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HEALTH ALERT

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

Considered several times more potent than the fentanyl class of opioids (phenylpiperidines), these compounds can make an existing opioid epidemic much worse or introduce an epidemic to unsuspecting countries and regions.

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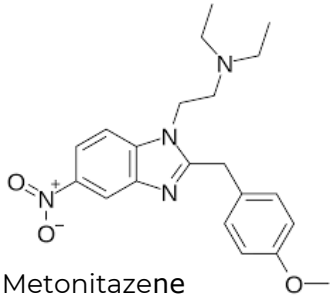
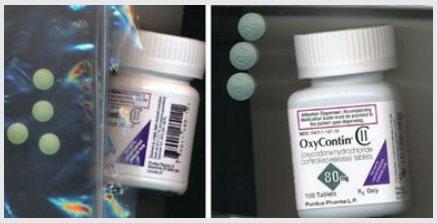
Emerging Global Synthetic Opioid Threat:

Increasing Reports of Nitazene Toxicity

In 2023, nitazene tablets destined for Florida, Connecticut, and Brazil containing an average of 29 mg of metonitazene across multiple shipments were seized in the U.S. from international express mail. This amount is equivalent to 290 mg of fentanyl in a single tablet (or 145 times the DEA's estimated fatal dose of fentanyl), which would be highly lethal.

- At a recent international symposium on emerging global synthetic drug threats sponsored by the Colombo Plan and CFSRE, a number of countries reported the emergence of nitazenes around the world.
- Benzimidazoles, also known as "nitazenes" (nai-ta-zeens), are a potent class of synthetic opioids estimated to be 1.5X - 20X more potent than fentanyl compounds (Vandeputte et al. 2024).
- An alarming increase in the number of deaths linked to nitazene use has been reported worldwide: North America, Brazil, Europe, Australia, New Zealand, West Africa (see boxes on pages 2-3).
- Nitazenes are distributed in powder or tablet form and are often mixed with other synthetic and traditional drugs and adulterants in unregulated drug markets, creating additional risk and danger for people who use drugs (See Table 1, page 4). Combinations of nitazenes and designer benzodiazepines are most common, especially the co-occurrence with Bromazolam.
- In testing of nitazene samples from US Crime Laboratories, 2.6% of cases (55 exhibits) contained 19 or more substances besides the principal component, usually fentanyl.
- Primary adverse effects associated with synthetic opioids are sedation and respiratory depression, leading to death.
- Naloxone is effective in the reversal of nitazene toxicity; multiple doses may be necessary, however.
- A number of nitazene analogs began to appear in the United States: isotonitazene (2019), metonitazene (2020), butonitazene, etodesnitazene, flunitazene, N-pyrrolidino etonitazene, protonitazene, metodesnitazene, and N-piperidinyl etonitazene (2021), N-desethyl isotonitazene (2022), N-pyrrolidino metonitazene, N-pyrrolidino protonitazene, N-desethyl etonitazene (2023), and 5-methyl etodesnitazene, and methylenedioxynitazene (2024).
- The NPS Discovery program at the CFSRE reports on a quarterly basis the most common nitazene drugs in the US, which in the third quarter of 2024 include protonitazene, metonitazene, and N-pyrrolidino protonitazene.

COUNTRY	REPORTED ACTIVITY
AUSTRALIA	• The Victorian Institute of Forensic Medicine (VIFM) at Monash University in Melbourne has reported deaths linked to isotonitazene (2021), and etodesnitazene (2022). There are indications of an increase in nitazene deaths across Australia in 2023 and 2024, with the most commonly detected drugs being protonitazene, metonitazene, and N-pyrrolidino etonitazene, with some cases testing positive for multiple nitazenes, including butonitazene.  • Cases of intoxication have also been confirmed in emergency department patients in Victoria. These cases are being reported to the Emerging Drugs Network of Australia (EDNA). The Australian Alcohol and Drug Foundation in 2024 has also reported several cases of counterfeit drugs containing nitazenes often mixed with designer benzodiazepines such as Bromazolam (Photo: Australian Border Force).
BRAZIL	• Nitazenes were the most frequent drugs detected in the opioid seizures that took place in the State of São Paulo, Brazil between July 2022 and April 2023. This was reported by health agencies in Brazil andscientists at the University of Campinas. There were a total of 140 cases of opioids seizures with 95 % of those belonging to the nitazene class, while only 5 % consisted of other opioids (morphine and fentanyl). Some of the exhibits were nitazenes mixed with other active compounds, including the synthetic cannabinoid MDMB-4en-PINACA (30 % of the samples). Metonitazene was the most frequent drug seized, appearing in 125 (72 %) of the cases.  Metonitazene
EUROPEAN UNION	• The European Union Drugs Agency (EUDA) has been tracking the presence of nitazenes in EU countries since 2019, and has issued multiple reports on the substances detected, including a 2024 update on the drug situation in Europe. While rates of use in EU countries still appear to be low, several specific outbreaks have been reported, including those in Ireland (see below) and France.  • The EU Early Warning System reported six new nitazene compounds in the European drug supply in 2023. The presence of nitazenes is concentrated in Lithuania, Latvia, Estonia, Poland, Sweden and Finland. Nitazenes were present in a counterfeit oxycodone seizure in Sweden, and in a seizure of counterfeit buprenorphine tablets in Finland. (Photo: Swedish Customs Laboratory).
IRELAND	• Several high profile outbreaks of nitazene intoxications have been reported in Ireland in 2023 and 2024, although nitazenes (metonitazene and butonitazene) were first detected in Ireland in 2022. In 2023 outbreaks in Dublin City, and Cork City, were linked to N-pyrrolidino protonitazene, and involved 57 and 20 non-fatal overdoses, respectively.  • In 2024 additional outbreaks both fatal and non-fatal, related to protonitazene were reported including one in a prison involving N-pyrrolidino protonitazene. Some seized exhibits containing protonitazene were yellow tablets packaged in counterfeit blister packs and labelled as alprazolam (Photo: www.drugs.ie).

COUNTRY	REPORTED ACTIVITY
NEW ZEALAND	• High Alert, a New Zealand based drug checking service reported in May 2024 the presence of N-desethyletonitazene in a counterfeit tablet being sold as a benzodiazepine (diazepam). https://www.highalert.org.nz/alerts-and-notifications/highly-potent-synthetic-opioid-detected-in-fake-diazepam-tablet/. • The group has previously reported metonitazene in yellow tablets and powders (possibly crushed tablets) as early as 2022, and either N-pyrrolidino-protonitazene or N-pyrrolidino-isotonitazene in an orange powder. The group advises extreme caution with respect to the possible presence of these drugs in the New Zealand drug supply. 
UNITED KINGDOM	• Nitazene drugs were first detected sporadically in the UK drug supply as early as 2019 but have become more prevalent in recent years. In 2023 the number of deaths linked to nitazenes had begun to increase, but more recently the UK's National Crime Agency has confirmed over 179 deaths involving nitazenes in the UK between June 2023 and May 2024. Recent UK media reports indicate nitazenes are proliferating rapidly. • The most commonly reported nitazenes in these cases were protonitazene, N-desethyl isotonitazene, metonitazene, and N-pyrrolidino protonitazene. Nitazenes are scheduled in the UK as Class I drugs (Photo: EUDA). 
UNITED STATES	• CFSRE/NPS Discovery regularly updates positivity rates in the US for nitazenes in its trend reports and includes analytical data on each new emerging opioids in its drug monographs. • A collaboration between CFSRE, US Customs and Border Protection and the Colombo Plan recently identified in one seizure a highly potent counterfeit oxycodone tablets (OC80's) containing on average 24 mg of metonitazene (together with amphetamine, PCE, 2-fluoro-2-oxo-PCE, pentylone, N,N-dimethylpentylone, and N-pyrrolidino protonitazene). Another set of metonitazene only tablets contained an average of 35 mg, which would be equivalent in potency to approximately 350 mg of fentanyl in a single tablet and highly lethal. For comparison a typical counterfeit fentanyl tablet contains less than 2 mg of fentanyl. 
WEST AFRICA	• Kush, a derivative of cannabis mixed with suspected synthetic drugs and other traditional drugs and adulterants, has been causing deaths in West African countries for the past six years. Recently, the DEA Special Testing & Research Laboratory (in collaboration with the Colombo Plan) conducted the first ever confirmatory analysis of Kush, highlighting the lethal nature of the drug and public health implications for the region.  • Samples from Sierra Leone were found to contain a lethal mixture of nitazenes (protonitazene), synthetic cannabinoids (MDMB-4en-PINACA, ADB-BUTINACA), and cocaine, providing a plausible explanation for the cause of death among Kush users. (Photo: Melissa Phillip/AP Images/picture alliance).

Table 1.

Examples of complex mixtures or contamination of regular street drug supply with trace amounts of multiple drugs, adulterants, and contaminants. Red = Nitazene compounds, precursors, contaminants, or by-products and other synthetic opioids; Purple = Fentanyl compounds, precursors, contaminants, or by-products; Green = Synthetic benzodiazepines; Blue = Synthetic cathinones; Black = Traditional Drugs; Brown = Veterinary adulterant; Orange = Other adulterants, licit/illicit drugs, or impurities; Pink = Naloxone

Seized Drug Case: Peoria County, IL	**Toxicology Case: Grand Rapids, MI**
Fentanyl, Xylazine, Quinine/Quinidine, 4-ANPP, Ethyl 4-ANPP, Heroin, Phenethyl 4-ANPP, Diphenhydramine, Cocaine, 6MAM, Lidocaine, N-phenethyl-N-phenylpropionamide, Acetyl fentanyl, N-pyrrolidino iso/protonitazene, Acetylcodeine, Clonazolam, N-pyrrolidino metonitazene, Papaverine, Brorphine, Morphine, Iso/Protonitazene, Noscapine, N-propionyl, Norfentanyl, Eutylone, Methamphetamine, N-pyrrolidino etonitazene, Codeine, Norfentanyl, Butonitazene, Para-bromo 4-ANPP, Flualprazolam and Acetaminophen	Isotonitazene, para-Fluorofentanyl, Fentanyl, Heroin (Morphine, Codeine, Noscapine), Cocaine, Benzoylecgonine, Methamphetamine, Amphetamine, Diazepam, Alprazolam, 7-Amino Clonazepam, Nordiazepam, Oxazepam, Temazepam, Xylazine, Levamisole, Lidocaine, Monoethylglycinexylidide, Phenacetin, Diphenhydramine, Norfentanyl, O-Desmethyltramadol, 4-ANPP, N-propionyl Norfentanyl, Quinine/Quinidine, N-Desethyl Isotonitazene, Phenethyl-4-ANPP, Naloxone

Web Resources:
https://pharmaceutical-journal.com/article/feature/everything-you-need-to-know-about-nitazenes

https://www.oas.org/ext/DesktopModules/MVC/OASDnnModules/Views/Item/Download.aspx?type=1&id=1045&lang=1

https://www.euda.europa.eu/publications/eu-drug-markets/new-psychoactive-substances/distribution-and-supply/new-opioids_en

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