The Tox Lab

Episode Transcript
NSO Update

Edited transcript

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Clean Transcript

I'm Rob. This week we're going to 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 going to be doing an update 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 provides 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 2679 synthetic opioid samples to the UNODC early warning advisory. Nitazenes were most frequently detected in tablet form followed by powders while orphine analogues 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. They've 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 synthesised 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 etodezitramide.

There have also been nitazene 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 in two emergency department attendances in 2023 and two of them were expecting cannabinoids but got nitazenes instead. In August 2025 a 20 year old in New South Wales was charged with commercially supplying a vape liquid containing nitazenes. He was marketing these as supercharged vape liquids and 2.1 kilos of nitazenes 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 nitazenes 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 nitazenes in vapes but that these vapes were not being sold as nitazene vapes. People thought they were buying cannabinoid vapes and two kilos of nitazene is just so hard to comprehend given the potency of these nitazene compounds and that potentially a single milligram or less could be a dose.

A kilo is a million doses potentially we're looking at two 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 amine to control the youth vaping epidemic 96.1% of individuals who vape in Australia source then 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 in 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 supercharge vapes actually containing nitazenes suddenly it gets a whole lot worse. I want to circle back a little bit to the German article you mentioned about etodezitramide in vapes. Now etodezitramide is an orphine analogue?

Yeah. 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. Counterfeit 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 yellow tablets containing cychlorphine and methiodone being sold as alprazolam tablets.

And methiodone which is also known as IC26 or when 1161-3 is a structural analogue 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 alprazolam. It's really unclear what that's supposed to be. There's some chatter on some German reddit pages where it's suggested that this is being marketed as an alprazolam analogue or an alprazolam pro drug. 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. Cychlorphine is another orphine analogue and we'll talk a bit about cychlorphine in a little bit. Methiodone is interesting. This is an analogue 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 uses 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 SCRAs have been detected in the US in 2023. Blotting papers in Germany in 2025 were also found to contain orphines and nitazenes.

Yeah, 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, SCRAs. Now we're starting to see it with opioids as well. Novel opioids have also been seen in powders thought to be or 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 was less of a surprise. Yep, so the appearance of novel opioids in more traditional street drugs. It's 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. It's 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 protonitazene which is a nitazene 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 and 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 cough and so on. That was quite a recent spot in the US and a range of nitazenes including N-pyrrolidino protonitazene. 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 cases where N-pyrrolidino protonitazene 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 UK has recently put out an addendum report looking at the rise in orphine opioids in the UK. 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 cychlorphine and spirochlorphine were the most commonly involved. Other orphines detected in the UK include chlorphine, cychlorphine, spirochlorphine, five-six, dichloro, desmethylclophine, ethydezitramide, spirobrorphine and five-six dichlorobrophine. We do need to come up with a better name in conventions. It's really confusing. Some data from the national programme on substance use mortality have found 14 cases of orphines with 11 detections involving cychlorphine and 3 involving chlorphine.

So orphine opioids are here in the UK 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-propionitrile chlorphine or cychlorphine has also been spotted in the US. The CFSRE or the Centre 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-propionitrile 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 has 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 cychlorphine or N-propionitrile chlorphine has also now made it across to the US. It's also been co-detected with other NPS such as novel benzoes including phenazolam, another orphine analogue such as spirochlorphine, a nitazene analogue and carfentanil. 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 orphines but we have managed to find a fairly short case report haven't we? 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 intranasally with a partial response. An emergency medical services gave another one milligrams of naloxone intranasally. 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. When crime scene investigators found a purple glove containing a headphone case and a small black plastic bag with a tan crystallised powder. The LC-MS identified the presence of xylazine fentanyl and cychlorphine and cychlorphine was predominant substance found in this case. Not an awful lot really to go on with this case but it does show a 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 want to 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 want to 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 orphines. So let's unpack that one to begin with. So potency of the orphine compounds. Currently the very little published data is another sum on brorphine. Which we've talked about in the past. 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 brorphine, we do have some potency data from cell-based assays or chlorphine, iodorphine, fluorofine and orfine I believe.

But there isn't any potency data as of yet for the cychlorphine or the N-propionitrile derivatives or the desitramide 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, I might be. So some of these compounds are not new. Some of these compounds were synthesised 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's a good point. New ones keep emerging, but the old ones do still keep cropping up from time to time. That is a really a 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.

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 a tool 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 they really are to justify updating your screening library. Another thing that we don't really know is how a lot of these other opioids are metabolised.

There is a bit of work that we've done for some of the nitazene 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 orphines. So 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 orphine 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 talked about what we know, we 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? That is a good question.

I think orphines are definitely gaining in popularity. So I'm thinking we're going to see more orphines and more orphine analogues. I don't think nitazenes are going to go anywhere anytime soon. I do think we'll start seeing the same ones occurring in a little bit less variation. It's my prediction.

I could be completely wrong. We will 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 nitazene compounds. We have now seen the rise in the orphines that dodged that ban. But whether things will loop back around and we will see older nitazenes again. I think that's a real possibility.

And as you say, perhaps there's undiscovered nitazene analogues 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 benzodiazepines were benzodiazepines. 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 Chemical. 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.