

# SCDAT

## Guidelines for Drugs of Abuse Testing

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## Glossary

<b>FEDRO</b>	<b>Federal Roads Office (Switzerland)</b>
<b>BSV</b>	<b>Federal Social Insurance Office (Switzerland)</b>
<b>CAP</b>	<b>College of American Pathologists</b>
<b>Compliance</b>	<b>A patient's adherence to a recommended course of treatment</b>
<b>CSCQ</b>	<b>Quality Control Center, Switzerland</b>
<b>Cut-off</b>	<b>Medical and/or Legal Decision Value, pos/neg</b>
<b>DIN</b>	<b>German Industrial Standard</b>
<b>Donor</b>	<b>Person who donates something voluntarily</b>
<b>EJPD</b>	<b>Federal Department of Justice and Police (Switzerland)</b>
<b>EN</b>	<b>European Standard</b>
<b>fedpol</b>	<b>Federal Office of Police (Switzerland)</b>
<b>GC-MS</b>	<b>Gas Chromatography with Mass Spectrometric Detection</b>
<b>GC-NPD</b>	<b>Gas Chromatography with Nitrogen Phosphorus Detection</b>
<b>GLP</b>	<b>Good Laboratory Practice</b>
<b>HPCE-UV</b>	<b>High-Performance Capillary Electrophoresis with Ultraviolet Detection</b>
<b>HPLC-DAD</b>	<b>High Performance Liquid Chromatography with Diode-Array Detection</b>
<b>HPLC-MS</b>	<b>High Performance Liquid Chromatography with Mass Spectrometric Detection</b>
<b>ID</b>	<b>Identification</b>
<b>ISO/IEC</b>	<b>International Organization for Standardization/International Electrotechnical Commission</b>
<b>IUPAC</b>	<b>International Union of Pure and Applied Chemistry</b>
<b>KLV</b>	<b>Health Care Benefits Ordinance (Switzerland)</b>
<b>KVG</b>	<b>Federal Health Insurance Act (Switzerland)</b>
<b>KVV</b>	<b>Health Insurance Ordinance (Switzerland)</b>
<b>LSD</b>	<b>Lysergic Acid Diethylamide</b>
<b>MQ</b>	<b>Association for Medical Quality Control (Switzerland)</b>
<b>MS</b>	<b>Mass Spectrometry</b>
<b>NIDA</b>	<b>National Institute on Drug Abuse (U.S.A.)</b>
<b>OECD</b>	<b>Organisation for Economic Co-operation and Development</b>
<b>On Site</b>	<b>Done or located at the site</b>
<b>Peak</b>	<b>Portion of a differential chromatogram recording the detector response when a single component is eluted from the column</b>
<b>Prodrug</b>	<b>Inactive (or significantly less active) form of a drug</b>
<b>QC</b>	<b>Quality Control</b>
<b>QUALAB</b>	<b>Swiss Commission on Quality in the Medical Laboratory</b>
<b>SAMHSA</b>	<b>Substance Abuse and Mental Health Services Administration (U.S.A.)</b>
<b>SAS</b>	<b>Swiss Accreditation Service</b>
<b>SCDAT</b>	<b>Swiss Committee for Drugs of Abuse Testing</b>
<b>Spiker</b>	<b>Person pretending compliance in a drug substitution program</b>
<b>Spot</b>	<b>Spontaneous urine, urine specimen</b>
<b>SULM</b>	<b>Swiss Union for Laboratory Medicine</b>
<b>TDM</b>	<b>Therapeutic Drug Monitoring</b>
<b>THC</b>	<b>Delta(9)-tetrahydrocannabinol</b>
<b>TLC</b>	<b>Thin-Layer Chromatography</b>
<b>UP</b>	<b>Urine specimen/sample</b>
<b>UVEK</b>	<b>Federal Department of Environment, Transport, Energy and Communications (Switzerland)</b>
<b>Workplace Testing</b>	<b>Drug Testing Programs in the Workplace</b>

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## Foreword

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These revised SCDAT Guidelines were originally published by the Work Group on Drugs of Abuse Testing (AGSA). The SCDAT, successor to AGSA, is a work group composed of members of the following institutions:

- Swiss Association of Pharmacists (pharmaSuisse)
- Swiss Society of Clinical Chemistry (SGKC)
- Swiss Society of Legal Medicine (SGRM)
- Swiss Association of the Diagnostic Equipment and Product Industry (SVDI)
- University of Bern.

These guidelines are intended as recommendations. They are not legally binding in nature. Harmonization in drug analyses is the objective.

The use of drug analysis for the various questions in the therapeutic and forensic sectors as well as in specific workplaces can have far-reaching consequences of a professional and social nature for those affected. For this reason, the greatest possible care must be taken when conducting analyses and interpreting the results. These guidelines support analytical laboratories in their adherence to requisite quality assurance measures.

The guidelines are periodically revised and enlarged.

In addition, the SCDAT provides consultation both to the laboratories that conduct drug testing and the Swiss Quality Control Centers (inter-laboratory test centers).

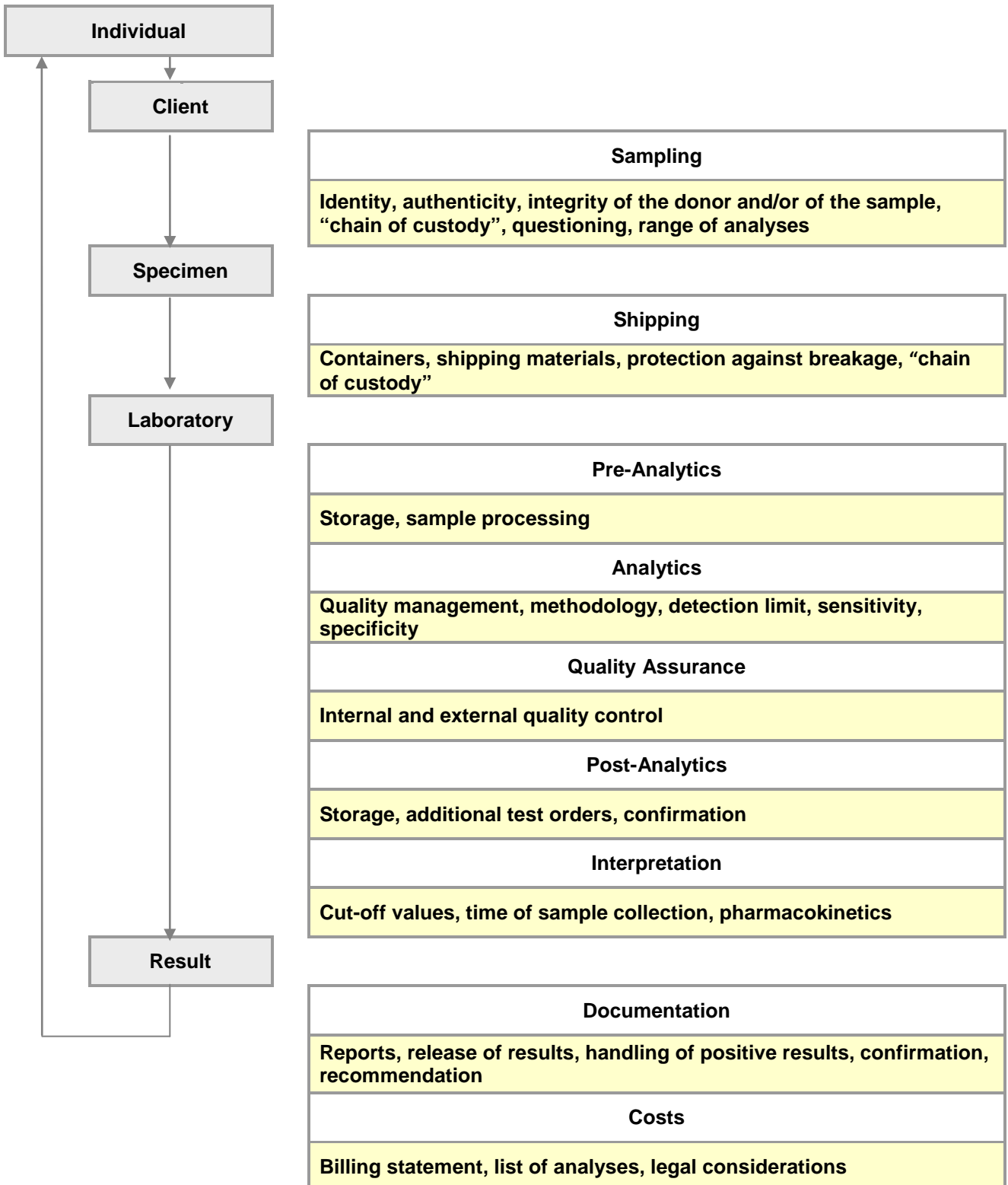
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# 1. Scope of the Guidelines

The following guidelines encompass the different stages of drug analyses, from the individual to be tested, through the client, to the result. The guidelines specifically deal with sampling, shipping, preanalytical, analytical, and postanalytical aspects, quality assurance, interpretation and documentation of the results of the analyses, as well as the costs (Fig. 1).

**Figure 1** Scope of the Guidelines



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## 2. Scope of Application of the Guidelines

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The guidelines are recommended for use in the clinical, socio-medical and forensic areas of application (Fig. 2: A-D).

**Figure 2**      Scope of Application of the Guidelines

<b>A</b>	<b>Testing for drugs of abuse associated with differential diagnosis</b>
<b>B</b>	<b>Testing for drugs of abuse during substitution therapy, heroin-based (HeGeBe) therapy, and/or detoxification treatment</b>
<b>C</b>	<b>Testing for drugs of abuse in forensic cases</b>
<b>D</b>	<b>Testing for drugs of abuse in the workplace/in educational facilities</b>

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## 3. Sample Collection, Shipping and Handling (“Chain of Custody”)

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The different stages in testing for drugs of abuse (Fig. 1) are described in detail below.

**Individuals - Collecting/Submitting a Sample**

### Objectives

- The identity, authenticity, and integrity of the individual and the specimen (urine\*, blood, serum, sweat, saliva, hair, etc.) must be ensured.  
\*e.g., Beverages containing identifiable markers are dispensed ½ hour prior to collecting sample [Gauchel 2003].
- Respect privacy.
- Identify and prevent any medical, chemical and/or physical tampering with the urine or hair specimen (urine: endogenous or exogenous dilution, additives, submission of another’s urine specimen, substitution of an analyte).

### Measures for urine specimens

- Check identity<sup>1</sup>
- Temperature 32-38 °C, measured within 4 min<sup>1</sup> (point of collection)
- Check consistency, odor, and color<sup>3</sup>
- Add dye to toilet water; keep washbasin, soap, and disinfectant outside restroom.<sup>3</sup>
- Conduct visual inspection.<sup>3</sup>
- Instruction and advice on obtaining urine are provided by the laboratory.<sup>1</sup>



## Measures for other sample sources

- Check identity.<sup>1</sup>
- Blood, sweat, saliva, hair, etc. in accordance with the information provided by the testing laboratory.
- Instruction and advice on obtaining specimen are provided by the laboratory.<sup>1</sup>

### Sample, Material

#### Objectives

- Identity, authenticity and integrity of the specimen must be assured.
- Identify and prevent chemically and/or physically induced changes (decomposition, contamination, breakage, etc.), tampering, mix-ups and/or loss of the specimen.

#### Measures

- Minimum of 30 mL for urine samples whenever possible; minimum of 2.5 mL for blood samples; please refer to applicable information pertaining to other sample sources.
- Container (supplied by the laboratory), if possible, must have a tamper-proof closure<sup>2</sup>, must be leak-proof, unbreakable; label must have a legible identification number<sup>1</sup>; other sample sources must be in accordance with the recommendations of the laboratory doing the testing.
- Order form (simple, easy to understand): identification number, last name, first name, date of birth, gender, date/time of sampling.
- Adhere to “chain-of-custody” procedure.

### Laboratory

#### Objectives

- The identity of the specimen as well as the traceability of all steps in the analytical procedure must be ensured.
- Sample handling and the quality of the analytical methods must comply with the accreditation requirements in accordance with SAS or the certification requirements in accordance with the OECD (GLP) and QUALAB.

#### Measures

- Limited and controlled access to the laboratory.<sup>1</sup>
- Receipt of the samples by authorized personnel only.<sup>1</sup>
- Urine samples: Record the color<sup>1</sup>, consistency<sup>1</sup>, odor<sup>3</sup>, pH<sup>1</sup>, creatinine<sup>1</sup>, specific gravity/density<sup>3</sup> and refraction index<sup>3</sup>.
- Storage (locked away): + 4 °C pre-analytical, - 20 °C post-analytical.
- Duration of sample storage: not defined for A and B (6 months recommended), minimum of 1 year for C and D.

<sup>1</sup> Compulsory for A – D

<sup>2</sup> Compulsory for C and D

<sup>3</sup> Optional

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## 4. Factors Interfering with Results of Analytical Testing, Tampering with Urine Specimens and Other Sample Sources

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Adhering to essential pre-analytical measures (Chapter 3) ensures proper response and can lead to the discovery of intentional or unintentional interference resulting in an inaccurate reading that aggravates the interpretation of test results (Chapter 10: Interpretation).

Most forms of tampering involve urine submission. The collection of blood, saliva or sweat (by means of controllable sweat patches only) ensures complete sample integrity, as collection of these sample sources is performed by the staff of the institution ordering the test. Tampering is usually not possible with these sample sources. Hair, for example, can be manipulated by intense washing, bleaching and dyeing.

### 4.1 Types of Interfering Factors

#### 4.1.1 Interference Due to Therapeutic Drugs

- Interference due to drugs taken for therapeutic purposes (e.g., antidepressants and antipsychotics) may in some cases interfere with analytical methods. The data provided by reagent manufacturers do not always make this clear.

#### 4.1.2 Interfering Factors

- Physiological factors (*in vivo* interference with the result) are, for example, ingestion of excessive amounts of water, ingestion of food containing opiates (e.g., poppy seeds), or the ingestion of multivitamin preparations.
- Substances that are added to urine and can interfere with one or several compounds (analytes) or with the test procedure for such compounds.
- Substances that modify the addictive drug to be detected, thereby preventing detection of said addictive drug with a confirmation test.
- Replacing urine with another's drug-free urine sample, commercially available urine, or other liquids to which coloring has been added.

### 4.2 Identification of Interfering Factors

The following table lists several forms of tampering and describes how tampering can be detected by analytical methods or visual inspection of the sample.

**Table 1**            **Interfering Factors and How to Identify Them in the Laboratory**

Interfering Factors in Urine Samples	Laboratory Test
Dilution: Excessive drinking, diuretics, addition of fluids	Creatinine/density, color
Bleaching agents (toilet cleansers) containing hypochlorite	pH, Check <sup>1</sup> , odor, color, test strips <sup>2</sup>
Liquid soap	Check <sup>1</sup> , foam build-up
Aldehydes, e.g. glutaric aldehyde	Check <sup>1</sup> and test strips <sup>2</sup>
Strong acids and bases	pH, Check <sup>1</sup>
Nitrite	NO <sub>2</sub> <sup>-</sup> on test strips <sup>2</sup>
Ascorbate	pH, Check <sup>1</sup>
Therapeutic drugs, special herbal teas	Chromatography
Chromates	Color test, test strips <sup>2</sup>
Peroxides and peroxidase (Stealth)	Check <sup>1</sup> , test strips <sup>2</sup>
Vitamins (multivitamin preparations)	Chromatography
Miscellaneous (eye drops, etc.)	Chromatography and other methods

Forms of Tampering in Hair Samples	Laboratory Test
Special shampoos	---
Chemicals used in permanents	Consistency of the material
Hair bleaching, hair dye	Consistency of the material
Intense UV exposure (tanning beds)	---

<sup>1</sup> Check = Test method specifically intended for a particular analytical procedure, e.g., "Sample Check".

<sup>2</sup> Test strip, e.g., Adultacheck 4, 6, 10 (pH, NO<sub>2</sub><sup>-</sup>, creatinine, aldehyde, chromates, oxidants, specific gravity, halogens, peroxidase/oxidants).

Please note that the form of tampering may change relatively rapidly, often in keeping with the analytical method used.

### 4.3 Definitions of Adulteration According to SCDAT, SAMHSA and ASNZ

- According to SCDAT and ASNZ [Australien/New Zealand Standard<sup>TM</sup> 2008] an urine is defined as diluted (does not implicate adulteration), if: creatinine <1.8 mmol/L (SCDAT) and <20 mg/dL (ASNZ), respectively, but >0.4 mmol/L (>5.0 mg/dL, ASNZ)\*.
- According to SCDAT and ASNZ an urine is defined as adulterated (SAMSHA, diluted), if: creatinine <0.4 mmol/L (SCDAT) and <5 mg/dL (ASZN, SAMHSA [SAMHSA 2008]), respectively\*.
- SCDAT and SAMHSA define an urine as adulterated if:
  - The nitrite-concentration is >500 mg/L
  - The pH is <3 oder >11
  - Exogenous substances are detectable which can lead to interferences (see chapter 4.2)
  - Endogeneous substances in non-physiological concentrations are detectable.

\*These concentrations are based on new, well documented studies recommending lower limits of the creatinine reference values [Arndt 2007a, Arndt 2007b, Arndt 2009]. This holds true for detecting urine manipulation in clinical chemistry as well as in drug testing.

## 5. Specimens

This guideline chiefly discusses urine, serum, and plasma as specimens. For the sake of providing a complete overview, all specimens are listed in the table below.

**Table 2: Specimens and Their Different Areas of Application**

Specimens	Area of Application			
	A	B	C	D
Urine	X	X	X	X
Serum, plasma	X	X	X	X
Whole blood	X	-	X	-
Sweat	-	X	X	X
Post-mortem blood	-	-	X	-
Saliva	X	X	X	X
Gastric content	X	-	X	-
Aspirated fluids and secretions	X	-	X	-
Dialysate	X	-	-	-
Tissue samples	-	-	X	-
Hair	-	X	X	X
Substance samples	X	-	X	X

## 5.1 Specimen Stability and Preservation

### 5.1.1 General Information

A negligible decrease in stability is of little consequence for qualitative testing. In general, for quantitative determinations, e.g. in forensic cases, somewhat more restrictive conditions should be maintained while checking the applicable literature. Depending on the substance, the laboratory has to perform its own validations, since only sparse amounts of data are available in the literature.

### 5.1.2 Storing and Packaging Specimens

Practically all common drugs of abuse and their metabolites are stable in urine for 7 days at 4 °C when kept in a dark place. In the literature [Baselt 2011], an increased GHB concentration in forensic samples has been described that can lead to a misinterpretation of results, since the heightened concentration leads to an excess in endogenous concentration, thus mimicking exogenous administration. However, this phenomenon could not be confirmed by several laboratories that determine GHB and keep the urine samples at -20 °C.

For further information, please consult the applicable guidelines [NCCLS 1999; USP 1990] and Table 3.

Plastic materials (polypropylene, polycarbonate, and polyethylene) are recommended for sampling and storing samples. Any other plastic materials adsorb analytes (e.g. THC) and some metabolites and should, therefore, not be used [Roth 1996].

The stability of standards that cannot be obtained commercially in lyophilized form along with a declaration of stability, should be verified on a regular basis.

It is recommended that the pH of the urine samples be adjusted to 5 – 7 after thawing and before analysis [USP 1990]. Please note: Mix urine samples vigorously after thawing!

**Table 3 Stability and Storage of Urine Samples**

Substance or Substance Group	Stability in Urine (≤ 6 months = assured up to 6 months)
Alcohol / ethyl glucuronide (EtG)	5 days at +4 °C
Amphetamines, incl. MDMA	7 days at +4 °C, -20 °C: ≤ 6 months
Barbiturates	7 days at +4 °C, -20 °C: ≤ 6 months
Benzodiazepines	7 days at +4 °C, -20 °C: ≤ 6 months
Buprenorphine	7 days at +4 °C, -20 °C: ≤ 6 months
THC-carboxylic acid (Cannabis)	7 days at +4 °C, -20 °C: ≤ 6 months; warning: Stability is dependent on the container used
Cocaine + metabolites	7 days at +4 °C, -20 °C: ≤ 6 months
Codeine	7 days at +4 °C, -20 °C: ≤ 6 months
Ethanol	7 days at +4 °C, -20 °C: ≤ 6 months; store in gastight containers.
GHB	At < -20 °C, several (≤ 6) months
LSD	7 days at +4 °C, -20 °C: ≤ 6 months
Methadone	7 days at +4 °C, -20 °C: ≤ 6 months
Methadone metabolite (EDDP)	7 days at +4 °C, -20 °C: ≤ 6 months
Methaqualone	7 days at +4 °C, -20 °C: ≤ 6 months
Nicotine, cotinine	2 days at +4 °C, -20 °C, ≤ 2 months
Opiates	7 days at +4 °C, -20 °C: ≤ 6 months
6-Acetylmorphine	7 days at +4 °C, -20 °C: ≤ 6 months
Phencyclidine (PCP)	7 days at +4 °C, -20 °C: ≤ 6 months
Psilocybin/psilocin	7 days at +4 °C, -20 °C: ≤ 6 months

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## 6. Use of Non-Instrument Rapid Tests – New Technologies

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With few exceptions (see chapter 6.3) "rapid tests" for drug screening in urine, oral fluid and sweat are non-instrument immunoassays that are unsuited for mass screening (chapter 7) and permit fast (within 5-10 min) yes/no decisions outside the laboratory ("on site"). Saliva and sweat tests have been used for some time, chiefly in forensic cases.

### 6.1 General Remarks

- As with instrument immunoassays, non-instrument immunoassays are merely indicative and not evidential in nature. All manufacturers' instructions for use point out this fact, but many users fail to or barely pay attention to it.
- Despite their simplicity and lack of reliance on an instrument, these non-instrument immunoassays as well as the instrumental onsite tests should only be conducted by trained personnel who are skilled in the interpretation of the results and any irregularities.
- In the case of a positive result, do not discard the sample. It must be retained for any confirmation analysis that may be required. In special forensic cases, an additional specimen of saliva can be taken after an oral fluid test has yielded a positive result. In so doing, the special collection tubes (e.g., salivettes) are to be used.
- Most of these analytical systems have a test quadrant that displays any irregularity in the reaction sequence. Nevertheless, irregularities that are not indicated through internal checks still may occur (in urine tests, for example, certain methods of tampering, interference with any one of the test quadrants, or irregularities caused by medication). When using oral fluid tests, please be aware that despite unrelenting continued development by manufacturers, test results far too frequently yield false negative or false positive results. For this reason, confirmation analysis e.g. in blood is mandatory in all such forensic investigations.
- Quality control samples generally used for testing the quality of screening tests are artificial. Therefore, discrepancies may be found when comparing the results of individual test quadrants of different manufacturers (e.g., varying cross-reactions with optical isomers, mainly amphetamines). False negative results may also occur due to an antigen excess (High-Dose Hook Effect).

### 6.2 Areas of Application

- A:** Chiefly in emergency departments - Instrumental immunoassays using equipment calibrated according to SCDAT guidelines are preferable. Depending on order requirements, differential and confirmation analyses are necessary. Please be aware that qualitative results may lead to false differential diagnoses and that quantification will be needed in addition.
- B:** Mainly in medical practices and pharmacies for verifying patient testimony or compliance monitoring (methadone). It is recommended that the rapid test be conducted in the presence of the patient. If a patient disputes a result, the result must be verified using a method based on a different analytical principle.
- C:** Non-instrument immunoassays for oral fluid and urine are generally used by law enforcement in forensic investigations, chiefly for road patrols. Therefore, the recommendations listed in chapter 6.1 must be adhered to in oral fluid testing. For all other forensic matters non-instrument immunoassays should not be used. Sweat tests are used in rare cases for long-term monitoring, such as when investigating individuals suspected of drug use.
- D:** Non-instrument immunoassays should only be used as screening tests. Instrument immunoassays on equipment calibrated according to SCDAT guidelines are the tests of choice. When testing urine in the workplace (workplace testing), any positive results require confirmation.

### 6.3 New Technologies

New technologies are mostly updated or changed detection systems of established immunoassays. As an example of instrument immunoassays the spot analytics with bioluminescence markers should be mentioned.

Transportable detection systems with the possibility of semi-quantitative determinations of specific substance assays, such as THC-carboxylic acid, are new on the market. In addition, they allow quantifications after calibration with a standard curve. The basic principles of detection for these assays are spectroscopic detection such as measuring the intensity of colored bands (visible detection) on plates or strips. Other methods are based on the measurement of the fluorescence after reaction in a fluorescence immunoassay on plates.

Detection systems for immunochemical reactions with electrodes (chip technology) did not prove themselves in contrast to analytical methods in clinical chemistry. Promising are methods including a specific reaction between the analyte and a nanoparticle dye followed by optical detection on microtiter plates or on microarray systems. They allow the determination of single substances without antigen-antibody reaction. The principle is a specific shift in the optical spectrum of a particular nanoparticle dye after reaction with the analyte. Basically, this technique should enable to specifically determine thousands of substances, but currently only as positive/negative result in aqueous solution. However, this promising technology has to be tested yet.

## 7. Immunochemical Analyses in Urine

This term applies to all variants of analytical systems have an antigen-antibody reaction regardless of the detection system being used.

### 7.1 Single-Substance Analyses

Immunoassays of single substances are designed to detect a substance and/or its metabolites. Examples of single-substance analyses are Cannabis (THC-carboxylic acid), the cocaine metabolite (benzoylecgonine), methadone, 2-ethyliden-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP, a metabolite of methadone), LSD, methaqualone, 6-acetylmorphine (6-AM), buprenorphine, ethyl glucuronide (EtG) and cotinine.

#### Indications

Immunoassays of single substances are recommended depending on the areas of application (Table 4). Particularly in the case of methadone, interpretation requires due care.

**Table 4: Single-Substance Analyses in Different Areas of Application**

Class		A	B	C	D
Single	Buprenorphine	X	X	X <sup>2</sup>	-
	THC carboxylic acid (Cannabis)	X	X	X <sup>2</sup>	X
	Benzoylecgonine (cocaine)	X	X	X <sup>2</sup>	X
	LSD	X	-	X <sup>2</sup>	X
	Methadone	X <sup>1</sup>	X <sup>1</sup>	X <sup>2</sup>	-
	EDDP (methadone)	X <sup>1</sup>	X <sup>1</sup>	X <sup>2</sup>	-
	Methaqualone	X	X	X <sup>2</sup>	-
	6-Acetylmorphine (6-AM, heroin)	X	X	X <sup>2</sup>	X
	Ethyl glucuronide (EtG)	-	X	X <sup>2</sup>	X
	Cotinine (nicotine, tobacco)	-	X	X <sup>2</sup>	X

X *Recommended indication*

<sup>1</sup> *Negative results are not necessarily conclusive, since most assays detect methadone alone and not its main metabolite, EDDP. EDDP may be detected by itself in urine. This is due either to its rapid metabolism ("Fast Metabolizers") or to enzyme induction of the metabolizing enzymes (interaction with, e.g., rifampicin, carbamazepine phenytoine, etc.). In such situations, it helps to determine EDDP.*

<sup>2</sup> *For use only as a screening test.*

## 7.2 Substance Group Analyses

Substance-group analyses using immunoassays detect a range (but not all) structurally related substances in one analytical process.

The antibodies react with a more or less large number of structurally related substances or metabolites (Chapter 8). The results in each case are only qualitative (from one to several substances that react with the antibody can either be detected or not). Depending on the manufacturer, calibration of the analytical systems for substance-group testing is based on different standard substances, leading to varying specificity in terms of the results.

Examples of such substance-group analyses are methods for detecting benzodiazepines, opiates, amphetamines, barbiturates and tricyclic antidepressants.

Depending on the method used, urine specimens exhibiting high concentrations of analyte (> measuring range) must not be diluted. There is a correlation between antibody affinity and the concentration of the substance.

### Indications

Substance-group analyses using immunoassays are recommended depending on the areas of application (Table 5) and are to be subjected to critical interpretation.

**Table 5: Substance-Group Analyses in Different Areas of Application**

Substance Group		A	B	C	D
Group	Amphetamines	X <sup>1,2</sup>	X <sup>2</sup>	X <sup>3</sup>	X <sup>2</sup>
	Barbiturates	X <sup>1,2</sup>	X <sup>2</sup>	X <sup>3</sup>	X <sup>2</sup>
	Benzodiazepines	X <sup>1,2</sup>	X <sup>2</sup>	X <sup>3</sup>	X <sup>2</sup>
	Opiates	X <sup>1</sup>	X	X <sup>3</sup>	X
	Tricyclic antidepressants	X <sup>1,2</sup>	-	X <sup>3</sup>	-

X Recommended area of application

<sup>1</sup> Problems due to the varying reactivity of the antibodies with individual substances within a substance class. Therefore, it is not possible to obtain quantitative data.

<sup>2</sup> Negative results are not necessarily always conclusive since, depending on the method used, individual substances of the substance class or their metabolites will not react. This also applies to the metabolites of a substance in single-substance tests (e.g. methadone).

<sup>3</sup> For use only as a screening test.

### Comment Regarding the Immunoassays:

Whatever the case, a chromatographic test method is more conclusive than most immunoassays. However, the latter are the methods of choice for rapid results, since chromatographic procedures are usually work-intensive. Immunochemical group testing is indicated when rapid detection of presumably ingested substances within a certain substance class (which may cover a large number of substances) and serial analyses are needed. Please note that there is still a potential for false positive and false negative.

Whenever there are numerous metabolites, the sensitivity of immunoassays is better than that of individual chromatographic methods (e.g., HPLC) since the metabolites are measured cumulatively in the immunoassays and as single peaks in the chromatographic method.

Since detection with immunoassays normally yields "yes/no" cut-off levels, the results require critical interpretation and, depending on the case, additional measurements may have to be performed (Chapter 11).

### 7.3 Long-Term Monitoring

If the excretion of a specific drug of abuse requires monitoring, the easiest way to do so is by comparing creatinine quotients. The creatinine quotients of the individual addictive drugs are calculated as shown in Fig. 3.

**Figure 3: Creatinine Quotient**

$\frac{\text{Concentration of drug in urine } (\mu\text{g/L})}{\text{Creatinine concentration in same urine specimen (mmol/L)}} = \frac{\text{Drug } (\mu\text{g})}{\text{Creatinine (mmol)}}$
------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

This quotient can prove interim consumption (quotient sample 1 → consumption → quotient sample 2) or depict the elimination rate of one-time consumption. Calculation of these quotients is allowed only with analytes determined by chromatography (e.g., THC-carboxylic acid, oxazepam following deglucuronidation, lorazepam following deglucuronidation, etc.). In the case of THC-carboxylic acid, the two urine samples must not be collected before at least 24 h have elapsed and must be collected within 7 days at most. The following formula is used for interpretation:  $Q2/Q1 \geq 1.5 =$  recent consumption likely [Huestis & Cone 1998].

### 7.4 Recommended Cut-off Concentrations for Instrument Immunoassays of Urine Specimens Without Prior Hydrolysis

Table 6 shows the cut-off concentrations that vary depending on the different areas of application for single substances and substance groups. They apply to instrument immunoassays of urine specimens that have not undergone prior hydrolysis.

**Table 6: SCDAT-Recommended Cut-off Concentrations for Instrument Immunoassays of Urine Specimens without Prior Hydrolysis**

Single Substances		A	B	C	D <sup>1</sup>
Single	Buprenorphine (µg/L)	LOD	10	X	-
	THC carboxylic acid (Cannabis) (µg/L)	LOD	50	X	50
	Cocaine or cocaine metabolite (benzoylecgonine) (µg/L)	LOD	300	X	150
	GHB (mg/L)	5 <sup>2</sup>	5 <sup>2</sup>	5 <sup>2</sup>	-
	LSD (µg/L)	LOD	0.5	X	-
	Methadone (µg/L)	LOD	300	X	-
	EDDP (Methadone) (µg/L)	LOD	100	X	-
	Methaqualone (µg/L)	LOD	300	X	-
	6-Acetylmorphine (6-AM) (µg/L)	LOD	10	X	-
	Ethyl glucuronide (EtG)	X	X	X	X
	Cotinine (nicotine)	X	X	X	X
Substance Groups					
Group	Amphetamines (µg/L)	LOD	500	X	500
	Barbiturates (µg/L)	LOD	300	X	-
	Benzodiazepines (µg/L)	LOD	100	X	-
	Opiates (µg/L)	LOD	300	X	2000

LOD *Limit of detection.*

X *No recommendation.*

<sup>1</sup> *Cut-off concentration in accordance with NIDA / SAMHSA.*

<sup>2</sup> *The endogenous GHB concentration in urine is < 5 mg/L.*



Cut-off values cannot be recommended for non-instrument immunoassays because these values are established by the manufacturers and, hence, are constant.

Hydrolysis of the urine prior to analysis permits indirect determination of conjugated metabolites (e.g., morphine glucuronides, benzodiazepine glucuronides), thus improving the chances for positive detection.

## 7.5 Enzymatic alcohol test

In clinical laboratories alcohol (ethanol) is determined by enzymatic tests. In these tests alcohol will be converted by alcohol dehydrogenase. So alcohols like isopropyl alcohol which are also converted by ADH are co-determined. These alcohols can only be found in urine in case of an intoxication with these compounds. It has to be considered that after the consumption of ripe fruits alcohol concentrations of <3 mmol/L can be found in urine.

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## 8. Chromatographic Confirmation Analyses in Urine

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Confirmation analyses in drug analysis involve chromatographic methods (usually using spectroscopic detection) for determining one or several single substances and are used as a second analysis to back up a finding from an immunochemical test.

### 8.1 General Remarks

Confirmation analyses must be used both wherever an immunochemical screening process is insufficiently specific and where sanctions may be imposed on the person involved due to the result obtained. In so doing, it is imperative that a second method based on a different principle be used to confirm a screening result. Using just another immunochemical testing procedure for confirmation purposes is prohibited.

### 8.2 Methods

The following methods are suited for confirmation testing:

- |                                                                                             |          |
|---------------------------------------------------------------------------------------------|----------|
| • Gas chromatography with mass spectrometric detection (all substances)                     | GC-MS    |
| • Gas chromatography with nitrogen-phosphorus detection (e.g., methadone, cotinine)         | GC-NPD   |
| • Capillary electrophoresis with UV detection                                               | CE-UV    |
| • High-performance liquid chromatography with diode-array detection (e.g., benzodiazepines) | HPLC-DAD |
| • High-performance liquid chromatography with mass spectrometric detection (all substances) | HPLC-MS  |
| • Gas chromatography with flame ionisation detection (headspace) (alcohol)                  | GC-FID   |

Both gas chromatography and high performance liquid chromatography in conjunction with mass-spectrometric detection (GC-MS and LC-MS) are the established methods for confirmation analysis today. When used correctly, they yield the most reliable results in terms of limit of detection, sensitivity and specificity. Many drugs of abuse and/or metabolites are analyzed in gas chromatography (GC, GC-MS) as derivatives. Using deuterated internal standards, even variable extraction yields can largely be compensated with this method. The reference spectrum libraries available today facilitate evaluation to a major extent. However, this method must only be used by adequately trained personnel. Otherwise, misinterpretations may readily occur.

LC-MS provides a good alternative to GC-MS confirmation, since drugs of abuse, including their metabolites, can be determined without derivatization with this method.

Diode-array and mass spectrometry are detection systems that provide improved reliability for peak identification such that MS has a markedly better specificity.

### 8.3 Areas of Application

- A:** Depending on the requirements, differential and confirmation analyses are required (quantification in serum or plasma only).
- B:** Confirmation analyses are required only if the result of an immunochemical assay is disputed by a patient.
- C:** Confirmation analyses are necessary for all positive immunotests. Depending on the case, negative findings will also require confirmation (e.g., urine samples of drug runners).
- D:** Positive findings always require confirmation.

## 9. Blood Analyses

Blood analyses are generally performed in scopes of application A and C but not in B and D.

### 9.1 Blood Analyses in Differential Diagnostics (A)

Table 7 shows the circumstances under which immunological differential analyses are recommended for determining drugs and drug groups in blood, serum, and plasma (lithium heparinate, ammonium heparinate, sodium heparinate plasma).

**Table 7: SCDAT Recommendation for the Use of Immunoassays in Serum or Plasma**

Substances, substance groups	Specimen in Original Procedure	Specimen	Specimen Pretreatment	Test Results	Cut-off <sup>1</sup> in µg/L
<b>Amphetamines</b>	Urine	Serum or plasma	Necessary	Pos/Neg	Limit of detection
<b>Barbiturates</b>	Serum <sup>2</sup> , urine	Serum or plasma	None (necessary with whole blood only)	Pos/Neg	200 – 300 (depending on test)
<b>Benzodiazepines</b>	Serum <sup>2</sup> , urine	Serum or plasma	None (necessary with whole blood only)	Pos/Neg	15 – 300
<b>Cocaine (benzoylecgonine)</b>	Urine	Serum or plasma	Necessary	Pos/Neg	Limit of detection
<b>Methadone</b>	Urine	Serum or plasma	None (depends on manufacturer)	Pos/Neg or µg/L	Limit of detection
<b>Opiates</b>	Urine	Serum or plasma	Necessary	Pos/Neg	Limit of detection
<b>THC carboxylic acid</b>	Urine	Serum or plasma	Necessary	Pos/Neg	Limit of detection
<b>Tricyclic antidepressants</b>	Serum	Serum or plasma	None (necessary for whole blood only)	Pos/Neg	300

<sup>1</sup> *Methods according to the manufacturer.*

<sup>2</sup> *Only a few manufacturers offer reagents for the analysis of this parameter in serum.*

Few manufacturers of reagents for analyzing drugs of abuse supply reagents for the analysis of barbiturates, benzodiazepines and tricyclic antidepressants in serum/plasma as well.

The other substances or substance groups can be detected in serum by urine detection methods after special sample pretreatment.

It must be pointed out that, generally, these urine tests determine the main metabolites in urine but that these metabolites are not necessarily present in high concentrations in serum. Application of these methods is basically possible only if they are validated with due care for this use.

The problems relating to immunological detection methods, as addressed in Chapter 7, also apply to most of the serum/plasma determinations (varying cross-reactions of the antibodies in the group tests from manufacturer to manufacturer, different calibration substances).

The results only provide an indication of the presence of a drug or of a substance group and do not enable the concentration to be determined. Hence, it is not possible to make a distinction between a positive result “that is present at a therapeutic concentration level” or one that is “present at a toxic concentration level”.

### 9.1.1 Alcohol determination

In clinical cases alcohol (ethanol) is determined by enzymatic methods which are usually available around the clock. It has to be considered that all alcohols which are substrates of alcohol dehydrogenase are determined with this method. This applies to isopropyl alcohol (isopropanol) which is an ingredient of many disinfectants. In case of a blood sampling for an alcohol determination other disinfectants, e.g. aqueous solutions of iodine or chlorhexidine, have to be used.

## 9.2 Blood/Serum Analyses in Forensic Investigations (C)

Where forensic investigations are concerned, generally it does not suffice to test urine for drugs by means of an immunoassay. For example, in the case of traffic violations or other crimes, where it is necessary to establish the prevailing impairment of the individuals involved or to determine the cause of death if there have been fatalities, a quantitative determination of the drugs in blood/serum must be performed following qualitative urinalysis. The methods recommended in such situations are shown in Table 8:

**Table 8: Recommendation for Quantitative Analyses in Forensic Cases**

Substances, Substance Groups	Method
Opiates and opioids	GC-MS or HPLC-MS
Cocaine and metabolites	GC-MS, HPLC-MS
THC and THC metabolites	GC-MS, HPLC-MS
Methadone and metabolite	GC-MS, GC-NPD, HPLC-DAD, HPLC-MS
Amphetamines and designer drugs	GC-MS, HPLC-DAD, HPLC-MS
Benzodiazepines, zolpidem, zopiclone	GC-MS, GC-ECD, HPLC-DAD, HPLC-MS
Barbiturates	GC-MS, GC-NPD, HPLC-DAD
GHB	GC-MS
Alcohol / ethyl glucuronide (EtG)	GC-FID, ADH / GC-MS/MS, HPLC-MS
Cotinine (nicotine)	GC-MS, GC-ECD, HPLC-DAD, HPLC-MS

The use of deuterated internal standards is recommended for GC-MS and LC-MS analyses. Immunochemical procedures conducted on blood samples may be used for orientation purposes only in forensic investigations (normally after special sample pretreatment) and not for the purpose of quantification. In this context, no cut-off concentrations can be recommended.

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## 10. Interpretation of the Results

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The results of the analyses call for interpretation in terms of analytical, toxicological, and medical considerations. In so doing, pharmacokinetic factors, such as significance and consequences of the findings, must be taken into account.

## 10.1 Stages of Interpretation

### 10.1.1 Analytical Interpretation (Laboratory Experts)

- Verification and interpretation of the results with consideration given to any pre-analytical events, “chain of custody” documents, quality assurance data, outliers and, method specifications (sensitivity, specificity, cut-off, cross-reactivity, etc.).

### 10.1.2 Toxicological Interpretation (Laboratory Experts)

- Consideration given to dose, frequency of consumption, route of application, interactions, inter-individual variability, tolerance, pharmacokinetics, pharmacogenetics, and plausibility (Fig. 4).

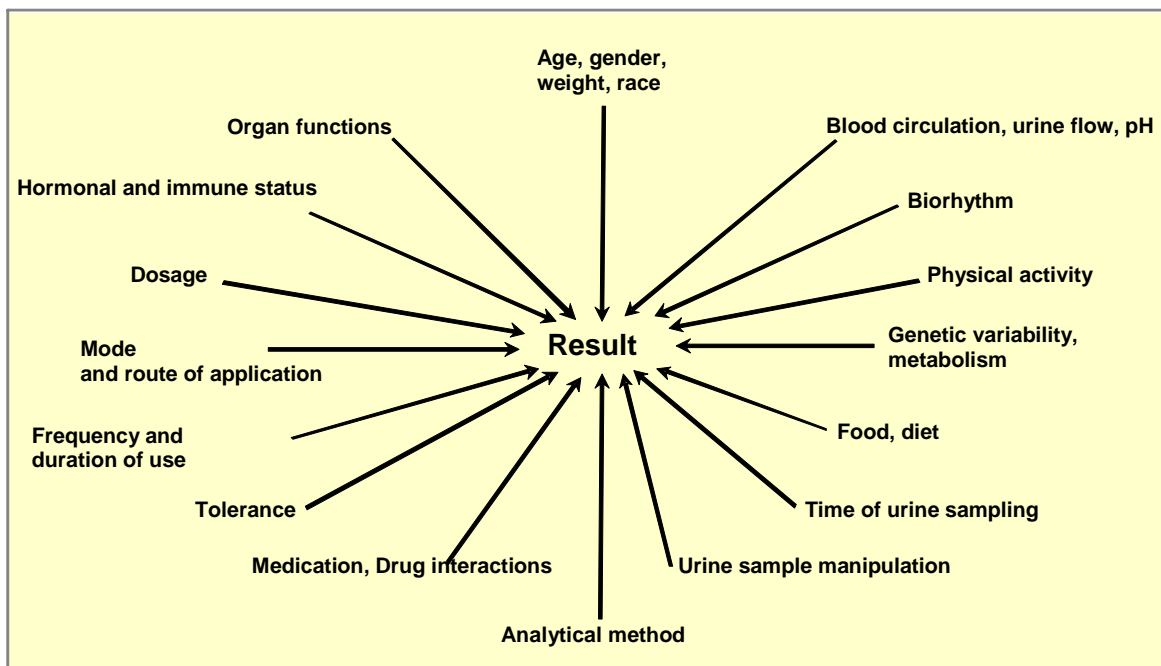
### 10.1.3 Medical Interpretation (Client, Medical Practitioner, Laboratory Experts)

- Consideration given to the patient’s medical history, e.g., any pre-existing conditions (organ function, enzyme deficiency, metabolic disorders, age).
- Evidence of drug influence at the time of the urine sample collection.
- Doctor’s prescription? Self-medication? Food?
- Plausibility check.

## 10.2 Factors Interfering with Pharmacokinetics and the Result of the Analysis

Figure 4 shows the exogenous and endogenous factors influencing pharmacokinetics, metabolism, and the analytical procedure and, ultimately, the result of the analysis.

Figure 4: Factors Influencing Pharmacokinetics and the Result of the Analysis



## 10.3 Significance of a Result

### 10.3.1 Questions to Ask When Using Immunochemical Methods

Negative finding:

- Hasn't there been any consumption to date?
- Hasn't there been any new consumption, or is there only occasional consumption?
- No consumption due to announced testing?
- Tampering with urine sample?

Positive finding:

- Confirmation using physicochemical methods?
- Chronic or occasional consumption?
- Passive inhalation (Cannabis, cocaine)?
- Cross-reactions with medication or foods?

### 10.3.2 Answers

The Immunochemical test is negative, meaning that no drugs of abuse and/or their metabolites are detectable with the applied methods:

- The individual is not consuming drugs of abuse detectable with the method used.
- The individual may possibly be consuming drugs of abuse that are not detectable.

Reasons:

- Sample mix-up
- Concentration too low
- Frequency of consumption too low
- Wrong time instant for sampling
- Manipulation of urine sample
- Method not sensitive enough, wrong reagent, faulty analytical method
- Wrong test requested.

Positive immunochemical test:

- Indication of presence of drugs of abuse and/or their metabolites in concentrations exceeding the cut-off level. Proof is established by confirmation analysis only.
- No conclusions possible concerning physical and mental state and behavior at time of incident.

Positive confirmation analysis:

- Proof of a minimum of one-time drug consumption.
- Proof of chronic drug of abuse consumption possible only in the case of long-term monitoring (multiple sampling and repeat positive results, taking clinical and social factors into consideration).

Negative immunochemical test – Positive confirmation analysis:

- The concentration of the drug of abuse established by confirmation analysis is below the cut-off level of the corresponding immunochemical test.
- The result of the immunochemical test is biased by other sample constituents and is therefore a false negative.
- The confirmation analysis was not performed correctly; the analysis has to be repeated.

## 10.4 Implications of the Finding

The findings obtained from analyses for drugs of abuse may have legal, financial, social, and medical implications. Each and every individual tested has the right to be properly tested:

- The quality of the analysis and the reliability of the result are essential not only in forensic testing but also in the socio-medical field.
- Critical interpretation of the result by the laboratory and quality assurance must be included.
- Critical interpretation of the result by the vendor (Chapter 12.1.3).

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## 11. Quality Assurance in Testing for Drugs of Abuse

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Testing for drugs of abuse should be performed in accredited laboratories. The corresponding applicable standards are ISO 15189 and ISO 17025. All measurement series are to be performed using internal quality controls. The analysis panel must be covered by external quality controls (Tables 10-11). The latter must be performed in accordance with QUALAB guidelines [[www.qualab.ch/CQI\\_d.htm](http://www.qualab.ch/CQI_d.htm) and [www.qualab.ch/EQK.htm](http://www.qualab.ch/EQK.htm)]. In the case of a method comparison, an adequate number of data points should be selected near the cut-off concentration as well.

## 11.1 Metrology Terms for Verification and Validation of Testing Procedures

The SCDAT relies on the International Vocabulary of Basic and General Terms in Metrology (VIM 2010), the Guidelines for the Validation of Physicochemical Testing Procedures and for the Determination of Measurement Uncertainty [GUM 2008] and the Guidelines and Recommendations of the GTFCh [www.gtfch.ch; Peters 2006].

Generally speaking, instruments used for laboratory analyses must undergo maintenance on a routine basis and be kept in good working order at all times. The manufacturers' operating instructions are to be heeded. In addition, laboratories must guarantee that their analyses are performed according to the current, recognized state of the art in analytical techniques.

The following parameters are to be understood as quality criteria for the methods and tests implemented and, as such, serve to document the suitability of analysis procedures for their intended purpose.

### 11.1.1 Trueness (VIM 2.14)

Trueness describes the proximity of agreement between the average of a large number of readings and a reference value. The trueness of the results of the immunochemical methods covered in these guidelines is influenced by various factors:

- Biological matrix
- Interference (documented as "selectivity" )
- Cross-reactivity (documented as "specificity" )
- Differing reactivity responses as a function of antibody concentration and affinity in the case of substance-group testing.

### 11.1.2 Precision (VIM 2.15)

Precision describes the random deviation of the values that are near the mean.. Precision is usually expressed in terms of "imprecision" and is calculated as a standard deviation of the readings obtained. High imprecision is expressed as a large standard deviation. A distinction is made between repeatability, laboratory precision, and comparative precision

*Repeatability* (in a series) describes the extent of agreement of repeated measurements of one and the same quantity, performed under the same experimental conditions. It is a measure of the random error component in a quantitative experiment.

*Laboratory precision* is obtained from a determination of one and the same sample within a laboratory, with the intentional change of one parameter (for instance, a person, an instrument, time of analysis, internal quality control on a day- to-day basis to the next).

*Comparative precision* describes precision under conditions such that readings are obtained by different individuals using different instruments, the same method, and identical sample sources in different laboratories (external quality control).

### 11.1.3 Accuracy (VIM 2.13)

Accuracy (measurement accuracy) describes the extent of the proximity of a reading to the true value of a measured quantity. It is qualified by a systematic (trueness) and a random (precision) error.

### 11.1.4 Selectivity (VIM 4.123) (Interference)

Selectivity is the capability of a measuring system to discriminate and unequivocally identify different analytes without interfering with each other or without interference due to other endogenous or exogenous substances (metabolites, contamination, degradation products, matrix).

### 11.1.5 Limit of Detection (VIM 4.18)

The limit of detection (LOD) is defined as the lowest concentration of an analyte in a sample for which the defined probability criteria are met. Neither qualitative nor quantitative results that are below this concentration are to be reported.

The limit of detection depends on:

- the analyte being sought

- the analysis method used
- the extraction that has been performed
- any possible matrix effects
- the noise level of the instrument.

#### 11.1.6 Lower Limit of Quantification

The lower limit of quantification (LLOQ) is the lowest concentration of an analyte in a sample matrix that can be determined with an acceptable measurement uncertainty (bias and imprecision), with a predefined performance uncertainty. Values below the lower limit of detection can only be interpreted on a qualitative basis.

#### 11.1.7 Sensitivity (VIM 4.12)

Sensitivity is defined as the quotient of the change in the signal of a measuring system and the change in the concentration of the substance measured. In a linear relationship, this corresponds to the sensitivity of the slope of the calibration curve. Sensitivity can be a function of the concentration of the measured substance.

#### 11.1.8 The “Cut-off”

So-called cut-off values (defined decision limits with respect to a measured quantity) are established in order to distinguish a positive result from a negative one. In group tests, a cut-off value applies to the substance used to calibrate the test procedure. The cut-off is usually set several times higher than the detection or measuring limit in order to prevent “false positive” results.

#### 11.1.9 Measurement Uncertainty (VIM 2.26)

Measurement uncertainty is a parameter of a result and signifies the dispersion of the values attributed to a measured quantity.

It can comprise the uncertainties in the different steps of an analysis:

- Sample collection
- Condition of the sample
- Sample preparation
- Size of an aliquot of the sample
- Calibration
- Reference materials
- Equipment and instruments
- Environmental conditions and tampering.

Estimation of measurement uncertainty can be specified, e.g., by way of inter-laboratory tests or with the aid of the laboratory precision computed from control samples. A standard measurement uncertainty results from the standard deviation for the measurement of quality control material across measurement days.

Measurement uncertainty constitutes an important parameter for all analyses. The narrower the range of values for a correct measurement happens to be, the more powerful is the analysis procedure [DIN 13005, Eurachem Guidelines, International Vocabulary of Metrology].

According to ISO 17025 and 15189, accredited laboratories must report any measurement uncertainties and include all results in the audit report [ISO/IEC 17025:2005, ISO 15189:2003].

#### 11.1.10 Diagnostic Sensitivity

Diagnostic sensitivity is a statistical quantity which describes the probability according to which a true positive fact will be recognized as being positive.

$$\text{Diagnostic Sensitivity} = \text{Number of (true positive)} / (\text{true positive} + \text{false negative})$$

#### 11.1.11 Analytical Specificity

Specificity is the ability of a method to determine an analyte or a substance class without being influenced by any adulterating compounds in the sample, thus identifying them conclusively.

Depending on the technology, different compounds sharing structural similarities can mimic positive results.

The lower limit of quantification in a quantitative confirmation method should, therefore, be lower than the one in the preceding test (screening test).

### 11.1.12 Diagnostic Specificity

Diagnostic specificity is a statistical quantity (hit rate) describing the probability with which a truly negative factor will be recognized as being negative in a test.

$$\text{Diagnostic specificity} = \text{Number of (true negative)} / (\text{true negative} + \text{false positive})$$

### 11.1.13 Stability

The chemical stability of an analyte in a given matrix under specific conditions should be ensured from the time instant of sample collection until the conclusion of the analysis.

Stability during storage and during possible refreezing and repeated thawing phases is independent of the method. Therefore, corresponding stability data can be carried over from the literature. The data must be collected in conjunction with method validation, should this information be unavailable.

## 11.2 Quality Control

**Table 9: Recommended Quality Assurance According to Area of Application**

	A	B	C	D
<b>Internal and external quality controls</b>	X	X	X	X
<b>Classification of the testing laboratory in accordance with the QUALAB concept, Federal List of Analyses, KVG, KVV, and KLV</b>	X	X	-	(X)
<b>In each case, confirmation analysis of positive samples</b>	-	-	X	X
<b>Depending on the case, confirmation analysis (especially in positive samples)</b>	X	X	-	-

### 11.2.1 Internal Quality Controls

According to the QUALAB guidelines, an internal quality control must be performed regularly for all medical laboratory analyses that are included in the Federal List of Analyses or that can be charged as part of a case-based lump compensation in accordance with the KVG.

A control sample must be analyzed as part of the internal quality control. It must be performed using the same reagents and sensors as those used to analyze patient samples.

[Guideline Pertaining to Internal Quality Control, Appendix Pertaining to the Quality Assurance Concept in the Medical Laboratory (QUALAB Concept), Internal Quality Control.

### 11.2.2 External Quality Control

When a laboratory performs analyses in accordance with Chapter 3 and 4.1.1 of the "QUALAB Guidelines for Compulsory External Quality Controls", it must register with a quality control center recognized by QUALAB for the number of inter-laboratory tests needed. Only the Swiss quality control centers are recognized for all primary care parameters (cf. Federal List of Analyses). Quality control centers from other countries can also be recognized for all of the other parameters upon the request of the scientific societies.

SCDAT recommends the following cut-off values in urine for the compulsory external quality checks (inter-laboratory tests):



Cannabis	50 µg/L	with respect to THC-carboxylic acid
Cocaine (metabolite)	300 µg/L	with respect to benzoylecgonine
Barbiturates	300 µg/L	with respect to secobarbital
Benzodiazepines	100 µg/L	with respect to nordiazepam
Amphetamines	1000 µg/L	with respect to amphetamine or methamphetamine
Opiates	300 µg/L	with respect to morphine
Methadone	300 µg/L	with respect to methadone

### 11.2.3 Providers of External Quality Control Programs

Table 10 contains a list of national and international institutions providing quality control programs.

**Table 10: Providers of External Quality Control Programs**

Country	Address	Area	Web Link
Switzerland CH-1	<b>Swiss Center for Quality Control (CSCQ)</b> 2 Chemin du Petit Bel-Air, CH - 1225 Chêne-Bourg	TDM Drugs of abuse Forensics Toxicology	<a href="http://www.cscq.ch">http://www.cscq.ch</a>
Switzerland CH-2	<b>MQ Verein für medizinische Qualitätskontrolle</b> Universitätsspital Zürich, CH - 8091 Zürich	Drugs of abuse	<a href="http://www.mqnet.ch">http://www.mqnet.ch</a>
Germany DE-1	<b>Arvecon GmbH</b> Kiefernweg 4 D-69190 Walldorf	TDM Forensics Toxicology	<a href="http://www.pts-gtfch.de">http://www.pts-gtfch.de</a>
Germany DE-2	<b>Institut für Standardisierung und Dokumentation im medizinischen Laboratorium e.V. (INSTAND)</b> Uwierstrasse 20, Postfach 250211, D - 40223 Düsseldorf	TDM	<a href="http://www.g-equas.de">http://www.g-equas.de</a>
Germany DE-3	<b>Deutsche Gesellschaft für Klinische Chemie und Laboratoriumsmedizin.V. (DGKL)</b> <b>Referenzinstitut für Bioanalytik (RfB)</b> Im Mühlenbach 52a, D – 53127 Bonn	TDM Drugs of abuse	<a href="http://www.dgkl-rfb.de">http://www.dgkl-rfb.de</a>
Finland FI	<b>Labquality Ltd</b> Ratamestarinkatu 11A, FI - 00520 Helsinki	TDM Drugs of abuse	<a href="http://www.labquality.fi">http://www.labquality.fi</a>
France FR	<b>Centre Lyonnais pour la Promotion de la Biologie et du contrôle de Qualité (ProBioqual)</b> 9 rue Professeur Florence, F-69003 Lyon	TDM Drugs of abuse	<a href="http://www.probioqual.com">http://www.probioqual.com</a>
The Netherlands NL	<b>Stichting Kwaliteitsbewaking Klinische Geneesmiddel-analyse en Toxicologie (KKGT)</b> P.O. Bos 43100, NL - 2504 AC Den Haag	TDM Drugs of abuse	<a href="http://www.kkgt.nl/programm.htm">http://www.kkgt.nl/programm.htm</a>

<b>United Kingdom GB</b>	<b>Cardiff Bioanalytical Services Ltd.</b> 16, Mount Stuart Square, UK Cardiff CF10 5DP, Wales	TDM Drugs of abuse	<a href="http://www.heathcontrol.com">http://www.heathcontrol.com</a>
<b>United States US</b>	<b>American College of Pathologists (CAP) Laboratory Accreditation program</b> 325 Waukegan Road, Northfield, IL 60093-2750 / USA	TDM Drugs of abuse	<a href="http://www.cap.org">http://www.cap.org</a>

#### 11.2.4 Available External Quality Control Programs

Table 11 summarizes test parameters and matrices available in various quality control programs.

**Table 11: Available External Quality Control Programs (Status as of 2010)**

Drug	CH-1	CH-2	DE-1	DE-2	DE-3	FI	FR	NL	GB	US
Alcohol	B		S		S	B			B	B
Amphetamines	BSU <sup>1</sup>	U	BSU	U	U	U	U	SU	U	BSU
Barbiturates	BSU	U	BU	SU	U	U	U	SU	U	SU
Benzodiazepines	BSU	U	BSU	SU	U	U	SU	SU	U	SU
Buprenorphine	U		SU		U	U				
Cannabis	BSU	U	BSU	U	U	U	U	SU	U	SU
Cocaine, Cocaine Metabolites	BSU	U	BSU	U	U	U	U	SU	U	BSU
EDDP	U		SU							
Ethanol	BSU	U	BSU	SU	SU	BS	S	SU	BSU	SU
Ketamine										BSU
LSD	U	U	SU	U	U				U	BSU
Methadone	BSU	U	SU	U	U	U	U	U	U	BSU
Methaqualone	BSU	U		U	U			SU	U	BSU
Opiates	BSU	U	BSU	U	U	U	U	SU	U	SU
Other Compounds										
Volatile compounds <sup>2</sup>	BS		(S)	S	S					
CDT <sup>3</sup>	S		S	SU	S					
Toxic compounds <sup>4</sup>	S		BSU		BSU		SU	SU	BSU	BSU

<sup>1</sup> S: Serum / Plasma; B: Whole blood; U: Urine.

<sup>2</sup> Acetaldehyde, acetone, ethanol, isopropanol, methanol.

<sup>3</sup> CDT marker for detecting alcohol abuse.

<sup>4</sup> Including special drugs and therapeutic drugs.

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## 12. Documentation of Results and Reports, Archiving

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The documentation serves as information while maintaining safety and confidentiality in the chain of custody. Electronic data storage media are equivalent to written material for the purposes of information and archiving.

### 12.1 Order for an Analysis

The order for an analysis, is issued using the form provided by the laboratory, The form should clearly document the analyses to be conducted. The order must include the following data:

#### 12.1.1 Precise Identification of an Order

- Name of the client<sup>2</sup>
- Date of the order<sup>1</sup> or date when received
- Signature of the client<sup>1</sup>.

#### 12.1.2 Reason and/or Clinical Details<sup>2</sup>

- Poisoning
- Substitution program or withdrawal treatment
- Forensic (e.g., traffic)
- Monitoring in the workplace, examination by company physician
- Physiological factors (e.g., pregnancy, liver or kidney ailment)
- Biological individuality (e.g., N-acetyltransferase)
- Prescribed and/or consumed drugs of abuse, therapeutic drugs, or other relevant substances
- Other clinical data (e.g. clinical status, dialysis, allergies).

#### 12.1.3 Sample Data<sup>1</sup> (in Forensic Investigations<sup>1</sup>)

- Date and time of sample collection (control)
- Sample source
- Type of sample (spot, timed urine collection)
- Special measures (emergency).

#### 12.1.4 Personal Data

- Precise identification (last name, first name, date of birth or code<sup>1</sup>)
- Address<sup>2</sup>
- Sample identification by the client<sup>2</sup>
- Gender<sup>2</sup>
- Height and Weight<sup>2</sup>.

#### 12.1.5 Tests Requested

- Correct designation of substance or substance group to be analyzed<sup>1</sup>
- Additional information, e.g., confirmation analysis<sup>2</sup>.

<sup>1</sup> *Compulsory information*

<sup>2</sup> *Optional information*

## 12.2 Report

If any non-compliant orders are received, they must be appropriately documented in the report.

### 12.2.1 Material<sup>1</sup>

- Type of sample source<sup>1</sup>
- Description of the sample prior to and subsequent to analysis<sup>2</sup>.

### 12.2.2 Result

Detection by immunochemical methods:

- Name of the single substance or substance group<sup>1</sup>
- Interpretation<sup>1</sup>
- Name of the reference substance<sup>2</sup>
- Cut-off for the reference substance<sup>2</sup>
- Obtained reading<sup>2</sup>
- Details about substances screened for but not found<sup>1</sup>
- Details about substances detected but not listed on the order form<sup>2</sup>.

Confirmation analyses (chromatographic methods):

- Name(s) of single substances found<sup>1</sup>
- Obtained reading<sup>2</sup>
- Limits of detection<sup>2</sup>, cut-off<sup>2</sup>
- Details of any measurement inaccuracies<sup>2</sup>
- Findings (Chapter 10)<sup>2</sup>
- Details about substances detected but not listed on the order form<sup>2</sup>.

### 12.2.3 Administrative Data

- Date of sample collection and/or receipt of order<sup>1</sup>
- Date of report (date when transmitted)<sup>1</sup>
- Date of analysis<sup>2</sup>
- Signature of the person responsible for the release of the report (may be in electronic form as well)<sup>1</sup>
- How transmitted (e.g., by phone, fax, email)<sup>2</sup>
- Reference to any copies<sup>1</sup>
- Reference to invoicing<sup>2</sup>
- Address of the laboratory (address for queries)<sup>1</sup>.

<sup>1</sup> *Compulsory information*

<sup>2</sup> *Optional information*

## 12.3 Archiving

All data listed under secs. 12.1 and 12.2 must be archived by the client (chapter 12.1, Order for an Analysis) and the laboratory (chapter 12.2, Report).

The data (order forms, extracts from the quality manual, measurement protocols, quality controls, calibrations, reports) must be archived in such a way that it is possible to obtain a copy of the analysis report at all times. Electronic storage media (e.g., CD-ROM or magnetic storage media) must be given preference over classic methods of archiving (on paper).

### 12.3.1 Data Retention Period

Data of an exclusively clinical nature must be kept for a minimum of 5 years (unless otherwise specified). Data protection criteria and the instructions issued by QUALAB shall also apply (Chapter 15).

Data of a forensic nature must be kept for a minimum of 10 years, unless explicitly directed by the authorities to destroy them or render them anonymous at an earlier date.

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## 13. Priority of the Results

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The priority status for obtaining results is broken down into three levels of priority, as shown in Table 12:

**Table 12**      **Priority of the Results**

Priority Level	Action	A	B	C	D
I:	Result should be available within 3 hours at most	X	-	-	-
II:	Result should be available within 24 hours at most	X	-		-
III:	Result should be available within a few days	-	X	X	X

Examples:

- I: Samples from hospitals with emergency departments. In cases of intoxication, it is vital to detect toxic substances without any loss of time (emergency situation).
- II: In extraordinary situations it is crucial for the physician to obtain a result without delay in order to be able to adjust a therapy immediately.
- III: For physicians and patients in substitution programs, it is important to be able to detect or exclude the use of any other drugs within a reasonable length of time.

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## 14. Costs, Reimbursements

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In general, when billing for drug analyses goes through health insurance companies, this must be done in keeping with the scale of rates listed in the Federal List of Analyses. This list is edited by the Swiss Federal Department of Home Affairs (FDHA) (cf. Appendix 3 of the “Kranken-Leistungs-Verordnung KLV” (“Health Care Benefits Ordinance”)).

<http://www.bag.admin.ch/kv/gesetze/e/index.htm>

The Federal List of Analyses is a “positive list”, meaning that health insurance companies need only reimburse the analyses documented in the list (Art. 34, sec. 1, KVG).

Analyses are reimbursed by the health insurance companies only if the laboratory performing the analyses takes part in the quality assurances program regulated by the KVG. The modalities of the quality assurance program must be defined in a contract with the health insurance companies (Art. 58 KVG and Art. 77 KVV). The “Schweizerische Kommission für Qualitätssicherung im medizinischen Labor” (QUALAB) (Swiss Commission for Quality Control in the Medical Laboratory) is responsible for the implementation of the quality assurance program.

### 14.1 Testing for Drugs of Abuse in the Clinical Sector and in Differential Diagnostics (A)

If the paying client is a social security agency, use of the Federal List of Analyses and its scale of rates is mandatory. Quality assurance (to be provided by the laboratory concerned) is included in this scale of rates in accordance with the guidelines prepared by QUALAB. The prerequisite for this is that the laboratory performing the analyses be accredited as a medical laboratory both by the Canton and the BSV and that quality assurance agreements be concluded between the paying clients and those performing the service, or that the laboratory or the laboratory director be members of an association that has signed said agreements on a collective basis. Billing statements are sent either to the patient’s home address or the hospital where the patient is staying as an inpatient.

## **14.2 Drugs of Abuse Testing in Substitution Programs or Withdrawal Treatment (B)**

If the paying client is a social security agency, implementation of the Federal Analysis List and its scale of rates is compulsory.

Billing statements are sent either to the patients or the institution providing treatment (lump compensation).

If the paying client is not a social security agency, individualized rates are acceptable.

A reimbursement should include the following details:

- Receipt of samples, controls, labeling and identification of the samples.
- Storage of the sample, if needed.
- Sample preparation
- The actual details of the analysis, including all costs for equipment, material, and staff
- Validation and interpretation of the results
- The actions to be taken for in-house and external quality assurance.

Any assessments or interpretations of the results of analyses are, therefore, included therein as part of the service performed.

The implementation of a scale of rates must be contractually stipulated. The billing statement is sent to the client or the representatives of the client institution as well as to any federal offices, as necessary.

## **14.3 Testing for Drugs of Abuse in Forensic Investigations (C)**

The forensic toxicology laboratories charge for analyses according to the scale of rates or schedule of fees of the institutes of legal medicine they belong to, or, as an exception, of another Institution. The latter institution has to be approved by the responsible Canton or university, as the case may be. The billing statement is sent to the client.

## **14.4 Testing for Drugs of Abuse in the Non-Traditional Sector (D)**

The billing statement for analyses shall be in accordance with the Federal Tariff List of Analyses.

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# **15. Legal Aspects, Standards, Data Privacy**

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General prerequisites are:

- The client requesting the drugs of abuse testing must be clearly identifiable.
- The legitimacy of said client to order the investigation must be known.
- The laboratory conducting the investigation must have the relevant qualifications and licenses.
- Traceability of the results must be guaranteed.
- The quality of the results must be provable.
- Results must only be made known to the person under investigation or to those whom he/she has authorized or otherwise legally entitled to obtain them.
- The laboratory conducting the investigation must disclose to the client the names of any sub-contractors.

### **15.1 Data Privacy**

Data privacy (raw data and results, patient data) must be guaranteed based on the Data Privacy Act ("Datenschutzgesetz") as well as the Health Insurance Act ("Krankenversicherungsgesetz", KVG).

On the whole, the following laws and standards are to be taken into account:

- Doctors' professional secrecy in accordance with the KVG
- Data Privacy Act
- Criminal law and official secrecy.

## **15.2 Ethical Aspects**

The ethical aspects are essentially based on Appendix C of ISO standard 15189 and the "Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine 1997-04-04".

### **15.2.1 General Information**

The laboratory defines the actions which it has to perform in a directive or in the quality manual (accredited in accordance with ISO 15189 or 17025).

### **15.2.2 Principles**

The general principle of medical ethics is primarily the well-being of the patient. The laboratory treats all samples equally and without discrimination.

### **15.2.3 Procuring Information**

The laboratory gathers sufficient information to safeguard patient and sample identification as well as the analysis and the interpretation of the results. The laboratory is not allowed to procure information that is not needed to carry out the requested laboratory investigation (e.g., religious affiliation, party affiliation, and social background of the patient). The patient will be informed about the reason for and the scope of the information gathered..

### **15.2.4 Sample Collection**

All intervention to be performed on the patient requires his/her consent.

### **15.2.5 Performing the Analysis**

The laboratory only performs those analyses for which it is qualified. Parameters not within the laboratory's scope of competence may be sent to a qualified subcontractor once the client's consent has been obtained. The laboratory analyzing the sample is responsible for the quality and interpretation of its results.

### **15.2.6 Transmitting the Results**

The laboratories have a written procedure outlining how the results are transmitted and how the patient is assured access to them.

### **15.2.7 Keeping Medical Documents**

A directive (Standard Operation Procedure, SOP) or the quality manual will provide information concerning how long the documents are to be kept and how the data are to be protected against loss, alteration, and retrieval by unauthorized individuals).

### **15.2.8 Accessing the Medical Data of the Laboratories**

The archive must be easily accessible for authorized individuals. The patient normally has access to his data via the investigator or another authorized person. If indicated in the order, the patient will have direct access to his own data as well.

### **15.2.9 Using the Samples for Other Purposes**

If the sample is used for purposes other than those requested by the client and without the prior agreement of the patient, the sample must be rendered anonymous.

### **15.2.10 Financial Aspects**

The laboratory and the investigator are not allowed to have financial agreements for the purpose of procuring additional services, repeat analyses, or for generating additional consultations, such that they compromise the independency of the interpretation and act counter to the interests of the patient.

### 15.3 Authorized Clients

Table 13 shows those individuals and institutions that are authorized to order testing for drugs of abuse and the area of application (A-D).

**Table 13: People and Institutions Authorized to Order Drug of Abuse Testing According to Area of Application**

<b>A</b>	<b>Medical personnel</b>
<b>B</b>	<b>Those authorized by withdrawal and substitution programs or who are authorized as caregivers</b>
<b>C</b>	<b>Authorized individuals and institutions who have been authorized by judiciary</b>
<b>D</b>	<b>Anyone who has a justified interest according to civil law standards, insofar as the person affected is informed and gives his or her consent. The laboratory conducting the investigation bears no responsibility.</b>

### 15.4 Laboratories Authorized to Conduct Analyses for Drugs of Abuse

Table 14 shows the institutions that are authorized to perform testing for drugs of abuse according to the area of application (A-D).

**Table 14: People and Institutions Authorized to Perform Drugs of Abuse Testing According to Area of Application**

<b>A</b>	<b>Cantonal and federally approved medical laboratories in accordance with the KVV and KLV</b>
<b>B</b>	<b>As in A, with the addition of other investigative agencies approved by the authorities</b>
<b>C</b>	<b>Forensic-toxicology departments of the Institutes for Legal Medicine, specifically laboratories approved by the authorities</b>
<b>D</b>	<b>As in B, approval in accordance with A would be desirable</b>

### 15.5 Accreditations and Authorizations for Laboratories as Required by Law

Table 15 shows the legally stipulated conditions and authorizations necessary for a laboratory.

**Table 15: Accreditation and Authorizations for Laboratories as Required by Law**

	<b>According to the Federal List of Analyses KVG</b>	<b>Compulsory quality assurance as contractually stipulated (QUALAB concept)</b>	<b>EJPD, UVEK (ASTRA) or Cantonal judicial authorities</b>
<b>A</b>	<b>X</b>	<b>X</b>	<b>-</b>
<b>B</b>	<b>X</b>	<b>X</b>	<b>-</b>
<b>C</b>	<b>-</b>	<b>-</b>	<b>X</b>
<b>D</b>	<b>-</b>	<b>-</b>	<b>-</b>



## 15.6 Confidentiality of Unsolicited Positive Results

In accordance with Article 10 of the “Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine 4 April 1997 [European Council 1997]”, every human being has the right to information concerning all details gathered about his or her health. All requested results must be transmitted to the person, or as the case may be, agency, person, or office designated by the legal system. In so doing, please note that the interest and welfare of the living human being have priority over the mere interest of society or science. Even results that have not been requested must be treated confidentially (Table16).

**Table 16: Confidentiality of Unsolicited Positive Results**

	<b>Routine check</b>	<b>Additional results permitting conclusions to be made with regard to additional drug use</b>
<b>A</b>	<b>1</b>	<b>1</b>
<b>B</b>	<b>1</b>	<b>2</b>
<b>C</b>	<b>1</b>	<b>2</b>
<b>D</b>	<b>1</b>	<b>2</b>

<sup>1</sup> *Inform the client.*

<sup>2</sup> *Disclose to attending (treating) medical personnel only.*

## 16. Pharmacokinetics, Detectability

The detectability of drugs of abuse depends on different factors. Unless otherwise indicated, the information below refers to detectability by immunochemical methods.

### 16.1 Alcohol (ethanol) and ethyl glucuronide (EtG)

Scene name: ---

Absorption: 20 min to 2 h (values in traffic cases).

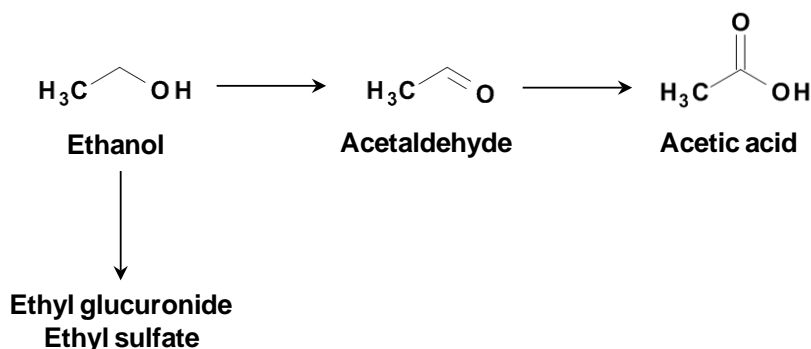
Elimination: 0.1 g/kg to 0.2 g/kg per hour.

Detectability: Alcohol: depends on dose.  
Ethyl glucuronide: 2-3 days in urine, up to 1 day in blood.

Metabolism: Ethanol is metabolized to acetaldehyde and acetic acid (Fig. 5). The conjugates ethyl glucuronide (specific biomarker for alcohol consumption) and ethyl sulfate (side product in small concentration) are produced by glucuronidation and sulfatation [Baselt 2011, Alt 1997, Abbott Laborlexikon].

T<sub>1/2</sub>\*: 2-14 h.  
\*Subsequently always defined as elimination half-life.

Figure 5: Metabolism of Alcohol (Ethanol)



### 16.2 Amphetamine and Derivatives

#### 16.2.1 Amphetamine

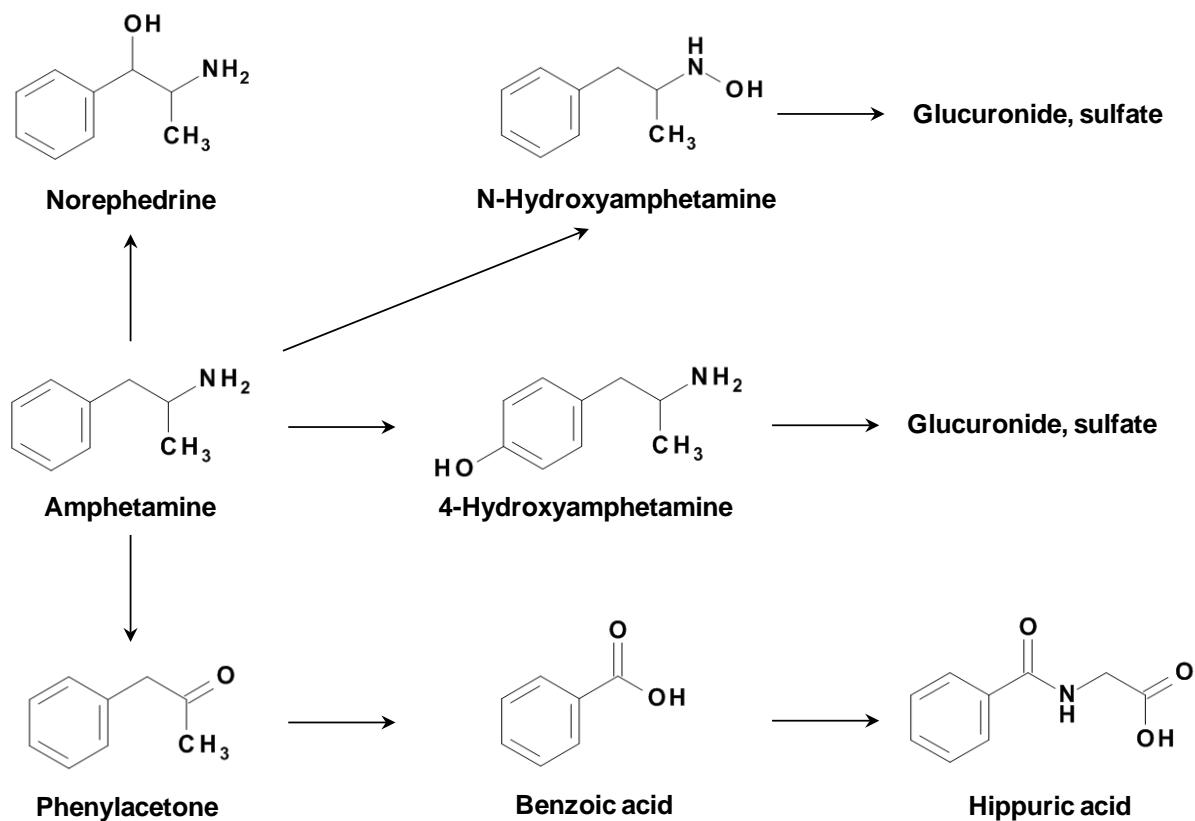
Scene name: Speed.

Metabolism: Rates of metabolism (Fig. 6) and excretion are pH-dependent: an acidic pH increases (e.g., amphetamine: up to 78% / 24 h, 68% unchanged), an alkaline pH lowers excretion in urine (45% / 24 h, 2% unchanged). It has to be noted that certain drugs (e.g., appetite suppressants) are metabolized to amphetamine (Fig. 9).

T<sub>1/2</sub>: 7 - 34 h, depending on urine pH [Baselt 2011]. Amphetamine appears in urine within 20 min after application.

Detectability: -72 h, depending on dose and frequency of use.

**Figure 6: Metabolism of Amphetamine**



### 16.2.2 Cathinone, Methcathinone, Methyldmethcathinone (Mephedrone, 4MMC)

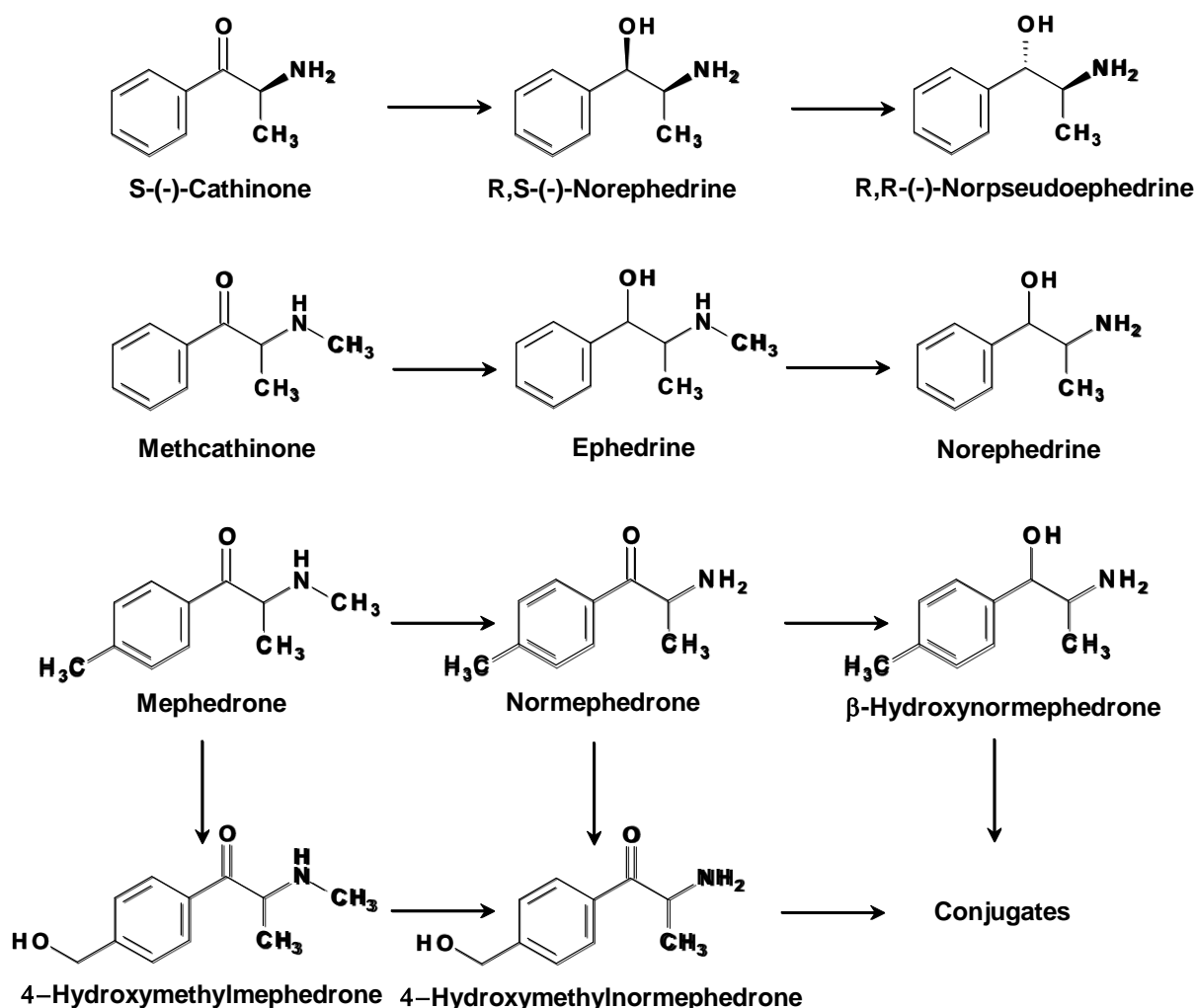
Scene names: Cat (methcathinone); M-Cat, Meouw (methyldmethcathinone).

Metabolism: Cathinone is rapidly metabolized by reduction (Fig. 7). After a single dose 2.4% are eliminated unchanged in the 24-h urine, 28% as norephedrine, and 3.8% as norpseudoephedrine [Brenneisen 1986]. Ephedrine and pseudoephedrine are the main metabolites of methcathinone [Paul 2001]. Methyldmethcathinone (mephedrone) is metabolized by demethylation, reduction and hydroxylation to normephedrone (methcathinone), hydroxymethylmephedrone and hydroxynormephedrone [Meyer 2010]. The hydroxylated metabolites are primarily eliminated as conjugates.

T<sub>1/2</sub>: Cathinone: 2.7 - 6 h.

Detectability: Cathinone: 4 - 8 h. Cathinone is the specific urine marker for the detection of khat consumption.

**Figure 7: Metabolism of Cathinone, Methcathinone and Methylnormcathinone**



### 16.2.3 Methamphetamine

Scene names: Meth, Crystal, Crystal Meth, Ice, Crank, Jaba.

Metabolism: Under normal conditions up to 43% of methamphetamine is excreted unchanged within 24 h, 4 - 7% as amphetamine and 15% as hydroxymethamphetamine (free or conjugated) (Fig. 8). In acidic urine up to 76% are excreted unchanged within 24 h and 7% as amphetamine. Basic urine reduces the excretion rate to 2% and <0.1%, respectively [Baselt 2011]. It has to be noted that a number of drugs are metabolized to methamphetamine (Fig. 9).

T<sub>1/2</sub>: 6 - 15 h, depending on the urine pH. Methamphetamine appears in urine within 20 min after application.

Detectability: -65 h, depending on dosis and frequency of use [Huestis 2007].

**Figure 8: Metabolism of Methamphetamine**

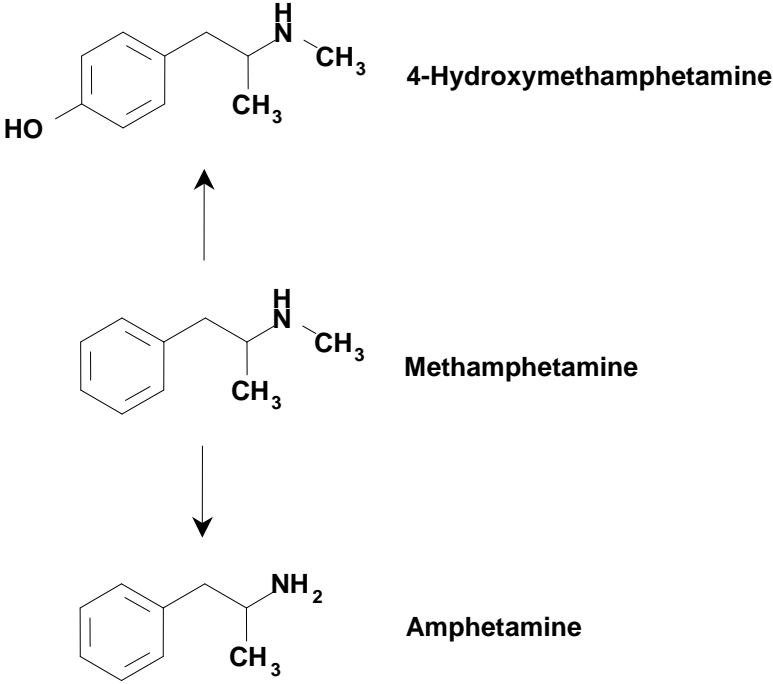
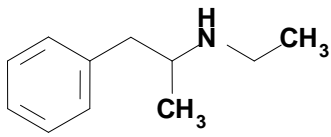
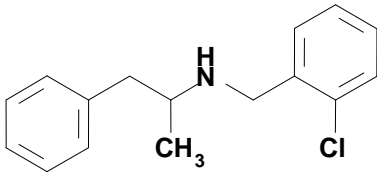


Figure 9: Drugs with Amphetamine or Methamphetamine as Metabolite

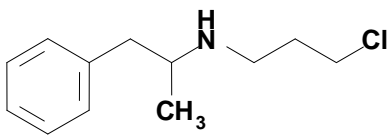
Amphetamine as Metabolite



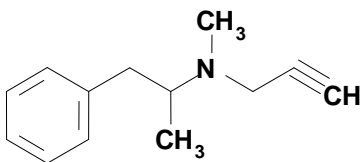
Ethylamphetamine



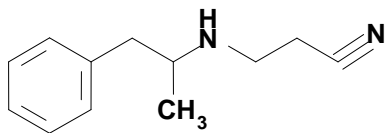
Clobenzorex



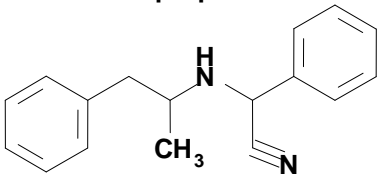
Mefenorex



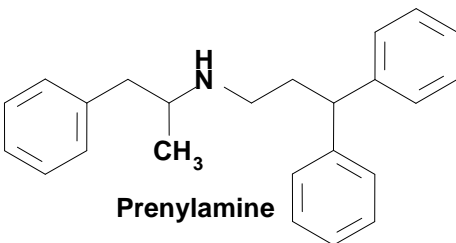
Selegiline



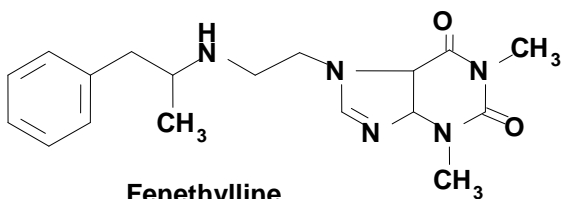
Fenproporex



Amfetaminil

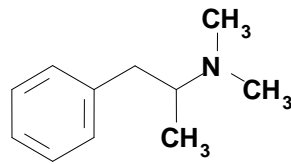


Prenylamine

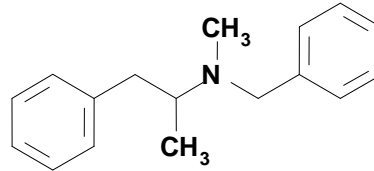


Fenethylline

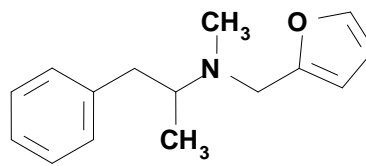
Methamphetamine as Metabolite



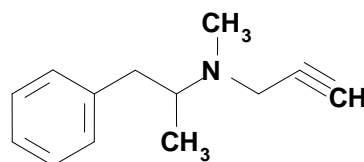
Dimethylamphetamine



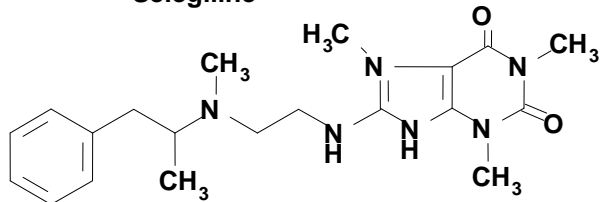
Benzphetamine



Furfenorex



Selegiline



Fencamine

## 16.2.4 3,4-Methylenedioxyamphetamine (MDMA)

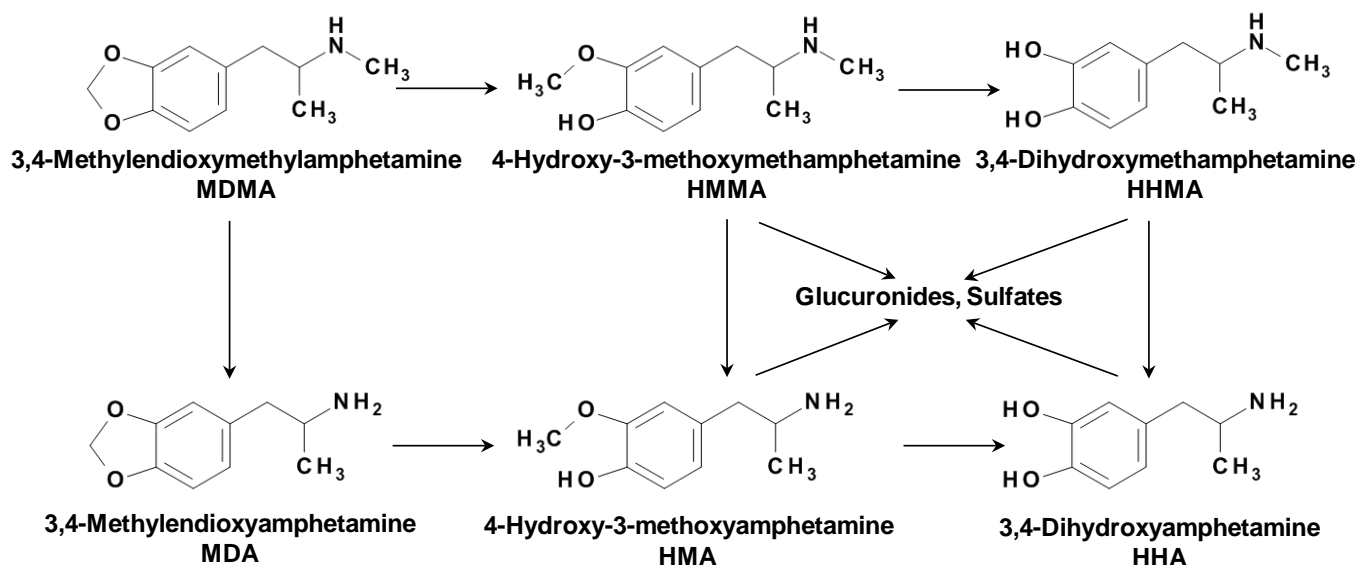
Scene names: Ecstasy, Exstasy, XTC.

Metabolism: MDMA is excreted predominantly unchanged. Metabolites (Fig. 10) are formed by D-demethylation, oxidative ring cleavage, methylation and glucuronidation. The main urinary metabolite is 4-hydroxy-3-methoxymethamphetamine (HMMA), which is mainly excreted as glucuronide [Helmlin 1996, Maurer 1996]. After oral application of 100-125 mg MDMA 26% of the dose is excreted unchanged within 24 h, 23% as HMMA, 20% as 3,4-dihydroxymethamphetamine, 1% as MDA and 0.9% as 3-hydroxymethamphetamine. 3,4-Methylenedioxyamphetamine (MDA) is mainly excreted unchanged. 3,4-Methylenedioxyethylamphetamine (MDE, "Eve") is metabolized by ring cleavage, conjugation, N-deethylation and deamination.

T<sub>1/2</sub>: 5 - 9 h.

Detectability: 1 - 4 days.

Figure 10: **Metabolism of 3,4 Methylenedioxyamphetamine**



## 16.3 Barbiturates

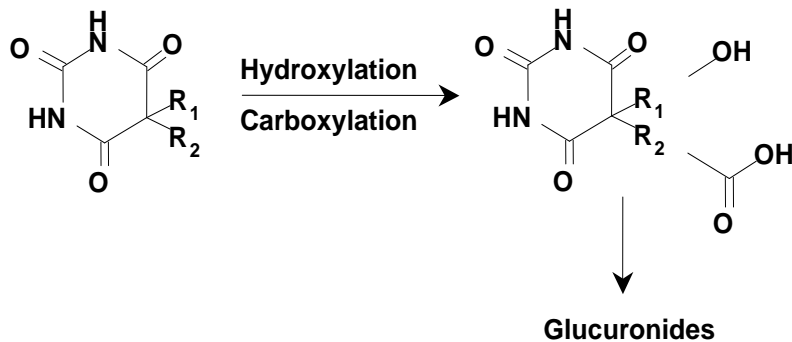
Scene names: Barbs, Barbies, Downers.

Metabolism: Phenobarbital, pentobarbital, cyclobarbital, etc.: oxidation of the substituents R1 and/or R2 at C-5' hydroxylation, carboxylation, etc. with subsequent conjugate formation (particularly glucuronides) (Fig. 11). Phenobarbital is excreted 25% unchanged, pentobarbital 50% unchanged. Thiobarbiturates: → desulphuration of S-2. Methylphenobarbital: → N-demethylation.

T<sub>1/2</sub>: 15 - 48 h (pentobarbital), 48 - 120 h (phenobarbital) 15 - 40 h (secobarbital).

Detectability: Pentobarbital: up to 5 days; phenobarbital: up to 8 days.

Figure 11: Metabolism of Barbiturates



## 16.4 Benzodiazepines

Scene names: Benzos, Downers; Rophies, Roofies, R2 (flunitrazepam).

Metabolism: 1,4-Benzodiazepines (diazepam, chlordiazepoxide, etc.): The main metabolites, nordiazepam and oxazepam, are formed as a result of desalkylation, oxydation, and hydroxylation and are eliminated via the kidneys as glucuronides following 3-hydroxylation (Fig. 12).  
7-Nitrobenzodiazepines (flunitrazepam, nitrazepam, etc.): Metabolization by reduction to 7-amino derivatives, N-acetylation, N-demethylation, 3-hydroxylation and 3-glucuronidation. Flunitrazepam is excreted less than 1% unchanged (Fig. 13).  
Triazolobenzodiazepines: 1- and 4-hydroxylation; also, formation of benzophenones (alprazolam) by ring cleavage (Fig. 14).

$T_{1/2}$ : 20 - 40 h (diazepam), 40 - 100 h (nordiazepam), 10 - 30 h (flunitrazepam), 8 - 20 h (bromazepam), 1 - 30 h (triazolam).

Detectability: Days to months (after long-term consumption).



Figure 12: Metabolism of 1,4-Benzodiazepines

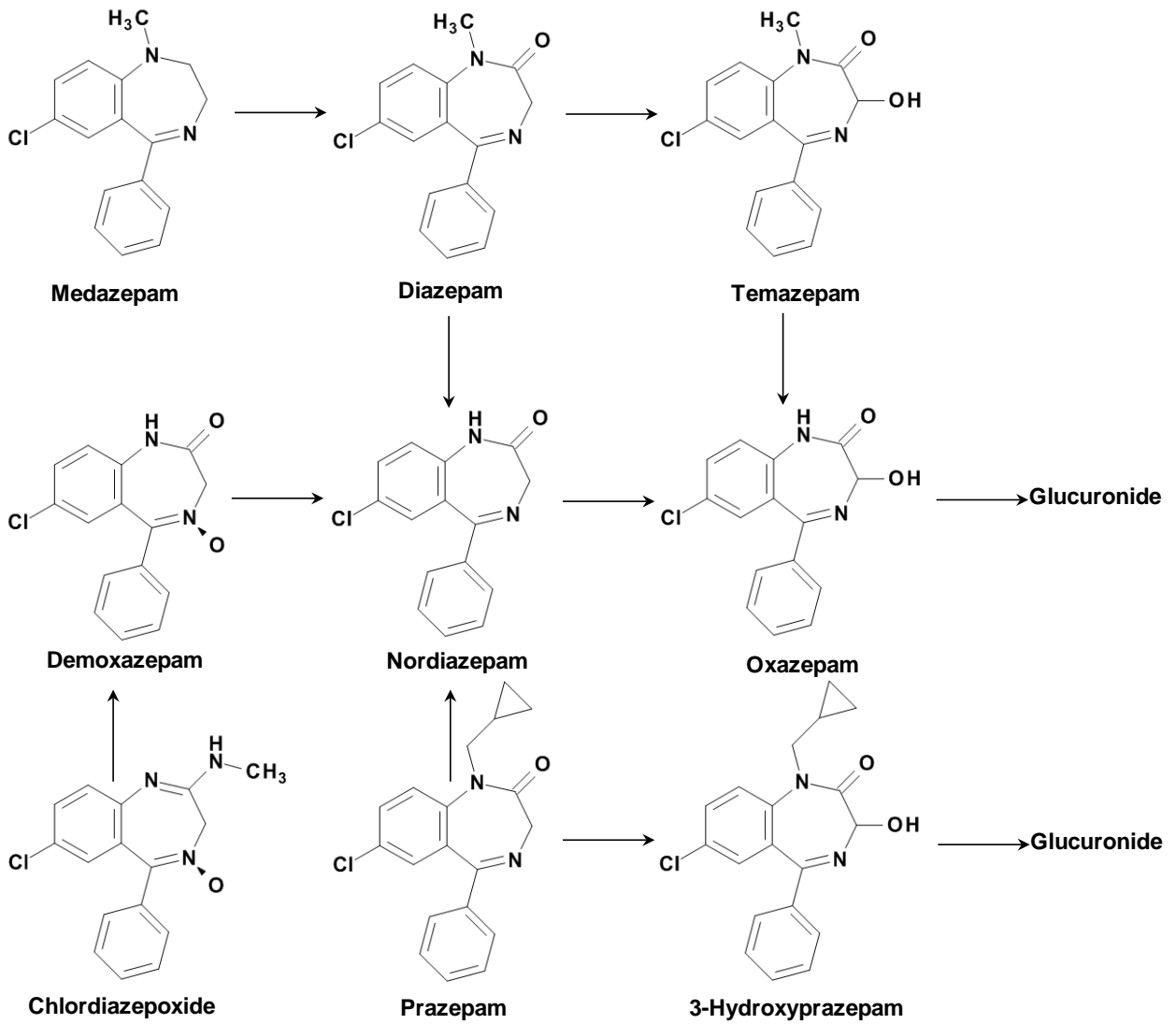


Figure 13: Metabolism of 7-Nitrobenzodiazepines

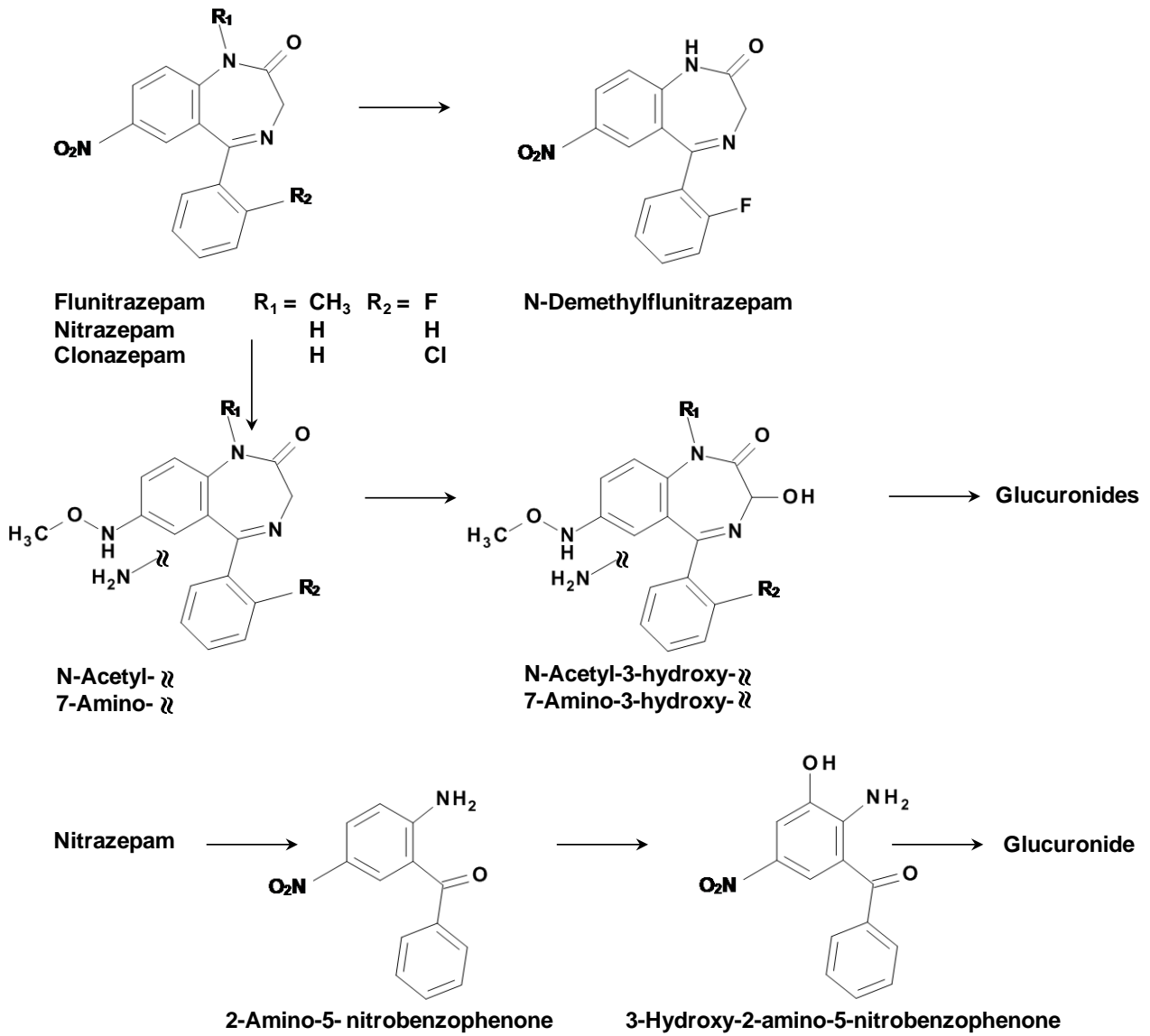
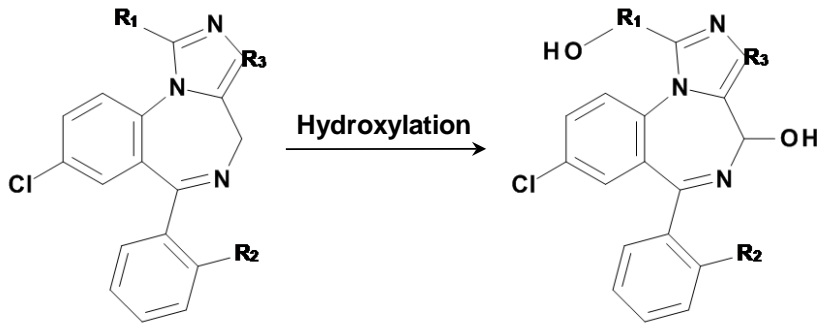


Figure 14: Metabolism of Triazolobenzodiazepines



Alprazolam	R <sub>1</sub> : CH <sub>3</sub>	R <sub>2</sub> : H	R <sub>3</sub> : N
Brotizolam	: CH <sub>3</sub>	: Cl	: N
Midazolam	: CH <sub>3</sub>	: F	: CH
Triazolam	: CH <sub>3</sub>	: Cl	: N

## 16.5 Cannabis

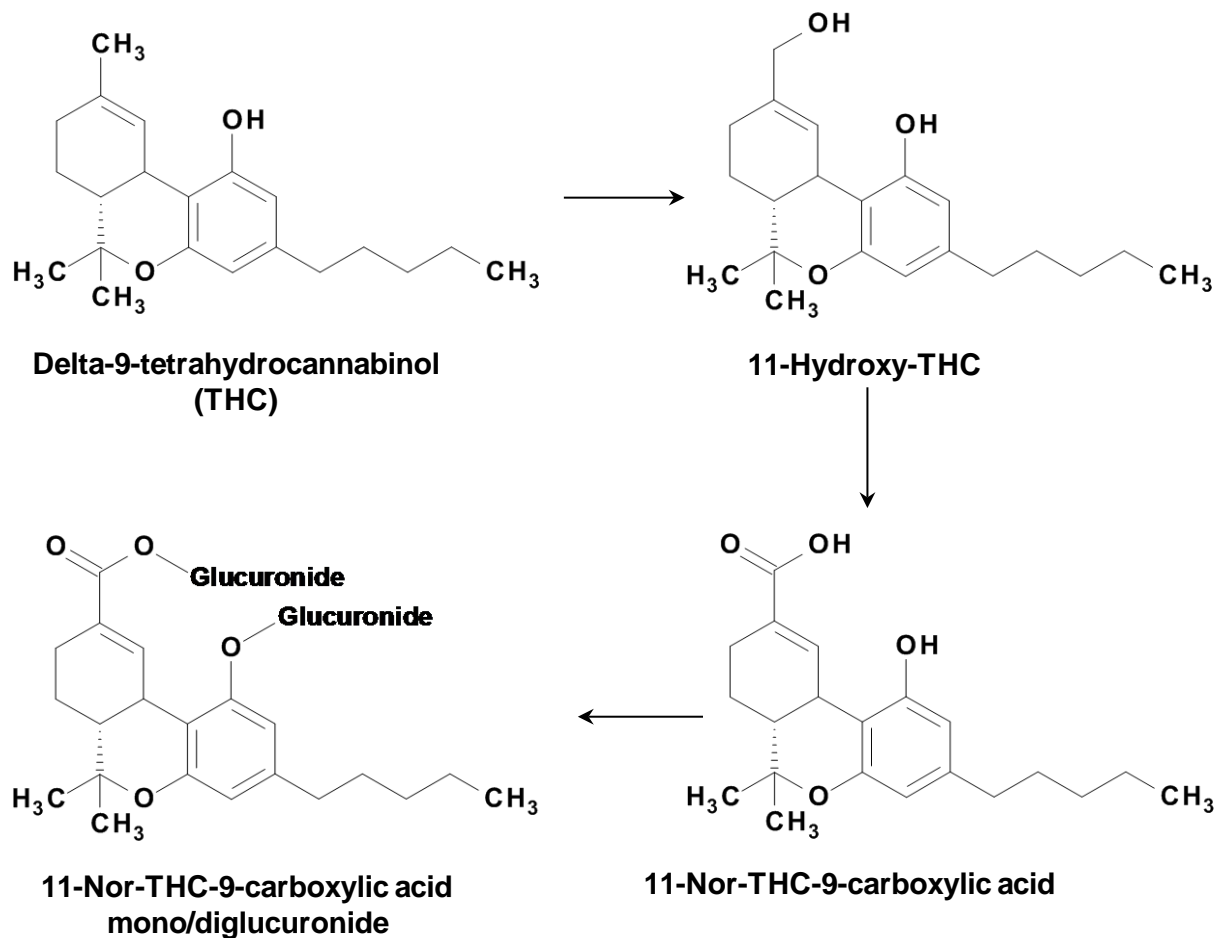
Scene names: Marijuana, Marihuana, Pot, Gras, Grass, Bhang (Cannabis leaves and flowers); Hash, Piece (Cannabis resin).

Metabolism: Oxidation of C-11 (of the side chain as well) results in the formation of hydroxy and carboxy metabolites, which are mainly excreted as glucuronides (Fig. 15). In addition, fatty acid conjugates have been identified as remaining in the body for an extended period of time. About one-third of the absorbed THC dose is excreted in urine and two-thirds via the feces [Huestis 1999, McGilveray 2005, Musshoff 2006, Iversen 2000].

T<sub>1/2</sub>: THC, plasma: 2 h to 4 days; 11-nor-THC-9-carboxylic acid: 1 - 3 days.

Detectability: Up to 3 days (one-time consumption), up to 30 days (occasional consumption, once a week), up to 80 days (continuous consumption). The long urinary detection window can primarily be attributed to multi-compartment kinetics, multi-phase distribution, and multi-phase elimination, as well as the high affinity of THC for adipose tissue. THC and 11-hydroxy-THC should be used as target urine analytes, instead of 11-nor-THC-9-carboxylic acid, to detect recent Cannabis consumption [Manno 2001, Brenneisen 2010]. However, this only applies to occasional consumption. Chronic users exhibit a correspondingly longer detection window [Karschner 2009].

Figure 15: Metabolism of Delta-9-Tetrahydrocannabinol (THC)



## 16.6. Cocaine

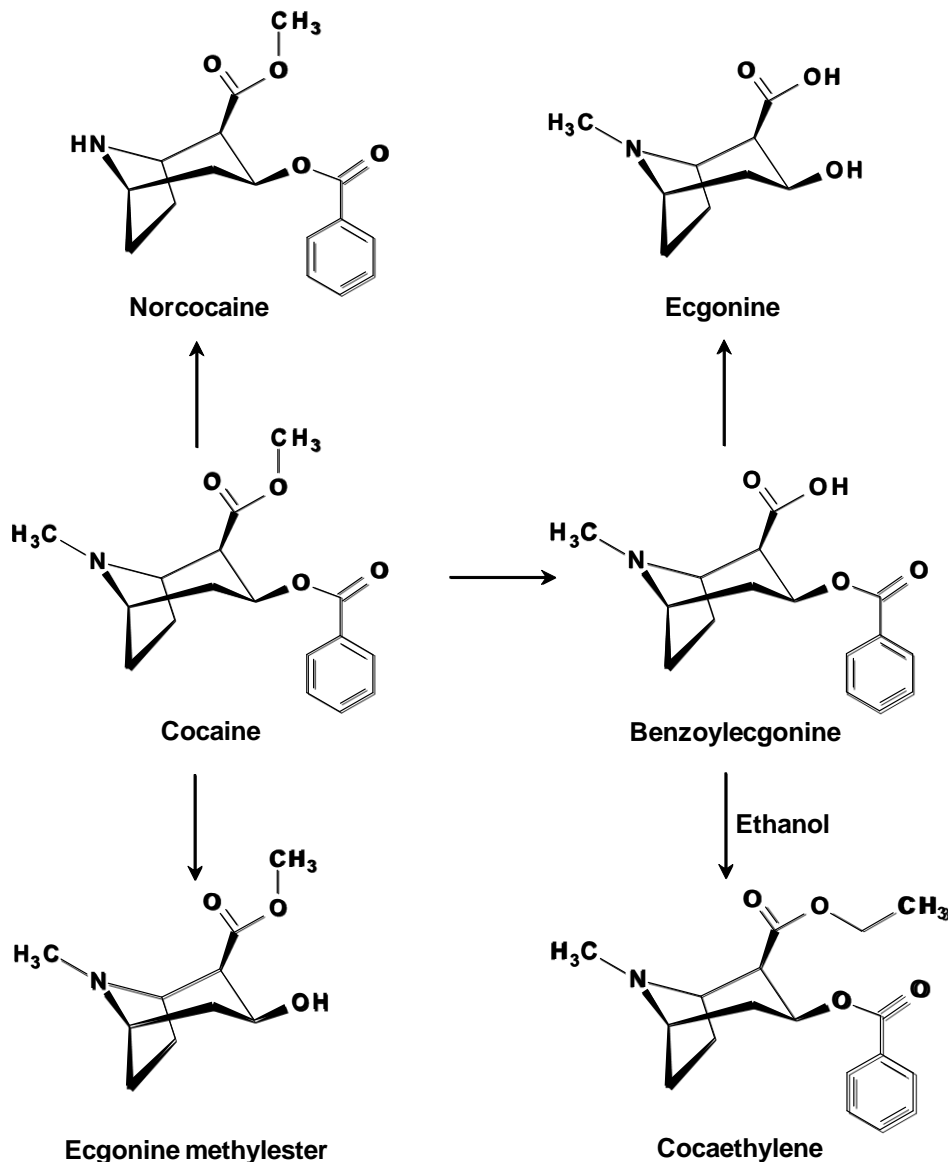
Scene names: Coke, Snow, Charlie, Crack.

Metabolism: The main metabolites of cocaine are benzoylecgonine and ecgonine methyl ester (methylecgonine) (Fig. 16). They are formed by enzymatic (pseudocholinesterase) or spontaneous hydrolysis. Anhydroecgonine methylester is a specific marker for "crack" consumption, while cocaethylene is detectable after the simultaneous consumption of alcohol.

T<sub>1/2</sub>: 0.5 - 1.5 h (cocaine), 3.5 - 8 h (benzoylecgonine), 3.5 - 6 h (ecgonine methyl ester).

Detectability: 4 - 12 h (cocaine), 1 - 4 days (benzoylecgonine), up to 5 days (benzoylecgonine, long-term consumption).

Figure 16: Metabolism of Cocaine



## 16.7 Gamma-Hydroxybutyrate (GHB)

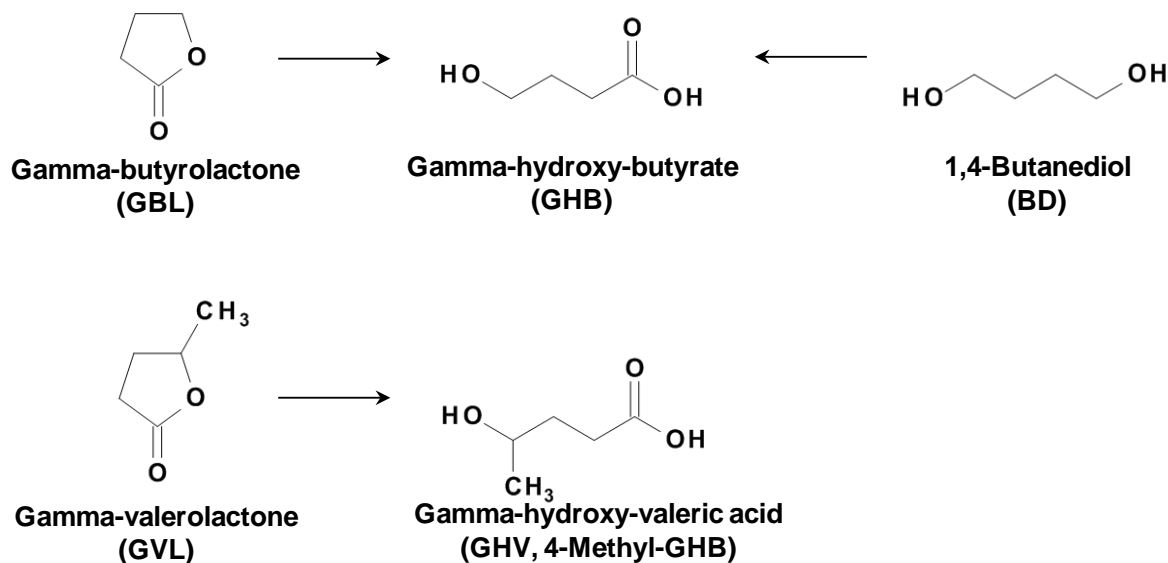
Scene names: GHB: Fantasy, G, K.O. Drops, Liquid Ecstasy, Natriumoxybate, Salty Water, Soap.  
 GBL: Renewtrient, Blue Nitro, Gamma G; BD: Borametz, BVM, Promusol, Thunder Nectar.

Metabolism: GHB is almost completely metabolized to water and carbon dioxide by alcohol dehydrogenase. Specific metabolites are not known. Generally less than 5% of a GHB dose is excreted unchanged in urine, ( e.g., only about 1% after 25 mg/kg GHB).  
 Gamma-butyrolactone (GBL) and 1,4-butanediol (BD) are substances which, after oral ingestion, are metabolized rapidly to very rapidly (GBL) in the body to become GHB (Fig. 17). The responsible enzymes are a lactonase for GBL and an alcohol dehydrogenase/aldehyde dehydrogenase for BD, respectively. The effect of GBL and BD is based on their transformation into GHB.  
 Gamma-valerolactone (GVL) is metabolized into gamma-hydroxy-valeric acid (GHV, 4-methyl-GHB).

T<sub>1/2</sub>: GHB 20 - 60 min.

Detectability: About 1 - 5% of the dose was recovered in urine after an oral dose of 25 mg GHB per kg, resulting in a detection window of 12 h at most (serum ≤6 h) [Brenneisen 2004, Baselt 2008].  
 Note: Enzymatic tests [Sciotti 2010], GC-MS [Brenneisen 2004], HPLC-MS/MS or HPCE-UV/MS [Baldacci 2003] can be used for the determination in plasma or urine.

**Figure 17: Metabolism of Gamma-butyrolactone (GBL) and Gamma-valerolactone (GVL)**



## 16.8 Ketamine

Scene names: K, Kate, Barbara, Ket, Kitty, Kiti, Special K, Multiketamine, Fiction, Keta.

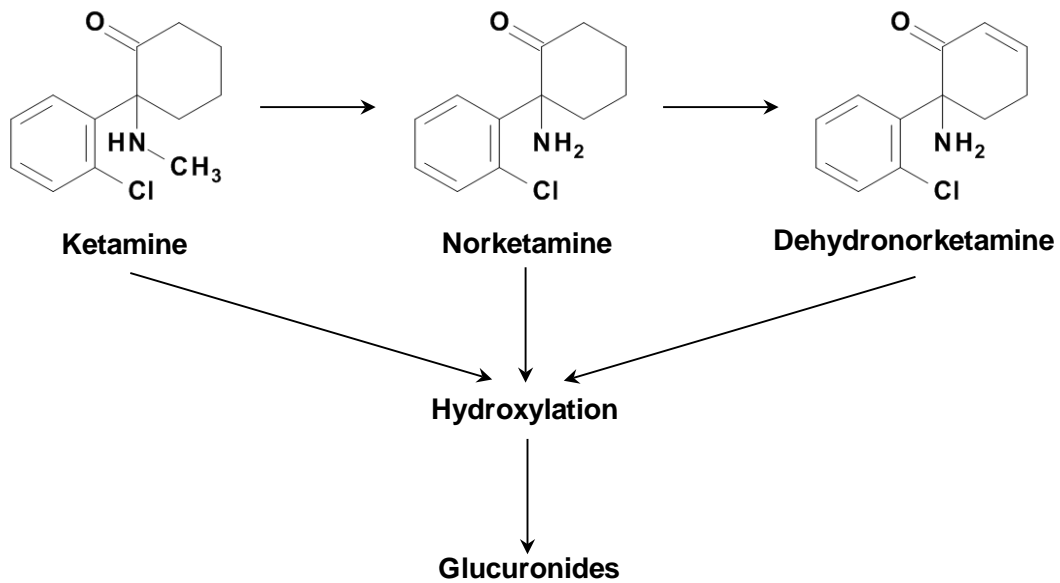
Metabolism: Ketamine is metabolized in the liver primarily via N-demethylation and hydroxylation and subsequent conjugation (Fig. 18). The main pathway consists of N-demethylation by cytochrome P<sub>450</sub> into norketamine, an active metabolite with one third of the anesthetic potency of ketamine [Baselt 2011].

T<sub>1/2</sub>: 3 - 4 h (ketamine), 240 min (norketamine).

Detectability: 1 day.

Note: No immunological methods are available; detectable in urine and blood with GC-MS or HPLC-MS (ketamine, norketamine, dehydro-norketamine, and conjugates) [Baselt 2011] only.

Figure 18: Metabolism of Ketamine



## 16.9 Lysergic Acid Diethylamide (LSD)

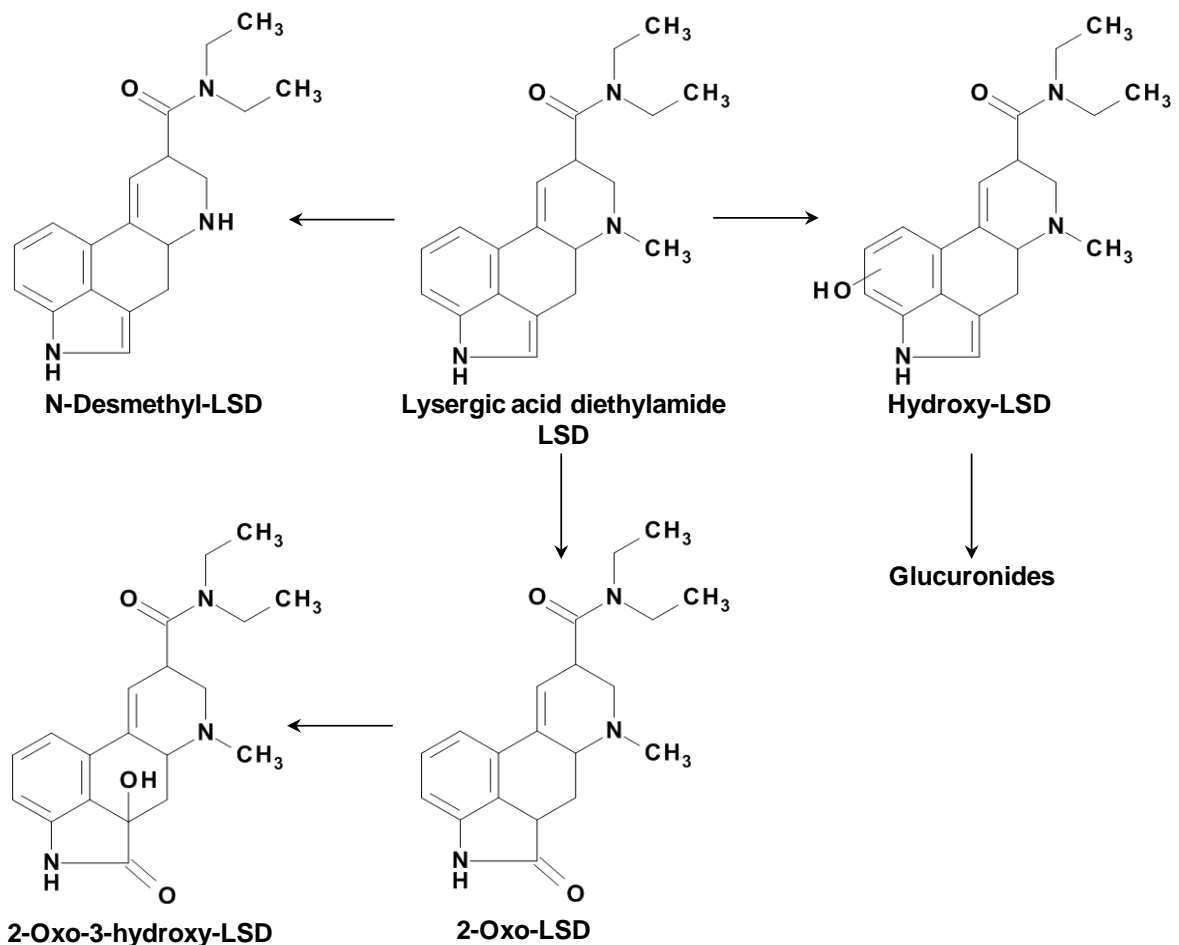
Scene names: Trips, Mikros, Acid.

Metabolism: N-demethylation, N-deethylation, hydroxylation and glucuronidation are the main metabolic pathways of LSD (Fig. 19). The predominant metabolites in urine are 2-oxo-3-hydroxy-LSD and nor-LSD. Additional metabolites are nor-iso-LSD, lysergic acid ethylamide, trioxylated-LSD, lysergic acid ethyl-2-hydroxyethylamide, and 13-/14-hydroxy-LSD as well as their glucuronides [Canezin 2001].

T<sub>1/2</sub>: 3 - 4 h.

Detectability: 1 - 2 days.

**Figure 19: Metabolism of Lysergic Acid Diethylamide (LSD)**



## 16.10 Methadone

Scene names: Dolly, Doll, Red Rock.

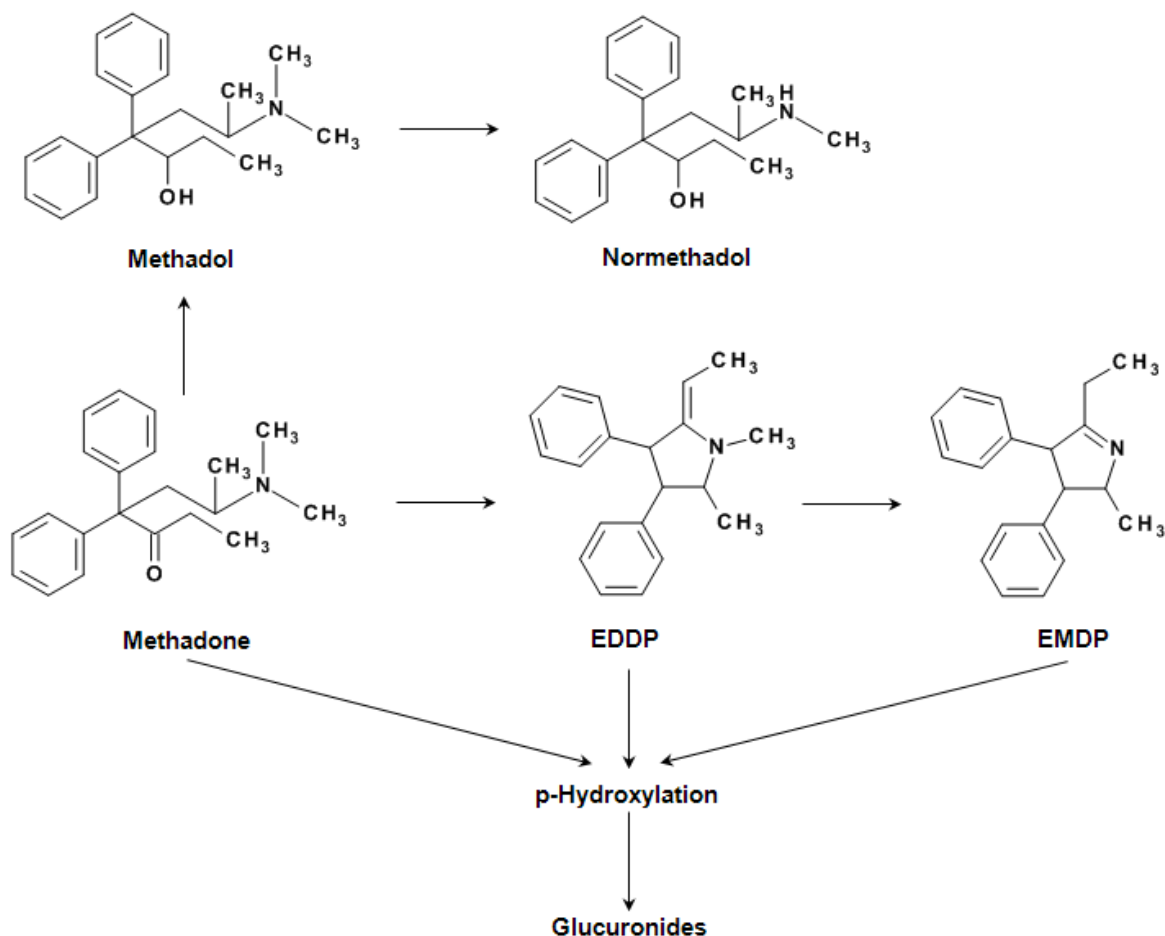
Metabolism: Methadone is metabolized by mono-, di-N-demethylation and subsequent spontaneous cyclization into 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), and 2-ethyl-5-methyl-3,3-diphenylpyrrolidine (EMDP) followed by glucuronidation (Fig. 20). The main metabolite is EDDP [Baselt 2008].

T<sub>1/2</sub>: 15 - 55 h.

Detectability: Methadone 1.5 - 3 days, EDDP 3 - 4 days.  
 The additional determination of EDDP is recommended for compliance testing as the metabolism of methadone is strongly accelerated by interaction with co-medications as well as in case of fast metabolizers (see chapter 10). This also enables to detect urine adulterations by addition of methadone (selling remaining methadone/spiker):  
 Methadone and EDDP negative: no methadone consumption.  
 Methadone and EDDP positive: methadone consumption.  
 Methadone negative, EDDP positive: fast metabolizer, interaction with co-medication.  
 Methadone positive, EDDP negative: spiker.



**Figure 20**      **Metabolism of Methadone**



### 16.11 Methaqualone

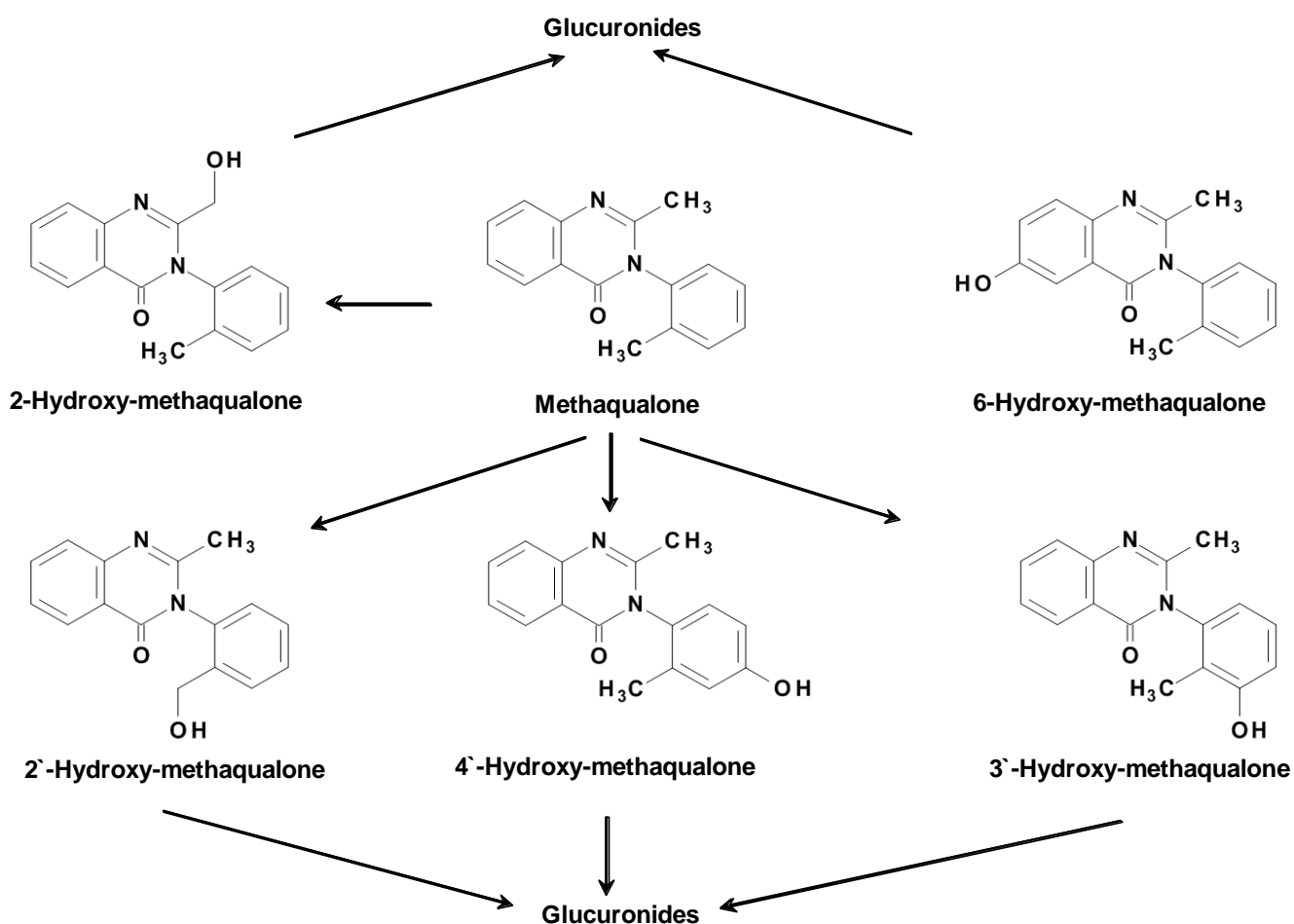
Scene names:      Seven-one-fours, Seventeen, Lemmon 714, Mandrax.

Metabolism:      Methaqualone is metabolized by hydroxylation at various positions, thus resulting in numerous metabolites, including a dihydroxy- and an N-oxidized derivative (Fig. 21) [Brenner 1996]. The main metabolites are methaqualone-N-oxide, 4'-hydroxy-methaqualone glucuronide, 2'-hydroxy-methyl-methaqualone glucuronide, 3-hydroxy methaqualone, 2-hydroxy-methyl-methaqualone glucuronide, 6-hydroxy-methaqualone glucuronide.

T½:                    20 - 60 h.

Detectability:      3 - 4 days.

Figure 21: Metabolism of Methaqualone



## 16.12 Methylphenidate

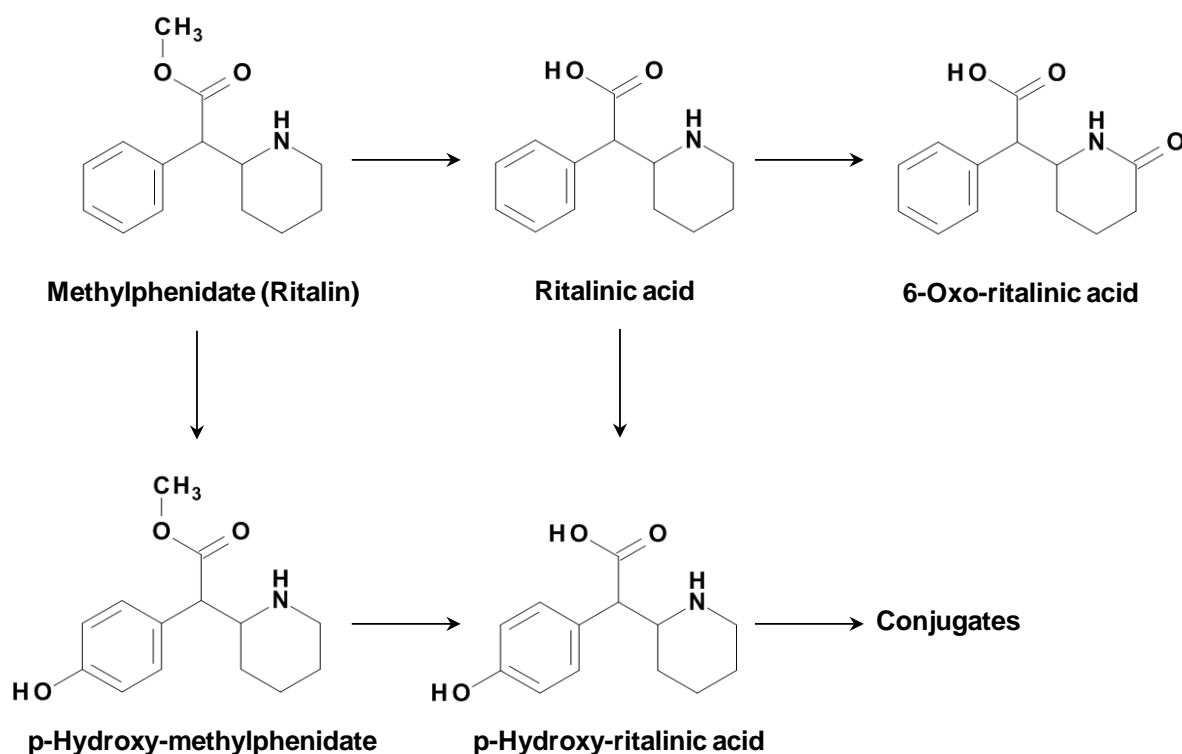
Scene names: Ritas, Pep.

Metabolism: Methylphenidate (Ritalin) is rapidly metabolized to the inactive ritalinic acid (Fig. 22). Other metabolites are formed by hydroxylation, methylation, oxidation and conjugation. Ethylphenidate can be detected after co-consumption of ethanol. 80% of a methylphenidate dose is excreted within 24 h, 60-81% as ritalinic acid and 5-12% as 6-oxo-ritalinic acid [Baselt 2011]. Less than 1% is excreted unchanged; however, the percentage can be higher at acidic urine pH.

T<sub>1/2</sub>: 1.4-4.2 h.

Detectability: At least 24 h (20 mg oral therapeutic dose [Solans 1994]). Note: Methylphenidate cannot be detected by amphetamine and methylamphetamine immunoassays [Taylor 2004]. Therefore, for the detection of use a specific ELISA, GC/MS or HPLC-MS/MS is required [Solans 1994, Eichhorst 2004, Paterson 2012].

**Figure 22: Metabolism of Methylphenidate**



### 16.13 N-Benzylpiperazine (BZP) and Related Substances

Scene names: A2, BZP.

Metabolism: N-Benzylpiperazine (BZP) is mainly metabolized by hydroxylation, N-desalkylation, O-methylation and conjugation (Fig. 23 and 24) [Balmelli 2001, Staack 2002, Antia 2009, Baselt 2011]. About 6% of a BZP dosis is excreted unchanged in urine, the 2 metabolites 3'-hydroxy-BZP and 4'-hydroxy-BZP only in traces (0.11%). So far, no other excretion pathways are known, therefore, a low bioavailability can be expected (about 12.5%) [Antia 2009]. Other piperazine derivatives are 1-(3,4-methylenedioxybenzyl)-piperazine (MDBP), 1-(4-methoxyphenyl)-piperazine (MeOPP), 1-(3-trifluoromethylphenyl)-piperazine (TFMPP) and 1-(3-chlorophenyl)-piperazine (mCPP). TFMPP is metabolized by hydroxylation, cleavage of the piperazine ring and conjugation. The main urinary metabolite is 4-hydroxy-TFMPP [Staak 2003].

T<sub>1/2</sub>: 4 - 6 h.

Detectability: 24 - 48 h.

Note: So far no immunological methods are available. Therefore, the detection of use can only be performed by chromatographic methods, such as HPLC-DAD, HPLC-MS oder GC-MS [Tsutsumi 2005, Moreno 2011].

Figure 23: Metabolism of N-Benzylpiperazine (BZP)

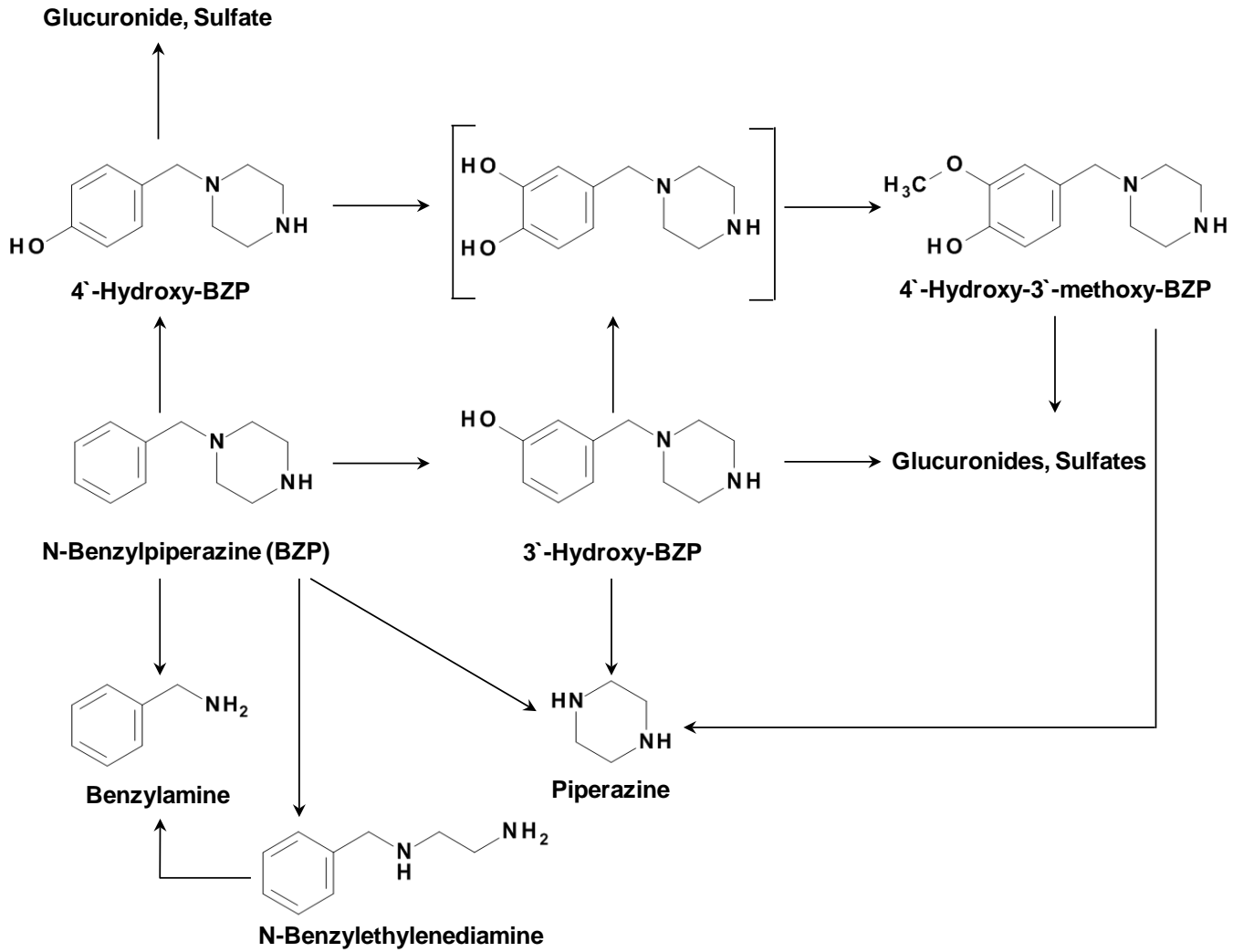
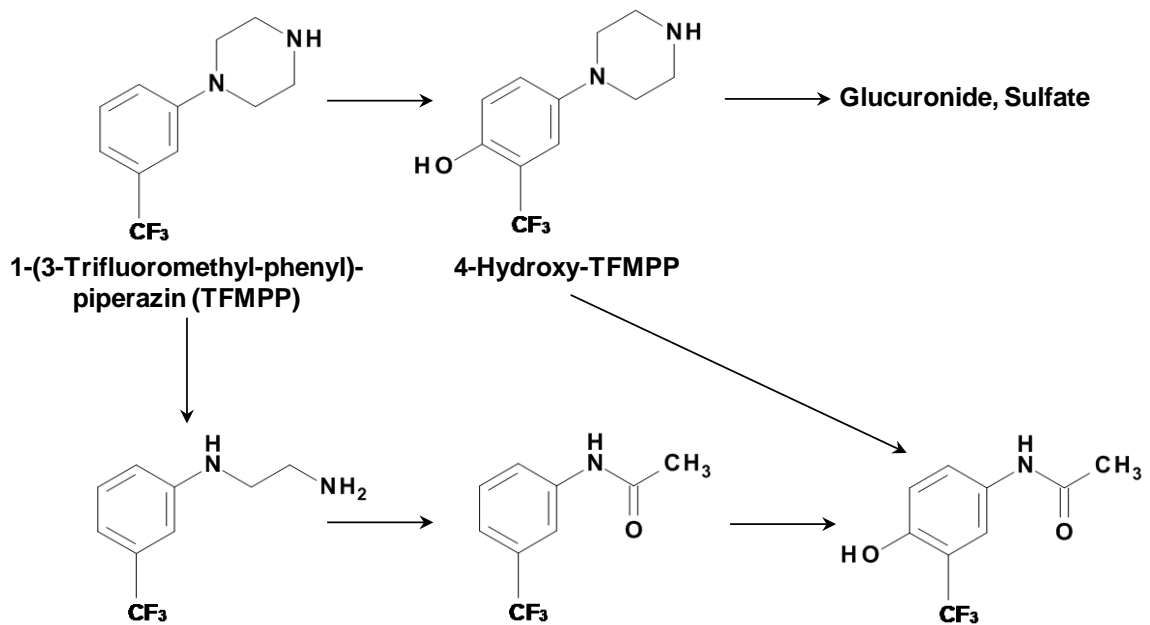


Figure 24: Metabolism of 1-(3-Trifluoromethylphenyl)-piperazines (TFMPP)



## 16.14 Nicotine

Scene names: --

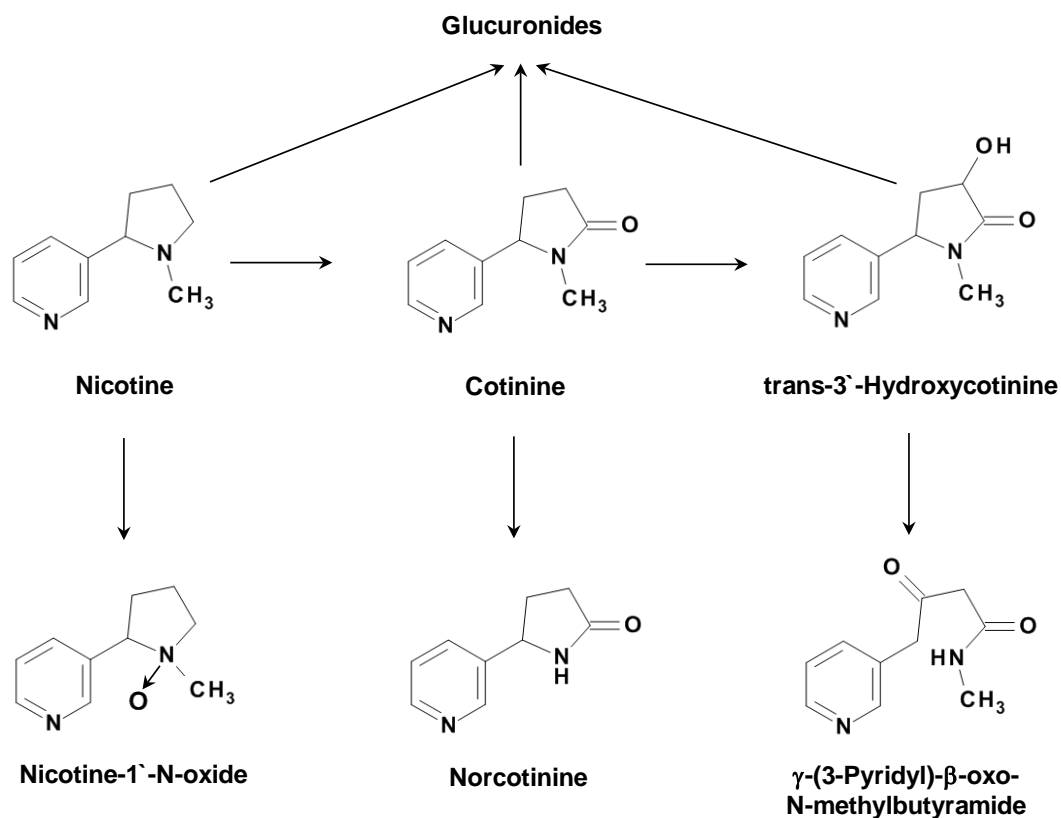
**Metabolism:** Nicotine is almost totally degraded by oxidation, ring cleavage, hydroxylation and glucuronidation to numerous, inactive metabolites (Fig. 25). In the 24-h urine, 35% is found as trans-3'-hydroxycotinine, 10% as cotinine, and 4% as nicotine-1'-N-oxide; only about 5% is excreted unchanged.

**T<sub>1/2</sub>:** Nicotine: 24 - 84 min (depending on pH); cotinine: 19 h.

**Detectability:** 8 - 48 h (depending on pH).

Note: The determination of cotinine, the main metabolite of nicotine, is used to detect active tobacco consumption and to differentiate between smokers and non-smokers. Passive and occasional smokers cannot be detected. The determination of nicotine in hair is recommended for the detection of continuous smoking, also by passive smoking.

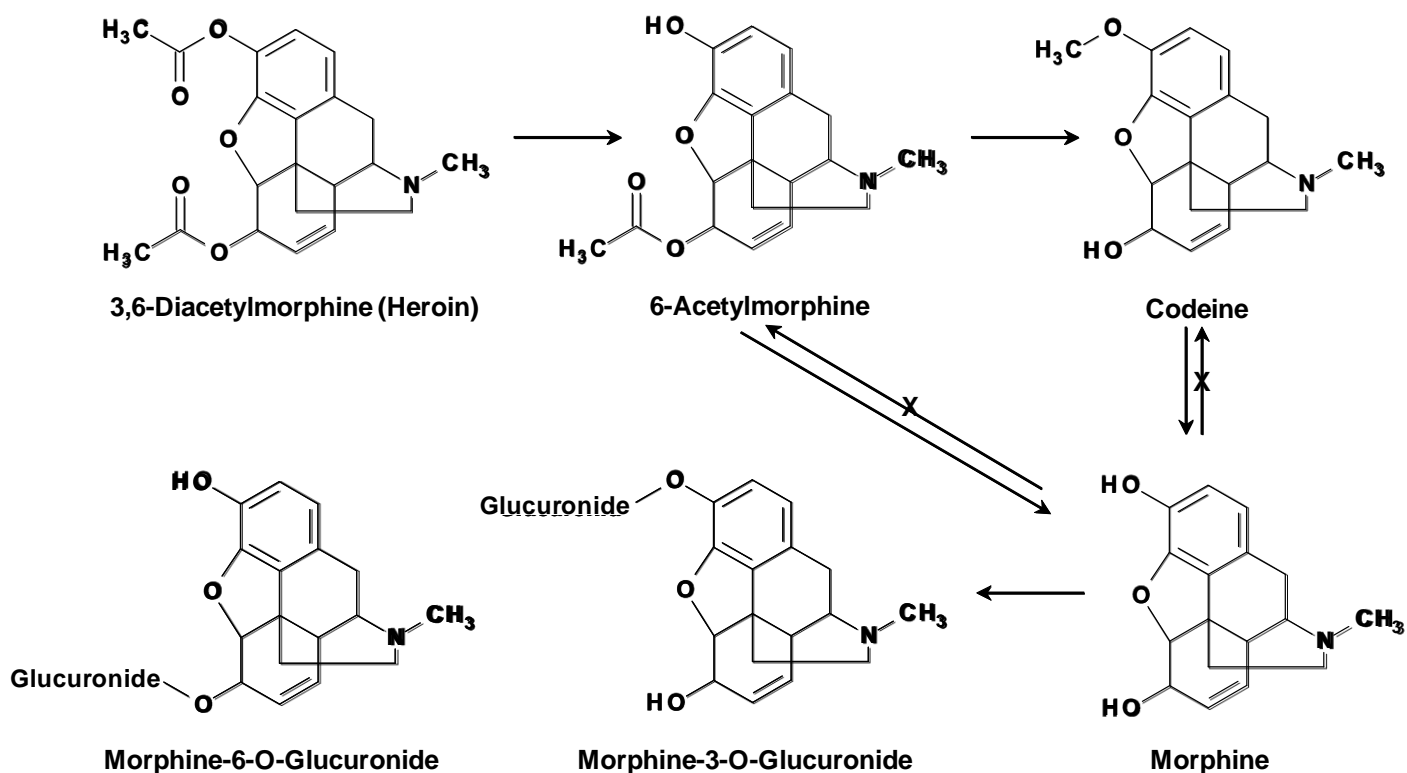
**Figure 25:** Metabolism of Nicotine



## 16.15 Opiates

Scene names:	Brown Sugar, H.
Metabolism:	Diacetylmorphine (heroin) is metabolized by esterases into 6-acetylmorphine and morphine and is primarily excreted as 3-O- and 6-O-glucuronide (Fig. 26).
T <sub>1/2</sub> :	3 - 20 min (diacetylmorphine), 9 - 40 min (6-acetylmorphine), 1 - 7 h (morphine).
Detectability:	<p>Morphine glucuronide up to 48 h (rarely up to 72 h), 6-acetylmorphine up to 8 to 12 h.</p> <p>Differentiation of opiate use: Immunochemically, the detection of heroin use is only possible via determination of the specific marker 6-acetylmorphine (see chapter 10), which must also be confirmed chromatographically due to the possibility of interfering substances. Particularly, the metabolism of codeine into morphine is subject to a high inter-individual variability. Therefore, codeine-morphine ratios must be interpreted with caution.</p> <p>Heroin use: daily doses of 20 - 200 mg result in urine levels of 2 - 150 mg/L morphine, 0.05 - 10 mg/L codeine (only in case of street heroin consumption, see below), and 0 - 10 mg/L 6-acetylmorphine. In case of the therapeutic use of morphine preparations, codeine can be detected as impurity with sensitive chromatographic methods (according to the Pharmacopeia &lt;0.2% codeine is allowed). Morphine does not metabolize to codeine [Baselt 2011].</p> <p>Codeine use: daily doses of 60 - 240 mg result in urine levels of 1 - 10 mg/L morphine and 5 - 50 mg/L codeine. Codeine-morphine-ratios &gt;0.5 result, if morphine concentrations are &gt;0.2 mg/L. In case of morphine use: codeine-morphine-ratios &lt;0.5 result, if morphine concentrations are &gt;0.2 mg/L.</p> <p>Heroin-assisted treatment: The parallel consumption of street heroin can only reliably be confirmed by the detection of its specific urine marker 6-acetylcodeine, formed during preparation of heroin from raw opium. Its detection window in urine is dependent on the sensitivity of the analytical method, for example, about 10 h after application when using GC-MS [Staub 2001, Brenneisen 2002].</p>

Figure 26: Metabolism of Diacetylmorphine (Heroin)



## 16.16 Psilocybin

Scene names: Psilos, Magic Mushrooms.

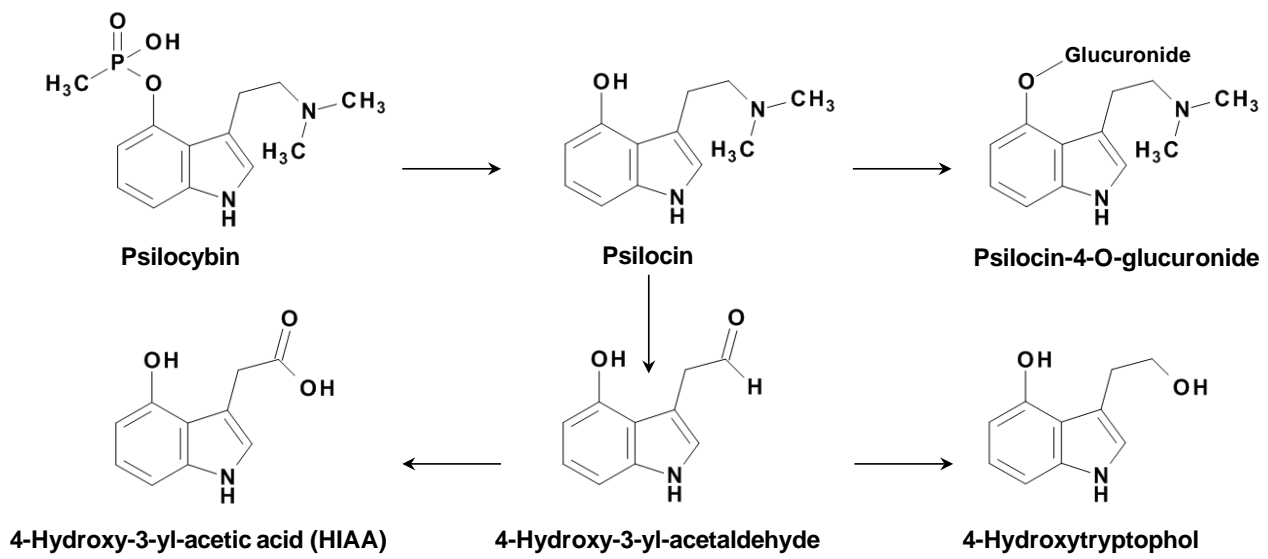
Metabolism: Psilocybin, an alkaloid occurring in many *Psilocybe* species, such as *P. mexicana*, *P. cubensis*, and *P. semilanceata* ("Magic Mushrooms"), is a phosphate derivative of N,N-dimethyltryptamine (DMT) [Hoffmann 1959]. Psilocybin acts as a prodrug and is rapidly converted by intestinal esterases to psilocin, which is the actual pharmacologically active substance formed by dephosphorylation (Fig. 27). Psilocin is then metabolized via an intermediate product (4-hydroxyindol-3-yl-acetaldehyde) into 4-hydroxytryptophol and, finally, into the inactive 4-hydroxyindol-3-yl-acetic acid (HIAA) [Hasler 1997]. HIAA is the dominant urinary metabolite. Within 24 h only 3% of the dose is excreted as free psilocin.

T<sub>1/2</sub>: 1.5 - 4.5 h.

Detectability: About 12 h.

Note: so far, no immunological tests are available. HPLC-DAD or HPLC-MS (for psilocybin and psilocin) and GC or GC-MS (only for psilocin), respectively, are the analytical methods suited for the detection of magic mushrooms consumption.

Figure 27: Metabolism of Psilocybin





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## 17. Literature

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## 17.2 Manuals, Monographs, Guidelines

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## 17.3 Websites

### 17.3.1 Guidelines of Other Institutions:

Forensic Toxicology Laboratory Guidelines, Society of Forensic Toxicologists (SOFT): <http://www.soft-tox.org>

Gesellschaft für Toxikologische und Forensische Chemie (GTFCh): <http://www.gtfch.org>

Kriterien zum Betreiben von med.-analyt. Labors: <http://www.qualab.ch/KBMAL.html>

Schweizerische Kommission für Qualitätssicherung im medizinischen Labor (QUALAB): <http://www.qualab.ch>

### 17.3.2 Federal Offices (Switzerland, Germany, USA):

Bundesamt für Gesundheit (BAG): <http://www.bag.admin.ch>

Bundesamt für Polizei (Fedpol): <http://www.fedpol.admin.ch>

Bundesamt für Sozialversicherungen (BSV): <http://www.bsv.admin.ch>

Bund gegen Alkohol und Drogen im Strassenverkehr: <http://www.bads.de>

US National Institute on Drug Abuse (NIDA): <http://www.nida.nih.gov>

### 17.3.3 General Information About Drugs of Abuse and Drugs of Abuse Testing:

Abbott Lab Compendium: [www.laborlexikon.de/Lexikon/Infotext/e/Ethylglucuronid.htm](http://www.laborlexikon.de/Lexikon/Infotext/e/Ethylglucuronid.htm)

Drugs: <http://www.drogen-wissen.de/>

Erowid: <http://www.erowid.org>

European Monitoring Centre for Drugs and Drug Addiction: <http://www.emcdda.europa.eu/publications/drug-profiles>

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