Episode 39: Plastic in the Fentanyl - Why should we care about BTMPS?

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Transcript

Welcome back to the Tox Lab. I'm Rebecca. I'm Rob. This week we're looking at something really strange, turning up in fentanyl samples across the US. And this is a compound called BTNPS.

It's not a drug, rather a plasticizer and a UV stabilizer. It was designed to keep plastics from degrading in the sun, but in cities like Los Angeles and Philadelphia, this stuff is turning up in as many as half the samples labeled as fentanyl. And in some of these cases, there's more BTNPS present in the sample than fentanyl by weight. So today, we're asking the questions, what is BTNPS?

Why is it here? Is it active? Is it dangerous? Is this just contamination?

Or is this something bigger? And before we jump in, I want to give a big shout out to our fellow Tox Podcasters, the Tox Pod. They recently talked about BTNPS in an episode a couple of months back and inspired us to cover it. Yeah, massive shout out to the Tox Pod.

They've been really supportive of us. So if you haven't already and you like toxicology podcasts, do check them out. If you want to stay up to date with our content, you can find us on Instagram at @the_tox_lab. We also have a page on LinkedIn, which we post on quite regularly.

And for those of you who don't use social media, but want to get in touch with suggestions or comments, you can email us at thetoxlab@gmail.com. So what is BTMPS? Well, its full name is a bit of a mouthful. This 2,2,6,6-tetramethyl-4-piperidyl sebacate, and it's commonly referred to by its trade name, which is Tinuvin 770.

And this is a fairly widely available industrial chemical. It's used as a UV stabilizer in plastic production. So you often then add it to plastics to basically prevent UV degradation, to stop UV causing damage to the plastics and make plastics last longer. And its structure is quite interesting.

It features two substituted piperidine rings chemically similar to the core of fentanyl. And we'll come back to this point a little bit later on, but really it's sore use in the industrial plastics industry. But I hear you ask, why are we talking about an industrial plasticizer on a toxicology podcast? Well, about a year or so ago, something very, very interesting happened.

And that was, it started appearing in the US drug supply. So we've talked a little bit in the last few weeks, haven't we, Rebecca, about contaminants in the drug supply and adulterants. We've talked about xylazine and medetomidine. We've talked a bit about novel opioids, nitazenes.

BTMPS is none of those things. And yet it was also appearing in the US drug supply. So Rebecca, why don't you take us through a recent paper that came out talking about the presence of BTMPS. So this paper is focused on the Philadelphia street opioid supply between March 2024 and March 2025.

260 dope samples from people who use drugs in the Kensington street market area of Philadelphia were sampled between March 2024 and March 2025. So specifically looking at dope, also known as tranq dope, so that's fentanyl with or without the presence of xylazine. Those using harm reduction programs in this area were invited to participate if they were in possession of dope at the time. And

they collected one sample per bag of dope and were looking at bags with unique stamps on them so they could identify where in this area they were coming from.

And the population we're looking at in this area, 62% white, 67% male, 83% of people who are involved in these programs are unhoused. And basically 10 milligrams of powder was taken, put in vials containing about half a mL of acetonitrile, and then sent to the NIST lab for testing, who analyzed these samples using Dart MS. And so Dart MS is direct analysis in real-time mass spectrometry. Samples sent after the 28th of April 2024 were quantitatively analyzed using LC-MS and components were reported as percentage by mass, and important to note not all components were quantified.

So out of the 260 samples that were looked at, there were 129 unique stamps. Fentanyl was present in 98% of samples, xylazine was present in 65% of samples, and the median concentration by mass was between 4% for fentanyl and 3% for xylazine, but there was lots of variation in this data set. From March 2024 to March 2025, the median fentanyl concentration did decrease from 9.6% by mass to 5.3%. In March 2024, xylazine was present in 100% of samples, and that did decrease to 58% of samples in March 2025.

Lidocaine and Tetracane did become more prevalent, increasing from about 3% of samples to 63% of samples, and medetomidine, which we've talked about previously, started appearing in April 2024. In June 2024, BTMPS started appearing on the scene, and by the end of the study period, 25% of samples contained BTMPS. So an article published in JAMA also looked at a similar thing and displays data from samples obtained from nine community drug checking programs across LA and Philadelphia.

They also include data from trace residues from a wipe of use paraphernalia obtained from two counties in California, Delaware, Maryland, Nevada, Washington and Puerto Rico. And their data spans 1st of June 2024 to the end of September 2074, with LA continuing into October 2024. And again, all of these samples were sent to the NIST lab for DART-MS analysis and quantitative analysis using LC-MS. 284 drug samples were collected from LA and Philly, and 98 or 35% of these contained BTMPS.

And this did increase from across the study period. So in June in LA, no samples contained BTMPS. This increased to about 56% of samples in September, and there was a slight drop off to 50% in October. And in Philadelphia, 25% of samples in June contained BTMPS, and this increased to 32% by September.

There were 486 trace samples collected as well, and BTMPS was identified in 13% of these. And this again increased from 3% in June to 32% in September. From the 98 drug samples that they had that contained BTMPS, the mean percentage by mass of BTMPS was 8.6%, and this varied quite widely from 0.1% to 56%. In those samples that contained BTMPS, the mean percentage of fentanyl by mass was also significantly lower, and was around 3.1% in samples that contained BTMPS versus 8.7%, which was typical for those without.

And a similar trend was seen in samples containing other drugs such as fluoro fentanyl, xylazine, 4ANPP, and lidocaine. And interestingly, 63% of these samples contained more BTMPS than fentanyl by mass, which I thought was quite a shocking statistic. 8 samples had no detectable fentanyl at all, and 14% had more BTMPS by a factor of 10 or greater. So there was no doubt, was there?

Pretty much overnight, BTMPS was appearing in fentanyl, and this wasn't just one-off, this wasn't just one state or one city, this was across the US, detections in various different parts geographically. Yeah. And so this was definitely a thing, but it did raise the question, why? And my first thought, bearing in mind this came off the back of the rise in xylazine and medetomidine, was is this some new adulterant designed to alter the effects of fentanyl or prolonged sedation like we proposed with xylazine and medetomidine.

And what is interesting about BTMPS is not only is it an industrial plasticizer, but it has got a history of some amount of pharmacological activity. And we were able to dig in the archives and find a couple of older papers looking at studies where they had tested BTMPS for its potential therapeutic value and also its toxicological nature. And so we did find a paper where they looked at BTMPS in the context of nicotinic acetylcholine receptors. And so the study design was relatively simple, rats were allowed to self administer nicotine intravenously via lever presses.

We talked a little bit a couple of weeks ago, didn't we, studies using controlled nose pokes to do rat administration studies. It was a very similar design with nicotine. They then gave the rats a period of abstinence, six weeks, and then re exposed the rats to the lever that delivered the nicotine without any drug reward to look for context induced drug seeking behavior. And they tested BTMPS versus a placebo.

And the rats treated with BTMPS redosed the nicotine less than the controls. So the conclusion really from this was that BTMPS did have some pharmacological activity on the nicotine sensitive acetylcholine receptor, and that it could potentially at least in this rat model actually serve a possible therapeutic use to reduce nicotine cravings. And what I did find actually interestingly in this was that there didn't seem to be any off target effects either. There wasn't any effect on other reward pathways, they still continue to eat as normal and things like that.

So actually the conclusion of this paper was that this could actually have potential therapeutic benefit. And so this did have me thinking a little bit, is this what's going on? Is this the logic behind the BTMPS? Now this study was nicotine, but actually, do you get a similar effect when you combine it with opioids, for example?

At this point, it was all speculation and really unknown. Now obviously, we don't have human data here. This is one isolated rat study. So another paper from 2003 was investigating in vivo myocardial changes in rats after exposure to BTMPS, as this has previously been shown in vitro to be cytotoxic to cardiac myocytes via calcium metabolism disruption.

So BTMPS has been shown to block L-type calcium channels and induce a time-dependent cytotoxicity, cause hyper contraction, reduce ATP and creatine phosphate, and lead to irreversible myocyte damage in cell cultures. So essentially, they split rats in different groups and gave them increasing doses of BTMPS, depending on the group they were in, and injected them 15 times in total over five weeks. The dose in group two was one microgram, group three, 10 micrograms, group four, 100 micrograms, and group five, one milligram. Group one was obviously controlled, and groups one to three didn't show any changes in behavior.

Groups four and five that were receiving a higher dose of BTMPS showed apathetic behavior, reduced food intake, and weight loss by week three. They also showed a poor response to stimuli, and one rat in group four and three rats in group five by week four of the study did die. When looking at the hearts, group one and two didn't show any significant changes. Group three that was receiving about 10 micrograms of BTMPS showed small hemorrhages, focal hyper contraction, interstitial edema, and myocytolysis.

Group four, these effects begin to increase. You see large hemorrhages, especially in the ventricular septum, loss of actomycin continuity, and calcium starts to accumulate in these areas, and you do get myofibril aggregation. Group five was receiving one milligram of BTMPS showed severe hyper contraction necrosis with overstretched sarcomeres, damage to inner mitochondrial membranes, and increased calcium present as well. And all the rats that died in the study showed severe changes like those exhibited in group five.

And they kind of hypothesized, based on some other data that showed an increase in catecholamines with increasing doses of BTMPS, that BTMPS triggers a catecholamine-induced myocardial damage. So you get a sudden catecholamine surge, which used to increase contractility, oxygen demand, and calcium influx, and then you get this energy collapse, depletion of ATP, calcium overload, and irreversible structural damage. So I think one thing was quite clear from these early papers looking at BTMPS was that it wasn't inert.

It was having effects possibly through reward pathways, but also through calcium channel effects, and clearly toxic effects as well, albeit relatively high doses, considering you're giving a milligram to a rat, that's quite a lot, at very high doses was showing severe cardiotoxicity. So two things at this point are quite clear. Firstly, that BTMPS was emerging. Secondly, that it wasn't benign.

So why was this happening? So as I say, my thought was that this could have been an attempt at altering the pharmacological profile of street fentanyl, similar to xylazine and medetomidine. I heard a lot of other theories at the time. Could it have just been a cheap bulking agent?

Because it certainly is cheap and widely available. One other theory I heard was that people were trading fentanyl and fentanyl precursors on marketplaces using pseudonyms. And the theory is that somebody bought what they thought was a pseudonym for a fentanyl precursor or fentanyl itself and actually turned out to be BTMPS. Whatever was going on was going on at quite a high level in the supply chain because of how rapidly it had spread across the US.

The current working hypothesis now is that it could actually be related to synthesis pathways, particularly for fentanyl and fentanyl compounds. And a very recent publication by the CSFRE showed that not only now have they detected BTMPS, they've also detected other related compounds to BTMPS, including compounds like tetramethyl nor fentanyl. And I think the current hypothesis is that it could be either a precursor itself or a compound which is being added to fentanyl synthesis mixtures to stabilize it. And so potentially this is all emerged due to clandestine labs actually exploring new synthesis pathways using different compounds.

And interestingly, actually CSFRE have provisionally identified a suspect of tetramethyl fentanyl, which is a new compound. And at time of recording, I believe still hasn't been confirmed with the reference standard. So it's possible therefore that BTMPS might be either an unintended byproduct or a stabilizing intermediate, or possibly actually deliberate scaffold in this synthesis pathway. As I said at the start, the structure of BTMPS, it's not a million miles away from fentanyl.

So it is entirely possible that it is being used as some intermediate or precursor. I think one of the most worrying things about the data we've looked at is, especially in those cases where the samples of dope contain no fentanyl or very little fentanyl and lots of BTMPS, that people are taking it, assuming it's the drug they are purchasing, and then we'll carry on slightly lose their tolerance and then take another sample that does have lots of fentanyl in it and then there are even high risk of overdose. And that is really concerning. For sure.

And inconsistent purity is one of the biggest risks actually of overdose. So you're absolutely right, especially some of these samples which were mostly BTMPS. And that logic applies if BTMPS is completely benign. And actually the rat data showed that it really wasn't.

So there's potentially also a toxicity element there as well. And I think there are some user perceptions that have been reported, haven't there? Some users of dope containing a lot of BTMPS saying how it is more plasticky than normal in terms of its smell and their vaporizing it and how users are considering it to be cheaper or less desirable. Yeah.

Yeah. I've heard effects like it burning on injection and things like that as well. Yeah. Difficulty breathing, following inhalation, that sort of thing.

I think it does just highlight as well, doesn't it? The hidden risks that people who use drugs face buying drugs on the street. Literally overnight, this new additive was present in the drug supply and an additive with unknown consequences. So as I say, this first hit the news, what, about a year ago?

I became aware of it. Certainly remember in September, October last year, thinking about BTMPS. And I think CSFRE had put out there really, really helpful, actually monograph showing its mass spectrum. So I went and added it to our library because at this point I didn't know it was related to fentanyl synthesis.

I thought possibly it was going to emerge like the new xylazine, new medetomidine. So I added it to our screening library. I reprocessed some data I had ran that week. And the first sample I looked at, I had a hit.

And I looked at the next sample and I had a hit. And I thought, something's going on here. It turned out every sample had a very, very small peak for BTMPS. As we say, it's a really common industrial plasticizer somewhere in our extraction process.

BTMPS is present, certainly not at the concentrations that have been reported where it's 50% of the drug sample that's tested. Very, very trace amounts. And actually every sample was positive for BTMPS. So I'm not sure it has made it to the UK yet, although obviously I've got my eyes open.

Only time will tell. I think if it is related to fentanyl synthesis, possibly we're not going to see it yet because we don't see that much fentanyl in the UK. But as this outbreak really shows, drug markets can change overnight. Yeah.

I think this case really does show the benefit of having programs like the US have got the MPS discovery program. The fact that they were able to detect this in samples and actually disseminate that information idea in a relatively short timeframe really, really is of huge benefit to people like us toxicologists. But also it does really help raise awareness on public health level as to what's going on on the street. And I guess really this just shows the power of drug checking services and real-time toxicological monitoring.

The fact that we even know about BTMPS at all is because labs shared that information and made it available. And that really is something we're really quite thankful for. Definitely. So what are the take-home messages here?

Well, BTMPS, particularly in the States, is definitely a thing. It's probably not inert or innocuous, although its true impact on people currently is unknown. We don't have good human toxicology studies or anything like that. We're really just inferring what we know from rodent studies.

And possibly it represents a changing synthesis landscape in the background of international controls to fentanyl precursors. But I think as always, it's a case of watch this space. Let's see what happens. As we said earlier, drug supplies and drug markets really can change very, very quickly as this case shows.

And I guess the lesson really here is expect the unexpected. Is that a lesson? I think so. As always, with anything toxicology.

Prepare to be surprised. So I hope you've enjoyed listening this week. If you've enjoyed what you've heard today, please do go and give us a like or a follow or tell your friends. Give us a five star rating on Spotify.

That would be amazing. I hope you all have an amazing week and we'll see you next time. Bye.