Adulterants: Lessons in History and Current Trends

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Disclosure Information

- JoAn Laes, MD
  - No Disclosures
- Daniel J. Sessions, MD, FACMT, FAAEM
  - No Disclosures
- Lewis S. Nelson, MD, MBA
  - No Disclosures
- Benjamin Swart, MD
  - No Disclosures

Learning Objectives

- Describe the recent epidemiological changes in the prevalence of adulterants and contaminants in the illicit drug supply as well as historical trends.
- Describe the pharmacology and toxicology of common adulterants and contaminants in illicit drugs.
- Identify strategies for bedside clinical and laboratory diagnosis of the presence of an unexpected adulterant or contaminant.
- Describe current strategies for community-level recognition and mitigation of adulterants and contaminants in illicit drugs.

“There is No New Thing Under the Sun”

600 AD
Ancient Rome
Colica pictonum
Lead sweetening &
preserving sour wine

1920-1930
Prohibition
Methanol, Lead
Diethyl ether, bromine
Formaldehyde

1800s
Opium Wars
Brick dust, poppy husk, ash
bulking
Lead acetate to cover taste

Today
Xylazine
Novel benzos
Fentanyl analogues
… tomorrow?

- Eisinger J. Lead and wine. Eberhard Gockel and the colica Pictonum. *Med Hist*. 1982;26(3):279-302.
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- Lovell, Julie. *The Opium War*. Harry N. Adams; 2018.
- Blum, Deborah. *The Poisoner’s Handbook*. Penguin Press; 2010.
- Alcohol as Medicine and Poison – Prohibition: An Interactive History. Accessed January 20, 2024. https://prohibition.themobmuseum.org/the-history/the-prohibition-underworld/alcohol-as-medicine-and-poison/

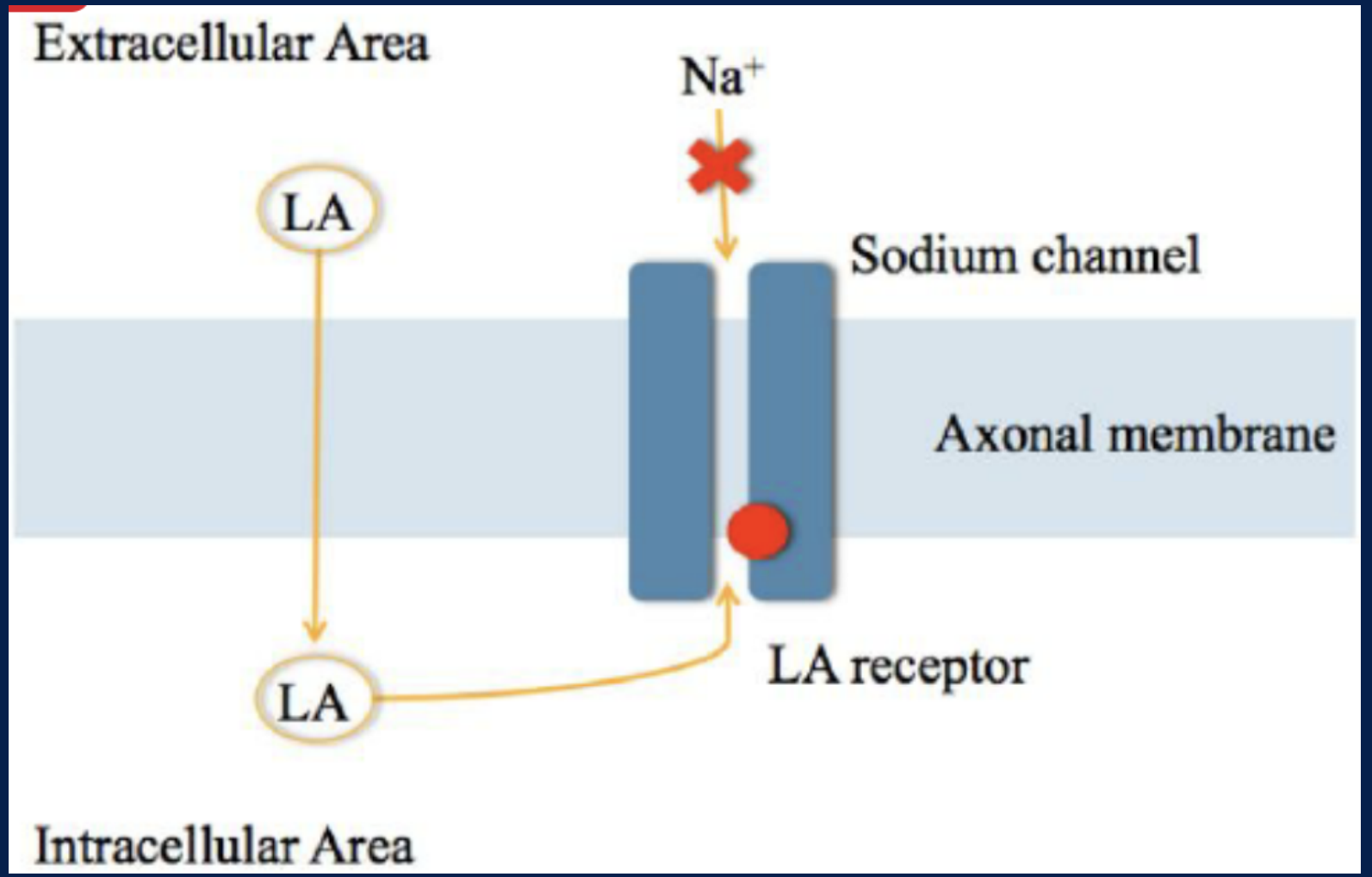
Definitions

- **Adulterant**
  - Pharmacologically active substance added to enhance or mimic the effect of the expected substance.
- **Contaminant**
  - Pharmacologically active, inert, or biologic substances unintentionally added during the manufacturing process.
- **Diluent**
  - Pharmacologically inactive substances intentionally added to increase bulk.

Intent

Adulterants, Contaminants and Co-occurring Substances in Drugs on the Illegal Market in Canada (CCENDU Bulletin) | Canadian Centre on Substance Use and Addiction. Accessed January 19, 2024. https://www.ccsa.ca/adulterants-contaminants-and-co-occurring-substances-drugs-illegal-market-canada-ccendu-bulletin

Local Anesthetics



https://www.researchgate.net/figure/Mechanism-of-action-of-local-anaesthetics_fig1_283724335

Local Anesthetics

June 2023

Local Anesthetics (Lidocaine and other 'Caines):
Toxic Adulterants Found in Illicit Street Drugs

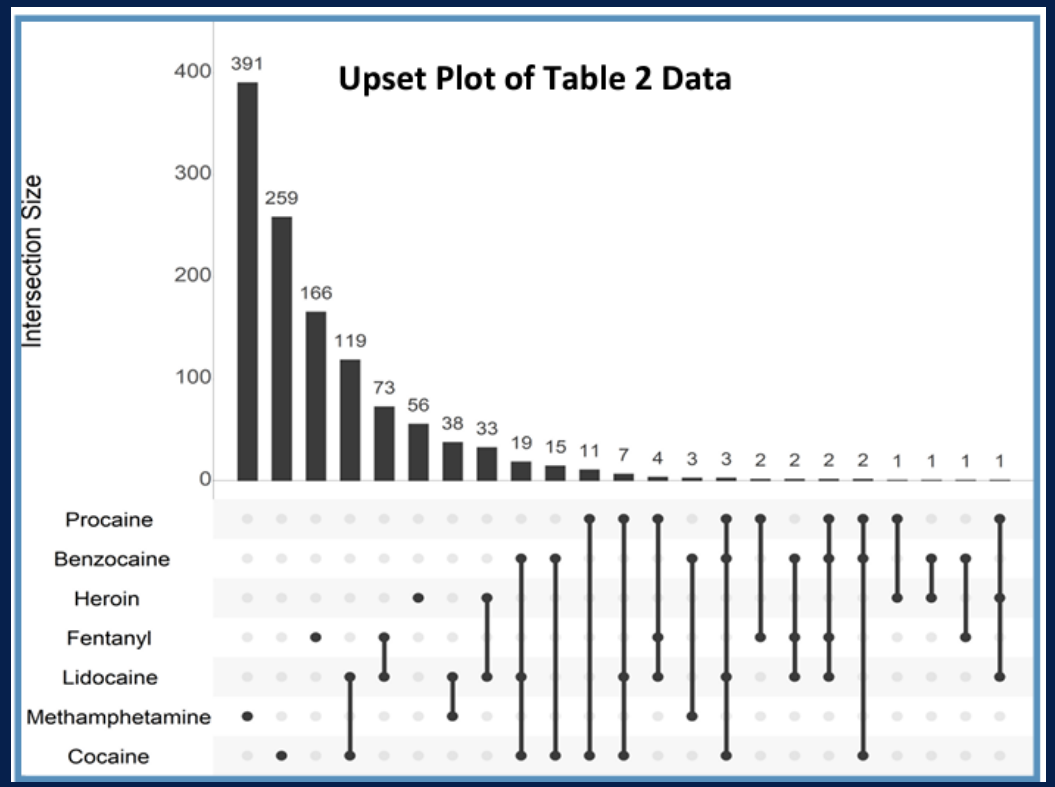


Table 2: Occurences of drugs in combination with LA compounds in CFSRE's Seized Drug Testing in the US (2016 - 2021; n = 2151)

Combination	Observations
Cocaine without LA	259
Cocaine, Lidocaine	119
Cocaine, Benzocaine, Lidocaine	19
Cocaine, Benzocaine	15
Cocaine, Procaine	11
Cocaine, Lidocaine, Procaine	7
Cocaine, Benzocaine, Lidocaine, Procaine	3
Cocaine, Benzocaine, Procaine	2
Fentanyl without LA	166
Fentanyl, Lidocaine	73
Fentanyl, Lidocaine, Procaine	4
Fentanyl, Benzocaine, Lidocaine	2
Fentanyl, Benzocaine, Lidocaine, Procaine	2
Fentanyl, Procaine	2
Fentanyl, Benzocaine	1
Heroin without LA	56
Heroin, Lidocaine	33
Heroin, Benzocaine	1
Heroin, Lidocaine, Procaine	1
Heroin, Procaine	1
Methamphetamine without LA	391
Methamphetamine, Lidocaine	38
Methamphetamine, Benzocaine	3

https://www.cfsre.org/nps-discovery/public-alerts/local-anesthetics-lidocaine-and-other-caines-toxic-adulterants-found-in-illicit-street-drugs#:~:text=While%20lidocaine%20is%20the%20LA,tetracaine%2C%20mepivacaine%2C%20and%20bupivacaine.

Local Anesthetics

- Reasons
  - Ease pain of injection
  - Add mass
  - Enhance euphoric effect

Local Anesthetics

Adverse Effects

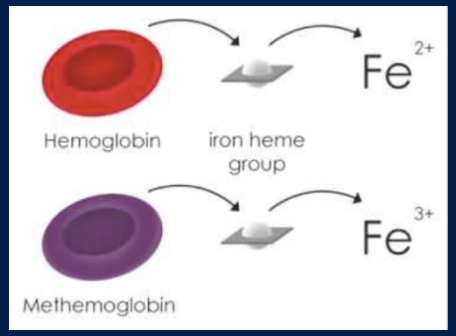
- Hypotension

- Seizure

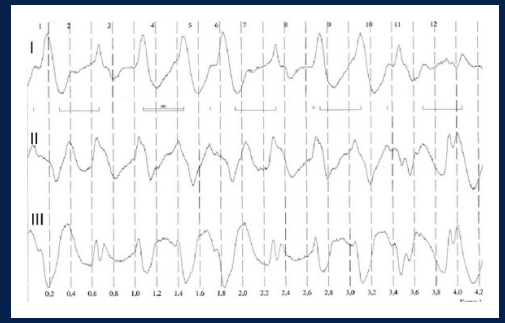
- Bradycardia

- Myocardial Depression

- Methemoglobinemia



- Arrhythmia



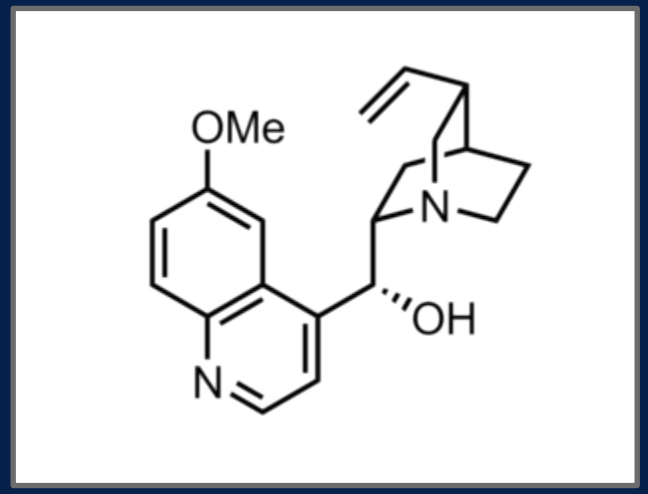
https://coreem.net/core/methemoglobinemia/; https://myheart.net/articles/what-is-heart-failure-everything-you-need-to-know/; https://en.wikipedia.org/wiki/Hypotension

Local Anesthetics

- Treatment
  - Supportive care
  - Sodium bicarbonate for arrhythmias

Quinine

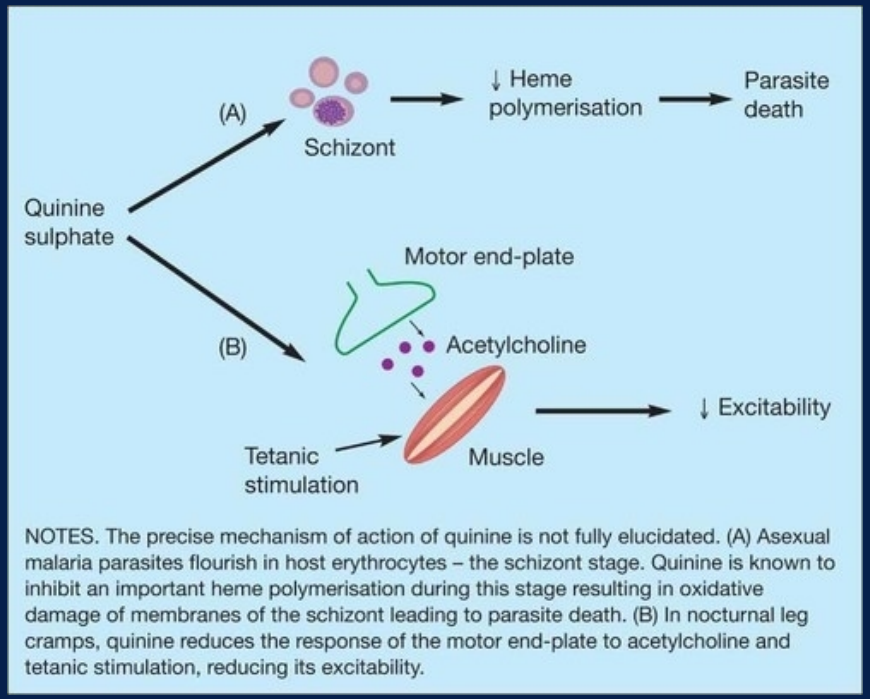
- Naturally-occurring alkaloid derived from the bark of the Cinchonca tree that grows in South America
- Bitter tasting white powder



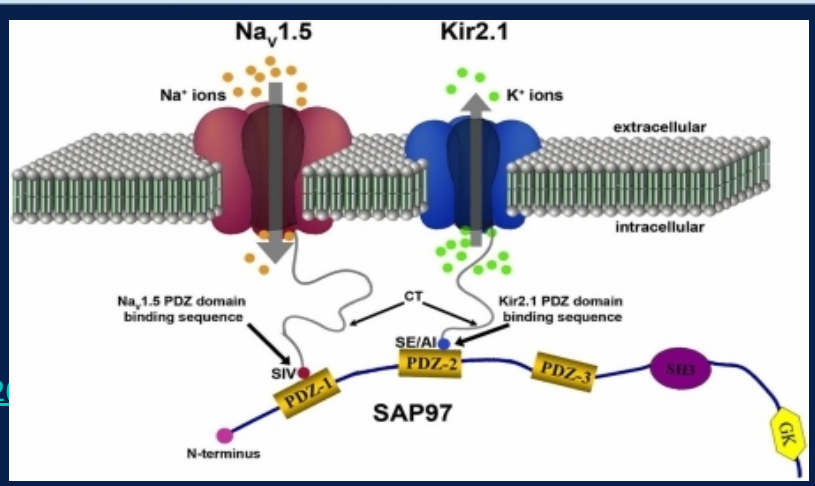
https://phys.org/news/2018-10-peru-danger-national-cinchona-tree.html;
https://en.wikipedia.org/wiki/Quinine

Quinine

- Anti-malarial
- Anti-pyretic
- Analgesic
- Skeletal Muscle Relaxant
- Smooth Muscle Relaxant
- Sclerosing agent
- Oxytocic
- Local anesthetic

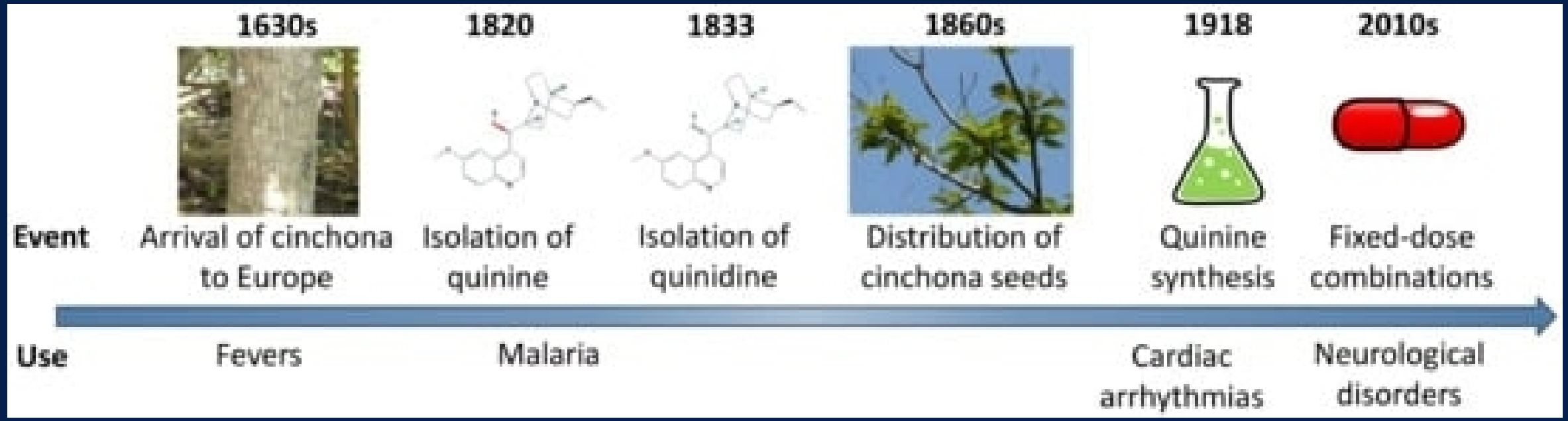


NOTES. The precise mechanism of action of quinine is not fully elucidated. (A) Asexual malaria parasites flourish in host erythrocytes – the schizont stage. Quinine is known to inhibit an important heme polymerisation during this stage resulting in oxidative damage of membranes of the schizont leading to parasite death. (B) In nocturnal leg cramps, quinine reduces the response of the motor end-plate to acetylcholine and tetanic stimulation, reducing its excitability.

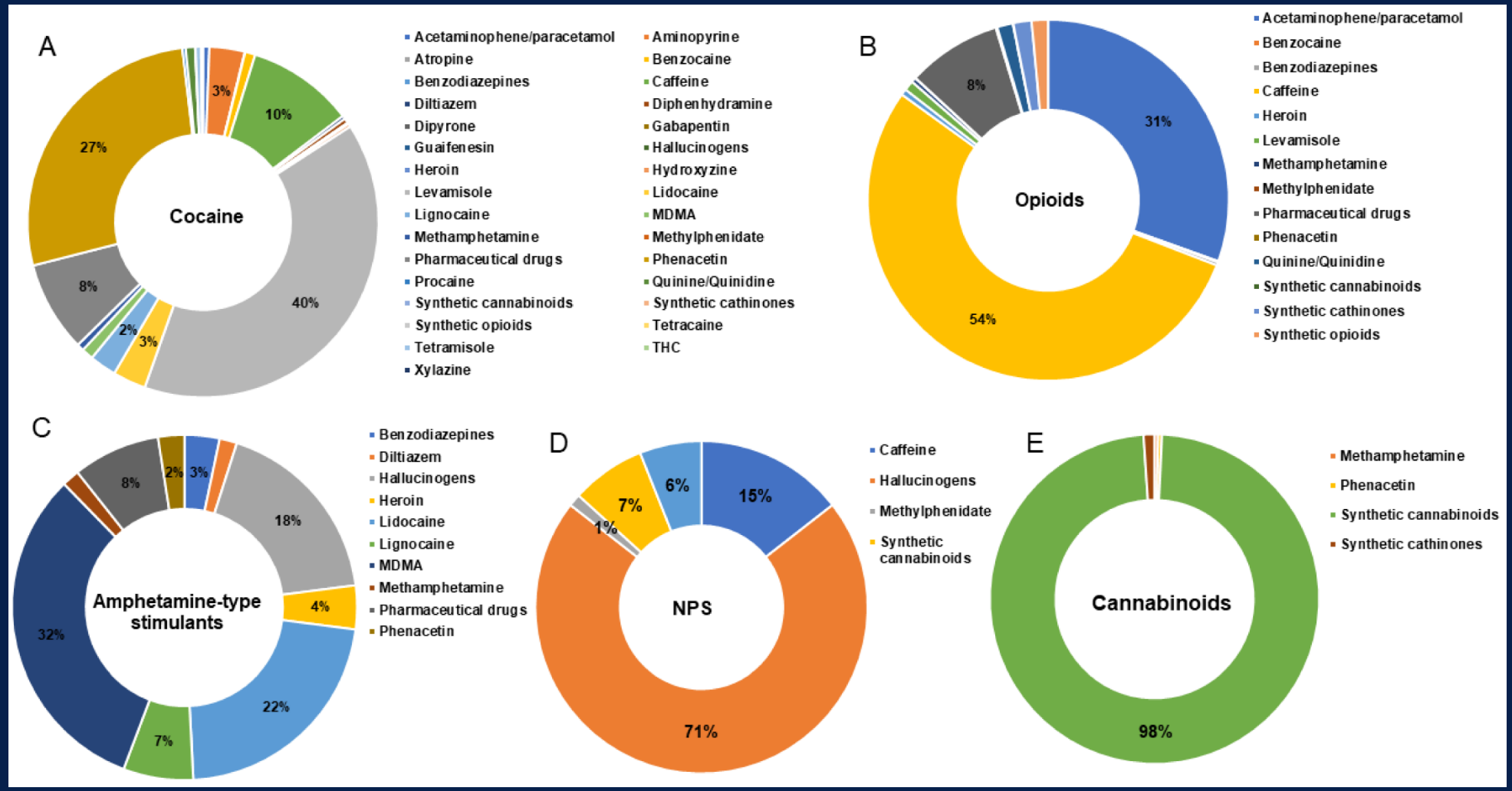


https://wchh.onlinelibrary.wiley.com/doi/pdf/10.1002/pdi.1536#:~:text=(B)%20In%20nocturnal%20leg,tetanic%20stimulation%2C%20reducing%20its%20excitability.

https://www.ahajournals.org/doi/10.1161/CIRCRESAHA.116.305017



Toxins **2018**, *10*(12), 491; **https://doi.org/10.3390/toxins10120491**
Submission received: 19 October 2018 / Revised: 14 November 2018 / Accepted: 15 November 2018 / Published: 23 November 2018



Di Trana, A.; Berardinelli, D.; Montanari, E.; Berretta, P.; Basile, G.; Huestis, M.A.; Busardò, F.P. Molecular Insights and Clinical Outcomes of Drugs of Abuse Adulteration: New Trends and New Psychoactive Substances. *Int. J. Mol. Sci.* **2022**, *23*, 14619. https://doi.org/10.3390/ijms232314619

Cinchonism

- Tinnitus
- Headaches
- Visual Disturbance
  - Blurred, visual field constriction, color perception
- Vertigo
- Nausea
- Vomiting
- Diarrhea

https://www.ebay.com/itm/256237326590

Quinine

- Tissue Irritant
  - Venous thrombosis
- Electrolyte
  - Hypokalemia, hypoglycemia
- Heme
  - Acute hemolytic anemia (G6PD Deficiency)
  - Thrombocytopenia
- Seizure
- Cardio toxicity
- Hypotension, QRSand QT prolongation

Quinine

- Heroin adulterant early 1940s
  - To stem Malaria epidemic in the early 1940s
  - Bitter taste prevented quality judgement
  - May cause rush due to hypotension
  - Thought to be a large factor in increase in overdose deaths

June 2022

Quinine & Quinidine: Toxic Adulterants Found in Illicit Street Drugs

THE COLOMBO PLAN

cfsre
The Center for Forensic Science Research & Education

Toxic Adulterant Alert

Table 1. Quinine Positivity in Seized Drug Cases in the United States

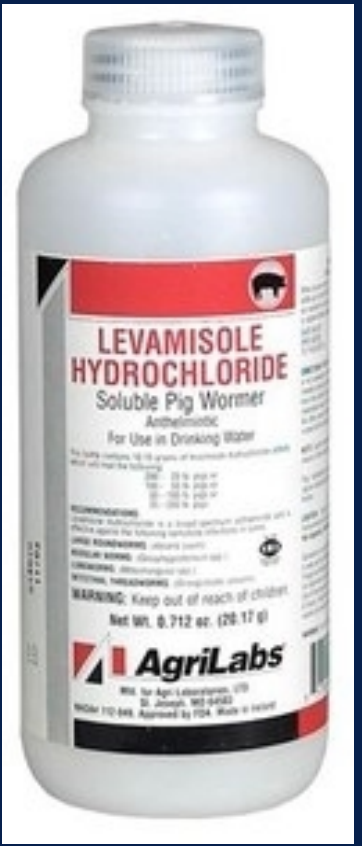
State	# of Quinine Positives	% Positivity for State	% Positivity Overall (n=2,151)
Vermont (n=244)	140	57.3	6.5
Washington, DC (n=91)	49	53.8	2.2
Kentucky (n=248)	51	20.5	2.3
Illinois (n=399)	74	18.5	3.4
Ohio (n=215)	38	17.6	1.7
New Hampshire (n=200)	19	9.5	0.8
Pennsylvania (n=106)	8	7.5	0.3
Florida (n=200)	14	7.0	0.6
Texas (n=274)	2	0.7	0.0
California (n=174)	0	0	0

ASAM

https://www.cfsre.org/nps-discovery/public-alerts/quinine-quinidine-toxic-adulterants-found-in-illicit-street-drugs

Levamisole

- Veterinary Antihelminthic
- Immunomodulator and adjuvant chemotherapy
- Nicotine Anticholinergic receptor agonist
  - Paralysis in soil transmitted helminths



Sanford, Shari. n.d. “Levamisole Hydrochloride.” Accessed February 7, 2024. https://www.loaches.com/disease-treatment/levamisole-hydrochloride-1.

Levamisole Epidemiology

- 2003 - United States Drug Enforcement Agency detected in seized cocaine samples
- 2004 – 44% of seized cocaine in US
- 2009 – 70% of seized cocaine in US
- 2010 – 70% of cocaine tested in Switzerland
- 2011 – 80% of seized cocaine in US

United Nations Publications. 2022. *World Drug Report 2022 (Set of 5 Booklets)*. UN.

Levamisole Epidemiology

- Identified in shipment of cocaine in Rome in 2007
- 28kg of seized cocaine
  - Levamisole and hydroxyzine identified by GC-MS

Unusual adulterants in cocaine seizured on Italian clandestine market

Nadia Fucci

Forensic Science International, 2007-10-25, Volume 172, Issue 2, Pages e1-e1, Copyright © 2007 Elsevier Ireland Ltd

Fucci, Nadia. 2007. "Unusual Adulterants in Cocaine Seized on Italian Clandestine Market." *Forensic Science International* 172 (2-3): e1.

Levamisole Epidemiology

- Australia – 2014 - 2016

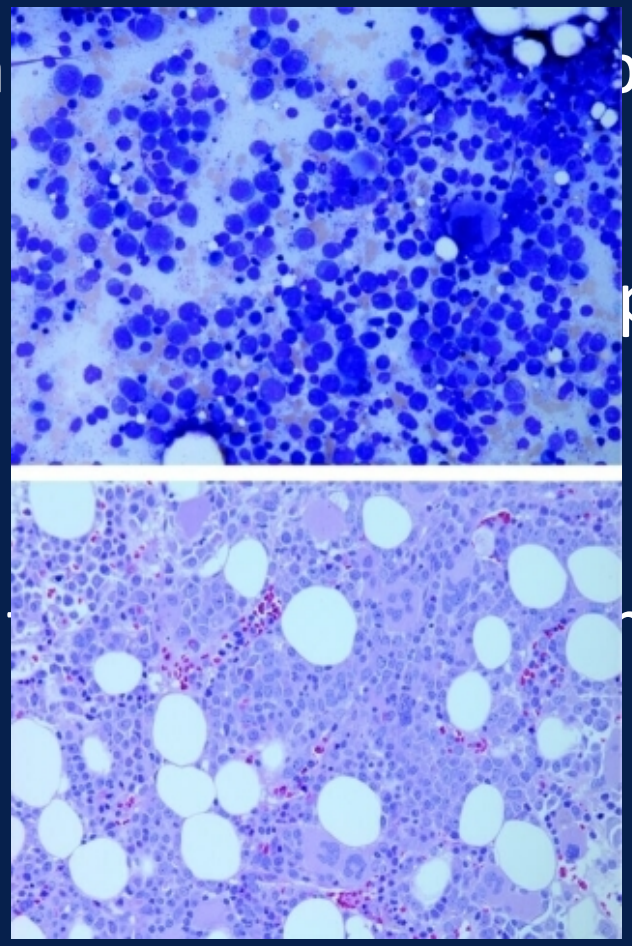
- 36 routinely obtained, cocaine positive urine immunoassays

Cocaine detected by immunoassay screening test (CEDIA, 300 µg/L cut-off) [b]	
Yes	26
No	10
Levamisole detected	27 (75%)

Pope, Jeffrey D., Olaf H. Drummer, and Hans G. Schneider. 2018. “The Cocaine Cutting Agent Levamisole Is Frequently Detected in Cocaine Users.” *Pathology* 50 (5): 536–39.

Levamisole Clinical Effects

- 20% incidence of agran beutic use
- Febrile agranulocytosis positive for cocaine and levamisole
- Documented response ng factors



Zhu, Nancy Y., Donald F. Legatt, and A. Robert Turner. 2009. “Agranulocytosis after Consumption of Cocaine Adulterated with Levamisole.” *Annals of Internal Medicine* 150 (4): 287–89.

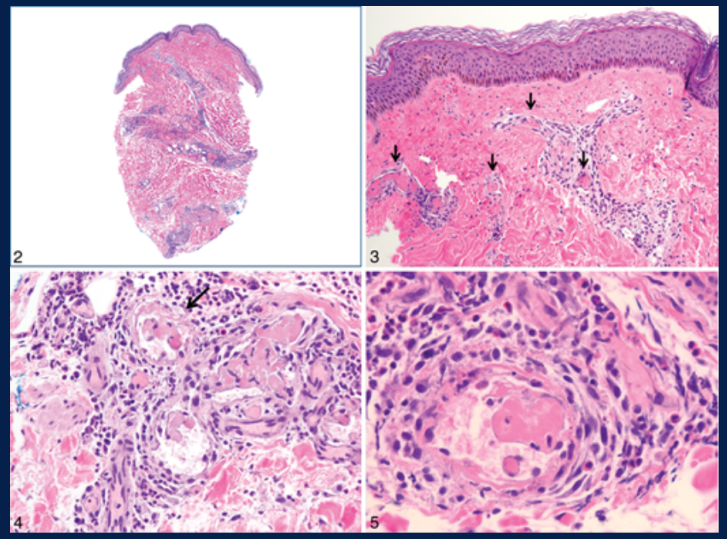
Levamisole Clinical Effects

- Cutaneous vasculitis
- 3:1 Female-to-Male ratio
  - Positive autoantibodies
- Mean age 44 years
- Smoked or insufflated cocaine

Sayadi, Lohrasb, and Donald Laub. 2018. “Levamisole-Induced Vasculitis.” *Eplasty* 18 (February): ic5.

Pathophysiology

- Leukocytoclastic vasculitis of small vessels
- Fibrin micro-thrombi in deep dermal vessels



Roberts, Jordan A., and Patricia Chévez-Barrios. 2015. “Levamisole-Induced Vasculitis: A Characteristic Cutaneous Vasculitis Associated With Levamisole-Adulterated Cocaine.” *Archives of Pathology & Laboratory Medicine* 139 (8): 1058–61.

Table 3. Time Course of Regional Effect of Lavamisol on Dopaminergic Parameters

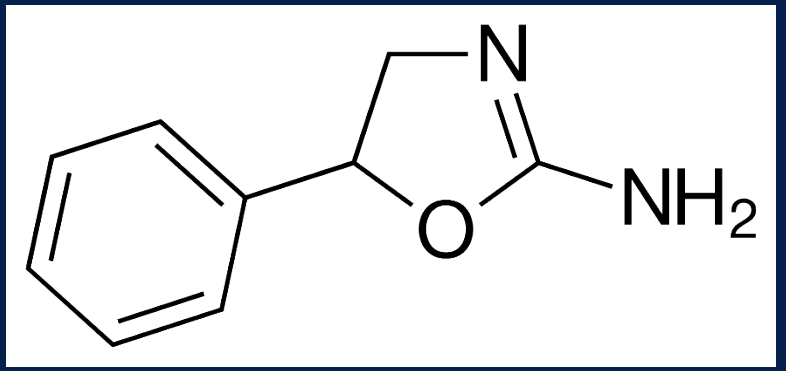
		Brain stem			Cerebellum			Cortex				Hippocampus		
		DOPAMINE	DOPAC***	HVA**	DOPAMINE**	DOPAC	HVA**	DOPAMINE	DOPAC***	HVA**	3-MT	DOPAMINE*	DOPAC*	HVA
Control	Mean	509.6	98.2	69.5	72.3	32.2	15.8	5680.5	349.4	222.5	123.1	340.6	42.9	0.0
	SEM	17.7	1.8	5.4	8.9	11.2	9.8	343.8	24.4	19.8	17.9	39.2	3.7	0.0
15 Min	Mean	987.6	148.0****	123.4****	206.6****	30.9	50.7	5864.0	218.3****	232.8	112.0	682.4	50.1	0.0
	SEM	17.8	5.4	6.6	24.1	2.0	4.0	453.0	17.1	20.7	9.5	99.9	4.9	0.0
30 Min	Mean	1135.0****	165.8****	182.0****	265.2****	41.3	108.6****	6593.7	203.0****	232.6	126.2	817.6****	66.9****	16.1
	SEM	30.9	7.6	9.8	34.5	3.7	11.7	916.8	12.7	27.9	22.0	167.7	3.5	16.1
60 Min	Mean	1046.1****	146.9****	162.0****	243.8****	33.8	98.1****	5710.3	188.9****	173.2	104.6	707.4	59.7	0.0
	SEM	45.2	6.7	11.9	10.3	2.0	11.8	463.3	16.2	6.2	2.9	81.9	5.9	0.0
120 Min	Mean	1058.1****	132.9****	143.9****	227.0****	36.0	110.0****	5930.1	197.5****	134.6****	89.6	626.5	59.1	0.0
	SEM	105.4	11.6	18.1	47.3	7.9	34.3	195.8	10.5	9.0	10.3	78.0	5.0	0.0

		Hypothalamus				Midbrain			Striatum			
		DOPAMINE*	DOPAC***	HVA**	3-MT***	DOPAMINE*	DOPAC	HVA	DOPAMINE	DOPAC***	HVA***	3-MT
Control	Mean	3035.4	286.7	60.1	22.9	2653.6	261.1	157.9	118378.2	6973.8	3973.0	2084.1
	SEM	570.6	10.4	11.7	6.0	191.0	11.7	4.9	6443.9	364.1	243.0	241.5
15 Min	Mean	6421.4	317.9	102.6	94.6****	5584.5****	246.7	213.1	137657.1	3838.7	3650.6	2046.5
	SEM	496.0	28.8	26.7	13.2	695.4	23.5	15.2	7509.0	305.9	279.7	161.1
30 Min	Mean	8451.2****	470.8****	207.7	94.0****	4171.2	203.2	164.9	130092.9	2917.4****	2465.4****	1960.0
	SEM	302.0	18.0	27.2	15.5	511.1	12.2	15.8	5028.1	164.9	279.2	126.6
60 Min	Mean	6145.3	352.5	129.4****	40.7****	5375.9	253.3	195.4	142572.0	3549.3****	2430.6****	1712.2
	SEM	350.2	20.4	16.6	3.9	1290.9	38.2	27.3	15373.4	404.3	197.4	298.4
120 Min	Mean	6247.3	321.2	90.1****	43.5	3749.0	221.0	150.2	125249.0	3348.0****	1729.1****	1598.1
	SEM	564.8	25.3	4.7	13.0	372.2	17.5	12.6	5780.0	400.5	214.5	260.2

Values are given as Fmoles/mg tissue.
$n = 6$ rats per group.
* = $p < .05$, ANOVA.
** = $p < .01$, ANOVA.
*** = $p < .001$, ANOVA.
**** = $p < .05$ vs. Control, Bonferroni's post hoc.

Rationale for Adulteration

- Aminorex active metabolite
  - Stimulant causing Norepinephrine and Dopamine Release
- Used in Horse Doping
- Previously prescribed as weight loss drug



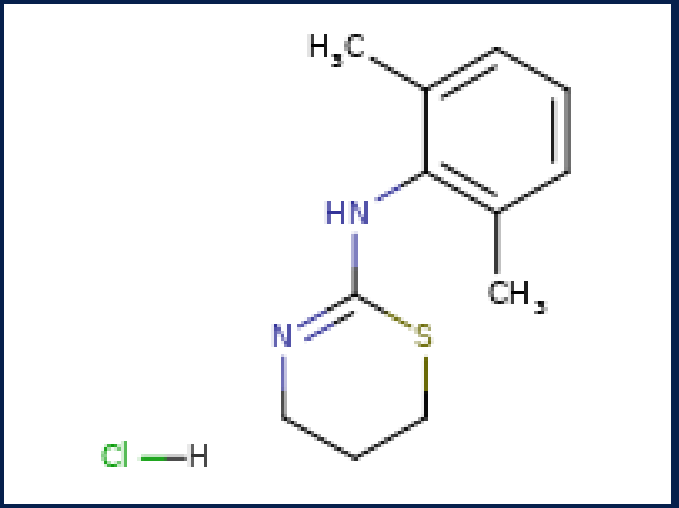
Hofmaier, Tina et al. 2014. “Aminorex, a Metabolite of the Cocaine Adulterant Levamisole, Exerts Amphetamine like Actions at Monoamine Transporters.” *Neurochemistry International* 73 (100): 32–41.

Xylazine and Alpha-2-Agonists

- Developed in Germany in 1962 as anti-hypertensive
- Veterinary sedative, analgesic, muscle relaxant, emetic
- Alpha-2-adrenergic receptor agonist
  - Feedback inhibition of norepinephrine and dopamine release in CNS

Xylazine

- Not FDA approved for human use
- Structural analog of clonidine, TCAs, and phenothiazines
- Pharmacokinetics well established in animals, not humans
  - IV, IM, SC



Ruiz-Colón, Kazandra, Carlos Chavez-Arias, José Eric Díaz-Alcalá, and María A. Martínez. 2014. "Xylazine Intoxication in Humans and Its Importance as an Emerging Adulterant in Abused Drugs: A Comprehensive Review of the Literature." *Forensic Science International* 240 (July): 1–8.

Xylazine

- Rose to prominence in Puerto Rico in early 2000s

"I opened up the bag and when I threw it in the cooker, a really fucking strong medicine smell. [...] That was the first heroin that they cut with *anestesia* (xylazine) in Puerto Rico, the "Blue Demon". [...] What those people did was that they would place heroin inside, they would then fold the paper the first time, the first fold, there outside they would put the *anestesia* and then the fold.

They would call that, *el regalito* (the small gift). And when you would open the bag, you would open the first fold and there was a half a bag [...] [of] *anestesia* and you would put some. And when you would open [the rest of] the bag you would put the other [heroin]. [...] It was later when they started to mix it, [...] 80% *anestesia* and 20% heroin."

Torruella, Rafael A. 2011. "Xylazine (veterinary Sedative) Use in Puerto Rico." *Substance Abuse Treatment, Prevention, and Policy* 6 (April): 7.

Xylazine and Alpha-2-Agonists

- Epidemiology

> *"Xylazine is making the deadliest drug threat our country has ever faced, fentanyl, even deadlier," said Administrator Milgram. "DEA has seized xylazine and fentanyl mixtures in 48 of 50 States. The DEA Laboratory System is reporting that in 2022 approximately 23% of fentanyl powder and 7% of fentanyl pills seized by the DEA contained xylazine."*

"DEA Reports Widespread Threat of Fentanyl Mixed with Xylazine." n.d. Accessed February 21, 2024. https://www.dea.gov/alert/dea-reports-widespread-threat-fentanyl-mixed-xylazine.

Xylazine and Alpha-2-Agonists

- ***78%*** of fentanyl positive urine assays ***also xylazine positive***

- Philadelphia 2021

Korn, Warren R., Matthew D. Stone, Kaddie L. Haviland, Joanne M. Toohey, and Douglas F. Stickle. 2021. “High Prevalence of Xylazine among Fentanyl Screen-Positive Urines from Hospitalized Patients, Philadelphia, 2021.” *Clinica Chimica Acta; International Journal of Clinical Chemistry* 521 (October): 151–54.

Xylazine and Alpha-2-Agonists

- Clinical effects:
  - CNS Depression
  - Respiratory Depression
  - Bradycardia
  - Transient Hypertension
  - Hypotension

Xylazine and Alpha-2-Agonists

- November 8, 2 vere, necrotic skin ulcerations

- Higher prevale detectable xylazine in syringes

Dear Colleague. n.d. “FDA Warns about the Risk of Xylazine Exposure in Humans.” Accessed February 21, 2024. https://www.fda.gov/media/162981/download?attachment.

Xylazine

- Rationale for adulteration
- Enhanced street sale value
- Enhanced drug effect

Torruella, Rafael A. 2011. “Xylazine (veterinary Sedative) Use in Puerto Rico.” *Substance Abuse Treatment, Prevention, and Policy* 6 (April): 7.

New or Novel Psychoactive Substances (NPS)

"Subs
not co
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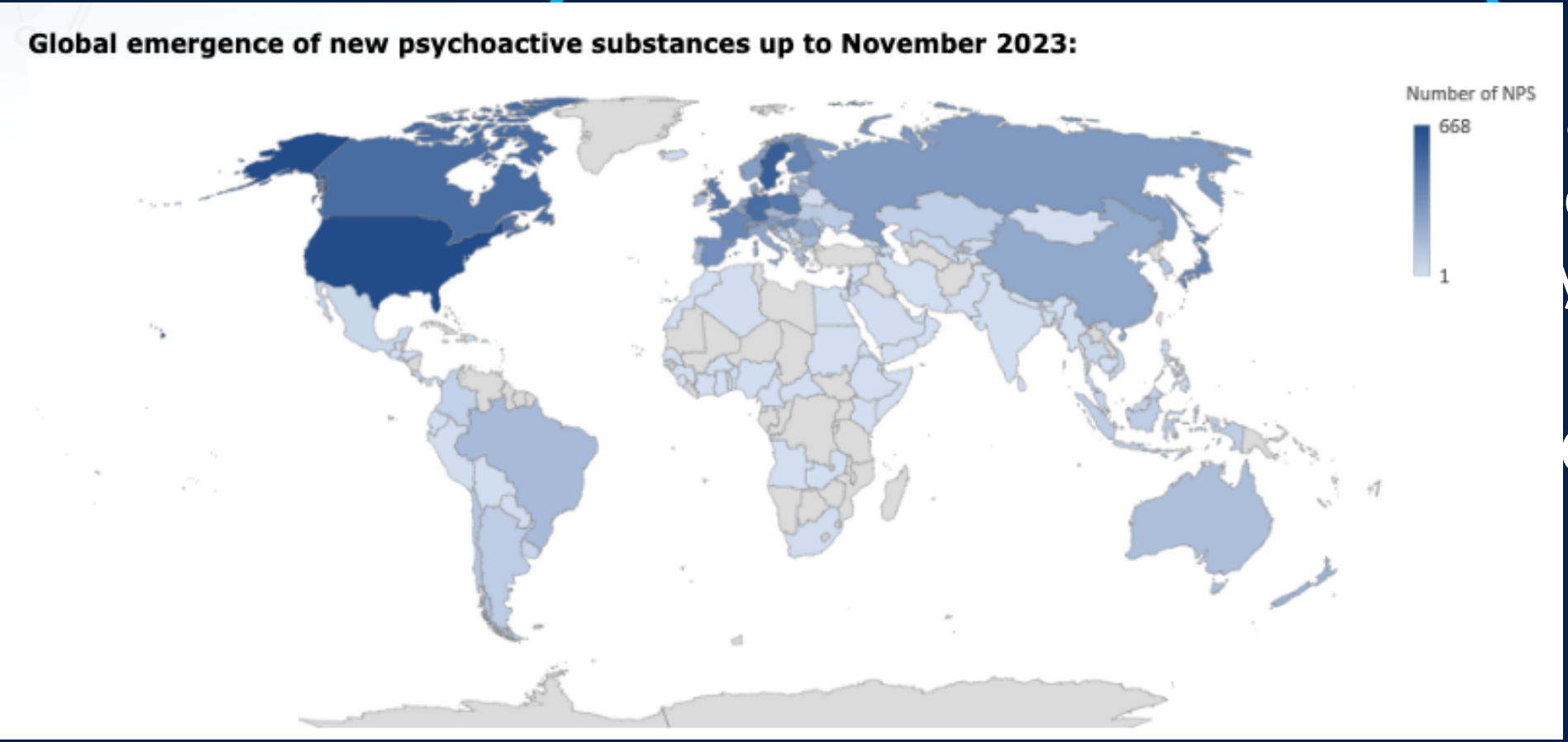
Crime



United Nations Office on Drugs and Crime, Early Warning Advisory on NPS, 2023

NPS Substance Groups

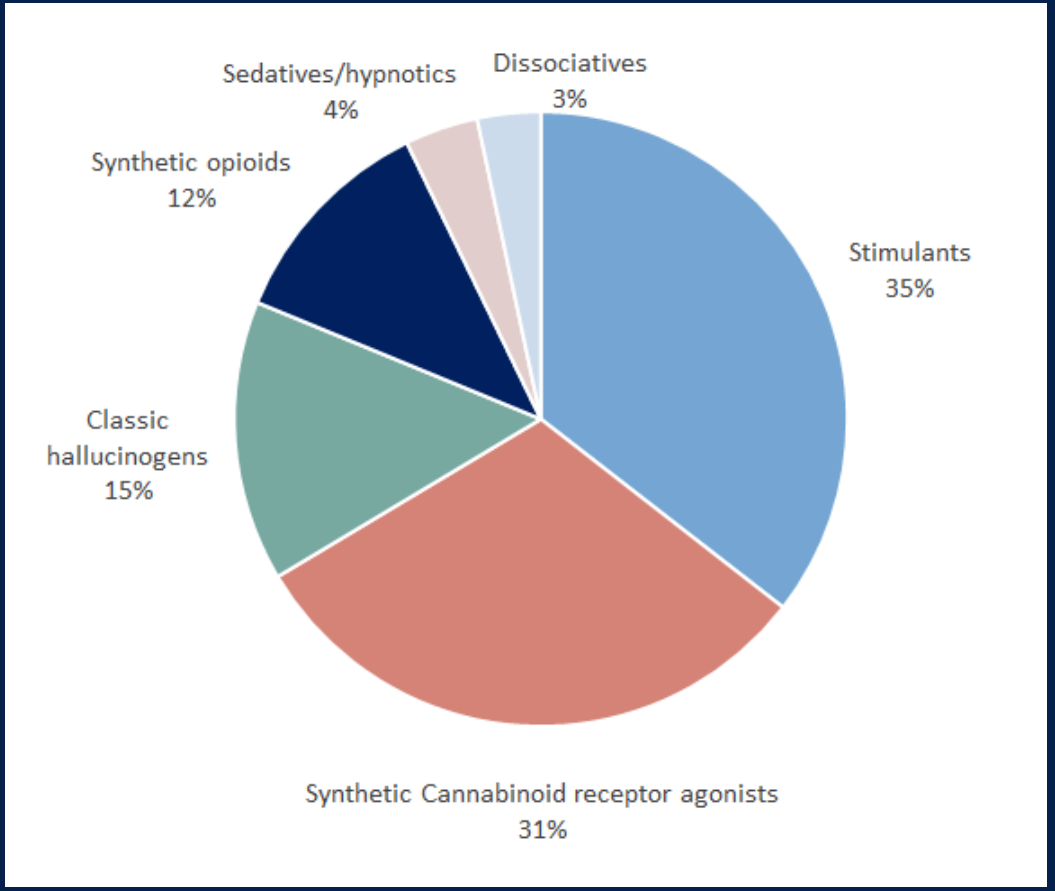
- Aminoindanes
- Benzodiazepines
- Fentanyl analogues
- Lysergamides
- Nitazenes
- Phencyclidine-type substances
- Phenethylamines
- Phenmetrazines
- Piperazines
- Plant-based substances
- Synthetic cannabinoids
- Synthetic cathinones
- Tryptamines
- Others

United Nations Office on Drugs and Crime, Early Warning Advisory on NPS, 2023

NPS

- Similar effects to controlled substances like cannabis, cocaine, opioids, hallucinogens, stimulants

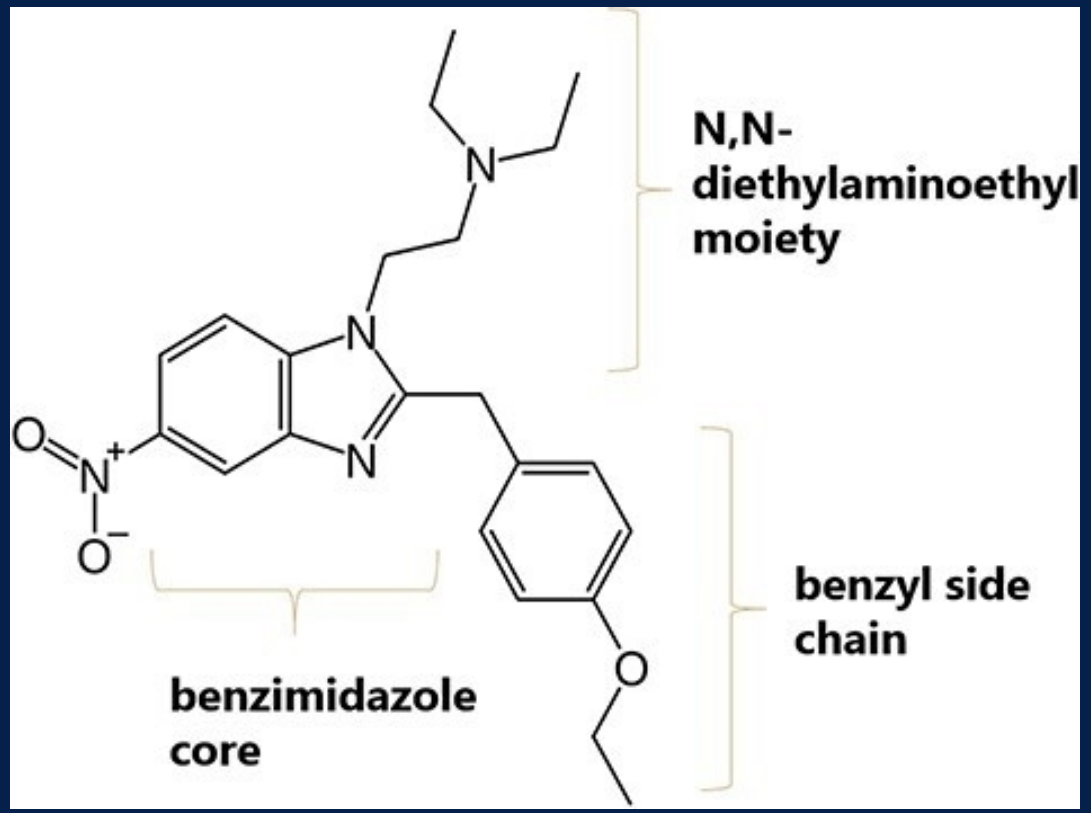
- Ideal candidates adulteration



United Nations Office on Drugs and Crime, Early Warning Advisory on NPS, 2023

New or Novel Psychoactive Substances (NPS)

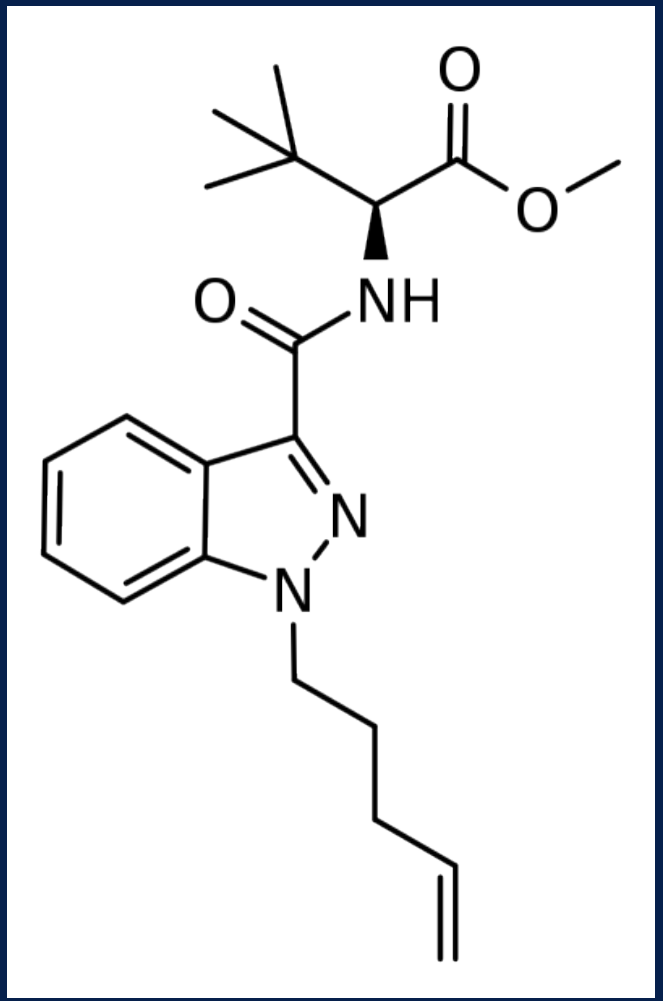
- Benzimidazole opioids aka Nitazenes
- Synthetic analogs of etonitazene
- Series of OD deaths in 2019



Di Trana, Annagiulia, Simona Pichini, Roberta Pacifici, Raffaele Giorgetti, and Francesco Paolo Busardò. 2022. "Synthetic Benzimidazole Opioids: The Emerging Health Challenge for European Drug Users." *Frontiers in Psychiatry / Frontiers Research Foundation* 13 (March): 858234.

New or Novel Psychoactive Substances (NPS)

- Low THC cannabis adulterated with SCRAs
  - 270/1142 samples contaminated with MDM-4en-PINACA
  - Vomiting, paranoia, hallucinations, agitation, and more

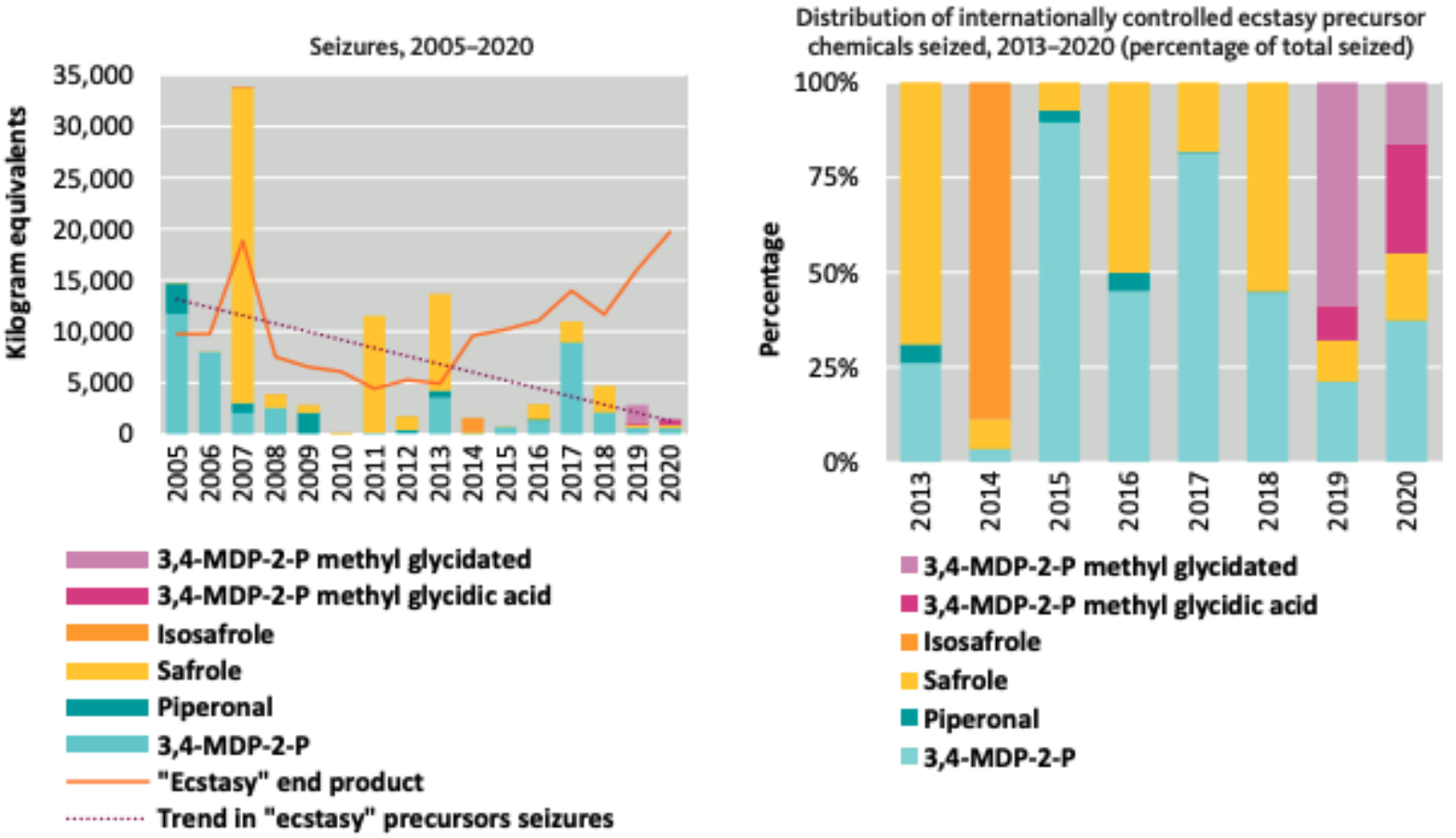


Oomen, Pieter E., Dominique Schori, Karsten Tögel-Lins, Dean Acreman, Sevag Chenorhokian, Anton Luf, Alexandra Karden, et al. 2022. “Cannabis Adulterated with the Synthetic Cannabinoid Receptor Agonist MDMB-4en-PINACA and the Role of European Drug Checking Services.” *The International Journal on Drug Policy* 100 (February): 103493.

New c (NPS)

- "Ecsta
  methy
  - Incre
    precu
  - Incre

FIG. 61 Seizures of "ecstasy" and of internationally controlled "ecstasy" precursors in kilograms of MDMA equivalents, 2005–2020, and as a percentage of total seizures, 2013–2020



Sources: INCB, Precursors and Chemicals Frequently Used in the Illicit Manufacture of Narcotic Drugs and Psychotropic Substances (E/INCB/2021/4), and previous years.

Note: the following conversion factors– as reported by INCB – were used to convert the MDMA precursor seizures into MDMA equivalents: 3,4-MDP-2-P: 1.1; piperonal: 2.1; safrole and isosafrole: 1.5; 3,4-MDP-2-P methyl glycidic acid and 3,4-MDP-2-P methyl glycidate: 2.1

WORLD DRUG REPORT 2022: INCB, Precursors and Chemicals Frequently Used in the Illicit Manufacture of Narcotic Drugs and Psychotropic Substances (E/INCB/2021/4), and previous years.

New or Novel Psychoactive Substances (NPS)

- Amphetamine-type stimulants adulterated with widest variety of compounds

- 19 different NPS identified in MDMA/Methamphetamine seized in US and Canada 2010 - 2015

Saleemi, Sarah, Steven J. Pennybaker, Missi Wooldridge, and Matthew W. Johnson. 2017. “Who Is ‘Molly’? MDMA Adulterants by Product Name and the Impact of Harm-Reduction Services at Raves.” *Journal of Psychopharmacology* 31 (8): 1056–60.

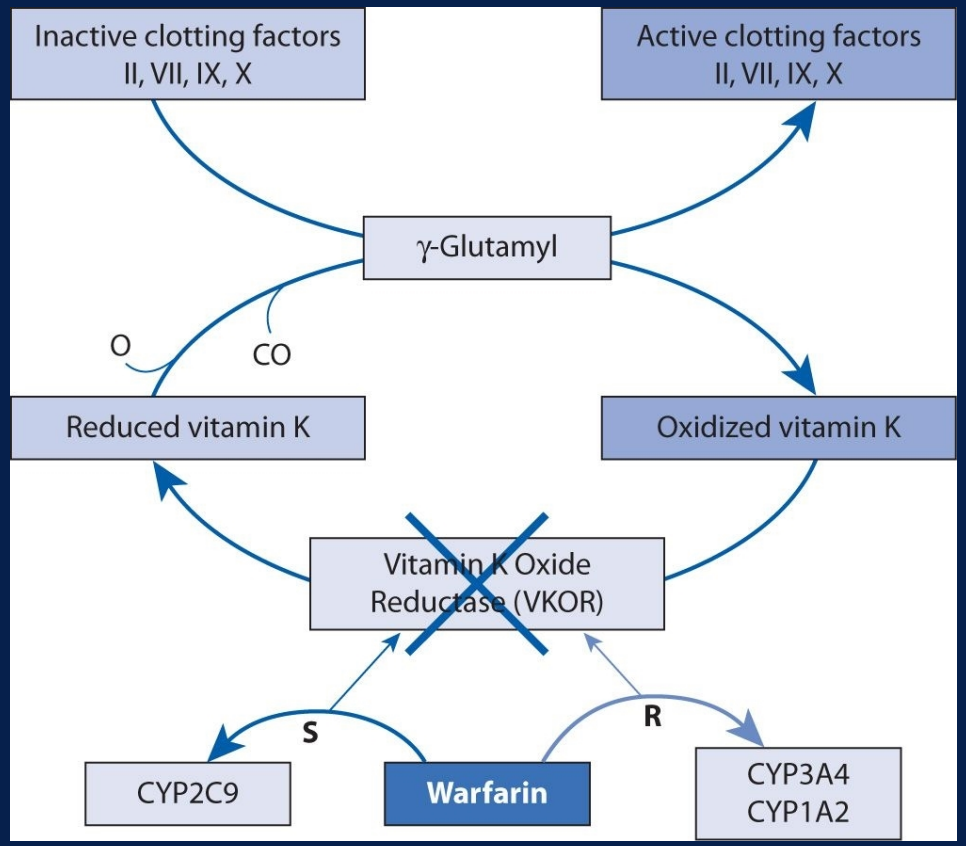
New or Novel Psychoactive Substances (NPS)

- 2017 – Chemsex intoxication with sildenafil as GHB adulterant
- 2018 - Lead intoxication in an opium user
- 2020 – Fatal etizolam intoxication in adulterated Xanax use
- 2020 – Heroin adulterated with the SCRA 5F-MDMB-PICA
- 2020 – Phenylethylamine associated intracranial hemorrhage in adulterated Kratom use
- 2021 – LSD poisoning cluster after insufflation of ‘cocaine’

Di Trana, Annagiulia et al. 2022. “Molecular Insights and Clinical Outcomes of Drugs of Abuse Adulteration: New Trends and New Psychoactive Substances.” *International Journal of Molecular Sciences* 23 (23). https://doi.org/10.3390/ijms232314619.

Long Acting Anticoagulant Rodenticides

- March-July 2018 outbreak in synthetic cannabinoids; 255 patients, 8 deaths
  - Brodifacoum, bromodialone, and difenacoum in combination
  - Adulterant vs contaminant? Altered CYP450 kinetics?
- Antagonist of vitamin K at VKOR
- Dx: Back/flank pain, bleeding, high INR
- Tx: FFP/PCC, IV/PO vitamin K, prolonged outpatient PO vitamin K



- Fasih A. Lethal coagulopathy resulting from the consumption of contaminated synthetic cannabinoids: the story of a public health crisis.*Journal of Public Health.* 2021;43(1):e1-e6. doi:10.1093/pubmed/fdz067
- Schulman S, Furie B. How I treat poisoning with vitamin K antagonists. *Blood*. 2015;125(3):438-442. doi:10.1182/blood-2014-08-597781
- Wright E, Hafner JW, Podolej G, et al. Severe Vitamin K-dependent Coagulopathy from Rodenticide-contaminated Synthetic Cannabinoids: Emergency Department Presentations. *West J Emerg Med*. 2021;22(4):1014-1019. doi:10.5811/westjem.2021.2.46317

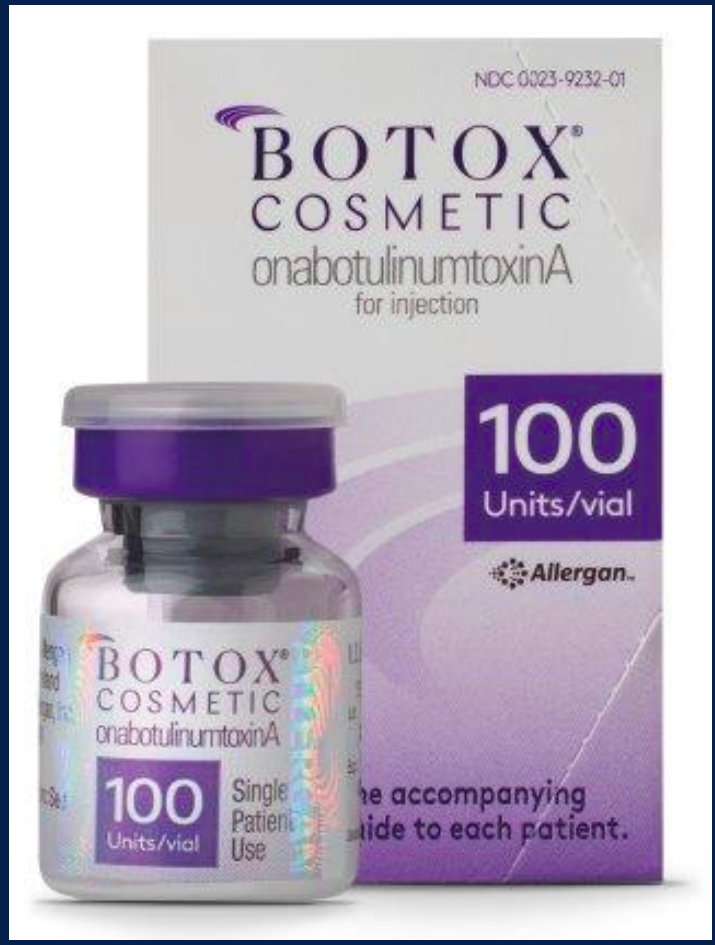
Clostridium tetani

- USA West Coast 1980-1990s
  - About 6 cases yearly
- Contaminant of black tar heroin
- 2003 cluster in the UK; 25 cases, 2 deaths
  - >90% reported active wound infection, IM or SubQ injection ("skin popping") or missing vein. Most partially vaccinated, ~1/4 unvaccinated
- Dx: Clinical >> wound culture, toxin ELISA
- Tx: Antitoxin, metronidazole, antispasmodics

- Hahné SJM, White JM, Crowcroft NS, et al. Tetanus in Injecting Drug Users, United Kingdom. *Emerg Infect Dis*. 2006;12(4):709-710. doi:10.3201/eid1204.050599
- Wurcel AG, Merchant EA, Clark RP, Stone DR. Emerging and Underrecognized Complications of Illicit Drug Use. *Clin Infect Dis*. 2015;61(12):1840-1849. doi:10.1093/cid/civ689
- Gonzales y Tucker RD, Frazee B. View from the front lines: an emergency medicine perspective on clostridial infections in injection drug users. *Anaerobe*. 2014;30:108-115. doi:10.1016/j.anaerobe.2014.09.005

Clostridium botulinum

- Similar epidemiology as *C. tetani,* but more common
  - About 30 cases wound botulism annually in USA
  - 1988-1992, only 2 cases among IV users outside California
- 1998 case-control study in CA (N=35)
  - Significantly associated with SubQ or IM injection (P<0.001)
- Diagnosis: Clinical, wound culture, toxin assay
- Treatment: Antitoxin, intubation



- Passaro DJ, Werner SB, McGee J, Mac Kenzie WR, Vugia DJ. Wound Botulism Associated With Black Tar Heroin Among Injecting Drug Users. *JAMA*. 1998;279(11):859-863. doi:10.1001/jama.279.11.859
- National Botulism Surveillance | Botulism | CDC. Published July 5, 2023. Accessed January 22, 2024. https://www.cdc.gov/botulism/surveillance.html
- Horowitz BZ. Botulinum toxin. *Crit Care Clin*. 2005;21(4):825-839, viii. doi:10.1016/j.ccc.2005.06.008

Bacillus anthracis

- Contaminated heroin, less SubQ/IM association
- 2000, Norway: First cutaneous anthrax in IV drug user
- 2009-2010: UK, 54 cases, 33% mortality
- 2012-2013: Europe, 15 cases, 47% mortality
  - Misdiagnosed as necrotizing fasciitis or compartment syndrome
  - Edema & blistering >> Eschar
- Diagnosis: Wound culture, ELISA assay, PCR
- Treatment: Combination antimicrobials & immune globulin, surgery

- Ascough S, Altmann DM. Anthrax in injecting drug users: the need for increased vigilance in the clinic. Expert Review of Anti-infective Therapy. 2015;13(6):681-684. doi:10.1586/14787210.2015.1032255
- Grunow R, Verbeek L, Jacob D, et al. Injection Anthrax—a New Outbreak in Heroin Users. Dtsch Arztebl Int. 2012;109(49):843-848. doi:10.3238/arztebl.2012.0843

Aspergillus species

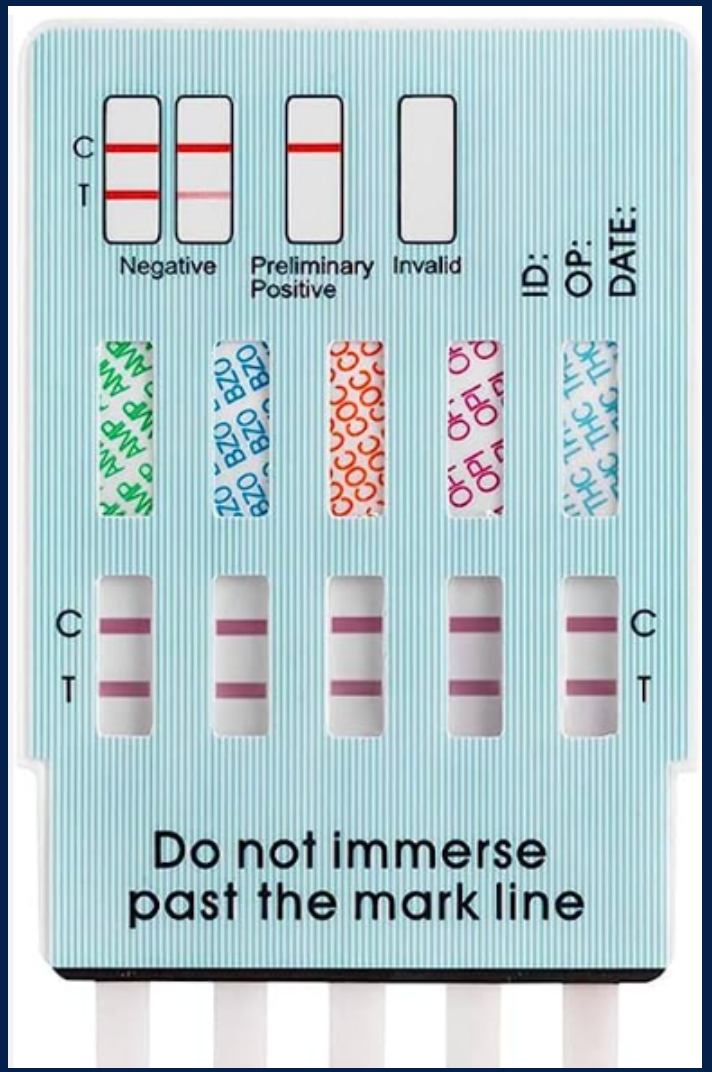
- Invasive pulmonary or disseminated disease in immunocompromised cannabis users
  - 2009 case series – 7 individuals, many on chemotherapy, 2 died
- Localized infection in IV drug users
  - Endophthalmitis, endocarditis, osteomyelitis, CNS
- Dx: Beta-D-Glucan, Galactomannan, Culture
- Tx: Amphotericin B, surgical debridement

- Trullas JC, Bisbe J, Miro JM. Aspergillosis in Drug Addicts. In: Comarú Pasqualotto A, ed. Aspergillosis: From Diagnosis to Prevention. Springer Netherlands; 2010:545-558. doi:10.1007/978-90-481-2408-4_32
- Aspergillus Endophthalmitis in Intravenous-Drug Users -- Kentucky. Accessed January 25, 2024.
- Oregon Court of Appeals Halts State's Aspergillus Testing Rules After Legal Challenge by Cannabis Industry. Willamette Week. Published August 25, 2023. Accessed January 25, 2024.

Strategies for Identification

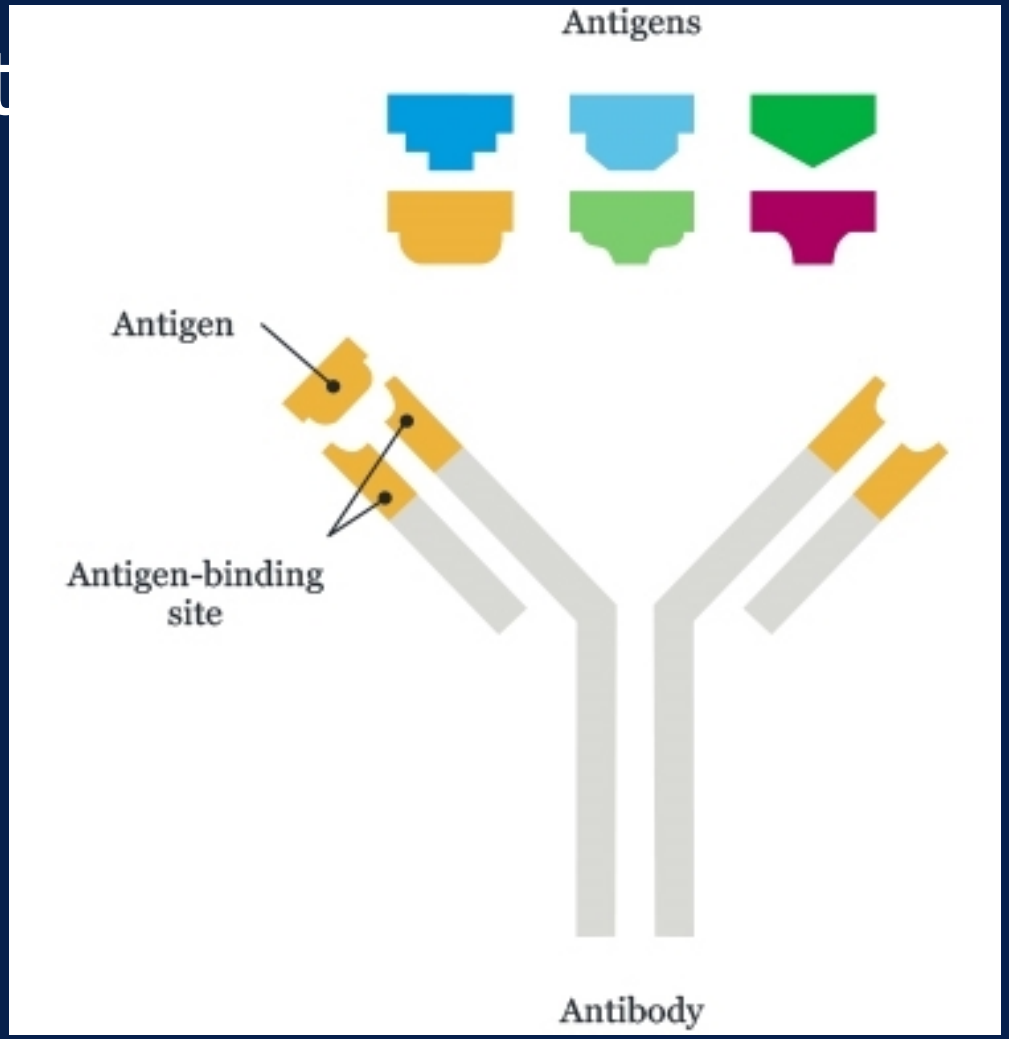
- Consumer Level
- Advanced Testing/Send Outs
- National Collation and Future Strategies

Consumer Level Testing



Drug Immunoassay testing

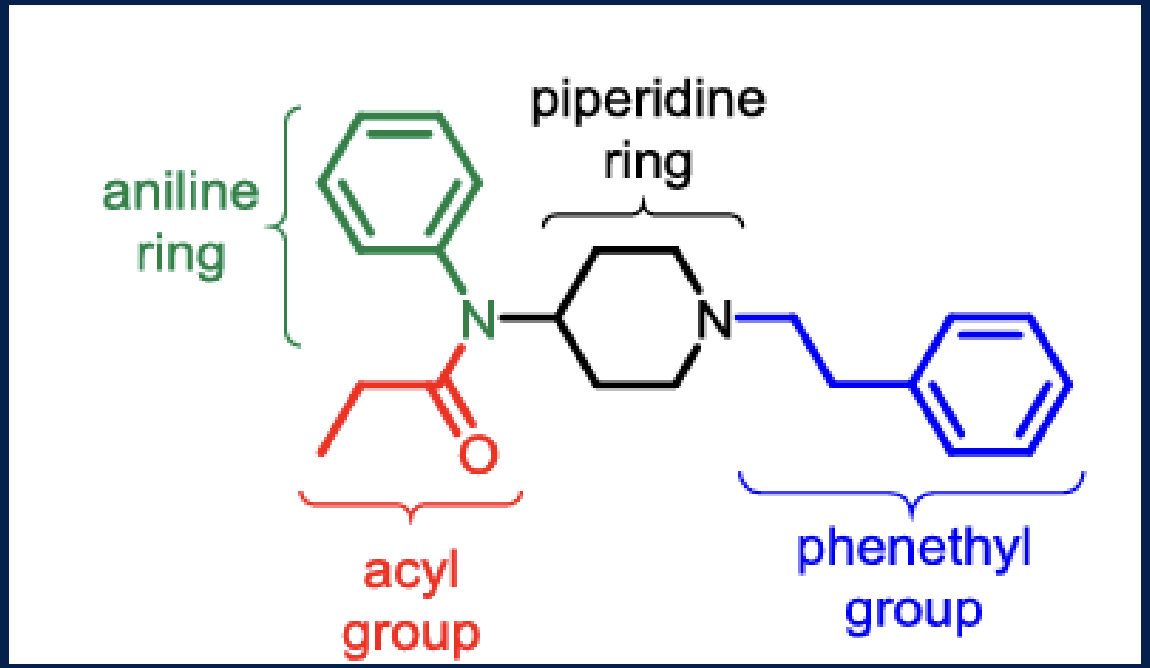
- Not generally able to detect adulterants
  - Xylazine
  - Fentanyl



https://www.toxicology.abbott/au/en/support/testing-explained.html

Fentanyl Test Strips

- 251 synthetic fentanyl analogues on 2 brands test strips
  - 121 compounds were detectable at or below 20,000 ng/mL by both
  - Large modifications on certain moieties inhibited detected
  - Phenethyl moiety inhibit detection by BTNX FTS while bulky modifications to the carbonyl (acyl) moiety inhibit detection by DanceSafe FTS.



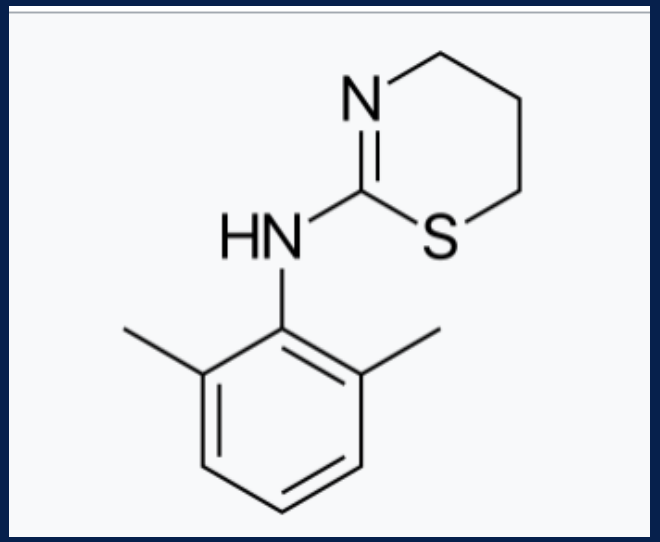
Fentanyl Sites of Substitution

Hayes, K.L., Lieberman, M. Assessment of two brands of fentanyl test strips with 251 synthetic opioids reveals “blind spots” in detection capabilities. *Harm Reduct J* **20**, 175 (2023). https://doi.org/10.1186/s12954-023-00911-w

Xylazine Test Strips

Performance

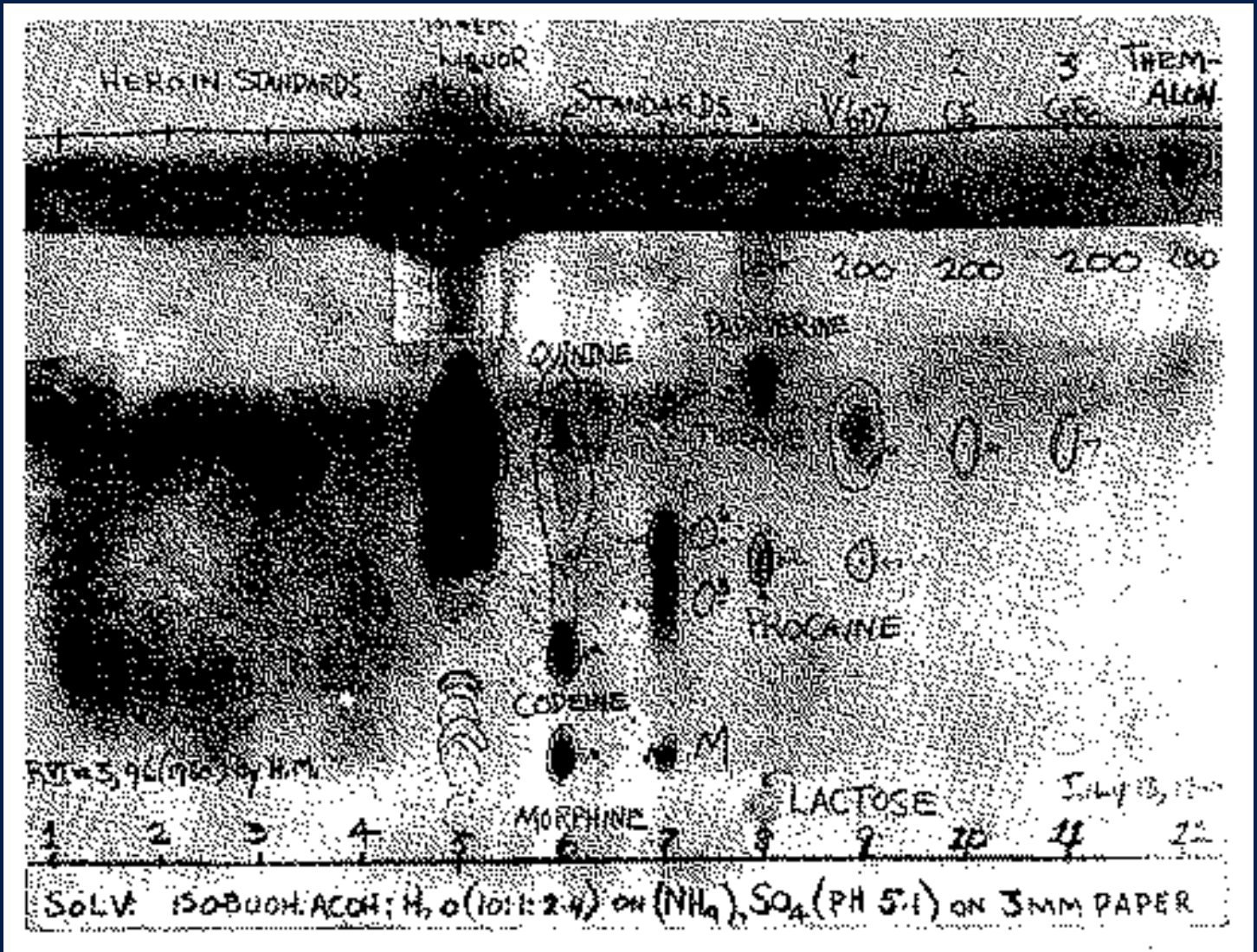
- Sensitivity (100%)
- Specificity (85%)
- Precision (91%).
  - Lidocaine potential false-positive results.

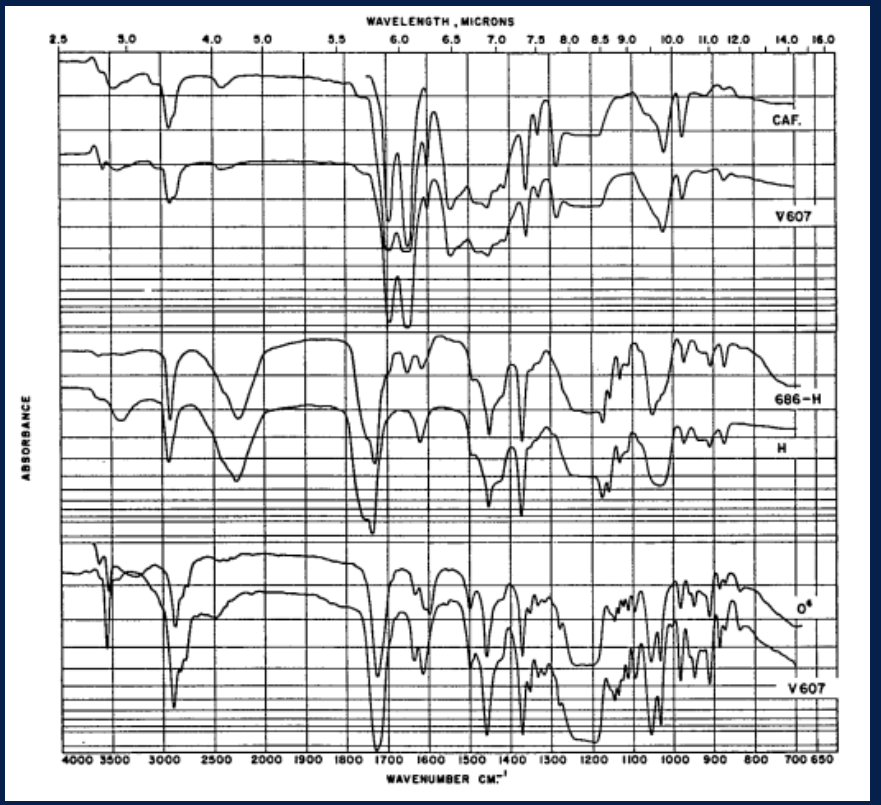


Jones S, Bailey S; Authors. Xylazine Test Strips for Drug Checking: CADTH Horizon Scan [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2023 Jul. Available from: https://www.ncbi.nlm.nih.gov/books/NBK595122/

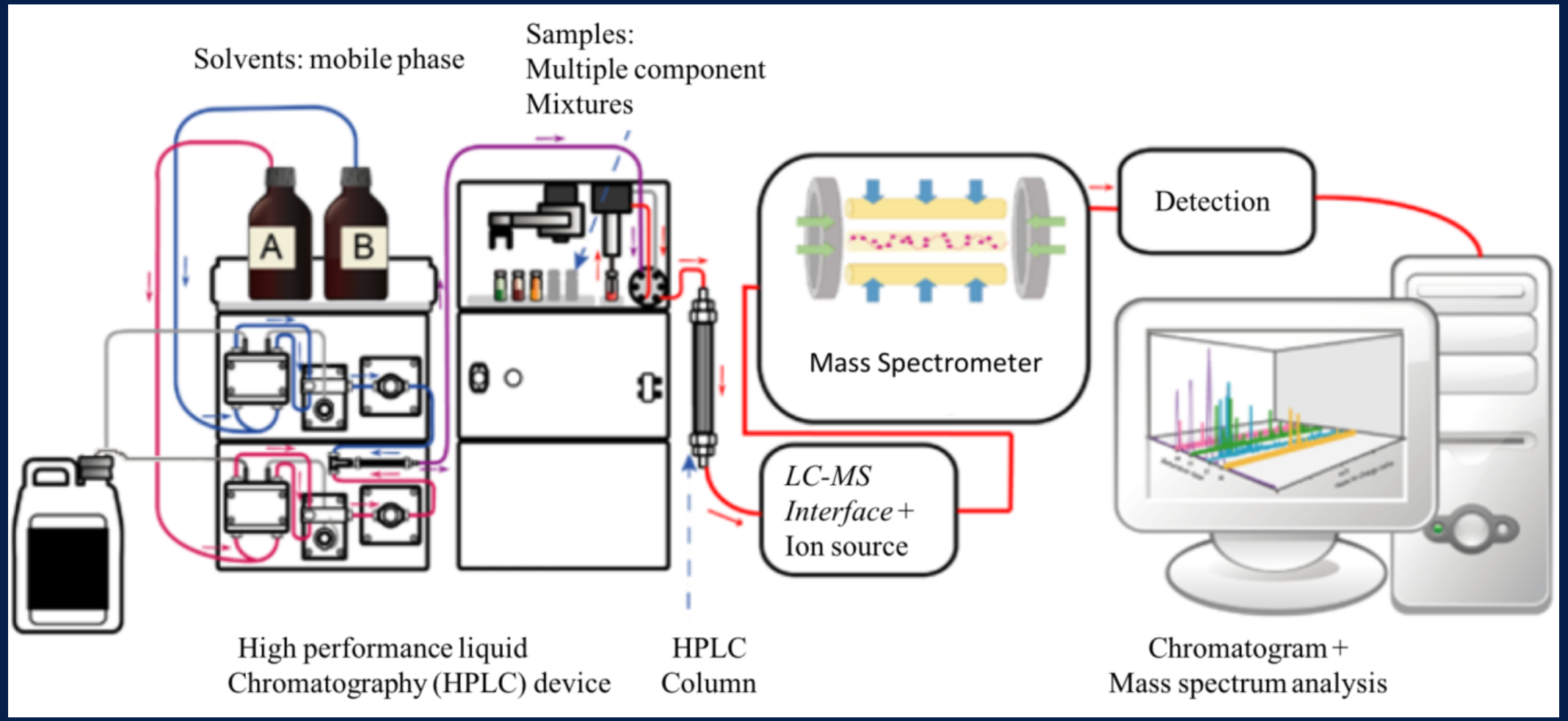
Other Drug Analysis Methods

- Capillary Electrophoresis
- Solid phase extraction (SPE)/ Thin-layered chromatography (TLC)
- Thin-layered chromatography (TLC)
- Gas chromatography and mass spectrometry
- High Performance Liquid Chromatography (HPLC)
  - Micro-HPLC

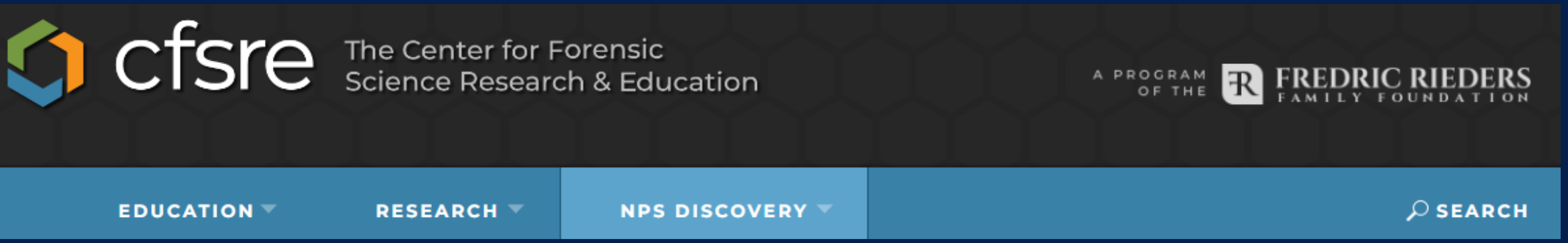




https://www.unodc.org/unodc/en/data-and-analysis/bulletin/bulletin_1962-01-01_3_page006.html



https://en.wikipedia.org/wiki/Liquid_chromatography%E2%80%93mass_spectrometry#/media/File:Liquid_Chromatography_Mass_Spectrometer.png



NPS DISCOVERY

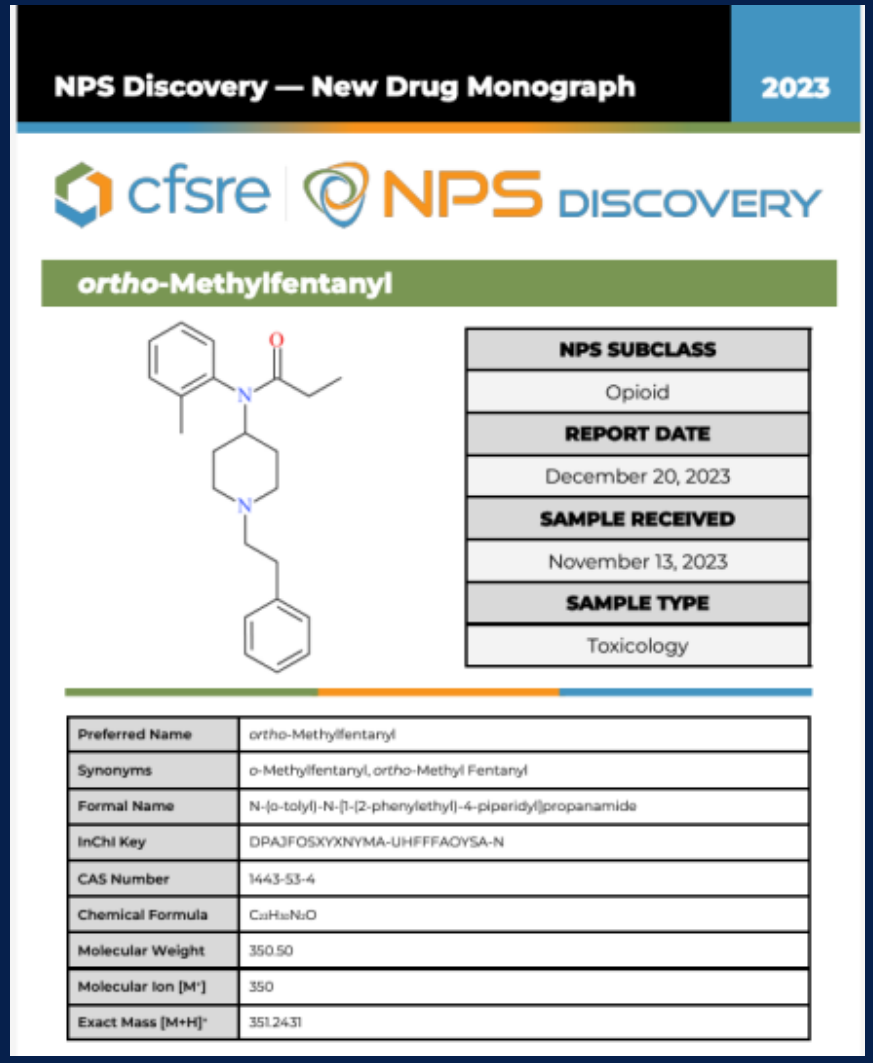
The CFSRE's NPS Discovery program is an open-access drug early warning system (EWS) operating in the United States. Our evidence-based approach leads the development of high impact reports for real-time action among public health and safety stakeholders.

We are working in collaboration with forensic science, public health, emergency medicine, and criminal justice agencies to rapidly identify emerging drugs, also known as Novel Psychoactive Substances (NPS), associated with intoxications and adverse events. Our data and results are consolidated into reports and resources to allow for the rapid dissemination of information to colleagues and affected communities.

Stakeholders interested in receiving up-to-date information and notifications can join our email listserv (be sure to select the NPS Discovery check box at the bottom).

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

Monographs



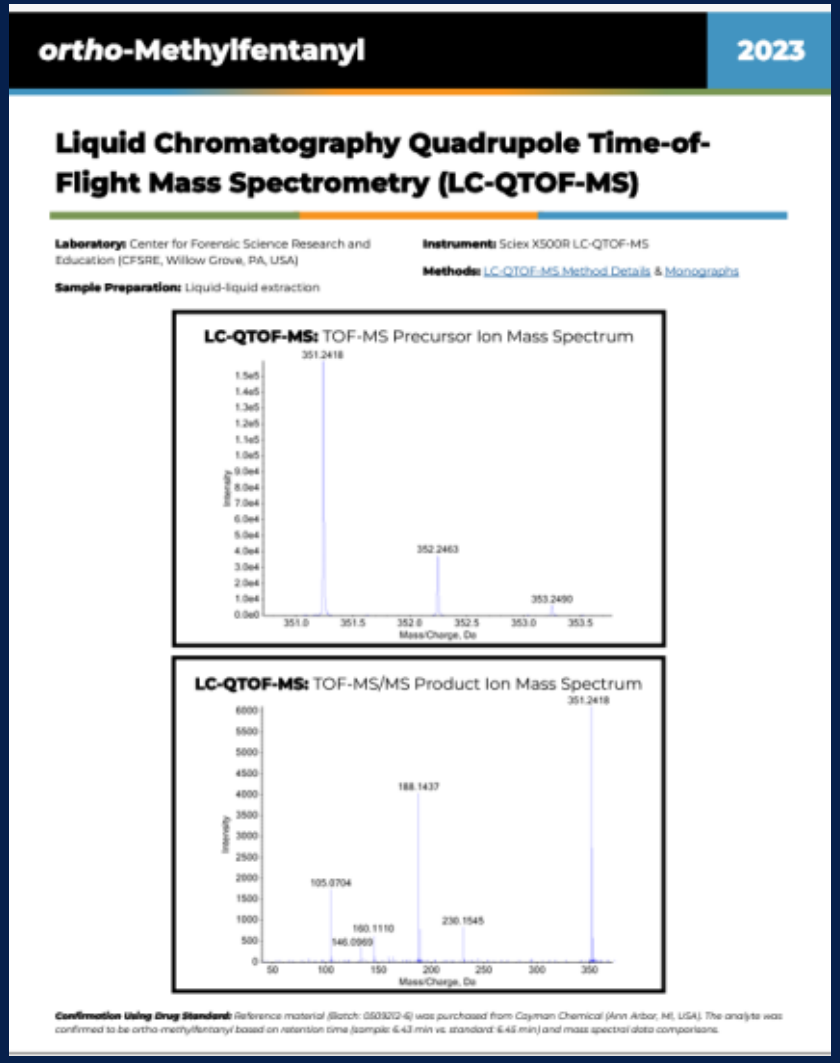
NPS Discovery — New Drug Monograph 2023

cfsre | NPS DISCOVERY

ortho-Methylfentanyl

NPS SUBCLASS
Opioid
REPORT DATE
December 20, 2023
SAMPLE RECEIVED
November 13, 2023
SAMPLE TYPE
Toxicology

Preferred Name	*ortho*-Methylfentanyl
Synonyms	o-Methylfentanyl, *ortho*-Methyl Fentanyl
Formal Name	N-(o-tolyl)-N-[1-(2-phenylethyl)-4-piperidyl]propanamide
InChI Key	DPAJFOSXYXNYMA-UHFFFAOYSA-N
CAS Number	1443-53-4
Chemical Formula	$C_{23}H_{30}N_2O$
Molecular Weight	350.50
Molecular Ion [M$^+$]	350
Exact Mass [M+H]$^+$	351.2431



ortho-Methylfentanyl 2023

Liquid Chromatography Quadrupole Time-of-Flight Mass Spectrometry (LC-QTOF-MS)

Laboratory: Center for Forensic Science Research and Education (CFSRE, Willow Grove, PA, USA)

Instrument: Sciex X500R LC-QTOF-MS

Methods: LC-QTOF-MS Method Details & Monographs

Sample Preparation: Liquid-liquid extraction

LC-QTOF-MS: TOF-MS Precursor Ion Mass Spectrum

LC-QTOF-MS: TOF-MS/MS Product Ion Mass Spectrum

Confirmation Using Drug Standard: *Reference material (Batch: 0503212-6) was purchased from Cayman Chemical (Ann Arbor, MI, USA). The analyte was confirmed to be ortho-methylfentanyl based on retention time (sample: 6.43 min vs. standard: 6.46 min) and mass spectral data comparisons.*

https://www.cfsre.org/nps-discovery/monographs/ortho-methylfentanyl#:~:text=Description%3A%20ortho%2DMethylfentanyl%20is%20a,%2D%2C%20and%20para%2Dmethylfentanyl.

QUARTERLY REPORT — PHILADELPHIA, PA

DRUG CHECKING | Q3 2022

cfsre | NPS DISCOVERY

Department of Public Health CITY OF PHILADELPHIA

Purpose: This report provides up-to-date information regarding the drug supply in Philadelphia, Pennsylvania, United States of America, and is our first Quarterly Drug Checking Report to include quantitative data on the purity of fentanyl, xylazine, cocaine, methamphetamine, and more.

Overview: Traditional drugs (e.g., heroin, fentanyl, cocaine, methamphetamine) are commonly identified among drug samples in cities across the United States, albeit at varying purities and combinations. Novel psychoactive substances (NPS) continue to appear within the drug supply, masked as traditional drugs or added to traditional drug preparations. Nationally, the drug supply remains a dynamic and evolving environment, especially relating to primary active drug components and cutting agents or adulterants added to drug preparations. The drug supply and drug use trends can be different from city to city or even within a given community, requiring specific regional or local assessments. Accurate understanding of drug materials and the drug supply in real-time is imperative for effective public health and public safety preparedness and response.

Objective: A partnership between the Center for Forensic Science Research and Education (CFSRE) and the Philadelphia Department of Public Health (PDPH) has been established to accurately assess the drug supply in Philadelphia, Pennsylvania. This initiative was established as a comprehensive effort examining various drug materials and drug forms. Select drug testing results from samples obtained within the city were compiled for preparation of this report. The results reported herein represent a subset of the drug supply and not its entirety.

Acknowledgements: This report was prepared by Alex J. Krotulski, PhD; Jen Shinefeld, MS; Joshua DeBord, PhD; Daniel Teixeira da Silva, MD; and Barry K. Logan, PhD, F-ABFT. The authors acknowledge CFSRE and PDPH personnel for their contributions and involvements. This work is funded by the Centers for Disease Control and Prevention (CDC) through an Overdose Data to Action grant awarded to the city of Philadelphia. The opinions, findings, conclusions, and/or recommendations expressed in this publication are those of the authors and do not necessarily reflect those of the CDC or other federal, state, local, or private agencies. For more information about drug checking services or NPS Discovery, please contact npsdiscovery@cfsre.org or visit www.npsdiscovery.org.

Summary and Key Findings:

- 219 samples were tested between May and September 2022
- Fentanyl-xylazine (tranq-dope) proportions varied greatly
- The average fentanyl purity was 11.7% (range: 0.3-34.8%)
- The average xylazine purity was 33.8% (range: 0-64.8%)
- Most dope samples (91%) contained fentanyl and xylazine
- Synthetic cannabinoids remain dynamic and unpredictable
- Counterfeit Xanax tablets tested positive for clonazolam
- Cocaine purity varied greatly (average: 37.8%, range: 0.2-81.8%)

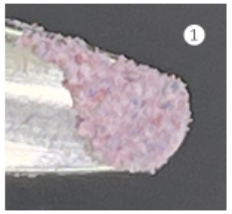
136 "Heroin" / Dope (Powder in Glassine Bag)

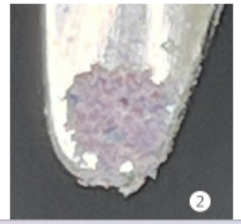
49 Powders / Crystals (E.g., Cocaine, Methamphetamine)

10 Pills / Tablets (E.g., Oxycodone, Xanax, Ecstasy)

24 Other (E.g., Cannabis, K2, "Unknown")

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





https://www.cfsre.org/nps-discovery/drug-checking/drug-checking-q3-2022-philadelphia-pennsylvania-usa

Final Takeaways/Summary

- Expect to encounter a changing landscape of adulterants and contaminants in clinical practice.
- Identification of adulterants/contaminants generally lags behind our clinical recognition and management of their effects.
- Adulteration typically meant to *increase potency* and drive *repeat use.*
- Trends change over time due to economic and enforcement stimuli.

Questions? Comments?

Thank You!

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