

the Cannabis Scientist™

Upfront

Adolescent cannabis use linked to cerebral cortical thinning

06

In My View

Without federal action, what is the future of device regulation?

08

In My View

European lessons from the US' journey to cannabis legalization

09

Sitting Down With

Baller & biologist: Annabelle Manalo Morgan

22 - 24

Do You Believe in Unicorns?

Why the cannabis industry needs to awaken from its delta-8 daydream

12 - 21





We
BELIEVE
in
UNICORNS
(*and* **DELTA-8**)

Contaminated product, negligent testing, consumer safety concerns... Why is the industry turning a blind eye to the hazards of synthetic delta-8 THC?

*By Christopher Hudalla, President and Chief Scientific
Officer of ProVerde Laboratories, US*

Delta-8 is one of the hottest topics in the US right now. The problem: Delta-8 does not exist – at least, not in the form you might think. Everybody is arguing about unicorns. Everyone believes a unicorn should be treated humanely but the problem is that unicorns, like delta-8-THC, don't exist – certainly not in the commercial market. What do exist are heavily contaminated delta-8 products – mixtures of synthetic chemicals with impurity levels of up to 47 percent. By shifting the focus of the conversation onto the legality of delta-8, we are obscuring the real argument that it doesn't even exist yet. So how did we get here?

The 2018 Farm Bill defines hemp as “the plant species *Cannabis sativa* L. and any part of the plant, including the seeds thereof and all derivatives, extracts, cannabinoids, isomers, acids, salts, and salts of isomers, whether growing or now, with a delta-9 tetrahydrocannabinol concentration of not more than 0.3 percent on a dry weight basis.” It is easy to see the industry's thought process. CBD extracted from hemp is natural and legal. Trace levels of delta-8 have been observed in biomass; therefore, delta-8 is a natural product. And since delta-8 is naturally occurring, a derivative pathway from CBD for production is legal.

But here's the catch: The conversion of CBD to delta-8 is not a natural process. Many of the isomers and byproducts formed during the conversion are not naturally occurring, produced in the synthetic reaction to isomerize CBD to THC, which leads to both legal and consumer safety issues arising from what are essentially unknown contaminants. Synthesis is not a singular chemical reaction, but rather a system of parallel competing reactions, resulting in multiple synthetic outcomes. Many of the isomers and byproducts formed are not found in nature and have not been tested for safety or efficacy. In fact, we have no real understanding of many of these compounds. Without safety studies, and with their toxicity unknown, we cannot say they are not a health risk. As such, it would be irresponsible to recommend these products for human consumption.



I remember the first time I saw delta-10 THC gummies submitted to our laboratory. I thought: “This is cool. People are thinking outside the box. I love to see innovation.” The next thing I did was consult the literature. What do we know about the toxicity of delta-10-THC? What is the metabolic fate of the delta-10-THC molecule? Does it clear the liver? Will it cause cancer with repeated long-term exposure? Will use of these products trigger a positive drug test? Might it interact with other pharmaceutical drugs that a person may be taking? Will these compounds cause birth defects if consumed during pregnancy? What about some of the other THC isomers formed in the process? What about other synthetic byproducts? What about residual synthetic reagents left over in the product? There are lots of unanswered questions here.

Why do isomers matter?

Many people in the US have never heard of the drug thalidomide – and luckily so. US pharmacologists at the FDA turned down several requests from the distributing company because they did not provide clinical evidence to refute reports of patients developing nerve damage in their limbs after long-term use. And that prevented the drug from ever being approved for use in the US. Unfortunately, this wasn’t the case in Europe, Canada, and Australia. First marketed in 1957 in West Germany, the drug was promoted for the treatment of anxiety, sleep disorders, tension, and morning sickness in pregnant women. It took five years for researchers to realize that the drug was affecting the development of the fetus 20–37 days after conception. It is estimated that over 10,000 babies were affected by the drug worldwide. Around half died within months of being born. The thalidomide babies who survived – and their families – live with the side effects, which include issues with limbs, brain, eyesight, and hearing. Can we say with certainty that the synthetic compounds and isomers found in delta-8 products won’t do the same?

I had a client who was in ICU for 10 days after using a counterfeit THC vape product – which turned out to be a mixture of delta-8-THC with vitamin E acetate – that caused her lungs to collapse. Though it is most likely it was the vitamin E acetate that landed her in the ICU, she almost lost her life because of an unregulated product, distributed illegally. Already, National Poison Control has received around 600 exposure cases, 77 percent of which involved minors. Eighteen percent required hospitalization, with some children treated in the ICU. Are these the statistics of a safe product? And this rise in adverse events has seen key industry groups release statements. The Centers for Disease Control and Prevention (CDC) have reported that delta-8 intoxication is similar to that of delta-9,

“ I H A D A C L I E N T
W H O W A S
I N I C U F O R 1 0
D A Y S A F T E R U S I N G
A C O U N T E R F E I T
D E L T A - 8 P R O D U C T –
M I X E D
W I T H
V I T A M I N E
A C E T A T E – T H A T
C A U S E D H E R L U N G S
T O C O L L A P S E . ”

resulting in lethargy, slurred speech, low blood pressure, difficulty breathing, sedation, and coma. The United States Pharmacopeia (USP) said, “The prevalence of synthetically derived delta-8 THC raises safety and quality concerns related to both identity and purity – given the unknown and untested nature of the synthetic analogs and the remaining compounds.” The US Hemp Authority has also distanced itself from hemp products marketed for their intoxicating effects, including delta-8. The Hemp Industry Association has taken a different tack, advocating for safer production methods and FDA regulation of delta-8 THC, along with CBD and other hemp compounds. The FDA, on the other hand, has released a carefully worded warning letter in which they don’t explicitly say that delta-8 is a hazard, but that the products associated with delta-8 represent a hazard. And from what we see in the products submitted to our lab for testing, I agree with this position. The problem is not delta-8, but the unregulated distribution of synthetic, contaminated products.

At least Walter White
was a chemistry teacher

So, why don’t we just remove these synthetic compounds? Removal of these contaminants can be costly and time consuming, resulting in increased production costs. And that means reduced profits. In addition, the synthesis uses toxic chemicals and organic solvents. The resulting mixtures, in addition to non-natural isomers and synthetic byproducts, can contain residuals of these toxic reagents.



Most producers are not testing for acids, residual solvents, neutralizing bases, and heavy metals. How adept are producers at removing these residual reagents from their process? Without more testing, we'll never know. And that brings us to another problem: The DEA has said multiple times that synthetic cannabinoids are illegal – but who is willing to say delta-8 is synthetic? Not politicians, lawyers, or regulators, who are focused on the legality of delta-8. Not law enforcement who are afraid to enforce sanctions, arrest people or confiscate products. To make matters worse, much of the product is found via the internet, in which the producer may be nebulous – and difficult to hold accountable. All this ambiguity has created a huge window of opportunity for producers – and, of course, delta-8 has become a money printing machine, which nobody wants to disrupt. But given that many of the isomers formed do not exist naturally, they can only be classified as synthetic.

Another issue: Producers are oftentimes unaware that they are distributing crude mixtures of synthetic contaminants. Right now, most laboratories providing cannabinoid testing for these producers are using HPLC as their primary methodology. But these methods were optimized for cannabinoids found in the cannabis plant, and as such, are incapable of resolving many of the synthetic cannabinoids and synthetic byproducts. It's like using a screwdriver to pound a nail; though I love screwdrivers, it's just not the right tool for the job. And so there are often multiple chromatographic peaks hiding behind the delta-8 signal. Recorded retention times of these peaks do not match exact cannabinoid reference standards, so their presence is often omitted from laboratory reports.

“ NOBODY WANTS TO SEND ME A SECOND VAPE CARTRIDGE FOR ANALYSIS WHEN MY FIRST REPORT CAME WITH A WARNING: NOT RECOMMENDED FOR HUMAN CONSUMPTION .”

Without chromatographic resolution of these chemical compounds, these contaminants are often integrated into the delta-8 signal. Consequently, products that claim to be 90 percent delta-8 typically contain contaminants that have been erroneously attributed to the delta-8 signal. Many of the cannabinoids have similar retention and UV absorbance, making it difficult to distinguish individual isomers. The similarity of these structures is part of the reason why they are so challenging to resolve in a singular chromatographic method. The use of orthogonal analytical methodologies, such as gas chromatography or supercritical fluid chromatography, can be used to separate some of the chemical contaminant signals from the delta-8 signal, but this takes extra time and extra resources.

There are no two ways about it, 100 percent of delta-8 products that have been tested by our lab are heavily contaminated with synthetic byproducts. Most labs are not telling producers that they have found synthetic isomers and/or contaminants whose signals cannot be resolved from delta-8. With labs not reporting what they are seeing, producers are being led to believe that they have high quality delta-8 distillate. Naturally, they go on to make that distillate into vapes, edibles, and so on, and carry those contaminants along in the process.

Why do so many labs ignore the presence of these compounds? Are they just not able to understand what the chromatography is telling them? Are they afraid of losing the testing business from these producers? Our lab has lost significant testing revenues based on our policy for delta-8 samples, which includes noting the presence of these contaminants on our Certificate of Analysis (COAs). Nobody wants to send me a second vape cartridge for analysis when my first report came with a warning: No toxicity data is available for these unknown compounds, and as such would not be recommended for human consumption.

Although labs are part of the problem, they are not the only guilty party. Producers can plead ignorance because labs have not been forthcoming with the truth – or incompetent with their testing. But when I show producers what is really in their sample, they don't stop making it, they don't stop distributing it – they just go to another lab who will not acknowledge the contaminants found. Few other labs in the US will call attention to contaminants in the products we test, providing a clear warning that a product may not be safe or recommended for human consumption. And when consumers are provided with test results to confirm safety, at least against agricultural contaminants of concern, they are misled by the omission of data indicating contaminants that would be of a synthetic nature and

“ THE SCIENTIFIC COMMUNITY, FOR THE MOST PART, HAS BEEN VERY SUPPORTIVE VERBALLY – BUT FEW PEOPLE ARE STEPPING UP TO TAKE A PUBLIC STANCE AGAINST SYNTHETIC DELTA-8 .”





therefore of concern. In reality, we cannot say these contaminants are harmful for human consumption, but – more importantly to me – I also cannot say they are safe. The scientific community, for the most part, has been very supportive of our stance on consumer safety – but few people are stepping up to take a public stance against synthetic delta-8 products and the associated contaminants.

The solution

So, what do we do about it? The answer is to look to industries dedicated to manufacturing and testing synthetic compounds for human consumption. How is Viagra manufactured? Trained people put chemicals together, perform several synthetic reaction steps, and finally get to the desired compound – but never with 100 percent yield. And that could mean a multitude of synthetic reaction byproducts. Those unintended synthetic compounds are treated one of two ways: i) They are either removed through a purification step – like chromatographic isolation, or ii) these compounds are studied to ensure they are safe for consumption, to ensure their presence in a final drug product will not cause harm. Nobody that I know of is doing that for delta-8.

“ WE HAVE BEEN WORKING COLLABORATIVELY WITH MULTIPLE EQUIPMENT MANUFACTURES THAT PROVIDE INSTRUMENTATION CAPABLE OF THE NECESSARY ISOLATION OR PURIFICATION OF CHEMICAL COMPOUNDS, LIKE DELTA - 8 . ”

In fact, we haven't even identified many of the resulting compounds from delta-8 synthesis. Each producer or each batch that uses different acids, different temperatures, or different reaction times creates a different mixture of contaminants – so contamination profiles in these products can differ greatly. But we do see some common foreign signals in many of the products, and with the application of multiple analytical techniques, we are starting to get bits and pieces of information. In one sample, the mass spec isotopic ratios observed are indicative of a chlorinated molecule, with the mass of hexahydrocannabinol. We don't have the complete picture, but chlorinated cannabinoids are probably not a good thing. Recently, researchers have published studies using nuclear magnetic resonance spectroscopy, along with chromatography and mass spectroscopy, to identify some of the structures they found in selected consumer products. Several of the structures found, including one compound that has not been previously identified, have not yet been studied for safety or toxicity.

We have been working collaboratively with multiple equipment manufactures that provide instrumentation capable of the necessary isolation or purification of chemical compounds, like delta-8. These collaborations demonstrate that there is hope for legitimate delta-8 products. I have presented much of our data and concerns at conferences, and while much of the data is not favorable for delta-8 product lines, I like to end my presentation with examples from these collaborations of what delta-8 could look like. That is, what delta-8 should look like. And yet, I'm left somewhat amazed after my presentations. I present an alternative to the current contaminant-produced products, but do not get asked for additional follow up information on the conditions, equipment or collaborators which were capable of producing a purified product. It seems that most producers just are not interested because of the additional resources necessary to pursue this alternate route.

And make no mistake, it will take time to gain clarity on these compounds. They all need to be purified, isolated, and characterized. If they cannot be removed by purification, then they need to be studied for biological safety. Unfortunately, my lab doesn't have the equipment to purify and study all these contaminants. But even for researchers that have access to this equipment, it will take years to get the full picture and understand these complex mixtures completely. With the unregulated, non-standardized industry, the contaminating compounds are part of a shifting landscape; as noted, every time we see variation in the process, there are subtle (or major!) differences in resulting contaminant profile. And as long as people continue to change their processes, there will be new contaminants and new risks. No wonder it takes millions of dollars to bring a regulated drug to market...

Self-regulate or die

I want the industry to self-regulate so outside organizations don't have to shut it down. But I don't see that happening... Many in the industry instead are trying to move regulation of delta-8 under the US Farm Bill so it is treated and regulated like hemp. But this delta-8 is not an agricultural product. I am frustrated when producers present a COA which includes pesticide screening results. Pesticides are contaminants of agricultural concern. As soon as the added acid starts changing the chemical structure of CBD, it leaves the world of agriculture and enters the realm of synthetic chemistry – but farmers are not synthetic chemists. And neither are cultivators, extractors, nor most processors. If delta-8 should be regulated, it should be overseen by the same organizations that regulate other synthetic chemistry products intended for consumption: In the US, most likely the FDA. But FDA regulation of CBD, and with it, delta-8, would be challenging because it would mean producers would have to follow legitimate processes to produce their goods. These processes, which would include GMP production, are neither easy nor inexpensive to implement and maintain. FDA-regulation means audits, paperwork, manufacturing practice guidelines, as well as safety and stability studies. The bureaucracy associated with an FDA-regulated program would crush most current CBD and delta-8 producers, inevitably forcing consumers to the black market. But without any regulatory oversight, many states have already started to shut delta-8 products down. At the last count, 17 US states had outlawed delta-8 products – with no oversight, no responsibility, and no integrity – driving producers and consumers underground. And that's especially disappointing because delta-8 (without the contaminants) has legitimate therapeutic potential.

The silver lining

Raphael Mechoulam was one of the first researchers to see the therapeutic potential of delta-8. It has significant neuroprotective properties. It is also an appetite stimulant – and it has analgesic properties in terms of neuropathic and inflammatory pain, as well as anxiolytic properties, binding to CB1 and potentially CB2 receptors. Its antiemetic effects have been studied with pediatric chemotherapeutic treatment in the reduction of nausea to great success. In fact, delta-8 has an almost identical therapeutic profile to

“THE BUREAUCRACY ASSOCIATED WITH AN FDA-REGULATED PROGRAM WOULD CRUSH MOST CURRENT CBD AND DELTA-8 PRODUCERS, INEVITABLY FORCING CONSUMERS TO THE BLACK MARKET.”





waiting for FDA approval of CBD. These are all incredible benefits, but they must be treated with caution.

It worries me that the synthetic version of delta-8 has become so palatable to the cannabis industry. So much so that the industry is now comfortable moving forward with additional chemical modifications.

In the last few months, we have seen hexahydrocannabinol (HHC), THCP, delta-8 THC acetate, and delta-9 THC acetate (THCO) – synthetic cannabinoids

that aren't even pretending to be phytocannabinoids. And yet these are being sold as legal hemp derivatives, "Farm Bill compliant," which, according to lawyers, is lawful.

To put that into context, if you could find a synthetic pathway to convert CBD into methamphetamine or heroin, that synthetic process would make those products legal – after all, it would still be a hemp derivative. Really?

As long as I feel that consumers need to be warned about the risks associated with delta-8 products, and as long as regulators and health care professionals need to understand what these are, I will continue to be a mouthpiece for unpopular opinions. I cannot deny that I am also driven by scientific curiosity; it is very frustrating to say that I've found compounds or chemical signals that I cannot identify, and include that note on our certificate of analysis. But the laboratories who are not prepared to acknowledge these unknown compounds are doing no benefits to producers and consumers.

We certainly have the means to produce a clean, uncontaminated delta-8 with proper post-synthesis isolation and purification. It will take time, money, research, and regulation, but it will be worth it. I just need more people – preferably the whole industry – to see the light.

In the meantime, I still want to believe, so I will keep watching for legitimate delta-8 (and unicorns).

delta-9, but with only 20 percent of the psychoactivity.

If prepared without contaminants and used correctly, it could allow healthcare providers to treat the most vulnerable with cannabinoids, without getting them high.

From a commercial perspective, delta-8 is relatively easy to produce from CBD (at least without regulatory oversight) – and that's currently in overabundance. It requires minimal capital investment for production equipment and supplies, making it incredibly attractive to suppliers – especially in our turbulent economy. With the exception of purification, delta-8 can be produced inexpensively. So once we find a way to scale the purification process, those costs will also be reduced. And because the oversupply of CBD isolate has resulted in lower margins for manufacturers, conversion to THC represents a significant financial opportunity and provides salvation for investors

Image Credits

Cocoparisienne/Pixaby.com

Kym Mackinnon/Unsplash.com

Tyler Lastovich/Pexels.com

Secret Garden/Pexels.com

Rikonavt/Pexels.com