Chemical Research in Toxicology
pubs.acs.org/crt
Rapid Report

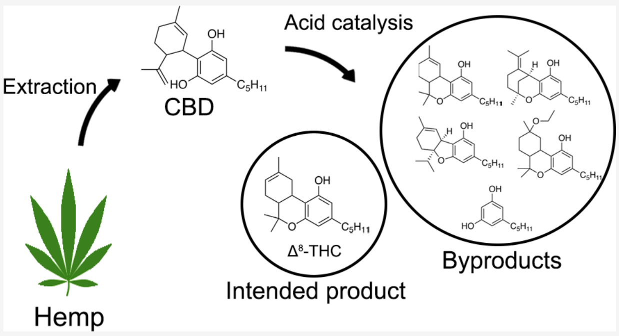
# Novel Δ8-Tetrahydrocannabinol Vaporizers Contain Unlabeled Adulterants, Unintended Byproducts of Chemical Synthesis, and Heavy Metals

Jiries Meehan-Atrash and Irfan Rahman*

Cite This: https://doi.org/10.1021/acs.chemrestox.1c00388 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

**ABSTRACT:** Cannabis e-cigarettes containing Δ8-tetrahydrocannabinol (Δ8-THC) produced synthetically from hemp-derived cannabidiol (CBD) have recently risen in popularity as a legal means of cannabis consumption, but questions surrounding purity and unlabeled additives have created doubts of their safety. Herein, NMR, GC-MS, and ICP-MS were used to analyze major components of 27 products from 10 brands, and it was determined none of these had accurate Δ8-THC labeling, 11 had unlabeled cutting agents, and all contained reaction side-products including olivetol, Δ4(8)-*iso*-tetrahydrocannabinol, 9-ethoxyhexahydrocannabinol, Δ9-tetrahydrocannabinol (Δ9-THC), heavy metals, and a novel previously undescribed cannabinoid, *iso*-tetrahydrocannabifuran.



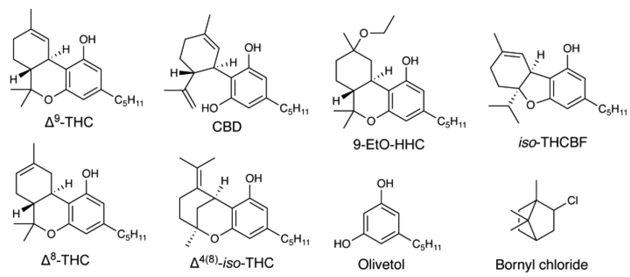



Cannabis e-cigarettes (CECs) are a noncombustion inhalation delivery method, which uses technology adapted from electronic nicotine delivery systems. CECs vaporize an oil rich in Δ9-THC, the psychoactive principle component of *Cannabis sativa*, and release hundreds of chemical breakdown products including carcinogenic and irritating gases such as isoprene, benzene, methacrolein, and methyl vinyl ketone.[1,2] CECs are popular with teens and young adults in the United States, with 23.7% of 12th graders having reported lifetime cannabis vaping in 2019.[3] CEC use was recently shown to be independently associated with higher odds of respiratory symptoms such as wheezing.[4] The 2019 outbreak of e-cigarette or vaping product use associated lung injury (EVALI) was centered around CECs, and though vitamin E acetate was identified as a potential causative agent, other ingredients or aerosol components were not ruled out.[5] Some CECs linked to EVALI were later found to contain unnatural cannabinoid distributions suggesting that these were of synthetic origin.[6,7] Niche online communities that recount intoxication experiences by minor or synthetic cannabinoids have existed likely for decades,[8] but it is only recently that cannabinoids other than those naturally occurring have reached broad commercial availability.[9] At the forefront of this trend is Δ8-THC (Chart 1).

Δ8-THC is an isomer of Δ9-THC not produced biosynthetically[10] but present at low levels in most cannabis products as a result of spontaneous isomerization given its higher thermodynamic stability and resistance to oxidative degradation than Δ9-THC.[10] Recent federal regulations that are permissive of hemp-derived products[11] have resulted in a rapid growth in usage of Δ8-THC CECs that are abundantly available to consumers through brick-and-mortar and online sources. Extensive hospitalizations involving suspected Δ8-THC consumption have been recently documented.[12] Δ8-THC is synthesized via acid-catalyzed cyclization of CBD.[13,14] Though Δ9-THC is the direct product of CBD cyclization (Scheme 1), Δ8-THC is favored as a major product at longer reaction times.[15,16]

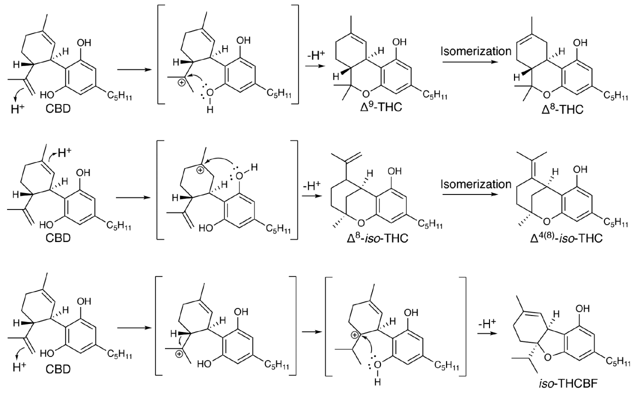
Hydrochloric acid (HCl), sulfuric acid, *p*-toluenesulfonic acid, boron trifluoride, and camphorsulfonic acid, among others, are viable catalysts, but the acids, solvents, and

**Chart 1. Relevant Structures**




**Received:** November 9, 2021

**Scheme 1. Routes of Formation of Δ[8]-THC (top), Δ[4(8)]-*iso*-THC (middle), and *iso*-THCBF (bottom) from CBD via Acid Catalysis**




purification steps used by manufacturers are not known.[15,16] In order to address this emerging class of products, available flavor formulations from different Δ[8]-THC brands were obtained. Proton nuclear magnetic resonance spectroscopy ($^1$H NMR) was chosen as the primary analytical tool given this instrument's ability to characterize analytically challenging vaporizer adulterants[17] without the need for derivatization or developing dedicated chromatographic methods, which may be necessary for complex samples. Quantitative $^1$H NMR (QNMR) was used to report component levels in these products, a facile and direct quantitative method whose limitations include the fact that some components cannot be identified or quantified due to spectral overlap of their resonances and its inherently low sensitivity precludes identification of ultratrace impurities.

Medium chain triglyceride oil was identified in B5 (3.71 ± 0.06%, $\bar{x}$ ± SEM), B6 (3.48 ± 0.06%), B8 (2.94 ± 0.05%), and B9 (5.6 ± 0.1%). Triethyl citrate (TEC) was identified in F20 (6.3 ± 0.06%), F21 (6.27 ± 0.03%), F22 (6.5 ± 0.1%), G23 (7.28 ± 0.05%), G24 (6.2 ± 0.1%), I26 (11.1 ± 0.1%), and J27 (5.34 ± 0.06%). Δ[4(8)]-*iso*-Tetrahydrocannabinol (Δ[4(8)]-*iso*-THC) is a previously described byproduct of acid-catalyzed CBD cyclization (Scheme 1)[18] and was detected in all 27 samples ranging from 2.36 ± 0.05% to 12.79 ± 0.06% with $\bar{x}$ ± SD of 5.4 ± 3.5% in $n$ = 16 where quantification was possible (see SI). Olivetol (5-pentyl-1,3-benzenediol, Chart 1) was identified in 22/27 products, but its quantification was not possible (see SI). Olivetol has been previously shown in EVALI-associated CECs that also contain unnatural cannabinoid distributions[7] and is likely a byproduct of chemical synthesis. Olivetol is a synthetic precursor to tetrahydrocannabinols,[19,20] and its presence could indicate the use of these pathways for production. 9-Ethoxyhexahydrocannabinol (9-EtO-HHC) is a known byproduct of CBD cyclization in ethanol[21] and was detected in D13 and D14. 9-EtO-HHC presence is correlated with lower levels of Δ[8]-THC ($p < 0.01$) and higher levels of Δ[4(8)]-iso-THC ($p < 0.01$) than in D15 and D16, suggesting that ethanol may favor Δ[4(8)]-*iso*-THC formation. Bornyl chloride (Chart 1), a known reaction product of HCl and *β*-pinene,[22] was tentatively identified by

**Table 1. Major Components of 27 Products (P) from 10 Brands (B)[a]**

| B | P | Δ[8]-THC reported | Δ[8]-THC measured | Δ[4(8)]-*iso*-THC | *iso*-THCBF |
|---|---|---|---|---|---|
| A | 1 | 83.2 | 76 ± 1 | 4.24 ± 0.07 | 1.22 ± 0.02 |
| | 2 | 83.2 | 79.5 ± 0.1 | 3.45 ± 0.03 | 1.25 ± 0.05 |
| | 3 | 86.15 | 81.2 ± 0.6 | 3.48 ± 0.03 | 1.31 ± 0.04 |
| | 4 | 84.66 | 79.5 ± 0.8 | 3.9 ± 0.1 | *d* |
| B | 5 | 93.0821 | 75 ± 2 | *c* | 0.88 ± 0.05 |
| | 6 | 93.0821 | 77 ± 1 | *c* | *e* |
| | 7 | 93.0821 | 62.7 ± 0.7 | 7.96 ± 0.09 | *d* |
| | 8 | 93.0821 | 77 ± 1 | *c* | *e* |
| | 9 | 93.0821 | 78 ± 2 | *c* | 0.63 ± 0.03 |
| C | 10 | 90 | 74.8 ± 0.2 | 4.79 ± 0.03 | 0.957 ± 0.004 |
| | 11 | 90 | 77.4 ± 0.4 | 4.23 ± 0.04 | 0.9 ± 0.02 |
| | 12 | 90 | 79.4 ± 0.4 | 3.74 ± 0.05 | 0.9 ± 0.02 |
| D | 13 | 90 | 54.8 ± 0.2 | 12.79 ± 0.06 | 1.67 ± 0.02 |
| | 14 | 90 | 53.6 ± 0.5 | 12.51 ± 0.05 | 1.65 ± 0.04 |
| | 15 | 90 | 78.0 ± 0.7 | 4.13 ± 0.04 | 1.6 ± 0.02 |
| | 16 | 90 | 79.9 ± 0.7 | 2.36 ± 0.05 | 0.73 ± 0.02 |
| E | 17 | 77.71 | 78.8 ± 0.4 | 3.01 ± 0.03 | 0.61 ± 0.02 |
| | 18 | 77.71 | 80.3 ± 0.7 | 2.851 ± 0.005 | 0.415 ± 0.008 |
| | 19 | 77.71 | 79.7 ± 0.2 | 2.75 ± 0.05 | 0.472 ± 0.005 |
| F | 20 | 80.85 | 76.8 ± 0.3 | *c* | *c* |
| | 21 | 84.02 | 77.1 ± 0.7 | *c* | *c* |
| | 22 | 81.87 | 77 ± 1 | *c* | *c* |
| G | 23 | 85.000 | 70.9 ± 0.7 | *c* | *c* |
| | 24 | 81.240 | 78.9 ± 0.9 | *c* | *c* |
| H | 25 | 78.43 | 61.6 ± 0.3 | 10.79 ± 0.05 | 1.54 ± 0.01 |
| I | 26 | *b* | 72.2 ± 0.3 | *c* | *c* |
| J | 27 | *b* | 73.4 ± 0.2 | *c* | *c* |

[a]Levels are mass % ± standard error of the mean (SEM). [b]No available data. [c]NQ: identified but not quantifiable. [d]Less than limit of detection (signal-to-noise ≤3). [e]Less than limit of quantification (signal-to-noise ≤ 12).

GC-MS (Figure S23) in A2 and A3 and is indicative of HCl as a cyclization catalyst. However, its absence in other products does not rule out the use of HCl, as its presence in A2 and A3 may simply be evidence of starting material contaminated with $\beta$-pinene. The potential for bornyl chloride to generate HCl gas when pyrolyzed[23] could present a significant inhalation hazard.

In addition to the above, a molecule which, to the best of the authors' knowledge, has never been previously described was also identified. The cannabinoid (5a*R*,9a*S*)-5a-isopropyl-8-methyl-3-pentyl-5a,6,7,9a-tetrahydrodibenzo[*b*,*d*]furan-1-ol or *iso*-tetrahydrocannabifuran (*iso*-THCBF, Chart 1) is likely the result of a hydride shift in the carbocation intermediate (Scheme 1). *iso*-THCBF was isolated from $\Delta^8$-THC CEC products and characterized by mass spectrometry and 1D and 2D NMR (see SI). *iso*-THCBF was present in nearly all products tested but was not quantifiable in products containing TEC due to spectral overlap.

CEC screening by inductively coupled plasma-mass spectrometry (ICP-MS) shows the existence of metals such as magnesium (599 ± 391 ppb, $\bar{x}$ ± SD, $n$ = 10), chromium (446 ± 758 ppb), nickel (380 ± 364 ppb), copper (509 ± 1143 ppb), zinc (1.8 ± 2.1 ppm), mercury (160 ± 162 ppb), lead (42 ± 28 ppb), and others (see SI). These metals are likely leachates from vaporizer components or production materials, and their inhalation could cause deleterious effects on the respiratory tract that stem from the generation of reactive oxygen species.[24,25] ICP-MS identified elevated levels of silicon (205 ± 108 ppm), a finding that has been previously shown for EVALI-associated CECs.[26] Silica gel may be used as a purification medium or decolorizing agent, and its potential delivery to the respiratory tract from these products is a subject of further investigation.

QNMR indicates that $\Delta^8$-THC levels can vary as much 40% from the labeled value (Table 1), suggestive of poor testing capabilities and falsified results. For brand A, the average of the sums of $\Delta^8$-THC and $\Delta^{4(8)}$-iso-THC for each product is not significantly different from the average reported $\Delta^8$-THC content ($p$ < 0.01), suggesting that the analysis method (HPLC-UV as stated in the certificate of analysis) cannot discriminate the two. Brands B−E appear to use one lab result for all their products when these not only have variable levels of $\Delta^8$-THC but also contain distinct levels of byproducts indicating different manufacturing methods in products that otherwise appear identical except for flavor formulation. Significant levels of understudied ($\Delta^{4(8)}$-*iso*-THC, 9-EtO-HHC) and novel (*iso*-THCBF) cannabinoids present a danger to users as these compounds are not well characterized pharmacologically and could cause unexpected levels of intoxication. High levels of unlabeled cutting agents present a further complication given the little safety information available. Further chemical, pharmacological, and toxicological testing of these and similar products is necessary.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.chemrestox.1c00388.

Analytical methodology, structural identifications, relevant spectra, and full ICP-MS data (PDF)

## ■ AUTHOR INFORMATION

### Corresponding Author

**Irfan Rahman** − *Department of Environmental Medicine, University of Rochester Medical Center, Rochester, New York 14642, United States;* orcid.org/0000-0003-2274-2454; Email: Irfan_Rahman@urmc.rochester.edu

### Author

**Jiries Meehan-Atrash** − *Department of Environmental Medicine, University of Rochester Medical Center, Rochester, New York 14642, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.chemrestox.1c00388

### Author Contributions

The manuscript was written through contributions of all authors.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

The National Institutes of Health (NIH) 1R01HL135613 and Toxicology Training Grant 5T32ES007026-43 supported this study. We thank Thomas Scrimale at the metal analysis core at the University of Rochester for performing the ICP-MS experiments.

## ■ ABBREVIATIONS

CEC, cannabis e-cigarette; EVALI, e-cigarette or vaping product use associated lung injury; CBD, cannabidiol

## ■ REFERENCES

(1) Meehan-Atrash, J.; Luo, W.; McWhirter, K. J.; Dennis, D. G.; Sarlah, D.; Jensen, R. P.; Afreh, I.; Jiang, J.; Barsanti, K. C.; Ortiz, A.; Strongin, R. M. The influence of terpenes on the release of volatile organic compounds and active ingredients to cannabis vaping aerosols. *RSC Adv.* **2021**, *11* (19), 11714−11723.

(2) Meehan-Atrash, J.; Luo, W.; McWhirter, K. J.; Strongin, R. M. Aerosol Gas-Phase Components from Cannabis E-Cigarettes and Dabbing: Mechanistic Insight and Quantitative Risk Analysis. *ACS Omega* **2019**, *4* (14), 16111−16120.

(3) Miech, R. A.; Patrick, M. E.; O'Malley, P. M.; Johnston, L. D.; Bachman, J. G. Trends in Reported Marijuana Vaping Among US Adolescents, 2017−2019. *JAMA* **2020**, *323* (5), 475−476.

(4) Boyd, C. J.; McCabe, S. E.; Evans-Polce, R. J.; Veliz, P. T. Cannabis, Vaping, and Respiratory Symptoms in a Probability Sample of U.S. Youth. *J. Adolesc. Health* **2021**, *69* (1), 149−152.

(5) Krishnasamy, V. P.; Hallowell, B. D.; Ko, J. Y.; Board, A.; Hartnett, K. P.; Salvatore, P. P.; Danielson, M.; Kite-Powell, A.; Twentyman, E.; Kim, L.; Cyrus, A.; Wallace, M.; Melstrom, P.; Haag, B.; King, B. A.; Briss, P.; Jones, C. M.; Pollack, L. A.; Ellington, S.; et al. Update: Characteristics of a Nationwide Outbreak of E-cigarette, or Vaping, Product Use-Associated Lung Injury - United States, August 2019-January 2020. *Morb. Mortal. Wkly. Rep.* **2020**, *69* (3), 90−94.

(6) Duffy, B.; Li, L.; Lu, S.; Durocher, L.; Dittmar, M.; Delaney-Baldwin, E.; Panawennage, D.; LeMaster, D.; Navarette, K.; Spink, D. Analysis of Cannabinoid-Containing Fluids in Illicit Vaping Cartridges Recovered from Pulmonary Injury Patients: Identification of Vitamin E Acetate as a Major Diluent. *Toxics* **2020**, *8* (1), 8.

(7) Ciolino, L. A.; Ranieri, T. L.; Brueggemeyer, J. L.; Taylor, A. M.; Mohrhaus, A. S. EVALI Vaping Liquids Part 1: GC-MS Cannabinoids Profiles and Identification of Unnatural THC Isomers. *Front. Chem.* **2021**, *9*, 746479.

(8) Zangani, C.; Schifano, F.; Napoletano, F.; Arillotta, D.; Gilgar, L.; Guirguis, A.; Corkery, J. M.; Gambini, O.; Vento, A. The e-Psychonauts' 'Spiced' World; Assessment of the Synthetic Cannabinoids' Information Available Online. *Curr. Neuropharmacol.* **2020**, *18* (10), 966−1051.

(9) Johnson-Arbor, K.; Smolinske, S. The current state of delta-8 THC. *Am. J. Emerg. Med.* **2021**, DOI: 10.1016/j.ajem.2021.06.066.

(10) Hanuš, L. O.; Meyer, S. M.; Muñoz, E.; Taglialatela-Scafati, O.; Appendino, G. Phytocannabinoids: a unified critical inventory. *Nat. Prod. Rep.* **2016**, *33* (12), 1357.

(11) Implementation of the Agriculture Improvement Act of 2018. In *21 CFR §1308 and §1312*; Drug Enforcement Administration, Department of Justice. US Government Publishing Office: 2020; Vol. RIN *1117-AB53*.

(12) Increases in Availability of Cannabis Products Containing Delta-8 THC and Reported Cases of Adverse Events. https://emergency.cdc.gov/han/2021/han00451.asp (accessed October 7, 2021).

(13) Adams, R.; Pease, D. C.; Cain, C. K.; Baker, B. R.; Clark, J. H.; Wolff, H.; Wearn, R. B. Conversion of Cannabidiol to a Product with Marihuana Activity. A Type Reaction for Synthesis of Analogous Substances. Conversion of Cannabidiol to Cannabinol. *J. Am. Chem. Soc.* **1940**, *62* (8), 2245−2246.

(14) Golombek, P.; Müller, M.; Barthlott, I.; Sproll, C.; Lachenmeier, D. W. Conversion of Cannabidiol (CBD) into Psychotropic Cannabinoids Including Tetrahydrocannabinol (THC): A Controversy in the Scientific Literature. *Toxics* **2020**, *8* (2), 41.

(15) Kiselak, T. D.; Koerber, R.; Verbeck, G. F. Synthetic route sourcing of illicit at home cannabidiol (CBD) isomerization to psychoactive cannabinoids using ion mobility-coupled-LC-MS/MS. *Forensic Sci. Int.* **2020**, *308*, 110173.

(16) Marzullo, P.; Foschi, F.; Coppini, D. A.; Fanchini, F.; Magnani, L.; Rusconi, S.; Luzzani, M.; Passarella, D. Cannabidiol as the Substrate in Acid-Catalyzed Intramolecular Cyclization. *J. Nat. Prod.* **2020**, *83* (10), 2894−2901.

(17) Meehan-Atrash, J.; Strongin, R. M. Pine rosin identified as a toxic cannabis extract adulterant. *Forensic Sci. Int.* **2020**, *312*, 110301.

(18) Gaoni, Y.; Mechoulam, R. Concerning the Isomerization of $\Delta^1$- to $\Delta^{1(6)}$-Tetrahydrocannabinol[1]. *J. Am. Chem. Soc.* **1966**, *88* (23), 5673−5675.

(19) Malkov, A. V.; Kočovský, P. Tetrahydrocannabinol Revisited: Synthetic Approaches Utilizing Molybdenum Catalysts. *Collect. Czech. Chem. Commun.* **2001**, *66* (8), 1257−1268.

(20) Razdan, R. K.; Dalzell, H. C.; Handrick, G. R. Hashish. X. Simple One-Step Synthesis of (−)-$\Delta^1$-Tetrahydrocannabinol (THC) from *p*-Mentha-2,8-dien-1-ol and Olivetol. *J. Am. Soc.* **1974**, *96* (18), 5860−5865.

(21) Gaoni, Y.; Mechoulam, R. Hashish—VII: The isomerization of cannabidiol to tetrahydrocannabinols. *Tetrahedron* **1966**, *22* (4), 1481−1488.

(22) Trukhin, A.; Kruchkov, F.; Hansen, L. K.; Kallenborn, R.; Kiprianova, A.; Nikiforov, V. Toxaphene chemistry: Separation and characterisation of selected enantiomers of the Polychloropinene mixtures. *Chemosphere* **2007**, *67* (9), 1695−1700.

(23) Bicknell, R. C.; Maccoll, A. The pyrolysis of bornyl chloride. *Chem. Ind.* **1961**, *190*, 715.

(24) Collin, F. Chemical Basis of Reactive Oxygen Species Reactivity and Involvement in Neurodegenerative Diseases. *Int. J. Mol. Sci.* **2019**, *20* (10), 2407.

(25) Ball, J. C.; Straccia, A. M.; Young, W. C.; Aust, A. E. The Formation of Reactive Oxygen Species Catalyzed by Neutral, Aqueous Extracts of NIST Ambient Particulate Matter and Diesel Engine Particles. *J. Air Waste Manage. Assoc.* **2000**, *50* (11), 1897−1903.

(26) Muthumalage, T.; Friedman, M. R.; McGraw, M. D.; Ginsberg, G.; Friedman, A. E.; Rahman, I. Chemical Constituents Involved in E-Cigarette, or Vaping Product Use-Associated Lung Injury (EVALI). *Toxics* **2020**, *8* (2), 25.


https://doi.org/10.1021/acs.chemrestox.1c00388
*Chem. Res. Toxicol.* XXXX, XXX, XXX−XXX