with daily cannabinoid news, research and opinions.

Current Affairs

Still Spinning in Circles: Fragments of a Harm Reductionist History of THC-O-Acetate

September 13, 2021 • Add Comment • by Carlton Bone, Upward Cannabis Kitchen • 635 Views

Written by Carlton Bone, Upward Cannabis Kitchen

Every harvest cycle, there is a new cannabinoid that comes to define the zeitgeist of the industry. The increase in cannabis extraction and isolation of compounds removed from *Cannabis sativa*, with both hemp and THC-dominant cannabis feeding the boom for concentrates, has also catalyzed tremendous enthusiasm and demand for cannabinoid science and chemistry.

In addition to the quest to genetically modify *C. sativa* to express particular traits, the concurrent project of processing flowers into increasingly refined extracts as a strategy for navigating ever changing regulatory paradigms has become commonplace. While growers work to identify genetics and cultivars expressing particular phenotypes, processors and manufacturers continue to explore ways to derive value from these traits. This has led to a resurgence of interest in cannabis stereochemistry, most evident in renewed exploration of the acetate ester of delta-9-tetrahydrocannabinol (THC) called THC-O acetate, the chemical that has been cryptically referred to as THC's more psychedelic sibling.

strategies surrounding THC remediation such as the nascent cannabinol (CBN) market. This minor cannabinoid has benefited from a meteoric rise in popularity

for sleep since the passage of the Farm Bill in December 2018. This phenomenon is less about the discovery of a new entity than the exploitation of marketing ploys alongside the surging market for cannabidiol (CBD). CBN was one of the first cannabinoids discovered during Roger Adam's initial isolation and synthesis of CBD [1], yet to the less-aware, it is advertised as a new and special cannabinoid with specialized benefit for sleep.

Contemporary interest largely relates to its chemical relationship to THC, and not its broader pharmacotherapy, and recent research into the effectiveness of CBD/CBN products aims to expand our understanding of the pharmacology of this compound. With the renewed US Food & Drug Administration (FDA) scrutiny of CBD and other cannabis derived supplements, it remains to be seen how the innovation around CBN will continue, and whether it will potentially come to supplement or replace the restrictions facing CBD.

Indeed, while interest and supplies for exotic cannabis compounds like tetrahydrocannabivarin (THC-V), cannabichromene (CBC), and even stable cannabinoid acid derivatives wax and wane, the legal dichotomy surrounding the regulation of *C. sativa* continues to hamper systematic inquiry into each of these compounds. And as long as scientific research is unable to keep up with the enthusiasm of consumers and the pace of technological development, our innovations will continue along this dialectic. While the cannabis science related to THC is worth exploring (and how this dialectic limits the potential of cannabis innovation), this essay takes a look at the recent "rediscovery" of THC-O-acetate and how contemporary discourse reveals tremendous ignorance of the past.

History

THC-O-acetate is not new. In fact, it is a reflection of some of the darkest corners of cannabis science, and parts of the past that the industry seems all too willing to neglect. Yet, it is readily available for study by anyone with a DEA I license.

A comprehensive history of THC-O-acetate is largely impossible to detail because some of these innovations, experimentations, and experiences were not documented, or the documentation has since been lost (as in the case of online forums and clandestine communications). Also, the US government comprehensively destroyed much of its early research into cannabinoids as part of the broader campaign to discredit Adams for his research into the plant [2] and to champion the international drug regime. This prohibition created a

timeline of significant events relating to THC-O-acetate has been constructed to illustrate the long and diverse history surrounding the moiety.

Timeline

- Starting in the 1940s, the US government conducted a series of military trials called the Edgewood Arsenal Experiments. During these experiments, they trialed a synthetic cannabinoid analog, dimethylheptylpyran, and its various isomers as non-lethal incapacitating agents. Program EA-2233 and its precursor, called EA-1476 (which explored red oil, or cannabis), was a non-success, finding only mild sedating and hallucinogenic properties associated with the compound and further identifying a heightened risk of low-blood pressure that creates confusion, fatigue, and dizziness at subclinical levels. Ultimately though, it was the overriding political context that drained support for the program most notably in the fact that only one sample of EA-2233 was ever created, and it took over a decade to separate particular stereoisomers. [3] As very little research was actually able to be conducted, and the optics of the program became increasingly unfavorable, the labs were closed in the 1970s after only a brief exploration of synthetic cannabinoids.
- The government's ill-guided experiments into the science of war, both in Vietnam and in the Edgewood laboratories, had the inadvertent effect of exacerbating both of these situations. In the context of cannabis use, the wave of soldiers returning from Vietnam brought an interest in intoxicants and drug cultures, the result of which helped catalyze the rise of cannabis as a counter-cultural symbol during the era. [4] In 1973, a clandestine chemist by the name of D. Gold published a book titled "Cannabis Alchemy: The Art of Modern Hashmaking" which would become a bible for cannabis chemists to this day. [5] Gold's project was aimed at undermining the efforts at regulating and controlling cannabis by democratizing the knowledge of how to process the plant drug. This is significant as the book would be republished and referenced periodically over the coming decades in both online forums about how to manufacture THC-O-acetate as well as in court cases about drug possession and distribution.
- The consistent context of THC-O-acetate throughout this period has been its categorization and appreciation as a synthetic cannabinoid, a term that first gained awareness in the general public through the rise of more noxious and harmful substances like Spice and K2 in the early 2000s. The sociopolitical and economic conditions that gave rise to these new drug

general public has been able to benefit from the resurgence of interest in more traditional synthetic cannabinoids, like THC-O-acetate.

Legality

THC-O-acetate is a pro-drug. Its pharmacological potential remains underexplored, and as an analogue, it has been soundly criminalized. This is an opinion shared by most legal minds in the cannabis field and, despite abstract discussions about both the law and chemistry, seems to accord with the enforcement history surrounding the compound. Indeed, despite US regulatory rescheduling of CBD, THC remains a Schedule I substance not just in the US but the world over according to the United Nations Convention on Psychotropic Substances (1971).

As a signatory state, the US is obligated to abide by the rules and regulations, and despite attempts by the US to have THC rescheduled as early as 1987, there remains little progress on rescheduling this substance internationally. The Commission on Narcotic Drugs overruled this recommendation as recently as last year, and while American consumers of cannabis may be confused as to the significance of international law for domestic law, it is worth noting how the broader category of "Designer Drugs," particularly as a cross-cultural framework for understanding illicit drug manufacturing, emerges in response to these conventions. We must keep in mind the global nature of these markets. The fact that Spice and K2 products emerged as the dominant forms of synthetic cannabinoids before the liberalization of cannabis policies in the 21st century and after the targeted criminalization of plant-derived analogues like THC-O-acetate in the second half of the 20th century indicates a recursive relationship between these drugs that deserves greater scrutiny and discussion.

Considering the emergence of D. Gold's *Isomerizer* in 1977 and the sustained global interest in the practice of cannabis isomerization and acetation within illicit cannabis cultures throughout the second half of the second century [6], it becomes clear how these synthetic cannabinoids are an inevitable feature of cannabis development, not just prohibition. As cannabis science finds its home in university and private labs across the globe while regulations continue to lag, the reality of THC-O-acetate (and other exotic cannabinoid products like 9-Nor-9β-hydroxyhexa- hydrocannabinol, HHC) are just the newest iteration of cannabinoid designer drugs, a fact further supported by the dynamics of grey-market product availability expanding. Understanding the rise in popularity of [illegible] encourages the proliferation of cannabinoid products) means resisting the knee-

jerk reaction to criticize it, and instead begs reflecting on the realities of drug use. [7]

Understanding the risk potential associated with products like THC-O-acetate is crucial, as adverse reactions and negative incidents are likely to undermine growing public confidence in the safety and tolerability of cannabis extracts. Stigmatizing users by appealing to the "unsafeness of the compound" and calling for overt criminalization of their manufacture exacerbates these risks by perpetuating an idea that there is a right way to use cannabis, as opposed to the reality that there are only less risky ways.

Users of designer drugs tend towards unique risk patterns (e.g., a greater tendency for polypharmacology). [8] This fact may have tremendous implications for understanding the safety and efficacy of cannabis-derived designer drugs. If THC-O-acetate is here, and likely to stay, ascertaining its safety and general toxicity is paramount. Fortunately, there is wealth of knowledge from harm reduction strategies to deal with designer drugs that can be drawn on for guidance as this process unfolds.

Harm Reduction Strategies for THC-O-Acetate

There is a tendency to approach anything unusual in cannabis with disdain. The visceral reaction to the "cannabumps" product is the tip of problematic drug chauvinism that has come to take hold in our industry and can be traced to the reactionary calls for regulation and criminalization of compounds like THC-O-acetate. This is because the push to normalize a particular kind of cannabis plant, consumer, and product inevitably perpetuates the stigmatization of certain kinds of drug users. Moreover, the overriding safety and legal concerns that motivate these beliefs neglect the basic reality of the matter, that there is no closing the Pandora's box of synthetic cannabinoids. We can't forget the "Iron Law of Prohibition" — that the potency of substances increases in line with enforcement [9] — when noting the coincidental emergence of THC-O-acetate during the peak of prohibition.

The general propensity to push consumers towards traditional cannabinoids and normative form factors is emblematic of the implicit moralizing that accompanies legalization. The paradigm of development that prioritizes safety, not as it relates to how consumers actually choose to use substances and relate to drugs, but instead anchored to legalistic ideas of health and wellbeing, is

substances and styles of consumption, we must let experience and compassion direct our response.

If cannabis advocates consider themselves harm reductionists, they should not view different drug products, practices, and markets antagonistically. The idea that there are good or bad cannabinoids inherent in the majority of the discourse surrounding THC-O-acetate is a microcosm of the same binary that enables criminalization in the first place.

Moreover, the dynamics of education and empowerment that underlie experimental drug use [10] (like New Psychoactive Substances (NPS) which encompass novel bio/synthetic cannabinoids) are invaluable examples of harm reduction in action that we can certainly learn from. Understanding what drives the use of new cannabinoid products is the goal of every marketing agency, yet there is a clear tension when these trends diverge from the developing stereotype of the cannabis consumer. It was literally within the last decade that the majority of Americans felt negatively about cannabis smokers, and we can't forget how much work remains to create a world where drug users are not stigmatized. This is why, rather than criminalize commoditizing novel or exotic cannabinoid compounds in a reactionary tendency, we might instead radically reconsider how we schedule cannabinoids themselves using new psychoactive substances or designer drug harm reduction principles as a guide.

References:

[1] Pertwee RG. Cannabinoid pharmacology: the first 66 years. *Br J Pharmacol*. 2006;147 Suppl 1(Suppl 1):S163-S171. [journal impact factor = 8.739; times cited = 471] [2] Campbell JN. *Bonds That Tie: Chemical Heritage and the Rise of Cannabis Research*. SpringerBriefs in Molecular Science. Springer: Springer Nature Switzerland. 2020.

[3] Ketchum J. S. *Chemical warfare secrets almost forgotten: A personal story of medical research testing of Army volunteers with incapacitating chemical agents during the Cold War (1955-1975)*. Santa Rosa, CA: ChemBooks, Inc. 2006.

[4] Chatterjee D. The mellow high and the psychedelic war. 2017

[5] Gold D. *Cannabis Alchemy: The Art of Modern Hashmaking*. Ronin Publishing: Oakland. 1973.

[6] Bone C. Spinning around in circles: Rediscovering THC-O-Acetate and

[7] Farre M, Gonzalez D, Ventura M, Caudevilla F, Torrens M, et al. Patterns of use of new synthetic drugs in a sample of research chemical users in Spain.