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New psychoactive substances – Implementations and pitfalls for forensic police and customs labs

Michael Pütz
Sára Harkai
Bundeskriminalamt, Germany
Forensic Science Institute, KT 34 - Toxicology

Legal implications of NPS:

narcotics act vs. medicines act

prosecution of possession (for private consume) vs.
prosecution of illicit trade, trafficking and manufacturing

Designer drugs – definition and legal status

Designer dugs are substances that are supposed to have optimized psychotropic effects as a consequence of modifications in the molecular structure and, even more important, that are produced with the **intention of by-passing the narcotics act**.

Only with the formal submission under the annexes of the narcotics act the (then former) designer drugs become narcotics (controlled substances).

but: illegal trade of designer drugs can be prosecuted as a violation of the medicines law (AMG) (**alternative state of offence when the narcotics act is not applicable**)

medicines law – drug registration and administration act

§2 AMG – definition of pharmaceutically active substances:

(1) Pharmaceuticals are substances and formulations of substances that are determined to influence the state or the functions of the organism or mental state when administered to the human or animal body.

§5 AMG – Prohibition of precarious pharmaceuticals:

(1) It is prohibited to put precarious pharmaceuticals into circulation.

(2) Those pharmaceuticals are precarious, which are reasonably suspected to cause harm beyond a scientifically accepted level even when they are applied as intended.

§6a AMG – Prohibition of pharmaceuticals intended for sports doping:

(1) It is prohibited to trade, to prescribe or to treat someone with pharmaceuticals/medicinal products that are suitable for doping in sports when doping in sports (increase of performance) is indeed intended.

European definition of medicinal products: EU directive 2001/83/EG

pharmaceuticals by presentation vs. function

Medicinal product by:

presentation

Any substance or combination of substances presented (by design, declaration) for treating or preventing disease in human beings.

(curative ?) function

Any substance or combination of substances which may be administered to human beings with an intention to make a medical diagnosis or to restore, correct or modify physiological functions in human beings is likewise considered a medicinal product.

Are NPS pharmaceuticals in the sense of functional medicinal products?

From the view of the toxicologist: without any doubt!

- All NPS that appeared on the drug market are undoubtedly active substances (meaning they bind to relevant effective receptors in the human organism).
- Many NPS were developed as candidates for pharmaceuticals by industry R&D.
- Many NPS have (limited) beneficiary/curative effects (e.g. as pain killers).
- The medicines law already includes non-curative active substances/products (e.g. contraceptives or even prescribable abortion tablets as mifegyne).
- The medicines law already includes abuse phenomena (for non-curative intention of use), especially doping to increase sports performance.

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Are NPS pharmaceuticals in the sense of functional medicinal products?

Possible points of concern:

- **non-prosecutability of possession**
  - ► criminalisation of consumers not desirable and not effective
  - ► definition of threshold amounts to discriminate consume from dealing is possible also within medicines law (as conducted in Germany for doping agents)

- **interference of research&trade of new pharmaceuticals (economic aspects)**
  - ► not really relevant for most of the NPS that appeared on the drug market up to now and the pharmaceutical R&D of new chemical entities is not hindered.

Consequence:

Application of the **medicines law** is a very important parallel approach to prosecute the **production and trade of NPS** (independent of specified substance classes).

The **general applicability of the medicines law** for all types of NPS is a highly relevant feature and motivation for state prosecutors to start new criminal prosecutions against internet shops and NPS producers and safeguards that, independent of the substances actually identified in the products, a NPS case can be brought to court!

Forensic Analysis of „Legal“ Highs

NPS: Implications and pitfalls for forensic analysis:

- non-applicability of sampling schemes for classic drugs
  (heterogeneous seizures, different compositon of equal-looking samples)
- necessity of high-end analytical instruments for identification
  (for „new“ NPS and differentiation of positional isomers)
- enormous expenditures for reference substances of NPS
- failure of standard presumptive tests for on-site testing

Myriads of new products and very complex composition of seizures

Example of recent case of big German NPS internet shop (Oktober 2013):

- seizure of a total of 15.000 bags of 18 different brands of Spice products in more than 100 packaging units
- previous test purchases revealed: different active substances in same products
- sampling strategy: clustering of products of same brand, sampling dependent on number of bags, on the average 5 % of the bags were chemically analyzed
- 5 % = ca. 800 samples to be analyzed, 90 % screening and 10 % MS-based
- only 6 % of the analyzed samples contained an active substance that was scheduled at the time of seizure (Manga XXL with XLR-11)
- state prosecutor only wants to prosecute only the violation of the narcotics law, so > 90 % of the seized products are not considered although the contained NPS are potentially more dangerous than XLR-11
- to date hardly any new prosecutions against NPS selling internet shops based on the suspected violation of the medicines law are started, pending prosecutions are suspended while the involved internet shops proceed to sell NPS products.

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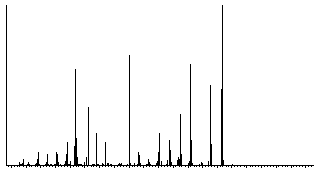
Scheme for substance identification

MeOH-extr.

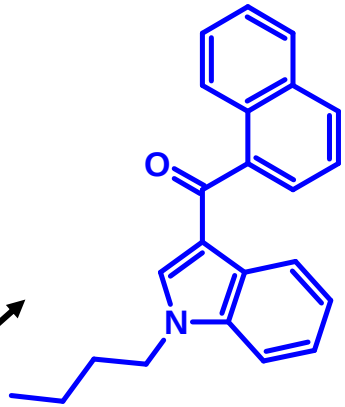
GC/MS
LC/MS



Library match

Unknown

HRMS,
MS^n



NMR analysis
(positional isomers!)

Pure substance
(reference material)

Isolation

prepHPLC, TLC,
column chromatography

- **Elemental composition**
- **Structural information**

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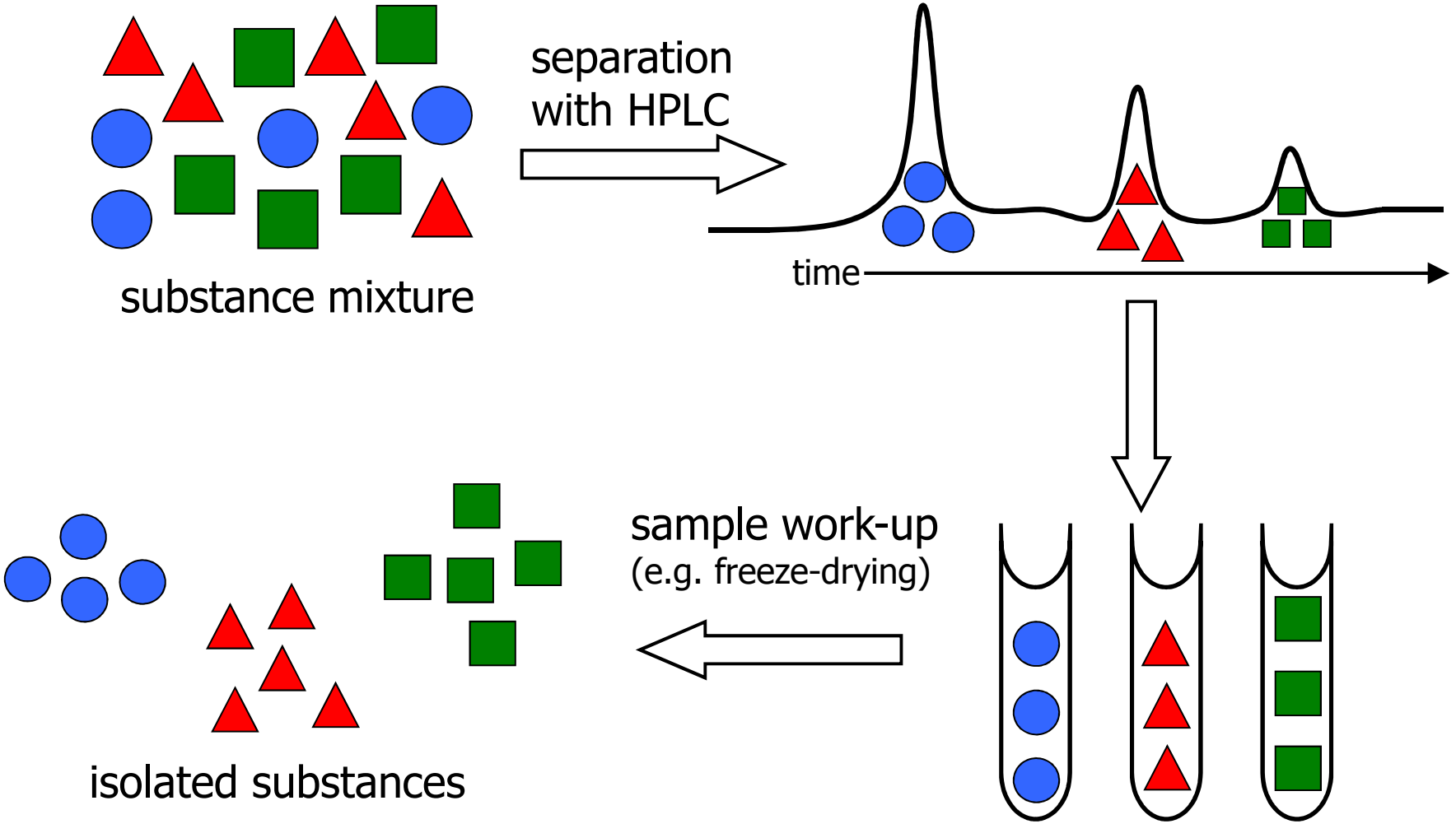
Isolation of pure active substances e.g. from herbal mixtures



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preparative HPLC-DAD-MS and freeze-dryer (lyophilization)

High resolution mass spectrometry: e.g. LTQ Orbitrap

- precise elemental composition (sum formula)
- calculation of double bond equivalents
- precise mass of fragments

but:

- expensive
- laborious calibration for high mass precision
- more technical service needed

NMR for designer drugs

Nuclear Magnetic Resonance Spectroscopy

- structure elucidation
- structure verification
- qualitative analysis of mixtures
- quantitative analysis of mixtures
- quantitative Deuterium NMR-spectroscopy

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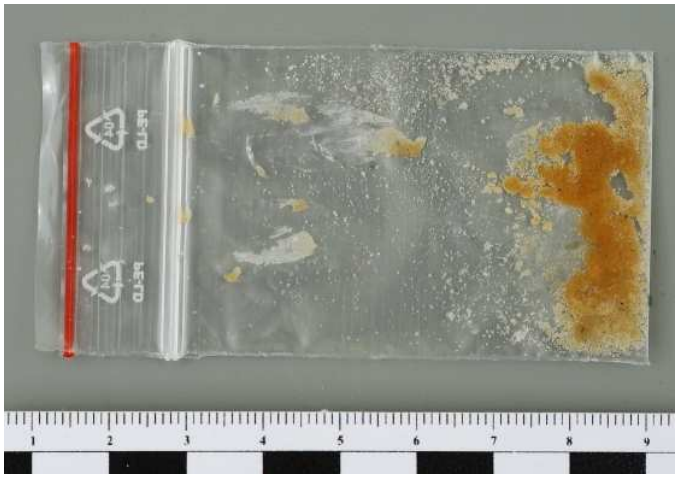
NMR – analysis of mixtures: cathinone derivatives in bath salts



seized in Polish headshop

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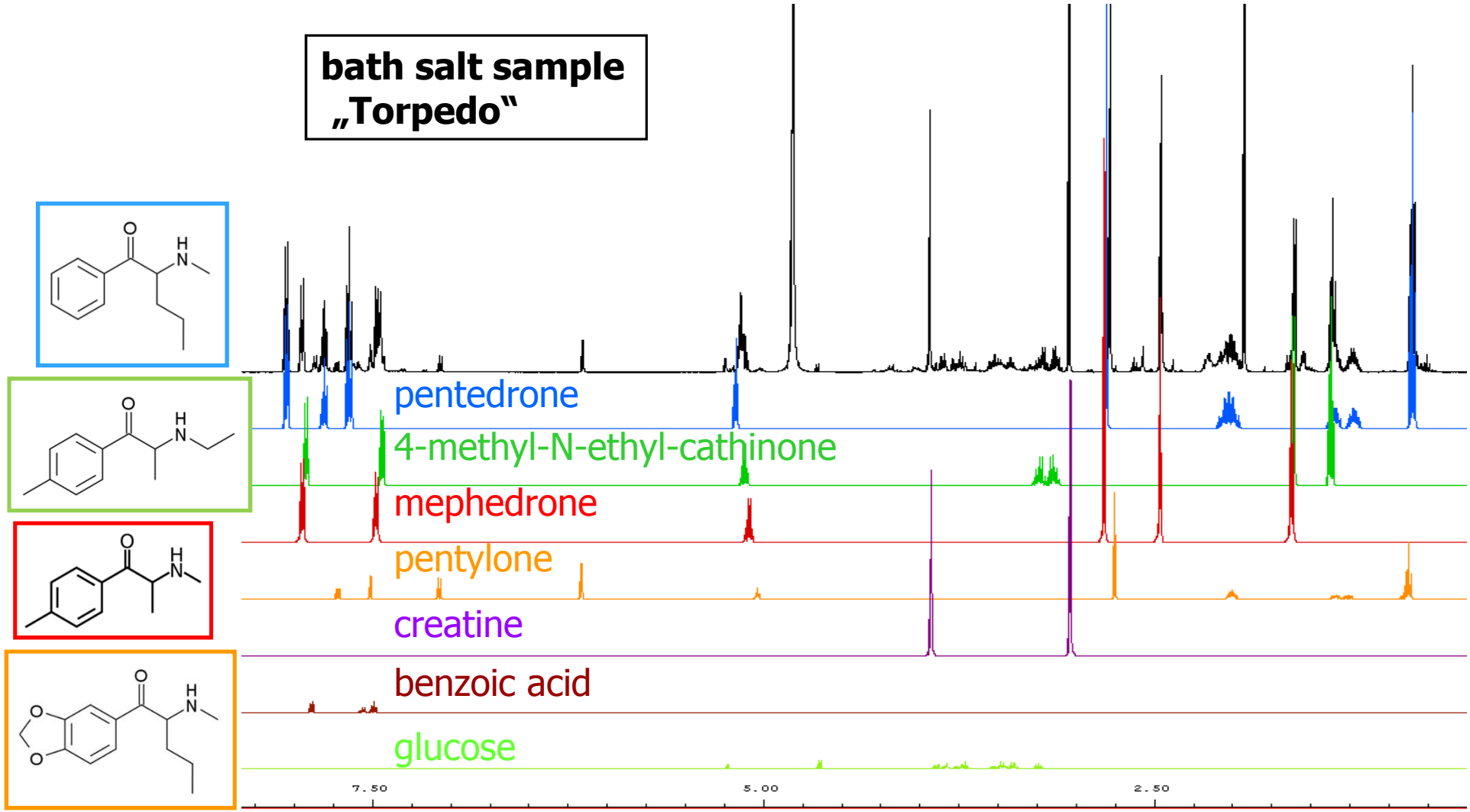
NMR – analysis of mixtures: cathinone derivatives in bath salts



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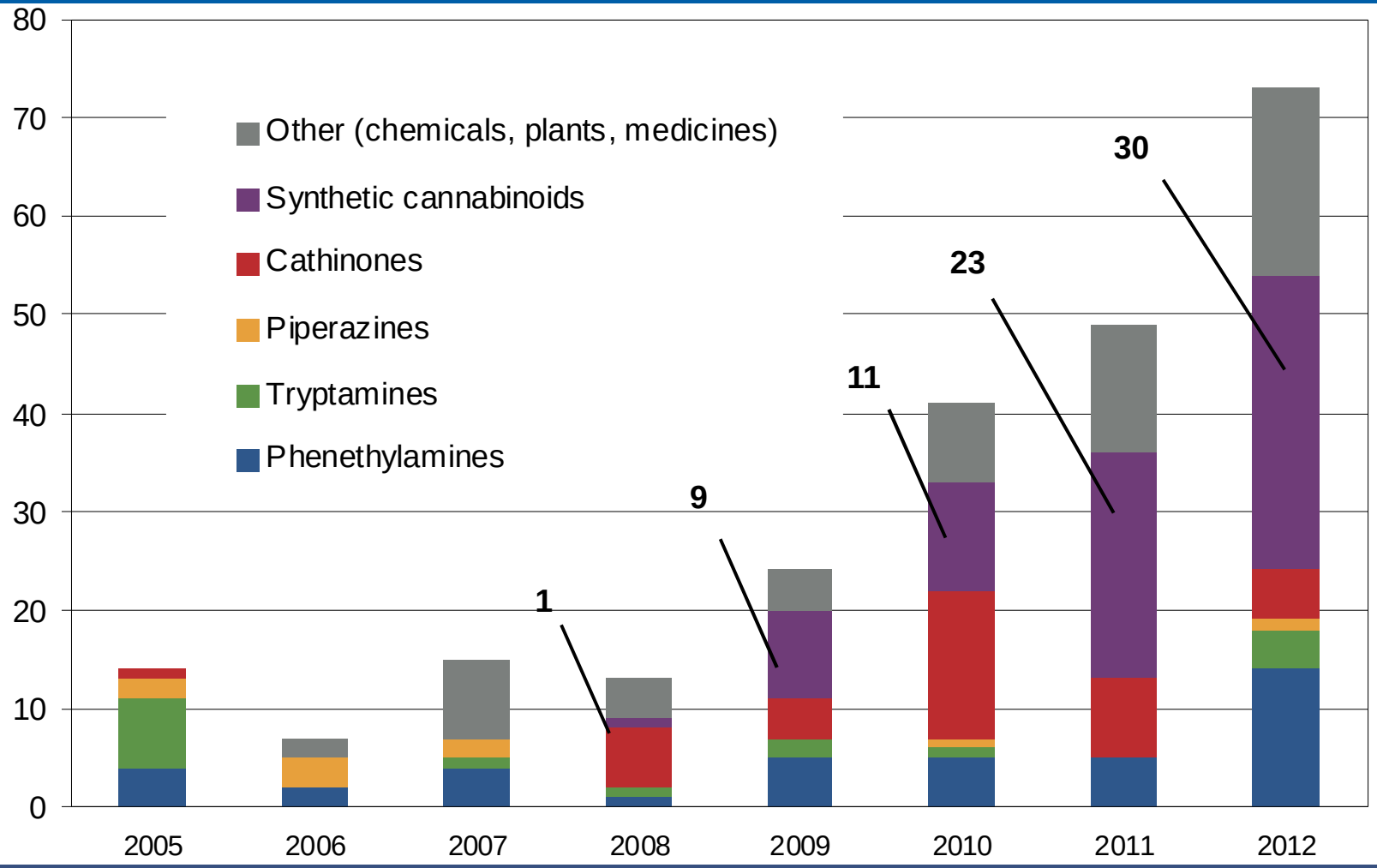
Cost-intensive supply of labs with reference standards of (350) NPS



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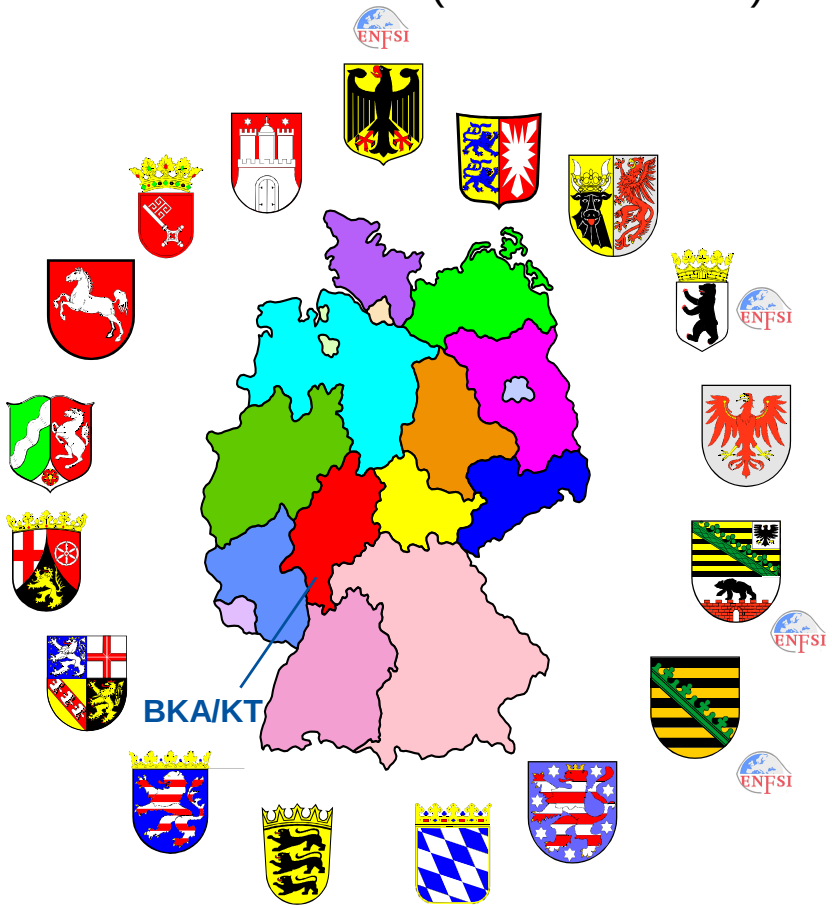
German and European forensic science institutes that analyze NPS samples

National Forensic Science Institutes

16 KTI of the Landeskriminalämter (LKÄ)
1 KTI of the Bundeskriminalamt (BKA)
6 customs laboratories (ZKA and 5 BWZ)



European Forensic Science Institutes

ENFSI – European Network of Forensic Science Institutes

Membership 2014:

* *64 Forensic Laboratories from 36 countries*

Reference standard problem - solutions

- Increasing use of techniques not requiring standards (NMR), e.g. by centralizing tasks (takes already partially place)
- Enforcing collaboration among NPS seizing police and customs labs – central collection of pure bulk NPS seizures, purification, analytical certification as secondary reference standard (e.g. by NMR) and timely redistribution to all (public) laboratories responsible for NPS analysis`

  In Germany plan to realize that as EU-funded ISF project (Horizon2020)
- Changing the legal treatment of NPS:

► inclusion of positional isomers when new substances are scheduled in the narcotics act (example: 3-FMC, automatic inclusion of 2- and 4-FMC)

► definition of threshold values for discrimination of consume/dealing based on typical single doses of products not individual values for all NPS, this way reduction of the number of samples that must be quantified.

Rapid on-site testing of NPS

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Rapid detection of NPS - do presumtive color test work?

Fluid reacts with specific chemical groups of a molecule

→ **color change**

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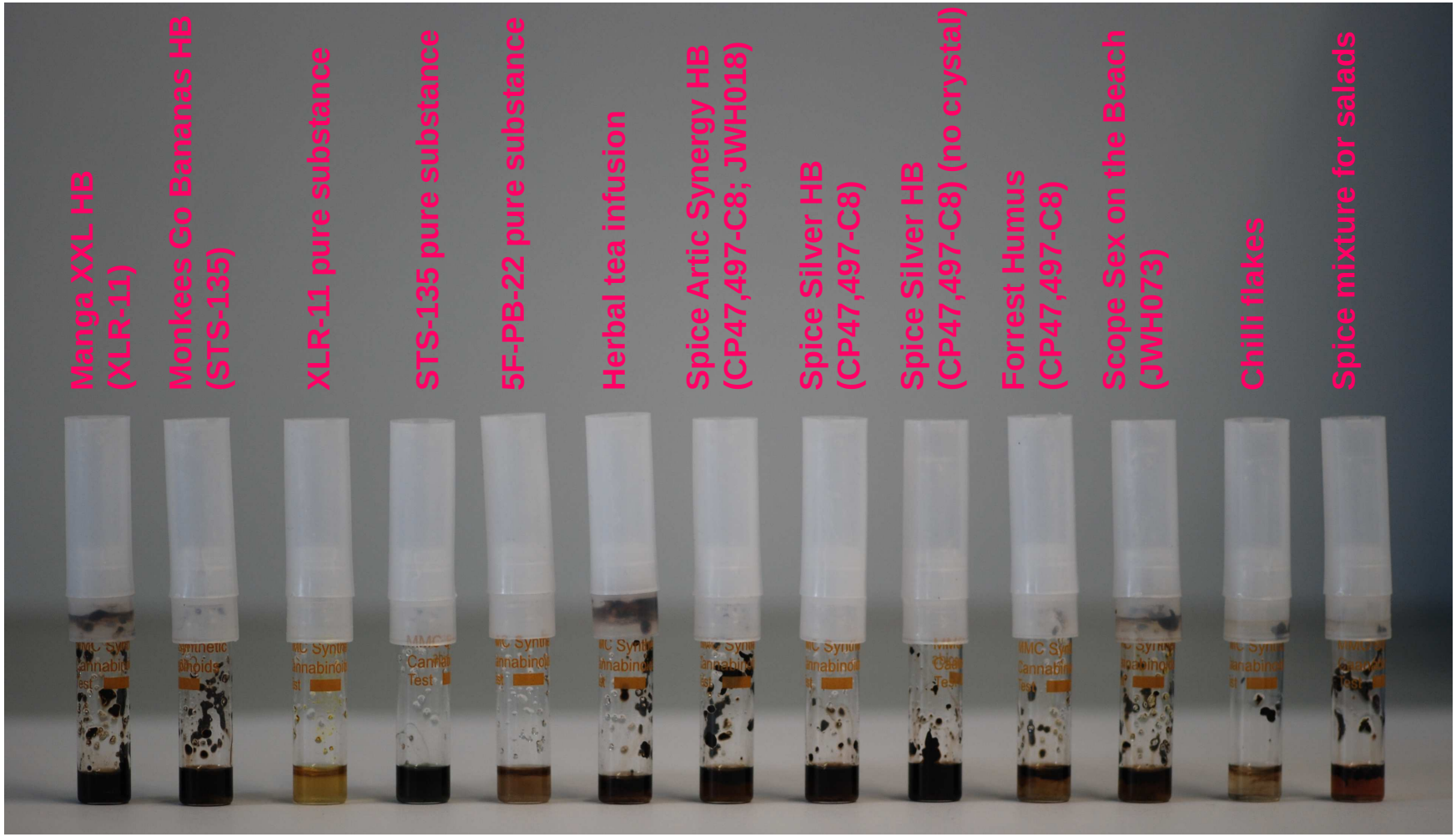
Rapid detection of synthetic cannabinoids in Spice products



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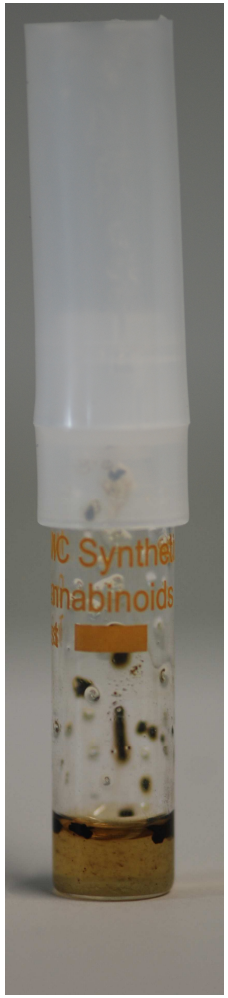
Rapid detection of NPS - Problems



Forest Humus
(CP47,497-C8)

Salad spice
herbal mixture

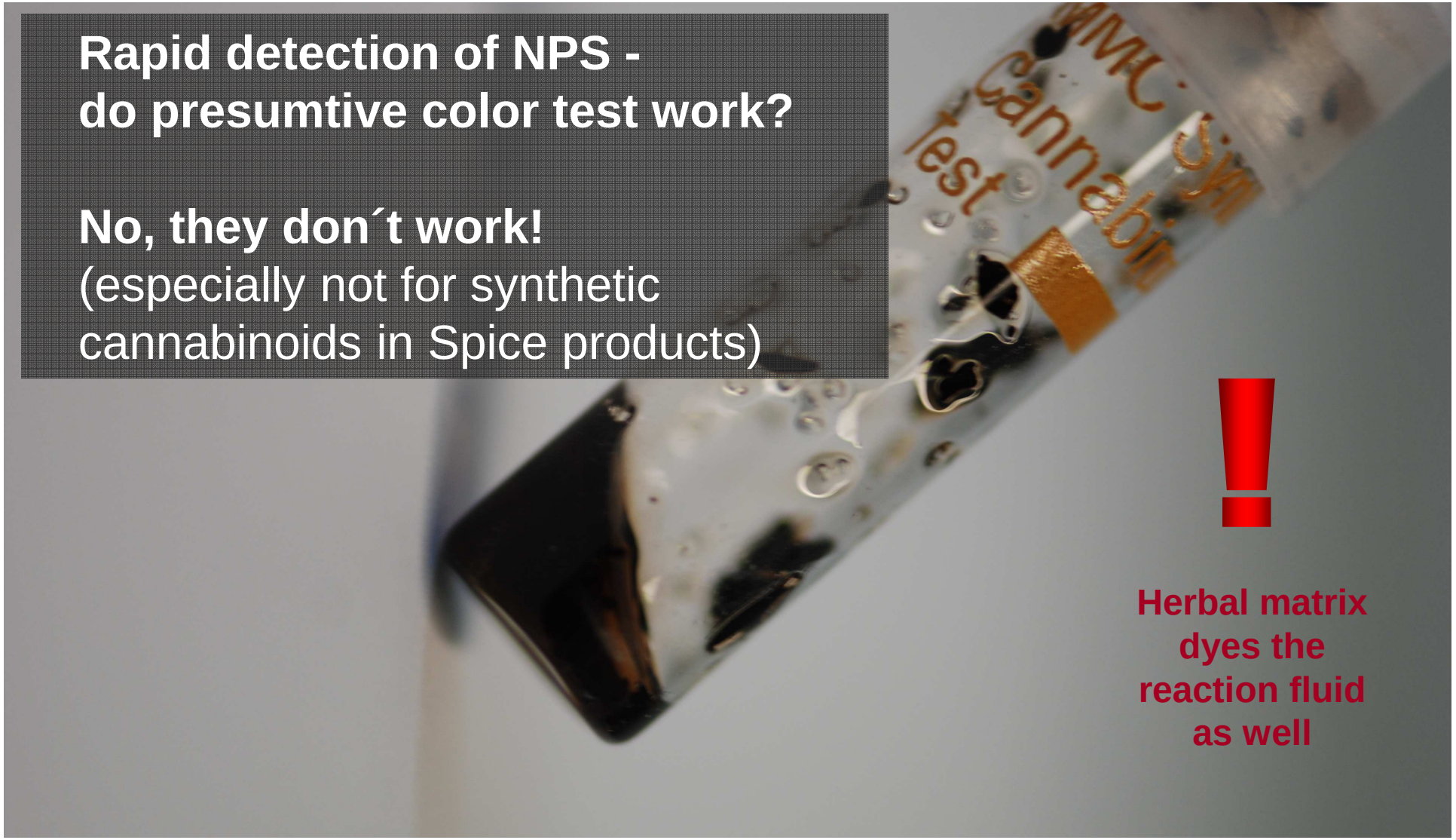
Tea

STS-135
Pure Substance

Fast detection of NPS - Problems

**Rapid detection of NPS -
do presumtive color test work?**

No, they don´t work!
(especially not for synthetic cannabinoids in Spice products)



Herbal matrix dyes the reaction fluid as well

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Detection of synthetic cathinones in bath salts – light and shadow

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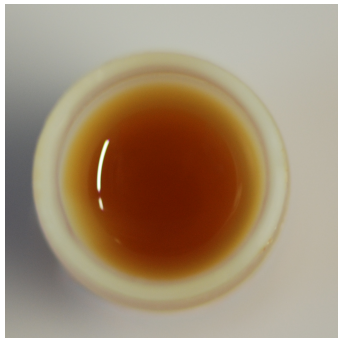
Fast detection of NPS - Problems

Dyed samples can change the color reaction

!



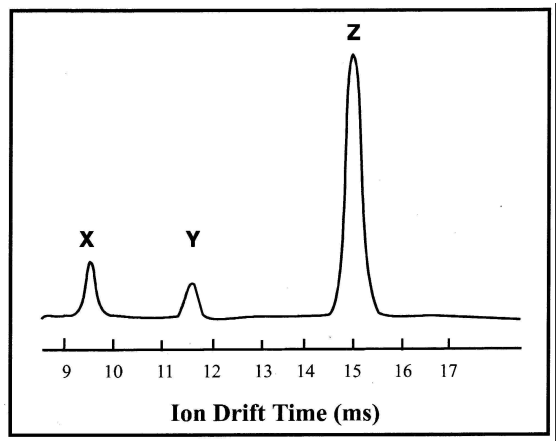
Investigation strategy (rapid analysis)

- **Why IMS**
  - High and fast sample throughput, field-suitable (portable)
  - Highly sensitive (trace technique), no sample work-up
  - First indication on a cannabimimetic substance
- **Why FT-IR**
  - Highly discriminative (fingerprint), field-suitable (portable)
  - Fast and identification technique for solids and liquids
  - Limited suitability for mixtures, not very sensitive
- **Why TLC**
  - Tolerates difficult matrices, no „instrument contaminations“
  - High sample throughput
  - Low cost, easy to use, present in every laboratory
- **Why DESI-MS^n**
  - High identification power
  - Fast and direct identification technique for solids
  - Can be perfectly combined with TLC

Rapid detection of NPS via IMS (ion mobility spectrometry)

Ionscan 400

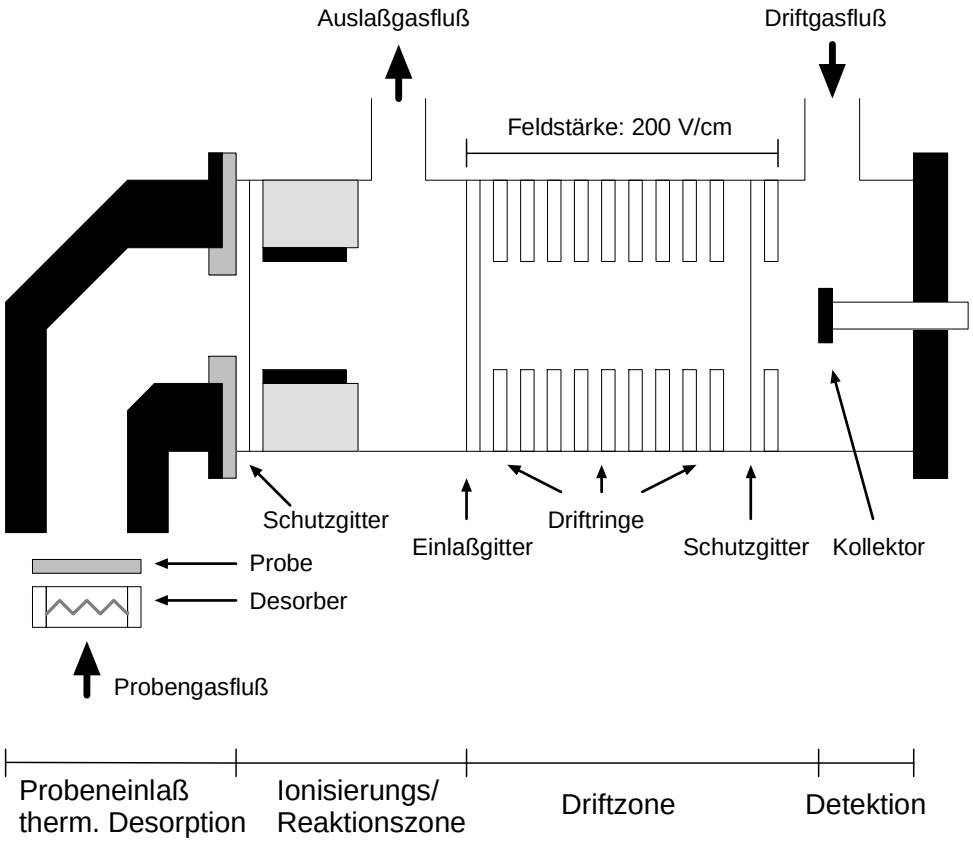
ion mobility spectrometry (IMS)



rapid and mobile detection of narcotics and explosives traces

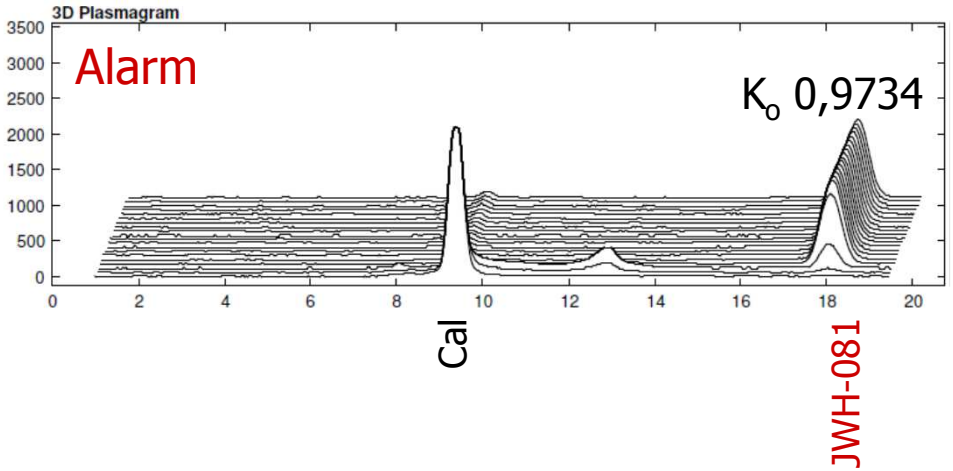
Narcotics detected by IONSCAN *

Narcotic	Detection Limit
Cocaine	0.5 ng
Heroin	3.0 ng
Amphetamine	0.3 ng
Methylenedioxy Amphetamine (MDA)	0.3 ng
Methamphetamine	0.3 ng
Methylenedioxy Methamphetamine (MDMA)	0.3 ng
Methylenedioxy Ethylamphetamine (MDEA)	0.3 ng
THC	1.0 ng

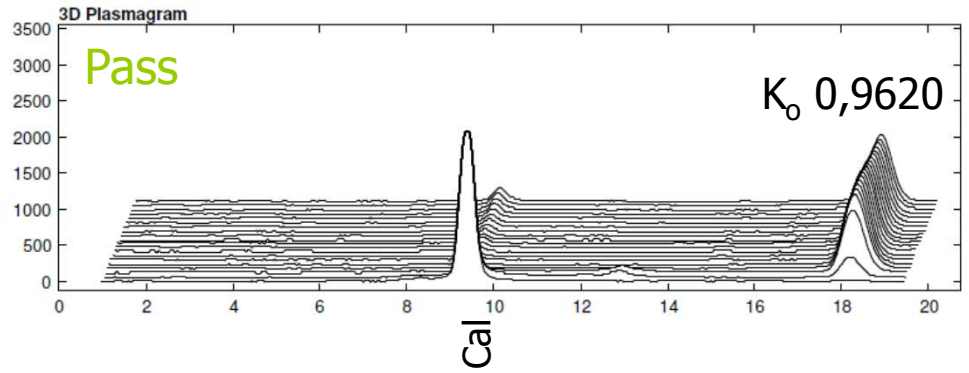


IMS results - Spice products

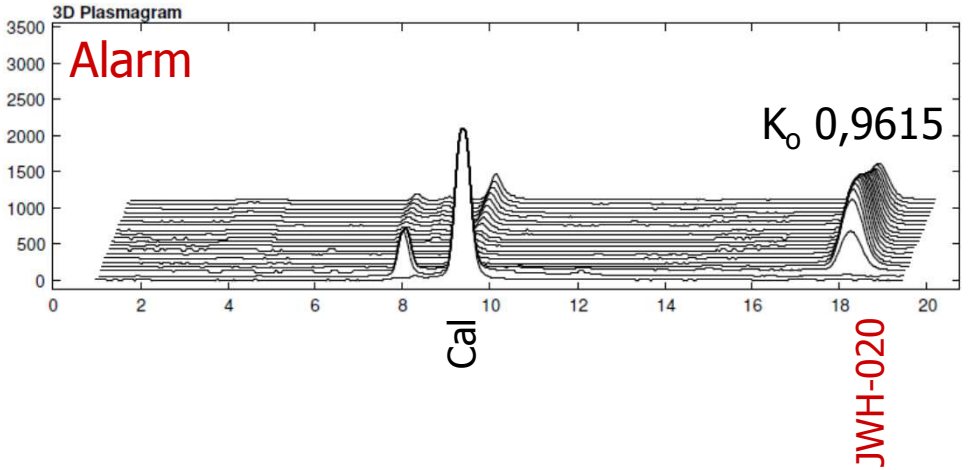
BooM



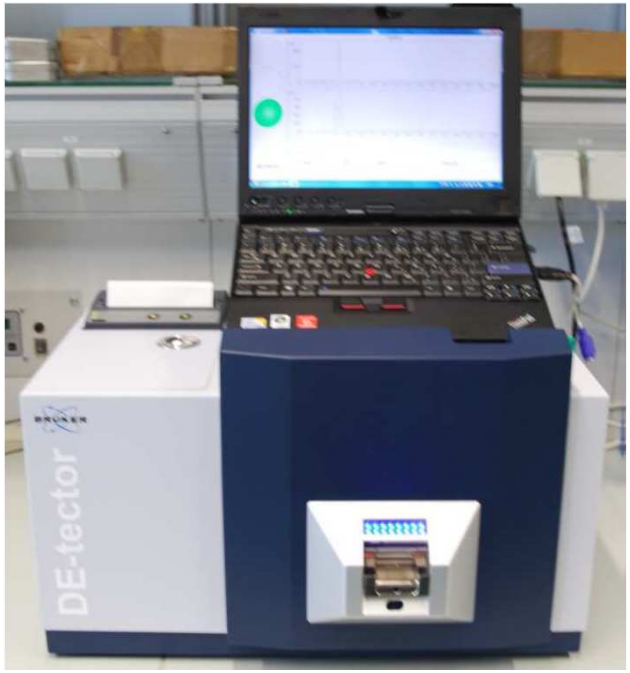
maya

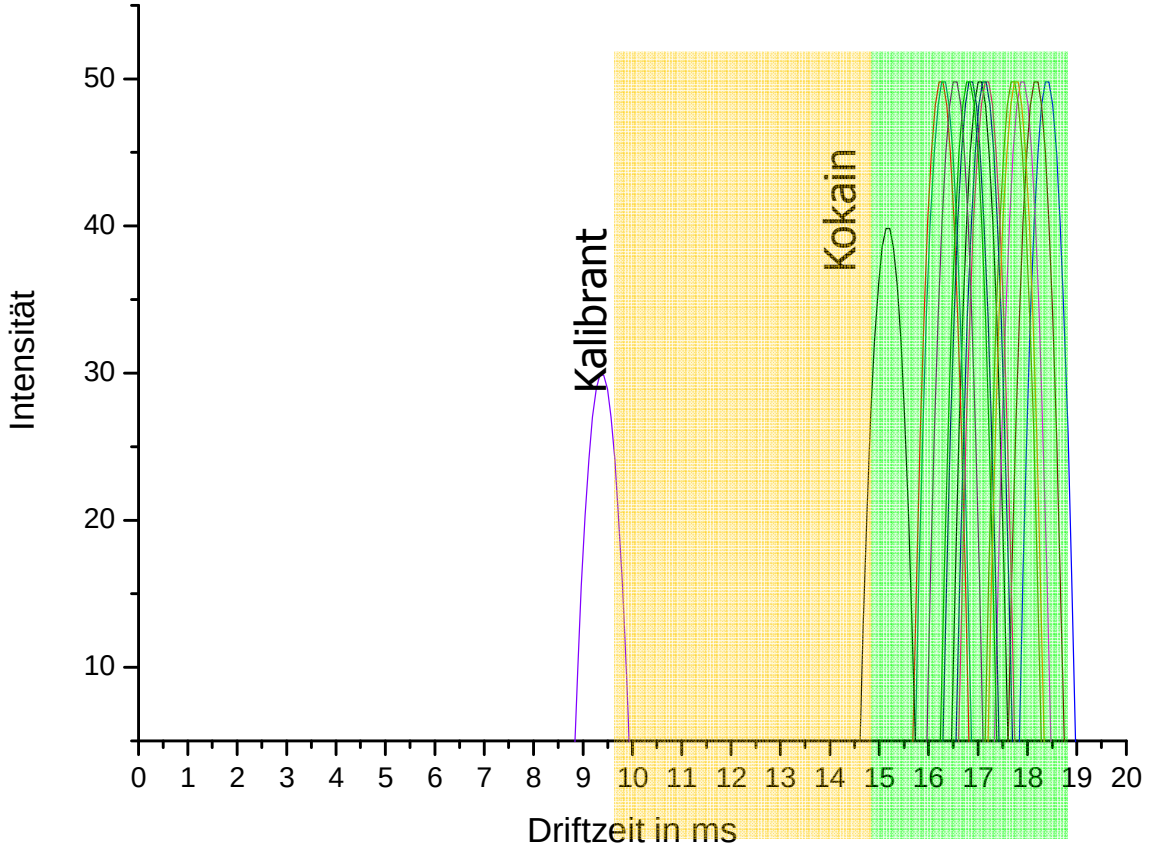


JWH-210



IMS – flexible and generally applicable tool for synthetic cannabinoids

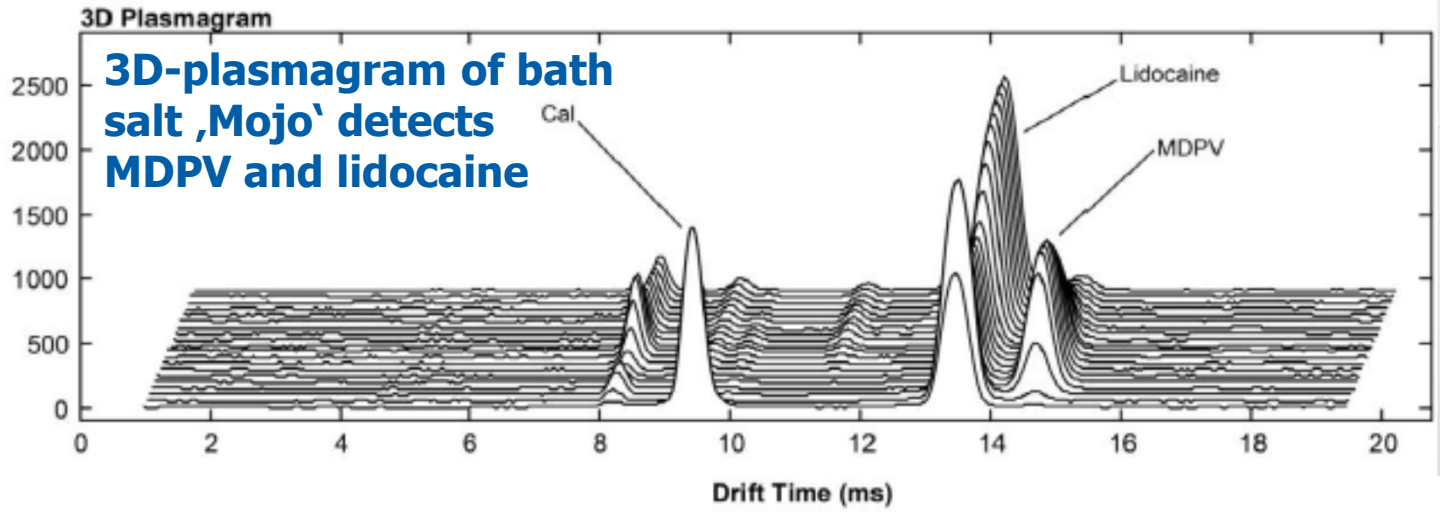




retention window for classic drugs

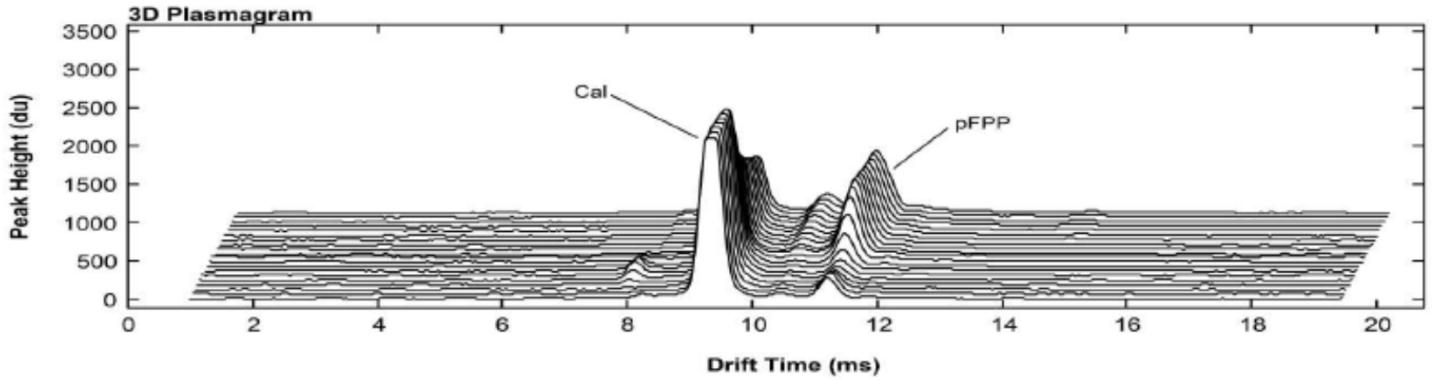
retention window for amino alkyl indoles etc.

IMS results – bath salts

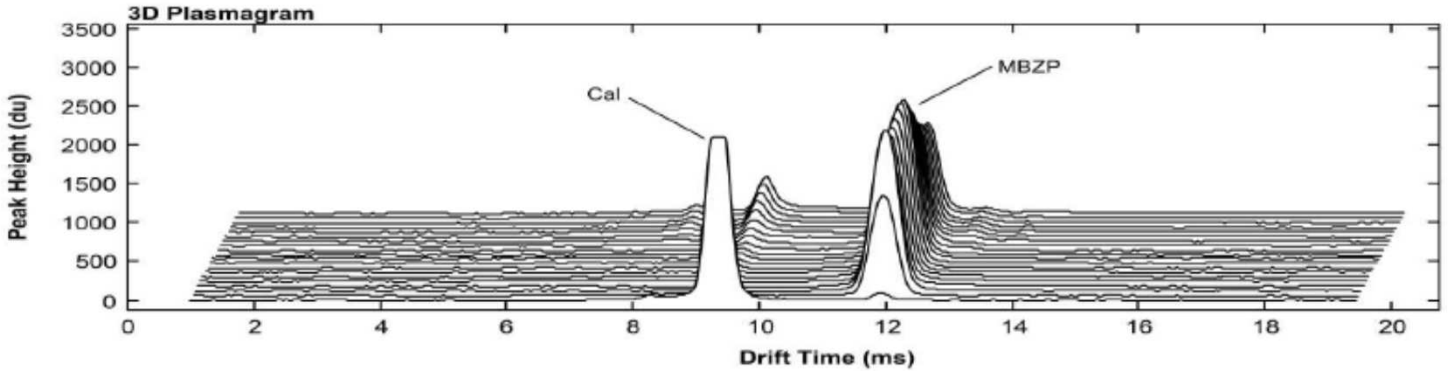


IMS results - herbal XTC/piperazines

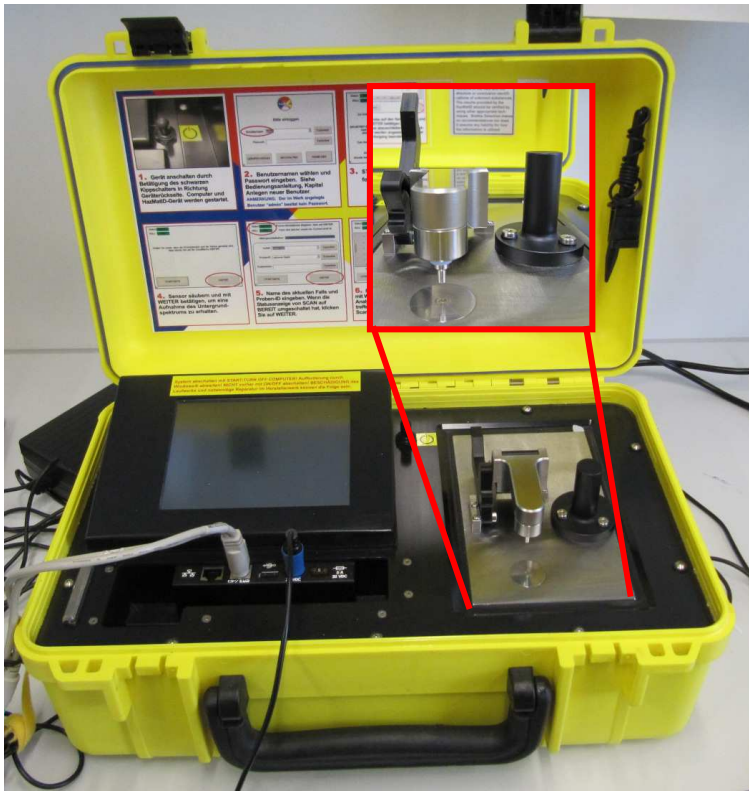
Cherries

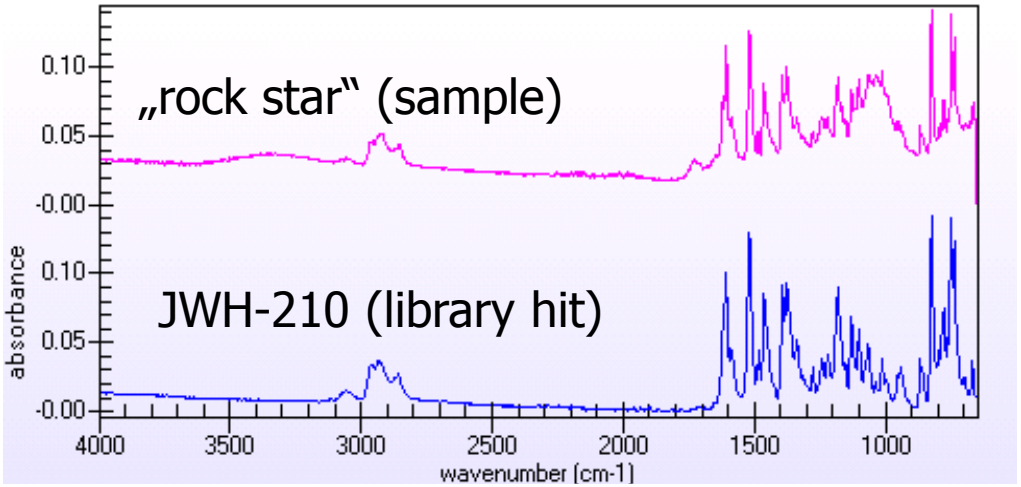


X4 Ecstasy

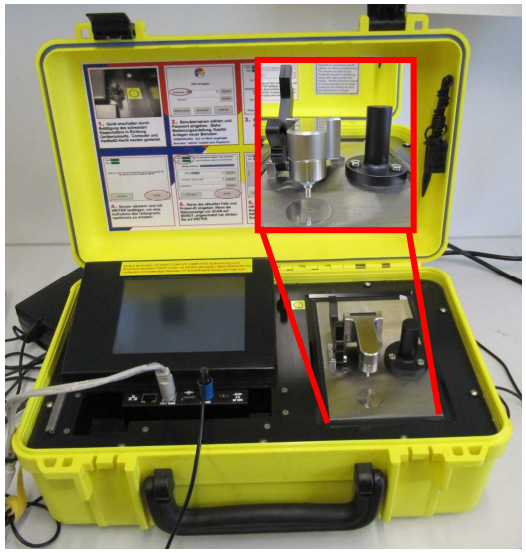


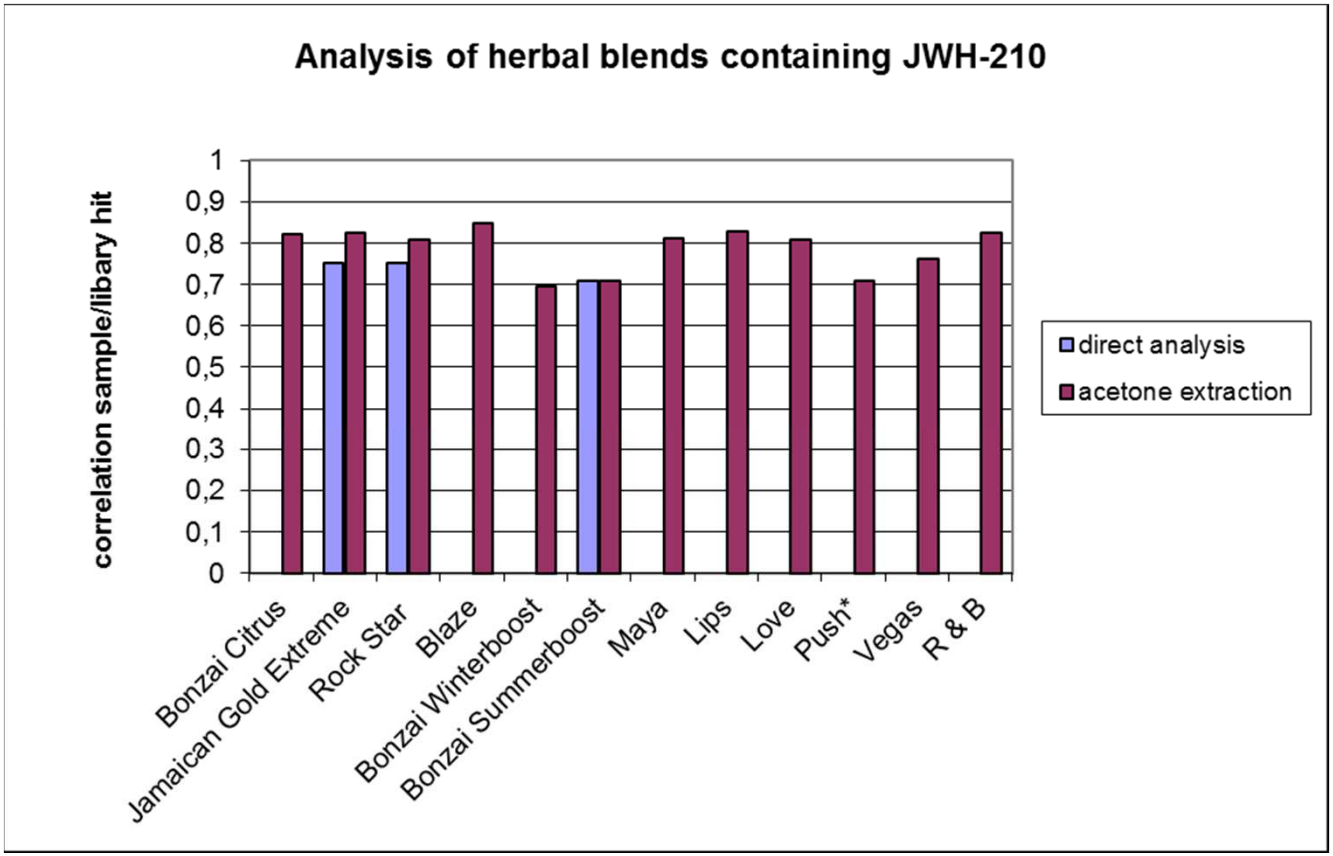
Mobile screening of „legal“ highs with FT-infrared spectroscopy (HazMatID)





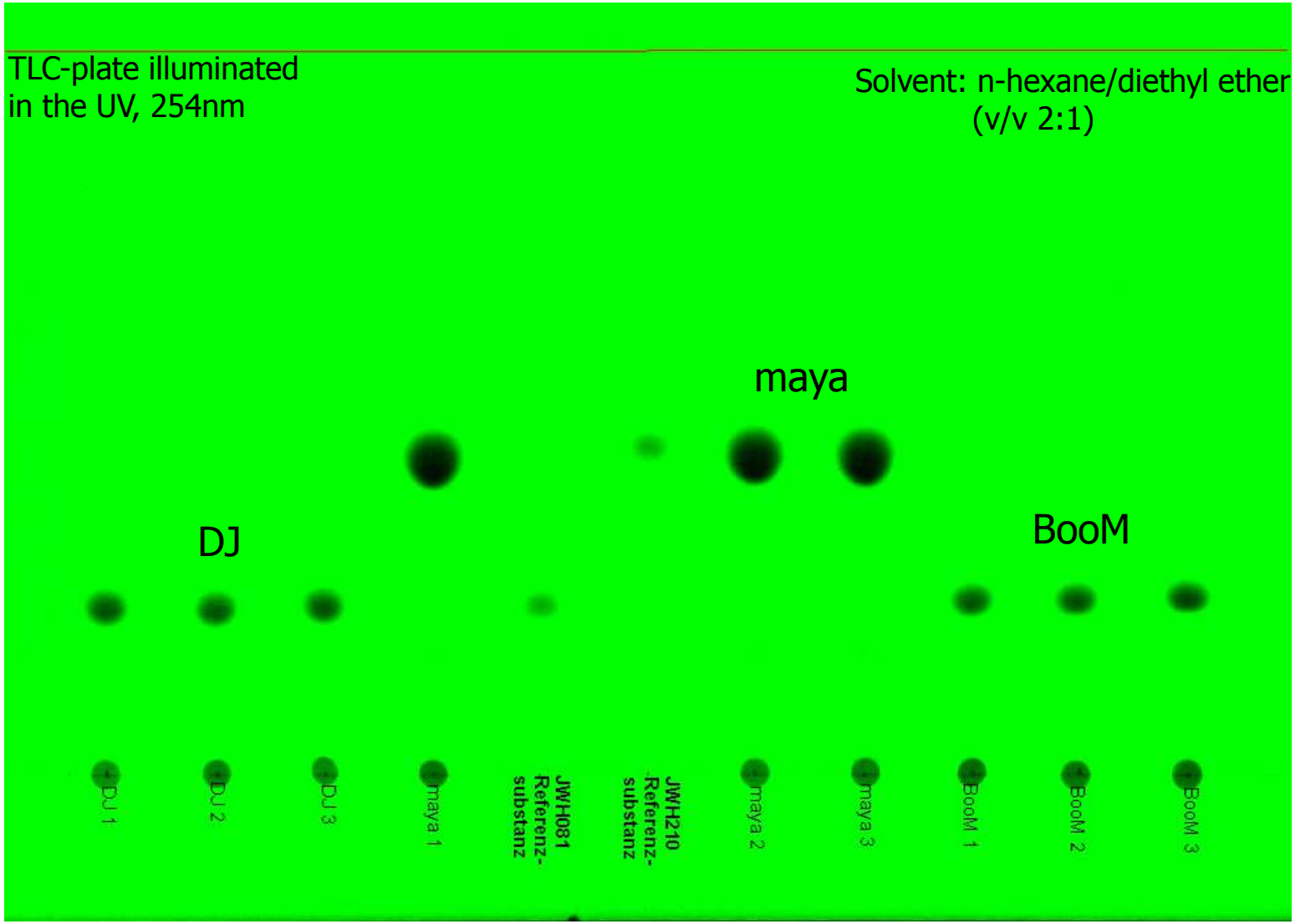
Mobile screening of herbal products after one-step extraction





Successfully applied to seized samples herbal products during outdoor events like techno event „Nature One".

TLC results


TLC-plate illuminated
in the UV, 254nm
Solvent: n-hexane/diethyl ether
(v/v 2:1)
maya
DJ
BooM
DJ 1
DJ 2
DJ 3
maya 1
JWH081
Referenz-
substanz
JWH210
Referenz-
substanz
maya 2
maya 3
BooM 1
BooM 2
BooM 3

Ambient ionization techniques

Applications of Desorptions-Electrospray-Ionization-Mass Spectrometry (DESI-MS) in forensic toxicological analysis of NPS

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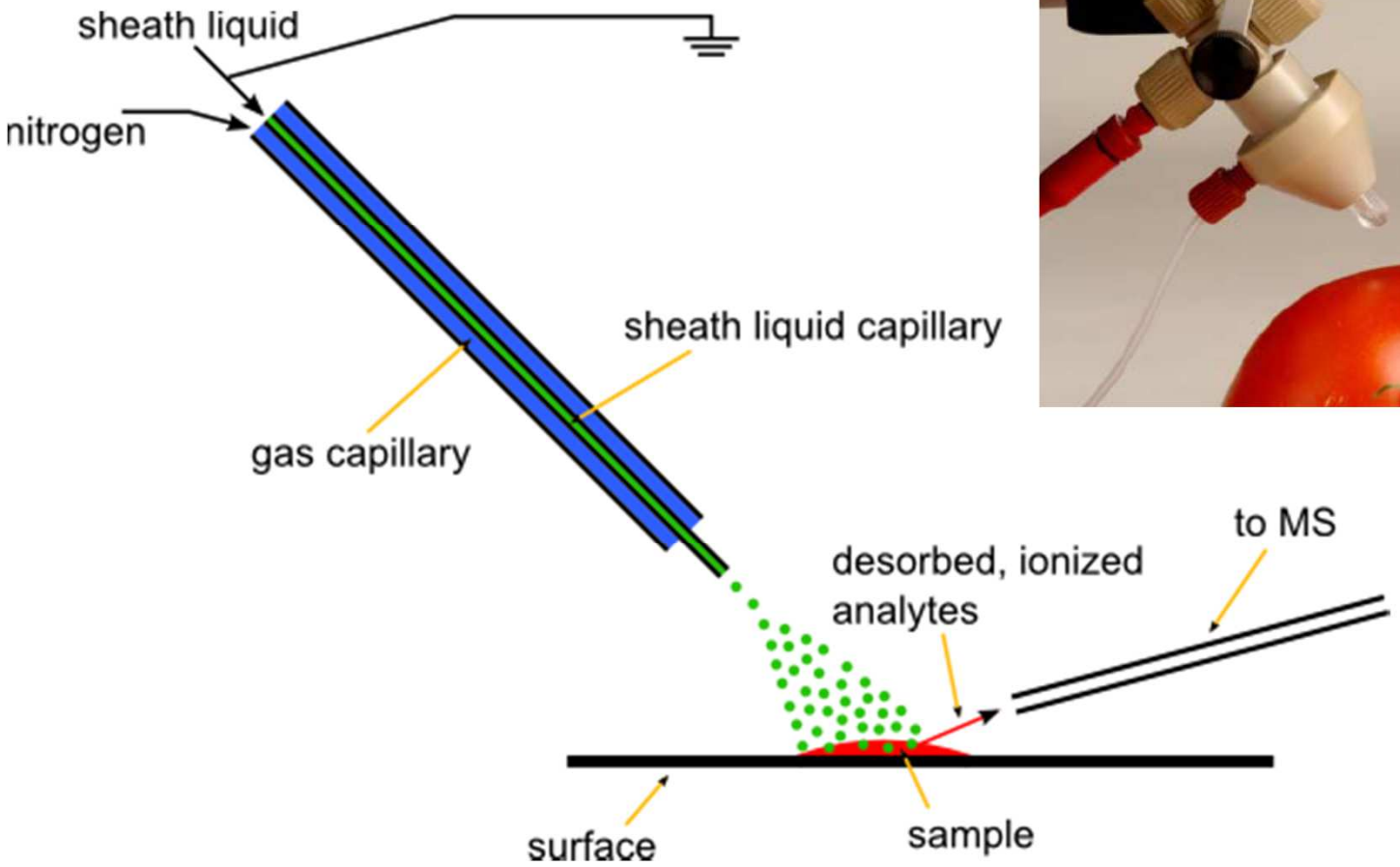
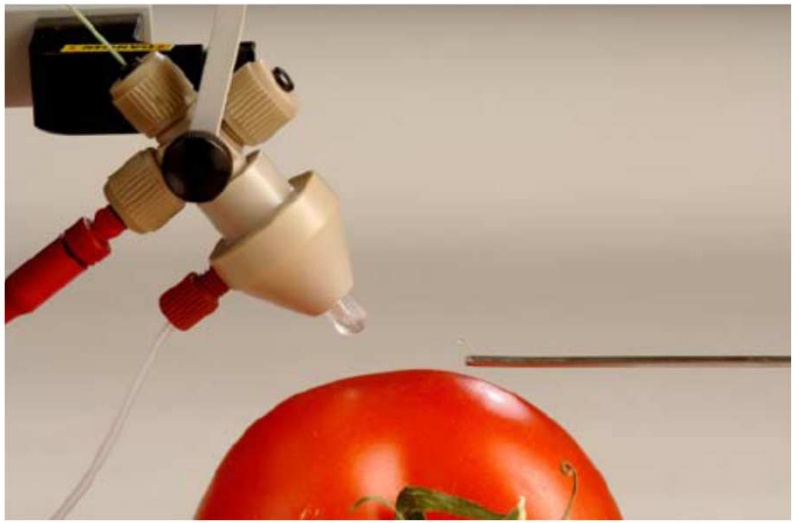
Ambient ionization MS techniques

ESI + Spray	Laser/Photoionisation	APCI
Desorption Electrospray Ionisation, **DESI**	Electrospray Laser Desorption Ionis., **ELDI**	Direct Analysis in Real Time (Helium plasma), **DART**
Extractive Electrospray Ionisation, **EESI**	Matrix-Assisted Laser DESI, **MALDESI**	Direct Atmospheric Pressure Chem. Ionisation, **DAPCI**
Neutral Desorption Extractive Electrospray Ionis., **ND-EESI**	Desorption Atm. Pressure Photon Ionisation, **DAPPI**	Helium Atm. Pressure Glow Dis-charge Ionisation, **HAPGDI**
Easy Ambient Sonic Spray Ionisation, **EASI**	Laser Ablation Electro-spray Ionisation, **LAESI**	Flowing Atmospheric Pressure Afterglow, **FAPA**
Jet Desorption Electrospray Ionisation, **JeDI**	Laser Desorption AP Chem. Ionisation, **LD-APCI**	Dielectric Barrier Discharge Ionisation, **DBDI**
Liquid Extraction Surface Analysis, **LESA**		Surface Activated Chemical Ionisation, **SACI**
Paperspray, **PS**		Atm. Solids Analysis Probe, **ASAP**
		Plasma-Assisted Des./Ionis., **PADI**
		Low Temperature Plasma, **LTP**
		Laser Diode Thermal Des., **LDTD**

DESI-MS principle





Schematische Darstellung der Desorptions-Elektrospray-Ionisations (DESI) Quelle

Why is DESI-MS helpful for forensics?

- Advantages:
  - Rapid and direct analysis technique
  - Screening method (rapid!)
  - High identification power
  - Spatial resolution (mass spectral imaging, e.g. fingerprints!)
  - Coupling with TLC
- Substances for examination:
  - Solid material (exception: powder, strong absorbent surfaces [e.g. dried leaves])
  - Liquids
  - Laboratory glassware or equipment

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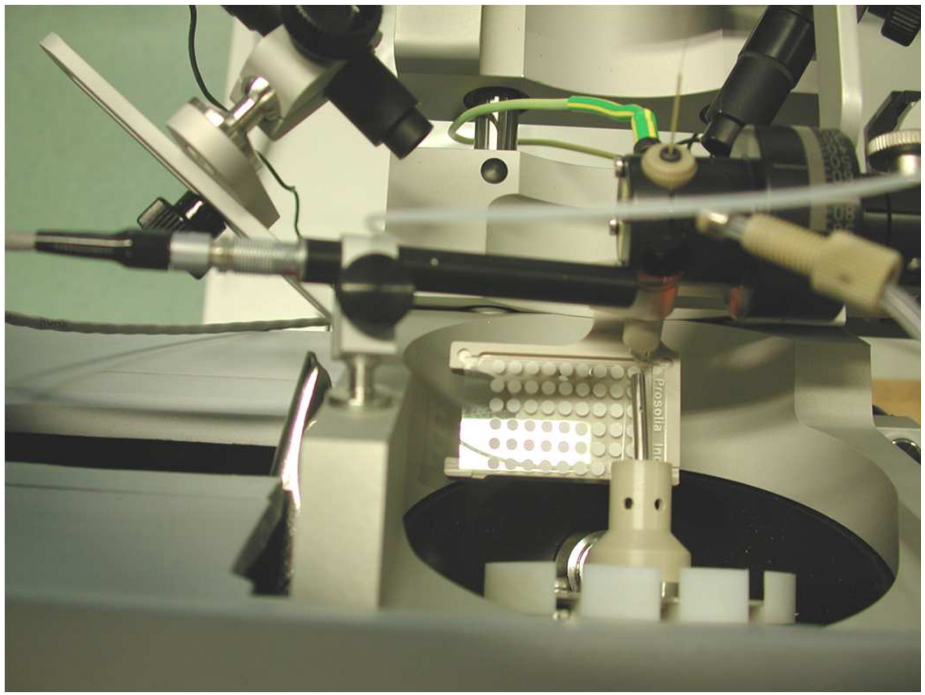
DESI-MS System



DESI-MS^n system:

DESI:
Prosolia OmniSpray DESI source

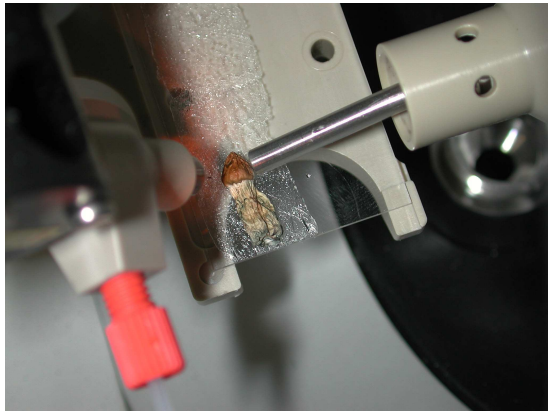
MS:
Bruker HCTplus
(high capacity ion trap)

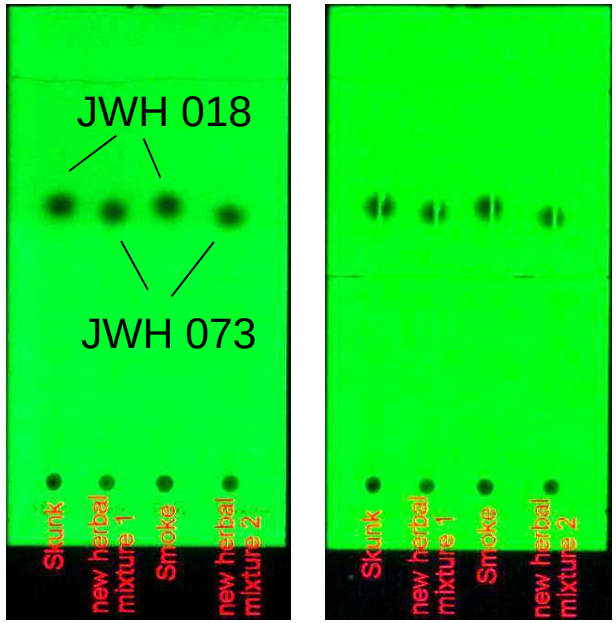
MS parameters:

Dry gas: 5 L*min^{-1}
Dry temperature: 250°C
Voltage: +4 kV

Investigated materials

- biogenic drugs
- TLC-DESI-MS
- Designer drugs
- pharmaceuticals
- Ecstasy tablets





Direct DESI-MS of Spice products I

herbal mixtures fixed to an adhesive tape

left: Spice product on teflon filter; middle: Spice product pressed between two teflon filters; right: teflon filter on glass slide for für DESI-MS (second filter optionally for IMS)

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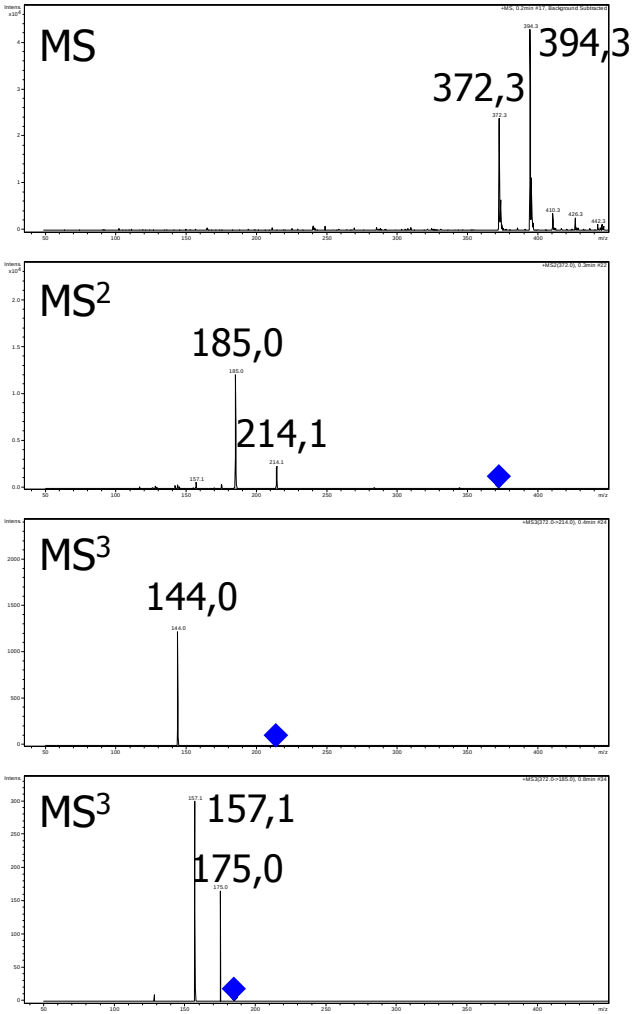
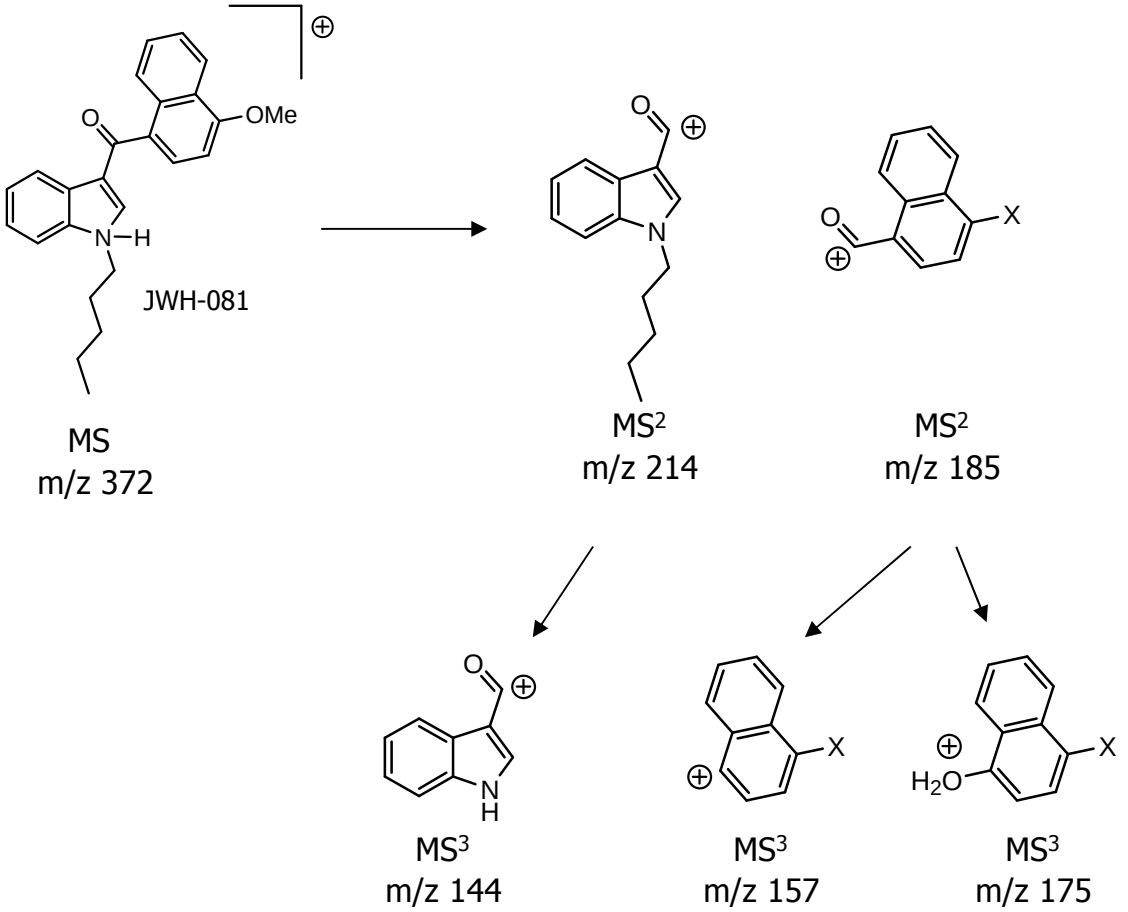
Direct DESI-MS of Spice products II

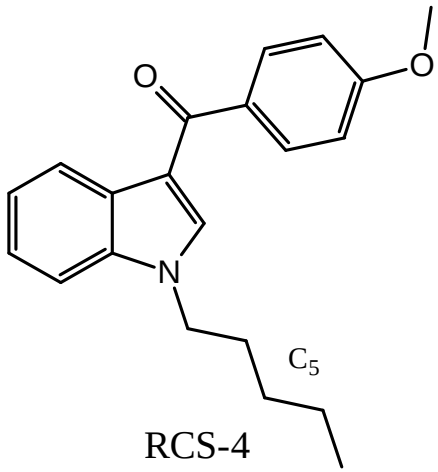
MS^n-spectrum of "BooM"



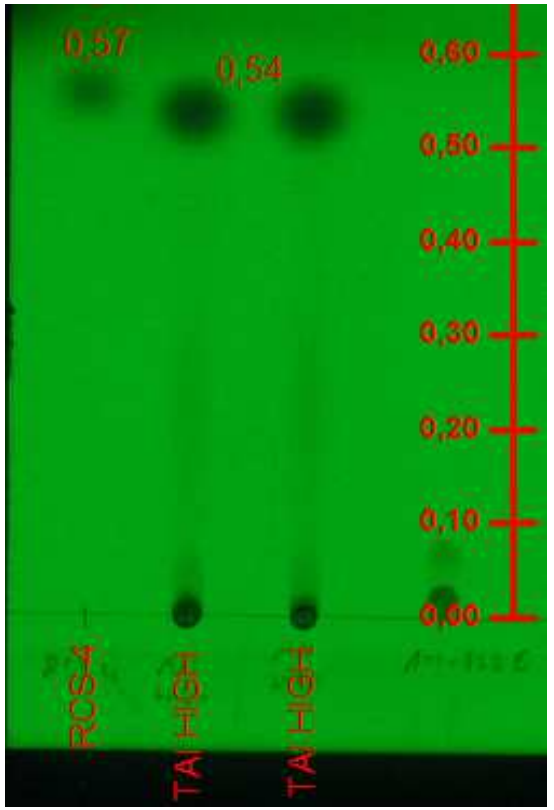


Unusual active ingredient in Tai High

Seizure in Saxonia
Suspicion: p-hydroxymethylene instead of p-methoxy



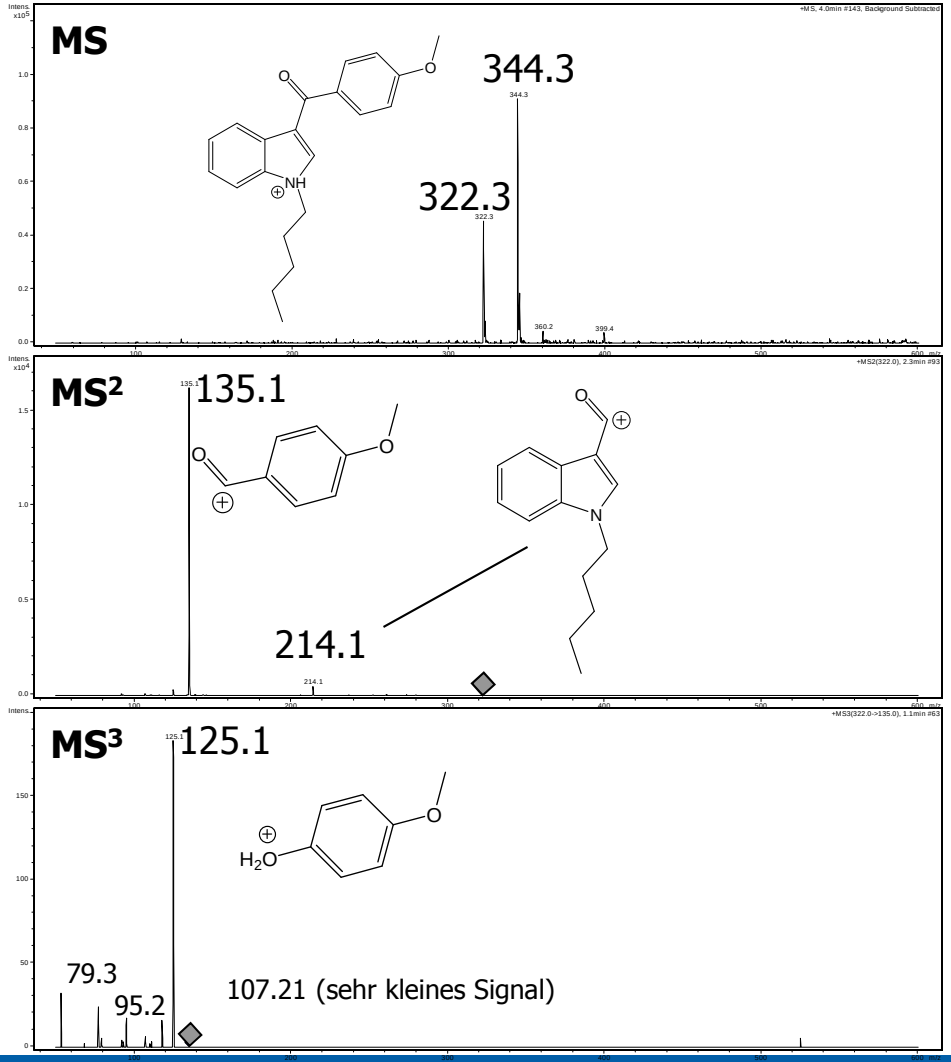
RCS-4
M = 321,4



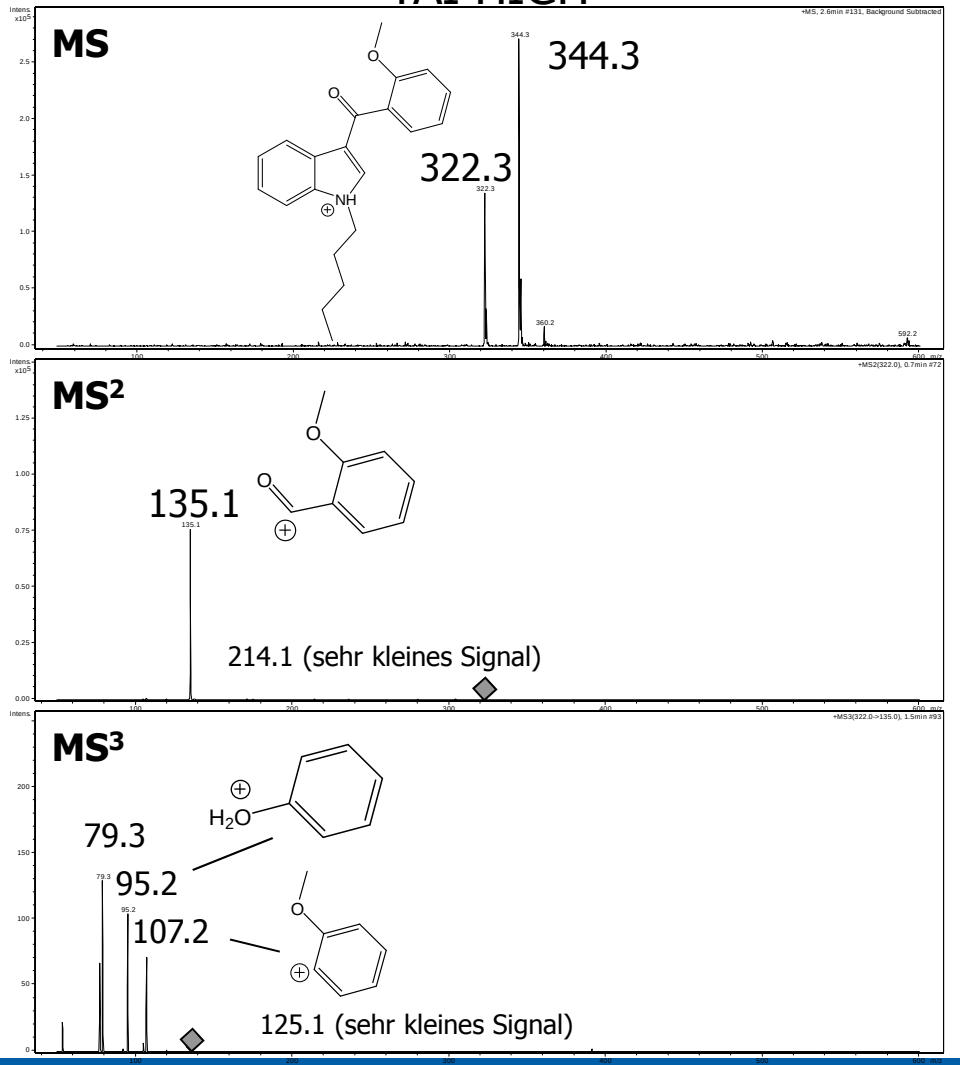
Bundeskriminalamt

Tai High – TLC-DESI-MS analysis identification of positional isomers

RCS-4



TAI HIGH



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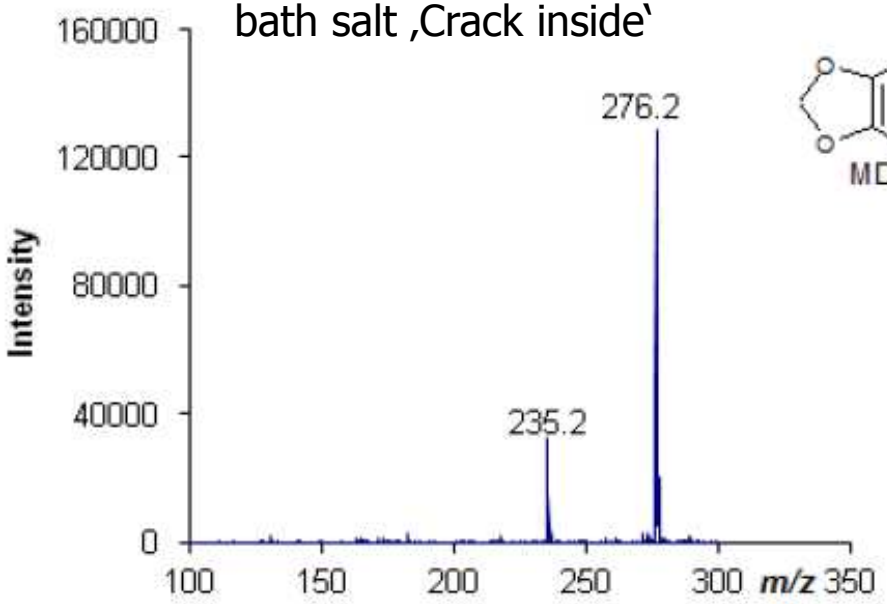
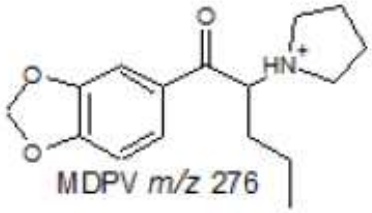
Legal highs – bath salts/herbal XTC
Rapid Identification via DESI-MS

(+) DESI-MS spectrum of bath salt ‚Crack inside'





Analysis of powdered samples for DESI-MS via Teflon filters

Results of direct DESI-MS analysis of powdered drug samples.

Sample	*m/z* signal	Identified substance
Mojo	235, 276	Lidocaine, MDPV
Charge plus	182, 235	4-MEC, Lidocaine
Mitseez	222, 235	Butylone, Lidocaine
Cherries	181, 231	pFPP, TFMPP
Loved up	181	TFMPP

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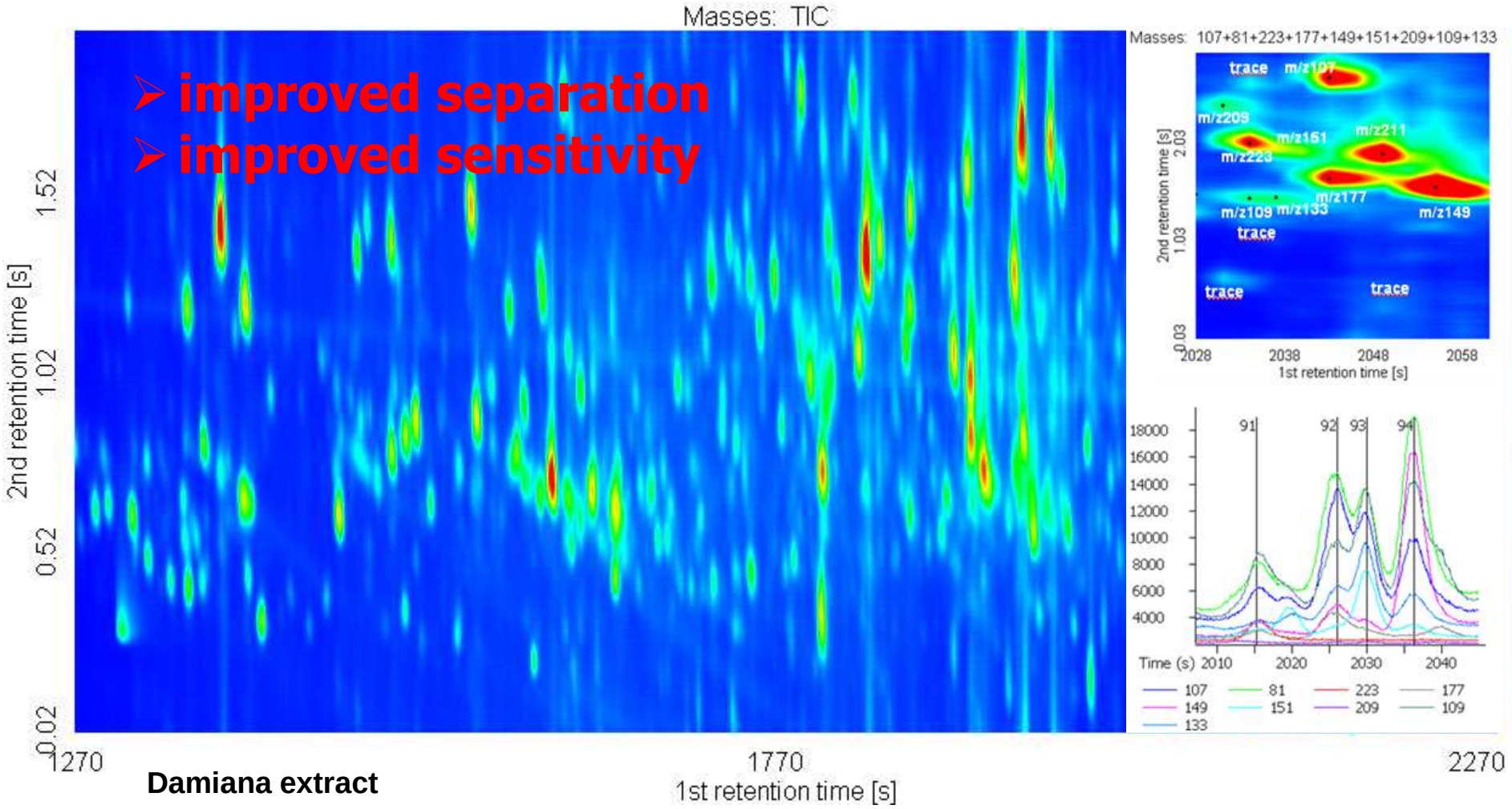
Outlook / future work: Spice profiling - linking products and production



Damiana extract

- 2D analysis (BPX50 × Rtx200ms)

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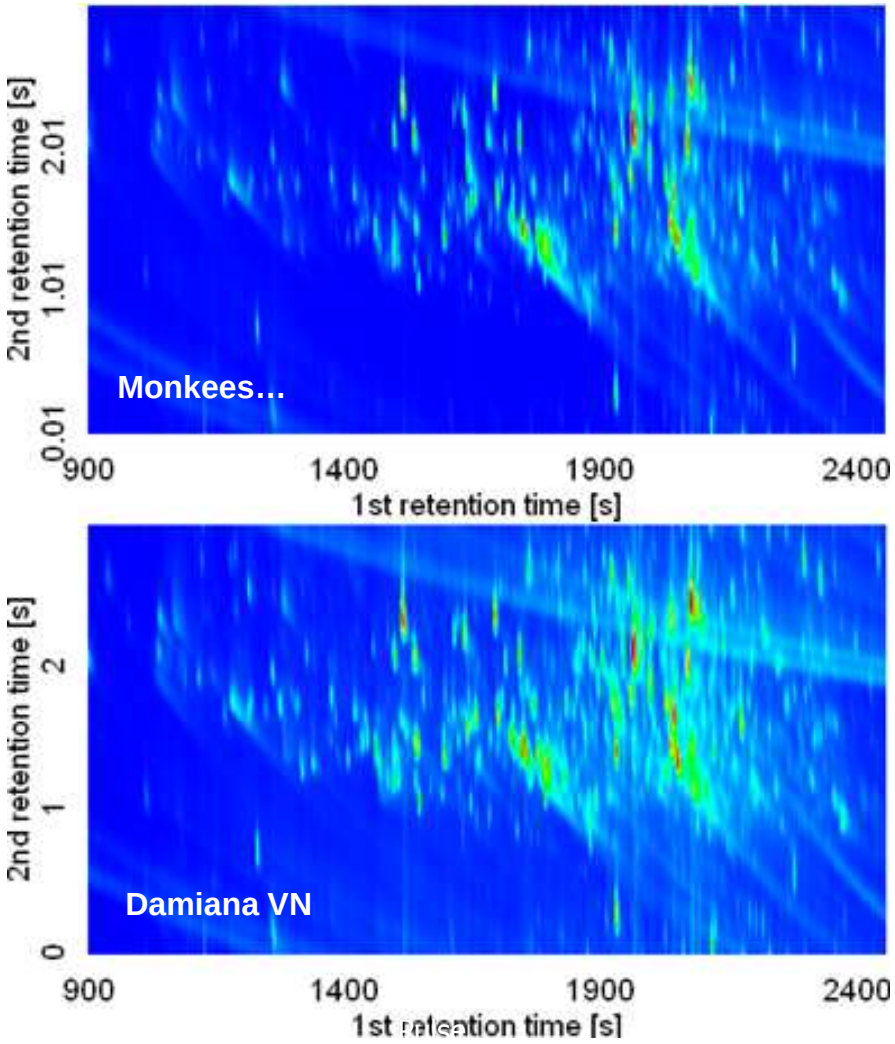
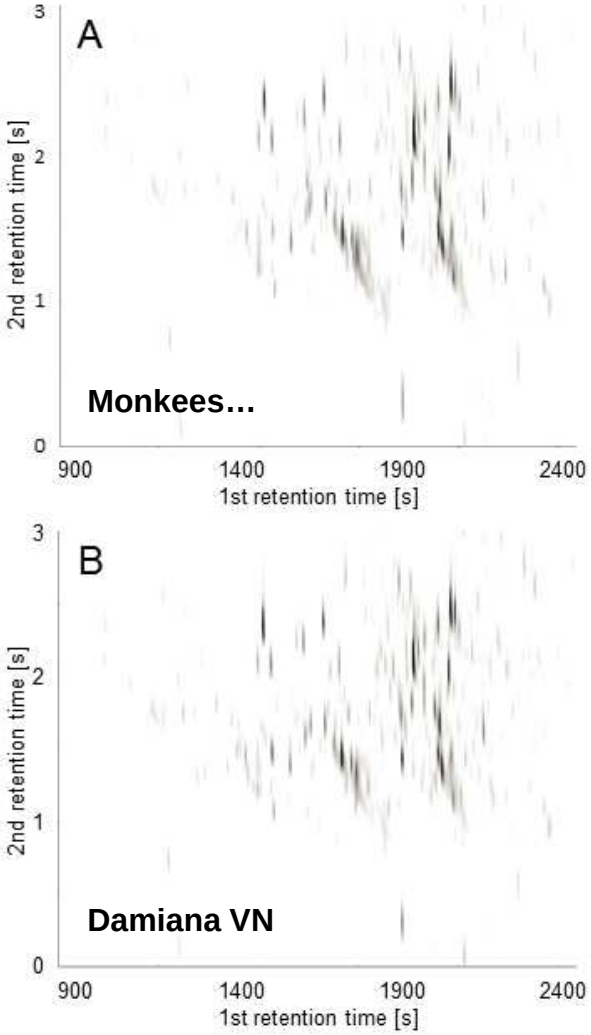
Damiana – main plant source in Spice products (even if undeclared)?





high similarity

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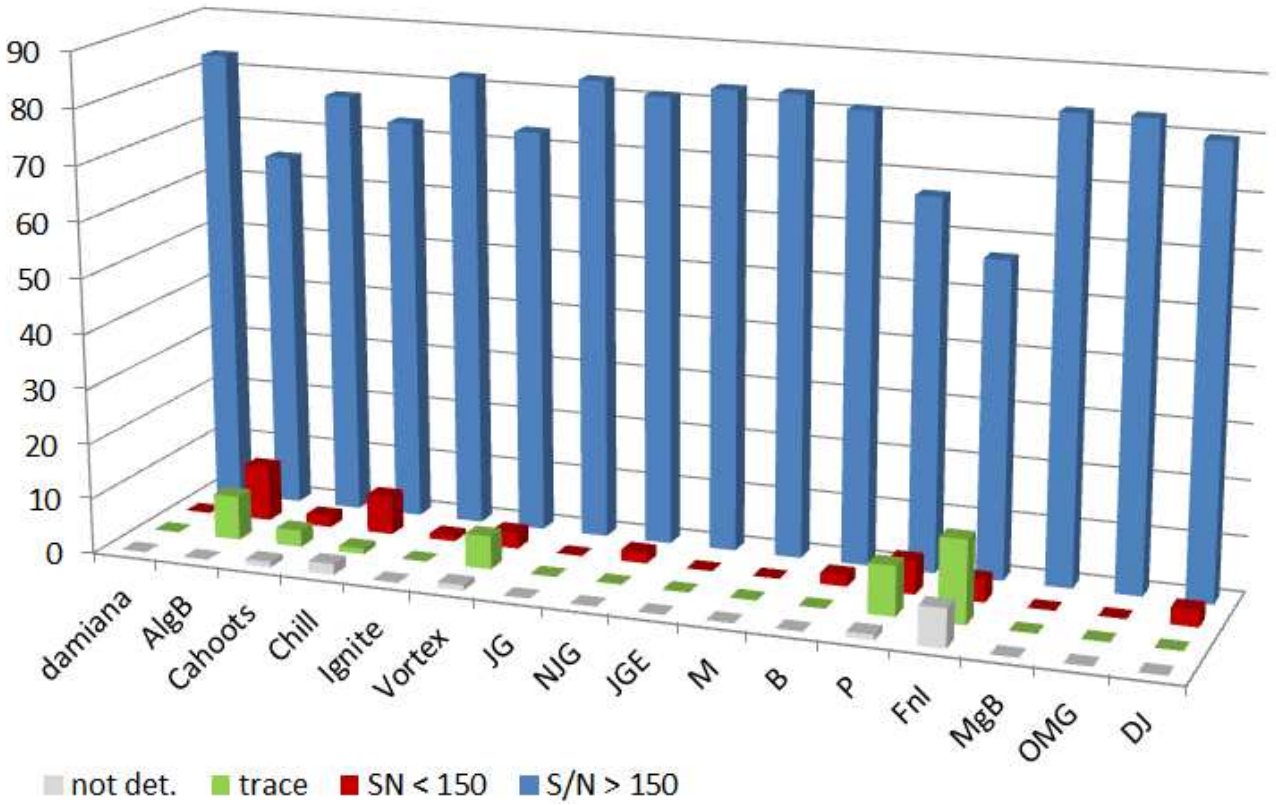
Damiana in Spice products profiling based on 83 marker compounds

'Jamaican Gold', 'New Jamaican Gold', 'Algerian Blend', 'Jamaican Gold Extreme', 'Maya', 'Boom', 'Experience Cahoots', 'Experience Chill', 'Experience Vortex', 'Experience Ignite', 'Pulse', 'Fire'n'ice', 'Monkees Go Bananas', 'OMG' and 'DJ'



→ Damiana present in all analysed herbal highs, some products, e.g. MgB showed exclusively the Damiana pattern

Conclusions

- „post event" submission of individual designer drugs is not very effective, should be focussed on substances that persist on the drug market (or even replace classic drugs)
- consequent application of pharmaceuticals law is expedient for effective criminal prosecution of NPS selling internet shops
- better co-operation between forensic customs, police and legal medicine labs (centralized special analyses, supply of reference substances, exchange of analytical data)
- continuation of NPS market monitoring as performed in the EU-projects SPICE and SPICE II plus
- conducting research to increase the knowledge base on the illicit production and supply chain of NPS (controlled syntheses, development of analytical profiling procedures

Thanks to the co-workers and for your attention!