World Health Organization

Critical Review Report:

N-Ethylnorpentylone

Expert Committee on Drug Dependence

Forty-first Meeting

Geneva, 12-16 November 2018

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

Acknowledgements

This report was prepared by the Secretariat of the Expert Committee on Drug Dependence (ECDD) within the Department of Essential Medicines and Health Products (EMP) of the World Health Organization (WHO), Geneva, Switzerland. The WHO staff involved in the production of this document, developed under the overall guidance of Mariângela Simão (Assistant Director General, Access to Medicines, Vaccines, and Pharmaceuticals), Suzanne Hill (Director, Essential Medicines and Health Products), Gilles Forte, (Secretary of the Expert Committee on Drug Dependence) were Dilkushi Poovendran (Technical Officer, WHO Essential Medicines and Health Products) and Wil De Zwart (Technical Officer, WHO Essential Medicines and Health Products).

This report was commissioned as a background document for a critical review for the 41st Expert Committee on Drug Dependence (ECDD). WHO would like to acknowledge Simon Brandt for drafting the report and Jurgen Rehm, Astrid Otto, and Jakob Manthey for the questionnaire analysis and writeup.

The WHO Secretariat would also like to thank the European Monitoring Centre for Drugs and Drug Addiction (EMCCDA) for providing data on *N*-ethylnorpentylone collected through the European Union Early Warning System, which includes data provided by Reitox National Focal Points in the EU Member States, Turkey and Norway, Bosnia and Herzegovina as well as the Europol National Units.

Executive Summary

Substance identification

N-Ethylnorpentylone (IUPAC name: 1-(2*H*-1,3-benzodioxol-5-yl)-2-(ethylamino)pentan-1-one) is a ring-substituted synthetic cathinone analog. It originally emerged in the 1960s during pharmaceutical drug development efforts. Another common name used widely is *N*-ethylpentylone. On the streets, *N*-ethylnorpentylone is most likely available as the racemic mixture and it might be obtained from Internet retailers. In the United States of America (USA), this substance was detected for the first time in 2014 but began to emerge more prominently in 2016 both in the USA and other UN Member States. Seizures indicate that *N*-ethylnorpentylone is available in powder, crystal, rock, capsule, and tablet forms. Examples exist where this drug has been surreptitiously sold as 'ecstasy'/MDMA.

WHO Review History

N-Ethylnorpentylone has not been previously pre-reviewed or critically reviewed.

Chemistry

There is no specific information available about the routes of synthesis employed for the *N*-ethylnorpentylone products circulating on the drug market but straightforward methods for its preparation exist without requiring access to precursors that are controlled internationally.

Ease of convertibility into controlled substances

There is no specific information available but it appears unlikely that *N*-ethylnorpentylone is converted into a substance currently controlled under the UN conventions.

Similarity to known substances / Effects on the central nervous system

The information currently available suggests that *N*-ethylnorpentylone is a psychomotor stimulant and that its molecular mechanism of action is also shared by other ring-substituted synthetic cathinones of the pyrovalerone type, such as MDPV (1-(2*H*-1,3-benzodioxol-5-yl)-2-(pyrrolidin-1-yl)pentan-1-one) and α-PVP (1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one), which are both listed in Schedule II of the Convention on Psychotropic Substances of 1971.

General pharmacology

The number of systematic studies available at this time is limited but it seems clear that *N*-ethylnorpentylone is a psychomotor stimulant. *In vitro*, it has been demonstrated to block the reuptake of dopamine, norepinephrine and serotonin using rat brain synaptosomal preparations with preference for the dopamine system, thus, behaving cocaine- and MDPV-like rather than amphetamine-like. Animal studies confirmed that *N*-ethylnorpentylone increases locomotor activity and that it substituted for methamphetamine and cocaine in drug discrimination studies.

Toxicology

The LD_{50} value for *N*-ethylnorpentylone in the mouse (route of administration not reported) was determined at 240 mg/kg.

Adverse reactions in humans

The detection of *N*-ethylnorpentylone in biological fluids collected from cases involving adverse effects (including deaths) confirmed that this drug is circulating on the market and used recreationally. Not all of the reported adverse effects could be causally linked to *N*-ethylnorpentylone alone but there are indications that the observed effects are consistent with those seen with other psychomotor stimulants. The fact that *N*-ethylnorpentylone has been identified in products believed by users to represent 'ecstasy'/MDMA means that users may be unaware of the additional risks of harm (e.g. potential exacerbation of a psychostimulant toxidrome) associated with the consumption of *N*-ethylnorpentylone either alone or in combination with other drugs.

Dependence potential

No studies carried out in humans or animals could be identified.

Abuse potential

In rodents, *N*-ethylnorpentylone fully substituted for methamphetamine and cocaine when using the drug discrimination paradigm. Mechanistically, results obtained from *in vitro* investigations confirmed that *N*-ethylnorpentylone inhibited the reuptake of the monoamines dopamine, norepinephrine and, to a lesser extent, serotonin, which is consistent with closely related pyrovalerone-type synthetic cathinones and cocaine with known abuse liability. The currently available data suggest that *N*-ethylnorpentylone might be liable to abuse.

Therapeutic applications / usefulness

N-Ethylnorpentylone is not known to have any therapeutic uses.

Listing on WHO Model List of Essential Medicines

N-Ethylnorpentylone is not listed.

Marketing authorizations

N-Ethylnorpentylone is not known to have any marketing authorizations.

Industrial use

N-Ethylnorpentylone is not known to have any agricultural, industrial or cosmetic uses even though it is available for purchase as a 'research chemical'.

Non-medical use

The mode of use may involve the combinational use (intentionally or unintentionally) of other drugs and users may be unaware of the exact dose or compound being ingested (by whatever route). The information currently available suggests that *N*-ethylnorpentylone has been found in products sold as 'ecstasy'/MDMA but there have been instances where other drugs have been detected in addition to *N*-ethylnorpentylone. *N*-Ethylnorpentylone may also be available in its own right and is advertised for sale by Internet retailers.

Nature and magnitude of public health problems

Use of *N*-ethylnorpentylone appears to be limited to recreational substance users rather than the general population. The mode of use may involve the combinational use (intentionally or unintentionally) of other drugs and users may be unaware of the exact dose or compound being ingested (by whatever route). The fact that *N*-ethylnorpentylone has been identified in products believed by users to represent 'ecstasy'/MDMA means that users may be unaware of the additional risks of harm (e.g. potential exacerbation of central nervous system effects resulting in a psychostimulant toxidrome) associated with the consumption of *N*-ethylnorpentylone either alone or in combination with other drugs.

Licit production, consumption, and international trade

N-Ethylnorpentylone is not known to have any agricultural, industrial or cosmetic uses even though it is available for purchase as a 'research chemical'.

Illicit manufacture and traffic

A dramatic increase in seizures and reports linked to the detection of *N*-ethylnorpentylone has been predominantly reported in the USA from 2016 onward. Purchase and importation of *N*-ethylnorpentylone is unproblematic in UN Member States that do not exercise legislative control measures. Increasing numbers of reports have appeared that document the detection of *N*-ethylnorpentylone on the drug market where it has been sold in the form of 'ecstasy'/MDMA-like products.

Current international controls and their impact

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

Current and past national controls

N-Ethylnorpentylone is controlled in some UN Member States.

1. Substance identification

A. International Nonproprietary Name (INN)

Not applicable.

B. Chemical Abstract Service (CAS) Registry Number

952016-47-6 (free base)
17763-02-9 (hydrochloride salt)

C. Other Chemical Names

1-(3,4-Methylenedioxyphenyl)-2-ethylaminopentan-1-one
1-(3,4-Methylenedioxyphenyl)-2-ethylamino-pentanone-(1)
1-(1,3-Benzodioxol-5-yl)-2-(ethylamino)-1-pentanone
1-(1,3-Benzodioxol-5-yl)-2-(ethylamino)pentan-1-one
1-(2*H*-1,3-Benzodioxol-5-yl)-2-(ethylamino)-1-pentanone
2-Ethylamino-1-(3,4-methylenedioxyphenyl)pentan-1-one
N-Ethylnorpentylone
N-Ethylpentylone [sic]

D. Trade Names

Not applicable.

E. Street Names

MDEVP; bk-EBDP; bk-ETHYL-K; bk-EPDP; ephylone; street names also include the chemical names.

F. Physical Appearance

The hydrochloride salt of *N*-ethylnorpentylone has been described as an off-white powder [1] and a neat solid. [2] In its pure form, *N*-ethylnorpentylone hydrochloride is expected to be odorless and white.

G. WHO Review History

N-Ethylnorpentylone has not been previously pre-reviewed or critically reviewed. A direct critical review is proposed based on information brought to WHO's attention that *N*-ethylnorpentylone is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any party. Preliminary data collected from literature and different countries indicated that this substance may cause substantial harm and that it has no medical use.

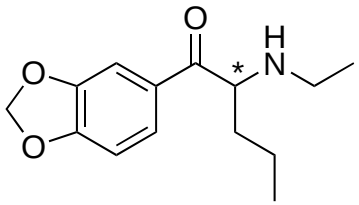
2. Chemistry

A. Chemical Name

IUPAC Name:
1-(2*H*-1,3-Benzodioxol-5-yl)-2-(ethylamino)pentan-1-one
CA Index Name:
N-Ethyl-α-propyl-1,3-benzodioxole-5-ethanamine

B. Chemical Structure

Free base:



Note: Asterisk (*) refers to a chiral center

Molecular Formula: $C_{14}H_{19}NO_3$
Molecular Weight: 249.31 g/mol

C. Stereoisomers

The presence of a chiral center at the α-carbon of the side chain gives rise to the enantiomeric pair of (*S*)-*N*-ethylnorpentylone and (*R*)-*N*-ethylnorpentylone, respectively. However, on the streets *N*-ethylnorpentylone is most likely available as the racemic mixture.

D. *Methods and Ease of Illicit Manufacturing*

There is no specific information available about the routes of synthesis employed for the *N*-ethylnorpentylone products circulating on the market. Two procedures described in a patent disclosed by the Boehringer Ingelheim pharmaceutical company employed the *N*-alkylation of the primary amine precursor 2-amino-1-(2*H*-1,3-benzodioxol-5-yl)pentan-1-one (a) using ethyl iodide/$NaHCO_3$ in 95% ethanol (step i) heated at reflux for 2 h (Figure 1A).[3, 4] An alternative reaction step employed an oxidation reaction using the 1-(2*H*-1,3-benzodioxol-5-yl)-2-(ethylamino)pentan-1-ol precursor (a) (Figure 1B) using a chromic acid-pyridine complex where the reaction mixture was left to stand over night.[4] Further details about the preparation of the precursors have not been disclosed. However, one convenient standard procedure frequently used for the synthesis of cathinones that might also be employable for the preparation of *N*-ethylnorpentylone (Figure 1C) could include the α-bromination (step i) of the 1-(2*H*-1,3-benzodioxol-5-yl)pentan-1-one precursor (a) and formation of the 1-(2*H*-1,3-benzodioxol-5-yl)-2-bromopentan-1-

one intermediate (b). Reaction with *N*-ethylamine (step ii) gives *N*-ethylnorpentylone (c), which may then be converted into a range of salts. This procedure has been employed for the preparation of *N*-ethylnorpentylone analogs.[3, 4] The ketone species (a) is accessible by various routes.

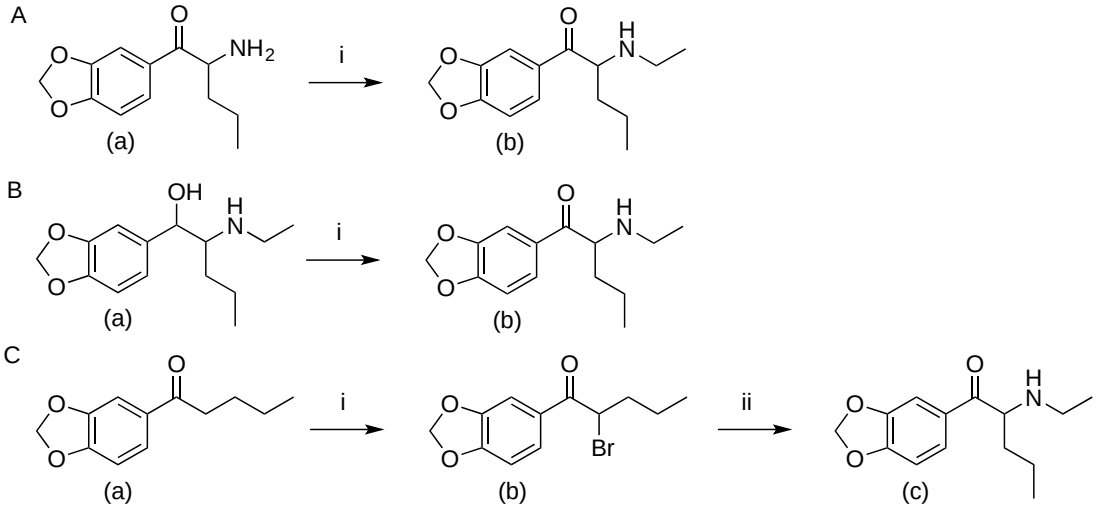


Figure 1. Examples of potential preparations of *N*-ethylnorpentylone.[3, 4]

E. Chemical Properties

Melting point

238–241°C (hydrochloride salt)[3, 4]
224 °C (salt form not reported)[5]

Boiling point

Information could not be identified.

Solubility

~ One mg/mL in phosphate buffered saline (pH 7.2) (hydrochloride salt).[6] A sample of the hydrochloride salt (containing some traces of a bromide counter ion) was reported to be soluble in dimethyl sulfoxide, methanol, water and partially in dichloromethane.[7]

F. Identification and Analysis

Identification, especially when available in larger quantities than normally encountered in forensic toxicological work, is straightforward. Presumptive colour test results performed on submitted samples determined to contain *N*-ethylnorpentylone have been published in the public domain.[8] Results from analytical studies have been published and include data on crystallography,[9, 10] gas

chromatography electron ionization mass spectrometry (MS),[1, 5, 7, 11-14] electrospray ionization tandem MS,[5, 11, 15] direct analysis in real time (DART) ionization based MS,[16] nuclear magnetic resonance spectroscopy,[5, 11] Fourier transform infrared spectroscopy,[5, 11 1, 7, 12] and separation by high performance liquid chromatography,[5, 15, 17]. A method on stable isotope ratio analysis of synthesized *N*-ethylnorpentylone has also been published.[18] Analytical challenges may arise, for example when dealing with closely related isomers such as *N*,*N*-dimethylpentylone (1-(2*H*-1,3-benzodioxol-5-yl)-2-(dimethylamino)pentan-1-one) or isopropylnorbutylone (1-(2*H*-1,3-benzodioxol-5-yl)-2-[(propan-2-yl)amino]butan-1-one). The implementation of adequate separation techniques might be needed to reduce the potential for misidentification, especially when dealing with samples (e.g. biological) that may only contain trace quantities.

3. Ease of Convertibility Into Controlled Substances

No information available.

4. General Pharmacology

The initial exploration of several synthetic ring-substituted cathinones carried out in the 1960s originated from the observation that many of these analogs were found to be stimulants of the central nervous system.[e.g.3, 4, 19-21]

A. Routes of administration and dosage

In patents disclosed by the Boehringer Ingelheim pharmaceutical company, the invented substances (including *N*-ethylnorpentylone and several other analogs) were claimed to be suitable for being used in various formulations such as oral (tablets, capsules or pills), parenteral (ampoules, vials or injectable liquids) or rectal administration (suppositories). Compound specific information was not provided but suggested dosage units for oral administrations were 1–150 mg (preferably 2–75 mg) and 0.3–30 mg (preferably 1–25 mg) for parenteral administration.[3] Generally speaking, synthetic cathinones can be consumed by oral, parenteral and rectal routes of administration. Information received by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) from reports on seized material suggests the existence of *N*-ethylnorpentylone-containing crystalline powders and pills containing logos normally associated with 3,4-methylenedioxy methamphetamine (MDMA, ecstasy) pills.[22] The Drug Enforcement Administration (DEA) reported seizures of powder, crystal, rock, capsule, and tablet forms,[23] suggesting its intended use for oral administration. Information published on user forums indicates that samples believed to be *N*-ethylnorpentylone were consumed by nasal insufflation, intravenous injection, oral and sublingual administration[e.g.24-26] but also rectal administration.[27] Interpreting the information on common *N*-ethylnorpentylone dosages based on descriptions shared on user forums is complicated by different routes of administration and examples of repetitive use ranging from low 10s to 100s mg.[e.g. 24-35]

B. Pharmacokinetics

Detailed information could not be identified. The incubation of *N*-ethylnorpentylone (37 °C, 2 h) with pooled mixed gender human liver microsomes revealed the detection of four metabolites arising from reduction of the keto group to the alcohol (1-(2*H*-1,3-benzodioxol-5-yl)-2-(ethylamino)pentan-1-ol), *N*-dealkylation to the primary amine (2-amino-1-(2*H*-1,3-benzodioxol-5-yl)pentan-1-one), demethylenation (1-(3,4-dihydroxyphenyl)-2-(ethylamino)pentan-1-one) and hydroxylation at one of the carbons of the α-carbon chain.[15] All four metabolites were detected in authentic blood and oral fluid samples obtained from casework with the alcohol being reported as the most abundant metabolite in both types of samples.[15]

C. Pharmacodynamics

The number of published *in vitro* and *in vivo* studies at this time is limited but the available data suggest that *N*-ethylnorpentylone acts as a psychomotor stimulant in a number of assays.

In vitro data:

In a monoamine transporter assay prepared from rat brain synaptosomes, *N*-ethylnorpentylone was shown to function as a potent inhibitor at the dopamine (DAT), norepinephrine (NET) and serotonin transporter (SERT) with IC_{50} values of 37 ± 2 nM, 105 ± 14 nM, and 383 ± 27 nM, respectively, which indicated a preference for the dopamine system. In comparison, the analog 1-(2*H*-1,3-benzodioxol-5-yl)-2-(methylamino)pentan-1-one (pentylone) was found to be less potent with IC_{50} values of 154 ± 11 nM (DAT), 401 ± 27 nM9 (NET), and 1198 ± 59 nM (SERT). In addition, *N*-ethylnorpentylone was found to be inactive as a transporter substrate, which meant that it was unable to induce neurotransmitter release.[36] Mechanistically, this property is consistent with some other synthetic cathinone psychostimulants such as 1-(2*H*-1,3-benzodioxol-5-yl)-2-(pyrrolidin-1-yl)pentan-1-one (MDPV) rather than, for example, 1-(2*H*-1,3-benzodioxol-5-yl)-2-(methylamino)propan-1-one (methylone) that acts as a non-selective releaser.[37, 38]

These results were consistent with studies investigating the binding, uptake and release of *N*-ethylnorpentylone compared to cocaine, methamphetamine and mazindol using HEK cells expressing human DAT, NET and SERT (Tables 1 and 2). *N*-Ethylnorpentylone was found to show highest affinity at DAT compared to SERT and NET. The affinity of mazindol for DAT was 6.5-times higher than that observed for *N*-ethylnorpentylone. *N*-Ethylnorpentylone was also confirmed to be an inhibitor of monoamine transport with a potency rank order of DAT (IC_{50} = 54.9 nM) > NET (IC_{50} = 114 nM) > SERT (IC_{50} = 460 nM) (Table 1). Superfusion release experiments furthermore confirmed that *N*-ethylnorpentylone behaved cocaine-like rather than methamphetamine-like given that it was not able to induce release (Table 2).

Table 1. Effects of *N*-ethylnorpentylone, cocaine, methamphetamine (METH) and Mazindol on [^{125}I]RTI-55 binding to, and [^{3}H]neurotransmitter uptake by, HEK- hDAT, HEK-hSERT and HEK-hNET cells (mean ± SEM). Modified from[39]

HEK-hDAT	*N*-Ethylnorpentylone	Cocaine	METH	Mazindol
[^{125}I]RTI-55 binding: Ki (nM)	102 ± 15	591 ± 78	2,580 ± 180	15.7 ± 5.0
[^{125}I]RTI-55 binding: IC_{50} (nM)	106 ± 16	–	–	–
Hill slope	-1.28 ± 0.08	-1.21 ± 0.15	-0.92 ± 0.10	-0.95 ± 0.05
[^{3}H]DA uptake IC_{50} (nM)	54.9 ± 7.3	314 ± 54	73 ± 16	–
HEK-hSERT				
[^{125}I]RTI-55 binding: Ki (nM)	893 ± 80	651 ± 52	172,000 ± 23,000	55 ± 17
[^{125}I]RTI-55 binding: IC_{50} (nM)	962 ± 86	–	–	–
Hill slope	-0.92 ± 0.08	-1.07 ± 0.10	-1.20 ± 0.09	-0.87 ± 0.04
[^{3}H]5-HT uptake IC_{50} (nM)	460 ± 120	286 ± 50	5,500 ± 1,400	–
HEK-hNET				
[^{125}I]RTI-55 binding: Ki (nM)	2,380 ± 620	4,000 ± 1,000	1,410 ± 120	-5.8 ± 1.7
[^{125}I]RTI-55 binding: IC_{50} (nM)	2,400 ± 630	–	–	–
Hill slope	-0.95 ± 0.05	-1.18 ± 0.22	-1.00 ± 0.10	-1.00 ± 0.12
[^{3}H]NE uptake IC_{50} (nM)	114 ± 29	373 ± 81	18.1 ± 4.4	–

Table 2. Effects of *N*-ethylnorpentylone and methamphetamine on [^{3}H]neurotransmitter release from HEK-hDAT, HEK-hSERT and HEK-hNET superfusion assays (mean ± SEM). Modified from[39]

HEK-hDAT	*N*-Ethylnorpentylone	Methamphetamine
[^{3}H]DA release EC_{50} (nM)	ND (>10 µM)	511 ± 46
E_{max} rel. to methamphetamine [a]	Minimal	103.4 ± 4.0%
HEK-hSERT		
[^{3}H]5-HT release EC_{50} (nM)	ND (>100 µM)	12,800 ± 2,300
E_{max} rel. to methamphetamine [a]	7.2 ± 1.4%	103.4 ± 4.6%
HEK-hNET		
[^{3}H]NE release EC_{50} (nM)	ND (>6.7 µM)	136 ± 42%
E_{max} rel. to methamphetamine [a]	15.6 ± 8.4%	109.4 ± 0.6%

[a] E_{max}: Maximal response relative to methamphetamine (100%: hDAT 10 µM; hSERT 0.3–1 mM; hNET 1–3 µM).

In vivo data:

The ED_{50} value determined for establishing central nervous stimulant action in the mouse (route of administration not reported) was of 2.75 mg/kg.[3, 4]

Intraperitoneal administration of *N*-ethylnorpentylone to Sprague Dawley rats induced significant locomotor activity (highest at 20 mg/kg) with the 5 mg/kg dose being comparable with 5 mg/kg methamphetamine. Repeated administrations of *N*-

ethylnorpentylone at 5 mg/kg led to increases in locomotor activity whereas 20 mg/kg and 50 mg/kg administrations led to stereotypy (backward moving and head weaving). Acute and repeated administrations of 20 mg/kg *N*-ethylnorpentylone led to increases in time spent in the elevated plus maze test (35 min post injection; exploration for 5 min) but this was not observed at 5 mg/kg and 50 mg/kg.[40]

Behavioral investigations comparing *N*-ethylnorpentylone with cocaine, (*S*)-(+)-methamphetamine, and 3,4-methylenedioxymethampetamine (MDMA) confirmed that all test drugs induced a dose dependent increase in locomotor activity in male Swiss-Webster mice (Hsd:ND4, aged 2–3 months) (Table 3).[41]

Table 3. Locomotor (horizontal) activity tests conducted over 8 h (10 min period).[a,41]

	N-Ethylnorpentylone [b]	Cocaine [c]	METH [d]	MDMA [e]
ED_{50} (mg/kg) [f]	0.73 (0–30 min)	9.4 (0–30 min)	0.50 (20–50 min)	6.7 (40–70 min)
Time	Within 10 min; lasted 30–130 min (0.5 to 2.5 mg/kg) [g]	Within 10 min; lasted 120 min (20 mg/kg) [h]	Within 10 min; lasted 180–270 min (0.25, 0.5, 1 and 2 mg/kg) [i]	Within 10 min; lasted 260 min (2.5 to 50 mg/kg) [j]

[a] Time course/dose response study using male Swiss-Webster mice (Hsd:ND4, aged 2–3 months); intraperitoneal administration.

[b] Administered doses: 0.25, 0.5, 1, 2.5, 5, 10 or 25 mg/kg; behavioral observations recorded on each mouse at 30, 120, and 480 min following 25 mg/kg *N*-ethylnorpentylone. It was stated that no unusual effects were observed following injection of this test drug.

[c] Administered doses: 5, 10, 20, or 40 mg/kg.

[d] METH: methamphetamine. Administered doses: 0.25, 0.5, 1, 2, or 4 mg/kg.

[e] MDMA: 3,4-methylenedioxymethampetamine. Administered doses: 1, 2.5, 5, 10, 25, or 50 mg/kg. Behavioral observations recorded on each mouse at 30, 120, and 480 minutes following 50 mg/kg of this test drug.

[f] Time period selected for analysis of dose-response data; time period in which test drug produced maximal effects. For *N*-ethylnorpentylone: 0–30 min selected for analysis of dose-response data; earliest time period in which maximal stimulation first appeared as a function of dose.

[g] Time- and dose- dependent stimulation of locomotor activity following 0.5 to 25 mg/kg.

[h] Time- and dose- dependent stimulation of locomotor activity following 20 and 40 mg/kg.

[i] Time- and dose- dependent stimulation of locomotor activity following 0.25 to 4 mg/kg dose range.

[j] Time- and dose- dependent stimulation of locomotor activity following 2.5 to 50 mg/kg.

5. Toxicology

The LD_{50} value for *N*-ethylnorpentylone in the mouse (route of administration not reported) was determined at 240 mg/kg.[3, 4]

6. Adverse Reactions in Humans

A number of case reports involving the detection of *N*-ethylnorpentylone have been reported in the scientific literature and are summarized in Table 4 below. The extent to which complete case histories were available differed and causal relationships to *N*-ethylnorpentylone alone could not be established in all cases. The examples provided in Table 4 include acute intoxications, death cases and analysis of oral fluid samples taken from recreational users of recreational substances.

According to the background information and evaluation of 'Three Factor Analysis' (Factors 4, 5 and 6) for temporary scheduling document prepared by the US Drug Enforcement Administration, *N*-ethylnorpentylone has been detected in 25 fatalities in Maryland (USA) that occurred between 2016 and 2017. In addition, approximately 125 toxicology reports confirmed the detection (urine and blood) of *N*-ethylnorpentylone in fatal cases observed between 2016 and 2018.[23] It is unclear whether any of these cases are included in the information published in the literature and included in Table 4 below.

Table 4. Case reports involving the detection of *N*-ethylnorpentylone

Year[a]	Patent, age	Comments (examples)	Ref
2016	M, 21	Death case. Suffered cardiac arrest following patient being described as agitated and diaphoretic with hot skin; haldol (5 mg) administered followed by cardiac arrest. CPR successful and vital signs at hospital showed hypotension and tachycardia. ECG showed sinus rhythm with premature atrial complexes and ST depression in inferior leads. Physical examination included sluggish pupillary reflexes, negative vestibulo-occular reflex, and myoclonus at the right lower extremity. Clinical laboratory analysis revealed hyperkalemia, hypoglycemia, rhabdomyolysis, liver failure, renal injury, elevated troponin, pH 6.80, and lactic acid of 28 mg/dL. Tox screen positive for cannabinoid and ethanol level of 12 mg/dL. MRI showed bilateral restricted diffusion in the posterior parietal and occipital regions; treatment initiated with hypothermia cooling measures, intravenous fluids, and bicarbonate. ECG revealed severe encephalopathy. Cardiac arrest at treatment day 4. Details about detection of *N*-ethylnorpentylone not reported.	[42]
2017	M, 29	Death case. Agitated and combative patient (history of bipolar disorder); initial treatment with 5 mg haloperidol; pulse needed restoring en route to hospital. Patient was hypotensive and tachycardic with temperature ~41°C. Clinical laboratory analysis showed elevated troponins, rhabdomyolysis, hypoglycemia, hepatic and renal injury,	[14]

		respiratory failure and disseminated intravascular coagulation. Patient went into cardiac arrest and pronounced dead ~36 h after admission. Tox screen positive for opiates, benzodiazepines, amphetamines and cannabinoids. *N*-Ethylnorpentylone and lidocaine detected in antemortem blood but not quantified. Total morphine concentration of 40 ng/mL detected. Confirmatory tests for benzodiazepines, amphetamine and methamphetamine were negative.	
2018	M, 34	Death case. Found dead on floor; behaving erratically night prior. Peripheral blood: cocaine (trace), cocaethylene (trace), *N*-ethylnorpentylone (953 ng/mL), Cause of death: complications of acute *N*-ethylnorpentylone intoxication.	[43]
2018	M, 34	Death case. Brought to hospital in full cardiac arrest and pronounced dead; history of marijuana and alcohol use. Peripheral blood: cocaine (33 ng/mL), fentanyl (3 ng/mL), methamphetamine (938 ng/mL), amphetamine (86 ng/mL). Autopsy significant for pneumonia and early microscopic evidence of acute myocardial infarction. Cause of death: methamphetamine, cocaine, fentanyl, and *N*-ethylnorpentylone toxicity.	[43]
2018	M, 25	Death case. Shot dead and found on street. Peripheral blood: hydrocodone (trace), alprazolam (30 ng/mL), *N*-ethylnorpentylone (45 ng/mL), Cause of death: homicide.	[43]
2018	M, 25	Death case. Shot dead at gas station. Peripheral blood: alprazolam (25 ng/mL), cocaine (trace), ecgonine methyl ester (detected), *N*-ethylnorpentylone (31 ng/mL), Cause of death: homicide.	[43]
2018	M, –	Death investigation. Blood analysis: *N*-ethylnorpentylone (positive), butylone (150 ng/mL), ketamine (870 ng/mL).	[15]
2018	M, –	Death investigation; alleged "Molly" [b] use. Blood analysis: *N*-ethylnorpentylone (50,000 ng/mL), dibutylone (14 ng/mL).	[15]
2018	M, –	Unknown case history. Blood analysis: *N*-ethylnorpentylone (1,200 ng/mL).	[15]
2018	M, 29	Unknown case history. Blood analysis: *N*-ethylnorpentylone (1,140 ng/mL).	[15]
2018	M, 35	Homicide. Blood analysis: *N*-ethylnorpentylone postmortem (833 ng/mL); antemortem: positive. Butylone, midazolam (8.9 ng/mL) and THC (0.78 ng/mL) also detected.	[15]
2018	M, –	Death investigation. Blood analysis: *N*-ethylnorpentylone (790 ng/mL), pentylone (96 ng/mL), dibutylone (13 ng/mL), butylone (12 ng/mL).	[15]

2018	M, 28	Death investigation, suspected drug overdose. Blood analysis: *N*-ethylnorpentylone (600 ng/mL).	[15]
2018	M, 49	Death investigation, suspected drug overdose, suspected "bath salts" use. Blood analysis: *N*-ethylnorpentylone (550 ng/mL), dibutylone (10 ng/mL), 4-chloro-α-PVP.	[15]
2018	M, –	Death investigation. Blood analysis: *N*-ethylnorpentylone (540 ng/mL), dibutylone (11 ng/mL).	[15]
2018	M, –	Death investigation, possible drug overdose. Blood analysis: *N*-ethylnorpentylone (430 ng/mL).	[15]
2018	M, –	Death investigation. Blood analysis: *N*-ethylnorpentylone (358 ng/mL).	[15]
2018	M, –	Death investigation following vehicular crash. Blood analysis: *N*-ethylnorpentylone (210 ng/mL), pentylone (200 ng/mL)	[15]
2018	F, –	Death investigation, homicide. Blood analysis: *N*-ethylnorpentylone (160 ng/mL).	[15]
2018	M, 31	Death investigation, suicide, gunshot wound. Blood analysis: *N*-ethylnorpentylone (150 ng/mL).	[15]
2018	M, 33	Case history unknown. Blood analysis: *N*-ethylnorpentylone (100 ng/mL), methamphetamine (49 ng/mL), amphetamine (14 ng/mL), lorazepam (40 ng/mL).	[15]
2018	M, 47	Death investigation, suspected drug overdose. Blood analysis: *N*-ethylnorpentylone (90 ng/mL), carfentanil (1.3 ng/mL).	[15]
2018	M, 23	Driving under the influence of drugs. Blood analysis: *N*-ethylnorpentylone (87 ng/mL).	[15]
2018	M, 53	Death investigation. Blood analysis: *N*-ethylnorpentylone (86 ng/mL), U-47700, U-49900, tetrahydrofuranylfentanyl, acrylfentanyl (0.4 ng/mL), 4-ANPP.	[15]
2018	M, 40	Driving under the influence of drugs. Blood analysis: *N*-ethylnorpentylone (41 ng/mL), fentanyl (7 ng/mL), norfentanyl (2.3 ng/mL).	[15]
2018	F, –	Death investigation, suspected drug overdose. Blood analysis: *N*-ethylnorpentylone (38 ng/mL), dibutylone (40 ng/mL), butylone (15.3 ng/mL), "fluoroisobutyrylfentanyl".	[15]
2018	M, –	Driving under the influence of drugs. Blood analysis: *N*-ethylnorpentylone (34.3 ng/mL).	[15]
2018	M, 25	Death investigation. Blood analysis: *N*-ethylnorpentylone (24 ng/mL), alprazolam (28 ng/mL), THC (1.6 ng/mL).	[15]
2018	M, 36	Driving under the influence of drugs. Blood analysis: *N*-ethylnorpentylone (23 ng/mL) methamphetamine (55 ng/mL), amphetamine (<5 ng/mL).	[15]
2018	M, 32	Driving under the influence of drugs. Blood analysis: *N*-ethylnorpentylone (21 ng/mL) clonazepam (23 ng/mL).	[15]

2018	M, –	Death investigation, suspected drug overdose, found deceased at home, suspected to have snorted cocaine or heroin. Blood analysis: *N*-ethylnorpentylone (18.4 ng/mL), furanylfentanyl, 4-ANPP, cocaine (130 ng/mL), THC (0.86 ng/mL).	[15]
2018	M, –	Death investigation. Blood analysis: *N*-ethylnorpentylone (12 ng/mL).	[15]
2018	M, 30	Recreation drug use ("Molly"); oral fluid sample collected from recreational user at dance music festival. Blood analysis: *N*-ethylnorpentylone (1,377 ng/mL), eutylone, MDA, alprazolam.	[15]
2018	M, 20	Recreation drug use ("Molly"); oral fluid sample collected from recreational user at dance music festival. Blood analysis: *N*-ethylnorpentylone (132.9 ng/mL), eutylone, THC (40.5).	[15]
2018	F, 24	Recreation drug use ("Molly"); oral fluid sample collected from recreational user at dance music festival. Blood analysis: *N*-ethylnorpentylone (35.2 ng/mL), alprazolam.	[15]
2018	F, 21	Recreation drug use ("Molly"); oral fluid sample collected from recreational user at dance music festival. Blood analysis: *N*-ethylnorpentylone (31.5 ng/mL), MDA (35.7 ng/mL), THC (2.7 ng/mL).	[15]
2018	F, 34	Recreation drug use ("Molly"); oral fluid sample collected from recreational user at dance music festival. Blood analysis: *N*-ethylnorpentylone (12.6 ng/mL), THC.	[15]
2018	M, 32	Death case. Patient displayed psychomotor agitation and aggressiveness, then fainted at rave party. External showed facial swelling, cyanosis at extremities and yellowish liquid emanating from mouth and nostrils. Internal examination showed generalized hemorrhage of pulmonary alveoli, abnormal increase in liver size and absence of urine in bladder. Whole blood analysis: *N*-ethylnorpentylone (170 ng/mL).	[36]
2018	M, 18	Intoxication case. Display of agitation and signs of several injuries at rave party. Patient presented with tachycardia (176 bpm) and mydriatic pupils, oscillated between psychomotor agitation and neurological depression. Serum analysis: *N*-ethylnorpentylone (7 ng/mL) and detection in urine. Patient recovered after a few hours; discharged after 12 h.	[36]
2018	F, 26	Intoxication case. Found unconscious in apartment with sphincter release, attended party in previous night and suspected to have consumed ecstasy pills and marijuana. At hospital, patient appeared confused, sleepy, displayed disconnected speech and episodes of visual hallucinations.	[36]

		Urine analysis: *N*-ethylnorpentylone and MDMA; not detected in serum. Patient discharged after 24 h observation.	
2018	M, 19	Intoxication case. Patient attended rave party, stayed 14 h consuming various drugs and alcohol. He reportedly consumed five ecstasy tablets, ingested one LSD blotter hit, smoked two packs of cigarettes and drank an undetermined amount of the Brazilian alcoholic beverage "catuaba". Patient experienced palpitations and visited hospital; at physical examination he appeared agitated, with palpitations and tachycardia (180 bpm). Urine tox screening showed MDMA, *N*-ethylnorpentylone, caffeine and cotinine; LSD not detected; serum analysis: alcohol (0.8 g/L), *N*-ethylnorpentylone (19 ng/mL), and MDMA. Patient treated with diazepam and metoclopramide and discharged 24 h later.	[36]
	M, 35	Intoxication case. Patient reported of having been consuming alcohol and other drugs of abuse for two consecutive days. He was found unconscious, with neurological depression (Glasgow 5) and anisocoria. At hospital, patient received fentanyl, midazolam for orotracheal intubation, tramadol and dipyrone. After 6 h of admission, patient evolved to neurogenic shock, and decerebration. Serum analysis: *N*-ethylnorpentylone (149 ng/mL). Symptoms remained unchanged. At 6 days vertebral artery dissection identified affecting brainstem; and cerebrovascular hemorrhage of the brainstem was diagnosed. Thirty-five days later, patient was discharged in a vegetative state with neurological damage to the third cranial nerve (oculomotor nerve), which made it impossible for the patient to open his eyes.	[36]
	M, 26	Intoxication case: patient with previous history of mental disorders admitted to psychiatry emergency unit for differential diagnosis of drug misuse; presented with symptoms of psychosis, paranoia, sleeplessness and inconsistent speech. Serum analysis: *N*-ethylnorpentylone (61 ng/mL). Patient required sedation with midazolam and started treatment with valproic acid, risperidone, haloperidol and levopromazine.	[36]

[a] Year of publication.
[b] "Molly": frequently referring to pure crystalline form of 3,4-methylenedioxymethamphetamine (MDMA) and/or drugs marketed as having MDMA-like effects.

7. Dependence Potential

A. Animal Studies

Studies could not be identified.

B. Human Studies

Studies could not be identified.

8. Abuse Potential

A. Animal Studies

Drug discrimination studies (male Sprague-Dawley rats; two-lever choice methodology; intraperitoneal administration; FR10 schedule) corroborated that *N*-ethylnorpentylone fully substituted for the discriminative stimulus effects of cocaine (ED_{50} = 1.98 mg/kg; 10 mg/kg cocaine used for training),[44] and (*S*)-(+)-methamphetamine (ED_{50} = 1.65 mg/kg; 1 mg/kg (*S*)-(+)-methamphetamine used for training).[45] Partial substitution (51% at 10 mg/kg *N*-ethylnorpentylone) was observed in rats trained to discriminate MDMA (1.5 mg/kg) from saline. It was also found that the response rate decreased following 10 and 25 mg/kg *N*-ethylnorpentylone, with the maximum effect (27% of vehicle control) following administration of 25 mg/kg.[46]

B. Human Studies

Studies could not be identified.

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

Information about therapeutic use could not be identified.

10. Listing on the WHO Model List of Essential Medicines

N-Ethylnorpentylone is not listed.

11. Marketing Authorizations (as a Medicinal Product)

N-Ethylnorpentylone was never marketed as a medicinal product.

12. Industrial Use

Information about recorded industrial use could not be identified.

13. Non-Medical Use, Abuse and Dependence

Use of *N*-ethylnorpentylone appears to be limited to recreational substance users rather than the general population. The mode of use may involve the combinational use (intentionally or unintentionally) of other drugs and users may be unaware of the exact dose or compound being ingested (by whatever route). Dependence-producing properties

in humans have not been studied. The information currently available suggests that *N*-ethylnorpentylone has been found in products sold as 'ecstasy'/MDMA.[8, 23, 47] but there have been instances where other drugs have been detected in addition to *N*-ethylnorpentylone.[8, 22] *N*-Ethylnorpentylone may also be available in its own right and is advertised for sale by Internet retailers.

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

Surveys that systematically assess the prevalence of *N*-ethylnorpentylone use within the general population are not available. The detection of *N*-ethylnorpentylone in biological fluids has been described in cases involving impaired driving (Section 6). The fact that *N*-ethylnorpentylone has been identified in products believed by users to represent 'ecstasy'/MDMA means that users may be unaware of the additional risks of harm (e.g. potential exacerbation of a psychostimulant toxidrome) associated with the consumption of *N*-ethylnorpentylone either alone or in combination with other drugs.

15. Licit Production, Consumption and International Trade

It is used as a reference material for scientific research. It is not known to have any agricultural, industrial or cosmetic uses even though it is available for purchase as a 'research chemical'.

Please refer to Annex 1: Report on WHO questionnaire for review of psychoactive substances.

16. Illicit Manufacture and Traffic and Related Information

Reports have been received from the European Early-Warning System on new psychoactive substances that *N*-ethylnorpentylone (first notified to EMCDDA in January 2016[48]) was encountered in seizures and collected specimen (crystalline powder, powder, urine, tablets) in Austria, Belgium, Bosnia and Herzegovina, Czech Republic, France, Germany, Greece, Italy, Hungary, Ireland, Latvia, Lithuania, Malta, Norway, Portugal, Romania, Slovenia, Spain, Sweden, Turkey, and United Kingdom.[22]

Reports about detections of *N*-ethylnorpentylone in the United States of America (USA) started to appear in May 2014[49]. The National Forensic Laboratory Information System (NFLIS), which is dedicated to the collection of drug cases submitted by State and local laboratories in the USA, is currently registering an increase in reports (Table 5). According to the background information and evaluation of 'Three Factor Analysis' (Factors 4, 5 and 6) for temporary scheduling document prepared by the US Drug Enforcement Administration, a total number of 6,035 reports (local and State forensic laboratories) on the identification of *N*-ethylnorpentylone were received between January 2013 and December 2017.[23] Seizures of *N*-ethylnorpentylone increased since 2016 from 2,074 reports (from 39 States) to 3,955 reports (from 39 States) in 2017. It was furthermore stated that seizures of *N*-ethylnorpentylone by the U.S. Customs and Border Protection emerged in 2016.[23] The net weight of 338 drug exhibits pertaining to trafficking,

distribution and abuse amounted to approximately 82 kg. Seizures indicate that *N*-ethylnorpentylone is available in powder, crystal, rock, capsule, and tablet forms. [23] The number of *N*-ethylnorpentylone identifications published in the Drug Enforcement Administration's (DEA) Special Testing and Research Laboratory's Emerging Trends Program increased from 63 (out of 347 cathinone identifications, 18.2%) in 2016[50] to 63 (out of 347, 18.2%) in 2016 to 201 (out of 369 cathinone identifications, 54.5%) in 2017.[51] In the first quarter of 2018, 17 out of 29 cathinone identifications (58.6%) were attributed to *N*-ethylnorpentylone.[52]

Table 5. Number of reports received by the U.S. National Forensic Laboratory Information System (NFLIS) related to detections of *N*-ethylnorpentylone in law enforcement operations

Year [a]	Numbers [b]	α-PVP [c]	MDMA [d]	Meth [e]	Ref
2013 (MY)	NR	1,202	2,423	100,045	NFLIS[53]
2013 (AR)	NR	2,440	4,798	206,784	NFLIS[54]
2014 (MY) [c]	NR	1,950	2,224	117,318	NFLIS[55]
2014 (AR)	NR	3,905	4,902	236,175	NFLIS[56]
2015 (MY)	NR	NR	2,421	133,374	NFLIS[57]
2015 (AR)	NR	NR	5,188	277,823	NFLIS[58]
2016 (MY)	457	666	2,901	155,535	NFLIS[59]
2016 (AR) [f]	1,720	1,036	5,726	314,872	NFLIS[60]
2017 (MY)	2,520	512	2,695	170,300	NFLIS[61]

[a] MY: mid-year report (January to June); AR: annual report (January to December).
[b] NR: not reported
[c] α-PVP: alpha-pyrrolidinopentiophenone
[d] MDMA: 3,4-Methylenedioxymethamphetamine
[e] Meth: methamphetamine
[f] Revised April 2018

Detections of *N*-ethylnorpentylone have also been reported to the United Nations Office on Drugs and Crime's (UNODC) Early Warning Advisory on New Psychoactive Substances. Identifications of *N*-ethylnorpentylone were reported by one country in 2015, 25 countries in 2016, 10 countries in 2017, and 3 countries in 2018 (as of 25 August 2018).[62]

Please also refer to Annex 1: Report on WHO questionnaire for review of psychoactive substances.

17. Current International Controls and Their Impact

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

18. Current and Past National Controls

Refer to Annex 1: Report on WHO questionnaire for review of psychoactive substances.

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

Detections of *N*-ethylnorpentylone may be under-reported given that the substance might not be routinely screened for in all laboratories receiving samples for analysis.

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