

NEW NITAZENE ANALOGUE *N*-PYRROLIDINO PROTONITAZENE IMPACTING DRUG MARKETS IN NORTH AMERICA AND EUROPE

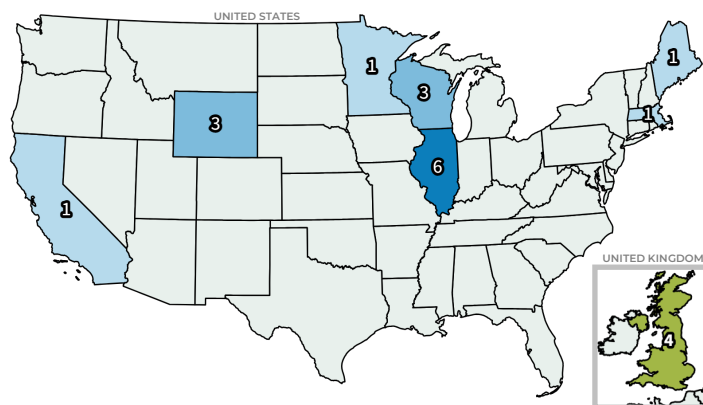
PURPOSE: The objective of this announcement is to notify public health and safety, law enforcement, first responders, clinicians, medical examiners and coroners, forensic and clinical laboratory personnel, and all other related communities about new information surrounding the emergent novel synthetic opioid *N*-pyrrolidino protonitazene (also referred to as “protonitazepyne”).

BACKGROUND: Synthetic opioids (e.g., fentanyl analogues, nitazene analogues) are chemically manufactured drugs, often having unknown potency and adverse effects or health risks. Synthetic opioids are frequently mixed with more traditional opioids (e.g., fentanyl, heroin) and other drugs in unregulated drug markets creating additional risk and danger for people who use recreational drugs. Synthetic opioids may be distributed in powder or tablet form. In the United States, an alarming increase in the number of deaths linked to synthetic opioid use has been observed. Deaths involving synthetic opioids in Europe, Oceania, and other regions continue to increase as well. Primary adverse effects associated with synthetic opioid use are sedation and respiratory depression, leading to death.

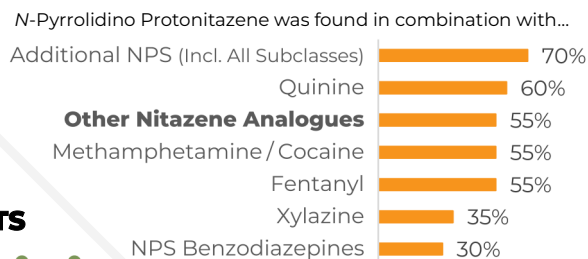
SUMMARY: *N*-Pyrrolidino protonitazene is a new synthetic opioid and the latest to emerge among the nitazene analogue (or 2-benzyl benzimidazole) subclass. *N*-Pyrrolidino protonitazene bears structural resemblance to both **protonitazene** and ***N*-pyrrolidino etonitazene**, two previously encountered nitazene analogues. *N*-Pyrrolidino protonitazene is dissimilar in chemical structure to fentanyl. New synthetic opioids, namely the nitazene analogues, have sustained proliferation following the 2018 scheduling of fentanyl related substances. Most nitazene analogues encountered among the recreational drug supply retain opioid receptor activity and exhibit potency similar to or greater than that of fentanyl. Recently acquired *in vitro* pharmacological data show that *N*-pyrrolidino protonitazene is an active opioid with potency approximately 25 times greater than that of fentanyl [source: L. De Vrieze and C. Stove, Ghent University].

To date in August 2023, *N*-pyrrolidino protonitazene has been confirmed in 20 forensic toxicology cases, all of which were medicolegal death investigations. *N*-Pyrrolidino protonitazene was first reported by CFSRE’s NPS Discovery in January 2023; however, the date of first sample collection was as early as December 2022. Cases originated from seven states across many regions within the United States, as well as the United Kingdom. Decedent age ranged from mid-20s to mid-70s (mean: 45 years, median: 44 years). Quantitative blood concentrations for *N*-pyrrolidino protonitazene ranged from 0.1 to 55 ng/mL (mean: 6.9 ng/mL, median: 1.1 ng/mL). The toxicity of *N*-pyrrolidino protonitazene has not been examined or reported but recent association with overdoses among people who use drugs leads professionals to believe that this synthetic opioid has the potential to cause harm and is of high public health concern globally.

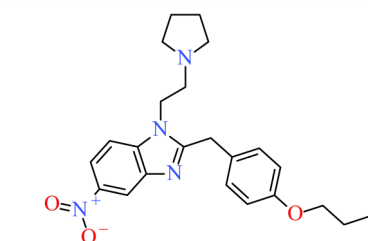
GEOGRAPHICAL DISTRIBUTION OF CASES



DRUG CO-POSITIVITY IN TOXICOLOGY SAMPLES



SEX OF DECEDENTS



***N*-PYRROLIDINO PROTONITAZENE**

RECOMMENDATIONS FOR CLINICIANS

- Become familiar with the signs and symptoms associated with synthetic opioid use (e.g., sedation, respiratory depression).
- Naloxone should be administered to reverse critical respiratory depression and repeated naloxone administration may be necessary. Be aware that clinical conditions may change rapidly and unpredictably after naloxone administration due to other drugs onboard or precipitation of withdrawal, which may be more severe with faster onset.
- Be mindful that drugs have limited quality control, containing undeclared substances that impact clinical effects or findings.
- Counsel about the harms and dangers of synthetic opioid products and other drugs.

RECOMMENDATIONS FOR PUBLIC HEALTH

- Implement surveillance for rapid identification of drug overdose outbreaks. Engage local poison centers and clinicians to assist with treatment of affected patients.
- Track and monitor geographical drug distribution and trends. Track demographics and Known risk factors.
- Raise awareness about the risks, harms, and dangers associated with opioid use.
- Make naloxone available to people who use drugs. Notify personnel that naloxone remains effective at reversing opioid overdose caused by nitazene analogues.
- Be aware that FTIR and fentanyl test strips are not effective for detecting nitazene analogues.

RECOMMENDATIONS FOR LABORATORIES

- Utilize analytical data available publicly for the identification of *N*-pyrrolidino protonitazene if a reference standard is not immediately available.
- Utilize previously developed non-targeted testing protocols or develop sensitive and up-to-date testing procedures for synthetic opioids and novel drugs.
- Prioritize analytical testing of drug materials obtained from drug overdose scenes during death investigations.
- Share data on synthetic opioid drug seizures with local health departments, medical examiners, coroners, and related communities.

RECOMMENDATIONS FOR MEDICAL EXAMINERS & CORONERS

- Test for new synthetic opioids and their biomarkers (if known) in suspected opioid overdose cases.
- Be aware that ELISA screening for synthetic opioids is not specific or specialized for the newest generations of drugs — Mass spectrometry-based screening is necessary.
- Be aware that concentrations of synthetic opioids in biological specimens can vary and GC-MS sensitivity may not be adequate.
- Consult with forensic toxicologists about novel opioid activity, potency, and association with overdose and/or death.

