Hemp Derivatives and Isomers:
Exploitation of an Unintended Loophole

CANNABIS
SCIENCE
CONFERENCE

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Baltimore, MD

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ProVerde Laboratories – analytical testing services

(1) ProVerde Laboratories, Inc. – Milford, MA

(2) Waters Corporation – Milford, MA

US Farm Bill

“Hemp” is defined by the 2018 Farm Bill as “the plant species *Cannabis sativa* L. and any part of that plant, including the seeds thereof and all **derivatives**, extracts, cannabinoids, **isomers**, acids, salts, and salts of isomers, whether growing or not, with a delta-9 tetrahydrocannabinol concentration of not more than 0.3 percent on a dry weight basis.”

Δ8 THC – A New Opportunity

Industry thought process:

- Hemp is legal under farm bill
- CBD extracted from hemp is natural and legal
- Trace levels of Δ8-THC have been observed in biomass and therefore is a natural product
- Since Δ8-THC is naturally occurring, a derivative pathway from CBD for production is legal

Problem:

- Conversion of CBD to Δ8-THC is not a natural process
- Many isomers formed are not naturally occurring
- There are both legal questions and consumer safety issues arising from these unknown contaminants

(+) Rationale

Different rationales for supporting Δ8-THC production

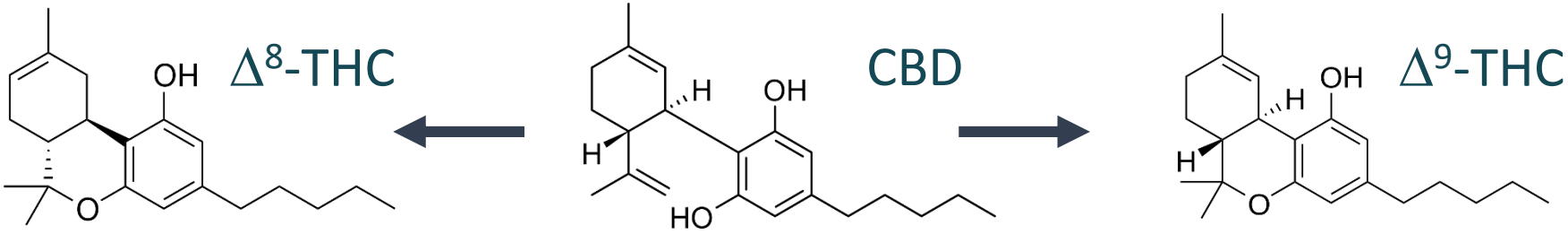
- High potential for therapeutic/recreational applications
  - Especially in markets where marijuana is not yet legal
- Scientifically interesting and relevant
  - Like many minor cannabinoids
- Relatively easy to produce, currently without regulatory oversight
  - Minimal capital investment for production equipment and supplies
- Oversupply of CBD isolate resulted in lower margins
  - Conversion to THC represents significant value add to products
  - Provides salvation for investors waiting for FDA approval of CBD

(-) Rationale

Different rationales for prohibiting (regulating) Δ8-THC production

- Potential for intoxication with Δ8-THC use
  - Much of hemp legislative success is based on absence of intoxicants
  - Could have negative consequences to future cannabis legislation
- Unregulated products cutting into regulated cannabis profits
- Consumer safety
  - Produced without regulatory oversight
  - Many unidentified contaminants observed in consumer products
  - No efficacy or toxicity information available for these contaminants

CBD into THC



First published in literature by Roger Adams in 1941

US 20040143126A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2004/0143126 A1**

Webster et al. (43) **Pub. Date: Jul. 22, 2004**

(54) **CONVERSION OF CBD TO DELTA8-THC AND DELTA9-THC**

(76) Inventors: **G. R. Barrie Webster**, Manitoba (CA); **Leonard P. Sarna**, Manitoba (CA); **Raphael Mechoulam**, Jerusalem (IL)

Related U.S. Application Data

(60) Provisional application No. 60/273,628, filed on Mar. 7, 2001.

Publication Classification

Most synthetic pathways employ acidic conditions (some with catalyst)

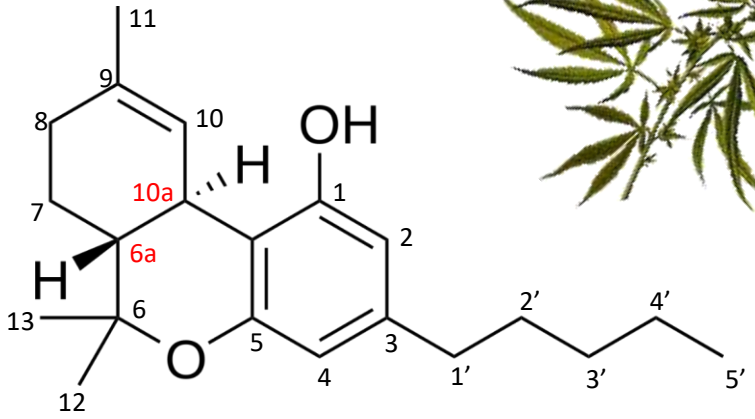
Isomers of THC

(6aR, 10aR)-Δ^9-Tetrahydrocannabinol

(6aR, 10aR)-Δ^9-THC

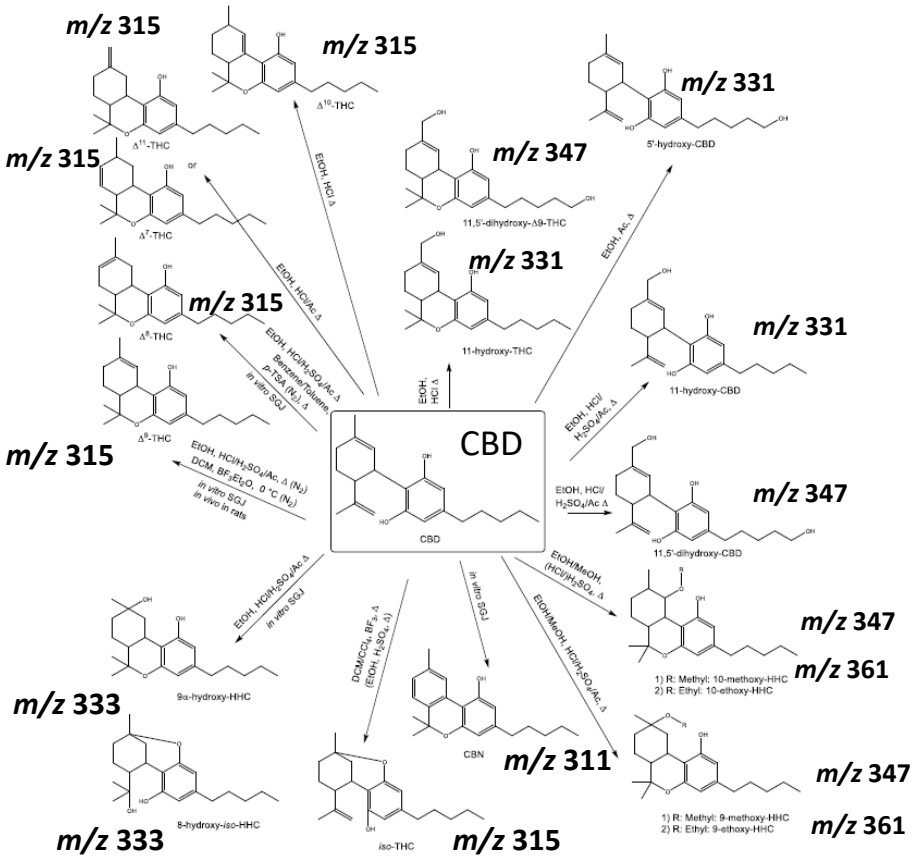
(-)-*trans*-Δ^9-THC,

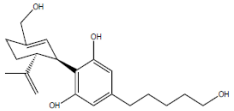
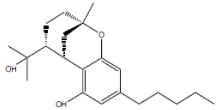
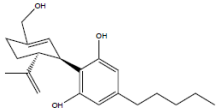
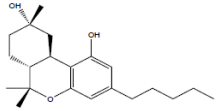
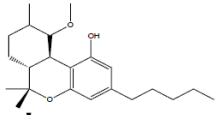
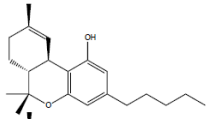
Δ^9-THC, D9-THC



Isomers	Double Bond	Stereoisomers
$\Delta^{6a,10a}$-THC	6a-10a	2
$\Delta^{6a,7}$-THC	6a-7	4
Δ^{7}-THC	7-8	8
Δ^{8}-THC	8-9	4 (1)
Δ^{9}-THC	9-10	4 (1)
Δ^{10}-THC	10-10a	4
$\Delta^{9,11}$-THC	9-11	4

THC from CBD

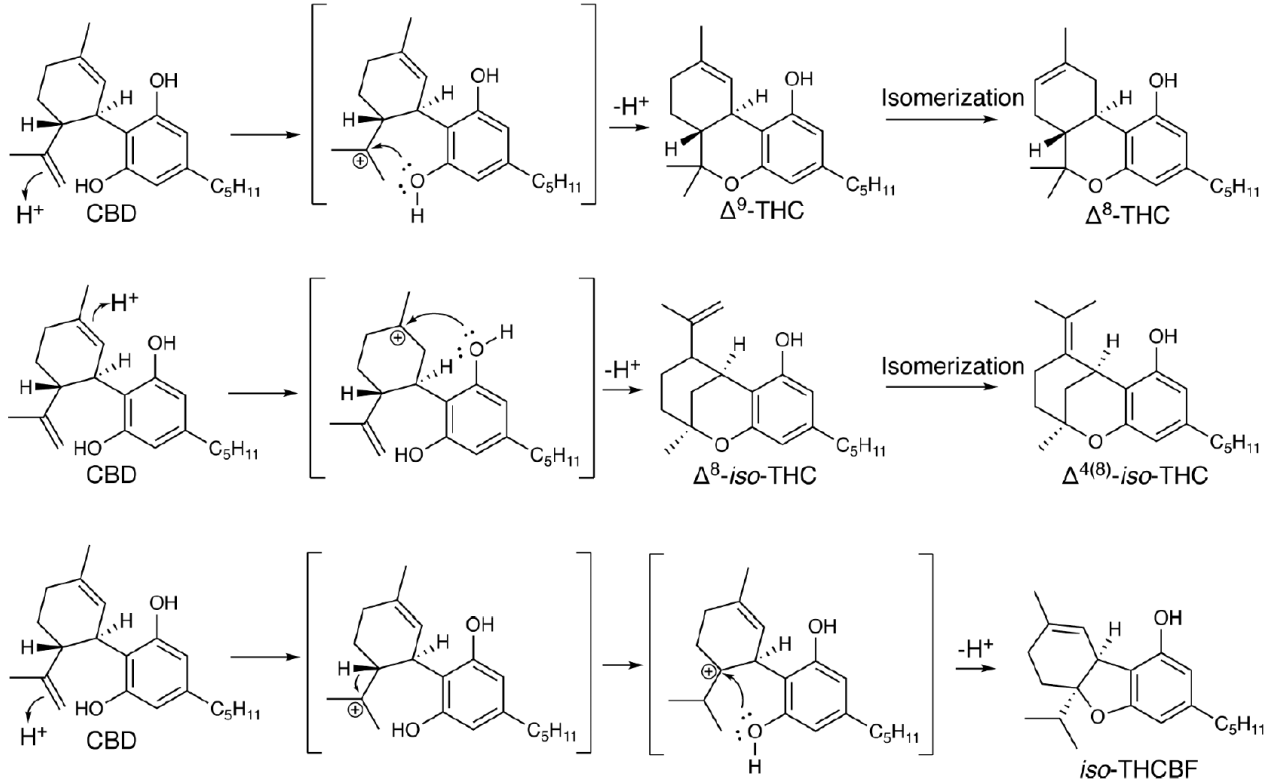


Retention Time (min)	Structure	*m/z*	Fragments
1.96		347.244	329.203, 311.197, 287.215, 271.167, 231.137, 217.118, 193.116, 107.069
2.54		333.232	315.230, 259.160, 193.116, 135.104, 93.0541
2.87		329.211	311.204, 287.201, 271.160, 231.130, 193.116, 107.074
3.25		333.232	315.230, 259.160, 193.116, 135.104, 93.0541
3.56		347.325	315.230, 259.167, 193.116, 135.104, 93.0541
3.97		315.23	259.167, 193.116, 135.099, 123.024, 107.069, 93.0499

Golombek, P., et al. (2020). "Conversion of Cannabidiol (CBD) into Psychotropic Cannabinoids Including Tetrahydrocannabinol (THC): A Controversy in the Scientific Literature." Toxics **8(2).**

Kiselak, T. D., et al. (2020). "Synthetic route sourcing of illicit at home cannabidiol (CBD) isomerization to psychoactive cannabinoids using ion mobility-coupled-LC-MS/MS." Forensic Sci Int **308: 110173.**

THC from CBD



(5aR,9aS)-5a-isopropyl-8-methyl-3-pentyl-5a,6,7,9a-tetrahydrodibenzo[b,d]furan-1-ol

Meehan-Atrash, J., et al. (2021). "Novel D8-Tetrahydrocannabinol Vaporizers Contain Unlabeled Adulterants, Unintended Byproducts of Chemical Synthesis, and Heavy Metals." *Chem. Res. Toxicol.* ***35 (1)***

Potential Contaminants

Isomers of Cannabinoids

- There are 30 THC isomers, most of which are not found in nature. Most have not been studied for safety or efficacy.

Synthetic Byproducts

- Synthesis is not a singular chemical reaction, but rather a system of parallel competing reactions, resulting in multiple outcomes.
- Many of these byproducts have not been identified.
- These have not been studied for safety = unknown toxicity.

Residual Synthetic Reagents

- Synthesis requires toxic chemical reagents and solvents.
- How adept are producers at removing these?

Regulatory and Consumer Safety Groups

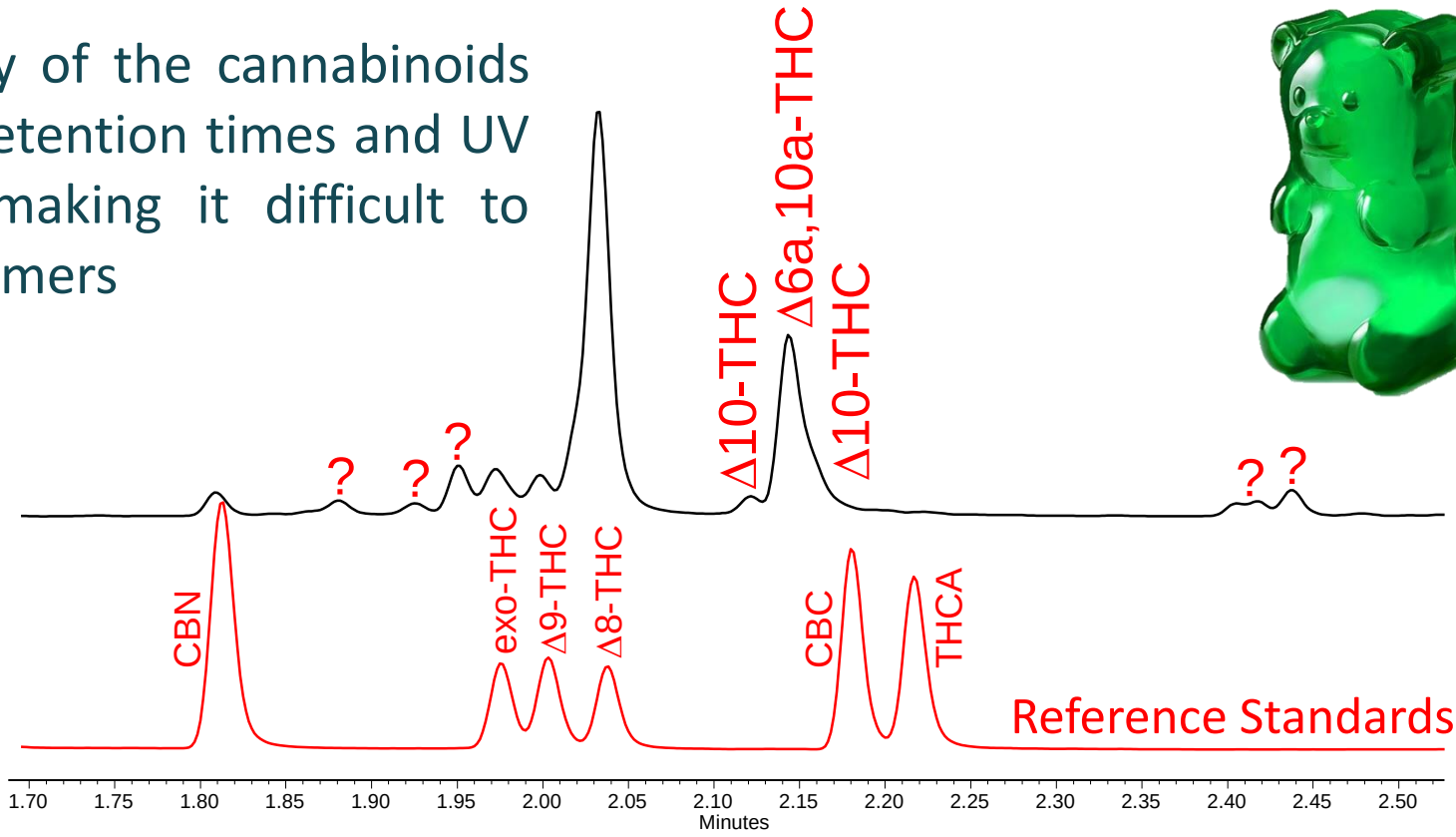
Regulatory, Safety and Industry Groups Have Issued Statements

- US Food & Drug Administration (FDA)
- Centers for Disease Control and Prevention (CDC)
- United States Pharmacopeia (USP)
- American Herbal Products Association (AHPA)
- US Hemp Authority
- Hemp Industry Association (HIA)

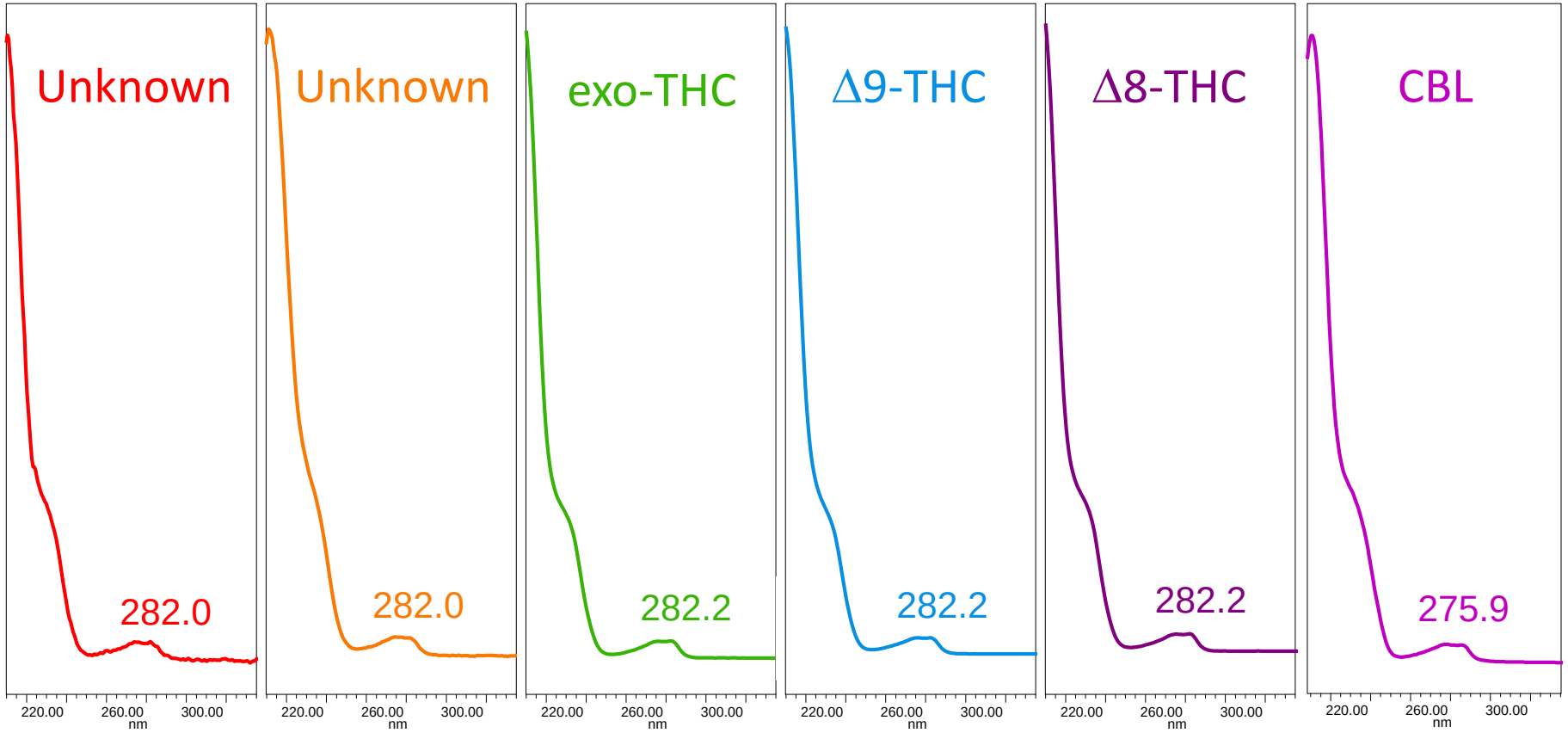
https://www.fda.gov/consumers/consumer-updates/
5-things-know-about-delta-8-tetrahydrocannabinol-delta-8-THC

Laboratory Challenges

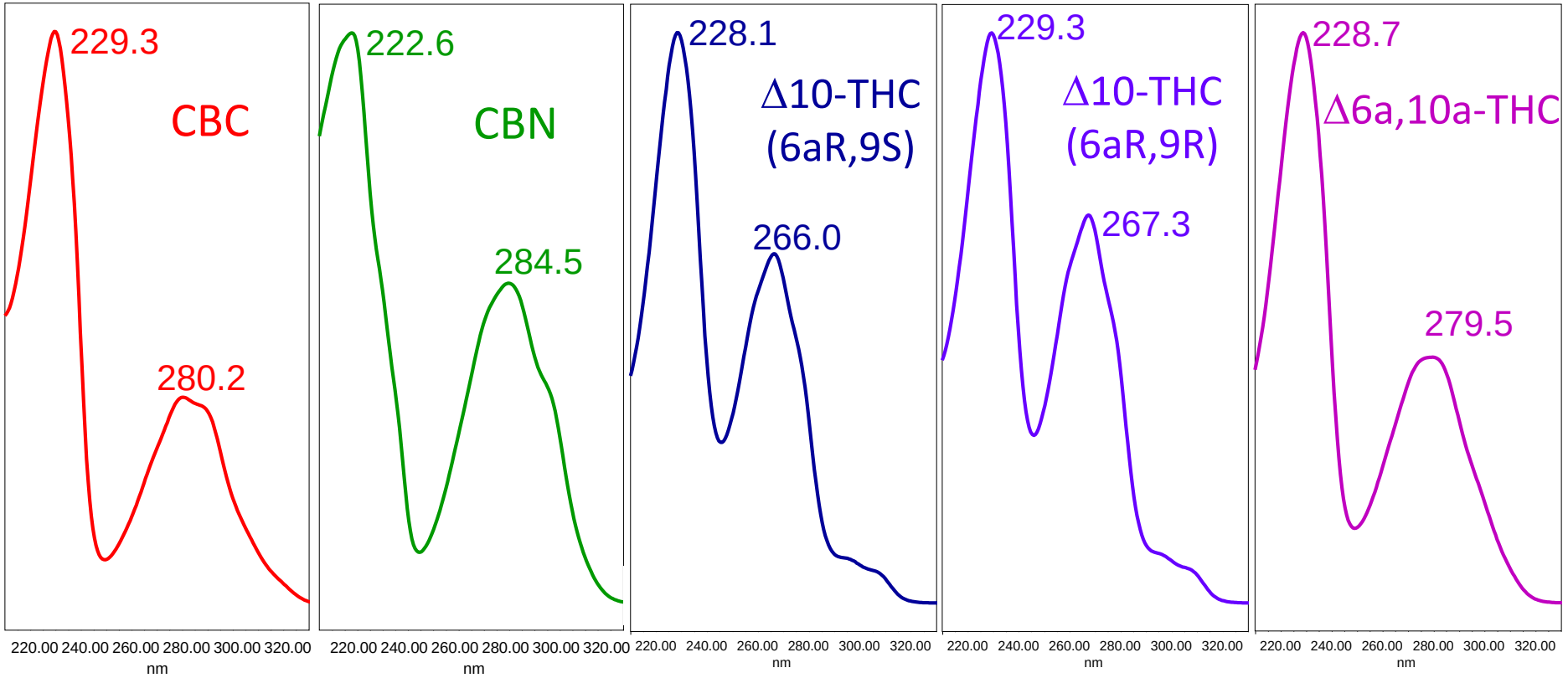
LC/UV - Many of the cannabinoids have similar retention times and UV absorbance, making it difficult to distinguish isomers



UV Absorbance for Isomers



UV Absorbance for Isomers

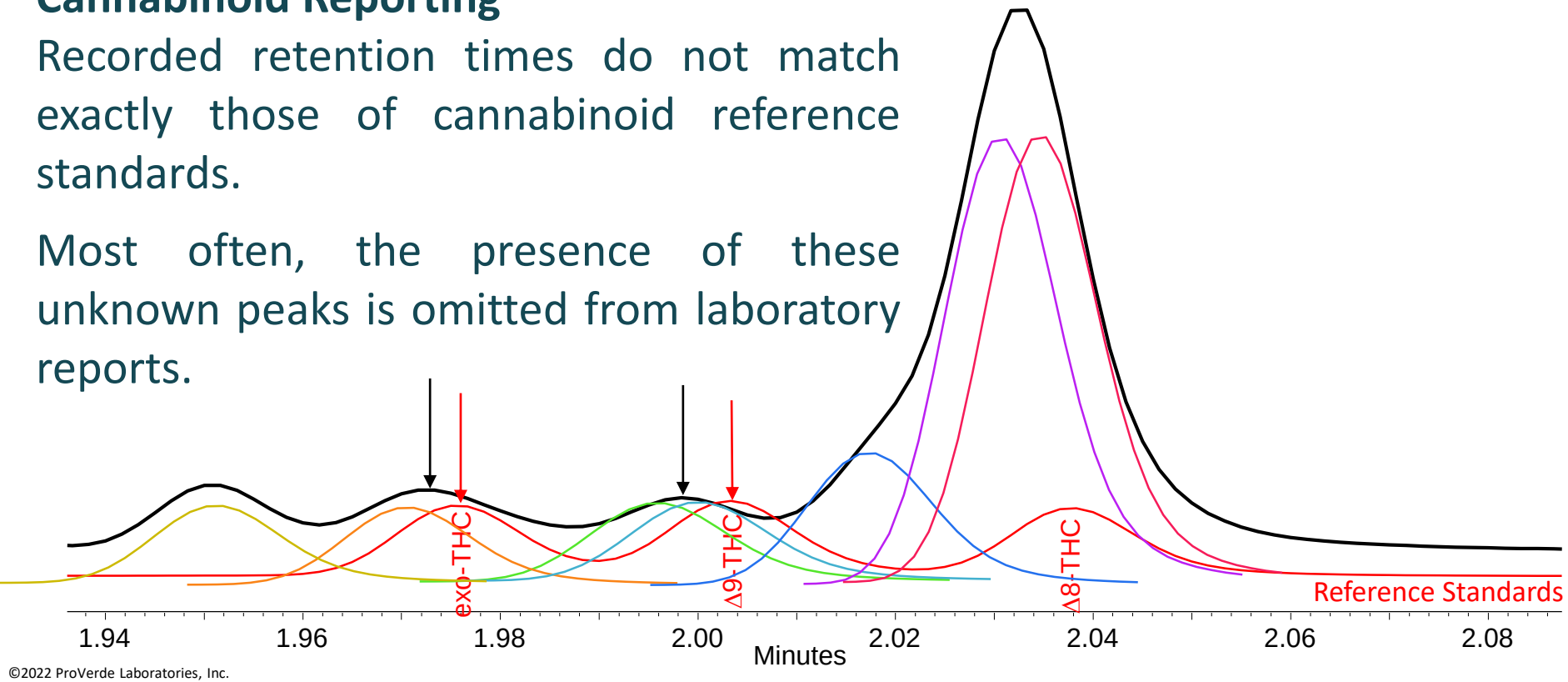


Laboratory Challenges

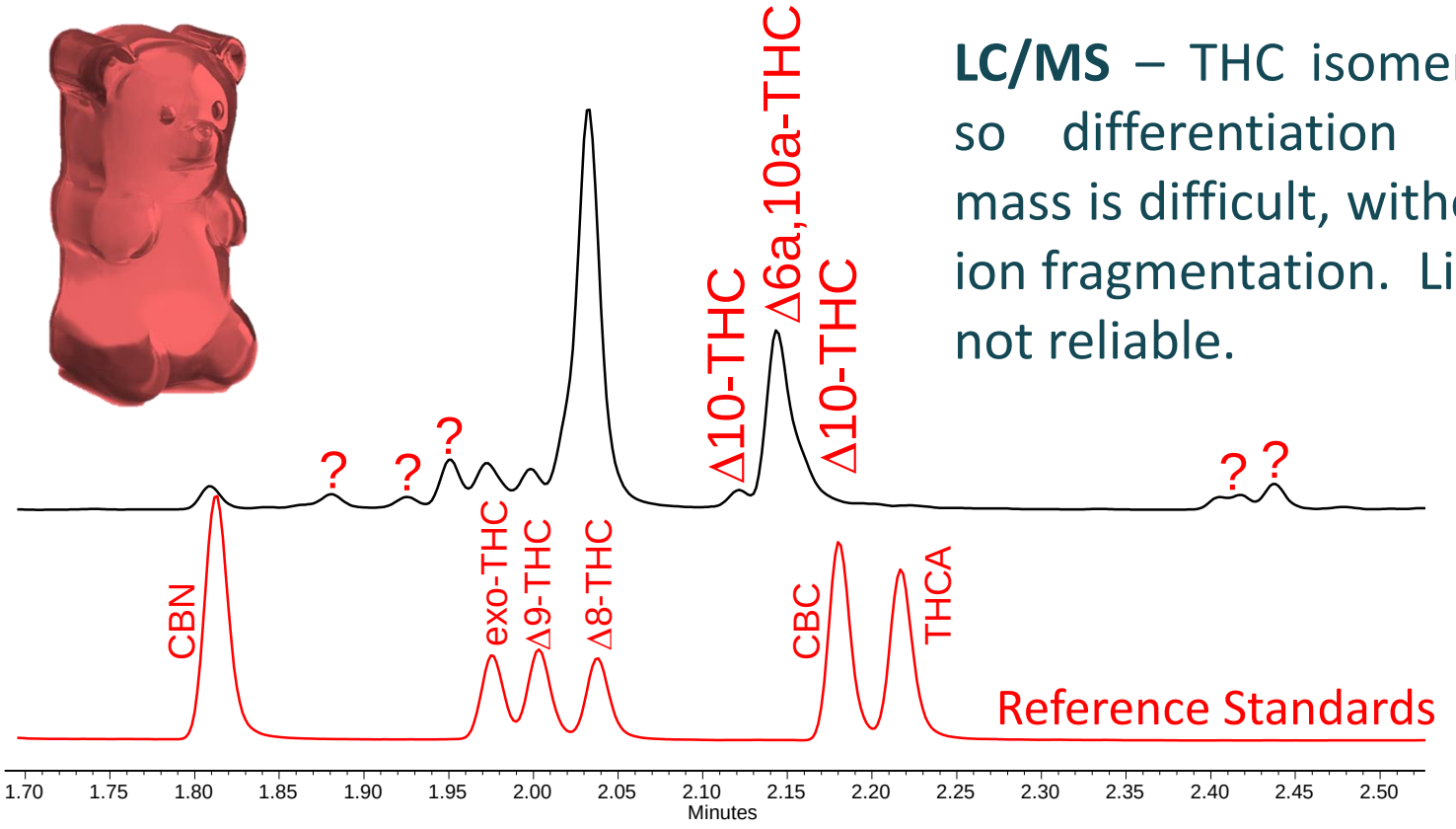
Cannabinoid Reporting

Recorded retention times do not match exactly those of cannabinoid reference standards.

Most often, the presence of these unknown peaks is omitted from laboratory reports.



Laboratory Challenges

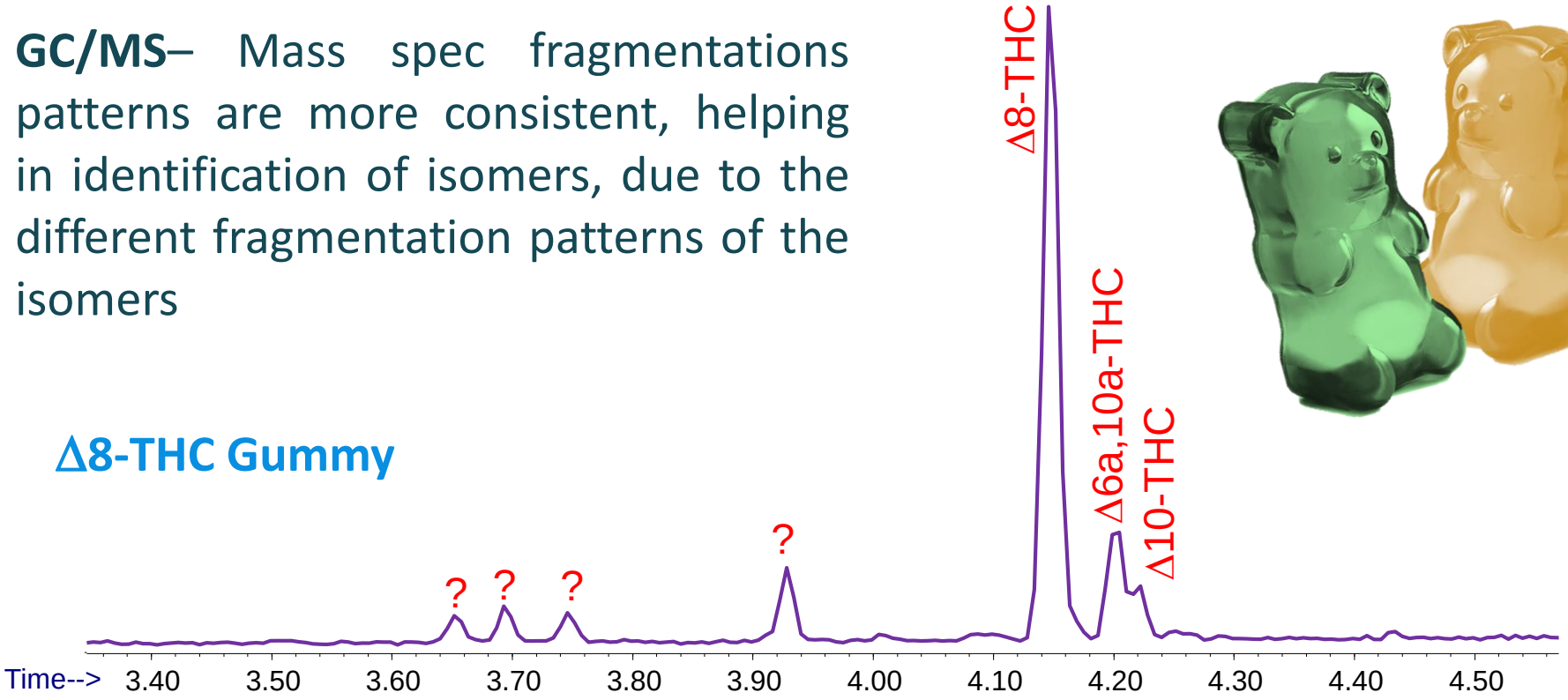


LC/MS – THC isomers are isobaric, so differentiation by compound mass is difficult, without considering ion fragmentation. Library searching not reliable.

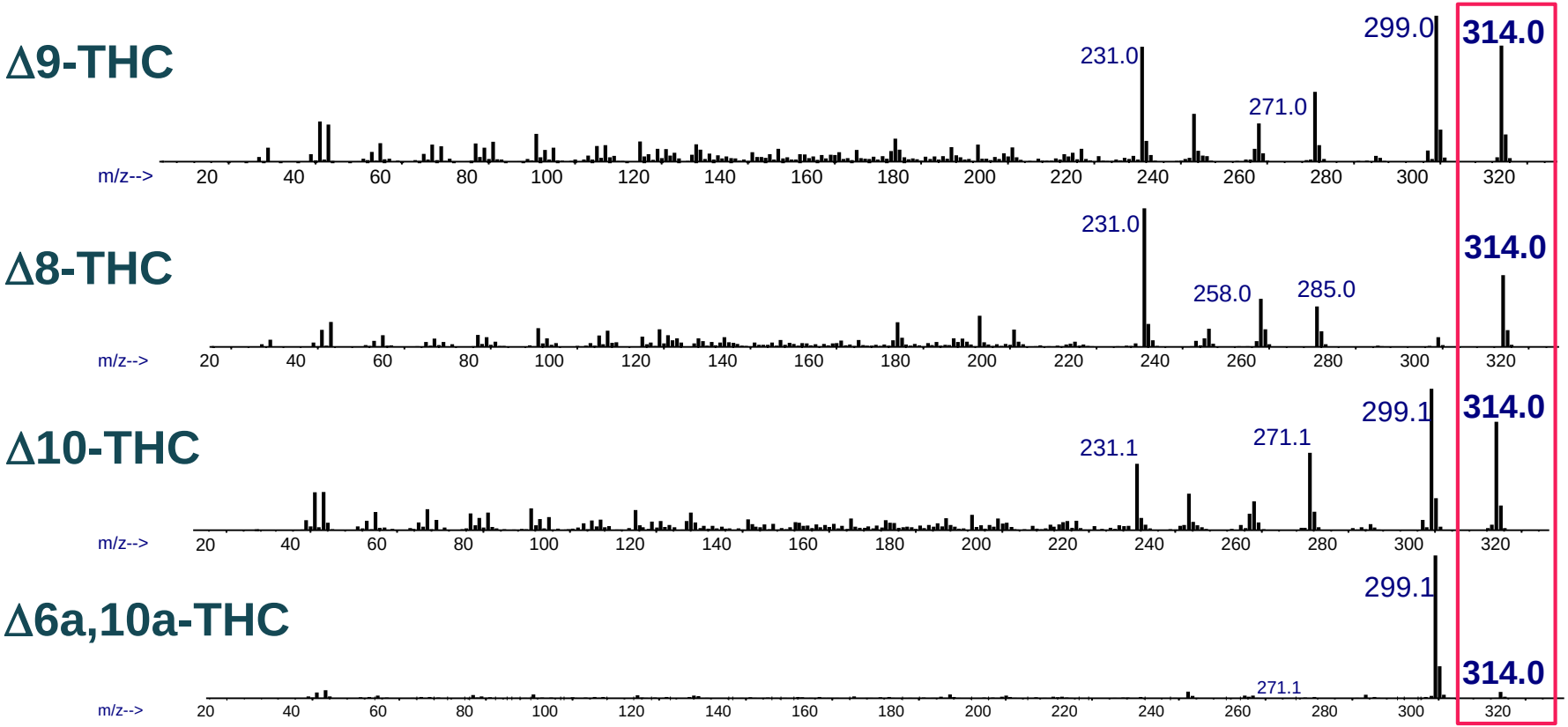
Laboratory Challenges

GC/MS– Mass spec fragmentations patterns are more consistent, helping in identification of isomers, due to the different fragmentation patterns of the isomers

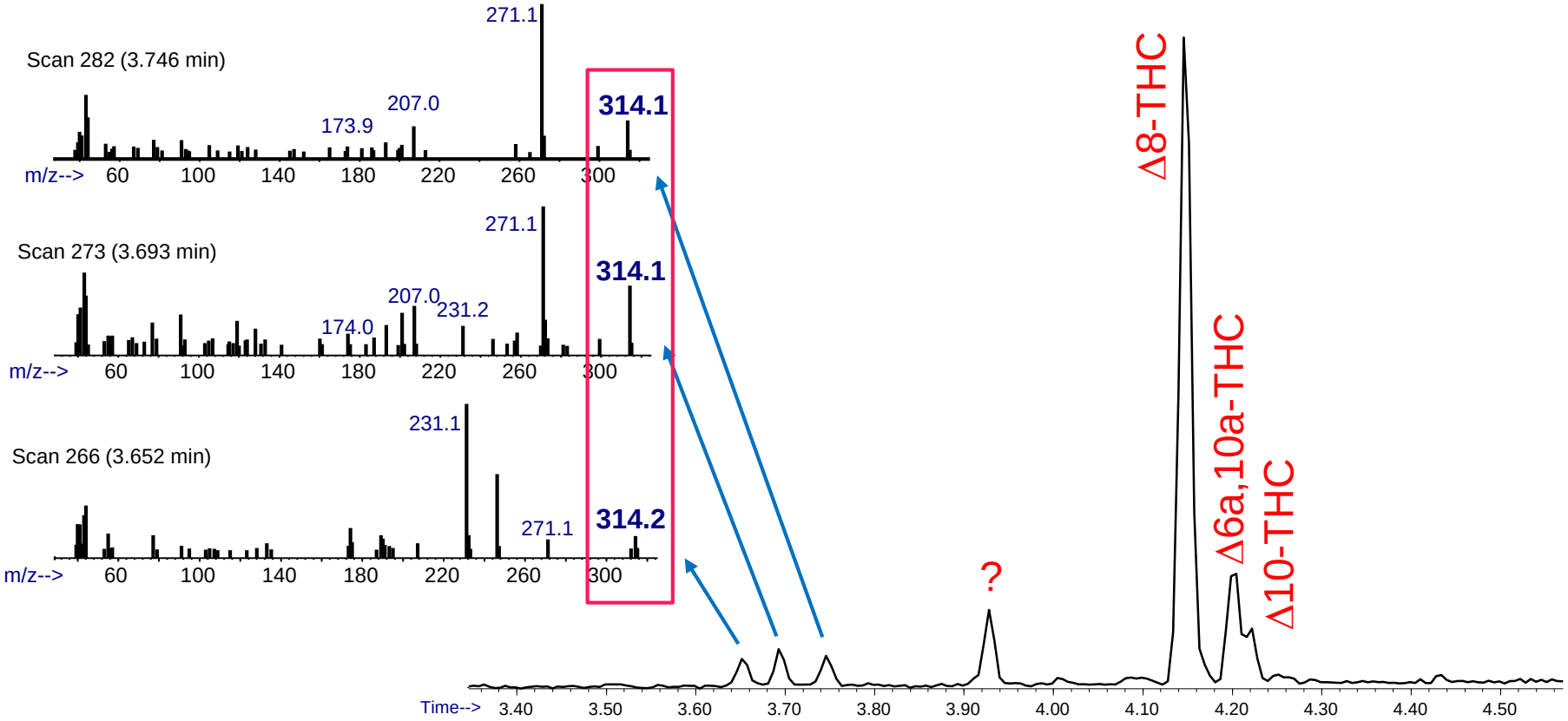
Δ8-THC Gummy



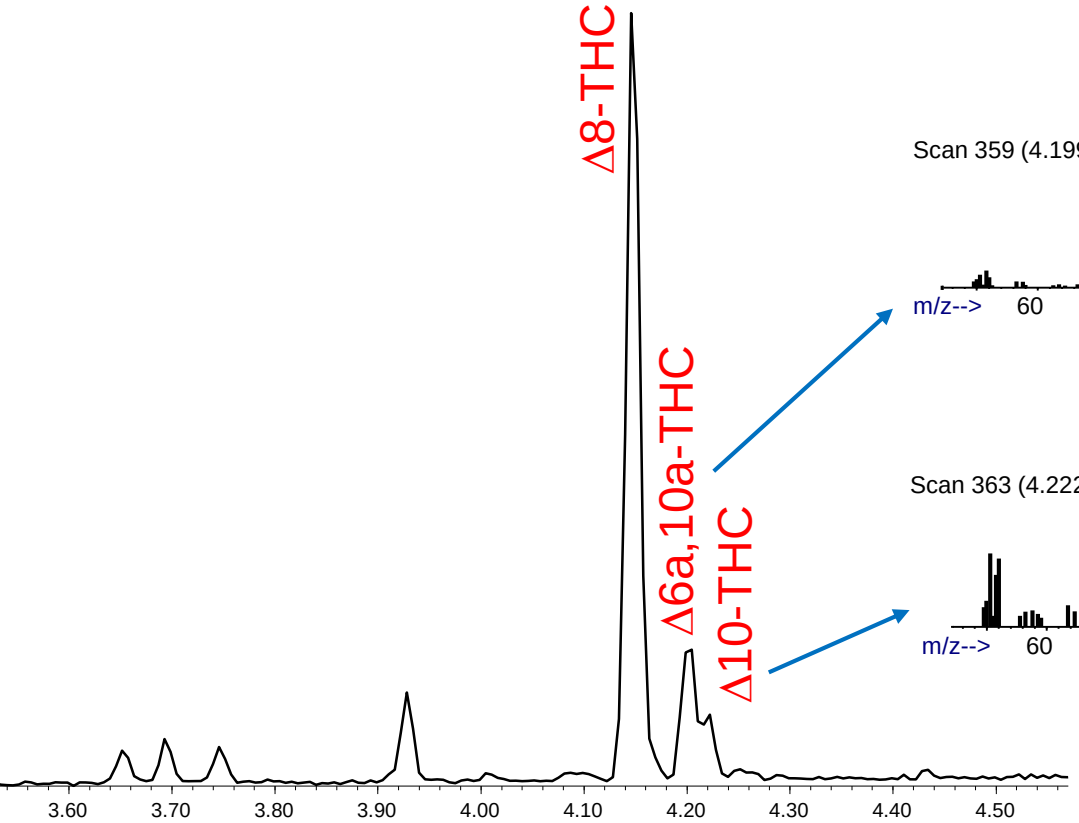
Mass Spec Fragmentation

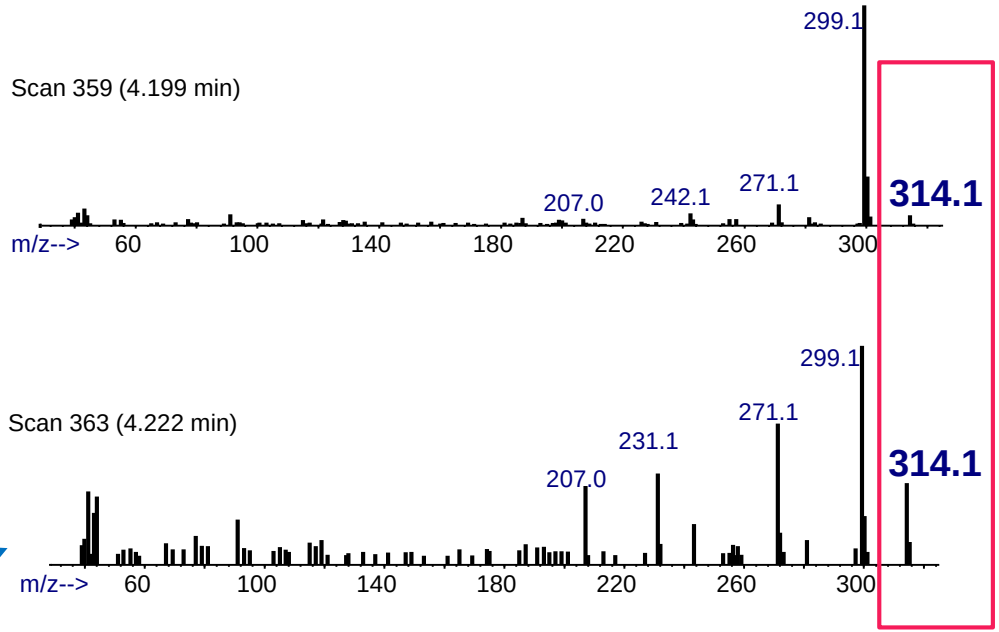


Mass Spec Fragmentation Patterns



Mass Spec Fragmentation Patterns





Isomers in Finished Products

CBD

THC

CBN

Δ9-THC

Δ8-THC

Δ10-THC

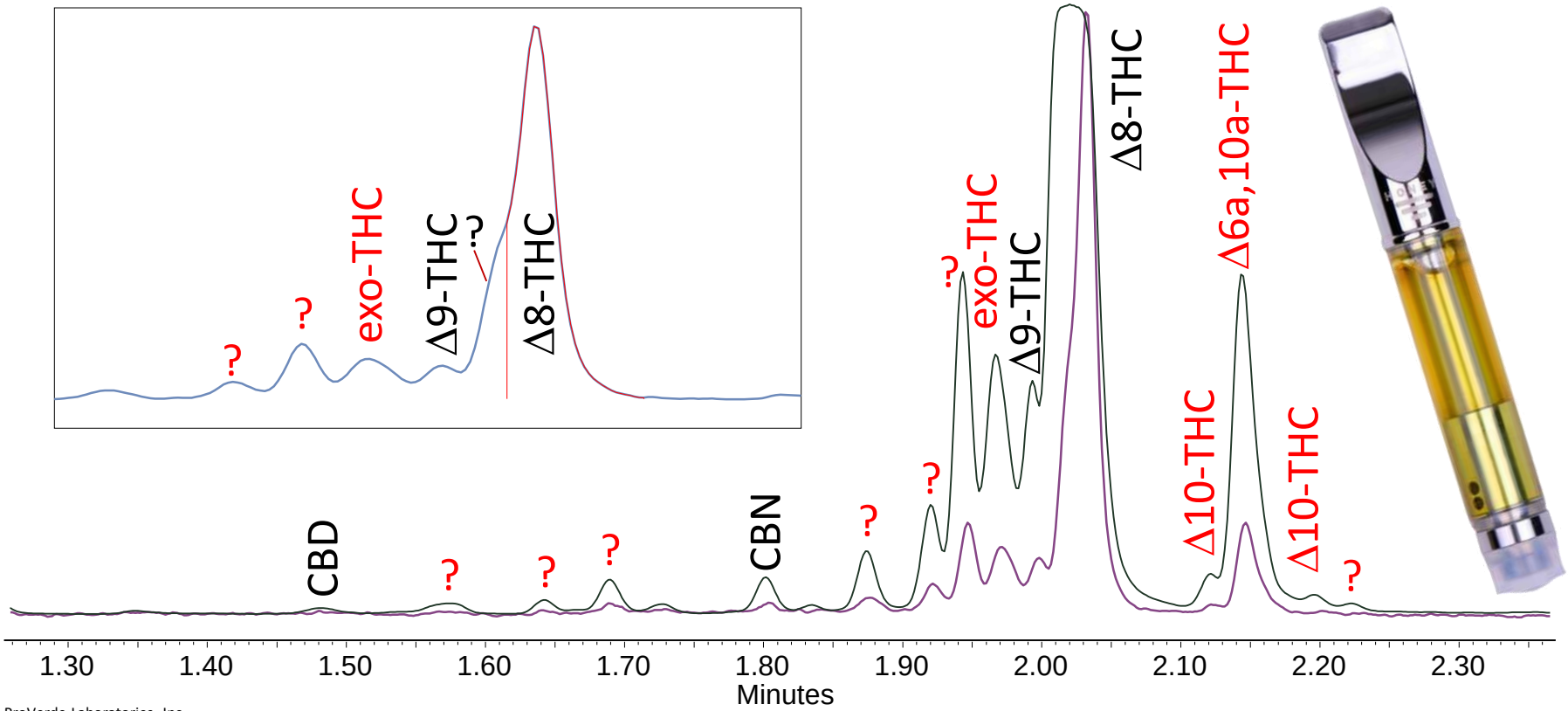
Δ6a,10a-THC

Δ10-THC

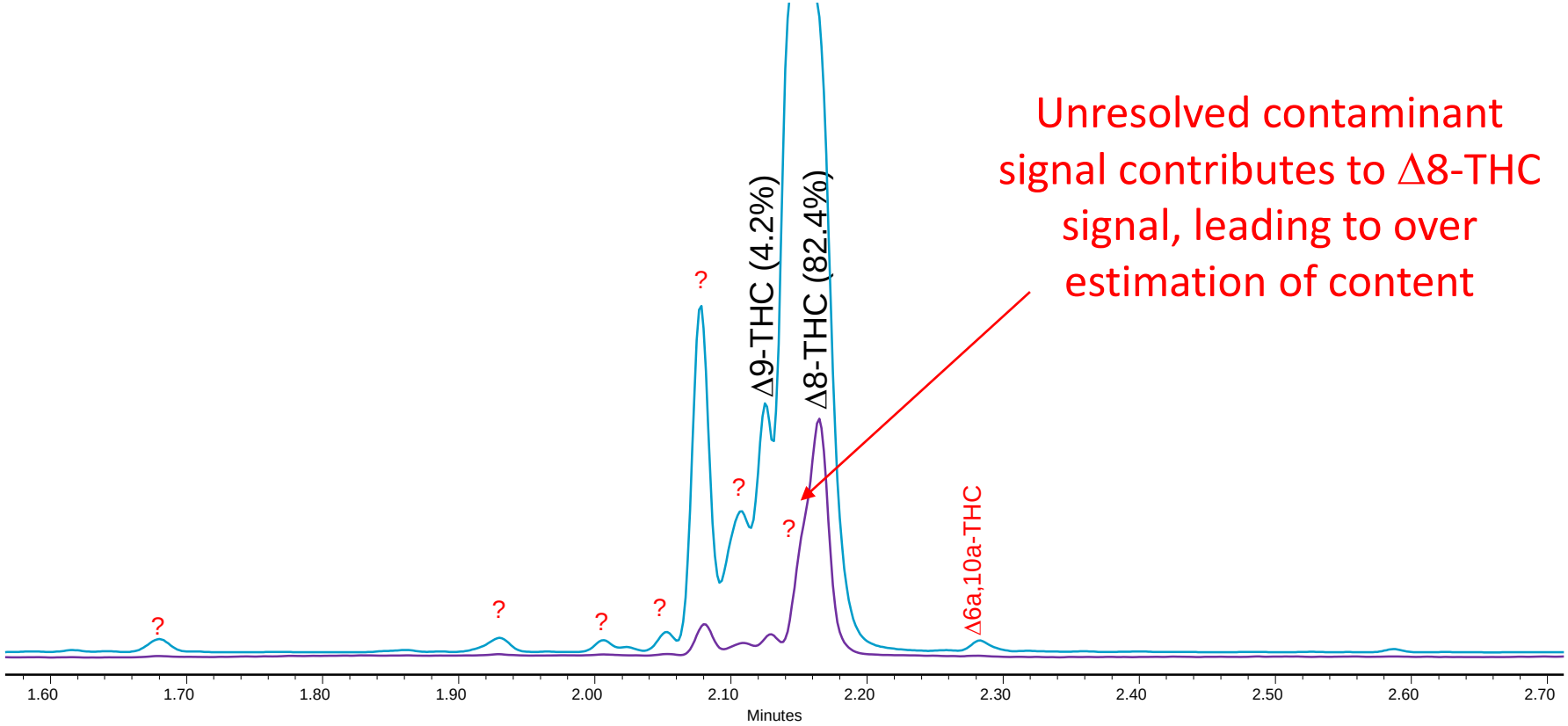
1.50 1.60 1.70 1.80 1.90 2.00 2.10 2.20 2.30 2.40 2.50

Minutes

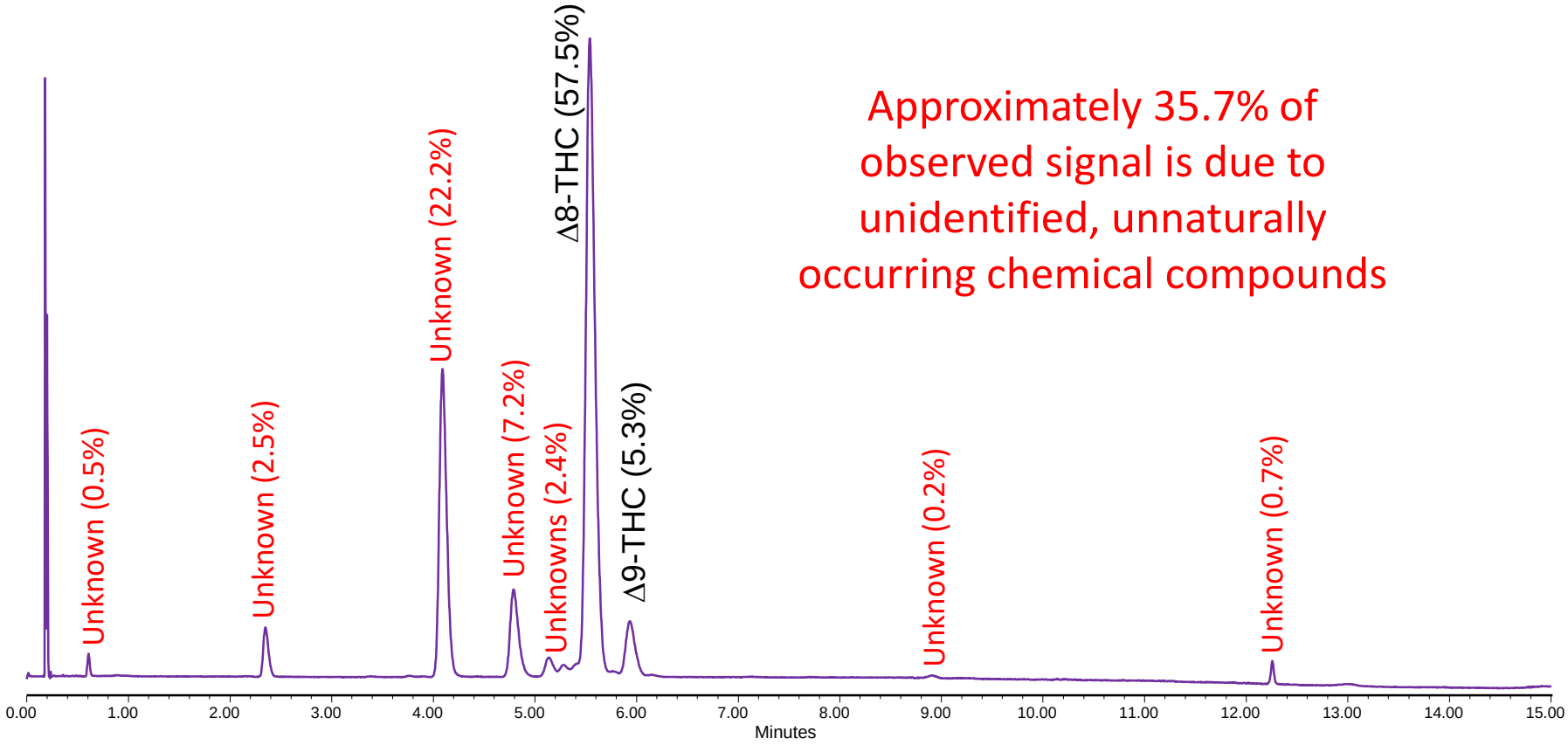
Lemon Drop Vape Cartridge Oil



Δ8-THC Distillate (LC/UV)



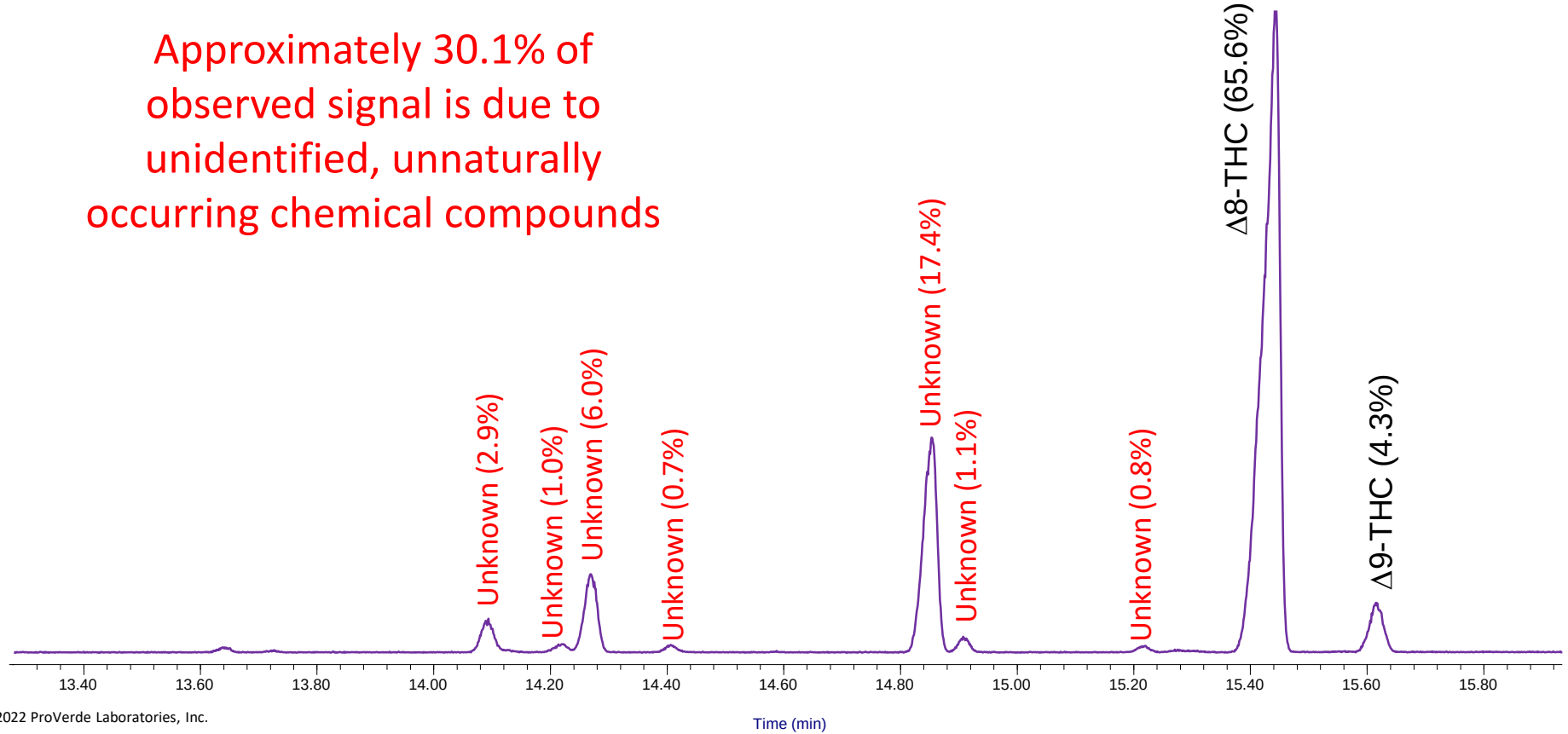
Δ8-THC Distillate (SFC/UV)



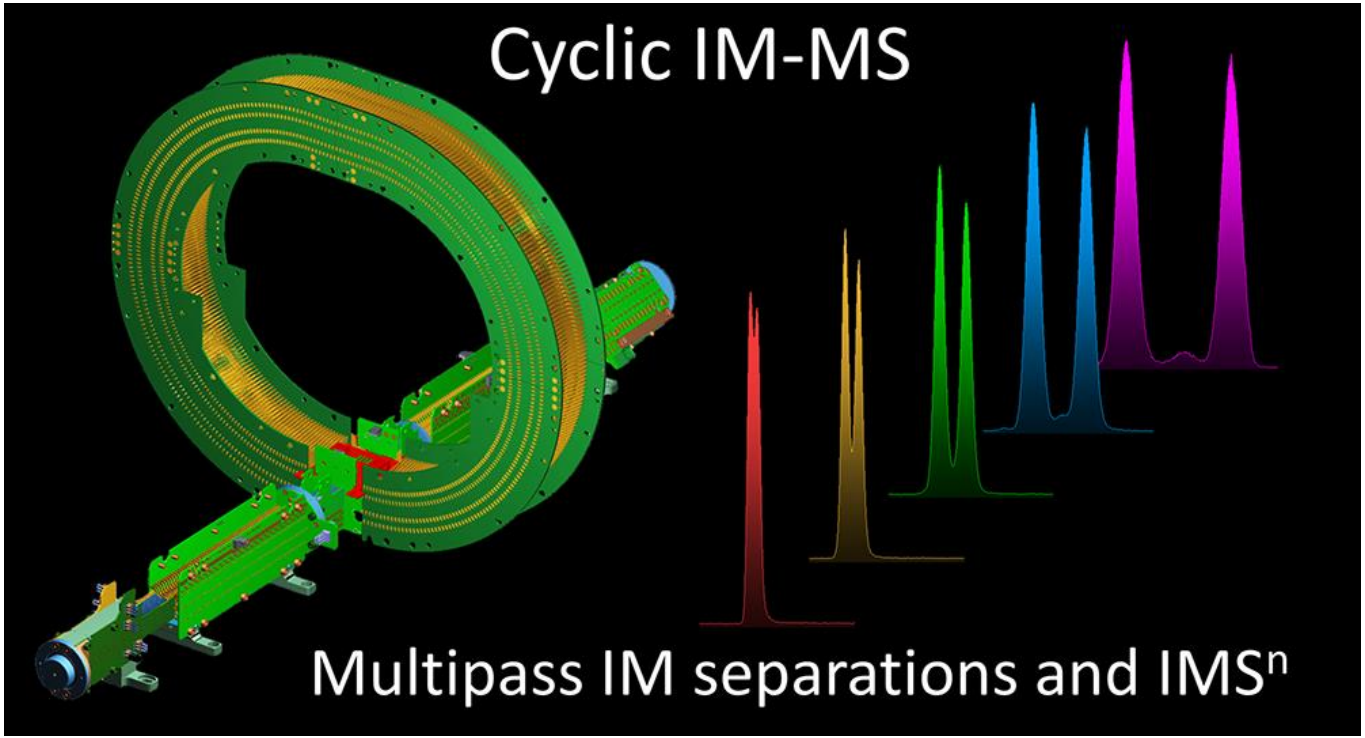
Approximately 35.7% of observed signal is due to unidentified, unnaturally occurring chemical compounds

Δ8-THC Distillate (GC/MS)

Approximately 30.1% of observed signal is due to unidentified, unnaturally occurring chemical compounds

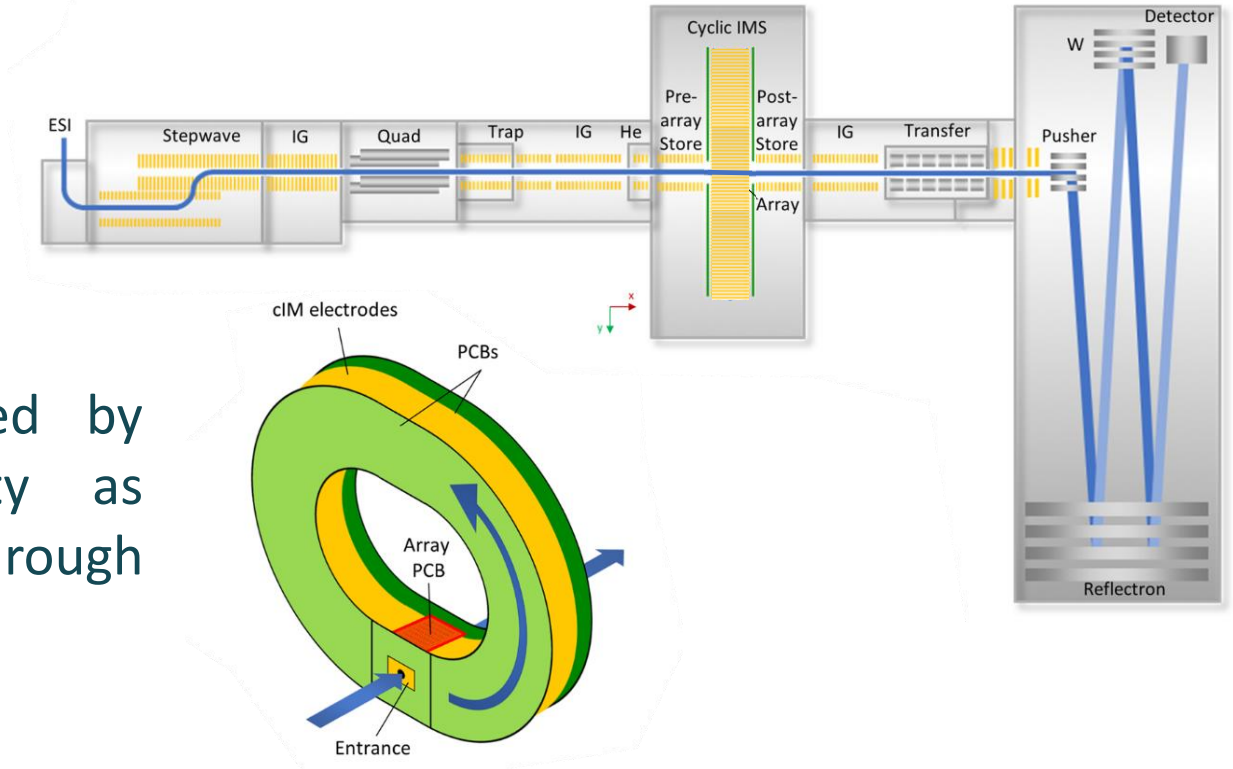


Additional Tool to Unravel the Complexity



Giles, K., et al. (2019). “A Cyclic Ion Mobility-Mass Spectrometry System." *Anal. Chem.* ***91***

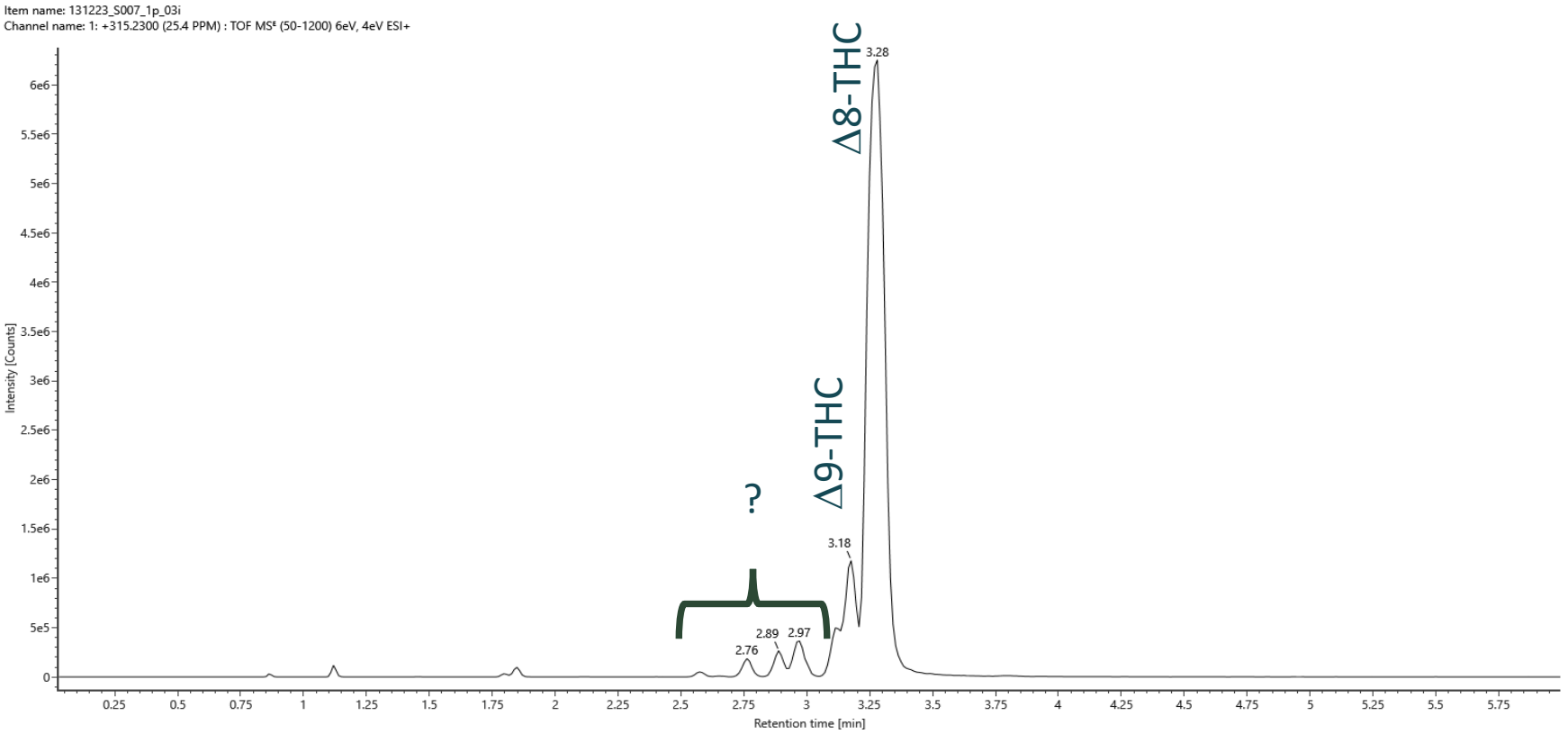
Cyclic Ion Mobility-Mass Spectrometry



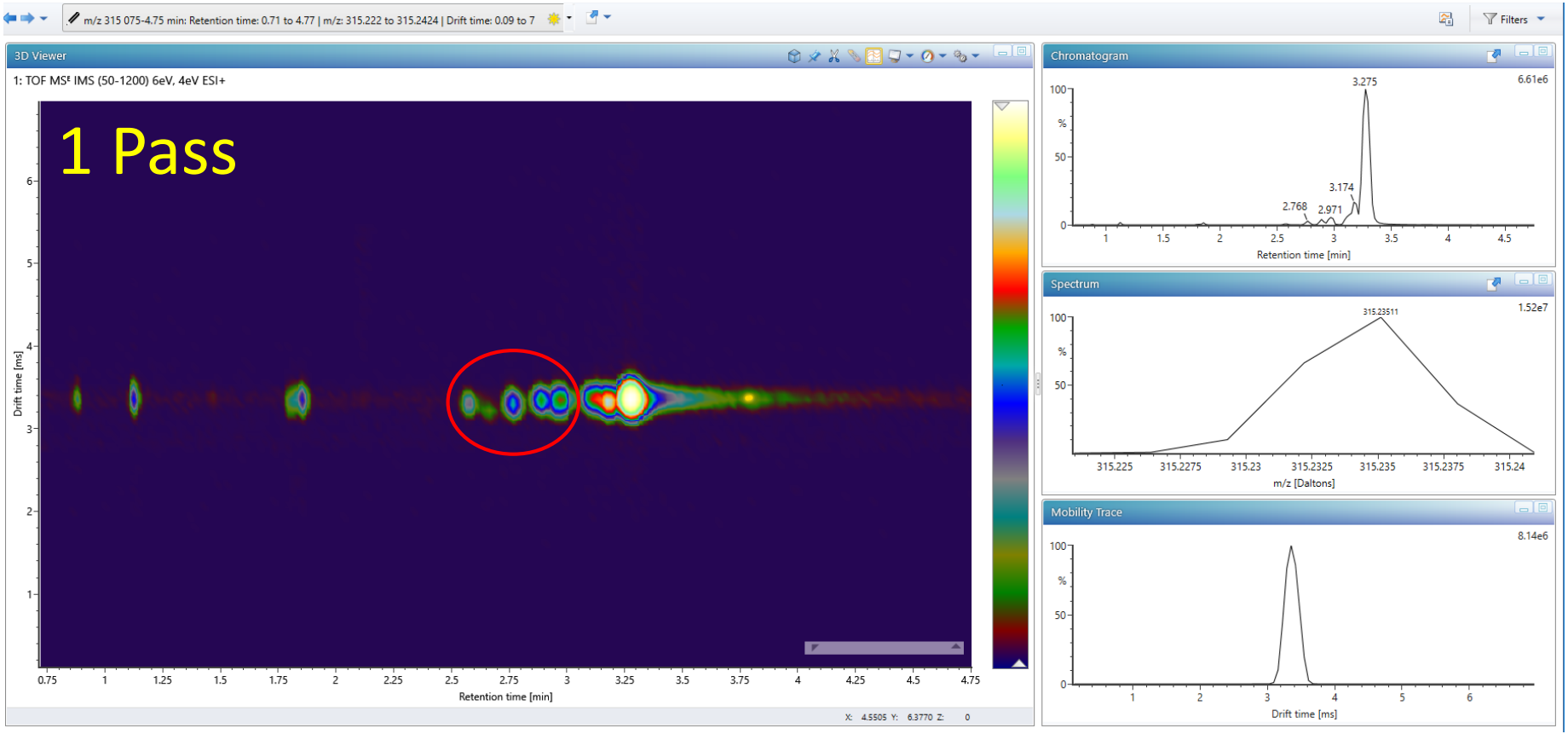
Ions separated by their mobility as they cycle through the drift tube

Giles, K., et al. (2019). “A Cyclic Ion Mobility-Mass Spectrometry System." *Anal. Chem.* ***91***

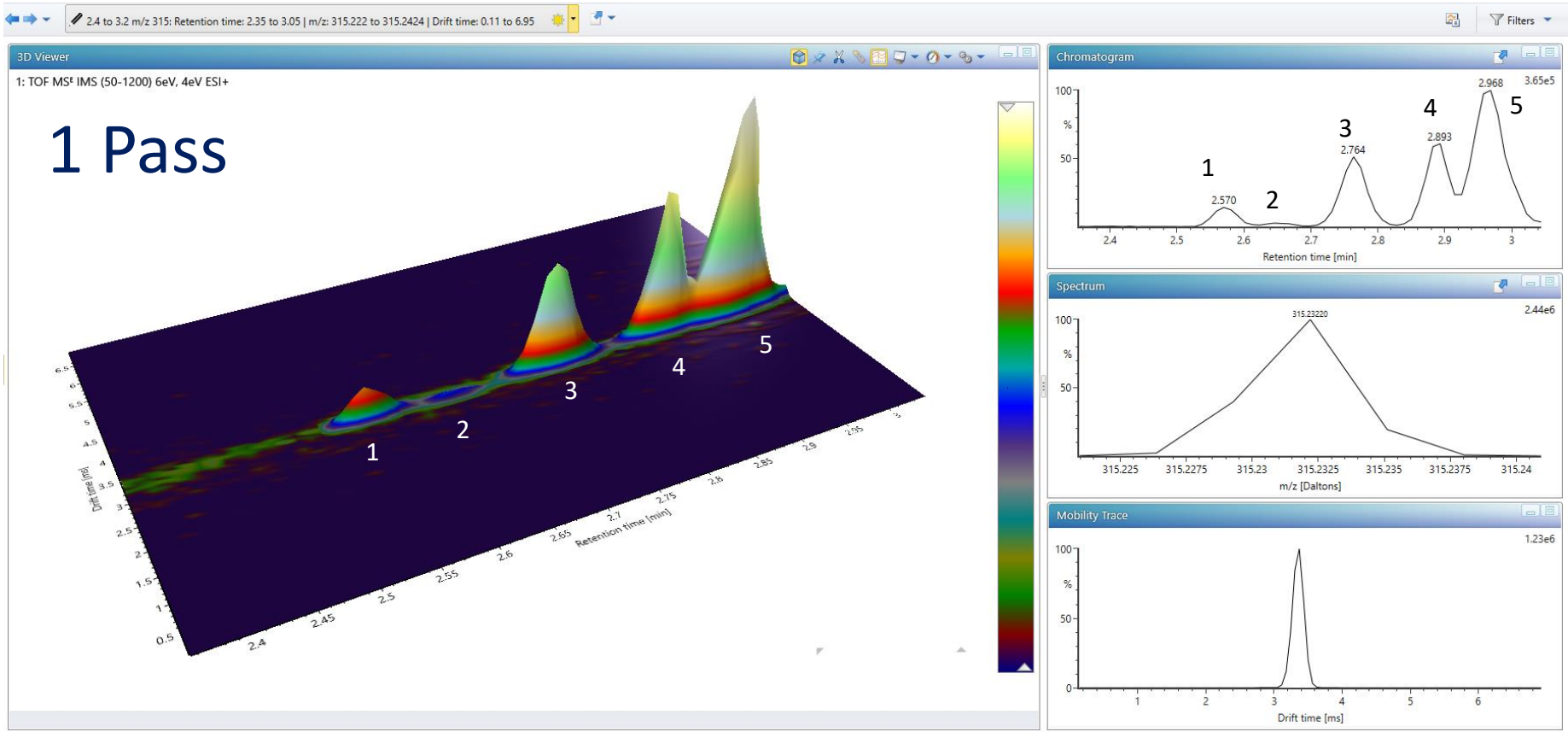
Analysis of Δ8-THC Distillate Sample A: XIC 315.23



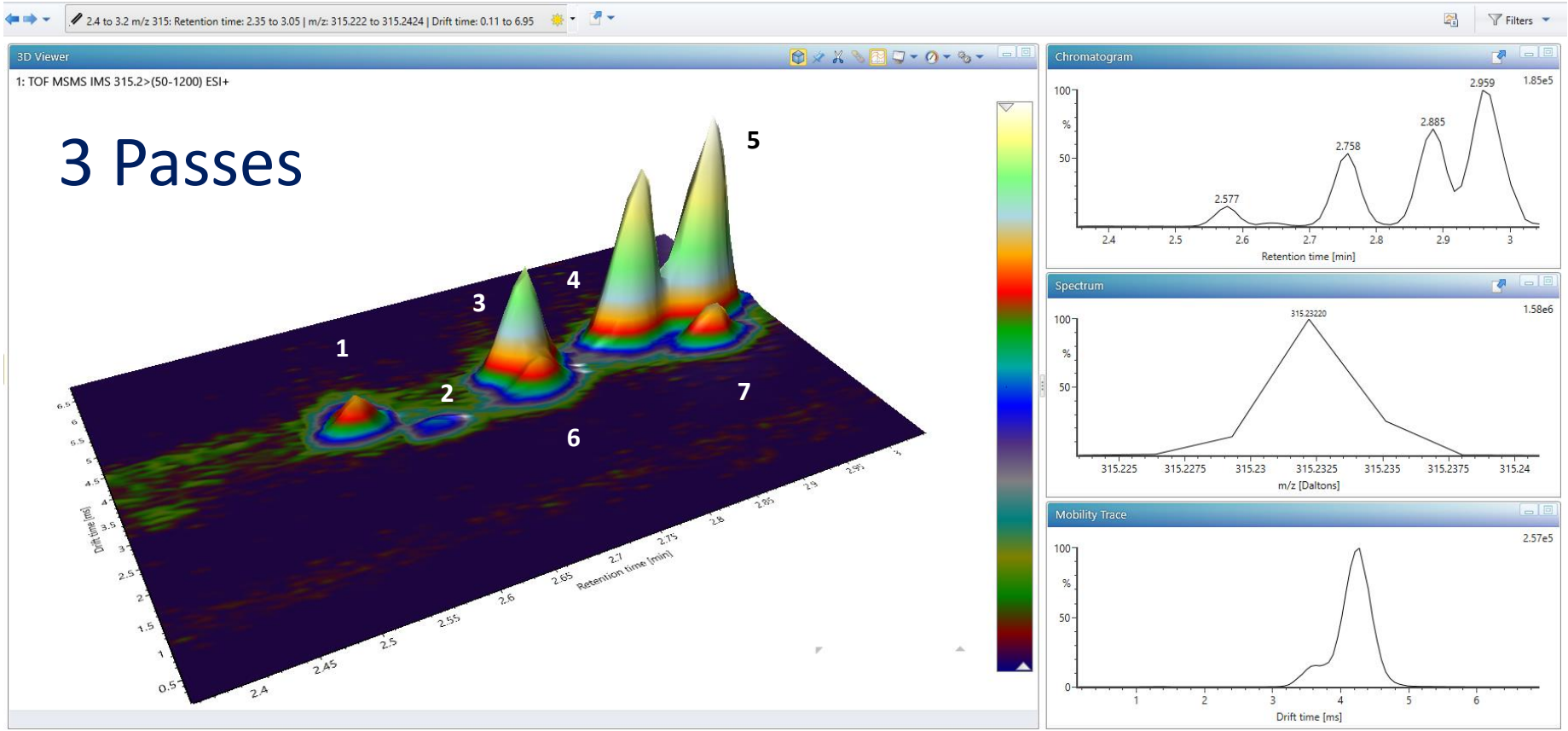
Analysis of Δ8-THC Distillate Sample A : XIC m/z 315.2



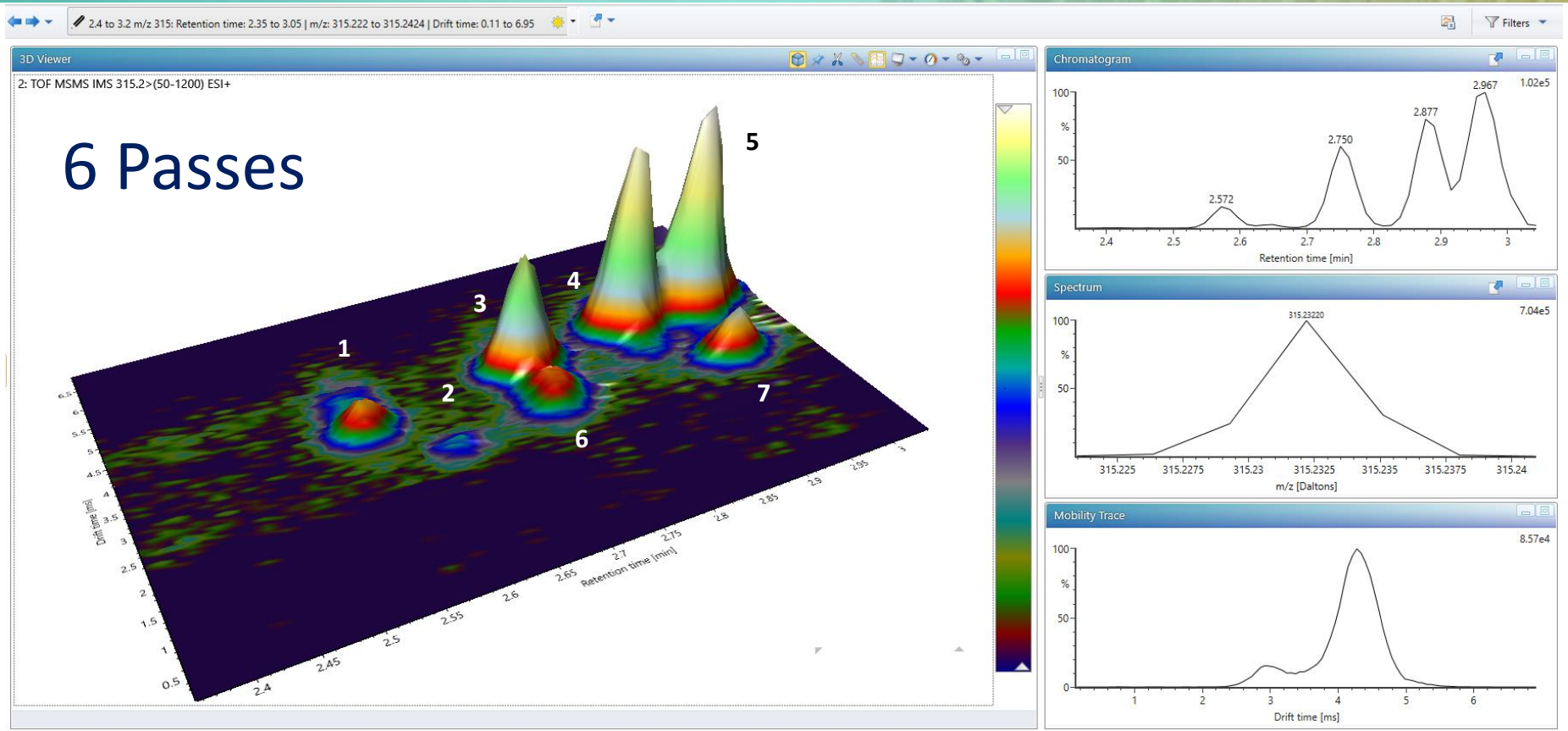
Analysis of Δ8-THC Distillate Sample A : XIC m/z 315.2



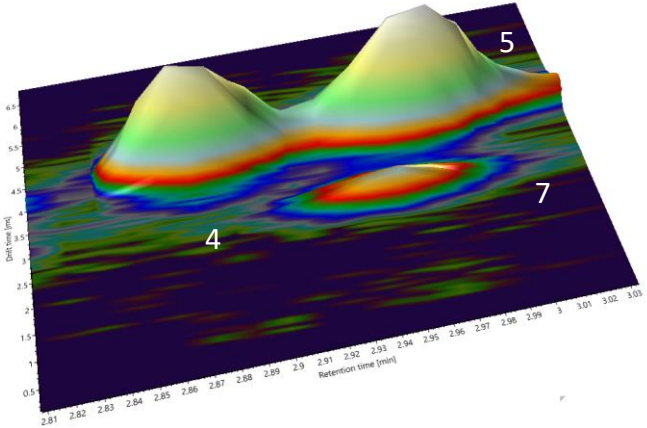
Analysis of Δ8-THC Distillate Sample A: MS/MS m/z 315.2

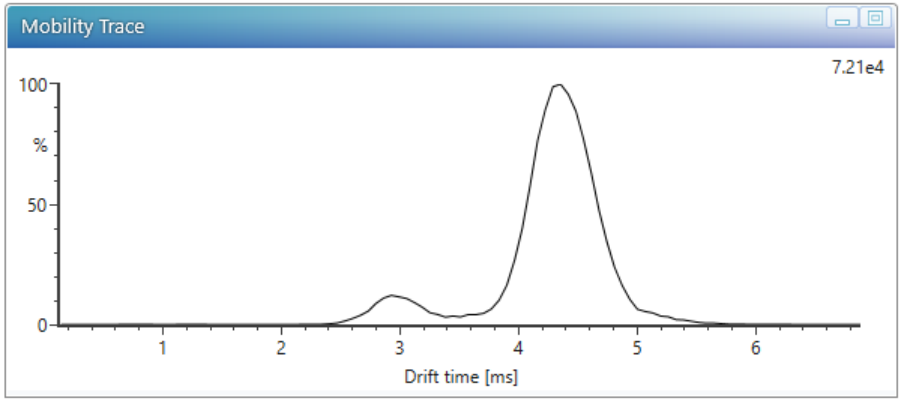


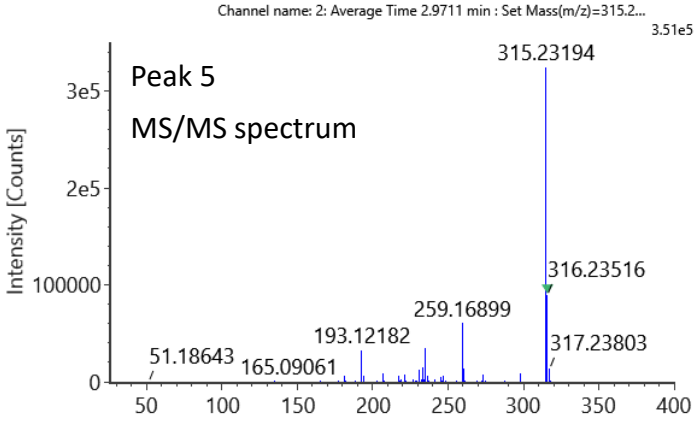
Analysis of Δ8-THC Distillate Sample A: MS/MS m/z 315.2

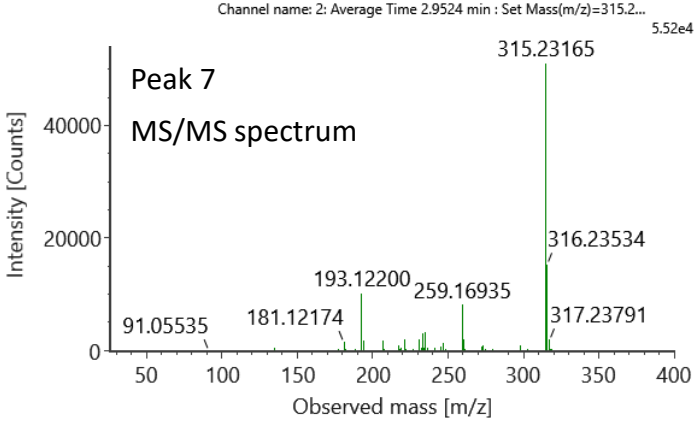


Analysis of Δ8-THC Distillate Sample A: 6-Passes-MS/MS spectra for Peaks 5 and 7









Δ^x – Wheel of Chance

- Commercially available Δ8-THC products represent complex synthetic mixtures
- Most laboratories are not reporting the unknown constituents
  - Certificates of Analysis are often unreliable
- Producers often do not know what they are producing and distributing
- Without regulatory oversight, consumers have no idea what they are consuming

Points to Ponder

For these unknown synthetic reaction byproducts in Δ8-Samples:

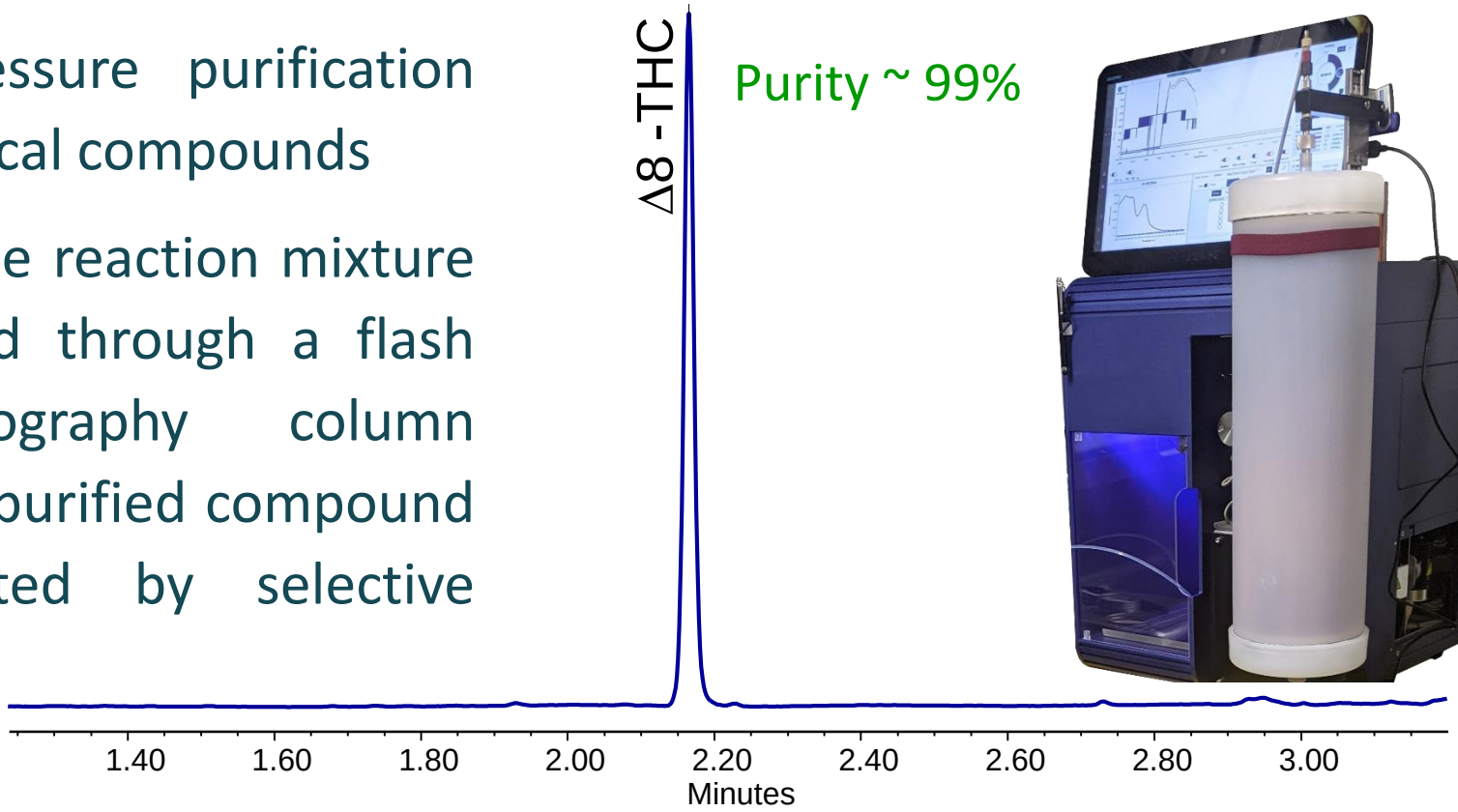
- Are they doing liver damage because the body does not know how to metabolize these unknown compounds?
- Will they cause cancer with repeated long term exposure?
- Might some of these compounds cause birth defects or miscarriage if consumed during pregnancy?
- Will some of these compounds interact with other medications that a patient may be taking?
- Will use of these products trigger a positive drug test?

Purification / Isolation

- Chromatographic methods are available for sample purification
- Facilitates the isolation and purification of individual chemical compounds
    - Typically by separation and collection of fractions
- Purified compounds can then be studied as individual compounds for efficacy and toxicity

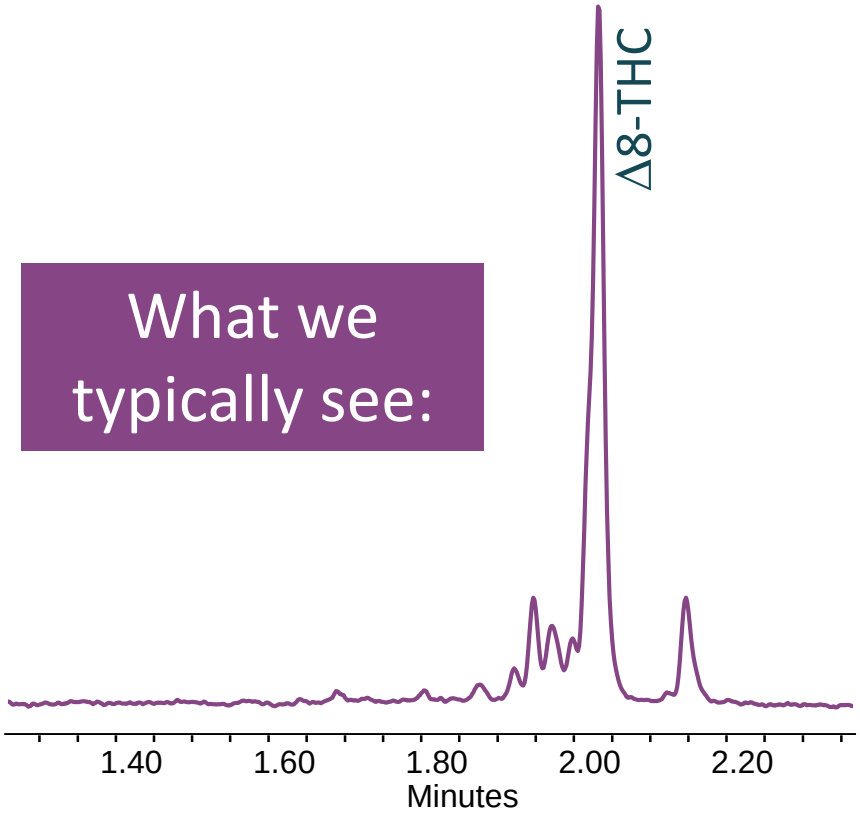
Flash Purification

- Low Pressure purification of chemical compounds
- The crude reaction mixture is passed through a flash chromatography column and the purified compound is isolated by selective elution

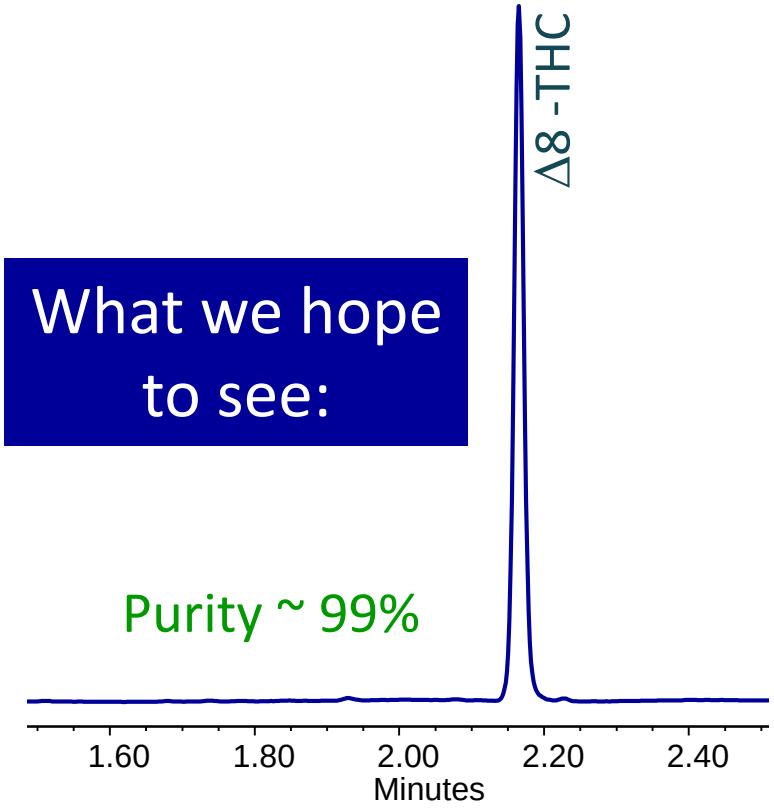


Δ8 Purification

What we typically see:

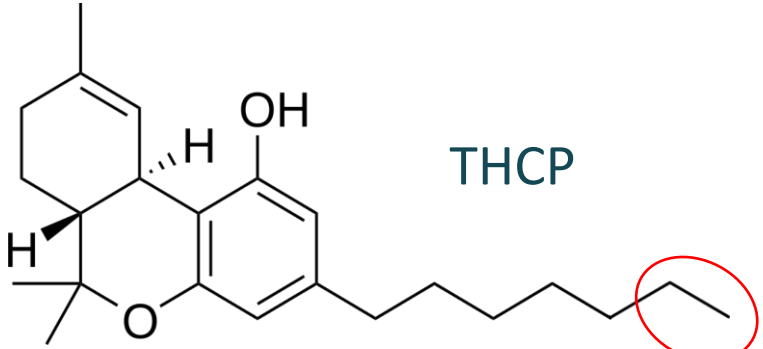


What we hope to see:



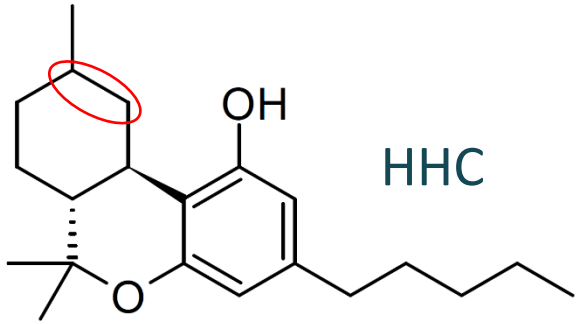
What's ~~Next?~~ Now?

- Other synthetic variants and analogs are already on the market:



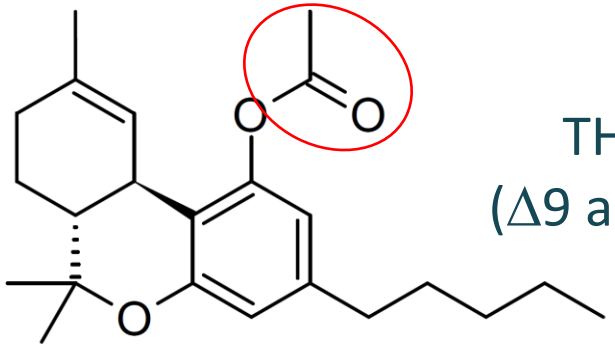
THCP

Δ9-Tetrahydrocannabiphorol



HHC

Hexahydrocannabinol



THCO

(Δ9 and Δ8)

Δ9-THC acetate

Δ8-THC acetate

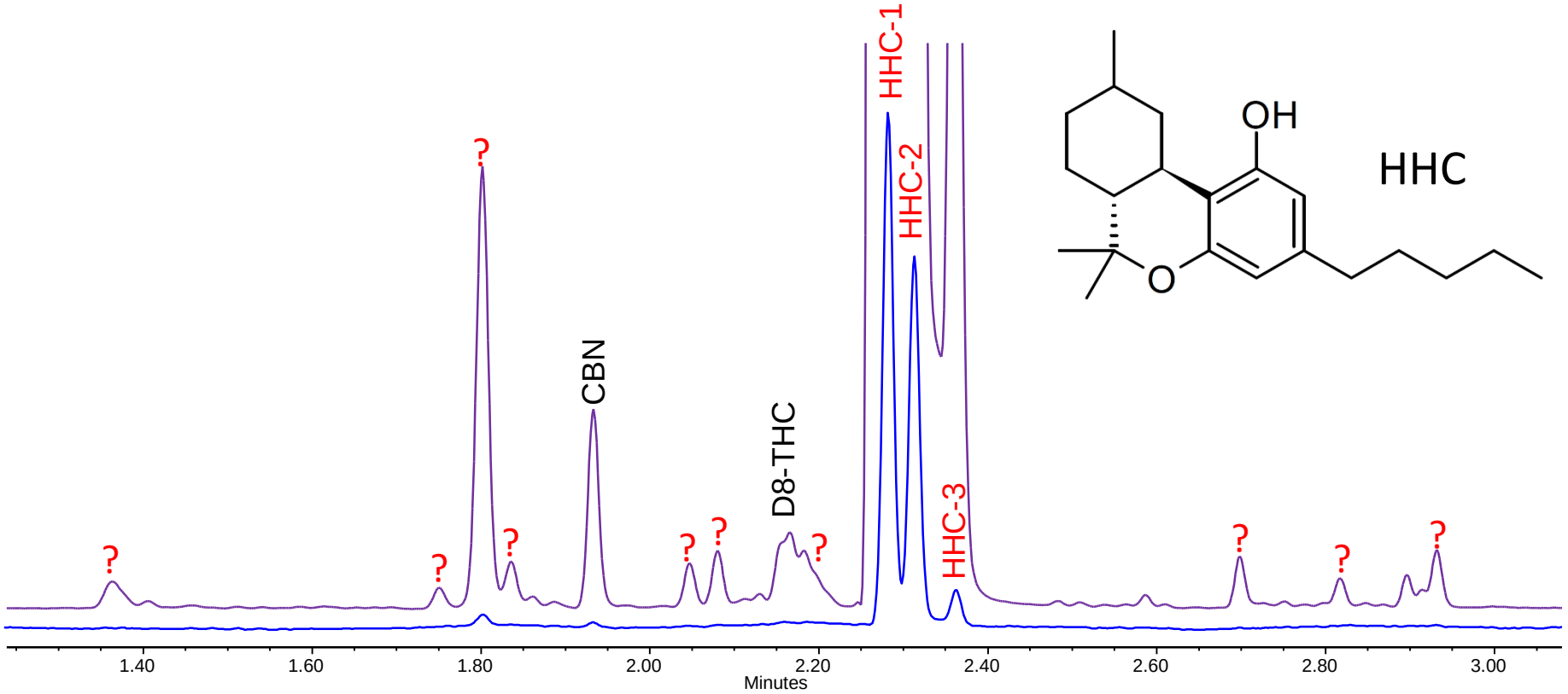
(Δ9 / Δ8)
THCb
THCh
THCp
THCO
THCPO

CBNO
HCC
HHCP
HHCO
HHCPO

THC-O-Acetate Vape

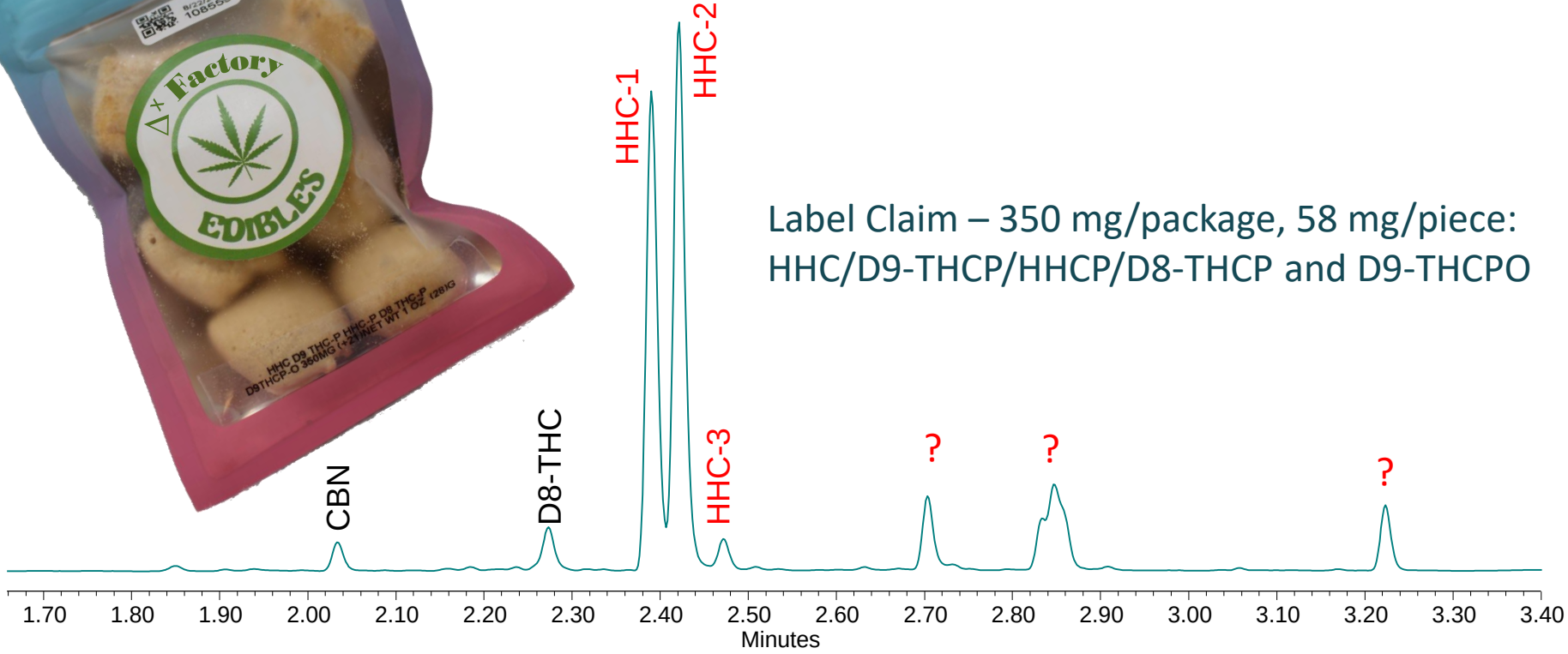
Δ8-THC
Δ8-THC-OAc
Δ9-THC-OAc
?
?
?
?
?
?
CBDV
CBDA
CBGA
CBG
CBD
THCV
CBN
exo-THC
Δ9-THC
Δ8-THC
CBD
THCA
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
Minutes

Hexahydrocannabinol (HHC)



Multi-Mix of Synthetics

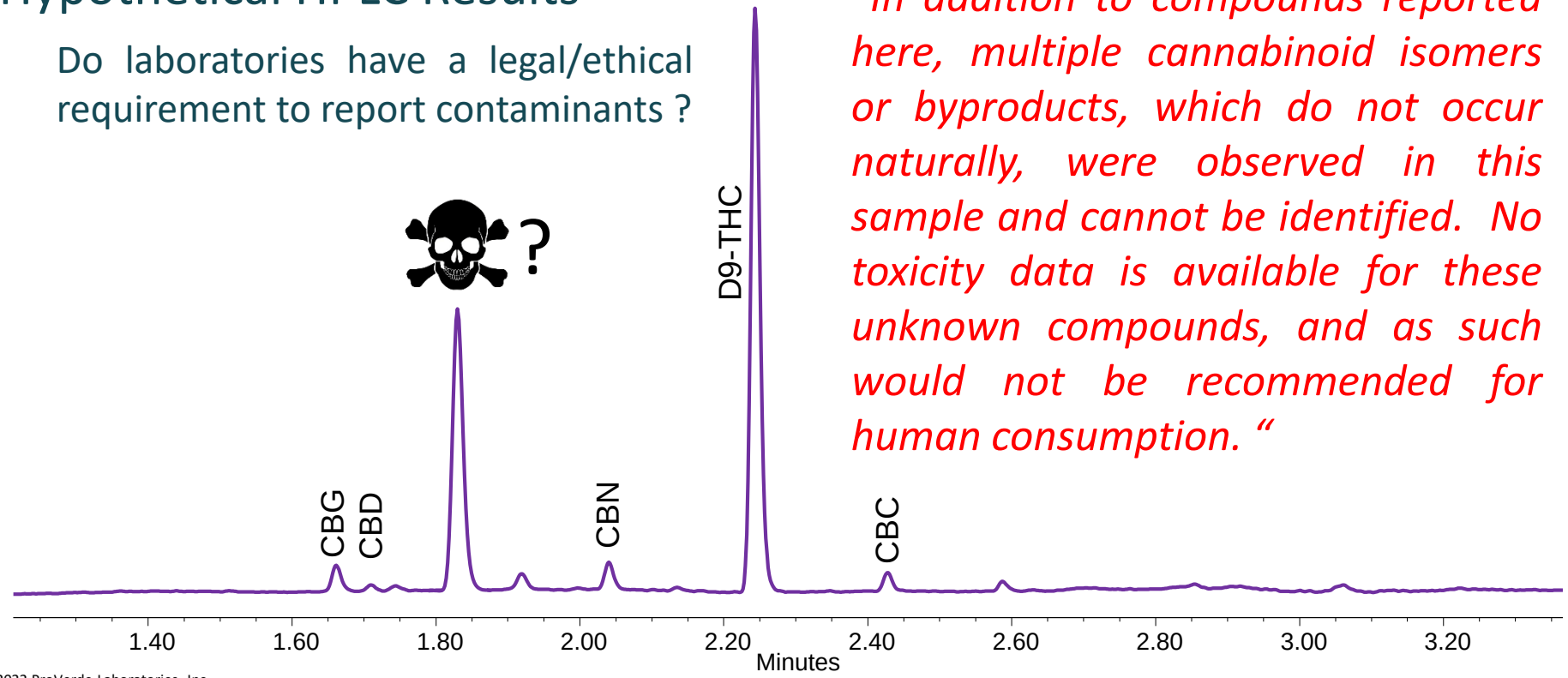
Label Claim – 350 mg/package, 58 mg/piece:
HHC/D9-THCP/HHCP/D8-THCP and D9-THCPO



Laboratory Responsibility

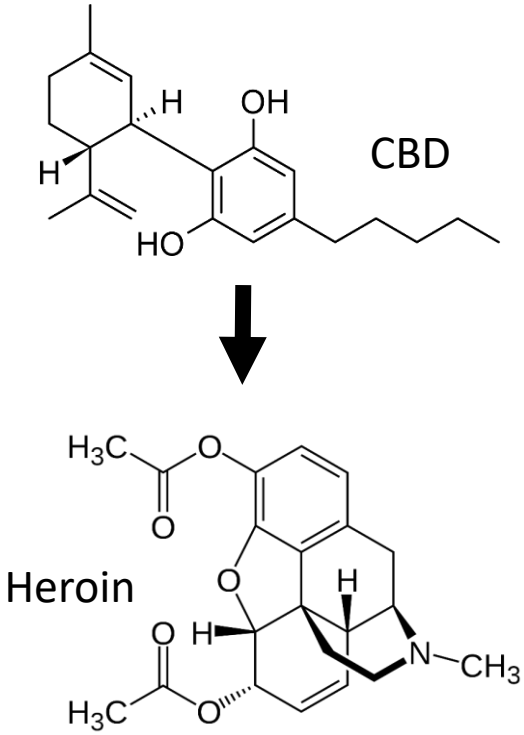
Hypothetical HPLC Results

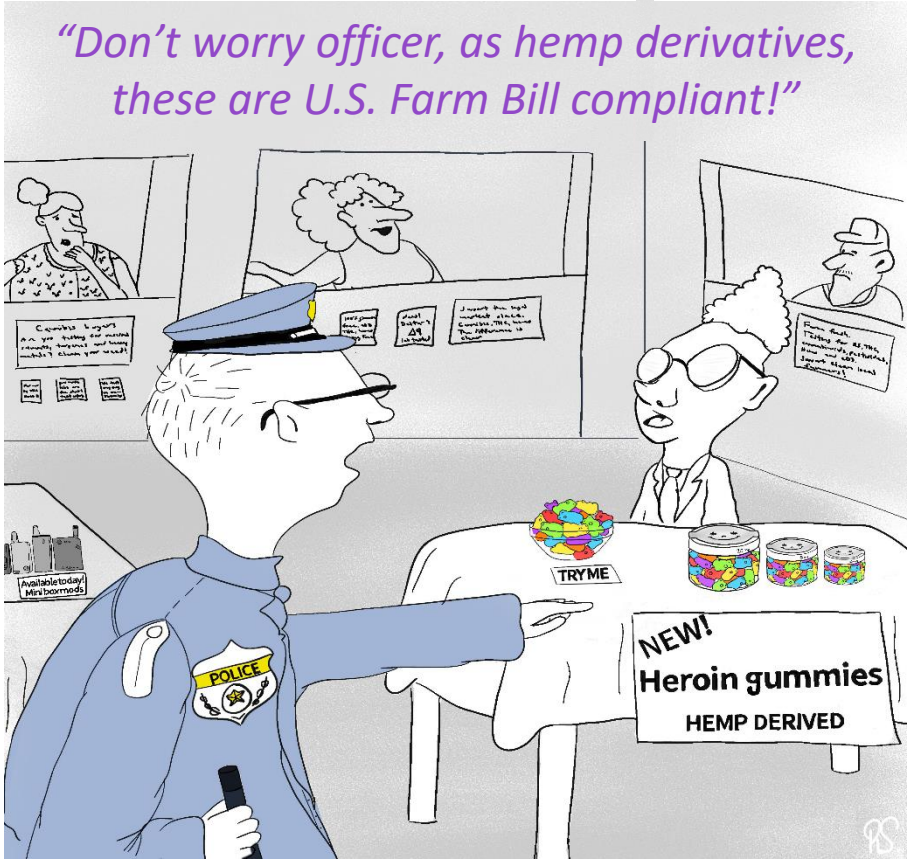
Do laboratories have a legal/ethical requirement to report contaminants ?



"In addition to compounds reported here, multiple cannabinoid isomers or byproducts, which do not occur naturally, were observed in this sample and cannot be identified. No toxicity data is available for these unknown compounds, and as such would not be recommended for human consumption. "

Legal Hemp Derivatives





Summary

- The US Farm Bill has provided the unintended loophole for synthetic transformations of CBD into other psychoactive compounds.
- While Δ8-THC is found in nature, natural sources are impractical, making synthetic preparation the most economical source.
- Currently, these synthetic products are synthesized in an unregulated environment, giving rise to multiple contaminants of concern.
- Many of these contaminants have not yet been identified, and most laboratories ignore their presence, making COAs unreliable.
- Additional or advanced analytical techniques and more research is required for a better understanding of these products.

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Waters

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Thank You!