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PUBLIC ALERT

JAN 2026

INCREASE IN FATAL OVERDOSES LINKED TO NOVEL SYNTHETIC OPIOID *N*-PROPIONITRILE CHLORPHINE (CYCHLORPHINE)

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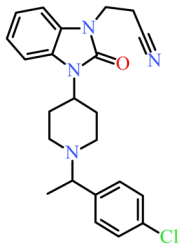
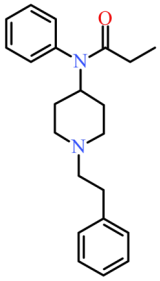
INCREASE IN FATAL OVERDOSES LINKED TO NOVEL SYNTHETIC OPIOID *N*-PROPIONITRILE CHLORPHINE (CYCHLORPHINE)

PURPOSE: The objective of this *Public Alert* is to notify public health and safety agencies, 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 novel synthetic opioid ***N*-Propionitrile Chlorphine** (also known as "Cychlorphine").

BACKGROUND: Synthetic opioids are chemically manufactured drugs, often having unknown potency and adverse effects. Synthetic opioids can be sold alone but are frequently mixed with more traditional opioids (e.g., fentanyl, heroin) and other substances in unregulated drug markets creating risks and danger for people who use recreational drugs. Synthetic opioids are commonly distributed in powder or tablet form. The United States has observed an alarming increase in deaths linked to synthetic opioids; Europe, Oceania, and other regions continue to observe increases as well. Primary adverse effects associated with synthetic opioid use are sedation and respiratory depression, which can lead to death if untreated with naloxone and/or other measures.



***N*-PROPIONITRILE CHLORPHINE**



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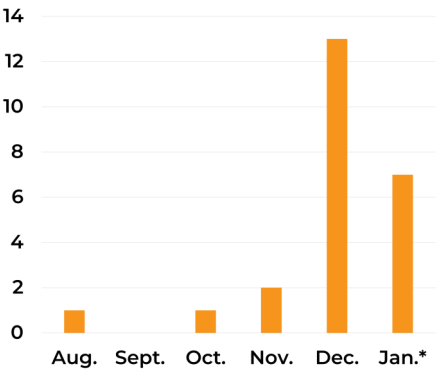
SUMMARY: *N*-Propionitrile chlorphine belongs to an emergent subclass of novel synthetic opioids often referred to as "orphine analogues" (or more simply "orphines") and bears structural similarity to other benzimidazolones (e.g., brorphine, chlorphine). These drugs have ties to pharmaceutical drug discovery conducted in the 1960s and 1970s, beginning with substances like bezitramide and R-6890 (now referred to as "spirochlorphine"). The orphine analogues first emerged in recreational drug markets in 2020 with the proliferation of **brorphine** (a drug first synthesized and published on in 2018). This novel opioid subclass continues to diversify, with at least six analogues confirmed in recent years. *N*-Propionitrile chlorphine was first detected at the **Center for Forensic Science Research and Education (CFSRE)** in mid-2024. *In vitro* pharmacology data show this drug to be approximately 10x more potent than fentanyl *[Vandeputte & Stove, personal communication]*. The positivity of *N*-propionitrile chlorphine, specifically in fatal drug overdoses, has increased since mid-2025. In July 2025, the Chinese government placed nitazene analogues under generic control. Since this announcement, overall positivity for nitazene analogues has declined as overall positivity for orphine analogues has increased, led in large part by *N*-propionitrile chlorphine.

N-Propionitrile chlorphine has been identified in 25 blood specimens from fatal overdoses tested at the CFSRE, the vast majority submitted in late-2025 and early-2026. In addition, *N*-propionitrile chlorphine has been tentatively identified in more than 100 toxicology cases at **NMS Labs**. Toxicology specimens originated from nine states across the United States, as well as three provinces in Canada. *N*-Propionitrile chlorphine was detected as the sole opioid in 11 of 25 cases, and alongside other opioids (e.g., fentanyl, oxycodone) and traditional stimulants (e.g., methamphetamine, cocaine). Co-detection with NPS was common (e.g., novel benzodiazepines [**phenazolam**], other orphine analogues [**spirochlorphine**], nitazene analogues, and carfentanil).

POSITIVE CASES SUBMITTED



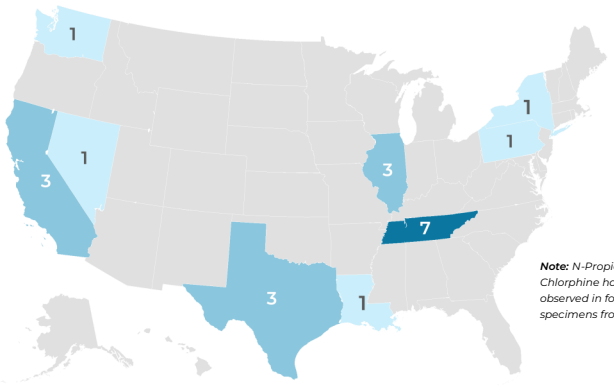
**Cases received through 1/13/2026.*

EMERGENCE OF ORPHINE ANALOGUES

DATE*	ANALOGUE
July 2020	Brorphine
Aug. 2024	5,6-Dichloro Desmethylchlorphine (SR-17018)
Dec. 2024	Chlorphine
Dec. 2024	***N*-Propionitrile Chlorphine (Cychlorphine)**
Oct. 2025	Spirochlorphine (R-6890)
Dec. 2025	5,6-Dichloro Brorphine (SR-14968)

**Date of NPS Discovery monograph issuance.*

DISTRIBUTION OF CONFIRMED CASES

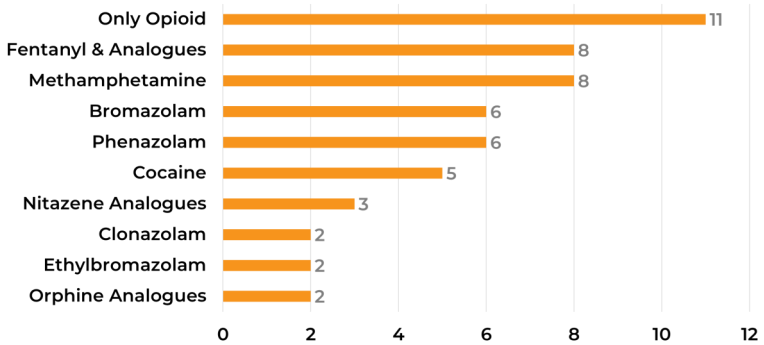


***Note:** N-Propionitrile Chlorphine has also been observed in four toxicology specimens from Canada.*

SELECTION OF TOXICOLOGY SPECIMEN RESULTS

DATE	STATE	RESULTS
Oct. 2024	New York	***N*-Propionitrile Chlorphine**, Phenazolam
Oct. 2025	California	***N*-Propionitrile Chlorphine**, Alprazolam, Caffeine
Nov. 2025	Illinois	***N*-Propionitrile Chlorphine**, *N*-Desethyl Metonitazene, Isotonitazene, *N*-Desethyl Etonitazene, Spirochlorphine, *N*-Pyrrolidino Metonitazene, Metonitazene, *N*-Pyrrolidino Etonitazene, *N*-Pyrrolidino Protonitazene, Alprazolam, Cocaine
Dec. 2025	Nevada	***N*-Propionitrile Chlorphine**, Bromazolam, Ethylbromazolam, Cocaine, Lidocaine, Caffeine
Dec. 2025	Pennsylvania	***N*-Propionitrile Chlorphine**, Acetaminophen
Jan. 2026	Tennessee	***N*-Propionitrile Chlorphine**, Phenazolam, Fentanyl, Xylazine, Alprazolam, Quinine, Caffeine
Jan. 2026	Texas	***N*-Propionitrile Chlorphine**, Bromazolam, Alprazolam, Oxycodone, Methamphetamine, Cocaine, Levamisole

CO-OCCURRENCE WITH DRUGS & OTHER NPS



ACKNOWLEDGEMENTS: This report was prepared by Alex J. Krotulski, Donna M. Papsun, Brianna N. Stang, Sara E. Walton, and Barry K. Logan at the Center for Forensic Science Research and Education (CFSRE) at the Fredric Rieders Family Foundation. The authors acknowledge staff at the CFSRE, NMS Labs, and collaborating agencies for involvements and contributions. For more information, please contact CFSRE's NPS Discovery at npsdiscovery@cfsre.org or visit www.npsdiscovery.org.

FUNDING: CFSRE's NPS Discovery is supported by the National Institute of Justice, Office of Justice Programs, U.S. Department of Justice (Award Number 15PNIJ-24-GK-00981-COAP "Implementation of NPS Discovery – An Early Warning System for Novel Drug Intelligence, Surveillance, Monitoring, Response, and Forecasting..."). 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.

SUGGESTED CITATION: Krotulski AJ, Papsun DM, Stang BN, Walton SE, Logan BK. (2026) Increase in Fatal Overdoses Linked to Novel Synthetic Opioid N-Propionitrile Chlorphine (Cychlorphine). Center for Forensic Science Research and Education, United States.

COLOMBO PLAN
HEALTH ALERT

FEBRUARY 2026

EMERGING GLOBAL SYNTHETIC OPIOID THREATS:

BENZIMIDAZOL-2-ONES – THE ORPHINES

COLOMBO PLAN
HEALTH ALERT

COLOMBO PLAN

cfsre
The Center for Forensic Science Research & Education

Public health and public safety officials worldwide should be aware of an emerging threat of the Benzimidazol-2-one (Orphine) class of opioids, which are causing increased mortality (death) and morbidity.

With potencies equal to or greater than the fentanyl class of opioids, these drugs can interact with other opioids to increase the risk of respiratory depression and death.

FEBRUARY 2026

Emerging Global Synthetic Opioid Threats:

Benzimidazol-2-ones – The Orphines

Following the recent core structure scheduling by China of the nitazenes (benzimidazoles), markets have seen a decline in these potent opioids in late 2025, and their replacement by a new class of synthetic opioids, the benzimidazol-2-ones, also known as the **"Orphines".** This alert describes the emergence of these potent opioids, and spotlights their detection in US and international drug markets.

- Brorphine was the first highly potent synthetic opioid of the **benzimidazol-2-one ("orphine") class**, detected in **European drug markets around 2019, and in the US in 2020**. It likely originated from **clandestine synthesis in China**, emerging as a fentanyl analog-replacement or opioid adulterant with potency similar to or slightly less than fentanyl.

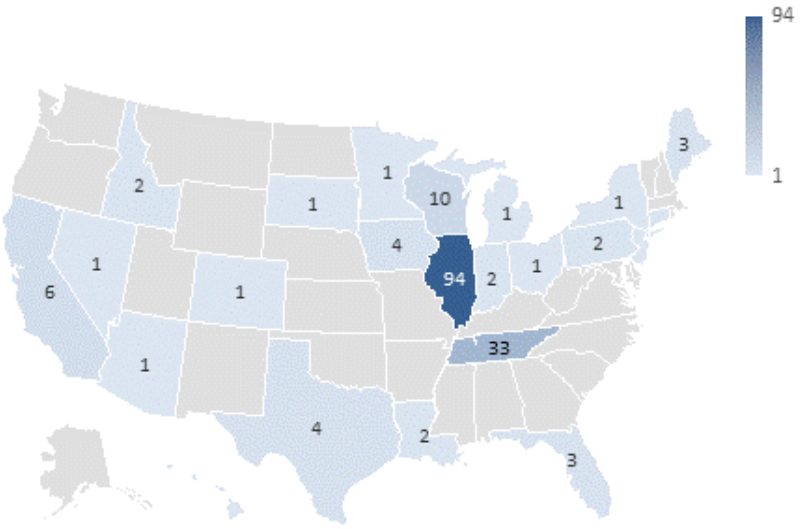
- Following initial alerts, brorphine was rapidly scheduled or emergency-controlled in multiple jurisdictions (e.g., EU, UK, US, Canada). This regulatory response appears to have accelerated structural diversification, with multiple halogenated and cyclized analogs appearing about four years after brorphine controls were put in place.

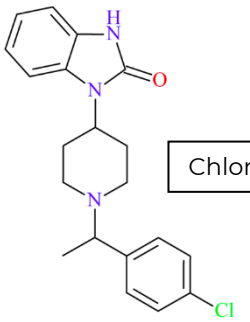
- As analytical reference standards have become more widely available, orphine analogs detected now include Chlorphine, N-Propionitrile Chlorphine (Cychlorphine), 5,6-Dichloro Desmethylchlorphine (SR-17018), Spirochlorphine (R-6890), Spirobrorphine and 5,6-Dicholoro Brorphine (SR-14968), various members of which have been reported in the UK, Europe, US, and Canada.

- Through collaboration with its partner laboratory NMS Labs, the Colombo Plan, the CFSRE and its NPS Discovery Program are working to develop methods for detecting and quantifying these new drugs, and tools to enable automated retrospective datamining of postmortem toxicology data to allow their identification as part of CFSRE's drug early warning system.

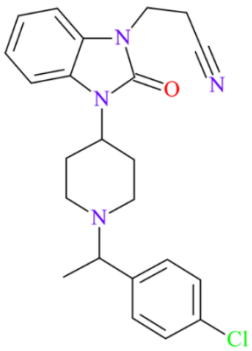
- Early data from this datamining process, obtained by scraping analytical mass spectrometric datafiles, have identified the following numbers of orphine analog cases between 2024 and 2025: 5,6-Dichloro Desmethylchlorphine (31 cases), Brorphine (81 cases); Chlorphine (8 cases); N-Propionitrile Chlorphine (84 cases); and Spirochlorphine (20 cases).

- The geographic spread of the presumptive positive cases is shown below:

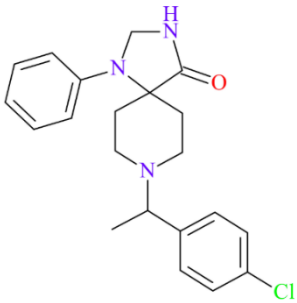




Chlorophine



N-Propionitrile Chlorophine (Cychlorphine)



Spirochlorophine (R-6890)

Polydrug Use and Adulteration

- The NMS Labs toxicology cases indicated that the most common adulterants and co-positivity included fentanyl, as well as other opioids and CNS depressants including nitazene analogs (e.g., metonitazene, N-pyrrolidino protonitazene, Isotonitazene, protonitazene, N-pyrrolidino metonitazene, and N-desethyl metonitazene) and illicit designer benzodiazepines (e.g., bromazolam).

- There were considerable geographic differences, with nitazene co-positivity being most common in Illinois. Methamphetamine, amphetamine, and diphenhydramine were most frequently found in Illinois, while fentanyl co-positivity was most frequently seen in Tennessee. Note that these positivity distributions reflect only jurisdictions in which NMS Labs performs testing.

Source of Synthetic Opioids:

- Following China's class-wide scheduling of fentanyl compounds in May 2019, the nitazene class of opioids originating from China, started appearing worldwide. Likewise, following China's core-structure scheduling of nitazene compounds in July 2025, the orphine class of opioids, most likely originating from China, are now appearing worldwide (see table page 3). This appears to be a recurring pattern with China following class-wide scheduling. In addition to already established drug classes including fentanyl, nitazene and orphine derivatives, **multiple potential future classes of synthetic opioids that warrant monitoring include benzamides, acetamides, piperidines/piperazines, and cinnamylpiperazines**.

Laboratory Analysis

- While standard reference materials for many of these analogs are now commercially available and can be added to laboratory testing scopes, very few forensic toxicology laboratories currently have comprehensive testing for orphine analogs within their scopes. In cases where the presence of an opioid is suggested based on history, scene and circumstances, but for which routine toxicology testing is negative, orphine class opioids should be considered. Please contact NPS Discovery for assistance with testing in these cases (supported by the National Institute of Justice, DOJ).

- Note that opioid and fentanyl immunoassays will not cross-react with orphine class compounds, and field test strips often used in harm reduction programs will not detect these compounds either.

- Based on preliminary data for a limited number of these drugs, toxicologically significant concentrations may be in the range of <1ng/mL to 10ng/mL and may be missed during routine screening. Comprehensive interpretive data on typical postmortem concentrations are currently lacking.

- As discussed above, the orphines are frequently present in toxicology cases or in seized drug samples, along with other opioids or sedating drugs.

First Responders and Emergency Room Response

- Responses are expected to be common to other mu-opioid agonists and to produce the classic triad of opioid effects:
  - ***CNS Depression***: lethargy, stupor and coma
  - **Respiratory Depression:** Slow respiratory rate (often **<8–10/min**), with shallow breathing.
  - **Miosis** (pinpoint pupils): typically, bilateral and symmetric
- ***Treatment should be supportive:*** Treat the airway and breathing first, followed by reversal with cautious administration of an opioid antagonist (e.g. naloxone), being careful not to precipitate acute withdrawal.

MAIN NPS OPIOID SUBCLASSES

FENTANYLS 2013 - PRESENT	NITAZENES 2019 TO PRESENT	ORPHINES 2025 - PRESENT
Fentanyl	Isotonitazene	Brorphine
3-Methylfentanyl	Metonitazene	Chlorphine
Carfentanil	Butonitazene	N-Propionitrile Chlorphine
Butyrylfentanil	Protonitazene	5,6-Dicholoro Desmethylchlorphine
Cyclopropylfentanyl	Flunitazene	Spirochlorphine
Isobutyrylfentanyl	Etodesnitazene	Spirobrorphine
Fluoro-Isobutyrylfentanyl	N-Pyrrrolidino protonitazene	5,6-dicholoro Brorphine
Methoxyacetylfentanyl	N-Pyrrolidino metonitazene	(others evolving rapidly)
O-methyl fentanyl	N-Pyrrolidino etonitazene	
P-Fluorofentanyl	N-desethyl isotonitazene	
Others (~65) ...	Others (~4)...	
All controlled either by name or through core structure scheduling.	Most currently controlled in the US permanently or temporarily, by name	Only Brorphine currently scheduled in the US Others are not scheduled

Acknowledgements: This report was prepared by Thom Browne, MA, Barry K. Logan, PhD, Alex Krotulski PhD, Amanda LA Mohr, MS, Sherri Kacinko PhD, and Madison Schackmuth PhD. Funding for preparation of this document was received by the Fredric Rieders Family Foundation via an MOA with the Colombo Plan. Information for this report was supplied by NMS Labs. Figures are courtesy of www.npsdiscovery.org.