



Millennium Health Signals Report™

Volume 6

The "Fourth Wave"

The Rise of Stimulants and the Evolution of
Polysubstance Use in America's Fentanyl Crisis

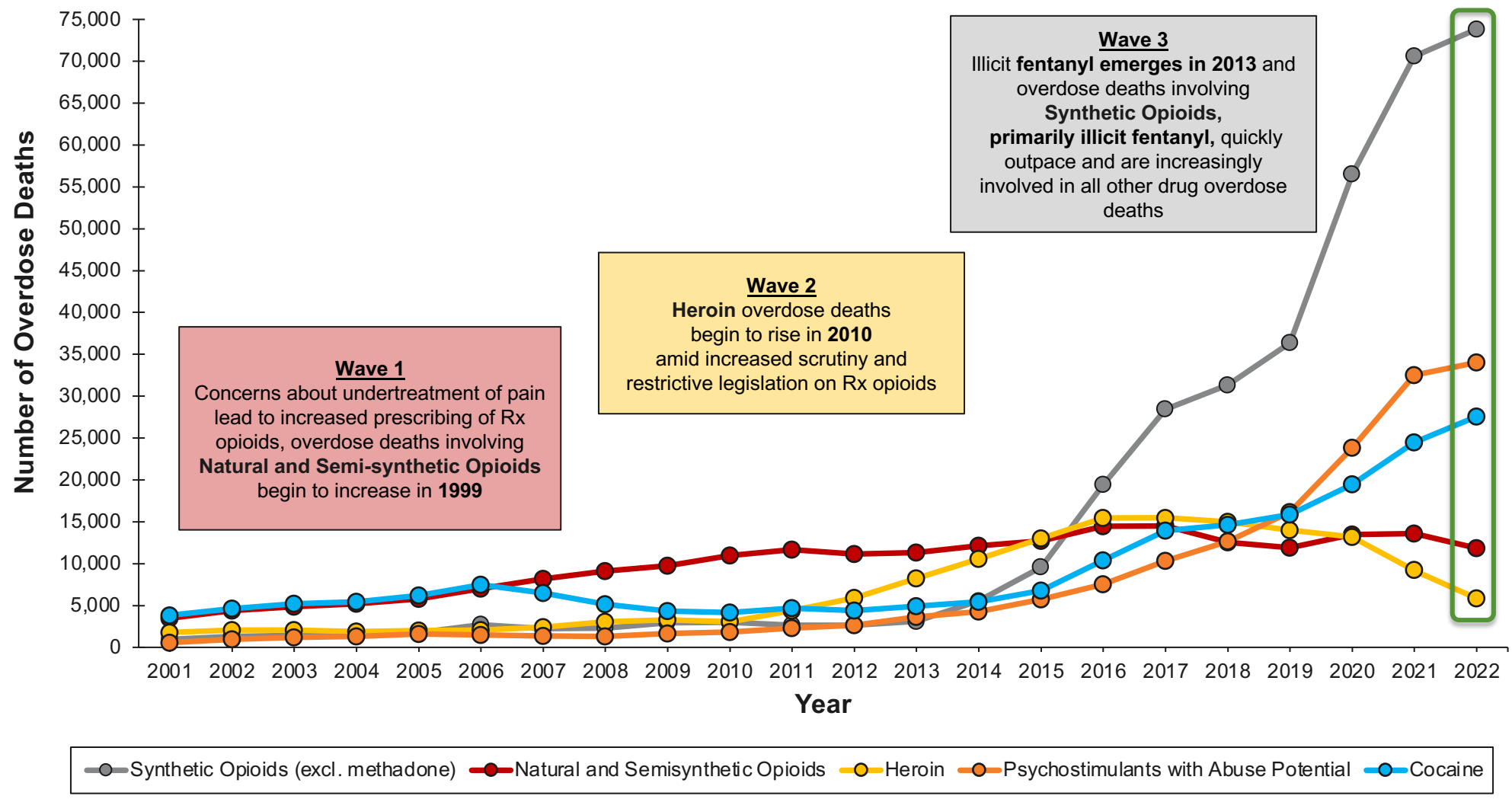
Eric Dawson, PharmD
Vice President, Clinical Affairs

- Clinical laboratory uniquely focused on providing clinical drug testing services for healthcare providers primarily in the areas of Substance Use Disorders, Behavioral Health, Pain Management and Primary Care
- With accounts in all 50 states and next day turn-around-time for laboratory results, Millennium provides clinicians with timely information to help guide individual treatment plans and has the capability to monitor large scale changes in drug use trends in real-time
- **Millennium's Emerging Threat Intelligence (ETI) Program™** provides timely surveillance data to help identify dangerous use patterns and support overdose prevention activities



107,941 total drug overdose deaths in 2022

Drug Overdose Deaths (2001-2022)



1. Spencer MR, Miniño AM, Warner M. Drug overdose deaths in the United States, 2001–2021. NCHS Data Brief, no 457. Hyattsville, MD: National Center for Health Statistics. 2022. DOI: <https://dx.doi.org/10.15620/cdc:122556>.

2. Spencer MR, Garnett MF, Miniño AM. Drug overdose deaths in the United States, 2002–2022. NCHS Data Brief, no 491. Hyattsville, MD: National Center for Health Statistics. 2024. DOI: <https://dx.doi.org/10.15620/cdc:135849>.

The “Fourth Wave”

- Non-opioid drugs are frequently involved in fatal opioid overdoses
- A “fourth wave” of drug overdose deaths involving fentanyl and stimulants (i.e., methamphetamine and/or cocaine) has emerged¹

Percentage of Fentanyl Overdose Deaths Involving Stimulants²

2010

<1%

2021


32.3%

1. Ciccarone D. The rise of illicit fentanyls, stimulants and the fourth wave of the opioid overdose crisis. *Curr Opin Psychiatry*. 2021;34(4):344-350. doi:10.1097/YCO.0000000000000717
2. Friedman J, Shover CL. Charting the fourth wave: Geographic, temporal, race/ethnicity and demographic trends in polysubstance fentanyl overdose deaths in the United States, 2010-2021. *Addiction*. 2023;118(12):2477-2485. doi:10.1111/add.16318

Risks Associated with Stimulants

- Today's methamphetamine is pure and potent
 - Greater euphoria...more toxic effects¹

Negative Consequences

- Abnormal heart rhythm
 - Chest Pain
 - Stroke
 - Agitation
 - Delirium
 - Trauma
 - Increased risk for HIV
- 

EMERGENCY DEPARTMENT

visits
INCREASED
by almost

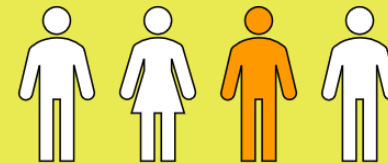


6x



from 2008 to 2018

With heavy use,
ONE in **FOUR**



will experience
AT LEAST **ONE**
PSYCHOTIC
EPIISODE

Psychiatric
Hospitalizations



NEARLY
DOUBLED
from 2015 to 2019

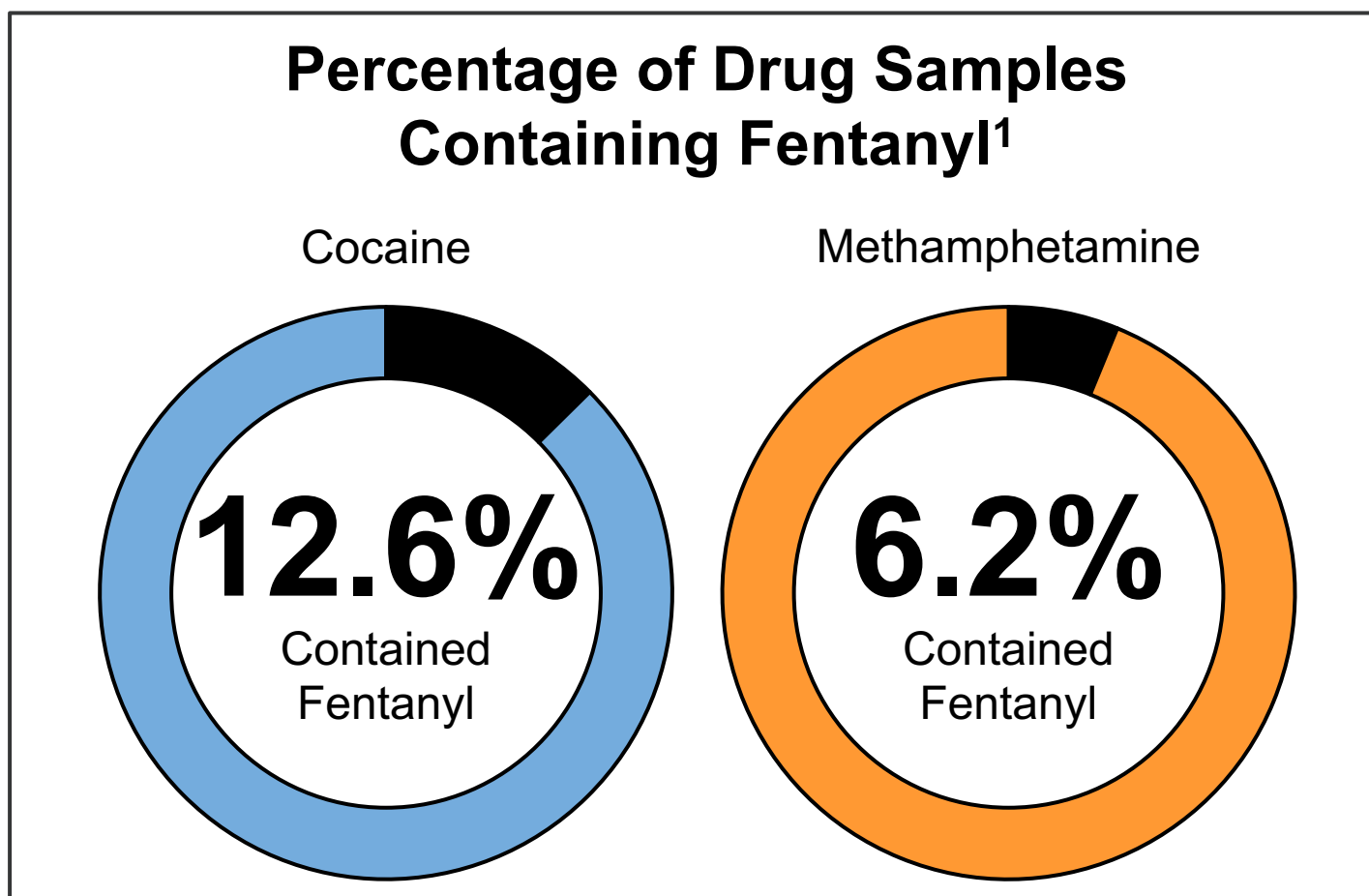
- Negative consequences of cocaine use are similar to those of methamphetamine²
 - May be less severe

1. Coffin PO, Suen LW. Methamphetamine Toxicities and Clinical Management. *NEJM Evidence*. 2023;2:12. doi:10.1056/EVIDra2300160

2. Rubin RB, Neugarten J. Medical complications of cocaine: changes in pattern of use and spectrum of complications. *J Toxicol Clin Toxicol*. 1992;30(1):1-12. doi:10.3109/15563659208994441

Inadvertent Exposure Risks

- Increased overdose risk from inadvertent exposure to fentanyl and other substances
 - More common in powder forms compared to crystalline forms¹



1. Wagner KD, Fiuty P, Page K, et al. Prevalence of fentanyl in methamphetamine and cocaine samples collected by community-based drug checking services. *Drug Alcohol Depend.* 2023;252:110985. doi:10.1016/j.drugalcdep.2023.110985

Methods

- Cross-sectional analysis of definitive urine drug testing (UDT) results from over 4.1 million unique patients
- Collected in health care practices in all 50 U.S. states between January 1, 2013, and December 15, 2023
- Specimens with reported prescriptions for any of the UDT drugs/categories evaluated were excluded from all analyses
- Fentanyl analogue testing began in July 2019, except parafluorofentanyl which began in August 2022
- Xylazine testing began in April 2023
- Testing for novel illicit opioids and illicit benzodiazepines began in August 2022



UDT Positivity Rates Significantly and Strongly Correlate with Overdose Mortality

JAMA Network | Open™



Original Investigation | Public Health

Analysis of Urine Drug Test Results From Substance Use Disorder Treatment Practices and Overdose Mortality Rates, 2013-2020

Penn Whitley, BA; Leah LaRue, PharmD, CMPP, PMP; Soledad A. Fernandez, PhD; Steven D. Passik, PhD; Eric Dawson, PharmD; Rebecca D. Jackson, MD

Abstract

IMPORTANCE Drug overdose deaths in the US are collected from public health surveillance sources associated with overdose mortality rates, but the testing (UDT) is one potentially underused source of timely data collection.

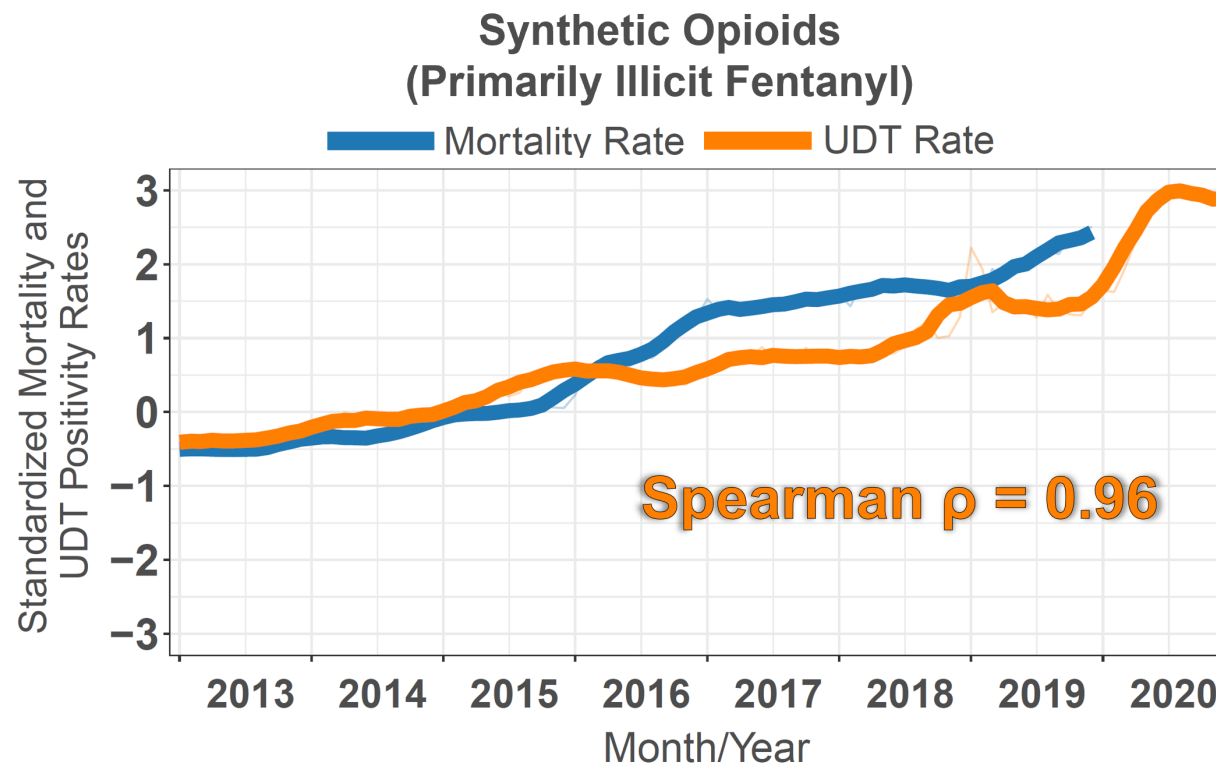
OBJECTIVE To evaluate the correlation between database and overdose mortality data from the N

DESIGN, SETTING, AND PARTICIPANTS This re 500 000 urine specimens submitted for UDT by practices and collected between January 1, 2013, obtained from the Millennium Health proprietary were obtained from the National Vital Statistics S Prevention (CDC WONDER). Specimens were an heroin, methamphetamine, synthetic opioids, ar tandem mass spectrometry. Participants were ad specimens at SUD treatment practices.

EXPOSURES Urine drug testing.

MAIN OUTCOMES AND MEASURES The prima positivity rates and overdose mortality rates at n multivariate regression models were also used to county-level overdose mortality and standardized UDT positivity rates.

RESULTS Among 500 000 unique patient specimens collected from SUD treatment practices between 2013 and 2020, 288 534 specimens (57.7%) were from men, and the median age of the study population was 34 years (IQR, 17-51 years). On a national level, synthetic opioids and



+ Supplemental content

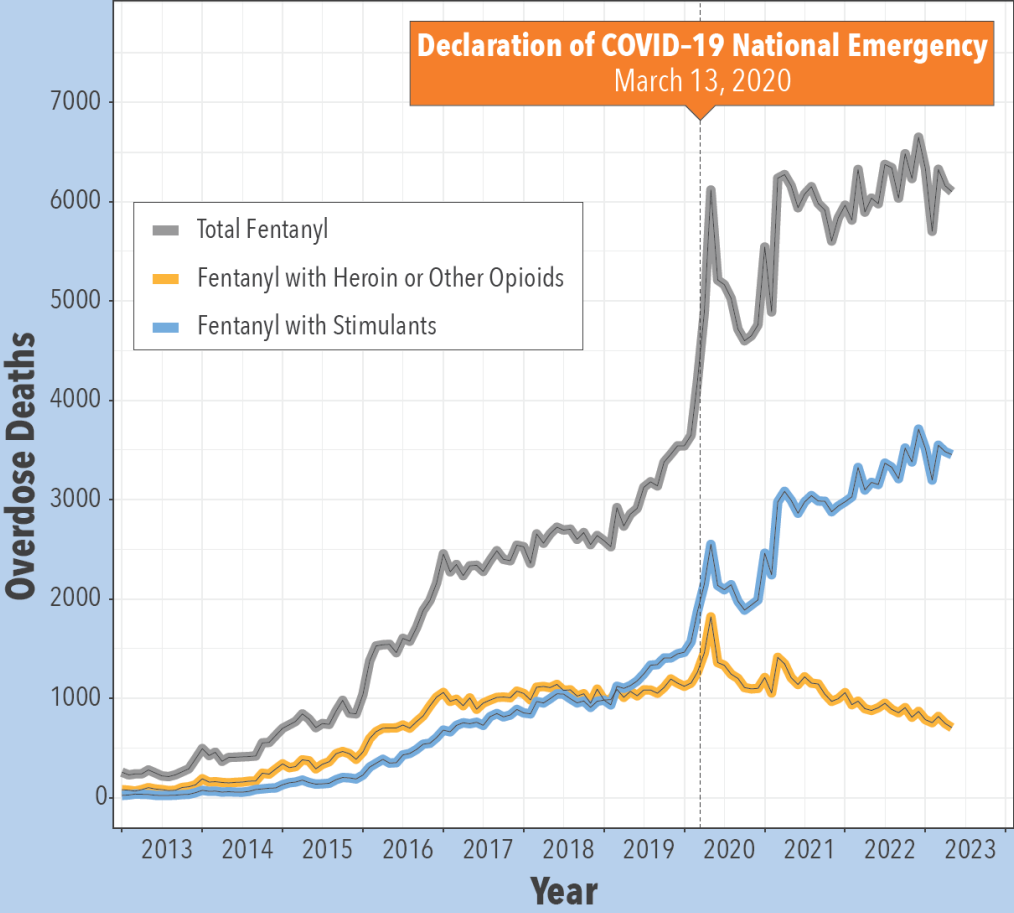
Author affiliations and article information are listed at the end of this article.

Comparison of Fentanyl UDT Data and Fentanyl-Related Overdose Mortality



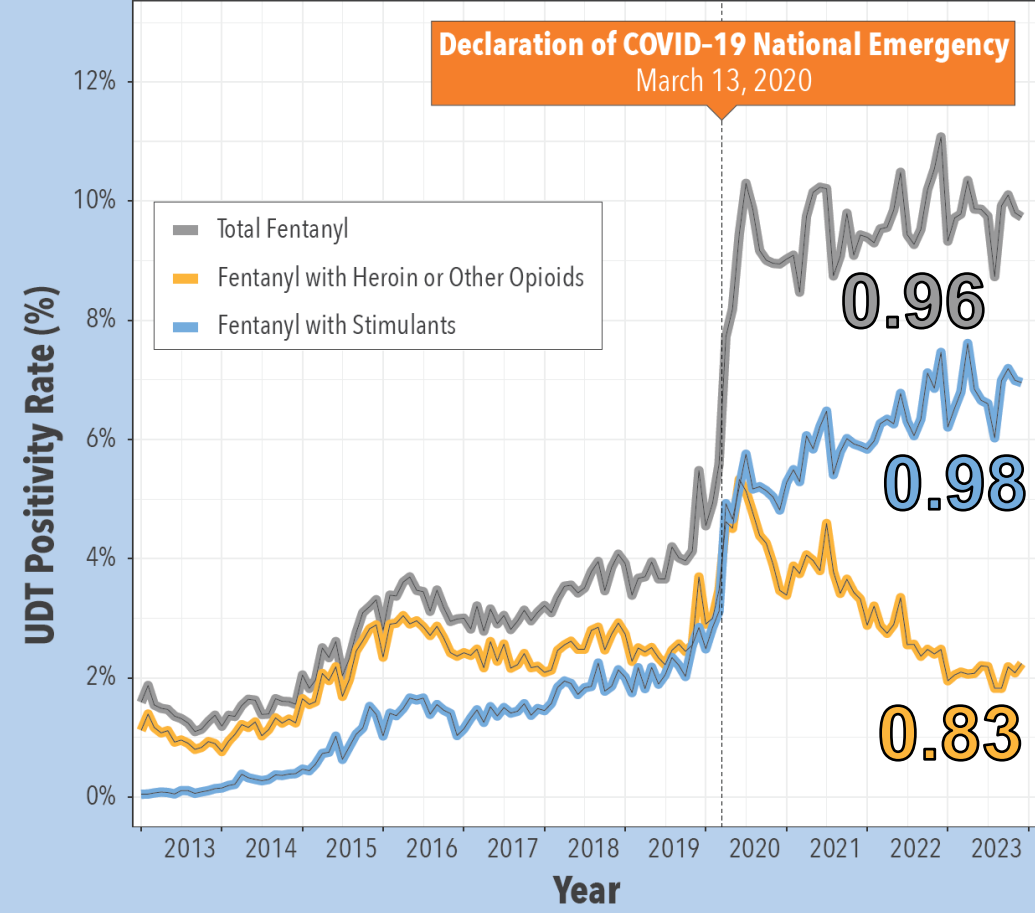
Overdose Mortality Data

Declaration of COVID-19 National Emergency
March 13, 2020



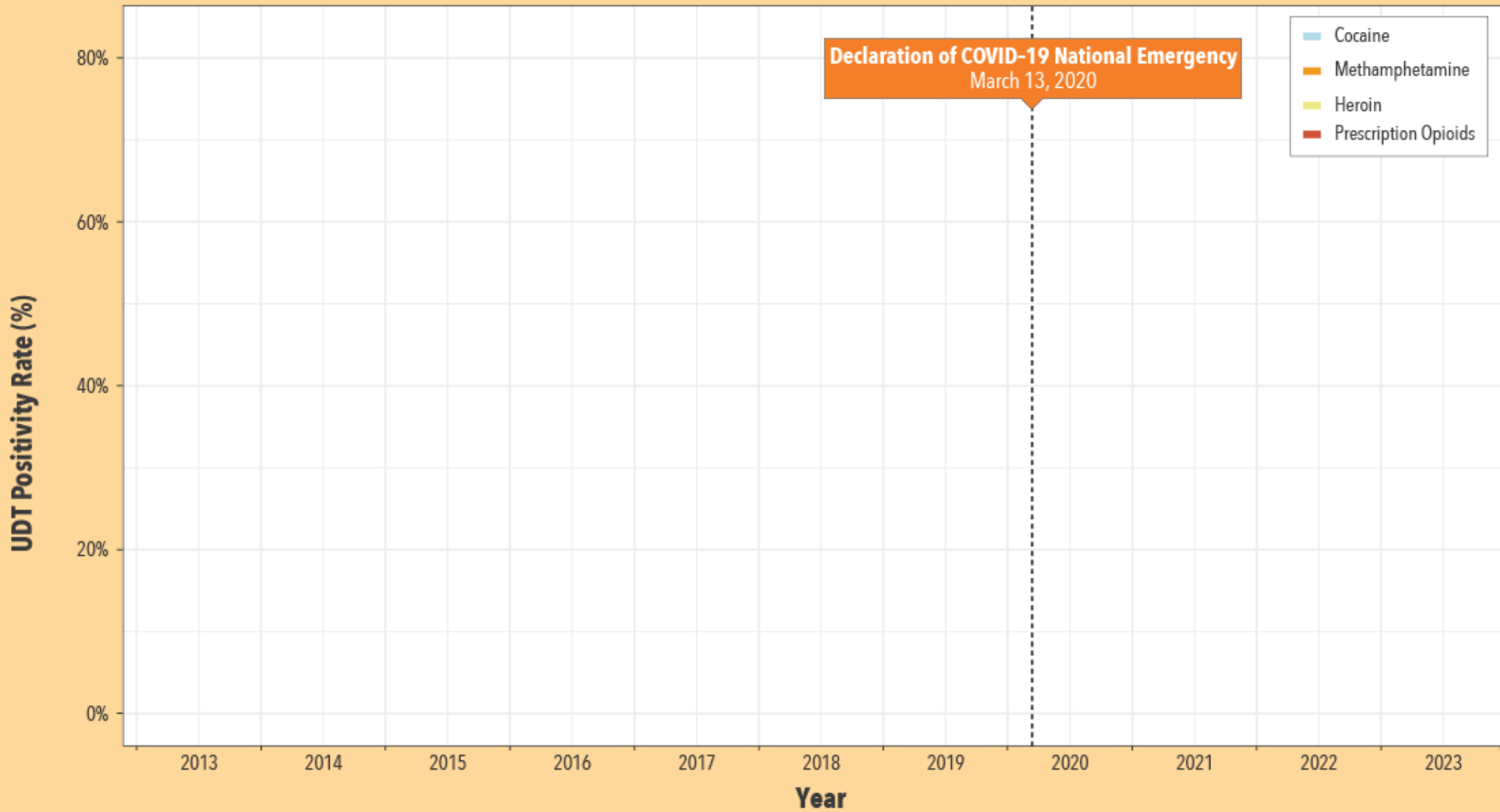
UDT Data

Declaration of COVID-19 National Emergency
March 13, 2020



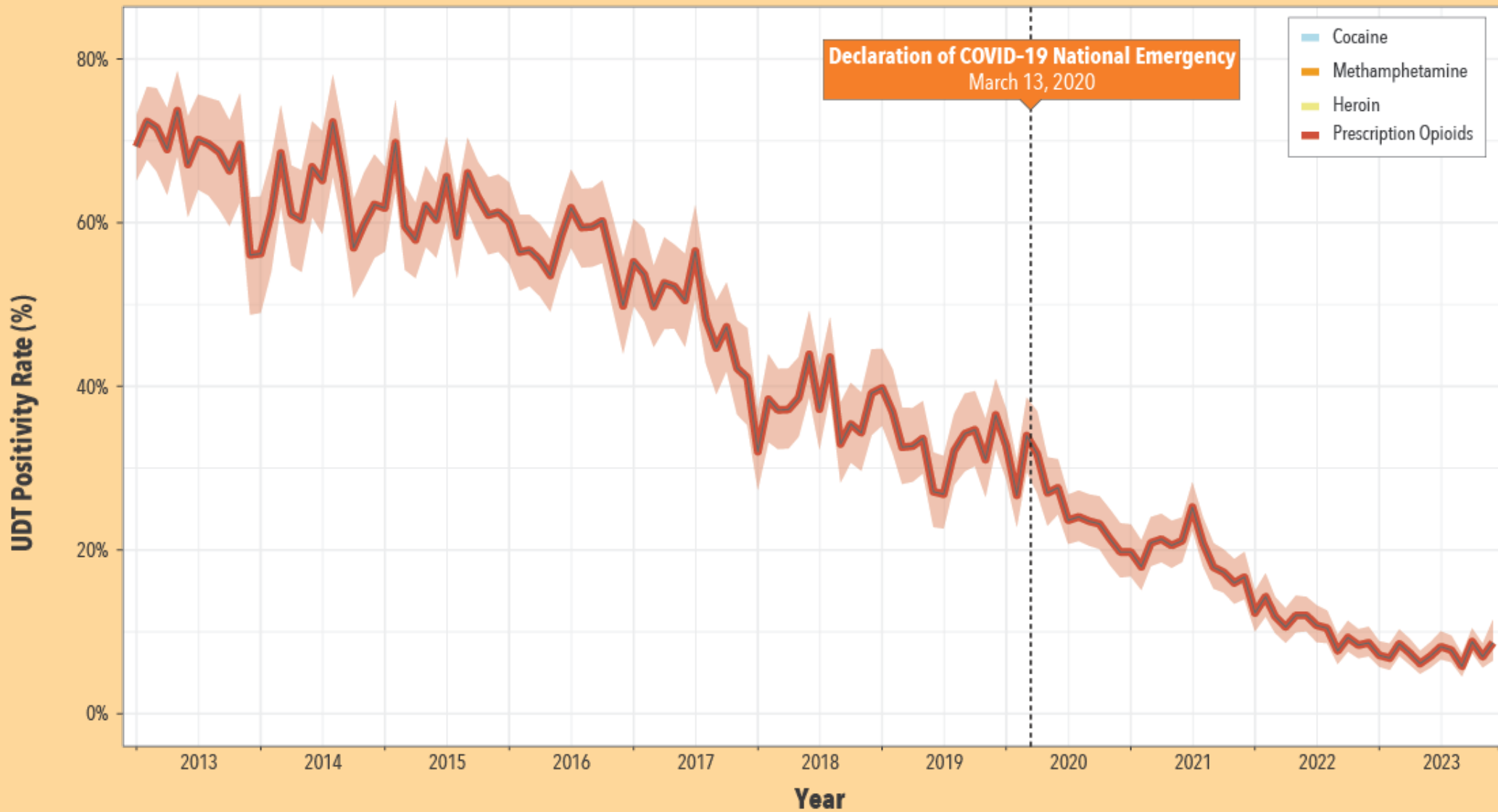
1. Millennium Health, LLC. Millennium Health Signals Report, Volume 6. *The "Fourth Wave" – The Rise of Stimulants and the Evolution of Polysubstance Use in America's Fentanyl Crisis*. Published: February 2024. Available at: <https://www.millenniumhealth.com/signalsreport/>

National Co-Detection of Prescription Opioids, Heroin, Methamphetamine, and Cocaine in Fentanyl-Positive Specimens



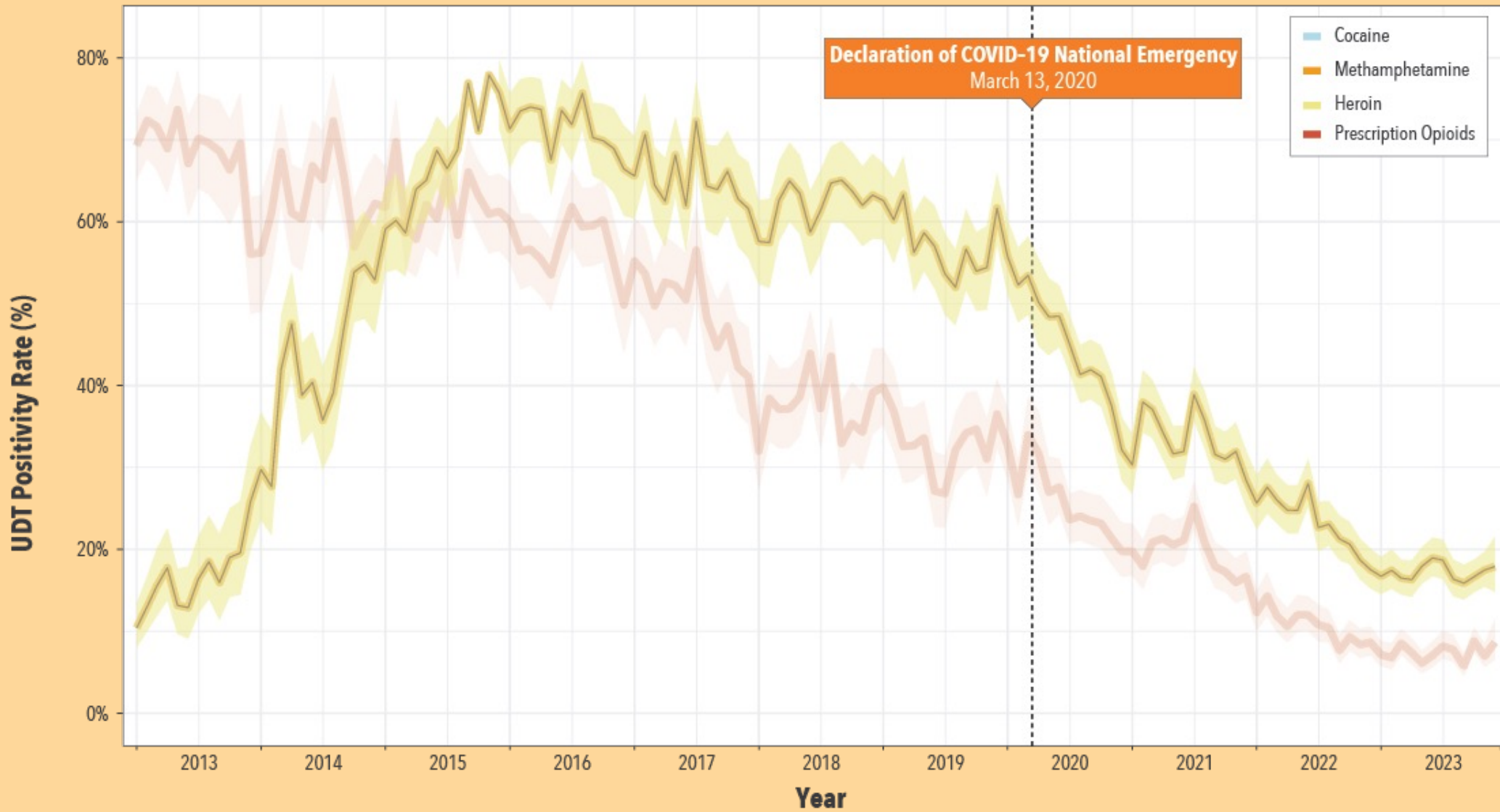
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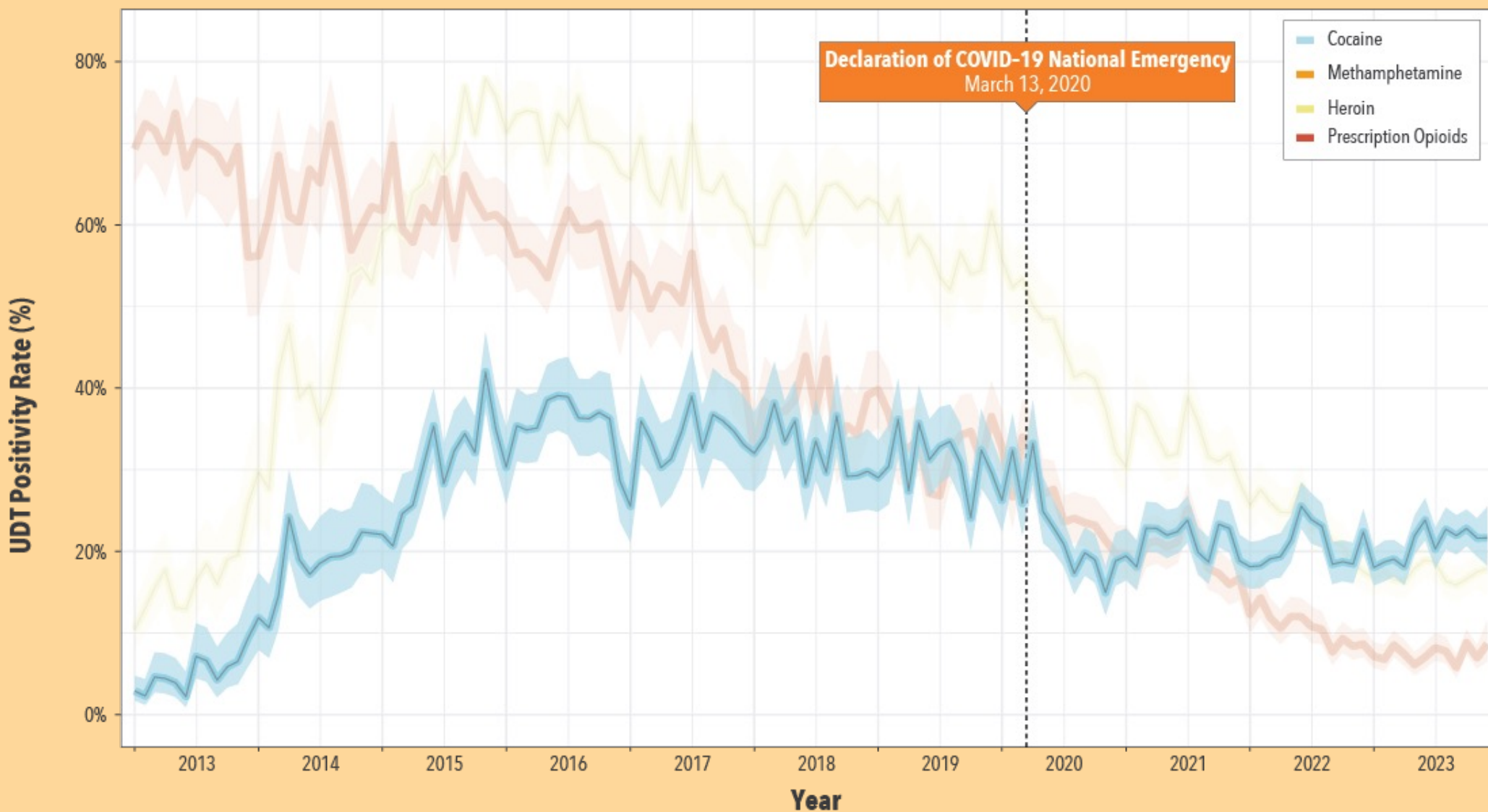
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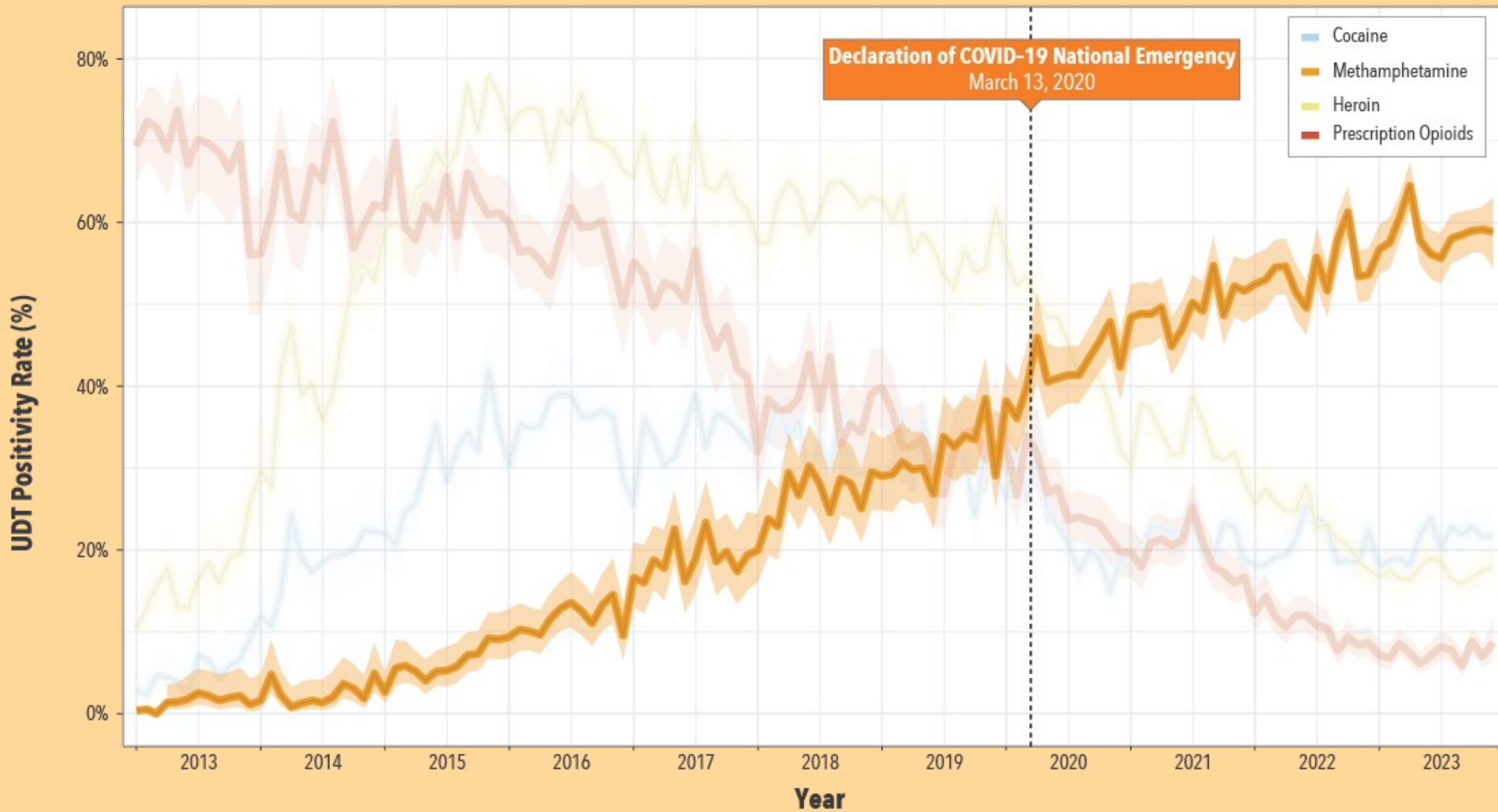
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National UDT Positivity Rates for Specific Drug Use Combinations Over Time



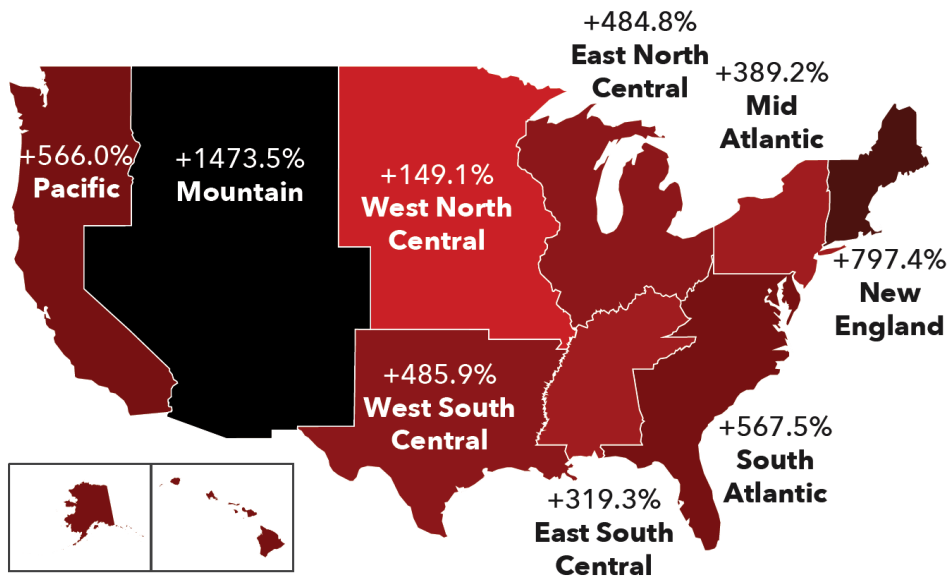
Drug Combination	2015	2019	2023
	0.76%	7.5%	53%
	1.5%	9%	9.8%
	0.1%	1.9%	8.5%
	28%	10%	1.1%
	1.7%	4.1%	0.79%
	21%	8.3%	0.71%

= Fentanyl
 = Prescription Opioids
 = Heroin
 = Methamphetamine
 = Cocaine

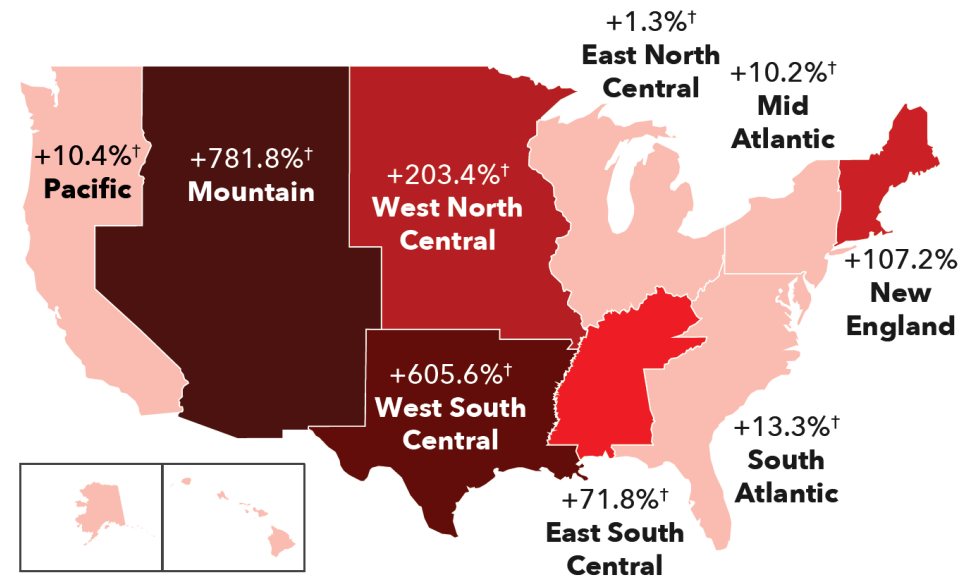
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Percent Change in Methamphetamine and Cocaine Detection in Fentanyl-Positive Specimens from 2015 to 2023

Methamphetamine in Fentanyl-Positive Specimens



Cocaine in Fentanyl-Positive Specimens



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Positivity Rates for Methamphetamine Co-Detection Over Time



Methamphetamine in Fentanyl-Positive Specimens by U.S. Census Division

	Pacific	Mountain	West North Central	West South Central	East North Central	East South Central	Mid Atlantic	South Atlantic	New England
2015	10.6%	4.9%	21.8%	7.1%	6.6%	11.4%	3.7%	4.0%	3.8%
2017	28.9%	14.4%	47.8%	16.3%	18.5%	37.1%	8.4%	7.4%	10.5%
2019	52.7%	36.3%	49.2%	33.0%	28.8%	46.5%	15.2%	14.8%	20.5%
2021	66.0%	62.0%	50.0%	36.9%	37.1%	50.4%	24.5%	26.0%	39.4%
2023	70.6%	77.1%	54.3%	41.6%	38.6%	47.8%	18.1%	26.7%	34.1%



1. Millennium Health, LLC. Millennium Health Signals Report, Volume 6. *The "Fourth Wave" – The Rise of Stimulants and the Evolution of Polysubstance Use in America's Fentanyl Crisis*. Published: February 2024. Available at: <https://www.millenniumhealth.com/signalsreport/>

Positivity Rates for Cocaine Co-Detection Over Time



Cocaine in Fentanyl-Positive Specimens by U.S. Census Division

	Pacific	Mountain	West North Central	West South Central	East North Central	East South Central	Mid Atlantic	South Atlantic	New England
2015	11.5%	1.1%	5.9%	3.6%	37.7%	14.2%	28.4%	38.4%	26.5%
2017	16.5%	10.8%	15.9%	15.4%	38.8%	22.4%	29.4%	45.9%	36.2%
2019	13.1%	12.2%	25.2%	29.0%	38.3%	18.0%	34.3%	43.1%	43.9%
2021	9.4%	10.4%	13.1%	30.4%	35.1%	20.8%	39.7%	36.2%	40.9%
2023	12.7%	9.7%	17.9%	25.4%	38.2%	24.4%	31.3%	43.5%	54.9%

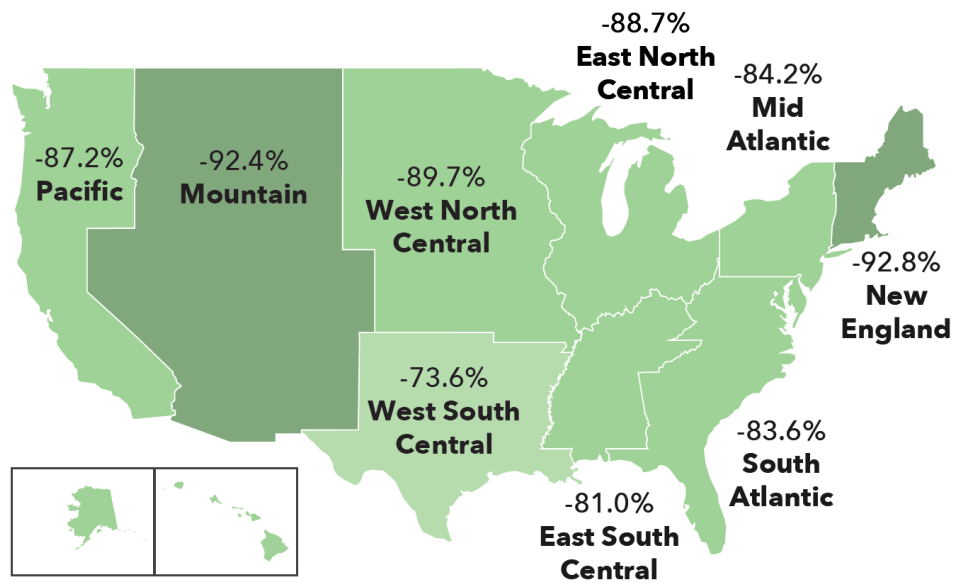


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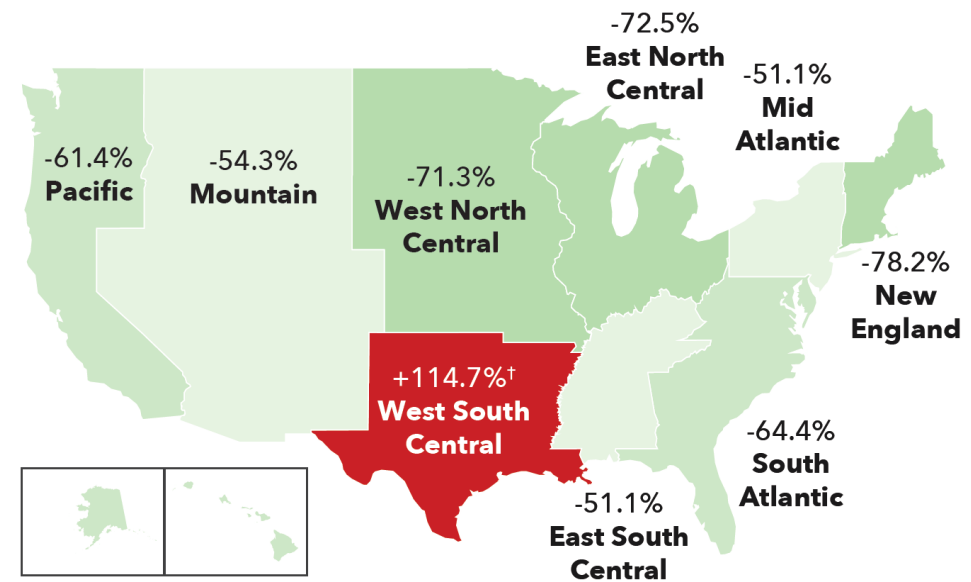
Percent Change in Prescription Opioid and Heroin Detection in Fentanyl-Positive Specimens from 2015 to 2023



Prescription Opioids in Fentanyl-Positive Specimens



Heroin in Fentanyl-Positive Specimens



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Positivity Rates for Prescription Opioid Co-Detection Over Time



Prescription Opioids in Fentanyl-Positive Specimens by U.S. Census Division

	Pacific	Mountain	West North Central	West South Central	East North Central	East South Central	Mid Atlantic	South Atlantic	New England
2015	54.8%	72.7%	56.3%	58.0%	61.8%	57.4%	64.7%	65.9%	51.1%
2017	53.8%	68.5%	57.7%	72.1%	39.9%	48.4%	63.0%	55.6%	33.5%
2019	54.1%	38.4%	40.3%	68.0%	25.1%	28.7%	40.4%	38.4%	18.7%
2021	34.4%	18.9%	19.8%	27.0%	11.8%	12.8%	21.9%	25.4%	7.2%
2023	7.0%	5.5%	5.8%	15.3%	7.0%	10.9%	10.2%	10.8%	3.7%



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Positivity Rates for Heroin Co-Detection Over Time



Heroin in Fentanyl-Positive Specimens by U.S. Census Division

	Pacific	Mountain	West North Central	West South Central	East North Central	East South Central	Mid Atlantic	South Atlantic	New England
2015	37.8%	20.8%	58.8%	17.0%	81.6%	40.3%	65.3%	72.7%	66.9%
2017	49.2%	29.7%	69.8%	38.5%	69.3%	68.2%	66.0%	74.9%	47.1%
2019	56.5%	33.7%	76.4%	67.0%	57.9%	62.1%	67.4%	62.3%	41.5%
2021	52.0%	25.1%	38.5%	54.6%	27.0%	35.0%	36.4%	37.6%	21.5%
2023	14.6%	9.5%	16.9%	36.5%	22.4%	19.7%	31.9%	25.9%	14.6%



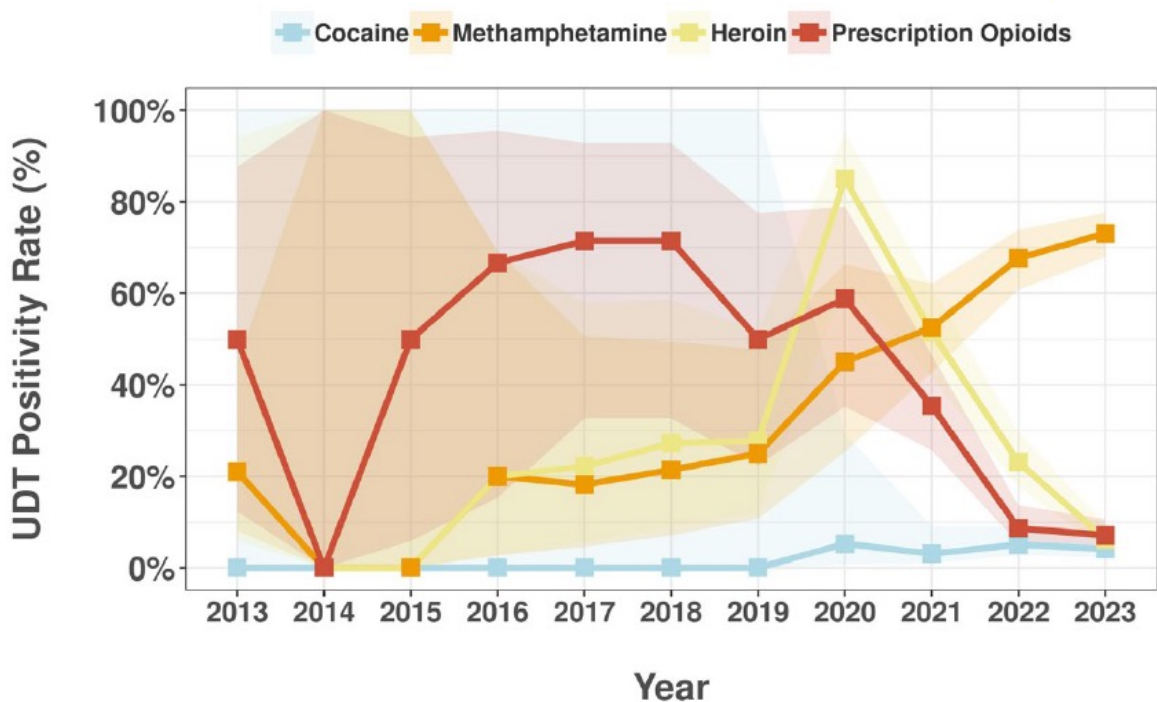
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The “Fourth Wave”: The Rise of Stimulants and the Evolution of Polysubstance Use in America’s Fentanyl Crisis

STATE-LEVEL SNAPSHOT: MONTANA



Figure 1. Detection of Prescription Opioids, Heroin, Methamphetamine, and Cocaine in Fentanyl-Positive UDT Specimens from 2013-2023

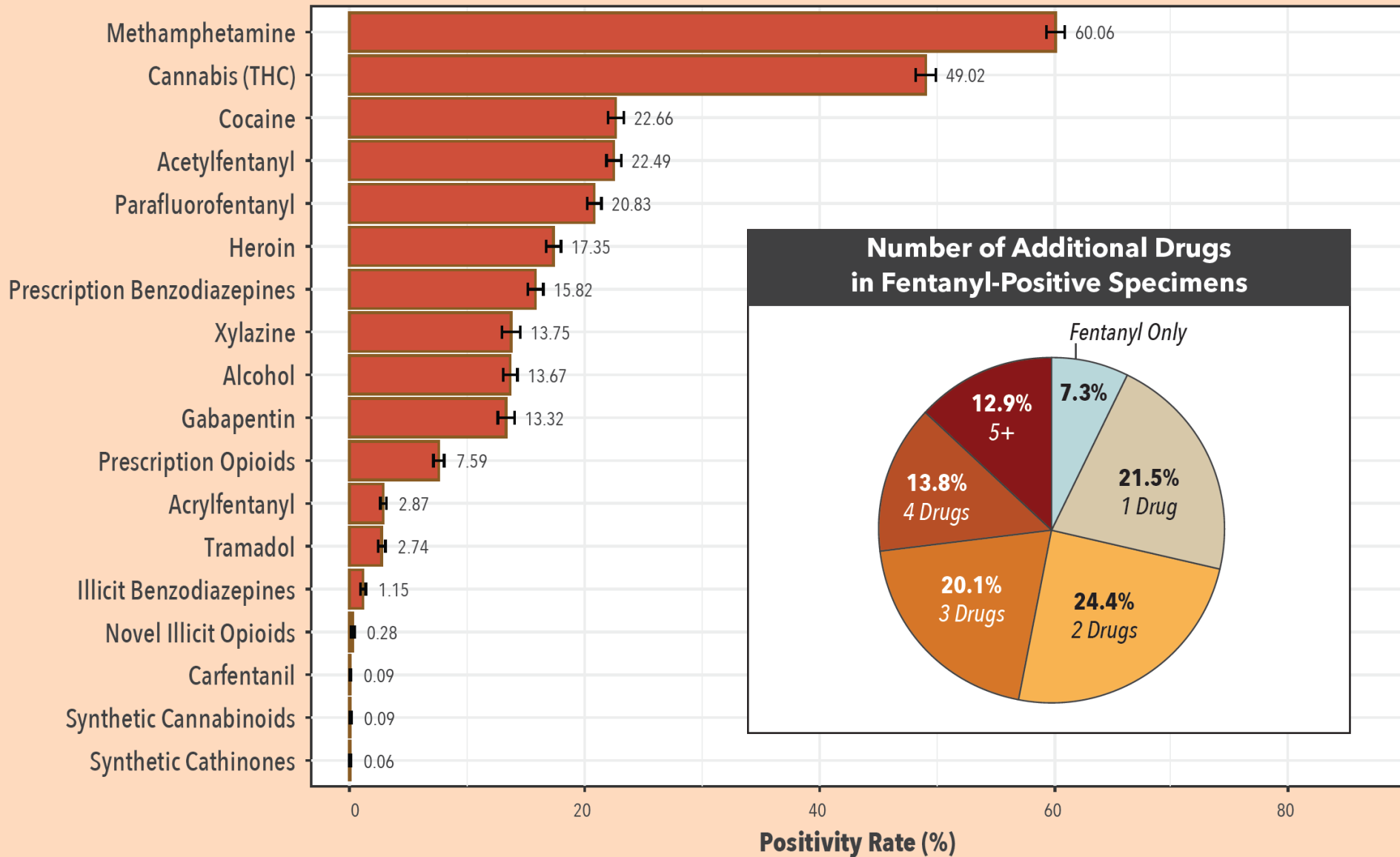


Yearly state-level urine drug test (UDT) positivity rates and 95% confidence interval values for prescription opioids (i.e., hydrocodone, hydromorphone, oxycodone and oxymorphone without a reported prescription), heroin, methamphetamine, and cocaine detected in fentanyl-positive specimens collected from 2013-2023.

Drug/Drug Class	2013	2023	Percent Change
Prescription Opioids	50.00%	7.10%	-86%
Heroin	50.00%	6.30%	-87%
Methamphetamine	21.10%	73.10%	+247%
Cocaine	Not Detected	4.10%	Over +5,000%

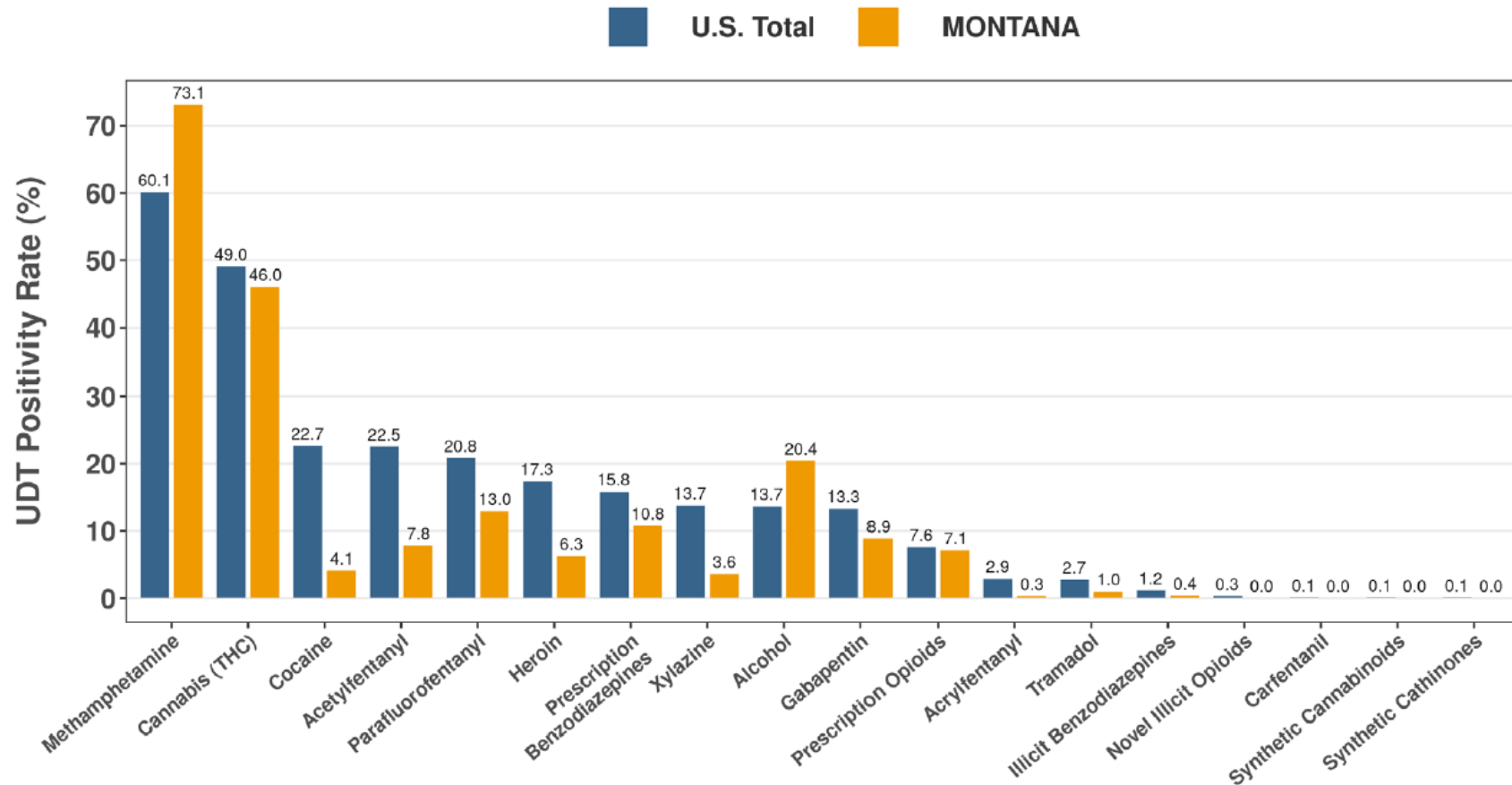
State-level urine drug test (UDT) positivity rates in 2013 and 2023 and percent change from 2013 to 2023 for heroin, prescription opioids, methamphetamine, and cocaine in fentanyl-positive specimens. Percent change was calculated as: % Change = (2023 positivity rate - 2013 positivity rate)/2013 positivity rate × 100. Percent change values (rounded to the nearest whole number) in red or green font indicate increases or decreases, respectively, in UDT positivity from 2013 to 2023.

National UDT Positivity Rates for Fentanyl-Associated Polysubstance Use in 2023



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Figure 2. State-Level UDT Positivity Rates for Fentanyl-Associated Polysubstance Use in 2023



The proportion of fentanyl-positive specimens that were positive for various illicit and non-prescribed drugs and drug classes at the national (U.S. Total) and state level. UDT positivity rates were estimated in fentanyl-positive specimens collected in 2023 and used to calculate the proportion of specimens also positive for the 18 drugs and drug classes shown. Each specimen had valid test results for all drugs and drug classes shown. See Methods in the full Signals Report for further detail on the drugs and drug categories analyzed.



Emerging Threat Intelligence (ETI)[™] State Focus

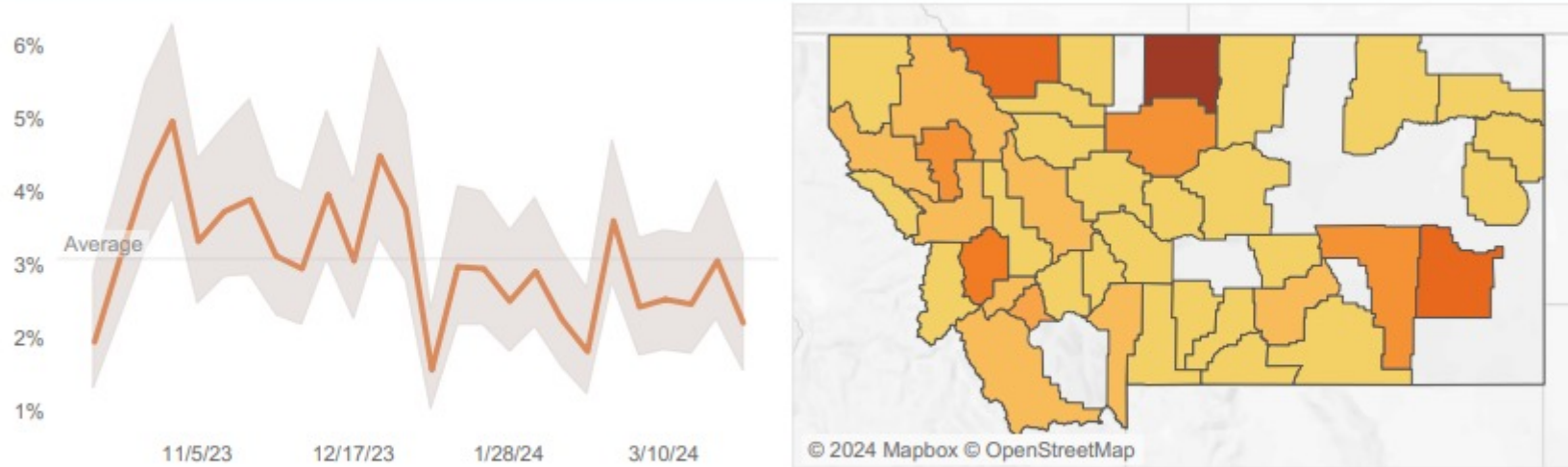
Reporting Period: 10/9/2023 to 4/6/2024

Prepared for State of: MONTANA



Analysis of 6 Month Non-Prescribed Fentanyl Positivity by County

Insights below are based on specimens collected in MONTANA between 10/9/2023 and 4/6/2024



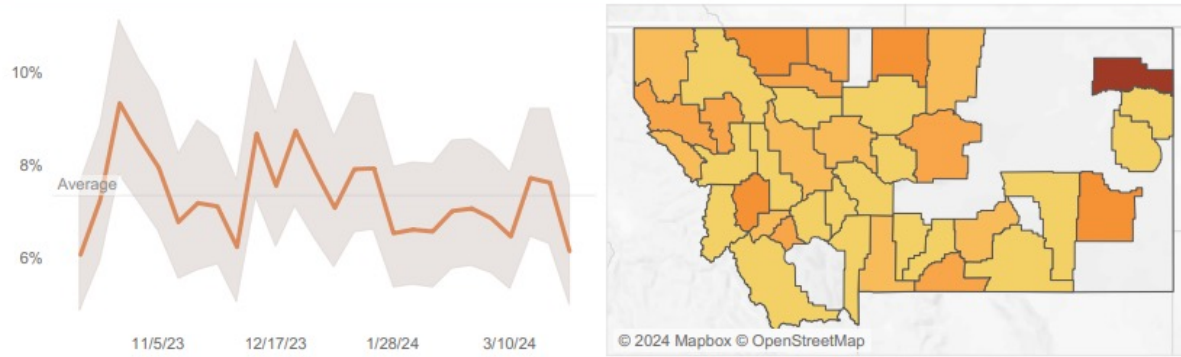
The graphs above display the positivity rate for non-prescribed fentanyl in MONTANA, where the average positivity rate is 3.0% [2.9% - 3.2%]. Gray bands show 95% confidence interval values. The legend shows the positivity rate color scale. Counties with less than 10 test(s) performed are not shown.



County	Tested Volume	Positivity Rate [95% CI]
HILL	1,001 - 10,000	17.4% [15.4% - 19.6%]
GLACIER	101 - 1,000	9.7% [7.1% - 13.0%]
CUSTER	101 - 1,000	9.0% [5.6% - 14.4%]
GRANITE	0 - 100	8.7% [2.4% - 26.8%]
LAKE	1,001 - 10,000	6.6% [5.5% - 7.9%]
ROSEBUD	0 - 100	5.7% [1.9% - 15.4%]
CHOUTEAU	0 - 100	5.3% [2.3% - 11.7%]
SILVER BOW	101 - 1,000	5.1% [3.5% - 7.3%]
BEAVERHEAD	0 - 100	3.2% [0.9% - 10.9%]

Analysis of 6 Month Methamphetamine Positivity by County

Insights below are based on specimens collected in MONTANA between 10/9/2023 and 4/6/2024



The graphs above display the positivity rate for methamphetamine in MONTANA, where the average positivity rate is 7.3% [7.0% - 7.6%]. Gray bands show 95% confidence interval values. The legend shows the positivity rate color scale. Counties with less than 10 test(s) performed are not shown.

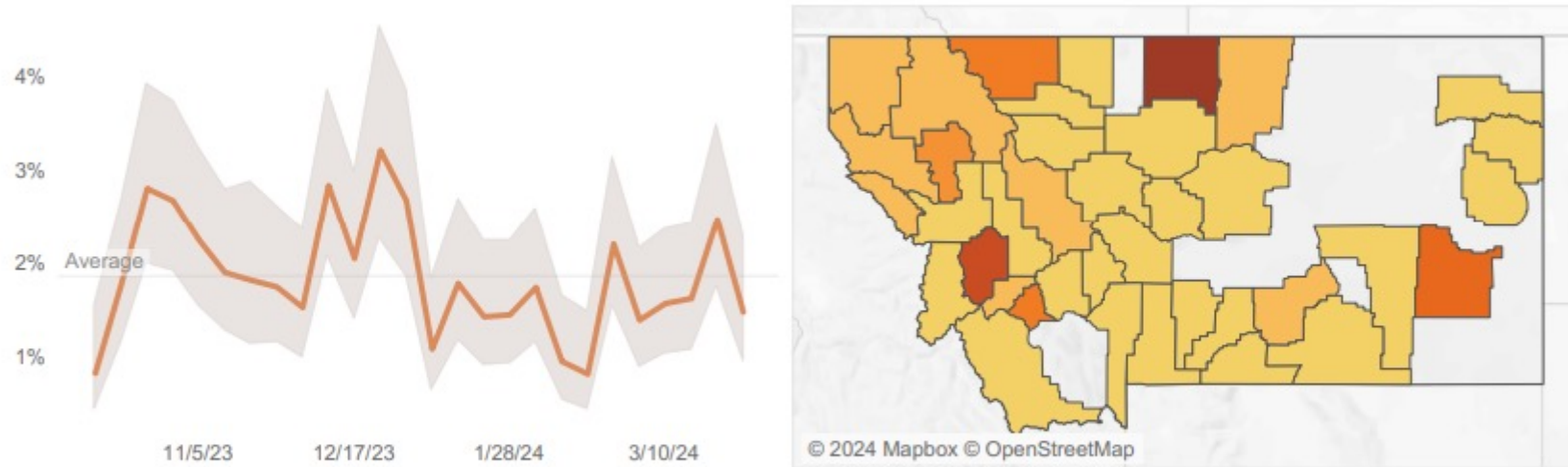


6 Month Methamphetamine Positivity by County

County	Tested Volume	Positivity Rate [95% CI]	County	Tested Volume	Positivity Rate [95% CI]
ROOSEVELT	0 - 100	60.0% [31.3% - 83.2%]	LINCOLN	101 - 1,000	6.7% [5.1% - 8.9%]
CUSTER	101 - 1,000	23.9% [17.8% - 31.2%]	FLATHEAD	1,001 - 10,000	5.1% [4.6% - 5.6%]
GRANITE	0 - 100	20.8% [9.2% - 40.5%]	MISSOULA	1,001 - 10,000	5.1% [4.5% - 5.7%]
HILL	1,001 - 10,000	19.6% [17.5% - 21.9%]	DAWSON	0 - 100	4.0% [0.7% - 19.5%]
GLACIER	101 - 1,000	19.4% [15.8% - 23.7%]	RAVALLI	101 - 1,000	3.9% [2.6% - 5.9%]
CARBON	0 - 100	17.2% [7.6% - 34.5%]	BROADWATER	0 - 100	3.8% [1.0% - 12.8%]
SANDERS	101 - 1,000	15.7% [10.8% - 22.3%]	JEFFERSON	101 - 1,000	3.3% [2.0% - 5.5%]
TOOLE	0 - 100	14.3% [5.7% - 31.5%]	STILLWATER	0 - 100	3.1% [0.6% - 15.7%]
PONDERA	0 - 100	13.3% [6.3% - 26.2%]	BIG HORN	0 - 100	3.1% [1.0% - 8.6%]
SILVER BOW	101 - 1,000	13.2% [10.4% - 16.5%]	SWEET GRASS	0 - 100	2.8% [0.5% - 14.2%]
LAKE	1,001 - 10,000	12.5% [10.9% - 14.3%]	GALLATIN	1,001 - 10,000	2.0% [1.3% - 2.9%]
FERGUS	0 - 100	12.0% [5.6% - 23.8%]	ROSEBUD	0 - 100	2.0% [0.3% - 10.3%]
PARK	101 - 1,000	11.6% [9.0% - 14.8%]	TETON	0 - 100	1.7% [0.3% - 9.0%]
DEER LODGE	0 - 100	10.6% [5.9% - 18.5%]	BEAVERHEAD	0 - 100	1.6% [0.3% - 8.7%]
BLAINE	101 - 1,000	10.6% [6.2% - 17.6%]	CHOUTEAU	0 - 100	1.1% [0.2% - 5.9%]
MINERAL	0 - 100	10.6% [5.2% - 20.3%]	JUDITH BASIN	0 - 100	0.0% [0.0% - 21.5%]
YELLOWSTO.	1,001 - 10,000	8.2% [7.4% - 9.0%]	MEAGHER	0 - 100	0.0% [0.0% - 16.8%]
LEWIS AND CLARK	1,001 - 10,000	7.7% [6.9% - 8.6%]	POWELL	0 - 100	0.0% [0.0% - 9.2%]
CASCADE	1,001 - 10,000	6.9% [6.2% - 7.6%]	RICHLAND	0 - 100	0.0% [0.0% - 15.5%]






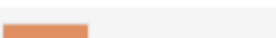
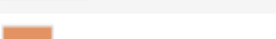
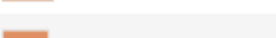
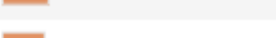
Analysis of 6 Month Non-Prescribed Fentanyl & Methamphetamine Co-Positivity by County

Insights below are based on specimens collected in MONTANA between 10/9/2023 and 4/6/2024



The graphs above display the co-positivity rate for non-prescribed fentanyl and methamphetamine in MONTANA, where the average co-positivity rate is 1.8% [1.7% - 2.0%]. Gray bands show 95% confidence interval values. The legend shows the co-positivity rate color scale. Counties with less than 10 test(s) performed are not shown.



HILL	1,001 - 10,000	11.8% [10.1% - 13.8%]	
GRANITE	0 - 100	9.1% [2.5% - 27.8%]	
CUSTER	101 - 1,000	6.5% [3.5% - 11.5%]	
GLACIER	101 - 1,000	5.5% [3.7% - 8.3%]	
SILVER BOW	101 - 1,000	5.0% [3.4% - 7.3%]	
LAKE	1,001 - 10,000	3.7% [2.8% - 4.8%]	
DEER LODGE	0 - 100	2.2% [0.6% - 7.5%]	
SANDERS	101 - 1,000	2.0% [0.7% - 5.6%]	
BLAINE	101 - 1,000	1.8% [0.5% - 6.2%]	



Millennium Health Signals Report™

Volume 6

The "Fourth Wave"

The Rise of Stimulants and the Evolution of
Polysubstance Use in America's Fentanyl Crisis

Eric Dawson, PharmD
Vice President, Clinical Affairs

Medical Necessity

Criteria to establish medical necessity must be based on patient-specific elements identified during the clinical assessment and documented in the patient's medical record by the provider.

Documenting Medical Necessity

- Orders must be individualized
- Tests ordered and reasons for testing must be documented in the patient's medical record
- Risk assessment and stage of treatment should match testing frequency

Documenting How the Test Results Were Used

- Review of results and use in the treatment plan