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Workplace Drug Testing for Today and Tomorrow – The Challenges with Amphetamines

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The Substance Abuse and Mental Health Services Administration (SAMHSA) in the United States provides guidelines for the measurement and detection of drugs commonly associated with workplace drug testing [1,2]. Of the five drugs on the workplace drug testing panel, the amphetamine drug constitutes a very unique class. Its structure is very simple and several drugs share similarity to the phenylethalamine skeleton structure (Figure 1), and may be found in nature (such as mescaline in cayote cactus, *Lophophora williamsii*) or licit amphetamine and designer drugs may be synthesized from it. As a result, myriads of pharmacological effects have been associated with amphetamines, including weight loss, vasoconstriction and as central nervous system stimulants. The routes of administration are also varied and include intravenous administration, smoking, snorting or oral ingestion. However, it's activity as a central nervous system stimulant that is of public health concern and the need to detect its presence during workplace drug testing provides challenges because of the possibility of licit drug use the false positive tests. Unlike drug tests for patient care where the physician makes clinical decisions based on test results measured only once, in forensic drug testing, specimens must first be screened and then confirmed before a test rest can be classified as positive. Table 1 shows the initial cutoffs for the five drug classes and table 2 shows the cutoffs during confirmatory testing. Because of ease of collection, urine is a favorite specimen used. However, it must be remembered that there is no clinical relationship between urine drug concentration and clinical symptoms. It only indicates that the drug was ingested and passed through an individual's body.

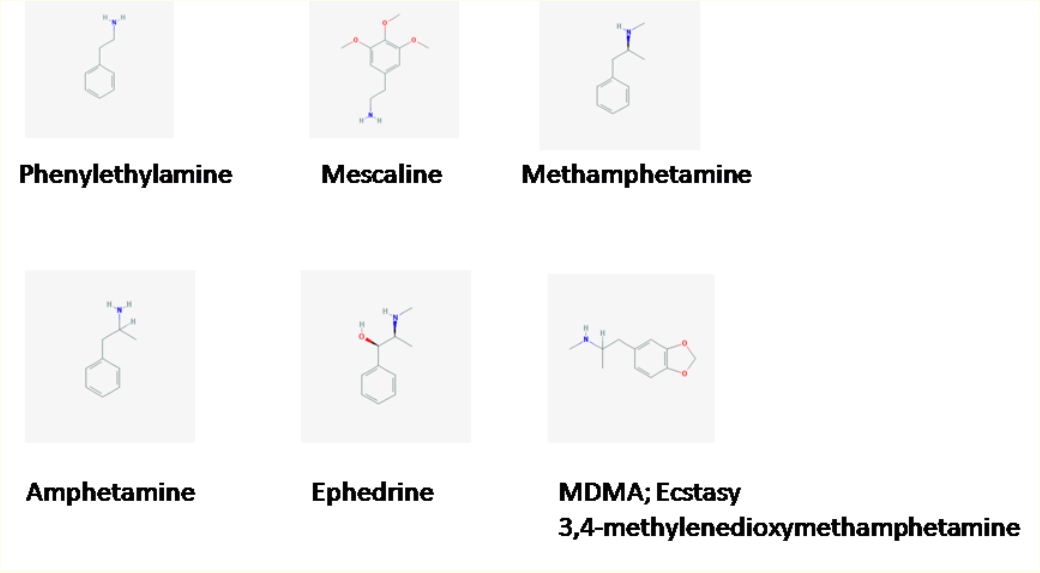

Figure 1: *Structurally related amphetamine compounds. The structures were accessed from PubChem, an open chemistry database* (https://pubchem.ncbi.nlm.nih.gov/). *An initial screen must be able to identify all these compounds as a class.*

Initial Drug Cutoff Levels	
Drug	Concentration (ng/ml)
Marijuana metabolites	50
Cocaine metabolites	150
Opiate metabolites	2000
Phencyclidine (PCP)	25
Amphetamines	500

Table 1: *Drug cutoff levels for the screen test.*

According to SAMHSA, an approved method for the initial screening urine drug screen may use one or more types of immunoassay and by design, it is best to use a polyclonal antibody-based assay so that drug classes rather than specific drugs may be detected at this stage. Maximum cross-reaction is best in order to detect the presence of amphetamine analogs such as ecstasy (3,4-Methylenedioxymethamphetamine, MDMA) or Eve (3,4-Methylenedioxy-N-ethylamphetamine, MDEA). This initial screen allows for the elimination of thousands of negative samples. If drug levels in the samples exceed the initial cut-offs, as shown in table 1, then one might proceed to confirm the identity of the drug/s, using a method based on a different scientific principle. The most common is using gas chromatography and mass spectrometry (GC/MS). Because the GC/MS technique identifies the finger print of the actual drugs, the confirmatory cutoffs are generally lower than the initial cutoffs (Table 2). Thus, whereas the screen cutoff for amphetamine is 500 ng/ml, the sample maybe reported as positive if it exceeds 250 ng/ml in the confirmatory test. SAMHSA guidelines also requires that the screening test used must be able to identify the d- enantiomer of amphetamine because of the different biological activities of the d- and l- enantiomers of amphetamine (Figure 2). Whereas the d-amphetamine is about ten times more potent as a central nervous system stimulant than the l-enantiomer, the l-enantiomer is more potent as a vasoconstrictor. Thus, l-methamphetamine is a common ingredient in over-the-counter medications for relief of nasal congestion. As stimulants, amphetamines are very attractive to athletes and the challenge is to be able to detect these substances when used illegally as performance enhancing drugs or when they are ingested legally, because amphetamines are common ingredients in appetite suppressant medications and medications such as Adderall which is used for treatment of Attention Deficit/Hyperactive Disorder (ADHD). As an illustration of a typical test and its interpretation, consider a urine result of about 13,200 ng/ml of amphetamine, which was solely the d-amphetamine, and the individual claiming that he was taking the prescription drug Adderall (20 mg/day) before providing the urine sample. One would like to know if he is telling the truth. Although it is conceivable that one could produce amphetamine levels that high on a chronic ingestion of Adderall, the fact that only the d-enantiomer was detected suggests that this amphetamine excretion was not from Adderall. Table 3 is a summary of some common drugs and their enantiomeric composition of methamphetamine and amphetamine enantiomers. Some drugs are preferentially metabolized to only amphetamine (e.g. Adderall, Clobenzorex and Fenproporex), whereas others (Benzphetamine, Deprenyl and Famprofazone) are metabolized to methamphetamine, leading to the urine toxicology detecting both methamphetamine and amphetamine. This can be a clue to determining if an individual is telling the truth or not.

Confirmatory Drug Cutoff Levels	
Drug	Concentration (ng/ml)
Marijuana metabolites	15
Cocaine metabolites	100
Opiate	
Morphine	2000
Codeine	2000
6-Monoacetylmorphine	10
Phencyclidine (PCP)	25
Amphetamines	
Methamphetamine	250
MDMA	250
MDA	250
MDEA	250

Table 2: *Drug levels exceeding these cutoffs may be reported as positive*.*

**Note that these cutoffs may be lower than the screen cutoffs because they detect specific compounds.*

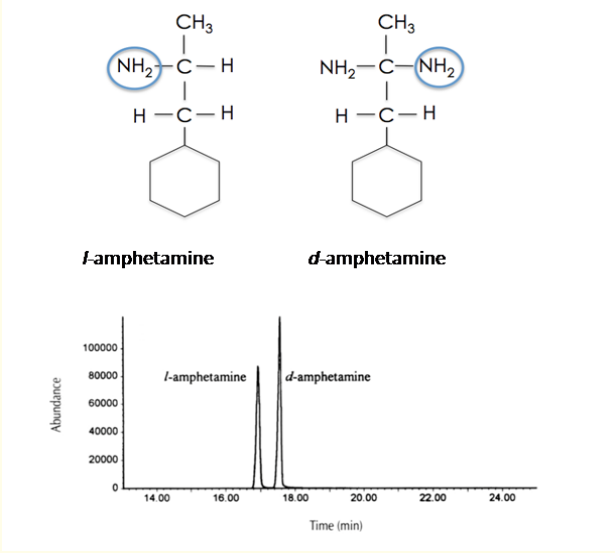

Figure 2: *Amphetamine d- and l- enantiomers which are easily separated by gas chromatography and mass spectrometry.*

Drug	Enantiomers
Adderall	d- and l-amphetamine
Dexedrine	d-amphetamine
Benzphetamine	d- and l-amphetamine
Benzedrine	d- and l-amphetamine
Selegiline	l-methamphetamine, l-amphetamine

Table 3: *Enantiomeric amphetamine composition of common medications.*

In conclusion, chemistry can be a useful tool for elucidating the mysteries surrounding urine drug test results. With drug peddlers apparently always one step ahead of toxicologists and the law in the synthesis of designer drugs because of the large market of avid users, both rich and poor, more studies in the metabolism of amphetamine-like licit drugs in particular is paramount now to help curb the continuing scourge of drug abuse on society. More importantly, routine measurement of the amphetamine enantiomers will save time especially for samples that are litigated.

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