

## EVIDENCE BRIEF

# Novel Non-Fentanyl Synthetic Opioids: Risk Assessment and Implications for Practice

10/08/2021

### Key Messages

- Novel non-fentanyl synthetic opioids (NSOs) in the benzimidazole-opioids group (e.g., isotonitazene, metonitazene, etonitazene; also known as “nitazenes”) have emerging presence in the unregulated drug supply, including samples from communities and deaths in Ontario.
- There is uncertainty in characterizing the specific risk of benzimidazole-opioids in Ontario due to the small body of relevant information, testing limitations, and overall volatility and toxicity of the unregulated drug supply (e.g., fentanyl/analogues, benzodiazepines and other novel psychoactive substances (NPS)).
- The risk of severe overdose with benzimidazole-opioids is moderate to high, with the potential to need higher doses of naloxone due to potency that may exceed fentanyl and co-occurrence with fentanyl/analogues. The presence of benzimidazole-opioids increases the need for testing and surveillance capacity in harm reduction, health and forensic settings.
- At this time, the available information supports continuing with current approaches to opioid overdose prevention and response, including not using drugs while alone, accessing drug checking and supervised consumption services where available, monitoring respiratory status after using, the use of naloxone if needed, and seeking emergency health care.
- As NSO/NPS continue to emerge, new and innovative public health approaches and community-led responses are needed to address the toxic drug supply to improve drug policy and safety for people who use drugs.

### Issue and Research Question

Reports of novel non-fentanyl synthetic opioids (i.e. benzimidazole-opioids group) in the drug supply are emerging in Ontario, British Columbia and internationally. In addition, increasing opioid-related deaths over the past several decades have escalated to unprecedented levels during the COVID-19 pandemic. Given the need for effective responses of the health system to reduce substance-related harms, it is important to consider the potential impact of novel non-fentanyl synthetic opioids on opioid-related morbidity and mortality in Ontario. While there are other groups of NSO, this review and risk assessment focus specifically on the benzimidazole-opioids group.

## Methods

This rapid evidence review and risk assessment is based on searches of the published and grey literature, relevant data sources, and documents referred from experts. Public Health Ontario (PHO) Library Services conducted searches on August 27, 2021 of published literature on novel synthetic opioids, including the class name benzimidazole-opioids (also known as nitazenes) and specific drugs within this class; etonitazepyne, etodesnitazene, metonitazene, and isotonitazene, using the MEDLINE and Embase databases (search strategies available upon request). English language peer-reviewed records that described novel synthetic opioids were included. Based on suggestions from library services at PHO, we conducted a search of the grey literature using custom search engines, including Ontario’s Public Health Units, Canadian Health Departments and Agencies, U.S. State Government Websites, International Public Health Resources, U.S. .Gov/.Org/.Edu domains, in addition to Google Canada. These six repositories were searched using search queries based on concepts of potency, opioids, adverse effects, and drug supply related to the nitazene/benzimidazole opioids group of drugs between September 14 and 16, 2021. Data from the Health Canada Drug Analysis Service (HC DAS) was analyzed by the Office of the Chief Coroner for Ontario, and Toronto’s Drug Checking Service provided a summary of results from their program data.

As information on this topic continues to evolve rapidly, the information provided in this document is current as of the date of the literature searches.

Novel synthetic opioid group	Examples
<b>Benzimidazole-opioids</b> <b>(also known as nitazenes)</b>	<b>Etonitazepyne, Etodesnitazene, Metonitazene, Isotonitazene</b>

## Background

- Benzimidazoles, including etonitazene, are substances that are active as mu opioid receptor agonists and reported as being first synthesized in Swiss pharmaceutical research laboratories in the late 1950’s.(1)
- In previous research benzimidazole-opioids demonstrated high potency (some are several times more potent than fentanyl) and also high toxicity. For example, metonitazene was 10 times more potent than morphine in humans, but was not studied further due to high risk of adverse effects including sedation and respiratory failure. (1) Naloxone has been shown to work in the presence of benzimidazole-opioids, such as isotonitazene.(1, 2)
- Substances in this group of novel non-fentanyl synthetic opioids (NSO) have not been approved as pharmaceutical products, but have been identified in the unregulated drug supply (e.g., isotonitazene identified March 2019), and have been involved in deaths in Europe and North America.(1, 2, 3, 4, 5)
- Recent literature reflects concern for NSOs as a contaminant in the unregulated drug supply due to fentanyl policy (e.g. production ban in China), regulation of precursors, low cost of production, and ease of concealment.(2)

# Increased Exposure

## Drug distribution

- A report based on the Belgian Early Warning System Drugs (BEWSD) described the identification and characterization of a sample of isotonitazene obtained in June 2019, that was sold online under the name etonizatine.(6)
- In a study of 35,196 opioid listings on darknet markets between June and August 2020, 17 NSOs (883 listings) were identified among 2.9% of the listings and 45.5% of the NSO listings were advertised as shipped from China. Of these NSOs, five were in the benzimidazole-opioids group, with etazene (also called etodesnitazene) listed most commonly (195 of 883 NSO listings). Fourteen of the NSOs were identified for the first time, indicating a shift in their availability.(7)
- Research using a web crawler called NPSfinder® between January and August 2020 identified 18 NPS for the first time, including 6 new opioids (3 benzimidazole-opioids: etazene, metodesnitazene, flunitazene).(8)
- In the US, a study evaluated the relationship between the on-line mention of eight novel psychoactive substances (NPS) and forensic investigations, including isotonitazene on Reddit forum discussions between 2013 and 2020. The study found 7 of the 8 included NPS showed an increased mention on Reddit prior to their implication in poisoning deaths. This may support monitoring of social media sites as potential predictors of future NPS exposures, including benzimidazoles-opioids.(9)

## Drug samples

### DRUG ANALYSIS SERVICE

- [Health Canada Drug Analysis Service](#) (HC DAS) operates laboratories across Canada that analyze suspected illegal drugs seized by Canadian law enforcement agencies, and reports on the detection of substances in submitted samples including several benzimidazole-opioids.
- These data are based on samples analyzed by DAS and should not be used as a basis for determining trends or making comparisons, as they are not representative of drug seizures in Canada or drugs circulating on the market. Also of note, multiple substances may be detected in a single sample, multiple samples can be drawn from the same seizure, the size of the seizure cannot be determined, and samples can include a variety of sources including tablets, powders, residue, or syringes.

**Table 1. Health Canada Drug Analysis Service (HC DAS) detection of Isotonitazene, Etodesnitazene, Metonitazene, Protonitazene in samples submitted in Ontario**

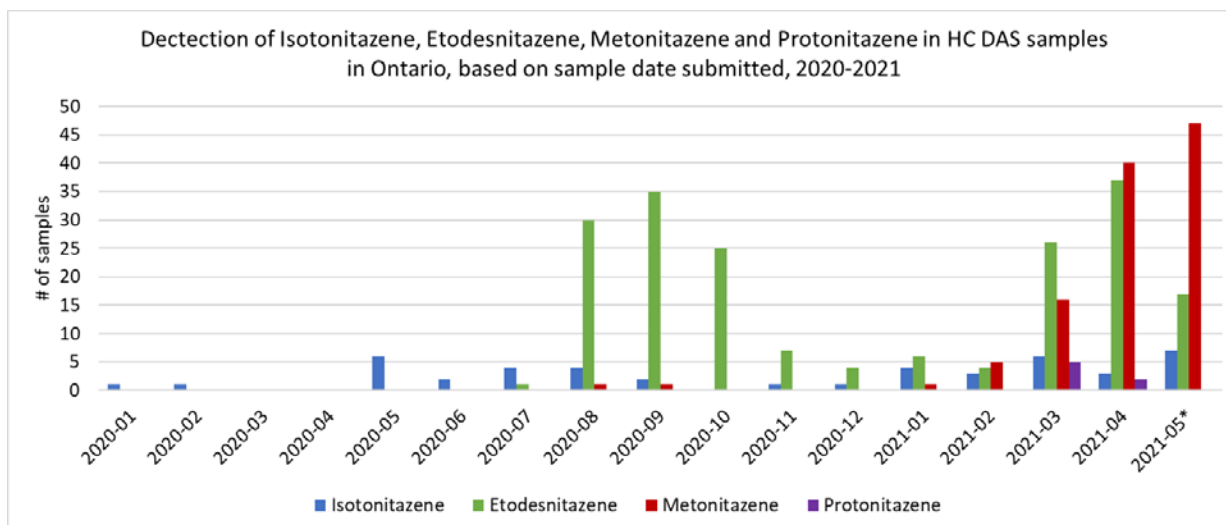
	Isotonitazene	Etodesnitazene	Metonitazene	Protonitazene
<b>Total samples</b>	<b>46</b>	<b>188</b>	<b>118</b>	<b>6</b>
<b>Sample submission date to HC DAS of first sample detected</b>	Jan 2020	Aug 2020	Aug 2020	Mar 2021
<b>Number of regions (submitting police detachments*) with positive samples</b>	20	40	24	3
<b>% of samples with fentanyl also detected</b>	17%	99%	89%	0%
<b>% of samples with benzodiazepine also detected</b>	7%	49%	57%	0%

\*Location reflects the police detachment/department not location of seizures

Note: Substance categories are not mutually exclusive

Source: Health Canada Drug Analysis Monthly Data – data effective Sept 8, 2021

**Figure 1. Health Canada Drug Analysis Service (HC DAS) detection of Isotonitazene, Etodesnitazene, Metonitazene, Protonitazene by month in samples submitted in Ontario, 2020-May 2021**



Samples may be counted in more than 1 substance category.

Source: Health Canada Drug Analysis Monthly Data – data effective Sept 8, 2021

- In Ontario, isotonitazene was first detected by HC DAS in samples submitted in January 2020 (first detection in Canada was in November 2019). Etodesnitazene was detected in the greatest number of samples (n=188). In samples where etodesnitazene and metonitazene were detected, fentanyl was also present in most whereas benzodiazepines were detected in approximately half of these samples.
- Over time since January 2020, patterns of sample results indicate higher numbers of samples with etodesnitazene detected were submitted between August and October 2020 and again between March and May 2021. Increasing numbers of samples with metonitazene were submitted between March and May 2021. A lower number of samples were submitted with isotonitazene detected over several months.
- Samples positive for isotonitazene, etodesnitazene, metonitazene or protonitazene were submitted from 48 locations across the province. Based on the August 2021 monthly report (most recent report available), the number of samples with detection of nitazene substances reported was greater in Ontario, 73 positive samples, compared to other provinces with 5 or fewer positive samples in Alberta, Manitoba or Quebec.(10)
- In April 2021, the Royal Newfoundland Constabulary (Newfoundland and Labrador's Provincial Police Service) warned the public of dangerous opioids after the national laboratory confirmed fentanyl and isotonitazene in pills seized by the Drug Investigation Unit. The pills were made to look like prescription opioid medication.(11)

## DRUG CHECKING SERVICES

**Table 2. Nitazene opioids identified in 73 samples checked in Toronto, October 10, 2019 – August 31, 2021\***

	Drug name	Estimated strength compared to fentanyl	First identified	Found in how many samples
1	<b>Isotonitazene/Protonitazene</b>	Up to 5x stronger	February 12, 2021	30
2	<b>Etonitazene</b>	10x stronger	May 5, 2021	3
3	<b>Metonitazene</b>	Similar strength	May 31, 2021	38
4	<b>Etodesnitazene</b>	Similar strength	June 24, 2021	2
5	<b>Etonitazepyne</b>	10x stronger	July 13, 2021	5

Source: [www.drugchecking.cdpe.org](http://www.drugchecking.cdpe.org)

- Using mass spectrometry technologies, Toronto’s Drug Checking Service has identified 73 samples with nitazene opioids (6 types overall), and has issued several related drug alerts.(12) The first detected was isotonitazene in February 2021.
- The highest number of samples involved metonitazene, which is estimated at a similar potency as fentanyl, while several other types detected are estimated as 2 to 10 times more potent than fentanyl.
- Among other observations, the only opioids found were nitazene opioids in 22% (16) of the samples, 8% (6) contained more than one nitazene opioid, 15% (11) were reported as being associated with an overdose, and samples varied in colour: brown, green, purple, blue, red, pink, yellow.

## FORENSIC SAMPLES

A case-control study of deaths in two US counties identified 40 deaths involving isotonitazene between January 1 and July 31, 2020, whereas 981 involved other synthetic opioids. When isotonitazene was present, deaths involved a significantly greater number of substances and were more likely to involve flualprazolam.(13)

## Overdose Severity

In 2021, an article was published documenting the synthesis and analytical characterization of ten nitazenes and four metabolites to evaluate mu opioid receptor (MOR) activity. In vitro MOR activity revealed nitazenes to be generally highly active with some analogues having potencies and efficacies greater than fentanyl. This study unexpectedly, identified a nitazene metabolite, N-desethylisotonitazene which has a potency greater than isotonitazene. These findings may have in vivo implications related to potentially increasing MOR activation and also provides an analytical framework for detection of emerging nitazenes.(14)

Although not specific to benzimidazole-opioids, new synthetic opioids (e.g., fentanyl derivatives and non-fentanyl opioids) can interact with other pharmaceutical drugs and non-medical substances, such as benzodiazepines and other central nervous system depressants, producing respiratory distress, coma and death.(15)

## Opioid mortality

- A March 2021 published case report from a region in the south of Switzerland describes the first three deaths reported in Europe involving isotonitazene (earliest isotonitazene detection March 2019). (16) With all other substances in the non-toxic range, two cases involved benzodiazepines and another involved ethanol. The authors discuss that the presence of isotonitazene could have been overlooked without the powder and pipe at the sites, due to very low toxic concentrations, and suggest qualitative screening for forensic laboratories.
- A June 2021 publication reports findings from a series of 20 deaths involving metonitazene investigated between November 2020 and February 2021 in the United States. (17) Metonitazene was the only opioid in 30% of cases; 55% of cases also involved fentanyl, while 45% of cases involved benzodiazepines, opioids, or hallucinogens. These deaths were all considered accidental, and metonitazene was a drug contributing to death. Authors suggest metonitazene should be included in forensic testing protocols.
- Also in June 2021, the NPS Discovery program at the Center for Forensic Science Research and Education (CFSRE) in the United States issued a public alert on etonitazene found in post-mortem samples from overdoses across the country between January to April 2021.(18)
- Public Health England issued a national patient safety alert in August 2021 after a 10-14 day period of increased overdoses with some deaths, with testing of 3 cases in two areas of the country detecting isotonitazene.(19)
- In Canada, Alberta reported the first death involving benzimidazole-opioids in October 2019.
- As of September 2021, the analytical capability of toxicology testing in Ontario for benzimidazole-opioids (also referred to as “nitazenes”) is limited. Qualitative detection of the following nitazenes is available: isotonitazene, metonitazene, protonitazene, flunitazene and N-pyrrolidino etonitazene. Validation is underway for other substances in this group.
- To date, one death in the fall of 2020 was attributed to metonitazene in Ontario. An ongoing investigation into the cause of another death in July 2021 involved isotonitazene (detected in post-mortem samples along with other substances).” Many death investigations for 2021 are ongoing; finalized investigations may identify additional deaths where there was involvement of these substances.

## Effectiveness of Interventions

- Overall, current overdose prevention and response strategies are likely effective in the context of benzimidazole-opioid exposure among people who use drugs, but higher doses of naloxone may be required to restore breathing in opioid-related overdoses.

## Harm reduction

### NALOXONE

- Although not specific to benzimidazole-opioids, naloxone may be required in higher doses for synthetic opioids than traditional opioids. (15) Often present with other sedating substances, such as benzodiazepines, overdoses involving benzimidazole-opioids may present as a mixed toxicity.

### OTHER

- We did not find information on the use or effectiveness other harm reduction education or services with specific consideration of benzimidazole-opioids, which may reflect the novelty of this area.
- Drug checking, supervised consumption services (SCS), or safer supply programs may play an even more important role in preventing opioid-related morbidity and mortality as a result of increased exposure to a more varied and toxic unregulated drug supply, including benzimidazole-opioids, fentanyl/fentanyl analogues, benzodiazepines, and other NPS. (13, 20)
- Other harm reduction strategies such as not using opioids while alone, and seeking emergency care for respiratory distress and prolonged sedation, remain a component of the standard-of-practice for opioid overdose prevention and response.(21)

## Treatment

### OPIOID AGONIST TREATMENT (OAT)

- There was no specific evidence found relating to benzimidazole-opioids exposure and OAT treatment. In the era of fentanyl and other synthetic opioids, there have been challenges to manage withdrawal and reduce overdose rates with traditional OAT options. This has prompted the adaptation of [treatment guidelines](#) for people who use fentanyl and discussion of alternative treatment options.

## Ontario Risk Assessment

- **Overall, the risk of novel non-fentanyl synthetic opioids in the benzimidazole-opioids group is likely moderate to high, with a high degree of uncertainty. The presence of these substances is increasing in Ontario and they pose an increased risk of severe overdose, particularly when present with other sedating substances.**
- The overall risk assessment may change as new evidence emerges ([Table 1](#)).



**Table 3. Risk Assessment for Novel Non-Fentanyl Synthetic Opioids**

Issue	Risk Level	Degree of Uncertainty
<b>Increased exposure</b>	<b>1) Moderate</b> <ul style="list-style-type: none"> <li>Increasing prevalence of benzimidazole-opioids in the unregulated drug supply in the US, Europe and Canada: Ontario, British Columbia and Alberta</li> <li>Other synthetic opioids such as fentanyl and its analogues represent a much greater exposure</li> </ul>	<b>High</b>
	<b>2) Moderate/High</b> <ul style="list-style-type: none"> <li>Spectrum of potency may exceed fentanyl</li> <li>Benzimidazole-opioids are often found in combination with other sedating drugs such as fentanyl/analogues and benzodiazepines</li> </ul>	
<b>Lowered effectiveness of interventions</b>	<b>3) Moderate</b> <ul style="list-style-type: none"> <li>Naloxone works, but may need higher doses, related to a spectrum of potency that may exceed fentanyl</li> <li>Prolonged sedation when other sedating drugs are involved</li> </ul>	<b>4) High</b>
	<b>5) High</b> <ul style="list-style-type: none"> <li>Conventional point of care testing (e.g., urine drug screen testing for fentanyl and other opioids) does not detect benzimidazole-opioids which requires lab based mass spectrometry testing that is not widely available (e.g., only available at drug checking services in Toronto)</li> <li>Need to develop testing methods that can be applied across the province in harm reduction, healthcare and forensic settings</li> </ul>	

## Practice Implications

- As NSOs continue to emerge in the unregulated drug supply, detection of NSOs will help to clarify patterns in their presence and association with outcomes, requiring improved testing and surveillance capacity across Ontario in harm reduction, healthcare and forensic settings.

- Available information supports continuing with current approaches to opioid overdose prevention and response, including the use of naloxone.(22) Due to the high potency of benzimidazole-opioids or combination with fentanyl/analogues, higher doses of naloxone may be needed to restore breathing in an opioid-related overdose (no specific guidance identified. In the presence of benzodiazepines, there is an elevated potential for prolonged sedation.
- With the recent emergence of benzimidazole-opioids, in the context of fentanyl/analogues, benzodiazepines, and other NPS, the unregulated drug supply is becoming more toxic and unpredictable.(23) New and innovative public health approaches and community-led responses are needed to address the toxic drug supply to improve drug policy and safety for people who use drugs.(24)

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## Community Opioid/Overdose Capacity Building

Community Opioid/Overdose Capacity Building (COM-CAP), started in 2019, is a four-year project funded by Health Canada's Substance Use and Addiction Program. The goal of COM-CAP is to support community-led responses to opioid/overdose-related harms in communities across Ontario. The supports focus on strengthening the knowledge, skills, and capacity of the key stakeholders involved.

- The Ontario College of Art & Design University (OCAD U) - Health Design Studio
- University of Toronto- Strategy Design and Evaluation Initiative
- Black Coalition for AIDS Prevention
- Chatham-Kent Public Health
- NorWest Community Health Centres
- Drug Strategy Network of Ontario
- The Ontario Network of People Who Use Drugs

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