

# Nitazenes: Surveillance of benzimidazole opioids and brrorphine in British Columbia and Canada

## Background:

- Benzimidazoles are a large group of heterocyclic, aromatic compounds that often show biological activity, including antiviral, antiparasitic, anticancer, and analgesic properties, and have been developed into several classes of important therapeutic drugs.
- Benzimidazole opioids (also known as nitazenes) were first discovered in the 1950s; however, they were never clinically approved for marketing.
- Benzimidazole opioids are selective mu opioid receptor agonists, and therefore can cause classic opioid overdoses.
- In the event of an overdose, naloxone will likely reverse the drug's effects, including respiratory depression.
- The potency of benzimidazole opioids can vary dramatically between drugs in the class, ranging from levels that are similar to morphine to those that are significantly stronger than fentanyl.
- Benzimidazole opioids and brorphine are structurally dissimilar from fentanyl, so fentanyl test strips will not detect them.
- Benzimidazole opioids have never been used in clinical medicine due to their increased risk of respiratory depression and death (Montanari et al. 2022). The therapeutic index between analgesia and respiratory depression is narrow, and therefore offers no advantage over morphine when given by injection. Consequently, benzimidazole opioids were not further developed for clinical use (Ujváry et al. 2021).
- 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).
- Benzimidazole opioids such as metonitazene and butonitazene began emerging on the illicit drug markets from 2020 onwards, while isotonitazene emerged earlier, in 2019 (Ujváry et al. 2021).
- Brorphine, a synthetic mu opioid receptor agonist structurally related to benzimidazole opioids, was developed in 2018 and emerged on the US illicit drug market in 2019 (Vandeputte et al. 2021b), while benzimidazole opioid protonitazene emerged later in the US illicit drug market, in 2021 (The Center for Forensic Science Research and Education 2021a).

## Original data sources used in this information sheet

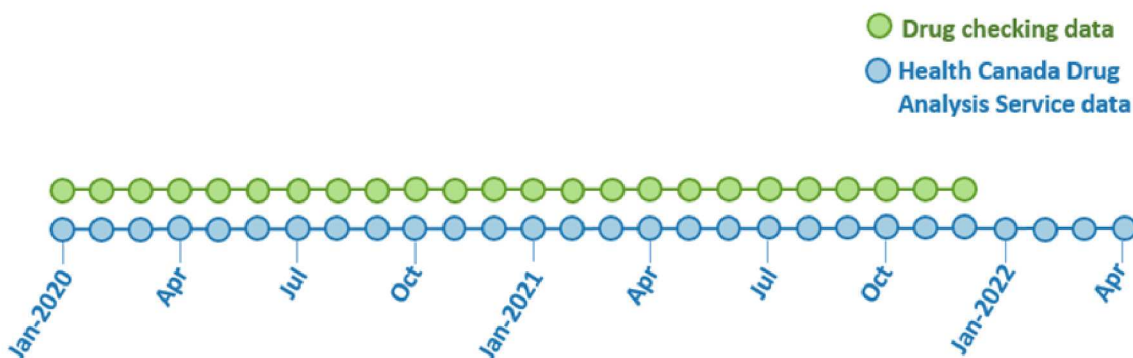
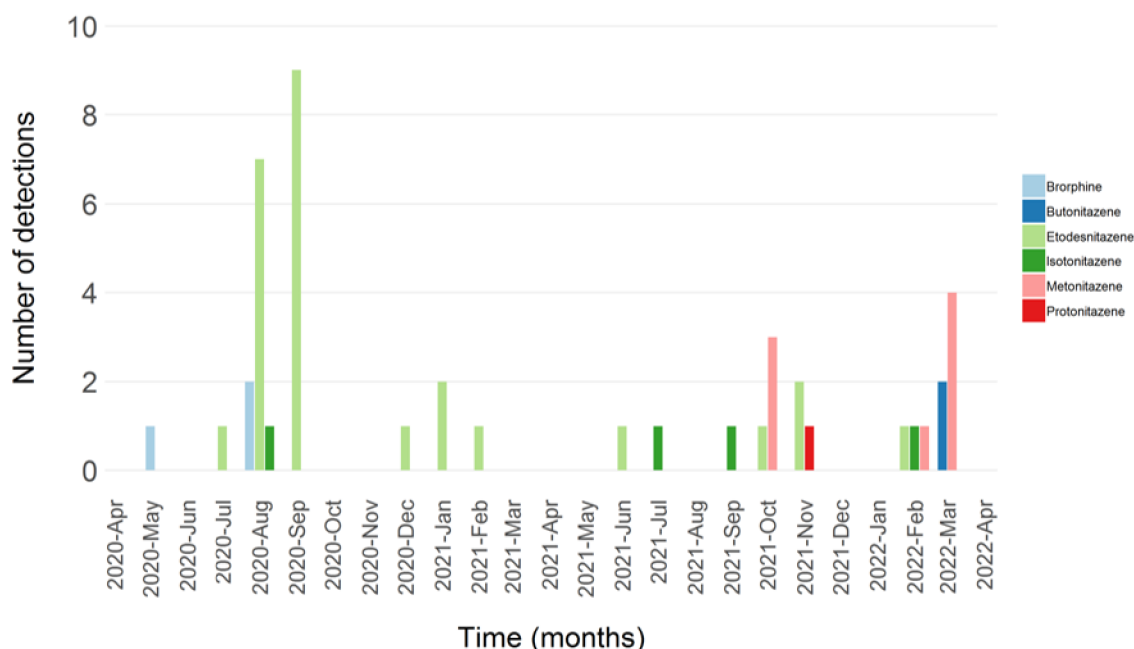


Figure 1. Date cut-offs for original data sources

# Benzimidazole opioids: surveillance of nitazenes and brorphine in British Columbia and Canada

- Health Canada Drug Analysis Services (HC DAS) receives substance samples seized by law enforcement. Results reported here include data for samples seized in British Columbia (BC) and Canada, and received by HC DAS for analysis to the end of April 2022.
  - Findings may differ from HC DAS data reported elsewhere as data may be analyzed and presented in a different manner.
  - Date ranges provided refer to the date that HC DAS received the samples - not the date law enforcement seized the samples. Only samples whose results have been returned to the submitting agency are depicted. Counts for previous months are subject to change as more testing is completed and reported.
  - Data is provided by HC DAS to BCCDC on a monthly basis.
- BC Centre on Substance Use (BCCSU) partners with 14 frontline drug checking services across BC, which conduct point-of-care Fourier-transform infrared spectroscopy (FTIR) at the sites. Some services send a subset of samples to HC DAS for confirmatory testing.
  - Data from BCCSU includes samples analyzed by Get Your Drugs Tested (GYDT).
- Vancouver Island Drug Checking uses FTIR, Raman spectroscopy, and Paper spray mass spectrometry (PS-MS) at a point-of-care testing site in Victoria, BC. Samples from Vancouver Island can also be mailed into Vancouver Island Drug Checking for analysis.

The following figure (Figure 2) shows benzimidazole opioids and brorphine detected among samples seized in BC and received by HC DAS for analysis between April 2020 and April 30, 2022. Time units on the x-axis refer to the date that HC DAS received the samples; therefore, there may be a lag between when these samples were circulating the illicit market and the dates listed. Data for recent months are subject to increase as more analyses are completed.



\*Date sample received by DAS or date result returned to client if date received unavailable  
 \*Number of detections may exceed number of unique samples where more than one type of benzimidazole is detected per sample

Figure 2. Benzimidazole opioids and brorphine detections in samples seized by law enforcement in BC, as of April 2022

# Benzimidazole opioids: surveillance of nitazenes and buprenorphine in British Columbia and Canada

## Acronyms

BCCSU: BC Centre on Substance Use

FTIR: Fourier-transform infrared spectroscopy

GC-MS: Gas chromatography mass spectrometry

GYDT: Get Your Drugs Tested

HC DAS: Health Canada Drug Analysis Service

PS-MS: Paper spray mass spectrometry

VIDC: Vancouver Island Drug Checking

## Isotonitazene

Isotonitazene is a potent benzimidazole opioid that was first identified by the Office of the Chief Medical Examiner of Alberta in March 2019, and became available on the illicit drug market in Europe in April 2019 (European Monitoring Centre for Drugs and Drug Addiction 2020; Vandeputte et al. 2021a).

### Identification:

Isotonitazene will not give a positive response on fentanyl test strips. It can be detected using FTIR or mass spectrometry.

### Potency:

In vitro analyses indicate that isotonitazene is more potent than fentanyl (World Health Organization 2020).

### Scheduling:

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 is a scheduled substance in the US and is internationally controlled (World Health Organization 2021).

### Prevalence:

Isotonitazene has been implicated in at least 250 fatalities in Europe and North America. (Ujváry et al. 2021; Vandeputte et al. 2021a). Krotulski and colleagues confirmed isotonitazene in 18 decedents, nine of whom were negative for other opioids, in samples collected between August 2019 and January 2020 in Midwest US (Krotulski et al. 2020). HC DAS laboratory detected isotonitazene in one sample seized in BC and received for analysis in 2020, two samples received for analysis in 2021, and one sample received for analysis in February 2022.

### Drug Checking in BC:

- Vancouver Island Drug Checking (VIDC) tests samples for isotonitazene with PS-MS, and confirms other benzimidazole opioids with PS-MS if detected through FTIR.
  - i. VIDC first detected isotonitazene in January 2021, and saw a total of 12 samples containing isotonitazene in 2021.
  - ii. In November 2021, nine isotonitazene-positive samples contained fentanyl, etizolam, and caffeine. Six of these nine samples also contained metonitazene and etodesnitazene.
- BCCSU and GYDT identified 15 samples containing isotonitazene in Vancouver in 2021. Thirteen of these were confirmed by HC DAS laboratory using confirmatory testing. Two samples of isotonitazene sold in Vancouver were sold as isotonitazene. As of April 2022, there have been no further samples with isotonitazene detected by BCCSU.

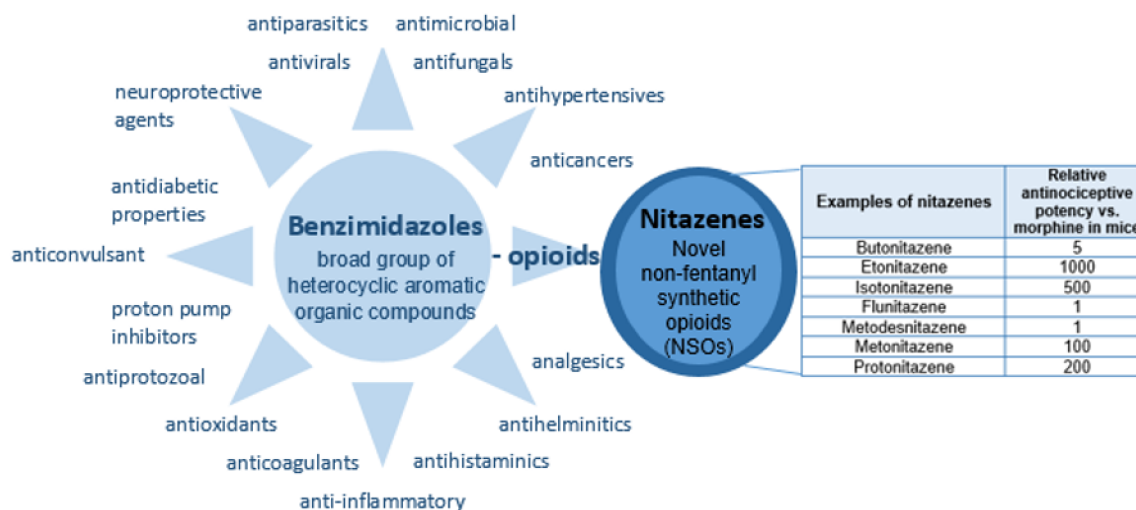


Figure 3. Benzimidazole opioids, nitazenes, and their relative antinociceptive potency. Adapted from Brishty et al. 2021; Ujváry et al. 2021.

## Etodesnitazene

Etodesnitazene (also called desnitroetonitazene, etazen and etazene, etazone) is classified as a novel opioid and can cause an opioid overdose.

### Identification:

Etodesnitazene will not give a positive response on fentanyl test strips. It can be detected using FTIR or mass spectrometry.

### Potency:

Recent in vitro data suggest that etodesnitazene is less potent than fentanyl.

### Scheduling:

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). Etodesnitazene is not a schedule I substance in US (although etonitazene and isotonitazene are scheduled).

### Prevalence:

As of April 2022, HC DAS has identified etodesnitazene in 135 samples across Canada in 2020 and in 261 samples in 2021. In 2020, HC DAS received 18 samples seized in BC that contained etodesnitazene, received an additional seven etodesnitazene-positive samples in 2021, and one sample in 2022, as of April 2022. Etodesnitazene was found in Northern Health for the first time in a sample analyzed in February 2021, where it was in combination with fentanyl, etizolam and caffeine.

# Benzimidazole opioids: surveillance of nitazenes and bupropion in British Columbia and Canada

## Drug checking in BC:

- GYDT in Vancouver has identified five samples containing etodesnitazene.
  - i. July 29, 2020 by FTIR and confirmed by HC DAS.
  - ii. Jan 2, 2021 by FTIR; DAS results detected etodesnitazene, clonazepam, phenacetin, and erythritol.
  - iii. October 29, 2021 by FTIR and confirmed by HC DAS.
  - iv. October 30, 2021 by FTIR.
  - v. February 7, 2022, a sample was found to contain etodesnitazene, along with caffeine and fentanyl.
- In November 2021, Vancouver Island Drug Checking detected etodesnitazene in six samples from Port Alberni, using FTIR and PS-MS. All six samples also tested positive for isotonitazene, metonitazene, fentanyl, caffeine, and etizolam, and were sold as opioid/down.

## Metonitazene

Metonitazene is classified as a novel opioid and can cause an opioid overdose.

### Identification:

Metonitazene will not give a positive response on fentanyl test strips. It can be detected using FTIR or mass spectrometry.

### Potency:

Metonitazene is more potent than fentanyl (World Health Organization 2021).

### Scheduling:

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). In October 2021, the World Health Organization's Expert Committee on Drug Dependence recommended metonitazene and bupropion become internationally controlled (World Health Organization 2021).

### Prevalence:

BCCSU and GYDT drug checking detected metonitazene in most months of 2021, starting in February 2021. In October 2021, HC DAS received a sample seized by law enforcement in Vancouver that contained metonitazene, in addition to fentanyl, caffeine, and diphenhydramine (an antihistamine). HC DAS detected metonitazene in three samples seized in BC and received for analysis in November 2021, and in five samples received for analysis in 2022.

## Drug checking in BC:

In November 2021, VIDC found that six samples from Port Alberni contained metonitazene, using FTIR and PS-MS. All six samples also tested positive for isotonitazene, etodesnitazene, fentanyl, caffeine, and etizolam, and were sold as opioid/down.

# Benzimidazole opioids: surveillance of nitazenes and brrorphine in British Columbia and Canada

- Between February 2021 and February 11th, 2022, BCCSU and GYDT identified 20 samples containing metonitazene in Vancouver using FTIR, 11 of which were confirmed by HC DAS laboratory with confirmatory testing.

## Protonitazene

### Identification:

Protonitazene will not give a positive response on fentanyl test strips. It can be detected using FTIR or mass spectrometry. Protonitazene is an isomer of isotonitazene, meaning they share the same molecular composition, but their molecules are arranged in different ways (The Center for Forensic Science Research and Education 2021a). Because of this, analyses with higher specificity are needed to differentiate protonitazene from isotonitazene (The Center for Forensic Science Research and Education 2021a).

### Potency:

Protonitazene is more potent than fentanyl (The Center for Forensic Science Research and Education 2021a).

### Scheduling:

Protonitazene is a controlled substance under the Controlled Drugs and Substances Act in Canada, and is also a controlled substance internationally (The Center for Forensic Science Research and Education 2021a).

### Prevalence:

Protonitazene has been detected a total of 15 times in North America to the end of December 2021, including nine times in post-mortem toxicology in North America, three of which were in British Columbia (The Center for Forensic Science Research and Education 2021a). HC DAS first identified protonitazene in law-enforcement seized samples in March 2021 in Quebec; DAS' first detection of protonitazene in BC was in one sample received for analysis in November of 2021.

### Drug Checking in BC:

- BCCSU and Get Your Drugs Tested detected protonitazene in one sample from Vancouver, in December 2021. It was confirmed by GC-MS at HC DAS laboratory.

## Brrorphine

Brrorphine is a novel synthetic mu opioid receptor agonist structurally related to benzimidazole opioids.

### Identification:

Brrorphine will not give a positive response on fentanyl test strips. It can be detected using FTIR or mass spectrometry.

### Potency:

Brrorphine is less potent than fentanyl, but more potent than morphine (World Health Organization 2021).

# Benzimidazole opioids: surveillance of nitazenes and bupropion in British Columbia and Canada

## Scheduling:

Bupropion is a controlled substance under the Controlled Drugs and Substances Act in Canada, the United States, and several European countries (Vandeputte et al. 2021b). In October 2021, the World Health Organization's Expert Committee on Drug Dependence recommended bupropion become internationally controlled (World Health Organization 2021).

## Prevalence:

The first detection of bupropion in North America was in August 2019, but it only became established in the US illicit drug market mid-2020 (Vandeputte et al. 2021b). It has been involved in over 50 deaths worldwide (Vandeputte et al. 2021b). The first detection of bupropion by HC DAS occurred in Alberta, in September 2019. In BC, bupropion was detected in three samples seized by law enforcement and received for analysis by HC DAS laboratory in May and August of 2020. As of April 2022, it has not been detected in any further samples seized in BC.

## Drug Checking in BC:

- Bupropion has not yet been detected in drug checking services in BC.

## Butonitazene

Butonitazene is classified as a novel opioid and therefore can cause an opioid overdose.

## Identification:

Butonitazene will not give a positive response on fentanyl test strips. It can be confirmed using FTIR or mass spectrometry.

## Potency:

Butonitazene is more potent than morphine, but less potent than fentanyl (Ujvary 2021).

## Scheduling:

Butonitazene is a controlled substance under the Controlled Drugs and Substances Act in Canada, and is scheduled in the US (Cayman 2022b). Butonitazene is not yet internationally controlled (International Narcotics Control Board 2021)

## Prevalence:

In BC, butonitazene has been detected twice in samples seized by law enforcement and received for analysis by HC DAS laboratory in March 2022. Butonitazene was also detected in post-mortem toxicology results in Ohio, in January 2021 (The Center for Forensic Science Research and Education 2021b).

## Drug Checking in BC:

Butonitazene has not yet been detected in drug checking services in BC.

## References

- Blanckaert P, Cannaert A, Van Uytfganghe K, Hulpia F, Deconinck E, Van Calenbergh S et al. Report on a novel emerging class of highly potent benzimidazole NPS opioids: Chemical and in vitro functional characterization of isotonitazene. *Drug Testing and Analysis*. 2020;12(4):422-430.
- Brishty S, Hossain M, Khandaker M, Faruque M, Osman H, Rahman S. A Comprehensive Account on Recent Progress in Pharmacological Activities of Benzimidazole Derivatives. *Frontiers in Pharmacology*. 2021;12.
- Cayman Chemical. Etodesnitazene (citrate) [Internet]. Cayman Chemical. 2022 [cited 18 February 2022]. Available from: [https://www.caymanchem.com/product/29916/etodesnitazene-\(citrate\)](https://www.caymanchem.com/product/29916/etodesnitazene-(citrate))
- Cayman Chemical. Butonitazene [Internet]. Cayman Chemical. 2022 [cited 26 April 2022]. Available from: <https://www.caymanchem.com/product/30278/butonitazene>
- Health Canada. Drug Analysis Service Analyzed Drug Report [Internet]. 2021 [cited 22 April 2021]. Available from: <https://health-infobase.canada.ca/drug-analysis-service/analyzed-drug-report.html?p=CA&y=2020&q=all>
- European Monitoring Centre for Drugs and Drug Addiction. Isotonitazene: EMCDDA initial report on the new psychoactive substance N,N-diethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1H-benzimidazole-1-ethanamine (isotonitazene) [Internet]. Luxembourg: European Monitoring Centre for Drugs and Drug Addiction; 2020 [cited 18 February 2022]. Available from: [https://www.emcdda.europa.eu/system/files/publications/13028/EMCDDA-Initial-report\\_Isotonitazene.pdf](https://www.emcdda.europa.eu/system/files/publications/13028/EMCDDA-Initial-report_Isotonitazene.pdf)
- International Narcotics Control Board. List of narcotic drugs under international control [Internet]. Vienna; 2021. Available from: [https://www.incb.org/documents/Narcotic-Drugs/Yellow\\_List/60th\\_edition/60\\_Yellow\\_List\\_EN\\_rev1.pdf](https://www.incb.org/documents/Narcotic-Drugs/Yellow_List/60th_edition/60_Yellow_List_EN_rev1.pdf)
- Krotulski A, Papsun D, Kacinko S, Logan B. Isotonitazene Quantitation and Metabolite Discovery in Authentic Forensic Casework. *Journal of Analytical Toxicology*. 2020;44(6):521-530.
- Montanari E, Madeo G, Pichini S, Busardò F, Carlier J. Acute Intoxications and Fatalities Associated with Benzimidazole Opioid (Nitazene Analog) Use. *Therapeutic Drug Monitoring*. 2022; Publish Ahead of Print.
- The Center for Forensic Science Research & Education. New Synthetic Opioid Protonitazene Increasing in Prevalence as "Nitazenes" Gain Traction Across the United States and Canada; 2021. Available from: [https://www.npsdiscovery.org/wp-content/uploads/2021/12/Public-Alert\\_Protonitazene\\_NPS-Discovery\\_121021.pdf](https://www.npsdiscovery.org/wp-content/uploads/2021/12/Public-Alert_Protonitazene_NPS-Discovery_121021.pdf)
- The Center for Forensic Science Research and Education. Butonitazene [Internet]. Willow Grove; 2021. Available from: [https://www.npsdiscovery.org/wp-content/uploads/2021/01/Butonitazene\\_011521\\_ToxicologyAnalyticalReport.pdf](https://www.npsdiscovery.org/wp-content/uploads/2021/01/Butonitazene_011521_ToxicologyAnalyticalReport.pdf)
- Ujváry I, Christie R, Evans-Brown M, Gallegos A, Jorge R, de Morais J et al. DARK Classics in Chemical Neuroscience: Etonitazene and Related Benzimidazoles. *ACS Chemical Neuroscience*. 2021;12(7):1072-1092.
- Vandeputte M, Van Uytfganghe K, Layle N, St. Germaine D, Iula D, Stove C. Synthesis, Chemical Characterization, and  $\mu$ -Opioid Receptor Activity Assessment of the Emerging Group of "Nitazene" 2-Benzylbenzimidazole Synthetic Opioids. *ACS Chemical Neuroscience*. 2021;12(7):1241-1251.
- Vandeputte M, Krotulski A, Papsun D, Logan B, Stove C. The Rise and Fall of Isotonitazene and Brophine: Two Recent Stars in the Synthetic Opioid Firmament. *Journal of Analytical Toxicology*. 2021;00:1-7.
- World Health Organization. Annex I. 44th WHO ECDD Summary assessments, findings and recommendations [Internet]. 2021. Available from: [https://cdn.who.int/media/docs/default-source/controlled-substances/44ecdd\\_unsg\\_annex1.pdf?sfvrsn=9c380ac2\\_5](https://cdn.who.int/media/docs/default-source/controlled-substances/44ecdd_unsg_annex1.pdf?sfvrsn=9c380ac2_5)



## References

- World Health Organization. Critical Review Report: ISOTONITAZENE [Internet]. Geneva; 2020. Available from: [https://www.who.int/docs/default-source/controlled-substances/43rd-ecdd/isonitazene-43rd-final-complete-a.pdf?sfvrsn=c98d9c9\\_2#:~:text=It%20has%20been%20identified%20in,seizures%20beginning%20in%20April%202019.&text=The%20single%20in%20vivo%20report,Isotonitazene%20is%20also%20highly%20lipophilic](https://www.who.int/docs/default-source/controlled-substances/43rd-ecdd/isonitazene-43rd-final-complete-a.pdf?sfvrsn=c98d9c9_2#:~:text=It%20has%20been%20identified%20in,seizures%20beginning%20in%20April%202019.&text=The%20single%20in%20vivo%20report,Isotonitazene%20is%20also%20highly%20lipophilic).