Neue Drogen - Herausforderungen für die Drogenanalytik

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MVZ Labor Dessau GmbH

LABOR®

LIMBACH GRUPPE

Missbrauchsrelevante Substanzen

Drogen (BtMG Anl. 1+2)

- Amphetamin, Methamphetamin
- Designerdrogen
- Heroin
- Cannabis
- Kokain
- LSD
- GHB
- Synthetische Cannabinoide
- .....

Medikamente

- Methadon, Buprenorphin, Morphin
- Barbiturate
- Benzodiazepine
- Opioide
- Narkotika (Propofol, Ketamin, PCP)
- Psychopharmaka (TCA, SSRI)

- Diuretika
- Anabole Steroide

"Naturdrogen"

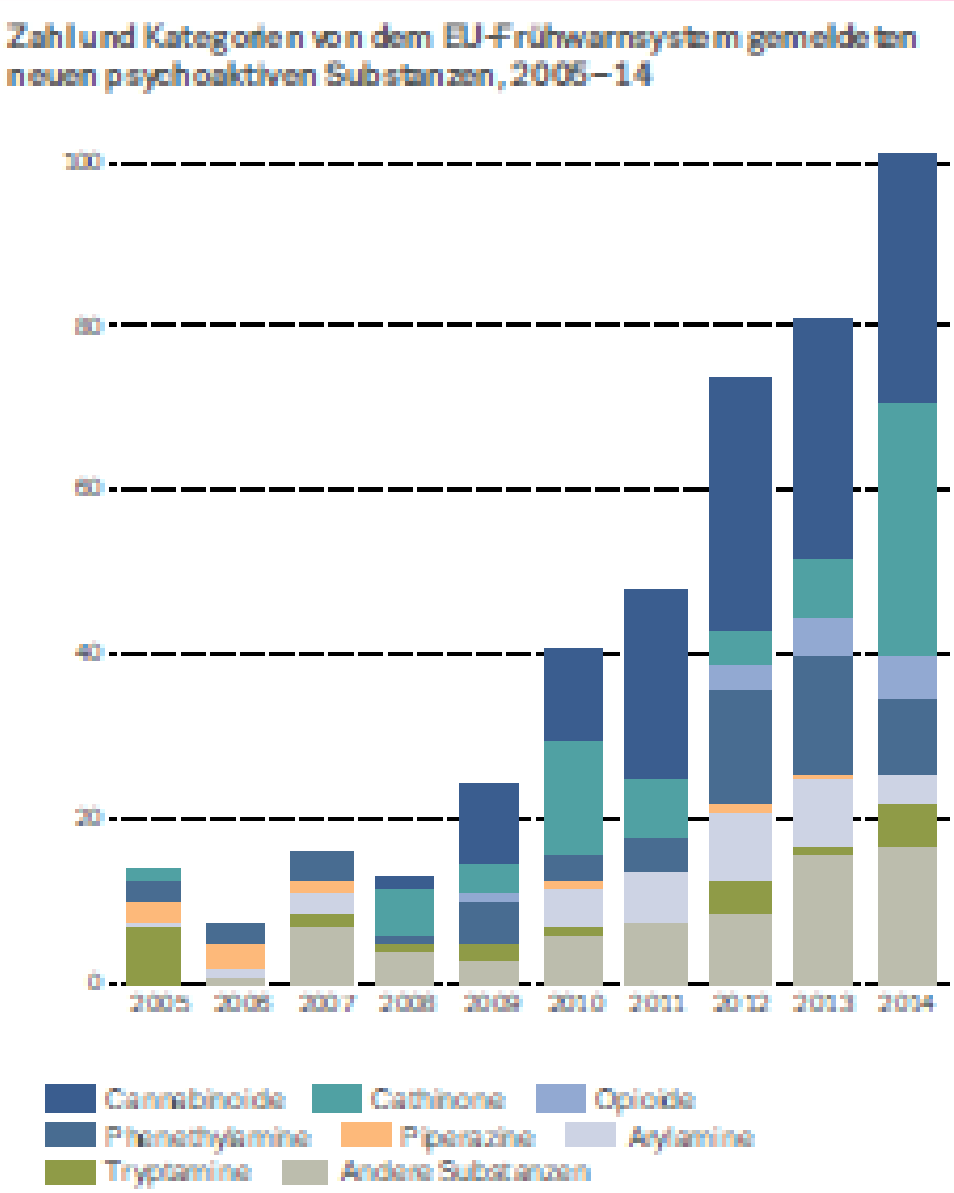
- Psilocybin
- Meskalin
- "Spice"
- Muscarin
- Myristicin
- Atropin
- Scopolamin
- Kratom / Krypton
- Khat (Cathinon)

"Internetdrogen/Legal Highs/RC"
"Badesalze"/Phenylethylamine
"Spice"
Tryptamine
Opioide
Designer Benzodiazepine

} **NPSG**

Pregabalin
"Z-Substanzen": Zopiclon, Zolpidem, Zaleplon
Methylphenidat
Lidocain
Loperamid

NPS, 2005-2014



Synth. Cannabinoide („Spice“)

Cathinone („Badesalze“)

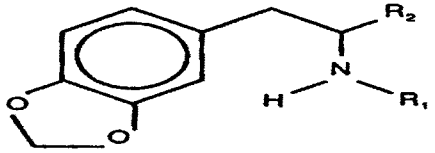
Opioide

Phenylethylamine

Europäischer Drogenbericht 2015
Europ. Beobachtungsstelle Für Drogen u. Drogensucht (www.EMCDDA.europa.eu)

Wirkbogen der Partydrogen

etwas stimulierend, etwas halluzinogen, besonders „herzöffnende
indirekt **Serotonerg**, > besonders in höheren Dosen auch Dopaminerg und > Noradrenerg



Entaktogene

Ecstasy-MDMA,
MDEE

MDPV

Mephedrone

Kokain

Amphetamin

Methamphetamin

MDA

Psylocibin

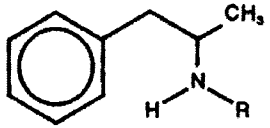
Meskalin

LSD

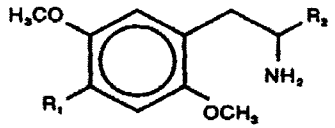
DOM, PCP

Aufputschmittel

Halluzinogene



indirekt **Dopaminerg**, > indirekt **serotonerg** und >noradrenerg



direkt Serotonerg

"Treibende Kräfte":

1. BtMG: Legaler Konsum/Vertrieb
2. AMG, LMG: Namensgebung!
3. Pharmakodynamik, -kinetik?!
4. Nachweisbarkeit (Dosierung, $T_{1/2\ Elim}$, Analytik)!

Drogenanalytik – Wie?

Geschwindigkeit, Preis, Empfindlichkeit

Immunoassays an Urinproben

-- Ausschluß von "Beikonsum" bei Patienten in Substitutionstherapie
-- Compliance von Patienten in Substitutionstherapie (EDDP, Norbupre.)

-- Ausschluß eines Drogenkonsum bei Suchtpatienten in "clean-Therapie" Einrichtungen (stationär oder ambulant)

-- Ausschluß eines Drogenkonsums in JVA`s, Massregelvollzug

-- "workplace testing“, Arbeitsmedizin

-- psychiatrische (Sucht-)Kliniken

-- Forensik, Rechtsmedizin

Welche Immunoassays (Urin!) gibt es?

-- Amphetamin and derivatives (!?)
-- Barbiturates
-- Benzodiazepines
-- Cocaine (Benzoylecgonine)
-- Methadone or better EDDP
-- Opiates
-- 6-Monoacetylmorphine
-- Cannabinoids (THC-COOH)
-- Tramadol
-- Oxycodone
-- Buprenorphine
-- Fentanyl
-- "Spice„ 2x

-- LSD

-- Ethanol

-- Phencyclidine
-- Propoxyphene
-- Methaqualone

-- Tricyclic Antidepr.
-- Paracetamol
-- Salicylates

-- Ethylglucuronide

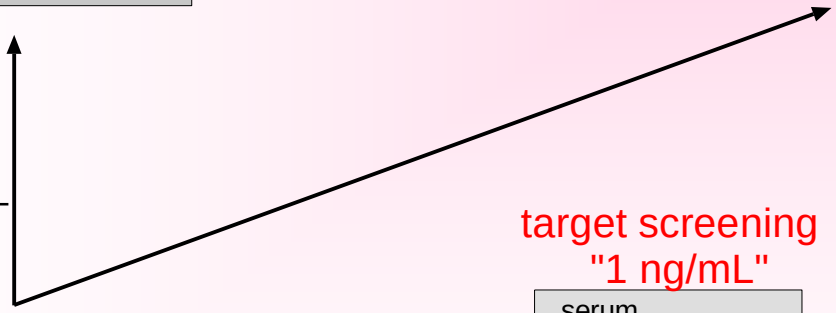
neu: Pregabalin

Drugs of abuse screening - urine

Immunoassay (CEDIA)

Amphetamines	500
Barbiturates	100
Benzodiazepines	100
Cocaine	50
Methadone/EDDP	100
Opiates	100
THC-COOH	25

0.5 **LSD**
5.0 6-MAM
2.0 **Bupren.**



confirmation or extended screening
GC/MS, GC/MS-MS or LC/MS-MS
after dedicated sample preparation

target screening
"1 ng/mL"

- serum
- postm. blood
- oral fluid
- gastric content
- hair
- capillary blood
- meconium

GC/MS "general unknown"

enzym. hydrolysis+ LLE+acetylation

Amphetamines Designer drugs

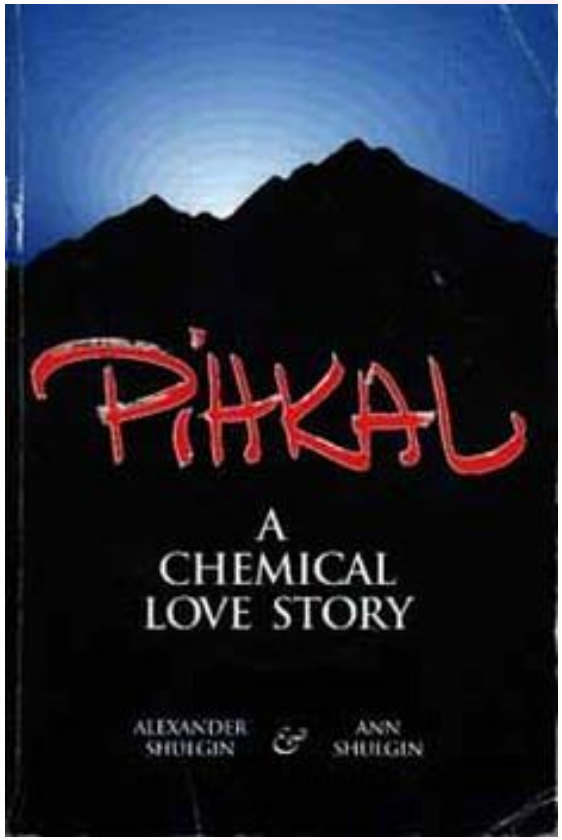
Methadone
Opiates

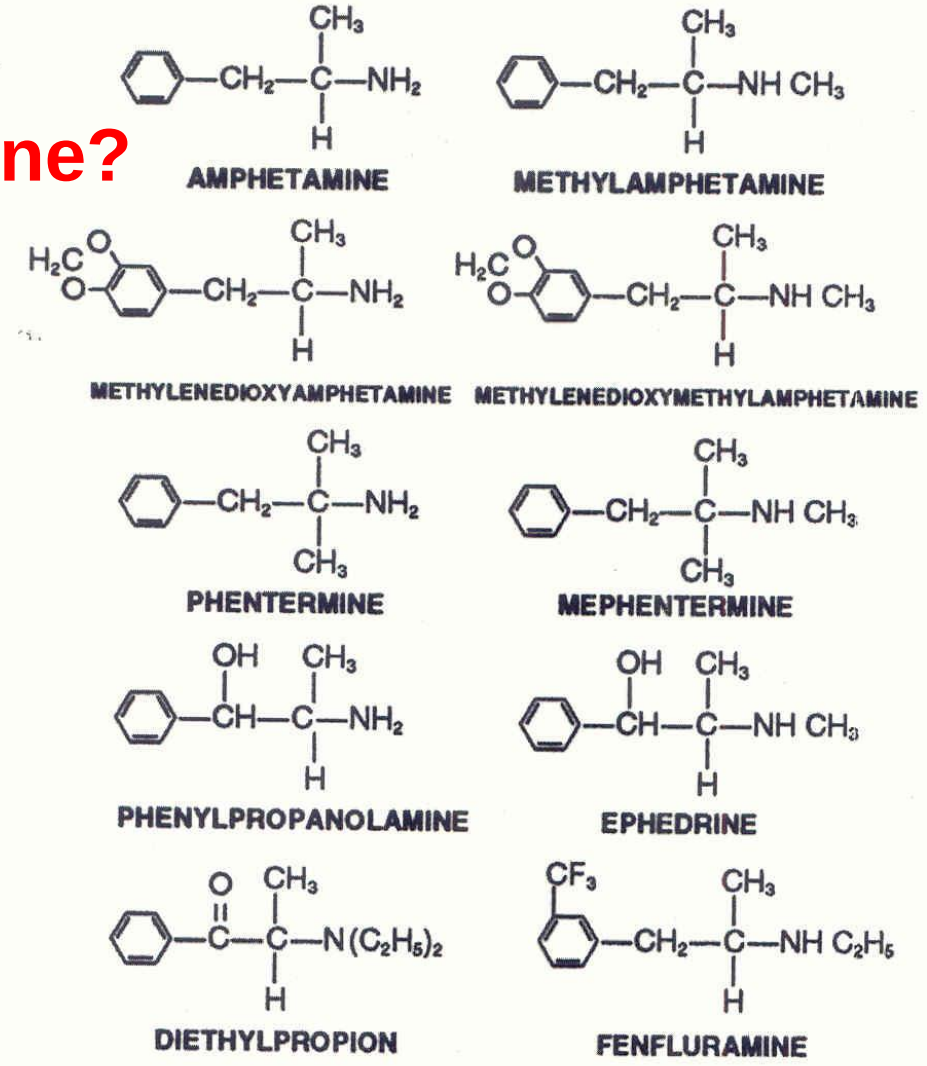
Analgesics (Tilidine, Oxycodone, etc.)
Antidepressants
Antiepileptics
Neuroleptics
NSAIDs
Zopiclone, Zolpidem, Zotepine
.
.
.
.
.
etc.

broad screening, "100 ng/mL"

Problem EIA:
falsch positiv/negativ

Was sind Amphetamine?





Phenethylamines **I** **H**ave **K**nown **A**nd **L**oved
1991
TiHKAL: **T**ryptamines.....
1997

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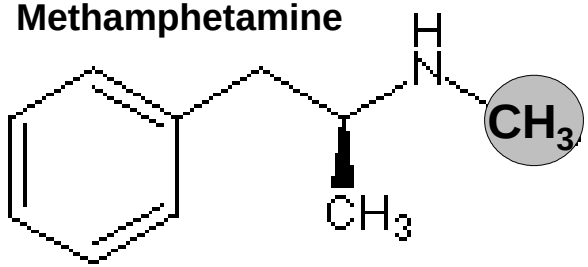
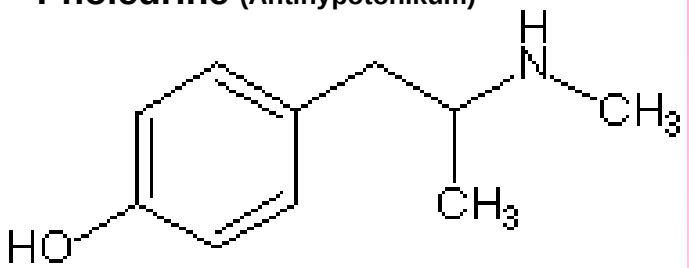
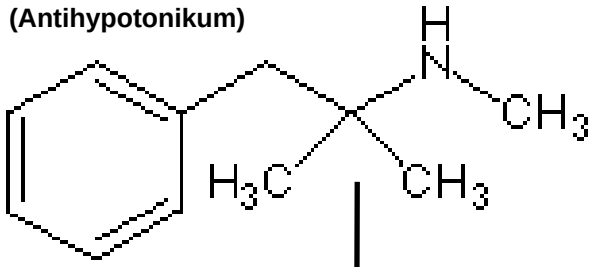
Methamphetamine



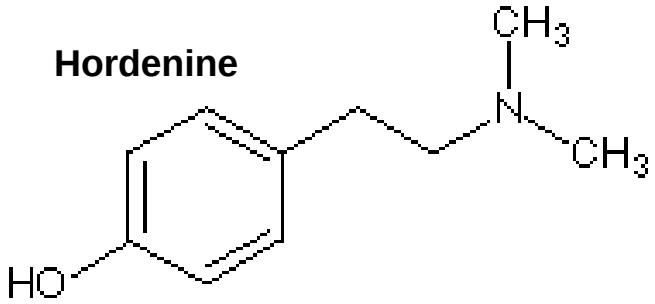
Pholedrine (Antihypotonikum)



Mephentermine
(Antihypotonikum)



Hordenine



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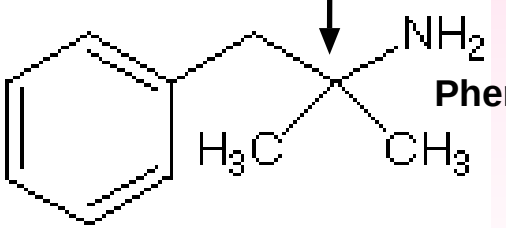
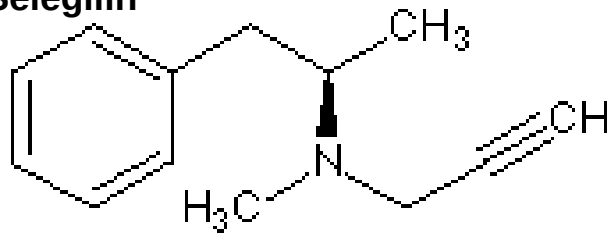
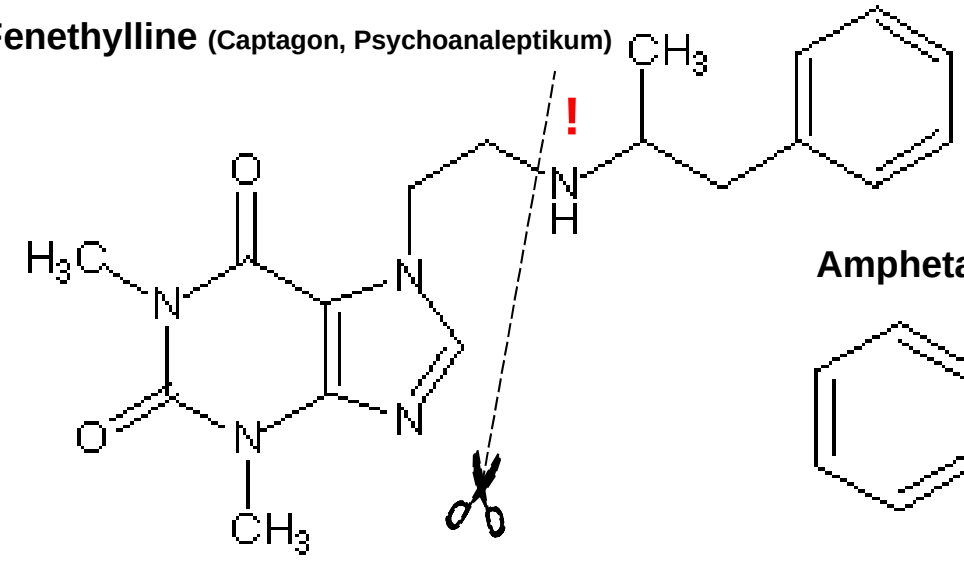


Phentermine

Selegilin

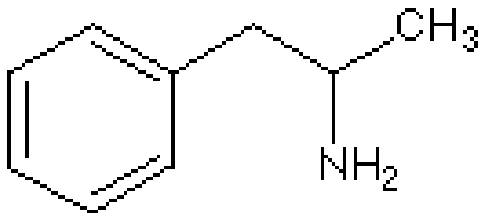


Fenethylline (Captagon, Psychoanaleptikum)

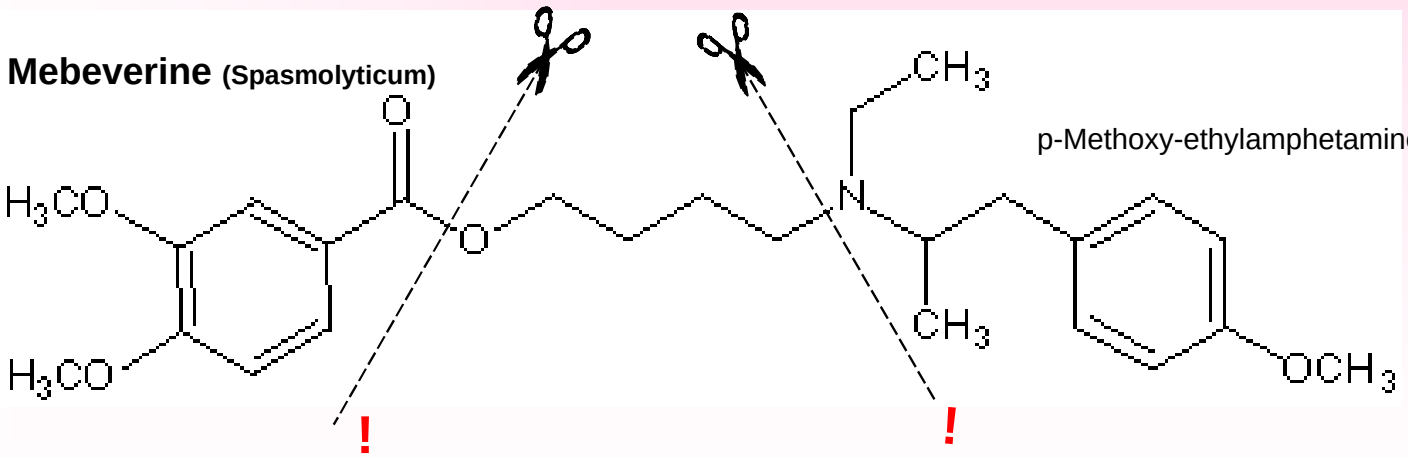


Amphetamine

Amphetamine



Mebeverine (Spasmolyticum)



p-Methoxy-ethylamphetamine

Crystal-Meth

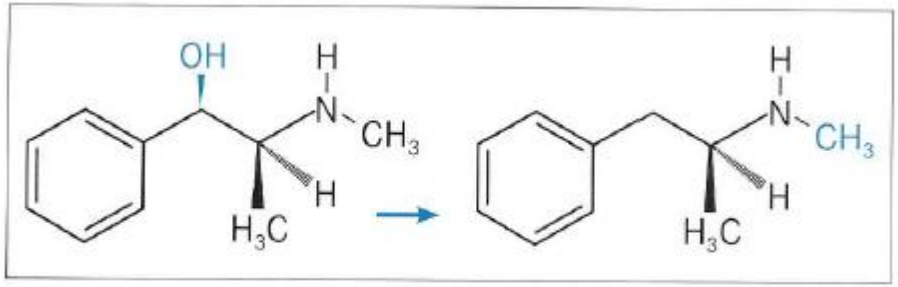


Abb. 43: Von der Ausgangssubstanz Ephedrin (links) zum zentral-wirksamen Stimulans Metamphetamin (1-Phenyl-2-methylamino-propan-Hydrochlorid) (rechts).

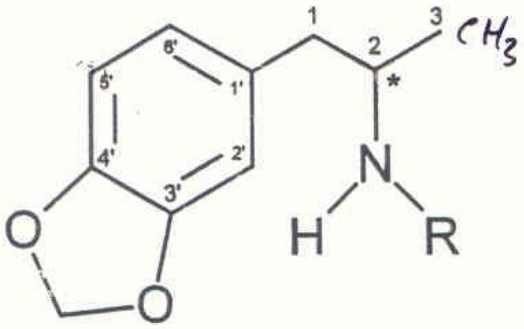
Crystal macht wach und schlank und bewirkt:

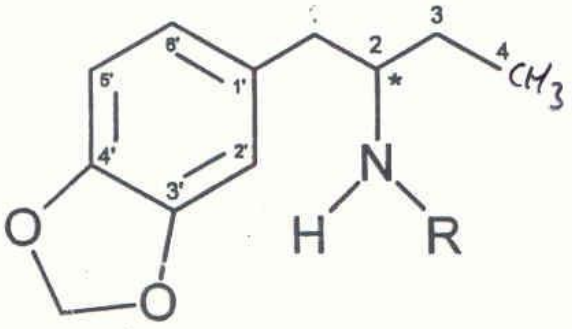
- ein Gefühl der Stärke, Euphorie
- gesteigerten Rededrang (Logorrhoe = „Sprechdurchfall“)
- eine psychische Stimulation, Antrieb
- Verlust der Schmerzempfindung
- erhöhte motorische Leistungsbereitschaft

Andererseits (insbes. bei chronischem Konsum):

- Schwächung des Immunsystems
- Hautentzündungen, Zersetzung d. Schleimhäute (Mund/Nase;Rauchen/Schnupfen)
- Haarausfall, Zahnausfall
- Herzrhythmusstörungen
- Schlafstörungen
- Hyperthermie
- Paranoide Wahnvorstellungen aufgrund des Schlafmangels
- Akutwerden einer latenten Schizophrenie
- Übersteigerte Egozentrik (Narzissmus)
- Agressivität

Designer drugs: Methylenedioxyphenylalkylamines





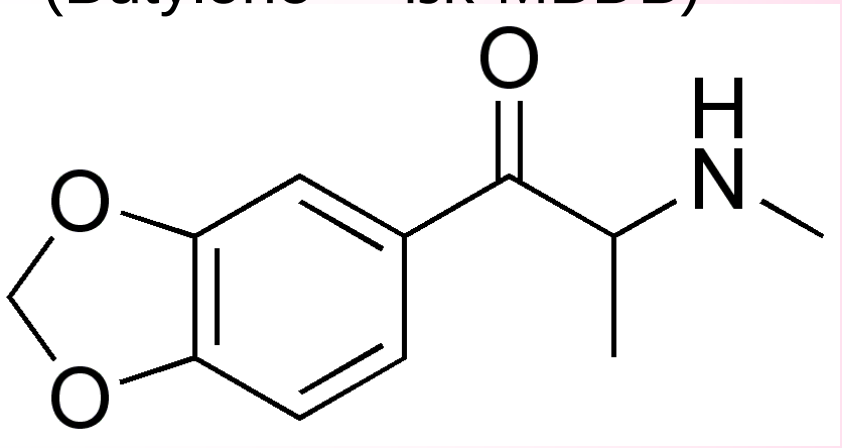
Propanamines (Amphetamines)
MDA: R = H
MDMA: R = CH_3
MDE: R = CH_2-CH_3

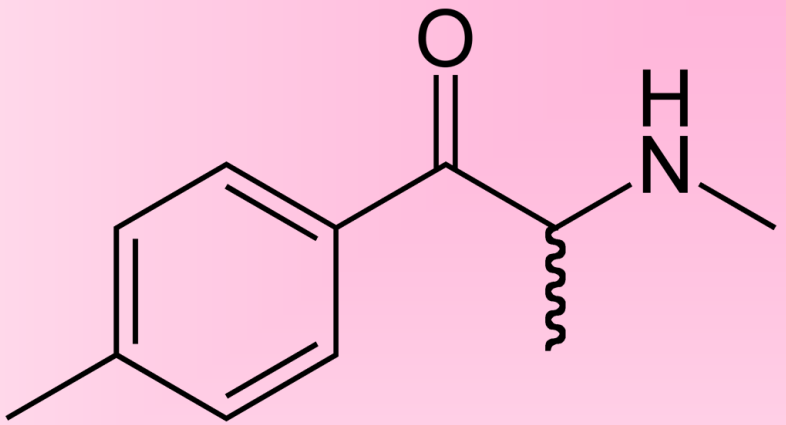
Butanamines
BDB: R = H
MBDB: R = CH_3

Entactogenic effect
Stimulating and hallucinogenic effect: MDA > MDMA > MDE > BDB > MBDB

Abb. 1. Formelübersicht der Designer Drogen vom Methylendioxyphenylalkylamin-Typ

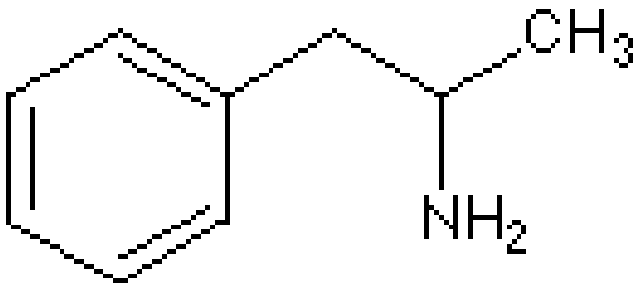
Methylone = ßk-MDMA
(Butylone = ßk-MBDB)





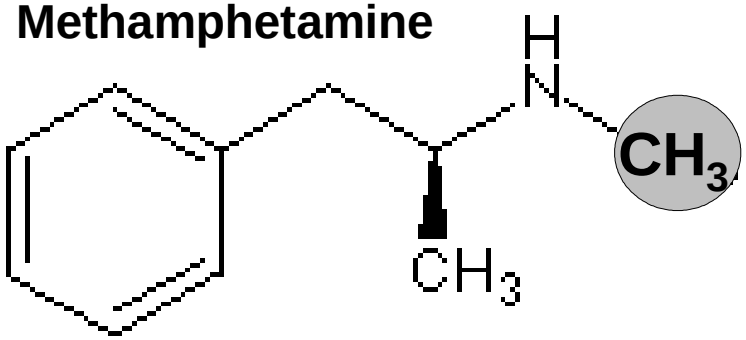
Mephedrone
(4-Methylmethcathinone, ßk-Methylmethamphetamine)

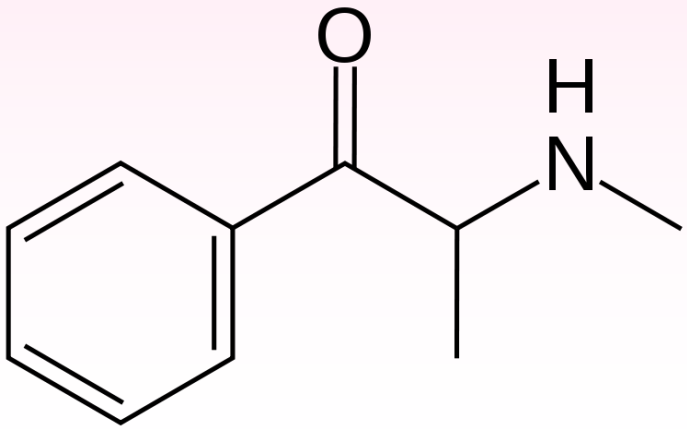
Amphetamine



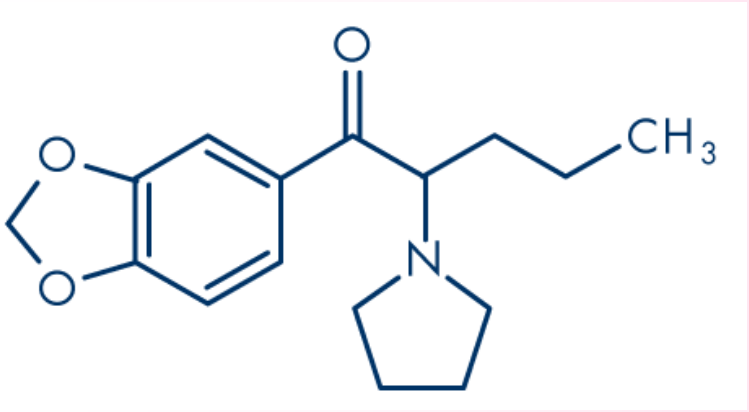
Ephedrone = Methcathinone

Methamphetamine

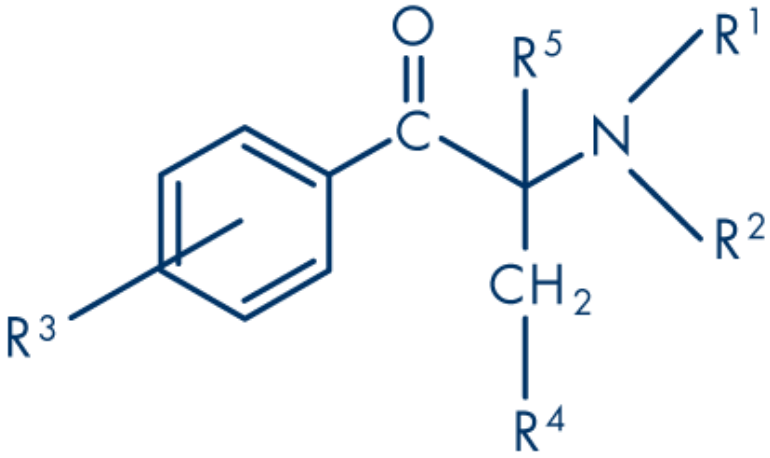




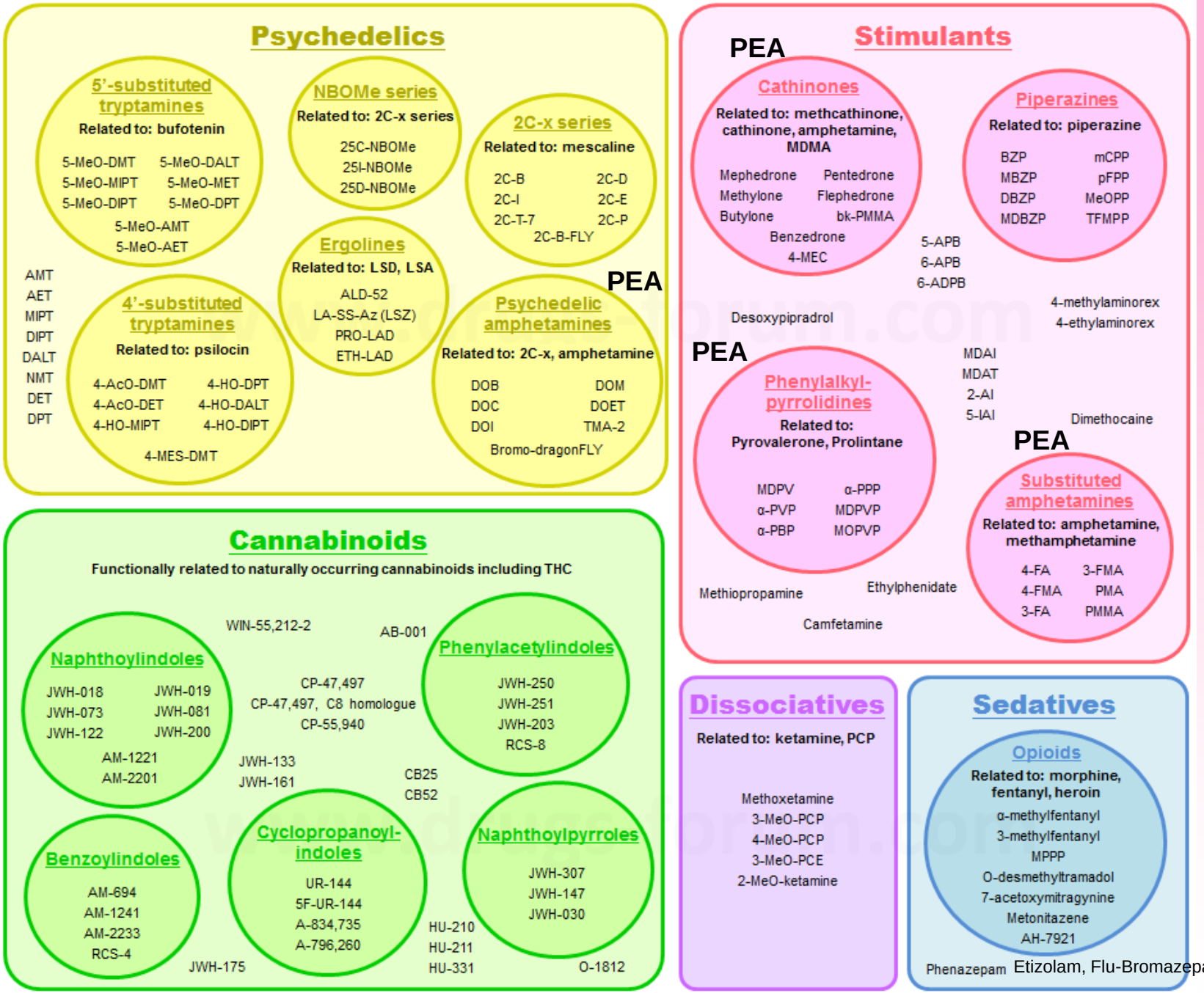
MDPV (3,4-methylenedioxypyrovalerone)



General structure of a cathinone derivative showing substitution patterns



R^1	R^2	R^3	R^4	R^5	Name
H	H	H	H	H	Cathinone
Methyl	H	H	H	H	Methcathinone (ephedrone)
Methyl	Methyl	H	H	H	N,N-Dimethylcathinone (metamfepramone)
Ethyl	H	H	H	H	N-Ethylcathinone (EC)
Methyl	H	H	Methyl	H	Buphedrone
Ethyl	H	4-Methyl	H	H	4-Methyl-N-ethylcathinone
Methyl	H	4-Methyl	H	H	Mephedrone (4-MMC; M-CAT)
Ethyl	Ethyl	H	H	H	Amfepramone
t-Butyl	H	3-Cl	H	H	Bupropion
Methyl	H	3.4-Methylenedioxy	H	H	Methylone (ßk-MDMA)
Ethyl	H	3.4-Methylenedioxy	H	H	Ethylone (ßk-MDEA)
Methyl	H	4-Methyl	Methyl	H	Butylone (ßk-MBDB)
Methyl	H	4-Methoxy	H	H	Methedrone (ßk-PMMA)
Methyl	H	4-F	H	H	Flephedrone (4-FMC)
Methyl	H	3-F	H	H	3-Fluoromethcathinone (3-FMC)
{pyrrolidino}	{pyrrolidino}	H	H	H	a-Pyrrolidinopropiophenone (PPP)
{pyrrolidino}	{pyrrolidino}	4-Methyl	H	H	4-Methyl-a-pyrrolidinopropiophenone (MPPP)
{pyrrolidino}	{pyrrolidino}	4-MeO	H	H	4-methoxy-a-pyrrolidinopropiophenone (MOPPP)
{pyrrolidino}	{pyrrolidino}	4-Methyl	Propyl	H	4-Methyl-a-pyrrolidino-hexanophenone (MPHP)
{pyrrolidino}	{pyrrolidino}	4-Methyl	Ethyl	H	Pyrovalerone
{pyrrolidino}	{pyrrolidino}	4-Methyl	Methyl	H	4-Methyl-a-pyrrolidino-butyrophenone (MPBP)
{pyrrolidino}	{pyrrolidino}	4-Methyl	H	Methyl	4-Methyl-a-pyrrolidino-a-methylpropiophenone
{pyrrolidino}	{pyrrolidino}	3.4-Methylenedioxy	H	H	3,4-Methylenedioxy-a-pyrrolidinopropiophenone (MDPPP)
{pyrrolidino}	{pyrrolidino}	3.4-Methylenedioxy	Ethyl	H	3,4-Methylenedioxypyrovalerone (MDPV)



www.drugs-forum.com/photopost/data/537/RCscheme.png

Spice-Varianten

HU = **H**ebrew-**U**niversity(Jerusalem), classical Cannabinoids

JWH = **J**. **W**. **H**uffmann (2005), Naphtylindole

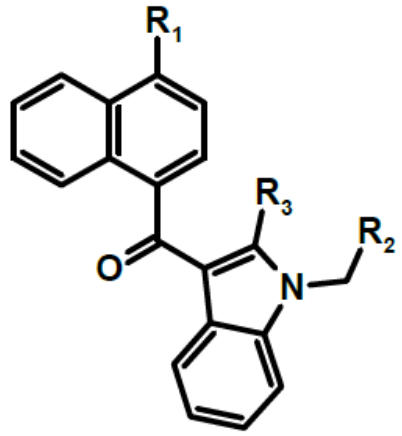
CP = von Pfizer entwickelt, **C**yclohexyl**p**henole

AM = **A**lexandros **M**akryannis, (Northeastern Univ. Boston)

WIN = Fa. **Win**throp-Sterling (heute Teil von Sanofi)

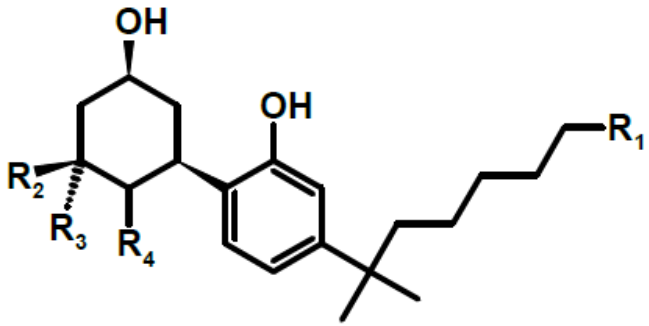
Synthetische Cannabinoide

a) Naphthoylindole



JWH-018
JWH-073
JWH-398
JWH-200
JWH-081
JWH-015
JWH-122
JWH-210
JWH-019
JWH-007
AM-2201
JWH-020
JWH-387
AM-1220
JWH-412
5-Fluoropentyl-JWH-122

b) Cyclohexylphenole



CP-47,497-C8

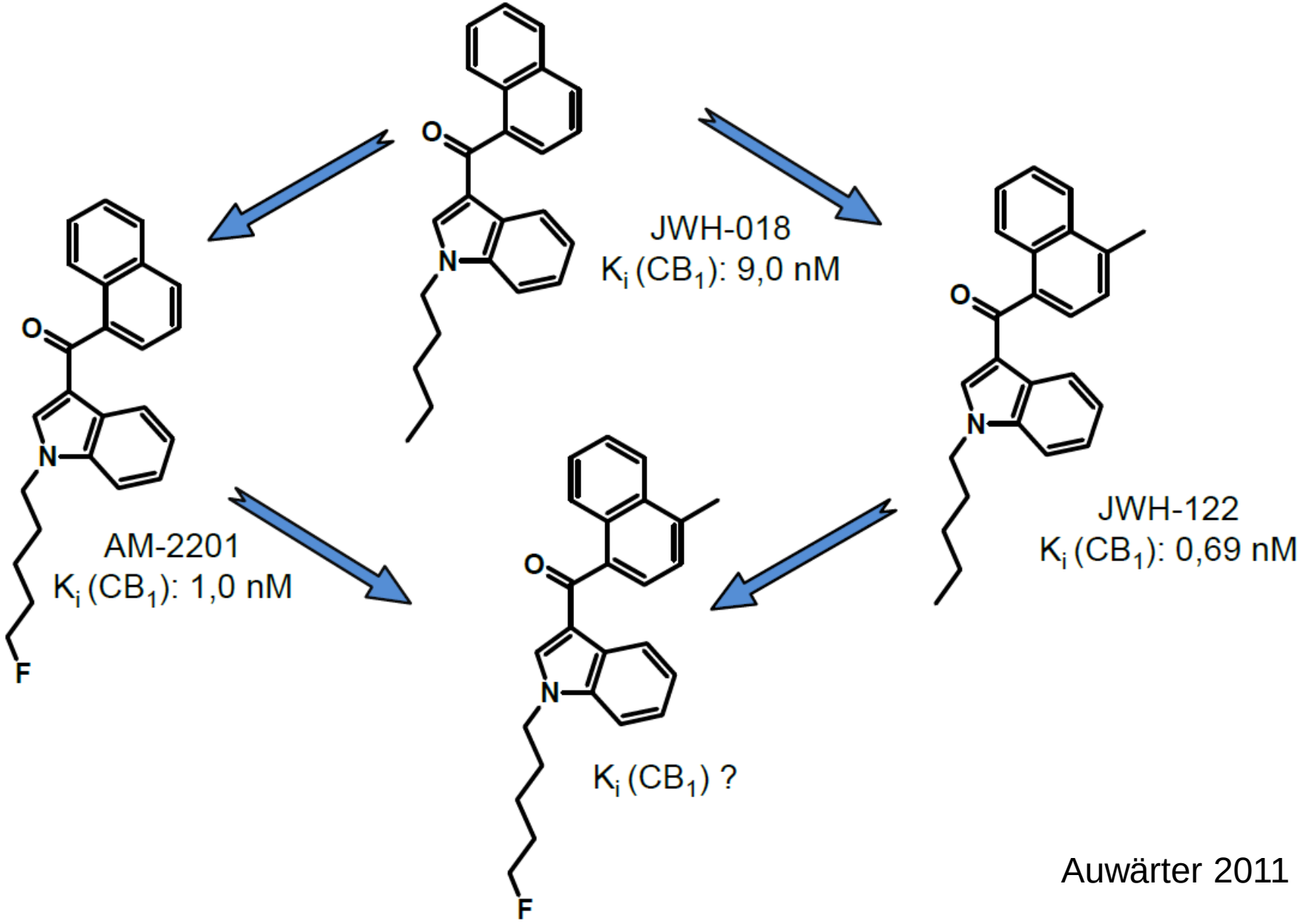
CP-47,497

Dimethyl-CP-47,497-C8

CP-55,940

Auwärter 2011

„Der Baukasten“



Auwärter 2011


H2
PINK
NOT FOR HUMAN CONSUMPTION
DOES NOT CONTAIN JWH018, JWH073,
JWH200, CP-73, 497, OR CANNABICYCLOHEXANOL

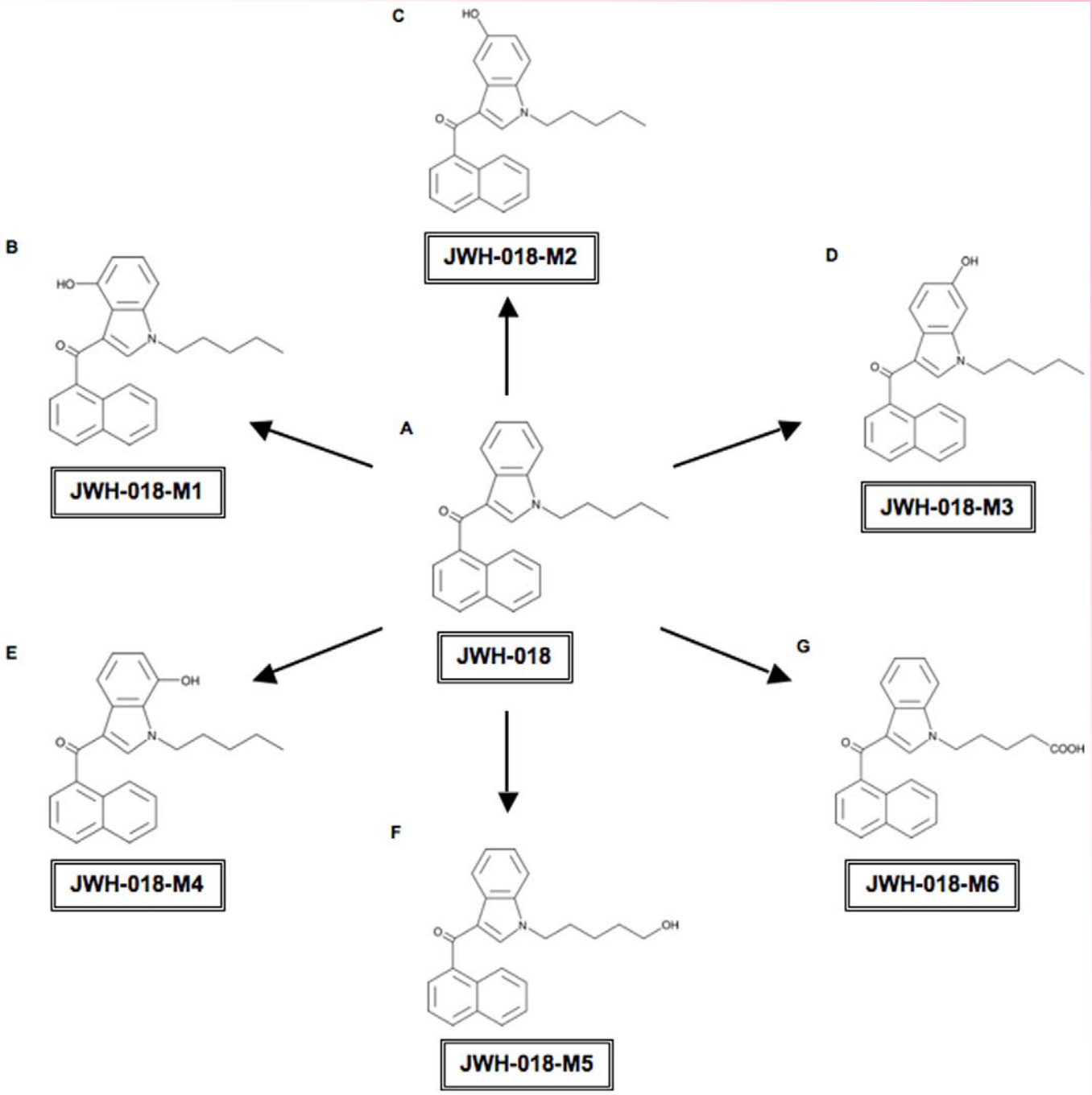

TIKI TIKI
PREMIUM HAWAIIAN BABY WOODROSE SEEDS


CAUTION
Super Strong In
Chronic
10X
3 gram


Unbannable
X X

JWH-122


ORGANIC
MNK
INFO@M-K-K-U
18+
INGREDIENTS:
Potpourri, dry leaves,
aromatic flowers and
tropical fruit extracts
This product is a car perfume.
Do not burn, Do not ingest,
Avoid contact with the skin,
Keep out of reach of children.


C
HO
O
N
JWH-018-M2
B
HO
O
N
JWH-018-M1
A
O
N
JWH-018
D
OH
O
N
JWH-018-M3
E
OH
O
N
JWH-018-M4
F
O
N
OH
JWH-018-M5
G
O
N
COOH
JWH-018-M6

„Liquid Ecstasy“

Was ist das ideale K.O.-Mittel?

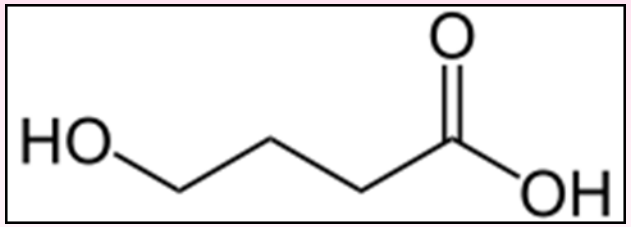
-- macht willenlos u./o. bewusstlos
-- anterograde und retrograde Amnesie
-- wirkt (vorhersehbar) schnell
-- schlecht (?) nachweisbar
-- schnell abgebaut
-- leicht erhältlich
-- leicht verabreichbar (wasserlöslich)

GHB („Liquid Ecstasy“)
Ketamin, Flunitrazepam und viele andere
in Kombination und oft mit Alkohol

ALLGEMEINES ZUR SUBSTANZ GHB

γ-Hydroxybutyrat, γ-Hydroxy-Buttersäure

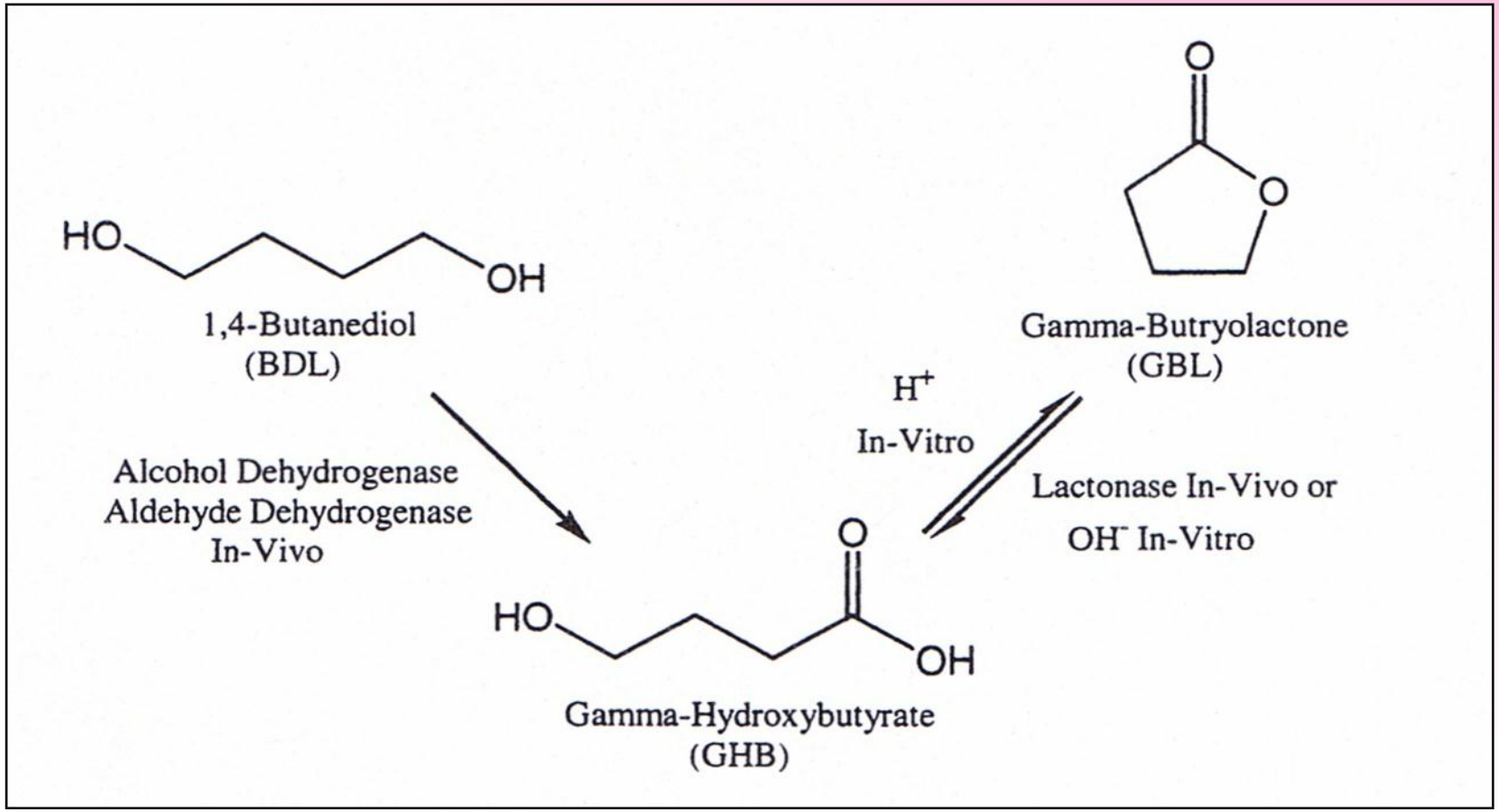
- Neben der freien Säure werden auch die Natrium-und Kaliumsalze als GHB bezeichnet.
- Strassennamen sind u.a. :
  Fantasy, K.O.-Tropfen, **Liquid Ecstasy**, Liquid X, Gamma, Salty Water.
  "Liquid Ecstasy " hat mit dem Amphetaminderivat " Ecstasy " (MDMA) nichts zu tun.
- Natriumsalz (Pulver)
- Farblose Flüssigkeit
- Salzig, leicht seifig, geruchlos
- GHB in Anlage III des BTMG



- WIRKUNG: - dosisabhängig
  - Euphorie, Sedierung, Relaxation, Amnesie, Atemdepression, Koma

METABOLISMUS VON GBL UND BDO

Exogene Aufnahme von:



Beispiel eines GBL-Produktes und Bezugsquellen

www.gblstarcleaner.com
www.cleanmagic.de
www.airfoxchemicals.com
www.buypowercleaner.com
www.magic-cleaner.com
www.gbl.de
www.cleanandsolve.com
www.ohne-rezept-kaufen.biz
www.alles-rezeptfrei.net

Sie wollen GBL kaufen, können es aber nirgends mehr finden? Das ist nicht verwunderlich, denn das Lösungsmittel mit der Bezeichnung Gamma-Butyrolacton unterliegt schon seit einiger Zeit einer freiwilligen Selbstkontrolle von Industrie und Handel.

Man darf aber in der EU nach wie vor legal GBL kaufen und verkaufen. GBL eignet sich als Lösungsmittel beispielsweise für die Reinigung von Wänden, die Graffiti-Sprayern zum Opfer gefallen sind. Außerdem werden damit elektronische Bauteile, Felgen und andere Metallteile gereinigt. In der Partyszene ist GBL als chemische Vorstufe für Liquid Ecstasy bekannt. Wenn Sie GBL kaufen wollen, dann wählen Sie aus den Produkten in unserem Shop.

GBL-GHB
GBL-GHB
in den Warenkorb
GBL GHB 30 ml
GBL-GHB, Schmerzfrei
€87.90

www.alles-rezeptfrei.net/gbl-kaufen/

GBL kaufen, bestellen Sie noch heute in unserem Shop. Durch die derzeit gültigen rechtlichen Regelungen ist GBL rezeptfrei und ohne Lizenz erhältlich. Wenn Sie GBL benötigen, wählen Sie aus den Produkten in unserem Shop. Wir liefern die gewünschte Menge GBL innerhalb von nur wenigen Werktagen an die von Ihnen angegebene Adresse im In- und Ausland. Gamma-Butyrolacton ist bekannt als industrielles Lösungsmittel, als Reinigungsmittel und als chemische Vorstufe von Liquid Ecstasy und von K.-o.-Tropfen.

Warten Sie mit der Bestellung nicht zu lange, denn es ist nicht absehbar, wie lange GBL noch rezeptfrei und legal in der Europäischen Union erhältlich sein wird.

WIRKUNG UND PHARMAKOLOGIE VON GHB

- Dosierungen von 0.5 -1.0 g:
  Alkoholähnlicher Zustand, Wohlgefühl sinnesverstärkend

- Dosierungen von 1.0 - 2.0 g:
  Stimulation (euphorisierend, MDMA und Cocain ähnlich)

- Dosierungen von > 2.5 - 5.0 g:
  Entspannung, Antriebssteigerung, Tanz fördernd, intensivere Wahrnehmung, Aggressivität in Einzelfällen, Schläfrigkeit, Verwirrtheit, Gedächtnisstörungen, motorische Probleme, Erbrechen

- Dosierungen > 5.0 g:
  Überdosierung, Koma

- Wirkungseintritt: peroral nach ca. 10-20 min

- Wirkungsdauer: 0.5 – 4 h Nachweisdauer >24 h

Individuell sehr verschieden und von Körpergewicht abhängig!

Nachweiszeit von GHB nach Einnahme von 1.5 mL GBL – **Serum**
Cutoff 5 µg/mL

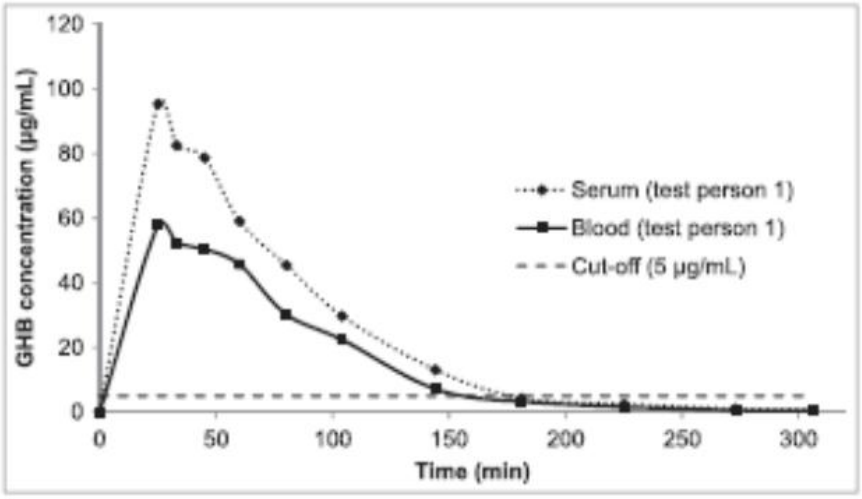


Figure 1. Serum and whole blood GHB concentrations of test person 1 (data are provided in supplementary information).

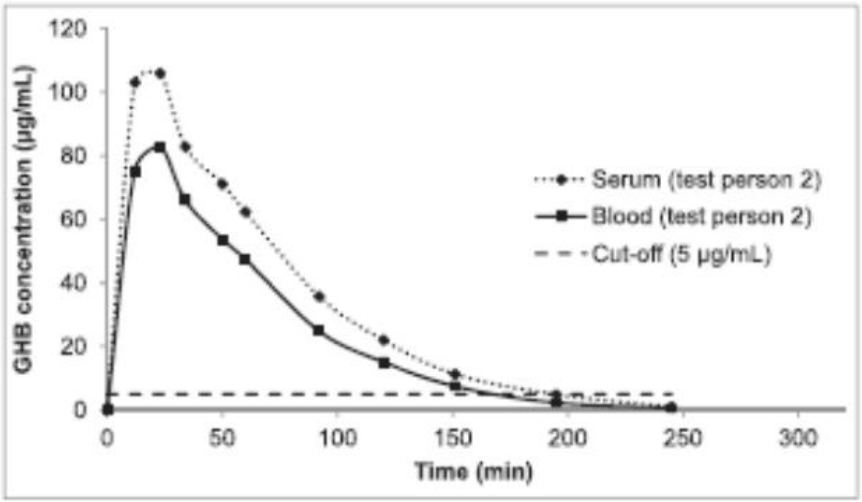


Figure 2. Serum and whole blood GHB concentrations of test person 2 (data are provided in supplementary information).

(www.drugtestinganalysis.com) DOI 10.1002/dta.1498 2013

Pharmacokinetics of GHB and detection window in serum and urine after single uptake of a low dose of GBL – an experiment with two volunteers

Alexandra Schröck,[a]* Yvonne Hari,[a] Stefan König,[a] Volker Auwärter,[b] Stefan Schürch[c] and Wolfgang Weinmann[a]

Nachweiszeit von GHB nach Einnahme von 1.5 mL GBL – **Urin,** Cutoff 10 µg/mL

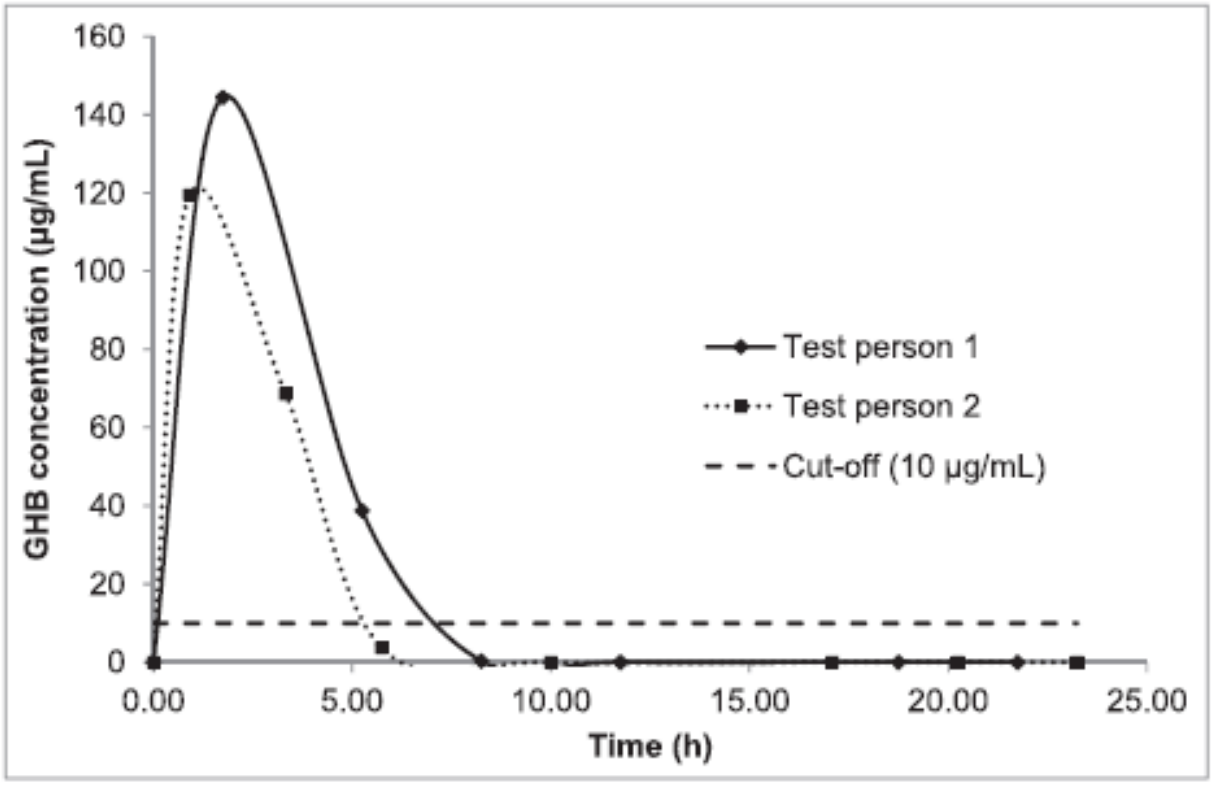


Figure 3. Urine GHB concentrations of both test persons (data are provided in supplementary information).

Wichtig bei entsprechendem Patienten:

-- Verdacht auf K.O.-Mittel: schnellstmögliche Probennahme

-- Serum + **Urin** gewinnen

-- ggf. Haarprobe: aktuell + in 4 Wochen (Hinterhaupthöcker)

-- Getränk o.a. Flüssigkeit asservieren (wenn möglich)

-- **Labor !!**
- viele verschiedene Substanzen
- mit maximaler Empfindlichkeit (Nachweisgrenzen verlangen)
- keine Teststreifen, Immunoassays etc.

- Empfehlungen:

UNODC
United Nations Office on Drugs and Crime

Guidelines for the

Forensic analysis of drugs facilitating sexual assault and other criminal acts

New York, 2011

Manipulation von Urinproben zum Drogenscreening

A Verdünnung:

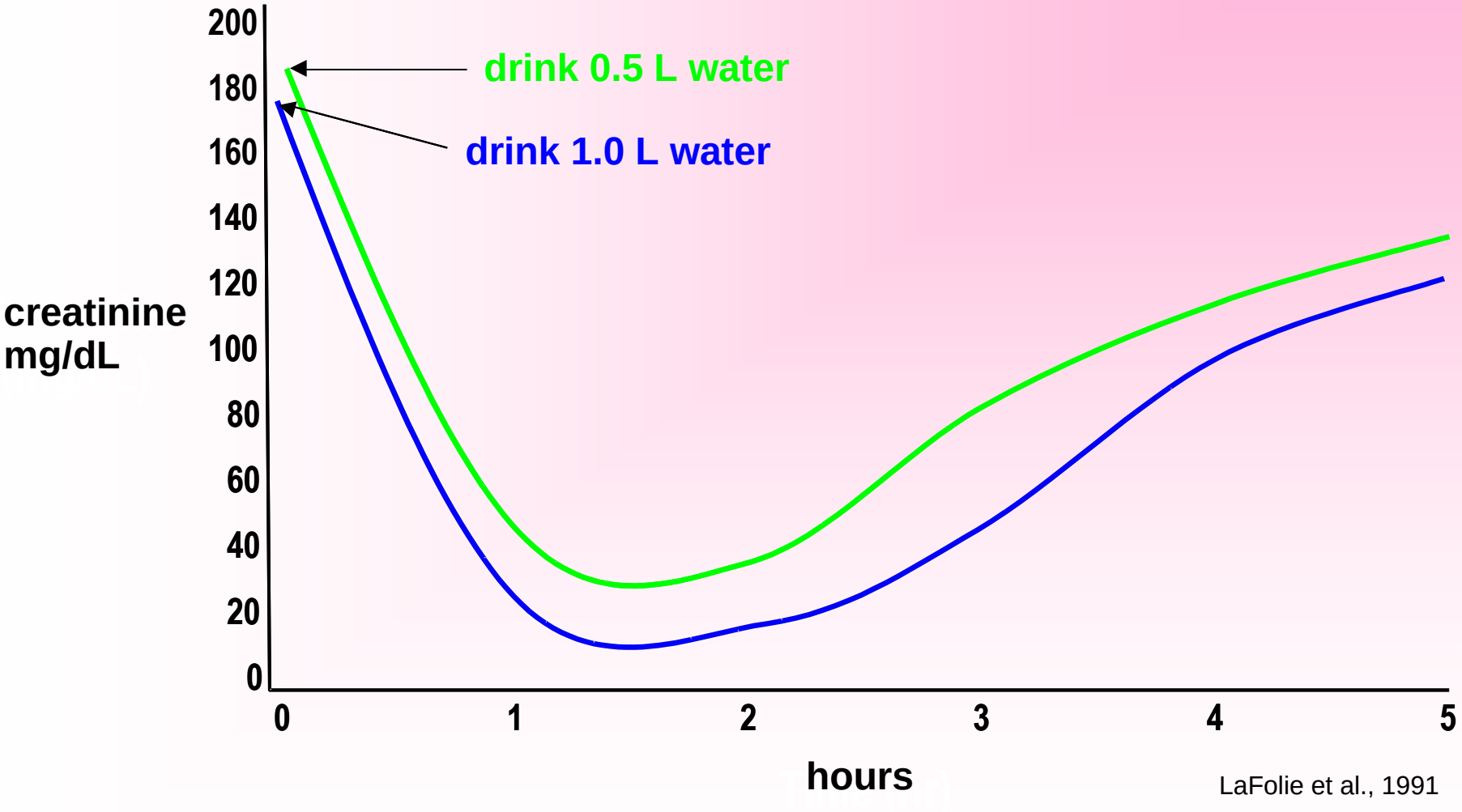
1. in vivo:
   a) Diuretika (forcierte Diurese)
   b) vermehrtes Trinken (u. Vit. B u. Kreatin)
   c) "Spezial Drinks" (Kräutertee, Zuckerlsg. etc.)

2. in vitro:
   a) Verdünnung mit (Toiletten-)Wasser
   b) Verdünnung mit Saft, mitgebrachtem Wasser
   c) Verdünnung mit Fremdurin (Negativurin)

Nachweis, Abhilfe

Direktnachweis d. Diuretika, Kreatinin
bzw. Dichte, Vit. B-Messung
Aufsicht, weitgehendes Ablegen d. Kleidung,
Kreatinin, Temperatur

Effect of water consumption on urinary creatinine



LaFolie et al., 1991

Manipulation von Urinproben zum Drogenscreening

B Manipulation d. Immunoassays:

1. Haushaltsmittel:
a) Detergentien: Seifen etc.
b) Salze
c) basischer pH: Soda, Ammoniak, Lauge
d) saurer pH: Essig, Säure
e) Oxidantien (z.B. Hypochlorit, Peroxid): "Rohrfrei" etc.

2. "Spezialprodukte":
a) Glutaraldehyd (Fixativ), z.B. "UrineAid"

Nachweis, Abhilfe

unter Aufsicht, "sample check"
keine derartigen Substanzen am Ort d. Probennahme
Schaum, Geruch
Dichte, Osmolarität
pH-Wert, Ausfällungen, Geruch, Dichte, Elektolyte

Manipulation von Urinproben zum Drogenscreening

C Manipulation(Oxidation) d. Analyten:

→ auch chromatographisch nicht nachweisbar

1. Na-Nitrit: z.B. "Whizzies"
2. K-Nitrit: z.B. "Klear"
3. Pyridin Chlorchromat: z.B. "UrineLuck"
4. Enzymatisch (!?): "Stealth"

Nachweis, Abhilfe

unter Aufsicht, Händewaschen !!, "sample check"?
Direktnachweise

4. ???


Stealth
51
Stealth
51
0.5mL
Micro-
Vial


Spectrum Labs
BAKE
N
SHAKE
DETOXIFYING BAG
200% Guarantee!
Easy To Use!
EFFECTIVE
IMMEDIATELY!
www.urineluck.com


GET CLEAN
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NET 4 FL. OZ.


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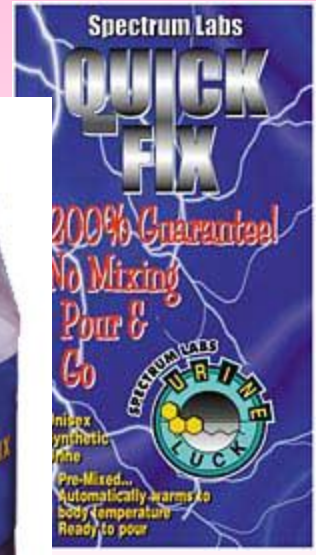
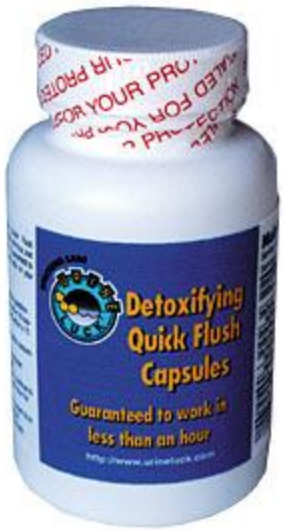
URINE LUCK
DETOXIFYING AGENT
DEVELOPED BY
SPECTRUM LABORATORIES, INC.
200% MONEY BACK GUARANTEE
URINE LUCK
DETOXIFYING AGENT


KHAKI
BLACK
OLIVE


Spectrum Labs
QUICK
FIX
200% Guarantee!
No Mixing
Pour &
Go
Pre-Mixed...
Automatically warms to
body temperature
Ready to pour


DETOXIFYING
CARBO-TEA MIX
GRAPE


NEW!
TECHNOLOGY
ABSOLUTE
DE-TOX


Detoxifying
Quick Flush
Capsules
Guaranteed to work in
less than an hour


Spectrum Labs
Quick
Fizz
EFFERVESCENT DETOXIFICATION
200% Guarantee!
WORKS IN
1 HOUR.
EFFECTIVE
UP TO 5
HOURS.
DIETARY
SUPPLEMENT
TWO TABLETS
www.urineluck.com

D
Abgabe eines negativen „Freundurins“

ClearTest

Continue Shopping
View Your Cart
Check Out
Add Item To Cart

Order This Product:

The Urinator - $149.95

Don't forget Extra Urine Samples when you Purchase *The Urinator*

1 Urine Sample - $10

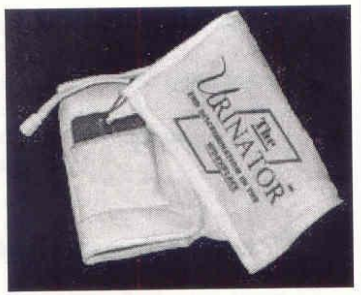
Continue Shopping

View Cart Contents

Check Out

THE URINATOR:

The Urinator is a small electronic module that maintains liquid (distilled water) within the correct testing temperature range for at least four hours.



The Urinator relies on the substitution method of passing a drug test, and is a fully self-contained unit. The Urinator is a thermostatically controlled state-of-the-art electronic device that uses two 9-volt batteries and a small electronic module to maintain liquid (distilled water) within correct testing temperature range for at least four hours. When using this device in a testing situation, the water is mixed with laboratory clean concentrated urine to provide the test facility with a clean toxin-free sample. The Urinator is small enough to hold in your hand and can be used many times- even shared with others.

Purchase The Urinator and it will last for years. It's small, easy to conceal size will keep you prepared for the random or pre-employment urine tests that are becoming so common today.

Includes:

- ELECTRONICALLY CONTROLLED HEATER
- 1 SAMPLE, TOXIN FREE CONCENTRATED URINE
- 4 SMALL LCD TESTING STRIPS
- CALIBRATED BOTTLE FILLING DEVICE
- SOFT FLEXIBLE FOLDING POUCH
- DISCREET PACKAGING AND

The Whizzinator

$ 149,99 plus Tax in
6 different colours

Drogenscreening (mit Immunoassay) im Urin -- Probleme:

-- in vivo/vitro Verdünnung! Kreatinin korrigierter Cutoff?!

-- pH-Wert: 4.5 bis 9.0!! pH-abhängige Resorption, Stabilität

-- Manipulation der Probe: Verdünnung, Detergenzien etc., Oxidantien, Abgabe „Freundurin“, Zugabe d. Medikamente: Probennahme unter Aufsicht

-- Cutoffs: insbes. Gruppenteste nicht standardisiert

-- Kreuzreaktivität: falsch positiv / **falsch negativ**

-- Zunehmende Zahl von Drogen, neue **Substanzklassen,** unbekannte Metaboliten

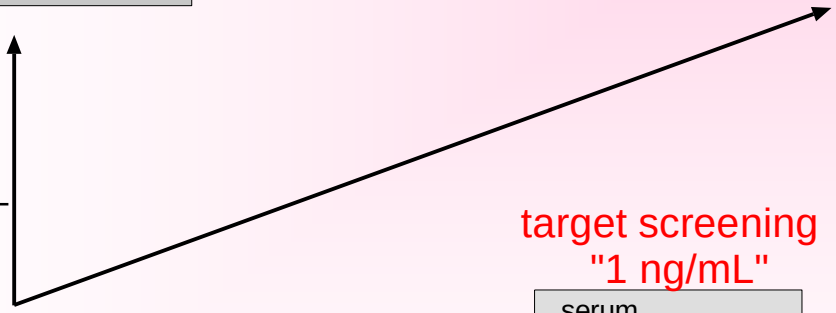
→ **andere Matrix** (Muttersubstanzen)
→ **andere** (sensitivere) **Methoden**

Drugs of abuse screening - urine

Immunoassay (CEDIA)

Amphetamines	500
Barbiturates	100
Benzodiazepines	100
Cocaine	50
Methadone/EDDP	100
Opiates	100
THC-COOH	25

0.5 **LSD**
5.0 6-MAM
2.0 **Bupren.**



confirmation or extended screening
GC/MS, GC/MS-MS or LC/MS-MS
after dedicated sample preparation

target screening
"1 ng/mL"

- serum
- postm. blood
- oral fluid
- gastric content
- hair
- capillary blood
- meconium

GC/MS "general unknown"

enzym. hydrolysis+ LLE+acetylation

Amphetamines Designer drugs

Methadone
Opiates

Analgesics (Tilidine, Oxycodone, etc.)
Antidepressants
Antiepileptics
Neuroleptics
NSAIDs
Zopiclone, Zolpidem, Zotepine
.
.
.
.
.
etc.

broad screening, "100 ng/mL"

Drugs screening - **serum**, meconium, hair, **oral fluid,** etc.

GC/MS "general unknown“ **LC/MS**
LLE+acetylation

Multi-Target-Screening
65 Substanzen
~1 ng/mL
LC-MS/MS

Amphetamines
Designer drugs

Methadone
Opiates

Analgesics (Tilidine, Oxycodone, etc.)
Antidepressants
Antiepileptics
Neuroleptics
NSAIDs
Zopiclone, Zolpidem, Zotepine
.
.
.
.
.
etc.

broad screening, **"25 ng/mL"**

confirmation / quantification

Multi-Target-Analysis

"Bath salts", Designer-drugs
Benzodiazepines
Opiates / Opioids
"Spice" (synth. Cannabinoids)
Psychopharm. drugs

TDM

Sensitive/comprehensive screening/confirmation methods:

-- Multi-Target-Screening, semi-quant.:

~65 substances from different classes
can be adopted to regional or setting specific needs
e.g.: pain management, opiates maintenance therapy etc.

-- Multi-Target-Analysis:

- Synthetic Cannabinoid Mimetics („Spice“): ~60 substances

- Opiates/Opioids/Analgesics: 60 substances (incl. metabolites), quantitative
  anticipates possible abuse from other drug classes, eg.: Ketamine

- Benzodiazepines: 55 substances (incl. metabolites), quantitative
  anticipates parallel abuse of other drug classes, eg.: Z-substances, Pregabalin

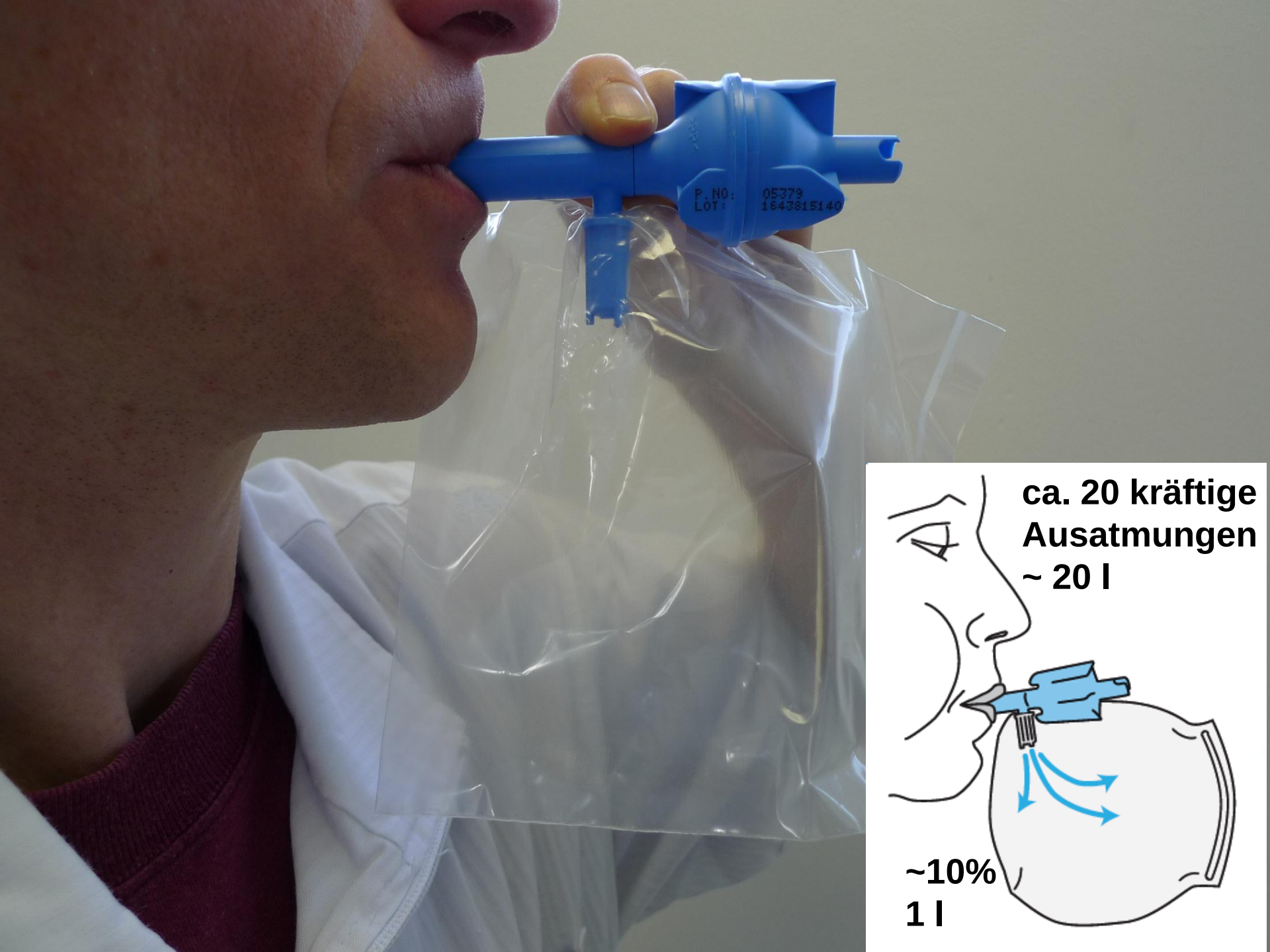
- Amphetamines/Piperazines/Cathinones: 55 substances, quantitative

- Psychoactive Therapeutic Drugs: under development, quantitative
  compliance / abuse testing and TDM

Alternatives Probenmaterial.....

Drogen in der Ausatemluft?

Sind Drogen flüchtig……???


P.NO: 05379
LOT: 1643815140
ca. 20 kräftige Ausatmungen
~ 20 l
~10%
1 l

Journal of Analytical Toxicology, Vol. 35, April 2011

Determination of Methadone in Exhaled Breath Condensate by Liquid Chromatography–Tandem Mass Spectrometry

Olof Beck[1,*], Sören Sandqvist[1], Paul Eriksen[1], Johan Franck[2], and Göran Palmskog[1]

[1]Department of Medicine, Section of Clinical Pharmacology and [2]Department of Clinical Neuroscience, Division of Psychiatry, Karolinska Institutet, Stockholm, Sweden

Journal of Analytical Toxicology, Vol. 35, June 2011

Study on the Sampling of Methadone from Exhaled Breath

Olof Beck[1,*], Sören Sandqvist[1], Michael Böttcher[2], Paul Eriksen[1], Johan Franck[3], and Göran Palmskog[1]

[1]Department of Medicine, Section of Clinical Pharmacology, Karolinska Institutet, Stockholm, Sweden; [2]Labordiagnostik und Hygien Dessau GmbH, Dessau, Germany; and [3]Department of Clinical Neuroscience, Division of Psychiatry, Karolinska Institutet, Stockholm, Sweden

Journal of Pharmaceutical and Biomedical Analysis 56 (2011) 1024–1028

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journal homepage: www.elsevier.com/locate/jpba

ELSEVIER

Demonstration that methadone is being present in the exhaled breath aerosol fraction

Olof Beck[a,*], Sören Sandqvist[a], Johan Franck[b]

[a] Department of Medicine, Section of Clinical Pharmacology, Karolinska Institutet, Stockholm, Sweden
[b] Department of Clinical Neuroscience, Division of Psychiatry, Karolinska Institutet, Stockholm, Sweden

The Detection of Δ⁹-Tetrahydrocannabinol in the Breath of Human Subjects

ANTONY MANOLIS, LINDA J. McBURNEY, and BRIAN A. BOBBIE

Defence and Civil Institute of Environmental Medicine, 1133 Sheppard Avenue West, P.O.Box 2000, Downsview, Ontario, Canada M3M 3B9

A. Manolis, L.J. McBurney and B.A. Bobbie. The detection of Δ9 tetrahydrocannabinol in the breath of human subjects. *Clin Biochem*. **16**: 229-233 (1983).

Developing exhaled breath as a matrix for the detection of Cannabinoids

O. Beck, TIAFT 2011

Journal of Analytical Toxicology, Vol. 34, June 2010

Amphetamines Detected in Exhaled Breath from Drug Addicts: A New Possible Method for Drugs-of-Abuse Testing

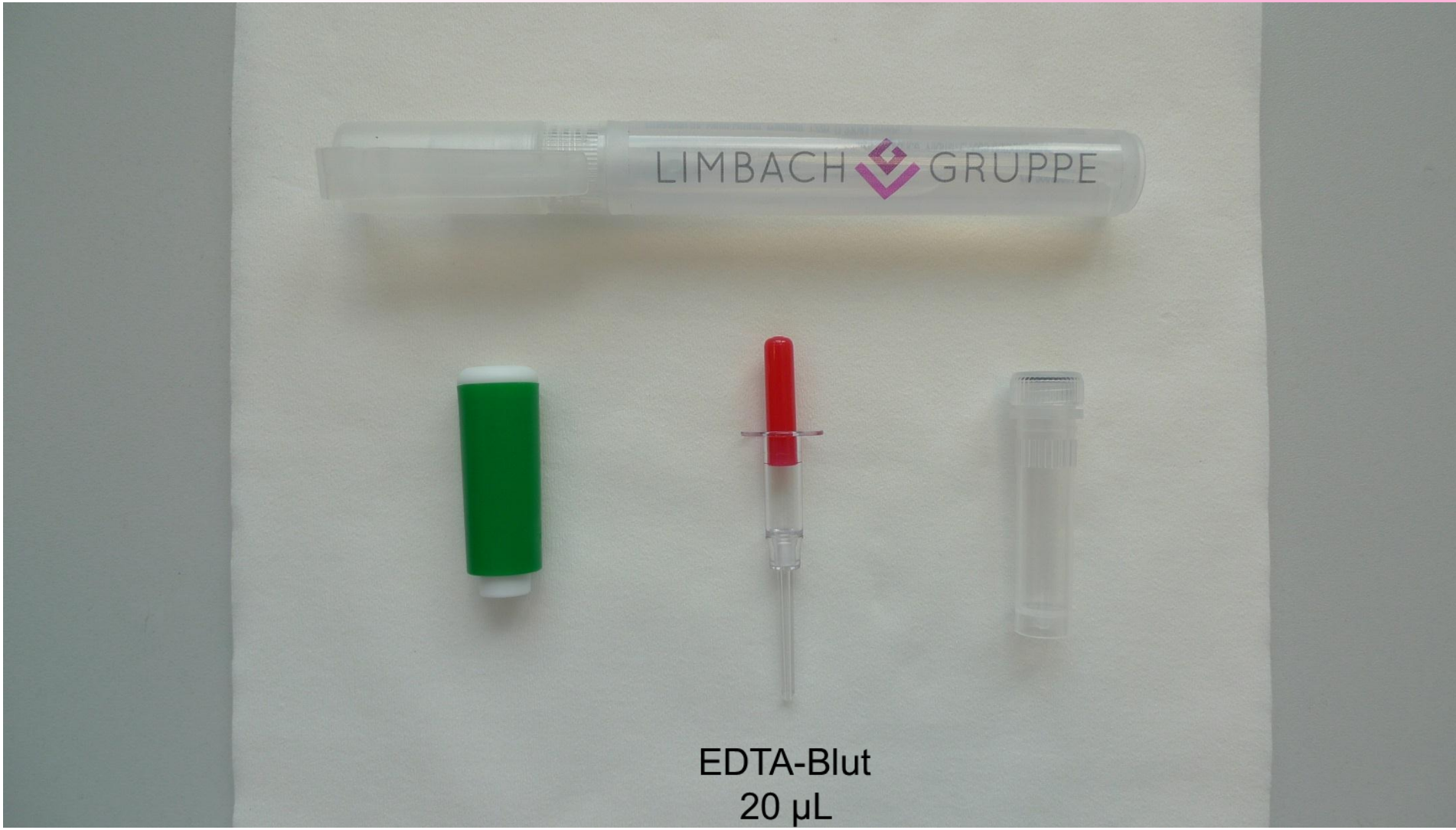
Olof Beck[1,*], Kathinka Leine[1], Göran Palmskog[1], and Johan Franck[2]

[1]Department of Medicine, Section of Clinical Pharmacology and [2]Department of Clinical Neuroscience, Division of Psychiatry, Karolinska Institutet, Stockholm, Sweden

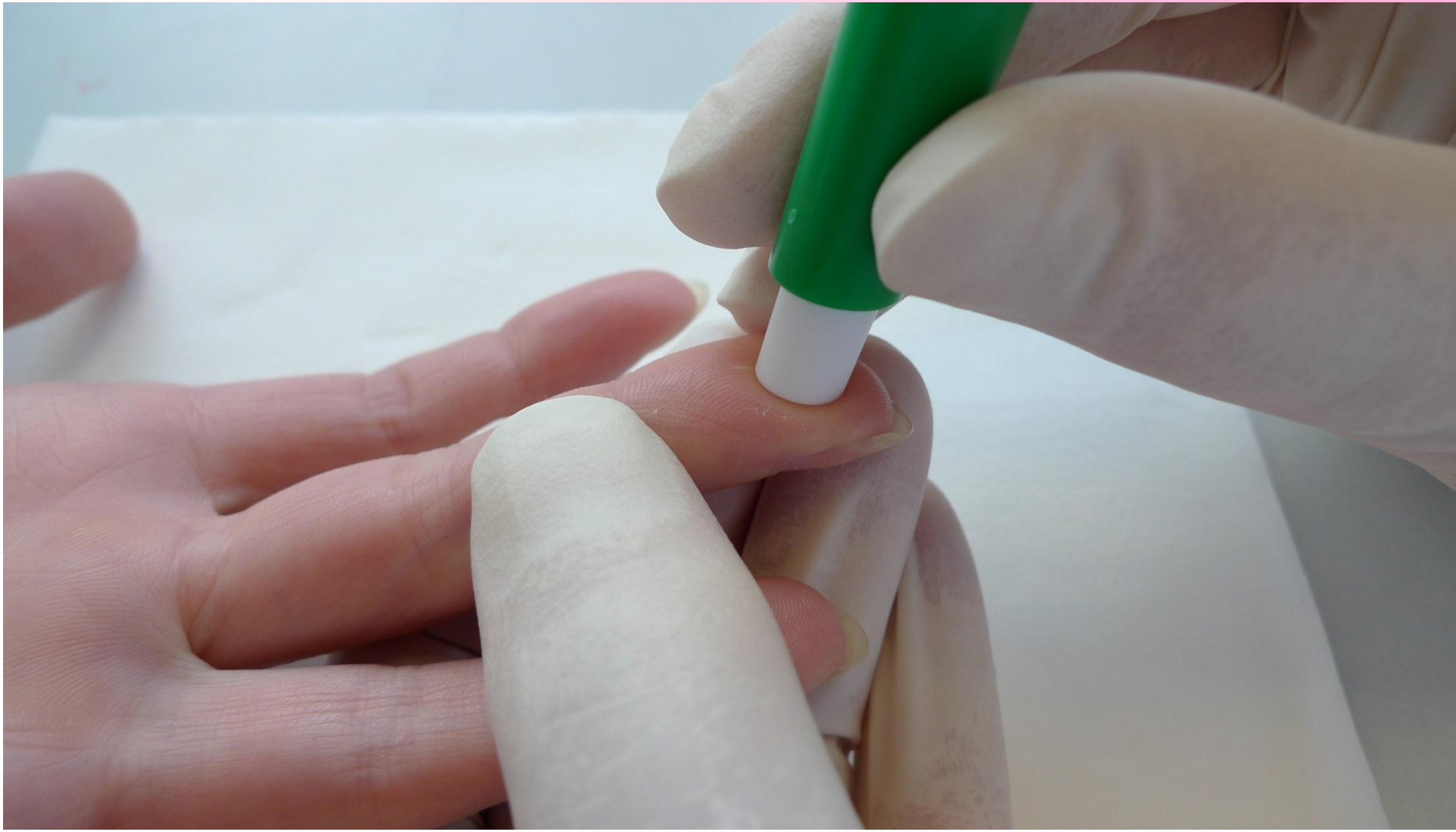
Nicht invasive Probennahmen, Nachw.fenster 1-7 d:
1. Kapillarblut, 2. Speichel („**O**ral **F**luid“)

Kapillarblutentnahme, EDTA Vollblut

- Multi-Target-Screening, 60 Subst.
- Multi-Target-Analysen, versch. Subst.klassen



EDTA-Blut
20 µL



0607262456

Wissenswertes zum Speichel

-- Produktion: bis 1.5 L/d, Fluss: 0.3-0.5 / 1.0-1.5 mL/min

-- Parotis(1) ~20%, Submandibularis(2) ~70%, Sublingualis(3) ~5%

-- Ruhesekretion: **pH 5.8 - 6.4**, Stimulation: bis 7.8

-- "Zutaten":

H_2O 99%
Enzyme: **Amylase**
Mucine
IgA u. a. Ig
Elektrolyte: $Na^{+,}$ K^{+}, Cl^{-}, HCO_3^{-}
bei niedrigem Fluss: hypoton
bei hohem Fluss: isoton

Vor- und Nachteile des Speichels

Vorteile:

•Probengewinnung

- Geringere Manipulationsmöglichkeit
- Privatssphäre wird gewahrt (größere Akzeptanz der Patienten)
- Nicht invasiv (kein medizinisches Fachpersonal notwedig)

•Relativ “saubere” Matrix (abhängig vom Entnahmesystem)

•Muttersubstanzen oftmals gut detektierbar

Nachteile:

•Probenmenge (Schwierigkeiten bei einigen Patientengruppen → Xerostomie)

•Einflussfaktoren auf die Analytkonzentration (Konzentrationsänderung durch Anregung des Speichel-flusses, unspezifische Bindung im Entnahmesystem)

Wie gelangen Drogen in den Speichel?

-- Orale Kontamination

-- aus dem Blut durch **passive Diffusion**

-- aktive Sekretion

-- Filtration

Faktoren mit Einfluß auf das S/P-Ratio:
-- **pKa** einer Substanz (sauer - alkalisch?)
-- Lipidlöslichkeit
-- **Plasmaprotein Bindung**
-- Molekulargewicht

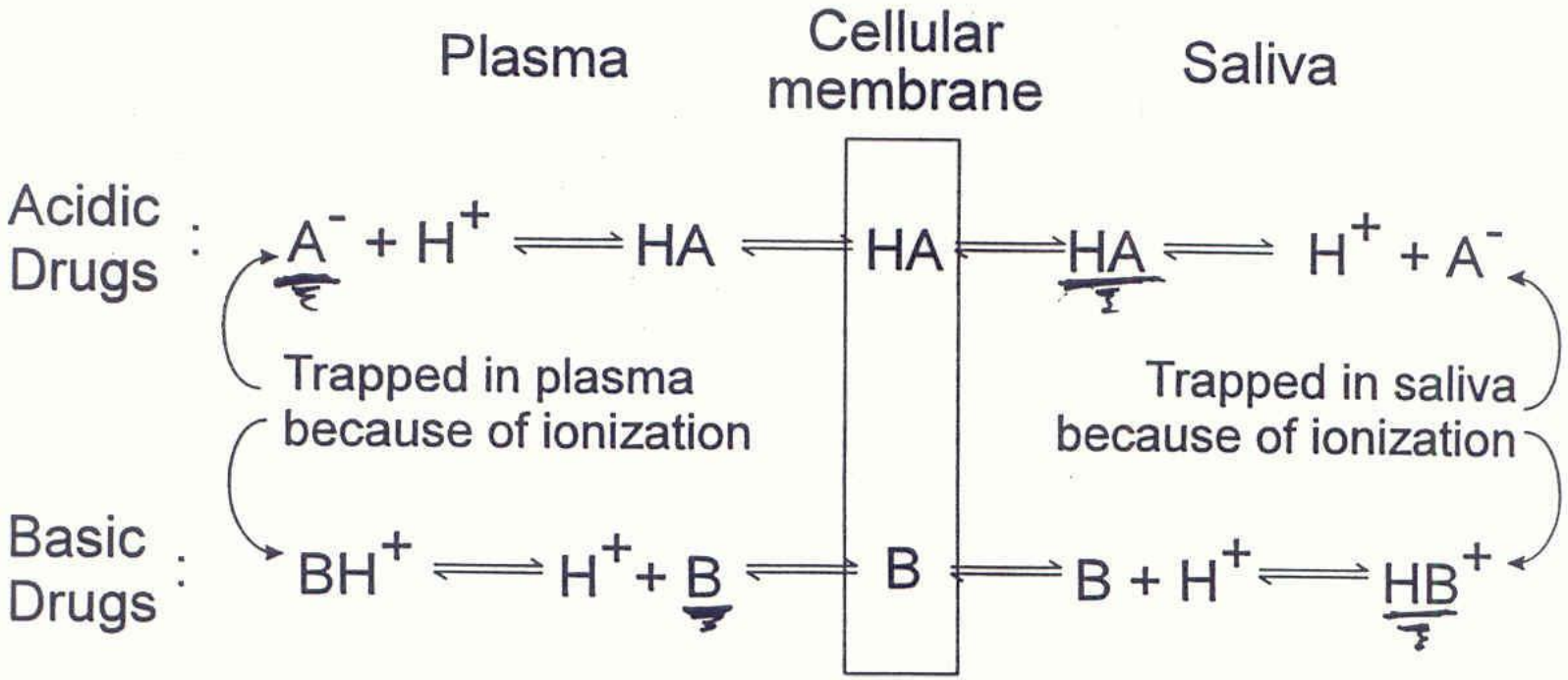


Fig. 1. Schematic diagram for transport of drugs into saliva or sweat.

Speichel/Serum-Ratio

- Das Speichel/Serum-Ratio (OF/SE-Ratio) einer Substanz erlaubt :

  1. Eine Abschätzung der generellen Nachweisbarkeit und deren Zeitfenster für eine Substanz

  2. Unter Berücksichtigung des therap. Bereichs für Serum/Plasma, Rückschlüsse auf den zu erwartenden Konzentrationsbereich einer Substanz im Speichel

- OF/SE-Ratio ist theoretisch ermittelbar

  Problem: schwierig und nicht unbedingt zuverlässig.

- Experimentelle Ermittlung ist zu bevorzugen

  Problem: das Speichelentnahmesystem könnte Einfluss auf die Ergebnisse haben (z.B. unspezifische Bindung)

  → möglicherweise der Grund für die unterschiedlichen Ergebnisse in der Literatur

Haeckel and Hänecke; Eur J Clin Chem Clin Biochem 1996:34:171-191
Samyn et al.; Forensic Sci Rec; 11:1; 1999

Table 10. Mean oral fluid-blood partition concentration ratios for specific drugs [117]

Substance	*Mean oral fluid-blood partition concentration ratios*
Amphetamines	
Amphetamine	23
Metamphetamine	29
Benzodiazepines	
7-Aminoclonazepam	0.43
Alprazolam	0.41
Bromazepam	0.31
Clonazepam	0.19
Diazepam	0.056
Lorazepam	0.10
Nordiazepam	0.053
Oxazepam	0.15

UNODC
United Nations Office on Drugs and Crime

2014

Guidelines for
Testing Drugs under International Control in Hair, Sweat and Oral Fluid

Table 10. *(continued)*

Substance	*Mean oral fluid-blood partition concentration ratios*
Z-drugs	
Zolpidem	0.43
Zopiclone	2.5
Cocaine	
Benzoylecgonine	3.3
Cocaine	20
Opioids	
Codeine	8.8
Methadone	2.9
Morphine	9.8
Tramadol	13
Cannabis	
THC	31
Others	
Amitriptyline	1.5
Mirtazapine	3.4
Trazodone	0.31

Different data in publications

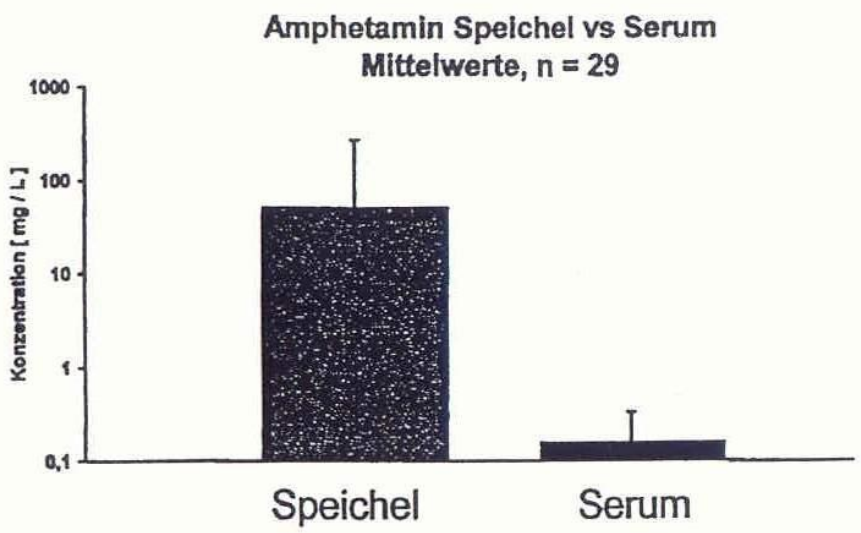
- Analytical methods
- Sampling
- Oral contamination

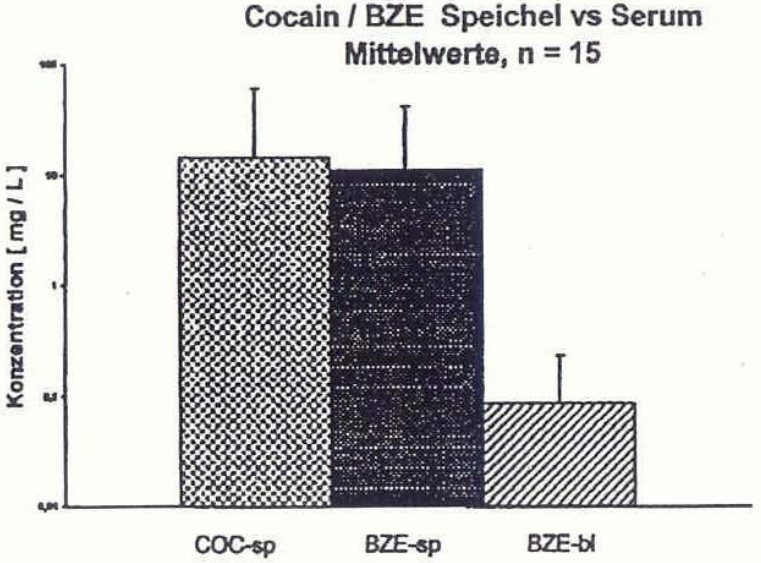
- No/small data on NPS

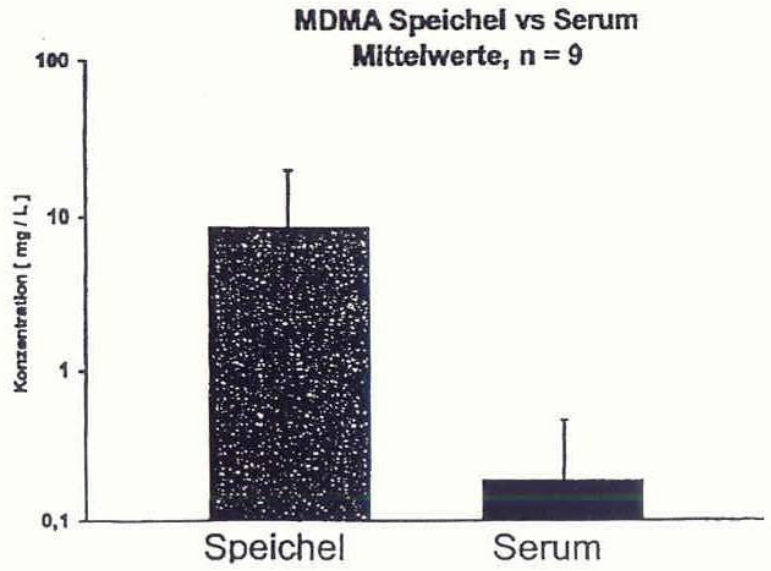
OF/SE-ratio: pKa values for some “new drugs”

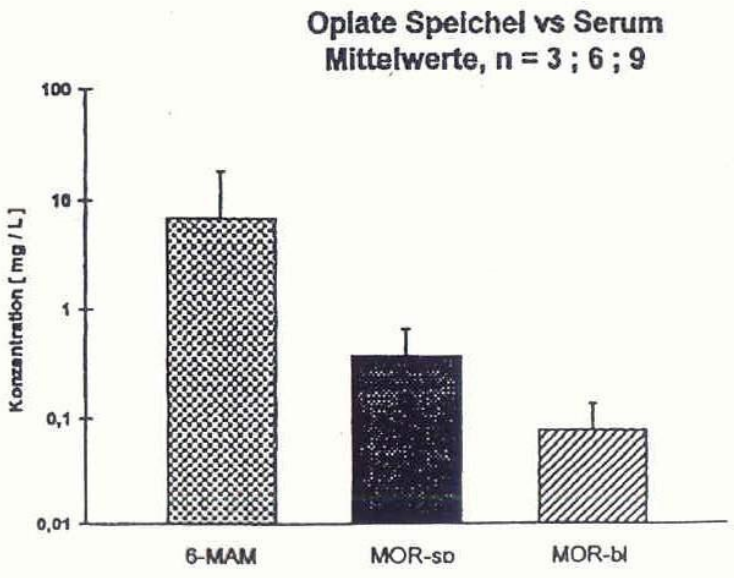
- Buphedrone: 7.1
- Butylone: 7.7
- Dimethylamphetamine: 9.8
- MDA: 9.7
- MDMA: 8.7
- MDPV: 8.4
- Methylfentanyl: 9.0
- Methylone: 7.7
- Methylphenidate: 8.8
- a-Methyltryptamine: 10.0
- PMMA: 9.5
- Sufentanyl: 8.0

R.C. Baselt, 10th Edition 2014, Disposition of Toxic Drugs and Chemicals in Man









Kauert, Blutalkohol 37, 2000

Saliva Collection System (SCS) pH 4.2
Greiner Bio-One

4 ml Saliva Extraction Solution (SES)

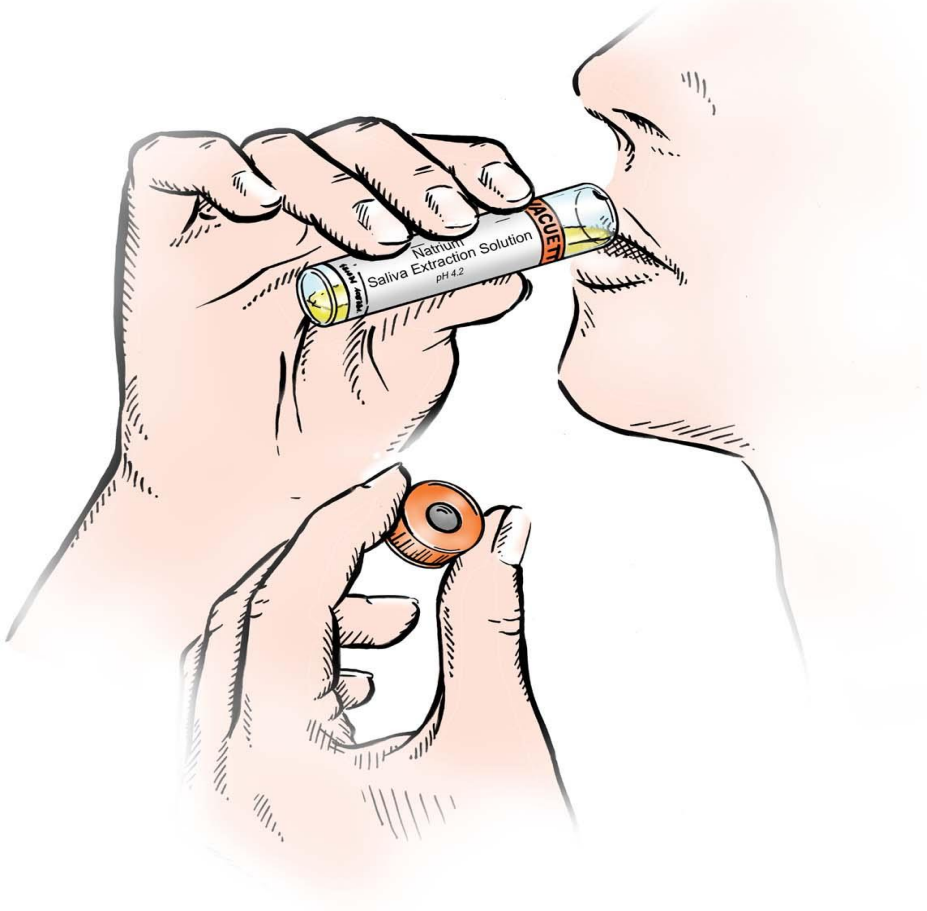
contains non-toxic yellow food color and buffer salts

Saliva Collection Beaker
with integrated saliva transfer device

Evacuated Saliva transfer tubes
contains stabilizing agents ; A+B sample!

OF sampling with the Greiner Saliva Collection System:

Step 1

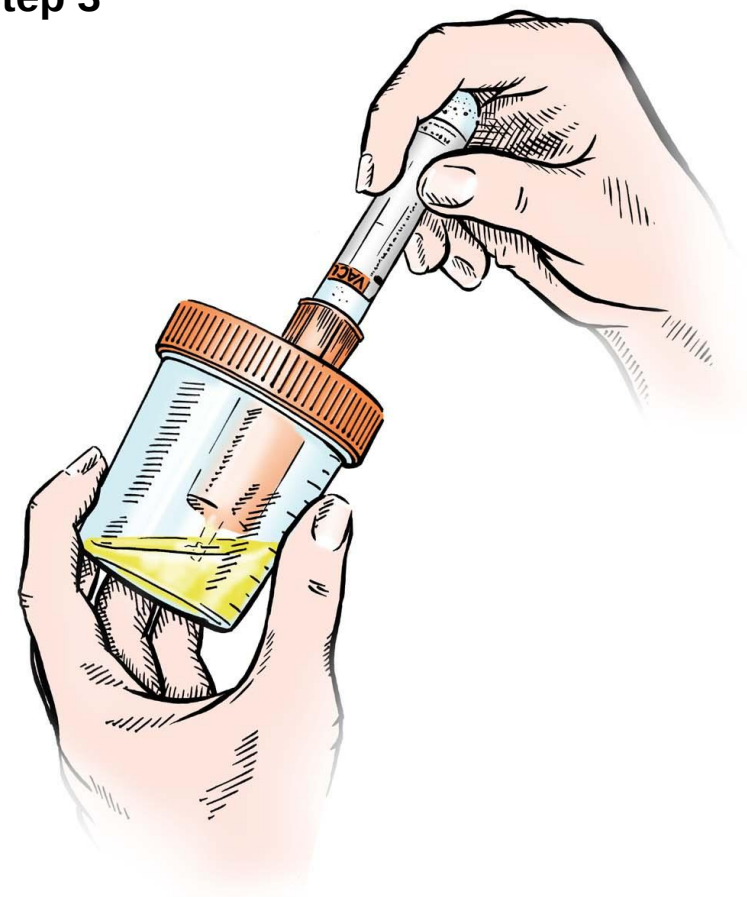


Rinsing of the oral cavity with Saliva Extraction Solution for 2 minutes

Step 2:

Spitting of the extracted oral fluid into the Saliva Collection Beaker

Step 3



Transfering of the extracted OF into the evacuated Saliva Collection Tubes

%OF is determined by photometry on Olympus AU680

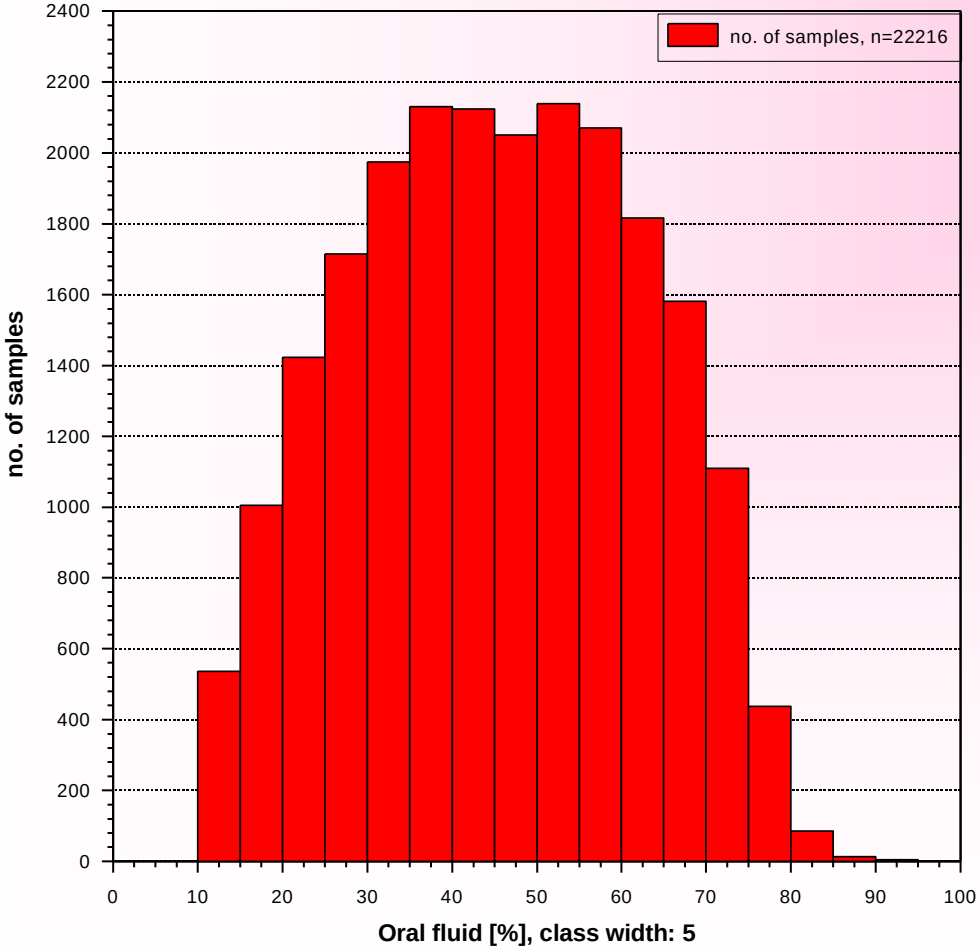
always A + B sample!

Advantages:

-- quick (Xerostomia!), standardized time
-- acidic pH during collection keeps pH difference to plasma
-- acidic pH: 6-AM, Cocaine, Zopiclone etc. are stable
-- aqueous matrix: less ion suppression, rapid SALLE possible

Oral fluid collection with the GBO Saliva Collection System

Distribution of oral fluid concentrations



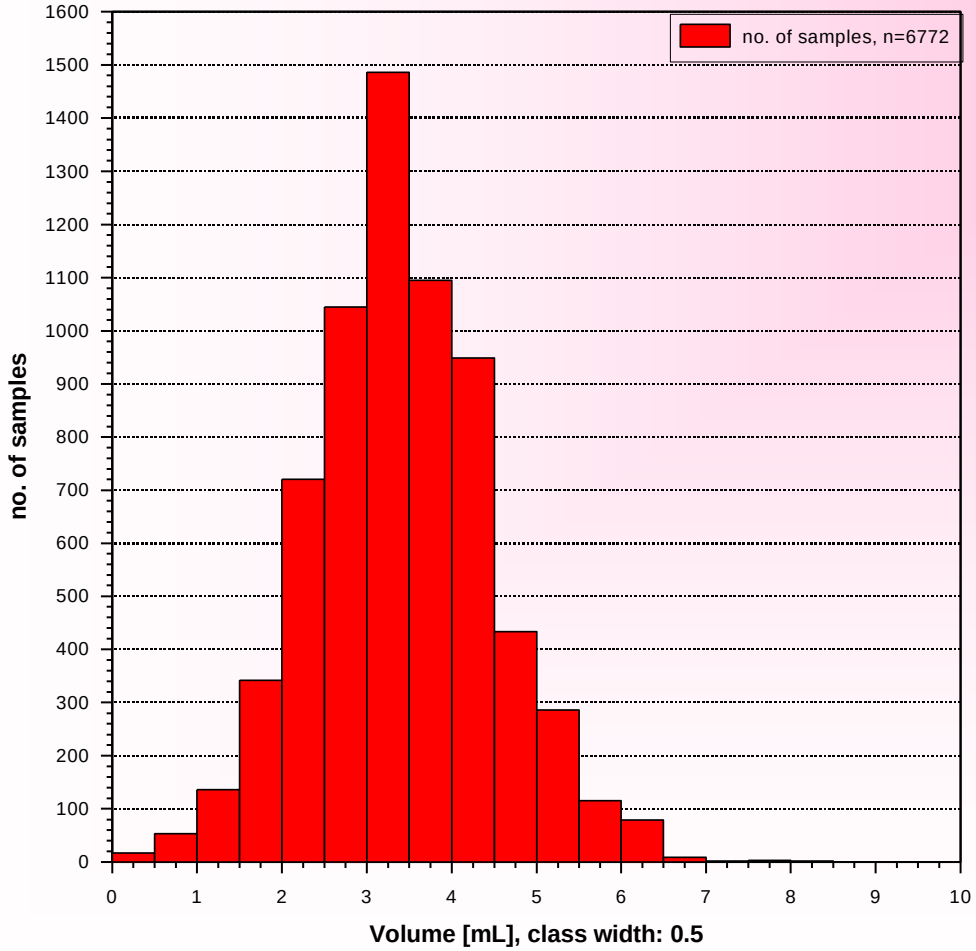
Statistics	Oral fluid [%]	n
mean	45.4	
median	45.4	
1% percentile	12.5	
5% percentile	18.1	
25% percentile	32.1	
75% percentile	58.7	
95% percentile	72.1	
99% percentile	77.9	
considered samples		22216
not considered	<10	252
not considered	nm*	52
all samples		22520

Samples from 4561 pats. (3313 male, 1248 female)
No gender information available for 219 pats.

- not measurable

Oral fluid collection with the GBO Saliva Collection System

Distribution of sample volume

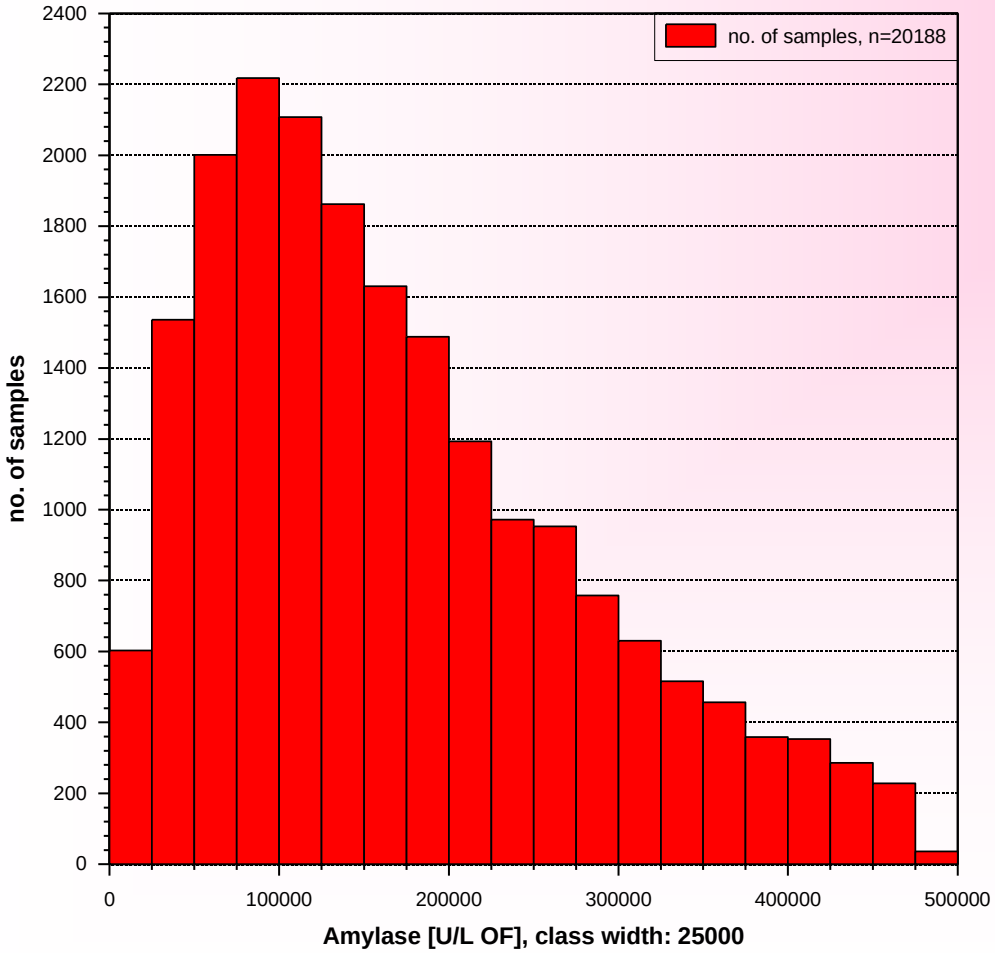


Statistics	Volume [mL]	n
mean	3.2	
median	3	
1% percentile	0.9	
5% percentile	1.5	
25% percentile	2.5	
75% percentile	4	
95% percentile	5	
99% percentile	6	
considered samples		6772
not considered	nm*	15748
all samples		22520

- not measurable

Oral fluid collection with the GBO Saliva Collection System

Distribution of amylase concentrations



Statistics	Amylase [U/L OF]	n
mean	170583	
median	146686	
1% percentile	15404	
5% percentile	33494	
25% percentile	85605	
75% percentile	236876	
95% percentile	392247	
99% percentile	456756	
considered samples		20188
not considered	>480000	1988
not considered	<10000	288
not considered	nm*	59
all samples		22520

- not measurable

Amylase activity + age: no change after 1 year

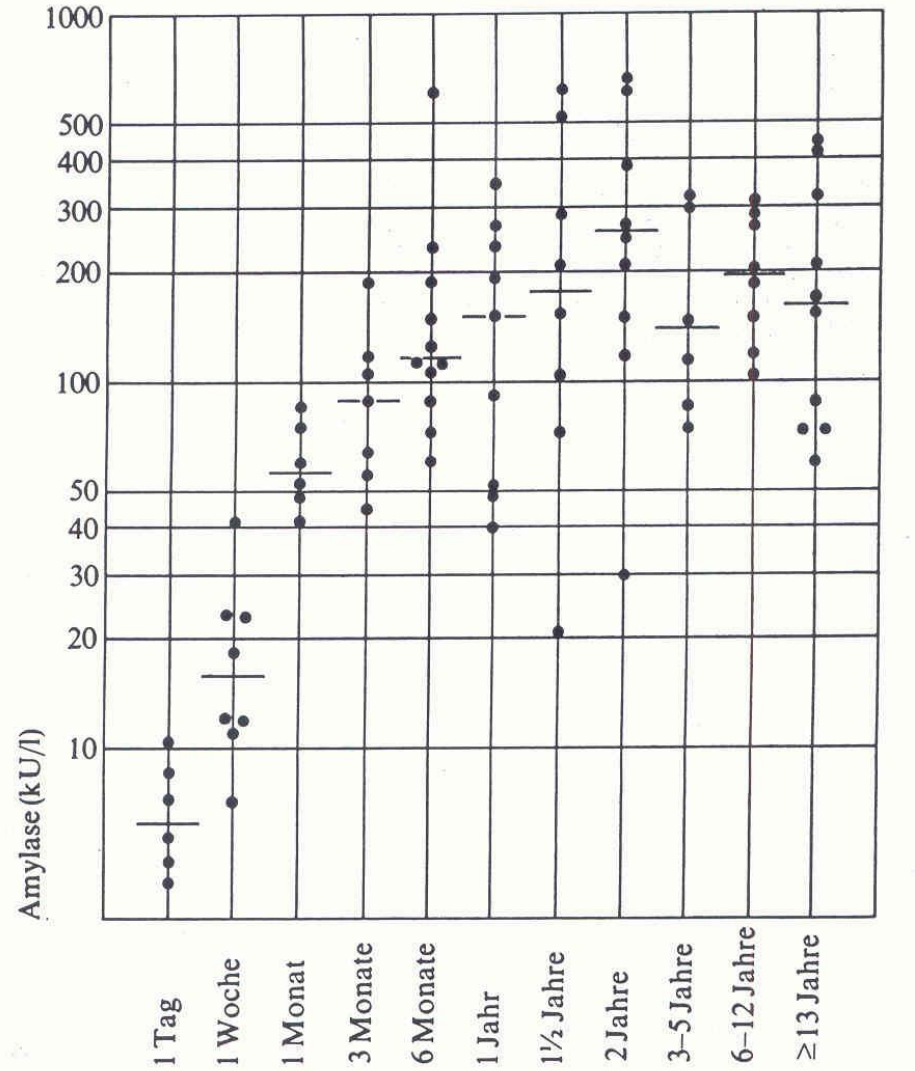


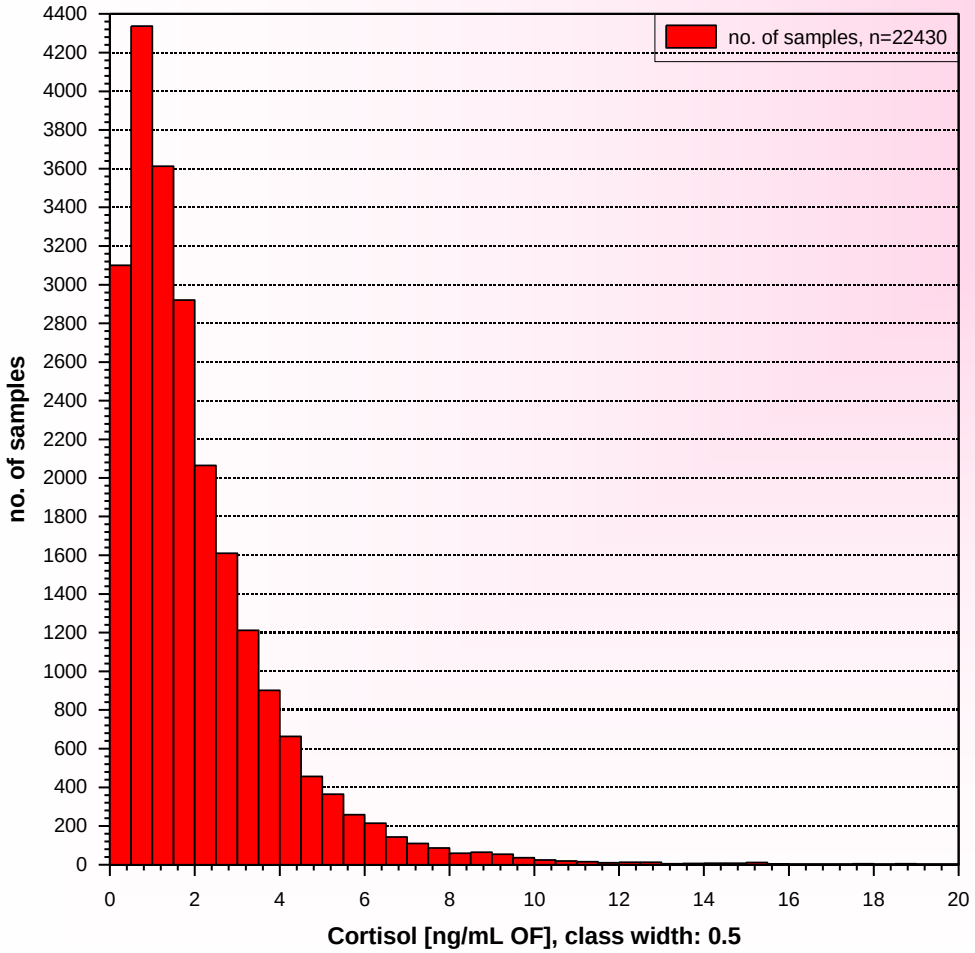
Abb.8. Amylaseaktivität in stimuliertem Gesamtspeichel in Abhängigkeit vom Alter[113].

Ciba Geigy, 1977

- There is no age related difference
- Is there a sex related reference range???
- Impact of medications?
- Impact of saliva flow?

Oral fluid collection with the GBO Saliva Collection System

Distribution of cortisol concentrations



Statistics	Cortisol [ng/mL OF]	n
mean	2.01	
median	1.5	
1% percentile	0.1	
5% percentile	0.2	
25% percentile	0.7	
75% percentile	2.7	
95% percentile	5.6	
99% percentile	9.2	
considered samples		22430
not considered	>20	46
not considered	<0.1	26
not considered	nm*	18
all samples		22520

- not measurable

Perianalytik

Perianalytik bezeichnet Überprüfung der Probe vor der eigentlichen Analytik (Echtheit, Verdünnung, Manipulationen etc.)

1. Probenvolumen

2. Photometrische Bestimmung des Speichelanteils (optische Dichte des Tartrazins)

3. Photometrische Bestimmung der Alpha-Amylase Konzentration durch die Messung der Alpha-Amylase Aktitvität (1. Authentizitätsmarker)

4. Bestimmung der Cortisolkonzentration (2. Authentiziätsmarker) mit UPLC-MS/MS

- Böttcher M., Preidel A., Beck O. “Peri-analytics” reference ranges for drug screening in oral fluid using the Greiner Bio-One collection device”; Poster: TIAFT, Bonn (2010)

Vorteile des Greiner Bio-One Speichelsammelsystems

- Anregung des Speichelflusses (Xerostomie als UAW vieler Psychopharmaka und Opiate/Opioide)
- ausreichendes Probenvolumen
- standardisierte Sammelzeit
- konstant saurer pH-Wert während des Sammelvorgangs (“Ionenfalle” für basische Substanzen)
- konstant saurer pH-Wert während der Lagerung (bessere Stabilität vieler Substanzen, z.B. “Badesalze”, Zopiclon oder 6-AM)
- A+B Probe entstammen demselben Sammelvorgang

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doi: 10.1093/jat/bkv123
Advance Access Publication Date: 29 October 2015
Article

OXFORD

Article

Influence of Sampling Procedure on Codeine Concentrations in Oral Fluid†

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†Preliminary results of this work were presented at the meeting on Alternative Sampling Strategies in Toxicology and Therapeutic Drug Monitoring in Ghent (Belgium) on 18–19 September 2014.
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Abstract

For many drugs, there is a poor correlation between the plasma and oral fluid (OF) concentrations, due to differences in OF pH, oral contamination, stimulation of OF flow and variability of the volume of sample taken. The aim of this study was to evaluate the OF/plasma ratio and variability in drug concentration in OF sampled by two commercially available collection systems: Saliva Collection System (SCS) and Quantisal. Blood and OF samples were collected from 12 volunteers after intake of 19.5 mg codeine phosphate. Six persons were sampled by SCS first, followed by Quantisal; six other participants used Quantisal before SCS. The OF content of SCS tubes was measured spectrophotometrically. The Quantisal devices were weighed to correct for the effectively obtained OF volume. Codeine was measured by gas chromatography–mass spectrometry. The mean codeine concentration at 1 h was 29.8 ± 18.8 µg/L in plasma, 72.8 ± 63.9 µg/L in SCS OF and 85.3 ± 72.6 µg/L in Quantisal OF. The mean OF/plasma ratio was 2.30 ± 0.77 (SCS) and 2.69 ± 1.94 (Quantisal). Pearson's correlation coefficient between OF and plasma codeine concentrations was statistically significantly ($P = 0.005$) higher for SCS ($R^2 = 0.745$) than for Quantisal ($R^2 = 0.403$). The variability in ratios with Quantisal was markedly reduced when used after SCS. Codeine concentrations measured in OF taken with SCS correlate better with plasma concentrations than in OF obtained with Quantisal, particularly when Quantisal was used first.

ABOR

Oral Fluid Levels of Nicotine and Metabolites in Smokers as a Function of Collection Device

Michael Böttcher, Andreas Peschel
MVZ für Mikrobiologie, Labordiagnostik und Hygiene Dessau GmbH, Dessau, Germany

IATDMCT 2011

ABOR

First experiments on the possible use of diphenhydramine as a model substance for the evaluation of oral fluid sample collection

J. Neumann, M. Böttcher
MVZ Labor Dessau GmbH, Germany

IATDMCT Sat.Symp. Ghent 2014

Journal of Analytical Toxicology, Vol. 35, January/February 2011

Oral Fluid is a Viable Alternative for Monitoring Drug Abuse: Detection of Drugs in Oral Fluid by Liquid Chromatography–Tandem Mass Spectrometry and Comparison to the Results from Urine Samples from Patients Treated with Methadone or Buprenorphine

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Abstract

Oral fluid is an alternative biological matrix that might have advantages over urine for drug analysis in treatment programs. A liquid chromatography–tandem mass spectrometry (LC–MS–MS) method has been used for screening 32 of the most commonly abused drugs and their metabolites in 0.5 mL preserved oral fluid, and the results were compared to results obtained from urine samples taken at the same time. In all, 164 pairs of oral fluid and urine were obtained from 45 patients stabilized on either methadone or buprenorphine. The total number of detections of drugs other than buprenorphine or methadone was 535 in oral fluid and 629 in urine. Morphine was found more often in urine (n = 66) than in oral fluid (n = 48), whereas the opposite was the case for 6-monoacetylmorphine (n = 20 in urine and n = 48 in oral fluid). Methadone showed the same detection frequency in urine and oral fluid (n = 75), whereas amphetamine (n = 45 in urine and n = 51 in oral fluid), methamphetamine (n = 39 in urine and n = 45 in oral fluid), and *N*-desmethyldiazepam (n = 37 in urine and n = 51 in oral fluid) were detected slightly more often in oral fluid. The other benzodiazepines, cannabis and cocaine were found more frequently in urine samples. If using a sensitive LC–MS–MS technique, oral fluid might be a good alternative to urine for detection of relatively recent use of drugs.

Table II. Comparison of the Results from Oral Fluid and Urine Showing that the Results from the Sample Pairs Primarily Correspond

Drug	Positive OF* and Urine	Negative OF and Urine	Corresponding Results OF and Urine	Positive OF Only	Positive Urine Only
3-OH-Diazepam	6	117	123 (75%)	0	41
6-MAM	19	115	134 (82%)	29 !	1
7-Aminonitrazepam	9	149	158 (96%)	0	6
7-Aminoflunitrazepam	59	83	142 (87%)	3	19
7-Aminoclonazepam	26	122	148 (90%)	2	14
Alprazolam	9	153	162 (99%)	0	2
Amphetamine	45	113	158 (96%)	6 !	0
Benzoylecgonine	1	158	159 (97%)	0	5
Buprenorphine	67	–†		–	22 ?
Codeine	34	122	156 (95%)	4	4
Cocaine	0	161	161 (98%)	2	1
Methadone	75	89	164 (99%)	–	0
Methamphetamine	39	119	158 (96%)	6 !	0
Morphine	45	95	140 (85%)	3	21
N-Desmethyldiazepam	35	111	146 (89%)	16 !	2
Oxazepam	41	71	112 (68%)	9	43 !
THC/THCCOOH‡	81	64	145 (88%)	1	18
Zopiclone	4	106	110 (99%)	1	0

* Oral fluid.
† There were analytical problems with the oral fluid analysis.
‡ THC was analyzed in oral fluid, and THCCOOH was analyzed in urine.

Routine Drogenscreening im Speichel mit UPLC-MS/MS: Analyten

Analytes in „**Module A“,** cutoff 0.1-1 ng/mL neat OF, IS = 0.5 ng/mL SA/SES:

- **Peri-analytics:** volume, % saliva in SES, Amylase (Roche AU680), Cortisol (incl. in LC-MS/MS)

- **Substitution drugs:** D-/L-Methadone, EDDP, Buprenorphine, Norbuprenorphine

- **Amphetamines:** Amphetamine, Methamphetamine, MDMA, MDA, MBDB, BDB, MDEA, PMMA, Butylone, Mephedrone, Methylone, MDPV, alpha-PVP, 4-Methylethcatinon, Pentedron

- **Benzodiazepines**: Diazepam, Nordiazepam, Oxazepam, Midazolam, Flurazepam, Desalkyl-flurazepam, Temazepam, 7-Aminoclonazepam, Alprazolam, Flunitrazepam, 7-Aminofluni-trazepam, Bromazepam, Lorazepam, Phenazepam

- **Cocaine:** Cocaine, Benzoylecgonine, Methylecgonine, Lidocaine

- **Opiates:** Morphine, Codeine, 6-Acetylmorphine, 6-Acetylcodeine, Norcodeine, Dihydrocodeine

- **Opioids:** Naloxone, Tilidine, Tramadol, O-Desmethyltramadol, Oxycodone, Noroxycodone, Fentanyl, Nortilidine, Hydromorphone

- **Cannabinoids:** THC

- **Others:** Zolpidem, Zopiclone**,** Zaleplone, Ketamine, Methylphenidate, Ritalinic acid, Pregabalin, Gabapentin, Bupropion

actual: N = 62 (3 transitions) **+ 60 deuterated IS** (2 transitions)

Assessment of the use of oral fluid as a matrix for drug monitoring in patients undergoing treatment for opioid addiction

Frank Kunkel, MD; Elizabeth Fey, MS; Damon Borg, PhD; Richard Stripp, PhD; Christine Getto, BS

ARTICLE INFO

Keywords:
oral fluid drug testing
opioid addiction
suboxone
buprenorphine
urine drug testing

DOI:10.5055/jom.2015.0293
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ABSTRACT

Drug testing is an important clinical tool that is available to physicians who are assessing the effectiveness of drug treatment as well as patient compliance to the administered program. While urine has traditionally been the matrix of choice for drug monitoring, oral fluid, a filtrate of the blood, has shown great promise as an alternative matrix for such applications. Oral fluid collection can be accomplished without the need for highly trained medical staff through the use of a simple, non-invasive oral fluid collection device, which obtains an adequate sample in only a few minutes. There has been a significant amount of research performed on the use of oral fluid for forensic toxicology application; however, more studies assessing the use of oral fluid drug testing are required to validate its ability to achieve clinical drug monitoring goals. Testing for various drugs in oral fluid may yield a different result when compared to the same drugs in urine, requiring an assessment of the utility of oral fluid for such practices. The purpose of this study was to examine the application of oral fluid drug testing in patients undergoing buprenorphine treatment for opioid dependence. A retrospective analysis of drug testing results obtained from 6,928 patients (4,560 unobserved urine collections and 2,368 observed oral fluid collections) monitored for heroin metabolite, amphetamine, benzodiazepines, buprenorphine, tetrahydrocannabinol, cocaine, codeine, hydrocodone, hydromorphone, methadone, morphine, oxycodone, and oxymorphone was completed. Results of this statistical exercise indicated that patients undergoing observed oral fluid collection tested positive more frequently than those unobserved urine collections for several illicit drugs and prescription medications targeted. Oral fluid was shown to detect illicit drug use as well as noncompliance in this patient population under the studied conditions more often than the urine specimens.

Table 2. LC/MS-MS oral fluid and urine cutoffs based on analyte		
Drug	**Oral fluid cutoff, ng/mL**	**Urine cutoff, ng/mL**
Amphetamine	2.5	250
Benzodiazepines		
α-Hydroxyalprazolam	N/A	25
Alprazolam	1	N/A
7-Aminoclonazepam	N/A	25
Clonazepam	1	N/A
Diazepam	1	50
Nordiazepam	1	50
Oxazepam	1	50
Temazepam	1	50
Lorazepam	1	50
α-Hydroxymidazolam	N/A	50
α-Hydroxytriazolam	N/A	50
Hydroxyethylflurazepam	N/A	50
6-MAM	4	10
Morphine	2.5	50
Codeine	2.5	50
Hydrocodone	2.5	50
Hydromorphone	2.5	50
Oxycodone	2.5	50
Oxymorphone	2.5	50
Methadone	2.5	100
EDDP	2.5	100
THC	2	15
Cocaine	8	N/A
Benzoylecgonine	8	100
Buprenorphine	0.25	2
Norbuprenorphine	0.25	2

Table 3. Unobserved urine vs observed oral fluid collection positivity (percent)		
Drug	**Urine positivity rate, percent**	**Oral fluid positivity rate, percent**
Amphetamine	0.5	3.5
Benzodiazepines	3.7	8.4
6-Acetylmorphine	1.4	7.4
Morphine	2.3	6.5
Codeine	0.7	3.8
Hydrocodone	0.18	2.4
Hydromorphone	1	0.25
Oxycodone	0.6	5.2
Oxymorphone	0.79	1.5
Methadone/EDDP	0.3	1.2
Buprenorphine/norbu-prenorphine	1.1	24
THC	2.9	4.8
Cocaine/benzoylecgonine	1.4	3
Urine and oral fluid specimens are not paired.		

1st Study: is OF of equal value?

Drug abuse testing of patients in substitution therapy: UPLC-MS/MS screening in OF vs. urine testing with EIA

-- three month observation period

-- urine cutoffs: Amphs 500 ng/mL, Benzos (enzym. hydrolysis) 100 ng/mL, Coca 50 ng/mL, Opi 100 ng/mL, EDDP 100 ng/mL, Bupre 2 ng/mL, THC-COOH 25 ng/mL.

-- saliva cutoffs: 0.1-1 ng/mL (neat OF)

-- Patients from:

1. an outpatient clinic **(OPC)** where the drug testing was stepwise moved from urine to SA.
   - **194 patients** (26 Bupre, 67 Metha, 101 Pola), **902 SA** samples.
   - **182 patients** (25 Bupre, 66 Metha, 91 Pola), **1119 urine** samples.

2. other outpatient clinics **(ALL)** with more random selection between the two matrices.
   - **612 patients** from 23 clinics (116 Bupre, 265 Metha, 231 Pola), **1072 SA** samples.
   - **1463 patients** from 40 clinics (285 Bupre, 673 Metha, 505 Pola), **9008 urine** samples.

Drug abuse testing of patients in substitution therapy: UPLC-MS/MS screening in saliva vs. urine testing with EIA

	OPC	OPC	OPC	ALL	ALL	ALL
	saliva % pos. spls.	urine % pos. spls.	urine no. of spls.	saliva % pos. spls.	urine % pos. spls.	urine no. of spls.
Amphetamines	9.3	3.3	1082	10.3	4.1	7396
Benzodiazepines	11.0	14.4	958	25.7	22.4	6891
Cocaine	5.2	3.9	1075	9.8	7.2	8295
Opiates	13.5	13.5	968	17.6	21.7	6977
Methadone saliva EDDP urine	86.6	85.2	953	85.4	88.0	8938
THC	26.9	-	-	30.5	31.3	598
Opioids	1.2	-	-	2.1	-	-
Others	0.8	-	-	1.4	-	-
Buprenorphine	12.3	-	-	16.9	73.1	640
	n = 902			**n = 1072**		

Methadone/EDDP was positive in both matrices where expected.
However, Buprenorphine was negative in 8 OF samples from 2 OPC patients in low dose therapy (0.4 and 1.0 mg/d).
Cutoff 0.1 ng/mL?

Opiates: detailed results OF

	OPC	OPC	ALL	ALL
	saliva % pos. spls.	saliva % from pos.	saliva % pos. spls.	saliva % from pos.
Opiates	13.5	100	17.6	100
Morphine	13.3	98.4	16.9	95.8
6-Acetylmorphine	10.3	**76.2**	13.4	**76.1**
Codeine	8.2	60.7	12.8	72.5
6-Acetylcodeine	3.7	**27.4**	4.8	**27.3**
Norcodeine	2.8	20.5	4.1	23.3
Dihydrocodeine	0.1	0.8	0.1	0.5

What is Heroin ?

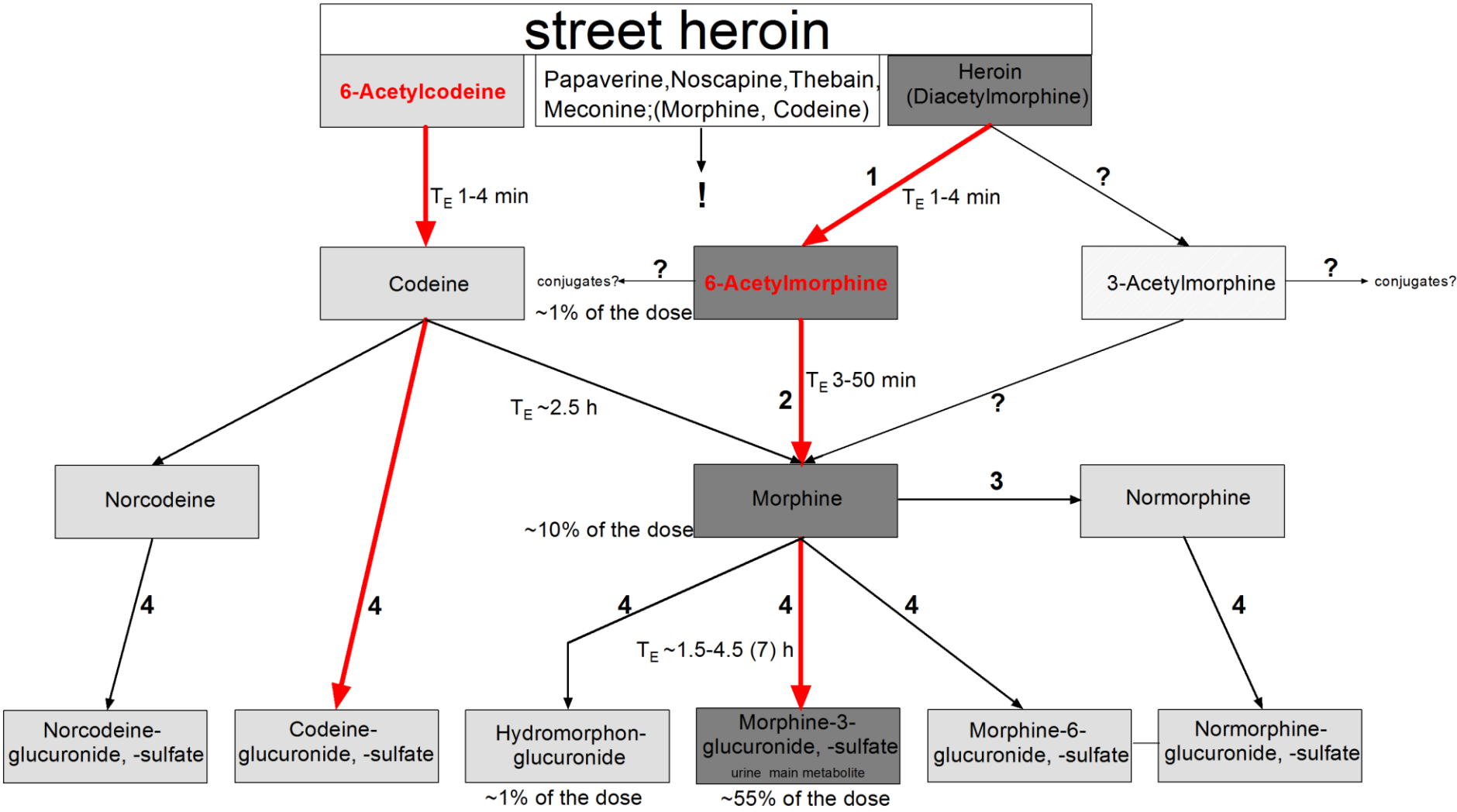
Heroin = Diacetylmorphine
penetrates blood-brain barrier ~25x faster than Morphine

clandestine/illegal labs derivatize Morphine (acetylation) from Opium

Opium:
Scratching the fruit of the of the poppy plant Papaver somniferum
the dried latex juice ("poppy tears") is then scraped off

Opium contains several alkaloids:
<0.1 - 450 µg/g Morphine
<0.1 - 57 µg/g Codeine
0.3 - 41 µg/g Thebaine
0.84 - 230 µg/g Noscapine
0.0 - 67 µg/g Papaverine

The latex juice contaminates the poppy seeds! Washing of the seeds is decisive…….



(1) enzymatic (serum: Butyrylcholinesterase, liver: Carboxylesterases) and chemical.
(2) Acetylcholinesterases (erythrocytes) and Carboxylesterases (liver)
Demethylation of Morphine to Normorphine (3) is a minor pathway
Phase-II-Metabolismus (4) is polymorph (UGT2B7, UGT1A)

DE GRUYTER OPEN

VOLUME 20 - No 2 - 2014 - Page 34-41 - doi: 10.2478/sjfs-2014-0004

Scandinavian journal of FORENSIC SCIENCE Nordisk rettsmedisin

Very long Detection Times after High and repeated intake of Heroin and Methadone, measured in Oral Fluid

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*Corresponding Author: E-mail: vigdis.vindenes@fhi.no

ABSTRACT

When detection times for psychoactive drugs in oral fluid are reported, they are most often based on therapeutic doses administered in clinical studies. Repeated ingestions of high doses, as seen after drug abuse, are however likely to cause positive samples for extended time periods. Findings of drugs of abuse in oral fluid might lead to negative sanctions, and the knowledge of detection times of these drugs are important to ensure correct interpretation. The aim of this study was to investigate the detection times of opioids in oral fluid. 25 patients with a history of heavy drug abuse admitted to a detoxification ward were included. Oral fluid and urine were collected daily and, if the patient gave consent, a blood sample was drawn during the first five days after admission. Morphine, codeine and/or 6-monoacetyl morphine (6-MAM) were found in oral fluid and/or urine from 20 patients. The maximum detection times in oral fluid for codeine, morphine and 6-MAM were 1, 3 and 8 days, respectively. Positive oral fluid samples were interspersed with negative samples, mainly for concentrations around cut off. Elimination curves for methadone in oral fluid were found for two subjects, and the detection times were 5 and 8 days. Oral fluid is likely to become a good method for detection of drug abuse in the future.

Keywords:
Oral fluid, opioid, detection time, heroin, methadone

2nd study: Cutoff considerations
All routine OF sampels, 3 month

Samples: 5355

from pats. in maintenance therapy:	4954 spls. = 92.5% of all spls.
from Methadone/Polamidone™ pats.:	3671 spls. = 68.5% of all spls.
from Buprenorphine pats.:	1283 spls. = 24.0% of all spls.

Patients: 2050

male: 1455 (71.0%), female: 595 (29.0%)

in maintenance therapy:	1877 pats. = 91.6% of all pats.
male:	1347 pats. = 65.7% of all pats.
female:	530 pats. = 25.9% of all pats.
Methadone/Polamidone™ pats.:	1315 pats. = 64.1% of all pats.

male: 924 (63.5%), female: 391 (36.5%)

Buprenorphine pats.:	562 pats. = 27.5% of all pats.

male: 423 (75.3%), female: 139 (24.7%)

Benzodiazepines :

CO 1 ng/mL: 731 pos. samples = 13.7% **CO 10 ng/mL: 415 pos. samples = 7.7%**

a sample was defined positive when at least one analyte was >= CO

Positive samples rate reduced by 43.2%

No. of spls.	**Analytes >= CO 1 ng/mL**	No. of spls.	**Analytes >= CO 10 ng/mL**	**reduced by**
663	Nordiazepam	336	Nordiazepam	49.3%
536	Diazepam	239	Diazepam	55.4%
343	Oxazepam	51	Oxazepam	85.1%
182	Temazepam	17	Temazepam	90.7%
38	Lorazepam	18	Lorazepam	52.6%
32	7-Aminoclonazepam	17	7-Aminoclonazepam	46.9%
30	Bromazepam	24	Bromazepam	20.0%
12	Alprazolam	5	Alprazolam	58.3%
5	7-Aminoflunitrazepam	0	7-Aminoflunitrazepam	100.0%
1	Midazolam	0	Midazolam	100.0%

Most of the positive samples are related to Diazepam ingestion. Because of its elimination half-life (~100 h) and its better OF/plasma-ratio when compared with the other Diazepam metabolites, Nordiazepam determines the positive sample rate. Nordiazepam is the target analyte in OF to detect Diazepam consumption. The Lorazepam cutoff should perhaps be lowered. For the other Benzodiazepines more data are needed.

Opiates :

CO 1 ng/mL: 610 pos. samples = 11.4% **CO 10 ng/mL: 397 pos. samples = 7.4%**

a sample was defined positive when at least one analyte was >= CO

Positive samples rate reduced by 34.9%

No. of spls.	Analytes >= CO 1 ng/mL	No. of spls.	Analytes >= CO 10 ng/mL	reduced by
597	Morphine	376	Morphine	37.0%
494	6-Acetylmorphine	237	6-Acetylmorphine	52.0%
396	Codeine	217	Codeine	45.2%
173	6-Acetylcodeine	100	6-Acetylcodeine	42.2%
129	Norcodeine	10	Norcodeine	92.2%
11	Dihydrocodeine	6	Dihydrocodeine	45.2%

81.0% of all Opiate positive samples contained 6-Acetylmorphine thus proving Heroin abuse.

34.7% of all 6-Acetylmorphine positive samples contained 6-Acetylcodeine thus proving "Street Heroin" abuse.

60.0% of all Opiate positive samples contained 6-Acetylmorphine thus proving Heroin abuse.

42.2% of all 6-Acetylmorphine positive samples contained 6-Acetylcodeine thus proving "Street Heroin" abuse.

Multi-Target-Screening Speichel

MVZ Labor Dessau GmbH

Geschäftsführer:
Dr. med. Juliane Böttcher-Lorenz

Bauhüttenstraße 6, 06847 Dessau

Drogen- und Medikamentenanalytik
Dr. rer. medic. M. Böttcher

Telefon : 0340/5405372
Funk : 0162/9071483

LABOR®

Befundbericht
- Archivbd. -
Blatt 1

10827 Berlin

Name des Patienten:	Gesch.	Geburtsdatum:	Kasse:	Eingangsdatum / Tagesnummer:
			K	04.05.2015 /SP000232
ID-Nr.: 0606205623 Ext.-Nr.:				Befundausgang: 05.05.15

Material: Speichel

Sonstige Medikation: Substitol

Drogen-/Medikamentenscreening im Speichel mit LC/MS-MS

Entnahmesystem: Greiner

Volumen A-Probe (Speichel/SES)	2.5	ml	
Volumen B-Probe (Speichel/SES)	1.0	ml	

Das Gesamtvolumen von A- und B-Probe sollte 2 - 7 ml betragen.

Speichelanteil in der Probe:	50.9	%	(20 - 80)
Amylase im Speichel:	127866	U/l	(> 10000)
Cortisol im Speichel:	2.4	ng/ml	(1.0 - 6.0)

Bei Cortisolsuppression durch entsprechende Substanzen wie z. B. Methadon werden Cortisolkonzentrationen von 0.1 - 6.0 ng/ml gemessen.

L-/D-Methadon:	**negativ**	ng/ml	(Cutoff 1)
Buprenorphin:	**negativ**	ng/ml	(Cutoff 0.1)

Amphetamine und Derivate: **negativ** ng/ml (Cutoff 1)

Berücksichtigte Substanzen:

D-/L-Amphetamin	MDA	BDB
D-/L-Methamphetamin	MDEA	MDPV
MDMA	MBDB	
Butylon	Mephedron	Methylon

Benzodiazepine: **negativ** ng/ml (Cutoff 0.1-1)

Berücksichtigte Substanzen:

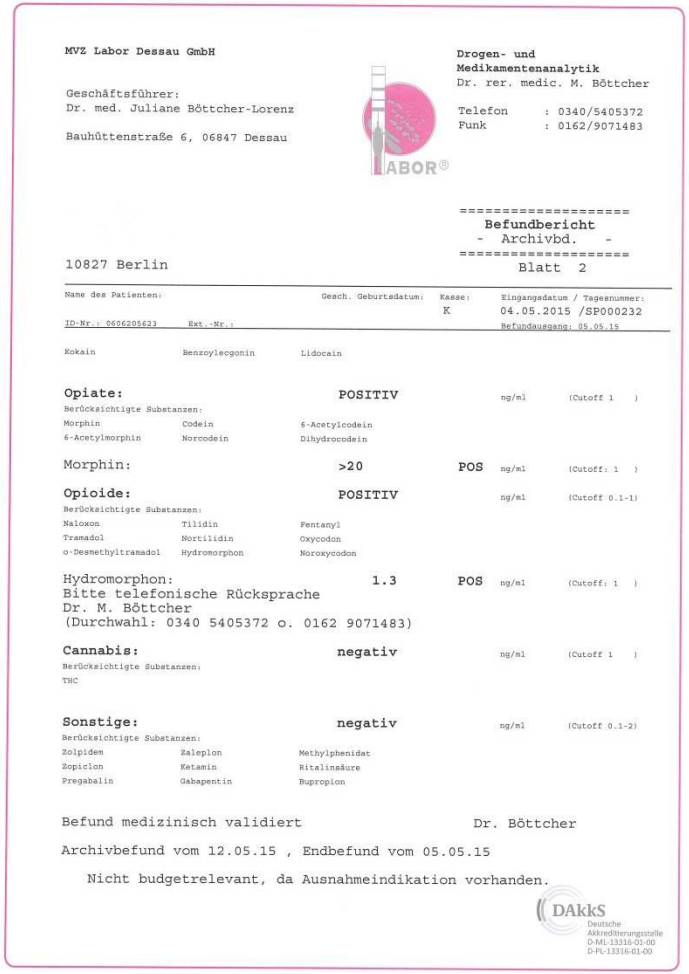
Diazepam	Temazepam	Midazolam
Nordiazepam	Alprazolam	7-Aminoclonazepam
Oxazepam	Lorazepam	Bromazepam
Flurazepam	Flunitrazepam	7-Aminoflunitrazepam
Desalkylflurazepam		

Kokain: **negativ** ng/ml (Cutoff 1)

Berücksichtigte Substanzen:

- Fortsetzung siehe nächstes Blatt -

DAkkS Deutsche Akkreditierungsstelle D-ML-13316-01-00 D-PL-13316-01-00



MVZ Labor Dessau GmbH

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Dr. rer. medic. M. Böttcher

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Funk : 0162/9071483

LABOR®

Befundbericht
- Archivbd. -
Blatt 2

10827 Berlin

Name des Patienten:	Gesch.	Geburtsdatum:	Kasse:	Eingangsdatum / Tagesnummer:
			K	04.05.2015 /SP000232
ID-Nr.: 0606205623 Ext.-Nr.:				Befundausgang: 05.05.15

Kokain Benzoylecgonin Lidocain

Opiate: **POSITIV** ng/ml (Cutoff 1)

Berücksichtigte Substanzen:

Morphin	Codein	6-Acetylcodein
6-Acetylmorphin	Norcodein	Dihydrocodein

Morphin: >20 POS ng/ml (Cutoff: 1)

Opioide: **POSITIV** ng/ml (Cutoff 0.1-1)

Berücksichtigte Substanzen:

Naloxon	Tilidin	Fentanyl
Tramadol	Nortilidin	Oxycodon
o-Desmethyltramadol	Hydromorphon	Noroxycodon

Hydromorphon: 1.3 POS ng/ml (Cutoff: 1)

Bitte telefonische Rücksprache
Dr. M. Böttcher
(Durchwahl: 0340 5405372 o. 0162 9071483)

Cannabis: **negativ** ng/ml (Cutoff 1)

Berücksichtigte Substanzen:
THC

Sonstige: **negativ** ng/ml (Cutoff 0.1-2)

Berücksichtigte Substanzen:

Zolpidem	Zaleplon	Methylphenidat
Zopiclon	Ketamin	Ritalinsäure
Pregabalin	Gabapentin	Bupropion

Befund medizinisch validiert Dr. Böttcher

Archivbefund vom 12.05.15 , Endbefund vom 05.05.15

Nicht budgetrelevant, da Ausnahmeindikation vorhanden.

DAkkS Deutsche Akkreditierungsstelle D-ML-13316-01-00 D-PL-13316-01-00

Multi-Target-Screening Speichel

Opiate:		**POSITIV**		ng/ml	(Cutoff 1)
Berücksichtigte Substanzen:					
Morphin	Codein	6-Acetylcodein			
6-Acetylmorphin	Norcodein	Dihydrocodein			

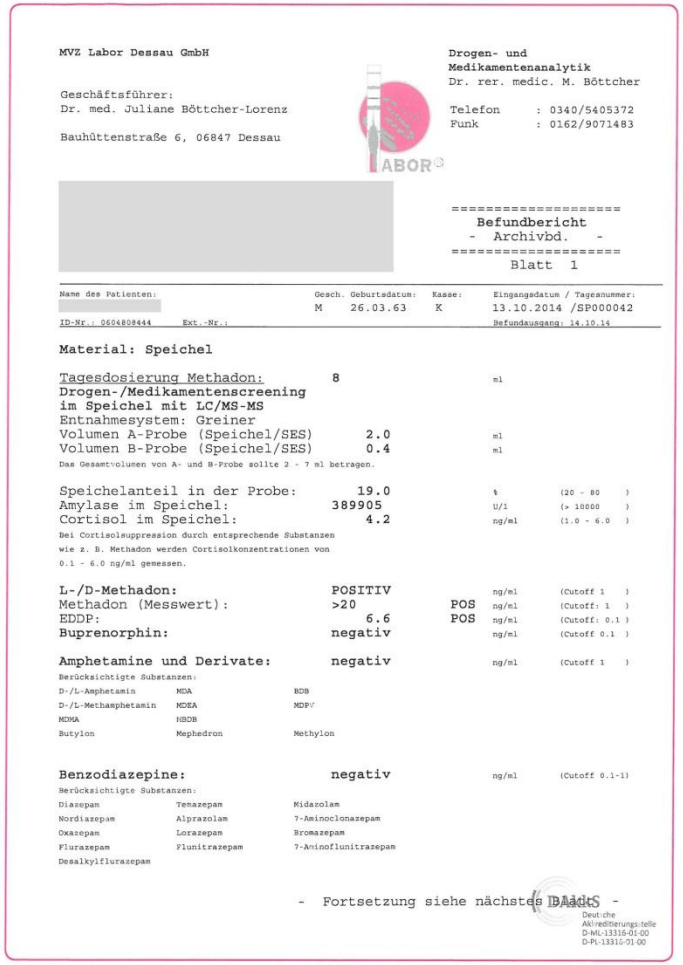
Morphin:	>20	POS	ng/ml	(Cutoff: 1)

Opioide:		**POSITIV**		ng/ml	(Cutoff 0.1-1)
Berücksichtigte Substanzen:					
Naloxon	Tilidin	Fentanyl			
Tramadol	Nortilidin	Oxycodon			
o-Desmethyltramadol	Hydromorphon	Noroxycodon			

Hydromorphon:	1.3	POS	ng/ml	(Cutoff: 1)
Bitte telefonische Rücksprache Dr. M. Böttcher				

Multi-Target-Screening Speichel

SUBSTITUTIONSPATIENT MIT METHADON



MVZ Labor Dessau GmbH

Geschäftsführer:
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Drogen- und Medikamentenanalytik
Dr. rer. medic. M. Böttcher

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Funk : 0162/9071483

Befundbericht
- Archivbd. -
Blatt 1

Name des Patienten:	Gesch.	Geburtsdatum:	Kasse:	Eingangsdatum / Tagesnummer:
	M	26.03.63	K	13.10.2014 /SP000042

ID-Nr.: 0604808444 Ext.-Nr.: Befundausgang: 14.10.14

Material: Speichel

Tagesdosierung Methadon:	8		ml	
Drogen-/Medikamentenscreening im Speichel mit LC/MS-MS				
Entnahmesystem: Greiner				
Volumen A-Probe (Speichel/SES)	2.0		ml	
Volumen B-Probe (Speichel/SES)	0.4		ml	
Das Gesamtvolumen von A- und B-Probe sollte 2 - 7 ml betragen.				
Speichelanteil in der Probe:	19.0		%	(20 - 80)
Amylase im Speichel:	389905		U/l	(> 10000)
Cortisol im Speichel:	4.2		ng/ml	(1.0 - 6.0)
Bei Cortisolsuppression durch entsprechende Substanzen wie z. B. Methadon werden Cortisolkonzentrationen von 0.1 - 6.0 ng/ml gemessen.				
L-/D-Methadon:	POSITIV		ng/ml	(Cutoff 1)
Methadon (Messwert):	>20	POS	ng/ml	(Cutoff: 1)
EDDP:	6.6	POS	ng/ml	(Cutoff: 0.1)
Buprenorphin:	negativ		ng/ml	(Cutoff 0.1)
Amphetamine und Derivate:	negativ		ng/ml	(Cutoff 1)

Berücksichtigte Substanzen:

D-/L-Amphetamin	MDA	BDB
D-/L-Methamphetamin	MDEA	MDPV
MDMA	NBDB	
Butylon	Mephedron	Methylon

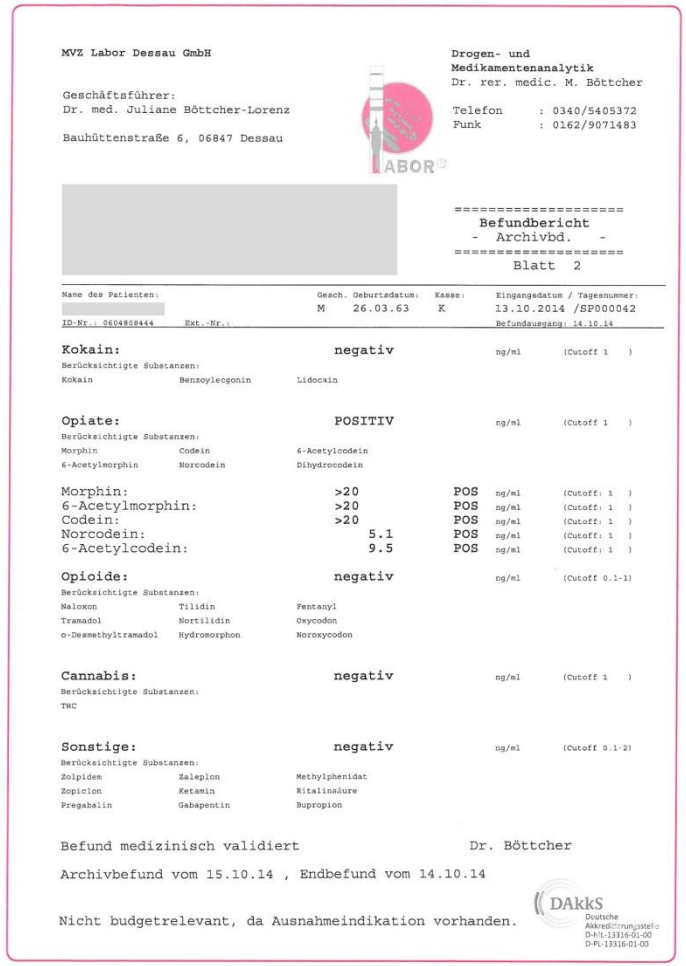
Benzodiazepine:	negativ		ng/ml	(Cutoff 0.1-1)

Berücksichtigte Substanzen:

Diazepam	Temazepam	Midazolam
Nordiazepam	Alprazolam	7-Aminoclonazepam
Oxazepam	Lorazepam	Bromazepam
Flurazepam	Flunitrazepam	7-Aminoflunitrazepam
Desalkylflurazepam		

- Fortsetzung siehe nächstes Blatt -

DAkkS Deutsche Akkreditierungsstelle D-ML-13316-01-00 D-PL-13316-01-00



MVZ Labor Dessau GmbH

Geschäftsführer:
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Drogen- und Medikamentenanalytik
Dr. rer. medic. M. Böttcher

Telefon : 0340/5405372
Funk : 0162/9071483

Befundbericht
- Archivbd. -
Blatt 2

Name des Patienten:	Gesch.	Geburtsdatum:	Kasse:	Eingangsdatum / Tagesnummer:
	M	26.03.63	K	13.10.2014 /SP000042

ID-Nr.: 0604808444 Ext.-Nr.: Befundausgang: 14.10.14

Kokain:	negativ		ng/ml	(Cutoff 1)

Berücksichtigte Substanzen:

Kokain	Benzoylecgonin	Lidocain

Opiate:	POSITIV		ng/ml	(Cutoff 1)

Berücksichtigte Substanzen:

Morphin	Codein	6-Acetylcodein
6-Acetylmorphin	Norcodein	Dihydrocodein

Morphin:	>20	POS	ng/ml	(Cutoff: 1)
6-Acetylmorphin:	>20	POS	ng/ml	(Cutoff: 1)
Codein:	>20	POS	ng/ml	(Cutoff: 1)
Norcodein:	5.1	POS	ng/ml	(Cutoff: 1)
6-Acetylcodein:	9.5	POS	ng/ml	(Cutoff: 1)
Opioide:	negativ		ng/ml	(Cutoff 0.1-1)

Berücksichtigte Substanzen:

Naloxon	Tilidin	Fentanyl
Tramadol	Nortilidin	Oxycodon
o-Desmethyltramadol	Hydromorphon	Noroxycodon

Cannabis:	negativ		ng/ml	(Cutoff 1)

Berücksichtigte Substanzen:
THC

Sonstige:	negativ		ng/ml	(Cutoff 0.1-2)

Berücksichtigte Substanzen:

Zolpidem	Zaleplon	Methylphenidat
Zopiclon	Ketamin	Ritalinsäure
Pregabalin	Gabapentin	Bupropion

Befund medizinisch validiert Dr. Böttcher

Archivbefund vom 15.10.14 , Endbefund vom 14.10.14

Nicht budgetrelevant, da Ausnahmeindikation vorhanden.

DAkkS Deutsche Akkreditierungsstelle D-ML-13316-01-00 D-PL-13316-01-00

Multi-Target-Screening Speichel

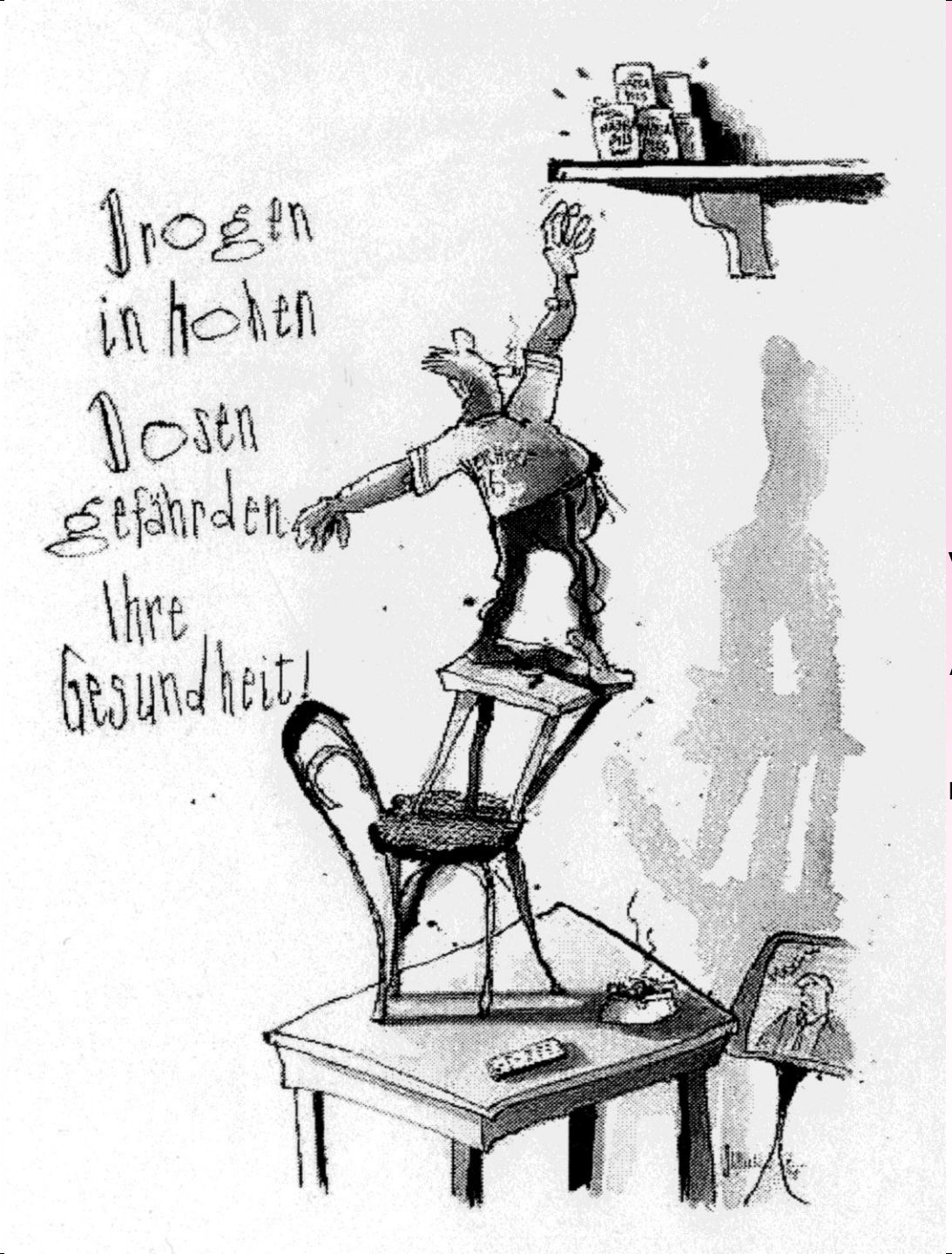
SUBSTITUTIONSPATIENT MIT METHADON

L-/D-Methadon:	**POSITIV**		ng/ml	(Cutoff 1)
Methadon (Messwert):	>20	POS	ng/ml	(Cutoff: 1)
EDDP:	6.6	POS	ng/ml	(Cutoff: 0.1)

- Substitution mit Methadon
  - Methadon positiv
  - EDDP positiv

Opiate:	**POSITIV**		ng/ml	(Cutoff 1)
Berücksichtigte Substanzen:				
Morphin	Codein	6-Acetylcodein		
6-Acetylmorphin	Norcodein	Dihydrocodein		
Morphin:	>20	POS	ng/ml	(Cutoff: 1)
6-Acetylmorphin:	>20	POS	ng/ml	(Cutoff: 1)
Codein:	>20	POS	ng/ml	(Cutoff: 1)
Norcodein:	5.1	POS	ng/ml	(Cutoff: 1)
6-Acetylcodein:	9.5	POS	ng/ml	(Cutoff: 1)

- Beweis von 6-Acetylcodein
  - Missbrauch von Straßenheroin



Vielen Dank für Ihre Aufmerksamkeit!

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