Trends in the Emergence of Novel Psychoactive Substances

CDC “Overdose Data to Action” Recipient Meeting – Atlanta, GA
Combined Surveillance Session – Thursday June 7, 2023 – 2:00 to 3:00 PM ET

Barry K. Logan, PhD, F-ABFT – Executive Director (CFSRE)

Alex J. Krotulski, PhD – Associate Director (CFSRE)

DISCLOSURES

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The Center for Forensic Science Research & Education

NPS DISCOVERY

- The Fredric Rieders Family Foundation (FRFF) is a 501(c)(3) non-profit operating foundation, funded by its activities in forensic science research and education.
- The Center for Forensic Science Research and Education (CFSRE) is a program of the FRFF and acknowledges the funding it receives from the Colombo Plan, the National Institute of Justice (NIJ), the Centers for Disease Control (CDC), National Network of Public Health Institutes (NNPHI), and the National Institutes of Health (NIH), among others.
- AJK is a paid employee of CFSRE
- BKL is also a paid employee of NMS Labs, a commercial reference laboratory for clinical and forensic clients, and Executive Director of CFSRE

PLANNING PROSPERITY TOGETHER
THE COLOMBO PLAN

NIJ | National Institute of Justice
STRENGTHEN SCIENCE. ADVANCE JUSTICE.

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

National Network of Public Health Institutes

NIH

NOVEL PSYCHOACTIVE SUBSTANCES (NPS)

- **Definition**
  - A new/novel psychoactive substance (NPS) is defined as 'a new narcotic or psychotropic drug, in pure form or in preparation, that is not controlled by the United Nations drug conventions, but which may pose a public health threat comparable to that posed by substances listed in these conventions'.
- **Additionally…**
  - Can also be a substance used in a **new or novel way**, differently dosed/administered, emerging from one culture into a different culture.
- **What they have in common…**
  - Difficult to identify, measure, detect, monitor, or surveille
  - Gaps in knowledge about toxicity or potency
  - Present risks to the user, not experienced with their use

TIMELINE OF CFSRE'S NPS DISCOVERY

NPS DISCOVERY

2017
- Development of LC-QTOF-MS assay for >400 drugs (including many NPS)
- Began charactering NPS using GC-MS, LC-QTOF-MS, and/or NMR workflows

2018
- Development and dissemination of first new drug monograph for NPS
- **Formally launched our NPS Discovery program**

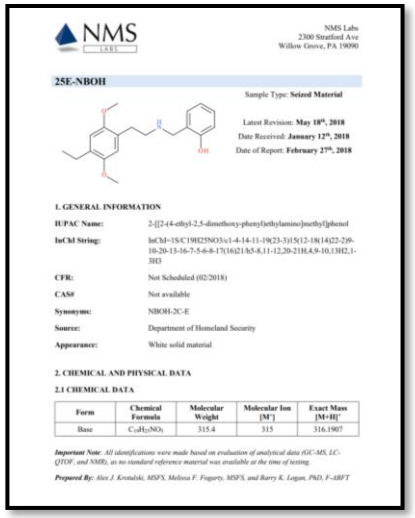
2019
- Launched first NPS Discovery website to archive reports and data
- Began issuing *Public Alerts* to scientific stakeholders and professionals

2020
- Expanded trend reporting to include all five major subclasses of NPS
- Continued data collections through onset of COVID-19 pandemic

2021
- Greatly expanding program outputs (including several new report types)
- Library database expanded to encompass >950 drugs and NPS

2022
- Advancements in *Drug Checking* initiatives (purity testing, potency index)
- Expansion of drug checking and clinical monitoring

2023
- Launch of Colombo Plan CBP Sentinel Strategy for deeper dive into chemical characteristics of illicit drug supply.


NMS

NMS Labs
2300 Stratford Ave
Willow Grove, PA 19090

25E-NBOH

Sample Type: Seized Material

Latest Revision: May 18th, 2018
Date Received: January 12th, 2018
Date of Report: February 27th, 2018

1. GENERAL INFORMATION

IUPAC Name: 2-[(2-(4-ethyl-2,5-dimethoxy-phenyl)ethylamino]methyl]phenol

InChI String: InChI=1S/C19H25NO3/c1-4-14-11-19(23-3)15(12-18(14)22-2)9-10-20-13-16-7-5-6-8-17(16)21/h5-8,11-12,20-21H,4,9-10,13H2,1-3H3

CFR: Not Scheduled (02/2018)

CAS#: Not available

Synonyms: NBOH-2C-E

Source: Department of Homeland Security

Appearance: White solid material

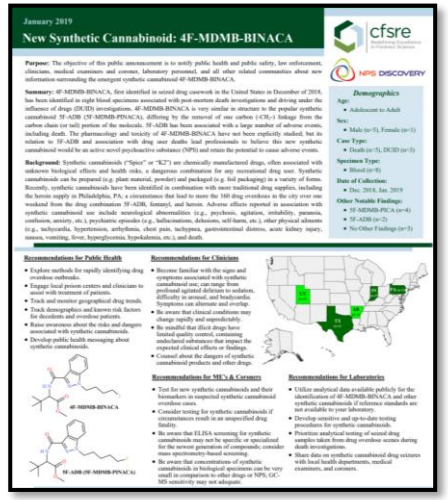
2. CHEMICAL AND PHYSICAL DATA

2.1 CHEMICAL DATA

Form	Chemical Formula	Molecular Weight	Molecular Ion [M+]	Exact Mass [M+H]+
Base	$C_{19}H_{25}NO_3$	315.4	315	316.1907

Important Note: All identifications were made based on evaluation of analytical data (GC-MS, LC-QTOF, and NMR), as no standard reference material was available at the time of testing.

Prepared By: Alex J. Krmanik, MSFS, Melissa F. Fogarty, MSFS, and Barry K. Logan, PhD, F-ABFT


January 2019

New Synthetic Cannabinoid: 4F-MDMB-BINACA

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NPS DISCOVERY

Purpose: The objective of this public announcement is to notify public health and public safety, law enforcement, clinicians, medical examiners and coroner, laboratory personnel, and all other related communities about new information surrounding the emergent synthetic cannabinoid 4F-MDMB-BINACA.

Summary: 4F-MDMB-BINACA, first identified in seized drug casework in the United States in December of 2018, has been identified in eight blood specimens associated with post-mortem death investigations and driving under the influence of drugs (DUID) investigations. 4F-MDMB-BINACA is very similar in structure to the popular synthetic cannabinoid 5F-ADB (5F-MDMB-PINACA), differing by the removal of one carbon (-CH2-) linkage from the carbon chain (or tail) portion of the molecule. 5F-ADB has been associated with a large number of adverse events, including death. The pharmacology and toxicity of 4F-MDMB-BINACA have not been explicitly studied, but its relation to 5F-ADB and association with drug user deaths lead professionals to believe this new synthetic cannabinoid would be an active novel psychoactive substance (NPS) and retains the potential to cause adverse events.

Background: Synthetic cannabinoids ("Spice" or "K2") are chemically manufactured drugs, often associated with unknown biological effects and health risks, a dangerous combination for any recreational drug user. Synthetic cannabinoids can be prepared (e.g. plant material, powder) and packaged (e.g. foil packaging) in a variety of forms. Recently, synthetic cannabinoids have been identified in combination with more traditional drug supplies, including the heroin supply in Philadelphia, PA, a circumstance that lead to more the 160 drug overdoses in the city over one weekend from the drug combination 5F-ADB, fentanyl, and heroin. Adverse effects reported in association with synthetic cannabinoid use include neurological abnormalities (e.g., psychosis, agitation, excitability, paranoia, confusion, anxiety, etc.), psychiatric episodes (e.g., hallucinations, delusions, self-harm, etc.), other physical ailments (e.g., tachycardia, hypertension, arrhythmia, chest pain, tachypnea, gastrointestinal distress, acute kidney injury, nausea, vomiting, fever, hyperglycemia, hypokalemia, etc.), and death.

Demographics

Age:
- Adolescent to Adult

Sex:
- Male (n=5), Female (n=1)

Case Type:
- Death (n=5), DUID (n=1)

Specimen Type:
- Blood (n=8)

Date of Collection:
- Dec. 2018, Jan. 2019

Other Notable Findings:
- 5F-MDMB-PICA (n=4)
- 5F-ADB (n=2)
- No Other Findings (n=2)

Recommendations for Public Health

- Explore methods for rapidly identifying drug overdose outbreaks.
- Engage local poison centers and clinicians to assist with treatment of patients.
- Track and monitor geographical drug trends.
- Track demographics and known risk factors for decedents and overdose patients.
- Raise awareness about the risks and dangers associated with synthetic cannabinoids.
- Develop public health messaging about synthetic cannabinoids.

Recommendations for Clinicians

- Become familiar with the signs and symptoms associated with synthetic cannabinoid use; can range from profound agitated delirium to sedation, difficulty to arouse, and bradycardia. Symptoms can alternate and overlap.
- Be aware that clinical conditions may change rapidly and unpredictably.
- Be mindful that illicit drugs have limited quality control, containing undeclared substances that impact the expected clinical effects or findings.
- Counsel about the dangers of synthetic cannabinoid products and other drugs.

Recommendations for ME's & Coroners

- Test for new synthetic cannabinoids and their biomarkers in suspected synthetic cannabinoid overdose cases.
- Consider testing for synthetic cannabinoids if circumstances result in an unspecified drug fatality.
- Be aware that ELISA screening for synthetic cannabinoids may not be specific or specialized for the newest generation of compounds; consider mass spectrometry-based screening.
- Be aware that concentrations of synthetic cannabinoids in biological specimens can be very small in comparison to other drugs or NPS; GC-MS sensitivity may not adequate.

Recommendations for Laboratories

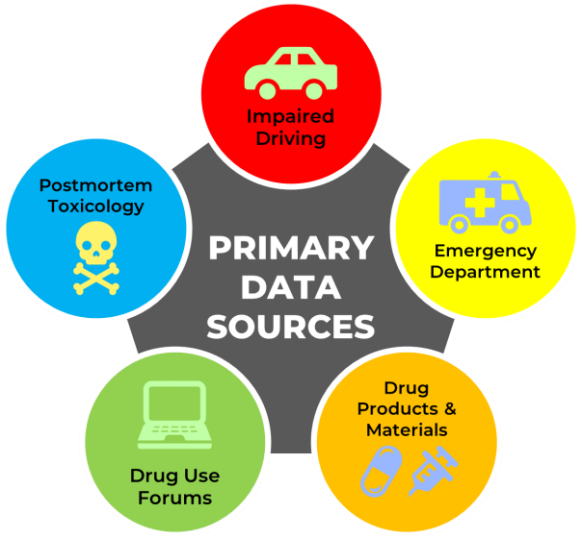
- Utilize analytical data available publicly for the identification of 4F-MDMB-BINACA and other synthetic cannabinoids if reference standards are not available to your laboratory.
- Develop sensitive and up-to-date testing procedures for synthetic cannabinoids.
- Prioritize analytical testing of seized drug samples taken from drug overdose scenes during death investigations.
- Share data on synthetic cannabinoid drug seizures with local health departments, medical examiners, and coroners.

4F-MDMB-BINACA

5F-ADB (5F-MDMB-PINACA)

CFSRE & NPS DISCOVERY

- Open-access national drug early warning system
  - Combine aspects of research & authentic cases
  - Analyze samples and generate data in-house
  - Develop a panel of high impact reports



Intelligence

- Information gathering
- Source analysis
- National data
- International data
- Literature & patents
- Surface & dark webs
- Forecasted drugs

Surveillance

- Drug discovery
- Significance assessment
- Seized drug testing
- Undetermined death
- Emergency departments
- Early notification
- Sharing analytical data

Monitoring

- Positivity & prevalence
- Implications & impact
- Drug use history
- Demographics
- Geographics
- Drug combinations
- Trend reporting

Response

- Information sharing
- Research & evaluation
- Intoxication vs. death
- Quantitation, potency, toxicity, metabolism, etc.
- Public alerts
- Scientific considerations

Forecasting

- Drug predictions
- Trends & use indicators
- Expert advisory
- Analogues & derivatives
- Scaffold-hoping
- Creative thinking
- Feeds intelligence efforts

NPS Lifecycle → >1 mo. → 1 mo. → 2-3 mos. → Approx. 6-9 mos. → >2-3 mo.

CFSRE & NPS DISCOVERY

Intelligence

Analysis:
- Drug use forums
- Reddit, Bluelight, Erowid
- Surface & dark webs
- U.S. government data
- DEA, CBP, NFLIS, etc.
- Forensic lab data
- International data
- EMCDDA, UNODC, etc.
- Literature & patents
- Publications
- Conference abstracts
- Standard manufacturers
- Drug use surveys

Development:
- "NPS Horizons"
- Online resource

Surveillance

Analysis:
- Database expansion
- GC-MS, LC-QTOF-MS
- Seized drug testing
- Toxicology samples
- Forensic investigations
- Clinical investigations

Data Processing:
- Sample-mining
- Data-mining* (discovery)
- Use of *Intelligence* data
- Analyst data review
- NPS interpretation

Report Generation:
- "NPS Monographs"

Monitoring

Analysis:
- LC-QTOF-MS, LC-TOF-MS
- Toxicology samples
- Forensic investigations

Data Processing:
- Sample-mining
- Data-mining* (trends)
- Data cleaning
- Data merge
- Demographic/geographic
- Positivity assessment
- Combinations

Report Generation:
- "NPS Trend Reports"
- "A Year in Review"

Response

Analysis:
- Drug checking
- Quantitation
- Metabolism
- Potency / activity
- Toxicity
- Human vs. animal model
- Heat maps
- Clinical data
- Autopsy data
- User experiences
- Additional research

Report Generation:
- "NPS Public Alerts"
- "NPS Factsheets"
- "NPS Toolkits"
- Drug product reports

Forecasting

Analysis:
- Trends & data
- Advisory team
- Review of literature
- Programming / AI

Report Generation:
- "NPS Forecast"

ESSENTIAL COMPONENTS OF NPS DISCOVERY

- **Technology for Structural Elucidation**
  - HRMS, LC-MS, GC-MS, FTIR, NMR
- **Access to populations & data sources**
  - Toxicology samples – forensic and clinical
  - Drug materials – various distribution points
  - Drug Checking Partners
  - Surveys and drug use information
  - Online sources – drug forums, gray market sites, etc.
- **Uniform reporting format and structure**
- **Research initiatives / research programs**
- **Dissemination avenues**
  - Scientific community
  - Public health and public safety
  - Drug consuming populations and general public
- **Scientific and health expertise**
  - Pharmacology
  - Toxicology
  - Medical treatment
- **Collaborations, cooperation, information sharing, and plan for action**
  - Drug control and scheduling actions

cfsre | NPS DISCOVERY

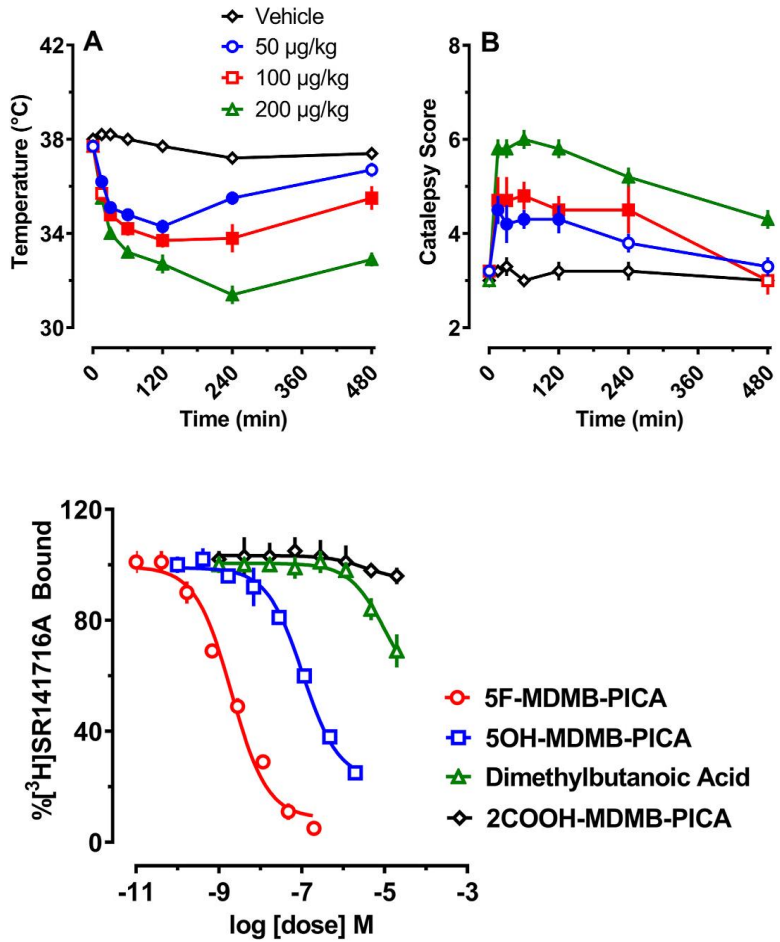
COLLABORATIONS

COLLABORATIONS & COLLABORATORS

- **Medical Examiners / Coroners → Casework**
  - Cause / manner of death determinations
  - Surveillance / monitoring / suspicion
- **Toxicologists → Human Performance Casework**
  - Assistance with new drug / NPS identification
- **Clinical Partners**
  - Drug intoxication outbreaks
  - Emergency Room Visits from NPS Intoxications
  - Public Health Drug Checking
- **Seized Drug Laboratories → Casework**
  - Border-to-street / Signature / Adulteration / Purity

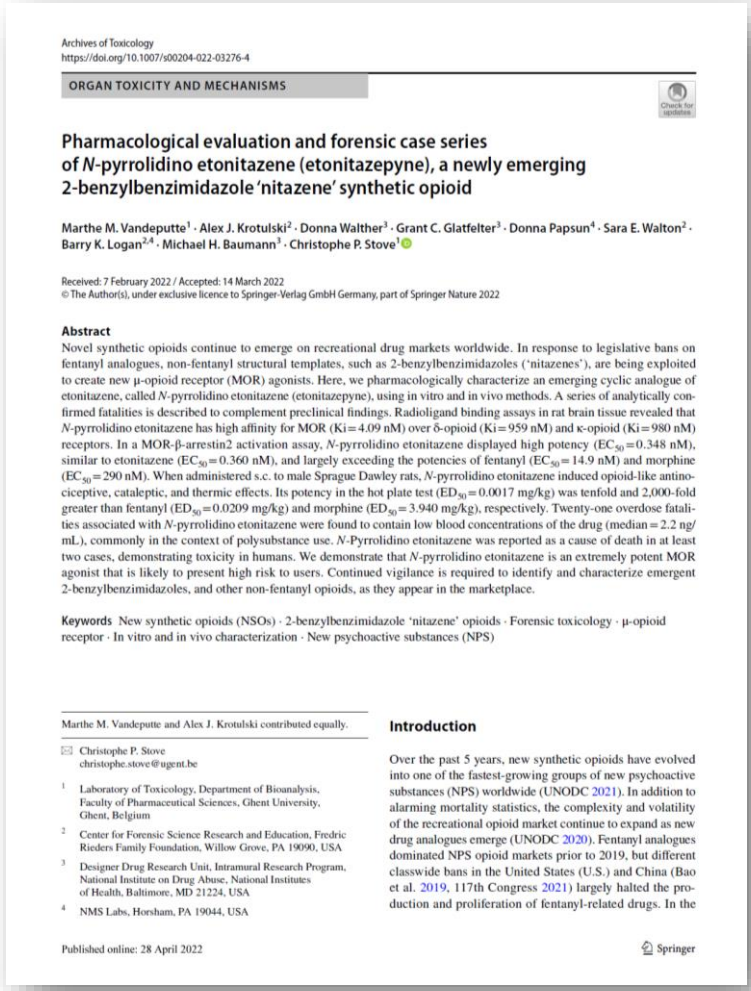
COLLABORATIONS & COLLABORATORS

- **NIDA DDRU (Mike Baumann & Team):**
  - *In vivo* assays to pharmacodynamic profiles
- **When NPS emerge, little is known about chemistry, pharmacology, and toxicology**
  - NIDA → Rat/mouse dosing studies, evaluate relative potency, physiological effects and behaviors (*in vitro* assays, as well)
  - CFSRE → Rapid development of toxicology methods and access to data (trends, intoxications, deaths)
- **Provides animal behavioral data to complement receptor binding information about the potential potency/toxicity of drugs within a new class**



COLLABORATIONS & COLLABORATORS

- **University of Ghent (Christophe Stove & Team):**
  - Pharmacological characterization through *In vitro* assays to assess activity and potency
- **When NPS emerge, little is known about chemistry, pharmacology, and toxicology**
  - UGhent → Quick assessment of activity and potency through receptor recruitment assays (MOR and CB)
  - CFSRE → Rapid development of toxicology method and access to data (trends, intoxications, deaths)
- **Receptor binding and functional effect (EC_{50}/EC_{Max}) allow toxicologists to better assess a drug's relative potency**



Archives of Toxicology
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ORGAN TOXICITY AND MECHANISMS

Pharmacological evaluation and forensic case series of *N*-pyrrolidino etonitazene (etonitazepyne), a newly emerging 2-benzylbenzimidazole 'nitazene' synthetic opioid

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Received: 7 February 2022 / Accepted: 14 March 2022

Abstract
Novel synthetic opioids continue to emerge on recreational drug markets worldwide. In response to legislative bans on fentanyl analogues, non-fentanyl structural templates, such as 2-benzylbenzimidazoles ('nitazenes'), are being exploited to create new μ-opioid receptor (MOR) agonists. Here, we pharmacologically characterize an emerging cyclic analogue of etonitazene, called *N*-pyrrolidino etonitazene (etonitazepyne), using in vitro and in vivo methods. A series of analytically confirmed fatalities is described to complement preclinical findings. Radioligand binding assays in rat brain tissue revealed that *N*-pyrrolidino etonitazene has high affinity for MOR (Ki = 4.09 nM) over δ-opioid (Ki = 959 nM) and κ-opioid (Ki = 980 nM) receptors. In a MOR-β-arrestin2 activation assay, *N*-pyrrolidino etonitazene displayed high potency (EC_{50} = 0.348 nM), similar to etonitazene (EC_{50} = 0.360 nM), and largely exceeding the potencies of fentanyl (EC_{50} = 14.9 nM) and morphine (EC_{50} = 290 nM). When administered s.c. to male Sprague Dawley rats, *N*-pyrrolidino etonitazene induced opioid-like antinociceptive, cataleptic, and thermic effects. Its potency in the hot plate test (ED_{50} = 0.0017 mg/kg) was tenfold and 2,000-fold greater than fentanyl (ED_{50} = 0.0209 mg/kg) and morphine (ED_{50} = 3.940 mg/kg), respectively. Twenty-one overdose fatalities associated with *N*-pyrrolidino etonitazene were found to contain low blood concentrations of the drug (median = 2.2 ng/mL), commonly in the context of polysubstance use. *N*-Pyrrolidino etonitazene was reported as a cause of death in at least two cases, demonstrating toxicity in humans. We demonstrate that *N*-pyrrolidino etonitazene is an extremely potent MOR agonist that is likely to present high risk to users. Continued vigilance is required to identify and characterize emergent 2-benzylbenzimidazoles, and other non-fentanyl opioids, as they appear in the marketplace.

Keywords New synthetic opioids (NSOs) · 2-benzylbenzimidazole 'nitazene' opioids · Forensic toxicology · μ-opioid receptor · In vitro and in vivo characterization · New psychoactive substances (NPS)

Marthe M. Vandeputte and Alex J. Krotulski contributed equally.

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Introduction

Over the past 5 years, new synthetic opioids have evolved into one of the fastest-growing groups of new psychoactive substances (NPS) worldwide (UNODC 2021). In addition to alarming mortality statistics, the complexity and volatility of the recreational opioid market continue to expand as new drug analogues emerge (UNODC 2020). Fentanyl analogues dominated NPS opioid markets prior to 2019, but different classwide bans in the United States (U.S.) and China (Bao et al. 2019, 117th Congress 2021) largely halted the production and proliferation of fentanyl-related drugs. In the

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COLLABORATIONS & COLLABORATORS

- **Philadelphia Department of Public Health**
  - Samples from recreational drug supply and adverse event scenarios
  - Data to complement toxicology and seized drug samples
- **New York City Overdose Prevention Program**
  - Surveillance of day-to-day changes in street drug supply
- **Additional tier of surveillance from people-using-drugs who don't go to the emergency room**
  - Street social workers, field epidemiologists, and other public health workers at wound clinics and on the street obtain drug user intelligence and collect drug materials and paraphernalia for analysis
- **Provides insights into drug use practices, motivation for drug use, harm reduction practices and adverse events**

COLLABORATIONS & COLLABORATORS

– Dr Alex Manini, Mt Sinai Icahn School, and the FENTALOG Project at ACMT

– American College of Medical Toxicologist (ACMT) & Clinical Partners

PITTSBURGH, PA
- 75% positive for at least one opioid
- Fentanyl (75%) commonly detected, followed by heroin (25%) and tramadol (25%)
- Opioid and stimulant use commonly observed (75%)
- NPS: *p*-Fluorofentanyl (25%), Clonazolam

BETHLEHEM, PA
- 97% positive for at least one opioid
- Fentanyl (88%) commonly detected
- Opioid and stimulant use observed (53%); benzodiazepine and opioid use less common (25%)
- *p*-Fluorofentanyl detected w/o fentanyl
- NPS: *p*-Fluorofentanyl (25%), *o*-Fluorofentanyl (6%), Valerylfentanyl, ADB-PINACA

NEW YORK, NY
- 88% positive for at least one opioid
- Fentanyl (65%) commonly detected, followed by methadone (26%), heroin (15%), and oxycodone (15%)
- Opioid and benzodiazepine use observed (32%); opioid and stimulant use (21%)
- PCP detected alongside fentanyl
- NPS: *p*-Fluorofentanyl (21%), Bromazolam, Flubromazepam, MDMB-4en-PINACA

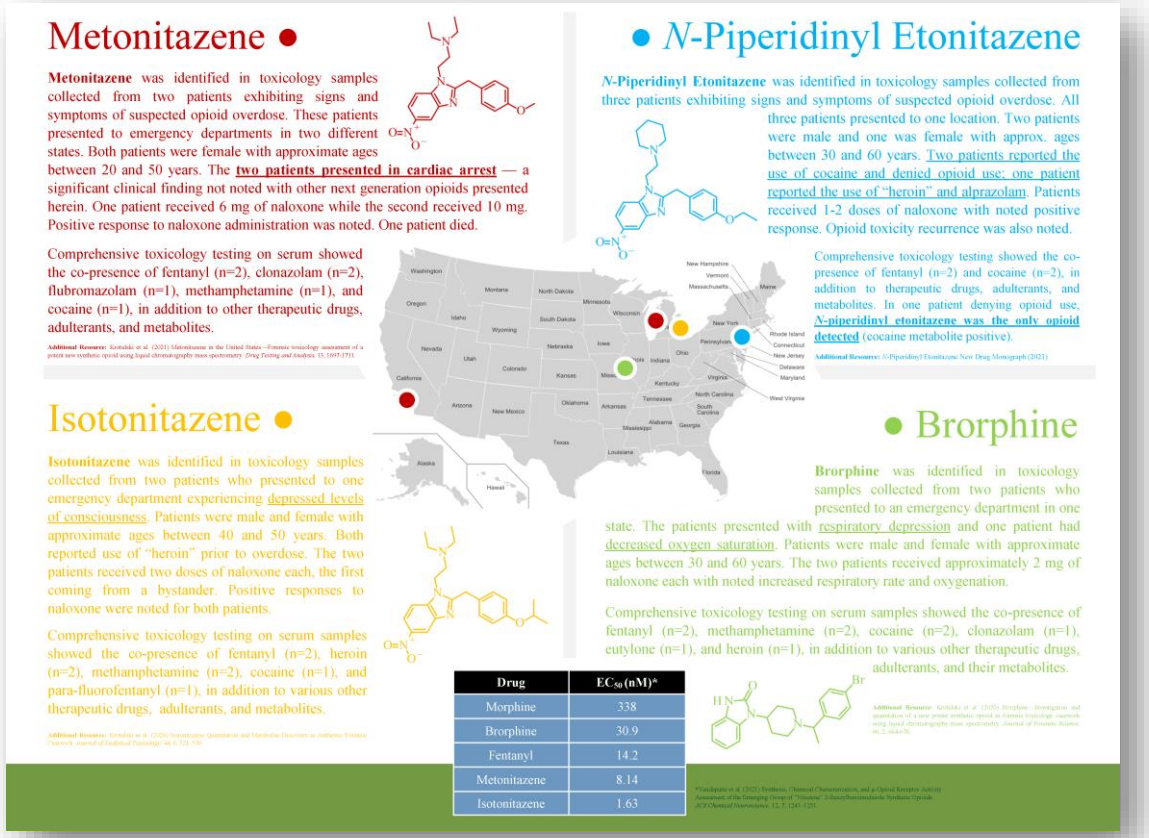
NEWARK, NJ
- 89% positive for at least one opioid
- Fentanyl (78%) commonly detected, followed by methadone and tramadol (11%)
- Opioid and stimulant use observed (44%); opioid and benzodiazepine use (17%)
- PCP detected alongside fentanyl
- NPS: *p*-Fluorofentanyl (11%), Clonazolam

ST. LOUIS, MO
- 95% positive for at least one opioid
- Fentanyl (93%) very commonly detected
- Opioid and stimulant use common (63%); opioid and benzodiazepine use was less common (15%)
- MDMA detected alongside fentanyl (5%)
- NPS: *p*-Fluorofentanyl (10%), Bromazolam, Flubromazepam

PORTLAND, OR
- 74% positive for at least one opioid
- Fentanyl (68%) commonly detected, followed by heroin (16%)
- THC and metabolites detected (32%)
- Opioid and stimulant use observed (53%); opioid and benzodiazepine use less

LOS ANGELES, CA
- 90% positive for at least one opioid
- Fentanyl (75%) commonly detected, followed by heroin (5%) & methadone (5%)
- Opioid and stimulant use observed (45%); opioid and cannabinoid use (15%); opioid and benzodiazepine use (10%)

GRAND RAPIDS, MI
- 89% positive for at least one opioid
- Fentanyl (74%) commonly detected, followed by tramadol (8%) and heroin (8%)
- Opioid and stimulant use observed (55%); opioid and benzodiazepine use (21%)
- *p*-Fluorofentanyl detected w/o fentanyl



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.

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).

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.

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.

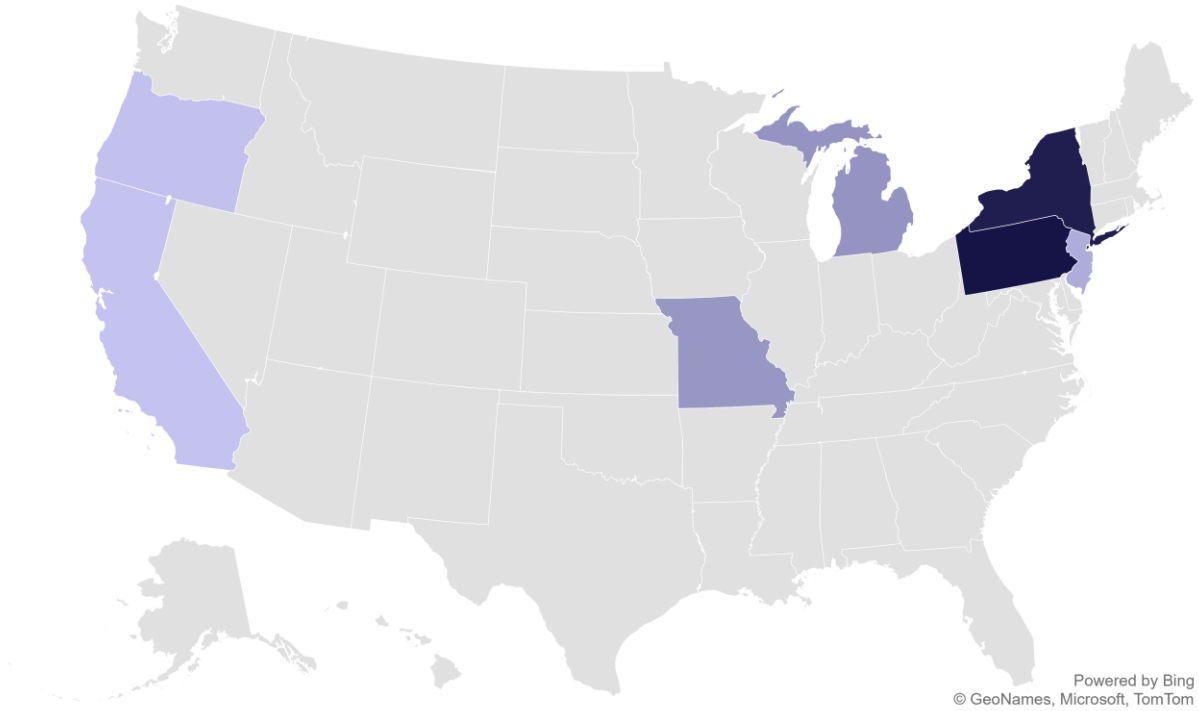
Drug	EC_{50} (nM)*
Morphine	338
Brorphine	30.9
Fentanyl	14.2
Metonitazene	8.14
Isotonitazene	1.63

ToxIC Toxicology Investigators Consortium

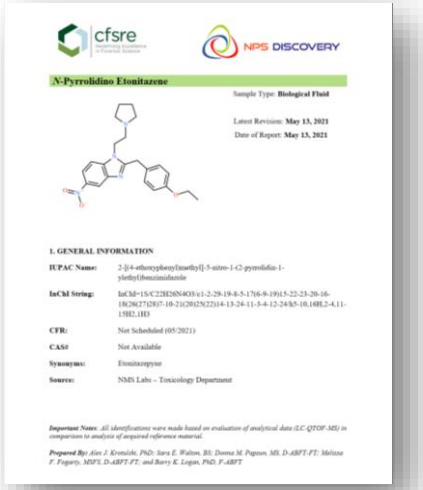
ACMT American College of Medical Toxicology

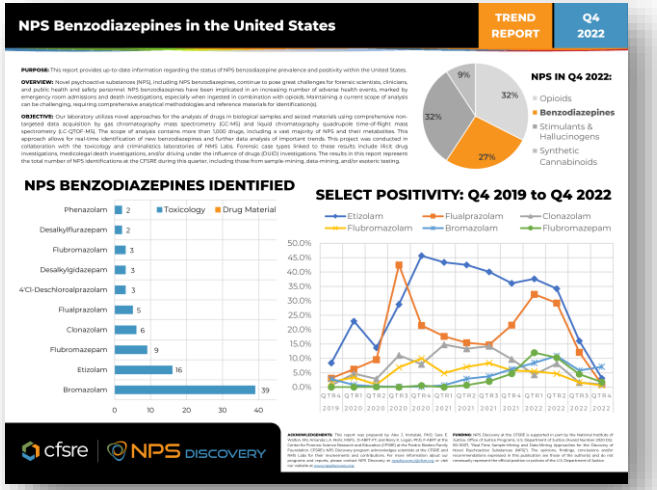
- Ongoing collaborative study with the **American College of Medical Toxicology (ACMT)**
  - Clinical reports, signs/symptoms, and toxicology samples collected
    - Antemortem blood and plasma/serum discarded samples
    - Samples sent to the CFSRE for comprehensive toxicology testing

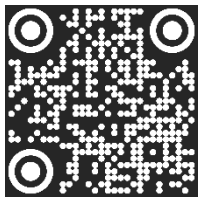
- Toxicological analysis (n=886)
  - Tested for the presence of NPS, traditional drugs, therapeutics, **adulterants**, and metabolites
  - **Xylazine prevalence (2023)**
    - Positive in 195 samples (22%)
    - Northeast (77%)
    - Midwest (20%)
    - West (1.5%)

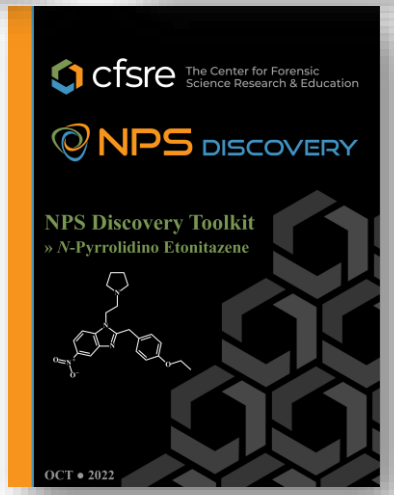


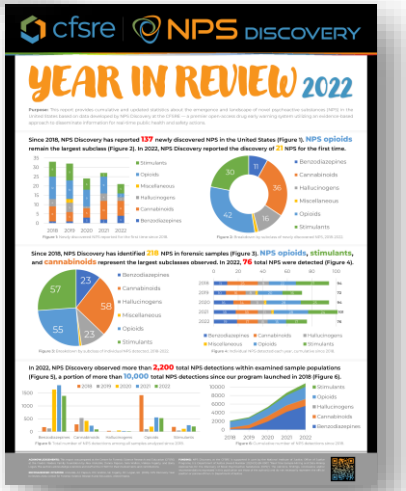
NPS DISCOVERY REPORTS → WWW.NPSDISCOVERY.ORG







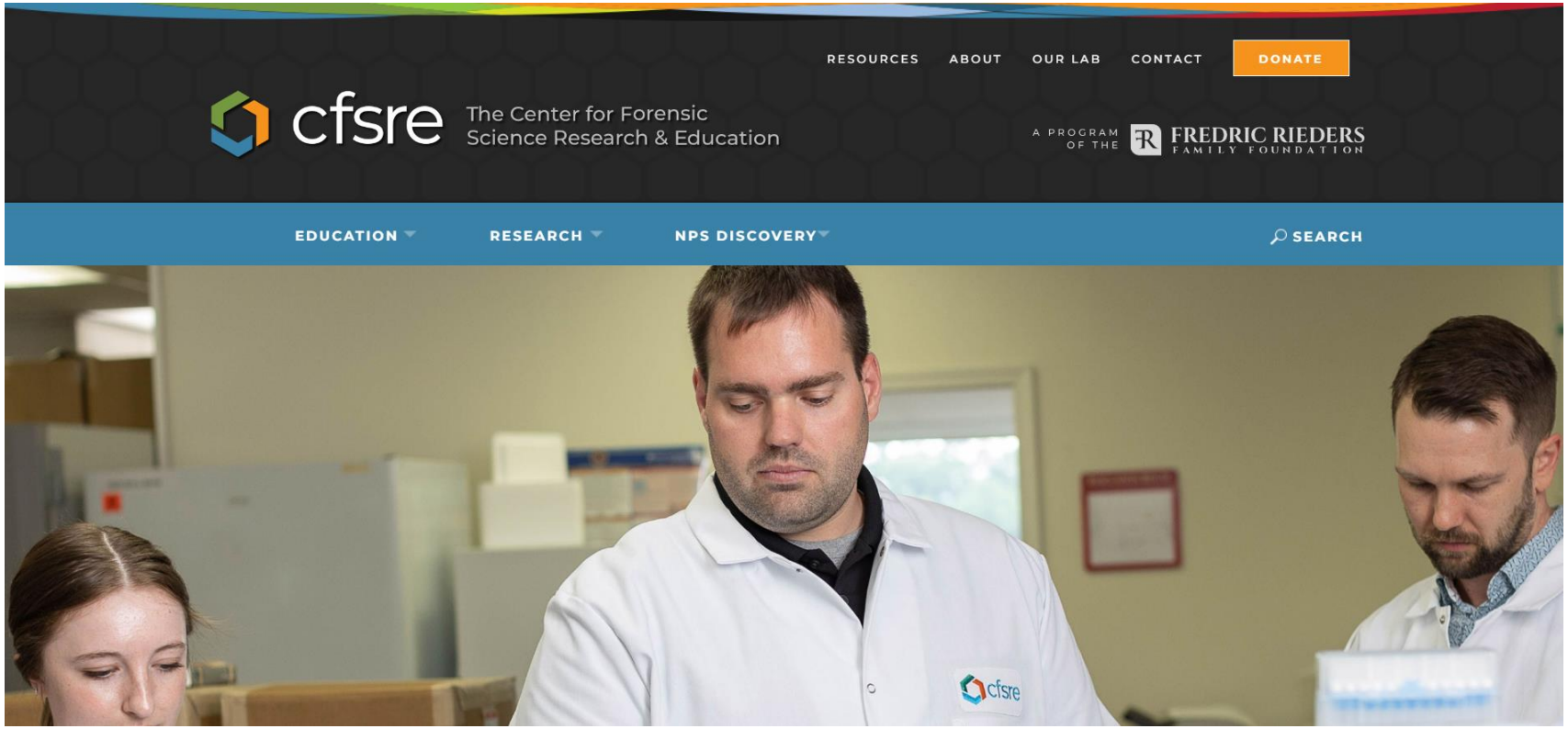




cfsre | NPS DISCOVERY

DISSEMINATION

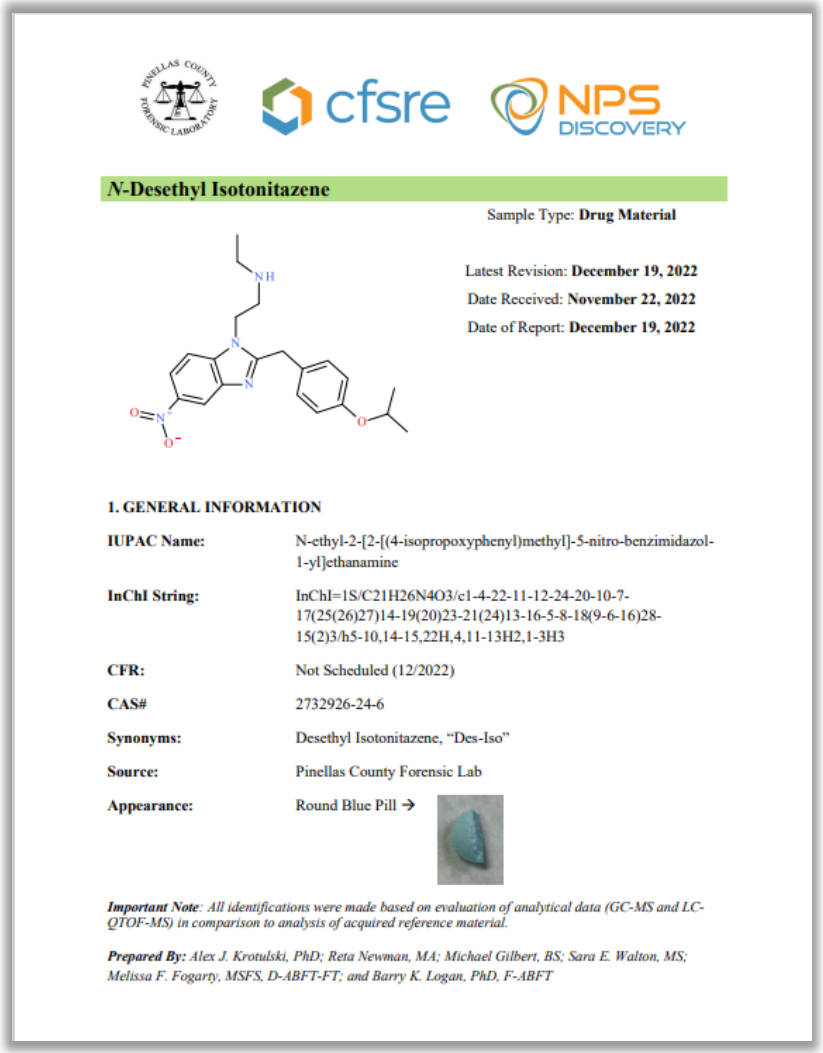
DISSEMINATION



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

DISSEMINATION → *N*-DESETHYL ISOTONITAZENE

Dec 19, 2022



PINELLAS COUNTY FORENSIC LABORATORY

cfsre NPS DISCOVERY

_N_-Desethyl Isotonitazene

Sample Type: **Drug Material**

Latest Revision: **December 19, 2022**

Date Received: **November 22, 2022**

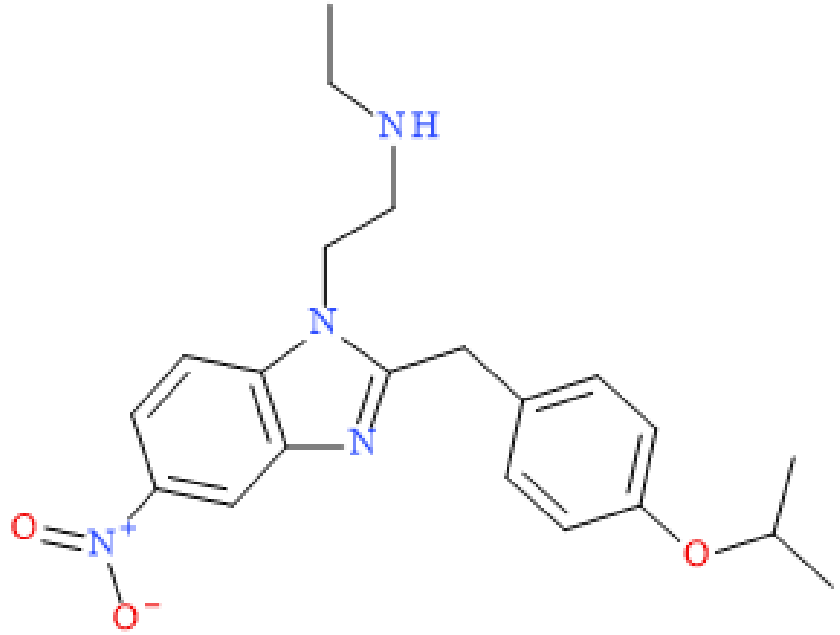
Date of Report: **December 19, 2022**

1. GENERAL INFORMATION

IUPAC Name:	N-ethyl-2-[2-[(4-isopropoxyphenyl)methyl]-5-nitro-benzimidazol-1-yl]ethanamine
InChI String:	InChI=1S/C21H26N4O3/c1-4-22-11-12-24-20-10-7-17(25(26)27)14-19(20)23-21(24)13-16-5-8-18(9-6-16)28-15(2)3/h5-10,14-15,22H,4,11-13H2,1-3H3
CFR:	Not Scheduled (12/2022)
CAS#	2732926-24-6
Synonyms:	Desethyl Isotonitazene, "Des-Iso"
Source:	Pinellas County Forensic Lab
Appearance:	Round Blue Pill →

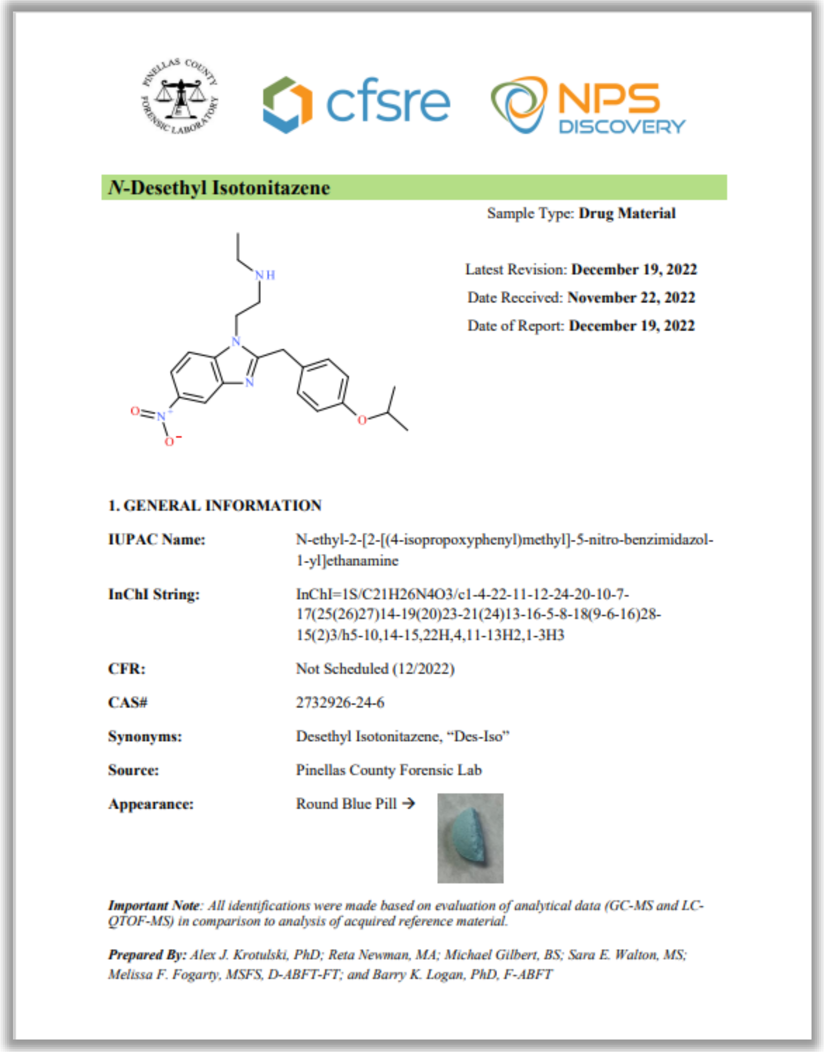
***Important Note**: All identifications were made based on evaluation of analytical data (GC-MS and LC-QTOF-MS) in comparison to analysis of acquired reference material.*

***Prepared By:** Alex J. Krotulski, PhD; Reta Newman, MA; Michael Gilbert, BS; Sara E. Walton, MS; Melissa F. Fogarty, MSFS, D-ABFT-FT; and Barry K. Logan, PhD, F-ABFT*

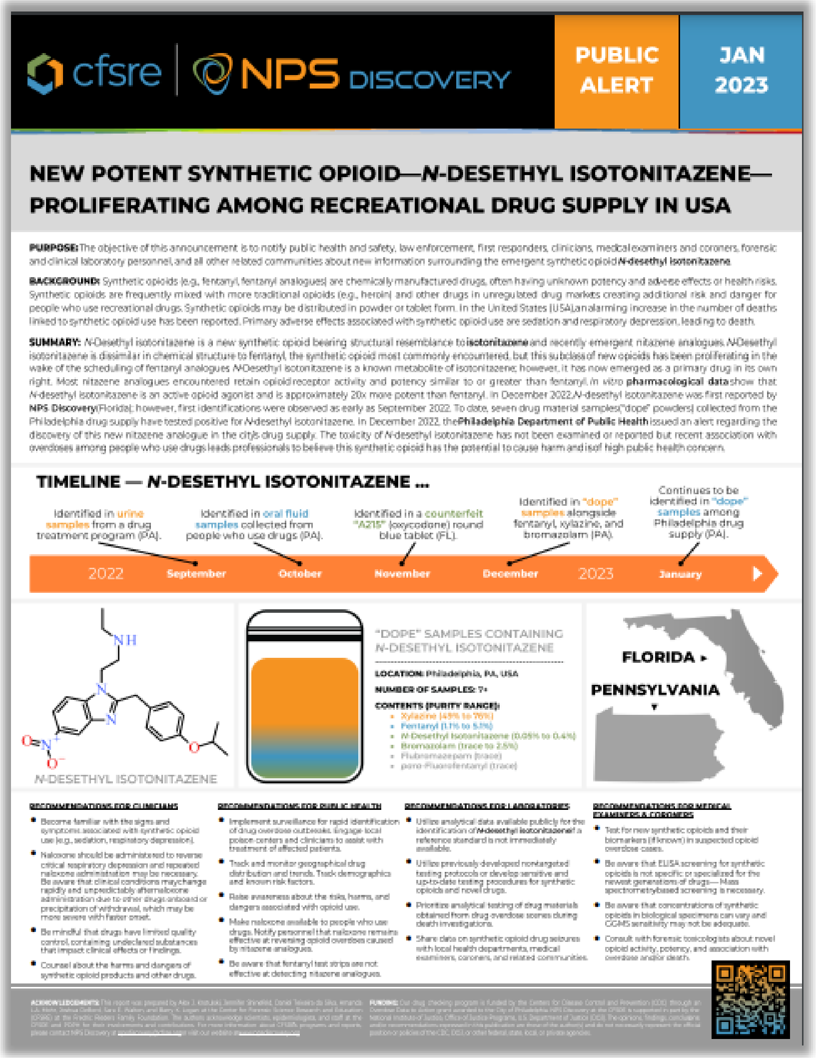


DISSEMINATION → *N*-DESETHYL ISOTONITAZENE

Dec 19, 2022



Jan 22, 2023



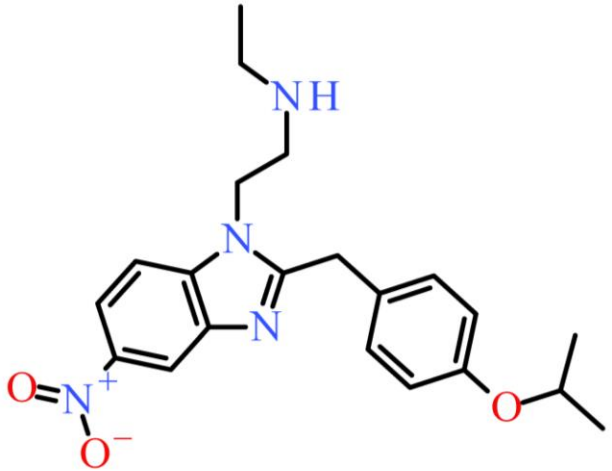
PUBLIC ALERT: *N*-DESETHYL ISOTONITAZENE

January 23, 2023

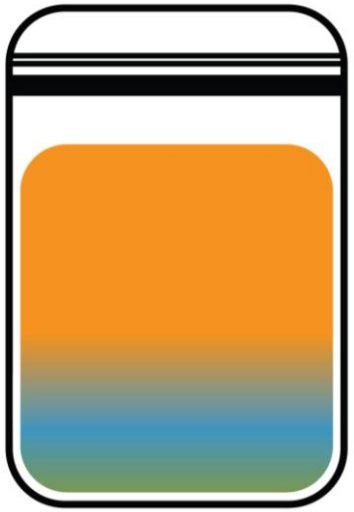
- New potent synthetic opioid proliferating among recreational drug supply in USA

TIMELINE — *N*-DESETHYL ISOTONITAZENE ...

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



N-DESETHYL ISOTONITAZENE



"DOPE" SAMPLES CONTAINING *N*-DESETHYL ISOTONITAZENE

LOCATION: Philadelphia, PA, USA

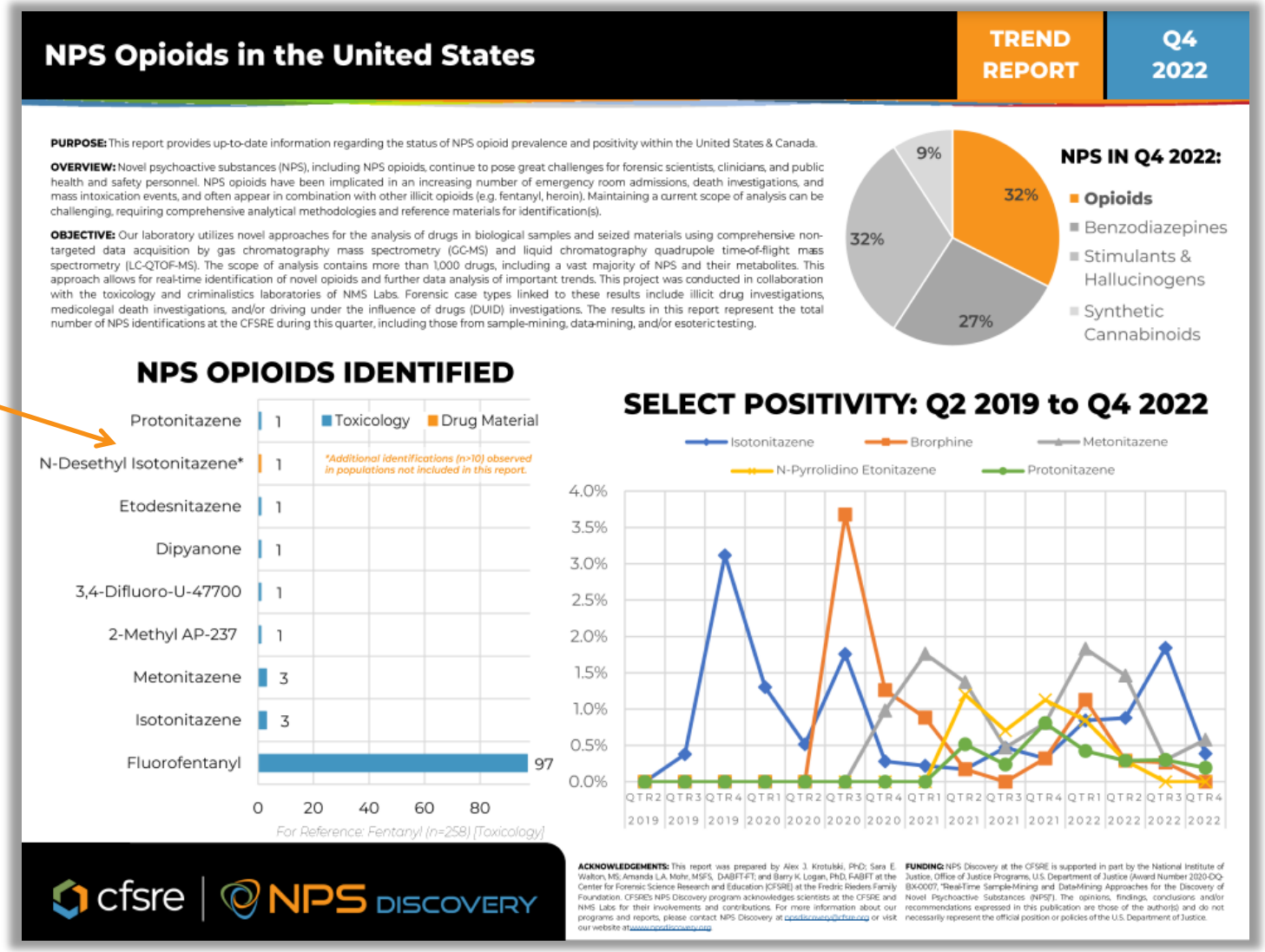
NUMBER OF SAMPLES: 7+

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)

DISSEMINATION → *N*-DESETHYL ISOTONITAZENE

January 30, 2023



NPS Opioids in the United States

TREND REPORT | Q4 2022

PURPOSE: This report provides up-to-date information regarding the status of NPS opioid prevalence and positivity within the United States & Canada.

OVERVIEW: Novel psychoactive substances (NPS), including NPS opioids, continue to pose great challenges for forensic scientists, clinicians, and public health and safety personnel. NPS opioids have been implicated in an increasing number of emergency room admissions, death investigations, and mass intoxication events, and often appear in combination with other illicit opioids (e.g. fentanyl, heroin). Maintaining a current scope of analysis can be challenging, requiring comprehensive analytical methodologies and reference materials for identification(s).

OBJECTIVE: Our laboratory utilizes novel approaches for the analysis of drugs in biological samples and seized materials using comprehensive non-targeted data acquisition by gas chromatography mass spectrometry (GC-MS) and liquid chromatography quadrupole time-of-flight mass spectrometry (LC-QTOF-MS). The scope of analysis contains more than 1,000 drugs, including a vast majority of NPS and their metabolites. This approach allows for real-time identification of novel opioids and further data analysis of important trends. This project was conducted in collaboration with the toxicology and criminalistics laboratories of NMS Labs. Forensic case types linked to these results include illicit drug investigations, medicolegal death investigations, and/or driving under the influence of drugs (DUID) investigations. The results in this report represent the total number of NPS identifications at the CFSRE during this quarter, including those from sample-mining, data-mining, and/or esoteric testing.

NPS OPIOIDS IDENTIFIED

SELECT POSITIVITY: Q2 2019 to Q4 2022

cfsre | NPS DISCOVERY

ACKNOWLEDGEMENTS: This report was prepared by Alex J. Krotulski, PhD; Sara E. Walton, MS; Amanda L.A. Mohr, MSFS, DABFT-FT; and Barry K. Logan, PhD, FABFT at the Center for Forensic Science Research and Education (CFSRE) at the Fredric Rieders Family Foundation. CFSRE's NPS Discovery program acknowledges scientists at the CFSRE and NMS Labs for their involvements and contributions. For more information about our programs and reports, please contact NPS Discovery at npsdiscovery@cfsre.org or visit our website at www.npsdiscovery.org.

FUNDING: NPS Discovery at the CFSRE is supported in part by the National Institute of Justice, Office of Justice Programs, U.S. Department of Justice (Award Number 2020-DQ-BX-0007, "Real-Time Sample-Mining and Data-Mining Approaches for the Discovery of Novel Psychoactive Substances (NPS)". 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 U.S. Department of Justice.

DISSEMINATION → *N*-DESETHYL ISOTONITAZENE

February 25, 2023

cfsre
The Center for Forensic Science Research & Education

Society of Forensic Toxicologists Inc.

TIAFT

Most Recent Recommendations from Q1 2023

Benzodiazepines		Opioids		Stimulants & Hallucinogens		Synthetic Cannabinoids	
TIER ONE *(STRONGLY RECOMMEND)*							
Etizolam	1-10	N-Desethyl Isotonitazene↑	<1	NN-Dimethylpentylone	>10	MDMB-4en-PINACA	<1
Flualprazolam	1-10	Isotonitazene	<1	Pentylone	>10	ADB-BINACA (-BUTINACA)	<1
Bromazolam	1-10	Metonitazene	<1	Eutylone	>10	ADB-5'Br-BINACA	<1
Flubromazepam	1-10	o/m/p-Fluorofentanyl	1-10	N-Propyl Butylone	>10	CH-PIATA↑	<1
Clonazolam	<1	Carfentanil	<1	alpha-PHP / alpha-PiHP↑	>10	ADB-FUBIATA	<1
TIER TWO *(RECOMMEND)*							
8-Aminoclonazolam	1-10	N-Pyrrolidino Etonitazene↓	<1	Fluoroexetamine↑	>10	5F-MDMB-PICA	<1
Flubromazolam	1-10	N-Pyrrolidino Protonitazene↑	<1	N-Cyclohexyl Butylone↓	>10	4F-MDMB-BINACA	<1
4'Cl-Deschloroalprazolam	1-10	N-Pyrrolidino Metonitazene↑	<1	N-Cyclohexyl Methylone	1-10	CH-FUBIATA	<1
Desalkylgidazepam↑	1-10	Protonitazene	<1	2F-Deschloroketamine	<1	ADB-5'Br-PINACA↓	<1
TIER THREE *(CONSIDER)*							
Desalkylflurazepam	1-10	Brorphine↓	<1	2/3/4-Methylmethcathinone	1-10	BZO-4en-POXIZID	<1
Deschloroetizolam	1-10	Etodesnitazene	1-10	3-HO-PCP / 4-HO-PCP↓	<1	5F-BZO-POXIZID	<1
Pyrazolam	1-10	2-Methyl AP-237	>10	3-MeO-PCP / 4-MeO-PCP	<1	BZO-POXIZID	<1
Phenazolam↑	1-10	AP-238↓	>10	MDPHP	>10	ADB-4en-PINACA↑	<1

Note: This may not be an all-inclusive list. Laboratories should consider additional NPS for inclusion (or exclusion) based on local, national, and/or international trends.

2022 – THE COLOMBO PLAN SENTINEL PROJECT

- Characterization of seized cross-border counterfeit dosage forms on the US Mexico Border
- Partnership with Customs and Border Protection
- Focus on Suspected Fentanyl and Methamphetamine tablets and powders
  - Identification
  - Purity determination
  - Signature:
    - Physical Characteristics (individualizing characteristics)
    - Active drugs (Toxicity)
    - Adulterants/Excipients (Toxicology and signature)
    - Residual precursor (supply chain intelligence)
    - Reaction by-products (Synthesis methods)

DRUG SIGNATURE PROJECTS

Fentanyl Profiling Program Report

CY 2021

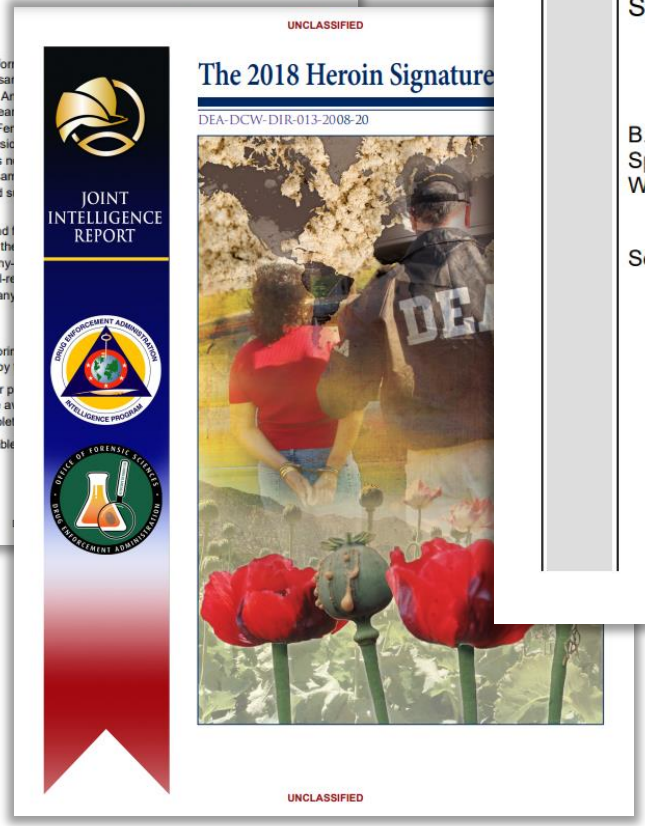
Drug Enforcement Administration
Special Testing and Research Laboratory

Summary and Key Findings

The Fentanyl Profiling Program (FPP) perfor
analyses on fentanyl and fentanyl-related sa
zures made throughout the United States. Ar
developed at the Special Testing and Resear
allow in-depth reporting on samples. The Fe
Report summarizes the results and conclusio
analyses on a bi-annual basis. FPP data is n
market share, but is rather a snapshot of sa
laboratory from the eight DEA regional and s
laboratories.

For this reporting period, 1,233 fentanyl and
seized during CY 2021 were examined by th
1,013 contained fentanyl as the only fentany
192 contained both fentanyl and a fentanyl-re
Twenty-eight samples contained only fentany

- The Gupta Method was the prin
fentanyl samples examined by
- The average fentanyl powder p
range of 0.1% to 75.6%. The a
a range of 0.01 to 8.4 mg/tablet
- Two hundred seven of the table
2 mg of fentanyl.



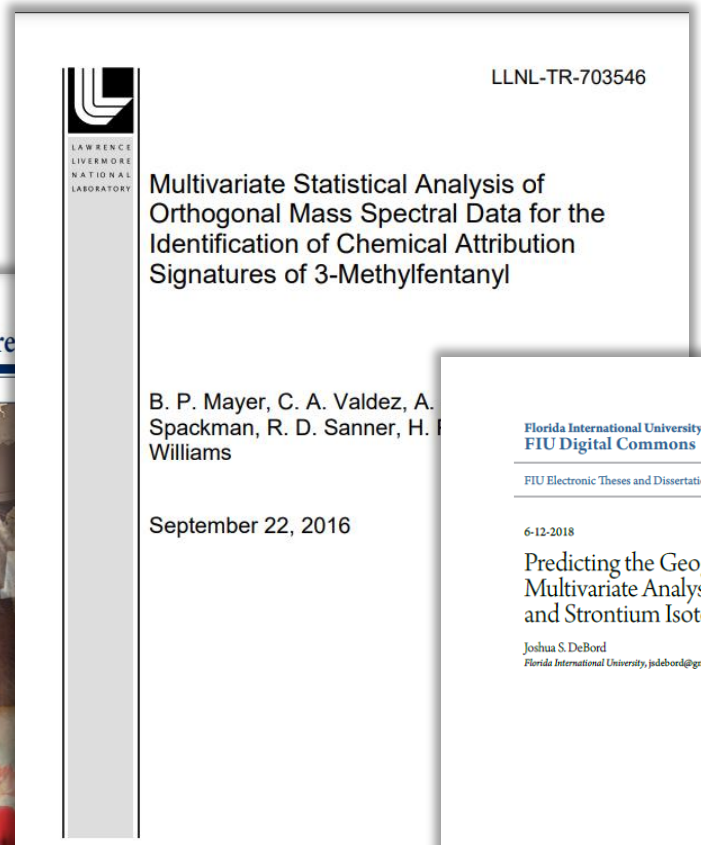
UNCLASSIFIED

JOINT INTELLIGENCE REPORT

The 2018 Heroin Signature

DEA-DCW-DIR-013-2008-20

UNCLASSIFIED



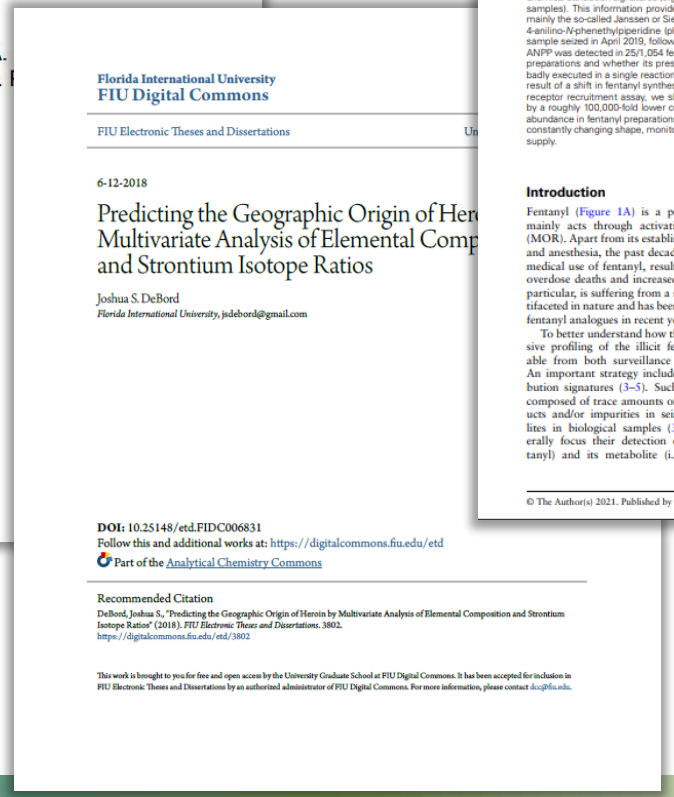
LLNL-TR-703546

LAWRENCE LIVERMORE NATIONAL LABORATORY

Multivariate Statistical Analysis of Orthogonal Mass Spectral Data for the Identification of Chemical Attribution Signatures of 3-Methylfentanyl

B. P. Mayer, C. A. Valdez, A.
Spackman, R. D. Sanner, H.
Williams

September 22, 2016



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6-12-2018

Predicting the Geographic Origin of Her
Multivariate Analysis of Elemental Comp
and Strontium Isotope Ratios

Joshua S. DeBord
Florida International University, jsdebord@gmail.com

DOI: 10.25148/etd.FIDC006831
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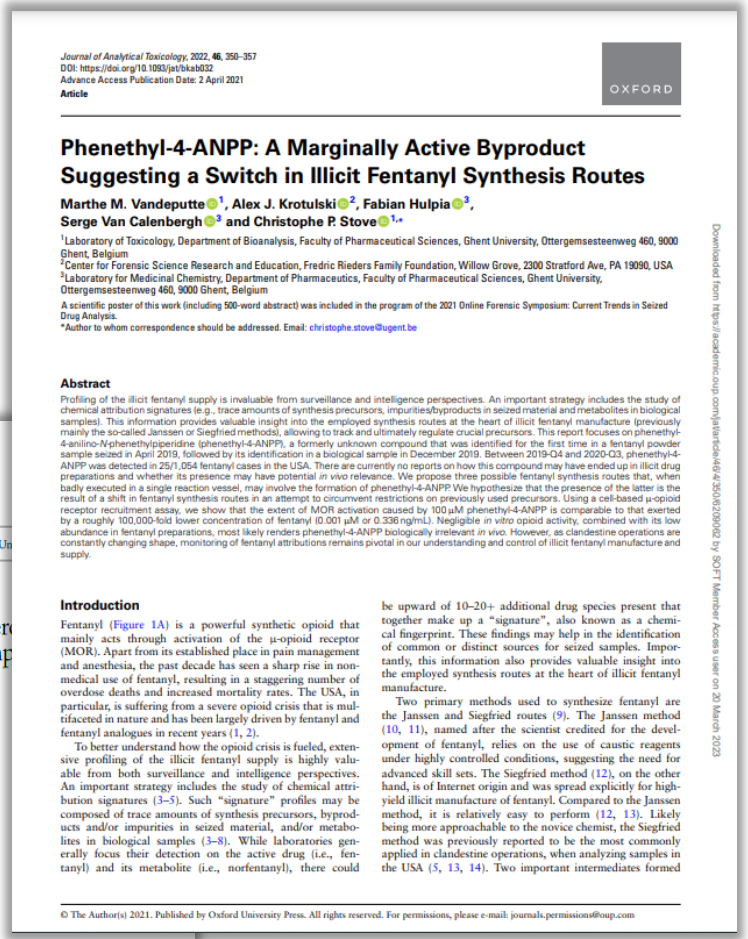

Journal of Analytical Toxicology, 2022, **46**, 350–357
DOI: https://doi.org/10.1093/jat/bkab032
Advance Access Publication Date: 2 April 2021
Article

OXFORD

Phenethyl-4-ANPP: A Marginally Active Byproduct Suggesting a Switch in Illicit Fentanyl Synthesis Routes

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[2]Center for Forensic Science Research and Education, Fredric Rieders Family Foundation, Willow Grove, 2300 Stratford Ave, PA 19090, USA
[3]Laboratory for Medicinal Chemistry, Department of Pharmaceutics, Faculty of Pharmaceutical Sciences, Ghent University, Ottergemsesteenweg 460, 9000 Ghent, Belgium

A scientific poster of this work (including 500-word abstract) was included in the program of the 2021 Online Forensic Symposium: Current Trends in Seized Drug Analysis.
*Author to whom correspondence should be addressed. Email: christophe.stove@ugent.be

Abstract

Profiling of the illicit fentanyl supply is invaluable from surveillance and intelligence perspectives. An important strategy includes the study of chemical attribution signatures (e.g., trace amounts of synthesis precursors, impurities/byproducts in seized material and metabolites in biological samples). This information provides valuable insight into the employed synthesis routes at the heart of illicit fentanyl manufacture (previously mainly the so-called Janssen or Siegfried methods), allowing to track and ultimately regulate crucial precursors. This report focuses on phenethyl-4-anilino-*N*-phenethylpiperidine (phenethyl-4-ANPP), a formerly unknown compound that was identified for the first time in a fentanyl powder sample seized in April 2019, followed by its identification in a biological sample in December 2019. Between 2019-Q4 and 2020-Q3, phenethyl-4-ANPP was detected in 25/1,054 fentanyl cases in the USA. There are currently no reports on how this compound may have ended up in illicit drug preparations and whether its presence may have potential *in vivo* relevance. We propose three possible fentanyl synthesis routes that, when badly executed in a single reaction vessel, may involve the formation of phenethyl-4-ANPP. We hypothesize that the presence of the latter is the result of a shift in fentanyl synthesis routes in an attempt to circumvent restrictions on previously used precursors. Using a cell-based μ-opioid receptor recruitment assay, we show that the extent of MOR activation caused by 100 μM phenethyl-4-ANPP is comparable to that exerted by a roughly 100,000-fold lower concentration of fentanyl (0.001 μM or 0.336 ng/mL). Negligible *in vitro* opioid activity, combined with its low abundance in fentanyl preparations, most likely renders phenethyl-4-ANPP biologically irrelevant *in vivo*. However, as clandestine operations are constantly changing shape, monitoring of fentanyl attributions remains pivotal in our understanding and control of illicit fentanyl manufacture and supply.

Introduction

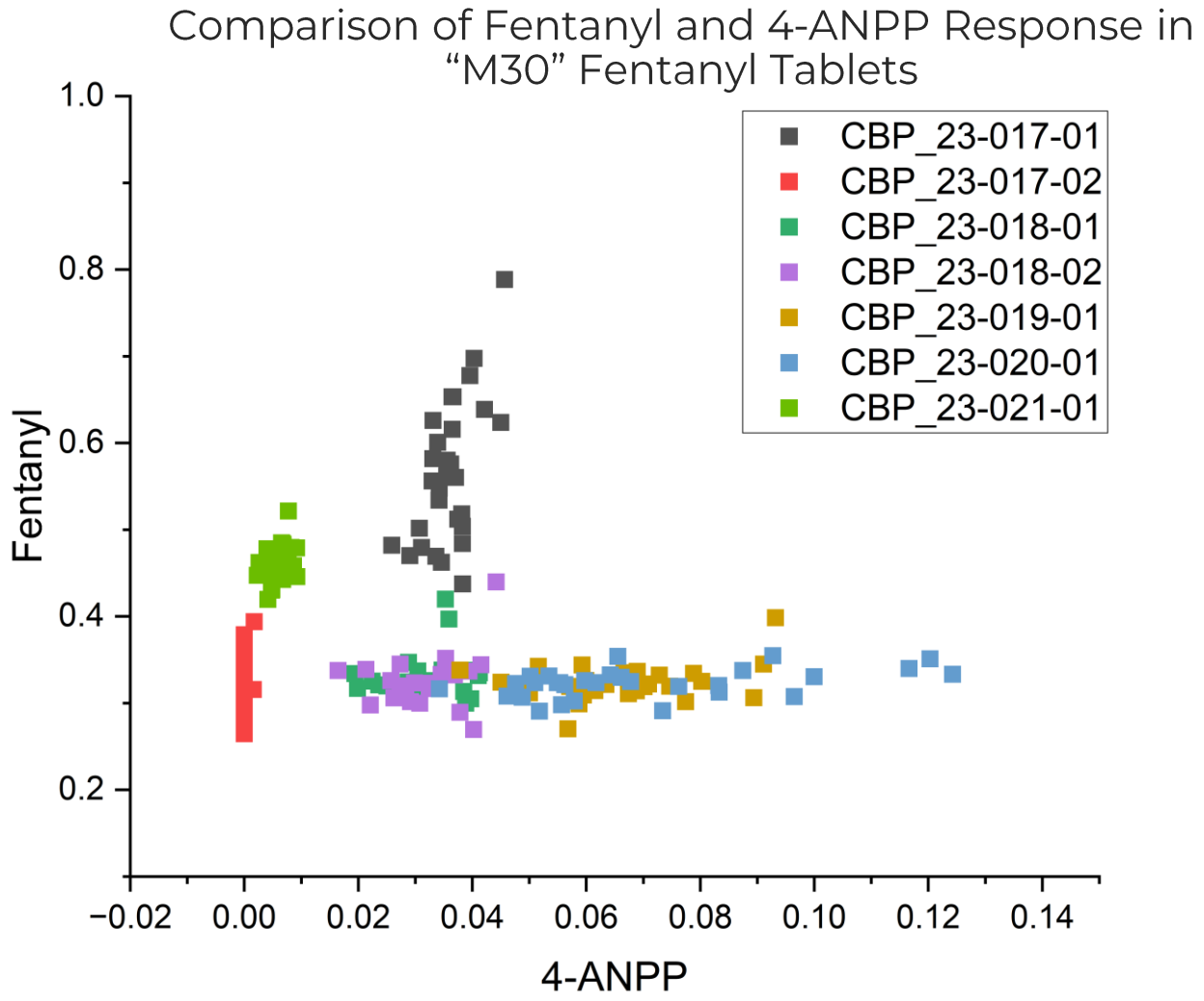
Fentanyl (Figure 1A) is a powerful synthetic opioid that mainly acts through activation of the μ-opioid receptor (MOR). Apart from its established place in pain management and anesthesia, the past decade has seen a sharp rise in non-medical use of fentanyl, resulting in a staggering number of overdose deaths and increased mortality rates. The USA, in particular, is suffering from a severe opioid crisis that is multifaceted in nature and has been largely driven by fentanyl and fentanyl analogues in recent years (1, 2).

To better understand how the opioid crisis is fueled, extensive profiling of the illicit fentanyl supply is highly valuable from both surveillance and intelligence perspectives. An important strategy includes the study of chemical attribution signatures (3–5). Such "signature" profiles may be composed of trace amounts of synthesis precursors, byproducts and/or impurities in seized material, and/or metabolites in biological samples (3–8). While laboratories generally focus their detection on the active drug (i.e., fentanyl) and its metabolite (i.e., norfentanyl), there could be upward of 10–20+ additional drug species present that together make up a "signature", also known as a chemical fingerprint. These findings may help in the identification of common or distinct sources for seized samples. Importantly, this information also provides valuable insight into the employed synthesis routes at the heart of illicit fentanyl manufacture.

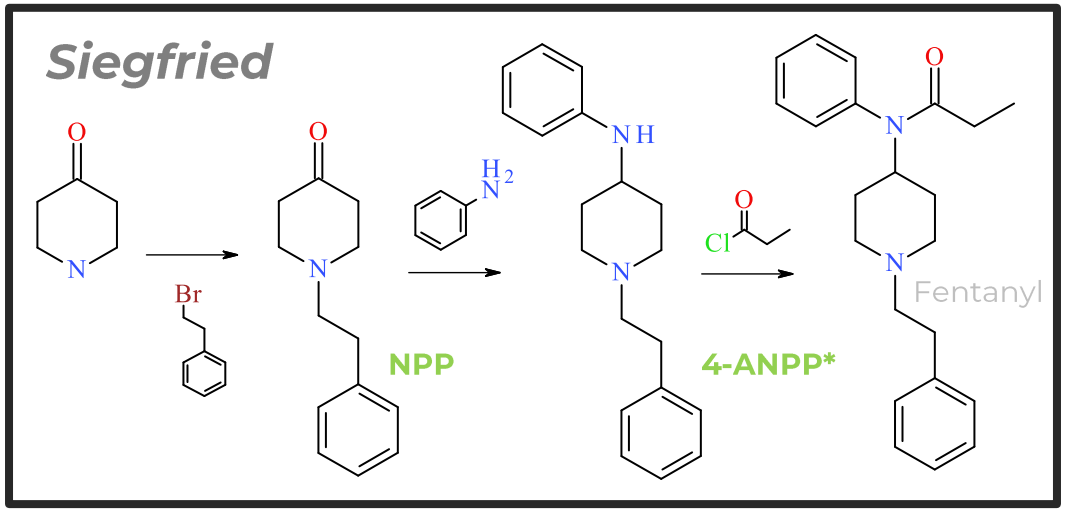
Two primary methods used to synthesize fentanyl are the Janssen and Siegfried routes (9). The Janssen method (10, 11), named after the scientist credited for the development of fentanyl, relies on the use of caustic reagents under highly controlled conditions, suggesting the need for advanced skill sets. The Siegfried method (12), on the other hand, is of Internet origin and was spread explicitly for high-yield illicit manufacture of fentanyl. Compared to the Janssen method, it is relatively easy to perform (12, 13). Likely being more approachable to the novice chemist, the Siegfried method was previously reported to be the most commonly applied in clandestine operations, when analyzing samples in the USA (5, 13, 14). Two important intermediates formed

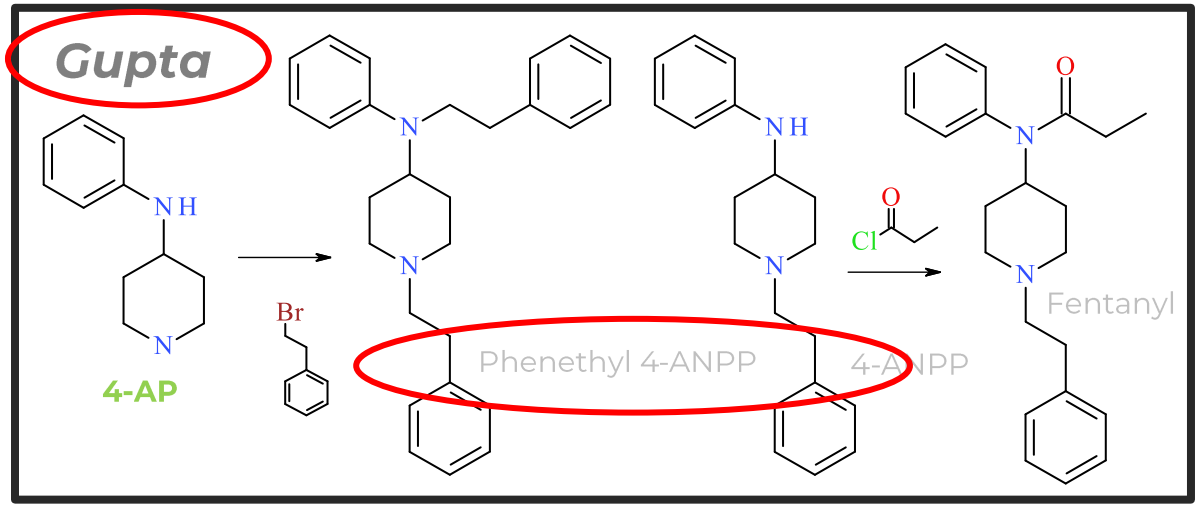
QUALITATIVE GC/MS ANALYSIS

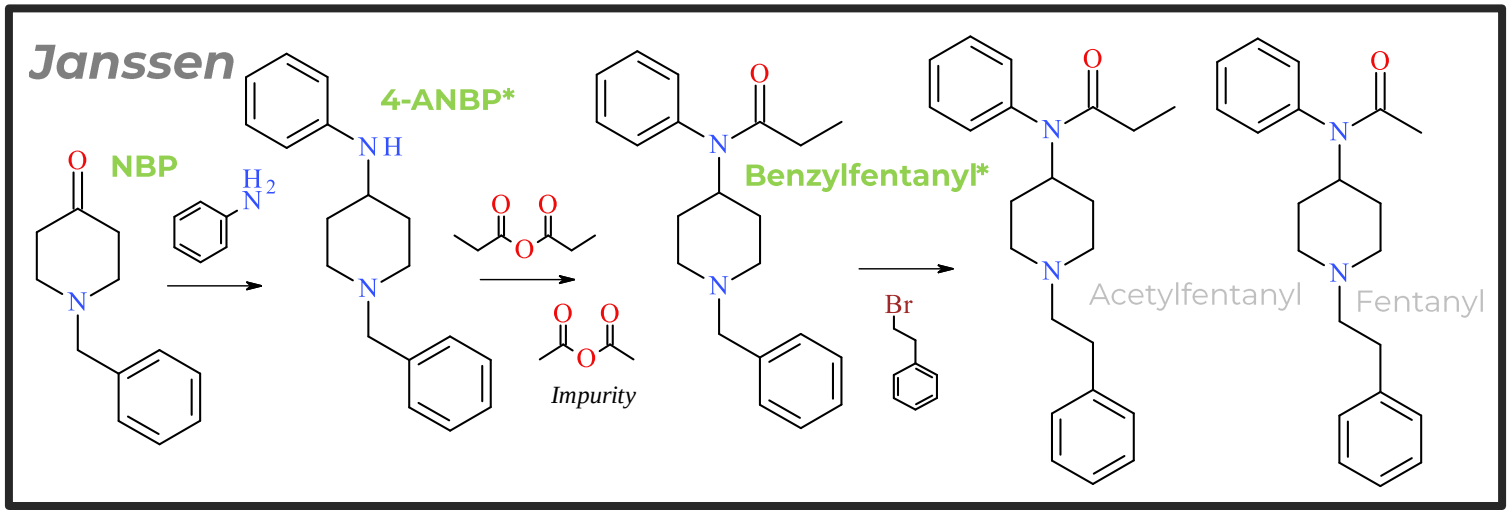
- Comparison of relative proportions of constituents can show similarities and differences between exhibits
  - 018-01 and 018-02 and 019-01 and 020-01 have similar proportions of Fentanyl to 4-ANPP
  - 4-ANPP is a fentanyl precursor
  - Differences in proportions could indicate differences in synthesis



SYNTHESIS ROUTES – PRECURSORS







- Detection of precursors allows for **determination of synthesis route used**
- Linked to control measures
- What are the health implications? Off target effects? Etc.

CFSRE AND NPS DISCOVERY

- A resource for analytical confirmation regarding the identity, composition, and purity/dosage strength of drugs associated with adverse human health outcomes.
- Capitalizing on data from multiple populations looking for temporal and geographic trends in drug composition and markets.
- Focusing on public health and safety aspects of drug threats.
- Early warning system for emerging drug threats.

cfsre | NPS DISCOVERY

NPS TRENDS IN THE U.S.

EMERGENCE OF NPS IN THE U.S.

- Since 2018, NPS Discovery has reported **137** newly discovered NPS in the United States (Figure 1). **NPS opioids** remain the largest subclass (Figure 2). In 2022, NPS Discovery reported the discovery of **21** NPS for the first time.

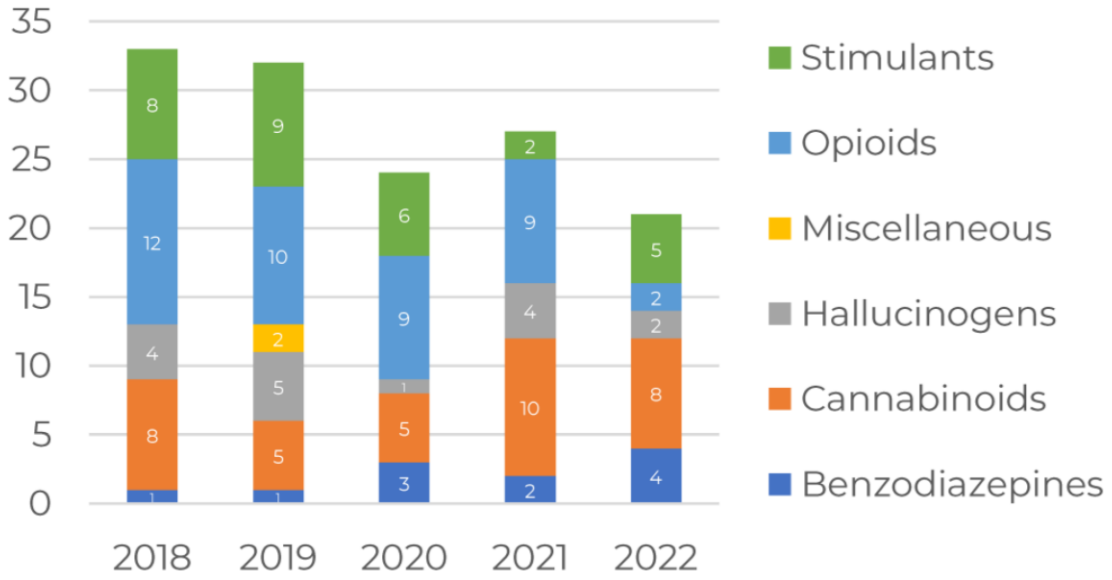


Figure 1: Newly discovered NPS reported for the first time since 2018.

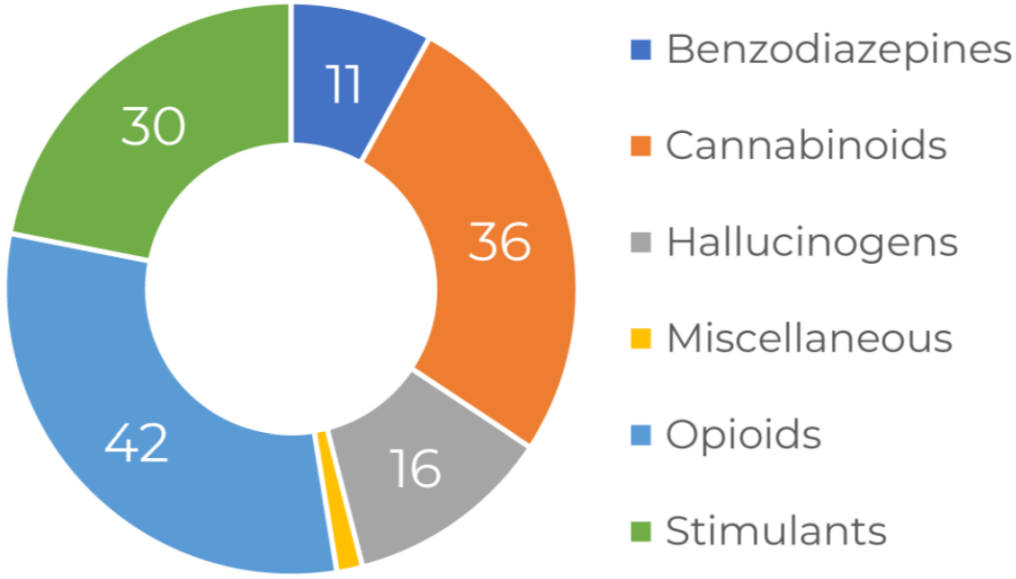


Figure 2: Breakdown by subclass of newly discovered NPS, 2018-2022.

LANDSCAPE OF NPS IN THE U.S.

- Since 2018, NPS Discovery has identified **218** NPS in forensic samples (Figure 3). **NPS opioids**, **stimulants**, and **cannabinoids** represent the largest subclasses observed. In 2022, **76** total NPS were detected (Figure 4).

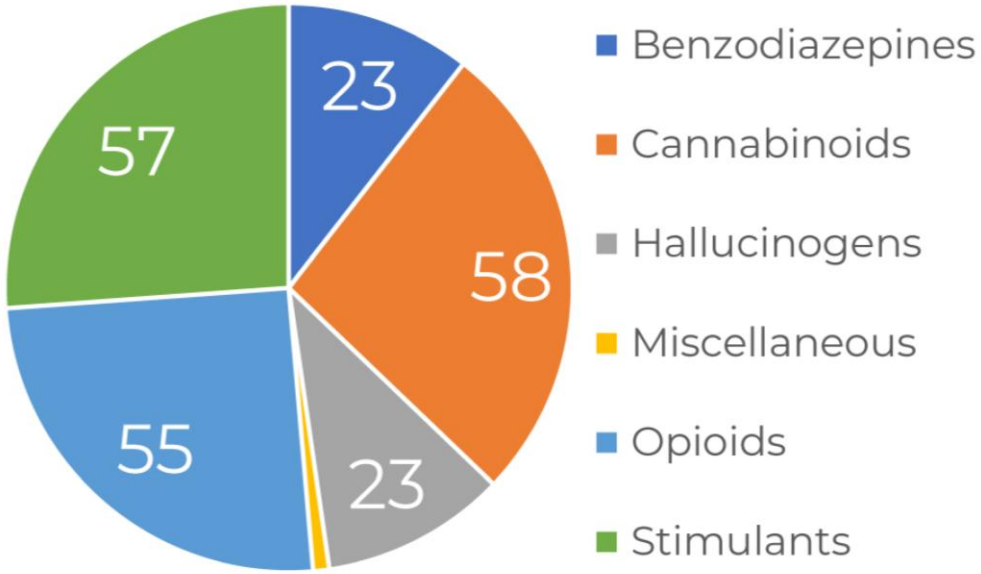


Figure 3: Breakdown by subclass of individual NPS detected, 2018-2022.

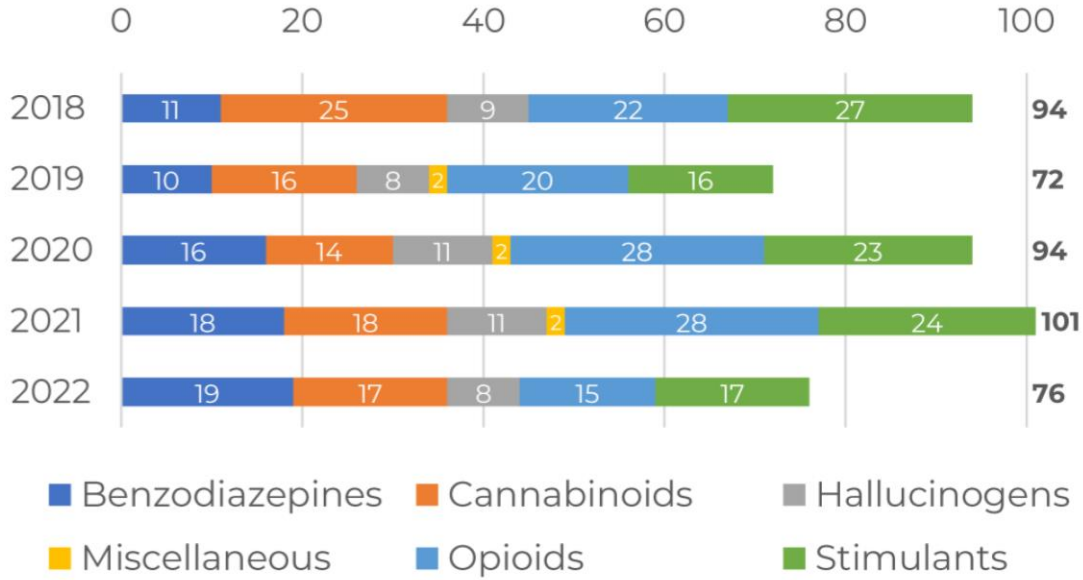


Figure 4: Individual NPS detected each year, cumulative since 2018.

PROLIFERATION OF NPS IN THE U.S.

- In 2022, NPS Discovery observed more than **2,200** total NPS detections within examined sample populations (Figure 5), a portion of more than **10,000** total NPS detections since our program launched in 2018 (Figure 6).

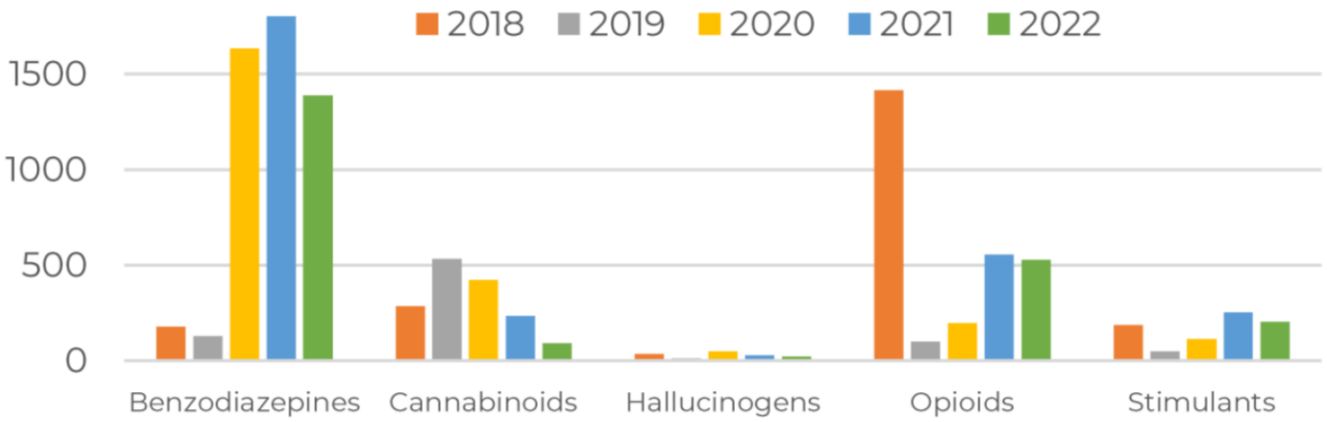


Figure 5: Total number of NPS detections among all samples analyzed since 2018.

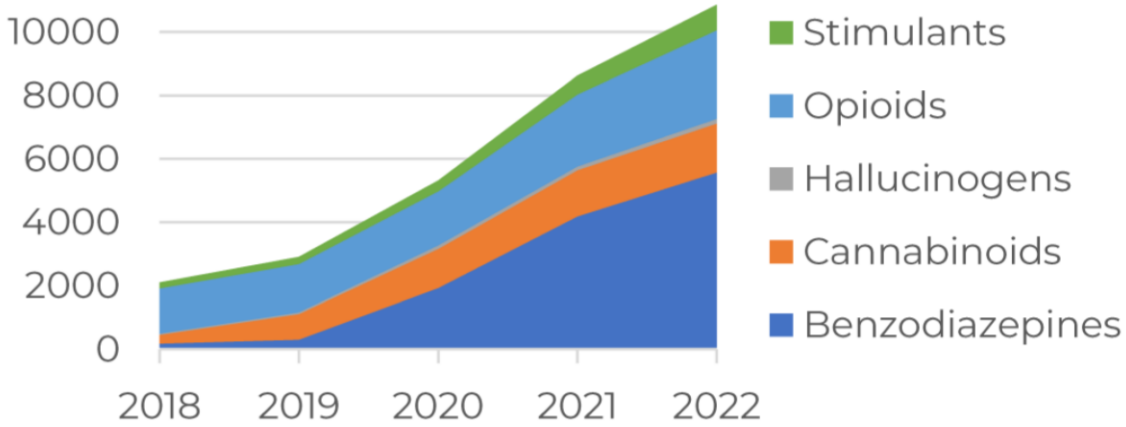
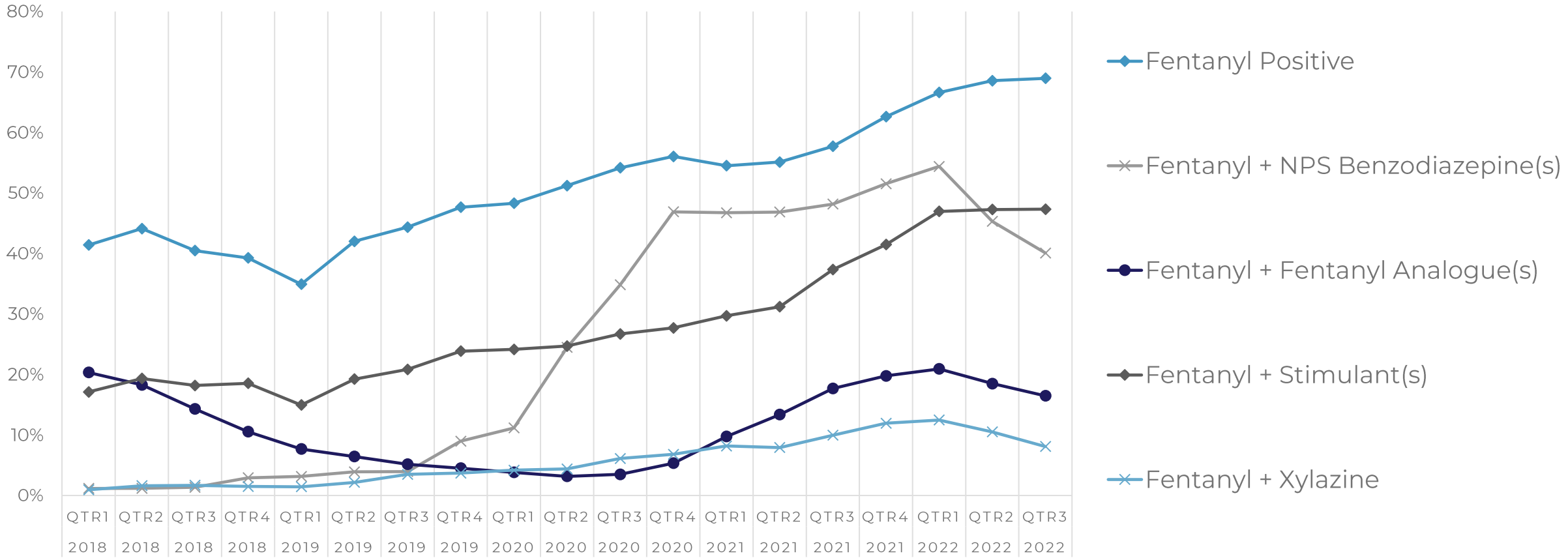


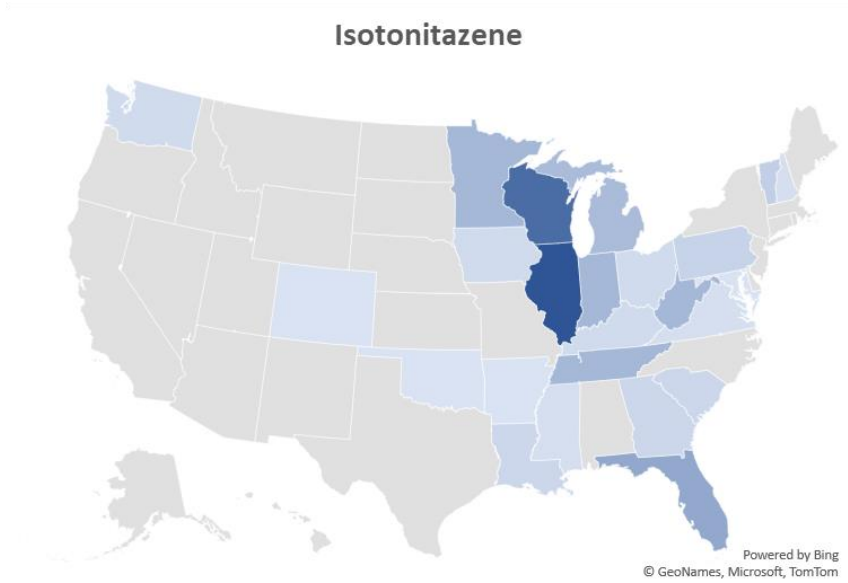
Figure 6: Cumulative number of NPS detections since 2018.

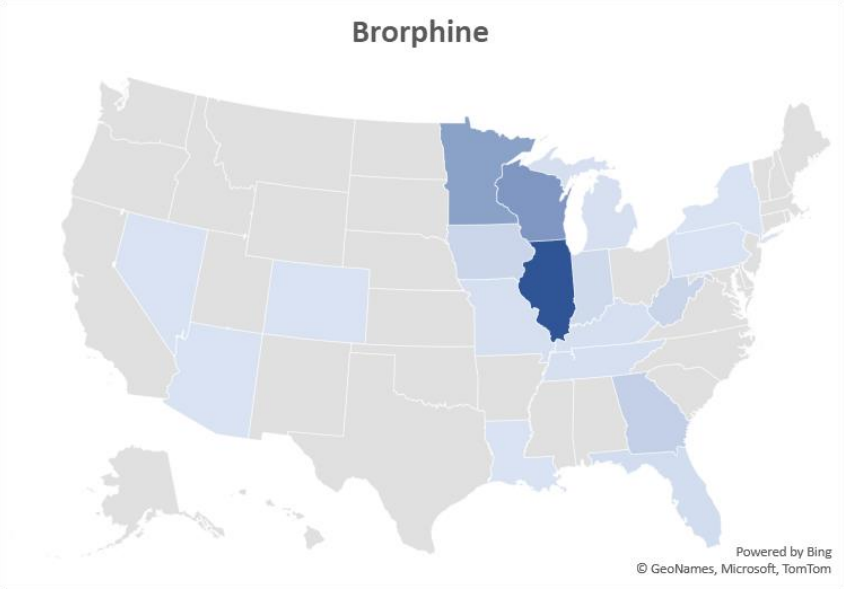
ENTERING THE POLYDRUG EPIDEMIC

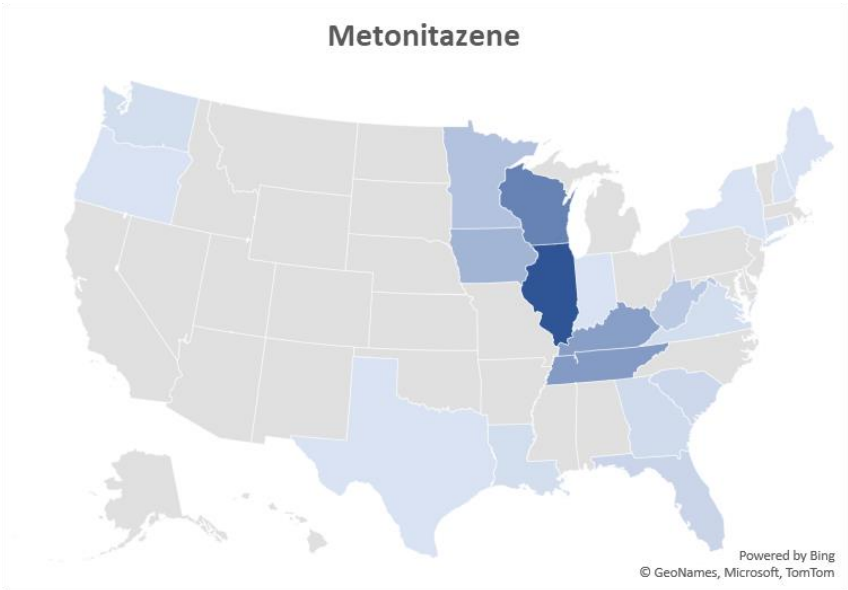
Fentanyl Co-Positivity – the "Nested Waves" Underlying Positivity and Prevalence

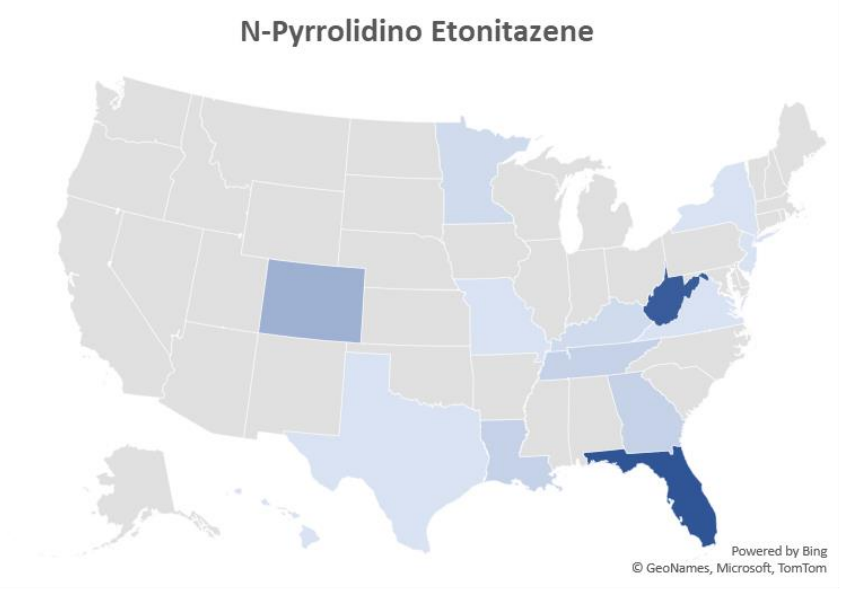


PROLIFERATION OF NITAZENE ANALOGUES →







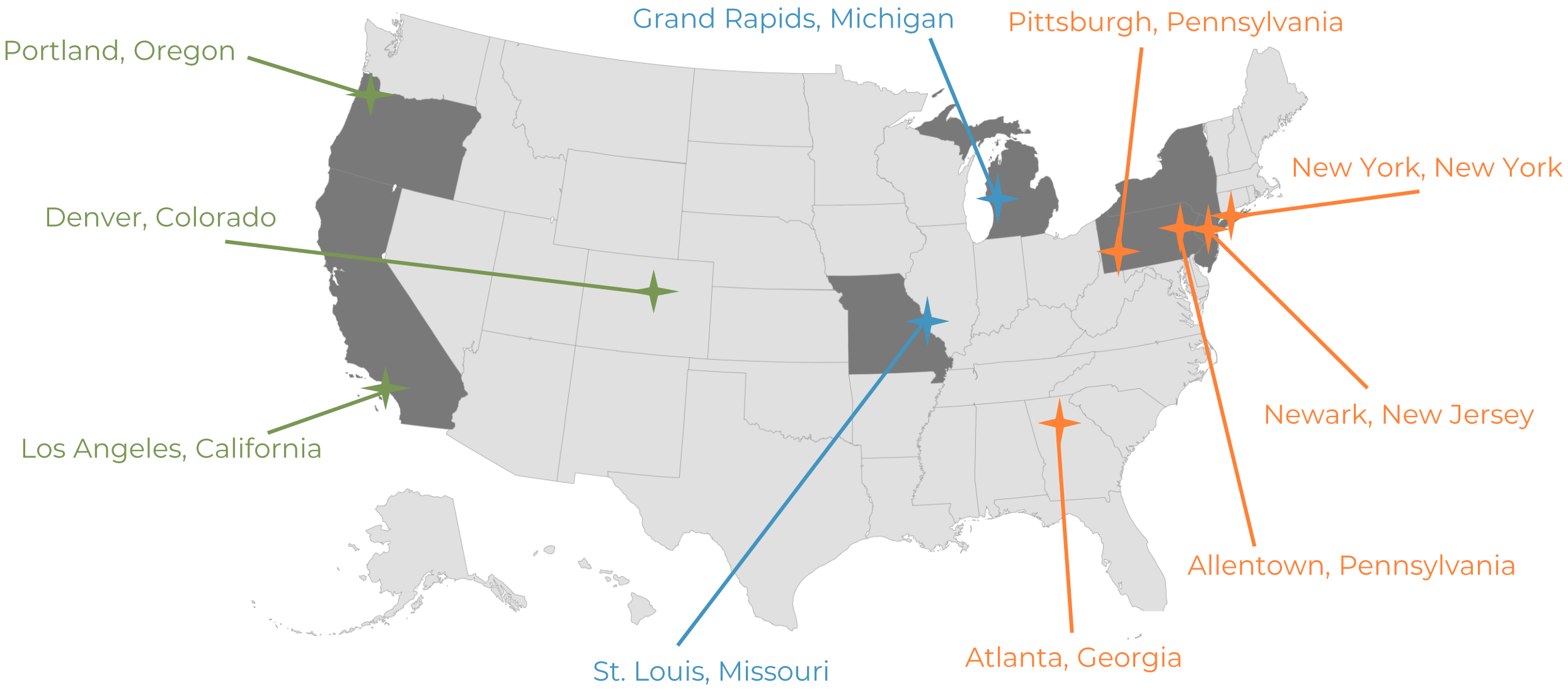


**Data from NMS Labs / cumulative identifications*

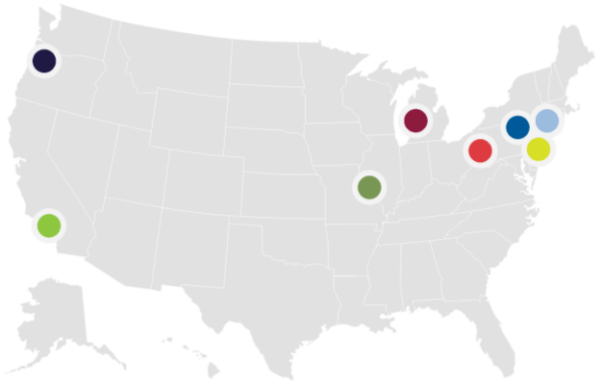
cfsre | NPS DISCOVERY

CLINICAL INVESTIGATIONS

CLINICAL SITES – EAST, MIDWEST, WEST



Q1 2023 →



PITTSBURGH, PA

- 75% positive for at least one opioid
- Fentanyl (75%) commonly detected, followed by heroin (25%) and tramadol (25%)
- Opioid and stimulant use commonly observed (75%)
- NPS: *p*-Fluorofentanyl (25%), Clonazolam

BETHLEHEM, PA

- 97% positive for at least one opioid
- Fentanyl (88%) commonly detected
- Opioid and stimulant use observed (53%); benzodiazepine and opioid use less common (25%)
- *p*-Fluorofentanyl detected w/o fentanyl
- NPS: *p*-Fluorofentanyl (25%), *o*-Fluorofentanyl (6%), Valerylfentanyl, ADB-PINACA

NEW YORK, NY

- 88% positive for at least one opioid
- Fentanyl (65%) commonly detected, followed by methadone (26%), heroin (15%), and oxycodone (15%)
- Opioid and benzodiazepine use observed (32%); opioid and stimulant use (21%)
- PCP detected alongside fentanyl
- NPS: *p*-Fluorofentanyl (21%), Bromazolam, Flubromazepam, MDMB-4en-PINACA

NEWARK, NJ

- 89% positive for at least one opioid
- Fentanyl (78%) commonly detected, followed by methadone and tramadol (11%)
- Opioid and stimulant use observed (44%); opioid and benzodiazepine use (17%)
- PCP detected alongside fentanyl
- NPS: *p*-Fluorofentanyl (11%), Clonazolam

ST. LOUIS, MO

- 95% positive for at least one opioid
- Fentanyl (93%) very commonly detected
- Opioid and stimulant use common (63%); opioid and benzodiazepine use was less common (15%)
- MDMA detected alongside fentanyl (5%)
- NPS: *p*-Fluorofentanyl (10%), Bromazolam, Flubromazepam

PORTLAND, OR

- 74% positive for at least one opioid
- Fentanyl (68%) commonly detected, followed by heroin (16%)
- THC and metabolites detected (32%)
- Opioid and stimulant use observed (53%); opioid and benzodiazepine use less common (21%)
- NPS: *p*-Fluorofentanyl (11%), Bromazolam

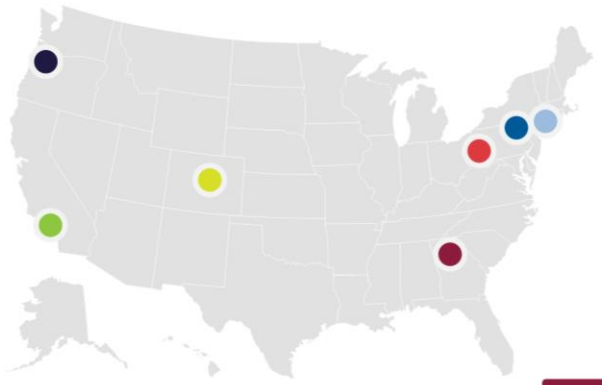
LOS ANGELES, CA

- 90% positive for at least one opioid
- Fentanyl (75%) commonly detected, followed by heroin (5%) & methadone (5%)
- Opioid and stimulant use observed (45%); opioid and cannabinoid use (15%); opioid and benzodiazepine use (10%)
- Xylazine not detected in opioid samples
- *p*-Fluorofentanyl detected w/o fentanyl
- NPS: *p*-Fluorofentanyl (15%), *o*-Fluorofentanyl (5%)

GRAND RAPIDS, MI

- 89% positive for at least one opioid
- Fentanyl (74%) commonly detected, followed by tramadol (8%) and heroin (8%)
- Opioid and stimulant use observed (55%); opioid and benzodiazepine use (21%)
- *p*-Fluorofentanyl detected w/o fentanyl
- NPS: *p*-Fluorofentanyl (11%), Clonazolam, Flualprazolam, BZO-POXIZID, ADB-5Br-INACA, MDMB-5Br-INACA, 4CN-CUMYL-BINACA, ADB-HEXINACA, 3,5-ADB-4en-PFUPPYCA

Q2 2023 →



NEW CLINICAL SITES!

Atlanta, GA &
Denver, CO

PORTLAND, OR

- 100% positive for at least one opioid
- Fentanyl (56%) commonly detected, followed by heroin (22%)
- Opioid and stimulant use commonly detected (67%); opioid and benzodiazepine use also common (44%)
- *Note: Xylazine and Fluorofentanyl not detected*
- **NPS: Clonazolam (11%)**

BETHLEHEM, PA

- 75% positive for at least one opioid
- Fentanyl (63%) only traditional opioid
- Opioid and stimulant (25%) and opioid and benzodiazepine (25%) use observed
- Xylazine found alongside fentanyl (25%)
- **NPS: Bromazolam (25%), *N*-Cyclohexyl Butylone (25%), *p*-Fluorofentanyl (13%), Flubromazepam (13%)**

ATLANTA, GA

- 93% positive for at least one opioid
- Fentanyl (83%) commonly detected, followed by oxycodone (10%) & heroin (7%)
- Opioid and stimulant use common (54%); opioid and benzodiazepine use (27%)
- Xylazine found alongside fentanyl (12%)
- **NPS: Flualprazolam (15%), *p*-Fluorofentanyl (12%), Metonitazene (9.7%), Eutylone (9.7%), Brorphine (7.3%), Bromazolam (4.9%), *N,N*-Dimethylpentylone (2.4%)**

DENVER, CO

- 90% positive for at least one opioid
- Fentanyl (76%) commonly detected, followed by oxycodone (23%)
- Opioid and stimulant use very commonly observed (76%); followed by opioid and benzodiazepine use (31%)
- *Note: Xylazine not detected*
- NPS: *N*-Cyclohexyl Butylone (8%), *p*-Fluorofentanyl (6%), Bromazolam (2%)

NEW YORK, NY

- 82% positive for at least one opioid
- Fentanyl (73%) most commonly detected, followed by methadone (14%)
- Opioid and stimulant use (37%) and opioid and benzodiazepine (27%) use observed
- Xylazine found alongside fentanyl (26%)
- NPS: *p*-Fluorofentanyl (8%), Bromazolam (8.2%), Flubromazepam (6.8%), Clonazolam (2.7%), Etizolam (1.4%)

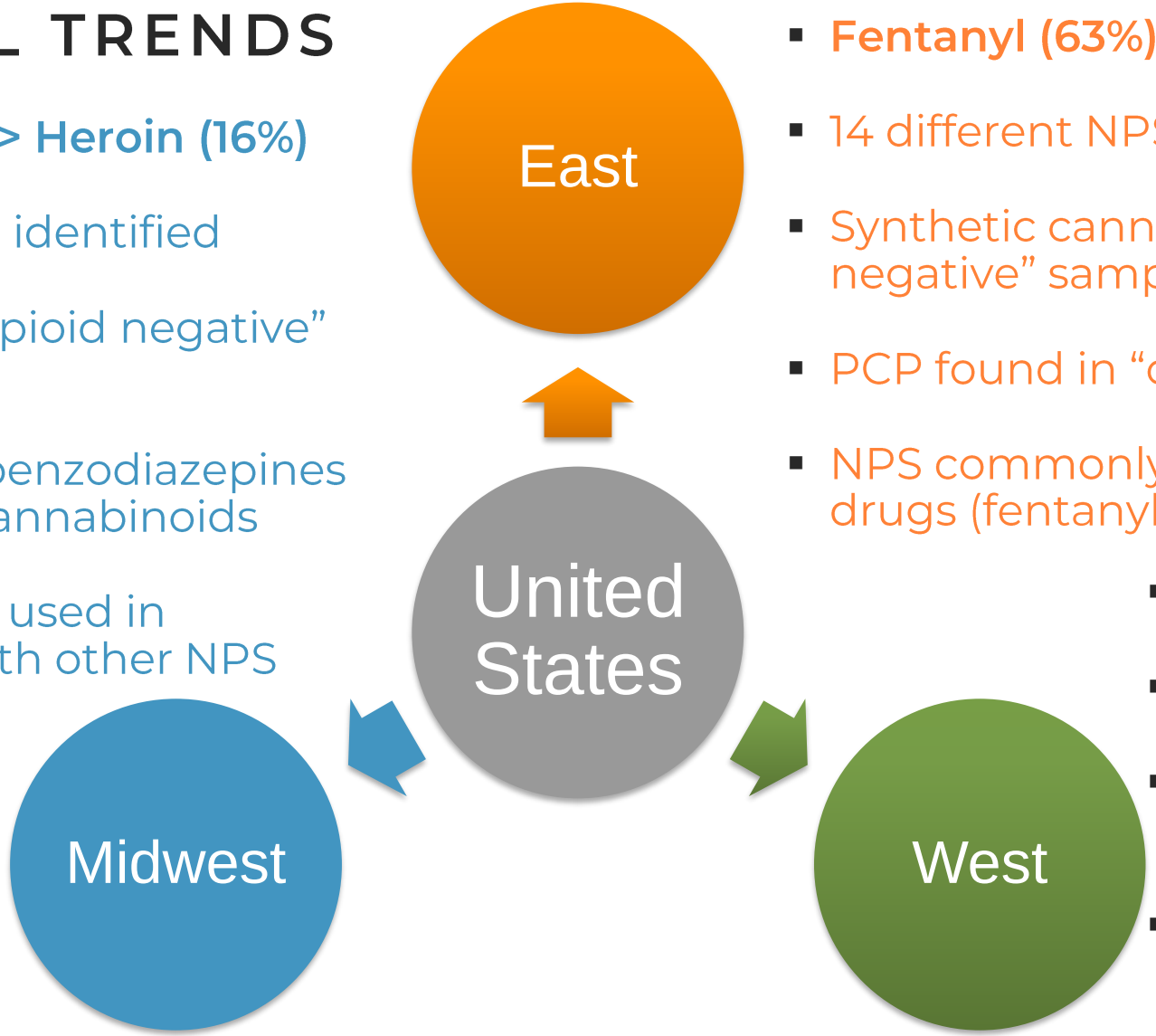
LOS ANGELES, CA

- 88% positive for at least one opioid
- Fentanyl (80%) commonly detected
- Opioid and stimulant use commonly observed (70%); while opioid and benzodiazepine use less common (25%)
- *Note: Xylazine not detected*
- NPS: *p*-Fluorofentanyl (15%), Bromazolam (5%), Flualprazolam (2.5%), Clonazolam (2.5%), *N,N*-Dimethylpentylone (2.5%), Metonitazene (2.5%)

PITTSBURGH, PA

- 90% positive for at least one opioid
- Fentanyl (88%) most commonly detected, followed by methadone (13%)
- Opioid and stimulant (33%) and opioid and benzodiazepine (23%) use observed
- Xylazine found alongside fentanyl (45%)
- **NPS: Bromazolam (10%), *p*-Fluorofentanyl (8%), Clonazolam (5%), Etizolam (2.5%), *N*-Desethyl Isotonitazene (2.5%)**

REGIONAL TRENDS



- **Fentanyl (63%) > Heroin (16%)**
- 19 different NPS identified
- PCP found in “opioid negative” samples
- Variety of NPS benzodiazepines and synthetic cannabinoids
- NPS commonly used in combination with other NPS

- **Fentanyl (63%) > Heroin (4.7%)**
- 14 different NPS identified
- Synthetic cannabinoids found in “opioid negative” samples
- PCP found in “opioid-negative” samples
- NPS commonly used with traditional drugs (fentanyl, methamphetamine)

- **Fentanyl (63%) > Heroin (25%)**
- 8 different NPS identified
- Xylazine less common in fentanyl positive samples
- Methamphetamine and fentanyl similar positivity
- NPS commonly used in combination with other NPS

*Overall: **fentanyl** most seen opioid found often with **xylazine***

DISCUSSION & OUTCOMES

- No opioids detected (n=44) spanning various clinical sites
  - Synthetic cannabinoids only drug present
  - **Synthetic cannabinoids can precipitate respiratory failure and depressant effects, emerging as an opioid overdose**

- Wide range of drugs detected
  - NPS, traditional drugs, therapeutics, adulterants, etc.
  - **33 different NPS identified**

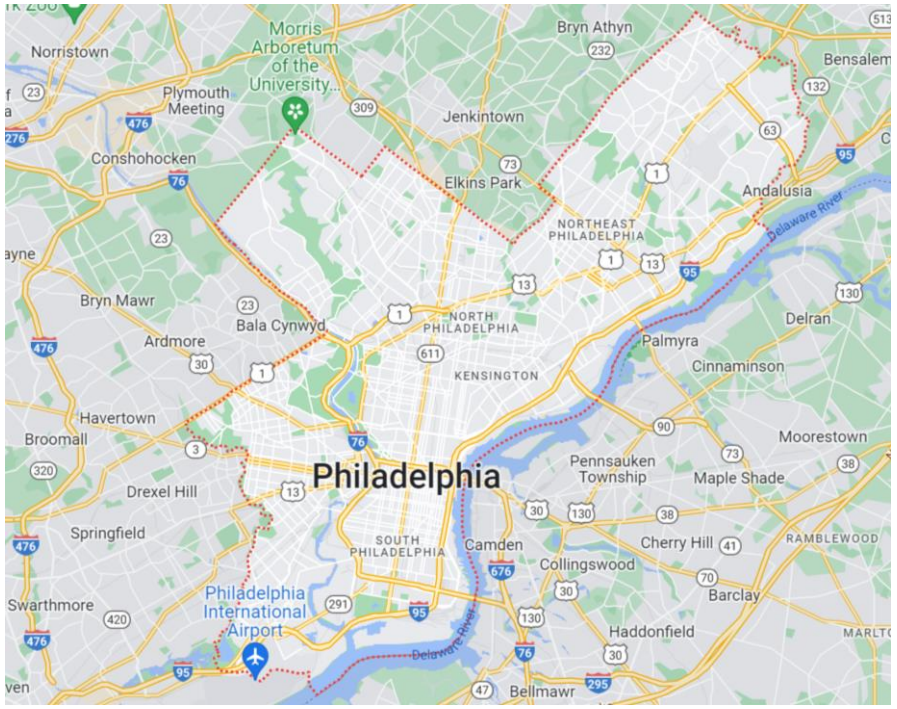
- Need for more collaborations between clinicians and forensic toxicologists
  - Help clinicians better understand **signs/symptoms of NPS intoxication**
  - **Outbreak investigations can serve as early indicators** for forensic investigations

cfsre | NPS DISCOVERY

DRUG CHECKING / SURVEILLANCE

PHILADELPHIA & ITS DRUG SUPPLY

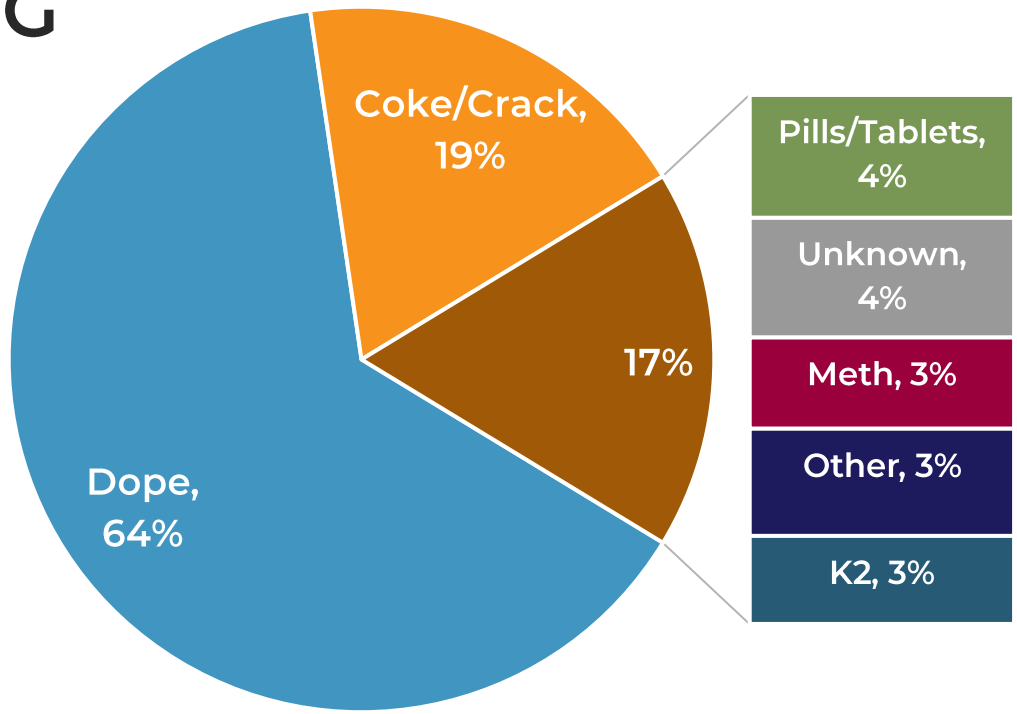
- Nestled in the center of the larger mid-Atlantic metropolitan region ("Northeast Corridor")
  - 6th largest city by population and 7th largest metro area
- **"Open air drug market"** (Kensington neighborhood)
- Drug markets → dope, crack/coke, meth, K2, etc.
- Continually changing and diverse drug environment
- Collaboration between the **CFSRE** and the **Philadelphia Department of Public Health (PDPH)**



PDPH/CFSRE DRUG CHECKING

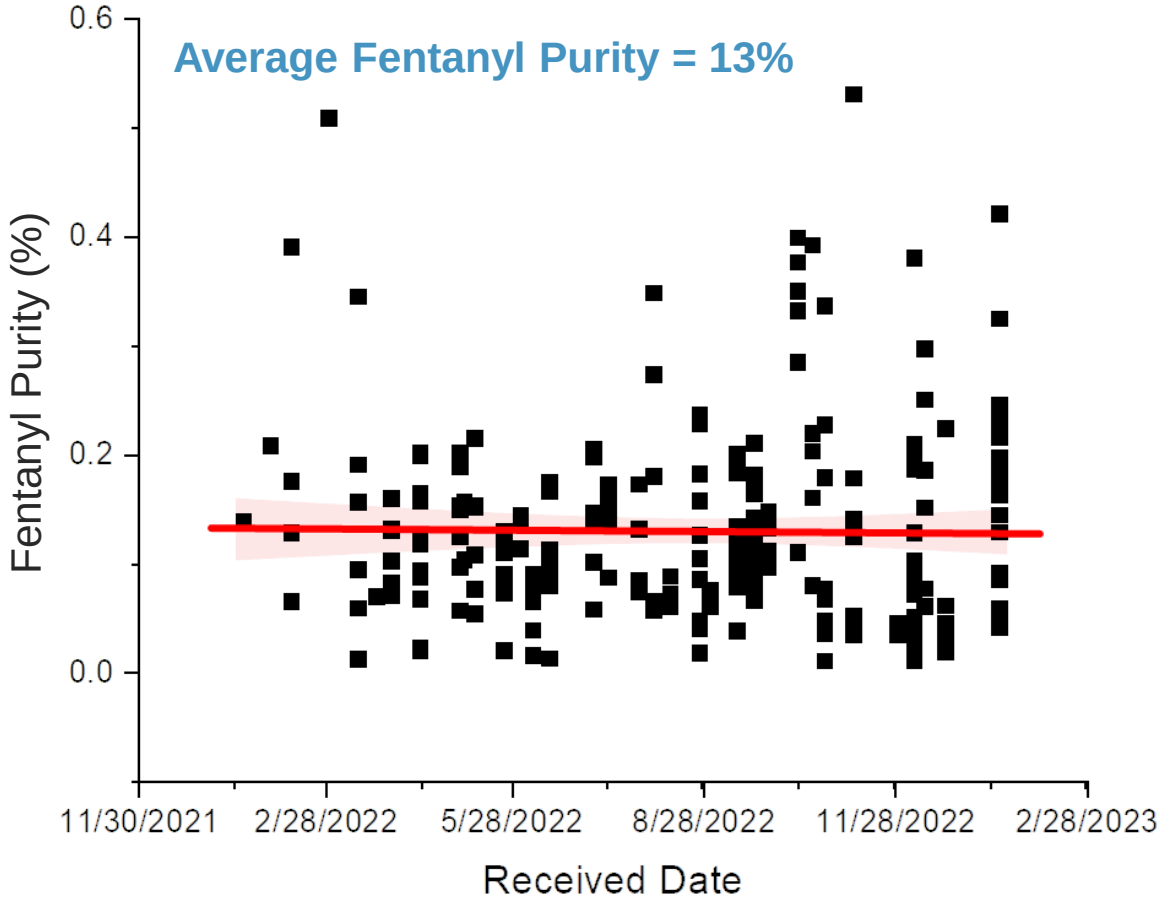
- **2020** → Partnership formally launched

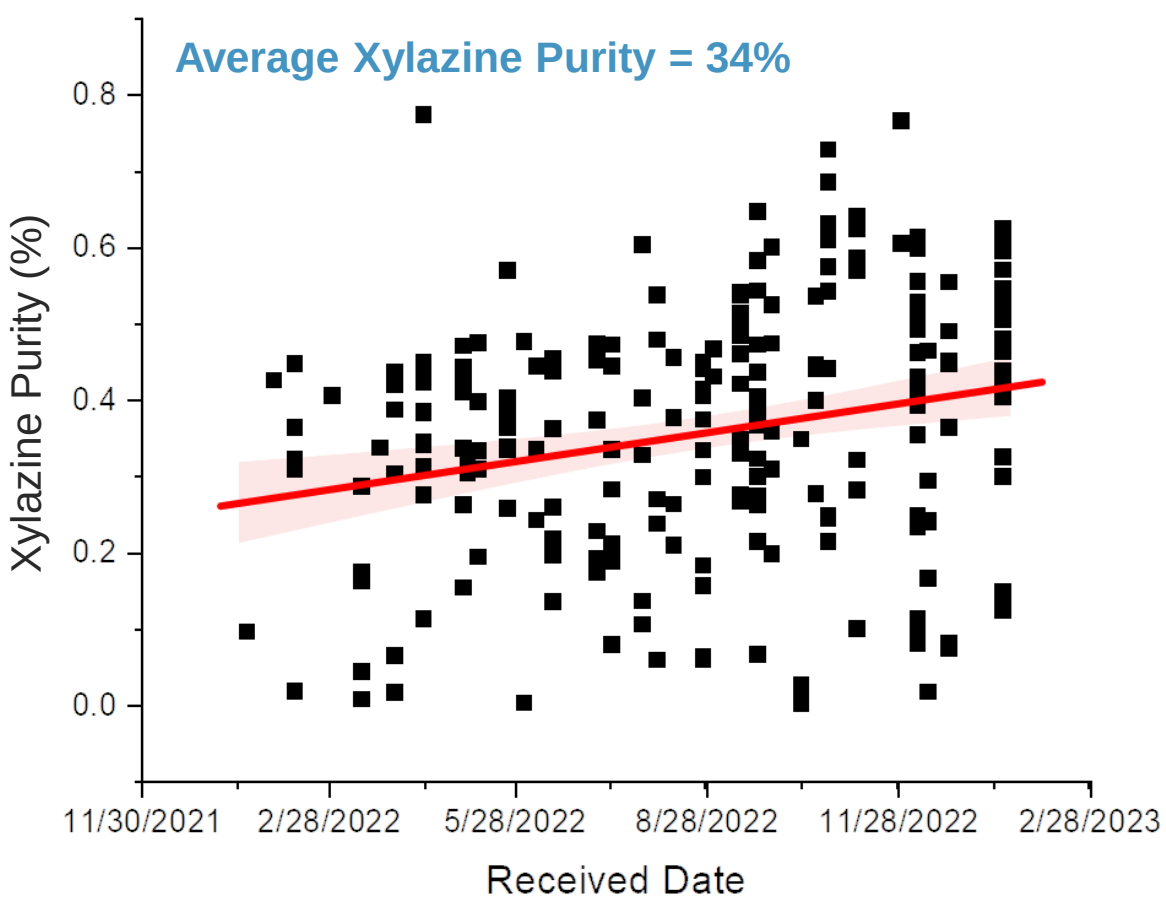
- **Sample Analyzed**
  - 950+ samples received since 2020
  - Variety of sample types (suspected contents) →
  - Paired FTIR and test strip results***



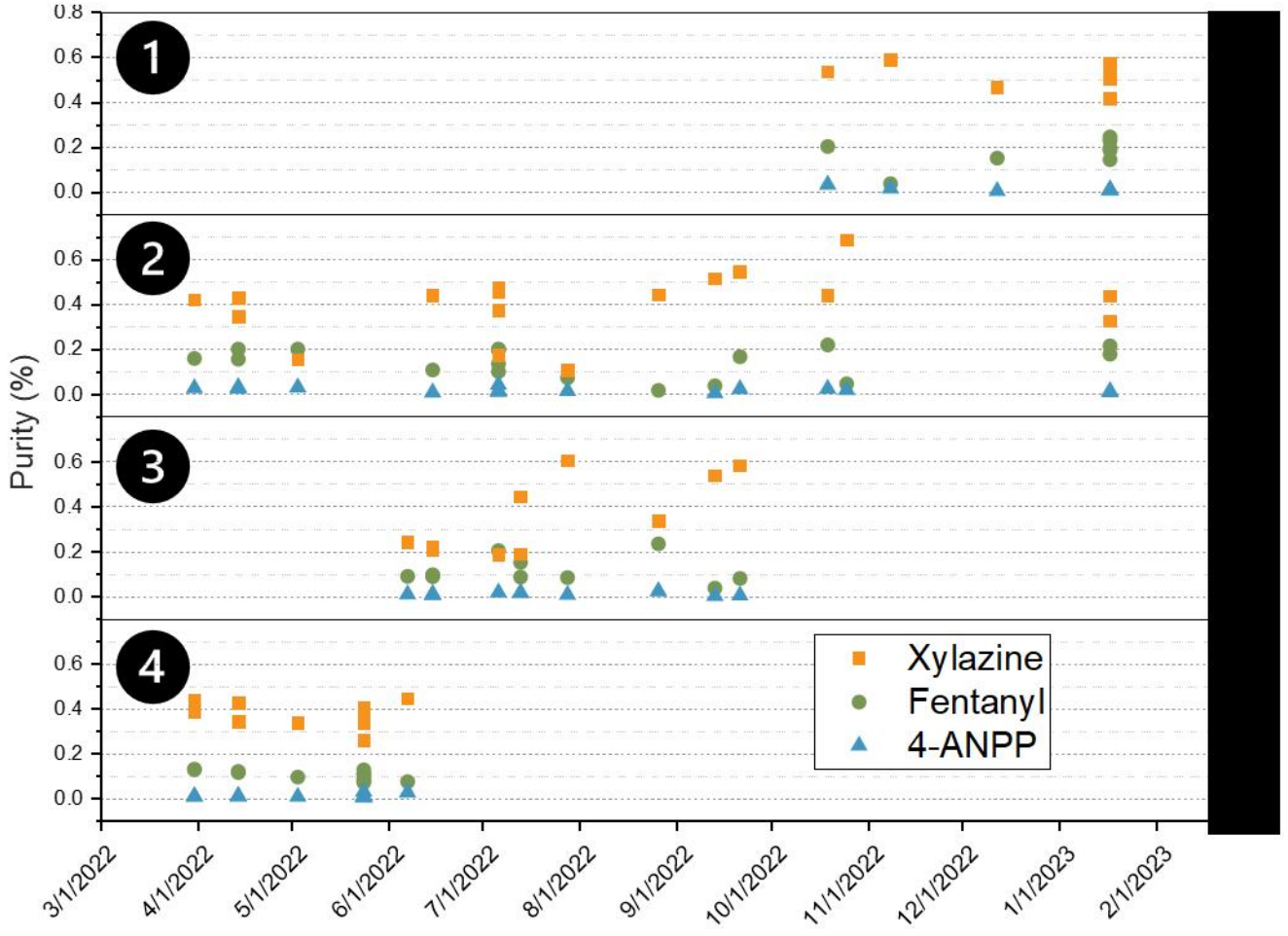
- **Key Findings**
  - "Dope": 99% contain fentanyl and ~90% contain xylazine
  - Methamphetamine – rarely adulterated or substituted
  - Cocaine – "coke" samples sometimes test positive for trace fentanyl
  - K2 – revolving door of synthetic cannabinoids

TEMPORAL CHANGES IN PURITY (2022)

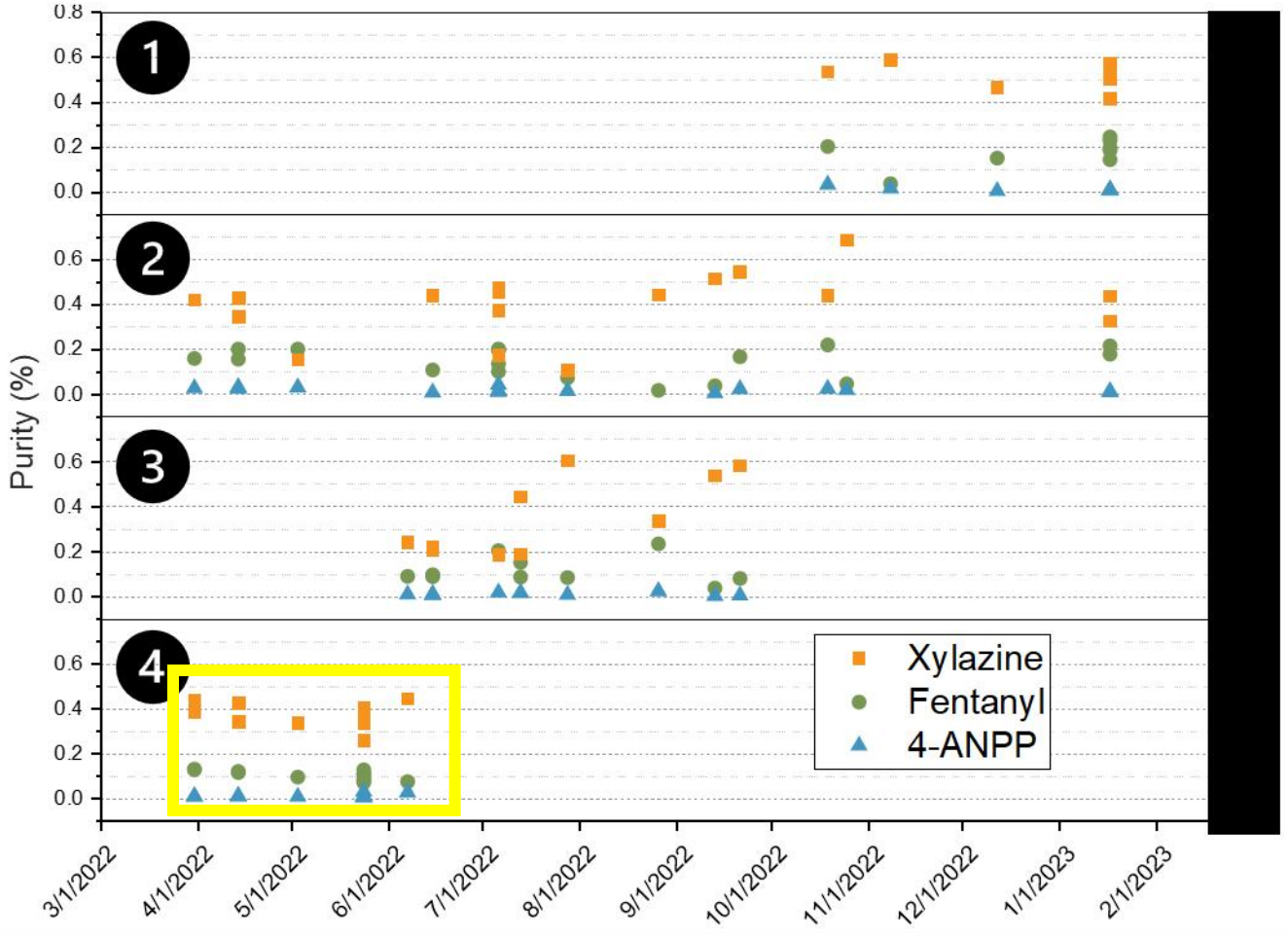




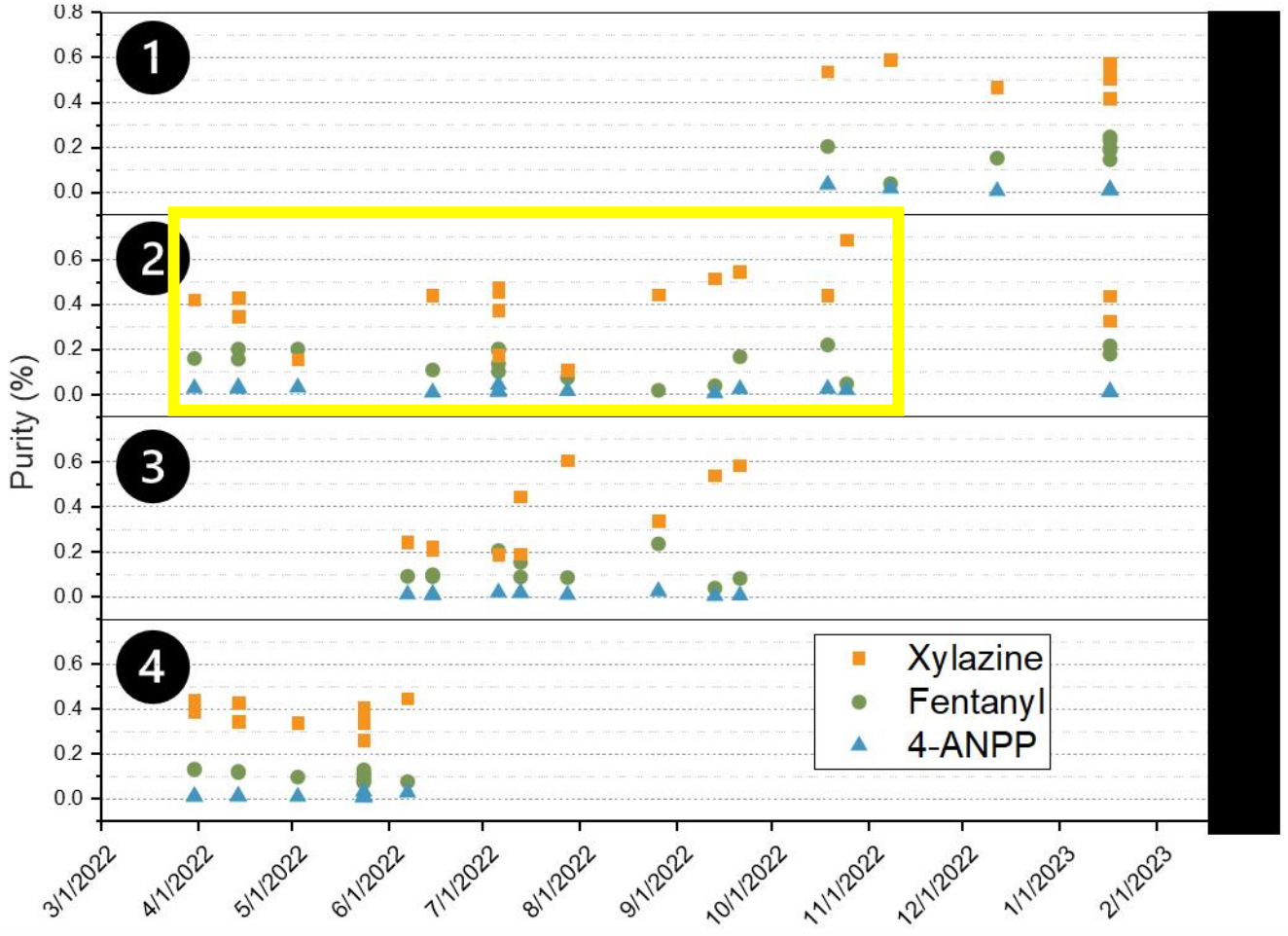
LONGITUDINAL ASSESSMENT OF DRUG PRODUCTS



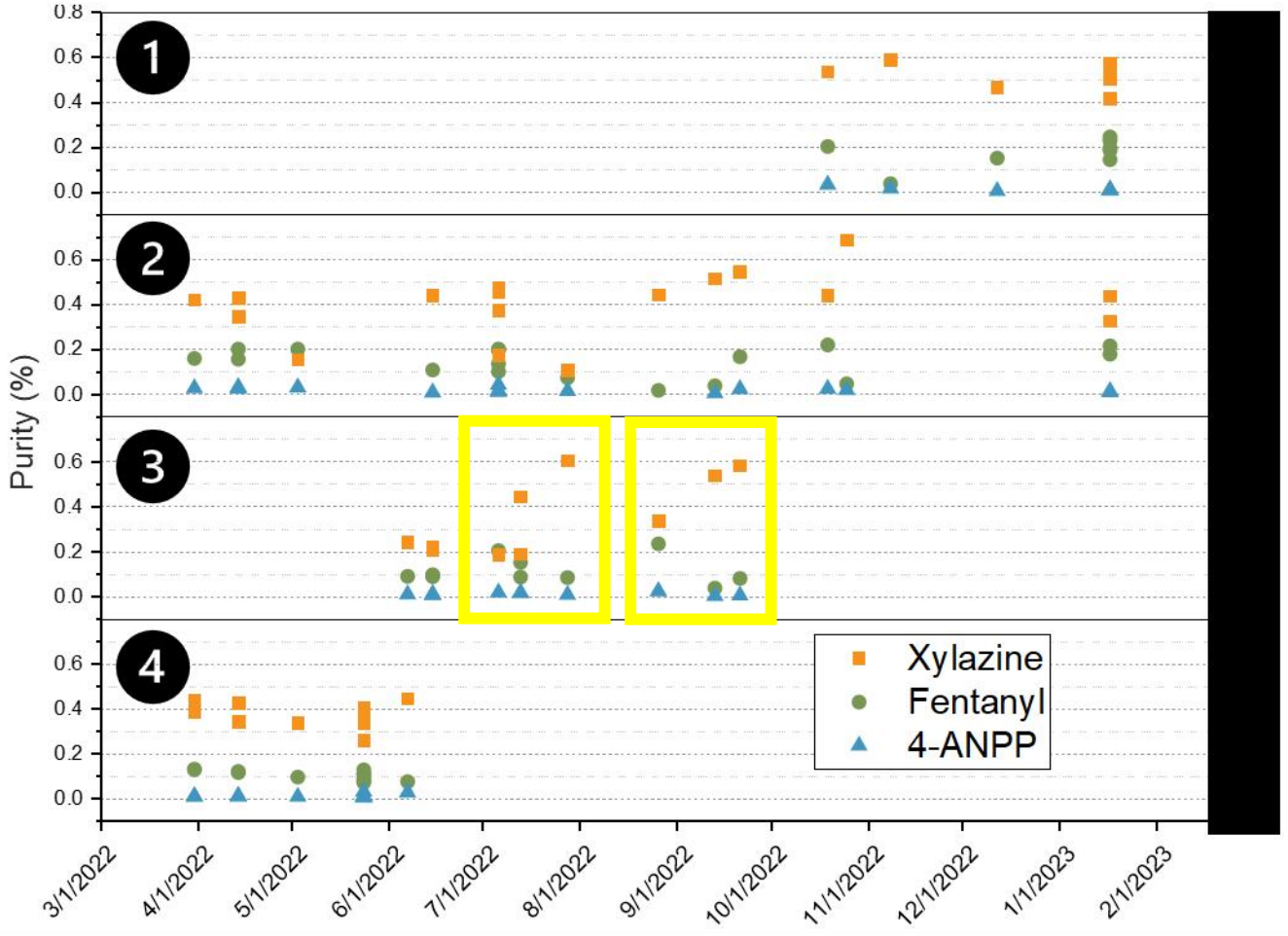
LONGITUDINAL ASSESSMENT OF DRUG PRODUCTS



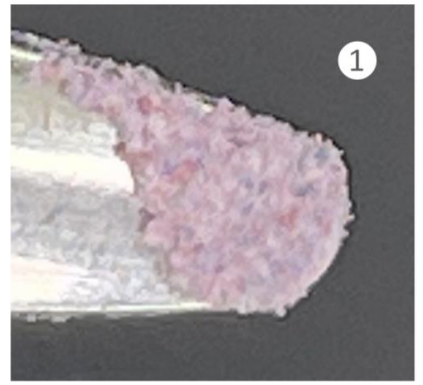
LONGITUDINAL ASSESSMENT OF DRUG PRODUCTS

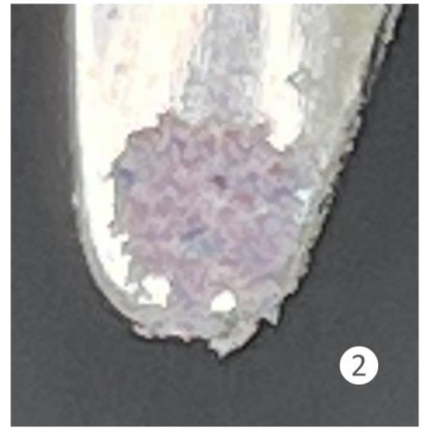


LONGITUDINAL ASSESSMENT OF DRUG PRODUCTS

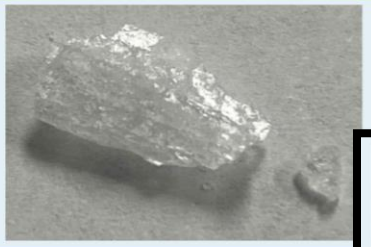


Date	Suspected	Drugs Identified
9/13/2022	Dope	Fentanyl (18.4%), Xylazine (26.9%), 4-ANPP (10.6%) *[OPI=1.84]*
9/21/2022	Dope	Fentanyl (6.6%), Xylazine (40.5%), 4-ANPP (1.0%), Procaine, Caffeine *[OPI=0.69]*
9/21/2022	Dope	Fentanyl (7.7%), Xylazine (32.4%), *para*-Fluorofentanyl (0.3%), 4-ANPP (0.7%) *[OPI=0.78]*
9/21/2022	Dope	Fentanyl (7.8%), Xylazine (26.6%), 4-ANPP (1.5%) *[OPI=0.78]*
9/21/2022	Dope	Fentanyl (8.2%), Xylazine (58.4%), 4-ANPP (0.6%) *[OPI=0.82]*
9/21/2022	Dope	Fentanyl (8.3%), Xylazine (26.3%), 4-ANPP (1.6%) *[OPI=0.83]* ❶
9/21/2022	Dope	Fentanyl (8.8%), Xylazine (30.1%), 4-ANPP (1.7%) *[OPI=0.88]*
9/21/2022	Dope	Fentanyl (10.0%), Xylazine (36.8%), 4-ANPP (1.7%) *[OPI=1.00]* ❷
9/21/2022	Dope	Fentanyl (11.2%), Xylazine (43.7%), 4-ANPP (1.7%) *[OPI=1.12]*
9/21/2022	Dope	Fentanyl (11.9%), Xylazine (38.0%), 4-ANPP (3.0%) *[OPI=1.19]*
9/21/2022	Dope	Fentanyl (13.2%), Xylazine (64.8%), 4-ANPP (2.0%) *[OPI=1.32]* ❸
9/21/2022	Dope	Fentanyl (14.3%), Xylazine (21.6%), 4-ANPP (7.7%) *[OPI=1.43]*
9/21/2022	Dope	Fentanyl (21.1%), Xylazine (40.2%), 4-ANPP (4.1%) *[OPI=2.11]*
9/21/2022	Dope	Fentanyl (18.2%), Xylazine (27.5%), 4-ANPP (8.8%) *[OPI=1.82]*
9/21/2022	Dope	Fentanyl (16.8%), Xylazine (54.4%), 4-ANPP (2.4%) *[OPI=1.68]*
9/21/2022	Dope	Fentanyl (16.5%), Xylazine (47.3%), 4-ANPP (2.0%) *[OPI=1.65]*
9/21/2022	Dope	Fentanyl (16.4%), Xylazine (6.8%), *para*-Fluorofentanyl (2.4%), 4-ANPP (3.3%), Heroin (trace), Caffeine *[OPI=1.72]*

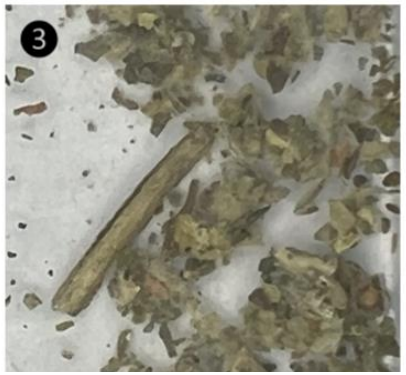




DRUG CHECKING RESULTS

			
Clonazolam	Etizolam	Etizolam	Desalkylflurazepam
		 	
Fentanyl, Gabapentin	*para*-Fluorofentanyl, Gabapentin	Methamphetamine MDA	
			
Cocaine, Lidocaine	Cocaine, Lidocaine	Methamphetamine, Caffeine	Methamphetamine

Methamphetamine



ADB-5'Br-IANCA

Methamphetamine

ADB-5'Br-IANCA

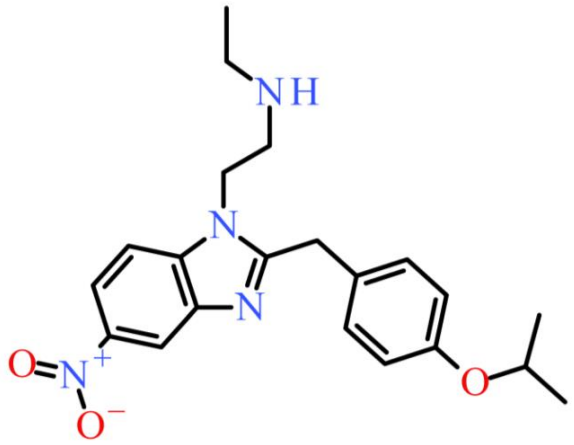
	
ADB-BINACA	ADB-BINACA

COMBINED SURVEILLANCE: *N*-DESETHYL ISOTONITAZENE

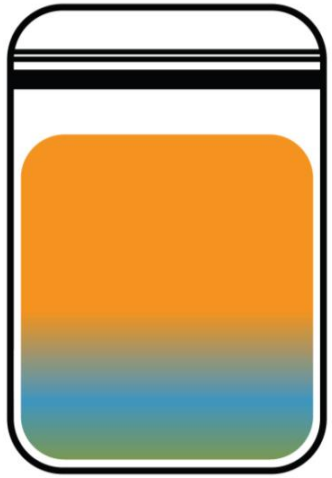
New potent synthetic opioid proliferating among recreational drug supply in USA

TIMELINE — *N*-DESETHYL ISOTONITAZENE ...

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



N-DESETHYL ISOTONITAZENE



"DOPE" SAMPLES CONTAINING *N*-DESETHYL ISOTONITAZENE

LOCATION: Philadelphia, PA, USA

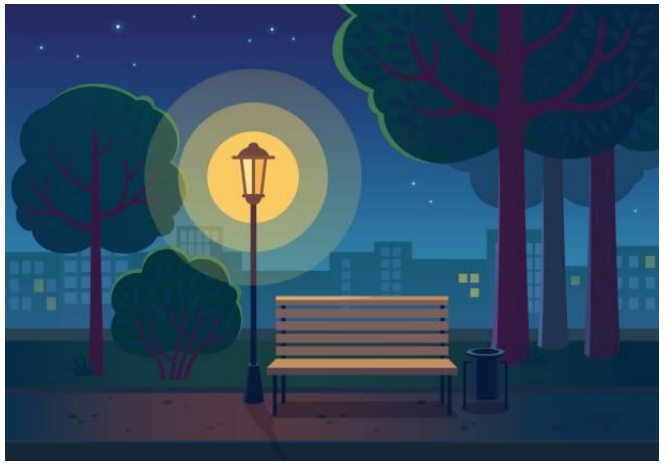
NUMBER OF SAMPLES: 7+

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)

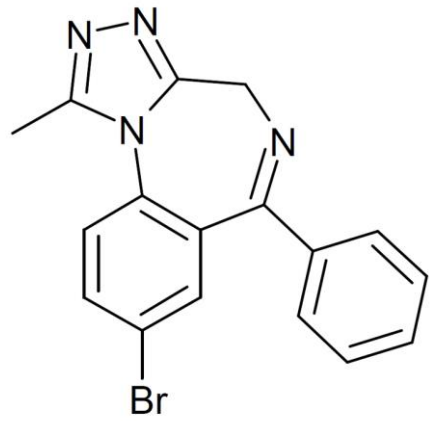
CASE EXAMPLE – ETODESNITAZENE

New synthetic opioid appearing on west coast, USA, and Canada



- One of many nitazene analogues to emerge in recent years
- Antemortem turned postmortem case from California
- 3 individuals unresponsive in park after snorting “cocaine” powder
- Transported to the hospital – 2 were revived and survived, 1 required advanced life support for persistent comatose state (suspected opioid OD)
- Hospital urine drug screen negative for opiates (fentanyl not performed)
- Patient died 3 days later → Body to coroner’s office
- Lab testing:
  - Urine → Fentanyl, cocaine, methamphetamine, etc.
  - Powders → Cocaine, cocaine, etodesnitazene
  - **Blood → Etodesnitazene**

CASE EXAMPLE – BROMAZOLAM



New benzodiazepine proliferating in the USA, Canada, and around the world

- Currently most encountered new benzodiazepine
- Brominated analogue of alprazolam (flualprazolam)
- Antemortem hospital case from New York
- 29-year-old male with polysubstance dependence
- Strange course of ED presentations
- Severe symptoms began after cessation of a new dark web drug
  - Waxing and waning delirium and aggression
- Admitted to the ICU for suspected benzodiazepine withdrawal
- **Pill testing → Bromazolam (~2.5-3 mg/tablet)**

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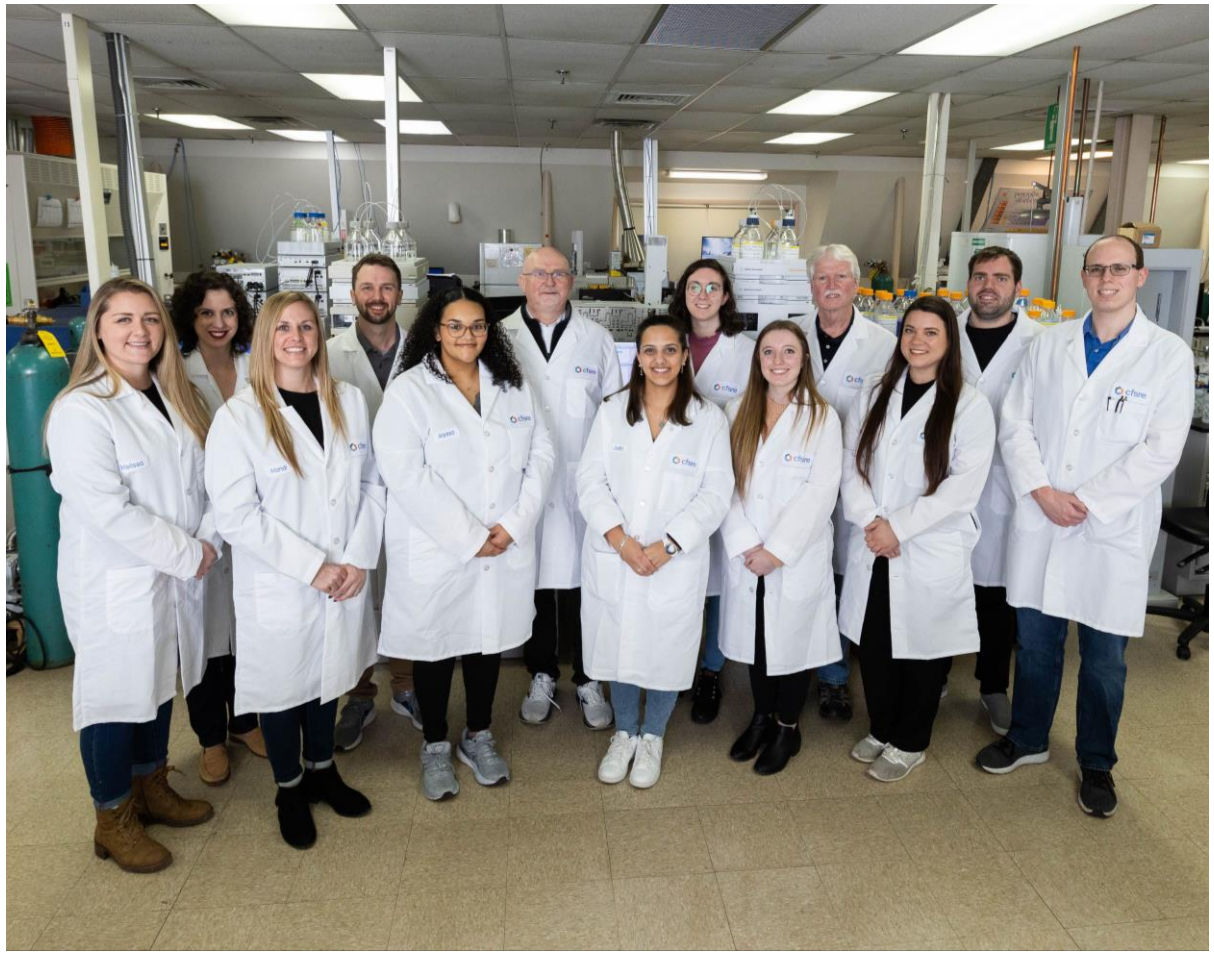
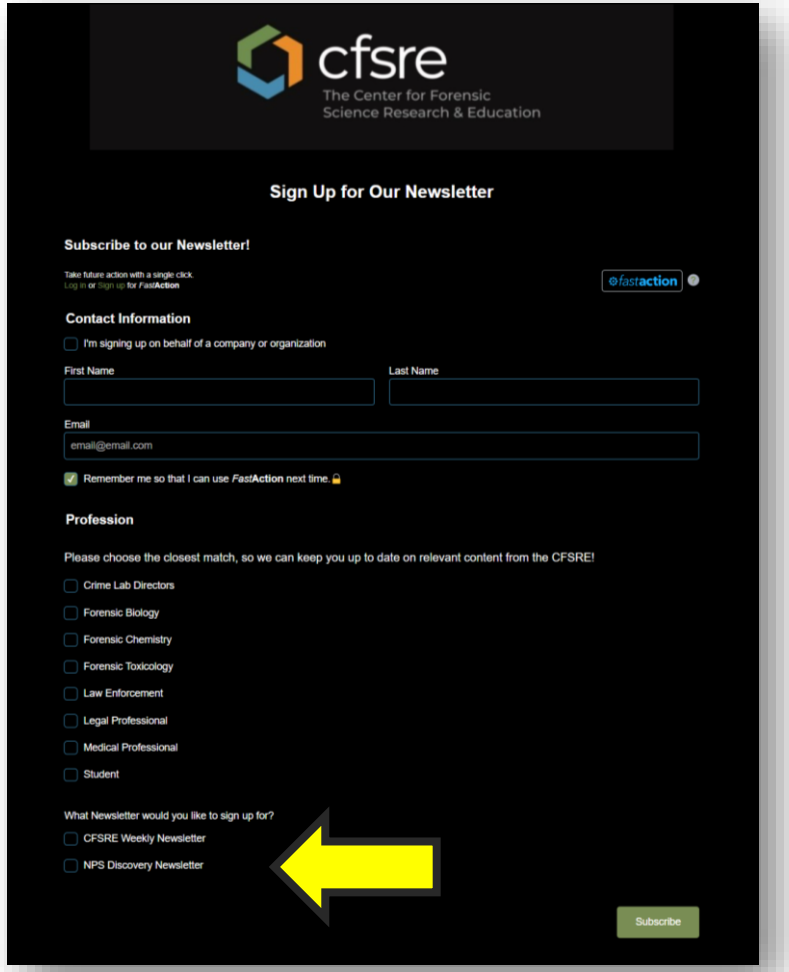
- **Funding Agencies**
- **Various Partners**
  - Forensic
  - Clinical
  - Medical Examiner
  - Coroner
  - Crime Lab
  - Public Health
  - Public Safety
  - Etc.



CFSRE'S NPS DISCOVERY – SIGN-UP TODAY!



Thank you!

Questions?

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