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INFORMATION BULLETIN

THE EMERGENCE OF NITAZENES IN THE AMERICAS

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¿WHAT ARE NITAZENES?

Nitazenes (benzimidazole-opioids) are a class of extremely potent novel synthetic opioids. First developed in the 1950s by researchers in Switzerland as an opioid analgesic alternative to morphine, nitazenes were never approved for medical use. For many years, nitazenes were not a regular part of the illicit drug market.[i] With a few isolated exceptions, prior to 2019, nitazenes were primarily known only to researchers studying opioid pharmacology. In fact, the most notable reports of recreational nitazene use prior to 2019 were from 10 deaths in Moscow in 1998[ii] and an isolated case of personal manufacture in Utah in 2003.[iii]

Beginning in 2019, nitazenes emerged more widely on the illicit drug market in Europe.[iii] Since then, nitazenes have been identified on nearly every continent, including North America, South America, Asia, and Oceania.[iv] Due to their recent emergence, comprehensive data on the spread of nitazenes are not available. Limited data described in this report suggest that nitazene use is a growing trend in North America and that availability is likely spreading across the Americas.

As they have emerged across the globe, illicit manufacturers have continuously synthesized new and chemically distinct types of nitazenes.[v] Today, at least 13 different types of nitazenes have been identified. The most prevalent nitazene is isonitazene (ISO), but other common nitazenes include: [ii,v]

- Metonitazene
- Protonitazene
- Butonitazene
- Etodesnitazene
- Flunitazene
- N-pyrrolidinio etonitazene

LEGAL STATUS OF NITAZENES

Clonitazene and etonitazene, two of the original nitazenes, are classified as Schedule 1 substances[1] under the United Nations 1961 Single Convention on Narcotic Drugs.[iv] However, this Convention applies only to these two nitazenes – not the larger set of nitazenes that exist today. Many member countries have enacted legislation that further restricts nitazenes, beyond the 1961 Convention. Some countries employ restrictions specific to nitazenes, whereas others use more general opioid control legislation.

In the United States, clonitazene and etonitazene were included in the original Controlled Substances Act of 1971 as Schedule 1 substances. In 2020, the U.S. Drug Enforcement Administration (DEA) classified ISO as Schedule 1, and since then, seven other nitazenes have been similarly scheduled. The United Kingdom also employs specific restrictions to control nitazenes, classifying them as Class A drugs.[viii] Canada does not list nitazenes in its controlled substances regulations, but nitazenes are de facto Schedule 1 due to their precursor chemicals.[viii] Nitazenes are similarly restricted in Brazil, falling within broader opioid restrictions rather than nitazene-specific laws.[ix]

1. Schedule 1 is the second-most restrictive category in the 1961 Single Convention. However, it is important to note that in many national drug scheduling systems, "Schedule 1" is the most restrictive category.

WHY AND HOW DO PEOPLE USE NITAZENES?

People may use nitazenes for the same reasons that they use other opioids, as nitazenes are synthetically engineered to mimic the effects of traditional opioids. Nitazene use may be motivated by self-treatment for physical, mental, or emotional disorders or by a desire to experience opioid effects, such as feelings of euphoria, relaxation, sleepiness, and reduced pain.

Nitazene consumption may also occur unintentionally. Nitazenes are frequently mixed with or counterfeited as other drugs (e.g., heroin, fentanyl, benzodiazepines, or other synthetic drugs) to increase potency and cut costs.[x] Many consumers may be unaware that they are consuming nitazenes, leaving them particularly vulnerable to the risks posed by nitazene use.[xi] This unintentional use is also one of the factors making comprehensive data on nitazene use challenging to collect.

Nitazenes are available in many forms, including pills, powders, and sprays – both in "pure" form and mixed with other drugs. Methods of nitazene ingestion include:[xii]

- Intravenously
- Intranasally
- Orally
- Sublingually
- Inhalation *(vaping)*

DANGERS OF NITAZENES

Nitazenes are highly addictive and continued use can lead to dependency. Although studies about nitazene dependence and withdrawal are limited, nitazene withdrawal has a high potential to be severe and painful. Nitazenes can also cause dizziness, nausea, vomiting, disorientation, loss of consciousness, and seizures.[xiii] Like other opioids, nitazenes present a high risk of central nervous system or respiratory depression, as well as cardiac arrest.[viii]

Nitazenes present an especially high risk for overdose and overdose mortality, due to their high potency. Nitazene potency varies significantly, but all nitazenes are much more potent than natural (non-synthetic) opioids, such as morphine. Table 1 shows that nitazenes range from slightly less potent to many times more potent than fentanyl. Fentanyl itself is generally 25 to 50 times stronger than heroin, which is about twice as strong as morphine.[xiii] The most common nitazene (ISO) is 250 to 900 times stronger than morphine, while the most potent nitazene is up to 4,300 times stronger than morphine.

Table 1: Nitazene Potency Relative to Fentanyl

Type of Nitazene	Potency Relative to Fentanyl[xiii xiv]
butonitazenes and etodesnitazenes	25% to 50% as strong
ISO— the most common nitazene	5X to 9X times stronger
N-pyrrolidino protonitazenes	Up to 25X times stronger
N-pyrrolidino etonitazenes	Up to 43X times stronger

Like other opioids, naloxone can reverse a nitazene overdose. However, because of their potency, multiple doses of naloxone may be required to reverse a nitazene overdose.[xv] Because they are frequently used unintentionally, many people who use nitazenes (and the people around them) may be unaware of the need for multiple naloxone doses – potentially increasing the risk of an overdose becoming fatal.

SCOPE OF USE IN THE AMERICAS

As an emerging substance of concern, we lack a complete picture of nitazene use across the Americas. Data are not currently available from surveys, administrative datasets, or clinical contexts – which are the core sources of drug use information. In the Americas, only the United States, Canada, and Brazil have data related to use, and those data are largely incomplete or proxy measures for actual use. A review of available information from the region did not reveal any data on nitazene use from Central America or the Caribbean.

The United Nations Office on Drugs and Crime (UNODC) Early Warning Advisory (EWA) system suggests that nitazenes are spreading across the Americas and Europe. The UNODC EWA reports that nitazenes were first identified in eight countries in 2019, rising to 19 countries by 2022.[v] The most frequent reports were (in order) from the United States, Canada, Latvia, Estonia, the United Kingdom, Sweden, and Germany. According to the UNODC EWA, up to February 2024, nitazenes have been reported from Asia, Europe, North America, Oceania, and South America.[xvi] However, detailed reports are not yet available. While the review of available literature on nitazenes in Latin America found a country-specific reference only from Brazil, nitazenes might be present in many other countries in the region that have not yet detected or reported them.

For substances with a high risk of overdose, overdoses can be an important proxy measure for use. Though nitazenes pose a high overdose risk, data on nitazene overdoses remain limited because nitazenes are not currently detected by the standard analyses employed by most jurisdictions following overdose events. Two journal publications noted evidence of nitazene overdose deaths globally, but neither could provide detailed estimates of their scope, and both are likely undercounts of the extent of nitazene overdose in the Americas. One study found that nitazenes were involved in at least 200 overdose deaths in Europe and North America from 2020 to 2021.[xvii] The second found 93 fatalities from 2022 data in eight case reports – primarily from the United States.[xviii]

NORTH AMERICA

Regional trends in the opioid epidemic are often first identified in the United States and Canada, including the prior emergence of fentanyl and xylazine. Both countries are recognized as the global epicenters of the opioid epidemic and support robust substance use surveillance systems. Nitazenes were first identified in the street drug supplies of both countries in late 2019 and early 2020[xix] Since then, other findings indicate that nitazene use is continuing to spread on the continent:[viii,xx] Since then, other findings indicate that nitazene use is continuing to spread on the continent:
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Nation	Key Information and Statistics
United States	▸ Nitazenes have been identified in at least 4,300 law enforcement drug seizures since 2019.[i] ▸ Nitazenes have been identified in US wastewater. A 2022/2023 study found protonitazene in samples from Washington & Illinois – indicating use in both states.[xxi] ▸ Nitazene-involved fatal overdoses in Tennessee increased from zero in 2019, to 10 in 2020, and 42 in 2021. All the overdoses co-occurred with other illicit substances and most (60%) included fentanyl.[xxii]
Canada[xxiii]	▸ **Quebec:** Nitazenes were first identified in the drug supply in 2019. ISO and protonitazene were detected as pure tablets. Other nitazenes were primarily found as powders and combined with fentanyl. From January 2020 to March 2022, ISO was detected in 25 overdose deaths and protonitazene was detected in seven. ▸ **Toronto:** Nitazenes were first identified in February 2021. Detection steadily increased through the year among samples expected to be fentanyl. In 2021, 165 checked samples contained nitazenes, 39 of which came from overdose events. ▸ There is currently no available information on the scope of nitazene use in Mexico.
Mexico	▸ There is currently no available information on the scope of nitazene use in Mexico.

SOUTH AMERICA

The UNODC EWA website refers to nitazenes in South America, but does not provide country-specific findings.[2] A review of available literature from the found a country-specific reference only from Brazil, but nitazenes might be present in many other countries in the region that have not yet detected or reported them. Current information suggests that the overall rates of nitazene use are likely low across most South American countries, but the high potency of this drug presents risks to people who use opioids on the continent.

Nation	Key Information and Statistics
Brazil[x]	São Paulo State Police report that 95% of opioid seizures contained nitazenes between July 2022 and April 2023. Most of the seized nitazenes (71%) were mixed with other opioids, though 29% were nitazenes with no other opioids present. Almost all (99%) of the reported seizures were of "herbal fragments" that were laced with opioids.

2. UNODC Early Warning Advisory on New Psychoactive Substances, February 2024 UNODC EWA: Nitazenes – A new group of synthetic opioids emerges; *https://www.unodc.org/LSS/Announcement/Details/cbec8f4c-73aa-49ee-9e2b-75620af8a910*

PRODUCTION AND TRAFFICKING OF NITAZENES

Because nitazenes are still emerging, very limited information is available on their production and trafficking. A pharmaceutical company in China and its alleged owner were indicted for importing nitazenes into the United States and Mexico, based on unsealed indictments by the U.S. Department of Justice.[xxiv] The European Drugs Agency (EUDA[3]) also reports that at least some of the ISO sold in Europe was manufactured by chemical companies based in China.[iii] However, the extent of these supply chains and their role in the global production of nitazene is currently unknown.

CONCLUSION

Nitazenes present a new and serious challenge for drug control policy. They are extremely potent and pose major health risks to consumers, including those who unintentionally encounter nitazene-contaminated substances. Meanwhile, illicit manufactures have continued to develop novel forms of nitazenes in the 50+ years since they were first synthesized. Though data remain limited, nitazene use appears to be growing – especially in the United States and Canada. Expanded nitazene surveillance capacity may be required to continue monitoring this emerging concern.

3. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) was formally rebranded under a new mandate as the European Drugs Agency (EUDA). At the time that this document was drafted, the agency was still known as EMCDDA.

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