World Health Organization

Critical review report

N-Desethyl-isotonitazene

Expert Committee on Drug Dependence

Forty-seventh Meeting

Geneva, 14–18 October 2024

This report contains the views of an international group of experts, which do not necessarily represent the decisions or the stated policy of the World Health Organization.

Contents

Executive summary

N-Desethyl isotonitazene (IUPAC name: *N*-ethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1*H*-benzimidazole-1-ethanamine, also known, for example, as Norisotonitazene) is a benzimidazole-derived synthetic opioid with a chemical structure and pharmacological similarities to drugs under Schedule I (under the 1961 United Nations Conventions), such as isotonitazene, and is a metabolite of isotonitazene. It is part of a series of 2-benzylbenzimidazole derivatives with analgesic properties that were originally synthesized in the late 1950s; however, no medical use of *N*-desethyl isotonitazene was identified. *N*-Desethyl isotonitazene has not been reviewed previously by the WHO Expert Committee on Drug Dependence.

N-Desethyl isotonitazene has been detected in seized material, typically of unknown purity or concentration. It sold as a reference material described as a crystalline solid. No reports on the main route used for its administration could be found, but two reports from the Welsh Emerging Drugs and Identification of Novel Substances (Wedinos) provided test results from samples containing *N*-desethyl isotonitazene that were smoked.

In vitro pharmacological studies showed that *N*-desethyl isotonitazene is an opioid agonist, with higher binding affinity to μ-opioid receptors than morphine and, arguably, than fentanyl or its parent compound, isotonitazene. Various warm-water tail-flick assays showed that *N*-desethyl isotonitazene is more potent than fentanyl in inducing analgesic effects.

N-Desethylisotonitazene was confirmed in 14 post-mortem cases in the United Kingdom and the USA, but its contribution to the cause of death was unknown in all cases. Because of its high potency, *N*-desethyl isotonitazene increases the risk of overdose as compared with other opioids.

No studies of its dependence potential in experimental animals or humans were found. In drug discrimination studies (two-lever choice method) in rats, *N*-desethyl isotonitazene fully substituted for the discriminative stimulus effects of morphine, suggesting abuse potential. No studies were found on the abuse potential of *N*-desethyl isotonitazene in humans.

N-Desethyl isotonitazene has no known therapeutic or industrial uses of and no marketing authorizations. It is used as a reference material in scientific research and forensic applications.

Reports from the US National Forensic Laboratory Information System indicate that *N*-desethyl isotonitazene was first detected in the USA in 2022, in Florida and Kansas. A total of 10 detections have been reported since then.

N-Desethyl isotonitazene is not controlled under the 1961, 1971 or 1988 United Nations Conventions.

1 Substance identification

A International Nonproprietary Name (INN)

Not available.

B Chemical Abstracts Service (CAS) Registry Number

2732926-24-6

C Other chemical names

N-Ethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1*H*-benzimidazole-1-ethanamine (ACI)

D Trade names

N-Desethyl Isotonitazene is sold under its name or as the hydrochloride salt, *N*-desethyl Isotonitazene (hydrochloride) *(1)*.

E Street names

N-Desethyl Isotonitazene is indicated under its name or as "Des-Iso", "Norisotonitazene" and "NDI" *(2,3)*.

F Physical appearance

N-Desethyl Isotonitazene hydrochloride as a synthetic standard is a crystalline solid *(1)*. It has also been detected in falsified pharmaceuticals, in round blue pills *(4)*.

G WHO review history

N-Desethyl Isotonitazene has not been formally reviewed by WHO and is not currently under international control.

2 Chemistry

A Chemical name

IUPAC name: *N*-Ethyl-2-[(4-(1-methylethoxy)phenyl]methyl]-5-nitro-1*H*-benzimidazole-1-ethanamine

CA Index Name: **1*H*-Benzimidazole-1-ethanamine,** *N*-Ethyl-2-[(4-(1-methylethoxy)phenyl]methyl]-5-nitro- (ACI)

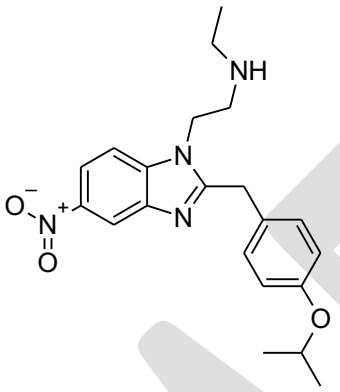
Canonical SMILES:
O=N(=O)C=1C=CC2=C(N=C(N2CCNCC)CC3=CC=C(OC(C)C)C=C3)C1

InChI:1S/C21H26N4O3/c1-4-22-11-12-24-20-10-7-17(25(26)27)14-19(20)23-21(24)13-16-5-8-18(9-6-16)28-15(2)3/h5-10,14-15,22H,4,11-13H2,1-3H3

InChI Key: HHBRZWRJZICFRP-UHFFFAOYSA-N

B *Chemical structure*

Free base:



Molecular formula: $C_{21}H_{26}N_4O$
Molecular weight: 382.46 g/mol

C *Stereoisomers*

No stereoisomers have been described for *N*-desethyl isotonitazene.

D *Methods and ease of illicit manufacture*

N-Desethyl isotonitazene was identified in vivo as an isotonitazene urinary metabolite by Krotulski et al. in 2020 *(4)*.

The literature reports synthesis of *N*-desethyl isotonitazene by Vandeputte et al. *(5)*. The activated halogen atom of 1-halo-2,4-dinitrobenzene (halo = F, Cl, or Br) can easily be substituted by *N*-Boc-*N*-ethylethylenediamine. Then, regioselective reduction of the nitro group in the ortho position to the resulting amino function is followed by condensation with 4-isopropoxyphenylacetic acid in the presence of *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline. Removal of the *tert*-butoxycarbonyl protecting group with trifluoroacetic acid affords the final product, *N*-desethyl isotonitazene, as the free base.

N-Desethyl isotonitazene can also be obtained through other synthetic routes with the methods established for the 5-nitro-2-benzylbenzimidazole analogues, with appropriate modifications to the reagents *(5–7)*.

While details of the production method and scale for recently identified *N*-desethyl isotonitazene are not available, use of the synthesis techniques for its nitazene

analogues suggests that the process is straightforward, cost-effective and does not require regulated precursors *(5,6)*.

E Chemical properties

Melting-point: No information was identified.

Boiling-point: No information was identified.

Solubility: N-Desethyl isotonitazene hydrochloride salt is soluble in dimethylformamide and in dimethyl sulfoxide at 30 mg/mL. It is soluble at 5 mg/mL in phosphate-buffered saline (pH 7.2) and at 30 mg/mL in ethanol *(1)*.

F Identification and analysis

Synthetic *N*-desethyl isotonitazene was characterized by nuclear magnetic resonance spectroscopy, high-performance liquid chromatography coupled to diode-array detection, gas chromatography coupled to mass spectrometry (GC-MS) and liquid chromatography (LC) coupled to high-resolution MS *(5)*.

N-Desethyl isotonitazene hydrochloride is available as reference material from commercial suppliers and used for routine analysis in forensic and clinical investigations *(1)*. It was detected in round blue pills by GC-MS, LC–quadrupole time-of-flight mass spectrometry (LC–QTOF-MS) and GC with infrared spectroscopy *(8)*.

N-Desethyl isotonitazene was detected as metabolite of isotonitazene in human post-mortem plasma and urine with LC–QTOF-MS *(4)*. It was detected in the plasma of rats after administration of isotonitazene by LC with tandem quadrupole mass spectrometry *(9)*. Recently, *N*-desethyl isotonitazene was detected and quantified in whole blood and urine from polydrug users admitted to a hospital in the United Kingdom by LC-MS/MS *(10)*.

3 Ease of conversion into controlled substances

It is not clear from the literature whether *N*-desethyl isotonitazene can be converted into a controlled substance.

4 General pharmacology

A Routes of administration and dosage

Two reports from Wedinos (W049751 and 000037166) *(11)* provided the results for samples that were smoked. No reports from participants in online discussion forums were found that provided information on the preferred routes of administration or dosage of *N*-desethyl isotonitazene.

B Pharmacokinetics

No data on the absorption, distribution, metabolism or excretion of *N*-desethyl isotonitazene were found. Although data on the metabolism of nitazenes are scarce, in a recent study on quantification of isotonitazene and identification of its metabolites in animals, the four main metabolites found after ingestion of isotonitazene included *N*-desethyl isotonitazene *(4)*. Isotonitazene is probably metabolized by *N*-dealkylation and *O*-dealkylation, like other benzimidazole opioids (a class of opioids that includes isotonitazene), which usually undergo *N*-dealkylation at the *N*-ethylamine chain and *O*-dealkylation at the phenylalkyl chain *(12).*

N-Desethyl isotonitazene has been identified by toxicological analysis as a major metabolite of isotonitazene *(9,12,13)*. In a recent study, *N*-desethyl isotonitazene was the main metabolite found, with isotonitazene, being detected in 96% of 64 samples from people driving under the influence of drugs and 47 post-mortem samples containing isotonitazene *(13)*. In all the cases analysed in the study, the presence of *N*-desethyl isotonitazene was evaluated only qualitatively, as its concentration was below the limit of quantification (0.5 ng/mL), further indicating that its presence was probably due to the metabolism of isotonitazene.

N-Desethyl isotonitazene was detected in the plasma of male Sprague-Dawley rats administered 10 or 30 μg/kg isotonitazene subcutaneously, at concentrations below the limit of quantification (0.5 ng/mL) *(9)*.

C Pharmacodynamics

Unpublished studies on the binding and functional activity of *N*-desethyl isotonitazene showed that it had a higher binding affinity to μ-opioid receptors than morphine and fentanyl and was more potent at μ-opioid receptors than at Δ- and κ-opioid receptors. Further details of the binding and agonism of *N*-desethyl isotonitazene at opioid receptors are presented in Annex 3.

Vandeputte et al. *(5)* analysed the biological μ-opioid receptor activity in vitro of 14 nitazenes, including *N*-desethyl isotonitazene, in two cell-based assays based on stable expression by HEK293T cells of either the human μ-opioid receptor-β-arrestin2-G protein-coupled receptor kinase 2 (MOR-βarr2-GRK2) or the human μ-opioid receptor-GTPase domain of the Gαi subunit (MOR-mini Gi). Both recruitment assays showed that *N*-desethyl isotonitazene was more potent at μ-opioid receptors (EC_{50} = 0.614 and 1.16 nM for β-arrestin-2 and mini-Gi systems, respectively) than any other benzimidazole opioid tested, morphine or fentanyl *(5)*.

Walton et al. *(9)* determined the binding affinity of *N*-desethyl isotonitazene for opioid receptors in rat brain membranes and compared it with that of its parent compound (isotonitazene) with the radioligands [^{3}H]DAMGO, [^{3}H]DADLE and [^{3}H]U69,593 used to label μ, Δ and κ opioid receptors, respectively. The authors observed that *N*-desethyl isotonitazene (K_i = 2.2 ± 0.4 nM) had seven and two times greater affinity for the μ-opioid receptor than isotonitazene (K_i = 15.8 ± 3.1 nM) and

fentanyl (K_i = 4.4 ± 1.0 nM) but was similar to that of morphine (K_i = 2.1 ± 0.4 nM). In these assays, *N*-desethyl isotonitazene also showed slightly higher affinity to the Δ-opioid receptor (K_i = 610.2 ± 108.0 nM) than isotonitazene (K_i = 745.8 ± 265.0 nM) and fentanyl (K_i = 932.1 ± 292.0 nM) and slightly lower than morphine (K_i = 442.1 ± 150.0 nM). Moreover, *N*-desethyl isotonitazene had less affinity to the κ-opioid receptor (K_i = 838.9 ± 120.0 nM) than isotonitazene (K_i = 691.0 ± 220.0 nM), fentanyl (K_i = 365.0 ± 113.0 nM) and morphine (K_i = 146.1 ± 61.9 nM).

Malcolm et al. *(14)* used optimized bioluminescence resonance energy transfer (BRET) G protein and β-arrestin2 recruitment assays and found that *N*-desethyl isotonitazene had sub-nanomolar potency and superagonism in both assays, similar to isotonitazene. In the BRET assay, *N*-desethyl isotonitazene was less potent (EC_{50} = 252 pM) than isotonitazene (EC_{50} = 107 pM). The authors correlated the potencies observed in the BRET assays with the high affinity of isotonitazene and *N*-desethyl isotonitazene at μ-opioid receptors.

In an unpublished study, *N*-desethyl isotonitazene was tested for its ability to produce analgesic effects in a warm-water tail-flick assay. *N*-Desethyl isotonitazene increased the latency of tail-flick in a dose-dependent manner. Results indicated *N*-desethyl isotonitazene was more potent than morphine and fentanyl and as efficacious as morphine and fentanyl. Subcutaneous injection of naltrexone before administration of *N*-desethyl isotonitazene blocked its analgesic effect, supporting the involvement of opioid receptors in its action. Further details of the analgesic effects of *N*-desethyl isotonitazene are presented in Annex 3.

The results of unpublished tail-flick assays in C57BL/6J mice demonstrated that *N*-desethyl isotonitazene has significant analgesic effects. A comparison of molar mass showed that the substance (ED_{50} = 40.1 μg/kg) was equipotent to fentanyl, whereas its parent compound, isotonitazene (ED_{50} = 11.3 μg/kg), had an analgesic potency almost four times higher than that of fentanyl (ED_{50} = 55.7 μg/kg) *(15)*. The same authors compared the respiratory depressant effects of *N*-desethyl isotonitazene and fentanyl by measuring phrenic nerve activity in a well-established decerebrate rabbit model in which pO_2 and pCO_2 were maintained constant throughout drug administration. *N*-Desethyl isotonitazene required less than half (3.5 ± 0.3 μg/kg, n = 6) of the dose required by fentanyl to cause complete apnoea (9.0 ± 0.5 μg/kg, n = 4, $P < 0.001$), indicating a doubling of the potency when given intravenously. A single equal dose (1 μg/kg) of *N*-desethyl isotonitazene induced greater respiratory depression (59 ± 2% of baseline respiratory rate, n = 6) than fentanyl (75 ± 3%, n = 3, $P < 0.001$). The time to the maximal effect for this dose was nearly four times longer for *N*-desethyl isotonitazene (10.5 ± 1 min) than for fentanyl (2.5 ± 0.5 min, $P < 0.001$). The time for recovery from apnoea to baseline respiratory rate was approximately three times longer with *N*-desethyl isotonitazene (208 ± 38 min) than with fentanyl (67 ± 9 min, $P = 0.018$). Injection of naloxone completely reversed apnoea induced by 3 μg/kg *N*-desethyl isotonitazene within 5.5 ± 0.6 min (n = 6), suggesting the involvement of opioid receptors in these processes.

5 Toxicology

According to a United Nations Office on Drugs and Crime (UNODC) Early Warning Advisory (EWA), *N*-desethyl isotonitazene was found in a total of 14 post-mortem cases (4 males, 10 females), with two in the United Kingdom and 12 in the USA in 2023 *(15)*. The blood concentrations of *N*-desethyl isotonitazene ranged between 0.7 and 290 ng/mL, but its contribution to the cause of death was unknown in all cases. Other substances found in six case were bromazolam (3), flubromazepam (1), metonitazene (3) and *N*,*N*-dimethylamphetamine (1).

In an observational case series of patients admitted to hospitals in the Sandwell and West Birmingham National Health Service Trust, United Kingdom, between July and October 2023 with suspected or declared substance use, 19 tested positive for *N*-desethyl isotonitazene, at a median concentration of 1.53 µg/L (range, 0.59–5.48, n=14) in whole blood and 27.75 µg/L (range 0.51–91.53, n=16) in urine. Other substances (which included cocaine, morphine, xylazine, gabapentinoids, methadone, 2-ethylidene-1, 5-dimethyl-3, 3-diphenylpyrrolidine, benzodiazepines and the synthetic cannabinoid MDMB-4en-PINACA) were detected in 18 of those patients. *N*-Desethyl isotonitazene was the only substance detected in one patient, who was admitted in coma and showed signs of miosis, bradypnoea and hypercapnia *(10)*.

The toxic dose of *N*-desethyl isotonitazene for humans has not been described.

6 Adverse reactions in humans

N-Desethyl isotonitazene belongs to the opioid chemical subgroup, 2-benzylbenzimidazoles, the most common effects of which include analgesia, euphoria, miosis, muscle rigidity, unconsciousness, sedation, and respiratory depression. A single report on adverse reactions to *N*-desethyl isotonitazene in humans was found, in which a patient was admitted to hospital in coma, with miosis, bradypnoea and hypercapnia *(10)*.

Unverified information from a participant in an online forum *(16)* referred to stimulant-like effects after taking *N*-desethyl isotonitazene intravenously. Self-reported effects from one report in Wedinos (W049751) *(11)* included euphoria, nausea and vomiting.

Because of its high potency, *N*-desethyl isotonitazene poses an higher risk of overdose than other opioids, such as fentanyl *(17,18)*. *N*-Desethyl isotonitazene was confirmed analytically in 14 post-mortem cases reported to the UNODC EWA, but the contribution of this substance to the cause of death was unknown *(15)*. A recent publication also mentioned identification of *N*-desethyl isotonitazene in 37 deaths between 2019 and 2021 in the USA. In all cases, *N*-desethyl isotonitazene was detected with isotonitazene, at lower blood concentrations, suggesting that the presence of *N*-desethyl isotonitazene was due most likely to metabolism of isotonitazene *(9)*.

7 Dependence potential

A Studies in experimental animals

No studies were identified.

B Studies in humans

No studies were identified.

8 Abuse potential

A Studies in experimental animals

In unpublished drug discrimination studies, *N*-desethyl isotonitazene fully substituted for morphine. It was more potent than morphine and slightly less potent than fentanyl, with similar efficacy to morphine and fentanyl.

Subcutaneous injection of naltrexone blocked the morphine-like discriminative stimulus effects of *N*-desethyl isotonitazene, indicating the involvement of opioid receptors in its discriminative stimulus effects. Details are presented in Annex 3.

B Studies in humans

No studies of the human abuse potential of *N*-desethyl isotonitazene were identified.

9 Therapeutic applications and extent of therapeutic use and epidemiology of medical use

Synthesis of a group of benzimidazole derivatives with analgesic properties was described in 1957 by the Swiss chemical company CIBA Aktiengesellschaft *(19)*, but none of the derivatives was medically approved. *N*-Desethyl isotonitazene is not known to have any medical use.

10 Listing on the WHO Model List of Essential Medicines

N-Desethyl isotonitazene is not listed on the 23rd WHO List of Essential Medicines or the 9th WHO List of Essential Medicines for Children.

11 Marketing authorizations (as a medicinal product)

N-Desethyl-isotonitazene is not known to be authorized for marketing.

12 Industrial use

N-Desethyl-isotonitazene is not known to have any industrial use.

13 Non-medical use, abuse and dependence

The Toronto (Canada) Drug Checking Service reported identification of *N*-desethyl isotonitazene by the Centre for Addiction and Mental Health (Clinical Laboratory and

Diagnostic Services) on 23 February 2024 in a sample collected in Toronto's west end. The sample was bought as fentanyl but consisted of *N*-desethyl isotonitazene and caffeine, with no fentanyl *(17)*.

A recent report from the Public Health Agency of Sweden indicated that *N*-desethyl isotonitazene is present in the country *(18)*.

Detection of *N*-desethyl isotonitazene has been cited in 10 reports of the US National Forensic Laboratory Information System (NFLIS-Drug) since 2022 *(20)*, suggesting its use.

N-Desethyl isotonitazene was detected in 19 people who had used several substances and were admitted to hospitals in Birmingham, United Kingdom, between July and October 2023 *(10)*.

N-Desethyl isotonitazene was identified by Wedinos in two samples received by purchaser(s) who intended to buy heroin *(11)*, suggesting its unintentional use.

14 Nature and magnitude of public health problems related to misuse, abuse and dependence

No information was found on the nature or magnitude of health problems associated with use of *N*-desethyl isotonitazene. *N*-Desethyl isotonitazene has been confirmed in at least nine fatal and one non-fatal overdose events in the USA *(20)*.

According to the UNODC Early Warning Advisory, *N*-desethyl isotonitazene was reported in 14 post-mortem cases during 2023 in the United Kingdom (2) and the USA (12) *(15).*

In 2022, *N*-desethyl isotonitazene was identified in falsified pharmaceutical tablets in the United Kingdom and the USA. Data from law enforcement agencies suggest that it is used as a recreational drug in the USA. The Center for Forensic Science Research and Education in the USA recently reported identification of *N*-desethyl isotonitazene in falsified oxycodone round blue tablets in Florida. In December 2022, *N*-desethyl isotonitazene was identified in samples referred to as ''dope'', with other substances (e.g. xylazine, fentanyl, parafluorofentanyl and designer benzodiazepines such as flubromazepam and bromazolam) in the drug supply in Philadelphia (PA) *(21)*.

15 Licit production, consumption and international trade

N-Desethyl isotonitazene is used as reference material in scientific research and forensic applications.

16 Illicit manufacture and traffic and related information

Reports from NFLIS-Drug indicate that *N*-desethyl isotonitazene was first detected in the USA in 2022 in Florida and in Kansas. Since 2022, there have been a total of 10 reports to NFLIS-Drug from four US states: Pennsylvania (5), Florida (3), Kansas (1) and Texas (1). Of those reports, 9 were of fatal overdoses and one of a non-fatal overdose. In 2023, six reports were made to NFLIS-Drug, only five of which reported weights, totaling 2.58 g *(20)*.

17 Current international controls and their impact

N-Desethyl isotonitazene is not currently controlled under the 1961, 1971 or 1988 United Nations Conventions.

18 Current and past national controls

In Germany, *N*-desethyl isotonitazene is classified as "Anlage II" (authorized trade only, not prescriptible).

Because of the negative effects of *N*-desethyl isotonitazene, the Public Health Agency of Sweden has recommended that it be included in Ordinance (1992:1554) on the Control of Narcotic Drugs *(18)*.

In the United Kingdom, *N*-desethyl isotonitazene is controlled under the Psychoactive Substances Act.

A notice of intent to control *N*-desethyl isotonitazene as a Schedule I substance was published in the US Federal Register on 25 October 2023 *(21)*.

19 Other medical and scientific matters relevant for a recommendation on scheduling of the substance

N-Desethyl isotonitazene remains a cause for concern due to its greater potency than the parent drug, the possibility that it aggravates the risks of isotonitazene use and its potential acquisition directly rather than isotonitazene.

As people who use *N*-desethyl isotonitazene are likely to obtain it from unregulated sources, its identity, purity and quantity are uncertain and inconsistent. This, combined with its high potency, may pose significant adverse health risks to people who use it *(21).*

References

1. *N*-Desethyl isotonitazene (hydrochloride). Ann Arbor (MI): Cayman Chemical; 2024 (https://www.caymanchem.com/product/30216, accessed 8 June 2024).
2. NDI or NDE? r/Opioid_RCs. San Francisco (CA): Reddit; 2024 (https://www.reddit.com/r/Opioid_RCs/comments/18xwea6/ndi_or_nde, accessed 8 June 2024).
3. 10g *N*-desethyl-isotonitazene. ChemicalGod24; 2024 (https://chemicalgod24.ru/product/10g-n-desethyl-isotonitazene, accessed 8 June2024).
4. Krotulski AJ, Papsun DM, Kacinko SL, Logan BK. Isotonitazene quantitation and metabolite discovery in authentic rorensic casework. J Anal Toxicol. 2020;44(6):521–30. doi:10.1093/jat/bkaa016.
5. Vandeputte MM, Van Uytfanghe K, Layle NK, St Germaine DM, Iula DM, Stove CP. Synthesis, chemical characterization, and mu-opioid receptor activity assessment of the emerging group of "nitazene" 2-benzylbenzimidazole synthetic opioids. ACS Chem Neurosci. 2021;12(7):1241–51. doi:10.1021/acschemneuro.1c00064.

6. 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 ChemNeurosci. 2021;12(7):1072–92. doi:10.1021/acschemneuro.1c00037.
7. Report on the risk assessment of N,N-diethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1H-benzimidazole- 1-ethanamine (isotonitazene) in accordance with Article 5c of Regulation (EC) No 1920/2006 (as amended). Lisbon: European Monitoring Centre for Drugs and Drug Addiction; 2024 (https://www.emcdda.europa.eu/publications/risk-assessments/isotonitazene_en, accessed 9 June 2024).
8. N-Desethyl Isotonitazene. Horsham (PA): Center for Forensic Science Research and Education; 2024 (https://www.cfsre.org/nps-discovery/monographs/n-desethyl-isotonitazene, accessed 13 June 2024).
9. Walton SE, Krotulski AJ, Glatfelter GC, Walther D, Logan BK, Baumann MH. Plasma pharmacokinetics and pharmacodynamic effects of the 2-benzylbenzimidazole synthetic opioid, isotonitazene, in male rats. Psychopharmacology (Berl). 2023;240(1):185–98. doi:10.1007/s00213-022-06292-5.
10. Pucci M, Singh Jutley G, Looms J, Ford L. *N*-Desethyl isotonitazene detected in polydrug users admitted to hospital in Birmingham, United Kingdom. Clin Toxicol. 2024;62(1):19–25. doi:10.1080/15563650.2024.2309321.
11. Sample results for N-desethyl isotonitazene. Cardiff: Welsh Emerging Drugs and Identification of Novel Substances; 2024 (https://www.wedinos.org/sample-results#mylocation, accessed 17 July 2024).
12. Montanari E, Madeo G, Pichini S, Busardò FP, Carlier J. Acute intoxications and fatalities associated with benzimidazole opioid (nitazene analog) use: a systematic review. Ther Drug Monit. 2022;44(4). doi:10.1097/FTD.0000000000000970.
13. Walton SE, Krotulski AJ, Logan BK. A forward-thinking approach to addressing the new synthetic opioid 2-benzylbenzimidazole nitazene analogs by liquid chromatography–tandem quadrupole mass spectrometry (LC–QQQ-MS). J Anal Toxicol. 2021;46(3):221–31. doi:10.1093/jat/bkab117.
14. Malcolm NJ, Palkovic B, Sprague DJ, Calkins MM, Lanham JK, Halberstadt AL et al. Mu-opioid receptor selective superagonists produce prolonged respiratory depression. iScience. 2023;26(7). doi:10.1016/j.isci.2023.107121.
15. United Nations Office on Drugs and Crime (UNODC) Early Warning Advisory (EWA) - Tox-Portal (https://www.unodc.org/tox/#/login, accessed 17 July 2024).
16. N-Desethyl isotonitazene. Campbells Creek (VIC): Bluelight Communities Ltd; 2024 (https://www.bluelight.org/community/threads/anyone-with-experience-with-nitazenes.912692/#post-15970367, accessed 16 July 2024).
17. N-Desethyl etonitazene and protonitazepyne: “New” nitazene opioids circulating in Toronto’s unregulated opioid supply. Toronto (Ont): Toronto’s Drug Checking Service; 2024 (https://drugchecking.community/wp-content/uploads/dlm_uploads/2024/03/2024-03_N-desethyl-etonitazene-and-protonitazepyne.pdf, accessed 24 July 2024).
18. N-Etyl-2-[2-(4-isopropoxibensyl)-5-nitro-1H-benso[d]imidazol-1-yl]etanamin med kortnamn N-desetylisotonitazen. Stockholm: Folkhalsomyndigheten; 2023 (https://www.aklagare.se/globalassets/dokument/narkotikapreparat/n/n-desetylisotonitazen.pdf, accessed 16 July 2024).

19. Hunger A, Kebrle J, Rossi A, Hoffmann K. Synthese basisch substituierter, analgetisch wirksamer Benzimidazol-Derivate [Synthesis of basic substituted, analgesically active benzimidazole derivatives]. Experientia. 1957;13(10):400–1. doi:10.1007/BF02161116.
20. N-Desethyl isotonitazene summary. Springfield (VA): National Forensic Laboratory Information System; 2024.
21. Schedules of controlled substances: temporary placement of N-desethyl isotonitazene and N-piperidinyl etonitazene in Schedule I (21 CFR Part 1308). Springfield (VA): Drug Enforcement Administration; 2023 (https://www.federalregister.gov/documents/2023/10/25/2023-23379/schedules-of-controlled-substances-temporary-placement-of-n-desethyl-isotonitazene-and-n-piperidinyl).