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PROCEEDINGS

Interpretation of Workplace Tests for Cannabinoids

Ken Kulig[1]

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Abstract Workplace urine drug testing for an inactive THC metabolite is common in both federally regulated and non-regulated drug testing. A positive result does not document impairment, or even recent use, when impairment is likely the most important parameter being searched for by the drug testing procedure. Most cannabinoid testing does not detect imported synthetics. Currently, urine is the most widely tested matrix, but blood, plasma, oral fluid, and hair may also be accepted in federally regulated testing in the future. This article will discuss the history, the status quo, and the possible near term future of workplace testing for marijuana in employees.

Introduction

Workplace Drug Testing in the United States has become common, both in Federally regulated programs and in private industries. Usually performed with urine as the matrix, and utilizing a two step process where an initial immunoassay is used as a screen with subsequent confirmatory testing if the screen is positive, an inactive marijuana metabolite THC-COOH in urine is most commonly used as the target analyte for marijuana use. Even though under this most commonly used procedure impairment cannot be directly determined, a positive confirmed test for this inactive metabolite may have profound consequences for both employers and employees. Workplace urine drug testing is commonly used in pre employment evaluations, post accident, reasonable suspicion (of impairment), and in random testing scenarios per company policy.

With the legalization of medical marijuana in many states and recreational marijuana in a few, workplace testing for marijuana metabolite has assumed legal and regulatory challenges that didn't exist until recently. Positive confirmed drug tests are reviewed by a physician trained and certified as a Medical Review Officer (MRO) whose role it is to determine if the reason for a positive test is a "legitimate medical explanation". Because marijuana remains a Schedule 1 drug under federal law, federally regulated testing does not consider any marijuana use to be legitimate, with the exception of prescription cannabinoids as discussed below. Private employers not subject to federal regulations can make other policies at their discretion.

The purpose of this article is to summarize cannabinoid drug testing in the workplace, and not to discuss the acute or chronic clinical effects of THC and related, nor the pros and cons of legalization.

Brief History of Workplace Drug Testing

In the United States, workplace drug testing became common after 1986 when Executive Order 12564 was signed, prohibiting federal employees from using illegal drugs [1]. The emphasis then, as now, is on illegal drugs, which has resulted in lack of regulatory testing for prescription drugs which can be impairing and commonly abused. Examples of these non tested drugs include oxycodone, hydrocodone, hydromorphone, fentanyl, methadone, barbiturates,

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✉ Ken Kulig
kkmedtox@msn.com

[1] Toxicology Associates, Prof LLC, Denver, CO, USA

benzodiazepines, and the Z drugs (prescription sleep aids). In addition, synthetic cannabinoids (with the exception of Marinol® which is synthetic THC) are not included in most testing programs despite their close structural relationship to THC. Private industry commonly does test for at least some of these classes of drugs.

In 1988 the Drugfree Workplace Act was passed by the US Congress establishing the 5 panel urine drug screen classes, which can be easily remembered by the mnemonic COMPA (the first five letters in the word company): Cocaine metabolite, Opiates (with morphine and codeine being the target analytes), Marijuana metabolite, Phencyclidine, and Amphetamines (as a class which includes amphetamine and methamphetamine). Procedures for urine collection, chain of custody, split specimens, and what to do if there is a refusal to test, a dilute or adulterated specimen, or when the employee cannot urinate were specified in 1989 with the Code of Federal Regulations 49 CFR Part 40 [2, 3]. In 2010 regulated testing began to include the heroin metabolite 6-MAM, and the substituted amphetamines MDMA, MDA, and MDEA. The current panel used in regulated testing including initial screening cutoffs and confirmatory cutoffs are listed in Table 1.

Under this model, a positive and confirmed urine drug test result is reviewed by a physician with extra training who has been certified as a Medical Review Officer (MRO), which requires both training and passing an exam specific to these procedures, with recertification every five years. The MRO contacts the employee to determine if they can provide proof of a legitimate prescription for the drug they tested positive for, and if they do the test may be deemed "negative". This may be problematic when the employee is in a safety sensitive position and is taking a prescription medication that may cause impairment. The employer should have policies to deal with this common scenario.

Private employers who do not have contracts with the federal government greater than or equal to $100,000 per year are not constrained by the above federal regulations. Alternative matrices for testing in these companies may include hair, oral fluid, breath, or blood. Additional classes of drugs can be assessed, which offers substantial advantage toward the goal of preventing prescription drug abuse in workers. However, because there has been such an extensive experience with federally regulated testing, many private companies choose to use the same model of urine testing used by the Department of Transportation model, which includes only the 5 panel urine-based test.

Table 1 Initial screen and Confirmatory cutoff concentrations in federally regulated testing

Initial test analyte	Initial test cutoff concentration	Confirmatory test analyte	Confirmatory test cutoff concentration
Marijuana metabolites	50 ng/mL	THCA[1]	15 ng/mL
Cocaine metabolites	150 ng/mL	Benzoylecgonine	100 ng/mL
Opiate metabolites	2000 ng/mL	Codeine	2000 ng/mL
Codeine/Morphine[2]		Morphine	2000 ng/mL
6-Acetylmorphine	10 ng/mL	6-Acetylmorphine	10 ng/mL
Phencyclidine	25 ng/mL	Phencylidine	25 ng/mL
Amphetamines[3] AMP/MAMP[4]	500 ng/mL	Amphetamine	250 ng/mL
		Methampethamine[5]	250 ng/mL
MDMA[6]	500 ng/mL	MDMA	250 ng/mL
		MDA[7]	250 ng/mL
		MDEA[8]	250 ng/mL

Analytes and their cutoffs

Effective date: October 1, 2010

Reference: Federal register, November 25, 2008 (73 FR 71858), Section 3.4

[1] Delta-9-tetrahydrocannabinol-9-carboxyclic acid (THCA)

[2] Morphine is the target analyte for codeine/morphine testing

[3] Either a single initial test kit or multiple initial test kits may be used provided the single test kit detects each target analyte independently at the specified cutoff

[4] Methamphetamine is the target analyte for amphetamine/methamphetamine testing

[5] To be reported as positive for methamphetamine, a specimen must also contain amphetamine at a concentration equal to or greater than 100 ng/mL

[6] Methylenedioxymethamphetamine (MDMA)

[7] Methylenedioxyamphetamine (MDA)

[8] Methylenedioxyethylamphetamine (MDEA)

Drug Testing for Cannabinoids

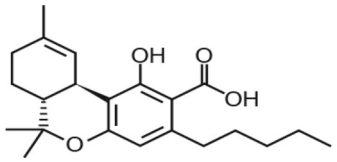
The nomenclature used in drug testing for cannabinoids can be confusing. The primary psychoactive agent in Cannabis, Δ-9-tetrahydrocannabinol (THC), has a naturally occurring inactive precursor tetrahydrocannabinolic acid, often referred to as THC acid, or THCa, THC carboxy, or 2-COOH-THC (see Fig. 1). The carboxyl group in the inactive precursor is on carbon #2. Heat and drying will decarboxylate the inactive precursor forming the psychoactive drug THC.

The primary metabolite of THC (the target analyte for urine marijuana testing) contains a carboxyl group (which differentiates it from parent compound THC) on carbon number #11, and in regulatory documents is often called THC Acid, or THCA, or THC carboxy, or 11-COOH-THC. To avoid confusion it may be valuable to use the words precursor and metabolite, or specify which carbon (#2 versus #11) has the carboxyl group, when discussing the inactive precursor versus the target analyte for Cannabis testing.

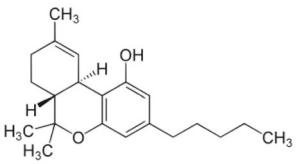
There are currently two FDA approved prescription oral cannabinoids - Marinol® (dronabinol, approved in 1992, Schedule III) and Cesamet® (nabilone, reapproved in 2006, Schedule II). Both are "synthetic cannabinoids", but should be distinguished from illicit synthetic cannabinoids such as JWH-108 as found in branded products like K2 or Spice. The illicit synthetic cannabinoids will not generally produce a positive drug test for THC or THC metabolite because their chemical structures are different from THC. Dronabinol (Marinol®) will cause a positive urine test for THC metabolite, because Marinol is actual THC albeit synthetic. Nabilone (Cesamet®) is structurally different enough from THC that it will not cause a positive urine THC metabolite test.

Sativex® is currently available in Europe but not yet the United States, and is a 1:1 mixture of THC and cannabidiol (CBD), that is used as an oral spray. Given its ingredients, it is clear why it would cause a positive THC/THC metabolite drug test. Epidiolex®, synthetic CBD, is currently in clinical trials in Europe, and should not produce a positive THC/THC metabolite urine drug test. CBD hemp oil, extracted from Cannabis hemp plants, may contain enough THC to cause a positive THC/THC metabolite drug test if ingested in very high doses.

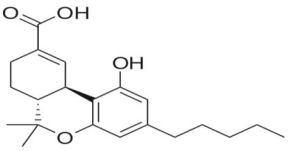
The current regulatory testing for cannabinoids uses as the target analyte in urine an inactive THC metabolite that may



Tetrahydrocannabinolic acid (**THCA**, **Δ9-THCA**, **2-COOH-THC**), is the inactive biosynthetic precursor of tetrahydrocannabinol (THC) and found in the Cannabis plant.



Tetrahydrocannabinol (**THC**), or more precisely its main isomer **(–)-*trans*-Δ⁹-tetrahydrocannabinol** ((6aR,10aR)-delta-9-tetrahydrocannabinol), is the principal psychoactive component of cannabis, formed when Cannabis plant material is dried out and combusted.



11-*nor*-9-Carboxy-THC (**11-*nor*-9-carboxy-delta-9-tetrahydrocannabinol**, **11-nor-9-carboxy-delta-9-THC**, **11-COOH-THC**, **THC-COOH**, **THC-11-oic acid)**, is the main secondary metabolite of tetrahydrocannabinol (THC) after cannabis is consumed and is inactive.

Fig. 1 Inactive naturally occurring precursor tetrahydrocannabinolic acid becomes active THC upon heating and drying, which is metabolized to the inactive metabolite 11-nor-9-Carboxy-THC, the target analyte for urine drug testing.

persist for weeks or even months in chronic users after last use (4). Because the concentration of THC in marijuana has progressively increased, passive inhalation has become more of a concern as a possible explanation for a positive test [5, 6]. The legalization of medical and recreational marijuana under state law in many states has added complexity to policy issues involving workplace drug testing. However, a recent survey of businesses found that only a small minority changed their drug testing policies based on changes in state law regarding legalization of medical or recreational marijuana [7].

The Concept or "False Negatives" and "False Positives"

Testing for drugs when there are potential serious negative consequences to the employee should not end at the initial screening immunoassay/colorimetric/point of care testing procedure. However, internet sites and medical literature often claim a false positive test result from unrelated substances when only the initial screen has been performed, or long after the technology has been improved to address these limitations. An example is the claim that ibuprofen causes a "false positive test for THC", when this was only by one type of initial immunoassay screen, EMIT, a technological issue addressed and fixed decades ago.

When the initial immunoassay screen is positive above the regulatory cutoff for THC metabolite of 50 ng/ml, but the confirmatory test has a THC metabolite concentration below the confirmatory cutoff of 15 ng/ml, this test is reported out as being negative. This is not a "false negative" but is negative by definition because the concentration is low enough that the lab may not properly distinguish signal from noise on the chromatogram.

When an MRO determines that an employee who has tested positive for THC metabolite has a legitimate recent prescription for dronabinol (Marinol®), in most cases that is sufficient to report the result to the employer as a negative. In this setting it is a matter of regulatory nomenclature, and is not a "false negative". In cases where it is important to distinguish dronabinol (Marinol®) use from marijuana use, GC/MS analysis of the specimen for tetrahydrocannabivarin (THCV) can be utilized, as THCV is not present or produced from dronoabinol (Marinol®) but is found in the marijuana plant [8].

It is best to be very specific regarding the technology when discussing the concepts of "false positives" and "false negatives". If the initial immunoassay is positive for a substance or class of drugs, but confirmatory testing is negative by GC/MS or LC/MS/MS, that is not a false positive or a false negative but a true negative result (ie initial screen unconfirmed).

However, when a drug concentration in any matrix is below the lab's limit of detection (or reporting limit), the negative result does not mean the drug concentration is zero. The negative result is laboratory nomenclature that medical toxicologists and all those who interpret drug test results should understand in detail. Specificity when describing which technology was used for testing, which analytes were targeted, and which were found in what concentration is important to avoid mischaracterizing results as being "false positives" or "false negatives".

A good practice is "when it doubt, and when it matters, call the lab". The lab that did the testing will likely know what cross reactivities exist, or can look it up in the testing manual, or can call the manufacturer for more information. If confirmatory testing has not yet been done, it should be under regulatory authority or if in private industry there will be negative consequences for the employee. If confirmatory testing has been done, by what technology, and what are the potential problems with it concerning this specific drug?

Recent Proposed Expansion of Cannabinoid Drug Testing Matrices Allowed under Federal Law

While urine has traditionally served as the matrix of choice for workplace drug testing, recent recommendations have been published advising that other matrices be accepted. On May 15, 2015 SAMHSA (Substance Abuse and Mental Health Services Administration) published in the Federal Register recommendations for using oral fluid, and for the inclusion of hydrocodone, oxycodone, and hydromorphone in federally regulated testing. For Cannabis testing in oral fluid the target analyte would be active THC with a proposed initial screen cutoff of 4 ng/ml and confirmation cutoff of 2 ng/ml.

On May 29, 2015 SAMHSA recommended in the Federal Register inclusion of hair testing in federally regulated testing. Although cutoffs were not included in the recommendation, common cutoffs in private industry for the inactive metabolite in hair include 1 pg/mg for the initial screen, and 0.05 pg/mg for the confirmatory test.

The merits of both of these proposals are still being debated. There has been a large amount of research and experience with drug testing in these alternative matrices since they were last proposed by SAMHSA in 2004.

The American College of Occupational and Environmental Medicine, which has been very involved in educational and regulatory activities regarding workplace drug testing, recently published two position statements [9, 10] that included recommendations for Cannabis testing. Although specifics varied somewhat, each emphasized documentation of impairment (which might include blood or plasma THC and active metabolite levels or neuropsychiatric testing of employees) as opposed to just the presence of an inactive metabolite in urine which is the status quo.

Synthetic cannabinoids such as those found in K2 and Spice pose a particular challenge in workplace testing. While clearly capable of causing severe impairment and life threatening medical problems [11], most workplace drug testing will not detect these substances because the initial screen target analyte 11-COOH-THC is structurally different enough that a positive initial screen will not occur. Private industry can add synthetic cannabinoids to their routine workplace testing, but at considerable expense. An ever changing array of chemical substitutions also makes detecting all currentlyl and potentially available products extremely difficult.

Recent Workplace Case Law in a State where both Medical and Recreational Marijuana Are Legal

Colorado voters approved medical marijuana in 2000 and recreational marijuana in 2014. On June 15, 2015 the Colorado Supreme Court [12] upheld the firing of a wheelchair bound employee who was using medical marijuana upon the recommendation of his physician to treat his spastic paraplegia from an automobile accident many years prior. The employee was never accused of being impaired from marijuana on the job, and claimed he only used marijuana after work. This occurred despite the fact that Colorado also has a lawful activities statute that protects workers from being fired for participating in legal activities when not at work.

The employee tested positive for THC in oral fluid in a random drug screen, and company policy (non federally regulated testing) guided his firing. The company argued that if the court ruled in favor of the employee that the company and others would risk losing federal contracts because they would no longer comply with federal drug free workplace statutes. The Colorado Supreme Court upheld the employer's right to fire the employee for the positive test result. The court ruled that "lawful activity" means under both federal and state law, not just state law. This important yet controversial ruling will likely be cited in future cases involving employee drug testing for cannabinoids in other states.

Conclusions

Workplace drug testing for cannabinoids remains common yet controversial from a regulatory, political, privacy, medical, and criminal justice viewpoint. It is rapidly evolving with likely future expanded regulatory testing of oral fluid and hair and not just urine, each matrix with its own advantages and challenges. The focus on cannabinoid testing appears to be shifting away from marijuana use of any kind at any time (testing urine for an inactive metabolite) to whether or not impairment from THC in the workplace exists. Driving under the influence criminal statutes where an inferred inference of impairment at 5 ng/ml whole blood THC (in Colorado and Washington) may serve as a model for "working while impaired by THC" policies. Impairment from illicit synthetic cannabinoids creates a whole different set of testing and policy challenges.

Compliance with Ethical Standards

Conflicts of Interest None

Sources of Funding None

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