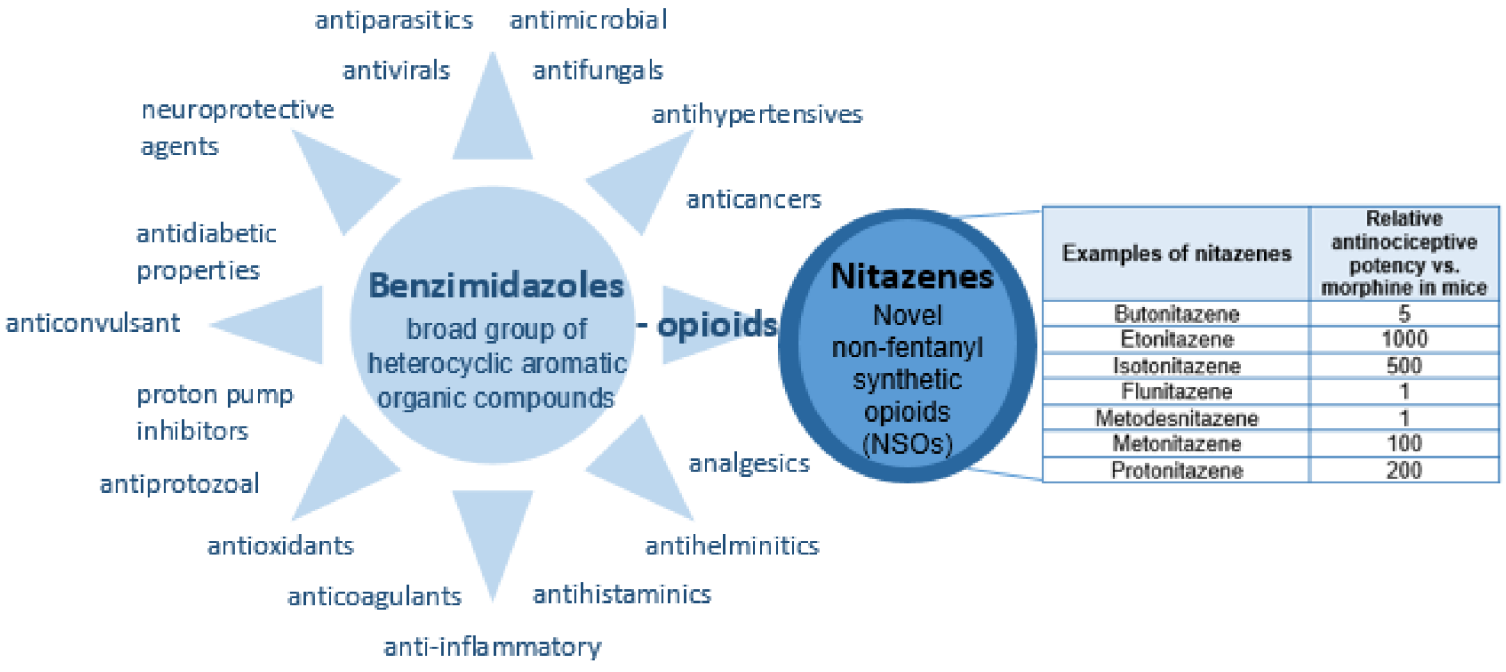
Nitazenes overview

Nitazenes are benzimidazole opioids, also known as novel non-fentanyl synthetic opioids (NSOs). They are selective mu opioid receptor agonists that have effects similar to other opioids. First synthesized in the late 1950's in Switzerland, benzimidazoles are a large group of compounds that span a range of properties. The synthesis of benzimidazole derivatives with analgesic activity was first reported in 1957. Benzimidazoles were also used to treat parasitic infections in domestic pets and some were trialed for use as analgesics, hypnotics, and anesthetics, but were never approved for clinical use in humans.

Benzimidazoles are currently labelled for research use only, not for veterinary or human clinical use.

Benzimidazoles, their salts, derivatives, and salts of derivatives are controlled as schedule I substances in the Canada Controlled Drugs and Substances Act (S.C. 1996, c. 19).

Isotonitazene, which is a type of nitazene, can be injected, smoked/vaporized, or inhaled, and has been found in liquid form, as a powder (yellow, brown, or white in colour), or pressed into tablets to look like Oxycodone or Dilaudid tablets.



Examples of nitazenes	Relative antinociceptive potency vs. morphine in mice
Butonitazene	5
Etonitazene	1000
Isotonitazene	500
Flunitazene	1
Metodesnitazene	1
Metonitazene	100
Protonitazene	200

Adapted from Brishty et al, 2021, and Ujváry et al, 2021.

Why should you be concerned?

Nitazenes have been detected with increased frequency in the unregulated drug supply in Canada. Some nitazenes have been reported to have greater potency over fentanyl. When mixed or used concurrently with other depressants (e.g., alcohol, benzodiazepines, ketamine, heroin, fentanyl), the risk of overdose greatly increases.

The synthetic opioid market continues to diversify at a rapid pace. At least 14 different nitazenes have been identified to date, with more emerging in the unregulated drug supply.

How much is considered dangerous?

It is not known. Potencies of some nitazenes are thought to be greater than fentanyl, however the unregulated supply of toxic substances continues to present wide fluctuations in reported content and potency.

What is the prevalence of nitazenes in BC's drug supply?

Benzimidazole opioids are structurally dissimilar from fentanyl, and will not give a positive response on fentanyl test strips. Nitazenes may be present in low amounts only detectable by gas chromatography/mass spectrometry methods and may not meet the 5% threshold needed to be detected by Fourier Transform Infrared spectroscopy currently used at drug checking sites in BC. Protonitazene is more difficult to detect, as it is an isomer of isotonitazene and a higher specificity is needed to differentiate the two.

Local and national findings:
See **Nitazenes: Surveillance of benzimidazole opioids and brorphine in British Columbia and Canada**

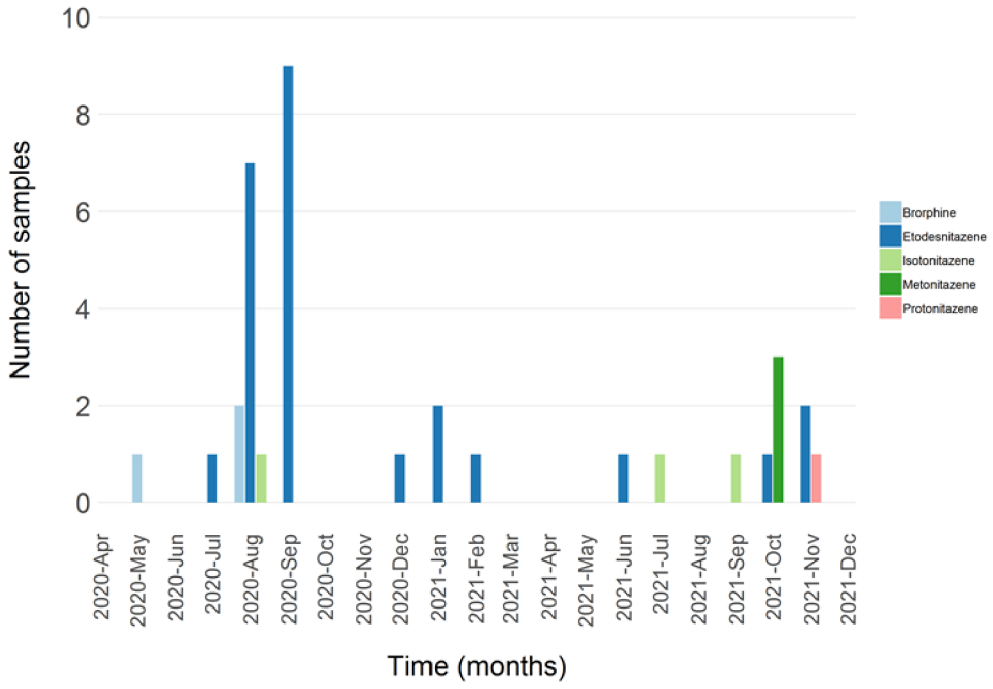


Figure 1. Presence of benzimidazole opioids and brorphine in samples seized by law enforcement in BC

Clinical presentation and treatment

Information is still emerging but nitazene toxicity likely presents similarly to opioid overdose. Nitazenes appear to potentiate the effects of other depressants, such as fentanyl and benzodiazepines, which could result in a more complex clinical presentation.

Etonitazene induced muscle rigidity and catalepsy has been reported in rat studies within 7 to 15 minutes. These adverse effects were successfully prevented by naloxone.

Nitazene Toxicity	
Typical overdose	**Complex overdose**
• Impaired breathing, such as choking, gurgling or snoring type sounds • Altered mental status due to changes in or loss of consciousness • Pinpoint pupils • Cold, clammy skin • Skin, lips and nailbeds may appear blue/purple or grey/ashen	• "Flailing limbs" • Seizures • Can remain standing, unable to sit down • Staring gaze, unable to speak • Severely hypoxic but able to follow simple commands • Decorticate posturing, with inwardly flexion at the wrists, elbows and feet • Bradycardia or arrhythmia • Vomiting (can also occur after larger doses of naloxone, from use of other substances, and/or related to acute withdrawal)
Cayman Safety Data Sheets Possible acute and delayed symptoms include: anemia, cough, CNS depression, drowsiness, headache, heart damage, weakness, exhaustion, liver damage, narcosis, and reproductive and teratogenic effects.	

How should you respond to an overdose with opioids including nitazenes?

Always give naloxone to reverse the effects of opioids when an overdose occurs. Higher doses of naloxone may be required.

Always place the person in the recovery position if you have to leave them alone, as increasing doses of naloxone can lead to vomiting. See the **Toward the Heart** website for the **Do I keep giving naloxone?** and **Opioids and Benzos or Etizolam** information sheets.

Recommend the **Lifeguard App** and the **Be Safe App**, a different drug supply, and drug-checking services:

- For current information and locations, see the **Toward the Heart** and **BCCSU Drug Checking BC** websites.
- For testing by mail or in person: **Getyourdrugstested.com**

Encourage not to use alone. Use the **Toward the Heart site finder tool** to help locate the nearest overdose prevention service/supervised consumption site and take home naloxone distribution sites.

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