Episode 77: Novel Synthetic Opioids - An Update on Emerging Trends

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Transcript

Hi everyone, welcome back to the Tox Lab. I'm Rebecca. I'm Rob. This week, we're gonna be taking a look at a subject that quite a few people have actually reached out to us and asked us to do an update on. And that is the subject of novel synthetic opioids.

And this week, we're gonna be doing an update on what has changed over the last few months and where we think things might be going in the future. And before we dive into the science this week, we do want to give a big shout out to this week's episode sponsor, Cayman Chemical. Cayman Chemical provide a wide range of resources for toxicology and forensic professionals. And in particular, we really want to mention their Synthetic Opioid Analytical Standards Panel.

This is a single product that contains 250 reference materials. And that includes a wide range of synthetic opioids, including fentanyls and some of the newer compounds like nitazenes as well. All available as a single 96 well plate. We'll put a link in the description.

Do go and check it out. So Rebecca, where do we start on this update? Where should we begin? So on the 24th of April this year, the UNODC published an announcement on unexpected forms of synthetic opioids.

Between 2024 and 2026, 12 countries reported 2,679 synthetic opioid samples to the UNODC early warning advisory. Nitazenes were most frequently detected in tablet form followed by powders while orphine analogs were more commonly reported as powders. So a lot of these things are things we've mentioned in the past, but really just a quick primer. Nitazenes are novel opioids that have increased in their prevalence.

And now we're starting to see the orphine compounds. They are their own class. And these are chemically different from nitazenes. A lot of these classes of compounds were first synthesized in the 1950s and 60s.

Subsequently were never approved for therapeutic use and are now starting to emerge in forensic toxicology casework. They're appearing in black market drug supplies. And this UNODC report really highlights the forms that they are coming in. One of the more unusual forms that synthetic opioids have been seen in is in vapes.

There was a notice from the Bavarian police released on the 25th of March this year where two deaths and two intoxications were reported in Bavaria associated with vapes containing the synthetic opioid, eta-de-zitramide. There have also been nytrazine adulterated vapes seen in Australia. So in late 2024 in New South Wales, three individuals presented with severe opioid withdrawal symptoms after cessation of prolonged use of illicitly sourced vape liquids. There was also one death and two emergency department attendances in 2023.

And two of them were expecting cannabinoids but got nytrazines instead. And in August, 2025, a 20 year old in New South Wales was charged with commercially supplying a vape liquid containing nytrazines, who's marketing these as supercharged vape liquids and 2.1 kilos of nytrazines were recovered. I mean, there is so much going on here, isn't there? We've talked a lot about vaping and

how vaping has emerged, not just as a popular alternative to traditional smoking but actually how it is becoming a novel way of delivering drugs.

And the idea of nytrazines being present in vapes really does worry me a bit. But I think perhaps for me, the bigger concern here is not just that there are nytrazines in vapes but that these vapes were not being sold as nytrazine vapes. People thought they were buying cannabinoid vapes. Yeah.

And two kilos of nytrazine is just so hard to comprehend given the potency of these nytrazine compounds and that potentially a single milligram or less could be a dose. A kilo is a million doses, potentially we're looking at 2 million doses here. It's insane. So nicotine vapes have been tightly controlled in Australia and up until 2024, nicotine vapes were only available with a prescription.

Since October 24, access to legal nicotine vape products have been limited to domestic pharmacies sold solely for smoking cessation and there have been controls on devices and flavors. And because of this really tight control over nicotine vape products in Australia aiming to control the youth vaping epidemic, 96.1% of individuals who vape in Australia source their nicotine vape products from the black market and are therefore more at risk of purchasing adulterated vapes.

These nicotine vape products typically contain significantly higher concentrations of nicotine than those products that are produced in controlled environments and 4.2% of samples on average were adulterated with hazardous substances. I think this is a classic case of an unintended consequence, isn't it? I can appreciate entirely why people would consider controls if you've suddenly got a youth vaping epidemic, you restrict access and you just push the market underground into a market that's much less regulated.

The concerns you raised about nicotine dose is bad enough but then when you factor in supercharged vapes actually containing nitazenes, suddenly it gets a whole lot worse. I wanna circle back a little bit to the German article you mentioned about Etodesitramide in vapes. Now Etodesitramide is an orthina analog. Currently we don't know very much about its relative potency or toxicity potential or anything like that at the moment but it is likely that it is a significantly potent opioid based on its chemical similarity to other orphine compounds.

And so you've got a situation here where you've got a brand new drug emerging in an unregulated market. Even we don't know how potent it is or what it's capable of. Here it is being sold on the street. Antifit benzodiazepines containing synthetic opioids have been spotted in Switzerland, the UK and Australia.

These are frequently being sold as Alprazolam or diazepam. In Germany in February of this year, there have been reports of deadly yellow tablets containing cyclothine and methiodone being sold as Alprovisofone tablets. And methiodone, which is also known as IC26 or WIN1161-3 is a structural analog of methadone where the carbonyl group is replaced with the sulfone group. So again, there's a lot going on with this report.

The compound it was claiming to be, Alprofirezone, it's really unclear what that's supposed to be. There's some chatter on some German Reddit pages where it suggested that this is being marketed as an Alprazolam analog or an Alprazolam prodrug. I can't even see that it's really an established chemical name. Although I don't speak German, I could be missing something.

So it's not necessarily even being marketed as a fake prescription pharmaceutical, but it is possibly being sold as a research chemical in its own right. And yet contains two different research chemicals, neither of which are benzodiazepines. Cyclothine is another orphine analog and we'll talk a bit about cyclothine in a little bit. Methiodone is interesting.

This is an analog of methadone. Now, methadone has its own toxicity risks. In particular, it's very long acting. We don't know if we know how long acting methiodone is currently, but long acting opioids can carry with them quite significant accumulation risks and redose risks.

So it's possible here that we have got quite a risky combination. And I think as we've mentioned many times in this podcast, the appearance of novel opioids in benzodiazepines is the bit that scares me the most because those who are looking for benzodiazepines aren't expecting to come across an opioid. Yeah, it's particularly risky in people who are perhaps regular users of benzodiazepines because they may have a degree of tolerance to benzodiazepines and therefore take more tablets than one should. And if what it contains isn't what you thought it was, that could have fatal consequences.

Impregnated papers found in correctional facilities containing nitazenes alongside scars have been detected in the US in 2023. Plotting papers in Germany in 2025 were also found to contain orphines and nitazenes. This is a concern, isn't it? We've been seeing impregnated papers for smuggling drugs into prisons for quite a long time.

Traditionally, it was synthetic cannabinoids, scars. Now we're starting to see it with opioids as well. Novel opioids have also been seen in powders thought to be all mixed in with cocaine in both North America and Australia. And we've also seen novel opioids in powders that are sold as heroin, which I felt like is less of a surprise.

Yep, so the appearance of novel opioids in more traditional street drugs. Its appearance in heroin is I think perhaps unsurprising given what's been going on in Afghanistan and the general global opium shortage. And therefore people stretching heroin stocks further by diluting it and then adding potent novel opioids. Its occurrence alongside cocaine is I think perhaps a little bit more concerning in the sense that whilst there will be some overlap between people who use cocaine and people who use heroin, quite a lot of people who use cocaine will only use cocaine and may not have opioid tolerance or indeed a desire to take opioids.

An N. pyrrolidino protonitocine, which is a nitticine has been spotted in MDMA tablets in Brazil, which is also quite shocking. I think that is perhaps the most shocking of all actually. The presence of nitazenes in MDMA tablets is particularly concerning, again, similar to the cocaine, you know, very different markets. Most likely individuals who procure MDMA tablets are not expecting opioids.

There have also been a range of opioids found in fake oxycodone tablets. And these have often been described as being in blue-green pills and they've contained a range of opioids, including carfentanil and that was quite a recent spot in the U.S. and a range of nitazenes including n. pyrrolidino iced nitticine. Carfentanil, one of the most potent opioids known. The idea that what can appear to be a pharmaceutical opioid tablet.

And some of these are really convincing, aren't they? Foiled blister packs sometimes that look for all intents and purposes to be prescription oxycodone actually containing these novel opioids. So we've recently published a paper looking at a cluster of places where n. pyrrolidino iced nitticine was detected and was thought to be in these blue-green tablets. But we will link that in the episode description below if anyone wants to have a read.

So a bit closer to home, the Advisory Council for the Misuse of Drugs in the U.K. has recently put out an addendum report looking at the rise in orphine opioids in the U.K. So this was the seventh addendum to the report published on the 30th of April, 2026. There have been 15 confirmed deaths where orphines have been involved since spring of 2025. And cyclothine and spiroclothine were the most commonly involved.

Other orphines detected in the U.K. include chlorphene, cyclothine, spiroclothine, 5,6-dichloro-desmuthylchlorphene, etodizitramide, spirobralphene, and 5,6-dichloro-bralphene. We do need to come up with a better naming convention. It's really confusing. Some data from the National Program on substance use mortality have found 14 cases of orphines with 11 detections involving cyclothine and three involving chlorphene.

So orphine opioids are here in the U.K., and they are clearly, sadly, killing people, being implicated in more and more deaths. I think another factor here to think about, though, is it isn't just, again, one compound. We're seeing a range of compounds detected, aren't we? Yeah.

The N-prophonitrile chlorphine, or cyclothine, has also been spotted in the U.S. The CFSRE, or the Center for Forensic Science Research and Education, put out a public alert on the 30th of January this year, and in that they had identified N-prophonitrile chlorphine in 25 blood specimens from fatal overdoses between late 2025 to early 2026. It's also been tentatively identified in over 100 toxicology cases at NMS labs, and the toxicology samples collected came from eight U.S. states, including New York, California, Illinois, Nevada, Pennsylvania, Tennessee, Texas, and Louisiana, and it's also been seen in three provinces in Canada.

It been detected as the sole opioid in 11 out of the 25 cases, but also found alongside other opioids like fentanyl and stimulants, such as methamphetamine and cocaine. So cyclothine, or N-prophonitrile chlorphine, has also now made it across to the U.S. It's also been co-detected with other NPS, such as novel benzos, including phenazepam, and other ophine analogs, such as spirochlorine, anitidine analogs, and carfentanyl.

Now, there's not a lot known currently about things like potencies of these compounds, and there's obviously not a lot yet published in things like the post-mortem literature relating to ophines, but we have managed to find a fairly short case report, haven't we? Yeah. The 36-year-old man was found unconscious on the bathroom floor with a GCS of three, and he was not breathing. Law enforcement officers attended and gave four milligrams of naloxone intranasalie with a partial response, and emergency medical services gave another one milligram of naloxone intranasalie.

On arrival to the emergency department, he was rousable, but was bradycardic with a heart rate of 53 beats per minute, and he was hypothermic. He refused all clinical investigations, including toxicology testing. The patient had stated that he had snorted what he believed to be alprazolam prior to his collapse, and crime scene investigators found a purple glove containing a headphone case and a small black plastic bag with a tan, crystallized powder. DCMS identified the presence of xylazine, vencinil, and cyclophene, and cyclophene was the predominant substance found in this case.

Not an awful lot, really, to go on with this case, but it does show the sort of typical presentation of the things we've been saying. Compounds appearing in the form that they're perhaps not expected, in this case, potentially alprazolam tablets, very rapid collapse, and classic opioid symptoms. Crucially, in this case, naloxone was given, and he did appear to have some naloxone response. We've talked about naloxone and novel opioids in the past.

Back in episode 61, if you wanna go and check that out. So that is a bit of a summary of what we know currently with regards to the current state of the novel synthetic opioid situation. I wanna now look at what we don't know, because I think this is perhaps a bigger question. I feel like we don't know more than we do at this point.

We don't really have much data to go on at the moment on potency of a lot of the olefins. So let's unpack that one to begin with. So potency of the olefin compounds. Currently, there's very little published data, isn't there?

There's some on broughin, which we've talked about in the past. The indications are they're likely to be very potent, but currently, in terms of how many orders of magnitude, we just currently really don't know. So as well as data on potency for broughin, we do have some potency data from cell-based assays for chlorothine, iodorothine, fluothine, and olefin, I believe. But there isn't any potency data as of yet for the cyclothine or the N-propionitrile derivatives, or the desertramide group, either, as far as I'm aware.

So having that will be quite valuable in allowing us to interpret our findings in post-mortem work and in clinical work as well. The other thing we don't really know anything about is how stable these are. I think that's a fair point. Stability is currently unknown.

We learned that nitazenes weren't particularly stable in the post-mortem interval. It remains to be seen whether orphines are more or less. There might be some hidden potency data. I was just thinking actually in the old Janssen patents.

Well, there might be. So some of these compounds are not new. Some of these compounds were synthesized, similar to nitazenes, in the 50s and 60s as potential experimental medicines that never saw use clinically. So there might be some potency data that was derived back when these compounds were first described.

So all in all then, the novel synthetic opioid world is getting more complicated, not less complicated. Yeah. In essence, the number of compounds keeps going up. And another point actually to bring up here is that old ones are not really disappearing.

No, they're not. That is a good point. New ones keep emerging, but the old ones do still keep cropping up from time to time. That is a really good point.

And with the scope of novel opioids that need to be lit for increasing, it becomes so much harder to stay on top of what is out there. And for a lot of labs, it's quite hard to keep an up-to-date library of all of these new and emerging compounds, depending on the bits of kit people have got. So there's every chance we're missing a whole load of cases. That's very true.

I mean, we are virtually always going to be behind the game, aren't we? Yeah. We're always responding to the market, not getting ahead of the market. I think one of the big things that we don't know regarding these, and this applies to the nitazenes as well as the new orphines now, is we really don't know the true prevalence.

You've mentioned the stability, and we don't know how stable they are. We don't know how many cases are occurring whereby nitazenes are either present and not detectable because they're not stable, or they're not tested for at all because either the methodology wasn't in place or the right compound wasn't in the library or the case just didn't fit the circumstances enough.

And then you look at what we've talked about today, this whole host of new chemicals, this whole host of new compounds, combine that with a whole host of new ways of these opioids being present in the drug supply, we're only going to underestimate more in the future, right? Yeah. The harder it gets, the harder it will be to target our testing. And I think because we're always responding, early cases may always slip through the net.

It's only when people start reporting compounds widely to people start to update their libraries, do you start to get better prevalence estimates. So for some of these really unusual compounds you've described, it's chicken and egg situation, isn't it? Yeah. Because on the one hand, there's not enough cases to justify the investment in updating your screening library.

On the other hand, if you're never looking for it, you'll never know how many cases there really are to justify updating your screening library. Another thing that we don't really know is how a lot of these double opioids are metabolized. There is a bit of work that we've done for some of the nittucine compounds looking for common metabolites that people can add to libraries to increase detection. But the same isn't known for a lot of the orthemes.

That'd be a really interesting area of research to see how they're broken down and whether there are common metabolites that people can look for. And help sort of make screening more efficient. Yeah. To add further complications to that, actually, some of the orthene compounds are actually pro-drugs.

The compound you detect in a street mixture is converted to an active drug in the body. So that, again, adds even more complexity to some of this. So we've talked about what we know. We've talked about what we don't know.

I guess we should look at perhaps an even bigger unknown. And that is, where are we going? What do you think the future holds? Oh, that is a good question.

I think orthene's are definitely gaining in popularity. So I'm thinking we're going to see more orthene's and more orthene analogs. I don't think nittesene's are going to go anywhere anytime soon. I do think we'll start seeing the same ones occurring and a little bit less variation.

It's my prediction. I could be completely wrong. We all have to see. I think that's fair.

I think one of the things we haven't talked about is international control. And there was a class-wide ban in China on nittesene compounds. We have now seen the rise in the orthene's that dodged that ban. But whether things will loop back around and we will see older nittesene's again, I think that's a real possibility.

And as you say, perhaps there's undiscovered nittesene analogs that still haven't quite made it to us yet that might occur. So I think you're right. I think it's going to get more complicated, not less complicated. Oh, for sure, yeah.

And I think the same is true of the different forms that these compounds are coming in. I think gone are the days where all opioids look like heroin and all benzos were benzos. Yeah. I think now it's a real mix of everything.

So I do hope you've enjoyed listening to us this week and that you found this update useful. Do go and check out our sponsor, Cayman Chemicals. Thank you again for sponsoring this episode. Do go and check out their synthetic opioid analytical standards panel.

And as always, if you have enjoyed listening to us this week, do give us a like, give us a follow, give us a share. Hope you all have an amazing week and we'll see you next time. Bye.