THE TOX LAB

Podcast Transcript

Episode 2: Semi-Synthetic Cannabinoids and N-Ethylhexedrone

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TRANSCRIPT

Hi everyone, welcome to The Tox Lab. I'm Rebecca.

I'm Rob. Today we're talking about three things: the UK drug-related death statistics for 2023, a paper on semi-synthetic cannabinoids found in cannabis products in Denmark, and a case series on N-ethylhexedrone.

Before we start, you said you had some banter.

I did, although I am not convinced it was good banter. Why did the toxicologist cross the road?

I have no idea.

To work out the real reason the chicken was dead.

That is terrible. Let's move straight on.

So the first topic is the new drug-related death statistics. What stood out to you?

Mainly that the numbers have gone up again. The Office for National Statistics reported 93 deaths related to drug poisonings per million people in 2023, compared with 84.4 per million in 2022.

So roughly a 10 percent increase.

About that, yes, and that is a substantial rise.

It is worth clarifying what these figures do and do not show. These are official mortality statistics, but when they break deaths down by drug, that only includes cases where a specific named substance was recorded. So if the cause of death is given more generally as mixed-drug toxicity, it may count toward the overall total but not necessarily toward the count for a specific drug.

Exactly, and that means people need to be careful with some of the headlines. I have seen a lot of reporting suggesting that cocaine is driving the increase in drug deaths, but this dataset cannot really prove that. It only tells you how often cocaine was mentioned on the death record, not whether it was the main cause of death.

And in many cases cocaine may simply be one of several detected drugs, alongside heroin, methadone, benzodiazepines, or a novel opioid.

That said, the cocaine trend is still striking. The graph is steep, and the increase over time is very clear, particularly in men.

Yes, and although the rise is less dramatic in women, the same broad trend is there. It probably reflects how normalised cocaine use has become in UK culture.

It is also probably relevant that cocaine remains relatively cheap and accessible compared with many other things.

Meanwhile, the opioid figures are also concerning. Deaths involving opiates or opioids rose from 39.1 per million in 2022 to 43.8 per million in 2023.

Which may reflect the impact of novel synthetic opioids, including nitazenes, although this specific dataset is not detailed enough to prove that on its own.

No, but it certainly fits with what we have been seeing elsewhere.

Another limitation is the delay. This is 2023 data and we are already close to 2025 as we record this, so there is always a lag between what is happening in the market and what the official statistics show.

That is one of the frustrating things with drug death data. It is valuable, but it is retrospective by nature.

I was also surprised by the benzodiazepine breakdown. Some novel benzodiazepines are mentioned by name, but bromazolam did not seem to feature in the way I expected, which I thought was interesting.

Yes, that stood out to me as well. I am not sure whether that reflects classification, reporting practice, or something else, but it would be worth looking into more closely.

So we will probably come back to these figures in more detail another time.

Definitely.

Let's move on to the paper on semi-synthetic cannabinoids. The title is The emergence of semi-synthetic cannabinoids in cannabis products in Eastern Denmark over a six-year period.

Do you want to start by explaining what we mean by semi-synthetic cannabinoids?

Yes. These are cannabinoid compounds derived from naturally occurring phytocannabinoids, but chemically modified. So they are related to compounds from the cannabis plant, but they are not simply the natural plant constituents as found in ordinary cannabis.

And the reason this market has grown is partly because CBD has become very widely available as a result of the legal hemp and wellness industries.

Exactly. CBD is now cheap and abundant, and that makes it a useful starting material for producing modified cannabinoids that may be more psychoactive or may sit in a legal grey area.

What are some of the main examples?

One of the earliest big ones was delta-8-THC, which became prominent in the US around 2019. Then you have compounds like HHC, THCP, HHCP, H4CBD, HHCB, and a range of others, including acetate derivatives.

And one of the key problems is that we do not know very much about the pharmacology of many of these compounds. We assume they act at CB1 and CB2 receptors in broadly similar ways to THC, but the evidence base is limited.

Yes, and there are also suggestions that some structural changes can increase potency. For example, longer side chains in certain THC analogues may increase receptor activity, and some HHC epimers may be more potent than others.

That is where the risk comes in. With the fully synthetic cannabinoids, the SCRAs, we learned that stronger receptor activity can produce severe and sometimes very unpredictable toxicity, including seizures, agitation, psychosis, and cardiovascular problems.

So if semi-synthetic cannabinoids become more potent than natural THC, we could end up seeing some of the same issues.

Exactly.

So what did this paper actually do?

The authors looked at 1,441 seized samples collected between 2018 and 2023 in Eastern Denmark. They analysed them by GC-MS and tracked which semi-synthetic cannabinoids were present, how often they appeared, and how that changed over time.

What proportion of samples were positive?

Fifteen percent of all seized materials contained at least one semi-synthetic cannabinoid, and the proportion increased over the six-year period.

That is quite a lot.

It is, especially because many labs are probably not routinely looking for these compounds yet.

What did the time trends look like?

Delta-8-THC first appeared in the third quarter of 2019, then was not seen again until the third quarter of 2021. HHC appeared in the first quarter of 2021 and then became more common, rising steadily until the second quarter of 2023 before dropping sharply in the third quarter of 2023.

And that decline probably reflects regulation.

Yes. HHC was scheduled in Denmark in May 2023, so it makes sense that it declined after that point. It suggests the market shifted toward other compounds once HHC became controlled.

That is a pattern we see repeatedly with novel psychoactive substances. One compound gets controlled, and the market moves on to another analogue.

Exactly.

One thing I found striking was the product types involved. The positive samples were not just obvious oils or vapes. A large proportion were plant materials.

Yes. Of the positive samples, 41 percent were plant material, 27 percent were edibles, and around 10 percent were concentrates or e-cigarette products.

Which suggests some products may effectively be CBD-rich plant material fortified with semi-synthetic cannabinoids.

That is the likely interpretation. It gives the appearance of cannabis flower, but the psychoactive effect may be coming partly or mainly from the added compound.

It makes me think we probably need comparable data from the UK.

I agree, although I do not think anyone is collecting it systematically at the moment.

No, and analytically that is a problem. If you are not looking for these compounds, you are not going to find them.

Exactly. They may already be more prevalent than we realise.

Any final thoughts on that paper?

Mainly that it is a useful early surveillance study and a reminder that the cannabis market is not static. The legal and semi-legal cannabinoid space is generating a lot of new compounds, and toxicology needs to keep up.

Agreed.

So let's move on to the second paper: N-Ethylhexedrone: a very long and bad trip. A case series.

Excellent title.

It is a very good title. First of all, what is N-ethylhexedrone?

It is a synthetic cathinone, so a stimulant in the same broad family as compounds like mephedrone.

Cathinones really emerged in the late 2000s and early 2010s as alternatives to established stimulants such as amphetamine, MDMA, and cocaine. N-ethylhexedrone appeared in Europe around 2016 and became fairly prevalent in some markets quite quickly.

Yes, and in some regions it was reported as one of the more common novel stimulants during that period.

Pharmacologically, cathinones are typically active at monoamine transporters, especially dopamine and norepinephrine transporters. Some also have serotonin activity.

And for N-ethylhexedrone specifically, this paper notes that in vitro it is more potent at the dopamine transporter than at the norepinephrine or serotonin transporters.

There are also animal data suggesting it has locomotor stimulant effects broadly comparable to cocaine, although not as strong as methamphetamine.

So what did the case series look at?

Three patients who presented to hospital with N-ethylhexedrone detected. The authors were interested both in the clinical presentations and in the metabolites that could be identified over time.

Which metabolites did they report?

They identified four: reduced NEH, dealkyl-NEH, reduced dealkyl-NEH, and hydroxy-NEH.

All four were found on day 1 in blood and urine across the three cases. Hydroxy-NEH and dealkyl-NEH were no longer detectable by day 4, whereas reduced dealkyl-NEH was still detectable in blood at day 10.

That is interesting, because it suggests there may be a relatively prolonged analytical window for at least some metabolites.

Yes, and it may also help explain the prolonged toxicity described in the paper.

What did the patients look like clinically?

They were all quite unwell. The paper describes reduced consciousness, confusion, disorientation, and in one case seizure activity. One patient developed coma. The broader adverse effects discussed include tachycardia, hallucinations, paranoia, depression, and insomnia.

Insomnia is an important feature with some stimulants like this. People can be awake for very long periods, redose repeatedly, and then eventually present to hospital after several days of deterioration.

Yes, and the paper's title reflects that prolonged course. This was not a short-lived stimulant intoxication in the simple sense.

There was also discussion of hypothermia and SIADH in at least one case, which is interesting because those features can make you think about MDMA-like mechanisms or broader monoaminergic effects.

Exactly. It raises the question of whether the parent drug is the whole story, or whether some metabolites may also contribute pharmacologically.

That is speculative, but it is plausible, especially when you have prolonged stimulation and delayed recovery.

Analytically, there is another problem, which is that some of these metabolites may overlap structurally with those of other cathinones. So if a lab has limited reference standards or is relying on partial information, interpretation can get messy.

Yes, and that is a good reminder that novel stimulant casework is not just clinically difficult, but analytically difficult as well.

Did the paper say much about dose and route of administration?

It did. Typical reported doses were in the tens of milligrams, around 50 to 60 milligrams, with routes including insufflation, smoking, and intravenous use. Intranasal use was associated with rapid onset, with peak effects reported at around 25 minutes and a duration of around two to three hours.

Which helps explain why people may redose frequently.

Exactly, and repeated dosing is where the risk escalates.

What is your main take-home from this paper?

For me, it is that N-ethylhexedrone may produce prolonged and quite severe toxicity, and that metabolite monitoring is likely to be important if you are trying to understand those cases.

I would agree. It is also a useful reminder that compounds which are no longer making headlines may still matter in clinical and forensic toxicology. Markets change quickly, but old substances can reappear.

Absolutely. Novel drug markets are cyclical. Compounds disappear, then re-emerge when someone still has stock or when a supply chain changes.

Any final thoughts before we wrap up?

No, I think that covers it.

Same here. Thanks for listening, everyone. Have a great week.

Take care, and we will see you next time.