Fentanyl and adulterants

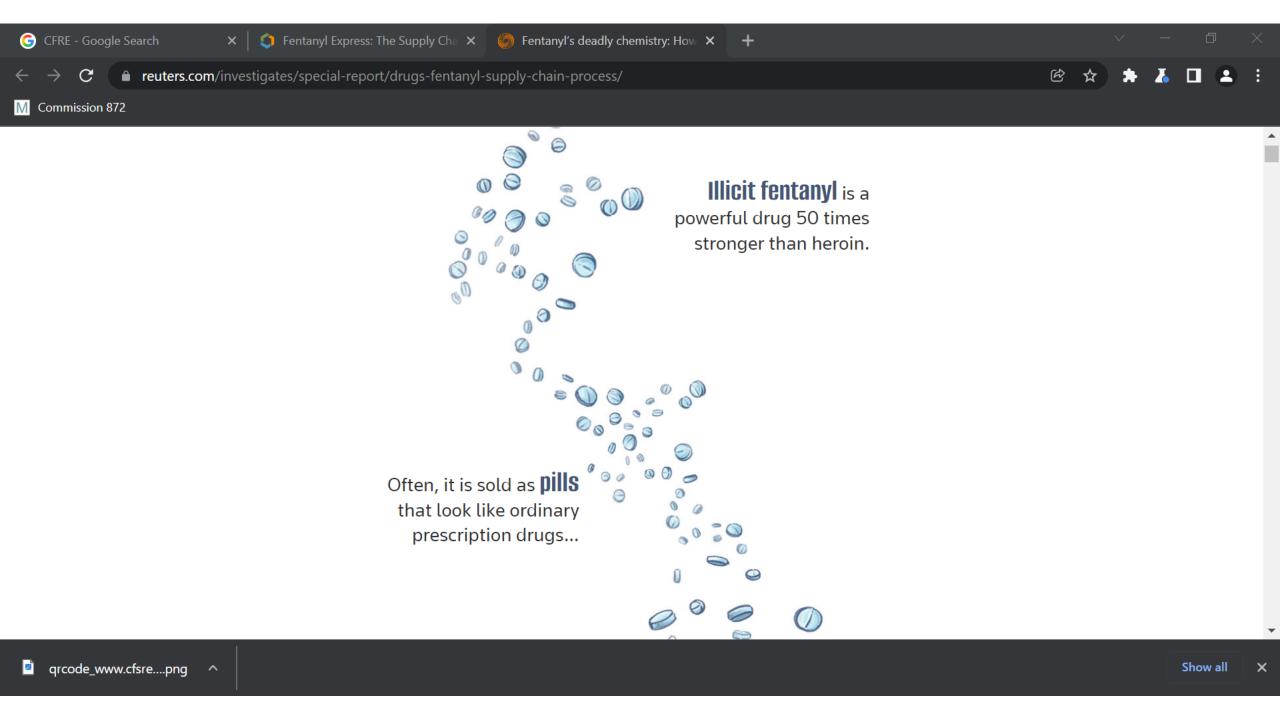
Tariffs and border militarization to stop the flow of fentanyl???

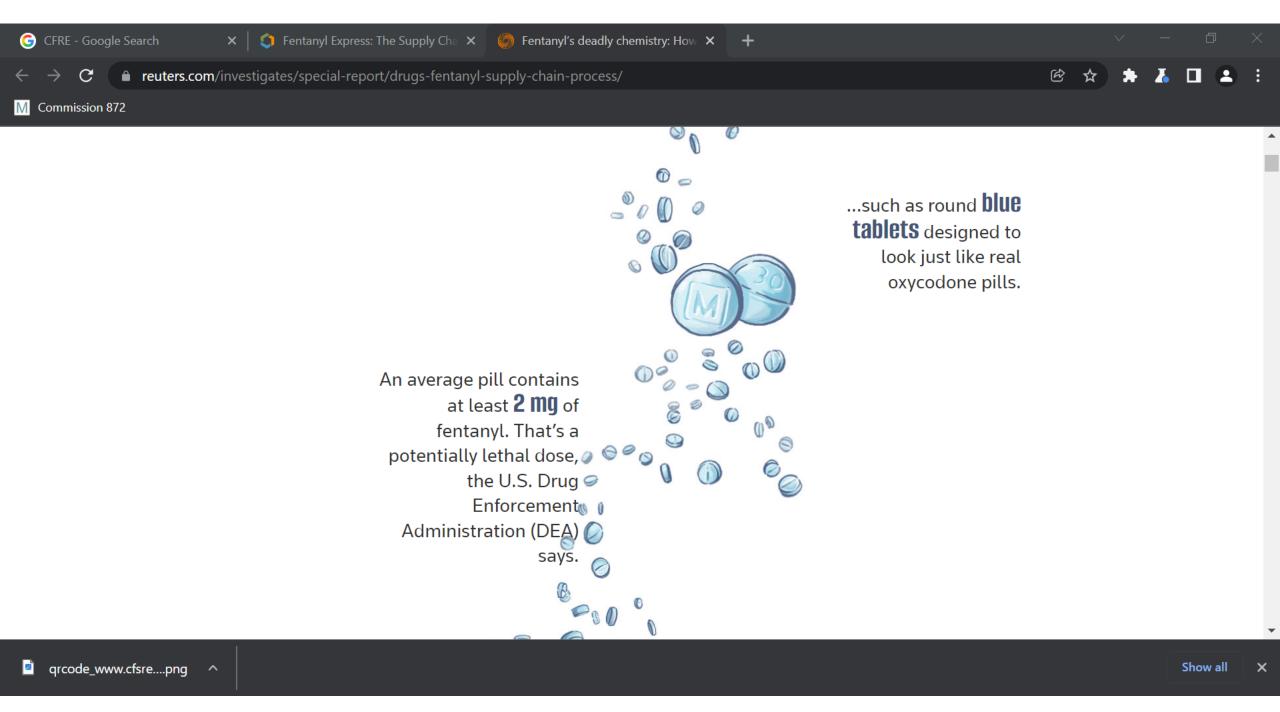
Dan Nauts, MD, FASAM

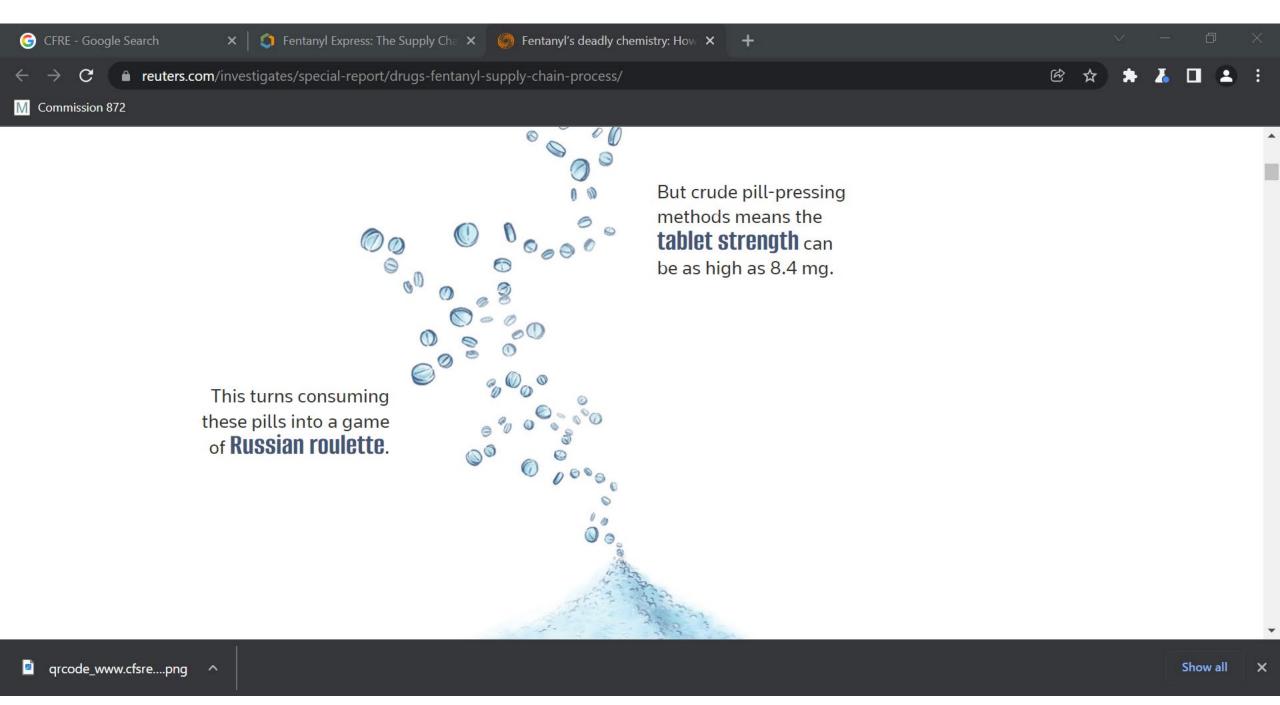
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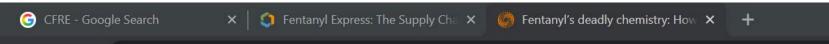


The ease with which our reporters bought the drug-making chemicals exposed holes in the world's regulatory framework and law enforcement.







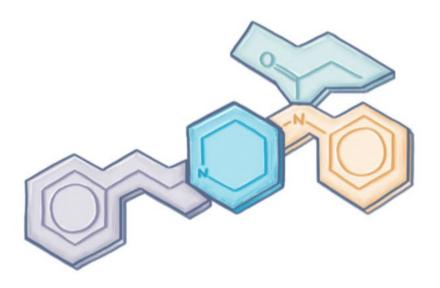






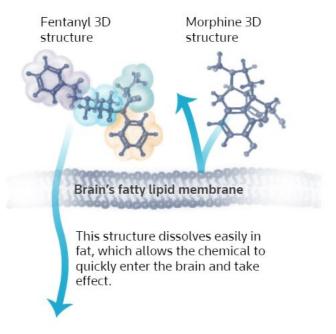


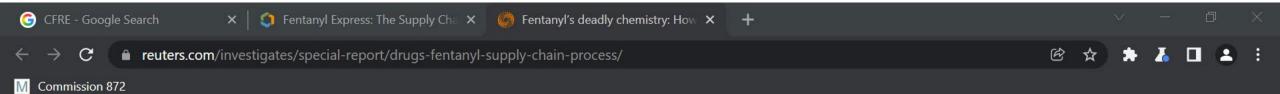
M Commission 872

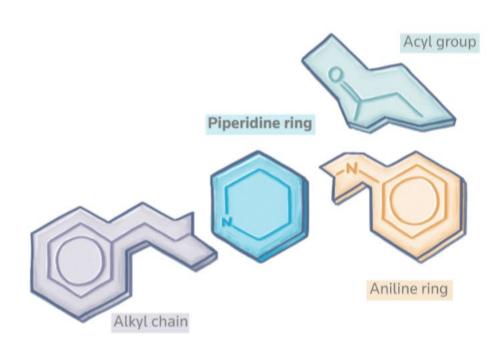


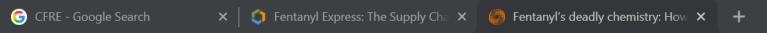
To understand these chemistry tricks, first consider the basic structure of fentanyl.

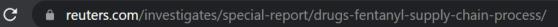
Fentanyl is much stronger than other opioids because its unique molecular structure allows it to easily enter parts of the brain that control pain and emotions.

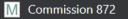


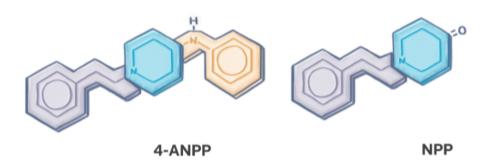




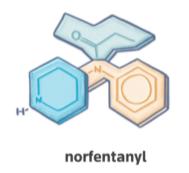






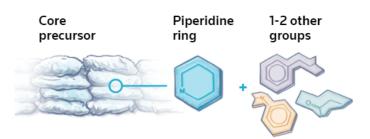






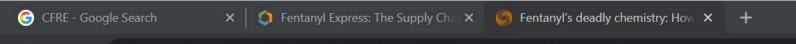
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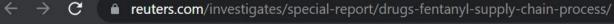
Core precursors are chemical compounds made up of a piperidine ring and one or more of fentanyl's three other molecular groups. Here are four examples used by illicit makers.

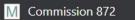


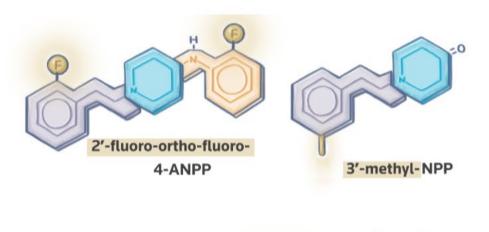
But among these are the precursors that governments have placed the toughest restrictions on because they make producing street fentanyl such a snap. For example, the U.S. government tightly controls 4-ANPP and norfentanyl since they're what are known as immediate precursors, only one chemical reaction away from fentanyl itself.

This is where creative chemistry comes in.







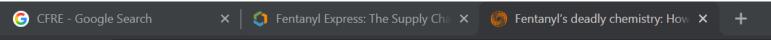


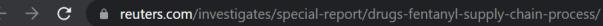


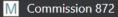
One way illicit fentanyl producers get around these regulations is to use **designer precursors** that have a similar, but slightly different chemical structure.

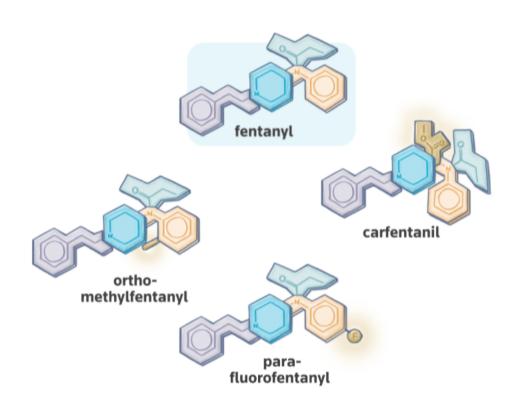
Imagine a Mr. Potato Head with its head, ears and nose – but in this case, the ears are gold, not the standard pink. The toy still looks and functions the same as the original.

The chemistry equivalent of that is, for example, replacing a hydrogen atom with a **fluorine atom** on the precursor chemical.









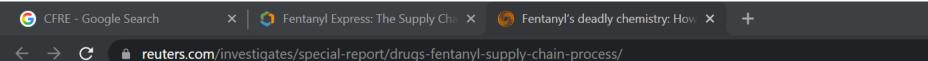
These changes help chemical sellers stay one step ahead of regulatory and interdiction efforts. The tweaked compounds can still be used to produce so-called **fentanyl analogs** that produce a similar high and are often just as dangerous — or even more dangerous — than fentanyl itself.

Here are three examples of fentanyl analogs common in the illicit drug market.

Carfentanil, which was initially developed to sedate elephants and other large animals, is 100 times more potent than fentanyl, according to the DEA.

Comparison of potentially lethal doses





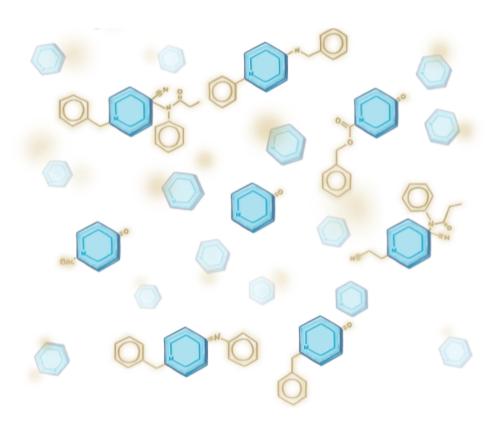








M Commission 872

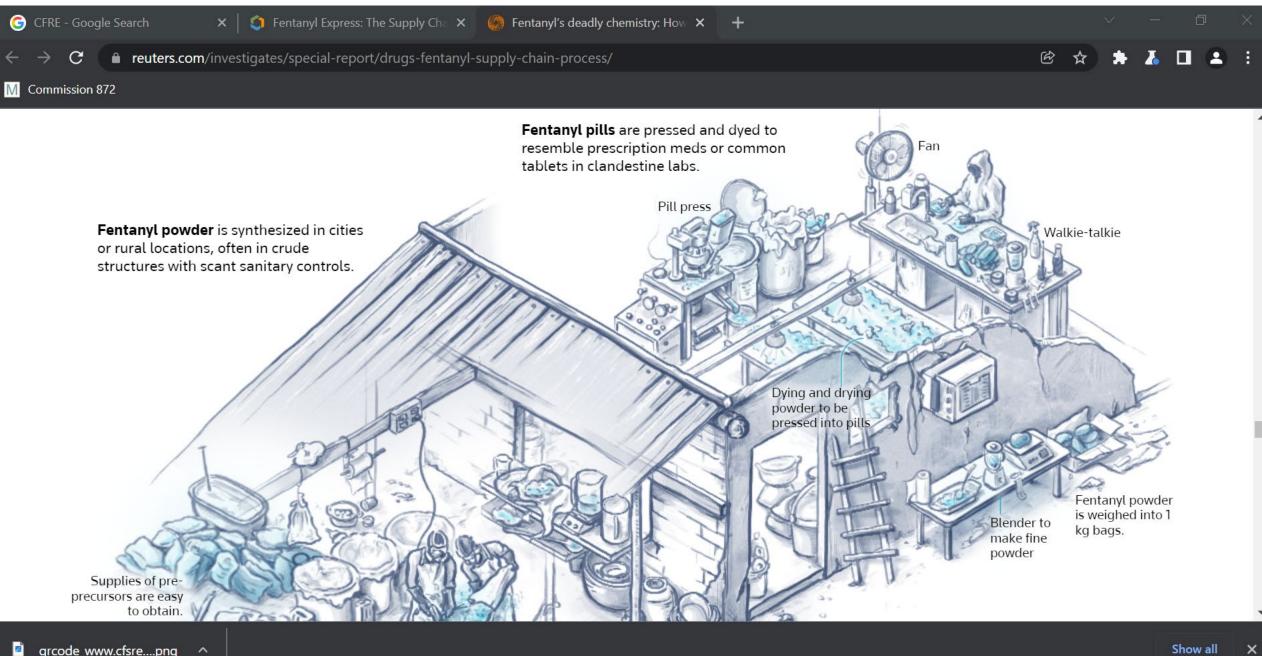


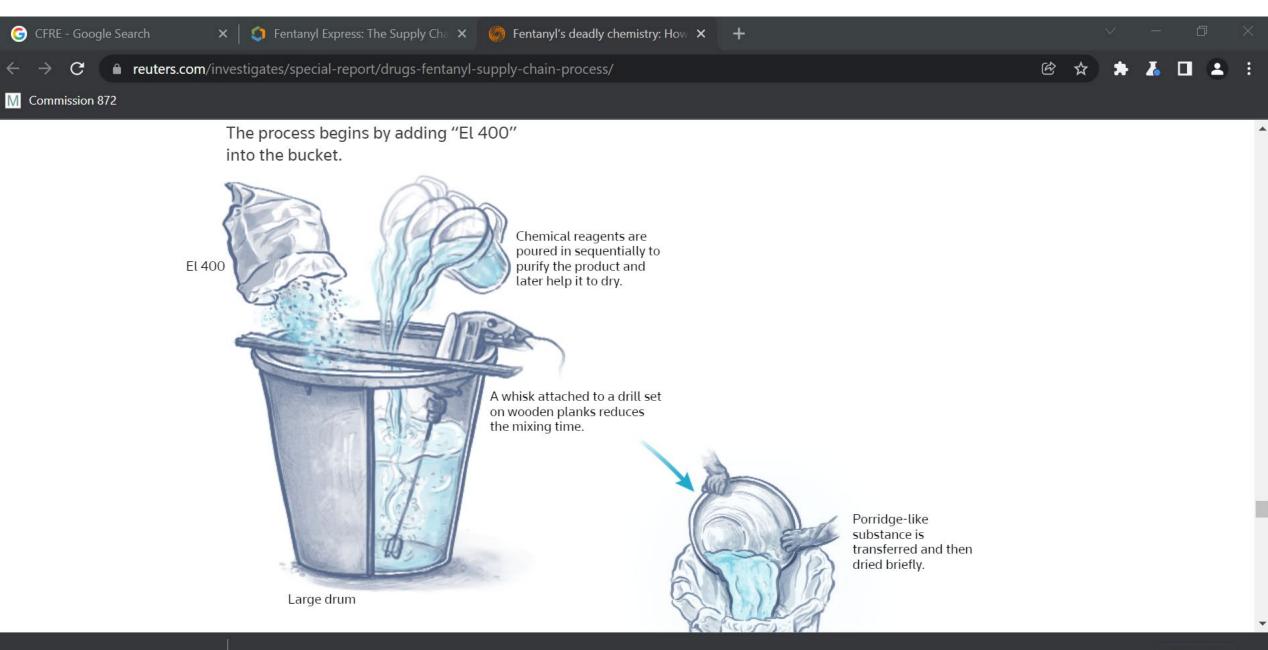
Pre-precursors

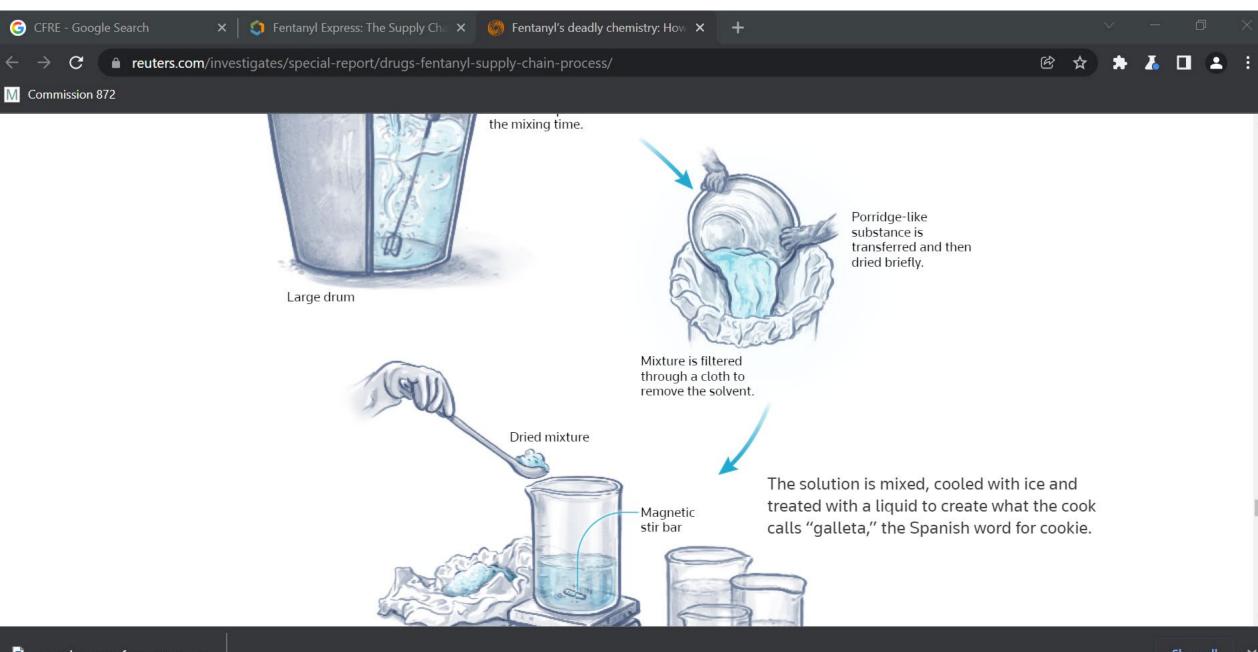
If packaged brownie mixes were banned, you could still make the dessert using eggs, chocolate, sugar and flour. That's the idea of **pre-precursors**.

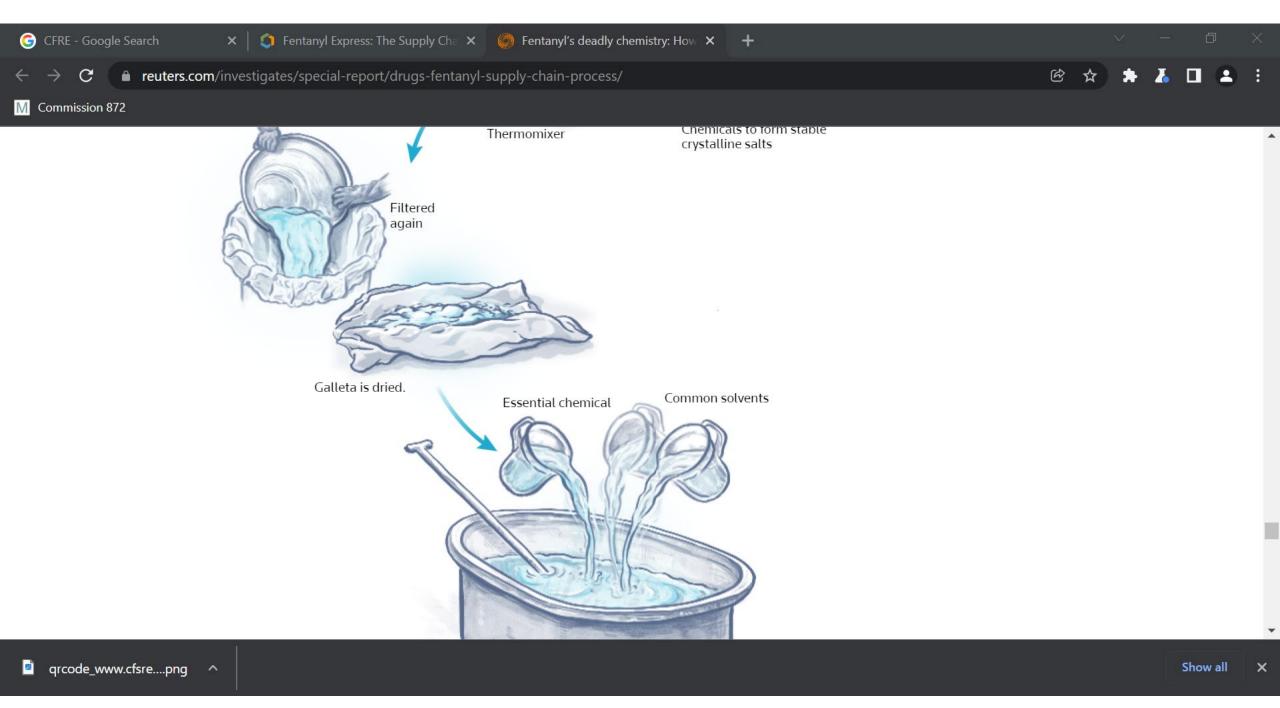
These chemicals contain the all-important **piperidine ring**, and are the ingredients that can be used to create immediate precursors.

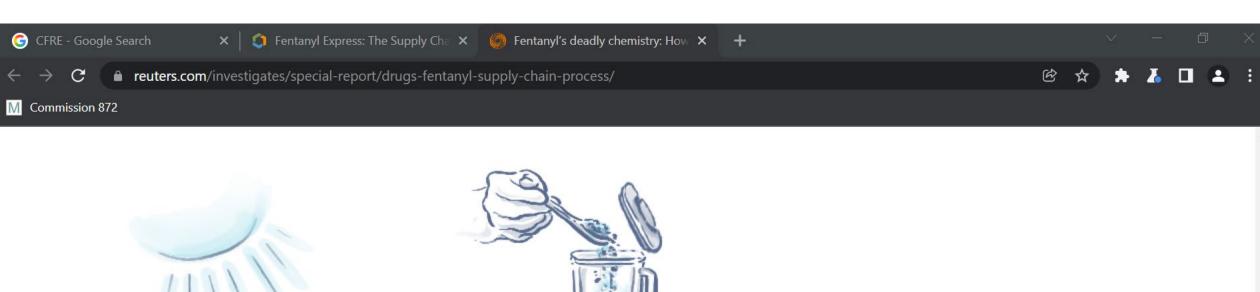
But legal industries also use pre-precursors to manufacture all sorts of goods, including fragrances, plastics, pesticides and lifesaving medications such as anti-tumor and anti-malarial drugs. That makes tightly regulating them much more complicated for authorities.

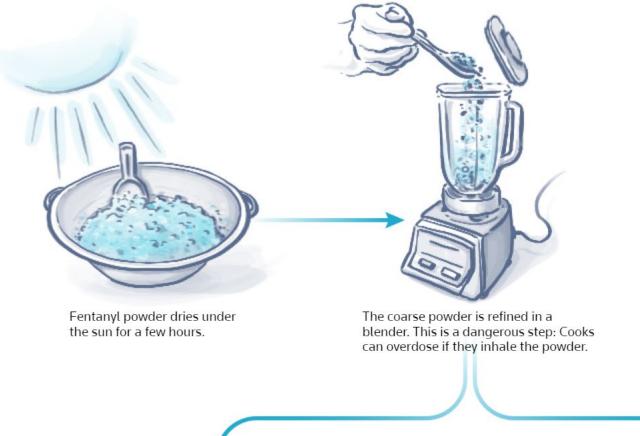


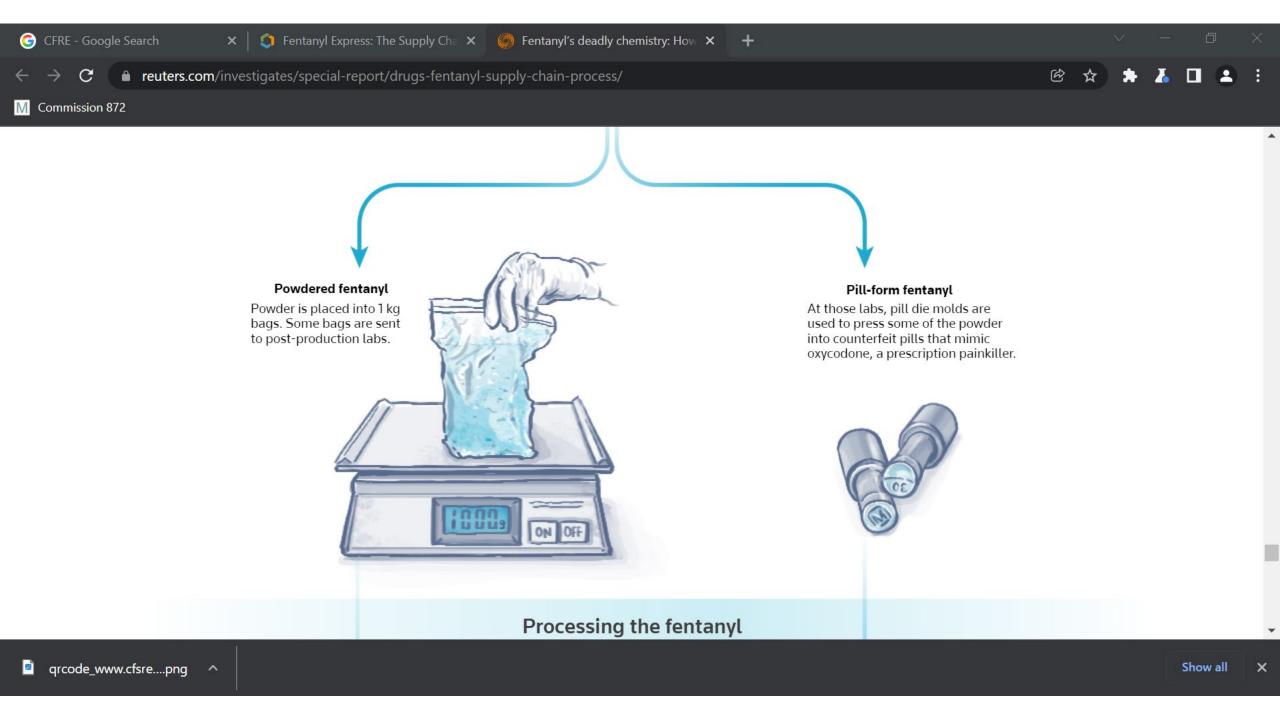


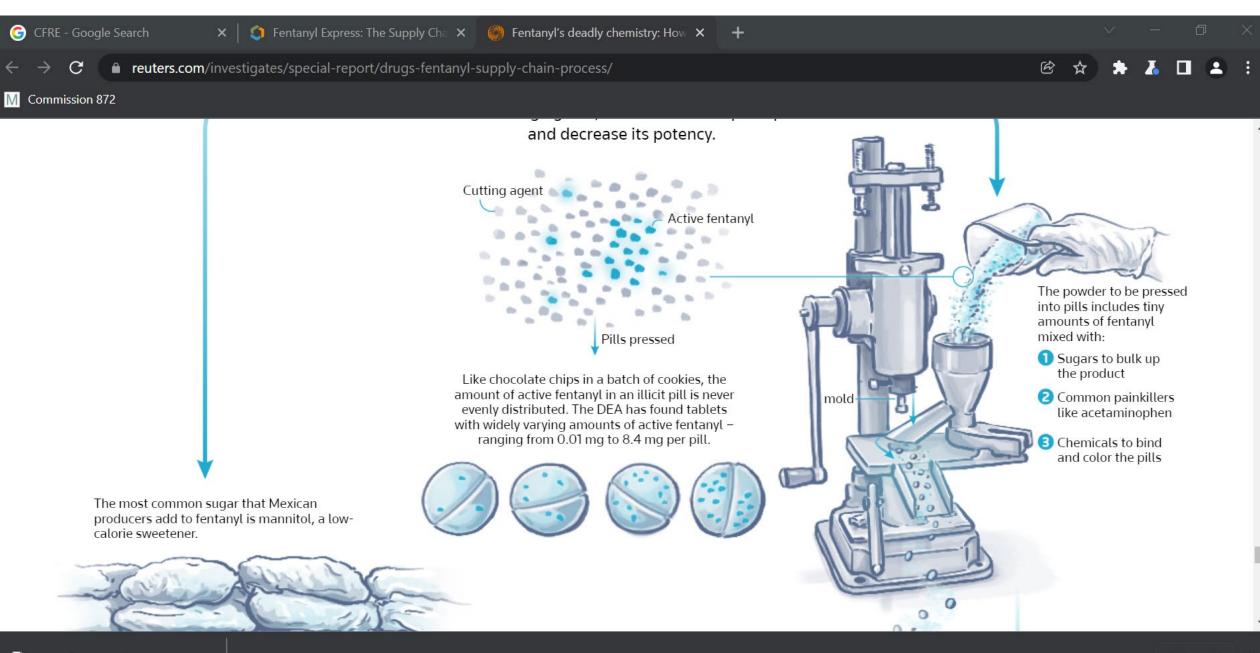


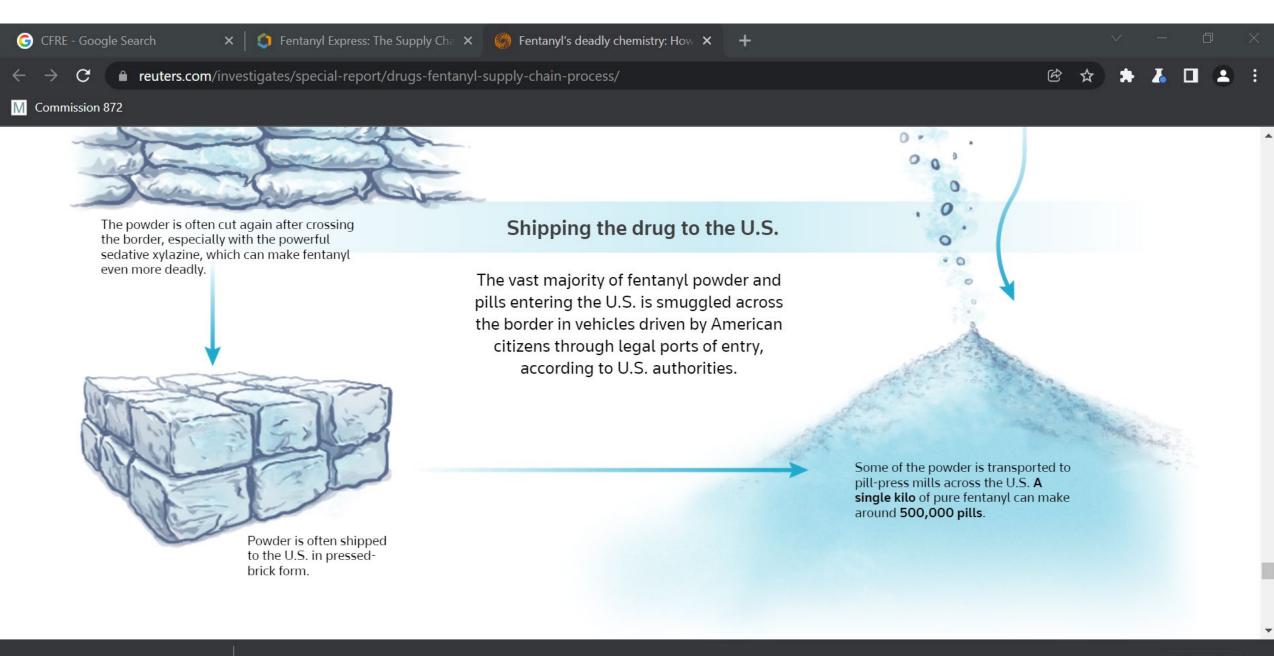














REUTERS VIDEO

CFSRE cfsre.org NPS Discovery

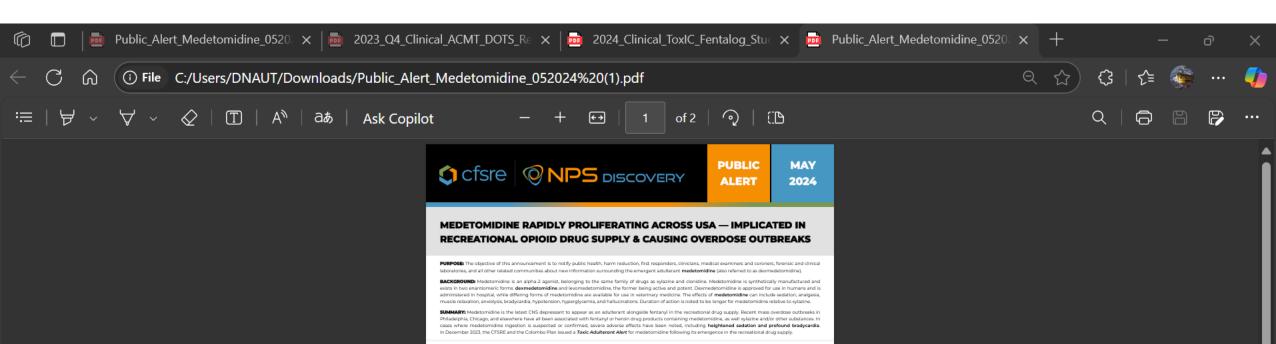


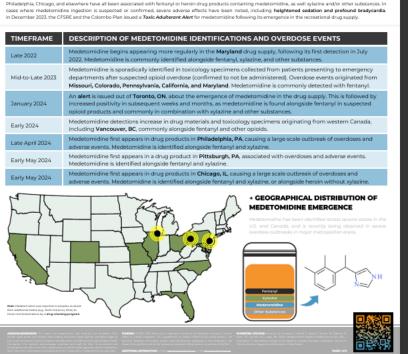


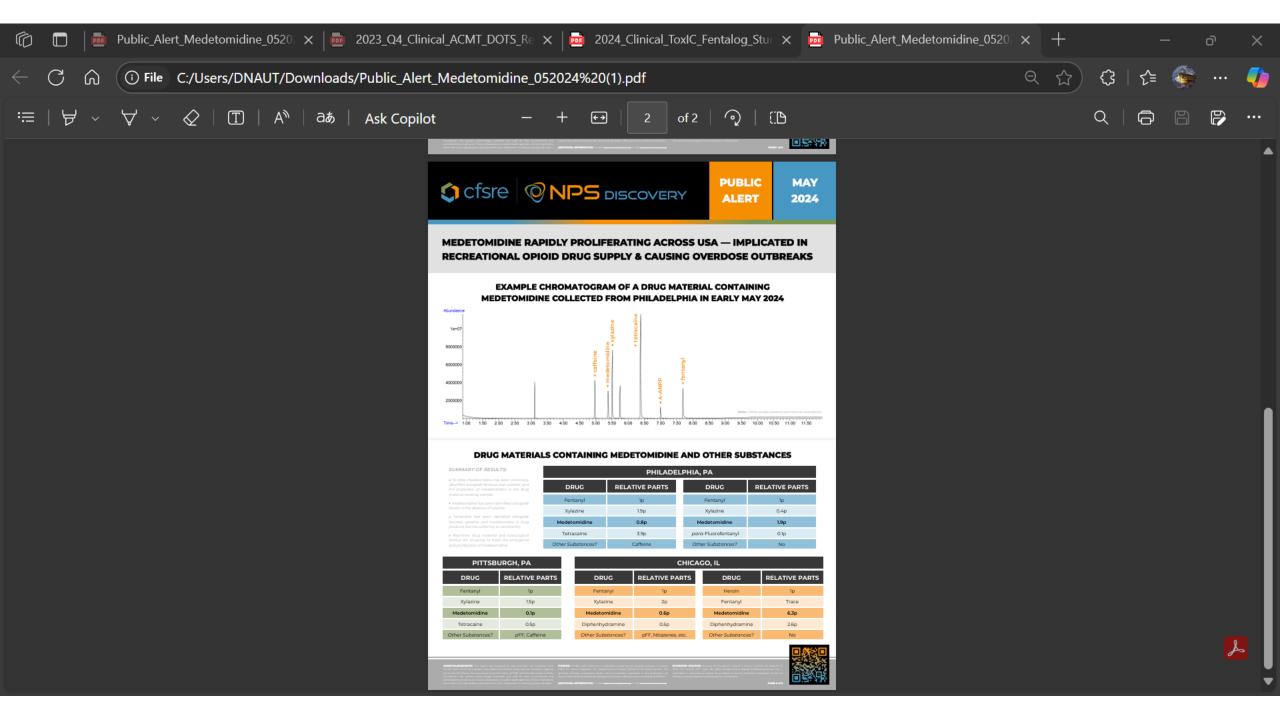
The Center for Forensic Science Research and Education Novel Psychoactive Substance Discovery

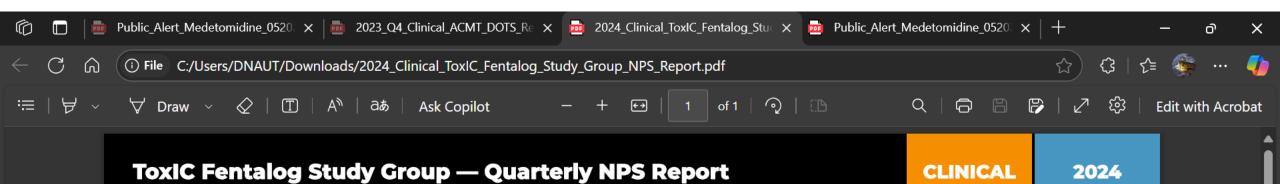


Early warning system in the US









PURPOSE: This report provides new information regarding comprehensive drug testing of clinical toxicology specimens collected after suspected opioid overdoses in cities across the United States (U.S.).

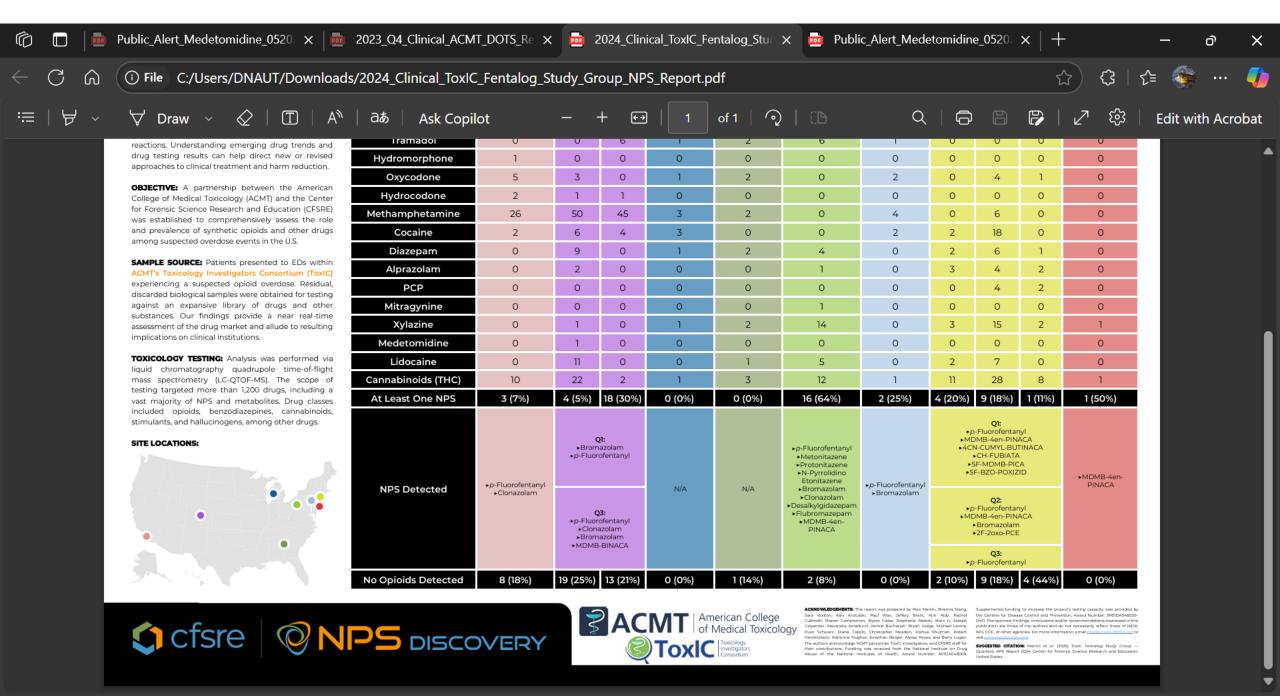
OVERVIEW: Drug use can lead to adverse events and overdose scenarios where individuals present to emergency departments (EDs) for clinical evaluation and/or treatment. The culprit can be traditional drugs (e.g., heroin, fentanyl, cocaine, methamphetamine) or novel psychoactive substances (NPS); however,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

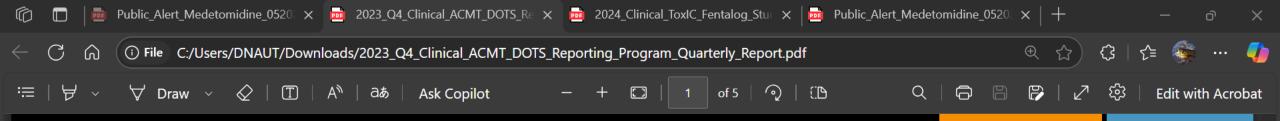
OBJECTIVE: A partnership between the American College of Medical Toxicology (ACMT) and the Center for Forensic Science Research and Education (CFSRE) was established to comprehensively assess the role and prevalence of synthetic opioids and other drugs among suspected overdose events in the U.S.

SAMPLE SOURCE: Patients presented to EDs within ACMT's Toxicology Investigators Consortium (ToxIC) experiencing a suspected opioid overdose. Residual, discarded biological samples were obtained for testing against an expansive library of drugs and other substances. Our findings provide a near real-time assessment of the drug market and allude to resulting implications on clinical institutions.

TOXICOLOGY TESTING: Analysis was performed via liquid chromatography quadrupole time-of-flight mass spectrometry (LC-QTOF-MS). The scope of testing targeted more than 1,200 drugs, including a vast majority of NPS and metabolites. Drug classes included opioids, benzodiazepines, cannabinoids,

Location >	Los Angeles, CA	Den C	ver, O	Grand Rapids, MI	Atlanta, GA	Pittsburgh, PA	Allentown, PA	Nev	w York Ci NY	ty,	Newark, NJ
Quarter >	Q2	Q1	Q3	Q3	Q3	Ć2	G2	Q1	Q2	Q3	Q3
Total Samples	45	75	61	7	7	25	8	20	51	9	2
At Least One Opioid	37 (82%)	56 (75%)	48 (79%)	7 (100%)	6 (86%)	23 (92%)	8 (100%)	18 (90%)	42 (82%)	5 (56%)	2 (100%)
Fentanyl	31	49	46	5	5	21	8	17	38	4	2
Heroin	0	0	1	2	0	1	0	1	1	0	0
Buprenorphine	1	0	1	0	0	0	0	0	0	0	0
Methadone	2	0	3	1	0	6	1	6	14	1	0
Tramadol	0	0	6	1	2	6	1	0	0	0	0
Hydromorphone	1	0	0	0	0	0	0	0	0	0	0
Oxycodone	5	3	0	1	2	0	2	0	4	1	0
Hydrocodone	2	1	1	0	0	0	0	0	0	0	0
Methamphetamine	26	50	45	3	2	0	4	0	6	0	0
Cocaine	2	6	4	3	0	0	2	2	18	0	0
Diazepam	0	9	0	1	2	4	0	2	6	1	0
Alprazolam	0	2	0	0	0	1	0	3	4	2	0
PCP	0	0	0	0	0	0	0	0	4	2	0
Mitragynine	0	0	0	0	0	1	0	0	0	0	0
Xylazine	0	1	0	1	2	14	0	3	15	2	1
Medetomidine	0	1	0	0	0	0	0	0	0	0	0
Lidocaine	0	11	0	0	1	5	0	2	7	0	0
Cannabinoids (THC)	10	22	2	1	3	12	1	11	28	8	1
At Least One NPS	3 (7%)	4 (5%)	18 (30%)	O (O%)	0 (0%)	16 (64%)	2 (25%)	4 (20%)	9 (18%)	1 (11%)	1 (50%)











PURPOSE: This report provides new information regarding comprehensive drug testing of toxicology specimens collected in clinical settings after suspected non-fatal opioid, stimulant, and other drug-related overdoses in cities across the United States (U.S.).

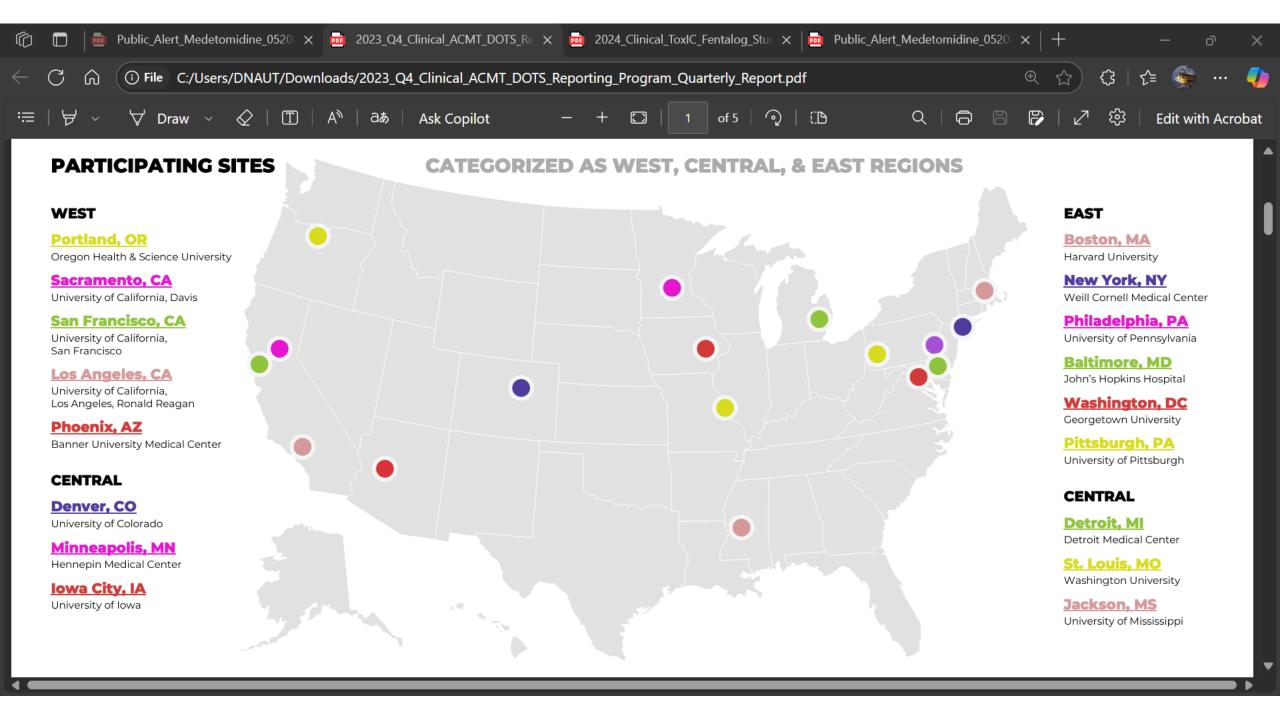
OVERVIEW: Drug use can lead to adverse events and overdose scenarios where individuals present to emergency departments (ED) for clinical evaluation and/or treatment. The culprit can be traditional drugs (e.g., heroin, fentanyl, cocaine, methamphetamine) or novel psychoactive substances (NPS); however,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

OBJECTIVE: A partnership between the American College of Medical Toxicology (ACMT) and the Center for Forensic Science Research and Education (CFSRE) was established to comprehensively assess the role and prevalence of drugs, adulterants, NPS, and other relevant substances among suspected overdose events in the U.S.

SAMPLE SOURCE: Patients presented to EDs within the Toxicology Investigators Consortium (ToxIC) Drug Overdose Toxico-Surveillance (DOTS) Reporting Program experiencing a suspected opioid or simulant related overdose. Blood samples were obtained for testing against an expansive library of drugs and other substances. Our findings provide near real-time assessment of drug markets and allude to resulting implications on clinical and forensic institutions.

TOXICOLOGY TESTING: Analysis was performed via liquid chromatography quadrupole time-of-flight mass spectrometry (LC-QTOF-MS) and liquid chromatography tandem quadrupole mass spectrometry (LC-QQQ-MS). The scope of LC-QTOF-MS testing targeted more than 1,200 drugs, including a vast majority of NPS and metabolites. Drug classes included opioids, benzodiazepines, cannabinoids, stimulants, and hallucinogens, among other drugs. The LC-QQQ-MS test was quantitative, targeting fentanyl, norfentanyl, methamphetamine, amphetamine, cocaine, benzoyleggonine, xylazine, and naloxone. Additional targets included for quantitative testing were NPS of interest (e.g., bromazolam, cathinones, nitazene analogues, and others).

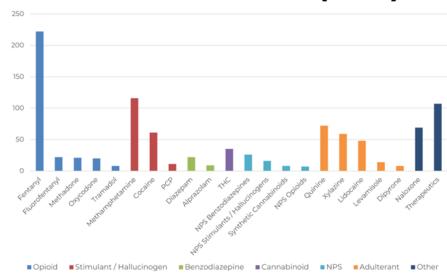
ACKNOWLEDGEMENTS: This report was prepared by Sara Walton, Alex Krotulski, Paul Wax, Jeffery Brent, Kim Aldy, Rachael Culbreth, Stephanie Abston, Sharan Campleman, Alyssa Falise, Alison Meyn, Maryann Amirshahi, Michael Chary, Jonathan Ford, Charlotte Goldfine, Robert Hendrickson, David Jang, Dana Jorgenson, Andrew King, Jacob Lebin, Michael Levine, David Liss, Brett Marlin, Daniel McCabe, Hoanvu Nguyen, Travis Olives, Jeanmarie Perrone, Anthony Pizon, Evan Schwarz, Craig Smollin, Meghan Spyres, Andrew Stolbach, Brianna Stang, Alyssa Reyes, and Barry Logan. The authors acknowledge ACMT personnel, ToxIC investigators, and CFSRE staff for their contributions. Funding was received by the US Food and Drug Administration (FDA) under Task Order 75F40122D00028/75F40123F19002. The views expressed are those of the authors and do not necessarily represent the position of, nor imply endorsement from, the US Food and Drug Administration or the US Government. For more information, contact npsdiscovery@cfsre.org or visit www.npsdiscovery.org





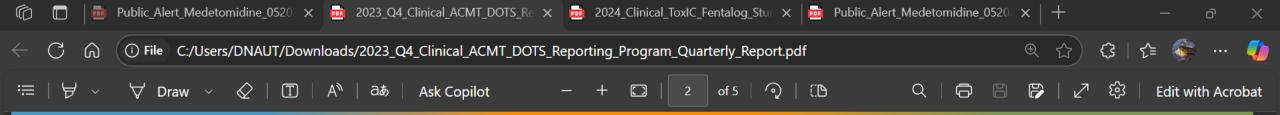
ALL SITE SUMMARY RESULTS (N=294)

University of Iowa



Tradit	iona	l Drugs (ı	ng/mL)		NPS (ng/mL)						
Drug	N	Mean ± Std Dev	Median	Range	Drug	N	Mean ± Std Dev	Median	Range		
Ethanol (mg/dL)	24	110±105	79	9.9-390	Bromazolam	21	81±85	50	<5-310		
Fentanyl	227	8.5±11	4.7	<1-100	Flubromazepam	2	-	-	<5->500		
Norfentanyl	207	8.4±21	2.8	<1-200	N,N-Dimethylpentylone	11	24±19	16	<10-63		
Methamphetamine	123	210±240	120	<1->1000	Pentylone	8	15±14	10	<10-54		
Amphetamine	116	35±51	19	<1-280	Eutylone	3	25±22	10	<10-57		
Cocaine	78	11±20	2.4	<1-67	N-Desethyl Isotonitazene	4	2.0±1.9	1.1	0.5-5.3		
BZE	160	240±240	160	<1->1000	Metonitazene	1	-	-	1.0		
Xylazine	58	14±28	4.9	<1-150	Protonitazene	1	-	-	<0.5		
Naloxone	101	15±59	5.2	<1-510							

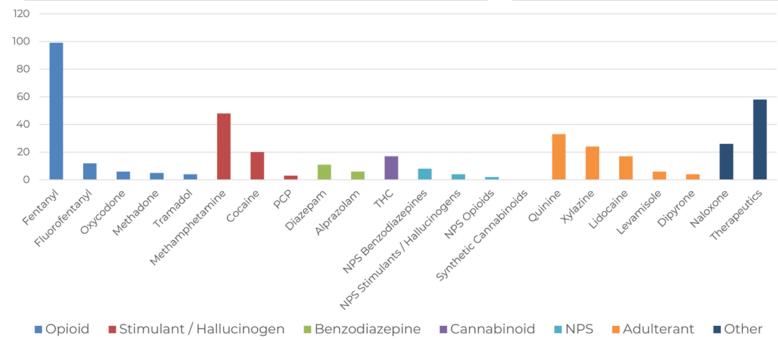
Jackson, MS University of Mississippi



CENTRAL REGION SUMMARY (N=130)

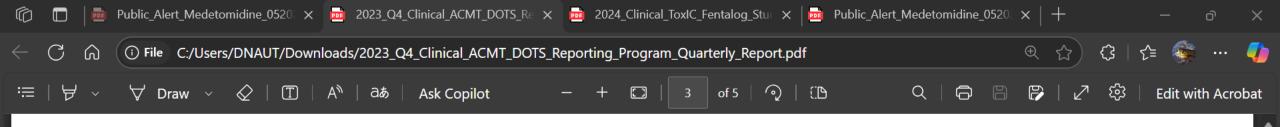
Traditi	ional	Drugs (ng	g/mL)	
Drug	N	Mean ± Std Dev	Median	Range
Ethanol (mg/dL)	9	170±140	130	20-390
Fentanyl	101	8.3±12	4.3	<1-100
Norfentanyl	89	9.2±27	2.8	<1-200
Methamphetamine	52	120±170	71	<1->1000
Amphetamine	47	23±30	11	<1-130
Cocaine	30	4.3±3.2	2.9	<1-9.4
BZE	66	260±249	175	<1->1000
Naloxone	44	6.2±4.0	5.0	<1-19
Xylazine	23	19±40	2.5	<1-150

	NPS (ng/mL)										
Drug N Mean ± Std Dev Median Range Drug N Range											
Bromazolam	6	61±37	55	<5-130		Flubromazepam	2	<5->500			

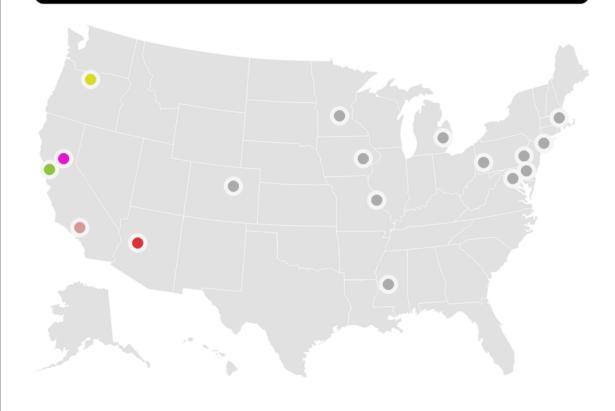


EAST REGION SUMMARY (N=90)

Tr	aditio	onal Drugs (ng/m	nL)		
Drug	N	Mean + Std Dev	Median	Dange	



WEST REGION



PORTLAND, OR (N=25)

- ▶ 96% positive for at least one opioid or stimulant
- ► Fentanyl (84%) was the primary opioid detected
- ► Methamphetamine (92%) was the primary stimulant detected, followed by cocaine (16%)
- ► Combined opioid and stimulant use was common (84%)
- ► THC and metabolites were detected (24%)
- Note: Xylazine and p-fluorofentanyl were not detected
- NPS: Bromazolam (4%)

Drug	N	Mean ± Std Dev	Median	Range	Drug	N	Mean ± Std Dev	Median	Range
Ethanol (mg/dL)	2	64±37	64	27-102	Cocaine	4	37±23	37	<1-61
Fentanyl	22	5.2±4.6	4.2	<1-22	BZE	7	53±39	65	<1->1000
Norfentanyl	21	2.0±1.1	1.6	<1-5.0	Naloxone	16	7.6±6.9	4.7	<1-28
Methamp.	24	270±240	230	2.3->1000	Amp.	24	38±52	25	<1-260
Bromazolam	1	43	-	-					

- ► Combined opioid and stimulant use was observed (53%)
- Xylazine was detected alongside fentanyl (31%)
- ► NPS: p-Fluorofentanyl (11%), 2-Fluoro-2-oxo PCE (5%), Bromazolam (4%), Flubromazepam (3%), N-Desethyl Etonitazene (1%)

Drug	N	Mean ± Std Dev	Median	Range	Drug	N	Mean ± Std Dev	Median	Range
Ethanol (mg/dL)	8	201±130	170	21-390	Cocaine	20	5.9±3.5	5.9	<1-9.4
Fentanyl	57	8.4±8.0	4.9	<1-32	BZE	45	280±260	215	<1->1000
Norfentanyl	53	6.7±11	2.8	<1-65	Xylazine	21	20±42	2.3	<1-150
Methamp.	26	95±110	52	<1-540	Bromazolam	3	82±33	63	55-130
Amp.	25	16±21	7.8	<1-83	Flubromazepam	2	-	-	<5->500
Naloxone	29	6.6±4.9	5.8	<1-19					

JACKSON, MS (N=12)

- ▶ 92% positive for at least one opioid or stimulant
- Fentanyl (67%) was the primary opioid detected, followed by methadone (8%) and oxycodone (8%)
- ▶ Methamphetamine (67%) was the only stimulant detected
- ► Combined opioid and stimulant use was identified (50%)

ı											
	Norfentanyl	15	4.8±3.6	4.2	<1-14	BZE	13	230±208	160	26->1000	
	Methamp.	2	70±70	70	<1-140	Xylazine	2	4.5±4.4	4.5	<1-9.1	
	Amp.	1	6.4	-	-	Naloxone	5	1.9±1.8	1.0	<1-4.9	

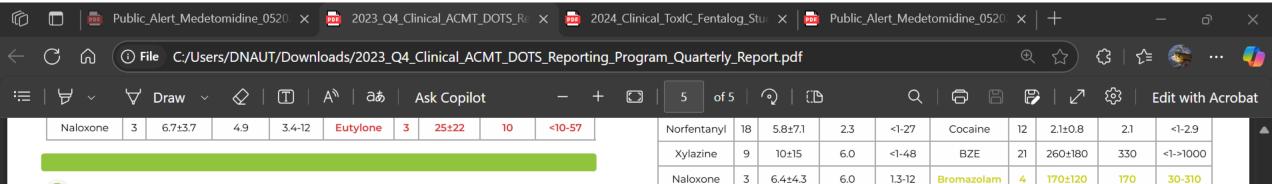
DENVER, CO (N=9)

- ▶ 89% positive for at least one opioid or stimulant
- ► Fentanyl (67%) was the only opioid detected
- Methamphetamine (56%) was the primary stimulant detected
- ► Combined opioid and stimulant use was observed (44%)
- No NPS were detected

Drug	N	Mean ± Std Dev	Median	Range	Drug	N	Mean ± Std Dev	Median	Range
Fentanyl	6	4.8±1.5	4.6	<1-7.4	Methamp.	6	101±86	110	2.5->1000
Norfentanyl	6	2.0±0.8	2.0	<1-2.9	Amp.	6	25±29	14	9.9-88
Cocaine	1	8.1	-	-	Naloxone	4	5.6±1.6	5.6	3.9-7.4
BZE	4	30±27	30	<1->1000					

IOWA CITY, IA (N=5)

- ▶ 80% positive for at least one opioid or stimulant
- Oxycodone (80%) was the primary opioid detected,



BALTIMORE, MD (N=27)

- ▶ 100% of samples positive for at least one opioid or stimulant
- ► Fentanyl (93%) was the primary opioid detected
- ► Cocaine (67%) was the only stimulant detected
- ► Combined opioid and stimulant use was common (67%)
- ► Xylazine was found alongside fentanyl (48%)
- ► NPS: Bromazolam (30%), *N*-Desethyl Isotonitazene (15%), *p*-Fluorofentanyl (15%), *N*,*N*-Dimethylpentylone (4%)

Drug	N	Mean ± Std Dev	Median	Range	Drug	N	Mean ± Std Dev	Median	Range
Ethanol (mg/dL)	3	43±26	45	10-75	Cocaine	16	2.0±0.5	2.4	<1-2.5
Fentanyl	26	13±16	8.3	<1-77	BZE	24	310±210	260	<1->1000
Norfentanyl	25	17±29	6.6	<1-120	Bromazolam	8	50±21	44	<5-84
Xylazine	13	13±15	5.9	<1-48	<i>N</i> -Desethyl Isotonitazene	4	2.0±1.9	1.1	0.5-5.3
Naloxone	5	4.1±1.2	3.3	<1-5.8					

PHILADELPHIA, PA (N=12)

- ▶ 100% positive for at least one opioid or stimulant
- ► Fentanyl (67%) & oxycodone (58%) were primary opioids detected
- ► Cocaine (58%) was the primary stimulant detected
- Xylazine was found alongside fentanyl (42%)
- NPS: Etizolam (25%), Bromazolam (8%), Metonitazene (8%), Protonitazene (8%)

Drug	N	Mean ± Std Dev	Median	Range	Drug	N	Mean ± Std Dev	Median	Range
Fentanyl	8	10±12	4.3	<1-38	BZE	7	210±230	120	4.7->1000
Norfentanyl	7	11±16	3.4	<1-48	Naloxone	3	1.8±0.4	1.9	1.2-2.3
Xylazine	5	7.1±4.0	7.0	<1-12	Bromazolam	1	46	-	-
Methamp.	1	28	-	-	Metonitazene	1	1.0	-	-
Amp.	1	14	-	-					