Clinical Update: December 2023

AN OVERVIEW OF TESTING CAPABILITIES TO IDENTIFY USE OF MARIJUANA (THC) AND OTHER NATURAL CANNABINOIDS

Following the passing of the 2018 Agriculture Improvement Act (a.k.a. Farm Bill), the cannabis industry has seen widespread growth in products that contain naturally occurring cannabinoids found in the *Cannabis sativa* plant. Aegis has expanded its marijuana analysis to include delta-8 THC and cannabidiol (CBD) for the purpose of providing a more informed assessment of patient use of cannabinoids. The information provided in this clinical update is intended to assist providers with understanding testing for naturally occurring cannabinoids at Aegis, how positive test results will be reported, and information related to CBD and delta-8 THC products. Concerns such as period of detection, oral fluid considerations, and passive inhalation are also discussed. Expanded cannabinoid analysis is currently only available in urine.

Cannabis Overview

The *Cannabis sativa* plant contains over 500 compounds, at least 100 of which are cannabinoids, the most prevalent and widely studied being delta-9-THC (THC) and CBD.[1] Hemp and marijuana are two varieties of *Cannabis sativa* and differ in THC content with hemp containing 0.3% THC or less by dry weight. Marijuana is the most commonly used federally illicit drug in the United States. The 2020 National Survey on Drug Use and Health reported that 59.3 million people aged 12 or older used illicit drugs in the past year, with 49.6 million (~84%) using marijuana.[2] In the 2021 National Survey on Drug Use and Health, 38.1 million people aged 18 or older used illicit drugs in the past month with 34.8 million (~91%) using marijuana.[3] In addition to being the most commonly used illicit substance, marijuana use has been increasing with decriminalization and/or legalization occurring in a growing number of states. The National Institute on Drug Abuse reported that in 2021, the proportion of adults aged 19-30 surveyed that reported past year marijuana use was 43%, up from 29% in 2011.[4] For adults aged 35 to 50 surveyed in 2022, percentages of those reporting use within the past year was 28%, up from 13% in 2012.[5] Daily marijuana use also increased with 11% of young adults surveyed in 2021 reporting daily use compared to 6% in 2011.[4] Marijuana is the drug with the highest prevalence in cases involving driving under the influence of drugs and the source of more positive results in workplace drug tests than any other drug of abuse.[6]

THC is the main psychoactive component in *Cannabis Sativa* and is responsible for the characteristic “high” of marijuana, whereas CBD has not been shown to have the same cognitive effects and is considered non-psychoactive. While THC is the most prevalent cannabinoid in cannabis plants grown for the purpose of psychoactive product development, CBD is the most abundant cannabinoid in hemp plants. It has been studied as a treatment for multiple disease states and health conditions, including bipolar mania, Huntington’s disease, inflammation, insomnia, multiple sclerosis, nausea, social anxiety disorder, schizophrenia, and seizures. Through the passing of the 2018 Agriculture Improvement Act, hemp was no longer considered a controlled substance in the USA, resulting in a burgeoning market of hemp-derived products having CBD as the predominant ingredient.

Recently other cannabinoids, such as delta-8 THC, have been found in a variety of commercially available products including liquids used for electronic cigarettes (i.e, vapes), edibles, and drinks. Like THC, delta-8 THC is a psychoactive cannabinoid of the *Cannabis sativa* plant. Delta-8 THC is nearly identical to THC in chemical structure, differing only in the placement of a double bond. Both THC and delta-8 THC have similar binding affinities at CB1 and CB2 cannabinoid receptors[7-8] and produce similar effects with the psychotropic potency of delta-8 THC being

estimated to be approximately two-thirds that of THC.[9] A recent survey of delta-8 THC users suggests delta-8 THC produces the same experiential effects as THC but with less cognitive distortion and distressing mental states such as paranoia and anxiety, than THC.[10] Delta-8 THC is not present in the *Cannabis sativa* plant in significant amounts. The percentage of delta-8 THC in cannabis plant material was determined to be on average 0.65% with a maximum observed percentage of 3%.[11] In a recent study, urine samples containing the THC metabolite delta-9 carboxy-THC were evaluated for the presence of the delta-8 THC metabolite, delta-8 carboxy-THC, which was detected in low concentrations (0.22-8.9 ng/mL), presumably from plant origin. The average percentage of delta-8 carboxy-THC to delta-9 carboxy-THC observed was 0.68% and ranged from 0.05 to 2.83%.[12]

Presumptive (i.e. Immunoassay) vs. Definitive Testing

The interpretation of cannabinoid results differs when considering presumptive vs. definitive testing methods and may also differ among laboratories. At Aegis, testing for marijuana use proceeds through immunoassay screening. When non-negative immunoassay results are obtained, then the specimen will proceed to definitive confirmatory testing using mass spectrometry. Specimens that produce a negative cannabinoid immunoassay result are considered negative and will not be tested further. Immunoassay screening is based on cross-reactivity to a target drug. Drugs similar in structure to the target drug may cross-react to produce a non-negative or presumptive positive result. Delta-8 and THC isomers, being nearly identical in chemical structure, are not able to be distinguished by cannabinoid immunoassay tests. Delta-8 THC and THC share the same metabolic pathways.[13] Thus as delta-9 carboxy-THC is the main metabolite for THC in urine, delta-8 carboxy-THC is the main metabolite for delta-8 THC in urine.[12] Recent studies have demonstrated that delta-8 THC and its metabolites cross-react with commercially available cannabinoid immunoassay tests.[14,15] Specifically, delta-8 carboxy-THC produced a high degree of cross-reactivity (87-112%) across different commercially available cannabinoid immunoassay platforms at a 50 ng/mL cutoff. This high degree of cross reactivity was also observed at 20 and 100 ng/mL cutoffs.[15] Thus delta-8 THC use is likely to produce a non-negative cannabinoid immunoassay test result. Conversely, CBD did not cross-react with any of the commercially available cannabinoid immunoassay tests.[14] Thus Aegis testing is not intended to be used to determine compliance with CBD-containing medications (i.e. Epidolex®) or use of CBD products. CBD-containing medications are not able to be indicated as prescribed.

Confirmatory testing using chromatography/mass spectrometry may not be able to distinguish between the delta-8 carboxy-THC and delta-9 carboxy-THC isomers unless they are separated in the test method.[15] Laboratories have reported an increasing number of specimens with interferences in testing for delta 9-THC due to the presence of delta 8-THC.[15-17] At Aegis, prior to reporting positive test results for naturally occurring cannabinoids including THC, delta-8 THC and CBD, analysis proceeds through definitive confirmatory testing by liquid chromatography tandem mass spectrometry (LC-MS/MS). Results of positive findings for delta-8 carboxy-THC, delta-9 carboxy-THC, and CBD will be reported individually (see Figure 1). Concentrations of these cannabinoids, when detected in urine, do not definitively indicate source of substance used or exposure that contributed to positive findings and will not be reported with interpretative differentiations.

Figure 1.

Medication Compliance

Drug and/or Metabolites	Result Interpretation	Result	Comment
Delta-9 Carboxy-THC	PRESENT	16 ng/mL	Test result may be due to ingestion or use of a product containing delta-9 THC, a psychoactive cannabinoid. Evaluate for medical use of dronabinol, an approved prescription medication. Additionally, delta-9 THC may be present in other cannabis-derived products or prescription medications (e.g., Epidiolex).
Delta-8 Carboxy-THC	PRESENT	16 ng/mL	Test result may be due to ingestion or use of a product containing delta-8 THC, a psychoactive cannabinoid. Delta-8 THC is a naturally-occurring cannabinoid.
Cannabidiol	PRESENT	16 ng/mL	Test result may be due to ingestion of a cannabidiol (CBD) containing product. Evaluate for medical use of cannabidiol (Epidiolex), an approved prescription medication. CBD is a naturally-occurring cannabinoid.

Marijuana False Positives on Immunoassay

Immunoassay, or point of care testing, has the highest risk of false positives among all testing methods.[18] The following medications and over-the-counter products have chemical structures similar enough to THC to trigger a presumptive positive result that would not confirm via LC-MS/MS on an Aegis test: Acetylsalicylic acid, baby wash/soaps[19], efavirenz[18,20], NSAIDs (ibuprofen, naproxen)[21-22], proton pump inhibitors (pantoprazole)[18,23], tolmetin[24], and more.

Marijuana False Negatives on Immunoassay

People using marijuana may attempt to tamper with urine samples to produce negative results. Addition of Visine® eyedrops to urine samples has been shown to cause false-negative results for THC. Chemical analysis of Visine® eyedrops has shown that the ingredients, benzalkonium chloride and the borate buffer, can directly decrease the concentration of the delta-9 carboxy-THC metabolite in the urine with no effects on the antibodies in the immunoassay. However, these ingredients do not chemically alter delta 9-carboxy-THC, which will still be detected by mass spectrometry.[22,25] Excess fluid ingestion has been shown to produce false-negative urine test results for delta-9 carboxy-THC metabolite.[26]

CBD Products

Since the passing of the 2018 Agriculture Improvement Act, there has been a burgeoning market of hemp-derived products having CBD as the predominant ingredient. The product descriptions “medical marijuana”, “high CBD,” and “low THC” are often used interchangeably, however no standard definition exists for these individual terms.[27] The legal limit for the amount of THC allowed in CBD products is variable, ranging from 0.3% to 5% depending on state-specific regulations.[28] Importantly, the manufacturing and purification processes for CBD products are not regulated by the Food and Drug Administration (FDA), leaving little opportunity for mandated CBD to THC ratios to be enforced.[27-28] In a study evaluating label accuracy of CBD products, 54% of products tested contained CBD concentrations within ±10% of the ingredient label claim, 15% contained <90% of the label claim with the lowest being 17%, and 31% contained >110% of the label claim, the highest being 159%.[29] A few studies have evaluated urinary cannabinoids following administration of CBD and CBD-dominant cannabis.[27,30,31] After dosing 15 volunteers with high CBD/low THC oils, capsules, and cigarettes, fourteen of the fifteen volunteers tested positive for both CBD and delta-9 carboxy-THC in urine.[27] Following vaporized and oral administration of 100 mg CBD, and vaporized administration of CBD-dominant (100 mg CBD/3.7 mg THC) cannabis, delta-9 carboxy-THC was > 15 ng/mL in 2 of 6 individuals between 4 and 8 hours only following administration of CBD-dominant cannabis.[30] In an expansion of

this study, of 12 additional participants, only one was positive for delta-9 carboxy-THC at >15 ng/mL following vaporized administration of CBD-dominant cannabis.[31] All of the specimens with delta-9 carboxy-THC >15 ng/mL, screened positive by immunoassay with a cutoff of 20 ng/mL.[31] Another study evaluated urinary delta-9 carboxy-THC concentrations in 14 individuals following a 4 week administration of a high CBD product. Of the 14 participants, 50% screened positive and 6 were confirmed by mass spectrometry to have delta-9 carboxy-THC concentrations > 15 ng/mL, with the highest concentration being 71.5 ng/mL.[32] THC content varies among unregulated hemp and cannabidiol products; the ability of these products to cause a positive marijuana result will depend on the amount of THC present in the product, the amount and frequency of the ingestion, and individual patient pharmacokinetics.[33-35] Given these factors, it is possible for the use of a CBD product to result in a THC-positive urine drug test. It is vital that healthcare providers use caution when recommending or reviewing CBD products for patients due to little regulation and inaccurate labeling of quantities within products.[36] Prescription CBD (Epidolex®) was developed to contain negligible amounts of THC (<0.1%)[37]; thus, it is unlikely to cause a marijuana positive.[38]

Delta-8-Tetrahydrocannabinol (delta-8 THC) Products

Although delta-8 THC is present in low abundance in the cannabis plant, it may be readily synthesized from CBD. Recently delta-8 THC products such as gummies and vapes are available over-the counter with some being marketed as “legal hemp” products. Due to the naturally low levels of delta-8 THC in hemp it is thought that delta-8 THC is being synthesized from CBD and added to hemp plant material in high concentrations that far exceed what is naturally found in cannabis and then sold as “legal hemp”.[8] There has been confusion regarding the legal status of such products because tetrahydrocannabinols, natural or synthetic, are classified as controlled in schedule I by the Controlled Substances Act (CSA). However, the CSA excludes from control tetrahydrocannabinols in hemp. Some states are choosing to define delta-8 THC as a controlled substance and others are prohibiting production and sale of delta-8 THC. It is important to note that like CBD products, some delta-8 THC products may contain THC and are not regulated by the FDA.[39-40] Thus depending on the amount of THC present in the product, the amount and frequency of the ingestion, and individual patient pharmacokinetics, it may be possible for the use of a delta-8 THC product to result in a THC-positive urine drug test. The content and labeling of twenty commercial delta-8 THC products has been evaluated. The only cannabinoids identified in the products were delta-8 THC, THC and CBD.[40] THC was detected in 35% of the delta-8 THC products and CBD was detected in one product.[40] A recent study determined the prevalence of delta-8 carboxy-THC in specimens submitted for workplace drug testing reported 24% of all cannabinoid-positive specimens were consistent with use of a delta-8 THC product, alone or in combination with cannabis.[41] For samples with a positive immunoassay test result (cutoff 50 ng/mL) and concentrations of delta-8 carboxy-THC and delta-9 carboxy-THC ≥15 ng/mL, 123 (~10%) contained delta-8 carboxy-THC only, 889 (~70%) contained delta-9 carboxy-THC only and 255 (~20%) contained both delta-8 carboxy-THC and delta 9-carboxy-THC.[60] Ratios were variable with 76% of specimens having <10% delta-8 carboxy-THC, 11% having >90% delta-8 carboxy-THC, and 13% were fairly evenly distributed across all other ratios between 10 and 90 but with somewhat more in the 10-20% delta-8 carboxy-THC range.[41]

Period of Detection Considerations

The detection time for delta-9 carboxy-THC in urine depends heavily on the body composition of the patient and the frequency of use. Daily use of marijuana is expected to be detectable in urine for a period up to 10 days; light use (such as one joint) may only be detectable for up to 3 days.[42] One study demonstrated that 73% of 37 chronic marijuana users had delta-9 carboxy-THC concentrations below a cutoff of 15 ng/mL within two weeks of last ingestion.[43] Patients with a large amount of adipose tissue and/or those with heavy use over a chronic period may store marijuana and excrete metabolites for a longer period of time. In such cases, marijuana has been reported

with a period of detection up to 30 days, with the longest period published as 95 days. Such a period of detection is the exception, not the rule.[18,42,44] During terminal elimination of delta 9-carboxy-THC, consecutive urine specimens may fluctuate between positive and negative as delta-9 carboxy-THC concentrations near the cutoff.[45] Normalization of urinary concentrations may facilitate interpretation of consecutive urine drug concentrations.[45]

Due to structural similarity between delta-8 carboxy-THC and delta 9-carboxy-THC, the period of detection of delta-8 carboxy-THC in urine may be similar to that of delta 9-carboxy-THC. Urinary excretion of CBD was evaluated following a single administration of 100 mg of CBD by different routes of administration and with different formulations.[31] CBD concentrations in urine were highly variable even within the same route of administration and formulation. For example, following vaporized administration of cannabis (100 mg CBD/3.7 mg THC), maximum concentrations of CBD in urine ranged from 27-808 ng/mL. In a few participants, specimens were >15 ng/mL for only few hours whereas other individual's last specimen >15 ng/mL was the 21-25 hour collection.[31] The authors concluded the data show that absorption and elimination of CBD is impacted by drug formulation, route of administration and gastric contents.[31]

Oral Fluid Considerations

Marijuana positives in oral fluid are generally due to a depot effect after smoking, which limits interpretation to recent use.[46] Using a 2 ng/mL threshold, detection times in oral fluid for last positive following smoking of a single 6.8% THC cigarette, in frequent and occasional smokers were 30 and 26 hours respectively.[47] Median detection times in frequent and occasional smokers was 21 and 13.5 hours respectively with earliest last positives being at 6 and 5 hours respectively.[47] In a placebo-controlled double-blinded randomized trial in which frequent and occasional users self-titrated while smoking 5.9 or 13.4% THC cannabis, THC in oral fluid was detectable >2 ng/mL in 74% of users at the study duration of 6 hours.[48] Maximum concentration of THC in oral fluid is greater following inhaled routes such as smoking and vaporization than after oral cannabis.[49] Oral ingestion of THC produces lower and later peak blood concentrations and effects than smoked THC, and only 6-20% of an orally administered dose reaches systemic circulation.[50-51] An increase in THC oral fluid concentrations was observed following oral dosing of a THC-containing brownie whereas that was not observed following administration of encapsulated synthetic oral THC (dronabinol).[49-50] Ingestion of dronabinol (Marinol®) is unlikely to cause a positive test for THC in oral fluid at a 2 ng/mL threshold, which is used at Aegis.[50] Using oral fluid as a specimen type may, therefore, be beneficial when assessing patients who claim to ingest Marinol® to explain marijuana positives in urine.

Passive Inhalation

A common issue that confuses the interpretation for marijuana testing is "passive inhalation." The argument presented is that exposure to marijuana smoke by a non-user will result in a positive urine cannabinoid test, and therefore, a person will be wrongfully accused of drug use. Historically, multiple studies were performed in the 1980s that demonstrated that passive exposure to marijuana in extreme conditions did sometimes result in positive delta-9 carboxy-THC in urine.[52-56] In the study by Cone *et al.* which reported concentrations obtained by chromatography/mass spectrometry methods, positive results were found under repeated exposure or exposure conditions so extreme that the study subjects were offered goggles to wear in order to prevent eye and mucous membrane irritation due to the test area being visibly saturated with marijuana smoke. Anecdotal evidence of study subjects who had taken off their goggles concluded that prolonged exposure would be unlikely to be tolerable to most subjects.[55] Most of the studies were conducted in unventilated areas (closed cars or specifically built rooms of small size). Furthermore, Cone *et al.* conducted a test of room air THC exposure levels in the same test room as their studies with ventilation, which resulted in THC levels <10% that of the room unventilated.[55]

One criticism of studies conducted in prior decades is that marijuana is available at increased potency today, which could influence drug test results. More recent studies conducted to investigate urinary concentrations of carboxy-THC following passive exposure include Rohrich *et al.* where subjects were exposed to marijuana smoke for three hours in a Netherlands coffee shop. Urinary concentrations of delta-9 carboxy-THC were no greater than 5 ng/mL (without hydrolysis) or 8 ng/mL (with hydrolysis).[57] A second study performed by Cone *et al.* evaluated passive exposure using high-potency marijuana (11.3%) being smoked by six smokers for one hour in the presence of six non-smokers in unventilated and ventilated conditions.[58] The researchers demonstrated that with ventilation consistent with typical air conditioning, some study subjects did excrete detectable delta 9-carboxy-THC. The maximum concentration observed in a non-smoker with unventilated conditions was 57 ng/mL, whereas with ventilated conditions the maximum was 15 ng/mL, both occurring at 4-6 hours following exposure.[58]

Cone *et al.* also researched the likelihood of positive oral fluid results under similar conditions as above. Maximum oral fluid concentrations of THC were present in non-smokers up to 308 ng/mL in unventilated conditions and 75 ng/ mL in ventilated conditions.[59] Maximum concentrations occurred immediately post exposure and dropped rapidly within 1-3 hours, with subjects in unventilated conditions testing below 2 ng/mL after 12 hours, and subjects in ventilated conditions after 2 hours. During the unventilated studies, smoke accumulation was rapid, and goggles were used to alleviate eye irritation, whereas ventilated sessions produced visible smoke at lower levels. Niedbala *et al.* measured THC in oral fluid following passive exposure to marijuana for 20 minutes in an unventilated van with four smokers and found THC concentrations did not exceed 1.2 ng/mL following exposure, with all specimens below 2 ng/mL. Urine concentrations of delta-9 carboxy-THC were also assessed and did not exceed 15 ng/mL.[60] Moore *et al.* measured THC in oral fluid following less extreme exposure in a Dutch coffee shop. Oral fluid specimens collected outside the coffee shop during exposure reached a maximum THC concentration of 17 ng/mL at 3 hours; in specimens collected 12-22 hours following exposure THC was either not present or less than 2 ng/mL.[61] Passive inhalation of marijuana is also unlikely to cause a positive test in oral fluid at typical laboratory thresholds, except in circumstances of heavy smoke exposure, long duration of exposure, lack of ventilation, and if exposure occurs on the same day as sample collection.[58,60]

Overall, the likelihood of positive marijuana results from passive inhalation will depend on the amount and duration of exposure, ventilation during exposure, and time since exposure. In circumstances of true passive inhalation, levels of THC (oral fluid) or delta-9 carboxy-THC (urine) would be expected to be low, and the exposure would have occurred very recent to the time of collection. Due to structural similarity between delta-8 carboxy-THC and delta-9 carboxy-THC, the possibility of positive delta-8 carboxy-THC results following passive inhalation may be similar to that of delta-9 carboxy-THC.

Please call our clinical scientists at 1-877-552-3232 if you require additional information.

NOTICE: The information above is intended as a resource for health care providers. Providers should use their independent medical judgment based on the clinical needs of the patient when making determinations of who to test, what medications to test, testing frequency, and the type of testing to conduct.

References:

1. ElSohly M, Gul W (2014): Constituents of cannabis sativa. In: Pertwee RG, editor. Handbook of Cannabis. Oxford: Oxford University Press, 3-22.

2. Substance Abuse and Mental Health Services Administration. (2021) Key substance use and mental health indicators in the United States: Results from the 2020 National Survey on Drug Use and Health (HHS Publication No. PEP21-07-01-003, NSDUH Series H-56). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. Retrieved from https://www.samhsa.gov/data/

3. SAMHSA. (2022) National Survey on Drug Use and Health, 2021. Table 1.3A – Types of Illicit Drug Use in Lifetime, Past Year, and Past Month: Among People Aged 18 or Older; Numbers in Thousands, 2021 Center for Behavioral Health Statistics and Quality, Retrieved from: https://www.samhsa.gov/data/sites/default/files/reports/rpt39441/NSDUHDetailedTabs2021/NSDUHDetailedTabs2021/NSDUHDetTabsSect1pe2021.htm

4. National Institute of Drug Abuse. Marijuana and hallucinogen use among young adults reached all time-high in 2021. https://nida.nih.gov/news-events/news-releases/2022/08/marijuana-and-hallucinogen-use-among-young-adults-reached-all-time-high-in-2021#:~:text=The%20proportion%20of%20young%20adults,2016%20and%2017%25%20in%202011.

5. National Institute of Drug Abuse. Marijuana and hallucinogen use, binge drinking reached historic highs among adults 35 to 50. https://nida.nih.gov/news-events/news-releases/2023/08/marijuana-and-hallucinogen-use-binge-drinking-reached-historic-highs-among-adults-35-to-50

6. Huestis MA. Cannabis. In: Levine B, ed. Principles of Forensic Toxicology. 3rd ed. Washington, D.C.: AACC Press; 2009:269.

7. Tagen and Klumpers 2022. Review of delta-8-tetrahydrocannabinol (Δ8-THC): Comparative pharmacology with Δ9-THC. Br J Pharmacol.2022;179:3915–3933.

8. Babalonis S, Raup-Konsavage WM, Akpunonu PD, Balla A, and Vrana K. Delta-8 THC: Legal status, widespread availability, and safety concerns. Cannabis Cannabinoid Res. 2021;6(5):362-365.

9. Hollister LE, Gillespie HK. Delta-8 and delta-9-tetrahydrocannabinol comparison in man by oral and intravenous administration. *Clin Pharmacol Ther*. 1973; 14:353-357

10. Kruger JS, Kruger DJ. Delta-8-THC: Delta-9-THC's nicer younger sibling?. *J Cannabis Res*. 2022;4(1):4. Published 2022 Jan 4. doi:10.1186/s42238-021-00115-8

11. Patel B, Wene D, Fan ZT. Qualitative and quantitative measurement of cannabinoids in cannabis using modified HPLC/DAD method. *J Pharm Biomed Anal.* 2017; Nov 30;146:15-23. doi: 10.1016/j.jpba.2017.07.021.

12. Rzeppa S, Große J, Rautenberg C, et al. Emergence of the less common cannabinoid Δ8-Tetrahydrocannabinol in a doping sample. *Drug Test Anal*. 2021;13(11-12):1936-1943. doi:10.1002/dta.3159

13. Watanabe K, Yamaori S, Funahashi T, Kimura T, Yamamoto I. Cytochrome P450 enzymes involved in the metabolism of tetrahydrocannabinols and cannabinol by human hepatic microsomes. *Life Sci*. 2007;80(15):1415-1419. doi:10.1016/j.lfs.2006.12.032

14. Wolf et al., 2023. The cross-reactivity of cannabinoid analogs (delta-8-THC, delta-10-THC and CBD), their metabolites and chiral carboxy HHC metabolites in urine of six commercially available homogeneous immunoassays. *Journal of Analytical Toxicology*, Volume 47, Issue 8, October 2023, Pages 732–736, https://doi.org/10.1093/jat/bkad059

15. Mullen et al., 2023. Delta-8-THC-COOH Cross-reactivity with cannabinoid immunoassay kits and interference in chromatographic testing methods. Journal of Analytical Toxicology, 2023, 47, 557-562.

16. Chan-Hosokawa et al., 2022. Emergence of Delta-8 Tetrahydrocannabinol in DUID Investigation Casework: Method Development, Validation and Application. J Anal Toxicol. 2022 Feb 14;46(1):1-9. doi: 10.1093/jat/bkab029.

17. Chan-Hosokawa et al., 2023. Estimation of Delta-8 Tetrahydrocannabinol (THC) Concentrations in DUID Investigation Casework. J Anal Toxicol. 2023 Feb 21;47(1):e14-e16. doi: 10.1093/jat/bkac068.

18. Gourlay DL, Heit HA, Caplan YH. Urine drug testing in clinical practice: the art and science of patient care. 6th ed. Stamford, CT: PharmaCom Group, Inc.;2015:1-32.

19. Cotten SW, Duncan DL, Burch EA, Seashore CJ, Hammett-Stabler CA. Unexpected interference of baby wash products with a cannabinoid (THC) immunoassay. *Clin Biochem*. 2012;45(9):605-609.

20. Rossi S, Yaksh T, Bentley H, van den BG, Grant I, Ellis R. Characterization of interference with 6 commercial delta9-tetrahydrocannabinol immunoassays by efavirenz (glucuronide) in urine. *Clin Chem* 2006;52:896-897.

21. Rollins, DE, Jennison, TA, and Jones, G. Investigation of interference by nonsteroidal anti-inflammatory drugs in urine tests for abused drugs. *Clin Chem*. 1990; 36: 602–606

22. Moeller KE, Lee KC, Kissack JC. Urine drug screening: practical guide for clinicians. *Mayo Clin Proc*. 2008;83(1):66-76.

23. Protonix [Package Insert]. Philadelphia, PA: Wyeth Pharmaceuticals Inc.; Feb 2017.

24. Reisfield GM, Goldberger BA, Bertholf RL. 'False-positive' and 'false-negative' test results in clinical urine drug testing. *Bioanalysis*. 2009;1(5):937-952.

25. Pearson, SD, Ash, KO, and Urry, FM. Mechanism of false-negative urine cannabinoid immunoassay screens by Visine eyedrops. *Clin Chem*. 1989; 35: 636–638

26. Cone et al., 1998. In vivo adulteration: excess fluid ingestion causes false-negative marijuana and cocaine urine test results. J Anal Toxicol. 1998 Oct;22(6):460-73. doi: 10.1093/jat/22.6.460.

27. Mead, A. The legal status of cannabis (marijuana) and cannabidiol (CBD) under U.S. law. *Epilepsy Behav*. 2017;70:288-91.

28. 17 States with Legal Cannabidiol (CBD). ProCon.org. https://medicalmarijuana.procon.org/view.resource.php?resourceID=006473. Updated July 12, 2019. Accessed August 26, 2019.

29. Johnson *et al. 2022.* Label accuracy of unregulated cannabidiol (CBD) products: measured concentration vs. label claim. *Journal of Cannabis Research (2022) 4:28* https://doi.org/10.1186/s42238-022-00140-1

30. Spindle et al., 2020. Urinary Pharmacokinetic Profile of Cannabinoids Following Administration of Vaporized and Oral Cannabidiol and Vaporized CBD-Dominant Cannabis. Journal of Analytical Toxicology, 2020;44:109-125

31. Sholler et al., 2021. Urinary Pharmacokinetic Profile of Cannabidiol (CBD), Δ^9-Tetrahydrocannabinol (THC) and Their Metabolites following Oral and Vaporized CBD and Vaporized CBD-Dominant Cannabis Administration Journal of Analytical Toxicology, 46, Issue 5, June 2022, Pages 494–503, https://doi.org/10.1093/jat/bkab059

32. Dahlgren et al., 2020. Urinary Tetrahydrocannabinol After 4 Weeks of a Full-Spectrum, High-Cannabidiol Treatment in an Open-label Clinical Trial. JAMA Psychiatry. 2021 Mar 1;78(3):335-337. doi: 10.1001/jamapsychiatry.2020.3567.

33. Meir U, Dussy F, Scheurer E, Mercer-Chalmers-Bender K, Hangartner S. Cannabinoid concentrations in blood and urine after smoking cannabidiol joints. *Forensic Sci Int*. 2018;291:62-7.

34. Hayley AC, Downey LA, Hansen G, et al. Detection of delta-9-tetrahydrocannabinol (THC) in oral fluid, blood and urine following oral consumption of low-content THC hemp oil. *Forensic Sci Int*. 2018;284:101-106.

35. Wertlake PT, Henson MD. A urinary test procedure for identification of cannabidiol in patients undergoing medical therapy with marijuana. *J Pain Res*. 2016;9:81-5.

36. VanDolah HJ, Bauer BA, Mauck KF. Clinicians' Guide to Cannabidiol and Hemp Oils. *Mayo Clin Proc*. 2019 Jun 12. pii: S0025-6196(19)30007-2.

37. Federal Register Volume 83, Issue 189 (September 28, 2018). 83 FR 48950- Schedules of Controlled Substances: Placement in Schedule V of Certain FDA-Approved Drugs Containing Cannabidiol; Corresponding Change to Permit Requirements

38. Schoedel KA, Szeto I, Setnik B, et al. Abuse potential assessment of cannabidiol (CBD) in recreational polydrug users: A randomized, double-blind, controlled trial. *Epilepsy Behav*. 2018;88:162-71.

39. U.S. Food and Drug Administration. 5 Things to Know about Delta-8 Tetrahydrocannabinol – Delta-8 THC https://www.fda.gov/consumers/consumer-updates/5-things-know-about-delta-8-tetrahydrocannabinol-delta-8-thc

40. Kaczor et al., 2023. Commercial Delta-8 THC Products: an Analysis of Content and Labeling. J Med Toxicol. 2023 Nov 2. doi: 10.1007/s13181-023-00974-y.

41. Vikingsson et al., 2023. Prevalence of delta-8 tetrahydrocannabinol carboxylic acid in workplace drug testing. Journal of Analytical Toxicology, 2023, 47, 719-725.

42. Heit HA, Gourlay DL. Urine drug testing in pain medicine. *J Pain Symptom Manage*. 2004;27(3):260-7.

43. Lewis J, Molnar A, Allsop D, Copeland J, Fu S. Rapid elimination of Carboxy-THC in a cohort of chronic cannabis users. *Int J Legal Med*. 2016;130(1):147-152.

44. Verstraete AG. Detection times of drugs of abuse in blood, urine, and oral fluid. *Ther Drug Monit*. 2004;26(2):200-5.

45. Heustis 2005. Pharmacokinetics and Metabolism of the Plant Cannabinoids,Δ9-Tetrahydrocannabinol, Cannabidiol and Cannabinol. HEP (2005) 168:657–690

46. Cone EJ, Presley L, Lehrer M, et al. Oral fluid testing for drugs of abuse: positive prevalence rates by Intercept™ immunoassay screening and GC-MS-MS confirmation and suggested cutoff concentrations. *J Anal Toxicol*. 2002;26:541-41.

47. Newmeyer et al., 2014. Cannabinoid Disposition in Oral Fluid after Controlled Cannabis Smoking in Frequent and Occasional Smokers. *Drug Test Anal*. 2014 October ; 6(10): 1002–1010. doi:10.1002/dta.1632.

48. Hoffman et al., 2021. Blood and Oral Fluid Cannabinoid Profiles of Frequent and Occasional Cannabis Smokers. Journal of Analytical Toxicology, 2021;45:851–862 doi:https://doi.org/10.1093/jat/bkab078

49. Swortwood et al., 2017. Cannabinoid disposition in oral fluid after controlled smoked, vaporized, and oral cannabis administration. Drug Test Anal. 2017 June ; 9(6): 905–915. doi:10.1002/dta.2092

50. Milman G, Barnes AJ, Schwope DM, et al. Disposition of cannabinoids in oral fluid after controlled around-the-clock oral THC administration. *Clin Chem*. 2010;56(8):126-9.

51. Lemberger L, Weiss JL, Watanabe AM, Galanter LM, Wyatt RJ, Cardon PV. Delta-9-tetrahydrocannabinol temporal correlation of the psychologic effects and blood levels after various routes of administration. *N Engl J Med.* 1972;286:685–8.

52. Perez-Reyes M, Di Guiseppi S, Mason AP, et al. Passive inhalation of marihuana smoke and urinary excretion of cannabinoids. Clin Pharmacol Ther. 1983;34(1):36-41

53. Law B, Mason PA, Moffat C, et al. Passive inhalation of cannabis smoke. J Pharm Pharmacol. 1984;36(9):578-81.

54. Morland J, Bugge A, Skuterud B, et al. Cannabinoids in blood and urine after passive inhalation of cannabis smoke. J Forensic Sci. 1985;30(4):997-1002.

55. Cone EJ, Johnson RE, Darwin WD, et al. Passive inhalation of marijuana smoke: urinalysis and room air levels of delta-9- tetrahydrocannabinol. J Anal Toxicol. 1987;11(3):89-96.

56. Mule SJ, Lomax P, Gross SJ. Active and realistic passive marijuana exposure tested by three immunoassays and GC/MS in urine. J Anal Toxicol. 1988;12(3):113-6.

57. Rohrich J, Schimmel I, Zorntlein S, et al. Concentrations of delta-9-tetrahydrocannabinol and 11-nor-9-carboxytetrahydrocannabinol in blood and urine after passive exposure to cannabis smoke in a coffee shop. J Anal Toxicol. 2010;34:196-203.

58. Cone EJ, Bigelow GE, Herrmann ES, et al. Non-smoker exposure to secondhand cannabis smoke. I. Urine screening and confirmation results. *J Anal Toxicol*. 2015;39(1):1-12.

59. Cone EJ, Bigelow GE, Herrmann ES, et al. Nonsmoker exposure to secondhand cannabis smoke. III. Oral fluid and blood drug concentrations and corresponding subjective effects. J Anal Toxicol. 2015;39(7):497-509.

60. Niedbala RS, Kardos KW, Fritch DF, et al. Passive cannabis smoke exposure and oral fluid testing. II. Two studies of extreme cannabis smoke exposure in a motor vehicle. *J Anal Toxicol*. 2005;29(7):607-15.

61. Moore C, Coulter C, Uges D, et al. Cannabinoids in oral fluid following passive exposure to marijuana smoke. Forensic Sci Int. 2011;11:227-30.