New Kinds of [Hash]tags: An Interdisciplinary Examination of Semi-Synthetic Cannabinoids

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ABSTRACT

The rise of distinct subcultures of cannabinoid users and the proliferation of new psychoactive substances derived from the hemp plant reflects a dynamic relationship between the development of new cannabis products and the growth of the markets for these goods. This research combines social science and analytical chemistry framework to explore the historical, linguistic, and chemical developments of cannabis acetates and related products over time Understanding the multiplicity of contexts that have influenced the trajectory of moieties like THC-O-Acetate is an attempt at detecting and identifying other new psychoactive substances with structural or functional similarities to Δ^9-THC through an interdisciplinary lens. The article concludes with a discussion on the potential implications of this kind of multidisciplinary research on new psychoactive substance research and regulation.

Introduction

The growth of the legal hemp industry has energized the market for cannabinoid infused products and increased the accessibility of cannabis extracts and isolates (Smart et al. 2017). The interest in these kinds of substances has led to the rise of distinct types of users, including consumers of cannabinoid concentrates (Cinnamon Bidwell et al. 2018; Daniulaityte et al. 2017). The commercial availability of CBN, CBG, CBC, and other distillates, in addition to infused products, such as terpene flavored vaporizers and gummies, reflects the popularization of specific compounds beyond just the familiar THC and CBD. The diversification of products can be correlated with the rise of manufacturing technologies and techniques that have increased the potency of cannabinoid concentrates over the past two decades (ElSohly et al. 2016).

A growing body of research on cannabinoids has accompanied the liberalization of hemp policy and the growing market for cannabinoid products (Strongin et al. 2021). Interest amongst both chemists and consumers has converged in the form of growing interest around what we term semi-synthetic cannabinoid products and digital communities vested in cannabinoid isomers (e.g., Δ^8-THC); acetate esters (e.g., THC-O-Acetate), and cannabinoid analogs like Hexahydrocannabinol (HHC). While research on synthetic cannabinoids has largely focused on the impact of completely synthetic cannabinoid products (Mills et al. 2015), like Spice, or oral pharmaceutical cannabinoid drugs, like Marinol (Calhoun et al. 1998), the proliferation of analog substances such as THC isomers and acetates in the form of hemp derived commodities, is only recently being explored (Kruger and Kruger 2021).

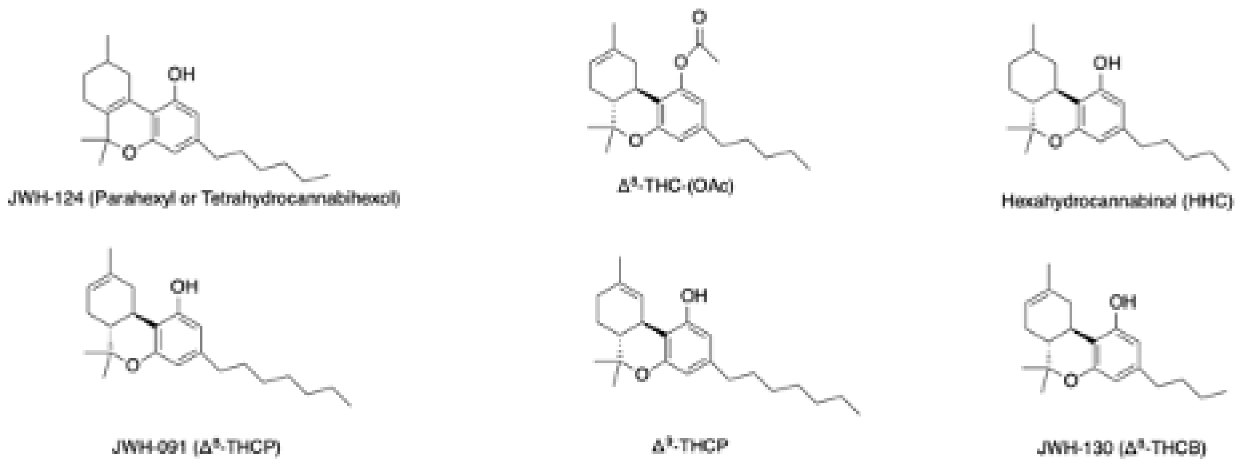

Figure 1. The overlap with between semi-synthetic and synthetic noids, especially surrounding emergent cannabinoids like THCP AND THCB is also an important consideration due to the existing networks for fully synthetic cannabinoid substances. Some of these moieties, such as JWH-124 were developed by synthetic organic chemists in the early 1900s, the most notable of which being Roger Adams. Recent developments in cannabis extraction have revealed the presence of minor cannabinoids in the plant itself that had previously only been synthesized outside of the plant. The growing overlap with existing categories for fully synthetic noids, as in the case of JWH-130 and JWH-091, is significant due to the International Scheduling of Parahexyl due to its functional and structural similarities to botanical tetrahydrocannabinol.

As the number of tetrahydrocannabinol analogs (Figure I) available for commercial consumption increases, the general confusion around the regulatory status, safety, and potency of cannabinoid concentrates only grows (Marcu 2020). The situation is exacerbated by an increasing number of states taking unilateral action to classify these compounds. Therefore, there is an urgent need to develop a comprehensive understanding of the identity of these substances and their intersection with both the legal cannabinoid industry and other drug using communities (Weiss et al. 2017). This research contributes to scholarship that aims to identify and detect harms associated with drug use through an interdisciplinary lens that combines chemical and anthropological insights to understand the materiality and language of new psychoactive substances like cannabinoid acetates (Zangani et al. 2020).

Methodology

In this article, we explore the shift in set, setting, and substance in the wake of the 2018 Farm Bill to understand the relationship between hemp regulations, markets, and cannabinoid products. "The set and setting hypothesis basically hold that the effects of psychedelic drugs are dependent first and foremost upon set (personality, preparation, expectation, and intention of the person having the experience) and setting (the physical, social, and cultural environment in which the experience takes place)" (Elcock 2021; Hartogsohn 2017). As the transformation of cannabis, and by extension the way consumers engage with cannabinoids, is likely to continue evolving rapidly (Caulkins 2021) there is a need to create a foundation for future research that engages with the multiplicity of contexts that influence cannabinoid product development, distribution, and consumption.

By collaboratively investigating the chemical and social dimensions of these substances we can provide deeper insights on both aspects of the phenomenon (Shapiro & Kirksey 2017). This approach demonstrates the utility of cross-discipline collaboration by examining the set, setting, and substance of the semi-synthetic cannabinoid THC-O-Acetate. Such collaboration is enabled by a shared understanding of the role of harm reductionist values in guiding research into new psychoactive substances (Des Jarlais 2017). This philosophy encourages us to engage with the drug users "where they are" to best meet their needs (Marlatt 1996), thus requiring us to develop a historically and materially informed understanding of specific drugs and drug using communities and their interrelated sets and settings (Dalgarno & Shewan 2005).

Social media analysis of online communities has emerged as an invaluable tool for public health experts (Hardon & Pool 2016) as demonstrated by the FDA's initiative to develop "Real World Evidentiary Standards" to regulate cannabinoids (Hahn & Abernethy 2021; Jaeger 2021). Hashtag analysis is an increasingly popular tool in the detection of novel online substances (Simpson et al. 2018) and has increased interest in the role of online forums in facilitating the rise and use of drugs (Gilbert and Dasgupta 2017). Importantly, the rise of online platforms and social media as an increasingly important fixture of emerging networks for new psychoactive substances presents new opportunities for exploring the impacts of linguistic and material changes on drug use communities.

Table 1. Emerging Terminology for Cannabis Acetates

Term	Comments
Cannabis Acetate	Includes substitutions for cannabis such as marijuana and hemp and extends to moieties like THC and CBD.
Marijuana Acetate	Less popular, but there are references to Hemp Acetate as well
THC-Acetate	Includes spelling variants such as "acitate" and conjunctions such as acetylation.
THC-O-Acetate	Increasingly shortened to THCO via variations overtime.
ATHC	N-Gram sequencing, spacing, and symbolism correlate with numerous variants such as THCA. Not to be confused with the lower-case variant, THCa which refers to cannabolic acid.
THCOA	Includes variant for CBD, as well as specification for delta 8,9, and 10.
THCO	Not to be confused with THCOA, this referent has emerged as the most popular signifier of the new substance.
Delta Zero	A mutation of isomer and acetate references, associated with THCO products
OAcetylTHC	Infrequent use, more associated with chemical processing than consumer products.
THC[O]Ace	Shortened, slang for THC Acetate.

On Instagram, hashtags are grouped with images and other meta-data that provides insights into the set, setting, and substance of each use case, making this a valuable platform for exploratory analysis (Cavazos-Rehg et al. 2016) In this study, the team created an account on the social media image-sharing platform Instagram and searched terms related to emerging cannabinoid products such as THC-O-Acetate (Table I). The search terms were identified through an examination of historical documents, internet forums, and industry related publications. The decision to use Instagram was motivated by the desire to understand the non-textual contexts (e.g., photos) that inform drug development and the language surrounding consumption and dissemination (Cleland & Macleod 2021). Due to ethical and logistical considerations, the team relied on a manual and iterative process of data collection where images were coded then stored in .JPEG format in an informal database. The search was predicated on an established list of terms visualized below (Figure II).

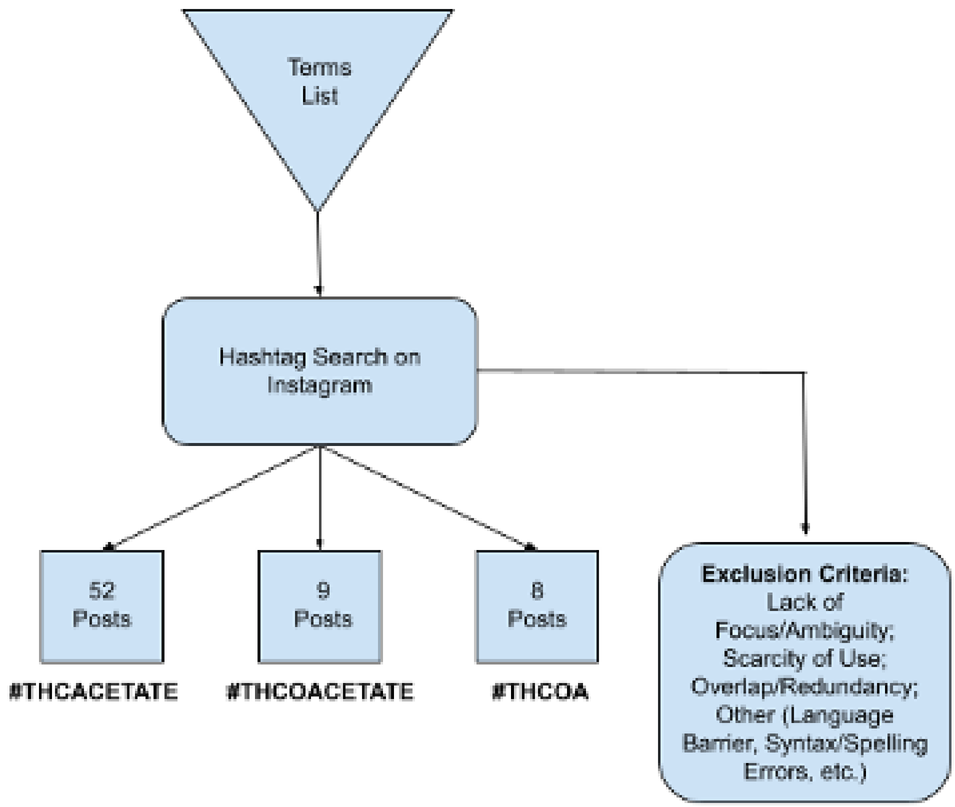

Figure 2. Diagram outlining the sampling process for the collection of data for the study. The focus on understanding how substances come to take on names and associations necessitates an investigation into the material and digital contexts that enable them. The focus on molecule specific conjugations is an important reflection of the emergence of specific cannabinoid commodities in line with the shift away from cannabis acetates to substances like THC-O-Acetate enabled by markets for hemp derived substances in the wake of the 2018 Farm Bill.

From this search, the research team identified three hashtags, with use cases dating back to 2016, that have been identified from this list, those being: #THCAcetate, #THCOAcetate, #THCOA. The Instagram filtered "Top Posts" algorithm helps focus analysis by creating a robust sample of posts that typify each hashtag. While the data collected reflects the sets, and settings of the online network associated with this THC-O-Acetate, the concurrent examination of substances and language bridges the gap between the digital and physical world. We believe this model of research enables a more rapid identification of harms and a more dynamic response by policymakers and community stakeholders.

Results

An increasing number of cannabinoids are being subject to acetalization to enhance their efficacy. The earliest innovations in cannabis acetates reflect both a transformation of the substance's potency, as well as its physical attributes (Bone 2018). The rise of commercial products in the form of concentrates and edibles has dovetailed with the rise in formulation chemistry as a means of transforming cannabinoids. Synthesis focused chemists have largely focused on the creation of new moieties or active ingredients, and formulation-based chemists look at how to blend active ingredients into form factors that are effective. The synthesis of new compounds is a different discipline from formulation or compounding of new drugs. The utilization of both methods to create new cannabinoid products has been a recursive process typifying the influence of "Green Chemists" -- a self-described term by chemists interested in the synthesis of cannabinoids.

Green chemists are critical to the product ontologies of many new psychoactive substance and exist as prosumers in this emergent network. Prosumers are individuals who have an influence over manufacturing and market trends because of their positioning as early adopters and explorers. This process facilitates a recursive process of co-production that must engage with the actions and beliefs of this constituency (De Rosis et al. 2020). Green Chemists exists across this network as both formal actors with careers in legal cannabinoid industries and as consumers of cannabinoid products. The various trajectories of different Green Chemists illustrate how socio-cultural contexts and community values ground individual practices and serve as overarching considerations when understanding the health antecedents and effects of new psychoactive substance use.

Sub-Section A: Chemical Analysis

The influence of "Green Chemists" is evidenced by two trends, those being formulations involving liposomal technologies (Ewell et al. 2021) and the creation of new moieties to enhance the potency of cannabinoid products. Early characterizations of THC-O -Acetate as a pro-drug – able to metabolize in the bloodstream – reflects a discourse on potency tied to chemical understandings (Bone 2021). The innovation of new kinds of edible formulations, e.g., beverages, with purported increased potency laid the groundwork for future experimentation and development of new cannabinoid products in ways that would take advantage of chemical enhancement or formulation to improve the efficacy of products. The current proliferation of new cannabinoids, new cannabinoid products, and new form factors can be traced back to these early efforts, however examination of the language surrounding these products reveals further evolutions in the wake of the passage of the 2018 Farm Bill.

Aside from having the potential to be confused with THC-O-Acetate, THCA is an important chemical because it is the naturally occurring compound in cannabis plant and the types of products that can be catalyzed from cannabinoids, including some of the isomers and analogs, revolve around this structure (Figure III). Understanding the degradation products of cannabinoids and their structural similarities, in context of the linguistic evolution of terminology for novel cannabinoid substances, can illustrate the nuances that exist in the current regulatory framework for cannabinoids. Unpacking the significant differences elucidates how complex it can be, distinguishing what kinds of structural or functional chemical changes are significant, the major legal challenge of liberalization, in the post Federal Analogue Act world (Fels 2021).

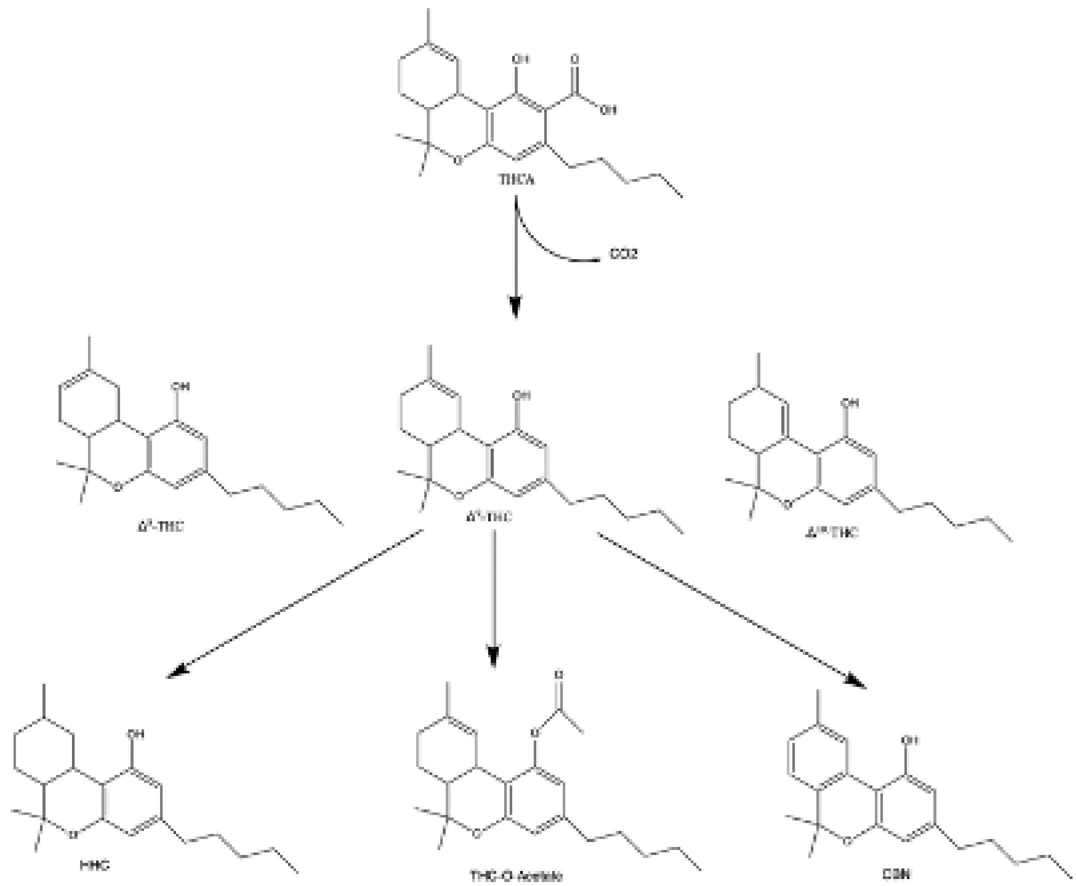

Figure 3. THCA harvested from the cannabis plant and various products that can be made from its decarboxylation. Decarboxylation of THCA leads to Δ^{9}-THC which can then undergo various reactions such as acetylation (forming the acetate seen above) or degradation (forming compounds like CBN). These are just two THC-like compounds that are commonly found on the market and used by consumers, although their potency and psychoactive effects differ from each other. It should be noted that analogous products displayed above such as Δ^{8}-THC and Δ^{10}-THC are commonly derived from CBD but many of the same chemical reactions are still being applied to these new compounds.

Sub-Section B: Social Analysis

There is a strong indication that Colorado and the Pacific Northwest (British Columbia to Oregon) are important places for the integration of “green chemistry” into the hemp and marijuana industries, both in the form of cannabinoid synthesis and molecular formulation. Notable examples of these formulations are the Adabinol and Adrapinol products, created by Dirty Arm Farms in Southern Oregon around 2016 (Jardine 2018), which have both linguistic and chemical similarities to oral synthetic cannabinoid pharmaceuticals such as Marinol and Nabilone. This is strengthened by the similarity in form factors. Strong similarities in branding and manufacturing techniques amongst competitors is further evidence of the common threads that unify these developments. As seen in Δ^{9}-THC in Marijuana Markets, the eventual rise of standardized branding, packaging, and the adoption of form factors popular to Hemp CBD products reveals a shared influence.

For instance, Colorado based firm, the Honest Marijuana company, launched an explicitly branded “THC-O-Acetate" product under the formula Nanobidiol, in 2019, with the CEO aiming to make Colorado the home of further innovation of cannabis acetates and isomers in a press release at the time of launch. Barriers on the export of marijuana limit the market potential and scope of influence of this product. Meanwhile, developmental trends seem to be shifting as Canadian based cannabis firm NextLeaf Solutions has acquired more than one patent on the technologies related to the production and synthesis of cannabis acetates since 2020, which further complicate the political-economic contexts of cannabis chemistry. As Oregon regulators have become the first state to create a path to market for these substances there is strong evidence that the linguistic evolution of the substance THC-O-Acetate and the interrelated network of sets and settings evidence how the liberalization of cannabis policy and the industrial hemp industry has helped catalyze this most recent phenomenon.

Figure 4. Top Posts from the hashtag "#thcacetate" aggregated by Instagram as of September 1st, 2021, based on their level of engagement, interest, and overall attention. Note the recurrence of photos depicting "Cannabis Alchemy".

Understanding the setting in which these transformations take place takes us to the first hashtag in our analysis, #THCAcetate (Figure IV) which is first used shortly after the passage of the 2014 Farm Bill which included the Hemp Act. Consistent through the total of 52 posts sampled, this hashtag reflects some of the earliest linguistic frames and the disproportionate representation of "Green Chemists" amongst references to cannabis acetates on the platform. A significant amount of the content associated with this hashtag is the use of scientific contexts, and the depiction of raw materials (e.g., bulk concentrate, typically in jars) as opposed to finished products or formulations (e.g., cartridges, edibles, etc.). The explicit reference to scientific texts and laboratory equipment alongside discussions of technique and technology is a recurrent trend, as is the connection to recreational cannabis industry stakeholders during this stage of evolution, one of the most notable being Instagram posts from Chris Barone, founder of "The Clear™", showcasing synthesized distillate (Figure V).

Figure 5. Barone's Instagram and ensuing conversation reflect the importance of green chemists in demonstrating the feasibility of early methods for synthesizing new cannabinoid products, like THC-O-acetate. The utilization of digital networks to share information is evident in the response by user "smokemeoutbrah". The trace quantities shown in the post are a stark contrast to the quantities and finished products characteristic of more recent posts.

In 2018, Barone's post (Figure V) would be explicitly referenced in a popular post with heavy user engagement about better practices and methods for "THC-O-acetate synthesis" on the cannabis forum Future4200, which may help explain the diffusion of knowledge and interest across digital spaces while also explaining how the "O" in the term first originated. In this thread, the Original Poster would reference a republication of D. Gold's "Cannabis Acetates" found on the popular cannabis blog, Skunk Farm Research. The elevated status of cannabis concentrates, and, by extension, science, is a result of the unique role that "green chemists" play as both consumers and innovators of products, while the historical legacy of D. Gold's Cannabis Alchemy attests to the influence of chemists in the language used to describe cannabis acetates.

The conversations surrounding the #THCAcetate depict a degree of experimentation contextualized by the different individuals engaging in the production of these early versions of the substance interpedently. Shared settings and sets between Green Chemists and foreground different experiences that are navigated through conversation on these platforms and beyond. The significance of this hashtag development is its indication of a trend of mutating of the referents for this substance, in this case by the substitution of the previously popular term "Cannabis Acetates" for the specific chemical THC. This unfixed language and evolving substance is also a reflection of the fundamental ambiguity and uncertainty surrounding these chemicals during this period of discovery and development. The emergence of hashtags, such as THCOAcetate and THCOA reflect a shift in association towards consumer goods and positionalities, like that which has occurred for legal cannabinoid goods in the wake of the 2018 Farm Bill (Mead 2019).

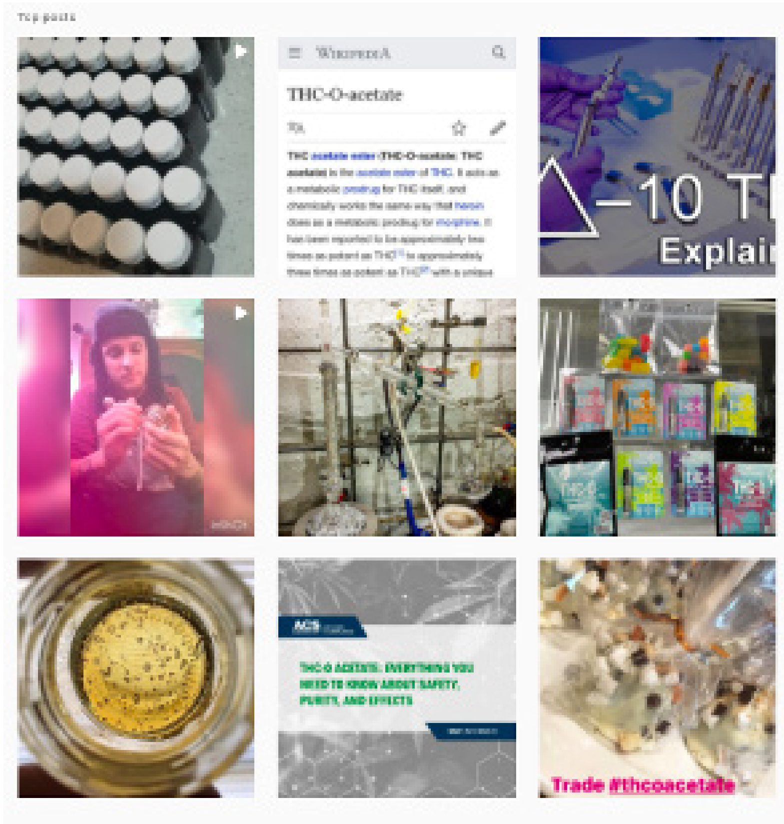

Figure 6. Collection of posts associated with the #thcoacetate on Instagram from September 1st, 2021.The lack of overlap with the Top Posts associated with the #THCAcetate and the qualitatively different content is significant.

Juxtaposed with the #THCAcetate hashtag that was oriented around the experience of green chemists, the change in imagery with #THCOAcetate (Figure V) is evidence of another class of stakeholders in this network, consumers, and distributors. This hashtag demonstrates the shift in experimentation from a scientific process to a consumer experience and becomes evident in the creation of new delivery systems and products. This shift is catalyzed by spread of knowledge and information from green chemists to communities of users interested in experimentation (Spillane et al. 2020) The nature of scientific discourse between posters in the one of the first posts associated with both hashtags back in 2017 (Figure VI) reflects how language is a mediating factor of the spread of new practices and beliefs.

Figure 7. The engagement on the post is dominated by a variety of other green chemists eager and interested in the process, and significantly the original poster currently works for a Canadian cannabinoid science company. The personal trajectory of this individual, as well as the discourse on the post itself, demonstrate the importance of these actors and networks to the integration of these substances into the legal cannabinoid industry via the proliferation of knowledge and expertise.

In contrast, the second use of the hashtag and is from a Colorado user sharing the first image depicting non-liquid, ingestible cannabinoid acetate products. In the text description for the 2017 post (Figure VI, bottom left square) seeks to trade "#thcoacetate #edibles for "sauce", a slang term for cannabis concentrates, an early indication of product variety. The wide spectrum of quality and quantity surrounding branded and packaged semi-synthetic cannabinoid consumer goods has accelerated rapidly since this time (Meehan-Atrash & Rahman 2022) suggesting a variety of distribution channels associated with the proliferation of these substances during this period. The shift from chemists to distributors is enabled by the integration of new substances into familiar form factors to make these substances, whereby substances become more intelligible in character and description and by extension more accessible to consumers.

A more recent post, (Figure VI, center left square) from July of 2020, reflects a more refined package and new form factor, indicating a distribution network with strong overlap with the market for hemp derived cannabidiol products. The emergence of cartridge vaporizers directly connects the two industries, materially by the shared reliance on the same form factors and technologies for these acetate products. As the markets for these products continue to grow, the relationship between green chemists, distributors, and consumers will likely continue to have a recursive effect on the language used to describe these substances. Trends like the shortening of terminology, evidenced in the next section exploring #THCOA as well as the creation of novel phrases like #THCOACE by users reflect the impact of this influence.

Terms like #THCOA, though not as historically prevalent as the previous hashtags are an important evolution in the network dynamics that constrain the evolution of this substance. Shortening of the term THC-O-Acetate in this way creates linguistic conformity with the multiplicity of other cannabinoids that are associated with hemp. As the terminology surrounding this substance continues to evolve, there is tremendous value in visualizing the chemical transformations involved in the degradation of THC. (Moreno-Sanz 2016; Wang et al. 2016).

Conclusion

In the past decade the scope and diversity of cannabinoids is rapidly changing, and the ability to understand the safety, toxicity, and potency of cannabinoid products depends on the ability to effectively identify not only chemical compounds, but also the contexts of their uses. How these substances are consumed, or their form factors, in turn intersect with the ways they are manufactured and how consumers come to understand their safety and potency (Berning and Hardon 2016). The capacity for any cannabinoid to be acetylated, coupled with the assumption that this process increases the potency of derived drugs, makes the potential harms of ketene formation more significant. Moreover, the identification of ketene formation during the decarboxylation of these acetate substances is an important harm that deserves further attention from both regulators and consumers considering the increasing commercial availability of these substances since the passage of the 2018 Farm Bill that legalized the cultivation of Hemp plants.

During the lung injury outbreak first recognized in the summer of 2019, research demonstrated that vaping vitamin E acetate led to the formation of ketene. Ketene is a highly reactive poison that was cited as a possible cause of e-cigarette or vaping product use-associated lung injury (EVALI). (Wu and O'Shea 2020). It has been known since 1938, that ketenes are created from thermolysis of phenol acetates, (Hurd and Blunck 1938) it is important to investigate its potential formation from the cannabinoid acetates. The team has recently found that all cannabinoid acetates investigated to date (Δ^8-THC, CBD and CBN as well as a commercial product containing Δ^8-THC-OAc), produce ketene under simulated vaping conditions (Munger et al. 2022).

Ketene reacts with biological molecules in a manner like phosgene, a chemical warfare agent (National Research Council 2014). One reported case described the development of symptoms of acute respiratory distress syndrome just 12 hours after a 5 min exposure to a concentrated mixture containing ketene (Huang et al. 2015). The acute effects were generally consistent with those observed in many EVALI patients (Attfield et al. 2020). Cyclic vomiting and nausea associated with cannabinoid use has been linked to EVALI (Spoons et al. 2021) and raises important questions about the intersection of Cannabinoid Hyperemesis and other vaping related illnesses. While the pathophysiology of Cannabinoid Hyperemesis is yet to be determined and there have been no cases explicitly associated with acetate products, there has been an association with heavy THC use, typical of dabbing (Pergolizzi Jr. et al. 2018), and it remains to be seen whether Ketene is implicated as a toxin that potentially contributes to this ailment (DeVuono & Parker 2020)

Discussion: From our analysis of social media images, we believe that green chemists have played an important role in influencing the evolution of semi-synthetic cannabinoids. The way language about these substances, product form factors, and packaging has developed since the passage of the 2018 Farm Bill reflects the scope and nature of this influence as it extends to the THC-O-Acetate. The significance of image-based analysis is that it enables a contextual understanding of the linguistic and material trends of developing new psychoactive substances (Fung et al. 2020). Providing context around the scientific processes of identifying these chemical substances with an anthropological perspective helps stakeholders at a variety of scales understand the relationship of these substances, sets, and settings to other drug practices, such as synthetic cannabinoids (Wiley et al. 2011) and botanical cannabis.

The identification of ketene formation during the decarboxylation of acetates at high temperatures is a unique harm identified with this emerging class of substances, highlighting the need for more research on semi-synthetic cannabinoids and the networks and actors that circulate them. In the face of ignorance and misinformation, consumer-led self-regulation has become an important force in shaping the growing market for semi-synthetic cannabinoids. This dynamic relationship between consumer and manufacturer is reified through the digital platforms that connect the multiplicity of contexts involved in consumption and production of cannabis highs (Belackova 2020). The identification of harms associated with semi-synthetic cannabinoid use both validates the interdisciplinary model utilized by the researchers which implicates the role of green chemists in the future of this substance's evolution (Ellis et al. 2019).

Product marketing has influenced increasing the perceived safety of semi-synthetic cannabinoids (Kruger & Kruger 2022), notably through their associations with botanical hemp and cannabis, in ways that mirror discourse around research chemicals and new psychoactive substances like fully synthetic cannabinoids (Cohen & Weinstein 2018). Our research demonstrates that these substances are not without risk of harm, and the need for due diligence by consumers and regulators is crucial in navigating this unfolding phenomenon. Peer-reviewed data is needed to establish the safety and efficacy of these substances and to compete with the misinformation being generated to sustain the markets for these products, as semi-synthetic cannabinoids are here to stay.

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Keywords: 2018 Farm Bill and Hemp Farming Act; Hemp; Federal Analogue Act; Cannabis Acetates; THCO and THC-O-Acetate Tetrahydrocannabinol (THC); Semi-Synthetic Cannabinoids; New Psychoactive Substances; Cannabis Chemistry, Medical Anthropology, Interdisciplinary Research, Chemo-Ethnography and Netnography