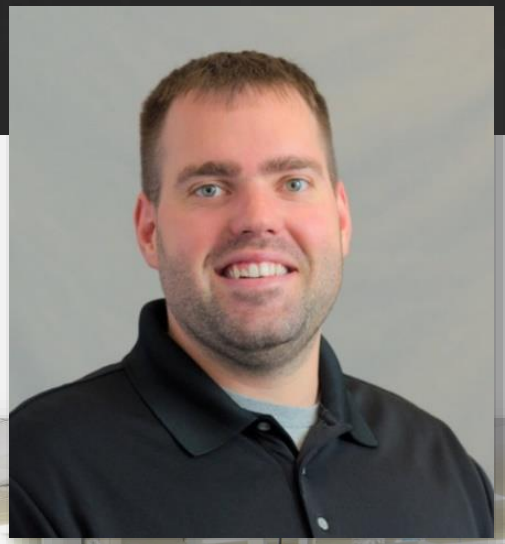
Implementation of CFSRE's NPS Discovery Program and Usefulness in Medicolegal Death Investigations

2023 Forensic Toxicology Symposium – Wednesday November 8, 2023, from 9:15 to 10:30 AM ET
Developments and Collaborations in Forensic Toxicology in North America

Alex J. Krotulski, Ph.D. – Center for Forensic Science Research and Education (CFSRE)

INTRODUCTION



- **Center for Forensic Science Research & Education**
  - Associate Director
    - Toxicology & Chemistry
  - Program Manager
    - NPS Discovery

- **Thomas Jefferson University**
  - Program Director
    - MS in Forensic Toxicology
  - Faculty / Lecturer

FUNDING DISCLOSURE

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  - Award Number: 15PNIJ-22-GG-04434-MUMU
  - 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.

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PRESENTATION OUTLINE

- The CFSRE and NPS Discovery
  - Analytical Workflows and Our Approach
- NPS Trends, Positivity, and Prevalence
- Impacts, Outcomes, and Reporting
  - NPS Opioids
  - Synthetic Cannabinoids
  - Xylazine
  - Drug Checking Surveillance
- Case Examples

THE CFSRE & NPS DISCOVERY

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THE CFSRE & OUR LAB

- The Center for Forensic Science Research and Education (CFSRE)
  - 501(c)(3) non-profit research and educational facility
  - Home to *NPS Discovery* and other programs

Waters Xevo® G2-S LC-QTOF-MS

Sciex X500R LC-TOF-MS

Sciex TripleTOF® 5600+ LC-TOF-MS

Agilent 6495 LC-QQQ-MS

Agilent 6430 LC-QQQ-MS

Waters TQS LC-QQQ-MS

Waters TQD LC-QQQ-MS

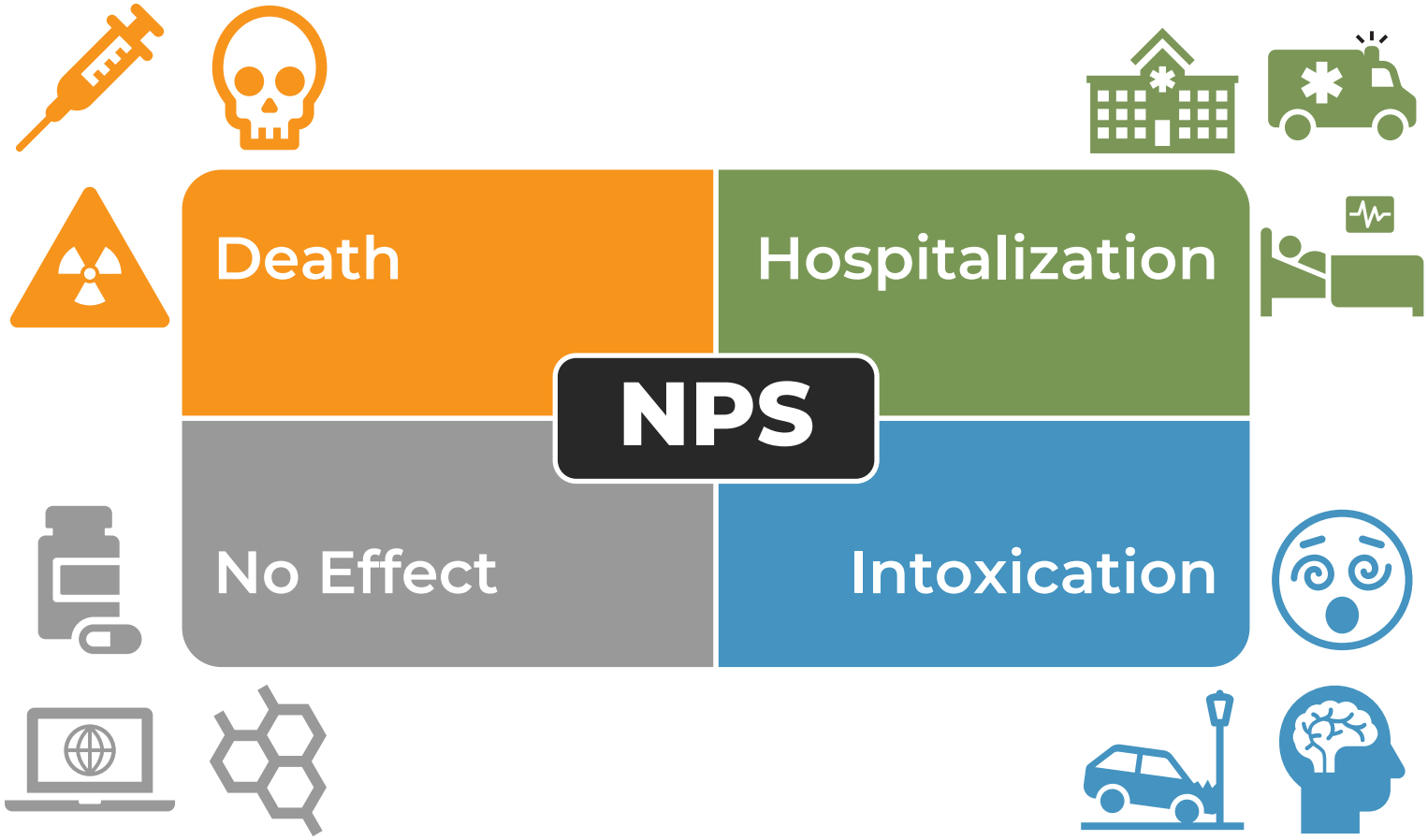
Agilent 5975 GC-MS

Agilent 5975 GC-MS

EXAMPLES OF SAMPLE "POPULATIONS"

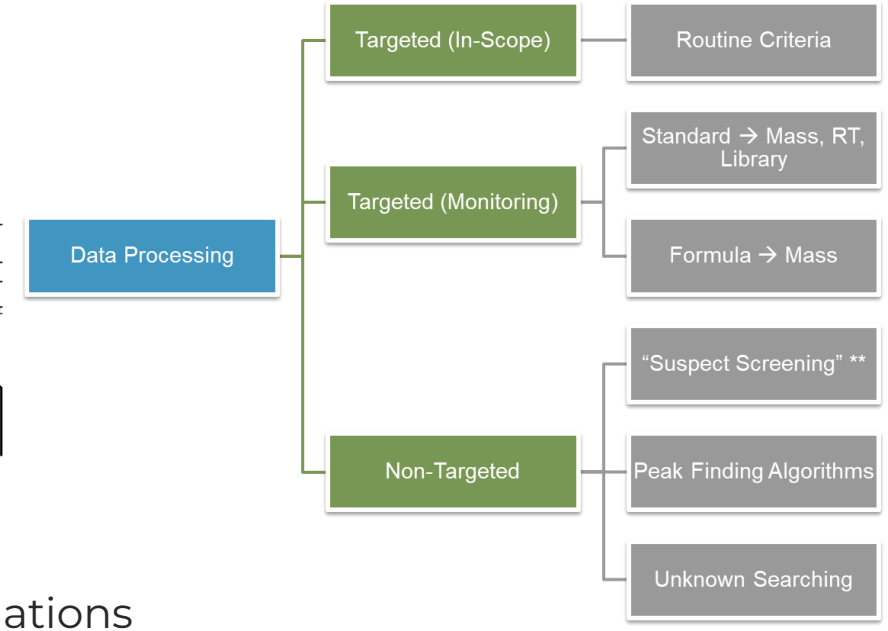
- **Important → Right populations paired with good intelligence**
- **Toxicology Specimens:**
  - Collaborations with medical examiner and coroner offices, other toxicology labs, clinical partners, and other
  - Example: Initial toxicology testing negative but "suspected overdose"
- **Drug Materials:**
  - Collaborations with crime labs, law enforcement agencies public health partners, and others
  - Routine analysis vs. chemical characterization (structural elucidation)
- **Intelligence & Surveillance:**
  - Monitor online surface web gray market sites, drug use forums, etc.
  - Some correlation between sites and drug markets but delayed

WHERE DO NPS “POP UP”?



ANALYTICAL WORKFLOWS & STRATEGIES

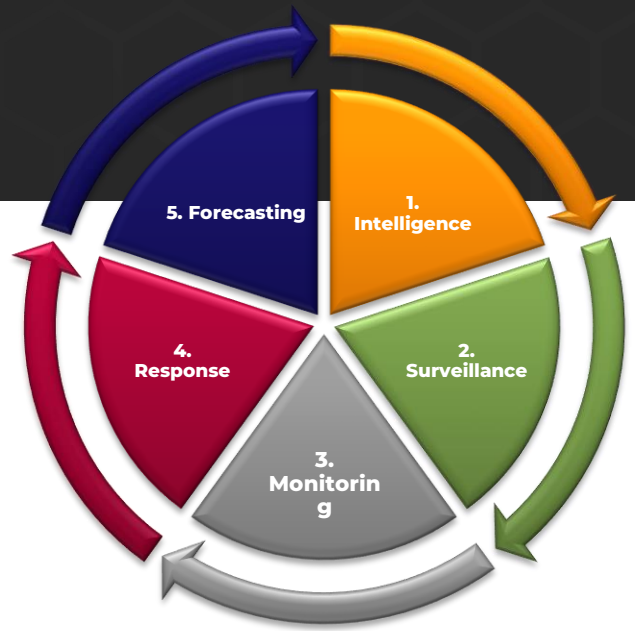
- **Sample-Mining (Prospective):**
  - Use of discarded authentic sample extract vials
  - High-*ish* volume, higher rate of incidence
  - Best for trend data (consistency)
- **Data-Mining (Retrospective):**
  - Use of electronic datafiles
  - Gives historical perspective
  - Not ideal way to discover NPS



- **Real-Time Surveillance / Case Analysis:**
  - Analysis of toxicology/chemistry samples from forensic investigations
  - Individual case basis but often can give insights into trending information

NPS DISCOVERY – THE CFSRE'S EWS

- Open-access drug early warning system (EWS)
  - Combine aspects of research & authentic cases
  - Analyze samples and generate data in-house
  - Develop a panel of high impact reports
  - Disseminate results and reports widely to stakeholders



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.

NECESSARY COMPONENTS OF A DRUG EARLY WARNING SYSTEM

- **Access to sample populations & data sources**
  - Toxicology samples – forensic and clinical
  - Drug materials – various distribution points
  - Surveys and drug use information
  - Online sources – drug fora, gray market sites, etc.
- **Framework that defines drugs of interest**
  - NPS vs. traditional drugs vs. adulterants, 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

BRIEF HISTORY & TIMELINE

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**

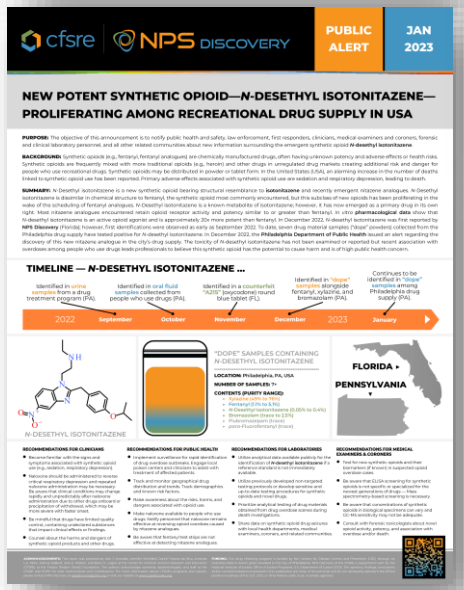
2019
- Launched first NPS Discovery website pages to archive reports and data
- Began issuing *Public Alerts* to scientific stakeholders and practitioners

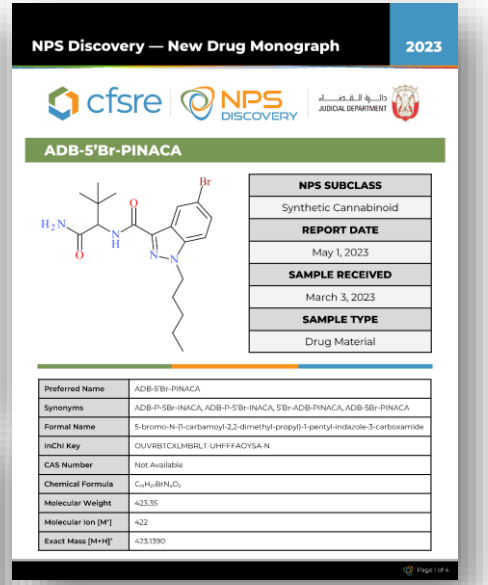
2020
- Expanded *Trend Reporting* to include all five major subclasses of NPS
- Continued data collections through onset of COVID-19 pandemic

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

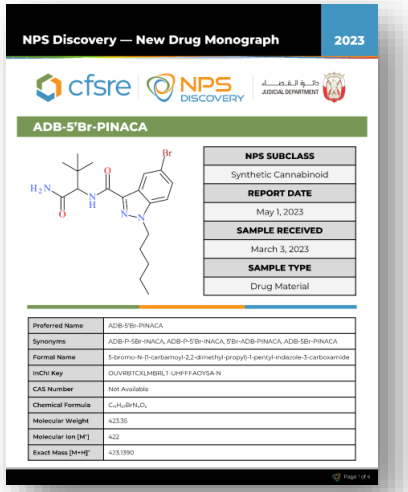
2022
- Advancements in *Drug Checking* initiatives (e.g., purity testing, potency index)
- Expansion of drug checking and clinical monitoring with new collaborators

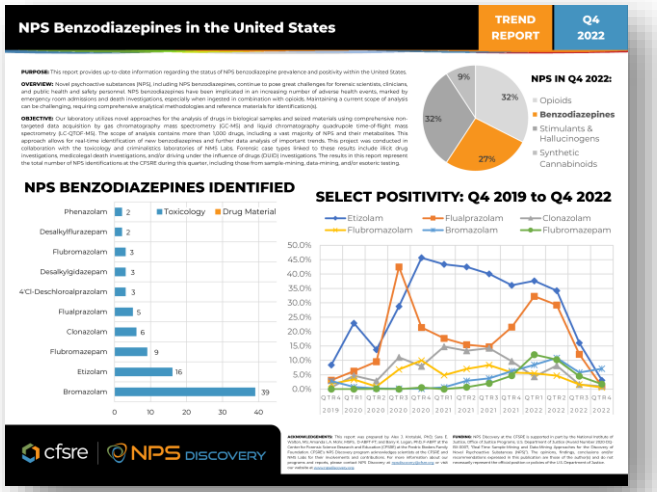
2023
- Continued expansion of *Clinical* NPS investigations (database >1,100 drugs)
- **Launch of *NPS Discovery Quarterly Webinar Series***

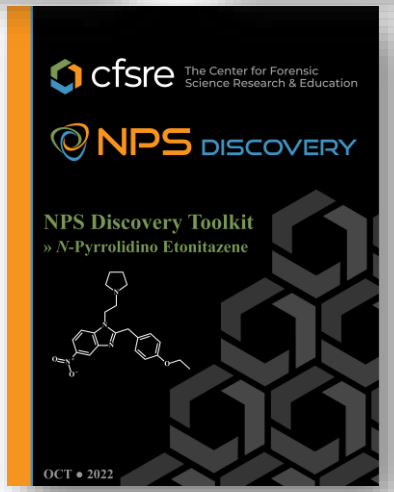


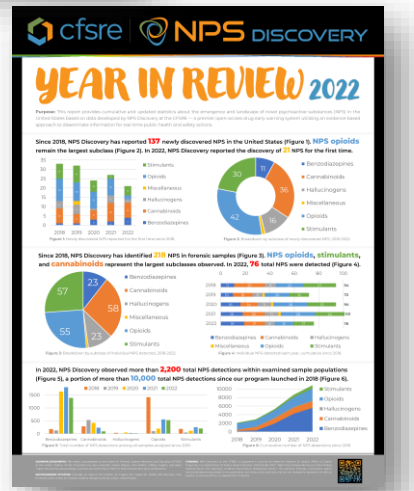


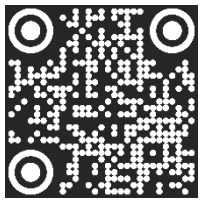
NPS DISCOVERY REPORTS











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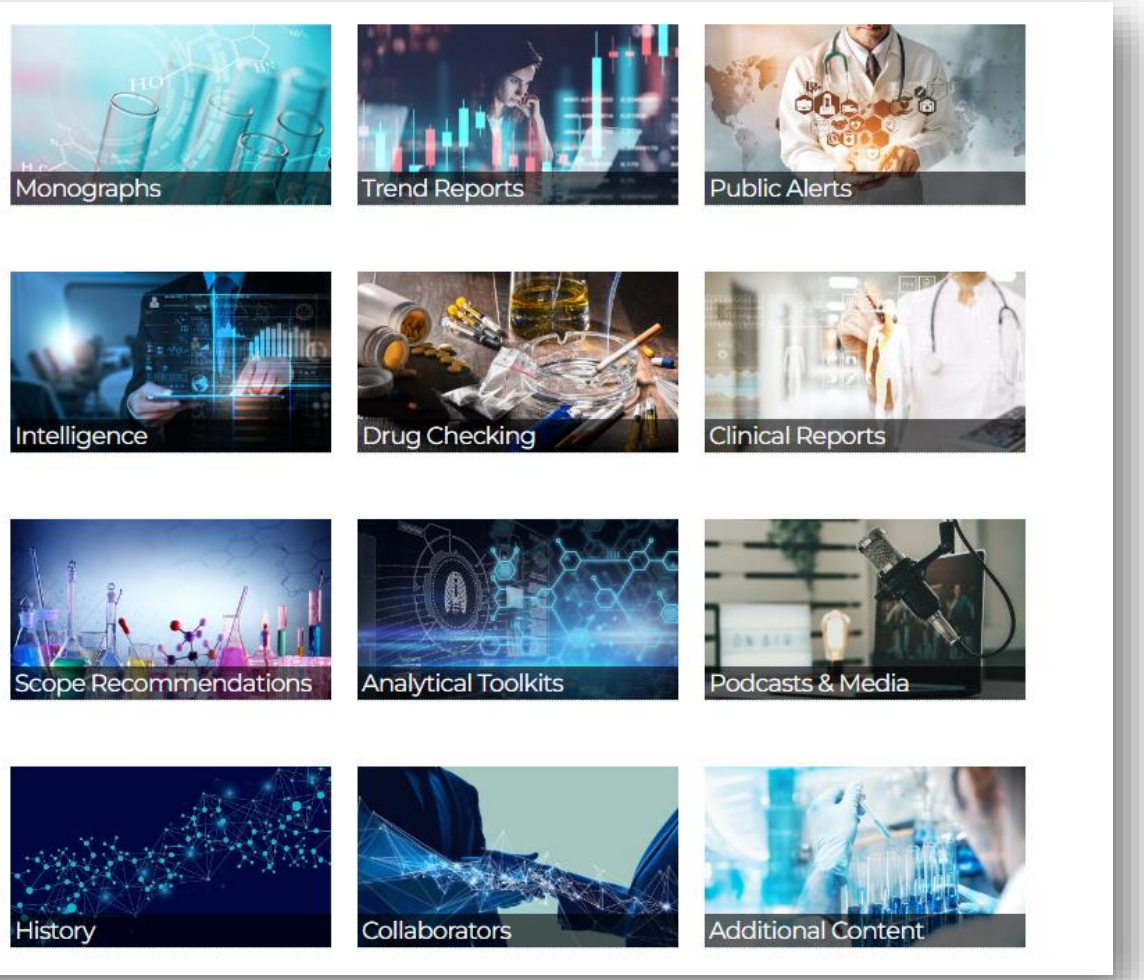
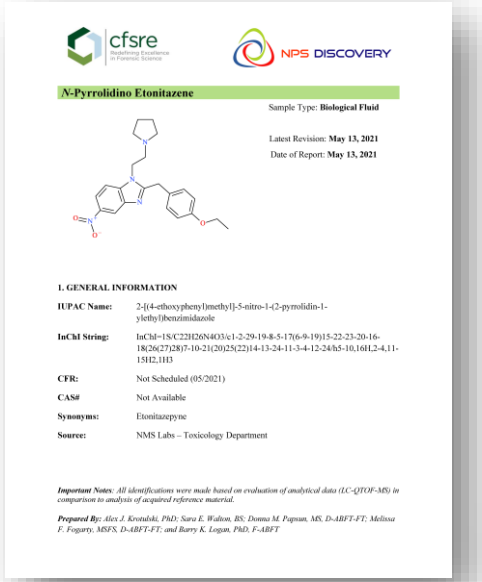
WEBSITE ▸ WWW.NPSDISCOVERY.ORG



EXAMPLE ▸ *N*-PYRROLIDINO ETONITAZENE



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NPS DISCOVERY

***N*-Pyrrolidino Etonitazene**

Sample Type: **Biological Fluid**

Latest Revision: **May 13, 2021**

Date of Report: **May 13, 2021**

1. GENERAL INFORMATION

IUPAC Name: 2-[(4-ethoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)benzimidazole

InChI String: InChI=1S/C22H26N4O3/c1-2-29-19-8-5-17(6-9-19)15-22-23-20-16-18(26(27)28)7-10-21(20)25(22)14-13-24-11-3-4-12-24/h5-10,16H,2-4,11-15H2,1H3

CFR: Not Scheduled (05/2021)

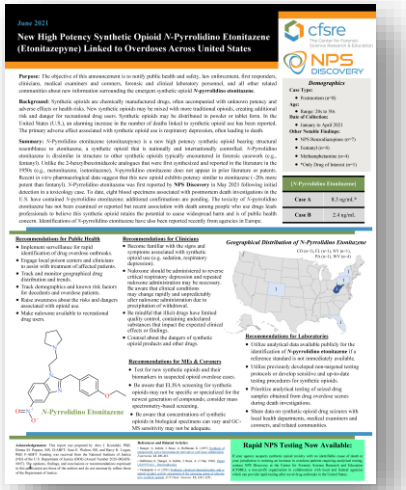
CAS# Not Available

Synonyms: Etonitazepyne

Source: NMS Labs – Toxicology Department

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

***Prepared By**: Alex J. Krotulski, PhD; Sara E. Walton, BS; Donna M. Papsun, MS, D-ABFT-FT; Melissa F. Fogarty, MSFS, D-ABFT-FT; and Barry K. Logan, PhD, F-ABFT*



June 2021

New High Potency Synthetic Opioid *N*-Pyrrolidino Etonitazene (Etonitazepyne) Linked to Overdoses Across United States

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NPS DISCOVERY

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*-pyrrolidino etonitazene.**

Background: Synthetic opioids are chemically manufactured drugs, often accompanied with unknown potency and adverse effects or health risks. New synthetic opioids may be mixed with more traditional opioids, creating additional risk and danger for recreational drug users. Synthetic opioids may be distributed in powder or tablet form. In the United States (U.S.), an alarming increase in the number of deaths linked to synthetic opioid use has been reported. The primary adverse effect associated with synthetic opioid use is respiratory depression, often leading to death.

Summary: *N*-Pyrrolidino etonitazene (etonitazepyne) is a new high potency synthetic opioid bearing structural resemblance to etonitazene, a synthetic opioid that is nationally and internationally controlled. *N*-pyrrolidino etonitazene is dissimilar in structure to other synthetic opioids typically encountered in forensic casework (e.g., fentanyl). Unlike the 2-benzylbenzimidazole analogues that were first synthesized and reported in the literature in the 1950's (e.g., metonitazene, isotonitazene), *N*-pyrrolidino etonitazene does not appear in prior literature or patents. Recent *in vitro* pharmacological data suggest that this new opioid exhibits potency similar to etonitazene (~20x more potent than fentanyl). *N*-Pyrrolidino etonitazene was first reported by **NPS Discovery** in May 2021 following initial detection in a toxicology case. To date, eight blood specimens associated with postmortem death investigations in the U.S. have confirmed *N*-pyrrolidino etonitazene; additional confirmations are pending. The toxicity of *N*-pyrrolidino etonitazene has not been examined or reported but recent association with death among people who use drugs leads professionals to believe this synthetic opioid retains the potential to cause widespread harm and is of public health concern. Identifications of *N*-pyrrolidino etonitazene have also been reported recently from agencies in Europe.

Biographics

Case Type:
- Postmortem (n=8)

Sex:
- Male
- Range: 20s to 50s

Date of Collection:
- January to April 2021

Other Notable Findings:
- NPS Benzodiazepines (n=7)
- Fentanyl (n=4)
- Nitrobenzbromine (n=4)
- Newly Drug of Interest (n=1)

N-Pyrrolidino Etonitazene	
Case A	8.3 ng/mL*
Case B	2.4 ng/mL

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 distinguishable and known risk factors for individuals at drug overdose patients.
- Raise awareness about the risks and dangers associated with opioid use.
- Make naloxone available to recreational drug users.

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 (e.g. hypoxia) and polysubstance ability affect naloxone administration due to precipitation of withdrawal.
- 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 opioid products and other drugs.

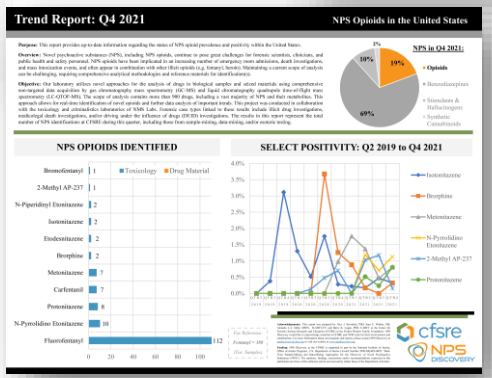
Recommendations for MEs & Coroners
- Test for non-synthetic opioids and their biomarkers in suspected opioid overdose cases.
- Be aware that ELISA screening for synthetic opioids may not be specific or specialized for the newest generation of compounds; consider mass spectrometry-based screening.
- Be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

***N*-Pyrrolidino Etonitazene**

Geographical Distribution of *N*-Pyrrolidino Etonitazene

Recommendations for Laboratories
- Utilize analytical data available publicly for the identification of ***N*-pyrrolidino etonitazene** 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.
- Prioritize analytical testing of seized drug samples obtained from drug overdose scenes during death investigations.
- Share data on synthetic opioid drug seizures with local health departments, medical examiners and coroners, and related communities.

Rapid NPS Testing Now Available:



Trend Report: Q4 2021 — **NPS Opioids in the United States**

NPS in Q4 2021:
- Opioids
- Benzodiazepines
- Stimulants & Hallucinogens
- Synthetic Cannabinoids

NPS OPIOIDS IDENTIFIED

	Toxicology	Drug Material
Bromofentanyl	1	
2-Methyl AP-237	1	
N-Piperidinyl Etonitazene	2	
Isotonitazene	2	
Etodesnitazene	2	
Brorphine	2	
Metonitazene	7	
Carfentanil	7	
Protonitazene	8	
N-Pyrrolidino Etonitazene	10	
Fluorofentanyl	112	

SELECT POSITIVITY: Q2 2019 to Q4 2021

Isotonitazene, Brorphine, Metonitazene, N-Pyrrolidino Etonitazene, 2-Methyl AP-237, Protonitazene

ToxIC Fentalog Study Group — Quarterly NPS Report — CLINICAL — Q2 2023

NEW CLINICAL SITES! Atlanta, GA & Denver, CO

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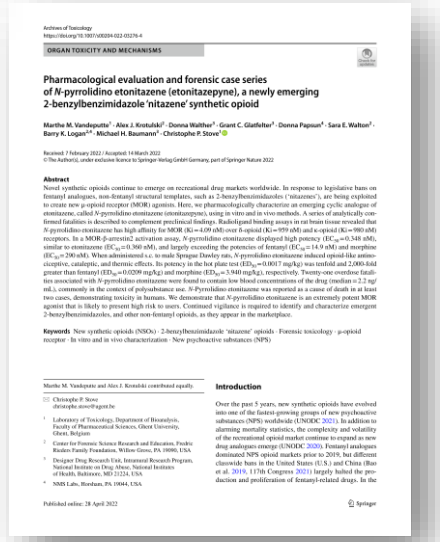

Archives of Toxicology
https://doi.org/10.1007/s00204-022-03276-4

ORGANTOXICITY 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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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 (K_i = 4.09 nM) over δ- opioid (K_i = 959 nM) and κ- opioid (K_i = 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)

Martha 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 2018, but different chemotypes bans in the United States (U.S.) and China (Bao et al. 2019, 113th Congress 2021) largely halted the production and proliferation of fentanyl-related drugs. In the

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NPS DISCOVERY

NPS Discovery Toolkit

» *N*-Pyrrolidino Etonitazene

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NEW

YEAR IN REVIEW ▸

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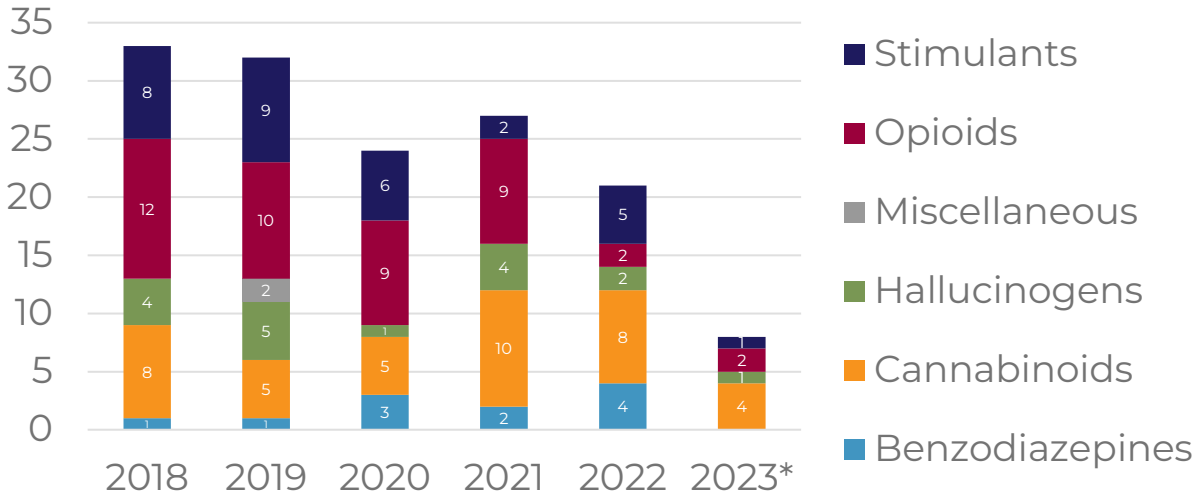
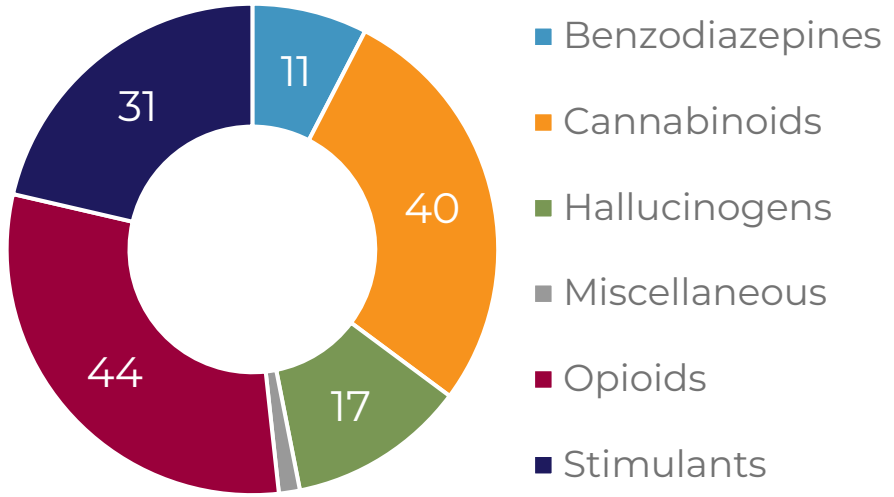
EMERGENCE OF NPS IN THE U.S.

- Since 2018, NPS Discovery has reported **145** newly discovered NPS (and counting)
- **NPS opioids** remain the largest subclass of newly emerging drugs encountered
- As of June 2023, NPS Discovery has reported **8** NPS for the first time this year





NEW DRUG MONOGRAPHS – 2023

Date	NPS Class	Drug Name	Formula	[M+]	[M+H]+
06/28/2023	Cannabinoid	**CHO-4'Me-5'Br-FUBOXPYRA**	C20H22BrFN2O2	420	421.0921
06/27/2023	Cannabinoid	**MDMB-BINACA**	C19H27N3O3	345	346.2125
06/26/2023	Cannabinoid	**MDMB-INACA**	C15H19N3O3	289	290.1499
06/23/2023	Opioid	***N*-Pyrrolidino Metonitazene**	C21H24N4O3	380	381.1921
06/22/2023	Opioid	***N*-Pyrrolidino Protonitazene**	C23H28N4O3	408	409.2234
06/21/2023	Hallucinogen	**25B-NBOH**	C17H20BrNO3	365	366.0699
06/20/2023	Stimulant	**4-Methylmethylphenidate**	C15H21NO2	247	248.1645
05/01/2023	Cannabinoid	**ADB-5'Br-PINACA**	C19H27BrN4O2	422	423.1390

Pending: Medetomidine, NMBMSB, MDMB-PICA, Rilmazafone, etc.

LANDSCAPE OF NPS IN THE U.S.

- Since 2018, NPS Discovery has identified **more than 225** NPS in forensic samples
- **NPS opioids**, **stimulants**, and **cannabinoids** represent the largest subclasses observed

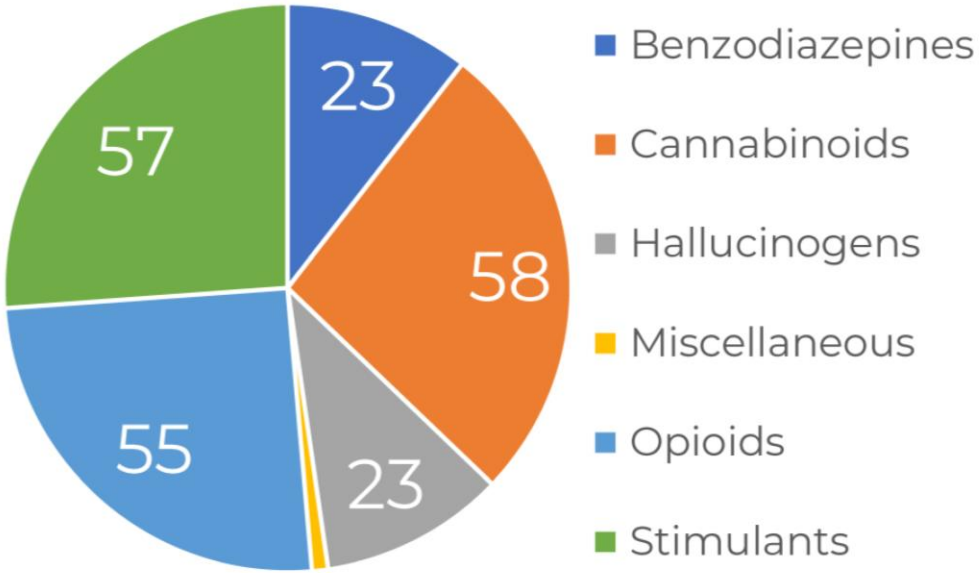


Figure 3: Breakdown by subclass of individual NPS detected, 2018-2022.

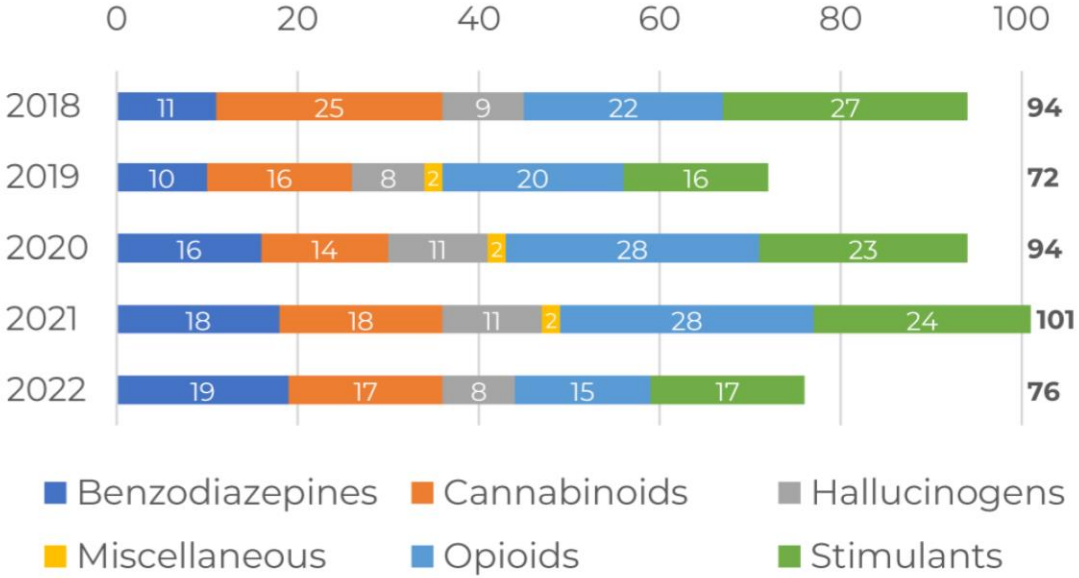


Figure 4: Individual NPS detected each year, cumulative since 2018.

PROLIFERATION OF NPS IN THE U.S.

- In 2022, NPS Discovery observed more than **2,200** total NPS detections
- A portion of more than **10,000** total NPS detections since 2018

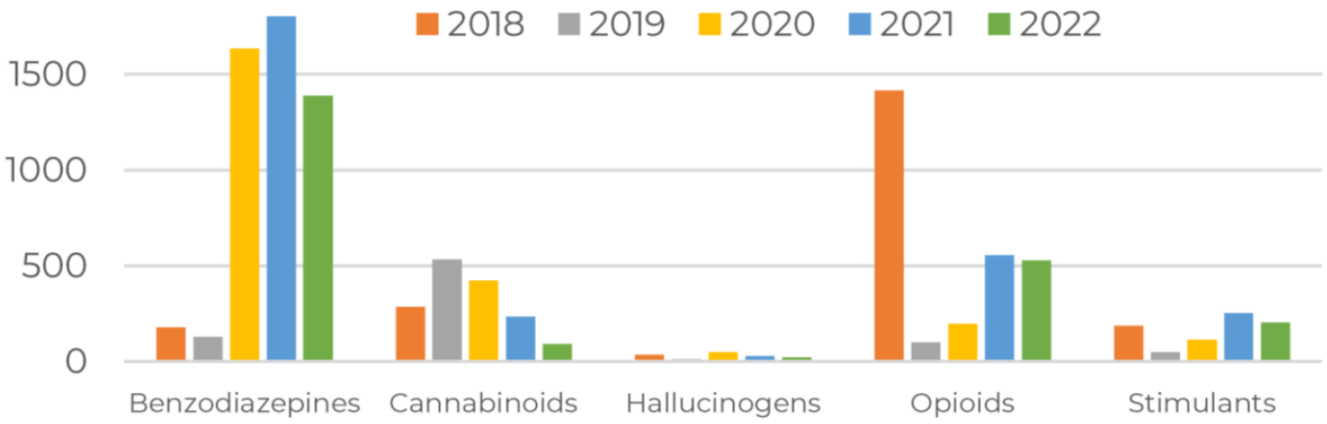


Figure 5: Total number of NPS detections among all samples analyzed since 2018.

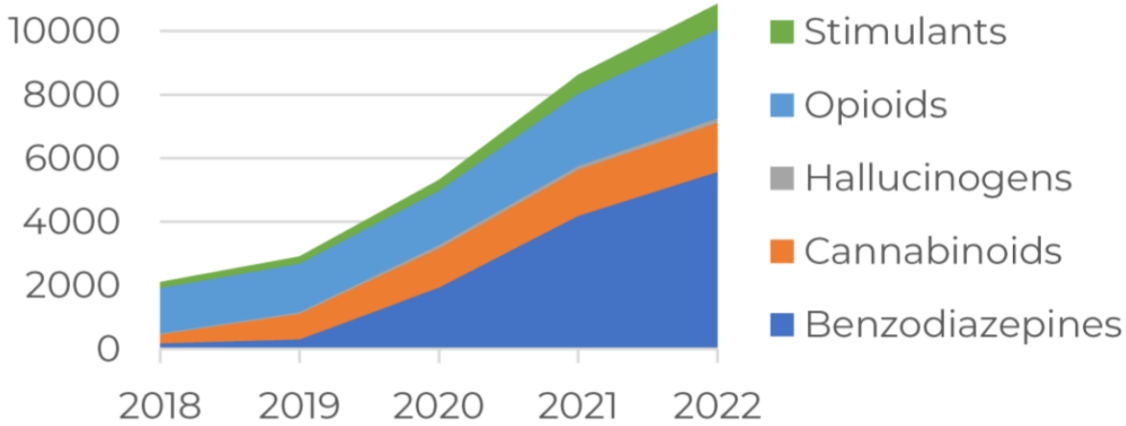


Figure 6: Cumulative number of NPS detections since 2018.

POSITIVITY PLOTS SINCE 2018

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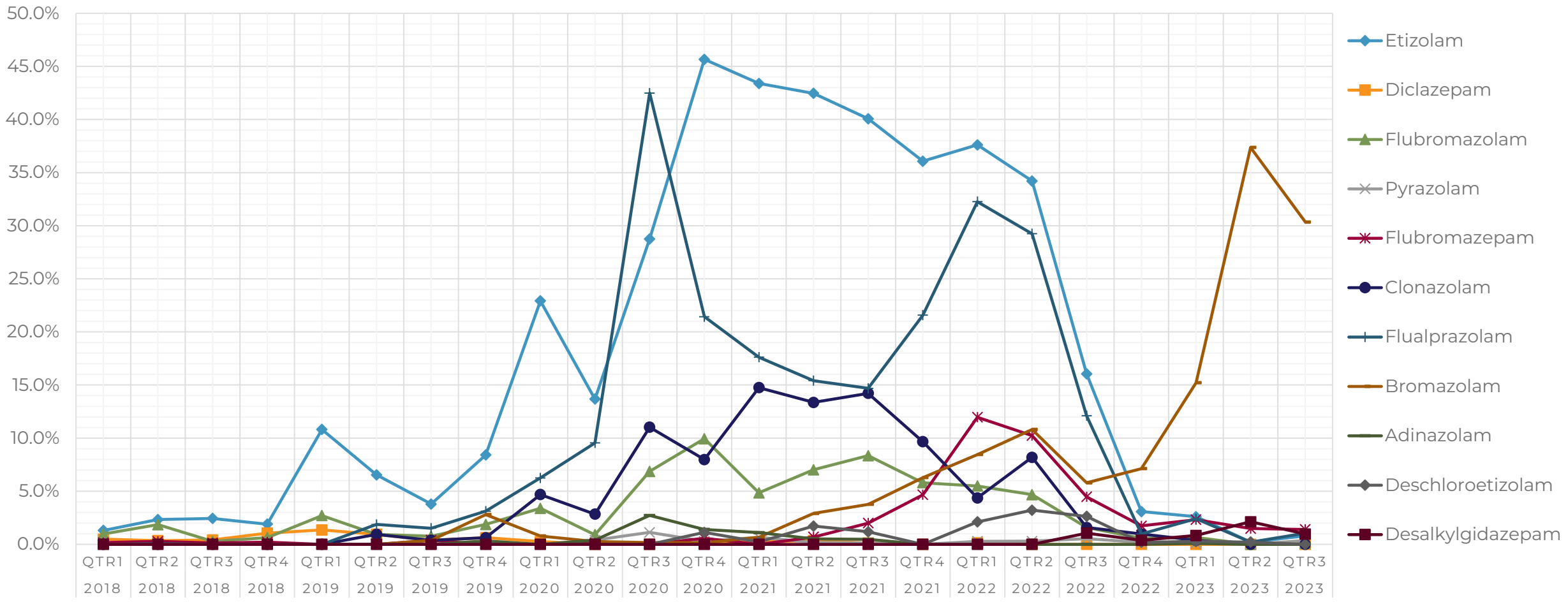
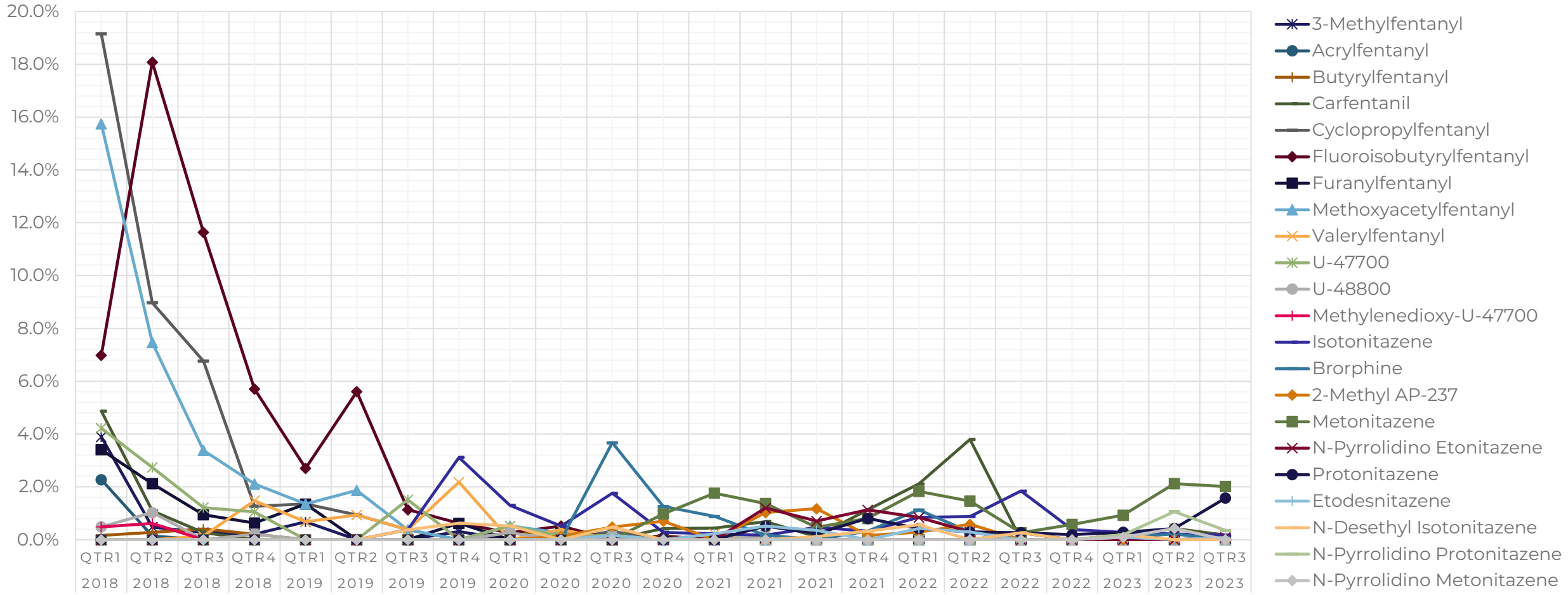
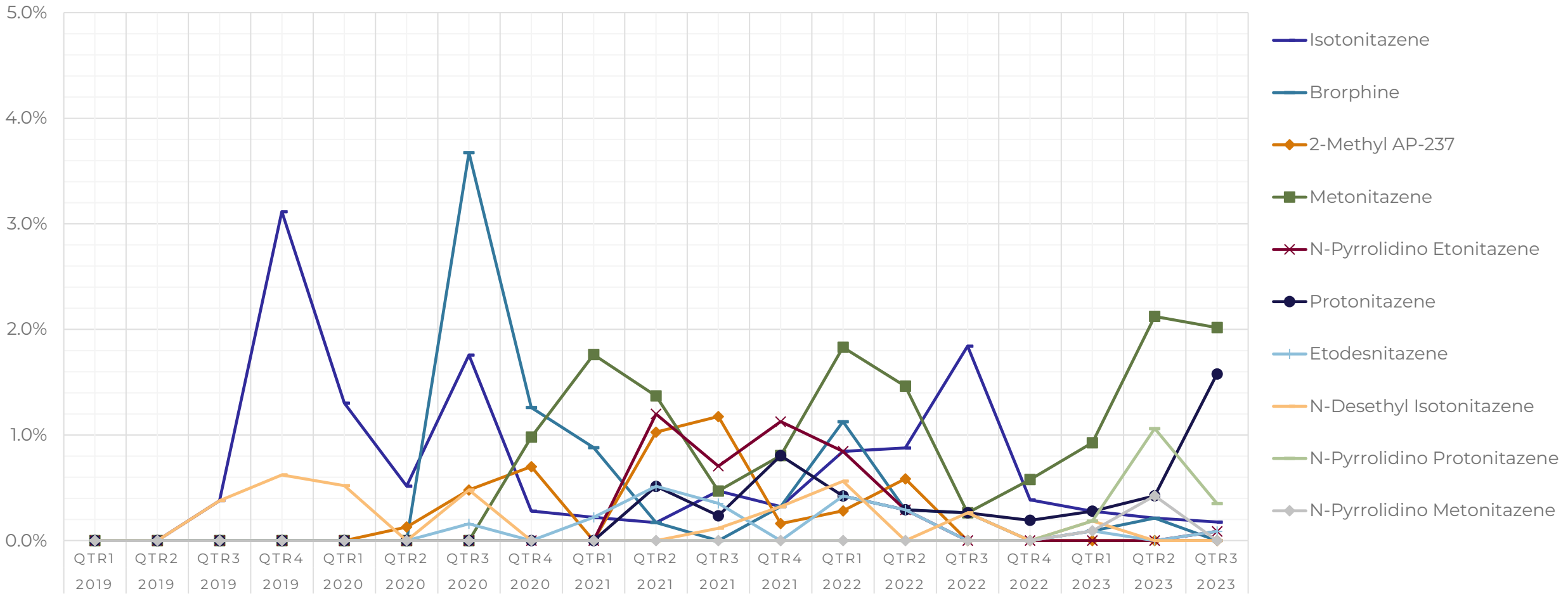
NPS BENZODIAZEPINES



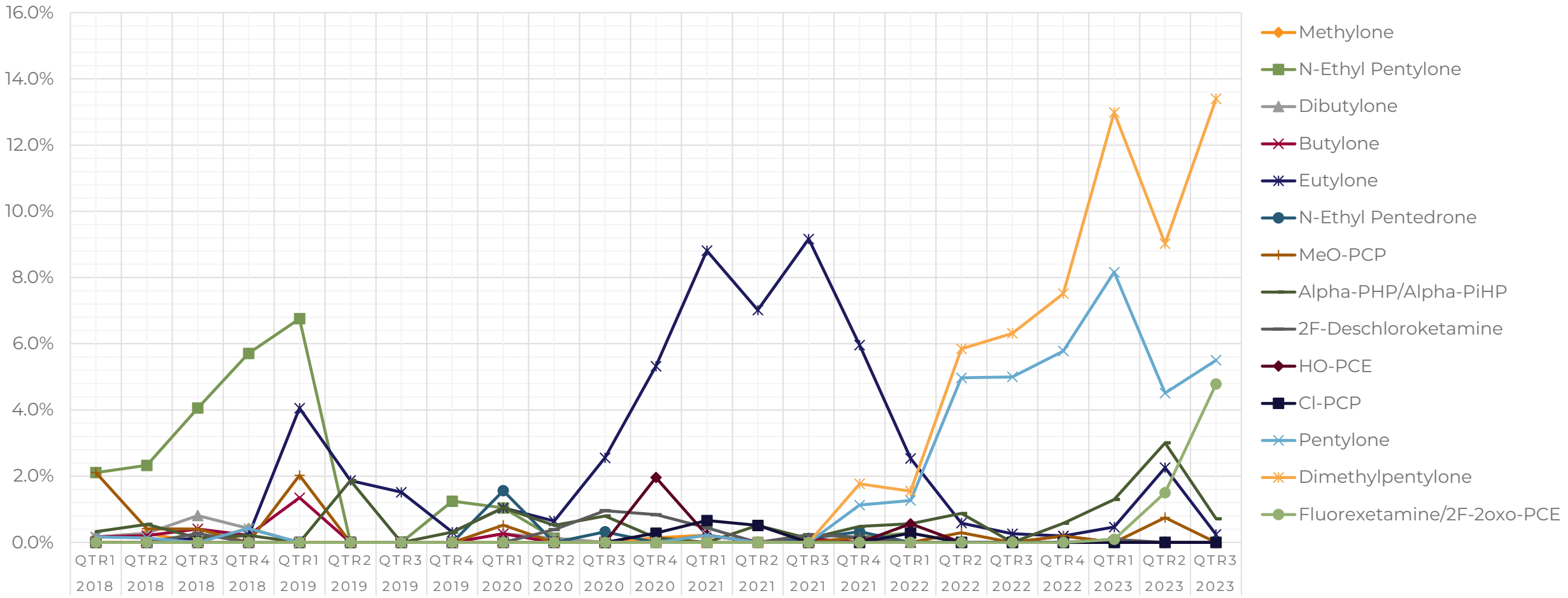
NPS OPIOIDS


20.0%
18.0%
16.0%
14.0%
12.0%
10.0%
8.0%
6.0%
4.0%
2.0%
0.0%
QTR1 2018
QTR2 2018
QTR3 2018
QTR4 2018
QTR1 2019
QTR2 2019
QTR3 2019
QTR4 2019
QTR1 2020
QTR2 2020
QTR3 2020
QTR4 2020
QTR1 2021
QTR2 2021
QTR3 2021
QTR4 2021
QTR1 2022
QTR2 2022
QTR3 2022
QTR4 2022
QTR1 2023
QTR2 2023
QTR3 2023
3-Methylfentanyl
Acrylfentanyl
Butyrylfentanyl
Carfentanil
Cyclopropylfentanyl
Fluoroisobutyrylfentanyl
Furanylfentanyl
Methoxyacetylfentanyl
Valerylfentanyl
U-47700
U-48800
Methylenedioxy-U-47700
Isotonitazene
Brorphine
2-Methyl AP-237
Metonitazene
N-Pyrrolidino Etonitazene
Protonitazene
Etodesnitazene
N-Desethyl Isotonitazene
N-Pyrrolidino Protonitazene
N-Pyrrolidino Metonitazene

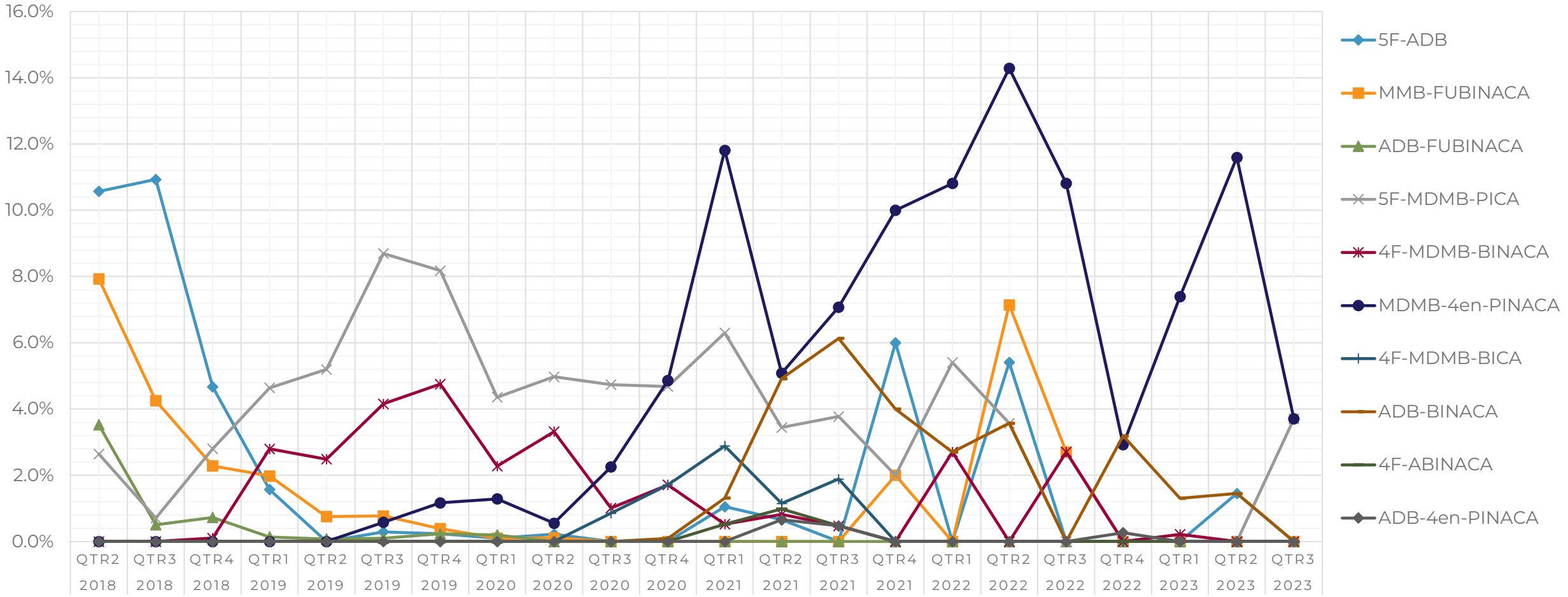
NPS OPIOIDS (NEW GENERATION ONLY)



NPS STIMULANTS AND HALLUCINOGENS

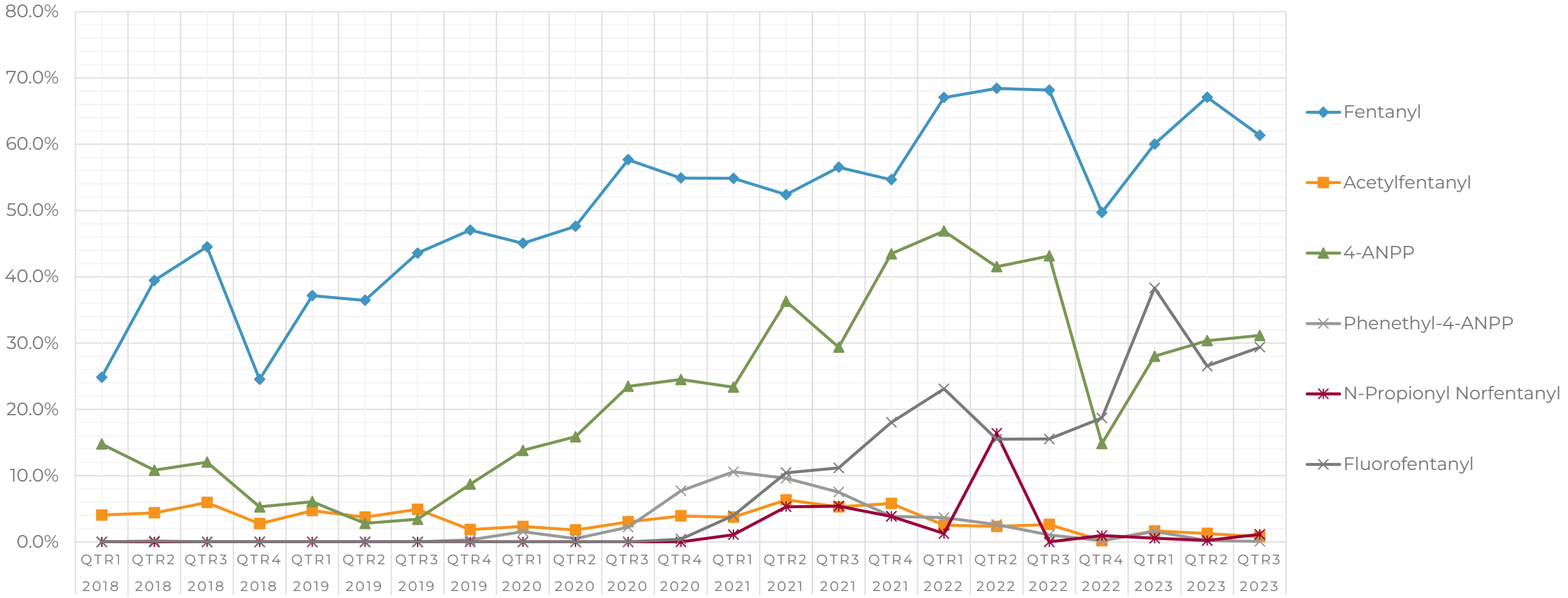


SYNTHETIC CANNABINOIDS

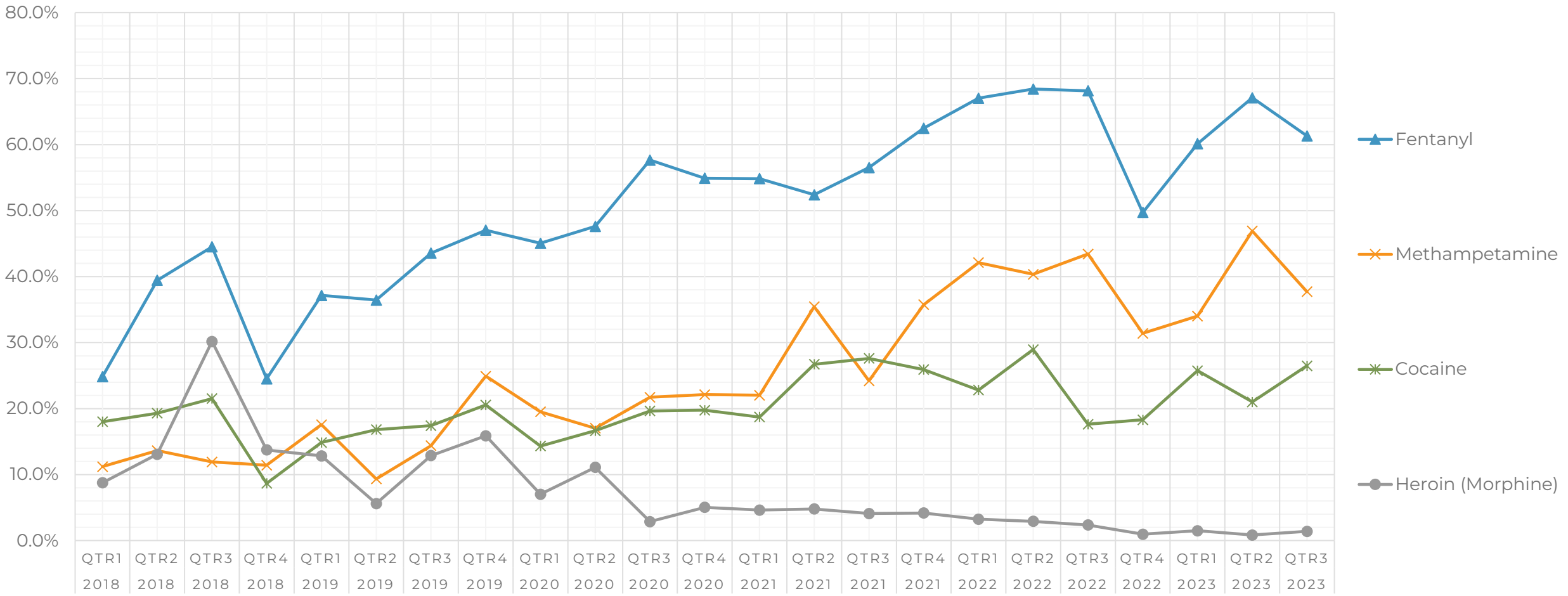


Note: Data is recent quarters is skewed due to low sample volume.

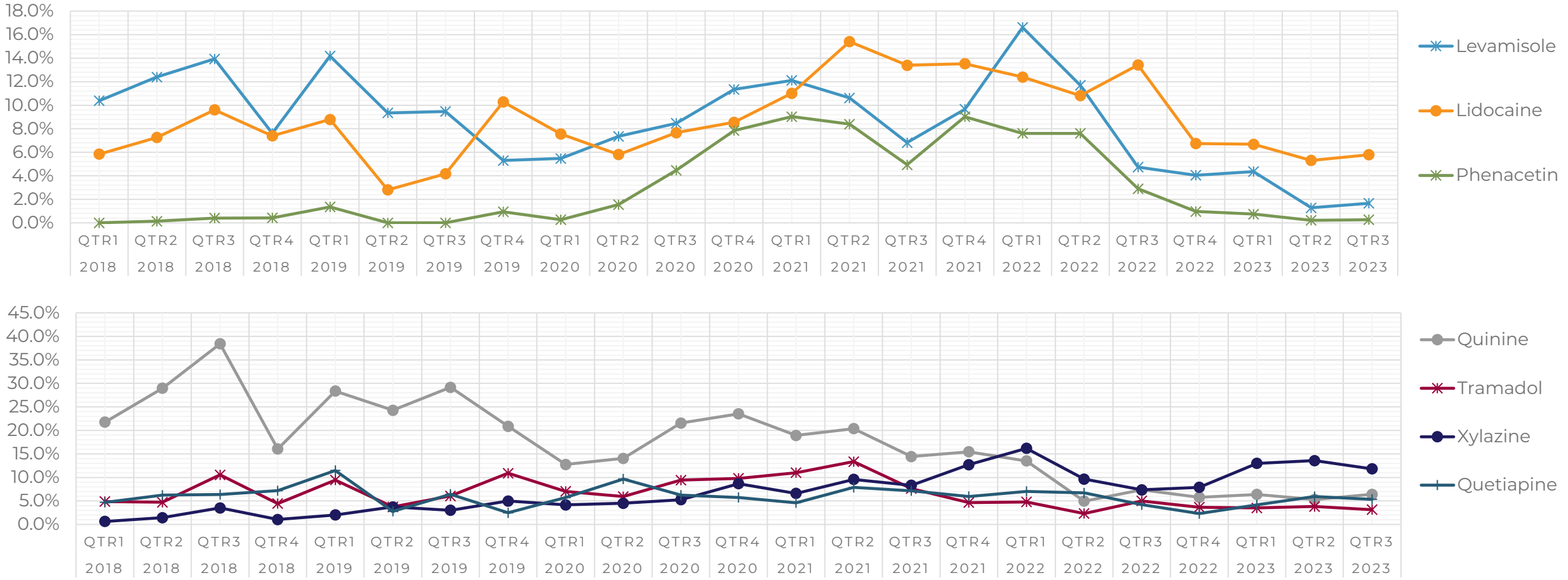
FENTANYL, FLUOROFENTANYL, & FENTANYL PROFILING



TRADITIONAL DRUGS

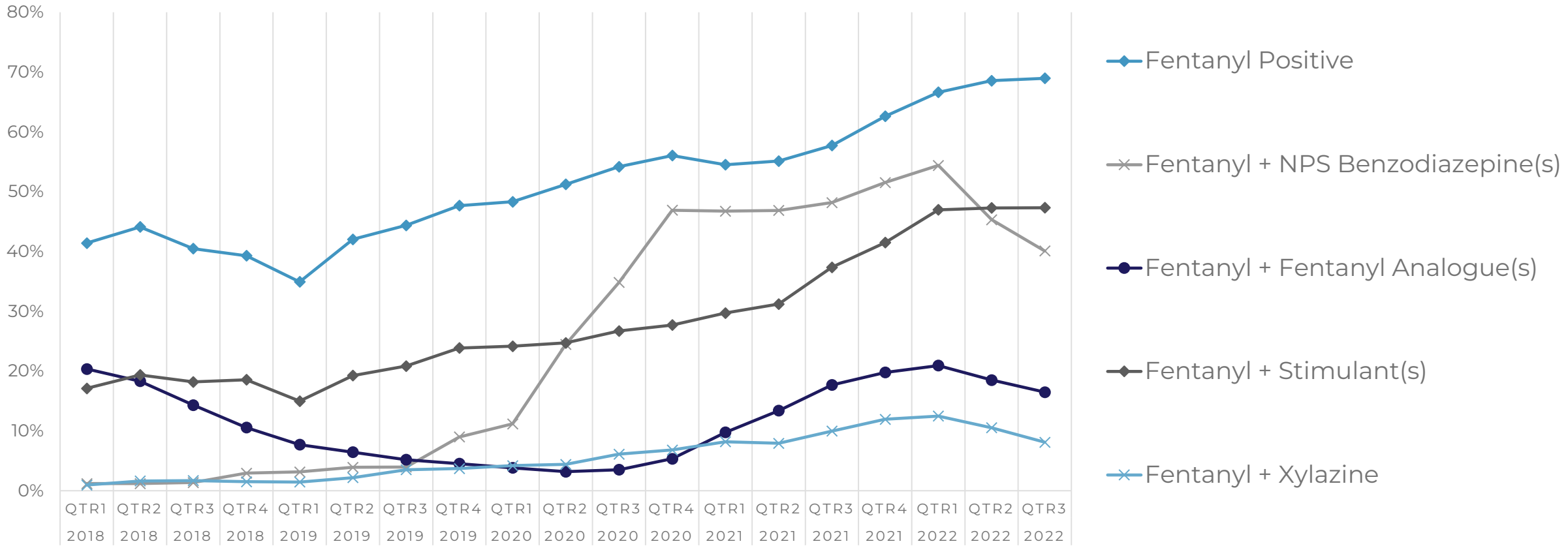


ADULTERANTS



ENTERING THE POLYDRUG STAGE OF OPIOID EPIDEMIC

Fentanyl Co-Positivity – the “Nested Waves” Underlying Positivity and Prevalence



NPS OPIOIDS

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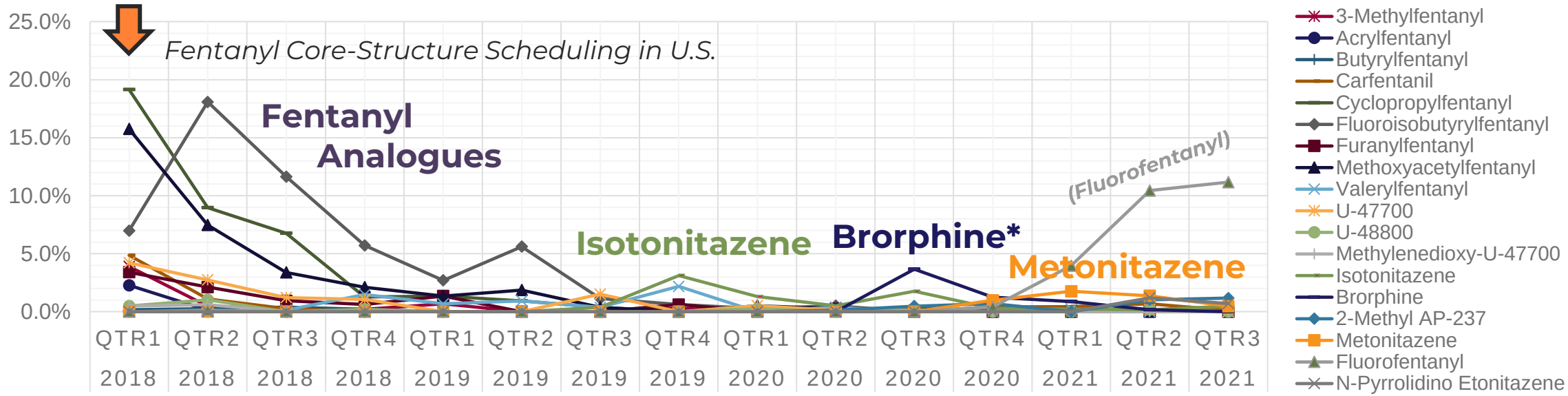
FENTANYL ANALOGUES → NITAZENE ANALOGUES

- In 2018, the DEA placed all **fentanyl-related substances** in Schedule I
  - Role of EWS → track what the impact of this scheduling action might be
- Between 2019 and 2021, NPS Discovery observed the **emergence of "nitazene analogues"**
  - And this has continued into 2023



*Not a "nitazene" analogue

NPS OPIOID DISCOVERIES SINCE 2018

2018

- MD-U-47700
- Phenylfentanyl
- U-47931E

2019

- Fluorofuranylfentanyl
- p-MeO-Fu-Fentanyl
- 2',5'-DiMeO-Fentanyl
- 2-Methyl AP-237
- AP-237
- Piperidylthiambutene
- 2F-Viminol
- **Isotonitazene**
- N-Methyl U-47931E
- p-Me-Cpr-Fentanyl

2020

- 3,4-Difluoro-U-47700
- N-Ethyl-U-47700
- para-Methyl AP-237
- Brorphine
- **Metonitazene**
- AP-238
- Fluorofentanyl
- Chlorofentanyl
- Bromofentanyl

2021

- **Butonitazene**
- **Etodesnitazene**
- **Flunitazene**
- ***N*-Pyrrolidino Etonitazene**
- **Protonitazene**
- **Metodesnitazene**
- ***N-Piperidinyl Etonitazene***

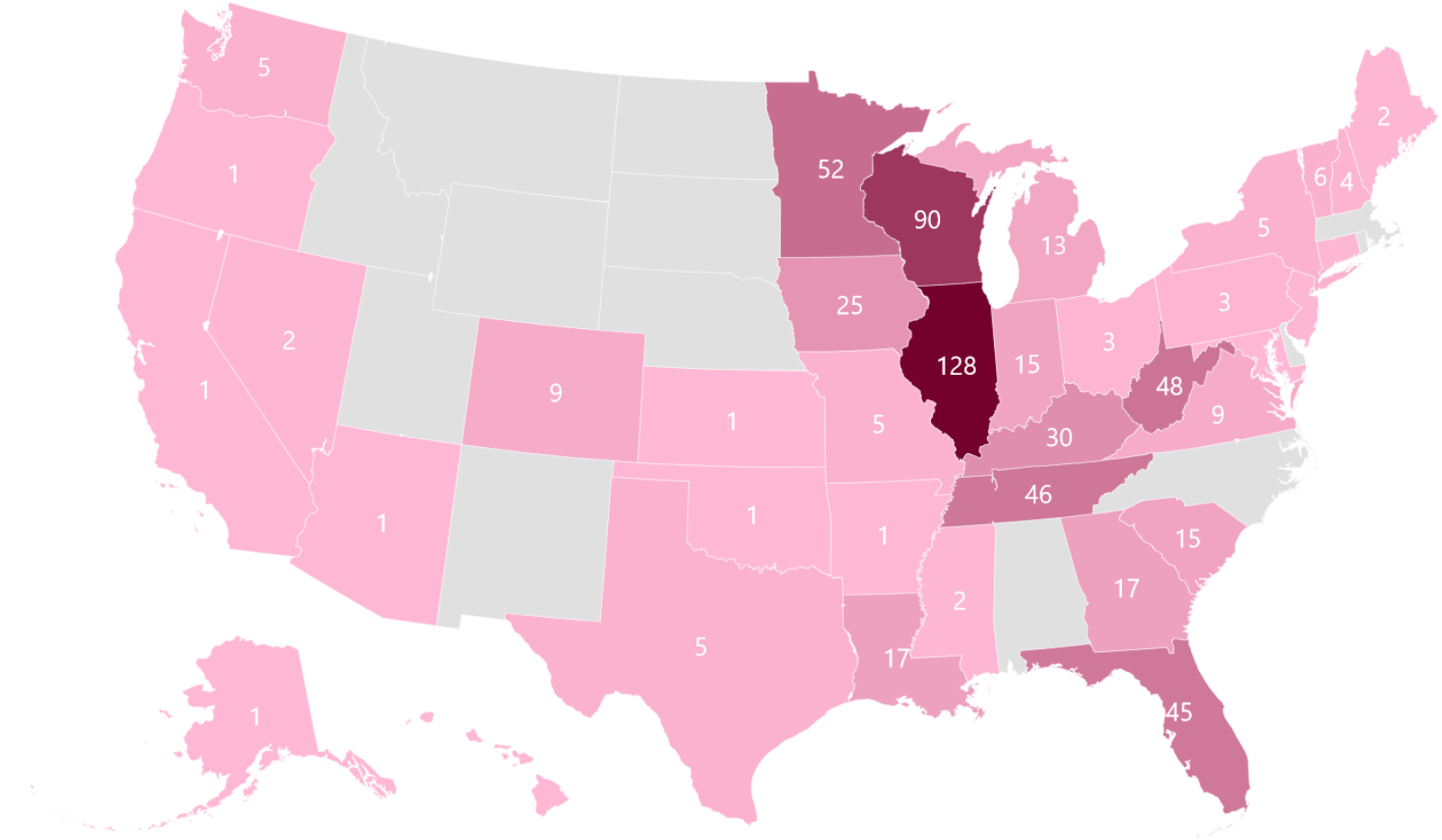
2022

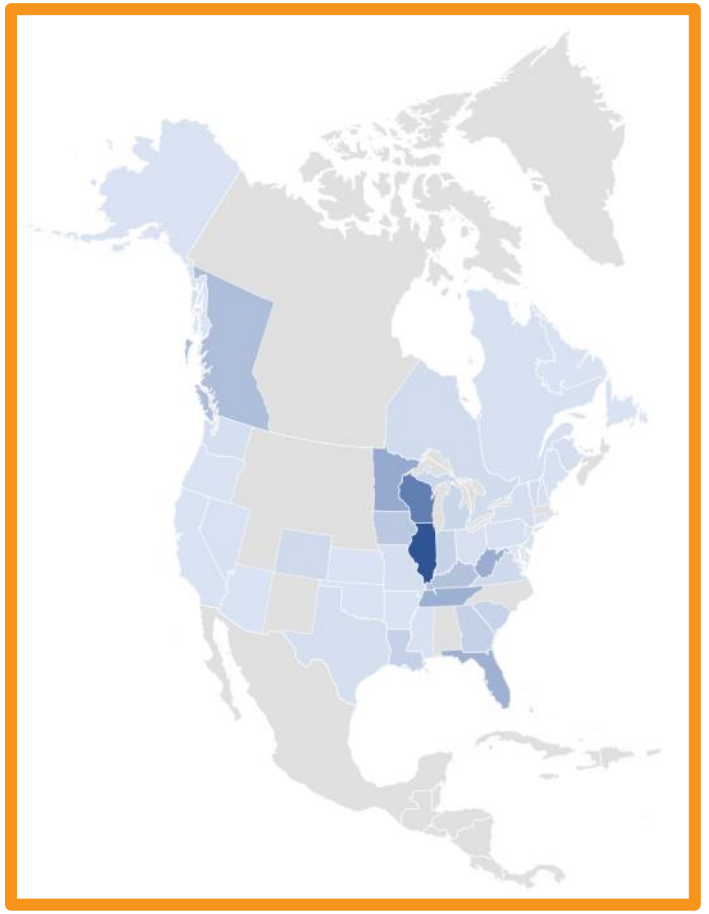
- Dipyanone
- ***N*-Desethyl Isotonitazene**

2023

- ***N*-Pyrrolidino Metonitazene**
- ***N*-Pyrrolidino Protonitazene**

PROLIFERATION OF NITAZENE ANALOGUES

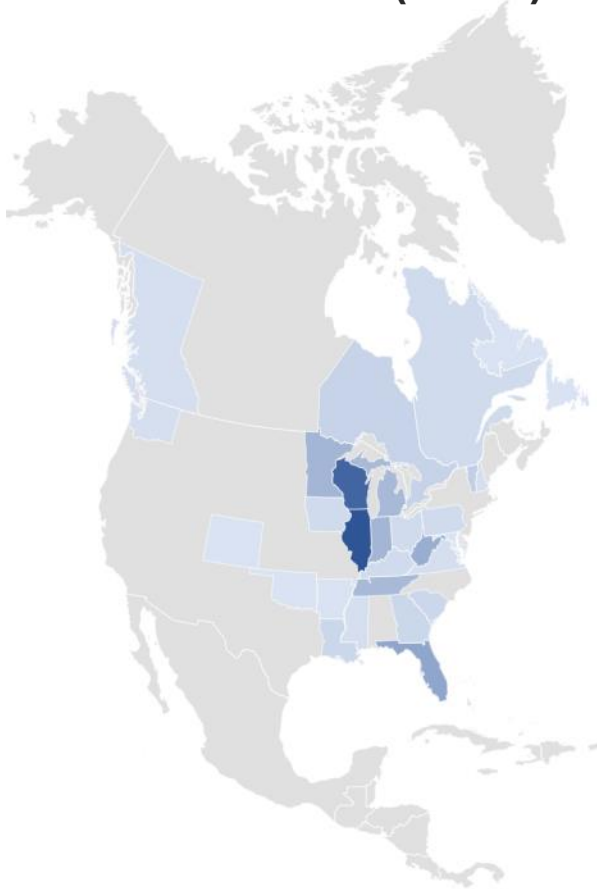




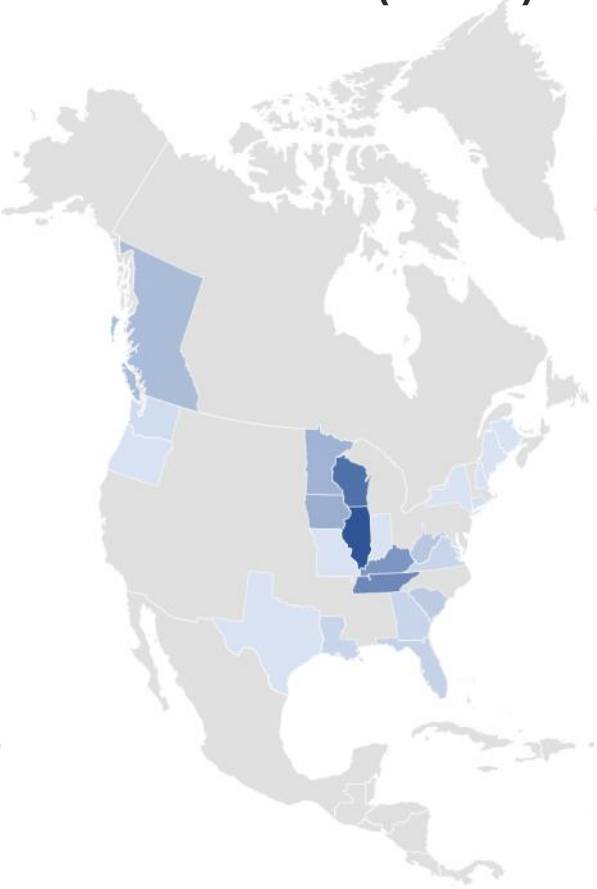
*Forensic toxicology cases. Data from NMS Labs representing cumulative identifications.
*Includes: isotonitazene, brorphine, metonitazene, N-pyrrolidino etonitazene, protonitazene

VARIED GEOGRAPHICAL DISTRIBUTION

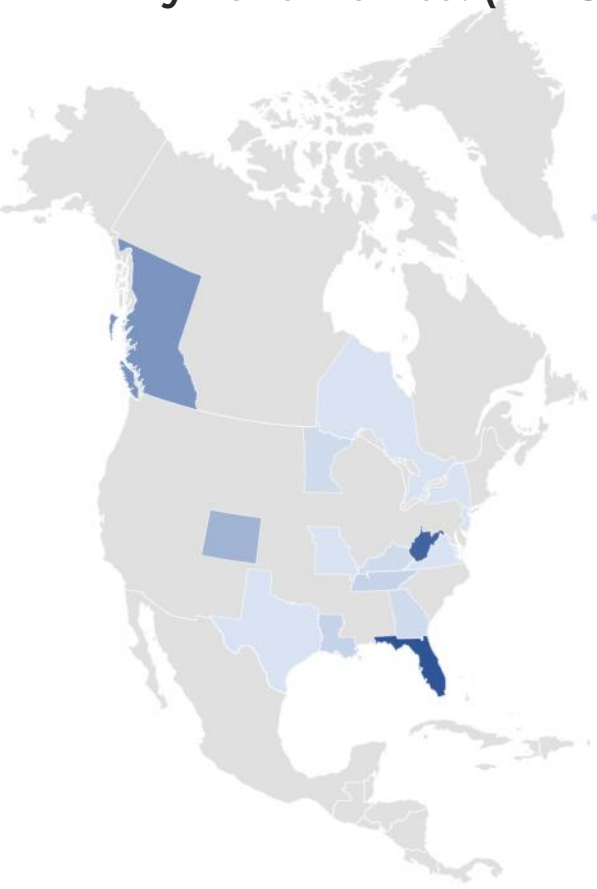
Isotonitazene (n=197)



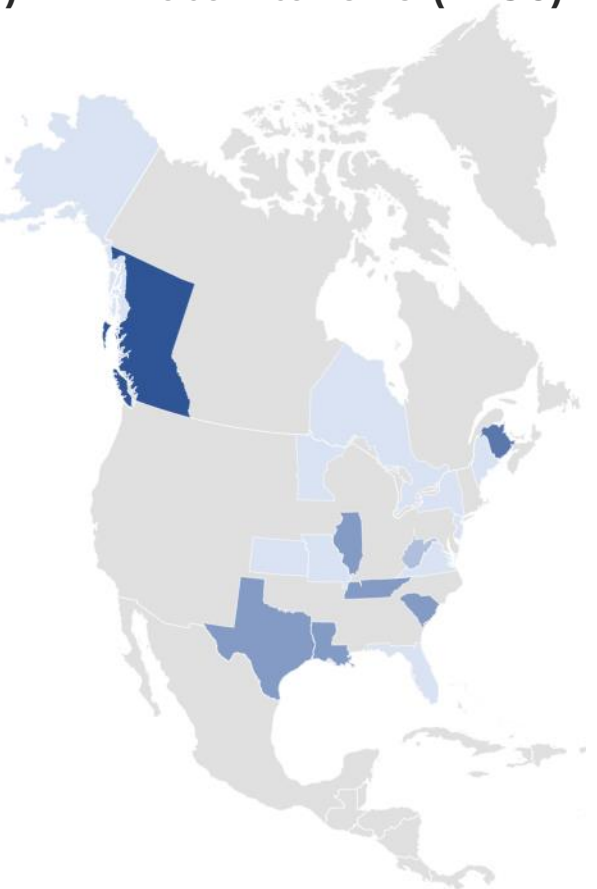
Metonitazene (n=220)



N-Pyrrolidino Eto. (n=73)



Protonitazene (n=36)



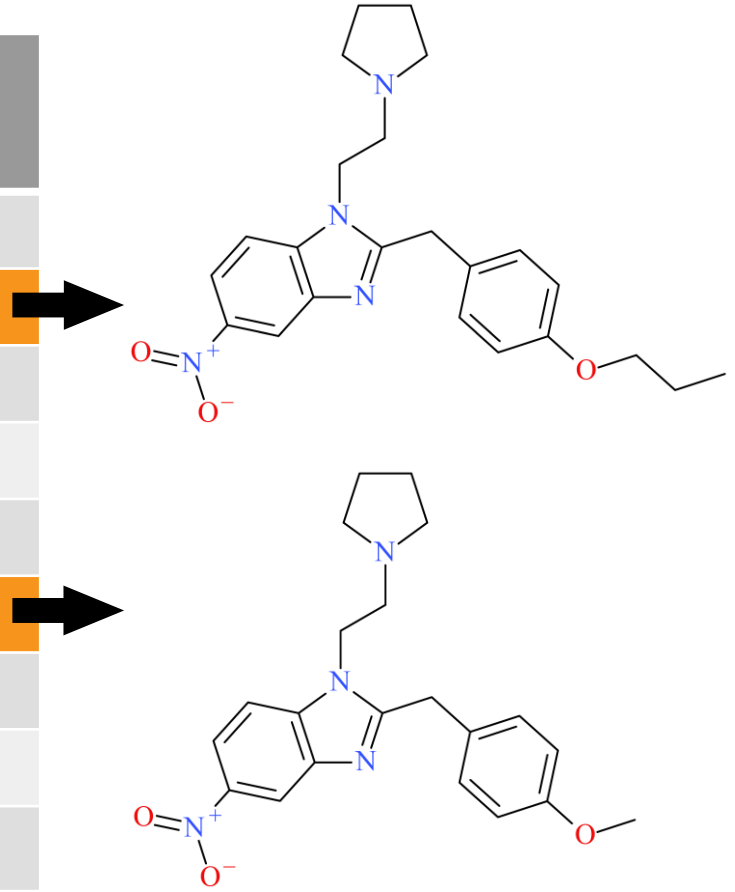
IN COMBINATION WITH OTHER DRUGS

Analogue	% Co-Positivity of Nitazene Analogue with...				
	Fentanyl	NPS Benzo.	Methamp.	Cocaine	Xylazine
Isotonitazene	57%	89%	30%	32%	11%
Brorphine	84%	100%	43%	29%	10%
Metonitazene	51%	94%	37%	16%	20%
N-Pyrro. Eto.	59%	89%	48%	37%	15%
Protonitazene	60%	87%	87%	13%	0%
Etodesnitazene	50%	92%	58%	17%	17%

*Forensic toxicology cases. Data from the CFSRE.

THE NEWEST NITAZENE ANALOGUES

Analogue	CFSRE Cases	Estimated Potency Compared to Fentanyl
N-Pyrrolidino Etonitazene	15	43x more
_N_-Pyrrolidino Protonitazene	**9**	**25x more**
Isotonitazene	69	9x more
Protonitazene	3	4x more
Metonitazene	18	2x more
_N_-Pyrrolidino Metonitazene	**5**	**2x more**
Fentanyl	-	-
Butonitazene	1	2x less
Etodesnitazene	15	4x less



SYNTHETIC CANNABINOIDS

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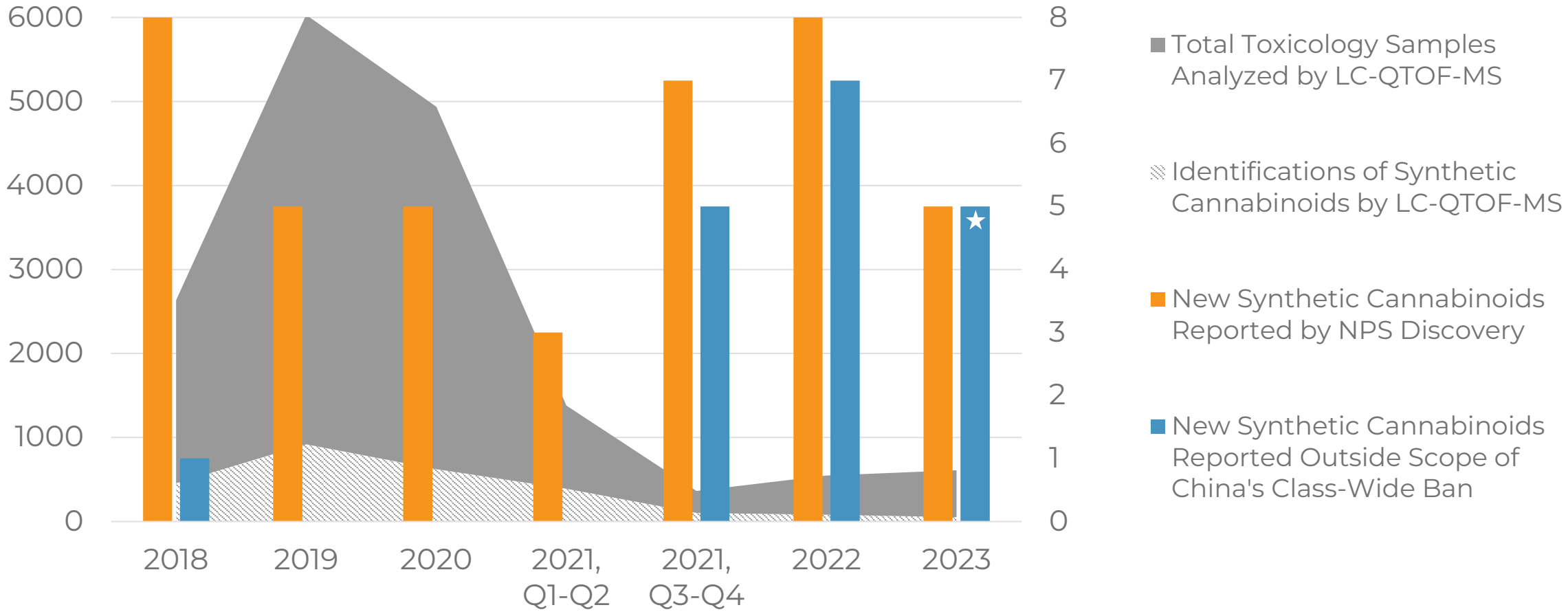
SHIFTING TIDES IN THE UNITED STATES



SYNTHETIC CANNABINOID DISCOVERIES SINCE 2018

- NPS Discovery now (almost exclusively) sees new synthetic cannabinoids that fall **outside** the scope of the 2021 Chinese class-wide ban; however, expectation remain (as with all NPS).

2018

- Adamantyl-CHMINACA
- 5Cl-AKB48
- 5Br-AKB48
- 5F-EDMB-PINACA
- 5F-MDMB-PICA
- 5Cl-AB-PINACA
- **5F-AB-PFUPPYCA**
- MFUBINAC

2019

- 4F-MDMB-BINACA
- 5F-MPP-PICA
- APP-BINACA
- MDMB-4en-PINACA
- MMB-4en-PICA

2020

- 5F-CUMYL-PINACA
- 5F-EMB-PICA
- 4F-MDMB-BICA
- ADB-BINACA
- 5F-MDMB-PICA

2021

- 4F-ABINACA
- ADB-4en-PINACA
- ADB-HEXINACA
- **BZO-HEXOXIZID**
- **BZO-POXIZID**
- **5F-BZO-POXIZID**
- **ADB-FUBIATA**
- **BZO-CHMOXIZID**
- ADB-PHETINACA
- EDMB-PINACA

2022

- **CH-PIATA**
- **ADB-5Br-INACA**
- **MDMB-5Br-INACA**
- **BZO-4en-POXIZID**
- **ADB-5'Br-BINACA**
- **CH-FUBIATA**
- CUMYL-TsINACA
- **ADB-INACA**

2023

- **ADB-5'Br-PINACA**
- **MDMB-INACA**
- MDMB-BINACA**
- **CHO-4'Me-5'Br-FUBOXPYRA**
- **NMDMSB**
- **MDMB-5Me-INACA**
- **MDMB-ICA**
- MDMB-PICA**

CLASS-WIDE BAN ON SYNTHETIC CANNABINOIDS

UNODC Laboratory and Scientific Service Portals

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- NPS Data Visualisations
- Pharmacology
- Legal Responses
- Publications
- Global SMART Programme
- EWA Partners
- ICE-Portal
- NPS-Portal

May 2021- China: Announcement to place synthetic cannabinoids under generic control

BEIJING, China – May 2021: On 11 May 2021, the Office of China National Narcotics Control Commission (NNCA) announced to place synthetic cannabinoids under national control using a generic definition as well as additional 18 substances using an individual listing approach. The control measure will be effective as of 1st of July 2021. Details on the definition and substances listed have been included in the legal database of the UNODC Early Warning Advisory on NPS (EWA) under China (accessible here: China Generic Legislation).

Photo: Announcement of the Office of China National Narcotics Control Commission

Source: Office of China National Narcotics Control Commission

AP

U.S. News World News Politics Sports Entertainment Business Technology Health Science Oddities

China issues total ban on synthetic cannabinoids

May 11, 2021

cfsre | NPS DISCOVERY

DIY SYNTHETIC CANNABINOIDS

Home \ Cannabinoids \ ADB-BUTINACA PRECURSOR (SEMI-FINISHED)

ADB-BUTINACA PRECURSOR (SEMI-FINISHED)

$2,400.00 – $15,000.00

Since the finished product is already illegal in China, the laboratories there have found a solution and can provide us with a precursor to the good old adb butinaca.

Quantity

Choose an option

1 Add to cart

SKU: N/A

Category: Cannabinoids

You need:

1kg ADB-BUTINACA PRECURSOR (SEMI-FINISHED) – 3500$

3L DMF (CAS 68-12-2)

850g anhydrous potassium carbonate (CAS: 584-08-7)

680g of bromobutane (CAS: 109-65-9)

Instructions:

1. They were successively added into the reaction bottle;

2. The temperature was raised to 70-80℃ for 5h; after the reaction, it was cooled to room temperature.

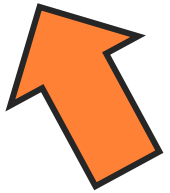
3. Prepare a bucket in advance and add 15L water;

4. Then pour the reaction solution into the bucket, cool to room temperature, filter the solid, wash the solid to neutral and dry.

DIY SYNTHETIC CANNABINOIDS

IMPORTANT NOTES:

Be very careful of imposters!! Our Email is only info@thegratefulmail.com If are you planning big order. Highly recommend to use PGP KEY always to be sure you are actually talking with us!! We are getting many questions about "which is your best cannabinoid?" It's hard to say. Some customers said "5BRO-ABB" and "5C-AKB-48" are very strong and great product. But some others do not like them. Please remember, we are not any kind of users. If you do not sure, we highly recommend you to make small order first. You also can order our semi-finished 5f-adb or semi-finished 5cl-adb and finish the product by yourself. It will be strong as the cannabinoids sold in China before the ban!

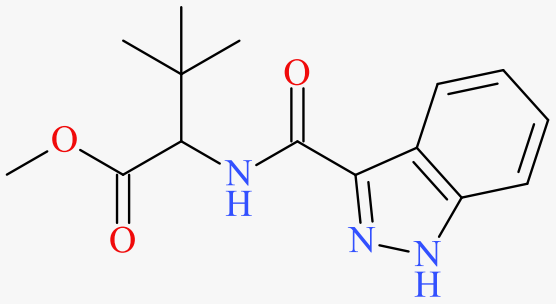


Now you can order 100 grams of our ADBB semi-finished and not only 1kg!
Now you can order 250 grams of our JWH-018 semi-finished and not only 1kg!

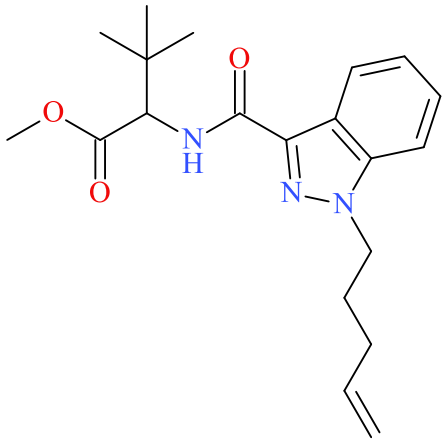
NEW UPDATE (24/09/2023)
4-FPO - back in stock!
5F-PiHP - new product!
2-Me-PVP - New product. Most similar to the original a-PVP!
Magical Mountain - TOP new OPIOID.

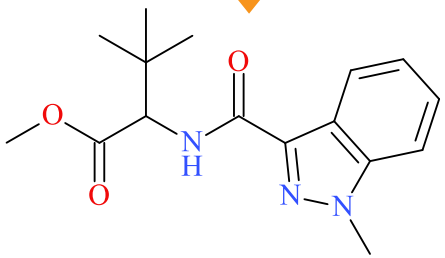
SYNTHETIC CANNABINOIDS PRECURSORS

MDMB-INACA



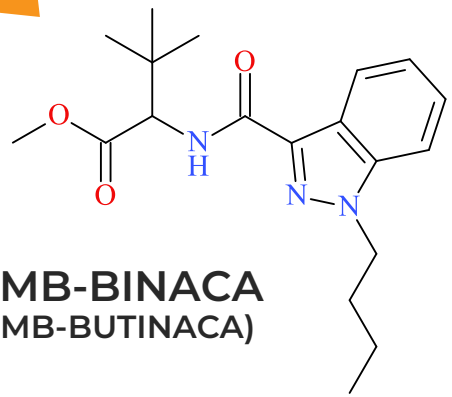
MDMB-4en-PINACA



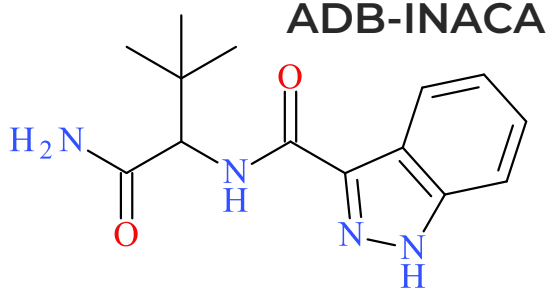


MDMB-???INACA ?

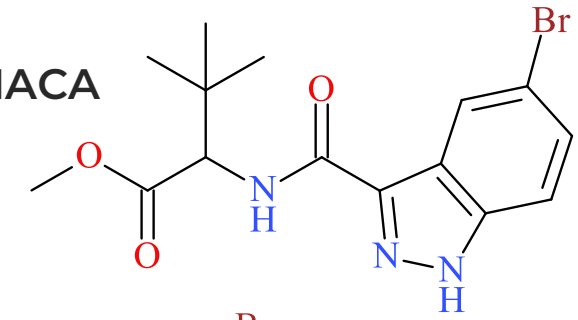
MDMB-BINACA
(MDMB-BUTINACA)

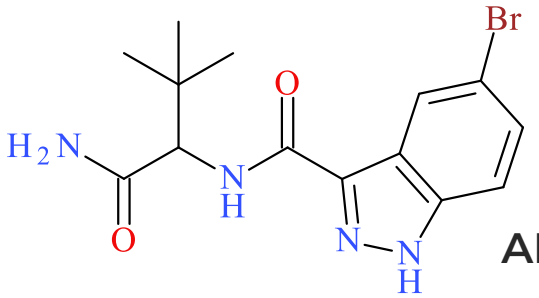


ADB-INACA



MDMB-5Br-INACA

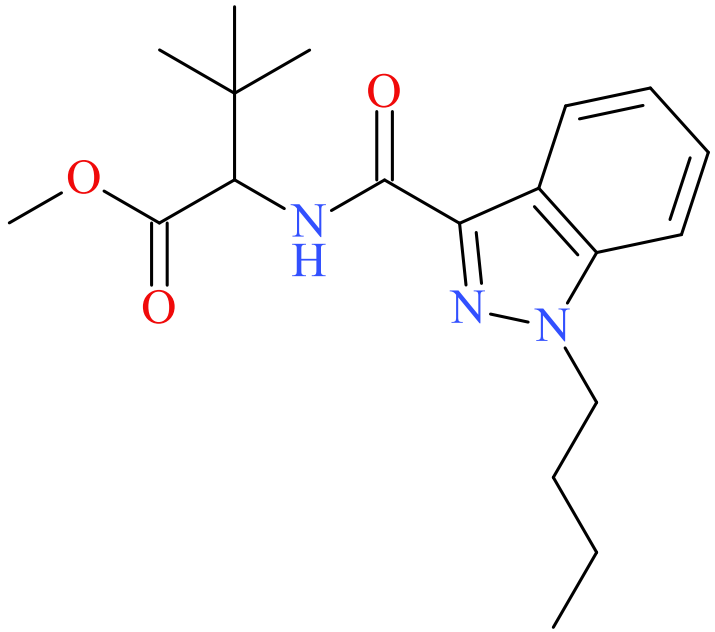




ADB-5Br-INACA

MDMB-BINACA (MDMB-BUTINACA)

- **First reported** → June 2023
- **Locations:**
  - United States
  - United Kingdom
- **Case Types:**
  - Suspected drug overdose
  - In-custody death
- **Toxicology:**
  - One case also contained MDMB-4en-PINACA
  - MDMB-BINACA 3,3-Dimethylbutanoic Acid
  - MDMB-BINACA Concentrations: 0.3 ng/mL and 0.6 ng/mL



XYLAZINE

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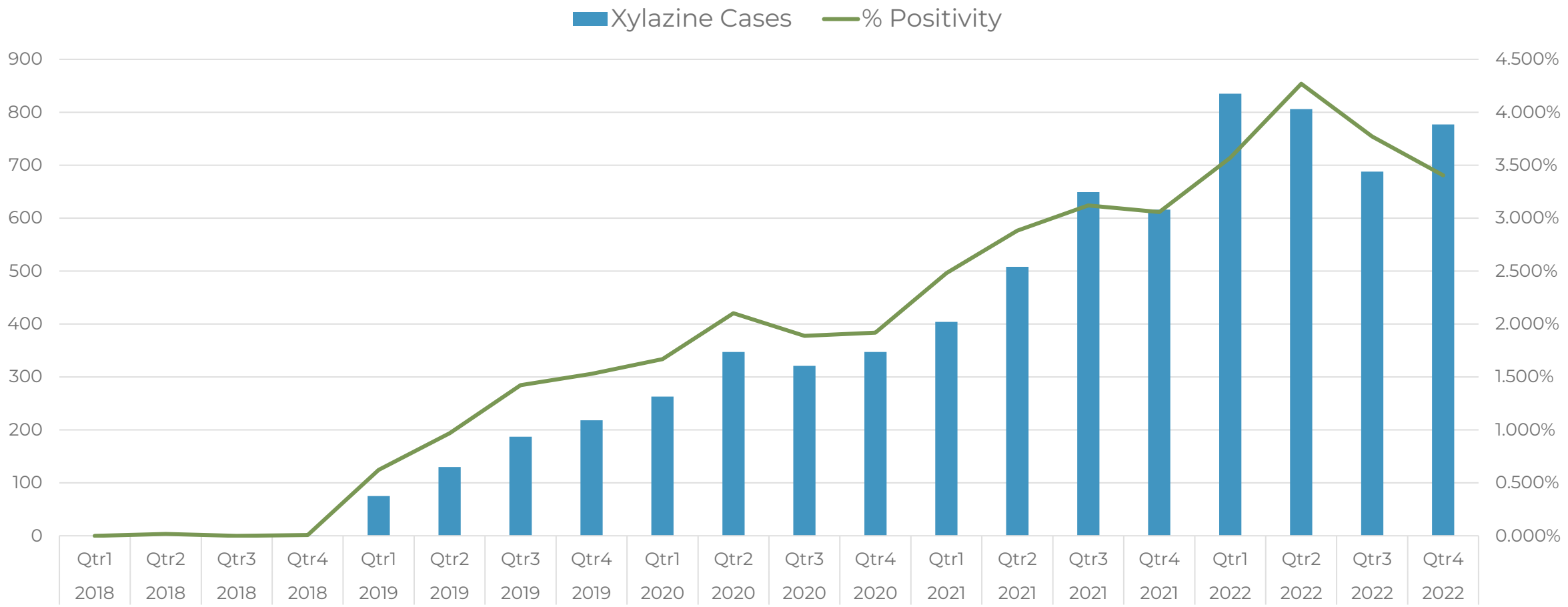
PREVALENCE OF XYLAZINE IN THE U.S.



*Data from NMS Labs / Not final numbers

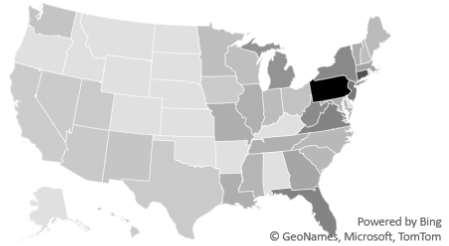
SPREAD OF XYLAZINE ACROSS THE U.S.

2020 Q1

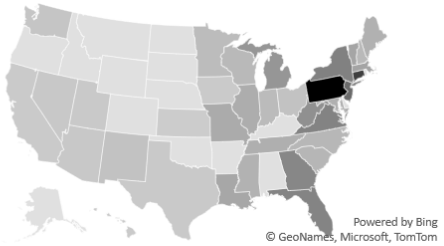
2020 Q2

2020 Q3

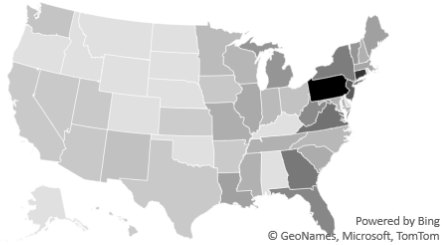
2020 Q4



2021 Q1



2021 Q2



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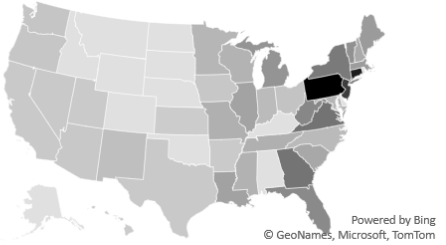

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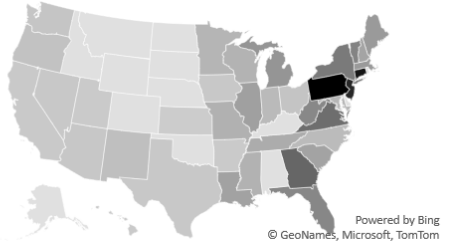

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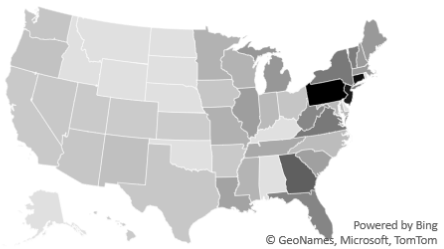

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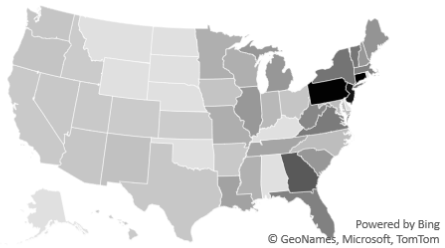

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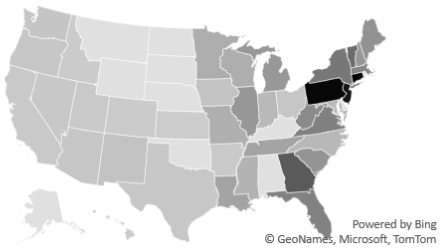

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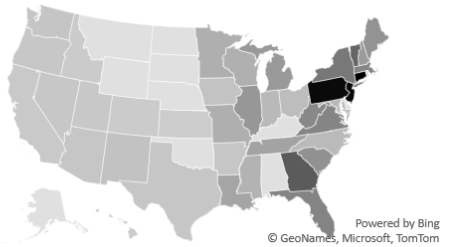


cfsre | NPS DISCOVERY

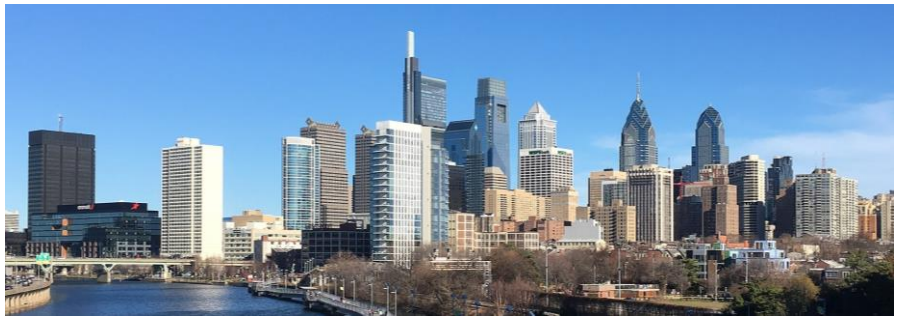
**Data from NMS Labs / Crude analysis with other necessary caveats*

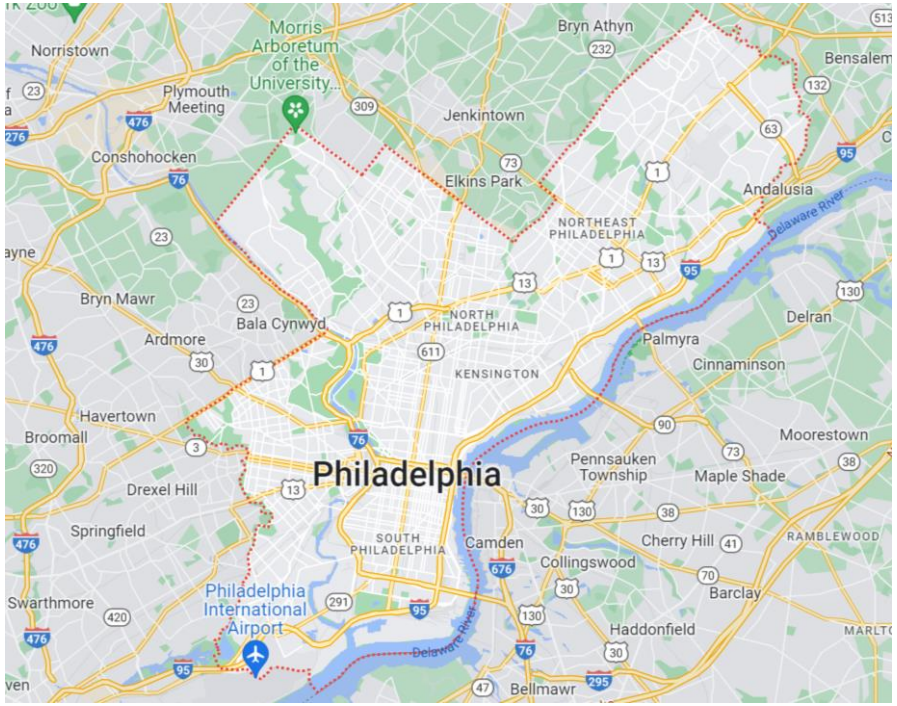
DRUG CHECKING SURVEILLANCE

cfsre | NPS DISCOVERY

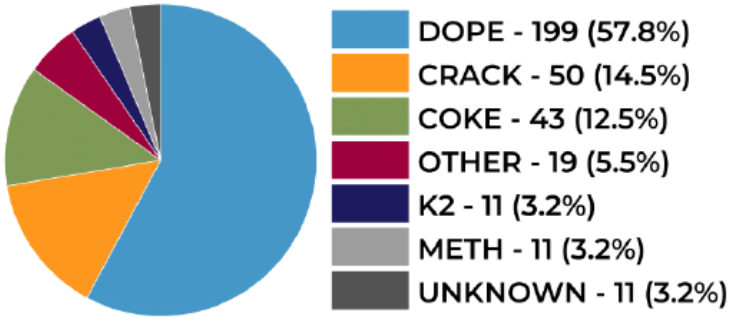
PHILADELPHIA & ITS DRUG SUPPLY

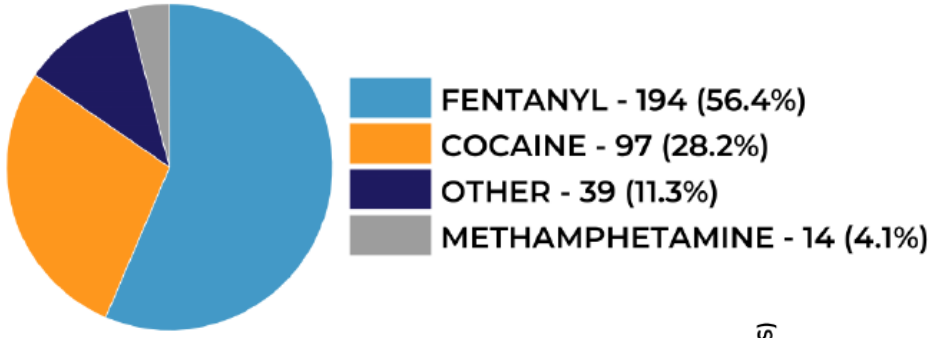
- Nestled in the center of the larger mid-Atlantic metropolitan region ("Northeast Corridor")
  - 6th largest city by population and 7th largest metro area
- **"Open air drug market"** (Kensington neighborhood)
- Drug markets → dope, crack/coke, meth, K2, etc.
- Continually changing and diverse drug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

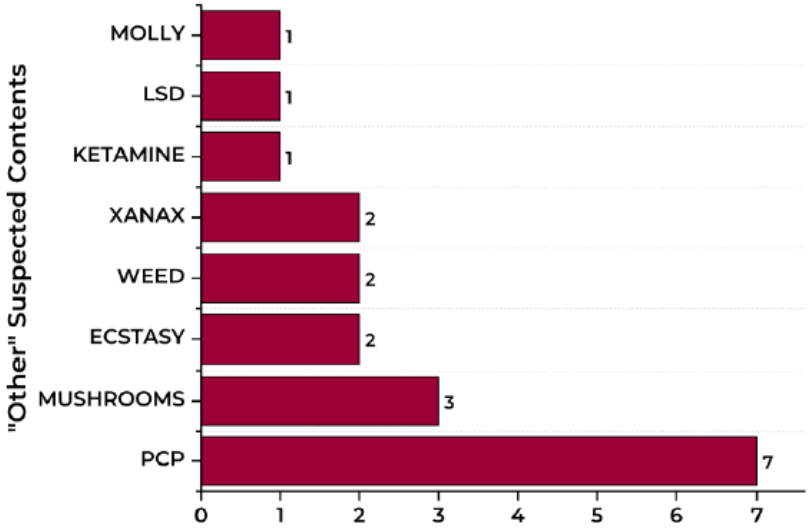


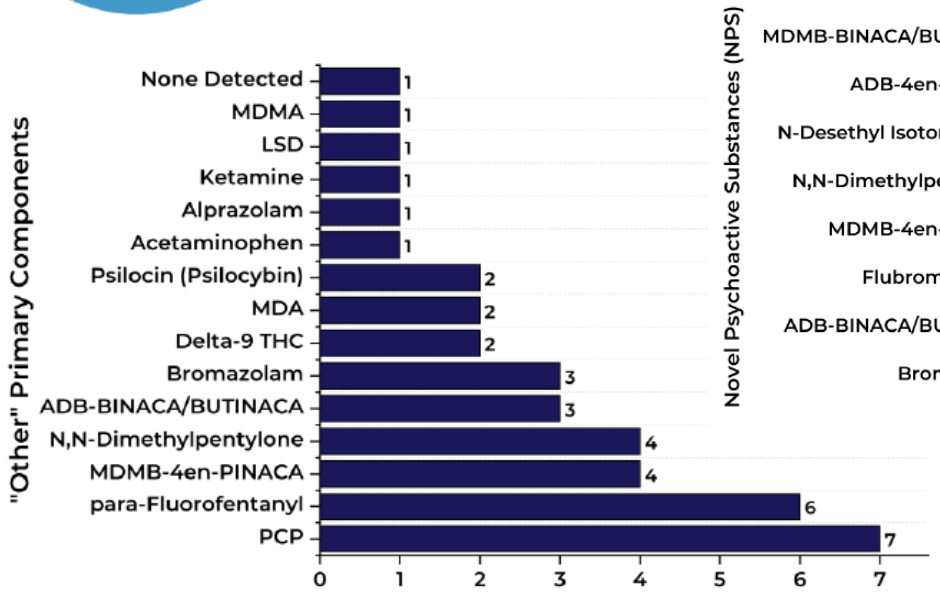


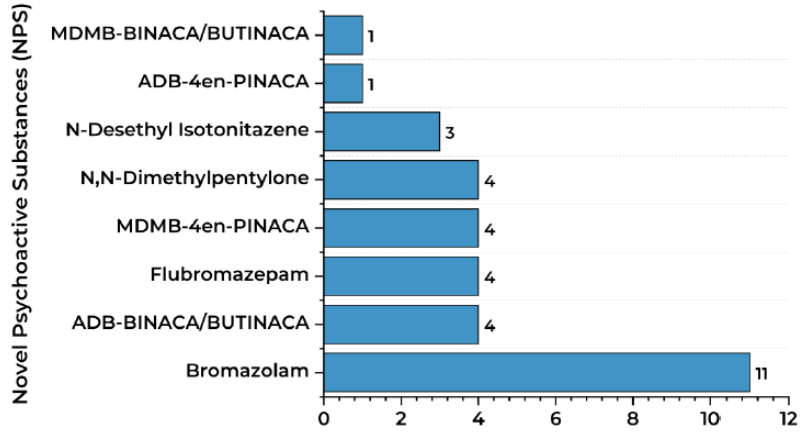
PDPH/CFSRE DRUG CHECKING



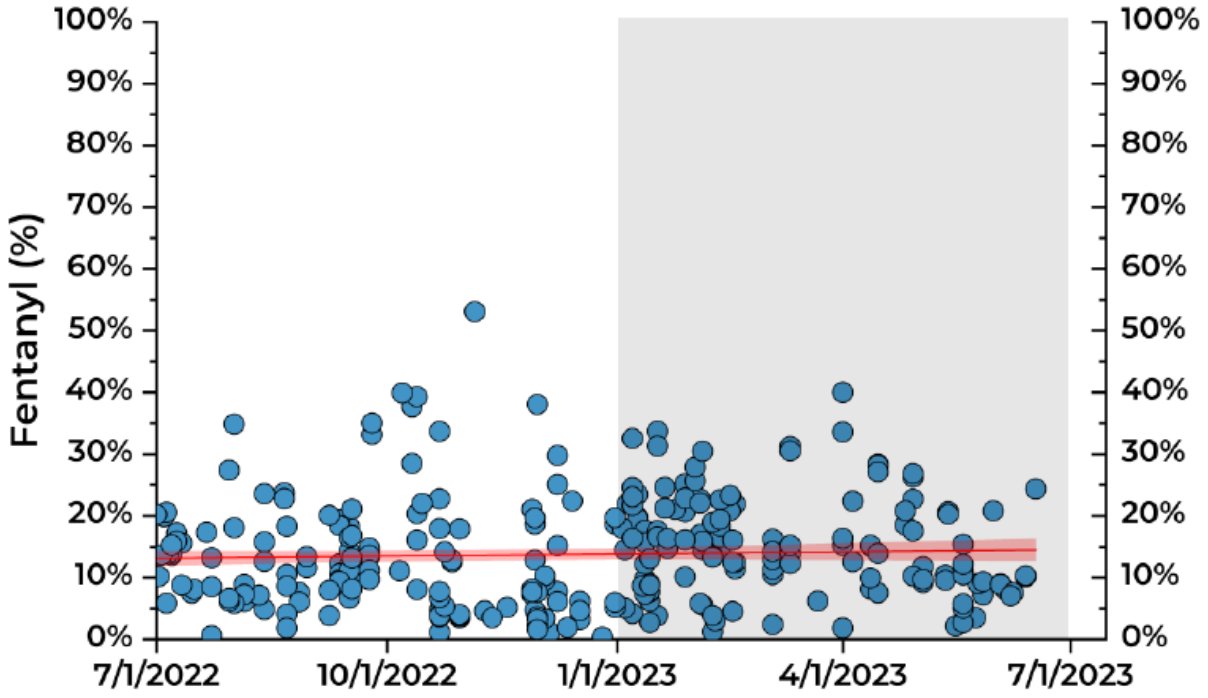


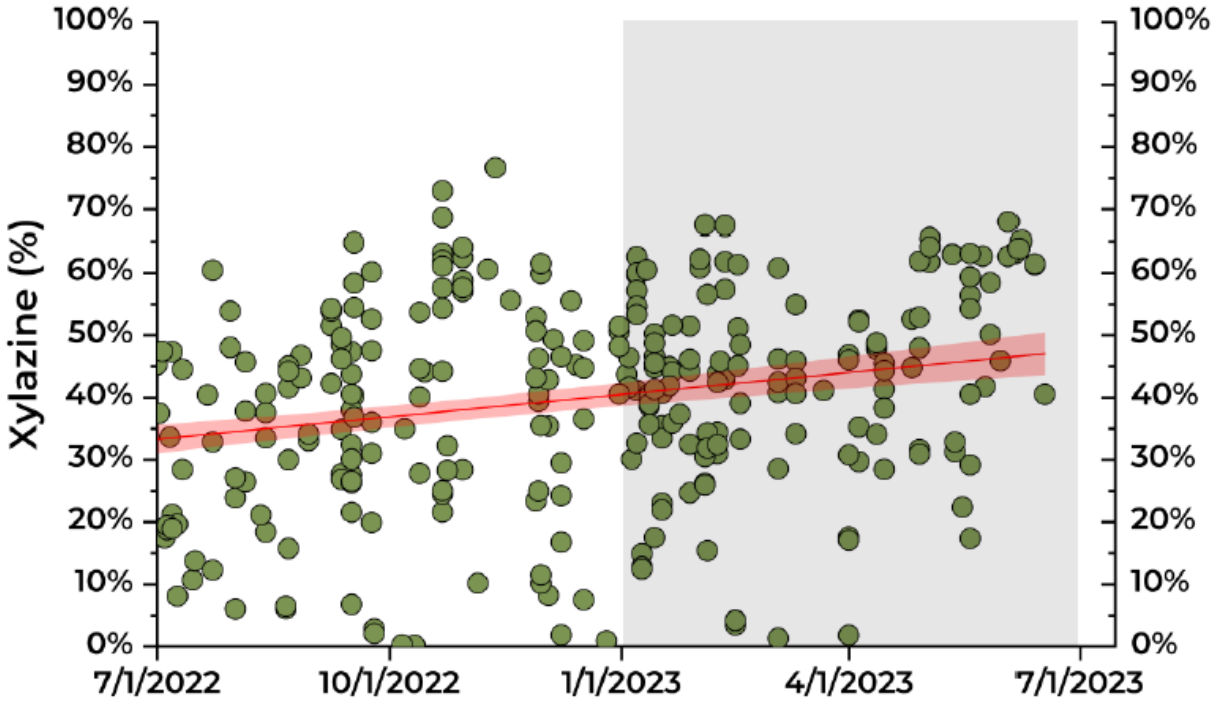




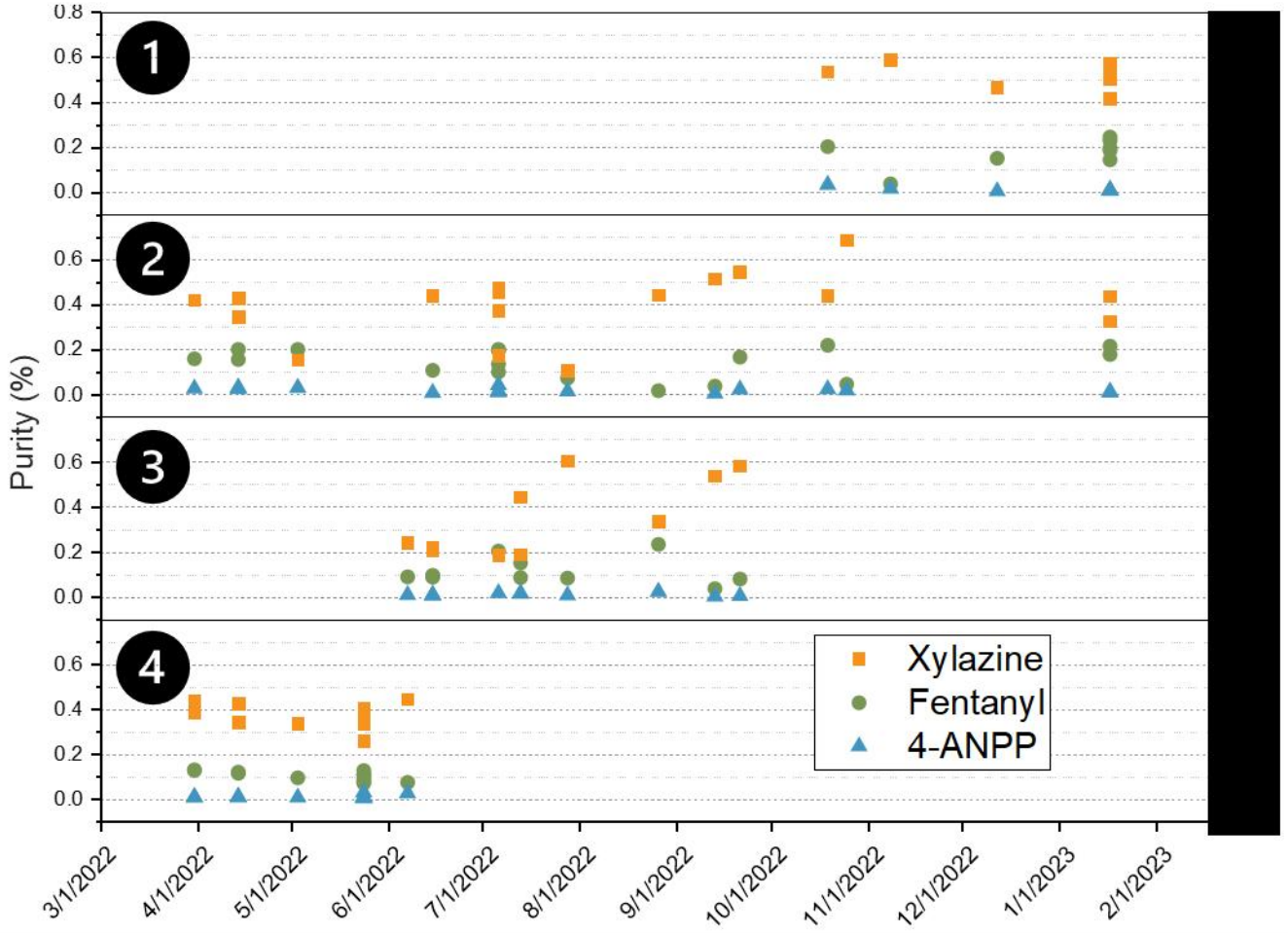


TEMPORAL CHANGES IN PURITY





LONGITUDINAL ASSESSMENT OF DRUG PRODUCTS



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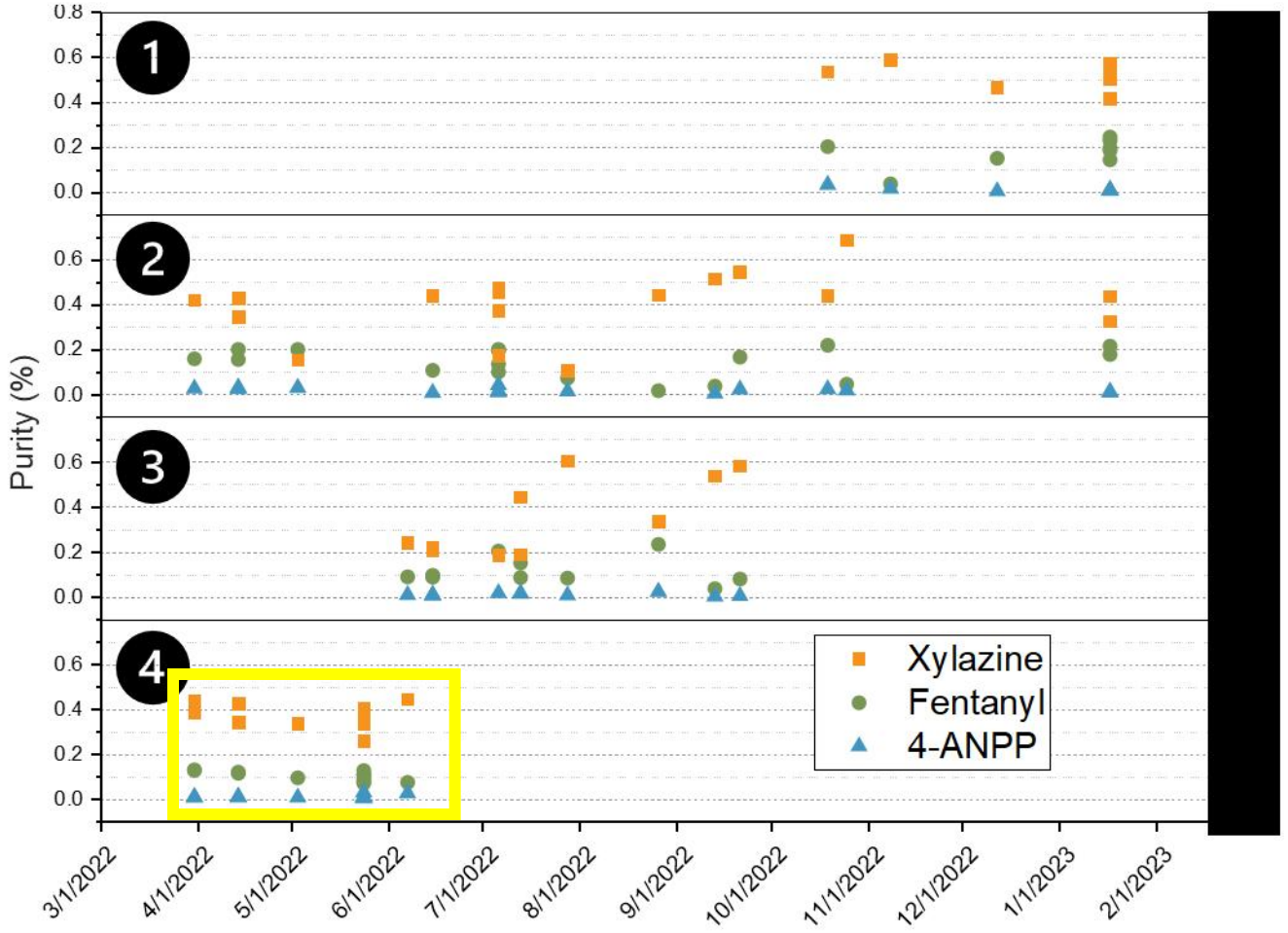

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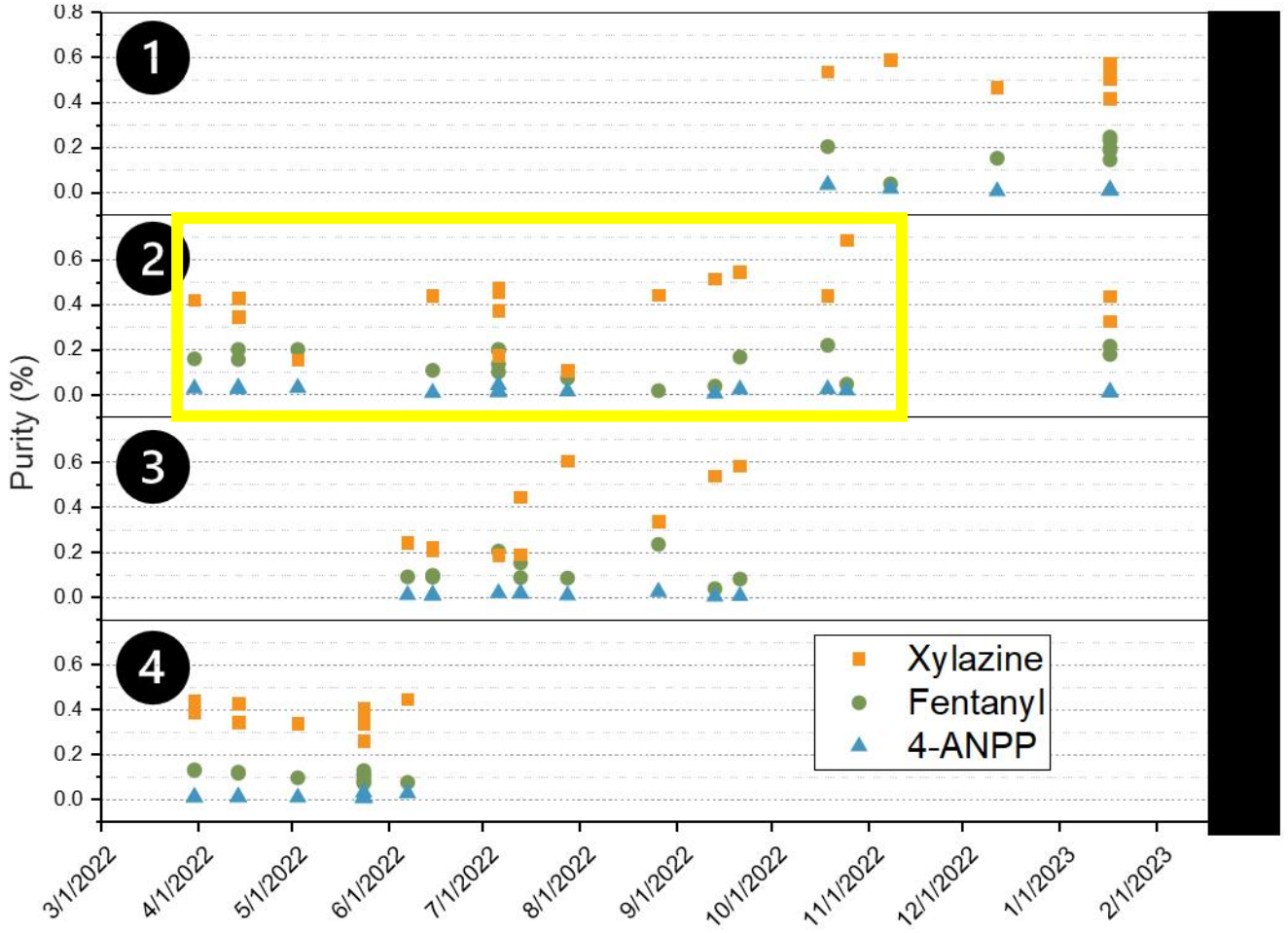

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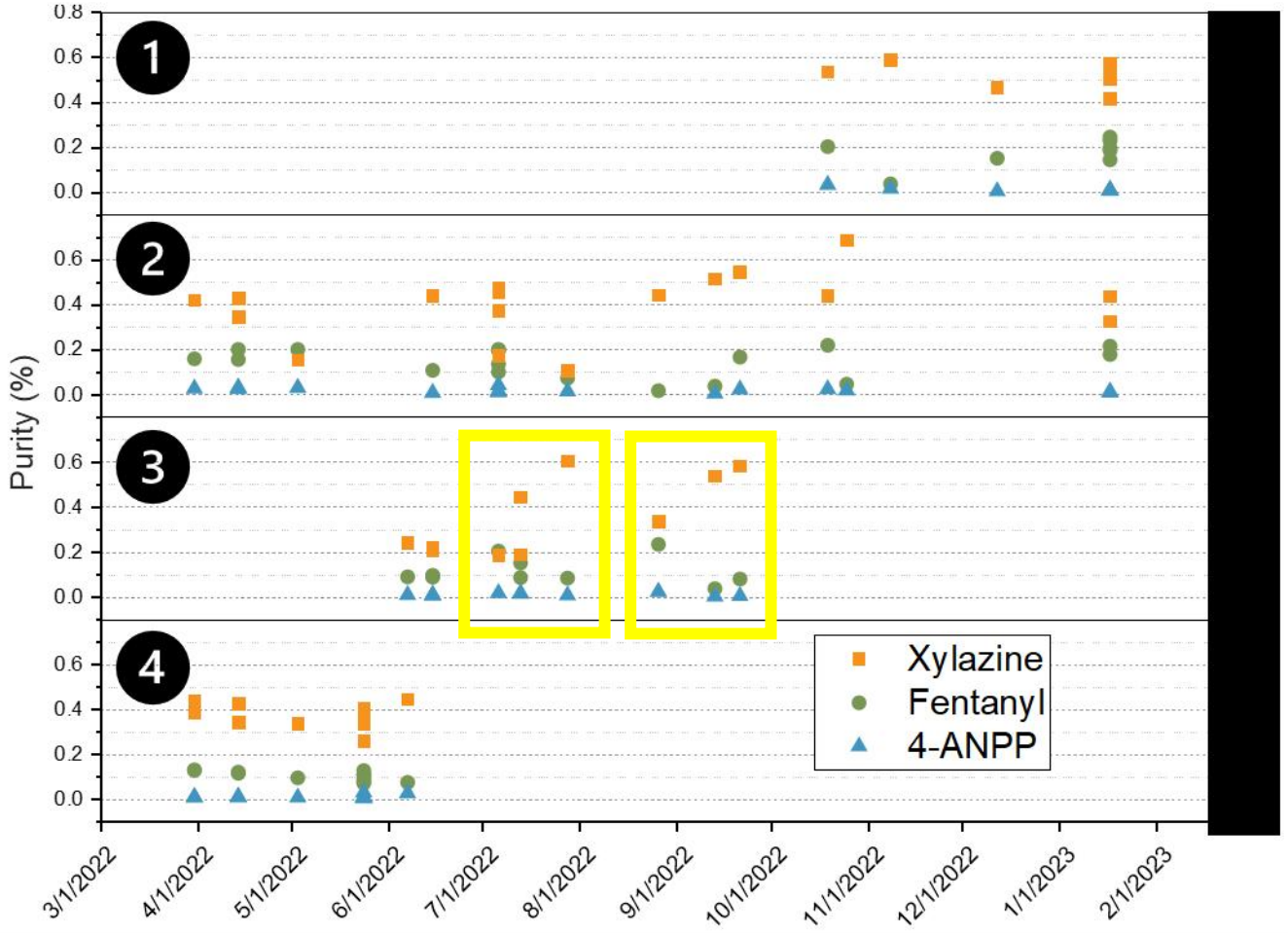


CASE EXAMPLES

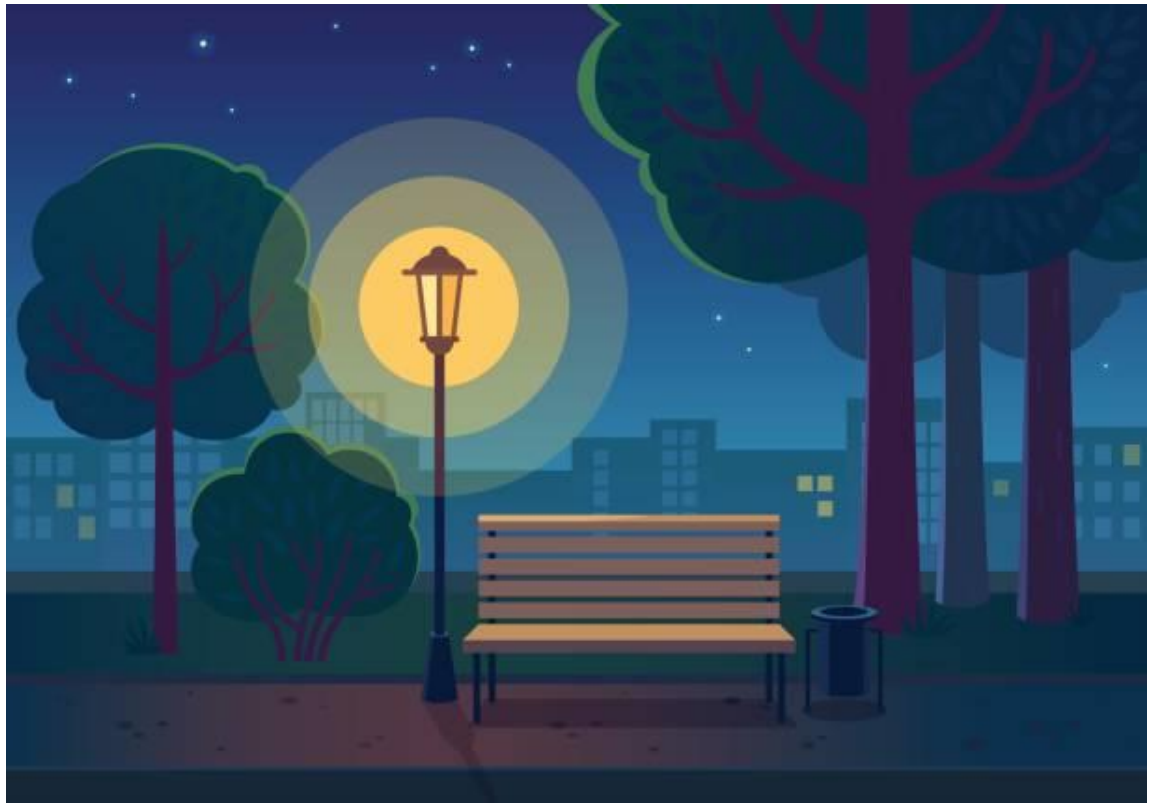
cfsre | NPS DISCOVERY

CASE #1

cfsre | NPS DISCOVERY

CASE #1 – HISTORY

- October 2021 (California)
- **Three individuals unresponsive in park**
  - Snorting suspected cocaine powder
- Two women purchased cocaine from a trusted dealer who sells “untainted” drugs
  - Used drugs the night prior without incident
- Met up with a guy who purchased more cocaine from unfamiliar dealer

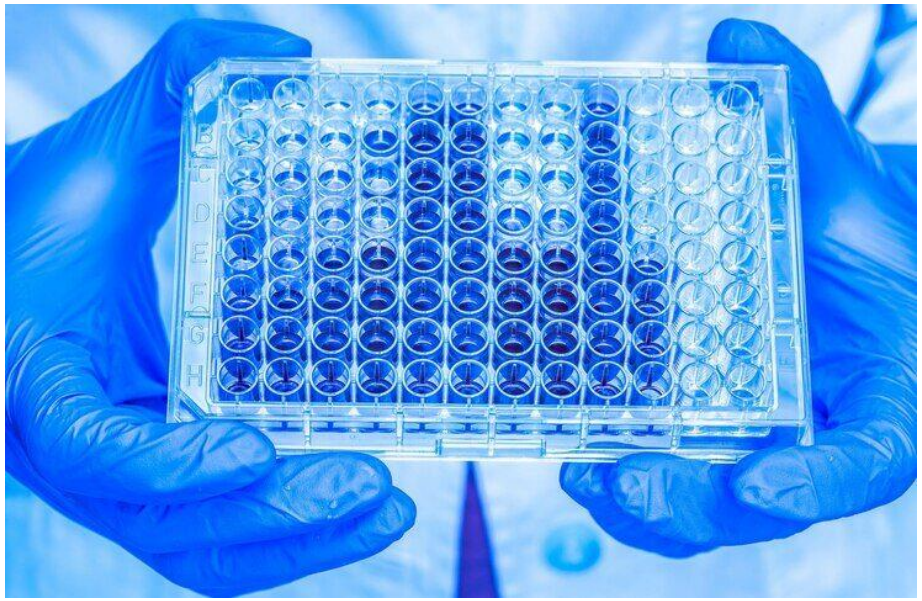


CASE #1 – HISTORY

- All were transported to the hospital
  - Two were revived with naloxone and survived
  - Third required advanced life support for persistent comatose state (suspected opioid OD)

- Hospital urine drug screen:
  - Positive → Amphetamine, cocaine, benzodiazepines
  - Negative → Opiates
  - **Not performed → Fentanyl**

- Patient died three days later
  - Body transferred to coroner's office
  - Hospital specimens transferred as well



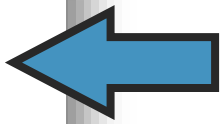
CASE #1 – CORONER'S OFFICE

- The body of the decedent was transported to the Santa Cruz County Sheriff-Coroner's Office
- The pathologist performed an external examination
- **Hospital admission blood and urine samples were sequestered for toxicological analysis**

CASE #1 – INITIAL TOXICOLOGY TESTING

- Specimens first sent to NMS Labs (Horsham, PA)
- Analysis performed by LC-TOF-MS, LC-QQQ-MS, and GC-MS
- **Results:**

Compound	Result	Units	Matrix Source
Naloxone	Positive	ng/mL	005 - Urine
Nicotine	Positive	ng/mL	005 - Urine
1-Hydroxymidazolam	>5000	ng/mL	005 - Urine
Benzoylecgonine	14000	ng/mL	005 - Urine
Cocaine	780	ng/mL	005 - Urine
Cocaethylene	610	ng/mL	005 - Urine
Amphetamine	300	ng/mL	005 - Urine
Methamphetamine	5400	ng/mL	005 - Urine
Fentanyl	63	ng/mL	005 - Urine
Norfentanyl	17	ng/mL	005 - Urine



- *Blood: Negative for fentanyl*

CASE #1 – TOXICOLOGY TESTING

- Specimens first sent to NMS Labs (Horsham, PA)
- Analysis performed by LC-TOF-MS, LC-QQQ-MS, and GC-MS

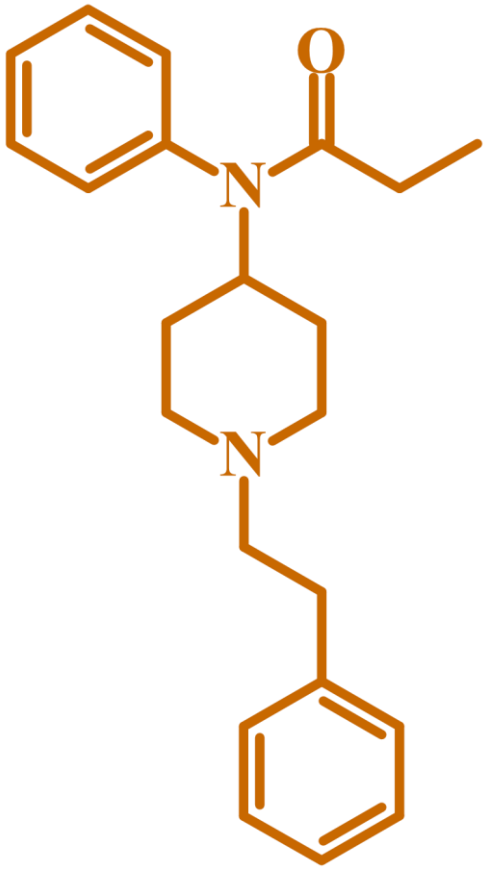
- **Results:** Fentanyl, methamphetamine, and cocaine (urine)

- Review of medical records → Fentanyl administered by medical staff
  - **Was the cocaine laced with fentanyl??**

- Other toxicology results are insufficient to explain the death
  - **What's the next step??**

CASE #1 – IS FENTANYL ALWAYS THE ANSWER?

- Fentanyl can be administered in the hospital for various reasons
  - Examples: Intubation or post-intubation sedation
- Handful of cases to date with this type of scenario
- Are there ways to distinguish hospital fentanyl vs. illicit fentanyl?
- ***Was fentanyl really the culprit in this case?***



CASE #1 – DRUG MATERIAL TESTING

- **Three white powders** sent to the CFSRE (Willow Grove, PA)
  - Sample preparation → Methanol dilution
  - Qualitative Analysis → GC-MS and LC-QTOF-MS

- **Results:**
  - Powder #1 – Cocaine (ziplock)
  - Powder #2 – Cocaine (ziplock)

(Examples of the drug evidence)

CASE #1 – DRUG MATERIAL TESTING

- **Three white powders** sent to the CFSRE (Willow Grove, PA)
  - Sample preparation → Methanol dilution
  - Qualitative Analysis → GC-MS and LC-QTOF-MS

- **Results:**
  - Powder #1 – Cocaine (ziplock)
  - Powder #2 – Cocaine (ziplock)
  - Powder #3 – **Etodesnitazene** (cellophane)

(Examples of the drug evidence)

CASE #1 – TOXICOLOGY TESTING

- Secondary toxicological analysis performed at the CFSRE for **etodesnitazene**
- Blood and urine samples were submitted
  - Sample preparation → Basic liquid-liquid extraction
  - Analysis → LC-QTOF-MS and LC-QQQ-MS
  - Quantitation → Standard addition (ISTD: fentanyl-D5).
- **Results:**

Results and Conclusions:

Exhibit #	Analyte	Concentration
1 (Blood)	Etodesnitazene	72 ng/mL
2 (Urine)	Etodesnitazene	68 ng/mL

CASE #1 – TOXICOLOGY TESTING

- Secondary toxicological analysis performed at the CFSRE for **etodesnitazene**
- Blood and urine samples were submitted
  - Sample preparation → Basic liquid-liquid extraction
  - Analysis → LC-QTOF-MS and LC-QQQ-MS
  - Quantitation → Standard addition (ISTD: fentanyl-D5).

- **Results:** Blood = 72 ng/mL, Urine = 68 ng/mL

- **Reference Blood Concentrations:**
  - Eleven MDI cases / **Mean = 33 ng/mL**, Median = 11 ng/mL, **Range = 0.53 to 120 ng/mL**

CASE #1 – REVIEW OF CASE FINDINGS

- **Case History:**
  - Three individuals ingested misrepresented “cocaine”
  - Two non-fatal overdoses, one fatal overdose
- **Drug Material Testing:**
  - Powder #3 → Etodesnitazene
- **Toxicology Testing:**
  - Blood & Urine → Etodesnitazene
- **Death Certification:**
  - Manner of Death – Accident
  - Cause of Death – Acute Etodesnitazene Intoxication

CASE #2

cfsre | NPS DISCOVERY

CASE #2 – JANUARY 2023

- **Circumstances:**
  - 57-year-old male, discovered unresponsive after taking shallow breaths
  - Possible drug paraphernalia was observed
  - CPR performed, pronounced dead on the scene

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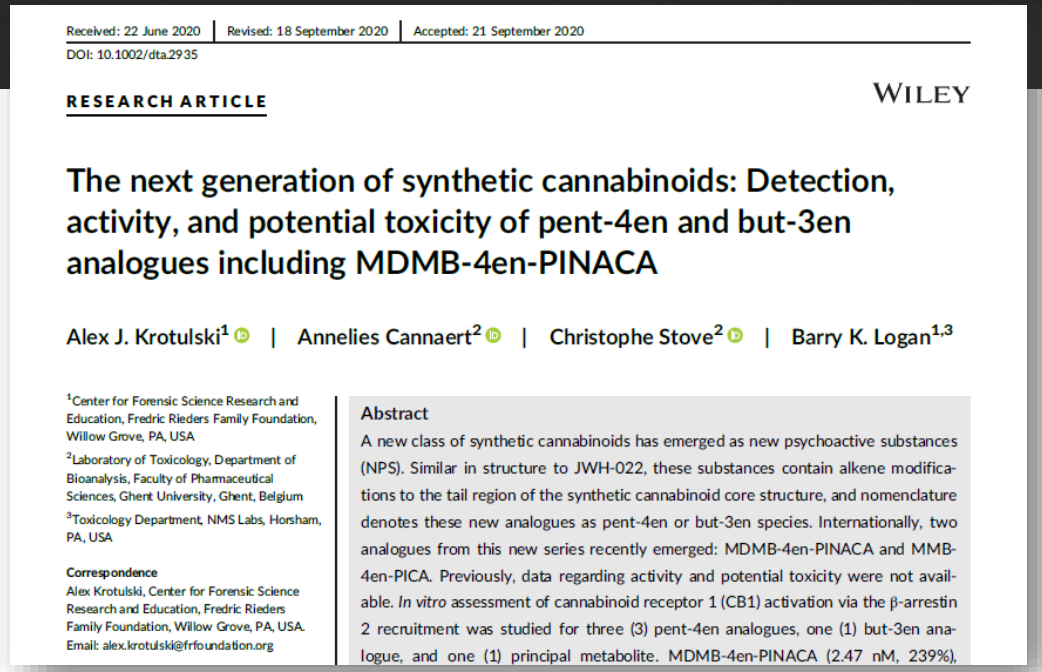
  - CPR performed, pronounced dead on the scene

- **Autopsy Findings:**
  - No evidence of significant antemortem injury
  - Mild coronary atherosclerosis and liver steatosis
  - Pulmonary edema and cerebral edema
- **Toxicology (Central Blood):**
  - Initial Toxicology – Naloxone, Lamotrigine (5.6), Aripiprazole (50), Citalopram (730)
  - **CFSRE – MDMB-4en-PINACA (0.75 ng/mL)**

CASE #2 – JANUARY 2023

- **“Old” synthetic cannabinoid**
  - First emerged in September 2019
  - Literature available – toxicology, cases, etc.



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RESEARCH ARTICLE

WILEY

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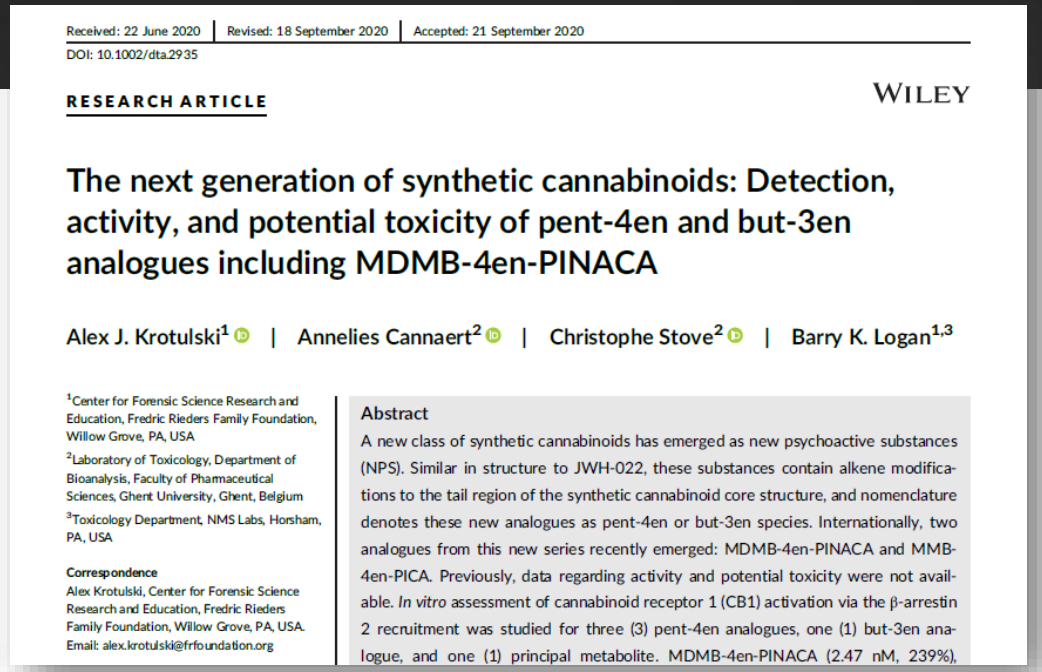
CASE #2 – JANUARY 2023

- "Old" synthetic cannabinoid
  - First emerged in September 2019
  - Literature available – toxicology, cases, etc.

- **Pharmacology** → potent CB1 agonist



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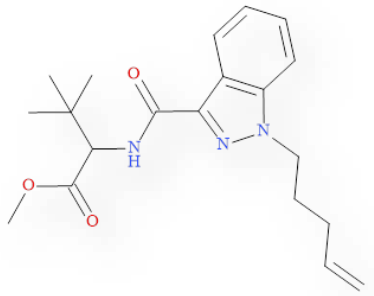
  - Literature available – toxicology, cases, etc.

- Pharmacology → potent CB1 agonist

- **What does the quantitative value mean?**
  - MDMB-4en-PINACA (0.75 ng/mL)
  - Cardiac blood
  - Known SCRA instability
  - No reference ranges



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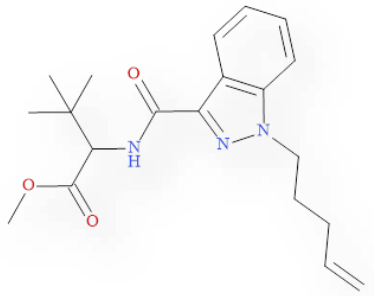

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- **Death Certificate:**
  - MOD – Accident
  - COD – MDMB-4en-PINACA toxicity

CASE #3

cfsre | NPS DISCOVERY

CASE #3 – HISTORY

- Male in 20s found dead on friend's deck
- Suspected drug overdose
- Drug paraphernalia found on scene
  - White oval shaped "IP204" pill
- Reported history of polydrug abuse
- No additional information provided

CASE #3 – MEDICAL EXAMINER'S OFFICE

- Full autopsy performed

- Autopsy findings:
  - External examination – unremarkable
    - No evidence of injury
  - Respiratory system:
    - Lungs: R 575 g and L 470 g
    - Dried frothy fluid on face
    - Mild amount of aspirated vomitus
  - Other organs → no abnormalities noted

- Femoral blood, urine, and vitreous fluid collected and sent for toxicological analysis

CASE #3 – INITIAL TOXICOLOGY TESTING

DRUG SCREENING

- **Ethanol and Volatiles (Blood):**
  - None detected
- **ELISA (Blood and Urine):**
  - Opioids – Present
  - Oxycodone – Present
  - Cannabinoids / THC – Present
- **GC-MS Screen (Urine):**
  - Cotinine – Present
  - Acetaminophen – Present
  - Oxycodone – Present

DRUG CONFIRMATION

- **LC-MS (Blood):**
  - Opioids – None detected
- **LC-MS (Blood):**
  - **Oxycodone – 41 ng/mL**
  - Fatal Reference – 100-8,000 ng/mL (Baselt)
    - Average: ~400 ng/mL
- **LC-MS (Blood):**
  - Acetaminophen – Present (<10 ug/mL)
- **LC-MS (Blood):**
  - THC-COOH – Present

CASE #3 – SECONDARY FORENSIC TESTING

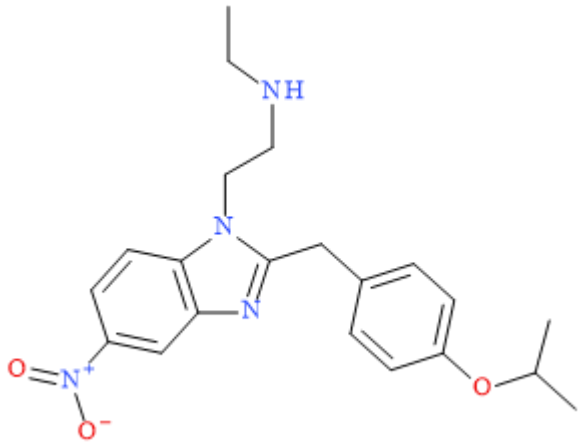
TOXICOLOGY RESULTS

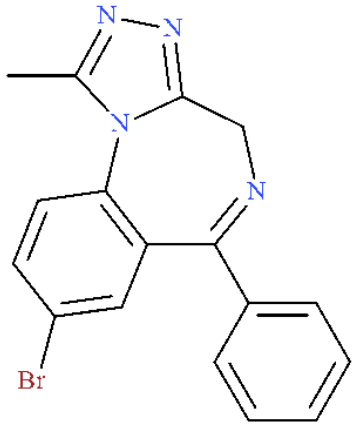
- **LC-QQQ-MS (Blood):**
  - – *N*-Desethyl Isotonitazene – 5.0 ng/mL
  - – Bromazolam – Positive (<5.0 ng/mL)
  - – Oxycodone – Positive *(@ 41 ng/mL)*
  - – Acetaminophen – Positive

- **LC-QQQ-MS (Urine):**
  - – *N*-Desethyl Isotonitazene – 1.7 ng/mL
  - – Bromazolam – Positive (<5.0 ng/mL)
  - – Oxycodone – Positive
  - – Noroxycodone – Positive
  - – Acetaminophen – Positive

CHEMISTRY RESULTS

- **GC-MS (Pills):**
  - – *N*-Desethyl Isotonitazene – Positive
  - – Bromazolam – Identified
  - – Acetaminophen – Positive
  - – ***[Counterfeit oxycodone tablets]***





CASE #3 – INTERPRETATION & DEATH CERTIFICATION

- **Toxicology Results:**
  - *N*-Desethyl Isotonitazene → novel opioid that is ~20 times more potent than fentanyl
  - Bromazolam → novel benzodiazepine suggested to be more potent than alprazolam
  - Polydrug use → Combined effects of opioids and benzodiazepines

- **Death Certification:**
  - Manner of Death:
    - Accident
  - Cause of Death:
    - Probable mixed drug intoxication (see toxicology)

Results and Conclusions:

Exhibit #	Analyte	Concentration
1 *(Blood)*	*N*-Desethyl Isotonitazene	5.0 ng/mL
1	Bromazolam	Positive (<5.0 ng/mL)
1	Oxycodone	Positive
1	Acetaminophen	Positive
2 *(Urine)*	*N*-Desethyl Isotonitazene	1.7 ng/mL
2	Bromazolam	Positive (<5.0 ng/mL)
2	Oxycodone	Positive
2	Noroxycodone	Positive
2	Acetaminophen	Positive
3 *(Pill)*	*N*-Desethyl Isotonitazene	Positive
3	Bromazolam	Identified
3	Acetaminophen	Positive

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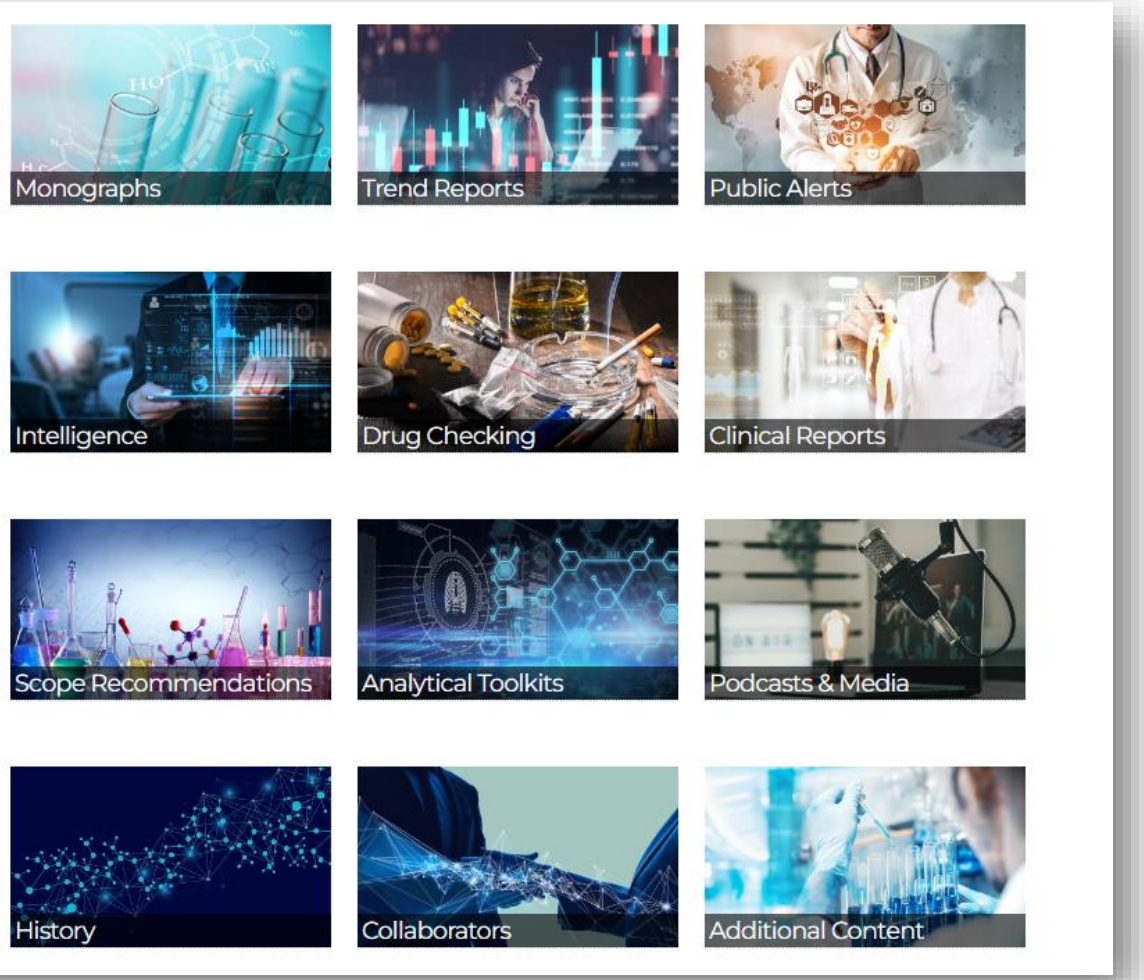

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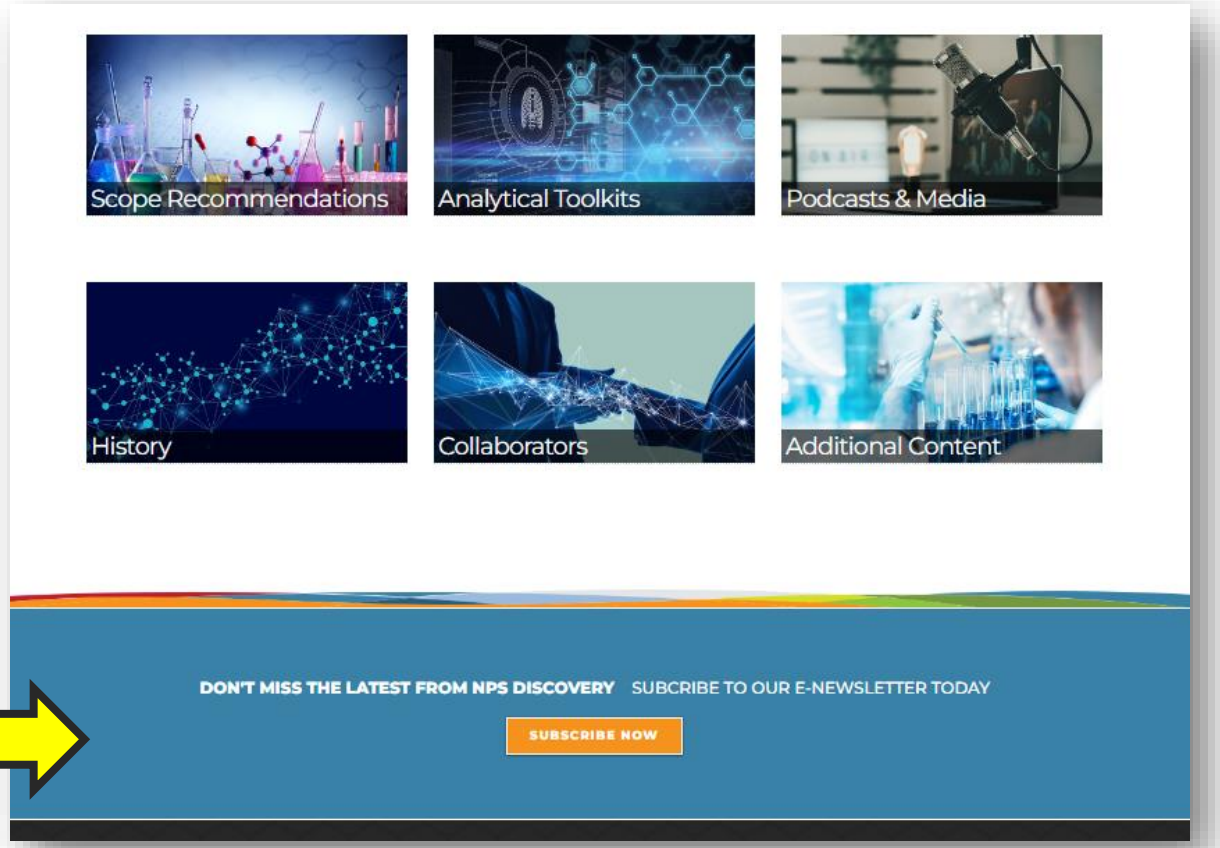

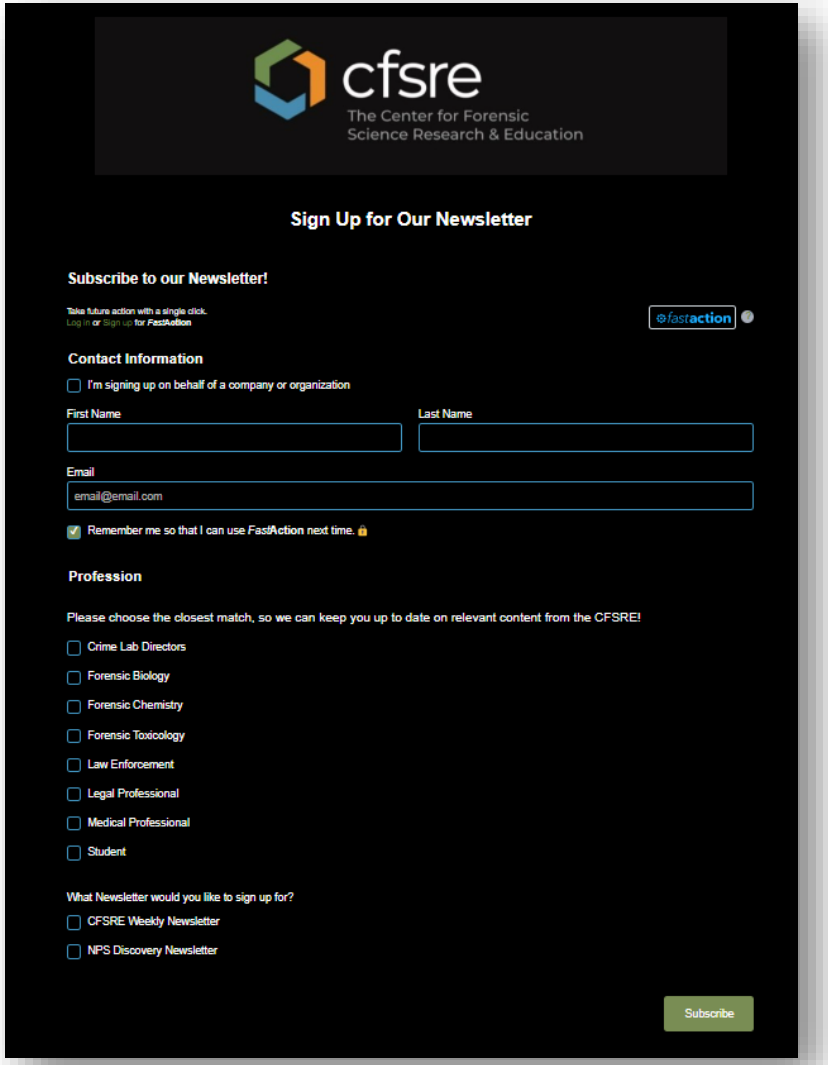

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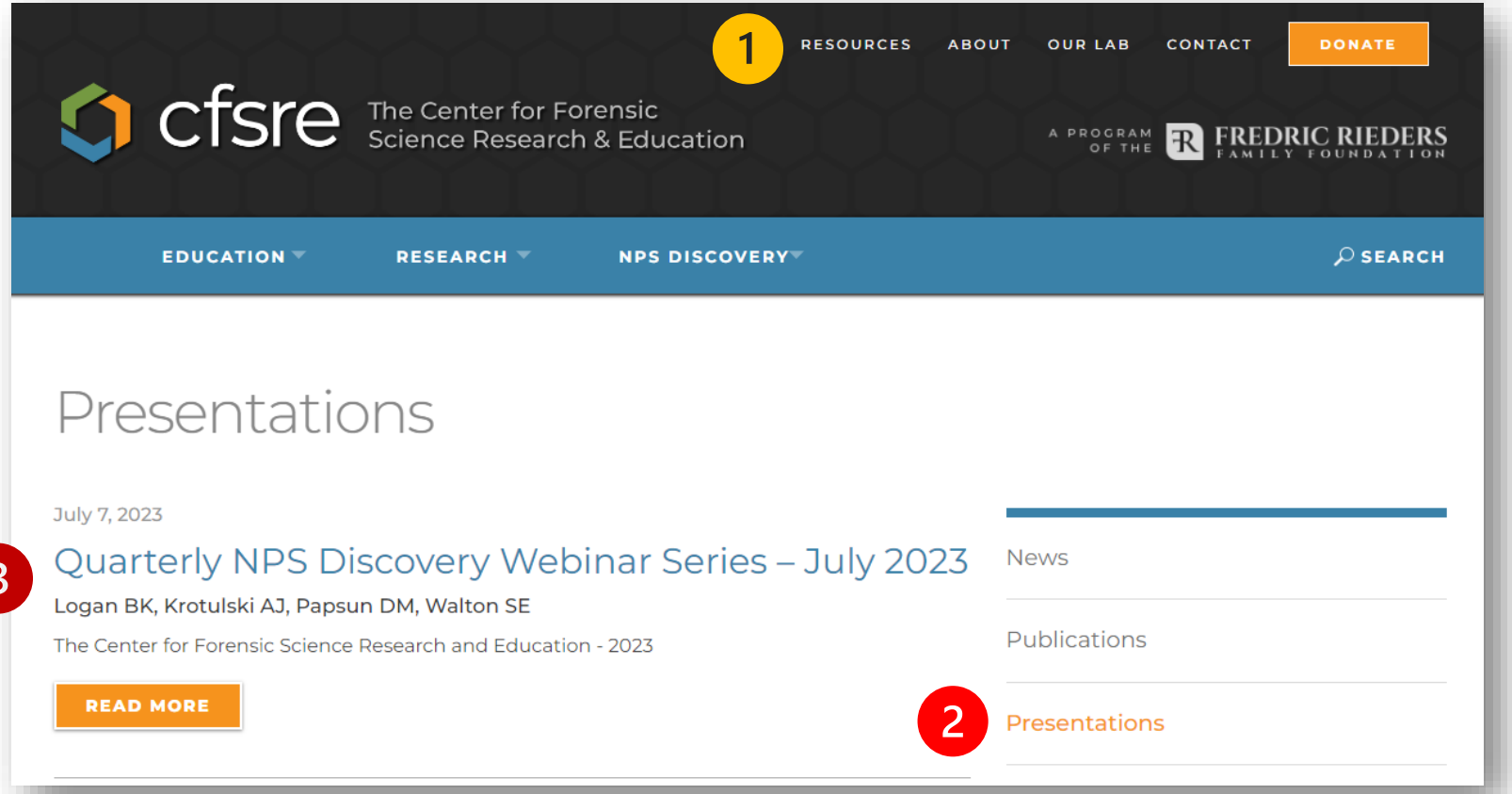

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SCAN ME

COLLABORATE WITH CFSRE & NPS DISCOVERY

- We accept toxicology samples and drug materials for NPS testing
- Contact Alex Krotulski for more information ▸ alex.krotulski@cfsre.org

BENEFITS OF TOXICOLOGY TESTING AT THE CFSRE:

- Perform routine testing for all NPS subclasses, including opioids, benzodiazepines, stimulants, hallucinogens, and cannabinoids.
- Assist medical examiners and coroners with determining cause of death when prior toxicology testing is negative or inconclusive.
- Analysis by state-of-the-art instrumentation and methodologies.
- Regularly updated, comprehensive in-house library database containing more than 1,000 drugs.
- Sample handling and analysis performed under chain of custody.
- Forensic quality data and individual reports generated per case.
- World-leading forensic toxicologists, chemists, and scientists.
- Laboratory follows forensic toxicology industry best practices.

TESTING CATALOG

NPS Opioids

Fentanyl Analogues, Nitazene Analogues, U-Series, AP-Series, Other Novel Opioids

NPS Benzodiazepines

Etizolam, Flualprazolam, Flubromazepam, Clonazolam, Bromazolam, Flubromazolam

NPS Stimulants

Empathogens, Cathinones, Amphetamines, Phenethylamines, Pyrrolidines

NPS Hallucinogens

Psychedelics, Dissociatives, PCP Analogues, Ketamine Analogues, LSD Analogues

Synthetic Cannabinoids

Classical, Indoles, Indazoles, Miscellaneous, Newly Emergent, & Many More!

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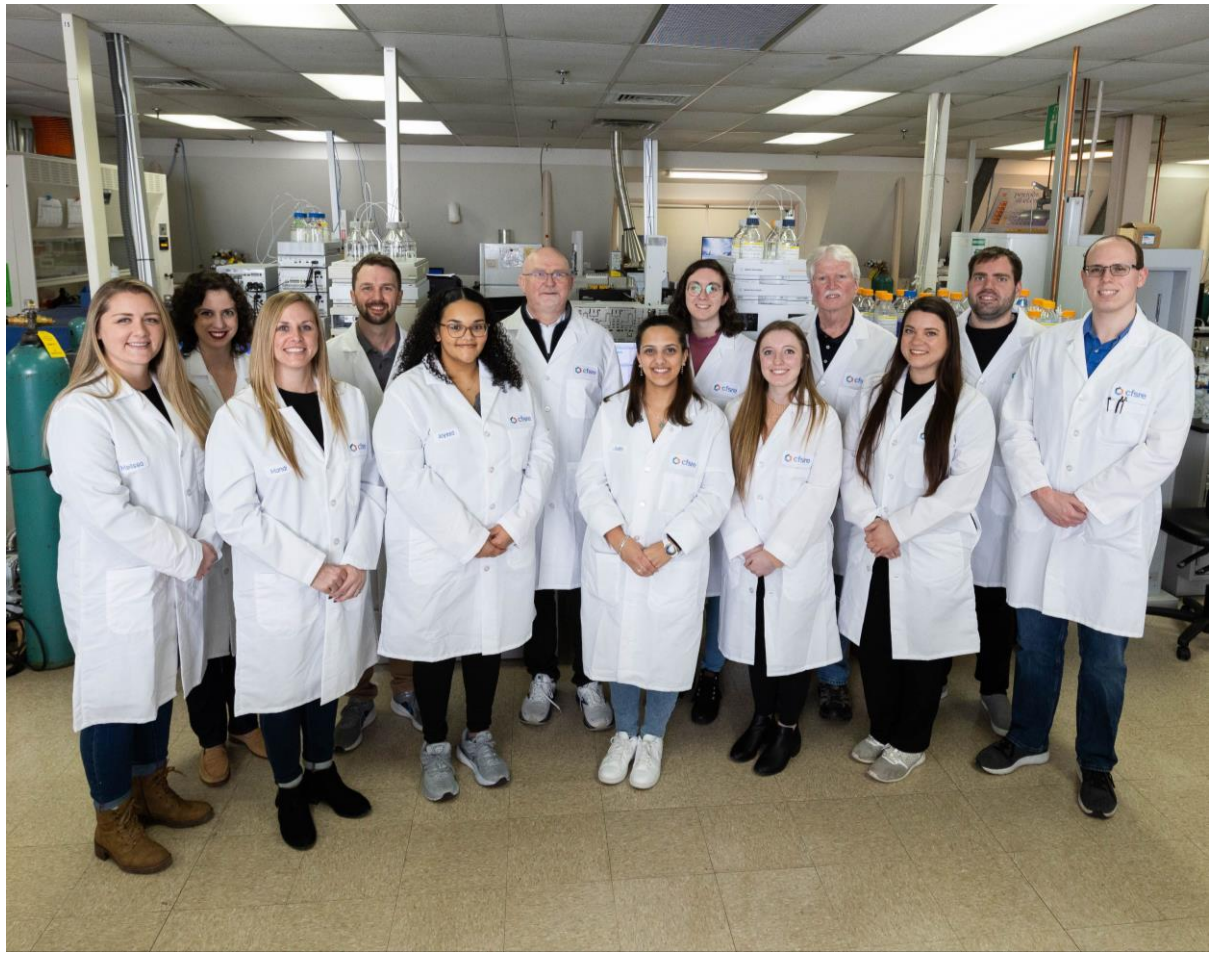
  - NIJ, CDC, NIH, etc.
- **Collaborators & Partners**
  - Forensic
  - Clinical
  - Medical Examiners
  - Coroners
  - Crime Labs
  - Etc.



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THANK YOU! QUESTIONS?

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