SPRING 2020 SYMPOSIA

PROCEEDINGS OF THE

CANNABIS CHEMISTRY SUBDIVISION

Assembled and Edited by Nigam B. Arora, PhD

CANN

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State of CANN

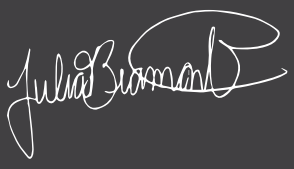
As 2020 has presented many challenges on a global scale, it has been met with great feats of adaptation and change. For CANN, this has meant evaluating and re-affirming our commitment to address racial and social injustices in our own community. This has also meant responding to the COVID-19 pandemic by providing alternate platforms and modes of connection for our members and affiliates. The CANN Spring Newsletter outlines our call to action, committee activities, and member resources. We encourage readers to follow the link to explore the various facets of our organization and what it has to offer.

CANN had a total of four symposia sessions planned for the Spring 2020 American Chemical Society (ACS) National Meeting scheduled to take place in Philadelphia, PA. While the in-person meeting was canceled due to the pandemic, CANN worked swiftly to offer our symposia virtually through a partnership with Cannabis Science and Technology. The resulting Spring 2020 CANN Virtual Symposium was comprised of three sessions: The 2nd Annual ElSohly Award Symposium; Advances in Cannabis Policy, Products, and Personal Use; and Breakthroughs: New Pathways for Cannabis Analysis. Each was a great success, bringing in over 300 attendees per session. While virtual meetings may not seem ideal compared to in-person, we found gratitude for the expanded outreach and dissemination of information that the virtual platform provided.

ACS, CANN's parent organization, has also adapted to holding events virtually. The upcoming Fall 2020 ACS National Meeting will be held completely online August 17–20. This meeting will include a full program of cannabis focused sessions hosted by CANN. Stay tuned on CANN social media channels for updates on schedule and registration information.

To continue the pursuit of information sharing, CANN in partnership with Analytical Cannabis is proud to provide the following proceedings from the Spring 2020 ACS National Meeting.

Sincerely,



Julia Bramante
Chair of CANN

The ElSohly Award

The ElSohly Award honors leading researchers, students, and industry professionals for their outstanding contributions to cannabis science. The award was named after Mahmoud A. ElSohly Ph.D., a leader at the forefront of cannabis chemistry and an active CANN member. Since the 1980s, he has run the only DEA sanctioned marijuana program at the University of Mississippi for the purposes of producing marijuana for research. He is also President and Laboratory Director of ElSohly Laboratories, Inc., and serves as Research Professor at the National Center for Natural Products Research and Professor of Pharmaceutics at the School of Pharmacy at the University of Mississippi. Through the work completed in his various roles, Dr. ElSohly holds over 30 patents and has authored over 250 scholarly articles, speaking to the tremendous impact he has had on the advancement of cannabis science.

The award is open to cannabis scientists from all walks of life–students, faculty, independent researchers, and professionals who work in the cannabis field are all encouraged to apply. Awardees receive travel funds to present their cannabis research at the American Chemical Society Spring National Meeting. Funds for the award were generously provided by Heidolph North America. Since inception, 16 researchers have received the award. The most recent 2020 awardees are listed on the right.

As we approach 2021, CANN is planning for the future of the award. 2019 ElSohly Award recipient Michael Coffin will be taking over as Chair of CANN Scholarship Committee which plans to continue offering the award through 2025 and beyond.

It has truly been an honor to help push the science of cannabis forward by providing a platform for dedicated researchers in the field to have their work recognized and shared. I am excited to see what the future holds for the award as the next generation of recipients tackle and address the ever-growing list of scientific questions being posed by this burgeoning industry.

Sincerely

Kyle Boyar

Kyle Boyar
Vice Chair &
Scholarship Committee Chair-CANN

2020
ElSohly Award Recipients:

Jacqueline von Salm, PhD

Jiries Meehan-Atrash

Justin Fischedick, PhD

Markus Roggen, PhD

Sang Hyuck-Park, PhD

Investigation of Chocolate Matrix Interference on Cannabinoid Analytes

David D. Dawson, PhD and Robert W. Martin, PhD
CW Analytical

As cannabis legalization continues to spread across the United States and abroad, legal markets are a patchwork of various rules and regulations. In an age where analytes, analyses, limits of detection, and even product types can vary from region to region,[1] it falls on third party cannabis testing laboratories to maintain highly precise, accurate, and rigorous analytical methods for the large and ever-expanding number of cannabis-infused matrices. As there are no standardized testing protocols in place, research into complex matrix testing in the cannabis industry is needed now more than ever. Our initial investigation of potency testing of complex cannabis-infused matrices begins with cannabis-infused chocolates, a ubiquitous product type in legal markets that accounted for 15% of retail sales in the combined legal markets of Arizona, Washington, Oregon, and California.[2] Relevant work in the field of allergen detection shows that components of dark chocolate can interfere with analyte detection, and understudied interactions between fats, sugars, and over seventy different organic flavoring compounds found in chocolate could cause deleterious matrix effects on cannabinoid extraction and analysis.[3–5]

In this study, several stock solutions of cannabinoids were prepared and subjected to various amounts of three different uninfused chocolate products: milk chocolate, dark chocolate, and non-Dutch cocoa powder. By creating stock solutions of Δ^9-tetrahydrocannabinol (Δ^9-THC), cannabidiol (CBD), cannabinol (CBN), and cannabigerol (CBG) at a known concentration in methanol, and measuring the percent recovery from varied amounts of chocolate products via HPLC analysis, a clear trend of matrix interference is revealed (Figure 1). For both milk and dark chocolates, the recovery rates for almost all cannabinoids decreased as more chocolate was added. Furthermore, the observed matrix interference is more pronounced for Δ^9-THC and CBN, which both contain a single phenolic –OH moiety, than it is for CBD and CBG, which contain 2 phenolic –OH groups (see Figure 2D). From the data in Figure 1, it was hypothesized that a cannabinoid containing zero phenolic –OH groups would have even lower recovery rates than the monophenolic Δ^9-THC and CBN.

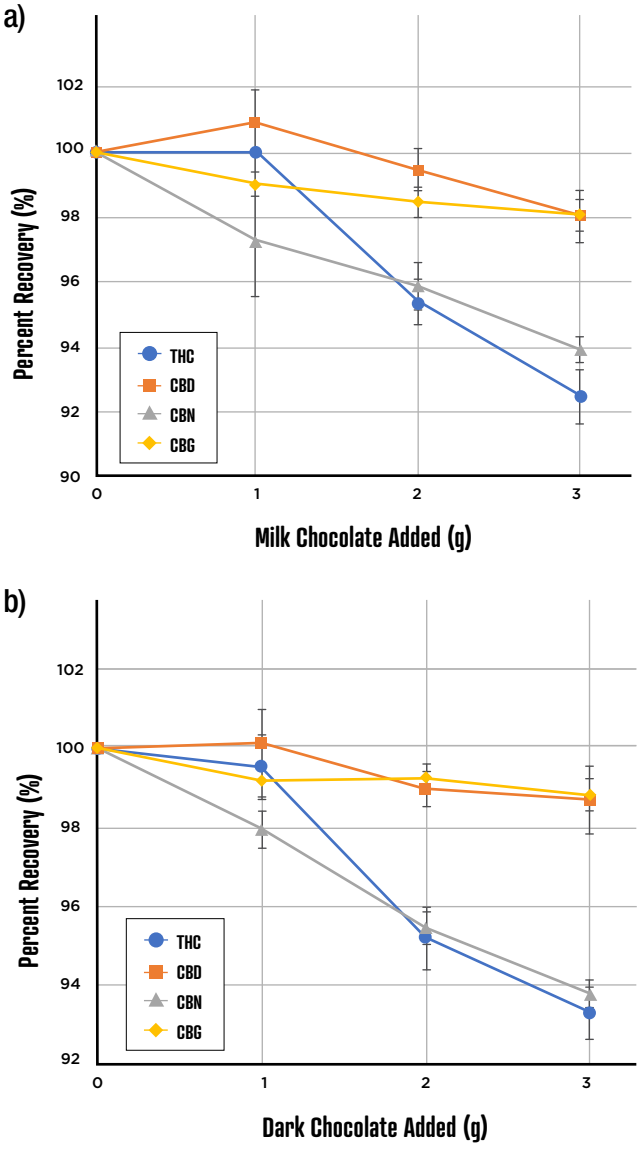
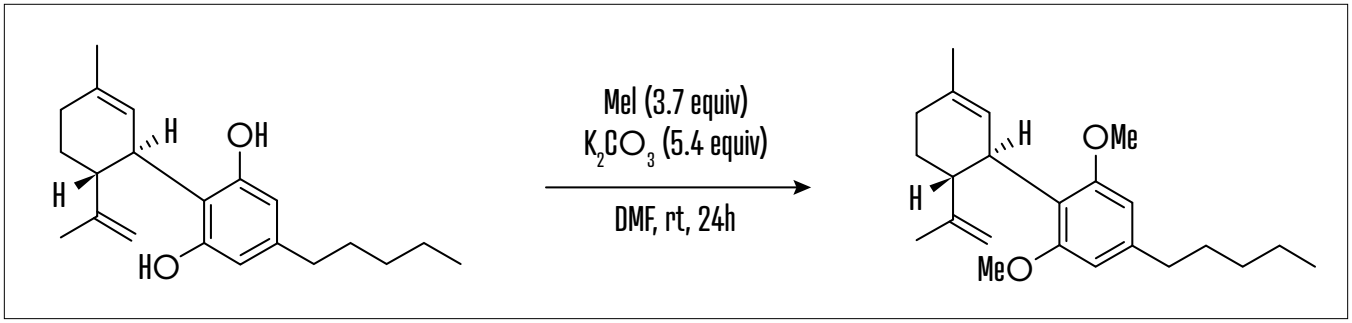
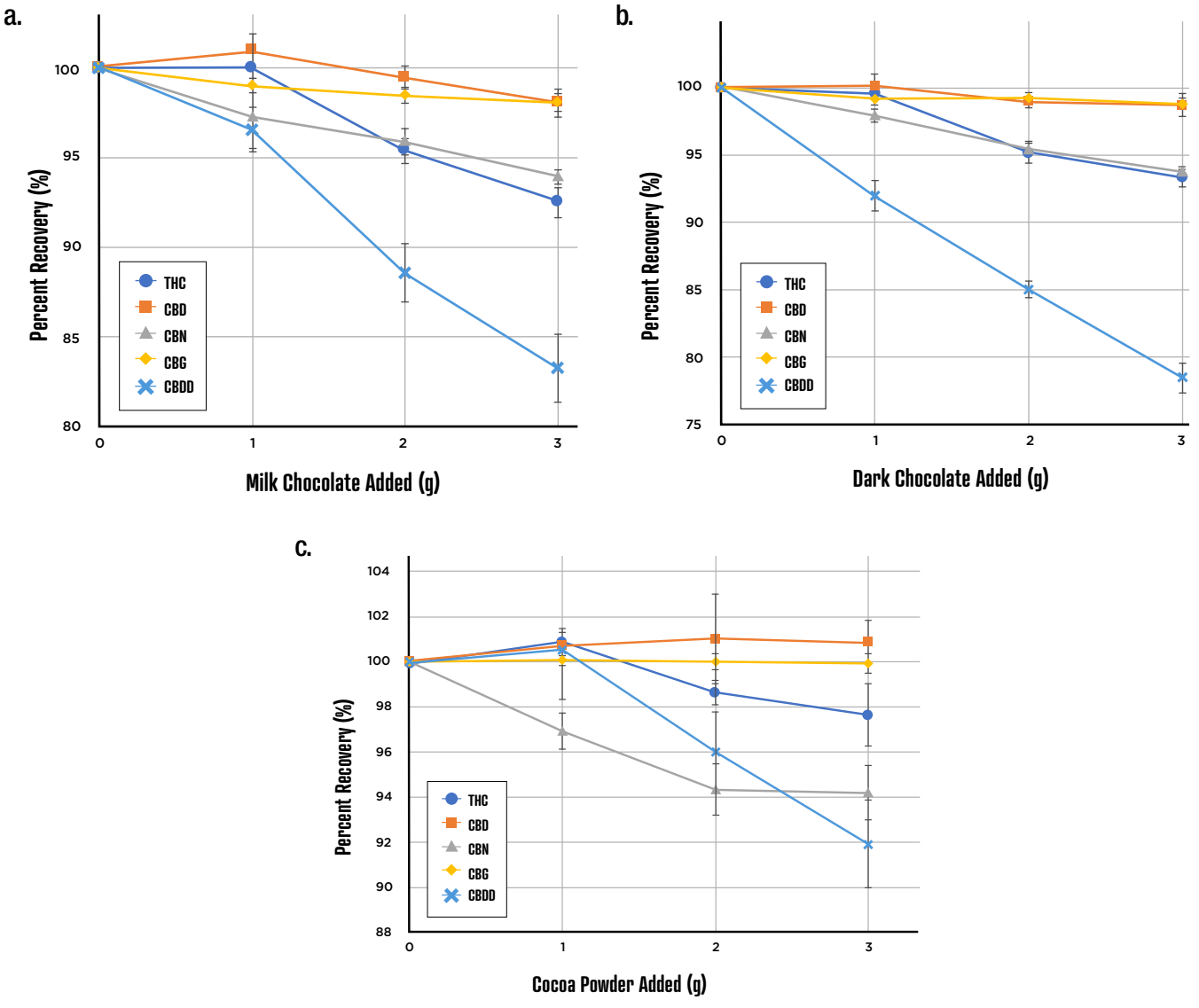


Figure 1: Investigation of matrix effects between four cannabinoids and A) Milk Chocolate and B) Dark Chocolate. All data an average of [n = 10] replicates.



Scheme 1: Conversion of CBD to CBDD; product was afforded in 78% yield.

To test this hypothesis, a synthetic modification was made to CBD according to a procedure by Mechoulam.[6] By methylating the two phenolic –OH groups, CBD is converted to the non-biogenic cannabidiol dimethyl ether (CBDD), which contains zero phenolic –OH groups (Scheme 1). When CBDD was subjected to the same experimental design as the other four cannabinoids (*vide supra*), our hypothesis was confirmed (Figure 2). Synthetic CBDD exhibits dramatically lower recovery rates than CBD; in fact, the 88% recovery seen with 2 g milk chocolate and 85% recovery with 2 g dark chocolate are lower than the lowest recoveries seen with either monophenolic cannabinoid. This data elucidates the outsized effect phenolic –OH groups play on cannabinoid recovery from the complex chocolate matrix.



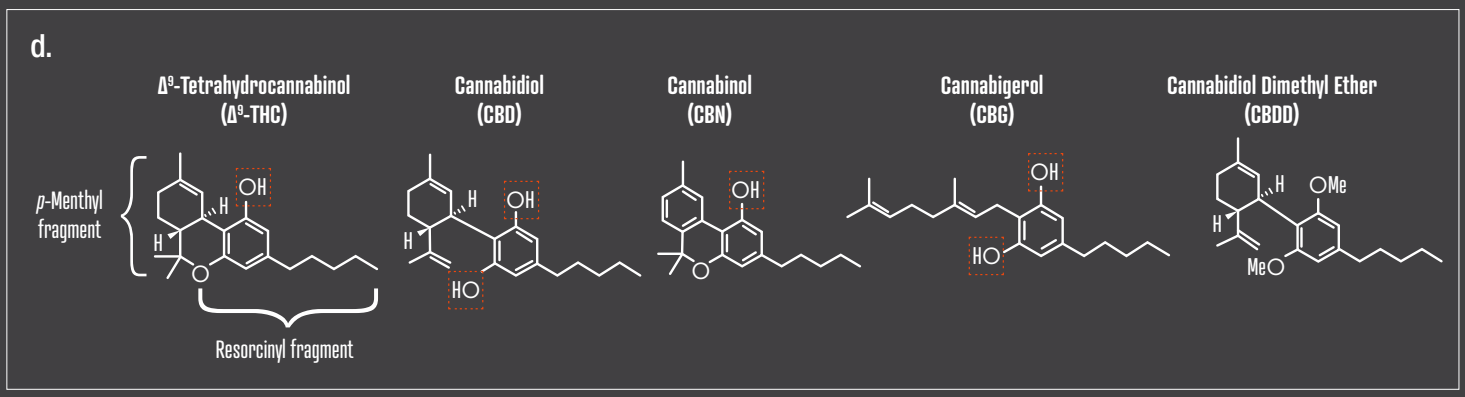


Figure 2: Percent recoveries for five cannabinoids from A) Milk Chocolate, B) Dark Chocolate, and C) Cocoa Powder. All data is the average of [n = 10] replicates. D) Cannabinoid structures, with fragments annotated and phenolic –OH groups outlined in red.

These experiments show that there are at least two major factors at play in determining the degree of matrix interference on cannabinoid analysis, both of which suggest the phenomenon is based on solubility differences between the cannabinoids. Cannabinoids with more phenolic –OH groups have increased polar character, which is likely to increase solubility in the polar, protic solvent (methanol), while also decreasing favorable interactions with the fatty, non-polar chocolate matrix. Thus, biphenolic cannabinoids such as CBD and CBG have an equilibrium state that lies closer to the solvent phase, which increases their recovery percentage. Conversely, a cannabinoid with no phenolic –OH groups has substantial non-polar character, decreasing favorable interactions with the solvent and pushing equilibrium towards the solid chocolate phase. The chocolate tested in this experiment is high in fats (~42% by weight), which has a well-documented affinity for the lipophilic cannabinoids.[7,8] This favorable cannabinoid-fat interaction is likely a cause of the significantly decreased quantities of analyte in solution, and thus the low recovery rates seen in Figure 2 for CBDD. Of note in Figure 2C is the uncharacteristically low recovery rates for CBN in the presence of cocoa powder. Breaking the trends seen for milk and dark chocolates, the suppressed recovery rate likely stems from interactions between the aromatized *p*-menthyl fragment of CBN and the high levels of flavan-3-ols found in cocoa solids, which has been shown to inhibit proteins via non-covalent London interactions between non-polar polarizable aromatic rings.[9]

The results disclosed herein represent the early stages of modern cannabis analytical research. In analogous fields such as pharmaceuticals, agriculture, and food chemistry, matrix effects on analyte testing is well documented, and testing methods are designed with these factors in mind. As the legal cannabis industry continues to make strides away from the black market and towards greater scientific legitimacy, any potential standardized testing methods must be based on detailed studies of the molecules and matrices involved.

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Quantitative and Qualitative Control of Cannabis Infused Products

Gene Ray, MSc
Garden Remedies Inc.

Quality assurance of cannabis infused products (CIP) are essential in both production and analytical screening. When performed correctly, production and qualitative testing can provide consumers with complete confidence in the labelled dosage. Due to the rapid innovation and growth in the edible sector of the cannabis industry, accurately formulating and analyzing products will consistently present challenges.[1,2]

Sample preparation is one of the main challenges as throughput decreases due to the complexity of matrices in most CIPs (i.e. chocolate, beverages, macaroons) compared to flower and extracts. Preparation of CIP samples require several steps prior to being analyzed. Depending on the type of product sample, several processes and/or preparative extractions are needed to achieve a clean finale sample for analysis. Selectivity ranges from different analytical instruments can also be an issue as they can show variance in final analysis results.

Processes such as appropriate use of standards, sample homogenization, phase separation, and complete compound extraction all play vital roles in proper analyses. Clean and well-prepared samples provide great baselines, reduced signal noise, less mystery peaks, and accurate reproducible methods for analysts.[3,4,5] Adhering to quality standards such as these gives manufactures the confidence to produce accurately dosed CIPs.

Another challenge is formulating to properly dose CIPs, which relies on current good manufacturing practices (cGMP), recipe management, and active ingredients analyses. Formulating with a complete tested concentrate or isolate of Δ^9-tetrahydrocannabinol (THC) and/or cannabidiol (CBD) maintains a standard and reproducible procedure to target a specific dosage. Infusing products with extracts containing a surplus of phytochemicals other than the active ingredients are prone to inconsistent test results, furthering the possibility of mislabeling. Testing samples throughout the formulating process is crucial to create quality assurance of each product. Inconsistent dosing levels of CIPs will cause consumers to experience a fluctuation of effects, which eliminates the possibility to adequately micro dose via titration. Consumers consuming more milligrams of THC than anticipated may experience adverse effects. The effects can include drowsiness, confusion, anxiety attacks, paranoia, and depression.[2]

Once THC is ingested the effects are delayed because the compound must be metabolized before crossing the blood brain barrier.[6] The variety of CIPs are vehicles that transports THC into the digestive tract where it undergoes first-pass metabolism inside the liver. THC is then hydroxylated to a more potent cannabinoid, 11-Hydroxy-Δ^9-tetrahydrocannabinol (11-OH-THC), which stays in the system longer.[7,8] The inaccuracies of CIPs will contribute to the uncertainty of psychoactivity and its prolonged effects.

The hurdles that remain related to variability of analytical test results, stringently reproducible formulations, the complexity of THC pharmacokinetics, and building consumer trust demonstrates the amount of proper growth that is needed for the industry. Dosage assurance should be commonplace when consumers choose to utilize CIPs. Providing the industry with standardized comprehensive procedures can produce uniform understanding and troubleshooting of these challenges across jurisdictions.

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Development and Optimization of Test Methods for Macro and MicroNutrients in Fresh Sap and Dry *Cannabis sativa* Leaves Using Microwave Digestion and ICP-MS

Amber Wise, PhD, Srinivasa Reddy Mallampati, PhD, Jessica Bailey, and Kyle Shelton
Medicine Creek Analytics

Many cannabis cultivators apply nutrients and fertilizers during the growth cycle in both indoor, greenhouse, and outdoor growing situations. A large challenge for cannabis growers is the lack of scientific research to back up production and application recommendations for this specific agricultural crop. By the time visual cues such as necrosis, discoloration or misshapen leaves are present, the imbalances can be difficult to correct with a short harvest cycle plant such as cannabis. By monitoring the micronutrient and macronutrient levels and ratios within individual plants, growers can use data-based decisions to ensure optimization of their nutrient application schedules, avoiding excessive run-off, undue costs, and potentially over-feeding plants.

This study was designed to optimize the microwave assisted acid digestion, sample preparation procedure, and inductively coupled argon plasma mass spectrometry (ICP-MS) analytical method for both macro and micronutrients in cannabis dry leaf and fresh sap (the fluid transported in xylem tubes or phloem cells of a plant). The macronutrients investigated include; calcium (Ca), magnesium (Mg), sodium (Na), potassium (K), phosphorous (P), and sulphur (S) while the micronutrients were boron (B), copper (Cu), iron (Fe), manganese (Mn), molybdenum (Mo), and zinc (Zn). Nitrogen was not analyzed because the elemental form that remains after microwave digestion is less important than the various molecular forms found in nature (NO_3^-, NH_4^+, etc.).

Two methods of sap extraction were investigated and a wheatgrass juicer was found to be more time efficient and create less cell damage over the garlic-press style extraction method. Microwave digestion parameters such as temperature, pressure and time were investigated and optimized to ensure full sample digestion. Further, given the nutrients are found at very different concentration ranges, two different dilutions were performed on digested samples before injecting to ICPMS to ensure injected solution concentration is within calibration ranges.

Nutrient	Isotope	Range of nutrient levels (avg)
Phosphorus	31	0.23-0.79% (0.54)
Potassium	39	1.5-3.1% (2.0)
Calcium	44	1.7-7.8% (3.6)
Magnesium	24	0.12-0.87% (0.50)
Sulfur	34	0.10-0.30% (0.21)
Boron	10	16-200 ppm (137)
Copper	63	1.9-14 ppm (7.0)
Iron	56	48-215 ppm (89)
Manganese	55	20-73 ppm (31)
Molybdenum	96	0.77-1.9 ppm (1.2)
Zinc	66	23-74 ppm (45)

Table 1: Isotopes monitored by ICP-MS and the ranges of values measured for various nutrients in dry leaf material from flowering stage cannabis plants.

Once sap sample preparation and analysis settings were optimized, assessment of two different types of client samples were performed: fresh sap for ratios of the nutrients in young vs. old leaves (data not shown here), and dry leaf samples for direct nutrient measurements (Table 1). The isotopes monitored using ICP-MS are also shown (Table 1). The data collected agreed well with previously published values of cannabis plants.[1, 2] Given that some nutrients can vary in plant tissues on an hourly basis as well as over the course of a growing or flowering cycle, it will be important to work with growers to develop standardized sampling methods to ensure data is comparable and relevant across different growing conditions and testing labs. Cultivators that want to utilize this kind of testing should work with a knowledgeable plant scientist to understand the relationships to soil pH, temperature, and levels of other nutrients in the cannabis plant's ability to uptake necessary nutrients. Baseline data of specific strains and growing conditions for healthy plants should be obtained in order to understand future measurements – a single one-off test is generally not useful to understand crop health.

This work has demonstrated the ability of microwave sample digestion combined with ICP-MS analysis to effectively analyze cannabis dry leaf and fresh sap samples for both macro and micro nutritional elements at a large range of concentration levels in cannabis leaves. Any lab with elemental testing capabilities could incorporate similar methods into their client offerings and as the industry continues to mature, more growers could utilize these types of tests to optimize nutrient applications and crop health.

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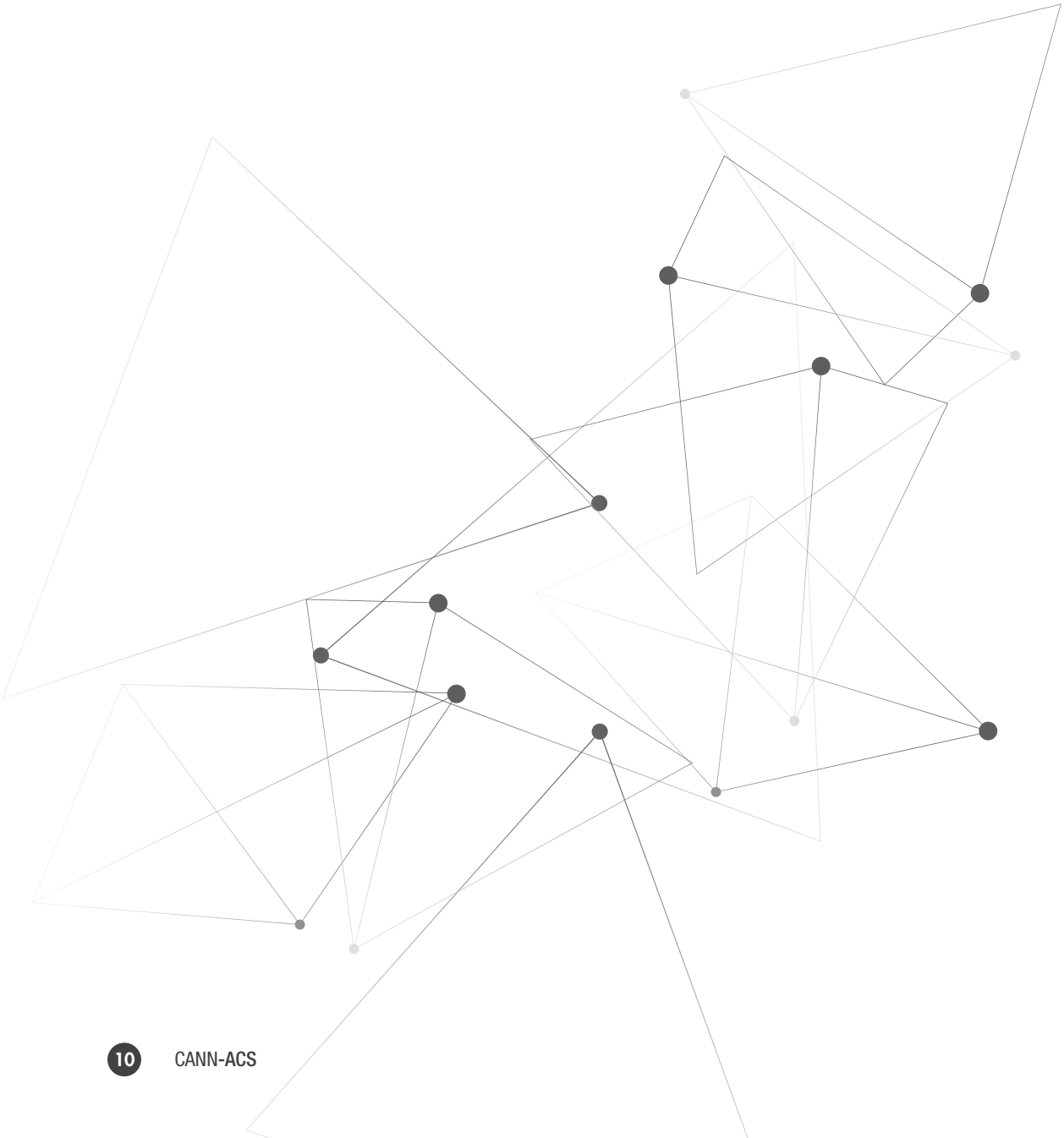


CannaClick™ CBD to THC Converter Personal Device

Alex Nivorozhkin, PhD
Arielium Health LLC

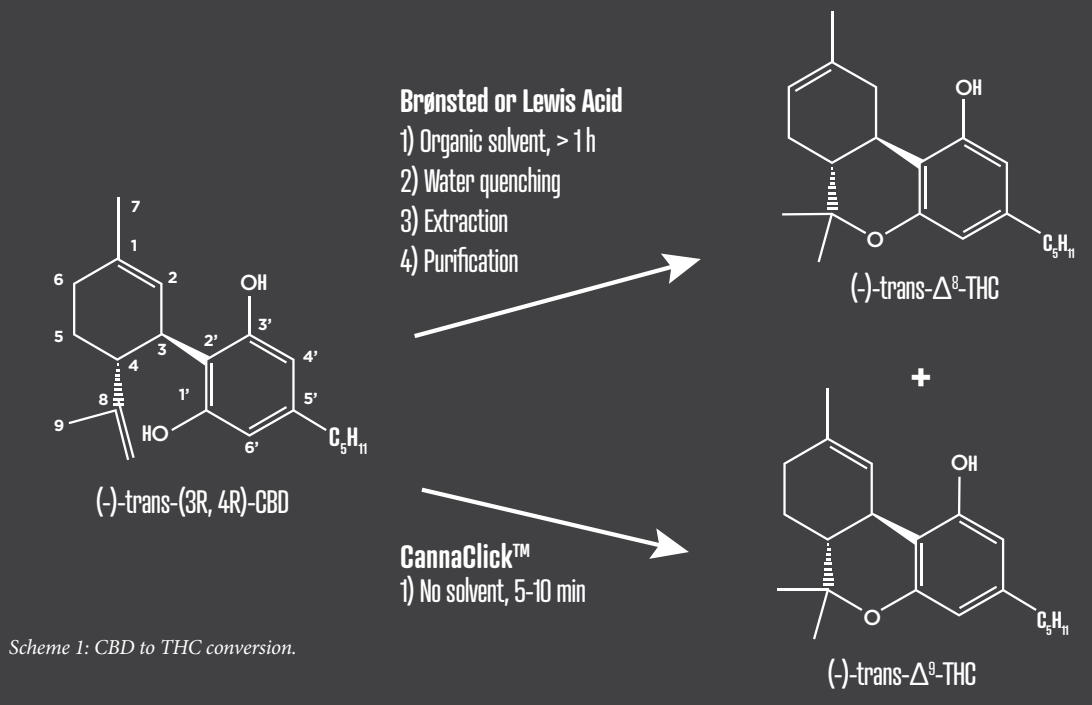
Combination of CBD and THC has recently become a staple modality for administration of phytocannabinoids. These combinations often times seek to alleviate psychotomimetic and other deleterious effects of THC and find an optimal ratio specific to the customer needs or medical conditions. The science of such combinations is still in its early days. However, it has rapidly expanded from a simple wisdom of 1:1 mixtures to a more complex view with shifts towards using lower THC, balanced dosing, and dose titration.[1] The actual relations between the effects of CBD and THC on the human body and associated dose response curves appear to be non-linear, with U-shape effects observed in multiple clinical studies[2]. Even in light of this, the only currently possible approach to choose and/or fine-tune the right "combination" product remains in scouring through the ever-changing offerings of specific dispensaries that are typically biased to very potent THC-rich products.

We sought to address this problem and provide on-demand access to well-controlled CBD/THC combinations by exploring the long-studied intrinsic proclivity of CBD to cyclize to THC. Conditions for this cyclization have been a subject of several investigations over decades since the dawn of the phytocannabinoid research in 1960s.[3,4] Although a transformation to THC does not occur in vivo through the consumption of CBD,[5] the motivation to explore the conversion under a variety of conditions has continued, culminating in the reaction chemistry as presented at the upper part of the Figure 1.

CBD exposure to BrØnsted acids such as toluene sulfonic in refluxed toluene has been found to lead to thermodynamically more stable THC-8. At the same time, Lewis acids (e.g., BF_3 Et_2O) in cold methylene chloride have produced predominantly Δ^9-THC-. Other Lewis acids such as zinc and iron chlorides have been later shown[6] to catalyze CBD to Δ^9-THC cyclization albeit proceeding sluggishly. Apparently, all these observations have had little practical implication or commercial applicability over the years other than an occasional reference to possible phytocannabinoid products degradation.[7]

We have revisited the chemistry of CBD-to-THC conversion and discovered a highly efficient process (also incorporated in related devices), which we have dubbed *CannaClick*™ technology (patent pending; depicted in the lower reaction of Scheme 1) with all the attributes of Click Chemistry, a term introduced by the Nobel Prize winner Barry Sharpless to define reactions that are fast, simple to use, easy to purify, versatile, regiospecific, and give high product yields.

Several iterations of the novel catalytic platform led us first to CBD-to-THC conversion solution chemistry under conditions more attractive than previously reported. We then increased a bias in this conversion towards formation of Δ^9-THC *vs.* Δ^8-THC. Ultimately, we have shown *CannaClick*™ technology affords a highly efficient solvent-free process with very fast reaction kinetics. Exemplary outcomes for one of our prototypic solvent-free transformations are presented in Table 1 (the reaction was run as a two-component mixture of CBD melt and a catalyst).



Scheme 1: CBD to THC conversion.

T, min	CBD, %	Δ^9-THC, %	Δ^8-THC, %	Total (CBD+ Δ^9-THC+Δ^8-THC), %*
1	67	27	6	95
2	52	37	11	93
3	37	47	16	91
4	15	56	29	91

Table 1: CannaClick™ reaction outcomes (Catalyst ARI-1342), 120°C (vs. total of detected cannabinoids).*

The mixtures with a CBD/THC ratio closest to 1:1 were produced in about 2 min at 120°C, with a good Δ^9-THC to Δ^8-THC selectivity of 3.4:1 and overall purity of total cannabinoids (CBD+ Δ^9-THC + Δ^8-THC) approaching 93%. The reaction outcomes were followed by HPLC and LC/MS that revealed only 2-3 minor side products, generated in a reproducible manner, all of them being structural isomers of CBD and THC, based on the universally observed m/z=315 dominant peak. The reaction can be driven to completion (<5% residual CBD) in about 8 min producing Δ^9-THC / Δ^8-THC mixtures (1.5:1 selectivity) with an overall purity close to 90% and maintaining a similar side products profile.

We have designed a prototype personal use converter device based on the described *CannaClick™* process to produce on-demand and tunable CBD/THC mixtures from CBD starting material that may be adapted in multiple ways, *e.g.*, suitable for vaping, (intra)oral, or topical use, which in turn may be complemented with add-on diluents, terpene blends, etc. In such a device, the phytocannabinoid product composition will be determined by a timer-controlled heating element used with a specialized CBD cartridge. Selected catalysts of the *CannaClick™* process are cost-effective as well as utilizing proven food compatible and leaching-resistant materials that can easily be separated from the mixture for discard.

After completion of the proper safety studies and regulatory clearance, it is expected that advancement of the *CannaClick™* converter into a consumer product will provide the potential to greatly benefit a community of medicinal cannabis users (as well as recreational users) through: (1) controllable/tunable access to CBD/THC products with standardized and predictable outcomes, (2) enablement of lower ratio THC combinations better suited for more balanced dosing and dose titration, and (3) improving the overall economics of phytocannabinoid products unaffordable for many in need. Furthermore, it may also equip medical professionals with a convenient precision delivery tool to enable flexible clinical trials and gain further insights into the fascinating pharmacodynamics of phytocannabinoids.

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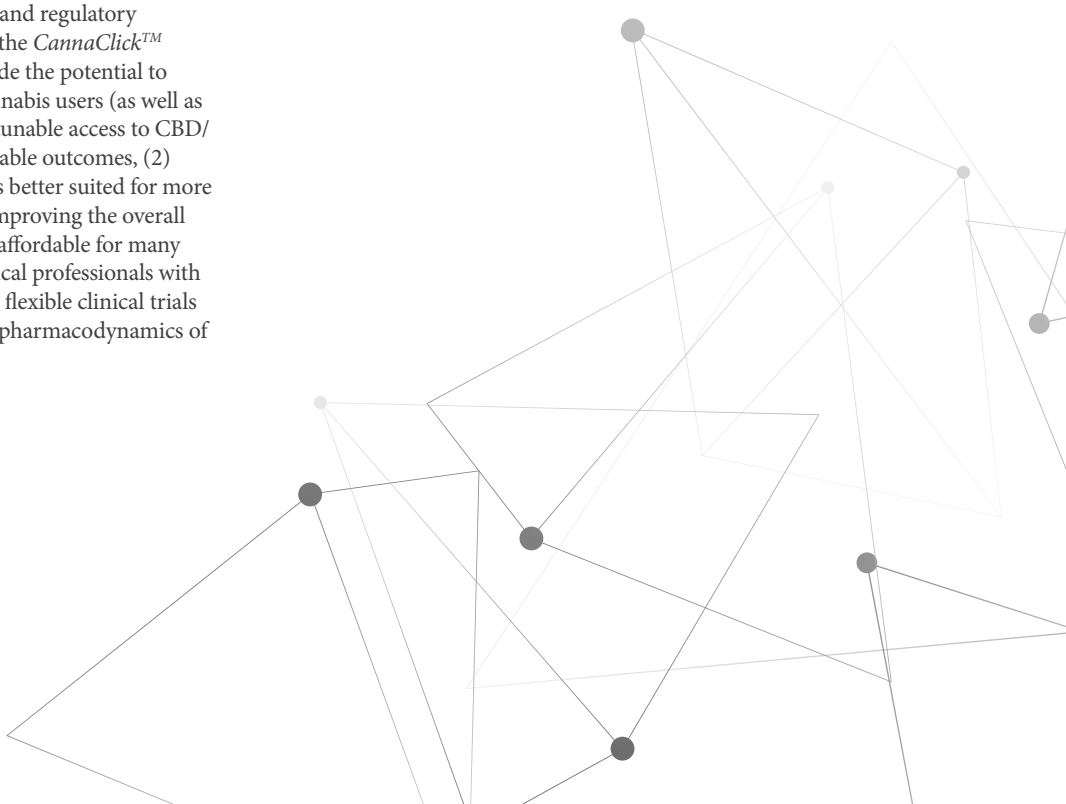


Detection and Differentiation of THC and CBD in the Palm of Your Hand with Organic Thin Film Transistors

Benoît H. Lessard, PhD
University of Ottawa

Organic semiconductors such polymers or small molecules. These active materials present some advantages over traditional silicon-based electronics such as the potential for relatively inexpensive manufacturing, easy flexible integration, and even biocompatible or implantable application. Over the past two decades, significant progress has been made in the development of organic electronic devices such as organic light emitting diodes (OLEDs), which can be found in most cellphone displays, flexible and curved TV displays and other wearable technologies. Organic thin film transistors (OTFT), are carbon-based logic gate operators which can be used as an electrical switching element such as pixel modulators in bendable active matrix OLED displays. OTFTs can also be used as sensors for the detection of different gases, liquids, chemical, or biological analytes. Specific interactions between the environment or the analyte and the semiconductor will lead to unique detectable electrical responses.[1–4] These responses can be tuned through engineering new semiconductors leading to ultra-sensitive and specific sensors. Being strictly electrical, the sensor can easily be miniaturized and manufactured at a fraction of the cost of other optical or chromatographic-based sensors on the market.

Recently we developed an OTFT based sensor for the detection of cannabinoids.[5] The sensor is based on the chemical reaction between primary cannabinoids, Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) and a common colorimetric trapping agent, Fast blue BB (4-amino-2,5-diethoxybenzanilide diazotated zinc double salt, or FBBB). Figure 1 illustrates a typical OTFT based sensor which uses FBBB. We report the detection and the differentiation of the resulting FBBB-CBD and FBBB-THC conjugates.[5] The sensor effectively characterized and differentiated THC and CBD in vapors, from a solution, and from a plant extract. Due to the unique two-dimensional electrical response obtained from the OTFT sensor we could even differentiate THC and CBD from known interfering compounds cigarettes, coffee, wood smoke, etc. The sensor could provide a ratiometric analysis of different CBD:THC ratios within 5% error of a standard analytical technique such as high-pressure liquid chromatography (HPLC). Current research efforts are focused on improving our understanding of the interactions between the THC and CBD conjugates and the semiconductor in the OTFT. Preliminary results are showing that modifying the semiconductor leads to predictable changes in sensor performance. Structure property relationships will facilitate the development of more sensitive sensors.

OTFT based cannabinoid sensors are a promising technology, which can lead to low cost detection and identification with a small footprint. The sensor could easily be adapted for hand held diagnostics and could therefore be useful by law enforcement as well as cannabis producers looking for plant-side analysis. The technology is currently patent pending and part of Ekidna Sensing Inc. a startup based on this technology.

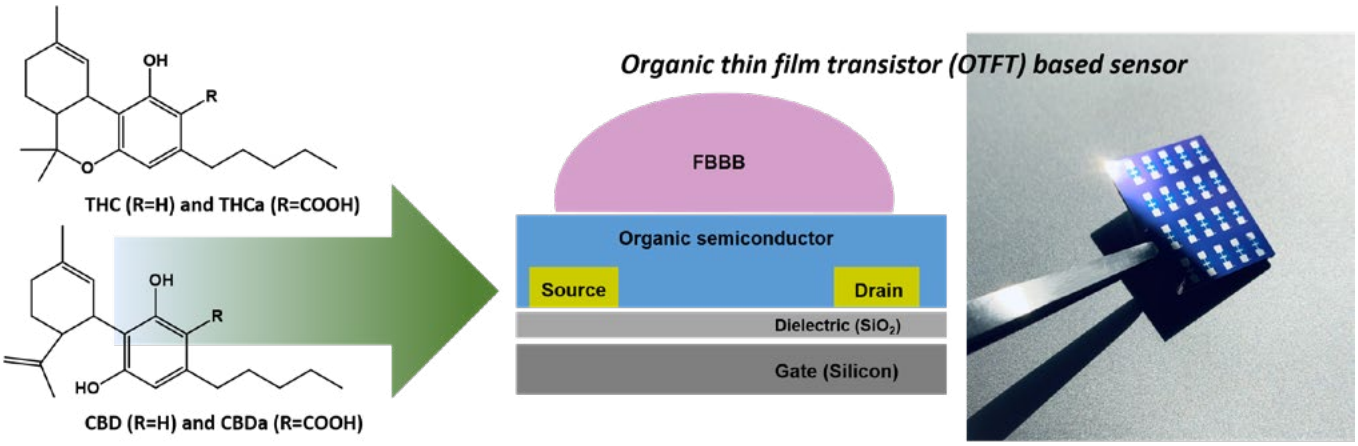


Figure 1: Chemical structure of Δ°-tetrahydrocannabinol (THC) and cannabidiol (CBD); side view of an organic thin film transistors (OTFT) based sensor as well as a picture of an actual sensor array.

1. *Boileau, N. T.; Cranston, R.; Mirka, B.; Melville, O. A.; Lessard, B. H. Metal Phthalocyanine Organic Thin-Film Transistors: Changes in Electrical Performance and Stability in Response to Temperature and Environment. RSC Adv. 2019, 9 (37), 21478–21485. https://doi.org/10.1039/C9RA03648B.*
2. *Brixi, S.; Melville, O. A.; Boileau, N. T.; Lessard, B. H. The Influence of Air and Temperature on the Performance of PBDB-T and P3HT in Organic Thin Film Transistors. J. Mater. Chem. C 2018, 6 (44), 11972–11979.*
3. *Boileau, N. T.; Melville, O. A.; Mirka, B.; Cranston, R.; Lessard, B. H. P and N Type Copper Phthalocyanines as Effective Semiconductors in Organic Thin-Film Transistor Based DNA Biosensors at Elevated Temperatures. RSC Adv. 2019, 9 (4), 2133–2142.*
4. *Samantha, B.; Melville, O. A.; Brendan, M.; He, Y.; Hendsbee, A. D.; Han, M.; Li, Y.; Lessard, B. H. Air and Temperature Sensitivity of N-Type Polymer Materials to Meet and Exceed the Standard of N2200. Sci. Reports (Nature Publ. Group) 2020, 10 (1).*
5. *Comeau, Z. J.; Boileau, N.; Lee, T.; Melville, O. A.; Rice, N.; Troung, Y.; Harris, C. S.; Lessard, B. H. .; Shuhendler, A. J. . On-The-Spot Detection and Speciation of Cannabinoids Using Organic Thin Film Transistors. ACS Sensors 2019, 4 (10), 2706–2715.*

Advanced Microsampling and Microfluidic-based Approaches for Cannabinoid Analysis in Blood

Laura Mercolini, PhD and Michele Protti, PhD
University of Bologna

Defining cannabis consumption levels and intoxication states currently represents a complex bioanalytical challenge. In some cases consumption can only be reliably demonstrated by using blood as the biological matrix. However, sampling is invasive, requires specialized environment, trained personnel, storage precautions, and complex handling, leading to potential logistical and analytical issues. For this reason, the use of miniaturized sampling approaches can be a promising alternative. Dried blood microsamples reflect the composition of circulating whole blood, but their sampling is much faster, less complicated, less invasive and, once dried can be stored at room temperature without any appreciable analyte loss. Dried blood spot (DBS) technology has been exploited in bioanalysis in place of plasma or serum to enable home-based and on-field applications,[1] however its implementation has been limited mainly by concerns related to hematocrit effect on method accuracy and sample homogeneity. Novel and advanced miniaturized sampling technologies, based on classic DBS (Figure 1a) and also on volumetric absorptive microsampling (Figure 1b) and capillary volumetric DBS (Figure 1c), have been developed in order to eliminate hematocrit effect, accuracy bias, and other disadvantages while still granting feasible sample processing and reliable quali-quantitative results.[2,3]

Among the research projects carried out at PTA Lab at the University of Bologna (Italy), multiple novel blood microsampling and microfluidic approaches have been developed and compared in order to study their potential for cannabinoid analysis. Original LC-MS/MS methodologies were developed and validated for the analysis of Δ^9-tetrahydrocannabinol (THC) and its main metabolites in whole blood dried microsamples (Figure 2).

THC blood levels decrease drastically after Cannabis consumption, being metabolized to 11-hydroxy-Δ^9-tetrahydrocannabinol (THC-OH). THC-OH is in turn metabolized to 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (THC-COOH) (Scheme 1).

The ultimate goal of these miniaturized approaches is to provide highly innovative blood microsampling analytical protocols, whose performances were extensively optimized and compared, in order to provide effective and alternative tools that can be exploited for cannabinoid determination. Immediate applicability lies in all the contexts where out-of-the-lab collection and impromptu processing are needed, *i.e.* clinical settings, workplace, roadside enforcement, forensic cases, or sport drug testing.

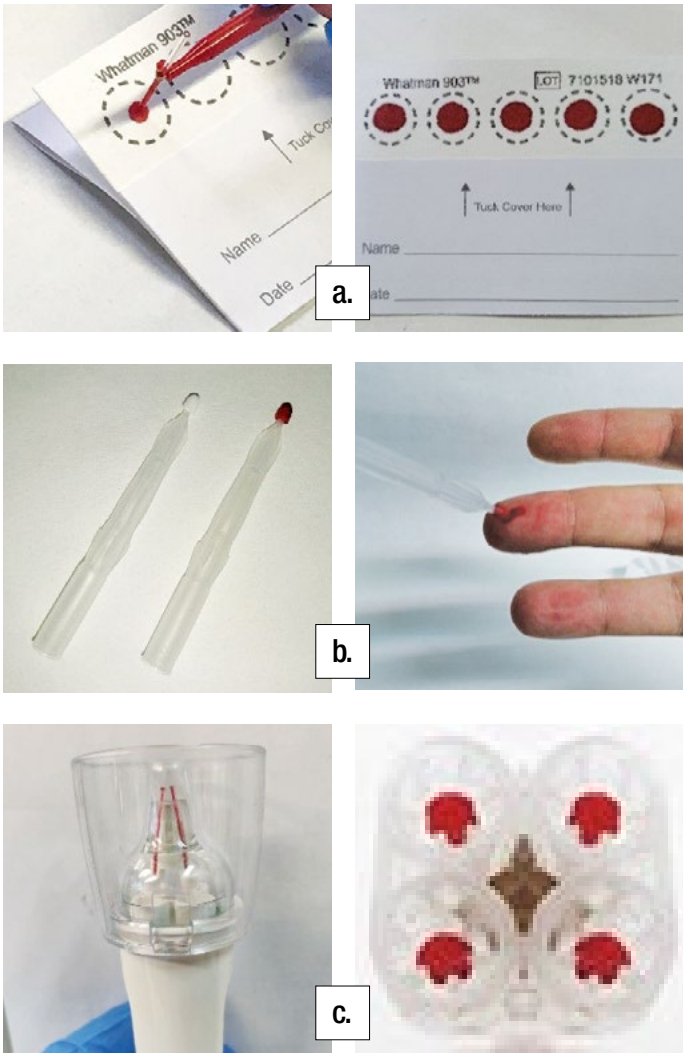


Figure 1: Examples of whole blood microsampling approaches developed at PTA Lab for cannabinoid analysis: classic DBS (a), VAMS (b) and capillary volumetric DBS (c).

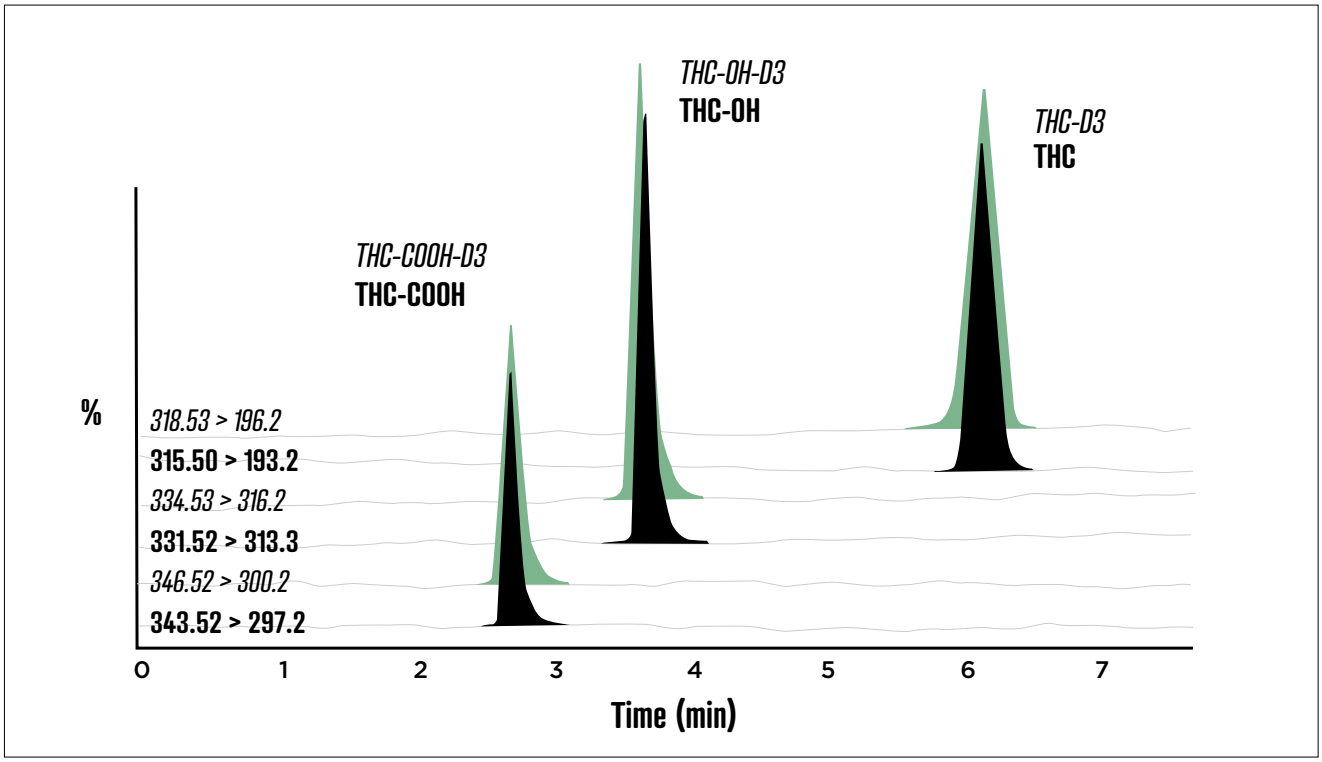
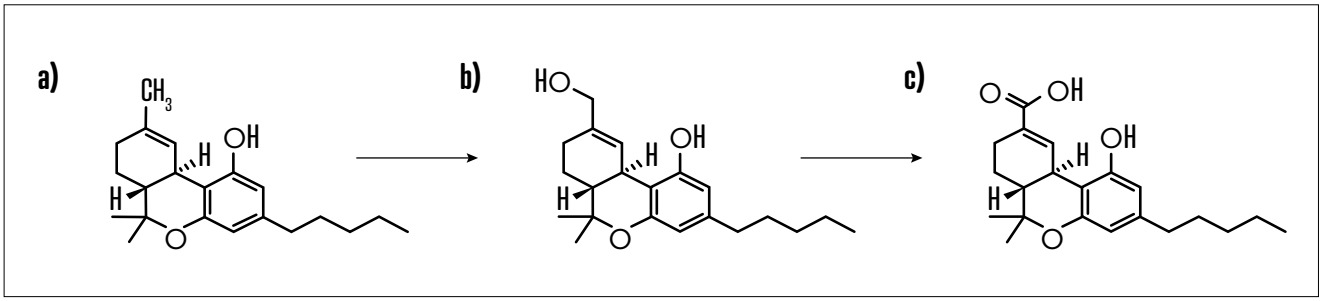


Figure 2: Example of an LC-MS/MS (multiple reaction monitoring) chromatogram of 10 µL whole blood VAMS sample.



Scheme 1: THC metabolic scheme. In vivo, THC (a) is hydroxylated to THC-OH(b), the primary and psychoactive metabolite. THC-OH is further oxidized to THC-COOH(c), an inactive metabolite and the major circulating cannabinoid metabolite found in blood.

1. *Mercolini L. et al. "Dried blood spots: liquid chromatography-mass spectrometry analysis of Δ9-tetrahydrocannabinol and its main metabolites" Journal of Chromatography A, 2013, Volume 1271(1):33-40.*

2. *Protti M et al. "Dried haematic microsamples and LC-MS/MS for the analysis of natural and synthetic cannabinoids" Journal of Chromatography B, 2017, Volume 1044-1045:77-86.*

3. *Protti M et al. "Tutorial: Volumetric absorptive microsampling (VAMS)" Analytica Chimica Acta, 2019, Volume 1046:32-47.*

A Modern Industry Redefining Federal Policy

Tami Wahl
Policy Advisor

The political climate in Washington, D.C., is finally amenable to discussing a federal regulatory framework for cannabis. The currently state-regulated industry has grown into a multi-billion-dollar economic contributor with a majority of the country residing in a jurisdiction with some type of regulated cannabis program and in support of these programs.[1]

Now is the time to advance a modern approach to federal oversight that will allow the industry to continue to flourish in a competitive manner and ensure a strategic entry into the global marketplace. Key considerations to be included in a federal regulatory model to ensure the U.S. cannabis industry can be positioned as a global leader without compromising innovation or inclusion are shown in Figure 1. These defined cornerstones are the result of looking to other non-related industries and examining their successes and failures,[2, 3] understanding the history of the cannabis plant, and exploring the existing federal pathways to market[4] while factoring in the current construct of the stateside cannabis industry.

The opportunity to develop a novel and forward-thinking framework for cannabis is upon us. Patients,[5, 6] consumers, the plant, and the economy demand we get this right. The key considerations shared here are designed to encourage thinking beyond known ways of doing business.

1. *As of March 2020, 47 states (plus D.C. and territories) have medical cannabis programs and/or adult-use cannabis programs or a limited program (low-THC, high-CBD). NORML, National Conference of State Legislatures (sites last accessed 23Jun2020). 'Two-thirds of Americans say the use' of cannabis should be legal.14.Nov.2019, Pew Research Center Survey*

2. *United States Department of Agriculture, Agricultural Marketing Service, U.S. Standards for Grades of Cultivated Ginseng.(May.2012) An example of how the AMS developed quality standards for cultivated ginseng roots, and as a result, American ginseng now demands a premium in foreign markets. See also, Farm Security and Rural Investment Act of 2002, Public Law 107-171, §10806(b), Ginseng Labeling.*

3. *Stoller, Matt. Goliath: The 100-Year War Between Monopoly Power and Democracy. Simon & Schuster, 2019. (pp. 158, 420).*

4. *Centers for Disease Control and Prevention (CDC), Alcohol and Public Health (last accessed 25.May.2020)*

5. *The National Academies of Sciences, Engineering, and Medicine. 2017. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. Washington, D.C.: The National Academies Press.*

6. *Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999-2010, JAMA Intern Med. 2014;174(10):1668-1673.*

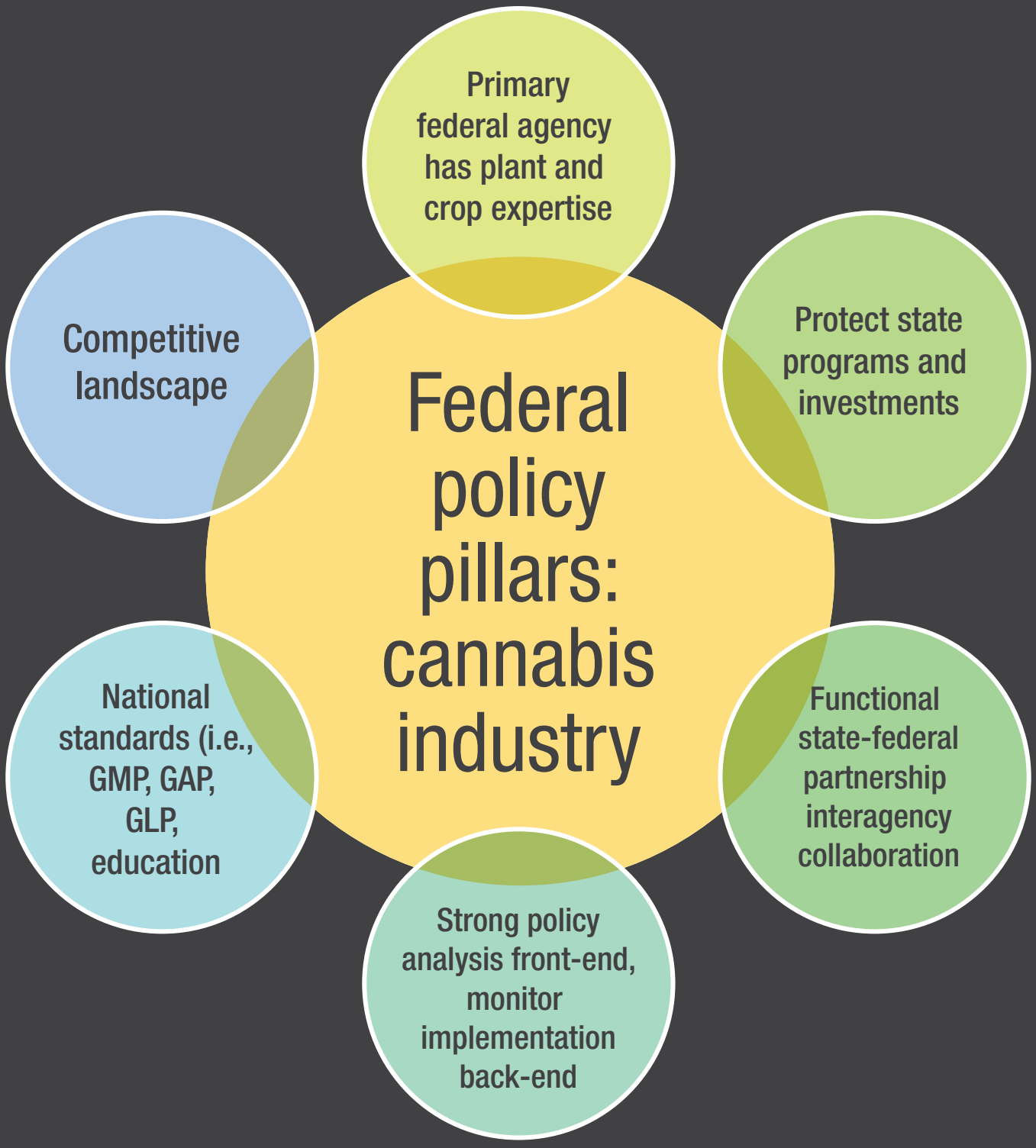


Figure 1: Federal policy pillars.

Identity Crisis: How to Employ a Risk-based Process to Identify What Factors Are Important to Assess During the Development and Production of New Cannabis Products

David Vaillencourt, MSc
The GMP Collective

As of February 2020, over 2,800 individuals had been hospitalized, with sixty-eight of these hospitalizations leading to death, due to e-cigarette or vaping product use-associated lung injury (EVALI).[1] Extensive research conducted by the Centers for Disease Control (CDC), Food and Drug Administration (FDA), as well as numerous public and private agencies concluded that there is a strong correlation between the EVALI cases and vitamin E acetate in the vaping liquid. As the vapor settles, this sobering reality raises the question – could manufacturers have known about the potential risks associated with using vitamin E acetate as a component of vape pens? After all, vitamin E acetate is generally regarded as safe (GRAS) by the US FDA. However, GRAS is limited to substances added to food which does not include inhalation as a route of administration, let alone heated or pyrolyzed.[2]

Unlike pharmaceutical and food manufacturers, cannabis and nicotine e-liquid companies are not currently required to perform risk assessments on their processes or raw materials. While not required, this fundamental system implemented properly, saves businesses millions of dollars per year. In its absence, manufacturers resign themselves to making uninformed decisions. These decisions, compounded over time, increase the risk of an adverse event or mistake occurring. Over time and as operations become more complex, the compounding of these decisions raises the probability of a significant negative event occurring.

Risk assessments are not inherently complicated, but they do require time and effort on the front end, before a product ever goes to market. The cost saved in skipping this fundamental step is erased with just one product recall. In the food industry, the average cost of a single recall

	Incubation Temperature (°C)					
	USP limit	VP^{180}	VP^{210}	VP^{240}	VP^{270}	VP^{300}
methanol	15	nd	nd	< 3	> 30	> 30
ethanol	5000	nd	nd	< 1000	< 1000	< 1000
formic acid*	5000	nd	nd	1448	> 10000	> 10000
acetone	5000	nd	< 1000	< 1000	> 10000	> 10000
acetic acid*	5000	nd	< 1000	5778	> 10000	> 10000
2-butanone (MEK)	5000	nd	nd	< 1000	1853	5249
benzene	2	nd	nd	nd	nd	< 0.4
4-methyl-2-pentanone (MIK)	5000	nd	nd	< 1000	< 1000	< 1000
toluene	890	nd	nd	nd	< 178	< 178
2-hexanone (MBK)	50	nd	nd	nd	89.5	> 100
m/p-xylene	1606	nd	nd	nd	< 321	< 321

Table 1: Result of solvents in parts-per-million (ppm) present in samples incubated at different temperatures, compared to the residual solvent limits for pharmaceutical drugs per the US Pharmacopeia. Data provided by Supra R&D.

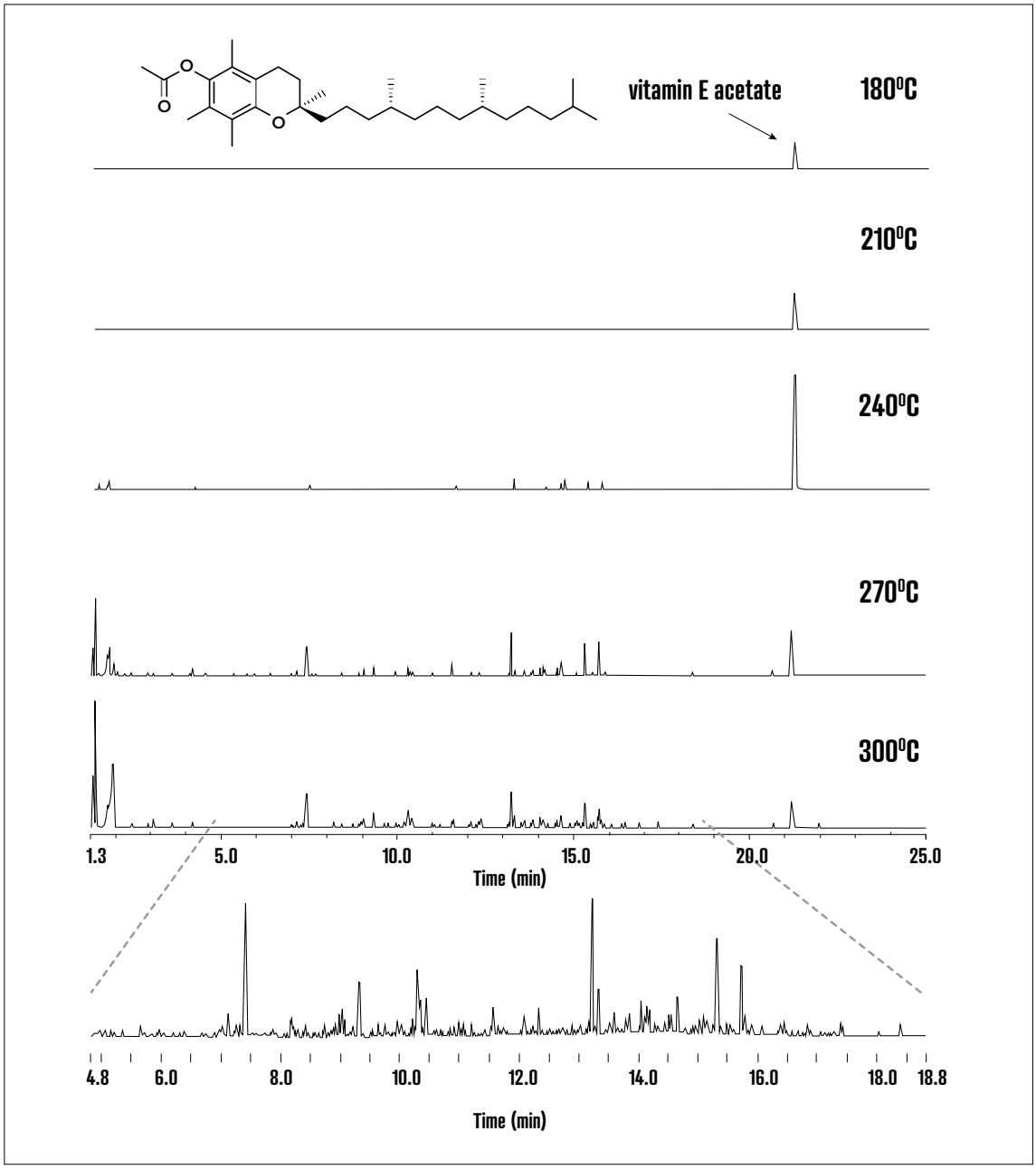


Figure 1: Full scan chromatograms of vitamin E acetate after being heated to different temperatures via headspace GC-MS. Data provided by Supra R&D.

is approximately $10M.[3] Applying a risk assessment, such as a preliminary hazard analysis (PHA) could have steered a company to discovering the carcinogenic compounds that are created upon heating of vitamin E acetate. These compounds do have research on their toxic properties when inhaled. As an example, a leading cannabis analytical testing company in British Columbia went ahead and assessed the breakdown products of vitamin E acetate when heated at several different temperatures from 180 °C to 300 °C (Figure 1).[4] As low as 240 °C, contaminants were identified in concentrations that exceed the US Pharmacopeia's limits for residual solvents (Table 1), highlighting the real risk of vitamin E acetate to convert into chemicals that are known to be harmful to health when using a typical e-liquid vaporizing device. This research highlights the criticality of conducting thorough risk assessments before bringing novel products to launch.

1. *https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html*
2. *https://www.fda.gov/food/food-ingredients-packaging/generally-recognized-safe-gras*
3. *https://www.foodsafetymagazine.com/signature-series/recall-the-food-industrys-biggest-threat-to-profitability/*
4. *Supra RnD http://suprarnd.ca/*

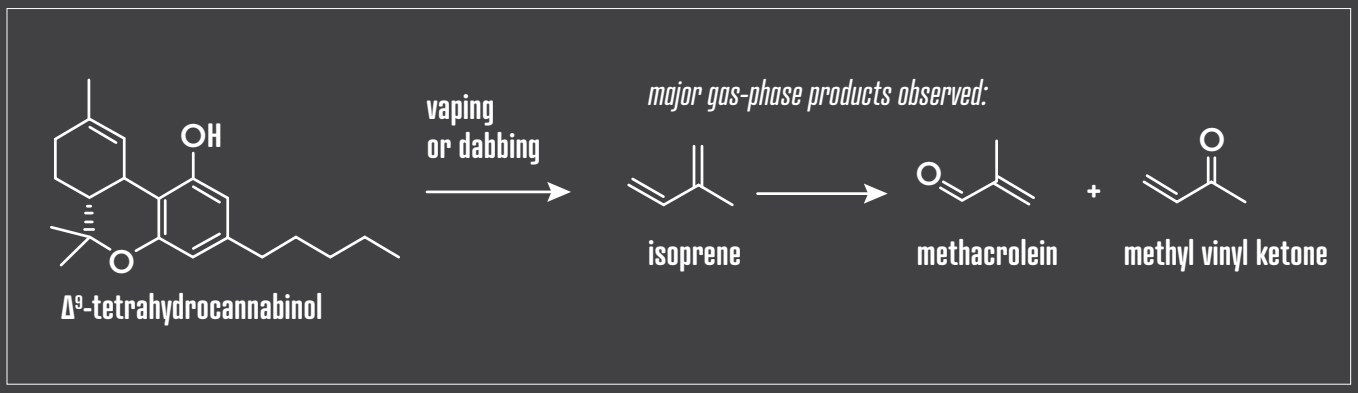
Vaping-induced Lung Injury and Vaping Chemistry

Robert M. Strongin, PhD
Portland State University

Vaping high potency cannabis extracts has emerged as a prevalent form of THC ingestion, particularly among US youth.[1] To date, it has been linked to disorders including psychosis and vaping-induced lung injury (EVALI).[2] However, there exists a large gap in current understanding of the health risks associated with these relatively new products and routes of administration. Importantly, basic knowledge is lacking, such as the chemical profiles of the inhaled aerosols and the factors that impact cannabinoid and terpene doses, as well as their degradation products. Toxic degradant levels vary significantly as a function of extract formulation and specific vaping devices and components, due to the relatively low volatility and high viscosity of cannabinoids. An additional confounding variable is the inclusion of miscellaneous additives and cutting agents, such as vitamin E acetate and several others, by both legal and illicit vendors. Additionally, the inhalation toxicology of cannabis extract aerosols and their components is virtually unknown.

To begin to address these challenges, our lab is undertaking extensive studies of the chemistry of cannabinoids and terpenes during vaping and dabbing to identify the origin and identities of inhaled aerosol components. Findings to date indicate that THC degrades in a similar manner to other terpenes, resulting in isoprene and oxidized derivatives (Scheme 1).[3] Terpenes are relatively more labile than THC. For example, a concentrate consisting of a 1:9 mixture of terpenes:THC produced a five-fold increase in isoprene levels compared to dabbing pure THC. In addition, a new illicit additive has been identified during this work, consisting of the respiratory toxin pine rosin mixed with medium chain triglycerides and the hypnotic oleamide.[4]

1. *Miech, R.A.; Patrick, M.E. O'Malley, P.M. Johnston, L.D.; Bachman, J.G. JAMA, 2020, 323, 475-476.*
2. *Chadi, N.; Minato, C.; Stanwick, R. Paediatrics & Child Health, 2020, 25, :S16-S20.*
3. *Meehan-Atrash J.; Luo, W.; McWhirter, K. J.; Strongin, R. M. ACS Omega, 2019, 4, 16111-16120.*
4. *Meehan-Atrash, J.; Strongin. R. M. Forensic Science International, 2020, 312, 110301-110304.*



Scheme 1: While most of the THC remains intact within the aerosol particulate phase, a portion of the THC as well as terpenes degrade to numerous similar gas-phase aerosol products upon vaping and dabbing cannabis concentrates.

Terpenoids of *Cannabis sativa* L., Analysis and Applications

Justin Fischedick, PhD
Integrated Analytical Solutions

In addition to cannabinoids, cannabis produces a variety of monoterpenoids and sesquiterpenoids. Similar to cannabinoids, terpenoids are mainly produced in the trichomes.[1] Terpenoids are largely responsible for the distinct aroma of cannabis. At least 94 monoterpenoids and 80 sesquiterpenoids have been identified in cannabis and products derived from cannabis such as hashish. From a chemotaxonomic perspective cannabis terpenoids have been studied as a potential means to determine geographic origin.[2] In development of cannabis markets, terpenoids are used as flavoring ingredients in cannabis products such as electronic vaporizer cartridges and cannabis extracts. As with many volatile organic compounds found in plants, cannabis terpenoids are typically analyzed by gas chromatography.

During my research at Leiden University, Institute of Biology, Natural Products Laboratory cannabis terpenoids were studied and gas chromatography methods for their analysis developed. In one study we identified cannabis terpenoids are components of cannabis smoke and vapor.[3] In another study of cannabis cultivars that were being grown as part of Dutch medicinal cannabis program we used multivariant data analysis techniques to chemically distinguishing cannabis varieties that had similar cannabinoid content based on their terpenoid content.[4] We again used this approach to analyze two common cannabis varieties sold in Dutch Coffeeshops. The results of this study demonstrated that even though the two varieties had similar cannabinoid they could be distinguished based on their terpenoid content.[5] The approach of distinguishing cannabis cultivars or "strains" as they are commonly called based on terpenoid content has been useful in the developing legal cannabis markets as well.[6,7]

1. *Booth, J.K., Page, J.E., Bohlmann, J., 2017. Terpene synthases from Cannabis sativa. PLOS ONE 12.*
2. *Hillig, K.W., 2004. A chemotaxonomic analysis of terpenoid variation in Cannabis. Biochemical Systematics and Ecology 32, 875–891.*
3. *Fischedick, J., Van Der Kooy, F., Verpoorte, R., 2010. Cannabinoid receptor 1 binding activity and quantitative analysis of Cannabis sativa L. smoke and vapor. Chem. Pharm. Bull. 58, 201–207.*
4. *Fischedick, J.T., Hazekamp, A., Erkelens, T., Choi, Y.H., Verpoorte, R., 2010. Metabolic fingerprinting of Cannabis sativa L., cannabinoids and terpenoids for chemotaxonomic and drug standardization purposes. Phytochemistry 71, 2058–2073.*
5. *Hazekamp, A., Fischedick, J.T., 2012. Cannabis - from cultivar to chemovar. Drug Test Anal 4, 660–667.*
6. *Elzinga, S., Fischedick, J., Podkolinski, R., Raber, J., 2015. Cannabinoids and Terpenes as Chemotaxonomic Markers in Cannabis. Natural Products Chemistry & Research 03.*
7. *Fischedick, J.T., 2017. Identification of Terpenoid Chemotypes Among High (−)-trans-Δ9- Tetrahydrocannabinol-Producing Cannabis sativa L. Cultivars. Cannabis and Cannabinoid Research 2, 34–47.*

Unique Terpene Metabolites as Descriptors of Cannabis Phenotypes and Products

Jacqueline von Salm, PhD[1,2]
(1) AltMed (2) Psilera Biosciences LLC

The focus of this research is to identify and emphasize the chemical diversity among *Cannabis sativa* plants and processed products. GC-MS metabolomics is a validated technique for monitoring and quantifying compounds in a mixture. For cannabis, most of these compounds include terpenes and terpenoids with four distinct regions in the analysis. In order of groupings from earliest to latest retention time these are monoterpenes, sesquiterpenes, diterpenes, and cannabinoids (modified terpenoid).

During our investigations of dozens of cannabis cultivars ("strains"), we noticed a terpene that is not often cited and never emphasized in cannabis metabolomics literature, *alpha*-thujene, also called thujene, since *beta*-thujene is much less common. This volatile monoterpene has been used to classify different species of frankincense trees (*Boswellia* spp.) along with the other well-known monoterpenes like *alpha*- and *beta*-pinene. We decided to do statistical analysis of our cultivars with the top 100 compounds from each GC-MS chromatogram (Figure 1).

The similarity and dissimilarity of the data via multi-dimensional scaling (MDS) and principle component analysis (PCA) were astonishing once the abundance of *alpha*-thujene was overlaid. The obvious distinction between two groupings of cultivars leads us to believe that this specific terpene could be a major chemical marker for differentiating between phenotypes and genotypes of cannabis (Figure 2). It further raises the question of what other compounds in the plant are not being appropriately focused on? Major terpenes like *beta*-myrcene, *beta*-caryophyllene, and limonene may not be as relevant as once believed for distinguishing cannabis variants or products. It also emphasizes the important of environment, since thujene appears less abundant in literature at other facilities around the world.

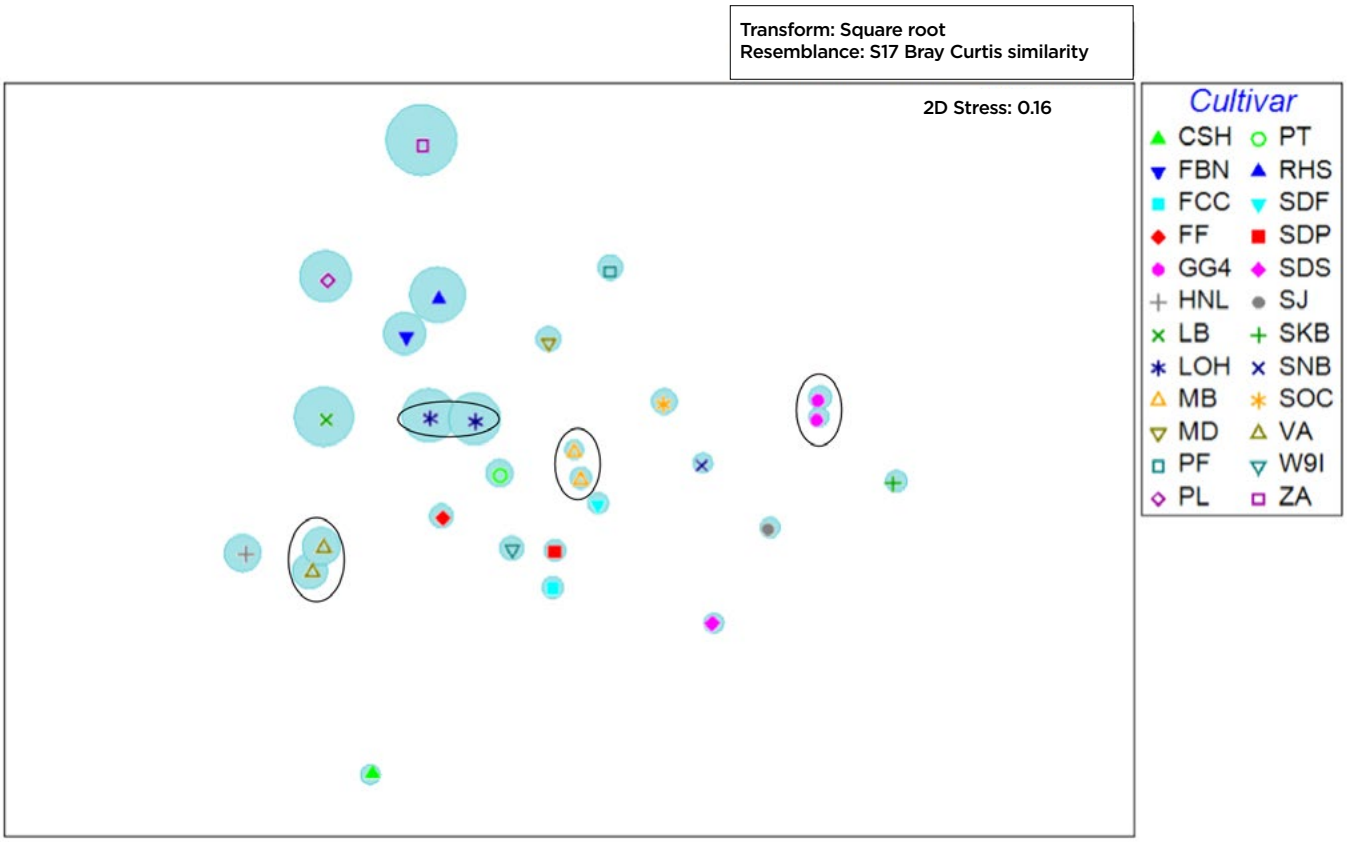


Figure 1: MDS Plot of top 100 compounds for 28 cannabis cultivars.

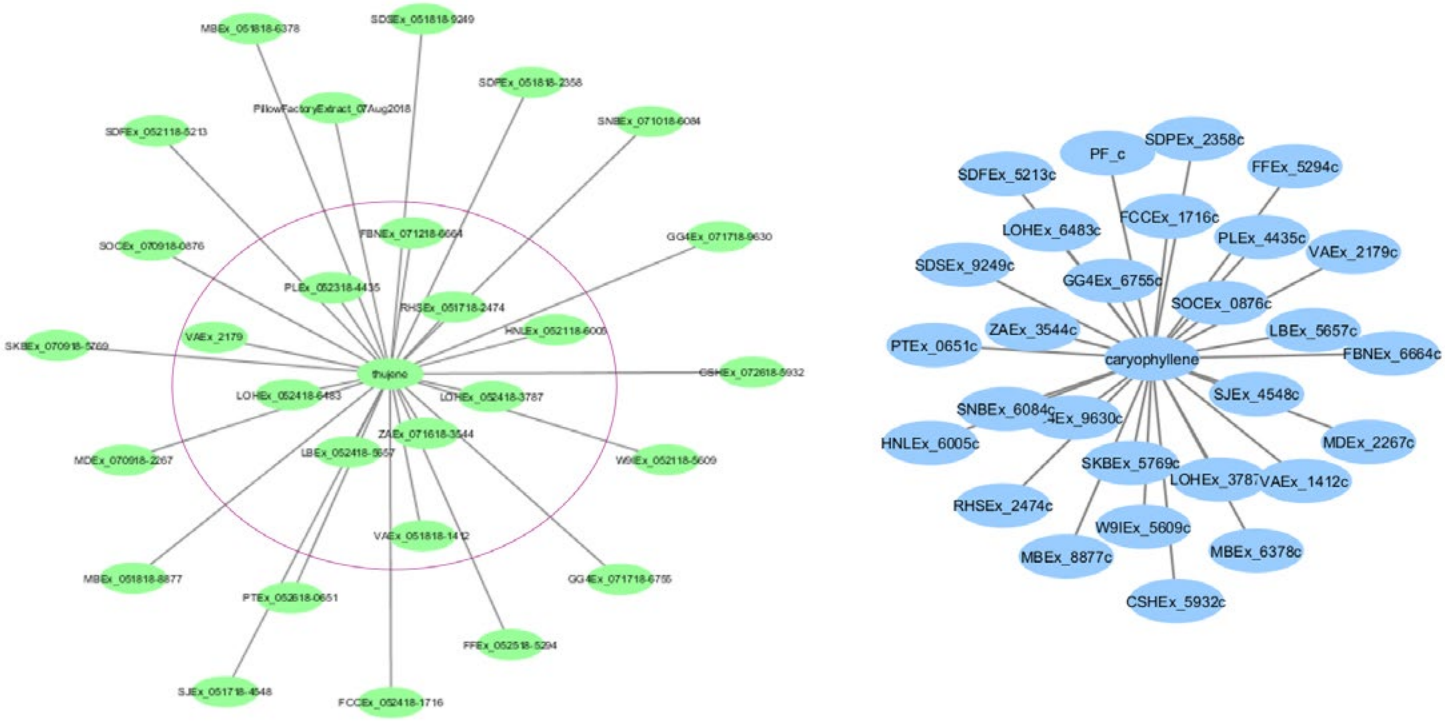


Figure 2: Graphical representations (generated using Cytoscape software) emphasizing significance of variability in the relative abundance of alpha-thujene (green) as compared to a major terpene metabolite of cannabis, beta-caryophyllene (blue). The relative distance from the center node represents abundance of the terpene in the extract. The closer to the central node, the more abundant that terpene is in that extract. The purple circle helps distinguish between cultivars with higher abundance of thujene (circled) versus those with abundance levels similar to what is typically published in literature.

We also took this data and did preliminary curing studies to show how important this aspect of manufacturing can be on the chemical complexity of cannabis products. Certain strains show different levels of terpene loss or gain depending on the curing techniques. We've also shown that chemically diverse or complex products like Rick Simpson Oil (RSO) contain significantly less monoterpenes than other concentrates, which raises questions about what is important in the "entourage effects" claimed by many companies and individuals throughout the cannabis industry. If the typical monoterpenes like pinenes, *beta*-myrcene, and limonene are much less abundant, other compounds must be contributing more to the renowned effects of RSO. Quantitative analysis of our ethanol extracted RSO showed that flavonoids and phytosteroids provide a much better picture of why RSO is so chemically unique and these compounds should be further investigated.

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