THE COLOMBO PLAN

PUBLIC HEALTH ALERTS

The Colombo Plan & CFSRE Global Toxic Adulterant and Sentinel Program

www.colombo-plan.org

FOREWARD

The **Colombo Plan's Global Toxic Adulterant and Sentinel Projects** are leading the charge in addressing one of the most urgent public health crises: the rise of synthetic drugs and toxic adulterants. Since their inception in 2016-2017, these initiatives have provided a crucial early warning system, enabling the identification of dangerous and often lethal substances entering drug supplies. Through the collaborative efforts of **The Colombo Plan** and the **Center for Forensic Science Research and Education (CFSRE),** these initiatives have helped in understanding and responding to the evolving threats posed by synthetic drugs.

The Sentinel Project has been instrumental in monitoring and issuing timely alerts, empowering law enforcement, healthcare professionals, and communities to take swift action against emerging drug threats. Substances such as Xylazine, first identified in U.S. drug supplies in 2020, and the newly discovered Nitazenes—substances that are 1.5 to 20 times more potent than fentanyl—are just a few examples of the evolving dangers tracked by the Sentinel Project. This invaluable resource continues to provide critical guidance on synthetic drug patterns and trends, ensuring that relevant partners are equipped with the knowledge to protect public health.

The public health alerts presented in this booklet are a direct result of the collective efforts of Thom Browne, M.A., CEO of The Colombo Plan, and the distinguished experts at CFSRE, including Barry K. Logan, Ph.D., MJ Menendez, Alex J. Krotulski, Ph.D.; Amanda L.A. and Mohr, M.S. Their dedication, supported by funding from the U.S. Department of State's Bureau of International Narcotics and Law Enforcement (INL), has been pivotal in releasing these public health alerts.

We would also like to express our deep gratitude to the leadership and unwavering support provided by His Excellency Dr. Benjamin P. Reyes, Secretary General of The Colombo Plan, and Ms. Oranooch Sungkhawanna, Director of The Colombo Plan Drug Advisory Programme (CPDAP). Their guidance has been integral to the success of these initiatives.

This ongoing work highlights the importance of continued vigilance, collaboration, and action to combat the synthetic drug epidemic, ultimately working toward a healthier and safer future for communities worldwide.

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THE COLOMBO PLAN

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EMERGING GLOBAL SYNTHETIC OPIOID THREATS: BENZIMIDAZOL-2-ONES – THE ORPHINES

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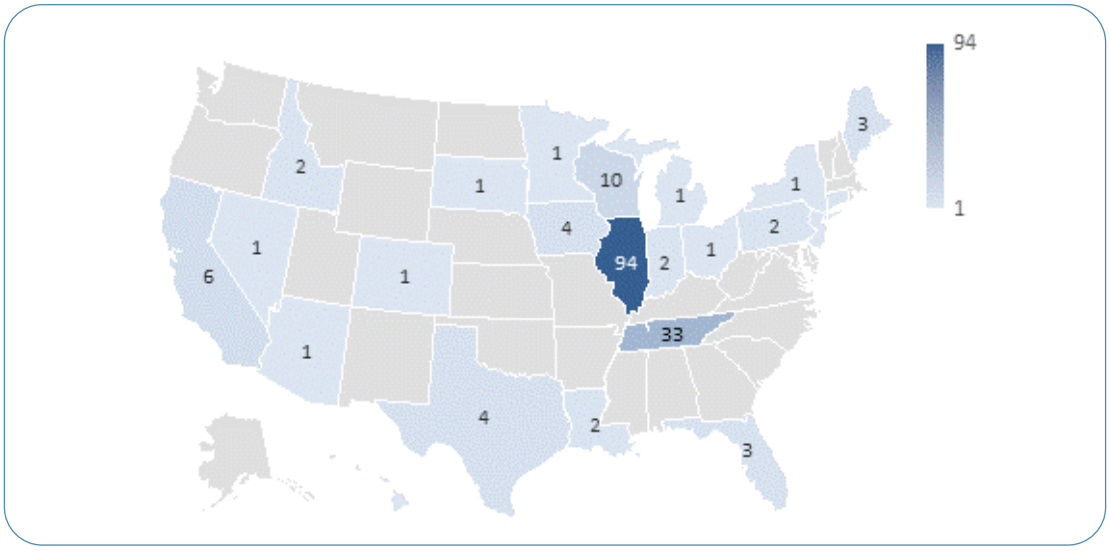
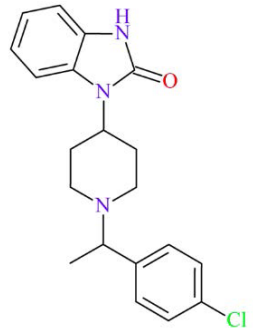
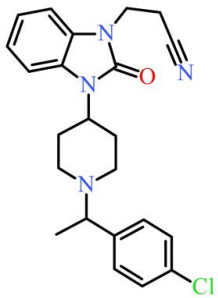
Following the recent core structure scheduling by China of the nitazenes (benzimidazoles), markets have seen a decline in these potent opioids in late 2025, and their replacement by a new class of synthetic opioids, the benzimidazol-2-ones, also known as the "Orphines". This alert describes the emergence of these potent opioids, and spotlights their detection in US and international drug markets.

- Brorphine was the first highly potent synthetic opioid of the **benzimidazol-2-one ("orphine") class**, detected in **European drug markets around 2019, and in the US in 2020**. It likely originated from **clandestine synthesis in China**, emerging as a fentanyl analog-replacement or opioid adulterant with potency similar to or slightly less than fentanyl.
- Following initial alerts, brorphine was rapidly scheduled or emergency-controlled in multiple jurisdictions (e.g., EU, UK, US, Canada). This regulatory response appears to have accelerated structural diversification, with multiple halogenated and cyclized analogs appearing about four years after brorphine controls were put in place.
- As analytical reference standards have become more widely available, orphine analogs detected now include Chlorphine, N-Propionitrile Chlorphine (Cychlorphine), 5,6-Dichloro Desmethylchlorphine (SR-17018), Spirochlorphine (R-6890), Spirobrorphine and 5,6-Dicholoro Brorphine (SR-14968), various members of which have been reported in the UK, Europe, US, and Canada.
- Through collaboration with its partner laboratory NMS Labs, The Colombo Plan, the CFSRE and its NPS Discovery Program are working to develop methods for detecting and quantifying these new drugs, and tools to enable automated retrospective datamining of postmortem toxicology data to allow their identification as part of CFSRE's drug early warning system.
- Early data from this datamining process, obtained by scraping analytical mass spectrometric datafiles, have identified the following numbers of orphine analog cases between 2024 and 2025: 5,6-Dichloro Desmethylchlorphine (31 cases), Brorphine (81 cases); Chlorphine (8 cases); N-Propionitrile Chlorphine (84 cases); and Spirochlorphine (20 cases).
- The geographic spread of the presumptive positive cases is shown below:

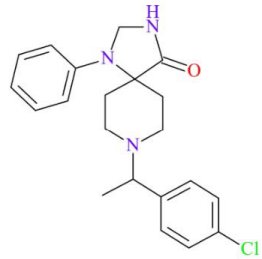




Chlorophine



N-Propionitrile Chlorophine (Cychlorphine)



Spirochlorophine (R-6890)

Polydrug Use and Adulteration

- The NMS Labs toxicology cases indicated that the most common adulterants and co-positivity included fentanyl, as well as other opioids and CNS depressants including nitazene analogs (e.g., metonitazene, N-pyrrolidino protonitazene, Isotonitazene, protonitazene, N-pyrrolidino metonitazene, and N-desethyl metonitazene) and illicit designer benzodiazepines (e.g., bromazolam).
- There were considerable geographic differences, with nitazene co-positivity being most common in Illinois. Methamphetamine, amphetamine, and diphenhydramine were most frequently found in Illinois, while fentanyl co-positivity was most frequently seen in Tennessee. Note that these positivity distributions reflect only jurisdictions in which NMS Labs performs testing.

Source of Synthetic Opioids:

- Following China's class-wide scheduling of fentanyl compounds in May 2019, the nitazene class of opioids originating from China, started appearing worldwide. Likewise, following China's core-structure scheduling of nitazene compounds in July 2025, the orphine class of opioids, most likely originating from China, are now appearing worldwide (see table page 3). This appears to be a recurring pattern with China following class-wide scheduling. In addition to already established drug classes including fentanyl, nitazene and orphine derivatives, multiple potential future classes of synthetic opioids that warrant monitoring include benzamides, acetamides, piperidines/piperazines, and cinnamylpiperazines.

Laboratory Analysis

- While standard reference materials for many of these analogs are now commercially available and can be added to laboratory testing scopes, very few forensic toxicology laboratories currently have comprehensive testing for orphine analogs within their scopes. In cases where the presence of an opioid is suggested based on history, scene and circumstances, but for which routine

toxicology testing is negative, orphine class opioids should be considered. Please contact NPS Discovery for assistance with testing in these cases (supported by the National Institute of Justice, DOJ).

- Note that opioid and fentanyl immunoassays will not cross-react with orphine class compounds, and field test strips often used in harm reduction programs will not detect these compounds either.
- Based on preliminary data for a limited number of these drugs, toxicologically significant concentrations may be in the range of <1ng/mL to 10ng/mL and may be missed during routine screening. Comprehensive interpretive data on typical postmortem concentrations are currently lacking.
- As discussed above, the orphines are frequently present in toxicology cases or in seized drug samples, along with other opioids or sedating drugs.

First Responders and Emergency Room Response

- Responses are expected to be common to other mu-opioid agonists and to produce the classic triad of opioid effects:
  - ***CNS Depression***: lethargy, stupor and coma
  - ***Respiratory Depression***: Slow respiratory rate (often <8–10/min), with shallow breathing.
  - ***Miosis*** (pinpoint pupils): typically, bilateral and symmetric
- ***Treatment should be supportive***: Treat the airway and breathing first, followed by reversal with cautious administration of an opioid antagonist (e.g. naloxone), being careful not to precipitate acute withdrawal.

MAIN NPS OPIOID SUBCLASSES

FENTANYLS 2013 - PRESENT	NITAZENES 2019 TO PRESENT	ORPHINES 2025 - PRESENT
Fentanyl	Isotonitazene	Brorphine
3-Methylfentanyl	Metonitazene	Chlorphine
Carfentanil	Butonitazene	N-Propionitrile Chlorphine
Butyrylfentanil	Protonitazene	5,6-Dicholoro Desmethylchlorphine
Cyclopropylfentanyl	Flunitazene	Spirochlorphine
Isobutyrylfentanyl	Etodesnitazene	Spirobrorphine
Fluoro-Isobutyrylfentanyl	N-Pyrrolidino protonitazene	5,6-dicholoro Brorphine
Methoxyacetylfentanyl	N-Pyrrolidino metonitazene	(others evolving rapidly)
O-methyl fentanyl	N-Pyrrolidino etonitazene	
P-Fluorofentanyl	N-desethyl isotonitazene	
Others (~65) ...	Others (~4)...	
All controlled either by name or through core structure scheduling.	Most currently controlled in the US permanently or temporarily, by name	Only Brorphine currently scheduled in the US Others are not scheduled

Acknowledgements:

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cfsre NPS DISCOVERY

PUBLIC ALERT:
INCREASE IN FATAL OVERDOSES LINKED TO NOVEL SYNTHETIC OPIOID N-PROPIONITRILE CHLORPHINE (CYCHLORPHINE)

Purpose:

The objective of this *Public Alert* is to notify public health and safety agencies, law enforcement, first responders, clinicians, medical examiners and coroners, forensic and clinical laboratory personnel, and all other related communities about new information surrounding the emergent novel synthetic opioid ***N*-Propionitrile Chlorphine** (also known as "Cychlorphine").

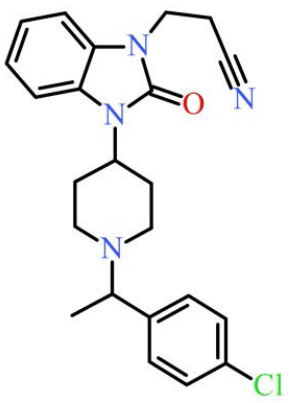
Background:

Synthetic opioids are chemically manufactured drugs, often having unknown potency and adverse effects. Synthetic opioids can be sold alone but are frequently mixed with more traditional opioids (e.g., fentanyl, heroin) and other substances in unregulated drug markets creating risks and danger for people who use recreational drugs. Synthetic opioids are commonly distributed in powder or tablet form. The United States has observed an alarming increase in deaths linked to synthetic opioids; Europe, Oceania, and other regions continue to observe increases as well. Primary adverse effects associated with synthetic opioid use are sedation and respiratory depression, which can lead to death if untreated with naloxone and/or other measures.

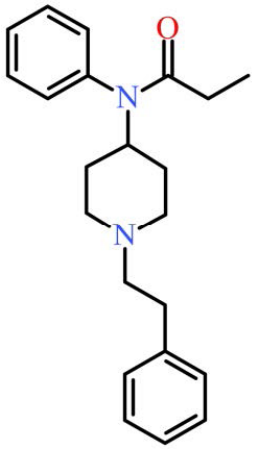
Summary:

N-Propionitrile chlorphine belongs to an emergent subclass of novel synthetic opioids often referred to as "orphine analogues" (or more simply "orphines") and bears structural similarity to other benzimidazolones (e.g., brorphine, chlorphine). These drugs have ties to pharmaceutical drug discovery conducted in the 1960s and 1970s, beginning with substances like bezitramide and R-6890 (now referred to as "spirochlorphine"). The orphine analogues first emerged in recreational drug markets in 2020 with the proliferation of brorphine (a drug first synthesized and published on in 2018). This novel opioid subclass continues to diversify, with at least six analogues confirmed in recent years. *N*-Propionitrile chlorphine was first detected at the Center for Forensic Science Research and Education (CFSRE) in mid-2024. In vitro pharmacology data show this drug to be approximately 10x more potent than fentanyl *[Vandeputte & Stove, personal communication]*. The positivity of *N*-propionitrile chlorphine, specifically in fatal drug overdoses, has increased since mid-2025. In July 2025, the Chinese government placed nitazene analogues under generic control. Since this announcement, overall positivity for nitazene analogues has declined as overall positivity for orphine analogues has increased, led in large part by *N*-propionitrile chlorphine.

N-Propionitrile chlorphine has been identified in 25 blood specimens from fatal overdoses tested at the CFSRE, the vast majority submitted in late-2025 and early-2026. In addition, *N*-propionitrile chlorphine has been tentatively identified in



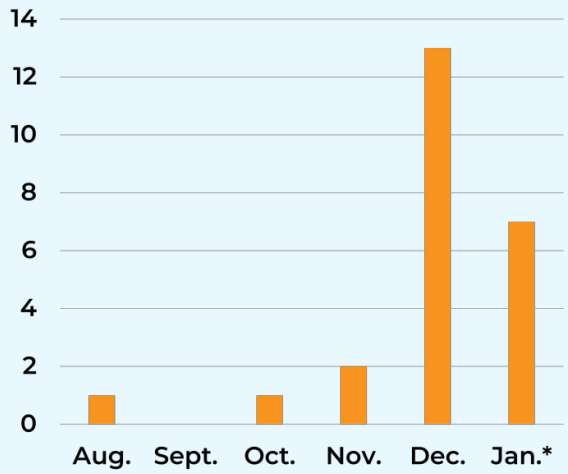
N-PROPIONITRILE CHLORPHINE



FENTANYL

more than 100 toxicology cases at NMS Labs. Toxicology specimens originated from nine states across the United States, as well as three provinces in Canada. *N*-Propionitrile chlorphine was detected as the sole opioid in 11 of 25 cases, and alongside other opioids (e.g., fentanyl, oxycodone) and traditional stimulants (e.g., methamphetamine, cocaine). Co-detection with NPS was common (e.g., novel benzodiazepines [phenazolam], other orphine analogues [spirochlorphine], nitazene analogues, and carfentanil).

POSITIVE CASES SUBMITTED



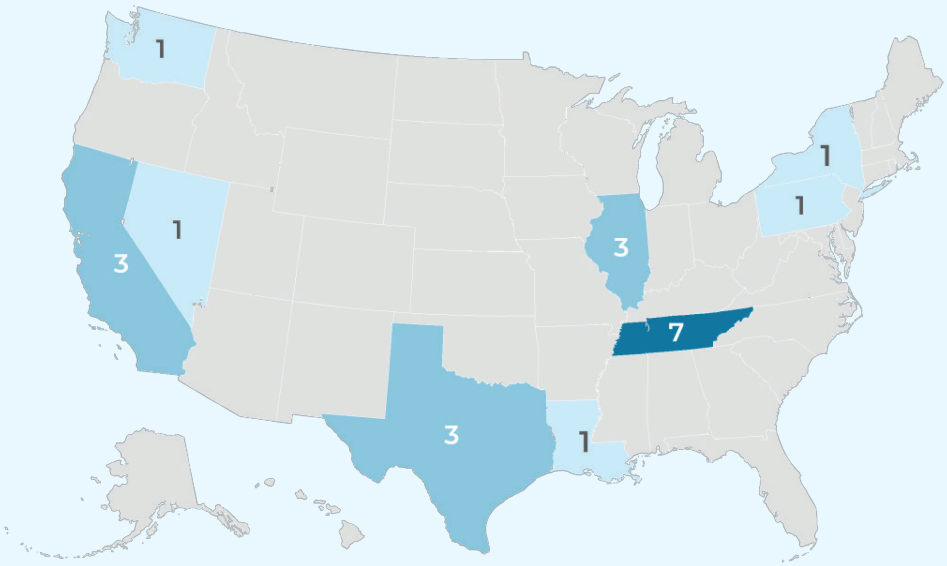
*Cases received through 1/13/2026

EMERGENCE OF ORPHINE ANALOGUES

DATE*	ANALOGUE
July 2020	Brorphine
Aug. 2024	5,6-Dichloro Desmethylchlorphine (SR-17018)
Dec. 2024	Chlorphine
Dec. 2024	N-Propionitrile Chlorphine (Cychlorphine)
Oct. 2025	Spirochlorphine (R-6890)
Dec. 2025	5,6-Dichloro Brorphine (SR-14968)

*Date of NPS Discovery monograph issuance.

DISTRIBUTION OF CONFIRMED CASES

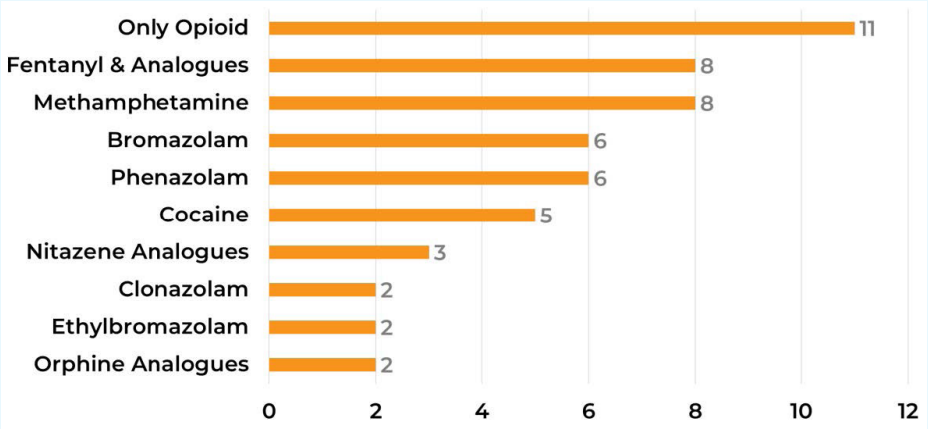


Note: N-Propionitrile Chlorphine has also been observed in four toxicology specimens from Canada.

SELECTION OF TOXICOLOGY SPECIMEN RESULTS

DATE	STATE	RESULTS
Oct. 2024	New York	***N*-Propionitrile Chlorphine**, Phenazolam
Oct. 2025	California	***N*-Propionitrile Chlorphine**, Alprazolam, Caffeine
Nov. 2025	Illinois	***N*-Propionitrile Chlorphine**, *N*-Desethyl Metonitazene, Isotonitazene, *N*-Desethyl Etonitazene, Spirochlorphine, *N*-Pyrrolidino Metonitazene, Metonitazene, *N*-Pyrrolidino Etonitazene, *N*-Pyrrolidino Protonitazene, Alprazolam, Cocaine
Dec. 2025	Nevada	***N*-Propionitrile Chlorphine**, Bromazolam, Ethylbromazolam, Cocaine, Lidocaine, Caffeine
Dec. 2025	Pennsylvania	***N*-Propionitrile Chlorphine**, Acetaminophen
Jan. 2026	Tennessee	***N*-Propionitrile Chlorphine**, Phenazolam, Fentanyl, Xylazine, Alprazolam, Quinine, Caffeine
Jan. 2026	Texas	***N*-Propionitrile Chlorphine**, Bromazolam, Alprazolam, Oxycodone, Methamphetamine, Cocaine, Levamisole

CO-OCCURRENCE WITH DRUGS & OTHER NPS



Acknowledgements:

This report was prepared by Alex J. Krotulski, Donna M. Papsun, Brianna N. Stang, Sara E. Walton, and Barry K. Logan at the Center for Forensic Science Research and Education (CFSRE) at the Fredric Rieders Family Foundation. The authors acknowledge staff at the CFSRE, NMS Labs, and collaborating agencies for involvements and contributions. For more information, please contact CFSRE's NPS Discovery at npsdiscovery@cfsre.org or visit www.npsdiscovery.org.

Funding:

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PUBLIC ALERT:
AN UPDATE ON THE PRESENCE OF BTMPS IN THE DRUG SUPPLY AND THE DISCOVERY OF TETRAMETHYLFENTANYL-RELATED SUBSTANCES

Purpose:

In collaboration with the Drug Enforcement Administration (DEA), the Center for Forensic Science Research and Education (CFSRE)'s NPS Discovery program has developed this report to notify public health, public safety, forensic and clinical laboratories, clinicians, medical examiners and coroners, and all other related communities about new information surrounding the emergent adulterant **BTMPS** and newly discovered **fentanyl-related substances**.

Background:

BTMPS, also referred to as bis(2,2,6,6-tetramethyl-4-piperidyl)sebacate or Tinuvin 770, is an industrial chemical that began appearing in June 2024 in the recreational opioid supply as an adulterant alongside fentanyl. BTMPS is used as a light stabilizer and was initially evaluated for use in plastic materials. Early on, the presence of BTMPS in the drug supply was perplexing to forensic scientists and chemists. Some suggested its use could be related to perceived enhancement of pharmacological effects of fentanyl or more simply as a cutting or bulking agent. The chemical structure of BTMPS is dissimilar from most forensically relevant drugs; however, it contains substituted piperidine rings — a similar core moiety to fentanyl.

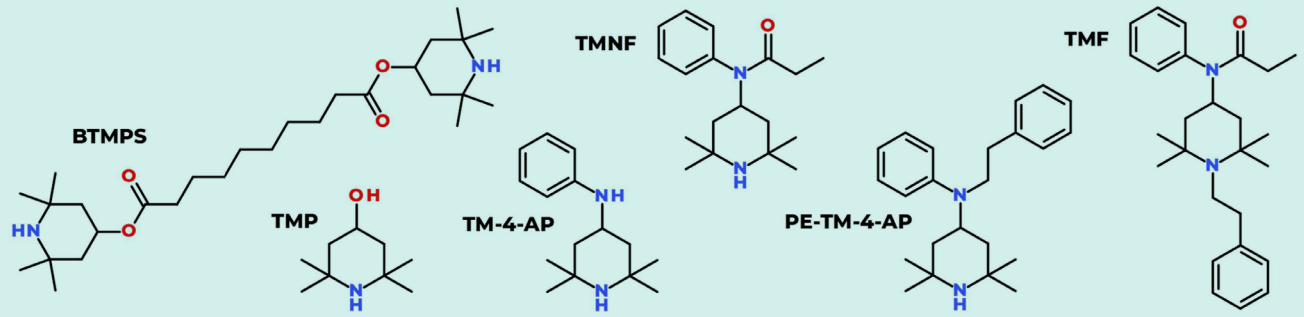
In early to mid–2025, forensic laboratories began detecting substances with chemical linkages to BTMPS, including tetramethyl-4-piperidinol, and soon after substances with ties to fentanyl, including 4-AP and norfentanyl variants. The emergence of these substances and relevant intelligence information indicate the manufacture of fentanyl-related precursors, byproducts, and perceived intermediates from BTMPS.

Summary:

BTMPS has been detected in all regions across the United States, demonstrating vast prevalence. BTMPS has appeared in more than 600 drug materials tested by our laboratory. Tetramethyl-4-piperidinol (TMP) was first detected in August 2024 and since has appeared in more than 20 drug materials. Tetramethyl-4-AP (TM-4-AP) and tetramethylnorfentanyl (TMNF) were first detected in April 2025 and since have appeared in more than ten drug materials, often together. To date, a substance suspected of being tetramethylfentanyl (TMF) has been identified in only small (or trace) amounts alongside these other related substances; however, confirmation of this substance is pending acquisition of a standard reference material.

SUBSTANCE	FORMULA	MOLECULAR ION [M+]	EXACT MASS [M+H]+	GC-MS FRAGMENT IONS
BTMPS	$C_{28}H_{52}N_2O_4$	480	481.4000 [2+: 241.2036]	342, 140, 124*, 98, 58
Tetramethyl-4-Piperidinol (TMP)	$C_9H_{19}NO$	157	158.1539	142*, 124, 98, 86, 58
Tetramethyl-4-AP (TM-4-AP)	$C_{15}H_{24}N_2$	232	233.2012	217, 175, 160, 140, 124, 98*, 77, 58
Tetramethylnorfentanyl (TMNF)	$C_{18}H_{28}N_2O$	288	289.2274	273, 140, 124*, 98, 77, 58
N-Phenethyl Tetramethyl-4-AP (PE-TM-4-AP)	$C_{23}H_{32}N_2$	336	337.2638	245, 140*, 115, 98, 77, 58
2,2,6,6-Tetramethylfentanyl (TMF)	$C_{26}H_{36}N_2O$	392	393.2900	301, 160, 105, 70 [Pending confirmation by standard]

CHEMICAL STRUCTURES



#	DATE	REGION	BTMPS	TMP	TM-4-AP	TMNF	PE-TM-4-AP	TMF	OTHER NOTABLE SUBSTANCES
1	Aug. 2024	East	X	X					Fentanyl, Tetracaine, Medetomidine
2	Aug. 2024	Midwest	X	X					Fentanyl
3	Oct. 2024	East	X	X	X	X	X		Heroin, Cocaine
4	Dec. 2024	East	X	X					Fentanyl, Xylazine, Lidocaine
5	Dec. 2024	West	X	X					Fentantyl, pFF
6	Dec. 2024	Southwest	X			X			Fentanyl, Lidocaine
7	Jan. 2025	East		X	X	X	X		N/A
8	Jan. 2025	Midwest	X	X	X	X	X		Fentanyl, Lidocaine
9	Feb. 2025	East		X					N/A
10	Mar. 2025	Southwest	X		X	X	X	X	Fentanyl, Lidocaine
11	Apr. 2025	East		X	X	X			Fentanyl, Lidocaine
12	Apr. 2025	East	X		X	X			Fentanyl, Lidocaine
13	Apr. 2025	East	X		X	X			Fentanyl, Xylazine, Lidocaine
14	Apr. 2025	West			X	X			Fentanyl, Lidocaine
15	May 2025	East	X	X					Fentanyl, pFF, Xylazine, Lidocaine
16	May 2025	East	X		X	X	X	X	Fentanyl, Carfentanil, Lidocaine
17	May 2025	East			X	X			Fentanyl, Tetracaine, Medetomidine

Acknowledgements:

This report was prepared by Alex Krotulski, Agnes Winokur, Steve Toske, David Guthrie, C. Luke Keller, Sandra Rodriguez-Cruz, Josh DeBord, Max Denn, Alexis Quinter, Mia Borrelli, and Barry Logan at the Center for Forensic Science Research and Education (CFSRE) at the Fredric Rieders Family Foundation (FRFF). The authors acknowledge scientists and staff at the CFSRE and DEA's Special Testing & Research Laboratory for their involvements and contributions, as well as many collaborators across a variety of public health, public safety, and forensic agencies.

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The opinions, findings, conclusions and/or recommendations expressed in this publication are those of the author(s) and do not

necessarily represent official position or policies of the NIJ, DEA, DOJ, DOS, INL, or any other entity.

For Additional Information:

Contact our laboratory via npsdiscovery@cfsre.org or visit www.npsdiscovery.org.

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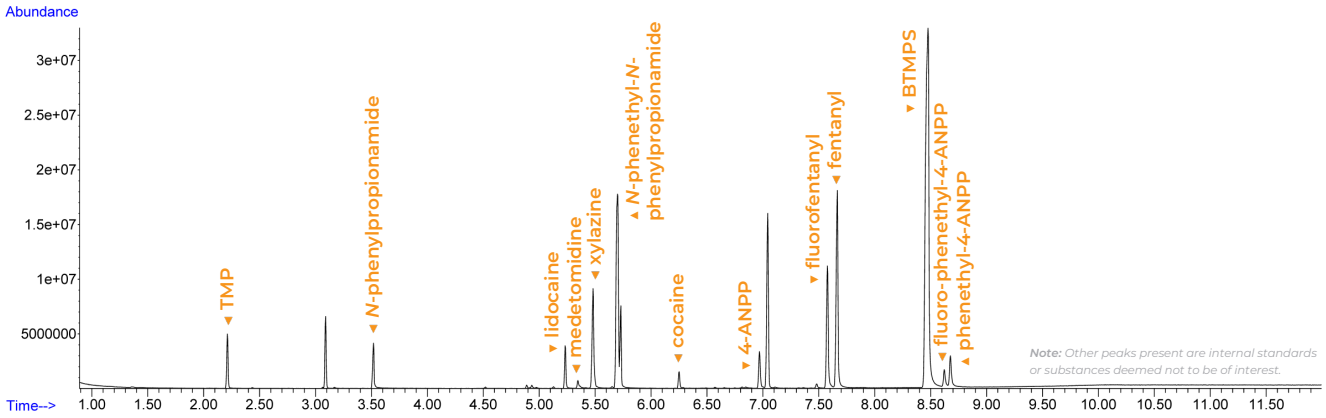
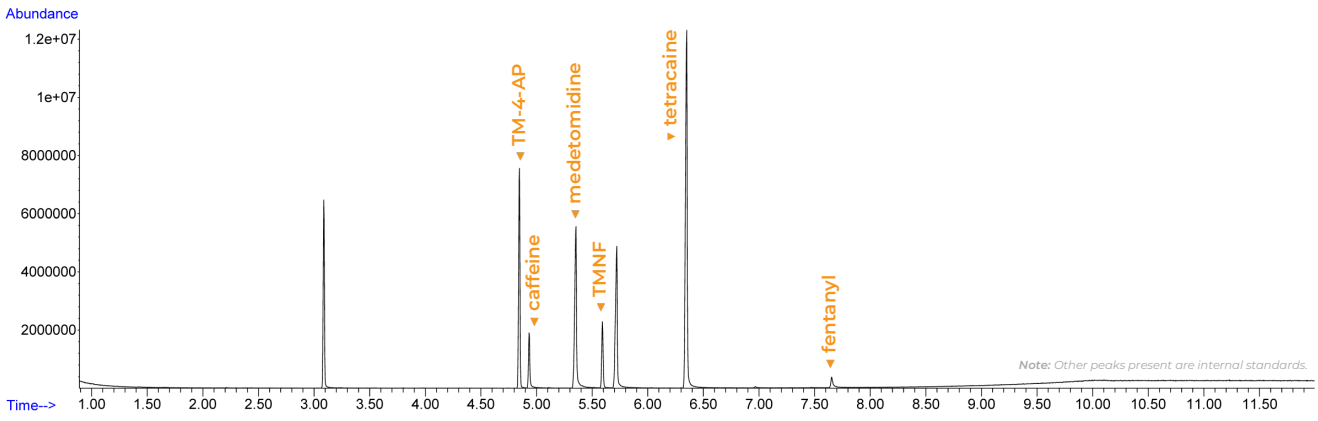
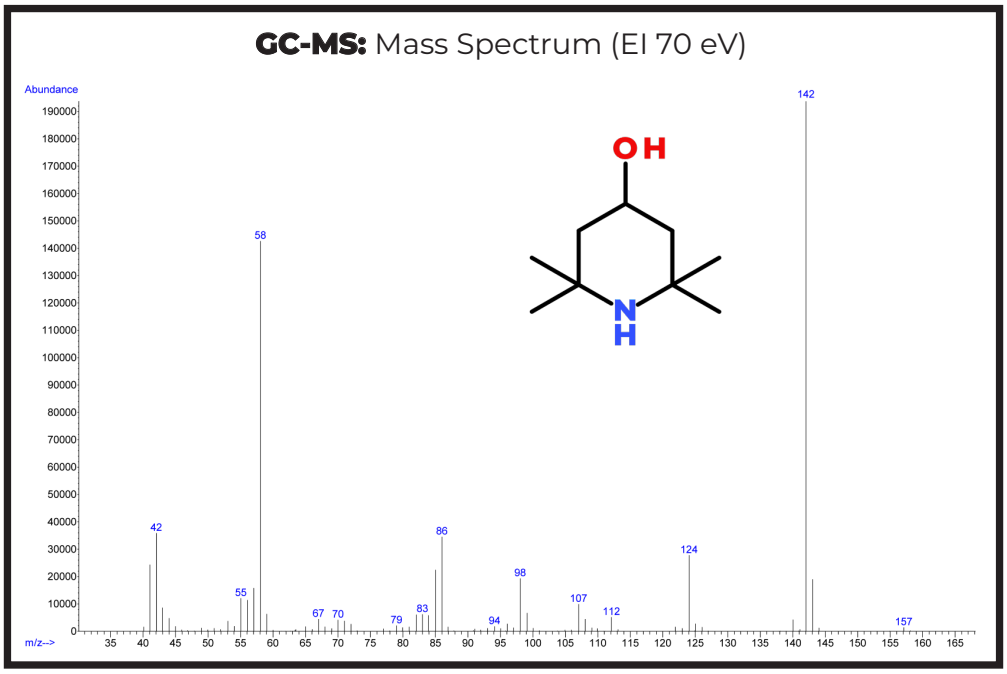
EXAMPLE CHROMATOGRAM OF A DRUG MATERIAL CONTAINING BTMPS, TMP, AND OTHER SUBSTANCES (MAY 2025)

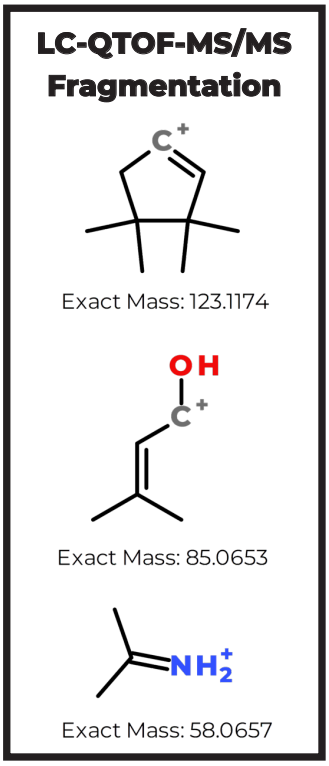


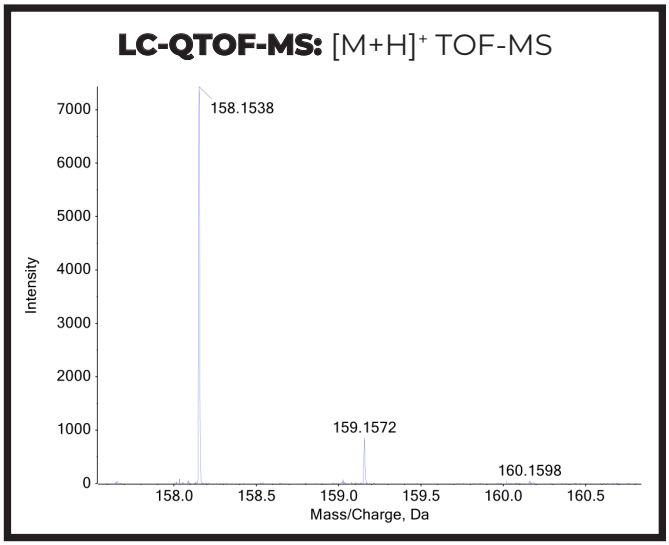
EXAMPLE CHROMATOGRAM OF A DRUG MATERIAL CONTAINING TM-4-AP, TMNF, AND OTHER SUBSTANCES (MAY 2025)

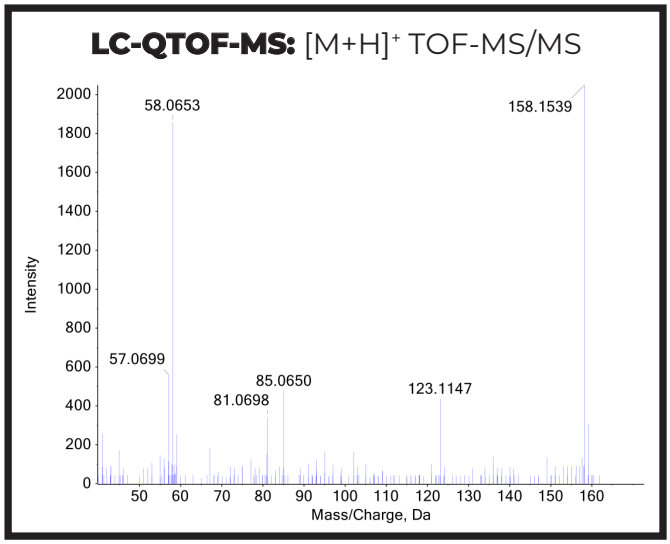


Tetramethyl-4-Piperidinol (TMP)



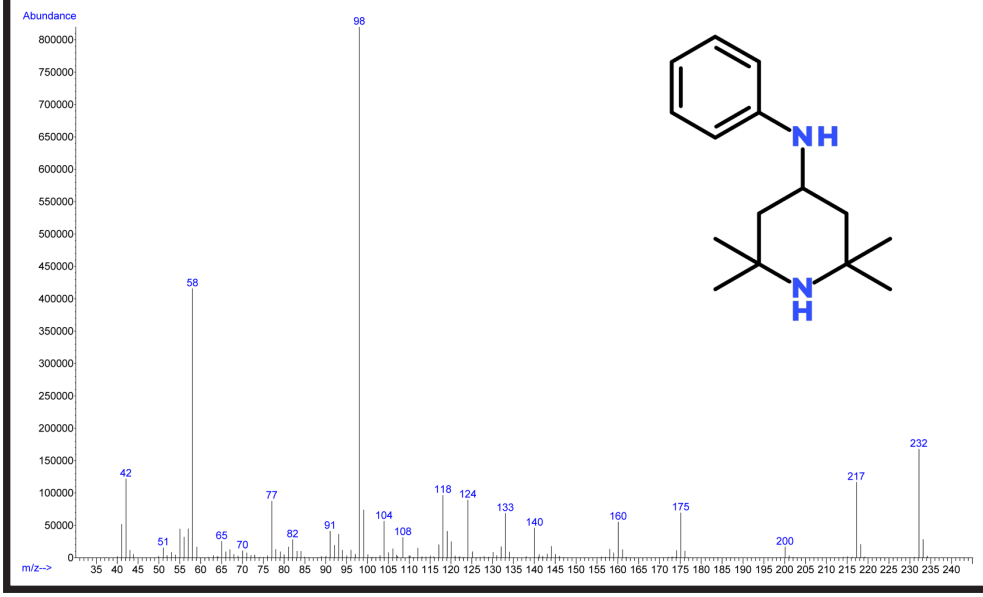




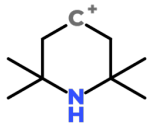


Tetramethyl-4-AP (TM-4-AP)

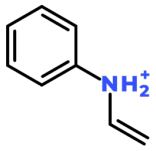
GC-MS: Mass Spectrum (EI 70 eV)



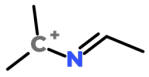
LC-QTOF-MS/MS Fragmentation



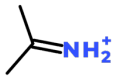
Exact Mass: 140.1439



Exact Mass: 120.0813

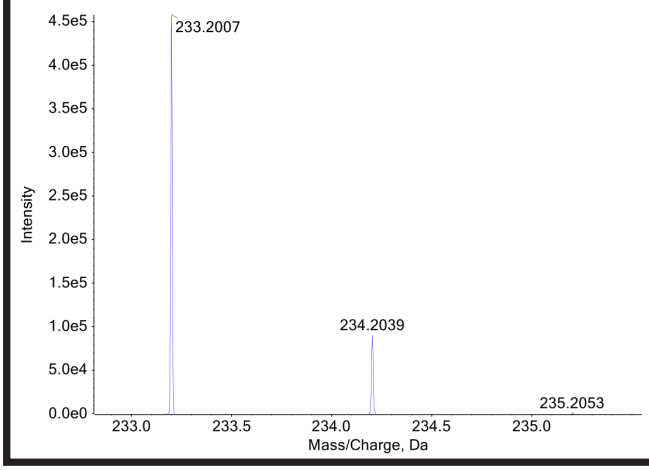


Exact Mass: 84.0813

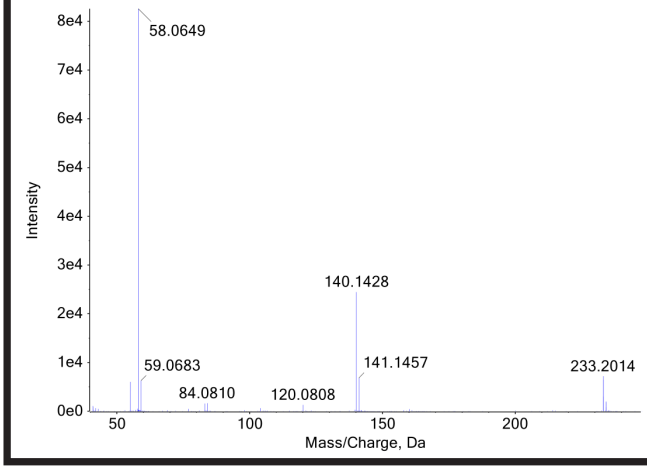


Exact Mass: 58.0657

LC-QTOF-MS: $[M+H]^+$ TOF-MS



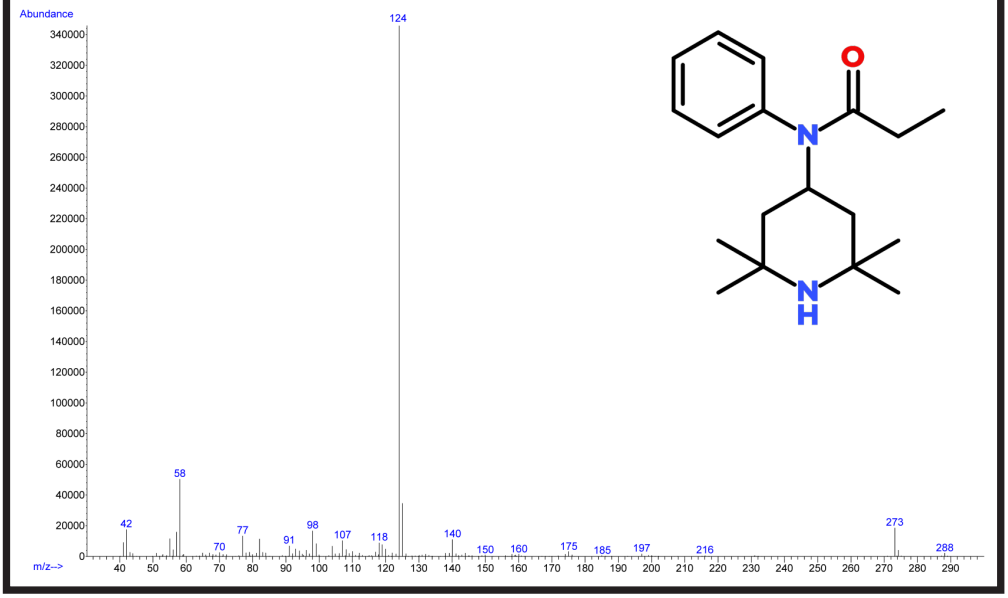
LC-QTOF-MS: $[M+H]^+$ TOF-MS/MS



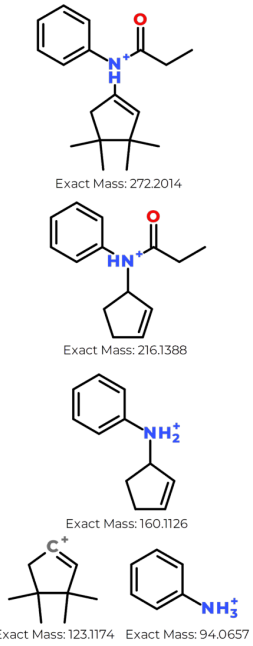
Tetramethylnorfentanyl (TMNF)

Tetramethylnorfentanyl (TMNF)

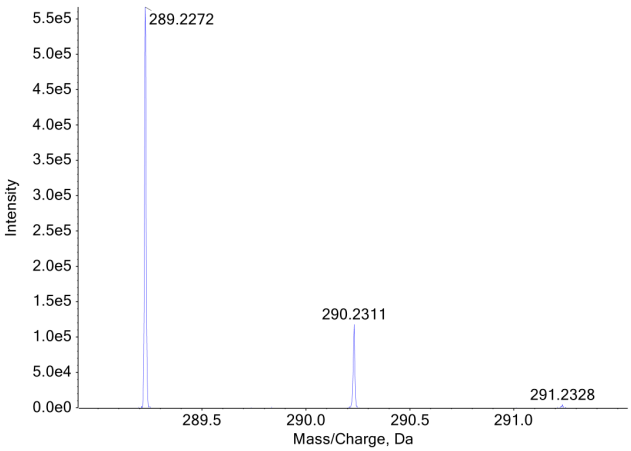
GC-MS: Mass Spectrum (EI 70 eV)



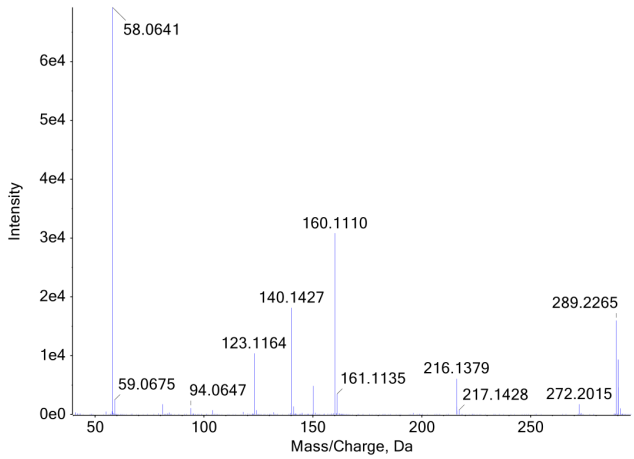
LC-QTOF-MS/MS Fragmentation



LC-QTOF-MS: [M+H]⁺ TOF-MS

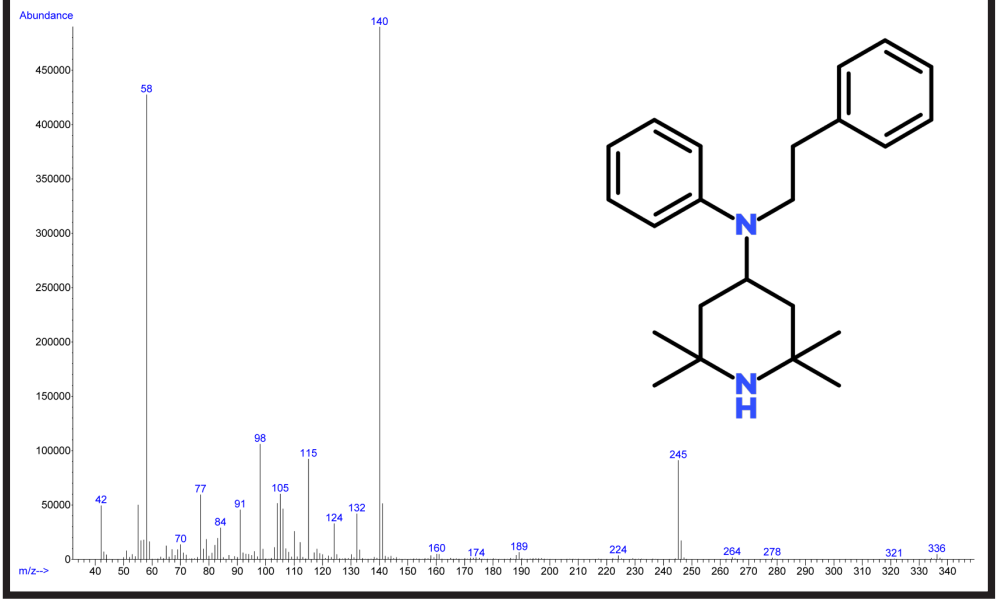


LC-QTOF-MS: [M+H]⁺ TOF-MS/MS

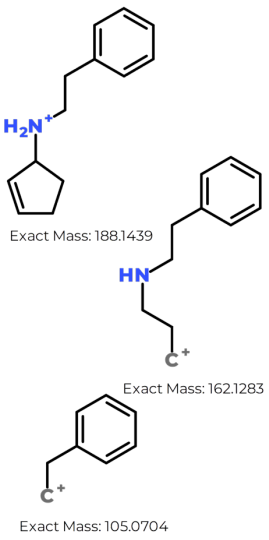


N-Phenethyl Tetramethyl-4-AP (PE-TM-4-AP)

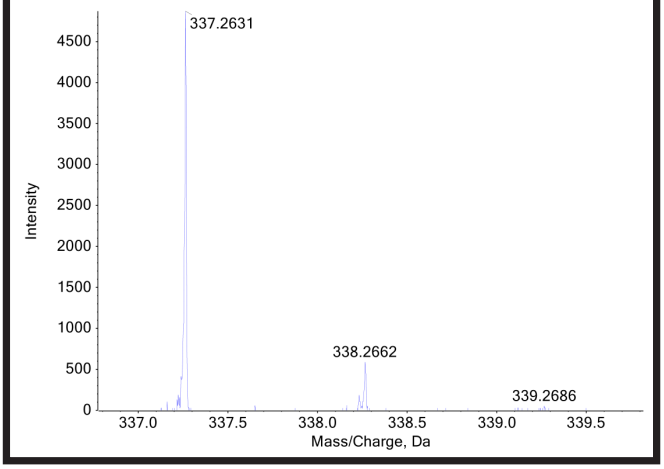
GC-MS: Mass Spectrum (EI 70 eV)



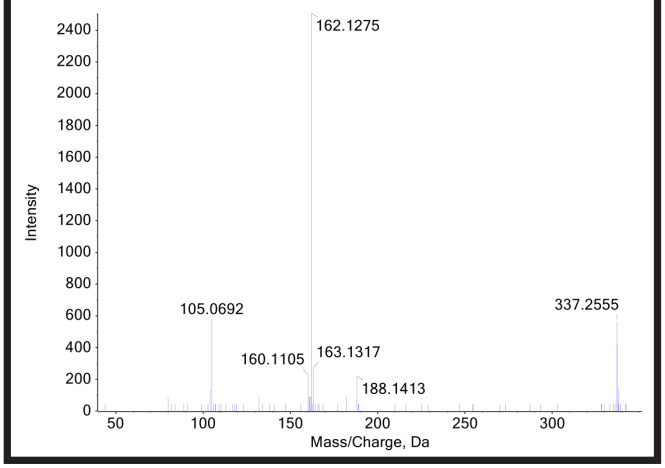
LC-QTOF-MS/MS Fragmentation



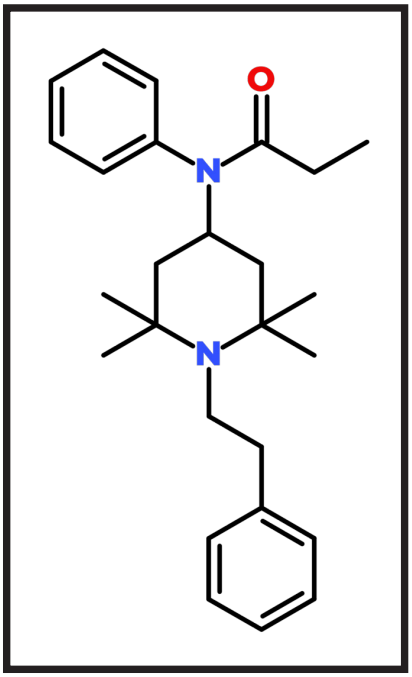
LC-QTOF-MS: $[M+H]^+$ TOF-MS

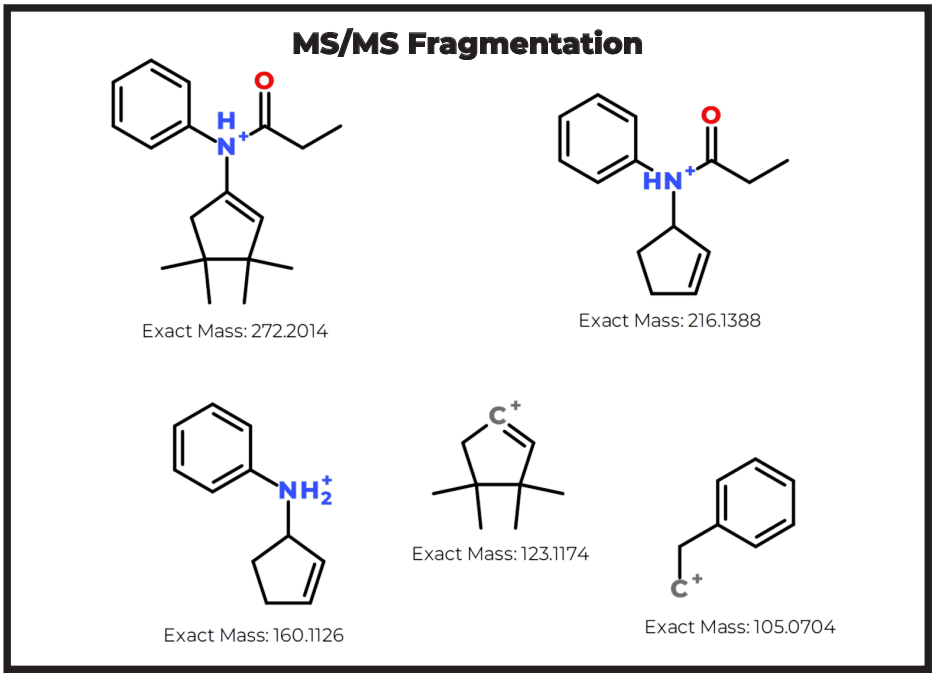


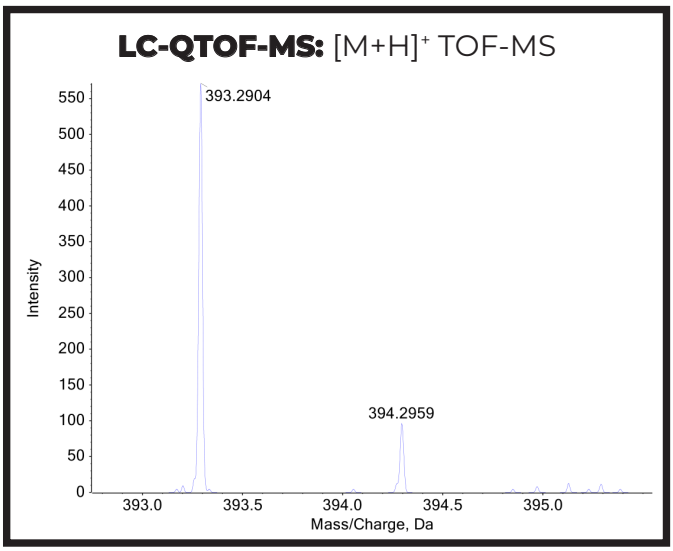
LC-QTOF-MS: $[M+H]^+$ TOF-MS/MS

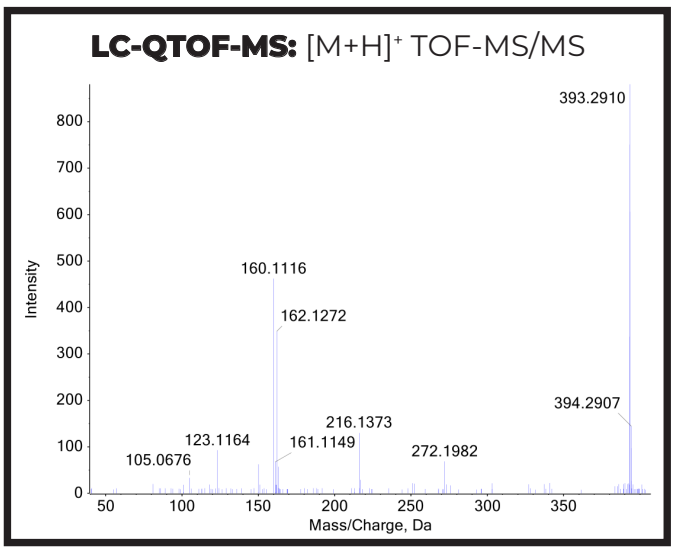


2,2,6,6-Tetramethylfentanyl (TMF)

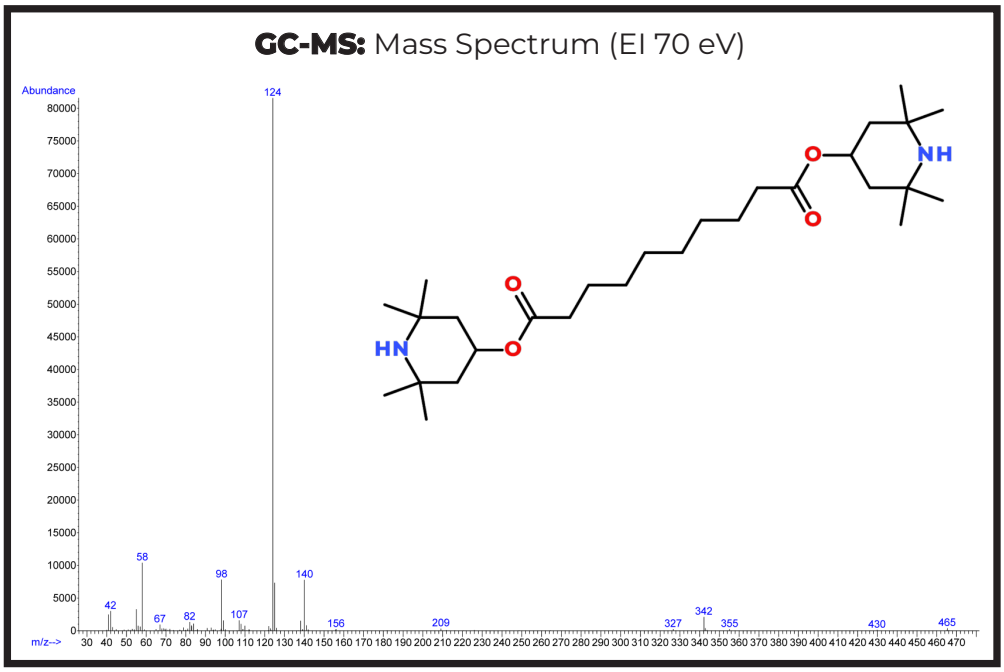




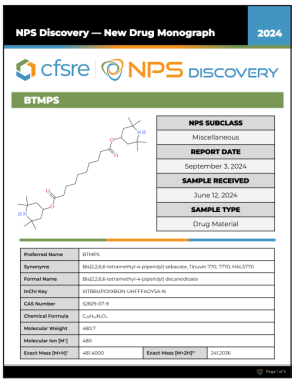


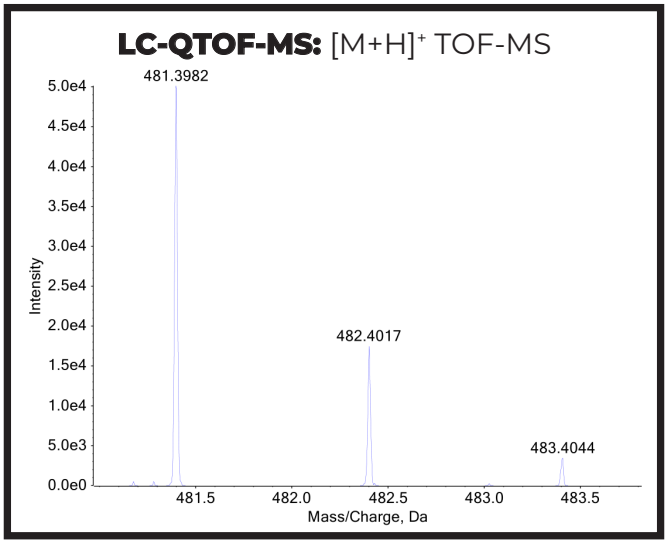


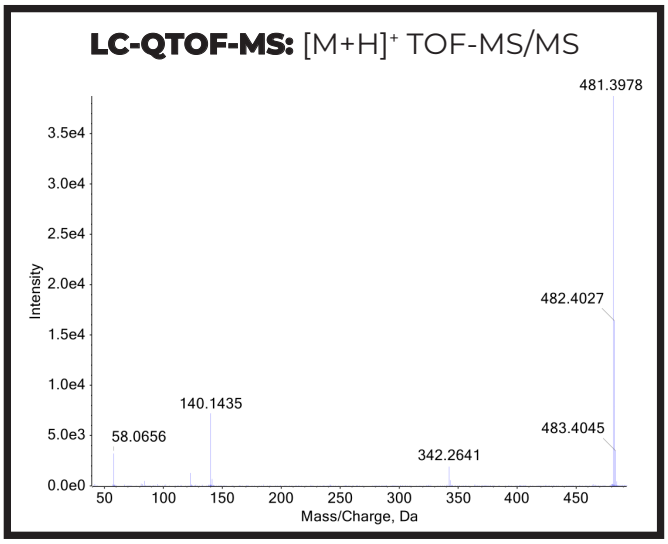
BTMPS



For More Information and Data, Access Our NPS Discovery New Drug Monograph For BTMPS (May 2024)







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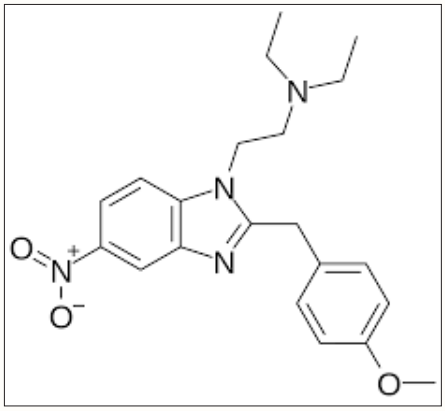
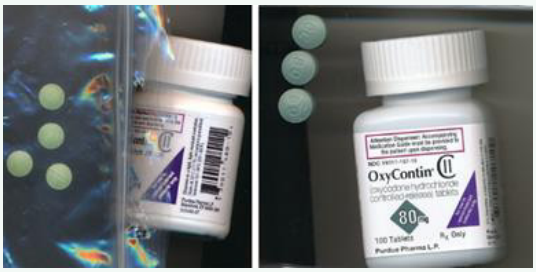
EMERGING GLOBAL SYNTHETIC OPIOID THREAT: INCREASING REPORTS OF NITAZENE TOXICITY

In 2023, nitazene tablets destined for Florida, Connecticut, and Brazil containing an average of 29 mg of metonitazene across multiple shipments were seized in the U.S. from international express mail. This amount is equivalent to 290 mg of fentanyl in a single tablet (or 145 times the DEA's estimated fatal dose of fentanyl), which would be highly lethal.

- At a recent international symposium on emerging global synthetic drug threats sponsored by The Colombo Plan and CFSRE, a number of countries reported the emergence of nitazenes around the world.
- Benzimidazoles, also known as "nitazenes" (nai-ta-zeens), are a potent class of synthetic opioids estimated to be 1.5X - 20X more potent than fentanyl compounds (Vandeputte et al. 2024).
- An alarming increase in the number of deaths linked to nitazene use has been reported worldwide: North America, Brazil, Europe, Australia, New Zealand and West Africa (see boxes on pages 14-16).
- Nitazenes are distributed in powder or tablet form and are often mixed with other synthetic and traditional drugs and adulterants in unregulated drug markets, creating additional risk and danger for people who use drugs (See Table 1, page 16). Combinations of nitazenes and designer benzodiazepines are most common, especially the co-occurrence with Bromazolam.
- In testing of nitazene samples from US Crime Laboratories, 2.6% of cases (55 exhibits) contained 19 or more substances besides the principal component, usually fentanyl.
- Primary adverse effects associated with synthetic opioids are sedation and respiratory depression, leading to death.
- Naloxone is effective in the reversal of nitazene toxicity; multiple doses may be necessary, however.
- A number of nitazene analogs began to appear in the United States: isotonitazene (2019), metonitazene (2020), butonitazene, etodesnitazene, flunitazene, N-pyrrolidino etonitazene, protonitazene, metodesnitazene, and N-piperidinyl etonitazene (2021), N-desethyl isotonitazene (2022), N-pyrrolidino metonitazene, N-pyrrolidino protonitazene, N-desethyl etonitazene (2023), and 5-methyl etodesnitazene, and methylenedioxynitazene (2024).
- The NPS Discovery program at the CFSRE reports on a quarterly basis the most common nitazene drugs in the US, which in the third quarter of 2024 include protonitazene, metonitazene, and N-pyrrolidino protonitazene.

Public health and public safety officials worldwide should be aware of an emerging threat of the Benzimidazole (Nitazene) class of opioids, which are causing increased mortality (death) and morbidity.

Considered several times more potent than the fentanyl class of opioids (phenylpiperidines), these compounds can make an existing opioid epidemic much worse or introduce an epidemic to unsuspecting countries and regions.

COUNTRY	REPORTED ACTIVITY
AUSTRALIA	• The Victorian Institute of Forensic Medicine (VIFM) at Monash University in Melbourne has reported deaths linked to isotonitazene (2021), and etodesnitazene (2022). There are indications of an increase in nitazene deaths across Australia in 2023 and 2024, with the most commonly detected drugs being protonitazene, metonitazene, and N-pyrrolidino etonitazene, with some cases testing positive for multiple nitazenes, including butonitazene.  • Cases of intoxication have also been confirmed in emergency department patients in Victoria. These cases are being reported to the Emerging Drugs Network of Australia (EDNA). In 2024, The Australian Alcohol and Drug Foundation has also reported several cases of counterfeit drugs containing nitazenes often mixed with designer benzodiazepines such as Bromazolam (Photo: Australian Border Force).
BRAZIL	• Nitazenes were the most frequent drugs detected in the opioid seizures that took place in the State of São Paulo, Brazil between July 2022 and April 2023. This was reported by health agencies in Brazil and scientists at the University of Campinas. There were a total of 140 cases of opioids seizures with 95 % of those belonging to the nitazene class, while only 5 % consisted of other opioids (morphine and fentanyl). Some of the exhibits were nitazenes mixed with other active compounds, including the synthetic cannabinoid MDMB-4en-PINACA (30 % of the samples). Metonitazene was the most frequent drug seized, appearing in 125 (72 %) of the cases.  Metonitazene
EUROPEAN UNION	• The European Union Drugs Agency (EUDA) has been tracking the presence of nitazenes in EU countries since 2019, and has issued multiple reports on the substances detected, including a 2024 update on the drug situation in Europe. While rates of use in EU countries still appear to be low, several specific outbreaks have been reported, including those in Ireland (see below) and France.  • The EU Early Warning System reported six new nitazene compounds in the European drug supply in 2023. The presence of nitazenes is concentrated in Lithuania, Latvia, Estonia, Poland, Sweden and Finland. Nitazenes were present in a counterfeit oxycodone seizure in Sweden, and in a seizure of counterfeit buprenorphine tablets in Finland. (Photo: Swedish Customs Laboratory).

COUNTRY	REPORTED ACTIVITY
IRELAND	• Several high profile outbreaks of nitazene intoxications have been reported in Ireland in 2023 and 2024, although nitazenes (metonitazene and butonitazene) were first detected in Ireland in 2022. In 2023 outbreaks in Dublin City, and Cork City, were linked to N-pyrrolidino protonitazene, and involved 57 and 20 non-fatal overdoses, respectively.  • In 2024, additional outbreaks both fatal and non-fatal, related to protonitazene were reported including one in a prison involving N-pyrrolidino protonitazene. Some seized exhibits containing protonitazene were yellow tablets packaged in counterfeit blister packs and labelled as alprazolam (Photo: www.drugs.ie).
NEW ZEALAND	• In May 2024, High Alert, a New Zealand-based drug checking service reported the presence of N-desethyletonitazene in a counterfeit tablet being sold as a benzodiazepine (diazepam). https://www.highalert.org.nz/alerts-and-notifications/highly-potent-synthetic-opioid-detected-in-fake-diazepam-tablet/.  • The group has previously reported metonitazene in yellow tablets and powders (possibly crushed tablets) as early as 2022, and either N-pyrrolidino-protonitazene or N-pyrrolidino-isotonitazene in an orange powder. The group advises extreme caution with respect to the possible presence of these drugs in the New Zealand drug supply. 
UNITED KINGDOM	• Nitazene drugs were first detected sporadically in the UK drug supply as early as 2019 but have become more prevalent in recent years. In 2023 the number of deaths linked to nitazenes had begun to increase, but more recently the UK's National Crime Agency has confirmed over 179 deaths involving nitazenes in the UK between June 2023 and May 2024. Recent UK media reports indicate nitazenes are proliferating rapidly.  • The most commonly reported nitazenes in these cases were protonitazene, N-desethyl isotonitazene, metonitazene, and N-pyrrolidino protonitazene. Nitazenes are scheduled in the UK as Class I drugs (Photo: EUDA).

COUNTRY	REPORTED ACTIVITY
UNITED STATES	 • CFSRE/NPS Discovery regularly updates positivity rates in the US for nitazenes in its trend reports and includes analytical data on each new emerging opioids in its drug monographs. • A collaboration between CFSRE, US Customs and Border Protection and The Colombo Plan recently identified in one seizure a highly potent counterfeit oxycodone tablets (OC80's) containing on average 24 mg of metonitazene (together with amphetamine, PCE, 2-fluoro-2-oxo-PCE, pentylone, N,N-dimethylpentylone, and N-pyrrolidino protonitazene). Another set of metonitazene only tablets contained an average of 35 mg, which would be equivalent in potency to approximately 350 mg of fentanyl in a single tablet and highly lethal. For comparison a typical counterfeit fentanyl tablet contains less than 2 mg of fentanyl.
WEST AFRICA	 • Kush, a derivative of cannabis mixed with suspected synthetic drugs and other traditional drugs and adulterants, has been causing deaths in West African countries for the past six years. Recently, the DEA Special Testing & Research Laboratory (in collaboration with The Colombo Plan) conducted the first ever confirmatory analysis of Kush, highlighting the lethal nature of the drug and public health implications for the region. • Samples from Sierra Leone were found to contain a lethal mixture of nitazenes (protonitazene), synthetic cannabinoids (MDMB-4en-PINACA, ADB-BUTINACA), and cocaine, providing a plausible explanation for the cause of death among Kush users. (Photo: Melissa Phillip/AP Images/picture alliance).

Table 1.

Examples of complex mixtures or contamination of regular street drug supply with trace amounts of multiple drugs, adulterants, and contaminants. Red = Nitazene compounds, precursors, contaminants, or by-products and other synthetic opioids; Purple = Fentanyl compounds, precursors, contaminants, or by-products; Green = Synthetic benzodiazepines; Blue = Synthetic cathinones; Black = Traditional Drugs; Brown = Veterinary adulterant; Orange = Other adulterants, licit/illicit drugs, or impurities; Pink = Naloxone

Seized Drug Case: Peoria County, IL	Toxicology Case: Grand Rapids, MI
Fentanyl, Xylazine, Quinine/Quinidine, 4-ANPP, Ethyl 4-ANPP, Heroin, Phenethyl 4-ANPP, Diphenhydramine, Cocaine, 6MAM, Lidocaine, N-phenethyl-N-phenylpropionamide, Acetyl fentanyl, N-pyrrolidino iso/protonitazene, Acetylcodeine, Clonazolam, N-pyrrolidino metonitazene, Papaverine, Brorphine, Morphine, Iso/Protonitazene, Noscapine, N-propionyl, Norfentanyl, Eutylone, Methamphetamine, N-pyrrolidino etonitazene, Codeine, Norfentanyl, Butonitazene, Para-bromo 4-ANPP, Flualprazolam and Acetaminophen	Isotonitazene, para-Fluorofentanyl, Fentanyl, Heroin (Morphine, Codeine, Noscapine), Cocaine, Benzoylecgonine, Methamphetamine, Amphetamine, Diazepam, Alprazolam, 7-Amino Clonazepam, Nordiazepam, Oxazepam, Temazepam, Xylazine, Levamisole, Lidocaine, Monoethylglycinexylidide, Phenacetin, Diphenhydramine, Norfentanyl, O-Desmethyltramadol, 4-ANPP, N-propionyl Norfentanyl, Quinine/Quinidine, N-Desethyl Isotonitazene, Phenethyl-4-ANPP, Naloxone

Web Resources:

https://pharmaceutical-journal.com/article/feature/everything-you-need-to-know-about-nitazenes

https://www.oas.org/ext/DesktopModules/MVC/OASDnnModules/Views/Item/Download.aspx?type=1&id=1045&lang=1

https://www.euda.europa.eu/publications/eu-drug-markets/new-psychoactive-substances/distribution-and-supply/new-opioids_en

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Vandeputte MM, Glatfelter GC, Walther D, Layle NK, St Germaine DM, Ujváry I, Iula DM, Baumann MH, Stove CP. Characterization of novel nitazene recreational drugs: Insights into their risk potential from in vitro μ-opioid receptor assays and in vivo behavioral studies in mice. Pharmacol Res. 2024 Nov 7;210:107503. doi: 10.1016/j.phrs.2024.107503. Epub ahead of print. PMID: 39521025.

Alhosan N, Cavallo D, Santiago M, Kelly E, Henderson G. Slow dissociation kinetics of fentanyls and nitazenes correlates with reduced sensitivity to naloxone reversal at the μ-opioid receptor. Br J Pharmacol. 2024 Oct 22. doi: 10.1111/bph.17376. Epub ahead of print. PMID: 39437833.

Amaducci A, Aldy K, Campleman SL, Li S, Meyn A, Abston S, Culbreth RE, Krotulski A, Logan B, Wax P, Brent J, Manini AF; Toxicology Investigators Consortium Fentalog Study Group. Naloxone Use in Novel Potent Opioid and Fentanyl Overdoses in Emergency Department Patients. JAMA Netw Open. 2023 Aug 1;6(8):e2331264. doi: 10.1001/jamanetworkopen.2023.31264. PMID: 37642962; PMCID: PMC10466160.

Gonçalves de Araújo KR, Fabris AL, Neves LF, Soares AL, Costa JL, Yonamine M. Synthetic illicit opioids in Brazil: Nitazenes arrival. Forensic Science International: Reports Volume 10, December 2024, 100375

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The opinions, findings, recommendations, and conclusions expressed in this publication are those of the authors and do not necessarily reflect those of the U.S. Department of State. Additionally, some aspects of the work are based upon work conducted under the U.S. Department of Homeland Security Cooperative Research and Development Agreement No. 23-CBP-001. Samples were submitted by U.S. Customs and Border Protection. Opinions, findings, recommendations, and conclusions expressed in this publication are those of the authors and do not necessarily reflect those of the U.S. Department of Homeland Security (DHS) and should not be interpreted as necessarily representing the official policies, either expressed or implied, of the DHS, and do not constitute a DHS endorsement of the equipment tested.

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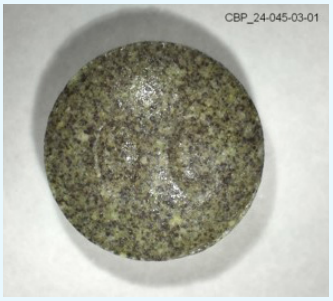
NITAZENE PILLS



Potency Compared to Fentanyl (Vandeputte et al.)	Compound
20x higher	N-desethyl-isotonitazene Etonitazene
1.5x – 10x higher	Isotonitazene **Metonitazene** N-desethyl-etonitazene Protonitazene
2x – 10x lower	Butonitazene Clonitazene Isotodesnitazene Etodesnitazene
12x – 50x lower	4'-OH-nitazene 5-aminoisotonitazene Flunitazene Metodesnitazene

THE COLOMBO PLAN

FREDRIC RIEDERS FAMILY FOUNDATION

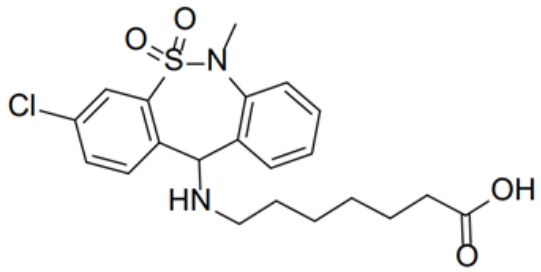
EMERGING DRUG ALERT:
TIANEPTINE

This notice is to alert substance abuse treatment providers, clinicians, public health agencies and testing labs that Tianeptine, an unapproved atypical antidepressant with opioid activity at higher doses, has been reported for sale in US gas stations and convenience stores, especially throughout the southeast United States. It has the potential to cause adverse opioid-like effects and has been linked to intoxication, overdoses, and death.

Background:

Tianeptine, popularly known as "gas station heroin" has been encountered in various forms including bulk powder and counterfeit pills mimicking hydrocodone and oxycodone. Tianeptine has been sold as "ZaZa",. "Tiana", "Neptune's Fix" and other brand names. Poison Control Center cases involving tianeptine exposure increased nationwide, from 11 total cases between 2000 and 2013 to 151 cases in 2020. As an antidepressant, tianeptine is prescribed to treat depression and anxiety in some European, Asian, and South American countries, but it is not approved for medical use in the United States. Tianeptine-containing products are marketed as dietary supplements or as "smart drugs" that allegedly enhance cognitive function. Tianeptine induces euphoria at high doses via activation of mu-opioid and dopaminergic receptors. It is also alleged to be useful to manage opioid consumption, with claims that it reduces the effects of opioid withdrawal and craving. Unregulated tianeptine is at an increased risk of contamination with adulterants, which may cause additional or unexpected side effects. Tianeptine is not currently controlled under the Controlled Substances Act, but has been scheduled in several states.

TIANEPTINE



Recommendations for Clinicians

- Since **tianeptine** activates opioid receptors, know that naloxone should be used in the acute management of **tianeptine** overdose with the conventional indication of respiratory depression.
- Be familiar with the signs and symptoms associated with **tianeptine** toxicity and withdrawal.
- Report adverse events to the FDA.

Indicators of Toxicity

Effects mimicking opioid toxicity

- Respiratory depression
- Sedation
- Loss of consciousness
- Coma

Withdrawal effects

- Agitation
- Nausea
- Vomiting
- Tachycardia
- Hypertension
- Diarrhea
- Tremor
- Diaphoresis

Recommendations for MEs & Coroners

- Consider testing for **tianeptine** when products suspicious for containing tianeptine are located at the scene, internet browsing history shows searches for tianeptine and/or analysis of seized drug evidence confirms its presence. Be alert for ZaZa, Tianna Red and other apparent supplement products at death scenes.

Recommendations for Forensic and Clinical Laboratories

- Consider toxicology testing for **tianeptine** when case history supports its use.
- Consider laboratory analysis of seized drug material or commercial products purported to contain **Tianeptine**.
- Share data with local health departments, medical examiners and coroners.

Health Impacts:

Tianeptine use carries a risk of misuse, dependence, tolerance, and overdose. A concentration of 15.5 mg/L was reported in a complex suicide case, and a concentration of 5.1 mg/L along with an ethanol concentration of 0.51 g/100mL in another fatality. Toxicological analysis has detected tianeptine in human performance impairment (e.g., intoxication, DUID) cases. In three cases submitted by Pennsylvania law enforcement for investigation of driving under the influence of drugs, tianeptine blood concentrations were found to range between 0.50 and 2.9 mg/L. The results of comprehensive toxicology testing performed on these cases are shown below.

Drug results in three human performance impairment cases where comprehensive toxicology testing was performed.	**Case 1** Amphetamine: 170 ng/mL Methamphetamine: 380 ng/mL Mitragynine: 11 ng/mL **Tianeptine: 1600 ng/mL**	**Case 2** O-desmethylvenlafaxine: 64 ng/mL **Tianeptine: 2900 ng/mL**	**Case 3** **Tianeptine: 570 ng/mL**

Tianeptine misuse has been associated with psychosis in supratherapeutic doses, particularly in individuals with a history of substance abuse or psychotic disorders. In one report, the authors describe a 28-year-old woman with a history of schizoaffective disorder, bipolar type, and polysubstance use who was admitted to inpatient psychiatry for aggressive behavior. She had also been experiencing somatic delusions with disorganized behavior and speech at the time of admission. Her symptoms were previously controlled with monthly long-acting paliperidone. During her admission, the patient reported procuring tianeptine from the Internet and friends to control her anxiety and depression, taking around 100 mg daily. The psychosis reportedly resolved after 2 days of abstinence.

Intentional ingestion of tianeptine as part of a successful suicide attempt has also been reported. In one case, a 26-year-old man was found dead in his apartment next to multiple packets of 12.5-mg tianeptine tablets. A suicide note confirmed the ingestion to be intentional. Analytical testing revealed elevated tianeptine concentrations in the blood, urine, liver, and stomach. The cause of death was attributed to suicidal ingestion of tianeptine in combination

with alcohol consumption (serum ethanol concentration: 53 mg/dL).

From 2018 to 2023 tianeptine was detected and quantified in 90 blood samples collected for death investigation purposes. In these cases, tianeptine blood concentrations ranged from 5.0 ng/mL to 47,000 ng/mL (mean: 3,841 ng/mL; median: 1,750 ng/mL). Other substances commonly co-detected in this population included amphetamine, fentanyl, gabapentin, mitragynine, and ethanol.

Analysis of Tianeptine Containing Exhibits Samples

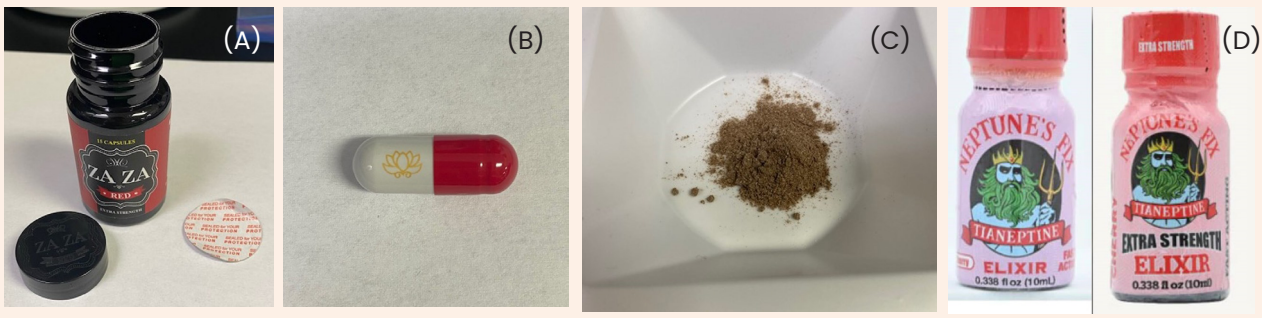
- An authentic sample of ZAZA was acquired from North Carolina. Labelling on the bottle indicates that the product contains *combretum quadrangulare leaf*, tianeptine and piper methysticum, also known as Kava. The contents of the capsule were analyzed at CFSRE via gas chromatography mass spectrometry (GC/MS) and liquid chromatography high resolution mass spectrometry (LC/QTOF-MS). Samples were diluted in solvent or mobile phase prior to analysis.
- Analysis of the product by GC/MS identified a peak consistent with a breakdown product of tianeptine. Results from the LC/QTOF-MS analysis identified tianeptine and the sedative natural product kavain, known to be present in the piper methysticum (kava) plant. Interactions between drugs with opioid effects and CNS depressant effects can be significant. In addition, more than 100 cases of liver toxicity related to the use of kava had been reported, some leading to liver transplant and some leading to death.
- The same methodologies were used by CFSRE to test another product labelled "Neptune's Fix", a flavored elixir shot associated with a series of severe clinical effects in New Jersey. The product was identified as being available at gas stations and online, and bottles were marked as containing kavain and tianeptine. Patients were described as having altered mental status, tachycardia, hypotension, seizure, and various heart rhythm changes that increase the risk of ventricular arrhythmia. In addition to tianeptine and kavain, some bottles tested positive for the synthetic cannabinoids MDMB-4en-PINACA, and ADB-4en-PINACA. More details were reported recently in the CDC's **Morbidity and Mortality Weekly Reports (MMWR).**

Evaluation of Seized Drug Samples from North Carolina Investigations

- A total of 59 random seized illicit drug samples from North Carolina were obtained and analyzed to evaluate the potential presence of tianeptine as an adulterant in the illicit drug supply. Twelve (20%) of the samples contained fentanyl, 16 (27%) were positive for cocaine, and 18 (30%) were positive for methamphetamine. Only one sample contained all three of those drugs in a mixture along with other opioids and/or adulterants. A majority of the fentanyl samples were highly lethal. Of the twelve fentanyl samples, seven (58%) contained 2 or more fentanyl compounds. None of these samples however contained tianeptine, suggesting that it is currently present in specific products (see below), and not mixed in with the general drug supply in North Carolina. This, however, should continue to be monitored.

Figure 1.

Images of (a) authentic ZAZA sample obtained from a convenience store in North Carolina; (b) intact capsule and; (c) contents from the capsule once broken open, and (d) Neptune's Fix bottle.



- In the North Carolina samples, 67% of the cases containing fentanyl also contained **xylazine**. Xylazine is a veterinary tranquilizer known to increase the sedative effects of fentanyl. These samples also contained varying amounts of other active drugs including opioids such as tramadol and heroin, and stimulants including cocaine and methamphetamine that if present in sufficient quantities could enhance the effects on the user and add to the potential lethality of the mixture.
- One North Carolina sample consisted of a combination of two designer benzodiazepines, flualprazolam and **clonazolam**, the latter posing higher risk than other designer benzodiazepines due to its ability to produce strong sedation and benzodiazepine intoxication at doses higher than 0.5 mg. Note: naloxone is not an antagonist for benzodiazepines.

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SENTINEL SNAPSHOT:
POLYDRUG COUNTERFEIT FENTANYL TABLETS

PURPOSE

Selected samples seized from the United States Southwest border are submitted to the Center for Forensic Science Research and Education (CFSRE) for testing for research purposes of qualitative and quantitative testing. The purpose of this report is provide information on an atypical batch of counterfeit tablets that was received and tested which contained multiple complex drug mixtures representing a significant health threat.

BACKGROUND

Seized tablets and powders suspected of containing fentanyl are analyzed at CFSRE using a workflow that includes microscopic imaging of tablets using the MiScope® Megapixel *MP3*, qualitative analysis by both gas chromatography mass spectrometry (GC/MS) as well as liquid chromatography quadrupole time-of-flight mass spectrometry (LC-QTOF-MS) for identification of novel substances, and quantitative analysis using Waters® Acquity UPLC coupled with a Waters Xevo® TQ-S micro.

Images of Six Different Counterfeit Tablets in a Single Atypical Case

Figure 1. The tablets pictured were differentiated from each other based on differing colors and/or monogramming. The "30" marking on Exhibits 4 and 5 appear to be similar, but were differentiated based on color comparison and diagonal of M square measurement, which for Exhibit 4 was 4.95mm and for Exhibit 5 was 5.85 mm. Exhibits 5 and 6 differed in the height of "0" measurement for the "30" monogram portion of the tablet. The height of zero measurement for Exhibit 5 was 1.50mm and for Exhibit 6 was 2.21 mm. Exhibit 3 differed from the other exhibits because it appeared degraded and the monogramming could not be visually compared to the rest of the exhibits.

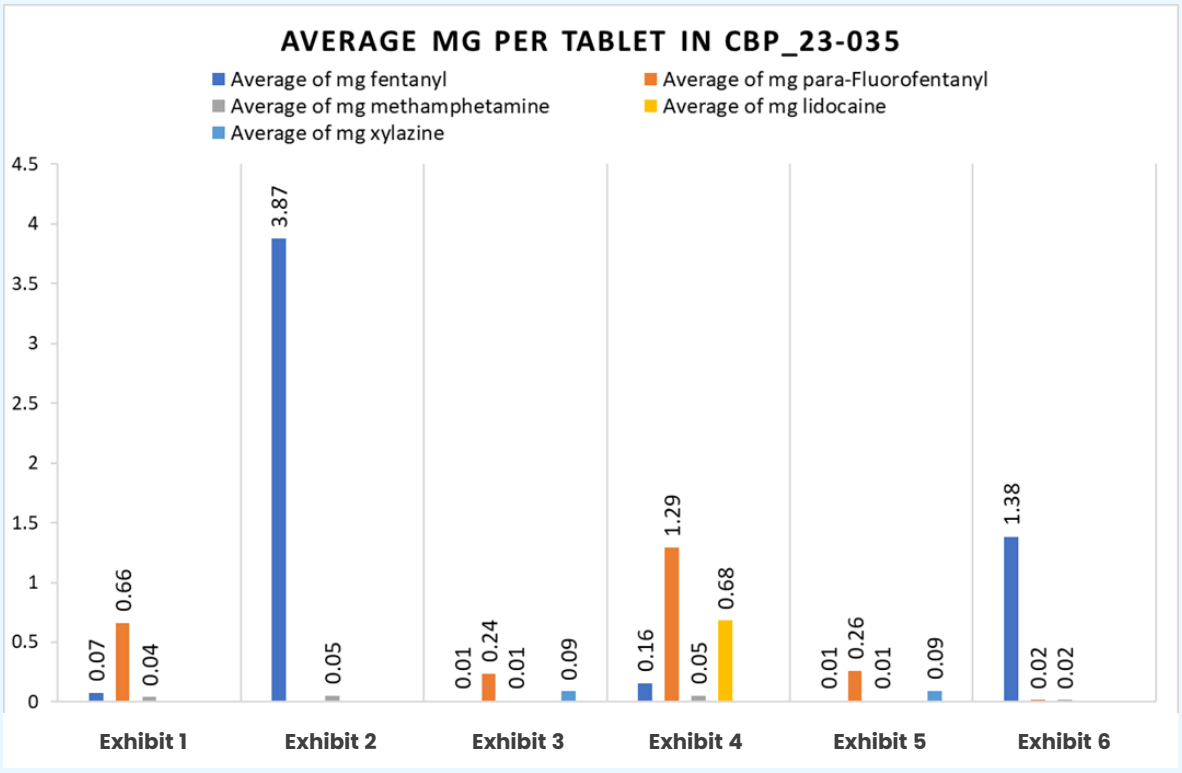
Combined Qualitative GC/MS and LC-QTOF-MS Results for All Exhibits Tested

	Fentanyl	Metamizole	Parafluoro fentanyl	Acetamino-phen	Methamphet-amine	Fluoro phenethyl 4-ANPP	Desproprionyl parafluoro-fentanyl	4-ANPP	Xylazine	Pentobarbital	Levamisole	Lidocaine
Exhibit 1	X	X	X		X	X	X					
Exhibit 2	X	X		X	X			X				
Exhibit 3	X	X	X	X		X	X		X	X		
Exhibit 4	X	X	X	X	X	X	X				X	X
Exhibit 5	X	X	X	X	X	X	X					
Exhibit 6	X	X	X	X				X	X	X		

CFSRE received a case involving suspected counterfeit tablets seized at the US Southwest Border. It consisted of six separate exhibits containing a total of 40 counterfeit tablets . One tablet was tested from Exhibits 1-3, ten tablets were tested from Exhibit 4, twelve tablets were tested from Exhibit 5, and fifteen tablets were tested from Exhibit 6.

All 40 tablets contained fentanyl and the banned analgesic metamizole. The fentanyl analog para -fluorofentanyl was present in 5 of the exhibits. Other substances present in the tablets were the psychoactive substances methamphetamine, xylazine (a veterinary sedative) and pentobarbital (a veterinary euthanasia agent). The samples also contained other adulterants including acetaminophen, lidocaine the banned anti-worming agent levamisole, and chemical reaction byproducts and precursors from illicit fentanyl manufacture.

NOTE: Although 2 mg is frequently considered a lethal fentanyl dose even in tolerant individuals, and the majority of cases analyzed contained less than 2 mg of fentanyl, almost all of these cases can still be considered potentially lethal due to the toxic and synergistic effects of adulterants such as para-fluorofentanyl, metamizole, xylazine, levamisole, methamphetamine, and pentobarbital. Much lower doses of fentanyl can also be lethal in individuals with less tolerance.



A total of 40 tablets were quantitatively tested for all six exhibits. The average mg of para-fluorofentanyl was greater than the average mg of fentanyl for 4 out of the 6 exhibits (exhibits 1, 3, 4, and 5). The average mg of acetaminophen per tablet was greater than 60% for exhibits 2-5.

EX	GC/MS FINDINGS
1	**Fentanyl**, **para-Fluorofentanyl**, **Methamphetamine** **Metamizole** Despropionyl para-Fluorofentanyl, para-Fluorofentanyl 4-ANPP
2	**Fentanyl**, **Methamphetamine** Acetaminophen, **Metamizole** 4-ANPP
3	**Fentanyl**, **para-Fluorofentanyl**, **Pentobarbital** Acetaminophen, **Metamizole** Despropionyl para-Fluorofentanyl, para-Fluorofentanyl 4-ANPP
4	**Fentanyl**, **para-Fluorofentanyl**, **Methamphetamine** Acetaminophen, **Metamizole**, Lidocaine, **Levamisole**, 4-ANPP, Despropionyl para-Fluorofentanyl, para-Fluorofentanyl 4-ANPP
5	**Fentanyl**, **para-Fluorofentanyl**, **Methamphetamine**, **Pentobarbital** Acetaminophen, **Metamizole**, **Xylazine** Despropionyl para-Fluorofentanyl, para-Fluorofentanyl 4-ANPP
6	**Fentanyl**, **para-Fluorofentanyl** Acetaminophen, **Metamizole** 4-ANPP

Fentanyl and metamizole were detected in every exhibit to a greater or lesser extent. In exhibits 1,3,4 and 5 however, the analog para-fluorofentanyl was the predominant opioid. Cutting agents highlighted in yellow can make the individual pills more potent and lethal.

	Information Regarding Adulterants Effects on Human Health
Acetaminophen	An over the counter analgesic which is used to reduce pain and fever. Overdose can result in acute liver failure. Symptoms of a possible acetaminophen overdose also includes loss of appetite, nausea, vomiting, extreme tiredness, sweating, unusual bleeding or bruising, yellowing of skin or eyes, and pain in the abdomen (especially in the upper right side). Acetaminophen was detected in 5 out of the 6 exhibits.
Levamisole	A de-worming drug that is used for veterinary practice. It is most commonly used as a cutting agent in cocaine to modify the stimulant effects of the drug. Adverse effects of levamisole use include unexplained fever and agranulocytosis (lowering of white blood cells), unexplained vasculitis (damage to blood vessels) with purple skin lesions over ear lobes, legs and thighs, persistent or recurrent fever and chills, worsening or persistent sore throat, worsening swollen glands. Levamisole may also increase the toxic effects of opioids.
Lidocaine	A local anesthetic drug approved for human use, lidocaine is added to drug samples as a filler so that not as much actual drug product is added.Because it produces a numbing effect, like cocaine, lidocaine is added to minimize the discomfort that injection or snorting of drugs usually comes with. Lidocaine toxicity can manifest as cardiotoxicity which includes symptoms of abnormal heart rhythms, low blood pressure, or altered mental status. It can also manifest as methemoglobinemia for which symptoms include, cyanosis, low blood oxygen, distressed breathing, headache, dizziness, delirium, and seizures.
Metamizole	A non-opioid analgesic that is used in Europe, South America, and Asia today to combat pain, fever, and muscle spasms. It is also commonly known as dipyrone. Metamizole was removed from the medical drug market in the United States due to frequency of agranulocytosis. Other adverse effects include nausea, vomiting, abdominal pain, diarrhea, headache, dizziness, renal dysfunctions, and others. Less common effects are aplastic anemia and anaphylaxis. Metamizole may increase toxic effects of opioids and affect naloxone ability to reverse overdose.
Pentobarbital	A barbiturate belonging to a class of sedative-hypnotic, seizure drugs which is widely used as a euthanasia agent in veterinary medicine. It has historically been used in humans as a medication used to treat or manage seizures, intercranial pressure control, and insomnia. Adverse effects of pentobarbital include altered mental status, agitation, confusion, drowsiness, respiratory depression, bradycardia, hypotension, cardiovascular collapse, dizziness, hallucinations, headache, insomnia, nausea, vomiting, hepatoxicity. Symptoms of pentobarbital toxicity include airway compromise, cardiovascular collapse, coma, and death.
Xylazine	Xylazine is a veterinary sedative used in animal surgery and sedation. It has never been approved in the US for human use due to its adverse effects. It is one of the most common adulterants in fentanyl powders in the eastern and midwestern United States. Xylazine can be dangerous when taken in combination with illicit drugs. Its toxicity symptoms include CNS depression, sedation, respiratory depression, bradycardia, skin lesions, and slowed wound healing. While naloxone can reverse opioid effects it does not reverse the contribution to sedation from xylazine.

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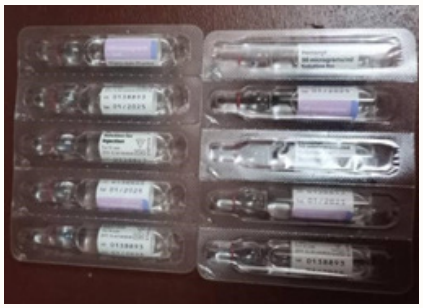
EMERGING THREAT:
INJECTABLE LIQUID FENTANYL

Public safety and public health officials worldwide should be aware of an emerging threat of diverted liquid pharmaceutical fentanyl, and other liquid forms.

This threat could have severe implications for the introduction of fentanyl into a country's illicit drug supply, or make an existing fentanyl epidemic worse.

- Fentanyl misuse or abuse typically involves injection or smoking of illicitly manufactured fentanyl (IMF). Illicit fentanyl is most commonly sold on the street as counterfeit tablets or as powders in folded glassine papers.
- Recently, however, diverted injectable solutions of pharmaceutical fentanyl have been reported in countries where IMF has not yet become established, such as Nigeria, Colombia and El Salvador (see details over); in addition to Argentina (500 vials), Brazil (72 vials), and Costa Rica (25 vials). Furthermore, there are reports of fentanyl injectable solutions being stolen or diverted from hospitals, clinics and medical supply houses in Panama (19,000 vials), the United States, and Europe.
- Pharmaceutical fentanyl citrate injection solution typically contains 50 micrograms of fentanyl citrate in each milliliter of solution (50 mcg/mL); a non lethal dose. However, injection of 5-10mL of these solutions can cause intoxication, and may lead to death in susceptible individuals or users without opioid tolerance.
- Diversion of pharmaceutical grade fentanyl in medicinal (non-lethal) doses has the potential to introduce fentanyl into local drug supplies in many countries that currently do not have a major illicit opioid problem, without attracting the attention of police and public health authorities following large overdose outbreaks.
- Not only can diverted medical fentanyl lead to opioid addiction, but when the source of diverted pharmaceutical fentanyl is shut off through interdiction or enforcement, local drug distributors and users may turn to the more dangerous powders and pills being produced by Mexican cartels to fill the demand, thereby increasing the risk of fatal overdose.
- IMF in powder and pill forms have been demonstrated to be difficult to produce consistently in non-lethal doses. The fentanyl content of these illicit pill and powder dosage forms has been shown to be highly variable which can lead to higher overdose death rates and lethal outbreaks.
- More recently, IMF in liquid (solution) form has also been seized in the United States in bulk quantities which are easier to conceal, transport and package for sale. These liquid solutions, however, can be as lethal as the standard powder and pill forms of the drug.
- Fentanyl can be recovered and concentrated in powder form from these IMF or diverted injectable solutions by chemical extraction or by evaporation, for example in a microwave, or the solutions can be directly injected. Recent U.S. seizures, however, indicate intent is for intravenous use in liquid form.
- Drug dealers may also mix adulterants (xylazine) and other drugs (e.g. cocaine, fentanyl analogs) into liquid fentanyl solutions creating complex lethal drug mixtures to mimic the effects of similarly adulterated fentanyl powders and pills.
- This health alert provides details of some of the liquid dosage forms that have been reported in international illicit drug markets. They may represent an emerging threat in countries that have not historically been exposed to illicit opioid use, or may exacerbate an existing IMF crisis like in the United States.

International Reports of Injectable Liquid Fentanyl

COUNTRY	REPORTED ACTIVITY
NIGERIA (May 2023)	• NDLEA reported the seizure of diverted pharmaceutical am-poules of fentanyl in an open-air shopping market. Each ampoule contained 50 micrograms of fentanyl in 1 ml of solution. The initial source of the fentanyl was a pharmaceutical firm in the United Kingdom. • **THREAT**: These individual ampoules represent non-lethal doses that could introduce illicit fentanyl use in countries not previously exposed to this substance. 
COLOMBIA (2023)	• Colombian National Police Antinarcotics teams intercepted shipments of medicinal fentanyl citrate in glass amber am-poules. The source of the fentanyl was a pharmaceutical manufacturer in Chile. Each ampoule contained 0.5 mg / 10 ml or 50 mcg / 1 ml of liquid fentanyl. Ampoules have been seized in Bogota, Medellin (280 vials), Tulua, and Cucuta. • **THREAT**: These individual ampoules represent non-lethal doses that could introduce illicit fentanyl use in countries not previously exposed to this substance. 
EL SALVADOR (May 2023)	• El Salvador National Police seized 500 ampoules of medici-nal fentanyl citrate along their border with Honduras. The source of the fentanyl was a health agency in Guatemala. Each ampoule contained 0.1 mg / 2 ml or 50 mcg / 1 ml of liquid fentanyl. • **THREAT**: These individual ampoules represent non-lethal doses that could introduce illicit fentanyl use in countries not previously exposed to this substance. 
HONDURAS (2023)	• In November, Honduran authoritiesseized 48,600 ampoules of medicinal-grade fentanyl packed into dozens ofsealed cardboard boxes. The shipment originated in the UK. • **THREAT**: These individual ampoulesrepresent non-lethal doses that couldintroduce illicit fentanyl use in countriesnot previously exposed to this substance. 

UNITED STATES (2023)	 • In October & November 2023, large quantities of liquid injectable fentanyl solutions were seized in Arizona. The first seizure totaled 54 gallons, while the latter totaled 64 gallons. Intent was for intravenous use, to be further broken down into vials for individual sale and consumption. In July 2023, 1.58 kg of liquid fentanyl was seized in Kentucky. • **THREAT**: Uniform individual doses of IMF liquid fentanyl would be extremely difficult to safely produce, resulting in similar risks for overdose as with traditional tablet or powder forms. The DEA estimates that only 16g of fentanyl out of the 691 kg U.S. 2022 fentanyl manufacturing quota was diverted from the medical supply. U.S. fentanyl nitrate injection solution typically contains 50 mcg / ml solution.
EUROPE (May 2021)	• In 2021, European Union member states reported to the EMCDDA approximately 140 deaths associated with fentanyl. A significant portion of these, however, were thought to be associated with fentanyl diverted from medicinal use rather than fentanyl from illicit production. https://www.emcdda.europa.eu/publications/European-drug-report/2023/drug-situation-in-europe-up-to-2023_en 

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See also:

https://www.cfsre.org/nps-discovery/public-alerts

Questions? Please email Barry.Logan@cfsre.org.

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THE COLOMBO PLAN

FREDRIC RIEDERS FAMILY FOUNDATION

TOXIC ADULTERANT ALERT:
MEDETOMIDINE/DEXMEDETOMIDINE

This alert is to warn substance abuse treatment providers, clinicians, public health agencies and testing labs that medetomidine/dexmedetomidine has been identified as an adulterant in illicit drug materials. It belongs to the same drug class as the adulterant xylazine, a veterinary tranquilizer, and has /similar adverse effects including bradycardia, hypotension, and CNS depression, however, medetomidine is considered more potent.

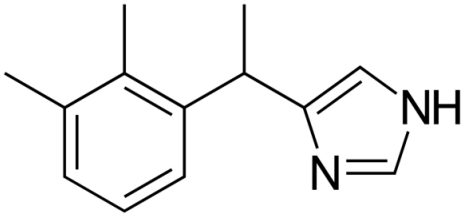
Medetomidine (Domitor®) has recently been identified as an adulterant in illicit drug material. Since July 2022, it has been detected in several seized drug samples across the state of Maryland, and in drug paraphernalia and illicit drug seizures submitted to public health and law enforcement agencies. It was most frequently observed in samples containing fentanyl and xylazine, though medetomidine has also been identified together with fentanyl analogs, heroin, and cocaine. Medetomidine has also been detected in overdoses in St. Louis and clandestine laboratory seizures in Ohio, Florida, and Canada. It is typically a minor component in the these samples, but is of toxicological concern.

Background:

Medetomidine is a potent surgical anesthetic approved for veterinary use in both large and small animals. Another form of the drug, its dextro-isomer dexmedetomidine (Dexdor®, Precedex®) is also utilized in human medicine. Clinically, it is used to induce sedation, analgesia, anxiolysis, and muscle relaxation in both humans and animals. The compound belongs to the class of α2-adrenoceptor agonists, which also includes xylazine, romifidine, and detomidine. Veterinary studies have shown medetomidine to be a more potent, selective, and specific agonist in the peripheral and central nervous systems than xylazine.

To date, reports involving human poisonings with medetomidine/dexmedetomidine are rare. An unintentional poisoning involving medetomidine and a related compound, detomidine, of a farmer working with livestock has been reported. The farmer experienced significant drowsiness, dizziness, CNS relaxation, bradycardia, and hypotension before making a full recovery. A three year old child accidentally administered 100ug of dexmedetomidine had bradycardia and reduced respiration and was unconscious for seven hours, before recovering.

MEDETOMIDINE



Recommendations for Clinicians

- Be aware that illicit drugs may contain **medetomidine** which can complicate the clinical presentation.
- Be familiar with the signs and symptoms associated with **medetomidine** intoxication.
- Be aware that most hospital-based clinical laboratories do not offer **medetomidine** toxicology testing.

Indicators of Toxicity

- Sedation
- Analgesia
- Dry mouth
- Respiratory depression
- Hypnotic/anesthetic effects
- Mydriasis
- Hypothermia
- Spontaneous muscle contractions (twitching)
- Bradycardia
- Initial hypertension, followed by prolonged hypotension

Recommendations for MEs & Coroners

- Test for common adulterating agents in suspected opioid– or fentanyl– related death cases where medetomidine may be present.

Recommendations for Forensic and Clinical Laboratories

- Consider monitoring for **medetomidine** during routine testing.
- Develop sensitive confirmatory procedures for common adulterating agents, including **medetomidine**.
- Consider laboratory analysis of seized drug samples taken from suspected drug overdose. investigations.
- Share data on adulterants in drug seizures in your jurisdiction with local health departments, medical examiners, and coroners.
- Share data with local health departments, medical examiners and coroners.

Health Impacts:

Medetomidine has been identified as a component in illicit drug samples.

Commonly known side effects of medetomidine include dose-dependent sedation, analgesia, anxiolysis, and muscle relaxation.

While dexmedetomidine is used frequently in human medicine, reports on medetomidine administration in humans is limited but demonstrates an α2-agonistic mechanism of action. In general, medetomidine studies in humans have shown dose-dependent hypotension and bradycardia. Both subjective and objective sedative effects have been observed after single intravenous doses, including sedation noted after a dose of 25 mcg. Medetomidine also reduces norepinephrine and increases human growth hormone levels in plasma.

Animal studies have shown the following adverse effects:

Cardiovascular effects: Initial, short-lived hypertension followed by dose-dependent hypotension and bradycardia.

Increased chance of arrythmias.

Respiratory effects: Decreased respiratory rates and overall respiratory depression.

At high doses, hypnotic or anesthetic effects as well as spontaneous muscle contractions can occur.

Induces dose-dependent mydriasis.

Medetomidine-induced sedative effects can be inhibited in animals with α2- adrenoceptor antagonists, including atipamezole and yohimbine, however this has not been formally evaluated in humans.

The adverse symptoms of medetomidine/dexmedetomidine over-exposure should be treated with supportive respiratory care and management of blood pressure. Medetomidine does not respond to naloxone (Narcan®). However, naloxone administration is recommended inillicit drug exposure because medetomidine is almost always found in combination with opioids.

Similar to warnings with xylazine, concomitant use of medetomidine with cocaine, opioids, or a combination may potentiate or prolong the effects of these drugs, which can lead to adverse consequences.

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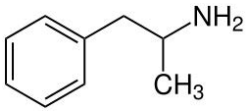
PUBLIC HEALTH ALERT:
COUNTERFEIT CAPTAGON

Synonyms: Captagon, fenethylline, amphetaminoethyltheophylline, amfetyline

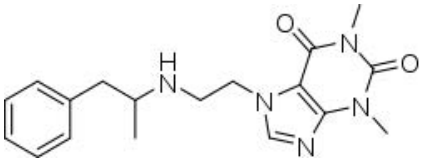
Captagon®, the trade name for fenethylline, an amphetamine prodrug, was originally developed by a German company in 1961 as a psychostimulant and eventually used in the treatment of narcolepsy and attention deficit disorder. Because of its side effects, fenethylline became a Schedule I controlled substance in the United States in 1981, was scheduled internationally in 1986, and its licit manufacture ceased. Most of the remaining stock of Captagon® was destroyed, but some was exported to the Middle East, where it became popular as an illicit stimulant. Once the original supply ran out and fenethylline was no longer available, counterfeit captagon tablets bearing the same monogramming of two offset stylized "C's" (photo), but containing amphetamine in place of fenethylline began to appear. Today, these tablets also contain a variety of adulterants as discussed below. Counterfeit captagon tablets containing amphetamine are now the major drug used illicitly in the Middle East, where they are predominantly manufactured, although their distribution has now spread to parts of Europe. Although there is illicit demand for amphetamine-type substances (ATS) in the US, as of August 2023, there is no evidence of widespread presence of counterfeit amphetamine-containing captagon tablets in the US. CFSRE and The Colombo Plan encourage vigilance for the emergence of these characteristic counterfeit dosage forms in the US drug supply and would encourage any investigators or laboratories who encounter them to notify us at contact@cfsre.org.

Composition of Counterfeit Captagon Tablets

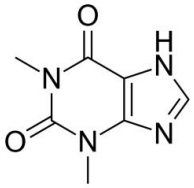
- Fenethylline was a co-drug and pro-drug of both amphetamine and theophylline (see figure) and although the EMCDDA and the UNODC report that amphetamine has replaced fenethylline in all seizures of counterfeit captagon tablets, some of these tablets do contain theophylline as an adulterant. Theophylline, has non-sympathomimetic CNS stimulant properties. Other adulterants identified in captagon tablets by CFSRE and the Forensic and Laboratories Department of the Public Security Directorate in Amman Jordan include caffeine, acetaminophen, diphenhydramine, quinine, methamphetamine, ephedrine,



Amphetamine



Fenethylline



Theophylline

chlorpheniramine and 8-chlorotheophylline. A significant percentage of tablets analyzed contain mostly caffeine and no amphetamine.

- In 2021, EU Member States reported 22,000 seizures of amphetamine, amounting to 7 tonnes.
- Türkiye seized 3.5 tonnes including 13.8 million tablets described as 'captagon' (2.9 million in 2020).
- The average purity of amphetamine at the retail level in European markets has increased by 41% over the past decade, while the price has remained relatively stable. Counterfeit captagon tablets seized in Saudi Arabia in 2021 were determined to contain between 16% and 41% amphetamine, along with significant levels of additives such as caffeine. The tablets also contained small amounts (<0.5%) of methamphetamine.
- Based on typical 170mg tablets, this would reflect an average dose of 27 to 71mg of amphetamine per tablet.

Effects of Amphetamine Psychostimulants:

The principal sympathomimetic stimulants in counterfeit captagon tablets are amphetamine, and to a much lesser extent, methamphetamine. These drugs promote the synthesis and release of the neurotransmitters dopamine, serotonin and norepinephrine. Amphetamine is used therapeutically to treat ADHD and narcolepsy. At therapeutic doses (0.25mg/Kg), the effects include wakefulness, improved alertness, increased pulse and blood pressure, elevated mood and increased motor activity.

Recreational use of amphetamines typically starts in the 50-100mg single dose range, characterized by marked excitability, euphoria, rapid speech, rapid flight of ideas, marked motor restlessness, tachycardia, and hypertension. Other effects include high blood pressure, rapid heart beat, seizures, and vasoconstriction. With chronic use, there can be paranoia, panic, and delusions. Following repeated high dose use, on cessation, users can experience withdrawal characterized by lethargy, sleepiness, CNS depression, anergia and anhedonia. Effects are more intense with IV or smoked routes of administration.

Adulterants in Counterfeit Captagon Tablets

Adulterants are added to illicit drugs as cutting agents to add bulk, and sometimes for their additive or synergistic effects. In the case of counterfeit captagon tablets, where only 16 to 41% of the tablet's content may be amphetamine, the remaining constituents will include binders (microcrystalline cellulose, sugars, starch) to help maintain the integrity of the tablet during tableting, but most pills also contain other active pharmaceuticals. In the case of captagon tablets, a number of adulterants have been identified, most commonly caffeine, acetaminophen, diphenhydramine, chlorpheniramine and others. These drugs can contribute to the effect of the amphetamine, or present their own constellation of symptoms. Below, we discuss some of the properties of the major adulterants in counterfeit captagon tablets.

Adulterant	Interactions
Theophylline	Theophylline is similar in chemical structure and effects to caffeine (see below), and is also a bronchodilator used to treat asthma. Side effects include tachycardia and cardiac arrhythmia, nausea/vomiting, stomach/abdominal pain, headache, trouble sleeping, diarrhea, irritability, restlessness, and nervousness. Theophylline can add to the excitatory effects of the amphetamine in counterfeit captagon. Fenethylline itself is broken down in the body to theophylline, so this may be the reason for its selection as an adulterant for counterfeit captagon. It is occasionally found as an adulterant in other drugs.
Caffeine	Caffeine is a non-sympathomimetic stimulant that improves wakefulness and alertness, and physical energy. Side effects of caffeine cause insomnia, nervousness, restlessness, nausea, increased heart rate, and other side effects (e.g., abnormal heart rhythm). Larger doses can cause headache, anxiety, and chest pain.
Diphenhydramine/ Chlorpheniramine	These drugs are over-the-counter antihistamines with sedative properties and will cause drowsiness. They can also cause dizziness, dry mouth/ eyes, blurred vision, and rapid heart rate. Sedatives and stimulants do not cancel out each others cognitive effects, but rather create a more complex impairment with contributions from excitation, euphoria, slowed or fuzzy thinking, impaired decision making, and impulsiveness. During amphetamine withdrawal, antihistamines can add to the depressant rebound effects of the abstinence syndrome.
Ephedrine	Ephedrine is a commonly used over-the-counter stimulant and precursor for amphetamine synthesis that can lead to increased alertness and energy. It can also result in side effects such as restlessness, nervousness, rapid heartbeat, and elevated blood pressure. Combining ephedrine with sedatives or other stimulants can create a more intricate cognitive impact, involving heightened arousal, potential euphoria, as well as challenges with focus, decision-making, and impulsiveness.
Allopurinol	Allopurinol is a widely used medication, primarily prescribed for managing conditions like gout and hyperuricemia. By reducing the production of uric acid in the body, allopurinol helps prevent the formation of painful urate crystals. While generally well-tolerated, it's important to be aware of potential side effects such as skin rash, gastrointestinal disturbances, and, rarely, severe hypersensitivity reactions. The drug has also been associated with rare but significant conditions such as leukopenia, thrombocytopenia, agranulocytosis, and renal function.
Local anesthetics	Local anesthetic agents such as lidocaine, benzocaine, and procaine are frequently used as adulterants in various drugs and have been detected in counterfeit captagon tablets. Large amounts of local anesthetic or rapid absorption into the bloodstream can potentially lead to cardiovascular effects like lowered blood pressure, an irregular heartbeat, or even cardiac arrest. Benzocaine has been associated with methemoglobinemia.
Trimethoprim	Trimethoprim is an antibiotic commonly used to treat bacterial infections. It has also been documented as an adulterant in counterfeit captagon tablets. Serious side effects from excessive exposure to trimethoprim can include lower white blood cell count and liver damage.

Adulterants in Counterfeit Captagon Tablets

Origins of Counterfeit Captagon in the Levant

Recent intelligence has spotlighted major production centers for counterfeit captagon tablets in the Levant, the region of the Middle East encompassing Syria, Jordan, Lebanon, Iraq and parts of Israel and Palestine. The clandestine production of this counterfeit drug has reached significant proportions, fueling a booming black market. The Levant, known for its porous borders and fragmented authorities, has become an ideal location for these illegal activities. Criminal syndicates exploit weak law enforcement, corrupt officials, and political instability, allowing them to establish sophisticated production networks. These networks span across multiple countries, enabling the transit of precursor chemicals and distribution of the final product. Consequently, the Levant is witnessing a surge in drug-related crimes and addiction, posing significant challenges and threats to the region's socio-economic stability. Major seizures of counterfeit captagon have been made in Turkey, Lebanon, Saudi Arabia and major port cities in Southern Europe.

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THE COLOMBO PLAN

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The Center for Forensic Science Research & Education

TOXIC ADULTERANT ALERT:
PHENYLBUTAZONE: A TOXIC ADULTERANT FOUND IN ILLICIT STREET DRUGS

Substance abuse treatment providers, clinicians, outreach workers, public safety and public health agencies should be aware of the following information. Phenylbutazone ("Bute", Phenylcare®) has been identified as an adulterant in illicit drug material. In a review of case data from NMS Labs from 2016-2021, 116 seized drug samples from Pennsylvania were identified as containing phenylbutazone. This represents a small percentage of total samples analyzed during the time frame. Xylazine, which is now a national concern, first emerged in the northeast (principally Pennsylvania) before spreading across the United States. As phenylbutazone has been gaining prominence in Pennsylvania over a five-year period, the possibility exists that it too can spread nationwide. This adulterant was most frequently observed in samples containing heroin, fentanyl and/or fentanyl derivatives. In addition to illicit drug samples, there have been reports in the literature of adulteration of herbal medicines and supplements with phenylbutazone and self-medication with phenylbutazone prescribed by veterinarians. The serious adverse effects of phenylbutazone can include gastrointestinal bleeding, liver and kidney damage, and blood disorders.

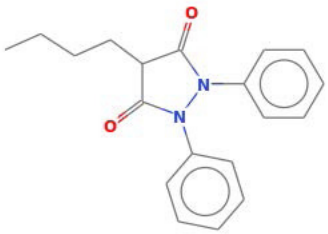
Background:

Phenylbutazone is a nonsteroidal anti-inflammatory drug (NSAID) introduced in the 1950s that has analgesic and anti-inflammatory properties. It inhibits the enzyme cyclooxygenase (COX), preventing prostaglandin creation. Phenylbutazone is highly absorbed when taken orally. It is highly bound to protein in plasma and has a low volume of distribution. Its half-life is widely variable but averages 70 hours. It is metabolized to oxyphenbutazone, 3'-hydroxyphenylbutazone, dihydroxyphenylbutazone, and glucuronides. Oxyphenbutazone is an active metabolite. Phenylbutazone was prescribed to treat arthritis, gout, and ankylosing spondylitis. Quickly after its introduction, side-effects were noted in patients using phenylbutazone both short and long term. **Phenylbutazone was largely discontinued from human use after reports of deaths caused by the medication**. It continues to be used in veterinary medicine, specifically for treating lameness, pain, and inflammation in horses.

Table 1. Phenylbutazone Positivity in Seized Drug Cases in PA 2016-2021

Year	No. of Positive Phenylbutazone Samples	Most Common Additional Findings
2016	15	Heroin, Fentanyl, Caffeine
2017	23	Heroin, Fentanyl, Xylazine, Additional Adulterants
2018	4	Heroin, Fentanyl, Xylazine, Additional Adulterants
2019	18	Heroin, Fentanyl, Xylazine, Additional Adulterants
2020	37	Heroin, Fentanyl, Acetylfentanyl, Xylazine, Additional Adulterants
2021	19	Heroin, Fentanyl, para-Fluorofentanyl, Valeryl Fentanyl, Cocaine, Tramadol, Xylazine, Additional Adulterants

PHENYLBUTAZONE



Recommendations for Clinicians

- Be aware that illicit drugs (mostly heroin or fentanyl) may contain **phenylbutazone** which can complicate the clinical presentation.
- Be familiar with the signs and symptoms associated with **phenylbutazone** toxicity.
- Be aware that most hospital-based clinical laboratories do not offer **phenylbutazone** toxicology testing.

Frequent Indicators of Toxicity

- Rash
- Blurred Vision
- Nausea/Vomiting/Diarrhea
- Edema
- Stomach pain
- GI bleeding
- Aplastic anemia
- Agranulocytosis
- Low blood pressure
- Confusion
- Incoordination
- Coma
- Convulsions
- Kidney failure
- Liver failure

Recommendations for MEs & Coroners

- If NSAID poisoning is suspected, conduct toxicology testing for **phenylbutazone** in opioid-related fatalities.

Recommendations for Forensic and Clinical Laboratories

- Consider including **phenylbutazone** in the routine scope of testing.
- Develop sensitive confirmatory procedures for common adulterating agents, including **phenylbutazone**
- Consider laboratory analysis of seized drug samples taken from suspected drug overdose investigations.
- Share data on adulterants in drug seizures in your jurisdiction with local health departments, medical examiners and coroners.

Health Impacts:

Phenylbutazone has been identified in illicit opioid drug samples. Adverse effects of phenylbutazone included rash, blurred vision, tinnitus, dizziness, headache, and edema. Gastrointestinal symptoms can include nausea, vomiting and diarrhea, stomach/abdominal pain, ulcers, and bleeding. Phenylbutazone overdose can also cause hepatitis, kidney failure, and congestive heart failure. Serious blood disorders like agranulocytosis, leukopenia, thrombocytopenia, and aplastic anemia have also occurred and, in some cases, led to death at therapeutic doses. Toxic effects are more frequently seen when daily doses are greater than 600 mg or serum concentrations are greater than 100 mg/L, but have been noted at lower levels.

Treatment of phenylbutazone toxicity is generally supportive care, similar to poisonings involving other NSAIDs. Supportive care can include maintaining an airway, correcting metabolic imbalances, and fluid resuscitation. There are mixed reports on the use of dialysis and hemoperfusion to treat phenylbutazone toxicity, as it is highly protein bound and elimination will be minimal. If phenylbutazone exposure occurs through a mechanism other than intravenous opioid use, such as ingestion of adulterated herbal supplements or diversion of veterinary medicine, gastric lavage and activated charcoal may be useful.

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The opinions, findings, recommendations, and conclusions expressed in this publication are those of the authors and do not necessarily reflect those of the U.S. Department of State. More information on phenylbutazone is available by contacting mandi.mohr@cfsre.org.

PUBLIC ALERT:

ADVERSE EFFECTS LINKED TO NEXT GENERATION OPIOIDS REPORTED IN PATIENTS PRESENTING TO EMERGENCY DEPARTMENTS AFTER SUSPECTED OPIOID OVERDOSE

Purpose:

The objective of this announcement is to notify public health and safety, clinicians, law enforcement, first responders, medical examiners and coroners, forensic and clinical laboratory personnel, and all other related communities about new information surrounding new generation synthetic opioids in clinical settings after suspected opioid overdoses and presentation to emergency departments, including: **metonitazene, *N*-piperidinyl etonitazene, isotonitazene, and brorphine.**

Overview:

Drug use can lead to adverse events and overdose scenarios where individuals present to emergency departments for clinical evaluation and/or treatment. The culprit can be traditional drugs (e.g., heroin, fentanyl, cocaine, methamphetamine) or novel psychoactive substances (NPS); however, proper drug testing methodologies must be employed for accurate identification and characterization. Street-level drug preparations can contain undeclared or unwanted substances, such as toxic adulterants or NPS, which can potentiate effects or lead to adverse reactions. Understanding emerging drugs can help direct new or revised approaches to clinical treatment and harm reduction efforts.

Objective:

A partnership between the American College of Medical Toxicology (ACMT) and the Center for Forensic Science Research and Education (CFSRE) was established to comprehensively assess the role and prevalence of synthetic opioids and other drugs among suspected overdose events in the United States. Patients with a suspected opioid overdose presented to an emergency department at a participating site within ACMT's Toxicology Investigators Consortium (ToxIC). Residual, discarded biological samples were obtained for testing against an expansive library of drugs and other substances. Our findings provide a near real-time assessment of the drug market and allude to resulting implications on clinical institutions. Analysis was performed via liquid chromatography quadrupole time-of-flight mass spectrometry (LC-QTOF-MS). The scope of testing targeted more than 950 drugs. Drug classes included opioids, stimulants, cannabinoids, and benzodiazepines, among others.

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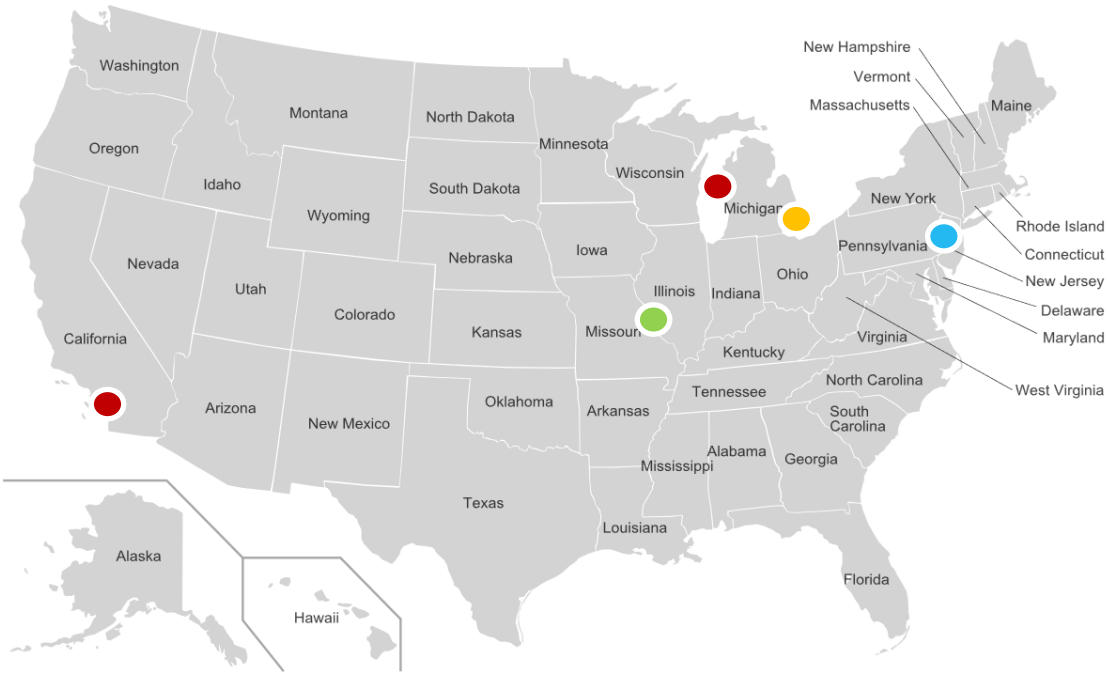
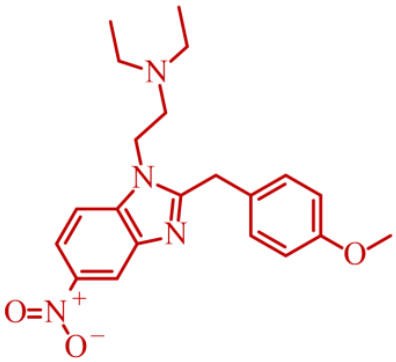


Metonitazene

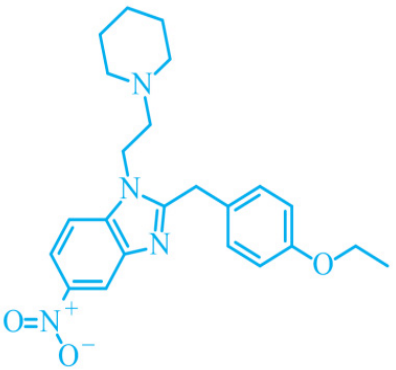


Metonitazene was identified in toxicology samples collected from two patients exhibiting signs and symptoms of suspected opioid overdose. These patients presented to emergency departments in two different states. Both patients were female with approximate ages between 20 and 50 years. The **two patients presented in cardiac arrest** — a significant clinical finding not noted with other next generation opioids presented herein. One patient received 6 mg of naloxone while the second received 10 mg. Positive response to naloxone administration was noted. One patient died.

Comprehensive toxicology testing on serum showed the co-presence of fentanyl (n=2), clonazolam (n=2), flubromazolam (n=1), methamphetamine (n=1), and cocaine (n=1), in addition to other therapeutic drugs, adulterants, and metabolites.

Additional Resource: Krotulski et al. (2021) Metonitazene in the United States—Forensic toxicology assessment of a potent new synthetic opioid using liquid chromatography mass spectrometry. Drug Testing and Analysis. 13, 1697-1711.

N-Piperidinyl Etonitazene

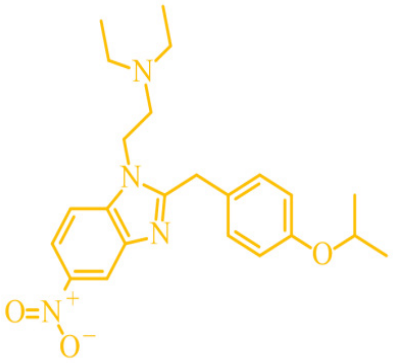


***N*-Piperidinyl Etonitazene** was identified in toxicology samples collected from three patients exhibiting signs and symptoms of suspected opioid overdose. All three patients presented to one location. Two patients were male and one was female with approx. ages between 30 and 60 years. **Two patients reported the use of cocaine and denied opioid use; one patient reported the use of "heroin" and alprazolam.** Patients received 1-2 doses of naloxone with noted positive response. Opioid toxicity recurrence was also noted.

Comprehensive toxicology testing showed the co-presence of fentanyl (n=2) and cocaine (n=2), in addition to therapeutic drugs, adulterants, and metabolites. In one patient denying opioid use, ***N*-piperidinyl etonitazene was the only opioid detected** (cocaine metabolite positive).

Additional Resource: *N*-Piperidinyl Etonitazene New Drug Monograph (2021)

Isotonitazene

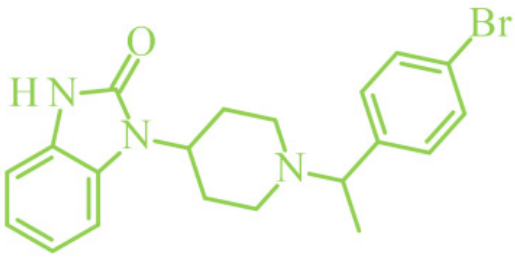


Isotonitazene was identified in toxicology samples collected from two patients who presented to one emergency department experiencing **depressed levels of consciousness.** Patients were male and female with approximate ages between 40 and 50 years. Both reported use of "heroin" prior to overdose. The two patients received two doses of naloxone each, the first coming from a bystander. Positive responses to naloxone were noted for both patients.

Comprehensive toxicology testing on serum samples showed the co-presence of fentanyl (n=2), heroin (n=2), methamphetamine (n=2), cocaine (n=1), and para-fluorofentanyl (n=1), in addition to various other therapeutic drugs, adulterants, and metabolites.

Additional Resource: Krotulski et al. (2020) Isotonitazene Quantitation and Metabolite Discovery in Authentic Forensic Casework. Journal of Analytical Toxicology. 44, 6, 521–530.

Brorphine



Brorphine was identified in toxicology samples collected from two patients who presented to an emergency department in one state. The patients presented with **respiratory depression** and one patient had **decreased oxygen saturation**. Patients were male and female with approximate ages between 30 and 60 years. The two patients received approximately 2 mg of naloxone each with noted increased respiratory rate and oxygenation.

Comprehensive toxicology testing on serum samples showed the co-presence of fentanyl (n=2), methamphetamine (n=2), cocaine (n=2), clonazolam (n=1), eutylone (n=1), and heroin (n=1), in addition to various other therapeutic drugs, adulterants, and their metabolites.

Additional Resource: Krotulski et al. (2020) Brorphine—Investigation and quantitation of a new potent synthetic opioid in forensic toxicology casework using liquid chromatography-mass spectrometry. Journal of Forensic Science. 66, 2, 664-676.

Drug	EC_{50} (nM)*
Morphine	338
Brorphine	30.9
Fentanyl	14.2
Metonitazene	8.14
Isotonitazene	1.63

*Vandeputte et al. (2021) Synthesis, Chemical Characterization, and μ-Opioid Receptor Activity Assessment of the Emerging Group of "Nitazene" 2-Benzylbenzimidazole Synthetic Opioids. ACS Chemical Neuroscience. 12, 7, 1241–1251.

THE COLOMBO PLAN

FREDRIC RIEDERS FAMILY FOUNDATION

JMJ Technologies
Medical Research and Development

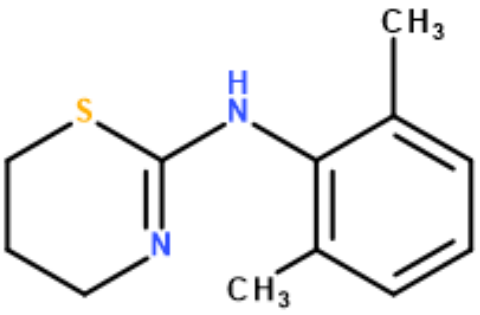
PUBLIC HEALTH ALERT
XYLAZINE: A TOXIC ADULTERANT FOUND IN ILLICIT STREET DRUGS

Substance abuse treatment providers, clinicians, outreach workers, public health clinics, etc. need to be aware of the following information.
Xylazine is commonly used as an adulterant in heroin. Xylazine is also frequently found in a combination with heroin and cocaine called a "speedball". Adulteration of illicit drugs with xylazine has become a serious health concern for public health officials and drug users.
The drug has been implicated as a cause, or contributing cause, of death in several cases both alone and in combination with other drugs.
The most common side effects in humans associated with xylazine poisoning include bradycardia, respiratory and CNS depression, hypotension, and other changes in cardiac output. **CONCOMITANT use of xylazine with heroin, cocaine and/or both can result in synergistic effects that may increase the risk of an overdose and/or of death.**

Background:

Xylazine was discovered as an antihypertensive agent in 1962 by Farbenfabriken Bayer in Germany. Due to its hazardous side effects, including sedation, hypotension and bradycardia, it was not approved by the Food and Drug Administration (FDA) for human use. The FDA did however approve it for veterinary use, and it is now used as an animal tranquilizer and a sedative, analgesic and muscle relaxant. It may be sold under the trade names Rompun®, Anased®, Sedazine®, and Chanazine®. Xylazine is not a controlled substance in the United States and only requires a veterinary prescription to obtain. It has emerged as an adulterating agent in many illicit drug products, including cocaine, heroin, fentanyl and combinations of these substances. Xylazine can be used as a drug of abuse alone and as a drug for attempted sexual assault or poisoning. Xylazine is referred to as "Tranq Dope" on the street in the United States or "Anestecia de Caballo" in Puerto Rico. The drug has been implicated as a cause, or contributing cause, of death in several cases both alone and in combination with other drugs.

XYLAZINE



Recommendations for Clinicians

- Be aware that illicit drugs may contain toxic adulterating substances that may complicate the clinical presentation.
- Become familiar with the signs and symptoms associated with xylazine toxicity.
- Be aware that routine hospital drug tests will not disclose the presence of xylazine, which requires a special test.

Frequent Indicators of Xylazine Toxicity

- CNS Depression
- Sedation
- Respiratory depression
- Initial hypertension followed by hypotension
- Bradycardia (Slow heart rate)
- Skin lesions
- Slowed wound healing
- Frequent, persistent or worsening skin infections
- Miosis
- Hyperglycemia

Recommendations for MEs & Coroners

- Test for common adulterating agents in suspected stimulant- or opioid-related death cases where xylazine may be present.

Recommendations for Forensic and Clinical Laboratories

- Include xylazine in the scope of testing.
- Develop sensitive confirmatory procedures for common adulterating agents, including xylazine.
- Consider laboratory analysis of seized drug samples taken from suspected drug overdose investigations.
- Share data on drug seizures in your jurisdiction with local health departments, medical examiners and coroners.

Xylazine Positivity Reported in Seized Drug Testing in the United States

State	*Xylazine Positives*	*% Positivity*
Pennsylvania (n=269)	32	10.8%
Maryland (n=32)	3	9.3%
Ohio (n=190)	26	8.8%
Vermont (n=315)	7	2.2%
Kentucky (n=200)	1	0.5%

- An ongoing project at the FRFF (2017-present), supported by The Colombo Plan and JMJ Technologies, is the analysis of seized drug extracts for the presence of toxic adulterants. A summary of the xylazine findings by state can be found below. Xylazine was commonly identified in cases containing fentanyl, heroin, or a combination of the two.

Xylazine Positivity Reported in Syringe Testing in the United States and Puerto Rico

- In a study by ***Fiorentin et. al. (2020)***, xylazine was identified in 2.2% of drug positive syringes tested. Syringes were obtained from the New York City Department of Health and Mental Hygiene in 2017. Xylazine was identified in combination with heroin only or heroin/fentanyl, heroin/cocaine combinations.
- In a study by ***Rodriguez et. al. (2008)***, xylazine was found in 37.6% of used-syringe collections. Syringes were collected at 29 sites located throughout Puerto Rico in 2005 and 2007. Xylazine was most commonly found in "speedball" preparations (90.6%). The study noted xylazine use was associated with the presence of a skin ulcer.

Health Impacts:

Ingesting xylazine alone or in combination with illicit drugs can cause severe hypotension and severe central nervous system depression.

In a study reviewing 76 xylazine reports to Texas Poison Centers between 2000-2014, the most common clinical effects were drowsiness or lethargy (47%), bradycardia (20%), hypotension (11%), hypertension (9%), puncture wound (8%) and slurred speech (8%). In 2019, Michigan, Ohio and Maryland poison centers reported opioid overdose deaths where xylazine may have contributed or was confirmed. The reports note naloxone may not reverse xylazine toxicity, but reverse respiratory depression associated with other opioids likely to be present.

Coadministration of xylazine and heroin produces a stronger high than administration of heroin alone. Research shows similar pharmacological effects of xylazine and heroin, may create synergistic toxic effects in humans. **Xylazine** alone has proven harmful to humans and even more so when combined with illicit drugs. **Concomitant use of xylazine with cocaine, opioids or a combination may potentiate or prolong the effects of these drugs, which can lead to adverse consequences. The risk of a fatality may increase with use of drugs adulterated with xylazine, especially when found in combination to opioid-related drugs due to the increased respiratory depression effects of opioids.**

The adverse symptoms of xylazine exposure should be treated with supportive respiratory care and management of blood pressure. There are mixed reports about whether xylazine responds to Naloxone (Narcan®). More severe cases of intoxication can lead to further complications and/or death.

Health providers should consider the possibility of exposure to xylazine in patients with the following symptoms: central nervous system symptoms, respiratory depression, cardiovascular effects, hyperglycemia and miosis. Additional effects that are rare but can occur include: hypotonia, dry mouth, urine incontinence, and changes in cardiac output.

COVID-19 Risks: Compromises the cardiovascular and respiratory systems.

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The opinions, findings, recommendations, and conclusions expressed in this publication are those of the authors and do not necessarily reflect those of the U.S. Department of State. More information on xyalzine is available by contacting mandi.mohr@frfroundation.org.

Xylazine Toxicity – Diagnosis and Treatment

Signs & Symptoms of Intoxication

Physical	Behavioral
Hypotension Bradycardia Miosis Hyperglycemia Sedation	CNS Depression Similar to opioid intoxication Appears high

Signs & Symptoms of Overdose

Physical	Behavioral
Hypotension or hypertension Bradycardia Hyperglycemia Sedation, respiratory depression or respiratory arrest Cardiac dysrhythmias Muscle relaxation	CNS Depression Similar to opioid overdose Obtundation

Provider Response

Physical	Behavioral
IV Fluids Manage hyperglycemia with insulin as needed If bradycardia severe, consider atropine ECG monitoring Supportive care	Avoid CNS Depressants

Provider Response

Physical	Behavioral
Naloxone (multiple doses may be necessary) Manage hyperglycemia with insulin as needed Oxygen Intubation if indication If bradycardia severe, consider atropine EGC monitoring Monitor K and Mg; replace as needed Supportive care	Avoid CNS Depressants

FURTHER TREATMENT NEEDED:

Naloxone has a short half life and multiple doses over 4-8 hours may be necessary.

TOXIC ADULTERANT PREVALENCE IN THE UNITED STATES ILLICIT DRUG SUPPLY: GEOGRAPHICAL TRENDS AND RAISING AWARENESS REGARDING THEIR DANGERS TO PROMOTE PUBLIC HEALTH

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Introduction

Adulterants are pharmacologically active substances which can readily be obtained and added to drug street samples to increase bulk. The addition of these agents can have dangerous and toxic effects to the consumer through additive or synergistic effects with the principal drug. The profile of adulterants in street drugs is in constant flux based on their availability and changes in market preference. Comprehensive testing of all substances in each sample allows for monitoring of emerging drug trends that ultimately impact the treatment and outcomes of acutely intoxicated patients.

Methods

Deidentified seized drug samples (n=2,031) were received from eleven forensic laboratories across the United States (U.S.) between March 2022 and July 2023. Sites included the Northeast (NH, PA, VT), Midwest (IL, IN, OH), Southeast (GA, WV, KY, FL), and Southwest (TX). All samples were shipped as dried extracts and reconstituted with 90:10 5mM ammonium formate in H2O: 0.1% formic acid in acetonitrile and analyzed using a Waters ACQUITY UPLC® I Class Waters Xevo® G2-S QTOF. Analytical separation was achieved using an ACQUITY UPLC® BEH C18 (2.1 mm x 150 mm, particle size 1.8 micron) column at 50˚C with a flow rate of 0.4 mL per minute and 5 µL injection. The Xevo® G2-S QTOF operated in positive electrospray ionization resolution mode (50-1000 m/z) with collision energy of 10-40 eV. Data was processed using UNIFI® Scientific Information System against an in-house library containing >1,000 drugs, including a wide range of adulterants, precursors, and by-products along with controlled substances and a broad range of novel psychoactive substances (NPS).

Results

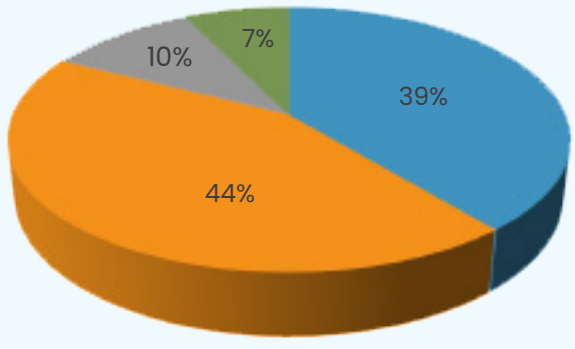


Figure 1. Overview of the Percentage of Adulterants in All Positive Samples (n=2,027)

- No Toxic Adulterants
- 1-4 Toxic Adulterants
- 5-8 Toxic Adulterants
- 9+ Toxic Adulterants

Figure 2. Most Prevalent Adulterant by State

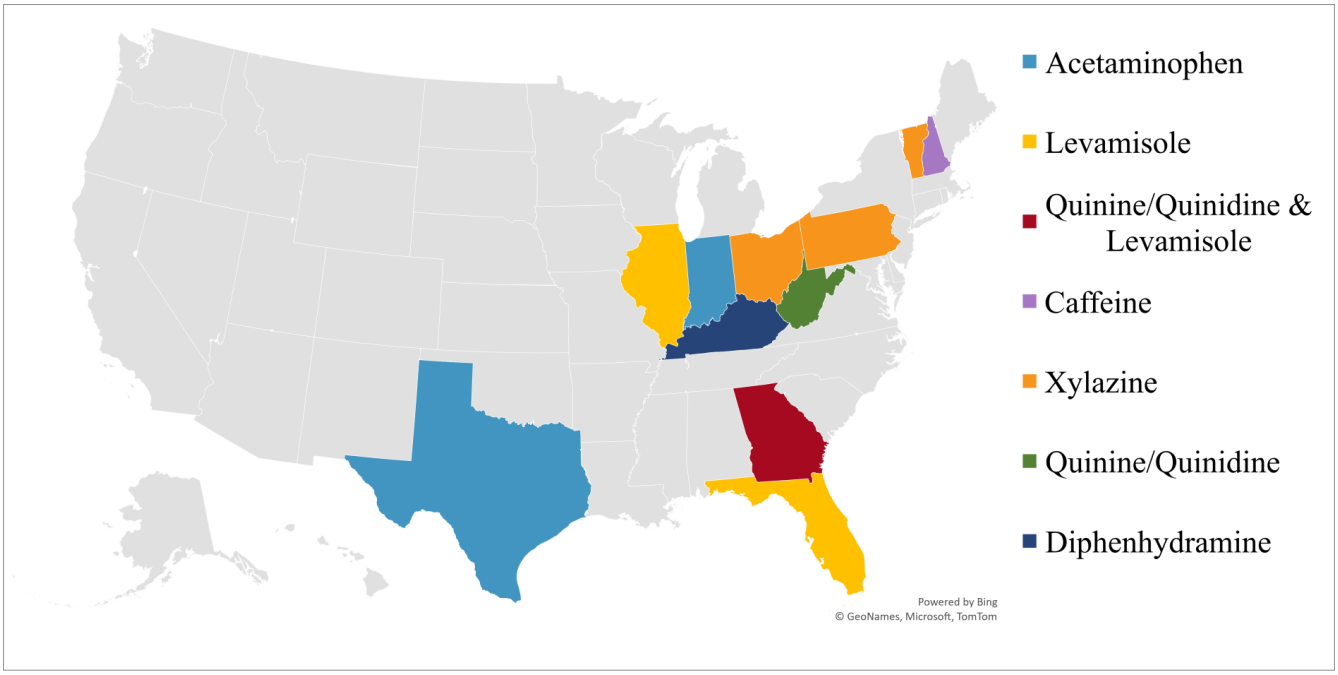


Figure 3. Overview of Adulterant Findings by State

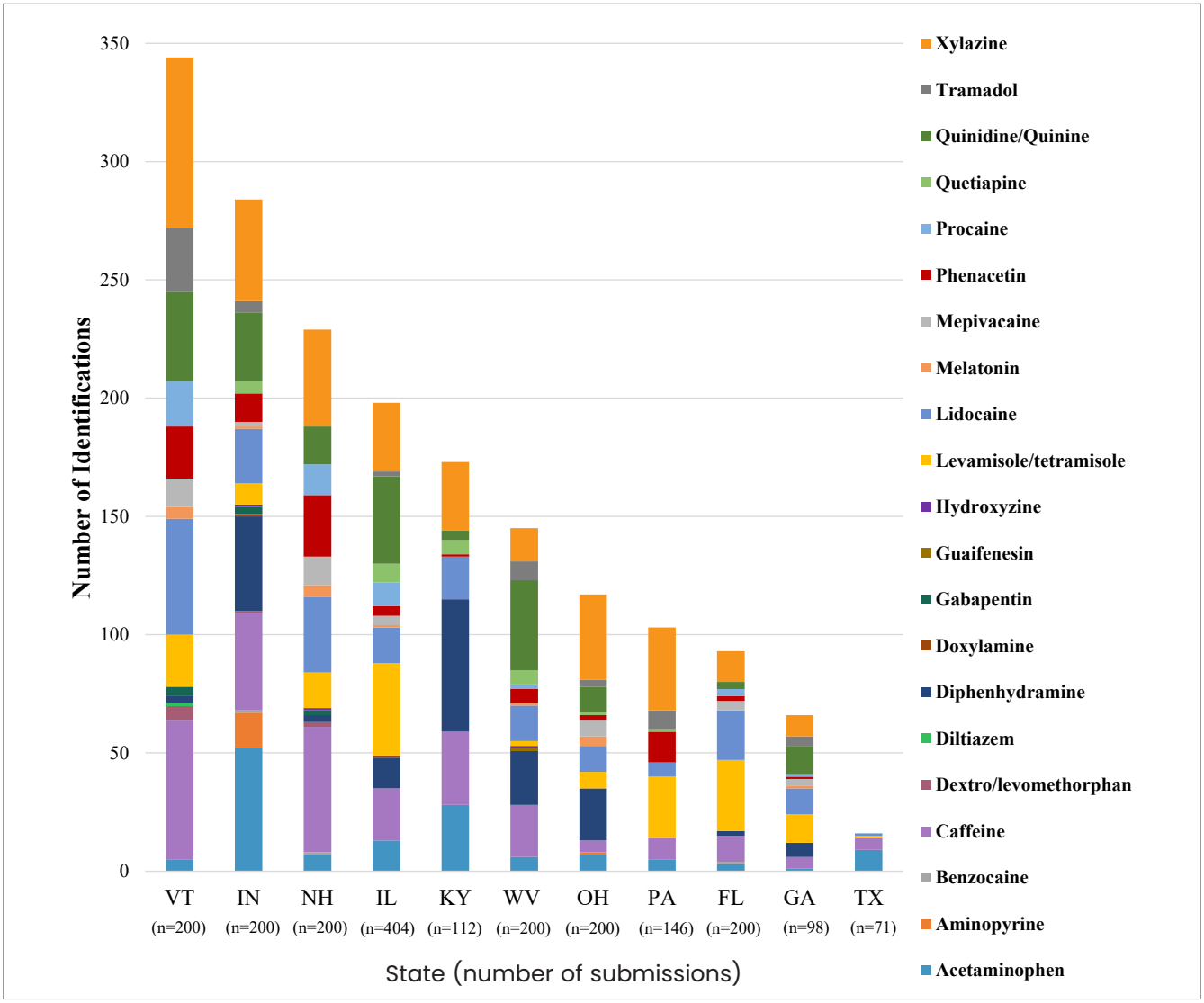
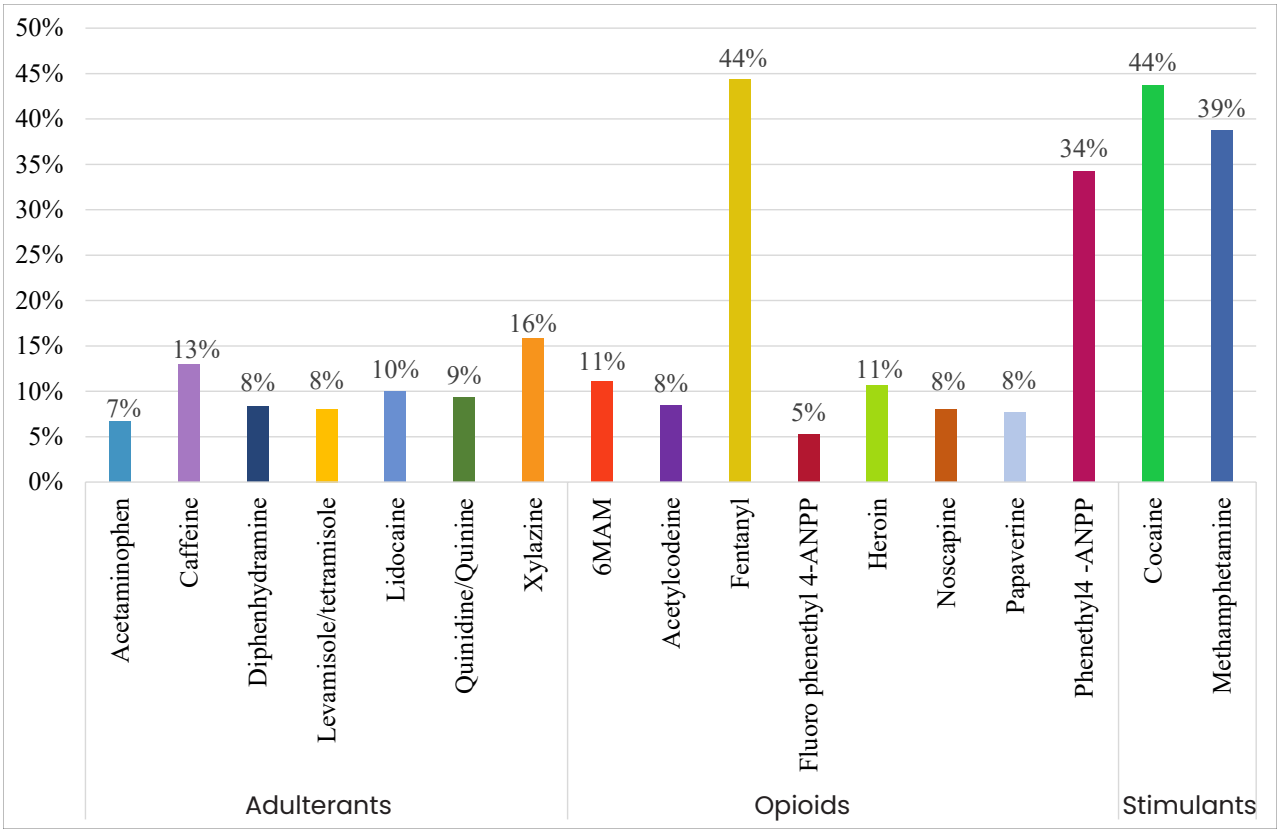


Figure 4. Percent Positivity by Drug Class



Drug Combinations

Table 1. Drug Combinations Observed

Principal Drug	In Combination With	Frequency of Combination within Principal Drug
Cocaine	Levamisole	31%
Cocaine	Lidocaine	19%
Cocaine	Phenacetin	14%
Fentanyl	Xylazine	36%
Fentanyl	Other Opioids	28%
Fentanyl	Caffeine	21%
Fentanyl	Quinine/Quinidine	20%
Fentanyl	Lidocaine	19%
Fentanyl	Diphenhydramine	18%
Fentanyl	Cocaine and Methamphetamine	9%
Fentanyl	Designer Benzodiazepines	4%
Fentanyl	Xylazine, Quinine/Quinidine, Caffeine, and Lidocaine	3%
Fentanyl	Heroin, Cocaine, and Methamphetamine	2%
Fentanyl	Nitazenes	1%
Heroin	Morphine and Codeine	10%
Methamphetamine	Caffeine	19%
Methamphetamine	Acetaminophen	4%

Discussion

Of the 2,031 samples analyzed, 2,027 returned positive results. There were four samples that had no compounds detected (all from West Virginia) in the data set. Constituents for the purpose of this project were defined as all positive findings, including drugs, adulterants, and related precursors and by-products. The peak with the greatest abundance was considered the main component, while all other constituents identified were considered to be adulterants. The sample that contained the most constituents was a sample from Illinois that contained 21 constituents other than the main component peak. These constituents included: benzyl fentanyl, quinidine/quinine, cocaine, quetiapine, xylazine, 6MAM, heroin, phenethyl 4-ANPP, protonitazene, noscapine, clonazolam, acetylcodeine, hydroquinidine, papaverine, nicotinamide, fluoro phenethyl 4-ANPP, doxylamine, morphine, cinchonine, risperidone, and lidocaine. The main component peak of this sample was fentanyl. For the samples that contained no toxic adulterants (n=790), 57% of the samples contained only methamphetamine and 34% contained only cocaine. Across all positive samples (n=2,027), fentanyl was the most frequent drug identified in 44% of the samples, with cocaine and methamphetamine identifications close behind. The profile of fentanyl positive samples were examined for combinations of fentanyl with other drugs and adulterants because fentanyl was the most prevalent drug identified in the samples. The nitazene category comprised of metonitazene, n-desethyl isonitazene, etonitazepyne, and protonitazene. Designer benzodiazepines included bromazolam, clonazolam, deschloroetizolam, diclazepam, etizolam, flualprazolam, and flubromazolam. The other opioid category consisted of acetyl fentanyl, benzyl fentanyl, chlorofentanyl, fluorofentanyl, heroin, tramadol, and valeryl fentanyl.

Conclusion/Impact

The identification of toxic adulterants is becoming more important in the field of drug chemistry as typically only controlled substances are reported. These identifications indicate a wide variety of dangerous compounds that are being added to street samples and unknowingly ingested by the user. Continued surveillance of these adulterants may lead to a better understanding of the illicit drug supply and can enable better information to be distributed to the public regarding the potential toxic effects. This can assist clinical health professionals in treating patients, as well as educate people who use drugs. Toxic adulterant testing results give additional perspective for understanding the toxic effects of recreational drug use and emerging trends. The information gathered regarding common adulterants in street samples helped to write public health alerts that are free to download here: https://www.cfsre.org/nps-discovery/public-alerts.

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Supplemental Information

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