World Health Organization

Critical Review Report:

N-desethyl etonitazene

Agenda item 3.3.2

Expert Committee on Drug Dependence

Forty-eighth Meeting

Geneva, 20-22 October 2025

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

Contents

Executive Summary

N-desethyl etonitazene was first synthesized in the 1950s during the development of a medication by CIBA Aktiengesellschaft in Switzerland and appeared in Europe and the United States as a novel psychoactive substance in 2023. The compound is a metabolite of etonitazene, another novel psychoactive opioid that is controlled under Schedule 1 of the 1961 Convention on Narcotic Drugs. To the extent that it has been investigated, available data suggest that *N*-desethyl etonitazene shares pharmacological properties with its parent compound and with other potent opioids such as fentanyl, in that it activates the m-opioid receptor with high affinity and full efficacy in several assays. Further, it does so at potencies that are at least ten-fold higher than fentanyl. Its potential for abuse and dependence has not been investigated in animal models. In humans, anecdotal evidence suggests that *N*-desethyl etonitazene is administered via several routes, including intravenously, vaping, and insufflation of nasal spray. Metabolites have been identified in vitro; however, they have not been verified in biosamples from people who have consumed *N*-desethyl etonitazene. Information on the physical and/or psychological effects specifically associated with the use of *N*-desethyl etonitazene (versus nitazenes as a general class) was not identified in published literature or in a search of several online forums that provide anecdotal reports of the effects of illicit drug use. Although the substance was present in one post-mortem sample in the UK and has been detected in thirteen toxicology samples in the US during 2023-2024, the degree to which *N*-desethyl etonitazene contributed to mortality or morbidity was unclear, as it was often consumed with other psychoactive substances, including other opioids and benzodiazepines. At least ten countries have reported detection of *N*-desethyl etonitazene within their borders. *N*-desethyl etonitazene is not currently under international control, but it is controlled nationally through regulations controlling nitazenes as a chemical class in Canada and Brazil. In addition, *N*-desethyl etonitazene was included in the list of new Class A substances published in 2024 in the United Kingdom. In 2025, an order for the temporary placement of *N*-desethyl etonitazene under Schedule 1 of the US Controlled Substances Act was published.

1. Substance identification

A. International Nonproprietary Name (INN)

Not available.

B. Chemical Abstract Service (CAS) Registry Number

2732926-26-8

C. Other Chemical Names

2-[(4-Ethoxyphenyl)methyl]-N-ethyl-5-nitro-1H-benzimidazole-1-ethanamine (ACI)

D. Trade Names

N-desethyl etonitazene is sold under its own name (Cayman Chemical, 2025).

E. Street Names

N-desethyl etonitazene is sold under its own name or as "*N*-Desethyletonitazene" or also "NDE" (EMCDDA, 2023).

F. Physical Appearance

N-Desethyl etonitazene, as a synthetic standard, appears as a crystalline solid (Cayman Chemical, 2025).

2. Chemistry

A. Chemical Name

IUPAC Name:
2-[(4-ethoxyphenyl)methyl]-N-ethyl-5-nitro-1H-benzimidazole-1-ethanamine

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

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

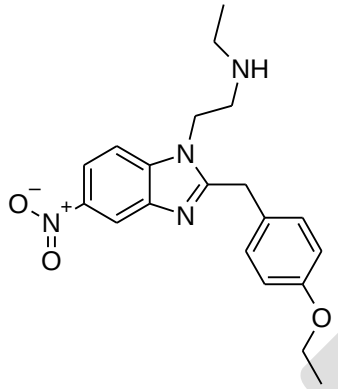
InChI

InChI=1S/C20H24N4O3/c1-3-21-11-12-23-19-10-7-16(24(25)26)14-18(19)22-20(23)13-15-5-8-17(9-6-15)27-4-2/h5-10,14,21H,3-4,11-13H2,1-2H3

InChI Key
RESPFUMJVJRUMB-UHFFFAOYSA-N

B. Chemical Structure

Free base:



Molecular Formula: $C_{20}H_{24}N_4O_3$
Molecular Weight: 368.43 g/mol

C. Stereoisomers

There are no stereoisomers described for *N*-desethyl etonitazene.

D. *Methods and Ease of Illicit Manufacturing*

Vandeputte et al. describe the synthesis of *N*-desethyl etonitazene (Vandeputte et al., 2021). 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, a regioselective reduction of the nitro group in the *ortho* position to the resulting amino function is carried out. This is followed by a condensation with 4-ethoxyphenylacetic acid in the presence of *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline. Lastly, removal of the BOC (*tert*-butyloxycarbonyl) protecting group with trifluoroacetic acid affords the final product, *N*-desethyl etonitazene, as the free base.

It is also possible to obtain *N*-desethyl etonitazene through other synthetic routes reported using the methods established for the 5-nitro-2-benzylbenzimidazole analogues, with appropriate modifications to the reagents (Vandeputte et al., 2021; Ujváry et al., 2021; EMCDDA, 2023).

While specific details about the production method and scale for the *N*-desethyl etonitazene are unavailable, based on the synthesis techniques known to be used for its nitazene analogues, it is likely that the process is straightforward, cost-effective, and does not require regulated precursors (Ujváry et al., 2021; Vandeputte et al., 2021; Caprari et al., 2025).

E. Chemical Properties

Melting point

No information could be identified.

Boiling point
No information could be identified.

Solubility
N-desethyl etonitazene is soluble in dimethyl sulfoxide (DMSO) at 20 mg/mL and at 25 mg/mL in dimethylformamide (DMF). It is soluble at 0.5 mg/mL in a mixture of 1:1 DMF: phosphate-buffered saline (PBS) (pH 7.2). In ethanol, it is soluble at 10 mg/mL (Cayman Chemical, 2025).

F. Identification and Analysis

N-desethyl etonitazene was characterized via nuclear magnetic resonance spectroscopy (^{1}H-NMR), high-performance liquid chromatography coupled to diode-array detection (HPLC-DAD), gas chromatography coupled to mass spectrometry (GC-MS), liquid chromatography coupled to high-resolution mass spectrometry (LC-HRMS), and liquid chromatography coupled to triple quadrupole mass spectrometry (LC-MS/MS) (Wachełko et al., 2025; Vandeputte et al., 2021).

N-desethyl etonitazene and its deuterated version, *N*-desethyl etonitazene-d_5, are available as reference materials from commercial suppliers and used for routine methods of analysis associated with forensic and clinical investigations (Cayman Chemical, 2025).

N-Desethyl etonitazene was detected in blood in a person using multiple substances by liquid chromatography time-of-flight mass spectrometry (LC-TOF-MS) (De Vrieze et al., 2024).

3. Ease of Convertibility Into Controlled Substances

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

4. General Pharmacology

A. Routes of administration and dosage

Data on the route of administration for *N*-desethyl etonitazene specifically were sparse. Intravenous use was suggested by the detection of *N*-desethyl etonitazene in three syringes collected in Maardu, Estonia, as part of a harm reduction effort (Abel-Ollo et al., 2024). Anecdotally, preparation for vaping, intranasal spray, or intravenous use was reported by people who have obtained tablets or powder containing the substance (Reddit, 2025). This information may not be representative of the most common route(s) of administration due to self-selection of whether or not to post to online forums;

however, it is consistent with the route of administration reported for nitazenes as a group (Inter-American Drug Abuse Control Commission, 2024). Information on dosage for *N*-desethyl etonitazene was not identified.

B. Pharmacokinetics

N-desethyl etonitazene was identified as a phase I metabolite of etonitazene, another psychoactive opioid, in human hepatocytes (Kanamori et al., 2025). Subsequently, its metabolism was studied in pooled human liver microsomes (Huang et al., 2024). Six metabolites were identified, with three produced through the process of oxidation, one produced via hydroxylation, and two isomers (N- and O-) followed by dealkylation. Verification of the presence of these metabolites after human use through analysis of biosamples was not obtained. No studies were identified on the absorption, distribution, or elimination of *N*-desethyl etonitazene.

C. Pharmacodynamics

Like fentanyl, *N*-desethyl etonitazene binds with high affinity to the m opioid receptor (MOR) [Ki = 0.317 nM (± 0.064 nM, standard error of the mean) (Abbas and Janowsky, 2024). By comparison, fentanyl's affinity for MOR was 8.8-fold less: Ki = 2.79 nM (± 0.45 nM, standard error of the mean) (Abbas and Janowsky, 2024). Both substances showed selective binding for MOR, with considerably lower affinity for kappa and delta opioid receptors. Further, *N*-desethyl etonitazene is a full, potent agonist at the m opioid receptor (MOR), as measured by activation of the MOR in a mini-Gi assay: EC50 = 6.38 nM (95% confidence interval: 4.64 ; 8.67 nM) (Vandeputte et al., 2021), and as measured by inhibition of forskolin-stimulated cyclic adenosine monophosphate (cAMP): EC50 = 0.172 nM (95% confidence interval: 0.09; 0.34 nM) and Emax = 101% (95% confidence interval: 94; 108 nM) (De Vrieze et al., 2024). By comparison, fentanyl had an EC50 of 2.20 nM (95% confidence interval: 1.06; 4.82) in the latter assay. At the MOR, N-desethyl-etonitazene also enhances b-arrestin 2 recruitment, with EC50 values ranging from 1.81 nM (95% confidence interval: 1.14; 2.94 nM) to 5.30 nM (95% confidence interval: 3.69; 7.54 nM) (De Vrieze et al., 2024; Monti et al., 2024; Vandeputte et al., 2021), and stimulates calcium release [EC50 = 0.468 nM (95% confidence interval: 0.347; 0.638 nM (Monti et al., 2024). No information on the in vivo pharmacology of *N*-desethyl etonitazene was identified.

5. Toxicology

No studies of the preclinical toxicology of *N*-desethyl etonitazene were found.

6. Adverse Reactions in Humans

Information on the physical and/or psychological effects specifically associated with the use of *N*-desethyl etonitazene was not identified in published literature or in a search of several online forums that provide anecdotal reports of the effects of illicit drug use (e.g., Bluelight). Although the substance was present in one post-mortem sample in the UK, the degree to which it contributed to the death was unclear (Office for Health Improvement and Disparities, 2024). A footnote to the table in which this death was noted stated that

other nitazenes were present for some deaths, but did not specify for which deaths/substances. In the US, *N*-desethyl etonitazene was detected in two toxicology cases in 2023 and in 11 toxicology samples (Drug Enforcement Administration, 2025) (see Section 14). The effects of the substance were not reported.

7. Dependence Potential

A. Animal Studies

No information was found.

B. Human Studies

No information was found.

8. Abuse Potential

A. Animal Studies

No information was found.

B. Human Studies

No information was found.

9. Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use

There are no known therapeutic uses for *N*-desethyl etonitazene.

10. Listing on the WHO Model List of Essential Medicines

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

11. Marketing Authorizations (as a Medicinal Product)

N-desethyl etonitazene has no known marketing authorizations.

12. Industrial Use

N-desethyl etonitazene has no known industrial use.

13. Non-Medical Use, Abuse, and Dependence

N-desethyl etonitazene was first synthesized in the 1950s during the development of a medication by CIBA Aktiengesellschaft in Switzerland; however, it was not submitted for regulatory approval or brought to the legal drug market. In 2023, *N*-desethyl etonitazene emerged on the illicit synthetic drug markets in Europe and the USA simultaneously (Krotulski et al., 2023; Monti et al., 2024). To date, the presence of this substance has been reported in at least ten countries (see section 16 for a listing). The prevalence of use and dependence of *N*-desethyl etonitazene has not been reported.

14. Nature and Magnitude of Public Health Problems Related to Misuse, Abuse, and Dependence

Since its emergence as a novel psychoactive substance in 2023, *N*-desethyl etonitazene was analytically confirmed in a post-mortem sample collected in the United Kingdom between June 2023 and May 2024 (Office for Health Improvement and Disparities, 2024). The degree to which the substance was responsible for the death is unclear, as the cases in which more than one nitazene was detected were not specified in the available data. *N*-desethyl etonitazene was also detected in two toxicology samples analyzed in the US (Krotulski et al., 2023). In one case (state of Colorado), *N*-desethyl etonitazene was the only substance identified; in the other (state of Missouri), the benzodiazepine flubromazepam was also detected. In the Colorado case, samples were obtained from the Colorado Coroner's Office, suggesting a fatal outcome. Trend reports from the Center for Forensic Science Research and Education (CFSRE) in 2024 indicate eleven cases in which *N*-desethyl etonitazene was identified in toxicology samples in the US (Drug Enforcement Administration, 2025). CFSRE collects these samples from one or more of the following situations: recreational drug use, medicolegal death investigations, clinical intoxications, and/or driving under the influence of drugs investigations.

15. Licit Production, Consumption, and International Trade

No information was found.

16. Illicit Manufacture and Traffic and Related Information

Countries in which the presence of *N*-desethyl etonitazene has been reported are Brazil (Centre for Studies on Drugs and Community Social Development, 2025), Canada (Toronto's Drug Checking Service, 2024), Estonia (Abel-Ollo et al., 2024; United Nations Office on Drugs and Crime, 2025), Israel (Ministry of Health, 2024), Latvia (United Nations Office on Drugs and Crime, 2025), New Zealand (Monti et al., 2024; United Nations Office on Drugs and Crime, 2025), Sweden (United Nations Office on Drugs and Crime, 2025), Switzerland (Monti et al., 2024), the United Kingdom (United Kingdom Home Office, 2024) and the USA (Drug Enforcement Administration, 2025). Information on the illicit manufacture and traffic of *N*-desethyl etonitazene specifically is difficult to parse, as most reports present data on nitazenes as a group; however, a report from the National Forensic Laboratory Information System (NFLIS) in the US is an exception: 114 encounters specifically with *N*-desethyl etonitazene occurred in over fourteen states since 2023 (Drug Enforcement Administration, 2025). The NFLIS database contains cases in which a substance was analyzed as part of an investigation of drug trafficking, distribution, or abuse. *N*-desethyl etonitazene has been detected in falsified prescription opioid tablets (Ministry of Health, 2024), in substances advertised as another illicit opioid (Monti et al., 2024), and in mixtures with other non-opioid novel psychoactive substances (e.g., benzodiazepines) (Drug Enforcement Administration, 2025).

17. Current International Controls and Their Impact

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

18. Current and Past National Controls

In 2025, an order for the temporary placement of *N*-desethyl etonitazene under Schedule 1 of the US Controlled Substances Act was published (Drug Enforcement Administration, 2025). *N*-desethyl etonitazene is controlled in Canada and Brazil through regulations controlling nitazenes as a chemical class (Inter-American Drug Abuse Control Commission, 2024). In the United Kingdom, *N*-desethyl etonitazene was included in the list of new Class A substances published in 2024 (United Kingdom Home Office, 2024).

19. Other Medical and Scientific Matters Relevant for a Recommendation on the Scheduling of the Substance

None

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