cfsre | NPS DISCOVERY

CFSRE’s NPS Discovery – A Timely Drug Surveillance Program

Emerging Drug Crises in America: a Criminal Justice and Public Health Nexus
NIJ Research Conference – Thursday May 25, 2023 – 12:00 to 1:15 PM ET

Alex J. Krotulski, PhD

Center for Forensic Science Research & Education (CFSRE)

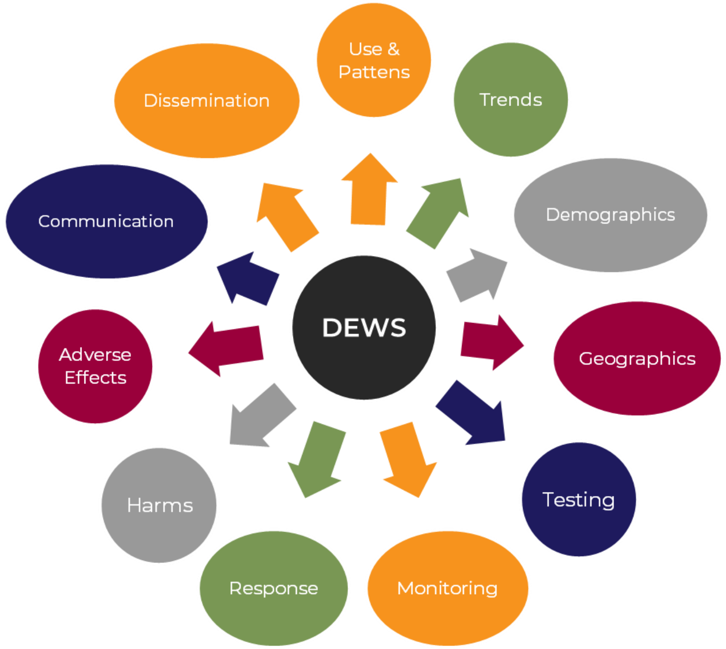
DISCLOSURES & FUNDING

NIJ National Institute of Justice
STRENGTHEN SCIENCE. ADVANCE JUSTICE.

- I have no conflicts of interest to disclose.
- I am a scientist and employee of FRFF / CFSRE, a 501(c)(3) non-profit research and educational facility.
- CFSRE's NPS Discovery is and has been supported by the National Institute of Justice, Office of Justice Programs, U.S. Department of Justice.
  - Award Number 15PNIJ-22-GG-04434-MUMU, "Implementation of NPS Discovery – An Early Warning Systems for Novel Drug Intelligence, Surveillance, Monitoring, Response, and Forecasting using Drug Materials and Toxicology Populations in the US".
  - The opinions, findings, conclusions and/or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect those of the Department of Justice.

NPS DISCOVERY – THE CFSRE'S DEWS

- Open-access drug early warning system (DEWS) →
- Combine aspects of research with authentic cases
  - – Forensic toxicology, drug materials, emergency departments, gray market sites, drug use forums, etc.
- Disseminate results and reports widely to stakeholders



DEWS

Use & Pattens

Trends

Demographics

Geographics

Testing

Monitoring

Response

Harms

Adverse Effects

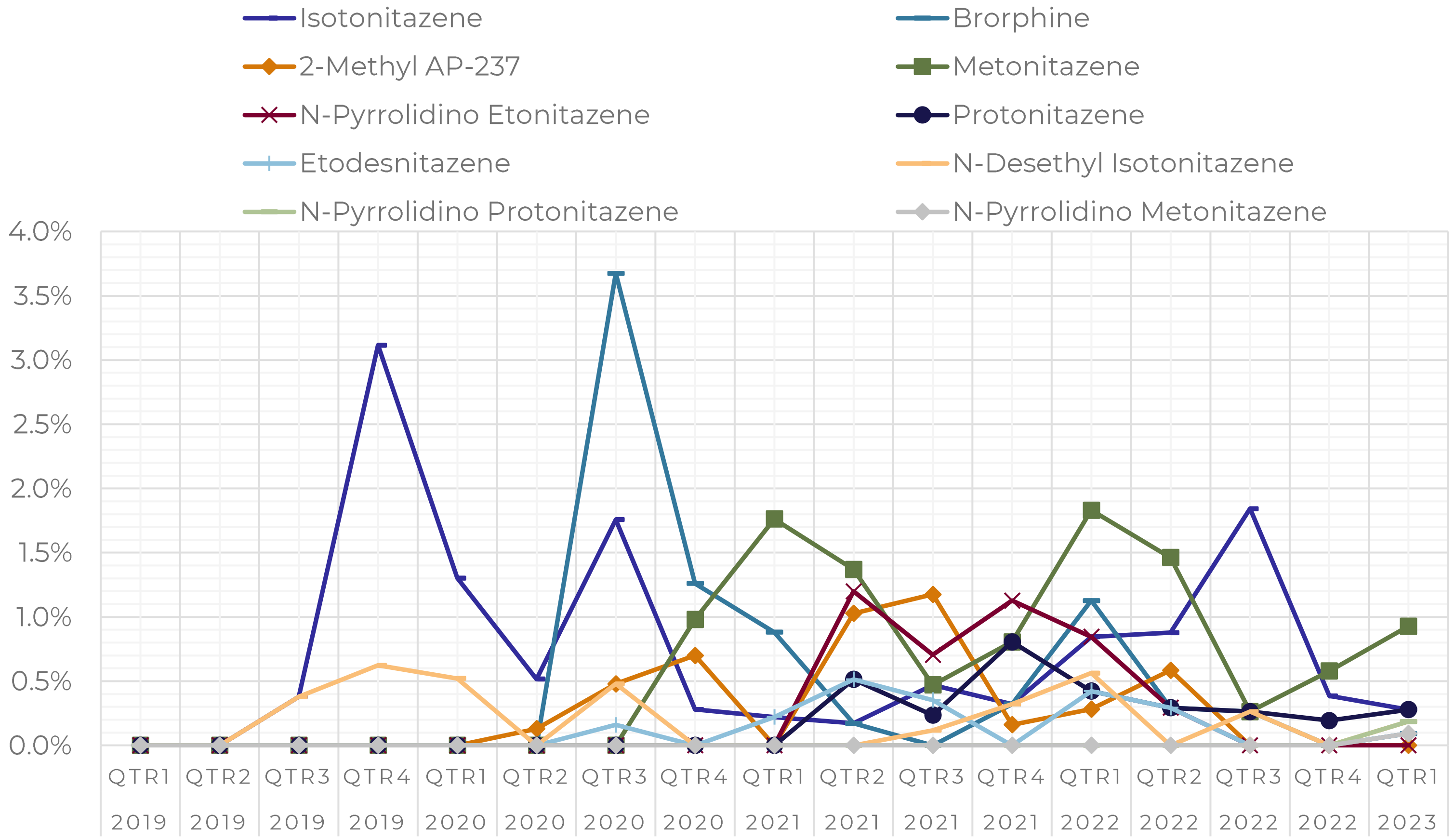
Communication

Dissemination

2016	2017	2018	2019	2020	2021	2022
U-47700 & Furanylfentanyl	***N*-Ethyl Pentylone**	**Cyclopropylfentanyl & Methoxyacetylfentanyl**	**Isotonitazene**	**MDMB-4en-PINACA**	**Metonitazene & Nitazene Analogues**	***N,N*-Dimethylpentylone**
Deadly outbreak investigation involving 20+ cases centralized in Midwestern states.	Investigation of deaths and impaired driving cases involving new stimulant drug linked to Ecstasy and Molly use.	Postmortem investigations involving new fentanyl analogues linked to 40+ deaths in Midwestern states and Florida.	First outbreak investigation in the U.S. involving 20+ deaths, primarily from Indiana and Illinois.	Investigation of 50+ cases involving deaths and hospitalizations from states in the South, Midwest, and Northeast.	Continued monitoring and investigations of 40+ deaths involving new nitazene analogues emerging in various regions across the U.S.	First outbreak investigations involving a new stimulant drug linked to 50+ cases, including deaths, primarily originating from Florida and Northeastern states.

DYNAMIC LANDSCAPE – NSO & NITAZENE ANALOGUES

Novel synthetic opioids (NSO) filling the void in the wake of the scheduling of fentanyl analogues



TOP 3 NSO PER YEAR

2018
- Fluoroisobutyrylfentanyl
- Cyclopropylfentanyl
- Methoxyacetylfentanyl

2019
- Fluoroisobutyrylfentanyl
- Valerylfentanyl
- Isotonitazene

2020
- Brorphine
- Isotonitazene
- Metonitazene

2021
- Metonitazene
- N-Pyrrolidino Etonitazene
- Carfentanil

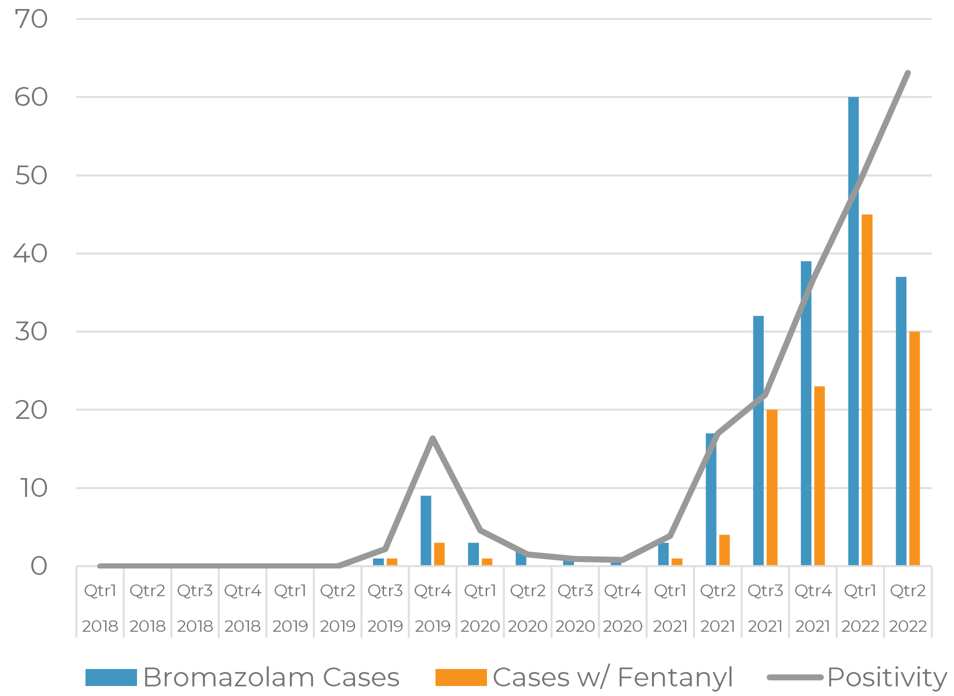
2022
- Carfentanil
- Metonitazene
- Isotonitazene

2023
- Metonitazene
- Isotonitazene
- Protonitazene

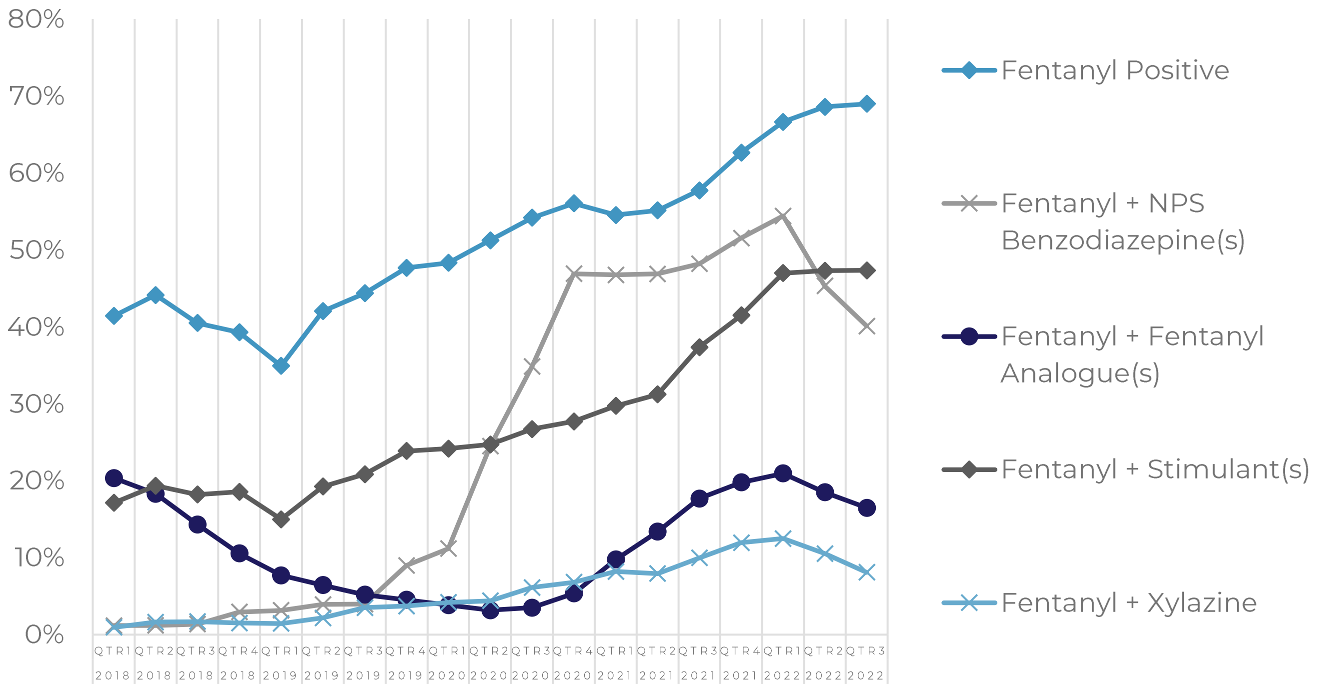
ENTERING THE POLYDRUG EPIDEMIC

Increasingly common to find multiple drugs, NPS, and/or adulterants in forensic samples

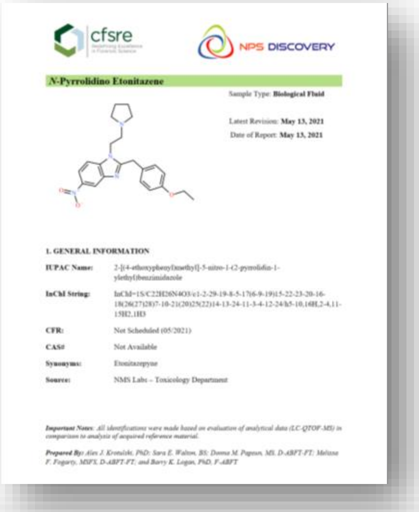
NPS Benzo: Bromazolam

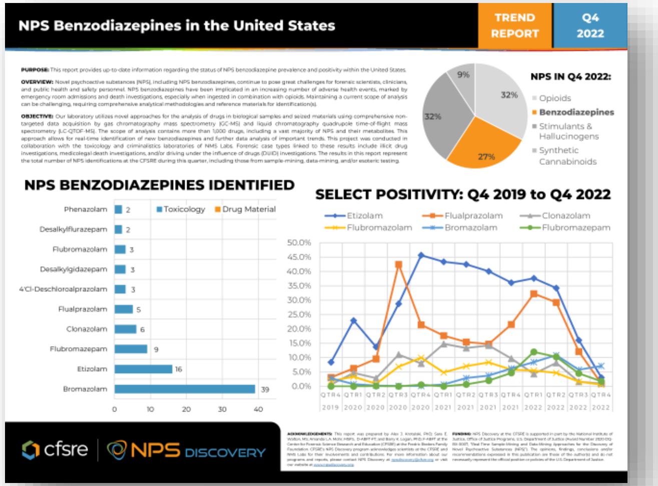


Fentanyl Co-Positivity ("Nested Waves")



NPS DISCOVERY REPORTS → WWW.NPSDISCOVERY.ORG


N-Pyrrolidino Etonitazene


NPS Benzodiazepines in the United States

TREND REPORT Q4 2022

NPS BENZODIAZEPINES IDENTIFIED

SELECT POSITIVITY: Q4 2019 to Q4 2022


April 2022

Synthetic Stimulant Market Rapidly Changing as N,N-Dimethylpentylone Replaces Eutylone in Drug Supply Typically Sold as "Ecstasy" or "Molly"


Recommended Scope for NPS Testing in the United States

NPS SCOPE Q3 2022


ToxIC Fentalog Study Group — Quarterly NPS Report

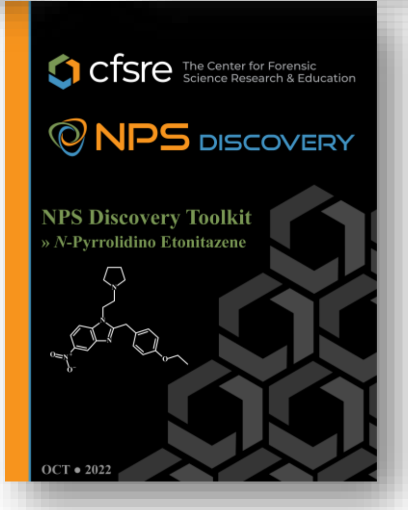
CLINICAL Q3 2022


QUARTERLY REPORT — PHILADELPHIA, PA

DRUG CHECKING Q3 2022


Fentanyl Purity, Potency, & Synthesis

Real-Time Testing of Opioid Drug Products in the United States

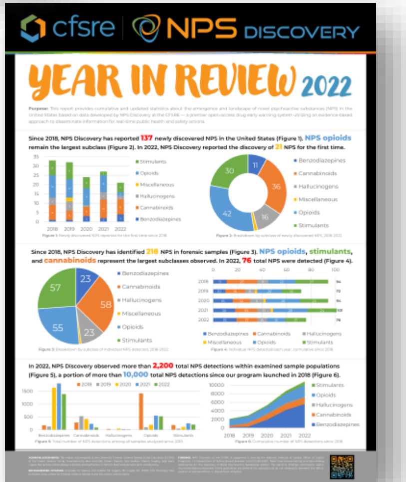

cfsre The Center for Forensic Science Research & Education

NPS DISCOVERY

NPS Discovery Toolkit

» N-Pyrrolidino Etonitazene

OCT • 2022


YEAR IN REVIEW 2022

NPS DISCOVERY REPORTS → PUBLIC ALERTS

April 2022

Synthetic Stimulant Market Rapidly Changing as *N,N*-Dimethylpentylone Replaces Eutylone in Drug Supply Typically Sold as "Ecstasy" or "Molly"

Purpose: The objective of this announcement is to notify public health and safety, 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 synthetic stimulant ***N,N*-dimethylpentylone**.

Background: Synthetic stimulants are chemically manufactured drugs with sub-classifications based on their structural relation to amphetamine or cathinone. Synthetic stimulants, including substituted cathinone analogues (e.g., eutylone), can retain both stimulant and hallucinogenic properties, and can cause associated health risks. Synthetic stimulants are often prepared and distributed in powder, capsule, or tablet form, and may be sold as "Ecstasy", "Molly", or "MDMA" (3,4-methylenedioxymethamphetamine) on recreational drug markets. In the United States (U.S.), synthetic stimulants have been associated with adverse effects and linked to cardiac effects resulting in death. Adverse effects can include hyperthermia, dehydration, arrhythmias, hallucinations, and serotonin syndrome.

Summary: In 2020 and 2021, the substituted cathinone **eutylone** was the most commonly encountered synthetic stimulant to appear in forensic casework, despite the drug being considered federally scheduled as an isomer of pentylone since March 2017 according to the U.S. Drug Enforcement Administration (DEA). In September 2021, eutylone was recommended for international control. It is this notice that likely created a shift in the NPS drug market, which would later be noted by declining eutylone positivity and increasing *N,N*-dimethylpentylone positivity. *N,N*-Dimethylpentylone was first identified in toxicology samples in the U.S. in Q3 2021, marking the initial insurgence of this drug into the supply and the beginning of its proliferation. To date, *N,N*-dimethylpentylone has been identified in 32 toxicology cases, including antemortem and postmortem investigations, in addition to drug material cases. *N,N*-Dimethylpentylone is not explicitly scheduled in the U.S.; however, it could be considered an isomer of ***N*-ethyl pentylone** (Schedule I). Of note, pentylone is a metabolite of *N,N*-dimethylpentylone.

Case Breakdown

Case Type:
- Postmortem (n=26)
- DUID (n=1)
- Unknown (n=5)

Date of Collection:
- August 2021 to March 2022

Other Notable Findings:
- Pentylone (n=23)
- Eutylone (n=5)
- Methamphetamine (n=11)
- Fentanyl / Opioids (n=13)
- No Other Drugs (n=8)

Recommendations for Public Health
- Implement surveillance for rapid identification of drug use and overdose outbreaks.
- Engage local poison centers and clinicians to assist with treatment of affected patients.
- Track and monitor geographical drug distribution and trends.
- Track demographics and known risk factors for people who use stimulant/hallucinogen drugs.
- Raise awareness about the risks and dangers associated with synthetic stimulant use.

Recommendations for Laboratories
- Utilize analytical data available publicly for the identification of ***N,N*-dimethylpentylone**.
- Utilize non-targeted testing protocols or develop sensitive and up-to-date testing procedures.
- Prioritize testing of drug material samples.
- Share data on synthetic stimulant identifications with local health departments, forensic scientists, and related communities.

Recommendations for Clinicians
- Become familiar with the signs and symptoms of synthetic stimulant use (e.g., agitation, hallucinations, excitement, elevated pulse, arrhythmias, serotonin syndrome).
- Be mindful that recreational drugs have limited quality control, containing undeclared substances that impact expected clinical effects or findings.
- Counsel about the potential harms of "Ecstasy", "Molly", and "MDMA" products and use.

Recommendations for MEs & Coroners
- Test for new synthetic stimulants and their biomarkers in suspected stimulant-related cases.
- Be aware that ELISA screening for synthetic stimulants may not be specific or specialized for the newest generation of drugs; consider mass spectrometry-based screening.
- Be aware that concentrations of synthetic stimulants in biological specimens can vary; however, GC-MS sensitivity may be adequate.

Conc. in Postmortem Blood [ng/mL] (n=5)			
***N,N*-Dimethylpentylone**		**Pentylone**	
Mean (±S.D.)	270 ± 400	**Mean (±S.D.)**	120 ± 170
Median	87	**Median**	37
Range	33 - 970	**Range**	10 - 420

Acknowledgements: This report was prepared by Alex J. Krotulski, PhD; Melissa F. Fogarty, MS, D-ABFT-FT; Donna M. Papsun, MS, D-ABFT-FT; Michael Lamb, MS, D-ABFT-FT; Sara E. Walton, MS; and Barry K. Logan, PhD, F-ABFT. Funding was received from the National Institute of Justice (NIJ) of the U.S. Department of Justice (DOJ) (Award Number 2020-DQ-BX-0007). The opinions, findings, and conclusions or recommendations expressed in this publication are those of the authors and do not necessarily reflect those of the Department of Justice.

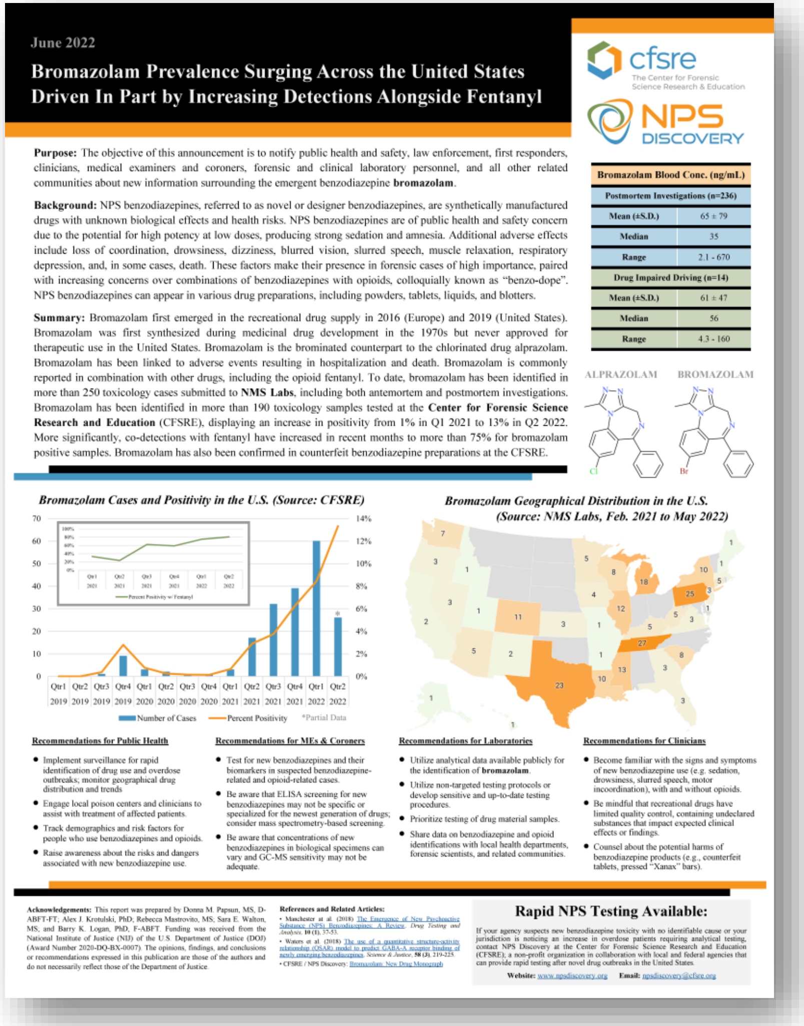
References and Related Articles:
- Koppe, H.; Ludwig, G.; and Zeile, K. (1964) Anti-alpha-Aminoketone Derivatives. CH Boehringer Sohn AG and Co KG, Boehringer Ingelheim GmbH, Assignee. Patent GB1085135A.
- World Health Organization (2021) Critical Review Report: Eutylone. Expert Committee on Drug Dependence 44th Meeting
- Krotulski et al. (2021) Eutylone Intoxications—An Emerging Synthetic Stimulant in Forensic Investigations. Journal of Analytical Toxicology, 45 (1), 8-20.

Rapid NPS Testing Now Available:

If your agency suspects synthetic stimulant toxicity with no identifiable cause of death or your jurisdiction is noticing an increase in overdose patients requiring analytical testing, contact NPS Discovery at the Center for Forensic Science Research and Education (CFSRE), a non-profit organization in collaboration with local and federal agencies which can provide rapid testing after novel drug outbreaks in the United States.

Website: www.npsdiscovery.org **Email:** npsdiscovery@cfsre.org

---



June 2022

Bromazolam Prevalence Surging Across the United States Driven In Part by Increasing Detections Alongside Fentanyl

Purpose: The objective of this announcement is to notify public health and safety, 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 benzodiazepine **bromazolam**.

Background: NPS benzodiazepines, referred to as novel or designer benzodiazepines, are synthetically manufactured drugs with unknown biological effects and health risks. NPS benzodiazepines are of public health and safety concern due to the potential for high potency at low doses, producing strong sedation and amnesia. Additional adverse effects include loss of coordination, drowsiness, dizziness, blurred vision, slurred speech, muscle relaxation, respiratory depression, and, in some cases, death. These factors make their presence in forensic cases of high importance, paired with increasing concerns over combinations of benzodiazepines with opioids, colloquially known as "benzo-dope". NPS benzodiazepines can appear in various drug preparations, including powders, tablets, liquids, and blotters.

Summary: Bromazolam first emerged in the recreational drug supply in 2016 (Europe) and 2019 (United States). Bromazolam was first synthesized during medicinal drug development in the 1970s but never approved for therapeutic use in the United States. Bromazolam is the brominated counterpart to the chlorinated drug alprazolam. Bromazolam has been linked to adverse events resulting in hospitalization and death. Bromazolam is commonly reported in combination with other drugs, including the opioid fentanyl. To date, bromazolam has been identified in more than 250 toxicology cases submitted to **NMS Labs**, including both antemortem and postmortem investigations. Bromazolam has been identified in more than 190 toxicology samples tested at the **Center for Forensic Science Research and Education** (CFSRE), displaying an increase in positivity from 1% in Q1 2021 to 13% in Q2 2022. More significantly, co-detections with fentanyl have increased in recent months to more than 75% for bromazolam positive samples. Bromazolam has also been confirmed in counterfeit benzodiazepine preparations at the CFSRE.

Bromazolam Blood Conc. (ng/mL)	
Postmortem Investigations (n=236)	
Mean (±S.D.)	65 ± 79
Median	35
Range	2.1 - 670
Drug Impaired Driving (n=14)	
Mean (±S.D.)	61 ± 47
Median	56
Range	4.3 - 160

Recommendations for Public Health
- Implement surveillance for rapid identification of drug use and overdose outbreaks; monitor geographical drug distribution and trends
- Engage local poison centers and clinicians to assist with treatment of affected patients.
- Track demographics and risk factors for people who use benzodiazepines and opioids.
- Raise awareness about the risks and dangers associated with new benzodiazepine use.

Recommendations for MEs & Coroners
- Test for new benzodiazepines and their biomarkers in suspected benzodiazepine-related and opioid-related cases.
- Be aware that ELISA screening for new benzodiazepines may not be specific or specialized for the newest generation of drugs; consider mass spectrometry-based screening.
- Be aware that concentrations of new benzodiazepines in biological specimens can vary and GC-MS sensitivity may not be adequate.

Recommendations for Laboratories
- Utilize analytical data available publicly for the identification of **bromazolam**.
- Utilize non-targeted testing protocols or develop sensitive and up-to-date testing procedures.
- Prioritize testing of drug material samples.
- Share data on benzodiazepine and opioid identifications with local health departments, forensic scientists, and related communities.

Recommendations for Clinicians
- Become familiar with the signs and symptoms of new benzodiazepine use (e.g. sedation, drowsiness, slurred speech, motor incoordination), with and without opioids.
- Be mindful that recreational drugs have limited quality control, containing undeclared substances that impact expected clinical effects or findings.
- Counsel about the potential harms of benzodiazepine products (e.g., counterfeit tablets, pressed "Xanax" bars).

Acknowledgements: This report was prepared by Donna M. Papsun, MS, D-ABFT-FT; Alex J. Krotulski, PhD; Rebecca Mastrovito, MS; Sara E. Walton, MS; and Barry K. Logan, PhD, F-ABFT. Funding was received from the National Institute of Justice (NIJ) of the U.S. Department of Justice (DOJ) (Award Number 2020-DQ-BX-0007). The opinions, findings, and conclusions or recommendations expressed in this publication are those of the authors and do not necessarily reflect those of the Department of Justice.

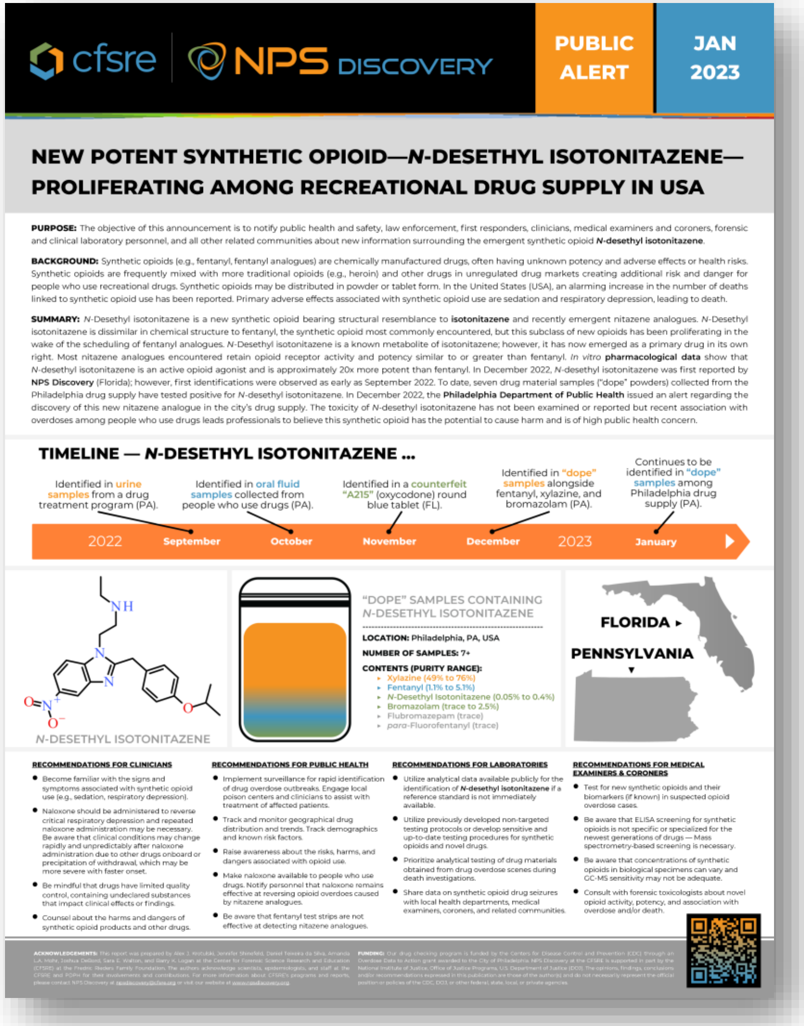
References and Related Articles:
- Manchester et al. (2018) The Emergence of New Psychoactive Substance (NPS) Benzodiazepines: A Review. Drug Testing and Analysis, 10 (1), 37-53.
- Waters et al. (2018) The use of a quantitative structure-activity relationship (QSAR) model to predict GABA-A receptor binding of newly emerging benzodiazepines. Science & Justice, 58 (3), 219-225.
- CFSRE / NPS Discovery: Bromazolam: New Drug Monograph

Rapid NPS Testing Available:

If your agency suspects new benzodiazepine toxicity with no identifiable cause or your jurisdiction is noticing an increase in overdose patients requiring analytical testing, contact NPS Discovery at the Center for Forensic Science Research and Education (CFSRE); a non-profit organization in collaboration with local and federal agencies that can provide rapid testing after novel drug outbreaks in the United States.

Website: www.npsdiscovery.org **Email:** npsdiscovery@cfsre.org

---



PUBLIC ALERT
JAN 2023

NEW POTENT SYNTHETIC OPIOID—*N*-DESETHYL ISOTONITAZENE—PROLIFERATING AMONG RECREATIONAL DRUG SUPPLY IN USA

PURPOSE: The objective of this announcement is to notify public health and safety, 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 synthetic opioid ***N*-desethyl isotonitazene**.

BACKGROUND: Synthetic opioids (e.g., fentanyl, fentanyl analogues) are chemically manufactured drugs, often having unknown potency and adverse effects or health risks. Synthetic opioids are frequently mixed with more traditional opioids (e.g., heroin) and other drugs in unregulated drug markets creating additional risk and danger for people who use recreational drugs. Synthetic opioids may be distributed in powder or tablet form. In the United States (USA), an alarming increase in the number of deaths linked to synthetic opioid use has been reported. Primary adverse effects associated with synthetic opioid use are sedation and respiratory depression, leading to death.

SUMMARY: *N*-Desethyl isotonitazene is a new synthetic opioid bearing structural resemblance to **isotonitazene** and recently emergent nitazene analogues. *N*-Desethyl isotonitazene is dissimilar in chemical structure to fentanyl, the synthetic opioid most commonly encountered, but this subclass of new opioids has been proliferating in the wake of the scheduling of fentanyl analogues. *N*-Desethyl isotonitazene is a known metabolite of isotonitazene; however, it has now emerged as a primary drug in its own right. Most nitazene analogues encountered retain opioid receptor activity and potency similar to or greater than fentanyl. *In vitro* **pharmacological data** show that *N*-desethyl isotonitazene is an active opioid agonist and is approximately 20x more potent than fentanyl. In December 2022, *N*-desethyl isotonitazene was first reported by **NPS Discovery** (Florida); however, first identifications were observed as early as September 2022. To date, seven drug material samples ("dope" powders) collected from the Philadelphia drug supply have tested positive for *N*-desethyl isotonitazene. In December 2022, the **Philadelphia Department of Public Health** issued an alert regarding the discovery of this new nitazene analogue in the city's drug supply. The toxicity of *N*-desethyl isotonitazene has not been examined or reported but recent association with overdoses among people who use drugs leads professionals to believe this synthetic opioid has the potential to cause harm and is of high public health concern.

TIMELINE — *N*-DESETHYL ISOTONITAZENE ...

- 2022 September: Identified in urine samples from a drug treatment program (PA).
- October: Identified in oral fluid samples collected from people who use drugs (PA).
- November: Identified in a counterfeit "A215" (oxycodone) round blue tablet (FL).
- December: Identified in "dope" samples alongside fentanyl, xylazine, and bromazolam (PA).
- 2023 January: Continues to be identified in "dope" samples among Philadelphia drug supply (PA).

"DOPE" SAMPLES CONTAINING *N*-DESETHYL ISOTONITAZENE

LOCATION: Philadelphia, PA, USA

NUMBER OF SAMPLES: 7+

CONTENTS (PURITY RANGE):
- Xylazine (49% to 76%)
- Fentanyl (1.1% to 5.1%)
- *N*-Desethyl Isotonitazene (0.05% to 0.4%)
- Bromazolam (trace to 2.5%)
- Flubromazepam (trace)
- *para*-Fluorofentanyl (trace)

RECOMMENDATIONS FOR CLINICIANS
- Become familiar with the signs and symptoms associated with synthetic opioid use (e.g., sedation, respiratory depression).
- Naloxone should be administered to reverse critical respiratory depression and repeated naloxone administration may be necessary. Be aware that clinical conditions may change rapidly and unpredictably after naloxone administration due to other drugs onboard or precipitation of withdrawal, which may be more severe with faster onset.
- Be mindful that drugs have limited quality control, containing undeclared substances that impact clinical effects or findings.
- Counsel about the harms and dangers of synthetic opioid products and other drugs.

RECOMMENDATIONS FOR PUBLIC HEALTH
- Implement surveillance for rapid identification of drug overdose outbreaks. Engage local poison centers and clinicians to assist with treatment of affected patients.
- Track and monitor geographical drug distribution and trends. Track demographics and known risk factors.
- Raise awareness about the risks, harms, and dangers associated with opioid use.
- Make naloxone available to people who use drugs. Notify personnel that naloxone remains effective at reversing opioid overdoes caused by nitazene analogues.
- Be aware that fentanyl test strips are not effective at detecting nitazene analogues.

RECOMMENDATIONS FOR LABORATORIES
- Utilize analytical data available publicly for the identification of ***N*-desethyl isotonitazene** if a reference standard is not immediately available.
- Utilize previously developed non-targeted testing protocols or develop sensitive and up-to-date testing procedures for synthetic opioids and novel drugs.
- Prioritize analytical testing of drug materials obtained from drug overdose scenes during death investigations.
- Share data on synthetic opioid drug seizures with local health departments, medical examiners, coroners, and related communities.

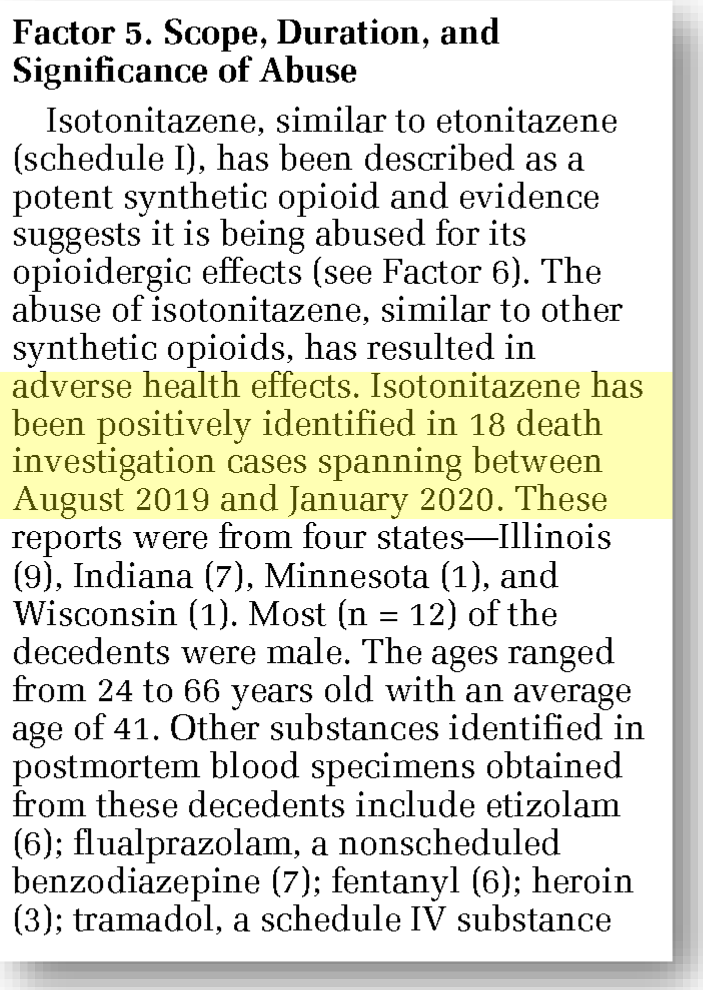
RECOMMENDATIONS FOR MEDICAL EXAMINERS & CORONERS
- Test for new synthetic opioids and their biomarkers (if known) in suspected opioid overdose cases.
- Be aware that ELISA screening for synthetic opioids is not specific or specialized for the newest generations of drugs — Mass spectrometry-based screening is necessary.
- Be aware that concentrations of synthetic opioids in biological specimens can vary and GC-MS sensitivity may not be adequate.
- Consult with forensic toxicologists about novel opioid activity, potency, and association with overdose and/or death.

ACKNOWLEDGEMENTS: This report was prepared by Alex J. Krotulski, Jennifer Shinefeld, Daniel Teixeira da Silva, Amanda L.A. Mohr, Joshua DeBord, 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 scientists, epidemiologists, and staff at the CFSRE and PDPH for their involvements and contributions. For more information about CFSRE's programs and reports, please contact NPS Discovery at npsdiscovery@cfsre.org or visit our website at www.npsdiscovery.org.

FUNDING: Our drug checking program is funded by the Centers for Disease Control and Prevention (CDC) through an Overdose Data to Action grant awarded to the City of Philadelphia. NPS Discovery at the CFSRE is supported in part by the National Institute of Justice, Office of Justice Programs, U.S. Department of Justice (DOJ). The opinions, findings, conclusions and/or recommendations expressed in this publication are those of the author(s) and do not necessarily represent the official position or policies of the CDC, DOJ, or other federal, state, local, or private agencies.

IMPACTS ON POLICY & PRACTICE

- Readily available information can:
    - Build greater understanding of **drug markets, drug trends, and use patterns**, etc.
    - Assist medical examiners and coroners (and toxicologists) determining **cause and manner of death**
    - Assist clinicians in understanding **sign, symptoms, and care**
    - Allow for **scheduling / control** of new synthetic drugs →
    - Allow people who use drugs to **make more informed decisions** and promote harm reduction
    - Steer future **NPS, scientific, and medical research**
    - *And so much more …*



Factor 5. Scope, Duration, and Significance of Abuse

Isotonitazene, similar to etonitazene (schedule I), has been described as a potent synthetic opioid and evidence suggests it is being abused for its opioidergic effects (see Factor 6). The abuse of isotonitazene, similar to other synthetic opioids, has resulted in adverse health effects. Isotonitazene has been positively identified in 18 death investigation cases spanning between August 2019 and January 2020. These reports were from four states—Illinois (9), Indiana (7), Minnesota (1), and Wisconsin (1). Most (n = 12) of the decedents were male. The ages ranged from 24 to 66 years old with an average age of 41. Other substances identified in postmortem blood specimens obtained from these decedents include etizolam (6); flualprazolam, a nonscheduled benzodiazepine (7); fentanyl (6); heroin (3); tramadol, a schedule IV substance cfsre | NPS DISCOVERY

Thank you! Questions?

alex.krotulski@cfsre.org

www.cfsre.org & www.npsdiscovery.org