



NATURAL PRODUCTS

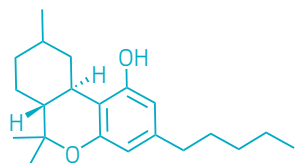
Waiting for CBD regulations in the US

Without oversight of hemp products, delta-8-THC, other cannabinoids flourish in unregulated market

BRITT E. ERICKSON, C&EN STAFF

A glowing CBD sign hangs in the store window. Inside are an array of products claiming to contain cannabinoids derived from hemp.

But the products for sale go far beyond nonintoxicating cannabidiol (CBD), known for its calming, antianxiety, and pain relief properties. Psychoactive chemicals like Δ^8 -tetrahydrocannabinol (delta-8-THC) and hexahydrocannabinol are for sale in gummies, tinctures, vaping oils, and other products intended to be ingested or inhaled.



Hexahydrocannabinol

Also for sale are products that have nothing to do with hemp. Some are analogs of delta-9-THC, the main ingredient in cannabis responsible for making users high. These chemicals differ only in the length of the molecule's carbon chain. The longer the chain, the more psychoactive—up to about eight carbons. Beyond eight carbons, the psychoactivity starts to decrease. Products containing tetrahydrocannabinophol (THCP) and tetrahydrocannabioctyl (THCjd), which have a seven-carbon and an eight-carbon chain, respectively, are more intoxicating than delta-9-THC, which has a five-carbon chain.

Companies that produce hemp-derived cannabinoids are also acetylating THC and THCP, making THC-O-acetate and THCP-O-acetate. These chemicals are potentially 100 times as psychoactive as delta-9-THC, warns Christopher Hudalla, president and chief scientific officer of ProVerde Laboratories, an analytical testing firm.

"It actually gets very scary with some of the modifications

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—**Christopher Hudalla**, president and chief scientific officer, ProVerde Laboratories

they're doing. There's no thought to consumer safety," Hudalla says. People who have eaten THCP-O-acetate gummies claim they were nonfunctional for 3 days, he says.

Some people say these emerging cannabinoids are exempt from the US Controlled Substances Act because they are made from hemp. But not all these products could possibly come from hemp, Hudalla argues. "There's no way you can make THCP from hemp," he says.

Hudalla explains that a cannabinoid with a seven-carbon tail can be synthesized only from a starting material with a seven-carbon tail. Hemp contains no chemical with a seven- or eight-carbon tail in any significant quantity, he says. THCP and THCjd are synthesized from commercial chemicals, he emphasizes.

Shops that sell intoxicating products under the guise of "hemp derived" are prevalent throughout the US. Unlike cannabis products sold in state-regulated marijuana dispensaries, these are not subject to quality and safety requirements.

Chemists like Hudalla have been sounding the alarm about contaminants in delta-8-THC products for several years. In the absence of federal regulations, they say the contamination problem has gotten worse and—with the proliferation of new cannabinoids—more urgent. "We see new structures all the time. There are 400 structures I've identified that might be in the consumer market," Hudalla says.

Delta-8-THC is typically made from

CBD. The process involves heating pure CBD in an organic solvent with a strong acid. Delta-8-THC is often considered a milder intoxicant than delta-9-THC. The only difference between them is the location of a double bond between two carbons. The chemical itself is unlikely to pose a safety risk, but contaminants and unintended reaction by-products are raising concerns.

Hudalla and colleagues have tested thousands of delta-8-THC items, including gummies and vape cartridges. They all contained by-products and impurities, he says. For some products, unintended cannabinoids made up as much as 40% of the total cannabinoids, according to Hudalla. Many of them do not exist naturally in cannabis and carry no safety information.

Some of those by-products are cannabinoids that are hard to identify using standard methods like high-performance liquid chromatography (HPLC) because their retention times and ultraviolet absorbance are similar to that of delta-8-THC, says Mark Scialdone, an organic chemist and founder of BetterChem Consulting, which specializes in the fine chemical and cannabis industries.

Two cannabinoids— Δ^8 -iso-THC and $\Delta^4(8)$ -iso-THC—are often confused with delta-8-THC when labs use HPLC, leading them to overestimate the amount of delta-8-THC in a product. But the three compounds can be distinguished by gas chromatography, Scialdone says. The R&D firm Cayman Chemical has even developed reference standards for the two iso-THC compounds to help commercial labs analyze delta-8-THC products.

One of the newer cannabinoids on the scene is hexahydrocannabinol (HHC). It is less common than delta-8-THC, but it is widely available online and increasingly showing up in vape shops. HHC can be synthesized from delta-8- or delta-9-THC. The reaction involves hydrogenation to remove the double bond in THC. It requires hydrogen gas, which is flammable, and metal catalysts, which can leave behind toxic metals.

Recent research by chemists at the University of California, Los Angeles, suggests that the R isomer of HHC has similar bioactivity to delta-9-THC but that the S isomer does not (*ACS Chem. Biol.* 2023, DOI: 10.1021/acscchembio.3c00254). HHC

products on the market are a mixture of the two isomers, and the amount of each varies widely, the researchers report.

HHC isomers were first synthesized in the 1940s, but until the UCLA study there was little information about their binding affinity to cannabinoid receptors and bioactivity in the human body.

“The compounds have been tested in animals before, but the basic binding assays of each isomer were somehow not done or not reported,” study author Neil Garg, an organic chemist at UCLA, says

in a press release. “That is unusual for a product that’s widely available to consumers, and it reflects the need for more fundamental research in this rapidly evolving field.”

The surge in synthetic cannabinoids began in 2018, when Congress legalized hemp in the farm bill. At the time, lawmakers were focused on unleashing the CBD market and giving farmers a new cash crop.

Major food and beverage manufacturers were anxious to start adding CBD and other hemp-derived ingredients to their products. But shortly after passage of the 2018 farm bill, the US Food and Drug Administration declared that it is illegal to add CBD to food and beverages or to sell it as a dietary supplement.

uptick in calls related to adverse effects of delta-8-THC products. From Dec. 1, 2020, to Feb. 28, 2022, the FDA says, it received more than 100 reports of such effects, including “hallucinations, vomiting, tremor, anxiety, dizziness, confusion, and loss of consciousness.” Even so, the agency has yet to regulate these products.

The FDA has a track record of going after only those companies that market products to children or that make unwarranted health claims. In July, the agency sent a handful of warning letters to firms for illegally selling foods that contain delta-8-THC and that mimic well-known snack food brands. Other than that, it has done little in the last few years to rein in the problem.

The hemp industry and some Republican lawmakers blame the current turmoil on the FDA, which maintains its position that CBD cannot be legally marketed as a dietary supplement or food additive. If the agency had allowed companies to add CBD to such products, the critics say, the industry would not have had the surplus that sparked the delta-8-THC craze.

Earlier this year, the FDA told Congress that it needs a new regulatory framework to regulate CBD. But many people say the FDA already has the authority it needs to regulate the substance in food and dietary supplements.

The agency’s inaction on hemp-derived cannabinoids came to a head during a July 27 subcommittee hearing of the Committee on Oversight and Accountability in the US House of Representatives.

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—Gillian Schauer, executive director, Cannabis Regulators Association

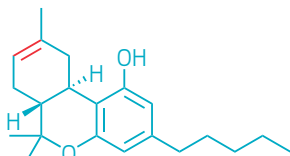
Although many small firms started marketing such products, the big companies stayed on the sidelines waiting for regulatory certainty. Some have now lost interest. Hemp farmers are struggling to find a market for their crop, and the price of CBD is at an all-time low.

While the CBD market languishes, firms have turned to delta-8-THC and other intoxicating cannabinoids that can be chemically synthesized from CBD.

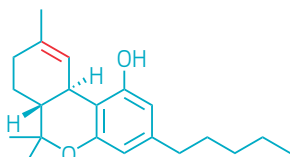
Poison control centers have seen an

The lack of federal regulations has severely impacted the hemp and CBD market, “resulting in a more than 90% commodity price decline,” Jonathan Miller, general counsel of the US Hemp Roundtable, testified at the hearing. The roundtable advocates for the hemp industry. The FDA’s inaction has crushed opportunities for hemp farmers, he noted. “It’s clearly time for Congress to act.”

“Beyond warning letters that mostly targeted illegal disease claims, the agency



Δ^8 -Tetrahydrocannabinol



Δ^9 -Tetrahydrocannabinol

has not engaged in meaningful enforcement,” Miller said. “This position, coupled with lack of action, has cast a cloud over the industry.”

The US Hemp Roundtable supports legislation that would provide a regulatory pathway for CBD as a food and beverage ingredient (H.R. 1628) and that would ensure hemp ingredients can be marketed as dietary supplements (H.R. 1629), Miller said.

The group also endorses regulation of intoxicating hemp-derived cannabinoids. “These products serve as a lifeline to US farmers and when manufactured properly can be of considerable value to adult consumers,” Miller said. “We oppose their ban or criminalization, but they need to be strictly regulated for safety and kept out of the hands of children.”

In the meantime, state regulators are stepping in. More than a dozen states have banned delta-8-THC, though they haven’t kept up with the alphabet soup of other cannabinoids on the market.

“Red states, blue states—every state is grappling with the public health and safety risks that come from unregulated, intoxicating hemp-derived cannabinoid products,” Gillian Schauer, executive director of the Cannabis Regulators Association

(CANNRA), testified at the July 27 hearing. CANNRA is made up of state government agencies that regulate cannabis and hemp.

These unstudied products are widely available “with no federally required testing for contaminants, no required packaging and labeling to tell consumers what is in the products or how they were manufactured, and no federal age-gating to ensure that intoxicating products are only sold to adults,” Schauer said. “This is in direct contrast to state-regulated marijuana or cannabis markets, which are regulated with consumer safety and youth prevention at the forefront.”

The 2018 farm bill does not specify which agency is responsible for regulating products that contain cannabinoids derived from hemp. The US Department of Agriculture has jurisdiction over hemp cultivation, but that authority ends once a plant is harvested.

Congress has a chance to fix the problem in the next farm bill, which is due later this year. The bill is renewed every 5 years. The current one expires Sept. 30, the end of the fiscal year. It is also the day the federal government will run out of money unless Congress passes a new budget or extends the current one.

Lawmakers left town for the month of August without giving much consideration to the farm bill, which has taken a back seat to budget negotiations this year. When they return in early September, they will have only a few weeks to reach a budget deal. A continuing resolution to prevent a government shutdown is likely, as is an extension to the farm bill to keep critical food and agriculture programs running until 2024.

With Congress at a standstill, and the FDA saying it can’t regulate even CBD under existing frameworks, it is unlikely that intoxicating hemp-derived cannabinoids will be regulated anytime soon.

“CBD is an easy one,” says Hudalla at ProVerde Laboratories. “If FDA won’t touch CBD, they’re certainly not going to touch the murkiness of the synthetics world.”

Some people have floated the idea of giving a different federal agency or a new agency authority over hemp-derived products. But no one expects that to happen anytime soon, either.

Others say Congress or federal agencies should just legalize cannabis. “End cannabis prohibition, and I think a lot of this will go away,” BetterChem Consulting’s Scialdone says. ■



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