Stability of new psychoactive substances

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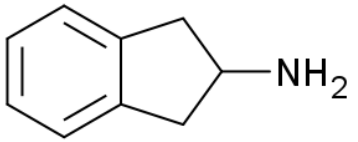
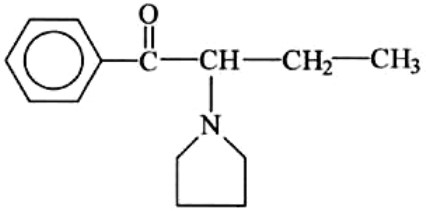
The evolution of drug types

Since 1980s, the nature of new psychoactive substances (NPS, “designer drugs”) have seemingly evolved each decade. This is a toxicological challenge.

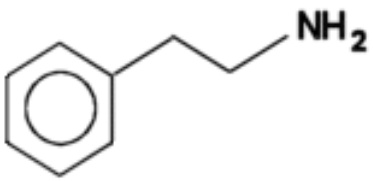
Aminoindanes



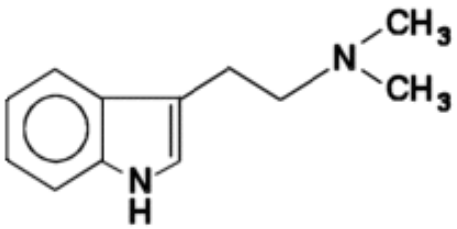
Pyrrolidinopropiophenones



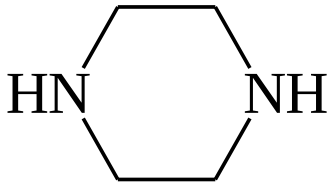
Phenethylamines



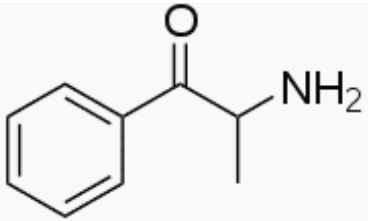
Tryptamines



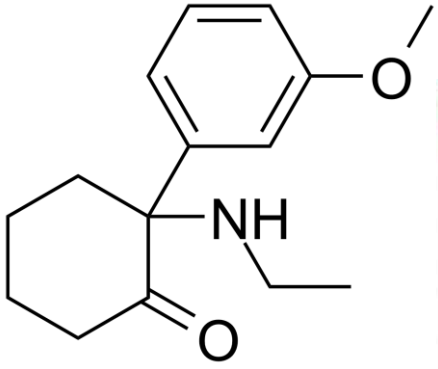
Piperazines



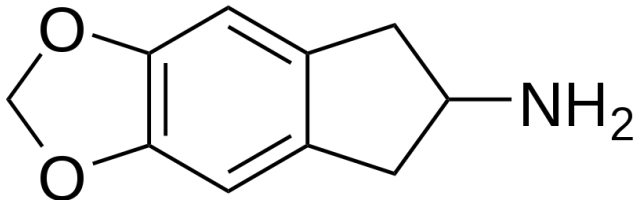
Cathinones



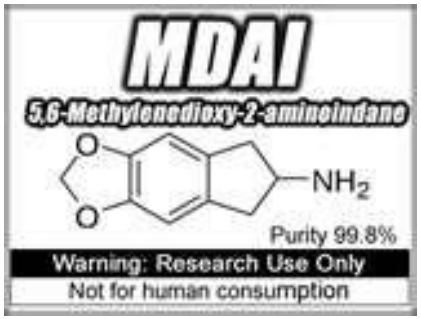
New New Designer Drugs

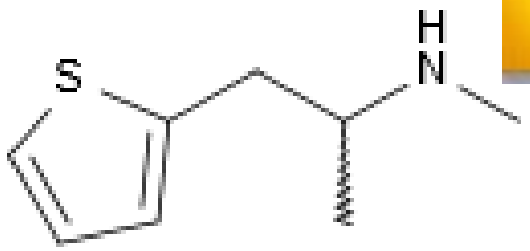


Methoxetamine



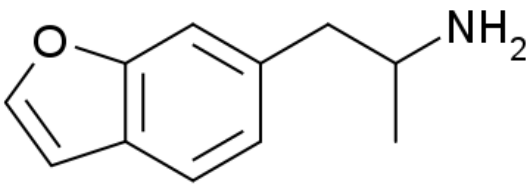
5,6-Methylenedioxy-2-aminoindane (MDAI)





Methiopropamine (MPA)

6-(2-aminopropyl)benzofuran (6-APB, “Benzo Fury”)



Challenges of NPSs

- Analytical – can you detect? can you identify?
  – can you confirm? can you measure?

- Interpretation – what does presence mean?
  – what does a concentration mean?

- Has anything affected any of the above?

STABILITY?

Stability/Instability

Drugs can breakdown in a sample even after collection, to form other compounds.

This involves chemical or enzymatic processes (e.g. hydrolysis, oxidation and de-esterification) typically in blood.

Depending on the process, this can be prevented or slowed by addition of a preservative or correct storage (e.g. sodium fluoride, freezing, enzyme-free matrix for standards).

Breakdown ultimately reduces the concentration of the original drug and increases the concentration of the instability/breakdown products. In extreme circumstances the original drug can completely disappear and no longer be detected in the sample.

It is useful to know what instability products to look for or be aware of to interpret the toxicology results.

Stability/Instability

Some instability products are also normal metabolites of the drug as the process may happen normally in the body as well.

It can therefore be difficult to determine if a compound is present as an instability product or as a metabolite, or both! e.g. cocaine breaks down to benzoylecognine and ecgonine methylester as well as forming these as normal metabolites.

Other examples include (drug = breakdown product/metabolite):

- Acepromazine = 2-hydroxy-ethylpromazine
- Diltiazem = desacetyldiltiazem
- Dosulepin = dosulepin sulphoxide
- Mebeverine = mebeverine alcohol + veratric acid
- 6-Monoacetylmorphine (6-MAM) = morphine
- Nitrazepam = nitrazepam benzophenone
- Zopiclone = 2-amino-5-chloropyridine

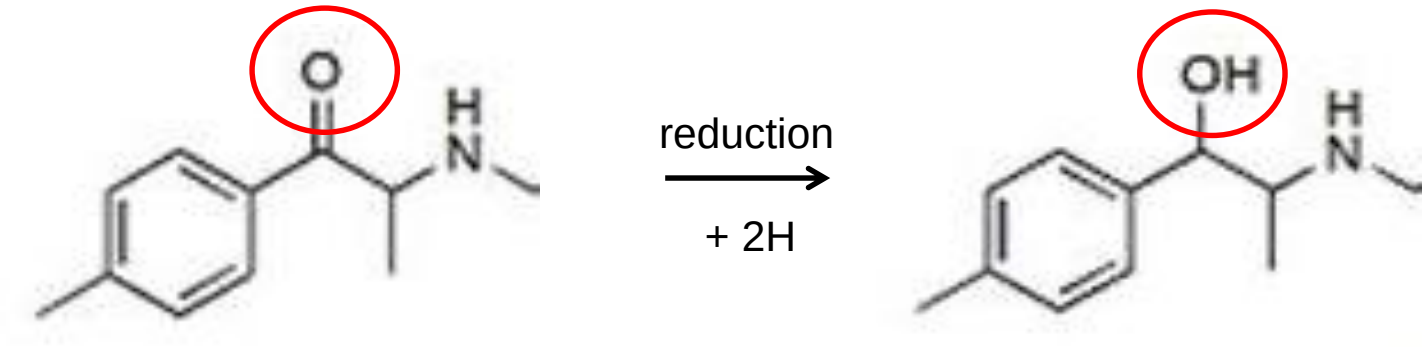
Mephedrone

Sørensen reported ~20–80% degradation of cathinones in 5 days at 20± 2°C and ~15–20% loss in 6 days at 5 ± 2°C in human blood, even in the presence of fluoride-oxalate preservative.

(2011- J. Chromatogr. B, 879, 727-736)

Tsujikawa et al reported an oxidation pathway of mephedrone and other methcathinones stored at 22°C in alkaline buffer with and without antioxidants.

(2012- Forensic Sci Int, 220(1-3), 103-110)

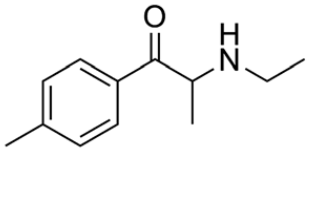


Mephedrone

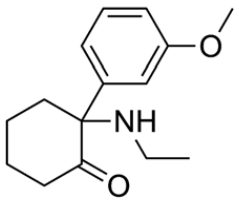
Dihydro-mephedrone

NPS Stability

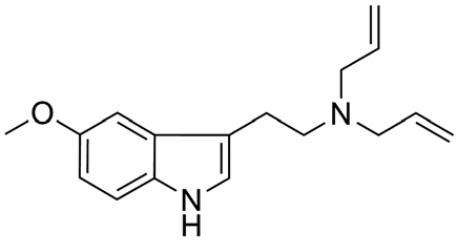
13 of the “new, new designer drugs” were selected.



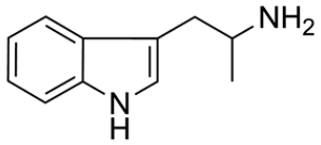
4-MEC



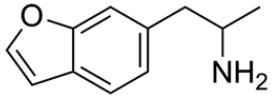
Methoxetamine



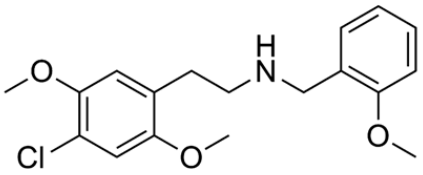
5-MeO-DALT



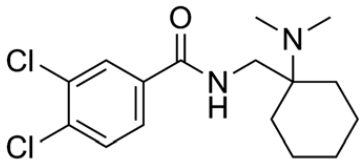
AMT



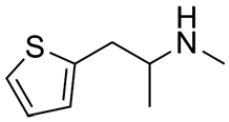
6-APB



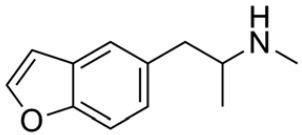
25C-NBOMe



AH-7921



MPA



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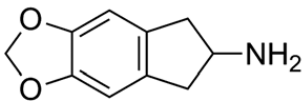
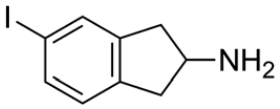
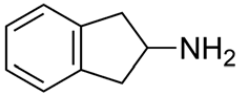


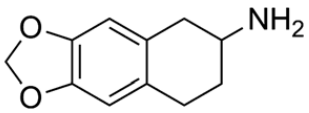
MDAI



5-IAI



2-AI



MDAT

NPS Stability

2 mg/L aqueous stds (inc. amitriptyline as stable control)

2 mg/L equine blood + plasma stds produced (inc. amitriptyline)

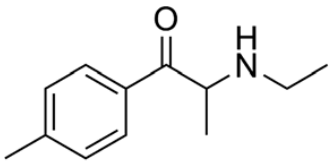
Kept at room temp (20-23^{o}C) to “encourage” instability

Analysed at Day 0, 1, 2, 3, 7, 14, 21, and 28 for AMT, 6-APB, MPA, 5-MAPB, 25C-NBOMe and AH-7921

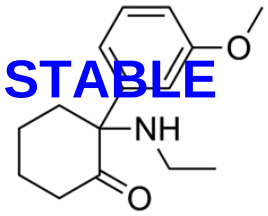
Extended to day 37 for 4-MEC (plasma), methoxetamine (blood and plasma) and 5-MeO-DALT (blood and plasma)

Aminoindanes analysed at time 0, 2, and 4 h and Day 1, 2, 7, 14, 21 (and 28 for MDAI + MDAT)

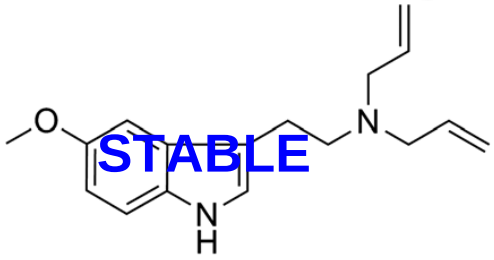
21 day stable



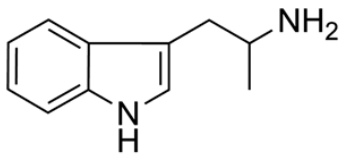
4-MEC



Methoxetamine



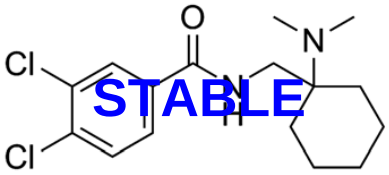
5-MeO-DALT



AMT

6-APB

25C-NBOMe



AH-7921

MPA

5-MAPB

MDAI

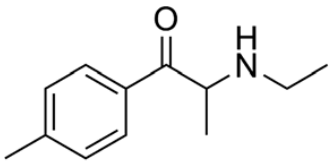
5-IAI

2-AI

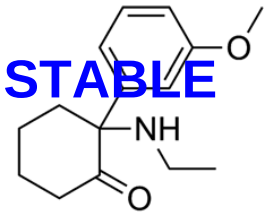
MDAT

ROAR Forensics

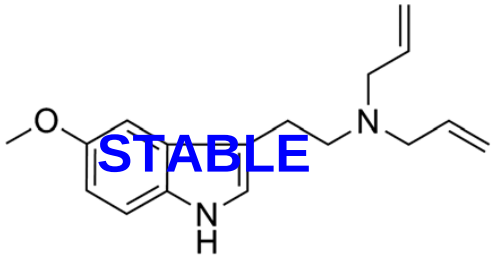
Unstable?



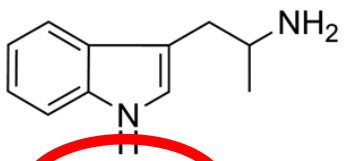
4-MEC



Methoxetamine



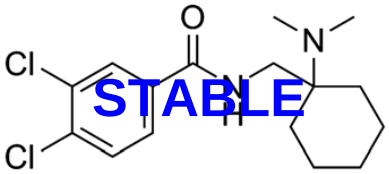
5-MeO-DALT



AMT

6-APB

25C-NBOMe



AH-7921

MPA

5-MAPB

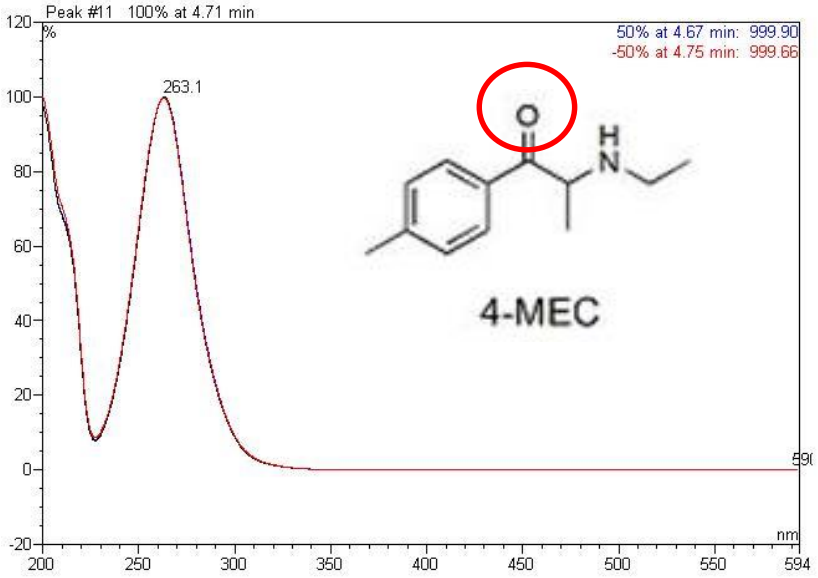
MDAI

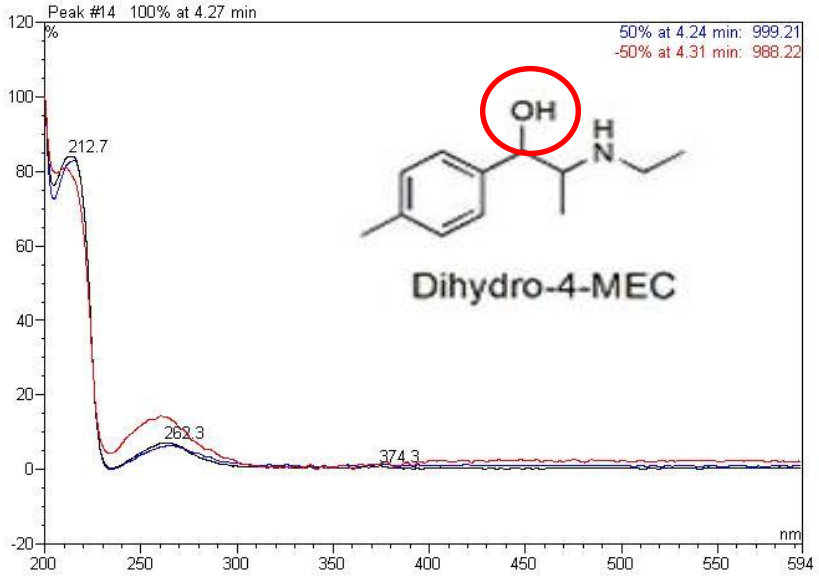
5-IAI

2-AI

MDAT

4-MEC

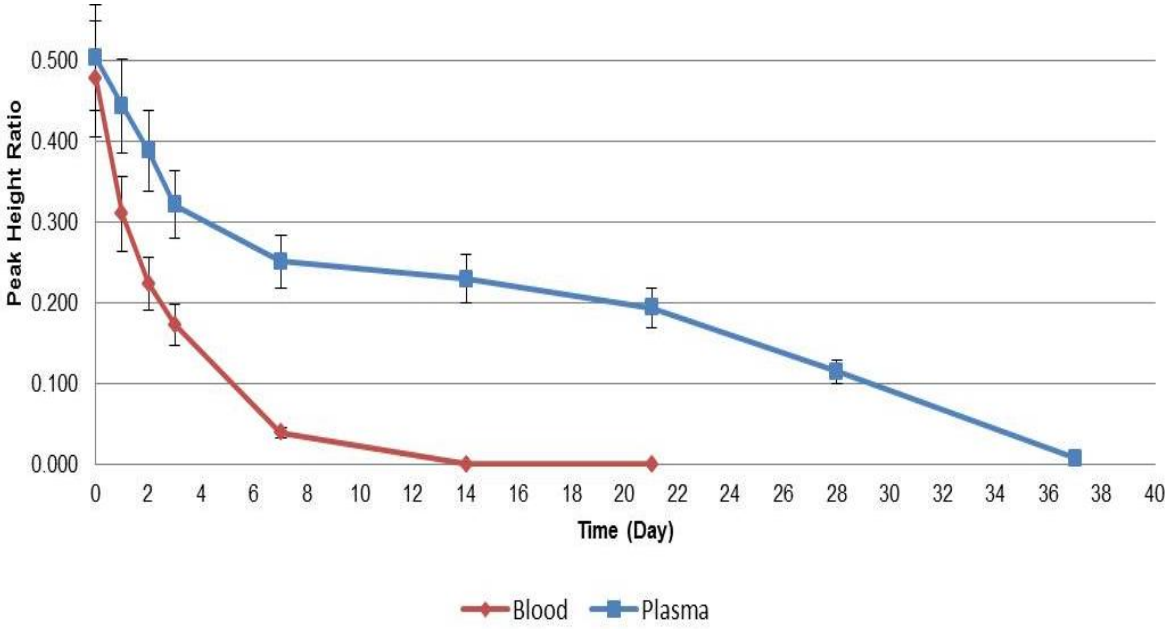




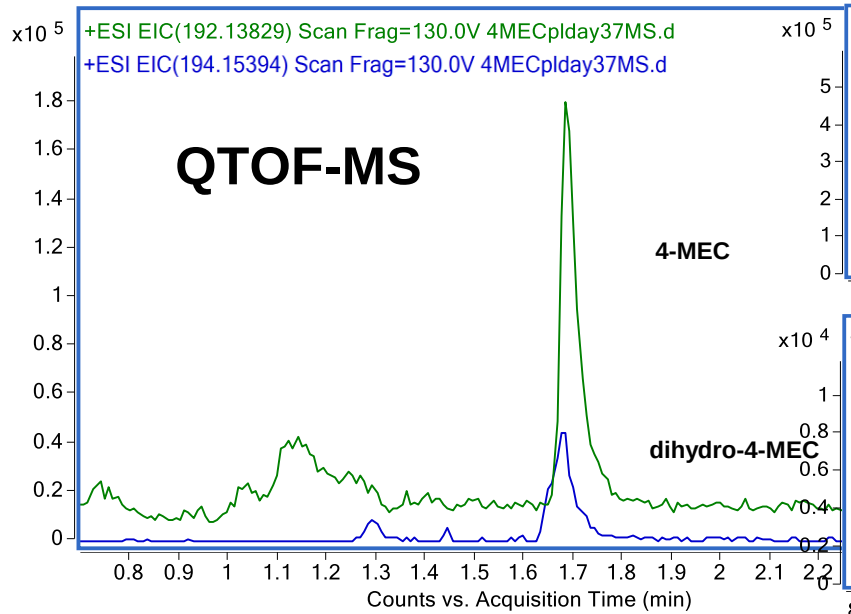
Undetectable in blood within 14 days

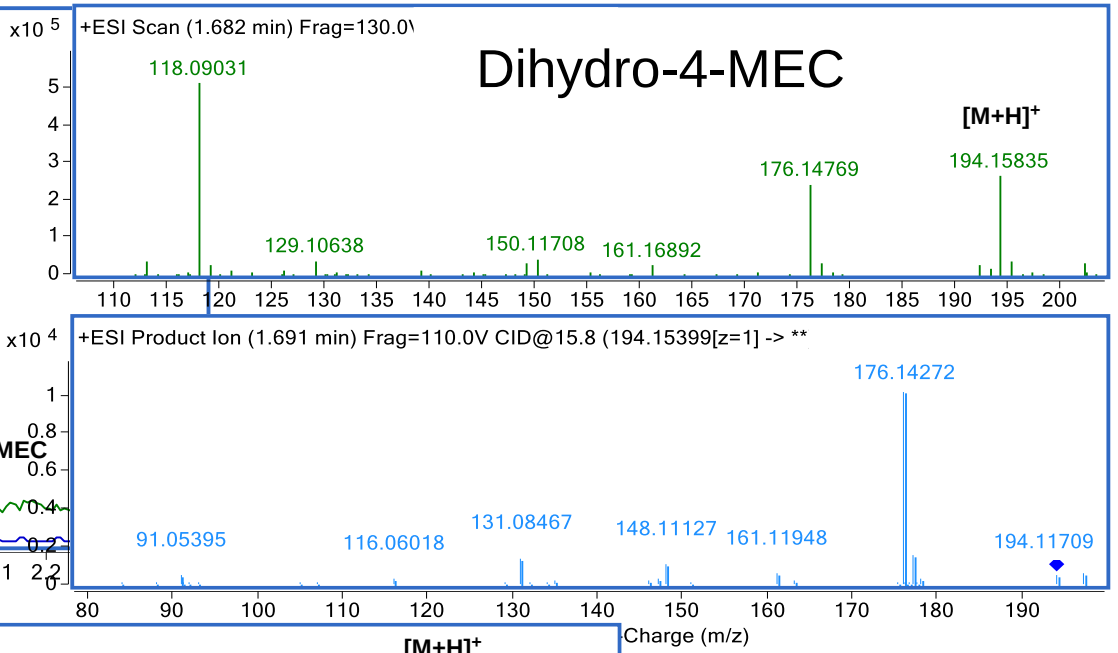
Corresponding loss of 54% in plasma

Dihydro-4-MEC did not account for proportional loss of 4-MEC

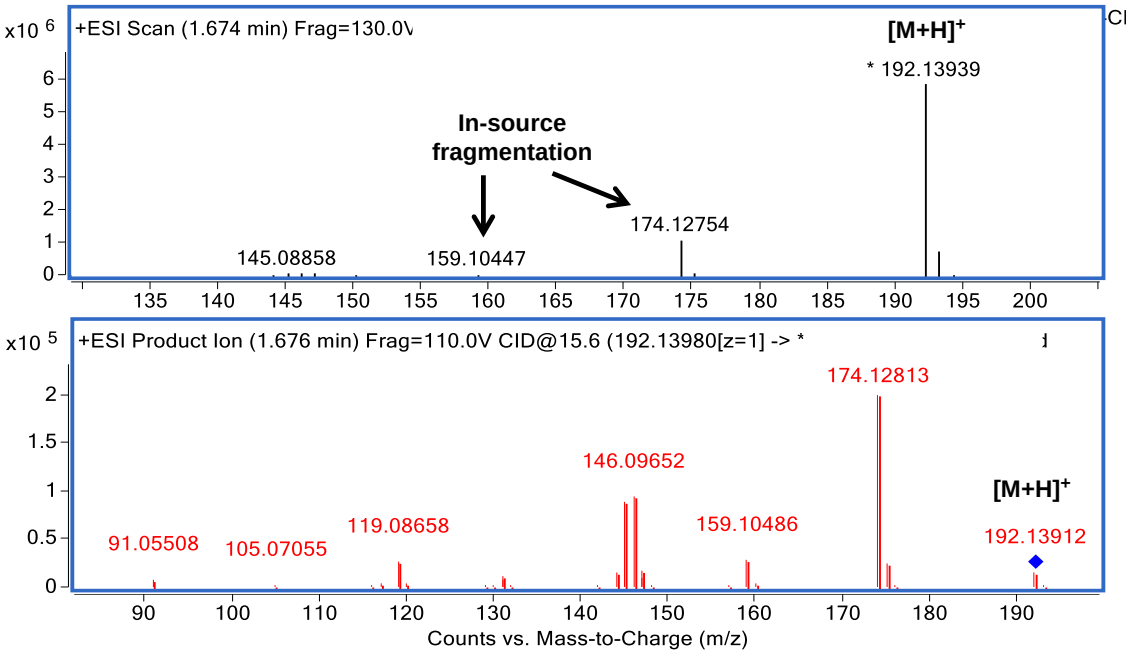


4-MEC



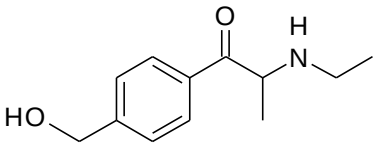


4-MEC

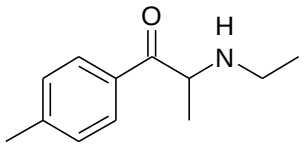


Dihydro-4-MEC later confirmed by $NaBH_4$ reduction of 4-MEC

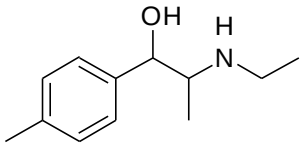
4-MEC metabolism



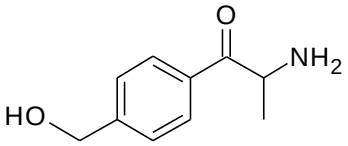
Hydroxytolyl-4-MEC



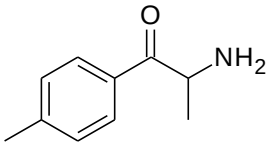
4-MEC



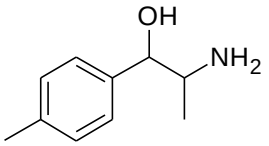
Dihydro-4-MEC



Nor-hydroxytolyl-4-MEC



Desethyl-4-MEC
(Nor-4-MEC)



Nordihydro-4-MEC

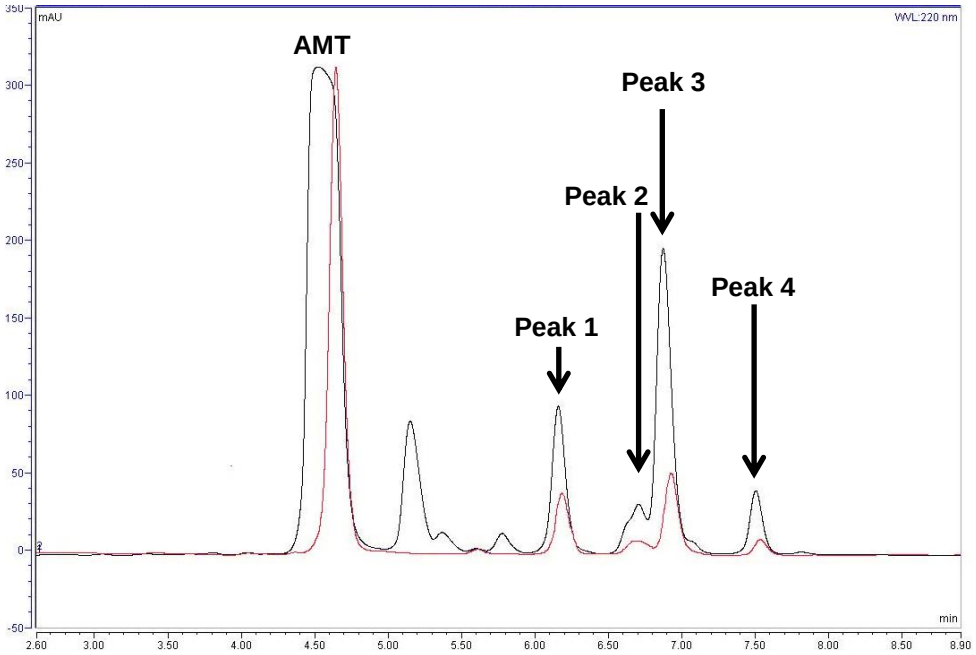
= N-Desmethylmephedrone

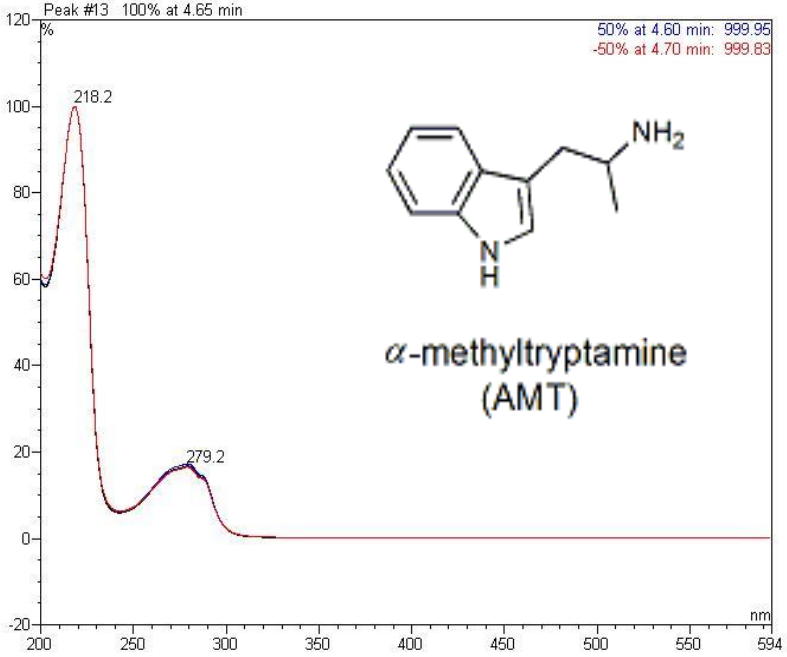
= Normephedrone

: degradation

: metabolism

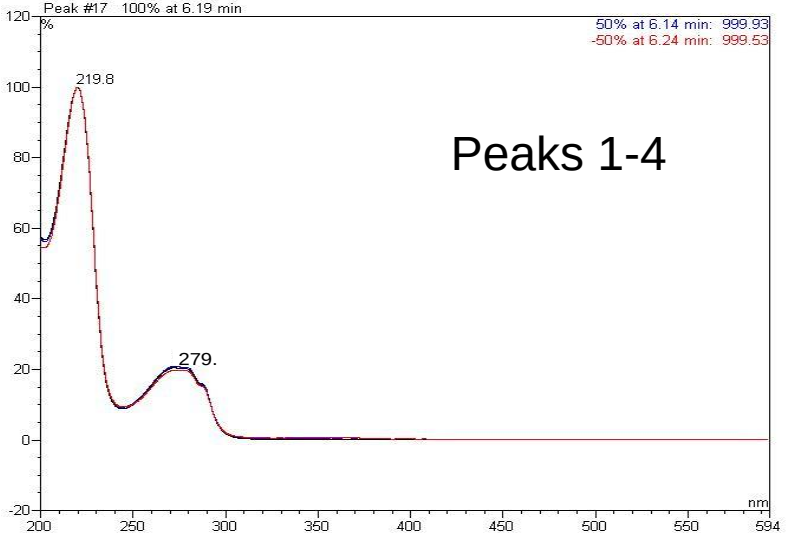
Alpha-Methyltryptamine (AMT)





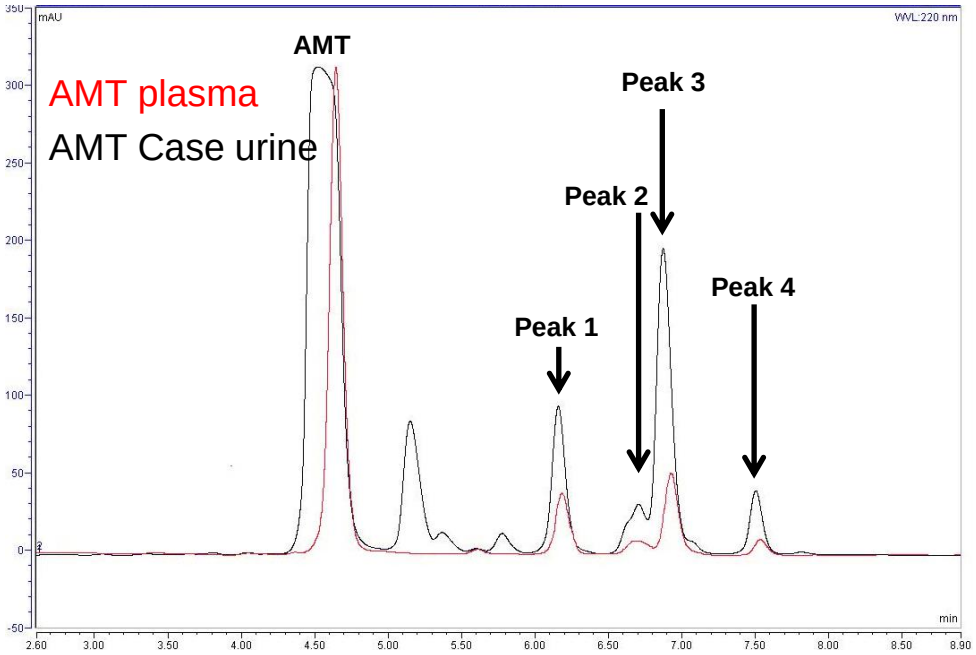
AMT plasma (instability incubate)

AMT Case urine

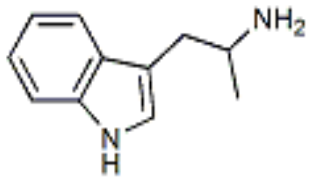


Peaks 1-4

Alpha-Methyltryptamine (AMT)



- AMT decreased day 0 to day 7, constant to day 28.
- Peaks 1 and 2: present at the same comparative levels for the entire 28 days of study.
- Peaks 3 and 4: 40% increased in relative concentration between day 0 and day 7 and then remained constant today 28.



AMT [M+H]+ calculated 175.12297 ($C_{11}H_{14}N_2$), m/z 175.12222 found
Fragmentation to m/z 158.09601, 143.07280, 130.06441

Peak 1 215.15404 m/z with fragments at m/z 172.11188, 157.08814, 144.08043 ($C_{14}H_{18}N_2$ and fragments $C_{12}H_{13}N$, $C_{11}H_{10}N$ and $C_8H_{19}N_2$)

Peaks 2-4 229.17021 m/z with fragments at m/z 186.12783, 144.08017 ($C_{15}H_{20}N_2$ and fragments $C_{13}H_{15}N$ and $C_{10}H_9N$)

CONCLUSIONS

- 6-APB, MPA, 5-MAPB, 25C-NBOMe, AH-7921, MDAI, 2-AI, 5-IAI and MDAT showed stability in blood and plasma after 28 days and after 37 days for methoxetamine and 5-MeO-DALT.

- Any additional compounds seen in casework, therefore likely metabolites and not breakdown products (e.g. AH-7921, 25C-NBOMe, methoxetamine)

- Could extrapolate results to other drugs in the groups (e.g. aminoindanes, APBs, NBOMes)

- 4-MEC showed significant degradation with a higher rate of decrease in the blood compared to plasma. Specifically, 92% loss by day 7 with complete degradation by day 14 in blood. Dihydro-4-MEC breakdown product did not account for the proportional degradation.

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Reference

- Yan Ni Annie Soh and Simon Elliott, "An investigation of the stability of emerging new psychoactive substances", Drug Testing and Analysis
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