Perspective

Drug Testing and Analysis

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Workplace drug testing, different matrices different objectives

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Drug testing is used by employers to detect drug use by employees or job candidates. It can identify recent use of alcohol, prescription drugs, and illicit drugs as a screening tool for potential health and safety and performance issues.

Urine is the most commonly used sample for illicit drugs. It detects the use of a drug within the last few days and as such is evidence of recent use; but a positive test does not necessarily mean that the individual was impaired at the time of the test. Abstention from use for three days will often produce a negative test result.

Analysis of hair provides a much longer window of detection, typically 1 to 3 months. Hence the likelihood of a falsely negative test using hair is very much less than with a urine test. Conversely, a negative hair test is a substantially stronger indicator of a non-drug user than a negative urine test.

Oral fluid (saliva) is also easy to collect. Drugs remain in oral fluid for a similar time as in blood. The method is a good way of detecting current use and is more likely to reflect current impairment. It offers promise as a test in post-accident, for cause, and on-duty situations.

Studies have shown that within the same industrial settings, hair testing can detect twice as many drug users as urine testing.

Keywords: drug testing; hair; urine; saliva

Drug analysis

The determination of drugs and metabolites in tissues and body fluids has been used for many years in various health-related sectors, including the workplace. In the 1970s, it became known that there is a correlation between the clinical effectiveness of drugs and their concentration in the blood. As a result, there was a growth in therapeutic drug monitoring using blood as the sample matrix. Then in the 1980s, there was an increased interest in the use of urine testing to detect and monitor the use of drugs of abuse, both in clinics and in the workplace. The big impetus for workplace drug testing was the signing of Executive Order 12564 in 1986 by US President Ronald Reagan, which effectively legalized testing of employees for drugs. The original order and subsequent Drug-free Workplace Act of 1988 was restricted to urine testing and it only applied to US Federal employees and Federal contractors but private-sector employers have been encouraged to follow the lead. Workplace drug testing has grown in the UK and Europe to reflect the implementation in the United States and increasingly in other less developed countries worldwide.

Drug testing is especially relevant where there are health and safety risks such as in heavy manufacturing, transportation, including airlines and railways, and the shipping and oil industries. There are enough growing statistics on the incidence and cost of accidents at work resulting from the use of drugs, including alcohol, to convince employers of the relevance of workplace testing.

In the USA and in Europe, it is common practice for employers to require pre-employment testing in order to identify those individuals that can pose risks to the safety of themselves and others.[1] The purpose of this practice is to reduce risks in the workplace that cause serious economic impacts (in the order of millions of dollars) due to drug use. This high cost includes loss of productivity due to absenteeism, delays, and increased numbers of occupational accidents.

There are other situations for drug testing in the workplace. Many workers are tested for illegal drugs each year for post-incident investigations (when coupled with random in-employment testing, post-accident, or randomly in employment but more commonly in the pre-employment selection process).

Consequently, due to the extensive demand, drug testing expanded rapidly in the 1990s and in parallel with this expansion there were also technological advances in the detection of drugs, both legal and illegal and their metabolites. Rapid tests based on immunochemical technology and the introduction of gas chromatography couples to mass spectrometry (GC-MS) made it possible to rapidly and accurately monitor the concentrations of drugs in a variety of matrices.

Biological matrices

Pharmacokinetic studies of drugs in the body following absorption show that, as a rule, the processes of metabolism, distribution, and elimination mean that there is a wide distribution of parent drugs and their metabolites between the various

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biological compartments. The bloodstream is the main vehicle for distribution of nutrients, drugs, and metabolites. The relationship between the various fluids and biological compartments depends on the kinetic parameters of each substance; for example, distribution volume, lipophylicity, half-life, and other pharmacokinetic factors.

The use of biological fluids is universally accepted for the detection and monitoring of drug use and blood or urine has been most commonly used for this purpose. All drug testing is to some extent invasive of personal privacy but some sampling raises special difficulties. The taking of samples of blood is considered particularly invasive as it involves taking blood with a syringe and requires trained phlebotomists to take it. Blood sampling is largely restricted to therapeutic drug monitoring and pharmacokinetic studies. In the early days of the detection of drugs of abuse, urine was the only choice because the amount of sample that can be obtained is relatively unlimited and the concentrations of drugs and metabolites found in urine are large. In those early days, the technology of detection was relatively less sensitive than that available today. Urine remains the most commonly used sample because of the ease of detection, the availability of on-site immunoassay kits that enable rapid screening and the extensive amount of information available on use and interpretation of the testing. There has also grown up an extensive knowledge of the ways drug users can subvert the testing. However urine is regarded as a test that is invasive of a person's privacy and is rather undignified.

However, with the refinement and sophistication of the analytical tools available, the use of alternative specimens such as saliva (oral fluid) began to be increasingly used, mainly due to the simplicity of sample collection.[2,3]

Similarly, the same technological advances allowed us to detect the presence of much lower levels of drugs and metabolites present in hair samples. Drug testing using hair began to be routinely used in the 1970s in the USA, where its use expanded in the 1980s; soon after, it was introduced in Europe.[4–9] In the last two decades, there has been a dramatic increase in the study and characterization of drug abuse through analysis of hair as evidenced by the subsequent publication of several studies and scientific reviews of the analysis of drugs in this matrix.[8,10–12]

Urine and saliva produce a transient spectrum of drug use for a relatively short period reflecting use that occurred hours before sample collection (24–72 h) depending on the drug. In contrast, hair provides information of use over a more extended period of the order of weeks or months.

The main benefit of hair analysis is the long window of detection that is able to demonstrate use retrospectively. The drugs and metabolites are locked into the hair post-elimination from the body and retained in the hair until it is cut or shed. So past use can be detected for months, not just for days as with urine or oral fluid. In addition, it is possible to study trends of past exposure. Also, while adulteration or substitution is a common issue when urine samples are used, it is difficult, if not impossible, when it comes to hair samples. Evasion is possible when people shave or use excessive cosmetic hair treatments, but both are usually very apparent to the collector.

The analysis of hair is used in a wide variety of organizations such as those dealing with drug addiction, clinics, hospitals, police (forensics), sports clubs and social services. It has been used increasingly in the workplace especially in pre-employment vetting.[8,9] In the case of treatment and rehabilitation of users, the analysis of drugs in hair allows easy verification of adherence to medical treatment without the requirement to attend a clinic every three days and thus enabling the donor to maintain employment and the physician to monitor therapy.[13,14]

Cutting the hair into segments allows the laboratory to detect changes in type of drug used and levels of use. This is useful to the physician as levels can indicate an increase or decrease in drug use by an individual over long periods of time, thus facilitating and improving the clinical treatment for the patient by the doctor. It can also give a history of prior drug use before the clinical interview. This single, simple fact is highly valuable to the clinical process.

The following examples offer three illustrations of the variety of applications of drug testing through the use of different biological matrices in the workplace:

1. In industries/institutions of higher risk where it is necessary to document that the job applicant is not a regular user of drugs. In these cases of pre-employment testing, a 3-centimetre hair sample covering a period of three months is ideal because the candidate will have to abstain from drugs for three months for the test to be negative. Most industries, however, still use a urine drug screen test as a requirement for employment. This can only provide a 3–5-day window of detection at maximum and if the candidate is pre-warned of the test, it is probably useless. There is also the perception that a hair test is expensive. However, this perception is illusory, for a sample of hair covering a period of approximately three months is equivalent to 18 urine tests in the breadth of coverage. It rather depends on whether the result of the test is important to the employer.
2. In industries/institutions that need to know whether a person is responsible and fit to perform specific tasks, it is possible to test to ensure that no drugs are present in the person's system that may impair performance or put others at risk. These tests are usually labelled 'random'. These tests do not accurately reflect or predict fitness to work. They only detect recent past use. They may be the best indicator available but it remains true that no drug test actually measures 'fitness to work'. The use of saliva (oral fluid) is ideal in such cases, when drugs are present in oral fluid samples actually reflects the use of drugs in the last 24 h, very relevant in assessing impairment.
3. In the post-accident situation, saliva (oral fluid) testing is best suited to assess very recent use of drugs when a blood test is not possible. However, a hair test may be useful to enable verification that the individual who had a urine test or oral fluid positive is actually a regular user of drugs, or if the positive result reflects only a single episode of use.

Nowadays, the use of three matrices – urine, saliva and hair – is widely accepted in scientific circles. They are complementary and each sample type has different advantages depending on the purpose of the test. It is well established that there is not a perfect sample for drug analysis, but the ideal sample for a particular purpose. In Table 1, there are examples of the use of different matrices highlighting the situations in which each is most appropriate. For example, in case of accidents, the use of hair is irrelevant in establishing the causal relationship between an individual's use of drugs and the event and the accident.

Table 1. Purposes of use for urine, saliva, and hair

Sector	Urine	Oral Fluid	Hair
Random drug test	+++	+++	+ (Useful when urine or oral fluid is positive to establish if individual is regular user)
Pre-employment			+++
Insurance			+++
Medical-legal	++	++	++
Child protection/custody	+ (Depending on specific case)	+ (Depending on specific case)	+++
Clinical monitoring			+++

Main benefits of drug analysis in hair

Each sample matrix will give a different perspective on drug use. The selection of a particular matrix depends on the purpose of the testing. The way a sample is collected is also important. Routine analysis of drugs in hair from a sample cut near the scalp can detect drug use from six days before collection. This means that drugs used six days, prior to collection may not be detected. However if the hair is pulled and hair with the roots attached is collected the window of detection extends to the day of collection. Pulling hair from cadavers to include the roots is common practice in cases of death investigations.

Drugs and metabolites remain fixed and trapped in the hair indefinitely after they are incorporated in the hair. As the hair grows, the drugs maintain their position and grow out with the hair, increasing the chronological window of detection.[15]

As a guide, the analysis of drugs of abuse in oral fluid or urine provides evidence of consumption in the last 24–48 h. As the hair covers a longer period of use that does not necessarily include the same period of a urine or oral fluid sample, it is possible that for the same individual, a hair sample can test positive while a urine test is negative. Urine and saliva are fluids that demonstrate recent exposure while hair generally represents what has been used in the past.

It is possible to get a rough indication of the frequency of use by analyzing multiple segments of hair.[9] Separate segments reflect use over several weeks, allowing the evaluation of the usage profile of drugs. It is possible to infer use of larger or smaller quantities over a prolonged period of time. One of the advantages of using hair analysis for drugs is the possibility of verifying a drug dose reduction over time. This can reveal a subject trying to reduce consumption whereas oral fluid testing and urine testing can only detect use or non-use.

Another advantage is in the sampling. The collection of hair is simple, non-invasive and more dignified than urine collection; urine collection is usually supervised and may be observed to ensure that no fraud occurs during the collection. Yet another important advantage of using hair to screen for drugs is that if there are any issues, a new sample can be cut that represents the same period of time, provided the hair has not been cut. This is not possible with oral fluid or urine testing and these samples need the collection of a second 'B' sample.

The main benefit of using hair as a sample for drugs of abuse is the longer window of detection and hence the greater sensitivity of detecting drug use. The identification of a non-drug user is much more secure with hair testing than with a random urine test because a drug user can abstain from use for 3–4 days prior to collection to produce a negative urine test. A hair test will require an abstention of three months for a typical 3-cm-long hair test.

Analytes commonly analyzed and levels detected

Groups of drugs most commonly analyzed with the respective cut-offs recommended for confirmatory testing in urine,[16] saliva,[17] and hair,[18] respectively, are shown in Table 2.

The term cut-off means a limit value, on which the results obtained in the analysis are compared and when found below the established levels of cut-off are considered as *not detected* or *negative*, and values above are considered *detected* or *positive*.

In the case of urine and saliva (oral fluid), the levels of cut-offs are used for the purpose of: (1) minimizing the detection of drugs taken involuntarily (passively), as is the case of drugs that are smoked; (2) eliminating the detection of drugs used in the earlier periods of interest (e.g. eliminating the detection of drugs used over the weekend outside the workplace). This is a very practical approach in the workplace, where it is important to know whether an individual is under the influence of drugs or not, so to minimize risk of injury to colleagues and the general public, beyond the individual.

In the analysis of drugs in hair, the main objective of the cut-off levels is to minimize the detection of drugs used in periods preceding the period of interest.

The cut-off values of different matrices usually reflect the levels of drugs that are found in them. For example, levels of cocaine and its major metabolite, benzoylecgonine, in a survey of over 7000 hair samples were in the range of 0.2 to 159.9 and 0.1 to 36.1 nanograms per milligram of hair respectively in 99% of the samples tested.[9] In the same study, 99% of the levels found in the results of the metabolite of delta-9-tetrahydrocannabinol (THC), 11-Nor-D9-THC-9-Carboxylic Acid (THC COOH), were in the range from 0.001 to 0.052 nanograms per milligram of hair. What is remarkable is the difference between levels of cocaine and THC COOH in hair. This difference is due to the different rates of incorporation of the analytes in hair, for example, cocaine has a rate of incorporation 3600 the rate of incorporation of THC COOH.[19] It has been a common finding that acidic drugs and metabolites have much lower rates of incorporation than basic drugs such as cocaine and the amphetamines.

Table 2. Drugs and metabolites commonly analyzed with the respective recommended cut-offs

Group	Drugs and metabolites	Recommended cut-offs		
		Urine (ng/ml)	Oral Fluid (Neat) (ng/ml)	Hair (ng/mg)
Amphetamines	Amphetamine	250	30	0.2
	MDMA (Ecstasy)	250	30	0.2
	MDA	250	30	0.2
	Methamphetamine	250	30	0.2
Benzodiazepines	Diazepam	-	-	0.05
	Lorazepam	-	10	0.05
	Nordiazepam	-	10	0.05
	Oxazepam	-	10	0.05
Cannabinoids	Delta-9-tetrahydrocannabinol (THC)	-	2	0.1
	11-Nor-D9-THC-9-Carboxylic acid (THC COOH)	15	-	0.0002
	11- hydroxy-D9-THC	-	-	0.0002
	Cannabidiol	-	-	0.1
	Cannabinol	-	-	0.1
Cocaine	Anhydroecgonine methyl ester	-	-	0.2
	Benzoylecgonine	150	8	0.2
	Cocaethylene	-	-	0.2
	Cocaine	-	-	0.2
Opiates	6-acetylmorphine	10	4	0.2
	Acetylcodeine	-	-	0.2
	Codeine	2000	40	0.2
	Dihydrocodeine	-	40	0.2
	Heroin	-	-	0.2
	Morphine	2000	40	0.2

The differentiation between the active use of drugs and external contamination when hair samples are tested

The differentiation between systemic exposure and external contamination is important in the analysis of drugs in hair as external contamination is always a possibility with hair samples.[7,20,21] Especially where drugs are smoked, it is possible that a non-user's hair could become contaminated by associating with users.

The detection of metabolites is the main approach in hair testing to confirm drug use, and exclude external contamination, since the presence in hair samples confirms the use of drugs as metabolism requires ingestion into the body. Difficulty in interpretation arises when metabolites are not detected. In the case of marijuana and cocaine, for example, metabolites are incorporated into the hair in relatively small quantities compared with the precursor drugs and may show levels below the detection limits of analytical methods, which means that the metabolites may not be detectable due to low doses of drugs used.

However, this problem is easily circumvented through the analysis of residues obtained from washing the hair during the process of decontamination prior to analysis.[22] Comparing the results of the sample with the wash residue can reduce the issues on the interpretation of results to manageable proportions.[7,21]

When low doses are used, the metabolites are present in the hair at levels too low to be detected, and only the precursor drugs are capable of being detected. A typical example is the detection of delta-9-tetrahydrocannabinol (THC) without the presence of a metabolite, 11-Nor-delta9-THC-9-carboxylic acid (THC-COOH) or 11-hydroxy-delta9-THC (THC-OH). This scenario is common in cases where there was the use of low doses; for example, sporadic use of cannabis. In these cases it is uncertain whether the source of the drugs in hair is caused by using low doses or is due to external contamination. Studies show that urine samples are unlikely to be positive due to passive inhalation (or involuntary) of certain drugs like marijuana, when the relevant cut-off levels are applied.[23]

Sectioning: Analysis of multiple segments

Generally a urine drug test will detect the use of most abused drugs within a 4-day window prior to the collection of the sample. An oral fluid sample will only detect drugs within a 2-day window. A hair drug test will cover a minimum of one month where a 1 cm section is analyzed, but the start of the evaluation is 6 to 7 days prior to the date of collection extending into the past by approximately 30 days. As a result, a single hair test is equivalent to many urine samples and the chances of confounding the test are greatly reduced.

The window of detection using hair depends on the length used. An evaluation study of patterns of drug use in the UK by hair analysis in more than 34 000 hair samples showed that segments of 3 cm is the most commonly used length. Other sectioning patterns are also used depending on the purpose of the analysis (Figure 1).[9]

It is not possible to know the exact time period covered by a hair sample because the rate of hair growth varies among individuals and calculation of the dates of the segments assumes a growth rate of 1 cm per month. This is especially important in forensics because it is impossible to precisely correlate an event with a residue of drug in a length of hair and thereby prove that someone was under the influence of drug when the event occurred.

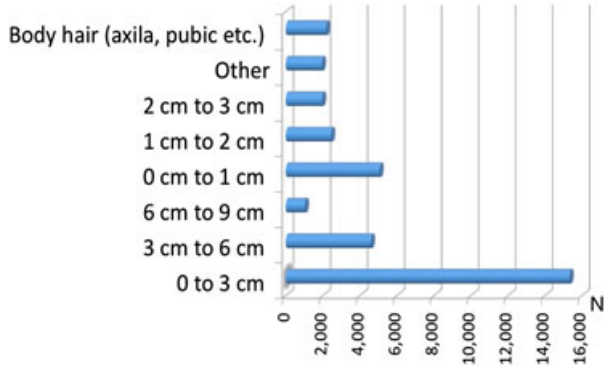

Figure 1. Usual sectioning patterns.

When multiple successive segments are tested, the results can be evaluated against each other to assess how long drugs have been taken and whether drug use is increasing or decreasing. The interpretation is not necessarily simple and requires consideration of when (and if) any cosmetic treatments were used, and the growth characteristics of hair. For example, when a subject stops taking drugs, the levels in hair fall rapidly to the levels in the telogen (resting) phase hair that may remain on the head for 4 to 5 months before being shed. In this situation, low levels of the drug may be found even after people have stopped taking it. To be confident that the hair will be free of drugs after a chronic drug user has stopped using, there needs to be a gap of at least 4 months after drug use has stopped. Urine and oral fluid are much more relevant in this period.

Factors that affect drug levels in hair

There are several factors that affect levels of drugs and metabolites in hair. For example, the incorporation of drugs in hair varies from person to person, mainly due to differences in metabolism between individuals. It is not possible to correlate exactly the levels detected in hair with the amount of drug ingested. The levels of drugs in hair are best used as a guide to the changes in drug use in an individual. However, it is possible to deduce that the same individual has used larger or smaller doses over several months, through the analysis of successive segments of hair, although it is not possible to compare data from hair analysis among individuals or extrapolate the dose used.[24]

The levels of drugs in hair, urine, or oral fluid are not correlated with the amount of drug used. The detection of drugs in oral fluid above certain levels can be presumptive proof of recent drug use, although it is not possible to determine how long before sampling the drug was consumed. The detection of drugs in urine provides a much weaker indicator of current drug use. Although it is not possible to correlate the levels of drugs in hair with the amount of drug used, it is possible to interpret the results compared with the results of a population of previous positive results.[9,24]

Another factor is the treatment by hair cosmetics. Hair treatments such as dyes and bleaches damage hair and can change the concentration of the drug in the hair. The implication is that a single dose within the period under review may not be detected due to the use of these products and may compromise the detection of eventual consumption. However, in cases where people use drugs regularly, the detection of drugs in hair is usually possible despite the use of cosmetics, although the drug level in hair is reduced. In a study consisting of 2957 hair samples, the median levels of cocaine found in hair treated with cosmetic products was 13% down when compared with untreated hair.[25]

Dark hair incorporates relatively more drugs and metabolites than lighter hair, mainly due to the binding of drugs to hair melanin.[26] Consequently, people with dark hair have a slightly higher chance of having a positive outcome than people with blonde hair using the same dose. However, data from scientific research to date have not elucidated whether the difference in hair colour has real significance in the incorporation of drugs and their detection in hair.[24] Studies consisting of a total of more than 60 000 samples showed no significant relationship between the categories of hair colour and the likelihood of a positive test.[25,27] In the study presented in 2001 using 2957 hair samples, the median levels of all studied drugs in dark hair were 11% higher than the median in light hair. The median levels of benzoylecgonine in dark hair showed approximately 20% higher, but in contrast the values of cocaine showed opposite values, where dark hair showed levels significantly lower than those found in light hair (approximately 40%).[25]

A positive result of a drug analysis confirms that a person has used or has been exposed to a drug. A negative result, however, does not categorically mean that the person did not use drugs in the last 24 h or 3 days (urine and oral fluid) and last 3 months (hair). Consequently, it is erroneous to think that drug tests are always clear-cut, whichever matrix –urine, saliva or hair – is used. It is important that the benefits and limitations of the tests are considered before the client assigns a contract for a drug screen. In reality, a negative drug test only indicates that a drug was not found above any cut-off level that may be applied.

When to use hair testing?

Hair analysis is not adequate to evaluate recent use and it is not possible to attribute drug use that occurred to a particular day or prove a causal connection between drug detected and a particular event.

If a drug user abstains from drug use for two or three days, a urine test usually provides a negative result, even if the individual is a regular drug user. However, a hair test will normally show a positive result in this case. When hair samples are used, a user will normally have to have abstained for at least three months for the result to be negative.[28,29]

Hair analysis becomes a very useful tool to confirm whether an individual who tested positive by using a urine test is a regular user, or has just used once. It is possible to find a positive urine result with a negative hair analysis, demonstrating that the individual is not a regular drug user. It is possible to have a negative urine test and a positive hair test, which implies that the individual is a drug user, but did not use recently.

Analyses in different matrices are therefore complementary to establish if an individual did or did not use drugs, but it is important to note that with any of the matrices, we cannot estimate the extent of drug addiction. While the urine provides information recent (2–3 days maximum), the hair provides long-term information, from months to years, both in frequency and identification of drugs. This is the great advantage of using hair samples. As for the costs of the examination, compared with the test in urine, hair analysis is more expensive; but four 3-cm sections of hair have the ability to monitor the use of substances over one year when spread evenly through the year (instead of one urine

sample every 3–5 days). The analysis of drugs in hair detects a greater number of drug users than urine samples. Studies in the USA and UK showed that the rate of detection of drugs in hair is often greater than the rate of detection in urine.[9,30]

One must also consider that a result of an isolated test in some cases may not be sufficient to produce a definitive interpretation. Like any chemical analysis, clinical laboratory tests have limitations and results must be considered together with other evidence, such as a clinical interview or regular monitoring of the individual.

Conclusions

The three matrices – urine, saliva and hair – are complementary and each sample type has different advantages depending on the purpose of the test.

Urine and saliva reflect drug use on a relatively short period before sample collection (24–72 h) depending on the drug.

The most important benefit of detecting drugs through hair analysis is to provide a retrospective detection window that can show the extent of the habit and identify which drugs were used during the preceding several months.

Tests for drugs using hair samples show positive for twice as many people as those using urine samples because of the detection window and difficulty of avoiding detection. The collection of hair is simple, non-invasive, and more dignified than urine collection.

Drug testing using hair is relatively more complex than urine testing. Not only does the testing laboratory need to be competent to deal with the difficulties in hair testing, but the laboratory needs specialized expertise for the interpretation of the results, if the benefits of hair testing are to be fully realized. Hair analysis is increasingly widely used, most commonly in cases of child protection and custody. In conclusion, hair analysis in the workplace is growing in importance especially in pre-employment settings, but the various matrices are not exclusive, but complementary.

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