CCENDU Drug Alert
Nitazenes

What Are Nitazenes?

- Nitazenes are potent synthetic opioids from a drug class known as benzimidazole-opioids.
- Some nitazenes are estimated to be several times more potent than fentanyl.
- They were developed 60 years ago as potential pain relief medication, but were never approved for clinical use.
- They were first identified in the unregulated drug supply in Canada in 2019.
- They typically appear unexpectedly in drugs expected to contain other, more traditional opioids (e.g., fentanyl, oxycodone tablets or "down"), often alongside non-medical benzodiazepines (NMBs).

Examples of nitazenes reported in Canada:

- Etodesnitazene
- Etonitazene
- Etonitazepyne
- Flunitazene
- Isotonitazene
- Metonitazene
- Protonitazene
- 5-Aminoisotonitazene

Why They Are a Concern

- The presence of nitazenes in the unregulated drug supply is rising. The frequency with which they are detected is increasing, but there is also an increasing number of nitazene analogs.
- They tend to be used unintentionally and in unknown quantities because the contents of drugs from the unregulated supply are unpredictable.
- Nitazenes can increase the risk of accidental overdose, especially when combined with other substances that suppress breathing and heart rate such as other opioids or benzodiazepines.
- Overdoses involving nitazenes may be difficult to reverse, potentially requiring additional doses of naloxone, but protocols around this are not yet clear.
- Fentanyl test strips cannot detect nitazenes, and detection of nitazenes by point-of-service drug checking requires sensitive equipment that is not always available.
- Nitazenes are not routinely tested for in post-mortem or urine toxicology, so their relationship to health risks and overdose deaths is difficult to monitor.

Reports from CCENDU

The following data were compiled from an information request about nitazenes sent to site leads of the Canadian Community Epidemiology Network on Drug Use (CCENDU). CCENDU is a pan-Canadian, sentinel surveillance network led by the Canadian Centre on Substance Use and Addiction (CCSA) and operating at the community level. The information was received between February 8 and February 22, 2022. The table presents a summary of the situation and responses in communities as reported by six CCENDU sites (for a list of all sites visit www.CCENDU.ca). The table is supplemented with data from Health Canada's Drug Analysis Service (HC DAS), which analyzes the contents of drugs seized by law enforcement agencies.

CCENDU Site	Local situation	Local responses
British Columbia	Drug checking services, including Vancouver Island Drug Checking (VIDC) and 14 sites coordinated by the B.C. Centre on Substance Use (BCCSU), first identified a nitazene in Jan. 2021. VIDC identified isotonitazene in 12 samples in 2021; of these, nine also contained fentanyl, etizolam and caffeine, and six of the nine also contained metonitazene and etodesnitazene. Most samples were expected to be other opioids or "down." BCCSU-partnered sites have also identified isotonitazene, etodesnitazene (in some cases alongside clonazolam, phenacetin, erythritol, caffeine or fentanyl), metonitazene and protonitazene. Protonitazene was linked to nine deaths in a 2021 report,[1] three of which were in B.C.	Distributing alerts locally, on the towardtheheart website, through social media and through the RADAR system Ensuring availability of overdose training and take-home naloxone Providing free drug checking and supervised consumption sites and overdose prevention services for people who inject and inhale substances Providing general harm reduction advice to reduce overdose risk[2]
Manitoba	No information was available on the presence or use of nitazenes in Manitoba. HC DAS data suggest that nitazenes are not prevalent in Manitoba as only one sample submitted from this province in 2020 contained isotonitazene and no samples contained a nitazene in 2021.	No targeted responses for nitazenes as of Feb. 22, 2022. General harm reduction services are available, including take-home naloxone and rapid access to addictions medicine clinics throughout the province.
Ontario – Toronto	Toronto's Drug Checking Service first identified a nitazene in Feb. 2021 and has since identified seven different analogs. In Oct.–Dec. 2021 a nitazene was identified in 16% (n=55) of samples expected to be fentanyl. This is in contrast to 5% (n=19) in Apr.–Jun. 2021. Nitazenes frequently occur alongside NMBs (approx. 66% of samples checked between Oct. 2019 and Aug. 2021). Some of the samples expected to be fentanyl contained no fentanyl at all, but instead etonitazepyne and flualprazolam (an NMB). Of the 165 samples checked in 2021 that contained nitazenes, 24% (n=39) were associated with an overdose. The Office of the Chief Coroner of Ontario detected a nitazene in two deaths: metonitazene in Sep. 2020 and isotonitazene in Jul. 2021.	8 Toronto Public Health alerts (May–Dec. 2021): • All available under Drug Alerts & Advisories Alerts from Toronto's Drug Checking Service: • Isotonitazene identified in Toronto's unregulated drug supply (Apr. 2021) • Etonitazene identified in Toronto's unregulated drug supply (May 2021) • "Ultra potent" opioids continue to circulate in Toronto's unregulated drug supply (May 2021) Ensuring availability of overdose training and take-home naloxone Providing free drug checking, free supervised consumption services and harm reduction advice to reduce overdose risk
Ontario — Thunder Bay	Etonitazene was detected in a sample submitted to HC DAS in Sep. 2021 and communicated as an advisory to community organizations in Jan. 2022.	Tracking and alerts through the Lifeguard App Issuing a Drug Strategy Advisory: Presence of Etonitazene identified in sample of drugs seized by Thunder Bay Police (Jan. 2021) Ensuring availability of and training on naloxone Providing supervised consumption services and harm reduction advice to reduce overdose risk
Quebec — Province	Isotonitazene was first detected in a sample submitted to HC DAS in 2019, and protonitazene in 2021. Since then, they have both been detected on a regular basis. These two are almost always detected alone and in tablet form, whereas other, less frequently detected nitazenes (etodesnitazene, metonitazene, etonitazepyne) tend to appear in powder form and alongside fentanyl or etizolam (an NMB). According to regional health advisories, several tablets sold as oxycodone or hydromorphone contained nitazenes instead of the expected substance. Since 2020, isotonitazene was detected in 25 suspected overdose deaths and protonitazene in seven.	Regional public health advisories: • Isotonitazène : nouvel opioïde de synthèse en circulation (Feb. 2020) • Risque de décès liés à la consommation de comprimés contenant de l'isotonitazène (Nov. 2020) • Risque de SURDOSE dû à des comprimés contenant de l'isotonitazène (toni) (Nov. 2020) • Risque de SURDOSE dû à des comprimés contenant de l'isotonitazène (toni) et du protonitazène (Mar. 2021) • Risque de surdoses sévères et de décès liés à la consommation d'un mélange de fentanyl et d'étodesnitazène présent dans les drogues de rue à MontréaL (Oct. 2021) Ensuring availability of and training on naloxone Providing harm reduction services and advice

Newfoundland and Labrador	Although the Office of the Chief Medical Examiner reported at least one overdose case involving isotonitazene, there is little evidence of nitazene presence in this province. This is corroborated by detection of a nitazene in only one sample analyzed by HC DAS between Jan. 2021 and Jan. 2022.	Regional public health alert: Newfoundland and Labrador CCENDU Drug Alert: Isotonitazene Ensuring availability of and training on naloxone Providing general harm reduction advice to reduce overdose risk

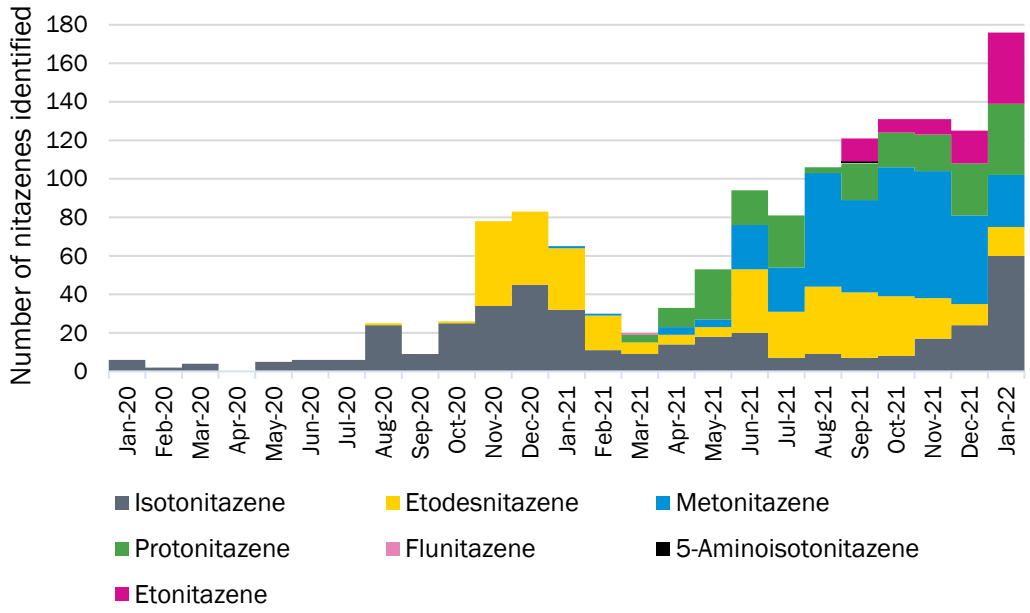
[1]The Center for Forensic Science Research and Education, see Resources section.
[2] General harm reduction advice includes recommendations to use with others, stagger use in a group, do small test doses, use one substance at a time and call 911 in an emergency.

Supplemental Data from HC DAS

The figure below shows the rise of nitazenes identified in samples analyzed by HC DAS, from a total of six nitazenes reported in January 2020 to 176 reported in January 2022. Note that more than one nitazene can be identified in a single sample; in 2021, approximately 14% of nitazene-positive samples contained two or more. Although nitazenes were only detected in 0.8% of all samples analyzed and reported in 2021 (872 of 108,374 total samples), this was a four-fold increase from 0.2% in 2020 (248 of 101,809 total samples).

In 2021, 64% of all samples containing nitazenes were submitted from Ontario, 27% from Quebec, 4% from New Brunswick and 2% from Alberta.

Figure 1: Counts (n) of nitazenes by month



Note: Dates displayed here are the month in which samples were analyzed and reported by HC DAS. Seizure and submission of the samples may have occurred several weeks prior. Results may differ from other data presented by HC DAS due to differences in how the data are analyzed and displayed.

Implications and Recommendations

- The unregulated drug supply is increasingly toxic and unpredictable. Drug checking services can help monitor the contents of drugs from the unregulated supply and mitigate risks for people who use drugs. Resources are needed to develop, implement and scale up these services.
- Expanding access to safer supply programs, based on evaluation of existing programs and synthesis of lessons learned, can also help create a more predictable and less toxic supply.
- People using fentanyl tests strips should be made aware that their drugs could unknowingly contain nitazenes, increasing risk even when the test strips are negative for fentanyl.
- Naloxone is a key harm reduction tool for reversing overdoses involving opioids. However, it is unclear what the appropriate naloxone response is to reverse an overdose involving a nitazene. Some services recommend administering multiple doses, but evidence is needed about the optimal delay between doses and how many are needed.
- Clinical and forensic toxicology labs should develop and implement testing protocols that can detect nitazenes. Communicating these results could help public health efforts to monitor the drug supply and associated risks.

Resources

- Benzimidazoles and analogues (nitazenes) including isotonitazene and etodesnitazene (BC Centre for Disease Control)
- "Ultra potent" opioids continue to circulate in Toronto's unregulated drug supply (Toronto's Drug Checking Service)
- Novel Non-Fentanyl Synthetic Opioids: Risk Assessment and Implications for Practice (Public Health Ontario)
- Learning Exchange: Risk of Novel Synthetic Opioids in Ontario (webinar) (Public Health Ontario)
- Public Health Alerts (Center for Forensic Science Research and Education)

CCENDU will continue to monitor the situation around opioids in Canada. If you have any questions, comments, information or corrections to this alert, or wish to subscribe and receive updates as new information becomes available, contact CCENDU@ccsa.ca. For more information on CCENDU and to review previous CCENDU Alerts and Bulletins, visit www.CCENDU.ca.

Prepared by the CCSA in partnership with the Canadian Community Epidemiology Network on Drug Use (CCENDU)

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