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Interpretation of Oral Fluid Tests for Drugs of Abuse

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Abstract

Oral fluid testing for drugs of abuse offers significant advantages over urine as a test matrix. Collection can be performed under direct observation with reduced risk of adulteration and substitution. Drugs generally appear in oral fluid by passive diffusion from blood, but also may be deposited in the oral cavity during oral, smoked, and intranasal administration. Drug metabolites also can be detected in oral fluid. Unlike urine testing, there may be a close correspondence between drug and metabolite concentrations in oral fluid and in blood. Interpretation of oral fluid results for drugs of abuse should be an iterative process whereby one considers the test results in the context of program requirements and a broad scientific knowledge of the many factors involved in determining test outcome. This review delineates many of the chemical and metabolic processes involved in the disposition of drugs and metabolites in oral fluid that are important to the appropriate interpretation of oral fluid tests. Chemical, metabolic, kinetic, and analytic parameters are summarized for selected drugs of abuse, and general guidelines are offered for understanding the significance of oral fluid tests.

Keywords

oral fluid; saliva; interpretation; testing; advantages; limitations

INTRODUCTION

Testing for drugs of abuse in biological fluids and tissues is an international phenomenon, practiced in many different settings for a variety of reasons. The majority of testing in the United States occurs in workplace programs, but a significant volume of testing also is performed in the United States and abroad in drug treatment centers, hospital emergency rooms, pain treatment clinics, sports organizations, and by courts and other legal authorities. Historically, urine has been the matrix of choice for testing, but recent advances in technology and the introduction of commercial oral fluid assays have effectively established oral fluid as a viable alternative. The popularity of oral fluid as a test matrix has arisen because of its distinct advantages over urine. Oral fluid collection can be performed in almost any location, with less embarrassment and under directly observed conditions. The noninvasiveness of collection and reduced opportunity for adulteration and substitution, in contrast to urine testing, are key factors to oral fluid's success. Some programs now use oral fluid as the test matrix of choice, especially in the private-sector workplace, drug treatment, and legal settings. The obvious advantages of oral fluid and concomitant advances in technology led the Department of Health and Human

Services (DHHS) to propose oral fluid analysis for inclusion in the federal workplace drug-testing program.¹

There is now a significant body of scientific literature on oral fluid testing. Several reviews document aspects of oral fluid testing including drug disposition,^{2–6} detection times,⁷ diagnostics,⁸ legal issues⁹ and application of state-of-the-art technologies.^{10–12} This review addresses chemical, physiological, and pharmacological factors that determine the outcome of oral fluid results and offers general guidelines for interpretation of positive tests and discussion of the limitations of oral fluid testing.

FACTORS INVOLVED IN INTERPRETATION OF ORAL FLUID DRUG TESTS

Interpretation of oral fluid drug results is dependent in part on the purpose of testing. Workplace drug testing is primarily performed as a means of identification of individuals, frequently in safety-sensitive positions, who are abusing drugs and as a deterrent to drug misuse by the general workforce. Drug treatment specialists perform drug testing to foster drug abstinence and compliance with program requirements. Testing in legal settings documents program violations, compliance, and provides evidence of impairment.

There are numerous considerations in drug test interpretation. Figure 1 illustrates the flow of the test process and factors important to accurate interpretation. Questions posed during the interpretational process depend upon the nature of the drug-testing program, and may be limited in scope, complex, and sometime seek answers that go beyond reasonable scientific certainty. Metabolic disposition patterns should be understood for each drug class. The body of evidence, including what is known with certainty and what is not known, must be brought to bear during the interpretation process.

Oral fluid is a composite tissue consisting primarily of saliva, mixed with gingival crevicular fluid, buccal and mucosal transudates, cellular debris, bacteria, and residues of ingested products. Salivary glands are highly perfused, allowing rapid transference of drug in blood to salivary glands. Within minutes of parenteral drug administration, drug can appear in oral fluid.¹³ Transfer of drug and metabolites from blood to saliva occurs primarily by passive diffusion and is dependent upon numerous factors, including chemical properties of the drug, salivary pH, concentration of un-ionized drug (ionized drug does not passively diffuse across cellular membranes), drug–protein binding (only the free fraction can diffuse), and membrane characteristics. Because of the relative acidity of saliva compared to plasma, basic drugs (e.g., amphetamine and cocaine) are frequently found in higher concentrations than in plasma, yielding saliva/plasma ratios (s/p) greater than unity.¹³ Although the terms “saliva” and “oral fluid” are used somewhat interchangeably in scientific literature, *oral fluid* more accurately describes the biological characteristics of this matrix. Thus, oral fluid is the term used predominantly in this review.

Interpretation of oral fluid tests requires an understanding of the unique features of this biological matrix, chemical and physiological factors that affect drug transfer into oral fluid, analytical factors, kinetics of drug disposition, drug metabolic patterns, and potential risks of oral contamination and passive exposure. Clearly, oral fluid tests are most useful in detection of recent drug use. Drugs and metabolites can generally be detected for a period of several hours to several days following drug exposure.⁷ Drug concentrations in oral fluid are generally related to content in blood, but also may be present as residual drug in the oral cavity. The frequently observed high correspondence of drug concentrations in oral fluid to blood makes oral fluid an attractive matrix for use in detection of recent drug use and in interpretation of possible drug-induced behavioral effects.

A table is included for each drug that summarizes key chemical, metabolic, kinetic and analytic parameters for each drug. Following each table, general guidelines are offered, although they should not be considered absolute criteria. A list defining each parameter and the usefulness of factors influencing oral fluid test outcome follows:

- Drug/metabolite(s) in oral fluid and urine: predominant drug or metabolite(s) most often detected in oral fluid and urine following drug exposure.
- Fb: free drug fraction in blood not bound to plasma protein. Only free unionized drug can passively diffuse across biological membranes; hence, highly protein-bound drugs generally will be present in lower concentration in oral fluid than in plasma.
- Plasma/oral fluid $t_{1/2}$: period of time required for drug concentration in plasma or oral fluid to decrease by 50%. Drugs with longer half-lives generally can be detected for longer periods of time.
- Plasma: oral fluid correlation: relationship between drug concentrations in plasma and oral fluid. A high plasma: oral fluid correlation reflects the close relationship between plasma and oral fluid.
- s/p and s/b: saliva (oral fluid) to plasma or blood ratio. Saliva to plasma ratios greater than unity (>1) generally are observed for drugs whose molecular structures contain a basic nitrogen moiety and exhibit low plasma-protein binding. Basic drugs tend to accumulate in oral fluid in higher concentrations than in plasma because of the lower pH of saliva. Values of s/p or s/b reported in this review are actual measured values of drug in saliva (oral fluid), plasma, and whole blood.
- P and log P: partition coefficient or logarithm of the partition coefficient of a drug. These parameters express the relative distribution of drug between oil and water under specified conditions, for example, octanol/water at 37°C and pH 7.4. Drugs with higher P or log P are more lipophilic and generally distribute more rapidly and to a greater degree into bodily tissues and fluids.
- pKa: negative logarithm of equilibrium coefficient of neutral and charged forms of a compound. pKa is a constant for each drug. For basic compounds, those with higher pKa constants exhibit greater ionization in plasma (pH 7.4) than drugs with lower pKa constants. For acidic drugs, those with lower pKa constants will exhibit greater ionization in plasma (pH 7.4) than drugs with higher pKa constants. A drug's pKa affects the transfer of basic drugs from plasma to saliva in two ways. Only un-ionized drug will transfer across epithelial membranes, and the acidic nature of saliva allows accumulation of greater concentrations of basic drugs than neutral or acidic drugs.
- Screening test: initial laboratory test commonly employed to rapidly eliminate negative specimens and identify presumptively positive specimens. Most screening procedures are commercial immunoassay-based tests; administrative cutoff concentrations are utilized to distinguish between positive and negative specimens; drugs that do not react sufficiently in these assays may, by necessity, be tested by chromatographic methods.
- Confirmation test: laboratory test utilized to confirm the presence of a specific drug analyte(s) at or above an administrative cutoff concentration(s).
- Detection time (cutoff, ng/mL): typical duration of time a drug can be detected in a biological specimen at a specified ng/mL cutoff concentration. This parameter serves as a useful guideline to establish the probable time that drug use occurred prior to specimen collection. This parameter is frequently determined following administration of a single drug dose and may underestimate detection times following

multiple drug administrations or chronic drug usage. Detection times also are highly influenced by cutoff concentrations employed in the analytical test.

- Interpretation resources: cites key clinical studies and reports that were used in development of interpretational guidelines for oral fluid.
- Possible drug/metabolite sources: potential sources of drug, or drug-associated metabolite(s), which might result in a positive oral fluid or urine test.
- Biomarkers: drug-related metabolites and analytes that predict or signal, with a high degree of reliability, additional information for interpretation, for example, identification of anhydroecognine methyl ester indicates that cocaine has been administered by the smoking route. It should be noted that biomarkers are only useful, however, if it can be established that they were not present originally as contaminants of the administered drug or produced as artifacts during specimen storage and analysis. Of additional note, many of the biomarkers proposed in this review are based on urine studies and have not been established as biomarkers in oral fluid tests. Further, when biomarkers are present, they offer additional assurances of drug use, but their absence does not lessen the value of a confirmed test.

DRUG INTERPRETATION

Amphetamines

Amphetamine

Overview: Amphetamine is a sympathomimetic amine with central nervous stimulant activity (Table 1). The d-isomer (dextro-amphetamine) is three to four times more potent than the l-isomer (levo-amphetamine) as a stimulant. It is prescribed for treatment of attention-deficit hyperactivity disorder (ADHD) and narcolepsy. Amphetamine is available in immediate-release and sustained-release formulations in doses ranging from 3 to 30 mg. Some formulations, such as Adderall®, contain combinations of d- and l-isomers.

Amphetamine is excreted intact in urine and also as metabolites. Amphetamine metabolites are produced primarily by oxidative enzymes, leading to mostly inactive products. The amount of amphetamine excreted in urine is highly dependent upon urinary pH. Under acid conditions, as much as 57–66% of the dose may be excreted unchanged, whereas under alkaline conditions, the amount may decrease to 1–5%.¹⁴ Analytical methods are available for determining the enantiomeric forms of amphetamine and methamphetamine.¹⁵ The mean elimination half-life of d-amphetamine is slightly shorter than that of l-amphetamine.¹⁶ Amphetamine also is produced as a metabolite of methamphetamine and from a variety of pharmaceutical products (see *Interpretation*).

Amphetamine appears rapidly in oral fluid following administration and parallels plasma drug concentrations. Wan *et al.*¹⁶ evaluated the influence of systemic administration of sodium bicarbonate and ammonium chloride on the disposition of amphetamine in plasma and oral fluid. Although salivary pH was relatively constant with both treatments, the half-lives of d- and l-amphetamine were reduced considerably under acidic conditions.

- Positive test for amphetamine (no methamphetamine)
 - Interpretation: amphetamine use; must rule out possibility that amphetamine presence is from metabolism of another drug. Determination of d/l-isomer ratio will assist interpretation.¹⁷ L-amphetamine only (no l-methamphetamine) would not occur from use of nasal inhaler.
- Possible sources of amphetamine

- Prescription products containing amphetamine
- Illicit amphetamine
- Drugs that are metabolized to amphetamine (and methamphetamine) include: amfetaminil (amphetamine only); benzphetamine (d-isomers of amphetamine and methamphetamine); clobenzorex (d-amphetamine only); dimethylamphetamine (d-isomers of amphetamine and methamphetamine); ethylamphetamine (amphetamine only); famprofazone (d/l-isomers of amphetamine and methamphetamine); fencamine (d/l-isomers of amphetamine and methamphetamine); fenethylline (d/l-amphetamine only); fenproporex (d/l-amphetamine only); furfenorex (amphetamine and methamphetamine); mefenorex (amphetamine only); mesocarb (amphetamine only); prenylamine (d/l-amphetamine only); and selegiline (l-deprenyl; l-isomers of amphetamine and methamphetamine).^{17–19}
- At present, although no oral fluid or urine studies have been reported on passive amphetamine smoke exposure, the risk of a positive test from passive exposure does not appear likely.
- Biomarkers
 - The confirmed presence of oxidative metabolites of amphetamine such as *p*-hydroxyamphetamine, norephedrine, and *p*-hydroxynorephedrine in oral fluid would be useful to substantiate use.²⁰

Methamphetamine

Overview: Methamphetamine is a sympathomimetic amine with central nervous stimulant activity similar to amphetamine (Table 2). The d-isomer (dextro-methamphetamine) is prescribed for treatment of ADHD and for exogenous obesity. It is available as an immediate-release formulation containing 5 mg of methamphetamine hydrochloride. The usual effective dose is 20 to 25 mg daily. The l-isomer (levmetamfetamine; l-desoxyephedrine), marketed as a nasal inhaler decongestant product, is sold over the counter (OTC). The nasal inhaler typically contains 50 mg of levmetamfetamine. Illicit methamphetamine is widely available and abused. Methamphetamine is easily manufactured in clandestine laboratories and is the most prevalent synthetic drug manufactured in the United States. The synthetic route determines which isomeric form of methamphetamine is produced. Currently, the most common route yields the d-isomer, but older methods primarily yielded a racemic mixture.

Methamphetamine is abused by numerous routes including smoking, snorting, injection, and oral administration. The l-isomer of methamphetamine, levmetamfetamine contained in nasal inhalers, also can produce positive results for methamphetamine in urine.²¹ Methamphetamine is excreted intact in urine and also as metabolites following enzymatic oxidation and conjugation. Like amphetamine, the amount of methamphetamine excreted is highly dependent upon urinary pH. Amphetamine, a metabolite of methamphetamine, is excreted in urine in variable amounts. Kim *et al.*²² reported that the ratio of amphetamine to methamphetamine in urine increased over time from 0.13 to 0.36 following oral doses of 10 or 20 mg of d-methamphetamine hydrochloride. Cook *et al.*²³ reported a similar finding for subjects administered intravenous and smoked d-methamphetamine.

Methamphetamine and amphetamine appear rapidly in plasma and oral fluid following administration. The relative amounts of amphetamine to methamphetamine in plasma and oral fluid were reported to be approximately 21% and 24%, respectively.²⁴ Oral fluid methamphetamine concentrations were higher than plasma concentrations by approximately fourfold.

- Positive test for methamphetamine (no amphetamine)
 - Interpretation: methamphetamine use; must rule out possibility that methamphetamine presence is from metabolism of another drug or from use of over-the-counter nasal inhaler. Determination of d/l-isomer ratio will assist interpretation¹⁷
- Positive test for methamphetamine and amphetamine (methamphetamine > amphetamine)
 - Interpretation: methamphetamine use; must rule out possibility that methamphetamine and amphetamine presence is from metabolism of another drug or from use of OTC nasal inhaler. Determination of d/l-isomer ratio will assist interpretation¹⁷
- Positive test for methamphetamine and amphetamine (methamphetamine < amphetamine)
 - Interpretation: possible combined use of methamphetamine and amphetamine; must rule out possibility that presence is due to metabolism of other drugs. OTC nasal inhaler use would not account for high abundance of amphetamine. Determination of d/l-isomer ratio will assist interpretation¹⁷
- Possible sources of methamphetamine
 - Prescription products containing methamphetamine
 - Illicit methamphetamine
 - Drugs that may be metabolized to methamphetamine (and amphetamine): include: benzphetamine (d-isomers); dimethylamphetamine (d-isomers); famprofazone (d/l-isomers); fencamine (d/l-isomers); furfenorex; and selegiline (l-deprenyl; l-isomers)^{17–19}
 - Nasal inhaler (l-methamphetamine)
 - At present, although no oral fluid or urine studies have been reported on passive methamphetamine smoke exposure, the risk of a positive test from passive exposure does not appear likely
- Biomarkers
 - The confirmed presence of oxidative metabolites of methamphetamine such as *p*-hydroxymethamphetamine in oral fluid would be useful to substantiate use²⁵
 - The confirmed presence of amphetamine in oral fluid would be useful to substantiate methamphetamine use. DHHS has proposed that a positive confirmed test for methamphetamine be accompanied by the confirmed presence of amphetamine at the assay's limit of detection.¹

3,4-Methylenedioxymethamphetamine (MDMA)

Overview: MDMA is a synthetic, ring-substituted amphetamine derivative that has become popular as an illicit recreational drug (Table 3). MDMA is one of numerous “designer” drugs, often referred to as “club drugs,” because of induction of feelings of euphoria, energy, and a desire to socialize. MDMA street names include “ecstasy,” “XTC,” “E,” and “Adam.” “Ecstasy” may also be used to denote the group of ring-substituted illicit amphetamines. MDMA exerts multiple effects on neurotransmitter systems and may produce acute toxic

reactions such as tachycardia, hypertension, arrhythmia, panic attack, and psychosis.²⁶ Recreational doses are generally in the range of 75 to 150 mg. Illicit synthetic routes generally produce a racemic mixture of R- and S-isomers. The S(+) isomer of MDMA is considered to be responsible for psychostimulant and empathic effects and the R(−) isomer for its hallucinogenic properties.²⁷

MDMA is typically administered by the oral route and reaches maximal blood concentrations in approximately 2 h.²⁷ It is metabolized by multiple pathways, primarily involving *N*-demethylation and *O*-demethylenation. *N*-demethylation of MDMA yields 3,4-methylenedioxyamphetamine (MDA), an active metabolite exhibiting similar pharmacological properties as the parent drug. *O*-demethylenation of MDMA and MDA produces 3,4-dihydroxymethamphetamine (HHMA) and 3,4-dihydroxyamphetamine (HHA), respectively. Additional metabolites are formed by *O*-methylation of HHMA to 4-hydroxy-3-methoxymethamphetamine (HMMA) and of HHA to 4-hydroxy-3-methoxyamphetamine (HMA), deamination, and conjugation. Nonlinear pharmacokinetics of MDMA was observed in humans; small increases in recreational doses gave rise to disproportionate increases in MDMA plasma concentrations.²⁸ Fallon *et al.*²⁹ reported that the plasma half-life in humans of (R)-MDMA (5.8 ± 2.2 h) was significantly longer than that of (S)-MDMA (3.6 ± 0.9 h). Approximately 15% of the dose of MDMA is excreted in urine in 24 h as intact MDMA, 1.5% as MDA, 17.7% as HHMA, 22.7% as HMMA, and 1.3% as HMA.²⁷

Oral administration of 100 mg of MDMA to humans yielded peak oral fluid and plasma concentrations of MDMA at 1.5 h after drug intake.³⁰ Oral fluid concentrations of MDMA were an order of magnitude higher than in plasma. HMMA, the major metabolite of MDMA, was detected in oral fluid in trace amounts, and MDA was present at approximately 4–5% of MDMA. Oral fluid concentrations of MDMA were highly correlated with plasma MDMA. The high concentrations of MDMA in oral fluid relative to plasma were attributed to the high pKa of MDMA and low plasma–protein binding.

- Positive test for MDMA (no MDA)
 - Interpretation: illicit MDMA use
- Positive test for MDMA and MDA
 - MDMA $\gg$ MDA
 - Interpretation: illicit MDMA use; presence of MDA likely due to metabolism of MDMA to MDA
 - MDA $\geq$ MDMA
 - Interpretation: combined use of illicit MDMA and illicit MDA, or illicit MDMA contaminated with MDA
- Possible sources of MDMA
 - Illicit MDMA
- Biomarkers
 - The confirmed presence of MDA or HMMA in oral fluid would be useful to substantiate MDMA use.³⁰ It should be noted that MDA could be present either from metabolism of MDMA or use of MDA.

3,4-Methylenedioxyamphetamine (MDA)

Overview: MDA is a synthetic, ring-substituted amphetamine derivative available as an illicit recreational drug (Table 4). It appears to produce similar pharmacological effects as MDMA. MDA street names include “love drug” and “love pill.” Recreational doses of MDA are similar to MDMA and generally in the range of 75 to 150 mg. Like MDMA, MDA has a chiral center (R- and S-isomers), and illicit synthesis leads to production of the racemic mixture. MDA also serves as a precursor in the synthesis of MDMA and 3,4-methylenedioxy-*N*-ethylamphetamine (MDEA).

Although MDMA has been extensively studied in humans, there are few metabolic data on MDA. MDA is an active metabolite of MDMA and is produced by *O*-demethylenation (see MDMA). HHA and HMA are metabolites of MDA. A number of studies have characterized the kinetics of MDA (as a metabolite of MDMA),^{18,28,31} but there appears to be little information on MDA administered under controlled clinical settings.

MDA has been reported to appear in oral fluid following the administration of MDMA in concentrations representing approximately 4–5% of MDMA.³²

- Positive test for MDA (no MDMA)
 - Interpretation: illicit MDA use
- Possible sources of MDA
 - Illicit MDA
 - Metabolite of illicit MDMA
 - Metabolite of illicit MDEA
- Biomarkers
 - The confirmed presence of HHA and/or HMA in oral fluid would be useful to substantiate MDA use.²⁷

3,4-Methylenedioxyethylamphetamine (MDEA)

Overview: When an ethyl group is substituted for the methyl group of MDMA, the synthetic analogue MDEA, is formed (Table 5). Like MDMA and MDA, MDEA has a chiral center and exists as two isomers. The S(+)-isomer appears to be primarily responsible for its psychotropic effect (higher affinity for presynaptic 5-HT transporters), whereas the R(–)-isomer appears to mediate the hallucinogenic effects.³³ MDEA is referred to by street names such as “eve” and “intellect.” Recreational doses of MDEA are generally in the range of 60 mg to 175 mg.

MDEA is metabolized by *O*-demethylenation and by *N*-dealkylation of the ethyl-group. The major metabolite is formed by *O*-demethylenation to yield *N*-ethyl-4-hydroxy-3-methoxyamphetamine (HME); *N*-dealkylation leads to formation of the active metabolite MDA.³⁴

MDEA has been reported in oral fluid of recreational drug users in concentrations ranging from 332 to 3320 ng/mL³⁵ and suspected users in concentrations > 100 ng/mL.³²

- Positive test for MDEA (no MDA)
 - Interpretation: illicit MDEA use
- Positive test for MDEA and MDA

- MDEA $\gg$ MDA

- Interpretation: Illicit MDEA use, presence of MDA likely due to metabolism of MDEA to MDA

- MDA $\geq$ MDEA

- Interpretation: combined use of illicit MDEA and illicit MDA, or illicit MDEA contaminated with MDA

- Possible sources of MDEA

- Illicit MDEA

- Biomarkers

- The confirmed presence of MDA or HME in oral fluid would be useful to substantiate MDEA use.³⁴ It should be noted that MDA could be present either from use of MDA or metabolism of MDEA.

Barbiturates

Overview: Barbiturates are sedatives used for seizure disorders, induction of anesthesia, and management of increased intracranial pressure. Barbiturate actions range from the short-acting, fast-starting pentobarbital and secobarbital to the long-acting, slow-starting phenobarbital, amobarbital, and butobarbital. Depending on the dose, frequency, and duration of use, one can rapidly develop tolerance, physical dependence, and psychological dependence on barbiturates. With the development of tolerance, the margin of safety between the effective dose and the lethal dose becomes narrow. Because of the risks associated with barbiturate abuse, and because new and safer drugs such as the benzodiazepines are now available, barbiturates are less frequently prescribed than in the past. Nearly all barbiturates are structurally related to barbituric acid. Although over 2,000 derivatives of barbituric acid have been synthesized, only about a dozen are currently used. Barbiturates available in the United States include amobarbital, aprobarbital, butobarbital, mephobarbital, pentobarbital, phenobarbital, and secobarbital. One preparation contains a combination of amobarbital and secobarbital. Barbiturate abusers appear to prefer the short-acting (e.g., pentobarbital, secobarbital) and intermediate drugs (e.g., amobarbital), but all barbiturates have significant abuse liability properties.

When used as sedative/hypnotics, barbiturates are typically administered orally. Barbiturates are efficiently absorbed from the gastrointestinal tract and exhibit high bioavailability. Generally, barbiturates are metabolized in the liver by oxidation and conjugation prior to renal excretion.

Studies of barbiturate disposition in oral fluid have been somewhat limited. Because amobarbital is one of the more commonly abused barbiturates and characterized most thoroughly, it is selected as the model compound for interpretation (Table 6). The disposition of amobarbital in oral fluid and serum of human subjects has been reported following ingestion of 120 mg of amobarbital.^{36,37} Peak concentrations of amobarbital were observed simultaneously in oral fluid and saliva at approximately 1 h and exhibited similar elimination curves. Concentrations were lower in oral fluid than serum with an average ratio of 0.35.³⁶ Amobarbital was detectable in oral fluid for approximately 50 h.

Studies on the detection of other barbiturates in oral fluid also have been reported including pentobarbital,³⁷ hexobarbital,^{38,39} and phenobarbital.^{40–45}

- Positive test for amobarbital

- Interpretation: amobarbital use
- Possible sources of amobarbital
 - Prescription amobarbital
- Biomarkers
 - The confirmed presence of oxidative metabolites of amobarbital in oral fluid would be useful to substantiate use.

Benzodiazepines

Overview: Benzodiazepines are a large class of structurally related compounds with anxiolytic, sedative, hypnotic, antipsychotic, and antiepileptic effects. Over 40 different drugs have been marketed worldwide and approximately 14 different benzodiazepines are marketed in the United States. The benzodiazepines, as a class, are generally lipophilic drugs with low solubility in water and exhibit efficient absorption from the gastrointestinal tract, first-pass metabolism, and high plasma–protein binding (70–99%). Potencies vary widely over this class of drugs; for example, the usual dose of triazolam is 0.125 mg, whereas 50–100 mg of chlordiazepoxide is usually taken for relief of symptoms of acute alcoholism.

A number of benzodiazepines share sufficient structural similarity such that metabolic conversions from one compound to another may occur. For example, diazepam may be metabolically converted in the human body to temazepam (3-hydroxydiazepam), nordiazepam, and oxazepam. In addition to this complexity, medazepam and ketazolam may be metabolically converted to diazepam. Thus, interpretation of benzodiazepine tests requires a thorough knowledge of the metabolic profiles of benzodiazepines. A number of benzodiazepines contain unique structural substitutions and use distinct metabolic pathways.

Studies of benzodiazepine disposition in oral fluid have been somewhat limited. Because diazepam has been studied most thoroughly, it is selected as the model compound for interpretation (Table 7). The disposition of diazepam and its metabolites in oral fluid has been reported following a single oral dose,^{46–51} multiple daily doses,^{48,51} and chronic dosing.^{49,52} Following oral diazepam, concentrations in plasma and oral fluid peak at approximately 0.75 h.⁴⁷ Metabolites identified in oral fluid include 3-hydroxydiazepam, nordiazepam, and oxazepam.⁵¹ At steady state, a significant correlation was observed between diazepam and nordiazepam in oral fluid.⁵² The metabolite, nordiazepam, typically is found in higher concentration than diazepam in oral fluid at steady state with a ratio of 1.58 (nordiazepam/diazepam).⁵² A significant correlation also was reported for diazepam concentration in oral fluid and CSF.⁴⁹

Studies on the detection of other benzodiazepines in oral fluid also have been reported including chlordiazepoxide,⁵³ clorazepate,⁴⁹ flunitrazepam,⁵⁴ midazolam,⁵⁵ nitrazepam,^{56,57} and oxazepam.⁵¹

- Positive test for diazepam (other metabolites of diazepam may be present including nordiazepam, oxazepam, and 3-hydroxydiazepam)
 - Interpretation: diazepam use, but also possible combined use of diazepam with nordiazepam, oxazepam, or 3-hydroxydiazepam
- Possible sources of diazepam
 - Diazepam
 - Metabolite of medazepam

- Metabolite of ketazolam
- Biomarkers
 - The confirmed presence of oxidative metabolites of diazepam such as 3-hydroxydiazepam (temazepam), nordiazepam, oxazepam⁵¹ in oral fluid would be useful to substantiate use, but it should be noted that these drug/metabolites may arise from use of other benzodiazepines.

Cannabis (Marijuana, THC)

Overview: Delta-9-tetrahydrocannabinol (THC) is a naturally occurring psychoactive constituent of *Cannabis sativa* L. (marijuana or cannabis; Table 8). Cannabis is the most widely used illegal substance in the world. THC also is found in pharmaceutical preparations, for example, dronabinol, a light yellow resinous oil insoluble in water and formulated in sesame oil. Dronabinol capsules are supplied as round, soft gelatin capsules containing either 2.5, 5, or 10 mg dronabinol for oral administration for the treatment of anorexia associated with weight loss in patients with AIDS and for treatment of nausea and vomiting associated with cancer chemotherapy. THC also is found in small amounts in cannabis products sold commercially such as hemp seeds and hemp oil and may produce positive urine tests for cannabinoid metabolite.⁵⁸

The primary route of administration of cannabis is by smoking, but ingestion of cannabis products as foodstuffs is not uncommon. THC appears rapidly in plasma following the smoking of cannabis products.⁵⁹ Oral ingestion generally produces lower blood concentrations and delays in time-to-peak effects.^{60,61} The highly lipophilic nature of THC allows rapid tissue uptake with concomitant decreases in plasma. THC appears to be released slowly from tissue resulting in a prolonged half-life of THC and metabolites. THC is metabolized by hydroxylation to an active metabolite, 11-hydroxy-THC, which in turn, is oxidized to 11-nor-9-carboxy- Δ^9 -tetrahydrocannabinol (THCCOOH). THCCOOH is excreted in urine as the water-soluble glucuronic acid conjugate.

THC is found in oral fluid following smoked^{62,63} and oral ingestion⁶⁴ of cannabis. THCCOOH is also found in oral fluid at very low concentrations. Extremely high (typically >200 ng/mL), but declining levels of THC, have been reported immediately after smoking cannabis.^{62,63,65} Thereafter, THC appeared to decline in similar fashion to plasma concentrations.⁶⁵ On the basis of evidence to date, it appears that THC is present in oral fluid primarily as a result of deposition in the oral cavity, rather than from transfer from blood.⁶⁵ Following ingestion of hemp oil liquid containing THC and capsules of dronabinol, positive oral fluid tests for THC did not occur.⁶⁶ Early studies on passive inhalation of cannabis smoke indicated a potential risk for detection of low concentrations of THC in oral fluid for up to 30 min following exposure,⁶³ however, a more recent study in which methods were taken to eliminate contamination during specimen collection indicated that passive inhalation did not produce positive oral fluid tests.⁶²

- Positive test for THC
 - Interpretation: cannabis use, but must rule out possibility that presence is due to use of pharmaceutical THC (Sativex[®]). Ingestion of Marinol[®] and hemp seed oil does not produce positive oral fluid tests for THC.⁶⁶
- Possible sources of THC
 - Illicit cannabis products
 - Hempseed products (does not give positive THC test)

- Sativex
- Marinol (does not give positive THC oral fluid test)
- A positive THC test from passive cannabis smoke exposure does not appear to be feasible on the basis of recent studies⁶²
- Biomarkers
 - The confirmed presence of oxidative metabolites of THC such as 11-hydroxy-THC and THCCOOH in oral fluid would be useful to substantiate use.
 - The confirmed presence of conjugates of THC and 11-hydroxy-THC in oral fluid would be useful to substantiate use.⁶⁷
 - The use of 11-nor-delta-9-tetrahydrocannabivarin-9-carboxylic acid (THCV-COOH) has been proposed as a biomarker in urine to distinguish the use of synthetic THC (Marinol) from cannabis use.⁶⁸ THCV-COOH is an oxidative metabolite of delta-9-tetrahydrocannabivarin found naturally in cannabis, but not in synthetic THC. The confirmed presence of THCV-COOH in oral fluid would be useful to differentiate cannabis use from synthetic THC.

Cocaine

Overview: Cocaine is a local anesthetic and vasoconstrictor found in abundance in leaves of the coca plant (Table 9). Pharmaceutical preparations are used primarily for topical anesthesia of the upper respiratory tract. Illicit cocaine is broadly available in illicit markets in two main forms, cocaine hydrochloride (for intravenous and intranasal administration) and free-base cocaine (for smoking). Self-administration of cocaine produces stimulation and short-lived euphoria and is frequently followed by a desire for more drug.

Cocaine has a short half-life (approximately 1 h) and is rapidly hydrolyzed by hepatic esterases to benzoylecgonine (BZE) and ecognine methyl ester (EME). A variety of other metabolites of cocaine also have been identified.⁶⁹ When cocaine is administered in concert with ethanol, a transesterification product, cocaethylene, is formed in minor amounts and is metabolized in a similar manner as cocaine. Cocaine and its metabolites appear rapidly in oral fluid following all routes of administration.⁷⁰ High concentrations of cocaine and BZE in oral fluid are observed shortly after intranasal and smoked administration. Cocaine concentrations decrease rapidly within approximately 1 h; thereafter, oral fluid concentrations appear to decline in parallel with blood.⁷⁰

- Positive test for cocaine (no BZE)
 - Interpretation: very recent cocaine use (e.g., within 8 h)
- Positive tests for cocaine and BZE
 - Cocaine concentration > BZE concentration
 - Interpretation: cocaine use likely within 2–8 h
 - Cocaine concentration < BZE concentration
 - Interpretation: cocaine use likely within 12 h for occasional users
 - Interpretation: cocaine use likely within 48 h for daily users
- Positive test for BZE (no cocaine)

- Interpretation: cocaine use likely within 48 h for occasional users
- Interpretation: cocaine use likely within 48–96 days for daily users

- Possible sources of cocaine

- Pharmaceutical cocaine, for example, use of cocaine as an anesthetic in surgery
 - Illicit cocaine
 - Coca tea
 - At present, no studies on oral fluid testing have been reported with passive cocaine smoke exposure; however, the risk of a positive test from passive exposure does not appear likely on the basis of urine studies.⁷¹
- Biomarkers
 - The confirmed presence of metabolites of oxidative metabolites of cocaine such as norcocaine, benzoylecgonine, and other hydroxy-metabolites in oral fluid would be useful to substantiate use.
 - The presence of cocaethylene in oral fluid may indicate combined cocaine and ethanol use; however, cocaethylene also may be present as a contaminant of both pharmaceutical and illicit cocaine.
 - The presence of anhydroecgonine methyl ester⁷⁰ or ecgonidine⁷² would be indicative of smoked administration of cocaine.

Nicotine/Cotinine

Overview: Nicotine is the principal alkaloid that accounts for the widespread human use of tobacco products throughout the world. Tobacco products come in different forms including cigarettes, cigars, pipe tobacco, chewing tobacco, and smokeless tobacco (snuff). Almost 30% of the population of the United States are current users of tobacco products, the majority being cigarette smokers. Passive smoking also delivers nicotine to nonsmokers. Passive smoking is exposure to tobacco smoke that occurs when a nonsmoker is exposed to the sidestream smoke of a cigarette. Nicotine in high doses can be toxic, but serious direct toxicity is rare. The major health effect of nicotine is by mediating tobacco use, which results in millions of premature deaths yearly. A number of nicotine replacement products have been developed as smoking cessation medications including nicotine gum, nicotine patches, and nicotine sprays.

Nicotine is efficiently absorbed during use of tobacco products and nicotine replacement medications. It has a half-life in blood of approximately 2 h and is readily distributed to tissues, metabolized, and excreted in urine as nicotine and metabolites. Quantitatively, the most important metabolites of nicotine are cotinine and 3'-hydroxycotinine. The metabolite, cotinine, exhibits a considerably longer half-life of approximately 17 h.⁷³

Nicotine appears in oral fluid at peak concentrations within 2–5 min following nicotine infusion in humans.⁷⁴ Oral fluid/plasma ratios were >1 for 60–120 min after nicotine administration. Cotinine also appears rapidly in oral fluid and is higher in concentration, but parallel to serum concentrations.⁷⁵ The higher concentration and longer half-life of cotinine makes it the preferred marker in plasma, oral fluid, or urine for monitoring nicotine intake after passive and active smoking (Table 10).⁷⁶ Passive smokers usually have cotinine concentrations in oral fluid <5 ng/mL, but heavy passive exposure can result in concentrations ≥ 10 ng/mL.⁷⁷ Cotinine concentrations in oral fluid between 10–100 ng/mL are seen in infrequent smokers and concentrations >100 ng/mL are generally associated with regular active smoking.⁷⁷

Trans-3'-hydroxycotinine concentrations in oral fluid of light- and heavy-smoking pregnant women have been reported to range from 14.4–117.7 ng/mL and 38.3–184.4 ng/mL, respectively.⁷⁸ A ratio of 0.41 for trans-3'-hydroxycotinine/cotinine was most effective in differentiating light from heavy tobacco use.

- Positive test for cotinine
 - Cutoff concentrations for cotinine in oral fluid to distinguish environmental smoke exposure from smoking have been suggested, but overlap between groups occurs.⁷⁷
 - Cotinine (0–10 ng/mL)
 - Interpretation: passive tobacco smoke exposure
 - Cotinine (>10–100 ng/mL)
 - Interpretation: passive tobacco smoke exposure or light smoking
 - Cotinine (>100 ng/mL)
 - Interpretation: light to heavy smoking
- Possible sources of cotinine
 - Metabolite of nicotine-containing replacement medications, for example, nicotine gum, nicotine patch, nicotine nasal spray
 - Metabolite of nicotine in tobacco products
 - Metabolite of nicotine from environmental tobacco smoke exposure
 - Metabolite of nicotine present in some foods (insignificant amounts compared with environmental tobacco smoke exposure)⁷⁹
- Biomarkers
 - The confirmed presence of oxidative metabolites of cotinine such as trans-3'-hydroxycotinine and norcotinine in oral fluid would be useful to substantiate use.⁷⁸

Opioids

Heroin: Overview: Heroin is a diacetyl derivative of morphine prepared from opium for the illicit drug market (Table 11). Illicit heroin contains minor amounts of other alkaloids including codeine and acetylcodeine. Pharmaceutical grade heroin is prepared from pure morphine and is generally free from impurities. Pharmaceutical heroin is used in some European countries for therapeutic treatment of heroin addiction.⁸⁰

Heroin is most commonly administered by intravenous and other parenteral routes and also may be smoked. The greater lipophilicity of heroin and 6-acetylmorphine, as compared to morphine, allows rapid entry into the central nervous system, resulting in fast onset of euphoria and other pharmacological effects. Heroin has an extremely short half-life (minutes) and is rapidly converted to 6-acetylmorphine and morphine.⁸⁰

Heroin and 6-acetylmorphine appear in oral fluid within 2 min following administration.⁸¹ Drug and metabolite concentrations in oral fluid generally are similar to blood concentrations following intravenous administration, but may be substantially higher than blood following smoking. The elevated drug and metabolite concentrations following smoking are presumably

due to residual drug deposited in the oral cavity. Thirty to sixty minutes after smoked heroin, concentrations in oral fluid diminish considerably and begin to reflect blood concentrations.

- Positive test for heroin, 6-acetylmorphine and morphine
 - Interpretation: heroin use
- Positive test for 6-acetylmorphine and morphine
 - Interpretation: heroin use
- Positive test for 6-acetylmorphine (only)
 - Interpretation: heroin use; consistent with very recent use by smoked or snorted route
- Positive test for morphine (only)
 - Interpretation: heroin or morphine use; possible poppy seed ingestion within last hour
- Positive test for morphine and codeine
 - Codeine concentration $\gg$ morphine concentration
 - Interpretation: codeine use
- Morphine concentration $\geq$ codeine concentration
 - Interpretation:
 - Possible heroin or morphine use. Codeine presence may arise as impurity of heroin or secondary use in combination with morphine, but generally in low concentration.
 - Possible recent poppy seed ingestion within hour
- Possible sources of heroin
 - Pharmaceutical heroin
 - Illicit heroin
- Possible sources of 6-AM
 - Pharmaceutical heroin
 - Illicit heroin
- Possible sources of morphine
 - Pharmaceutical heroin
 - Illicit heroin
 - Morphine
 - Poppy seeds
 - Metabolism of codeine to morphine
- At present, although no oral fluid or urine studies have been reported on passive heroin smoke exposure, the risk of a positive test from passive exposure does not appear likely.
- Biomarkers

- The confirmed presence of 6-AM in oral fluid is indicative of heroin use.
- The confirmed presence of 6-acetylcodeine in oral fluid would be useful to differentiate illicit heroin use from pharmaceutical grade heroin.⁸²

Morphine: Overview: Morphine, like most therapeutic opioids, produces effects through interaction with μ opioid receptors (Table 12).⁸³ The pharmacological actions of morphine encompass a wide range of effects including analgesia, mood alteration, and drug-seeking behavior. Historically, opioids have been the mainstay of pain treatment and continue to be widely used for this purpose. Numerous morphine prescription medications for treatment of acute and chronic pain are available in immediate-release formulations for oral and parenteral administration. Controlled-release formulations are available for oral administration.

Pharmaceutical morphine preparations have significant abuse liability. Drug abusers prefer immediate-release formulations that can be administered by the oral, intranasal, parenteral, and smoked routes. Controlled-release formulations generally contain higher doses, but may be more difficult to administer by alternate routes. Instructions may be found on the Internet for tampering with morphine formulations to allow faster administration, higher doses, and conversion of morphine to heroin.⁸⁴

Following parenteral morphine administration, morphine appears rapidly in saliva. Cone¹³ reported an approximate 45-min delay in equilibration of morphine concentrations in saliva compared to plasma following intramuscular administration of 10- and 20-mg doses; thereafter, saliva concentrations paralleled plasma concentrations. Kopecky *et al.*⁸⁵ measured morphine in saliva and plasma of pediatric patients following parenteral administration, but failed to demonstrate significant correlation. Although morphine is rapidly metabolized by conjugation, only free morphine has been reported in saliva. Morphine has been detected in oral fluid following intravenous and smoked heroin administration⁸¹ and poppy seed ingestion,⁸⁶ but has not been detected following codeine administration.⁸⁷

Morphine is a metabolite of heroin,⁸⁸ codeine⁸⁸ and a natural component of poppy seeds.⁸⁶ Pholcodine, a synthetic derivative of morphine with codeine-like effects, also has been reported to be metabolized to morphine in minor amounts.^{89–91} Interpretation of oral fluid morphine results must take into account these multiple sources of morphine (e.g., heroin, codeine, or poppy seeds).

- Positive test for morphine (no other opioids present)
 - Interpretation: possible use of heroin or morphine or ingestion of poppy seed
 - Although 6-AM is frequently detected in oral fluid, it has a shorter half-life, and may not be present.
 - Poppy seed ingestion may result in low concentrations of morphine for up to 1 h after consumption.⁸⁶
 - Codeine use has not been reported to produce detectable levels of morphine in oral fluid.⁸⁷
 - Pholcodine use has been reported to result in low concentrations of morphine in urine,^{89,90} but not likely to be found in oral fluid in absence of high concentration of pholcodine.
- Positive tests for morphine and 6-AM
 - Interpretation: heroin use

- Positive tests for morphine and codeine
 - Interpretation: codeine concentration $\gg$ morphine concentration
 - Codeine use
 - Interpretation: morphine concentration $>$ codeine concentration
 - Heroin or combined morphine/codeine use
 - Codeine presence may arise as impurity of heroin or secondary use in combination with morphine
- Possible sources of morphine
 - Pharmaceutical heroin
 - Illicit heroin
 - Morphine
 - Poppy seeds⁸⁶
 - Codeine
 - Pholcodine^{89,90}
- Biomarkers
 - The confirmed presence of oxidative metabolites such as normorphine in oral fluid would be useful to substantiate use.⁹²

Codeine: Overview: Codeine is an analgesic and cough suppressant usually marketed as an oral preparation, frequently in combination with additional active ingredients such as acetaminophen, aspirin, caffeine, guaifenesin, and ibuprofen (Table 13). Prescription doses range from 15 to 60 mg. Recreational drug users prefer higher doses and may attempt various purification methods available on the Internet, for example, “cold water extraction,” to eliminate unwanted active components and excipients present in over-the-counter and prescription formulations.⁸⁴ Codeine appears to be abused primarily by the oral route.

Following oral administration of 60 and 120 mg, codeine appeared in oral fluid within an hour and reached maximum concentration in approximately 1.6–1.7 h.⁸⁷ Concentrations in oral fluid correlated significantly with plasma concentration and were three to four times higher in oral fluid than plasma. Codeine could be detected in oral fluid for approximately 21 and 7 h at cutoff concentrations of 2.5 and 40 ng/mL, respectively.⁸⁷ Following intramuscular codeine of 60 and 120 mg, codeine appeared rapidly in oral fluid and reached maximal concentrations in 0.5–0.75 h.⁹³

Codeine is metabolized by oxidation to morphine and norcodeine and by conjugation. Codeine is not a metabolite of morphine.⁸⁸ Only free codeine and norcodeine have been detected in oral fluid; morphine was not detected.⁸⁷ Codeine is known to be present in minor amounts in illicit heroin and poppy seeds. 6-Acetylcodeine, a derivative of codeine produced during heroin manufacture, was proposed as a possible urinary marker of illicit heroin use,⁸² and has been identified in oral fluid of opioid-dependent women.⁹⁴ Interpretation of oral fluid codeine results must take into account possible sources of codeine (e.g., heroin or poppy seeds).

- Positive test for codeine (no other opioid present)
 - Interpretation: codeine use
- Positive tests for codeine and morphine

- Codeine concentration $\gg$ morphine concentration
 - Interpretation: codeine use
- Morphine concentration $>$ codeine concentration
 - Interpretation
- Possible heroin or morphine use. Codeine presence may arise as impurity of heroin or secondary codeine use in combination with morphine.
- Possible recent poppy seed ingestion within an hour
- Possible sources of codeine
 - Codeine
 - Illicit heroin
 - Poppy seeds
 - Codeine is not a metabolite of morphine
- Biomarkers
 - The confirmed presence of oxidative metabolites such as norcodeine in oral fluid would be useful to substantiate use.⁸⁷

Hydromorphone: Overview: Hydromorphone (Dilaudid®) is a hydrogenated ketone derivative of morphine sold as an opioid analgesic for relief of pain (Table 14). It is available commercially in various immediate-release forms such as injectable, oral liquid, tablets, and suppositories. Doses range from 1 to 10 mg. Hydromorphone is approximately seven times more potent than morphine when injected intravenously.⁹⁵

Following oral administration, hydromorphone reaches maximal plasma levels in approximately 1 h, demonstrates an elimination half-life of approximately 4.1 h, and has an absolute bioavailability of 50–60%.^{95,96} Hydromorphone is metabolized primarily by conjugation and to a lesser extent by 6-keto reduction to α - and β -isomers of hydromorphol.⁹⁷ Evidence for the metabolic transformation of morphine to hydromorphone in small amounts in subjects chronically treated with high-dose morphine has been reported.⁹⁸

Hydromorphone was reported to appear in saliva rapidly following intravenous administration.⁹⁶ Initial saliva/plasma (s/p) ratios were lower during the distribution phase (up to approximately 40 min post drug administration) than the elimination phase.

- Positive test for hydromorphone (no hydrocodone/morphine)
 - Interpretation: hydromorphone use
- Positive test for hydromorphone and morphine
 - Hydromorphone $>$ morphine
 - Interpretation: hydromorphone and morphine use
 - Hydromorphone $\ll$ morphine
 - Interpretation: possible hydromorphone use; possible occurrence of hydromorphone as a minor metabolite of morphine⁹⁸
- Possible sources of hydromorphone
 - Hydromorphone

- Hydrocodone metabolism to hydromorphone in minor amounts
- Chronic morphine administration with minor metabolic conversion of morphine to hydromorphone⁹⁸
- Biomarkers
 - The confirmed presence of reduced metabolites such as hydromorphol in oral fluid would be useful to substantiate use.⁹⁷

Hydrocodone: Overview: Hydrocodone is a semisynthetic opioid analgesic and antitussive with multiple actions qualitatively similar to those of codeine (Table 15). Misuse of hydrocodone appears to be primarily by the oral route, likely because most preparations are compounded with other active ingredients. Other routes of administration include intranasal, smoked, and rectal administration. Pharmaceutical hydrocodone is supplied as tablets, syrup, suspension, and oral solution, and as an extended-release formulation. Most formulations are immediate-release and contain hydrocodone in doses ranging from 2.5 to 10 mg.

Following oral administration, hydrocodone reaches maximal serum concentrations in approximately 1 h and has an elimination half-life of approximately 4–6 h. Hydrocodone is metabolized by *O*-demethylation to hydromorphone by CYP2D6, a genetically polymorphic enzyme.⁹⁹ Hydromorphone is a potent analgesic and may be primarily responsible for hydrocodone's analgesic effects. Additional hydrocodone metabolic pathways include *N*-demethylation, keto-reduction, and conjugation.¹⁰⁰ Evidence for human metabolic transformation in small amounts of codeine¹⁰¹ and dihydrocodeine¹⁰² to hydrocodone has been reported.

Although commercial testing services are available in the United States for hydrocodone in oral fluid, there appears to be little information on the time course of appearance and disappearance of this drug in oral fluid.

- Positive test for hydrocodone (no hydromorphone/codeine)
 - Interpretation: hydrocodone use
- Positive test for hydrocodone and hydromorphone
 - Hydrocodone > hydromorphone
 - Interpretation: hydrocodone use; presence of hydromorphone likely due to metabolism of hydrocodone to hydromorphone
 - Hydrocodone < hydromorphone
 - Interpretation: likely combined use of hydrocodone and hydromorphone, but could occur at low concentrations toward end of excretion following hydrocodone use¹⁰³
- Positive test for hydrocodone and codeine
 - Hydrocodone ≥ codeine
 - Interpretation: likely combined use of hydrocodone and codeine
 - Hydrocodone ≪ codeine
 - Interpretation: possible hydrocodone use; possible occurrence of hydrocodone as a minor metabolite of codeine¹⁰¹
- Possible sources of hydrocodone

- Hydrocodone
- Metabolite of codeine in minor amounts; but would occur only when codeine was present in very high concentration¹⁰¹
- Metabolite of dihydrocodeine in minor amounts; but would occur only when dihydrocodeine was present in very high concentration¹⁰²
- Hydrocodone is not a metabolite of hydromorphone
- Biomarkers
 - The confirmed presence of oxidative metabolites such as norhydrocodone and hydromorphone in oral fluid would be useful to substantiate use.¹⁰⁰
 - The confirmed presence of reduced metabolites such as hydrocodol in oral fluid would be useful to substantiate use.¹⁰⁰

Oxymorphone: Overview: Oxymorphone is a potent semisynthetic opioid substitute for morphine (Table 16). The approximate potency of oxymorphone is some 10 times that of morphine following parenteral administration.¹⁰⁴ Oxymorphone is available as an injection and as a suppository for relief of moderate-to-severe pain. Oxymorphone is available as an injection in concentrations of 1–1.5 mg/mL and as a 5 mg suppository.

Oral oxymorphone is approximately one-sixth as potent as injectable oxymorphone.¹⁰⁵ It is metabolized primarily by conjugation and to a lesser extent by 6-keto-reduction to oxymorphol. Oxymorphol has been shown in animal studies to have analgesic activity.¹⁰⁶ Following a 10-mg oral dose, approximately 46% of the dose was reported to be excreted in urine as free and conjugated oxymorphone.¹⁰⁷ 6-Keto-reduced metabolites accounted for an additional 2.7% of the dose.

Oral fluid testing for oxymorphone is quite feasible, but there appears to be no information currently available on the time course of appearance and disappearance of this drug in oral fluid.

- Positive test for oxymorphone (no oxycodone)
 - Interpretation: oxymorphone use
- Possible sources of oxymorphone
 - Oxymorphone
 - Oxycodone metabolism to oxymorphone in minor amounts
- Biomarkers
 - The confirmed presence of oxidative metabolites such as noroxymorphone in oral fluid would be useful to substantiate use.
 - The confirmed presence of reduced metabolites such as oxymorphol in oral fluid would be useful to substantiate use.¹⁰⁷

Oxycodone: Overview: Oxycodone is an opioid analgesic supplied as tablets, capsules, and oral solution (Table 17). It is available primarily as the hydrochloride salt with some formulations containing a combination of oxycodone hydrochloride and oxycodone terephthalate. Some formulations also contain aspirin or acetaminophen. Immediate-release formulations contain oxycodone doses ranging from 2.5 to 30 mg; a controlled-release formulation contains from 10 to 160 mg.

Oxycodone is effective orally and has a bioavailability of 50 to 90%.¹⁰⁸ It is metabolized by *O*-demethylation to oxymorphone, by *N*-demethylation to noroxycodone, and to minor metabolites by 6-keto-reduction.¹⁰⁹ CYP2D6 is the enzyme responsible for conversion of oxycodone to oxymorphone, a metabolite that is more potent than the parent drug. Although the analgesic potency of oxymorphone is higher, it is unclear how much activity is contributed to the actions of oxycodone by this metabolite. The analgesic potency of noroxycodone appears to be lower than that of oxycodone.¹⁰⁴

Oral fluid testing for oxycodone is quite feasible, but little information is currently available on the time course of appearance and disappearance of this drug in oral fluid.

- Positive test for oxycodone (no oxymorphone)
 - Interpretation: oxycodone use
- Positive test for oxycodone and oxymorphone
 - Oxycodone > oxymorphone
 - Interpretation: oxycodone use; presence of oxymorphone likely due to metabolism of oxycodone to oxymorphone
 - Oxycodone < oxymorphone
 - Interpretation: likely combined use of oxycodone and oxymorphone, but could occur at low concentrations toward end of excretion following oxycodone use¹⁰³
- Possible sources of oxycodone
 - Oxycodone
 - Oxycodone is not a metabolite of oxymorphone
- Biomarkers
 - The confirmed presence of oxidative metabolites such as noroxycodone and oxymorphone in oral fluid would be useful to substantiate use.¹⁰⁹
 - The confirmed presence of reduced metabolites such as oxycodol in oral fluid would be useful to substantiate use.¹⁰⁹

Methadone: Overview: Methadone is a long-acting opioid μ -receptor agonist with pharmacological properties similar to those of morphine (Table 18). Methadone is available as an oral concentrate and dispensable tablets for relief of chronic pain, treatment of opioid abstinence syndromes, and treatment of heroin dependence.

Methadone undergoes extensive metabolism in the liver to form cyclic metabolites, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) and 2-ethyl-5-methyl-3,3-diphenylpyrrolidine (EMDP), and other minor metabolites. The amount of methadone excreted in urine is increased when urine is acidified.¹¹⁰ EDDP is excreted in urine in approximately equal amounts to methadone, but with apparent less variability. Thus, there may be advantages in testing for EDDP when monitoring patient compliance.¹¹¹

Methadone and EDDP appear rapidly in oral fluid and correlate with plasma concentrations.¹¹² Oral fluid pH appears to be a factor in determining concentration of methadone in oral fluid, but is less important for EDDP detection.¹¹²

- Positive test for methadone (no EDDP)

- Interpretation: methadone use within 24–48 h or possible methadone doping
- Positive tests for methadone and EDDP
 - Interpretation: methadone use within 24–48 h
- Possible sources of methadone
 - Methadone
- Biomarkers
 - The confirmed presence of oxidative metabolites such as EDDP and EMDP in oral fluid would be useful to substantiate use.¹¹²

Buprenorphine: Overview: Buprenorphine is a thebaine-derived synthetic opioid whose actions are limited by a ceiling effect (Table 19). It is available in injectable form as an analgesic (0.3 mg) and as sublingual tablets (2 mg and 8 mg) for treatment of opioid dependence. One type of sublingual tablet contains only buprenorphine hydrochloride and the second contains buprenorphine hydrochloride in combination with naloxone hydrochloride in a ratio of 4:1 buprenorphine:naloxone (ratio of free bases).

Following sublingual administration, buprenorphine reaches maximal plasma concentrations in 1.3–1.6 h.¹¹³ The bioavailability of sublingual buprenorphine (ethanol solution) ranges from 28 to 36%. Sublingual bioavailability of buprenorphine tablets (relative to ethanolic solution) is 49% ± 25%.¹¹⁴ Buprenorphine is metabolized by conjugation and *N*-demethylation, and is excreted in urine primarily as conjugated metabolites.¹¹⁵

Cone reported measurement of buprenorphine in saliva following intramuscular and sublingual administration of single doses of buprenorphine.¹³ Drug concentrations in saliva were substantially lower than plasma at all times following intramuscular administration and were substantially higher following sublingual administration. The low s/p ratio following intramuscular administration is likely due to the high fraction of drug that is protein-bound in plasma. The high s/p observed following sublingual administration was attributed to an oral mucosal drug depot.¹¹⁶ Close correspondence in saliva and plasma buprenorphine concentrations was observed for subjects administered sublingual buprenorphine daily or on an every-other-day basis.¹³

- Positive test for buprenorphine
 - Interpretation: buprenorphine use
- Positive tests for buprenorphine and norbuprenorphine
 - Buprenorphine >> norbuprenorphine
 - Interpretation: acute buprenorphine use (suggested from plasma data)¹¹⁷
 - Buprenorphine ≤ norbuprenorphine
 - Interpretation: chronic buprenorphine use (suggested from plasma data)¹¹⁸
- Possible sources of buprenorphine
 - Buprenorphine
- Biomarkers

- The confirmed presence of oxidative metabolites such as norbuprenorphine in oral fluid would be useful to substantiate use.¹¹⁵

Phencyclidine (PCP)

Overview—PCP is a dissociative anesthetic reported in the 1950s to be effective in surgery without respiratory depression, but also produced unpleasant side effects leading to its discontinuation of clinical use (Table 20). It was used in veterinary medicine, but withdrawn in 1978, leaving only illicit synthesis as a source of the drug. PCP is illicitly marketed under a number of street names including Angel Dust, Supergrass, Killer Weed, Embalming Fluid, and Rocket Fuel. Among PCP's least desirable side effects are delirium, visual disturbances, and hallucinations and, occasionally, violence.

PCP is well absorbed and readily penetrates the central nervous system after intravenous, smoked, intranasal, oral, and percutaneous administration, and it can be passively absorbed from the environment.¹¹⁹ The plasma elimination half-life is 7–50 h (mean: 17.6 h) in normal volunteers.¹²⁰ PCP is excreted in urine in small amounts (approximately 10% of dose) along with a number of polar metabolites.¹²⁰ Acidification of urine by ingestion of ammonium chloride¹²¹ or by infusion of 0.1 N HCl¹²² increased PCP excretion in urine. Hydroxy-metabolites of PCP excreted in urine include 4-phenyl-4-(1-piperidiny)-cyclohexanol (PPC) and 1-(1-phenylcyclohexyl)-4-hydroxypiperidine (PCHP).¹²⁰

PCP has been measured by radioimmunoassay in oral fluid and serum specimens of emergency room patients suspected of PCP intoxication.¹²³ Of 74 patients with positive oral fluid tests, 73 were accompanied by positive serum result. Only two specimens were positive for serum and negative for oral fluid. Concentrations of PCP in oral fluid and plasma ranged from 2–600 ng/mL and 5–400 ng/mL, respectively. PCP also has been measured in oral fluid of humans following administration of small doses of radiolabeled drug.^{120,121,124} The radioactivity in oral fluid was principally (>90%) parent drug. Acidification or alkalinization of urine, respectively, increased and decreased urinary excretion of PCP but did not significantly alter concentration in oral fluid.

Interpretation of Oral Fluid PCP Tests

- Positive test for PCP
 - Interpretation: PCP use
- Possible sources of PCP
 - Pharmaceutical PCP
 - Illicit PCP
- Biomarkers
 - The confirmed presence of oxidative metabolites such as PPC and PCHP in oral fluid would be useful to substantiate use.¹²⁰

LIMITATIONS

Interpretation of biological tests for drugs of abuse will always be limited by available scientific evidence. At present, much of the available knowledge on oral fluid and urine tests has been generated from single- or multiple-dosing studies, but there is limited information in chronic users. Significant ethical issues exist in the study of many licit and illicit drugs that preclude their study under conditions that simulate “real-world use,” and relevant information may never be available. There also are significant cost and resource limitations for clinical studies that limit the number of drug studies that can be performed. Despite a substantial number of clinical

studies on drug disposition in oral fluid, many psychoactive drugs have not been studied. Many benzodiazepines and barbiturates and some opioid products have received limited or no evaluation in oral fluid; controlled dosing studies of hallucinogens in humans are virtually nonexistent.

Collection of oral fluid is an important process that deserves comment in the context of limitations to interpretation. The dynamic nature of oral fluid, especially pH, can substantially affect drug concentrations of basic drugs. For example, Kato *et al.*¹²⁵ showed that oral fluid collected from cocaine users under non-stimulated conditions produced substantially higher drug concentrations in oral fluid than under stimulated conditions. A similar finding has been reported for cotinine.¹²⁶ Collection of oral fluid with an absorptive device further introduces issues of drug/metabolite recovery. If drug/metabolite is not fully recoverable from the collection device, concentrations in oral fluid will be lower relative to neat oral fluid. If so, cutoff concentrations for oral fluid may, by necessity, be lower than for neat oral fluid. Obviously, comparison of oral fluid studies across different collection conditions is problematic if drug recovery is not equivalent.

Aside from collection, many other factors that may affect oral fluid test outcomes and interpretation have not been studied. Do adulterants exist that can be safely placed in the mouth and negate screening tests, thus producing false negative results? Observed collection, coupled with a waiting period, would likely be an effective procedure to overcome the risk of adulteration, but this remains to be clearly established. Does passive exposure to drug smoke result in positive oral fluid tests? Studies on passive inhalation of cannabis smoke indicate that the risk of a positive from exposure is equivalent to or less than that for urine testing.⁶² However, there is virtually no information on the risk of passive inhalation with heroin, methamphetamine, and PCP. Would passive exposure to these drugs result in positive tests in oral fluid? Experience in passive exposure studies with cannabis and cocaine suggests that passive exposure to other drugs is highly unlikely to produce positive oral fluid tests. Also, it should be noted that the limitation in information on the risk of passive inhalation for many drugs extends to urine testing as well.

Overall, it is clear that interpretation of oral fluid tests should be limited to available scientific knowledge. How oral fluid tests perform under many different conditions is not available, nor is it available for other biological matrices, for example, urine, sweat, and hair. It can be confidently predicted that scientific studies can never address all questions that may arise regarding how drug exposure affects test outcome. As always, science is an evolving process building upon prior knowledge that sometimes strikes out in new directions. Use of oral fluid as a test matrix is a relatively new science showing exceptional promise for detection of recent drug use. Informed interpretation of results requires a broad understanding of the unique characteristics of oral fluid.

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FIGURE 1.
Schematic of oral fluid drug testing and interpretation of results.

TABLE 1

Summary of chemical, metabolic, kinetic, and analytic factors important in interpretation of oral fluid tests for amphetamine

Factor	Amphetamine information
Drug/metabolite(s) in oral fluid	Amphetamine ¹⁶
Drug/metabolite(s) in urine	Amphetamine; <i>p</i> -hydroxy-amphetamine; norephedrine; <i>p</i> -hydroxynorephedrine ²⁰
Amphetamine Fb	16% (similar for d- and l-isomers) ¹⁶
Amphetamine plasma t _{1/2}	d-Amphetamine (acidic urine): 6.8 h d-amphetamine (alkaline urine) 17.0 h l-amphetamine (acid urine): 7.7 h l-amphetamine (alkaline urine) 23.7 h ¹⁶
Amphetamine oral fluid t _{1/2}	d-Amphetamine (acidic urine): 6.8 h d-amphetamine (alkaline urine) 17.2 h l-amphetamine (acidic urine): 8.5 h l-amphetamine (alkaline urine) 24.6 h ¹⁶
Amphetamine plasma: oral fluid correlation	Proportional to plasma in postabsorptive phase ¹⁶
Amphetamine s/p	2.76 (postabsorptive phase) ¹⁶
Amphetamine log P (HPLC)	0.82 ¹²⁷
Amphetamine pK _a	10 ¹⁶
Amphetamine screening test	Amphetamines
Amphetamine confirmation test	Amphetamine
Amphetamine detection time in oral fluid [cutoff, ng/mL]	Amphetamine GC, [10]: 20–50 h ¹⁶
Amphetamine detection time in urine [cutoff, ng/mL]	Single dose: EIA [1000] 24–72 h ^{7,128} ; chronic: EIA [300]: 9 days; EIA [1000]: 9 days ¹²⁹
Amphetamine oral fluid interpretation resources ¹⁶	—

HPLC=high-performance liquid chromatography; GC=gas chromatography; EIA=enzyme immunoassay.

TABLE 2

Summary of chemical, metabolic, kinetic, and analytic factors important in interpretation of oral fluid tests for methamphetamine

Factor	Methamphetamine information
Drug/metabolite(s) in oral fluid	Methamphetamine; amphetamine ²⁴
Drug/metabolite(s) in urine	Methamphetamine; amphetamine, <i>p</i> -hydroxy-methamphetamine ²⁵
Methamphetamine Fb	10–20% ¹³⁰
Methamphetamine plasma t _{1/2}	9.3–11.1 h ²⁴ ; 8.3–18.2 h ²³ ; 10.1 h ¹³¹
Methamphetamine oral fluid t _{1/2}	8.1–11.1 h ²⁴
Methamphetamine plasma: oral fluid correlation	$r^2 = 0.22$ ²⁴ ; $r^2 = 0.50$ ¹³¹
Methamphetamine s/p	Oral: 2 ²⁴ ; 7.76 ¹³¹ ; IV: 6 ²³
Methamphetamine log P (HPLC)	0.86 ¹²⁷
Methamphetamine pK _a	10.1 ²⁴
Methamphetamine screening test	Amphetamines EIA
Methamphetamine confirmation test	Methamphetamine; amphetamine
Methamphetamine/metabolite detection time in oral fluid [cutoff, ng/mL]	Single dose X4, methamphetamine: GC-MS [2.5]: 6–76 h; methamphetamine/amphetamine: GC-MS [50/2.5]: 24 h ²⁴
Methamphetamine detection time in urine [cutoff, ng/mL]	Single dose X4, methamphetamine: GC-MS [250]: 31–96 h; methamphetamine/amphetamine: GC-MS [250/100]: 25–96 h; me- thamphetamine/amphetamine: GC-MS [500/200]: 22–92 h ¹³²
Methamphetamine oral fluid interpretation resources ^{23,24,131}	

HPLC=high-performance liquid chromatography; GC-MS=gas chromatography-mass spectrometry.

TABLE 3

Summary of chemical, metabolic, kinetic, and analytic factors important in interpretation of oral fluid tests for MDMA

Factor	MDMA information
Drug/metabolite(s) in oral fluid	MDMA; MDA; HMMA ³⁰
Drug/metabolite(s) in urine	MDMA; MDA; HHMA; HMMA; HMA ²⁷
MDMA Fb	34–40% ¹³³
MDMA plasma t _{1/2}	8–9 h ²⁷ ; 7.2 h ³⁰
MDMA oral fluid t _{1/2}	5.6 h ³⁰
MDMA plasma: oral fluid correlation	0.81 ³⁰
MDMA s/p	6.4–18.1 ³⁰ ; 0.8–22.4 ³⁵
MDMA log P (octanol/water, 37°C, pH 7.4)	1.68 ¹³⁴
MDMA pK _a	10.4 ¹³³
MDMA screening test	Methamphetamine/MDMA
MDMA confirmation test	MDMA; MDA
MDMA/metabolite detection time in oral fluid [cutoff, ng/mL]	MDMA: GC-MS [LOD = 5.7]: 24 h; MDA: GC-MS [LOD = 1]: 24 h ³⁰
MDMA detection time in urine [cutoff, ng/mL]	MDMA/HMMA, GC-MS [20 ng/mL]: 48 h ⁷
MDMA oral fluid interpretation resources ^{30,31,35}	—

MDMA=3,4-methylenedioxymethamphetamine; MDA=3,4-methylenedioxyamphetamine; HHMA=3,4-dihydroxymethamphetamine; HMMA=4-hydroxy-3-methoxymethamphetamine; HMA=4-hydroxy-3-methoxyamphetamine; GC-MS=gas chromatography-mass spectrometry; LOD = limit of detection.

TABLE 4

Summary of chemical, metabolic, kinetic, and analytic factors important in interpretation of oral fluid tests for MDA

Factor	MDA information
Drug/metabolite(s) in oral fluid	MDA ³⁰
Drug/metabolite(s) in urine	MDA; HHA; HMA ²⁷
MDA Fb	34–40% ¹³³
MDA plasma t _{1/2}	24.9 h (metabolite of MDMA) ²⁷
MDA oral fluid t _{1/2}	MDA (MDMA dosed): 5.6–37.3 h ²⁸ ; MDA (MDEA administration): 3.4 h ³³
MDA plasma: oral fluid correlation	Not available
MDA s/p	Not available
MDA log P (octanol/water, 37°C, pH 7.4)	1.38 ¹³⁴
MDA pK _a	10.0 ¹³³
MDA screening test	Amphetamines/MDA
MDA confirmation test	MDA
MDA detection time in oral fluid [cutoff, ng/mL]	Not available
MDA detection time in urine [cutoff, ng/mL]	Not available
MDA oral fluid interpretation resources ³⁰	—

MDA=3,4-methylenedioxyamphetamine; HMA=4-hydroxy-3-methoxyamphetamine; HHA= 3,4-dihydroxyamphetamine.

TABLE 5

Summary of chemical, metabolic, kinetic, and analytic factors important in interpretation of oral fluid tests for MDEA

Factor	MDEA information
Drug/metabolite(s) in oral fluid	MDEA; MDA
Drug/metabolite(s) in urine	MDEA; MDA; HME ³⁴
MDEA Fb	Not available
MDEA plasma t _{1/2}	(R)-MDEA: 7.5 h; (S)-MDEA: 4.2 h ¹³⁵
MDEA oral fluid t _{1/2}	Not available
MDEA plasma: oral fluid correlation	Not available
MDEA s/p	Not available
MDEA log P (octanol/water, 37°C, pH 7.4)	Not available
MDEA pK _a	Not available
MDEA screening test	Amphetamine/MDEA
MDEA confirmation test	MDEA; MDA
MDEA detection time in oral fluid [cut-off, ng/mL]	Not available
MDEA detection time in urine [cut-off, ng/mL]	MDEA, FPIA [300]: 33–62 h; MDEA, GC-MS [5]: 33–62 h; MDA, GC-MS [5]: 32–36 h; HME, GC-MS [10]: 7–8 days ¹³⁶
MDEA oral fluid interpretation resources	—

MDEA=3,4-methylenedioxyethylamphetamine; MDA=3,4-methylenedioxyamphetamine; HME=*N*-ethyl-4-hydroxy-3-methoxyamphetamine; FPIA=fluorescent polarization immunoassay; GC-MS=gas chromatography-mass spectrometry.

TABLE 6

Summary of chemical, metabolic, kinetic, and analytic factors important in interpretation of oral fluid tests for amobarbital

Factor	Amobarbital information
Drug/metabolite(s) in oral fluid	Amobarbital ³⁶
Drug/metabolite(s) in urine	Amobarbital; 3'-hydroxyamobarbital; <i>N</i> -glucosyl amobarbital; 3'-carboxyamobarbital ¹³⁰
Amobarbital Fb	58% ³⁶
Amobarbital serum t _{1/2}	20.6 h ³⁶
Amobarbital oral fluid t _{1/2}	20.0 h ³⁶
Amobarbital plasma: oral fluid correlation	$r = 0.96$ ³⁶
Amobarbital s/p	0.35 ³⁶
Amobarbital log P (octanol/water, 37°C, pH 7.4)	2.07 [*]
Amobarbital pK _a	7.95 ³⁶
Amobarbital screening test	Barbiturates
Amobarbital confirmation test	Amobarbital
Amobarbital detection time in oral fluid [cutoff, ng/mL]	Amobarbital: GC [100]: 50 h ³⁶
Amobarbital detection time in urine [cutoff, ng/mL]	3'-Hydroxyamobarbital: GC [NR]: 5–6 days ¹³⁷
Amobarbital oral fluid interpretation resources ^{36,37}	—

GC=gas chromatography; NR=not reported.

* Source: Internet: Amobarbital: <http://chrom.tutms.tut.ac.jp/JINNO/DRUGDATA/22amobarbital.html> (accessed September 29, 2006).

TABLE 7

Summary of chemical, metabolic, kinetic, and analytic factors important in interpretation of oral fluid tests for diazepam

Factor	Diazepam information
Drug/metabolite(s) in oral fluid	Diazepam; 3-hydroxydiazepam (temazepam); nordiazepam; oxazepam ⁵¹
Drug/metabolite(s) in urine	Diazepam; nordiazepam; oxazepam conjugates ⁵¹
Diazepam Fb	96–98% ⁴⁷
Diazepam plasma t _{1/2}	21–37 h ¹³⁸
Diazepam oral fluid t _{1/2}	Not available
Diazepam plasma: oral fluid correlation	$r = 0.97^{47,48}$
Diazepam s/p	0.035 ⁴⁷
Diazepam log P (octanol/water)	2.99 ^a
Diazepam pK _a	3.3 ⁵²
Diazepam screening test	Benzodiazepines
Diazepam confirmation test	Diazepam; nordiazepam; oxazepam
Diazepam detection time in oral fluid [cutoff, ng/mL]	Diazepam GC [NR]: <5–50 h ³
Diazepam detection time in urine [cutoff, ng/mL]	Diazepam, EMIT [500]: 2–7 days ¹³⁹
Diazepam oral fluid interpretation resources ^{46–52,140,141}	—

GC=gas chromatography; NR=not reported; EMIT=enzyme multiplied immunoassay technique.

^a Source: National Toxicology Program, <http://ntp.niehs.nih.gov/index.cfm?objectid=7182FF48-BDB7-CEBA-F8980E5DD01A1E2D> (accessed September 27, 2006).

TABLE 8

Summary of chemical, metabolic, kinetic, and analytic factors important in interpretation of oral fluid tests for THC

Factor	THC information
Drug/metabolite(s) in oral fluid	THC; THCCOOH (minor) ^{62,65}
Drug/metabolite(s) in urine	THCCOOH; multiple minor metabolites; conjugates ¹⁴²
THC Fb	97% ¹⁴³
THC plasma t _{1/2}	THC: 0.75 h ⁶⁵ ; THC: (multiphasic): >20 h ^{144,145} ; THCCOOH: 5–6 days ¹⁴⁶
THC oral fluid t _{1/2}	0.8 h ⁶⁵
THC plasma: oral fluid correlation	High correlation ⁶⁵
THC s/p	1.18 (range 0.5–2.2) h ⁶⁵
THC log P (octanol/water)	6.97 ^a
THC pK _a	10.6 ¹⁴³
Cannabis screening test	Cannabinoids
Cannabis confirmation test	THC
THC detection time in oral fluid [cutoff, ng/mL]	Single doses, THC: RIA [1]: 2.0–24.0 h ⁶⁵
THCCOOH detection time in urine [cutoff, ng/mL]	Single dose: cannabinoid metabolites: EMIT [20]: 9.3–78.4 h ⁶⁵ ; cannabinoid metabolites: EMIT [50]: 6.4–54.0 h; THCCOOH: GC-MS [15]: 8.0–122.3 h ¹⁴⁷ ; chronic users: cannabinoid metabolites: EMIT [20]: up to 67 days ¹⁴⁸
THC oral fluid interpretation resources ^{62–65,149,150}	—

THC=delta-9-tetrahydrocannabinol; THCCOOH=11-nor-9-carboxy-delta-9-tetrahydrocannabinol; RIA=radioimmunoassay; EMIT=enzyme multiplied immunoassay technique; GC-MS=gas chromatography-mass spectrometry.

^aSource: National Toxicology Program, <http://ntp.niehs.nih.gov/index.cfm?objectid=7182FF48-BDB7-CEBA-F8980E5DD01A1E2D> (accessed September 27, 2006).

TABLE 9

Summary of chemical, metabolic, kinetic, and analytic factors important in interpretation of oral fluid tests for cocaine

Factor	Cocaine information
Drug/metabolite(s) in oral fluid	Cocaine; BZE; EME ⁷⁰
Drug/metabolite(s) in urine	BZE; EME; norcocaine; benzoylecgonine; hydroxylated metabolites ⁶⁹
Cocaine Fb	Cocaine: negligible binding; BZE: negligible binding ¹⁵¹
Cocaine Plasma t _{1/2}	Cocaine: 1.4–1.8 h; BZE: 5.4–7.6 h; EME: 2.7–5.6 h ¹⁵²
Oral fluid t _{1/2}	Cocaine: 1–2 h; BZE: 4.8–9.2 h; EME: 3.9–5.4 h ¹⁵²
Cocaine plasma:oral fluid correlation	$r = 0.89$ ¹⁵³
Cocaine s/p	0.4–9.7 ¹⁵²
Cocaine log P (octanol/water, 37°C, pH 7.4)	0.55 ¹⁵⁴
Cocaine log P (HPLC)	3.35 ¹²⁷
BZE log P (HPLC)	0.44 ¹²⁷
EME log P (HPLC)	0.72 ¹²⁷
Cocaine pK _a	Cocaine: 8.81; BZE: 2.1; 11.75 ¹⁵¹
Cocaine screening test	Cocaine metabolite
Cocaine confirmation test	Cocaine; BZE
Detection times in oral fluid [cutoff, ng/mL]	Single dose: cocaine, GC-MS [1]: up to 12 h; GC-MS [1]: BZE: >12 h ⁷⁰ ; Chronic: cocaine, GC-MS [1]: 8.0–48.0 h; BZE, GC-MS [1]: 36.0–72.0 h ¹⁵⁵
Cocaine detection time in urine [cutoff, ng/mL]	Single dose: BZE, EIA [300]: 14–59 h; BZE, GC-MS [150]: 21–59 h ⁶⁹ ; chronic: BZE, GC-MS [10]: 123–218 h ¹⁵² ; BZE, EIA [300]: 11–147 h ¹⁵⁶
Cocaine oral fluid interpretation resources ^{70,125,152,153,155}	—

BZE=benzoylecgonine; EME=ecognine methyl ester; GC-MS=gas chromatography-mass spectrometry; EIA=enzyme immunoassay.

TABLE 10

Summary of chemical, metabolic, kinetic, and analytic factors important in interpretation of oral fluid tests for nicotine/cotinine

Factor	Nicotine/cotinine information
Drug/metabolite(s) in oral fluid	Nicotine; cotinine; trans-3'-hydroxycotinine; norcotinine ⁷⁸
Drug/metabolite(s) in urine	Nicotine; cotinine; trans-3'-hydroxycotinine ⁷⁸
Nicotine Fb	5–20% ¹⁵⁷
Cotinine Fb	2.6% ¹⁵⁸
Nicotine plasma t _{1/2}	2 h ¹⁵⁹
Cotinine plasma t _{1/2}	16.6 h ¹⁶⁰
Nicotine oral fluid t _{1/2}	Not available
Cotinine oral fluid t _{1/2}	17.4 h ¹⁶⁰
Nicotine plasma:oral fluid correlation	None ⁷⁴
Cotinine plasma:oral fluid correlation	$r = 0.99$ ¹⁵⁹
Nicotine s/p	>1 ⁷⁴
Cotinine s/p	1.2; 1.3–1.8 ^{159,161}
Nicotine log P	0.93 ¹⁶¹
Cotinine log P	0.04 ¹⁶¹
Nicotine pK _a	9.13 ¹⁶¹
Cotinine pK _a	4.72 ¹⁶¹
Nicotine/cotinine screening test	Cotinine
Nicotine/cotinine confirmation test	Cotinine; trans-3'-hydroxycotinine; nicotine
Nicotine detection time in oral fluid [cutoff, ng/mL]	Not available
Cotinine detection time in oral fluid [cutoff, ng/mL]	light smokers: RIA [10]: 1–5 days ¹⁶² oral ingestion of 28 mg of nicotine/day: GC [<10]: 4 days ¹⁶⁰
Nicotine detection time in urine [cutoff, ng/mL]	Nicotine, GC [NR]: 16 h ¹⁶³
Cotinine detection time in urine [cutoff, ng/mL]	Cotinine, daily smokers: GC-MS [5]: > 5 days ¹⁶⁴ ; oral ingestion of 28 mg of nicotine per day: GC [<50]: 4 days ¹⁶⁰
Nicotine/cotinine oral fluid interpretation resources ^{73–78,159,162,165–167}	—

GC=gas chromatography; RIA=radioimmunoassay; NR=not reported.

TABLE 11

Summary of chemical, metabolic, kinetic, and analytic factors important in interpretation of oral fluid tests for heroin

Factor	Heroin information
Drug/metabolite(s) in oral fluid	Heroin, morphine; 6-AM ⁸¹
Drug/metabolite(s) in urine	Morphine; morphine-3-glucuronide; morphine-6-glucuronide; 6-AM; normorphine (minor); heroin (minor) ¹⁶⁸
Heroin Fb	Heroin: 20–39% ¹⁶⁹ ; 6-AM: not available; Morphine: 20–37.5% ^{170,171}
Heroin plasma t _{1/2}	Heroin: 3–4 min; 6-AM: 22–26 min; morphine: 177–184 min ⁸⁰
Heroin oral fluid t _{1/2}	Heroin (IV): 1–67 min; heroin (SM): 26–294 min ⁸¹
Heroin plasma:oral fluid correlation	Not available
Heroin s/b	Heroin s/b (IV): 0–1.9; heroin s/b (SM): 0–784; 6-AM (IV): 0–7.2; 6-AM (SM): 0–333; morphine (IV): 0–1.8; morphine (SM): 0–29 ⁸¹
Heroin log P (octanol/water, 37°C, pH 7.4)	Heroin: 1.076; 6-AM: 0.791; morphine: 0.083 ¹⁵⁴
Heroin log P (HPLC)	6-AM: 1.48; morphine: 0.5 ¹²⁷
Heroin pK _a	Heroin: 7.6 ⁸⁰ ; 6-AM: 8.19 ¹⁷² ; morphine: 7.9; 9.6 ¹⁷³
Heroin screening test	Opiates
Heroin confirmation test	Total morphine; 6-AM; morphine
Heroin detection time in oral fluid [cutoff, ng/mL]	Heroin, GC-MS [1]: 2–24 h; 6-AM, GC-MS [1]: 0.5–8 h; morphine, GC-MS [1]: 2–12 h ⁸¹
Heroin detection time in urine [cutoff, ng/mL]	Single dose: opiates, EMIT [300]: 7–54 h ¹⁷⁴ ; chronic: total morphine, GC-MS [25]: up to 270 h; 6-AM, GC-MS [10]: up to 34.5 h ¹⁷⁵
Oral fluid interpretation resources ⁸¹	—

6-AM=6-acetylmorphine; IV=intravenous; SM=smoked; GC-MS=gas chromatography-mass spectrometry; EMIT=enzyme multiplied immunoassay technique.

TABLE 12

Summary of chemical, metabolic, kinetic, and analytic factors important in interpretation of oral fluid tests for morphine

Factor	Morphine information
Drug/metabolite(s) in oral fluid	Morphine ¹³
Drug/metabolite(s) in urine	Morphine; morphine-3-glucuronide; morphine-6-glucuronide; normorphine (minor); hydromorphone (minor) ⁹²
Morphine Fb	20–37.5% ^{170,171}
Morphine plasma t _{1/2} (h)	2.9–4.5 h ¹⁷⁶
Morphine oral fluid t _{1/2} (h)	Similar to plasma ¹³
Morphine plasma:oral fluid correlation	High correlation ¹³ ; no correlation ⁸⁵
Morphine s/p	<1 ¹³
Morphine log P (octanol/water, 37°C, pH 7.4)	0.083 ¹⁵⁴
Morphine log P (HPLC)	0.5 ¹²⁷
Morphine pK _a	7.9; 9.6 ¹⁷³
Morphine screening test	Opiates
Morphine confirmation test	Total morphine
Morphine detection time in oral fluid [cutoff, ng/mL]	Morphine, GC-MS [0.6]: 24 h ⁹³
Morphine detection time in urine [cutoff, ng/mL]	Total morphine, GC-MS [300] 36–48 h ⁸⁸
Morphine oral fluid interpretation ^{13,93} resources	—

HPLC=high performance liquid chromatography; GC-MS=gas chromatography-mass spectrometry.

TABLE 13

Summary of chemical, metabolic, kinetic, and analytic factors important in interpretation of oral fluid tests for codeine

Factor	Codeine information
Drug/metabolite(s) in oral fluid	Codeine; norcodeine ⁸⁷
Drug/metabolite(s) in urine	Codeine; codeine-6-glucuronide; morphine-6-glucuronide; norcodeine ¹⁷⁷ ; hydrocodone (minor) ¹⁰¹
Codeine Fb	14.2–28.5% ¹⁷¹
Codeine plasma t _{1/2}	1.4–3.5 h ⁸⁷
Codeine oral fluid t _{1/2}	1.0–3.8 h ⁸⁷
Codeine plasma:oral fluid correlation	$r = 0.22$ ⁸⁷
Codeine s/p (range)	4.1 (1–17.2) ⁸⁷
Codeine log P (octanol/water, 37°C, pH 7.4)	0.54 ¹⁵⁴
Codeine pK _a	8.2 ⁸⁷
Codeine screening	Opiates
Codeine confirmation	Total codeine
Codeine detection time in oral fluid [cutoff, ng/mL]	Codeine, GC-MS [2.5]: 7–21 h ⁸⁷
Codeine detection time in urine [cutoff, ng/mL]	Codeine, GC-MS [300]: 24–48 h ⁸⁸
Codeine oral fluid interpretation resources ^{87,93,178}	—

GC-MS=gas chromatography-mass spectrometry.

TABLE 14

Summary of chemical, metabolic, kinetic, and analytic factors important in interpretation of oral fluid tests for hydromorphone

Factor	Hydromorphone information
Drug/metabolite(s) in oral fluid	Hydromorphone ⁹⁶
Drug/metabolite(s) in urine	Hydromorphone; hydromorphone-3-glucuronide; hydromorphol (α/β -isomers) ⁹⁷
Hydromorphone Fb	7% ⁹⁶
Hydromorphone plasma t _{1/2}	2.5–2.6 h ⁹⁵ ; 2.4–4.1 h ⁹⁶
Hydromorphone oral fluid t _{1/2}	2.12 h ⁹⁶
Hydromorphone plasma:oral fluid correlation	Not available
Hydromorphone s/p	0.25–2.32 ⁹⁶
Hydromorphone log P (octanol/water, 37°C, pH 7.4)	0.161 ¹⁵⁴
Hydromorphone log P (octanol/phosphate buffer, pH 7.4)	0.308 ⁹⁶
Hydromorphone pK _a	8.08; 9.47 ⁹⁶
Hydromorphone screening test	Opiates
Hydromorphone confirmation test	Total hydromorphone
Hydromorphone detection time in oral fluid [cutoff, ng/mL]	Single doses: hydromorphone, RIA [1]: 6 h ⁹⁶
Hydromorphone detection time in urine [cutoff, ng/mL]	Single doses: hydromorphone: EMIT [300]; 6.3–11.3 h; hydromorphone: GC-MS [300]; 12–24 h ¹⁰³
Hydromorphone oral fluid interpretation resources ⁹⁶	—

RIA=radioimmunoassay; EMIT=enzyme multiplied immunoassay technique; GC-MS=gas chromatography-mass spectrometry.

TABLE 15

Summary of chemical, metabolic, kinetic, and analytic factors important in interpretation of oral fluid tests for hydrocodone

Factor	Hydrocodone information
Drug/metabolite(s) in oral fluid	Hydrocodone
Drug/metabolite(s) in urine	Hydrocodone; norhydrocodone; hydrocodol (α/β -isomers); hydromorphone; hydromorphol (α/β -isomers); conjugated metabolites ¹⁰⁰
Hydrocodone Fb	Not available
Hydrocodone plasma t _{1/2}	Extensive metabolizers: 4.2 h; poor metabolizers: 6.2 h ⁹⁹
Hydrocodone oral fluid t _{1/2}	Not available
Hydrocodone plasma:oral fluid correlation	Not available
Hydrocodone s/p	Not available
Hydrocodone log P (octanol/water, 37°C, pH 7.4)	0.143 ¹⁵⁴
Hydrocodone pK _a	8.9 ¹³⁰
Hydrocodone screening test	Opiates
Hydrocodone confirmation test	Hydrocodone
Hydrocodone detection time in oral fluid [cutoff, ng/mL]	Expected to be similar to codeine
Hydrocodone detection time in urine [cutoff, ng/mL]	Single doses: hydrocodone: EMIT [300]: 12–36 h; hydrocodone: GC-MS [300]: 11–24 h; hydromorphone: GC-MS [300]: 0–11.8 h ¹⁰³
Hydrocodone oral fluid interpretation resources	—

EMIT=enzyme multiplied immunoassay technique; GC-MS=gas chromatography-mass spectrometry.

TABLE 16

Summary of chemical, metabolic, kinetic, and analytic factors important in interpretation of oral fluid tests for oxymorphone

Factor	Oxymorphone information
Drug/metabolite(s) in oral fluid	Oxymorphone
Drug/metabolite(s) in urine	Oxymorphone; conjugated oxymorphone; oxymorphol (α/β -isomers) ¹⁰⁷
Oxymorphone Fb	10–12% ^a
Oxymorphone plasma t _{1/2}	Parenteral: 1.3 h; oral: 7.3–9.4 h ¹⁷⁹
Oxymorphone oral fluid t _{1/2}	Not available
Oxymorphone plasma:oral fluid correlation	Not available
Oxymorphone s/p	Not available
Oxymorphone log P (octanol/water, 37°C, pH 7.4)	–0.105 ¹⁵⁴
Oxymorphone pK _a	8.5, 9.3 ¹³⁰
Oxymorphone screening test	Oxycodone
Oxymorphone confirmation test	Total oxymorphone
Oxymorphone detection time in oral fluid [cutoff, ng/mL]	Not available
Oxymorphone detection time in urine [cutoff, ng/mL]	Single doses: oxymorphone: opiate EMIT[300]: 0 h; oxymorphone: GC-MS [300]: 11.3–36 h ¹⁰³
Oxymorphone oral fluid interpretation resources ¹⁰⁷	—

EMIT=enzyme multiplied immunoassay technique; GC-MS=gas chromatography-mass spectrometry.

^aSource: http://www.opana.com/pdfs/Opana_IR_PI.pdf#search=%22oxymorphone%20plasma%-20binding%22 (accessed September 29, 2006).

TABLE 17

Summary of chemical, metabolic, kinetic, and analytic factors important in interpretation of oral fluid tests for oxycodone

Factor	Oxycodone information
Drug/metabolite(s) in oral fluid	Oxycodone
Drug/metabolite(s) in urine	Oxycodone; oxymorphone; conjugated oxymorphone; oxycodol (α/β -isomers); oxymorphol (α/β -isomers) ¹⁰⁹
Oxycodone Fb	0.45 ¹³⁰
Plasma t _{1/2}	Oxycodone: 2.25 h ¹⁰⁴ ; oxycodone 2.1–5.1 h ¹⁸⁰ ; oxymorphone: 2.40 h ¹⁰⁴ ; noroxycodone: 4.15 h ¹⁰⁴
Oxycodone oral fluid t _{1/2}	Not available
Oxycodone plasma:oral fluid correlation	Not available
Oxycodone s/p	Not available
Oxycodone log P (octanol/water, 37°C, pH 7.4)	0.243 ¹⁵⁴
Oxycodone pK _a	8.53 ¹⁸¹
Oxycodone screening test	Oxycodone
Oxycodone confirmation test	Oxycodone
Oxycodone detection time in oral fluid [cutoff, ng/mL]	Not available
Oxycodone detection time in urine [cutoff, ng/mL]	Single doses: oxycodone: opiate EMIT [300]: 0–6.6 h; oxycodone: GC-MS [300]: 12–36 h; oxymorphone: GC-MS [300]: 12–48 h ¹⁰³
Oxycodone oral fluid interpretation resources ¹⁸²	—

EMIT=enzyme multiplied immunoassay technique; GC-MS=gas chromatography-mass spectrometry.

TABLE 18

Summary of chemical, metabolic, kinetic, and analytic factors important in interpretation of oral fluid tests for methadone

Factor	Methadone information
Drug/metabolite(s) in oral fluid	Methadone; EDDP ¹¹²
Drug/metabolite(s) in urine	Methadone; EDDP; EMDP; minor metabolites ¹⁸³
Methadone Fb	88.1–89.1% ¹⁸⁴
Methadone plasma t _{1/2}	15–55 h ¹⁸⁵ ; 23–27 h ¹⁸⁶ ; 33–46 h ¹⁸⁵
Methadone oral fluid t _{1/2}	Not available
Methadone plasma:oral fluid correlation	$r = 0.81^{187}$; $r = 0.54^{112}$
Methadone s/p	0.51 ¹⁸⁸ ; 0.6–7.2 ¹¹² ; 1.3 ¹⁸⁷
Methadone P (chloroform/water, 25°C, pH 7.4)	Methadone: 14.56; EDDP: 2.38 ¹¹⁰
Methadone pK _a	Methadone 8.62 ¹¹⁰ ; 9.2 ¹⁸⁶ ; 8.2 ¹¹² ; EDDP: 10.42 ¹¹⁰
Methadone screening tests	Methadone; EDDP
Methadone confirmation test	Methadone; EDDP
Methadone detection time in oral fluid [cutoff, ng/mL]	Methadone, GC-MS [20]: 24 h ¹⁸⁸
Methadone detection time in urine [cutoff, ng/mL]	Methadone, EIA [300]: 24–96 h ¹⁸⁹
Methadone oral fluid interpretation resources ^{112,187,188}	—

EDDP=2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; EMDP=2-ethyl-5-methyl-3,3-diphenylpyrrolidine; EIA=enzyme immunoassay; GC-MS=gas chromatography-mass spectrometry.

TABLE 19

Summary of chemical, metabolic, kinetic, and analytic factors important in interpretation of oral fluid tests for buprenorphine

Factor	Buprenorphine information
Drug/metabolite(s) in oral fluid	Buprenorphine; norbuprenorphine ¹³
Drug/metabolite(s) in urine	Buprenorphine; conjugated buprenorphine; norbuprenorphine; conjugated norbuprenorphine ¹¹⁵
Buprenorphine Fb	95–98% ¹⁹⁰
Plasma t _{1/2}	Buprenorphine: 40.7 h; norbuprenorphine: 73.3 h ¹¹⁸
Buprenorphine oral fluid t _{1/2}	Not available
Buprenorphine plasma:oral fluid correlation	High correlation ¹³
Buprenorphine s/p	Intramuscular: 0.05–0.41; sublingual: >1 ¹³
Buprenorphine log P (octanol/water, 37°C, pH 7.4)	4.98 ¹⁷²
Buprenorphine pK _a	8.24, 10 ¹⁹⁰
Buprenorphine screening test	Buprenorphine
Buprenorphine confirmation test	Buprenorphine; norbuprenorphine; conjugates
Buprenorphine detection time in oral fluid [cutoff, ng/mL]	Buprenorphine, RIA [1]: up to 5 days ¹³
Buprenorphine detection time in urine [cutoff, ng/mL]	total buprenorphine/norbuprenorphine, GC [10/5]: 4–8 days ¹⁹¹ ; total buprenorphine/norbuprenorphine, GC-MS [0.25/0.2]: 4–8 days ¹⁹²
Buprenorphine oral fluid interpretation resources ¹³	—

RIA=radioimmunoassay; GC=gas chromatography; GC-MS=gas chromatography-mass spectrometry.

TABLE 20

Summary of chemical, metabolic, kinetic, and analytic factors important in interpretation of oral fluid tests for PCP

Factor	PCP information
Drug/metabolite(s) in oral fluid	PCP ¹²⁴
Drug/metabolite(s) in urine	PCP; PPC; PCHP ¹²⁰
PCP Fb	64% ¹²³ ; 68–69% ¹²⁰
PCP plasma t _{1/2}	7–50 h ¹²⁰
PCP oral fluid t _{1/2}	Not available
PCP plasma:oral fluid correlation	$r = 0.87$ ¹²⁰
PCP serum:oral fluid correlation	$r = 0.92$ ¹²⁴ ; $r = 0.4$ ¹²³
PCP s/p	1.5–3 ¹⁹³
PCP log P (octanol/water, 37°C, pH 7.4):	1.96 ¹⁵⁴
PCP pK _a	8.5 ¹²³
PCP screening test	PCP
PCP confirmation test	PCP
PCP detection time in oral fluid [cutoff, ng/mL]	Not available
PCP detection time in urine [cutoff, ng/mL]	Chronic: PCP; GC [5]: up to 30 days ¹⁹⁴
PCP oral fluid interpretation resources ^{120,121,123,124}	—

PCP=phencyclidine; PPC=4-(1-piperidiny)-cyclohexanol; PCHP=1-(1-phenylcyclohexyl)-4-hydroxypiperidine; GC=gas chromatography.