

New Synthetic Opioid Protonitazene Increasing in Prevalence as “Nitazenes” Gain Traction Across the United States and Canada

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 synthetic opioid **protonitazene**.

Background: Synthetic opioids are chemically manufactured drugs, often accompanied with unknown potency and adverse effects or health risks. New synthetic opioids may be mixed with more traditional opioids, creating additional risk and danger for recreational drug users. Synthetic opioids may be distributed in powder or tablet form. In the United States (U.S.), an alarming increase in the number of deaths linked to synthetic opioid use has been reported. The primary adverse effect associated with synthetic opioid use is respiratory depression, often leading to death.

Summary: Protonitazene is a new, potent synthetic opioid bearing structural resemblance to etonitazene, a synthetic opioid that is nationally and internationally controlled. Protonitazene is dissimilar in structure to synthetic opioids typically encountered in forensic casework (e.g., fentanyl, heroin); however, protonitazene is a structural isomer of **isotonitazene**, requiring increased analytical specificity during toxicological analysis. *In vitro* pharmacological data suggest that this new opioid exhibits potency similar to other recently emergent “nitazene” opioids, and is approximately three times more potent than fentanyl. Protonitazene was first reported by NPS Discovery in May 2021 following initial detection in a toxicology case. To date, nine blood specimens associated with postmortem death investigations in the U.S. were confirmed to contain protonitazene; however, at least six additional cases have been discovered through toxicological surveillance by NPS Discovery as of December 2021. Identifications of protonitazene have also been reported from organizations in Europe. The toxicity of protonitazene has not been examined or reported but recent association with death among people who use drugs leads professionals to believe this synthetic opioid retains the potential to cause widespread harm and is of public health concern.

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 for decedents and overdose patients.
- Raise awareness about the risks and dangers associated with opioid use.
- Make naloxone available to people who use drugs recreationally.

Recommendations for Laboratories

- Utilize analytical data available publicly for the identification of **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.
- Prioritize analytical testing of seized drug samples 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 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 precipitation of withdrawal.
- Be mindful that illicit drugs have limited quality control, containing undeclared substances that impact the expected clinical effects or findings.
- Counsel about the dangers of synthetic opioid products and other drugs.

Recommendations for MEs & Coroners

- Test for new synthetic opioids and their biomarkers in suspected opioid overdose cases.
- Be aware that ELISA screening for synthetic opioids may not be specific or specialized for the newest generation of compounds; consider mass spectrometry-based screening.
- Be aware that concentrations of synthetic opioids in biological specimens can vary and GC-MS sensitivity may not be adequate.

Acknowledgements: This report was prepared by Alex J. Krotulski, PhD; Donna M. Papsun, MS, D-ABFT; Sara E. Walton, MS; and Barry K. Logan, PhD, F-ABFT. Funding was received from the National Institute of Justice (NIJ) of the U.S. Department of Justice (DOJ) (Award Number 2020-DQ-BX-0007). The opinions, findings, and conclusions or recommendations expressed in this publication are those of the authors and do not necessarily reflect those of the Department of Justice.

References and Related Articles:

- Hunger, A; Kehrle, J; Rossi, A; Hoffmann, K. (1957) *Synthesis of analgesically active benzimidazole derivatives with basic substitutions*. *Experientia*, 13, 400-401.
- Hoffmann, K; Hunger, A; Kehrle, J; Rossi, A. (3 May 1960). *Patent US2935514A - Benzimidazoles*.
- Vandeputte et al. (2021) *Synthesis, chemical characterization, and μ -opioid receptor activity assessment of the emerging group of nitazene new synthetic opioids*. *ACS Chem. Neurosci.* 12, 1241–1251.

Case Breakdown

Case Type:

- Postmortem (n=9)

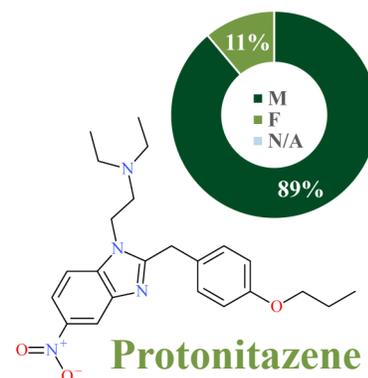
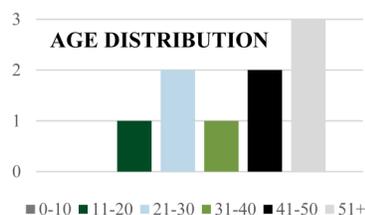
Date of Collection:

- April to July 2021

Other Notable Findings:

- NPS Benzodiazepines (n=5)
- Fentanyl (n=5)
- Methamphetamine (n=4)
- Other “Nitazenes” (n=3)
- *Only Opioid (n=1)

AGE DISTRIBUTION

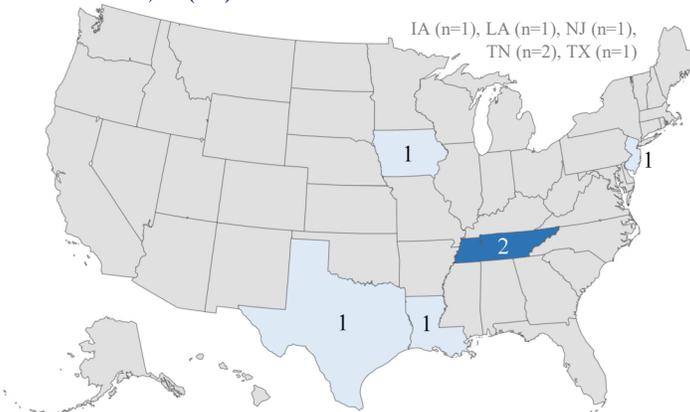


Protonitazene

| Conc. in Blood [ng/mL] | |
|------------------------|-----------|
| Mean (±S.D.) | 6.1 ± 8.5 |
| Median | 3.1 |
| Range | 1.3 - 25 |
| Outlier | 1,400 |

Geographical Distribution of Protonitazene in the U.S.

British Columbia, CA (n=3)



Rapid NPS Testing Now Available:

If your agency suspects synthetic opioid toxicity with no identifiable cause of death or your jurisdiction is noticing an increase in overdose patients requiring analytical testing, contact NPS Discovery at the Center for Forensic Science Research and Education (CFSRE); a non-profit organization in collaboration with local and federal agencies which can provide rapid testing after novel drug outbreaks in the United States.

Website: www.npsdiscovery.org Email: npsdiscovery@cfsre.org