World Health Organization

Critical review report

N-Ethylheptedrone (*N*-ethylnorheptedrone)

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-Ethylheptedrone (IUPAC name: 2-(Ethylamino)-1-phenylheptan-1-one, also known as *N*-ethylnorheptedrone, ethyl heptedrone or HEP) is a synthetic cathinone with a chemical structure and pharmacological properties similar to those of other Schedule II (under the 1971 United Nations Convention) synthetic cathinones (e.g. *N*-ethylhexedrone, pentedrone). No medical use of *N*-ethylheptedrone was identified. *N*-Ethylheptedrone has not previously been reviewed by the WHO Expert Committee on Drug Dependence.

Reports from law enforcement encounters and sample testing forums indicate that *N*-ethylheptedrone is usually snorted or sniffed, smoked or taken orally.

No reports on the absorption, distribution, metabolism or excretion of *N*-ethylheptedrone were found.

N-Ethylheptedrone completely inhibited the dopamine and norepinephrine transporters (DAT and NET, respectively) but was slightly less active against the serotonin transporter (SERT). It inhibited DAT and NET at significantly lower concentrations than cocaine. The inhibition ratio for DAT/SERT was 18 times higher than that for cocaine, suggesting that *N*-ethylheptedrone is associated with psychostimulant effects and has a high abuse potential.

N-Ethylheptedrone was identified in one case post-mortem, in which it was considered to have made a medium contribution to death. Self-reported effects include increased energy, increased confidence, irregular heartbeat and agitation.

No studies in experimental animals or humans on its dependence or abuse potential were identified, but its structural and pharmacological similarities to other synthetic cathinones and controlled substances indicate that it is expected to have abuse potential in humans.

There is no known therapeutic or industrial use for *N*-ethylheptedrone, nor any marketing authorization.

N-Ethylheptedrone was first detected in Hungary and Sweden in 2019. Since then, it has been detected in several other European countries, Australia, China, New Zealand and the USA. *N*-Ethylheptedrone is not controlled under the 1961, 1971 or 1988 United Nations Conventions.

1 Substance identification

A International Nonproprietary Name (INN)

Not assigned

B Chemical Abstracts Service (CAS) Registry Number

2514784-72-4

C Other chemical names

2-(Ethylamino)-1-phenyl-1-heptanone (ACI), NEHP

D Trade names

N-Ethylheptedrone hydrochloride is sold under the name *N*-ethyl heptedrone (hydrochloride) as an analytical reference standard *(1)*.

E Street names

N-Ethylheptedrone is sold under its name, as ethyl heptedrone or as HEP *(2)*.

F Physical appearance

N-Ethylheptedrone hydrochloride as a reference material has been described as a crystalline solid *(1)*.

G WHO review history

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

2 Chemistry

A Chemical name

IUPAC name: 2-(Ethylamino)-1-phenylheptan-1-one

CA index name: 1-Heptanone, 2-(ethylamino)-1-phenyl- (ACI)

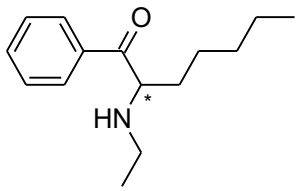
Canonical SMILES: O=C(C=1C=CC=CC1)C(NCC)CCCCC

InChI: 1S/C15H23NO/c1-3-5-7-12-14(16-4-2)15(17)13-10-8-6-9-11-13/h6,8-11,14,16H,3-5,7,12H2,1-2H3

InChI key: KCDBNUUMBCYCQC-UHFFFAOYSA-N

B Chemical structure

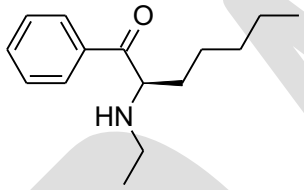
Free base:



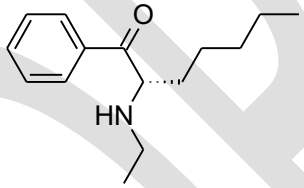
Molecular formula: $C_{15}H_{23}NO$
Molecular weight: 233.35 g/mol

C *Stereoisomers*

N-Ethylheptedrone contains a chiral centre; therefore, two enantiomers may exist: (*R*)-*N*-ethylheptedrone and (*S*)-*N*-ethylheptedrone. No information was available on the enantiomeric composition of *N*-ethylheptedrone on the drug market, but it is probably available as a racemic mixture of the (*R*)- and (*S*)- enantiomers, although the appearance of individual stereoisomers cannot be excluded.



(*R*)-*N*-ethylheptedrone



(*S*)-*N*-ethylheptedrone

D *Methods and ease of illicit manufacture*

No information was available on the routes of synthesis used for the *N*-ethylheptedrone products circulating on the market; however, chemical synthesis of cathinones is straightforward. Nadal-Gratacós et al. reported the synthesis of *N*-ethylheptedrone *(3)*. Benzonitrile was reacted with heptylmagnesium bromide Grignard reagent, followed by acidic hydrolysis, to achieve the intermediate ketone, which was α-halogenated by the addition of bromine. Reaction with ethylamine gave the synthetic cathinone *N*-ethylheptedrone, which was crystallized as a hydrochloride salt.

The synthesis reported in the literature, although simple, requires the equipment of a chemical synthetic laboratory and qualified personnel.

E *Chemical properties*

Melting-point: No information was identified

Boiling-point: No information was identified.

Solubility: N-Ethylheptedrone is soluble in dimethylformamide and in dimethyl sulfoxide at 15 mg/mL. Its solubility is 20 mg/mL in ethanol and 10 mg/mL in phosphate-buffered saline (pH 7.2) *(1)*.

F Identification and analysis

N-Ethylheptedrone (hydrochloride) is available as a reference material from commercial suppliers for use in routine methods of analysis in forensic and clinical investigations *(1)*.

Synthetic *N*-ethylheptedrone hydrochloride was characterized by thin-layer chromatography, proton and carbon nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR), infrared spectroscopy and liquid chromatography–mass spectrometry (LC-MS). Seized *N*-ethylheptedrone (hydrochloride) was described and characterized by gas chromatography–mass spectrometry (GC-MS), direct infusion electrospray ionization mass spectrometry (ESI-MS), high-resolution mass spectrometry (HRMS), IR spectroscopy, X-ray crystallography, thermogravimetric analysis, differential scanning calorimetry and ^{1}H NMR and ^{13}C NMR *(4)*.

Enatioseparation of racemic *N*-ethylheptedrone was reported by capillary electrophoresis, with single-isomeric cyclodextrin derivatives as selectors *(5)*.

An LC triple quadrupole MS method was validated for quantification of *N*-ethylheptedrone in wastewater *(6)*. A method for the quantification of synthetic cathinones, including *N*-ethylheptedrone, in urine was recently developed and validated, which comprised magnetic dispersive solid-phase extraction in combination with direct analysis in real time coupled to HRMS *(7)*.

3 Ease of conversion into controlled substances

No information was found the literature that *N*-ethylheptedrone can be converted into a controlled substance.

4 General pharmacology

A Routes of administration and dosage

Reports from the Welsh Emerging Drugs and Identification of Novel Substances (Wedinos) indicate that *N*-ethylheptedrone may be smoked, snorted or sniffed or taken orally *(1,8)*.

The Public Health Agency of Sweden indicated that participants on online drug forums self-reported taking doses of ≥ 50 mg *(9)*.

B Pharmacokinetics

No data were available on the absorption, distribution, metabolism or excretion of *N*-ethylheptedrone.

C Pharmacodynamics

The Public Health Agency of Sweden reported an in vitro study with transfected cells expressing human dopamine, serotonin and noradrenaline transporters (DAT, SERT and NET), which showed that *N*-ethylheptedrone completely inhibited DAT and NET but had slightly less activity on SERT (> 93% maximum inhibition of the receptor). *N*-Ethylheptedrone inhibited DAT and NET at significantly lower concentrations than cocaine in the test system, the concentration causing 50% inhibition of the receptor being 24.8 nM vs 94.5 nM for DAT and 155 nM vs 588 nM for NET. SERT was inhibited at significantly higher concentrations by both substances: 1430 nM and 300 nM for *N*-ethylheptedrone and cocaine, respectively. The inhibition ratio for DAT/SERT was 57.7 for *N*-ethylheptedrone and 3.17 for cocaine. The ratio indicates that *N*-ethylheptedrone is associated with psychostimulant effects and a high abuse potential *(9)*.

N-Ethylheptedrone has also been tested for its effects on the release of preloaded [^{3}H]dopamine, [^{3}H]serotonin and [^{3}H]norepinephrine from HEK cells expressing cDNA for the human dopamine (HEK-hDAT cells), serotonin (HEK-hSERT cells) and norepinephrine (HEK-hNET cells) transporters, respectively. These studies showed that release of [^{3}H]dopamine, [^{3}H]serotonin and [^{3}H]norepinephrine was barely detectable in HEK-hDAT, HEK-hSERT and HEK-hNET cells treated with *N*-ethylheptedrone, supporting its ability to inhibit all three monoamine transporters. Moreover, this substance was much less able to induce the release of all three [^{3}H]neurotransmitters than methamphetamine and methcathinone. Further details of the release activity at biogenic amine transporters are presented in Annex 3.

Unpublished data indicate that administration of *N*-ethylheptedrone to mice stimulated locomotor activity in a time- and dose-dependent manner. The maximal stimulant effect of *N*-ethylheptedrone was considered to be similar to the maximal stimulant effect of cocaine and methamphetamine. Further details of the locomotor activity of *N*-ethylheptedrone are presented in Annex 3.

5 Toxicology

A single occurrence involving *N*-ethylheptedrone was reported to the United Nations Office on Drugs and Crime (UNODC) Early Warning Advisory (EWA). The substance was detected with diclazepam, etizolam and *N*-ethylhexedrone in the femoral blood of a post-mortem case reported in 2020 in Australia *(10)*. The dose was unknown, and *N*-ethylheptedrone was considered to have made a medium contribution to the death.

No reports were found on the toxic doses of *N*-ethylheptedrone for humans.

6 Adverse reactions in humans

Information provided by the Swedish Poison Information Centre and posted by the Public Health Agency of Sweden in the Network for the Current Drug Situation in Sweden indicated that *N*-ethylheptedrone is sold as a stimulant, having been reported to have greater psychoactive effects than other cathinones. The same source noted that no deaths are known to have been linked to *N*-ethylheptedrone, although the patients in two hospital cases presented with symptoms such as seizures, tachycardia, hypertension, motor agitation, profuse sweating, nausea and vomiting *(9)*.

Three entries in Wedinos (W011119, W017185, W018181) indicated self-reports of increased energy. One (W011119) also included self-reports of increased confidence, irregular heartbeat and agitation. One (W019656) noted a self-report of no effect *(8)*.

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 studies of drug discrimination in rats trained to discriminate methamphetamine or cocaine from saline, *N*-ethylheptedrone fully substituted for methamphetamine or cocaine, demonstrating abuse potential. Further details of the are presented in Annex 3.

B Studies in humans

No studies were identified on the abuse potential of *N*-ethylheptedrone in humans.

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

N-Ethylheptedrone is not known to have any medical use.

10 Listing on the WHO Model List of Essential Medicines

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

11 Marketing authorizations (as a medicinal product)

N-Ethylheptedrone is not known to be authorized for marketing.

12 Industrial use

N-Ethylheptedrone is not known to have any industrial use.

13 Non-medical use, abuse and dependence

In a recent study, temporal trends were measured in new psychoactive substances (NPS) detected and quantified in wastewater collected from up to 57 wastewater treatment plants across Australia between February 2022 and February 2023 (avoiding public holidays and unusual events to determine trends in NPS use across the year) by LC–MS *(11)*. The authors detected *N*-ethylheptedrone in one (5%) of 20 capital city wastewater sites analysed in February 2022.

In May 2021, intensive monitoring of *N*-ethylheptedrone began in the European Union because of an increased number of seizures between 2019 and 2020 and the potential risk to public health posed by this substance *(12)*.

N-Ethylheptedrone has been detected frequently in products mislabelled and/or thought to be sold as other substances (e.g. *N*-ethylpentedrone, methamphetamine, MDMA, cocaine, imitation columbian, clonazolam, alprazolam, diclazepam, Vicodin/Norco, cannabidiol or *O*-desmethyltramadol), suggesting that most people who use *N*-ethylheptedrone may be unaware that they are using it *(8,13)*.

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

No information on the nature and magnitude of public health problems associated with the use of *N*-ethylheptedrone was identified other than that described in section 6 (Adverse reactions in humans).

15 Licit production, consumption and international trade

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

16 Illicit manufacture and traffic and related information

N-Ethylheptedrone was first identified in seizures in Sweden in May 2019, a total of 23 incidents being reported up to November 2022 *(9)*. It was also first identified in Hungary in 2019 and has since been identified in 22 biological samples in that country *(14,15)*.

N-Ethylheptedrone was formally listed with the European Monitoring Centre for Drugs and Drug Addiction in February 2019, having been identified in seizures in many European countries: Austria, Cyprus, Czechia, Denmark, Finland, France, Germany, Hungary, Latvia, Luxembourg, Netherlands (Kingdom of the), Romania, Slovakia, Spain and Sweden *(16)*.

N-Ethylheptedrone was first identified in New Zealand in 2020 *(17)*. According to the UNODC EWA, N-ethylheptedrone was first identified in Australia in 2020 *(11)*.

The DrugsData forum reported 17 entries involving *N*-ethylheptedrone in countries including Austria, China, Switzerland the USA *(13)*.

17 Current international controls and their impact

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

18 Current and past national controls

N-Ethylheptedrone was regulated in Sweden under Act 1999:42 on the Prohibition of Certain Health Hazardous Products on 28 April 2020. The Public Health Agency of Sweden recommended that the substance be included in Ordinance 1992:1554 on the Control of Narcotic Drugs, to prevent any negative consequences *(9)*.

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

As *N*-ethylheptedrone has been identified in products labelled as other substances, it is reasonable to expect that the prevalence of *N*-ethylheptedrone and *N*-ethylheptedrone-related intoxications is underreported. Moreover, since individuals are likely to obtain substances from unregulated sources, they may be unaware of the presence, purity and quantity of *N*-ethylheptedrone, posing significant risks of adverse health effects to users.

References

1. *N*-Ethyl heptedrone (hydrochloride). Ann Arbor (MI): Cayman Chemical; 2024 (https://www.caymanchem.com/product/27327, accessed 17 June 2024).
2. Anyone Know Anything About HEP? San Francisco (CA): Reddit; 2019 (https://www.reddit.com/, accessed 3 July 2024).
3. Nadal-Gratacós N, Ríos-Rodríguez E, Pubill D, Batllori X, Camarasa J, Escubedo E et al. Structure-activity relationship of N-ethyl-hexedrone analogues: role of the α-carbon side-chain length in the mechanism of action, cytotoxicity, and behavioral effects in mice. ACS Chem Neurosci. 2023;14(4):787–99. doi:10.1021/acschemneuro.2c00772.
4. Rojkiewicz M, Kuś P, Kusz J, Książek M, Staszek D. Spectroscopic and crystallographic characterization of two hydrochloride cathinones: 1-(4-fluoro-3-methylphenyl)-2-(pyrrolidin-1-yl)pentan-1-one (4-F-3-Me-α-PVP) and N-ethyl-2-amino-1-phenylheptan-1-one (N-ethylheptedrone). Crystals. 2023;13(6):934. doi:10.3390/ cryst13060934.
5. Ujj D, Kalydi E, Malanga M, Varga E, Sohajda T, Béni S et al. Sugammadex analogue cyclodextrins as chiral selectors for enantioseparation of cathinone derivatives by capillary electrophoresis. J Chromatogr A. 2022;1683:463506. doi:10.1016/j.chroma.2022.463506.
6. Bade R, Eaglesham G, Shimko KM, Mueller J. Quantification of new psychoactive substances in Australian wastewater utilising direct injection liquid chromatography coupled to tandem mass spectrometry. Talanta. 2023;251:123767. doi:10.1016/j.talanta.2022.123767.

7. Li Y, Lian R, Sheng Z, Mao J, Mao C, Liang C et al. Automatic MDSPE combined with DART–HRMS for the rapid quantitation of 21 synthetic cathinones in urine. J Am Soc Mass Spectrom. 2024;35(1):40–9. doi:10.1021/jasms.3c00299.
8. Sample results for N-ethylheptedrone. Cardiff: Welsh Emerging Drugs and Identification of Novel Substances; 2024 (https://www.wedinos.org/sample-results#mylocation, accessed 29 July 2024.
9. 2-(Etylamino)-1-fenylheptan-1-on med kortnamn N-etylnorheptedron (N-etylheptedron) [2-(Ethylamino)-1-phenylheptan-1-one, short name N-ethylnorheptedrone (N-ethylheptedrone)]. Solna: Public Health Agency; 2022 (https://www.aklagare.se/globalassets/dokument/narkotikapreparat/n/n-etylnorheptedron.pdf, accessed 29 July 2024).
10. Early Warning Advisory (EWA) – Tox-Portal. *N*-Ethylheptedrone. Vienna: United Nations Office on Drugs and Crime (https://www.unodc.org/tox/#/admin/search/detailed/%7B%22textQuery%22:%22N-Ethylheptedrone%22%7D, accessed 29 July 2024.
11. Jaunay EL, Bade R, Paxton KR, Nadarajan D, Barry DC, Zhai Y et al. Monitoring the use of novel psychoactive substances in Australia by wastewater-based epidemiology. Sci Total Environ. 2024;919:170473. doi:10.1016/j.scitotenv.2024.170473.
12. EU Early Warning System intensive monitoring. *N*-Ethylheptedrone under intensive monitoring as of 18 May 2021 (EU-EWS-IM-2021-0016). Lisbon: European Monitoring Center for Drugs and Drug Addiction; 2021.
13. N-Ethylheptedrone. DrugsData. Grass Valley (CA): Erowid Center; 2024 (https://www.drugsdata.org/, accessed 29 July 2024).
14. Lajtai A, Mayer M, Lakatos Á, Kuzma M, Miseta A. New psychoactive versus conventional stimulants – a ten-year review of casework in Hungary. Leg Med (Tokyo). 2020;47:101780. doi:10.1016/j.legalmed.2020.101780.
15. New psychoactive substances: global markets, glocal threats and the COVID-19 pandemic. An update from the EU Early Warning System. Lisbon: European Monitoring Centre for Drugs and Drug Addiction; 2020 (https://www.euda.europa.eu/publications/rapid-communication/new-psychoactive-substances-global-markets-glocal-threats-and-covid-19-pandemic_en).
16. European Information System and Database on New Drugs. Lisbon: European Monitoring Centre for Drugs and Drug Addiction; 2022.
17. New cathinone N-ethylheptedrone detected. Wellington: High Alert Drug Information and Alerts Aotearoa New Zealand; 2020 (https://www.highalert.org.nz/alerts-and-notifications/new-cathinone-n-ethylheptedrone-detected/, accessed 29 July 2024).