



Critical Review Report: N-Ethylhexedrone

Expert Committee on Drug Dependence

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Contents

Acknowledgements	5
Summary	5
1. Substance identification	7
A. International Nonproprietary Name (INN)	7
B. Chemical Abstract Service (CAS) Registry Number	7
C. Other Chemical Names	7
D. Trade Names.....	7
E. Street Names.....	7
F. Physical Appearance	7
G. WHO Review History	7
2. Chemistry	7
A. Chemical Name	7
B. Chemical Structure	8
C. Stereoisomers.....	8
D. Methods and Ease of Illicit Manufacturing	8
E. Chemical Properties	8
F. Identification and Analysis	8
3. Ease of Convertibility Into Controlled Substances	9
4. General Pharmacology	9
A. Routes of administration and dosage	9
B. Pharmacokinetics.....	10
C. Pharmacodynamics.....	10
5. Toxicology	10
6. Adverse Reactions in Humans	10
7. Dependence Potential	11
A. Animal Studies.....	11
B. Human Studies	11
8. Abuse Potential	11
A. Animal Studies.....	11
B. Human Studies	12
9. Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use	12
10. Listing on the WHO Model List of Essential Medicines	12
11. Marketing Authorizations (as a Medicinal Product)	12
12. Industrial Use	13
13. Non-Medical Use, Abuse and Dependence	13

14.	<i>Nature and Magnitude of Public Health Problems Related to Misuse, Abuse and Dependence</i>	13
15.	<i>Licit Production, Consumption and International Trade</i>	14
16.	<i>Illicit Manufacture and Traffic and Related Information</i>	14
17.	<i>Current International Controls and Their Impact</i>	15
18.	<i>Current and Past National Controls</i>	15
19.	<i>Other Medical and Scientific Matters Relevant for a Recommendation on the Scheduling of the Substance</i>	15
References		16

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Executive Summary

Although originally synthesized and described as a potential anorexigenic agent in a patent by Boehringer Ingelheim in 1964, N-ethylhexedrone has recently and quickly appeared on the global novel psychoactive substances (NPS) market starting in 2016. In 2017, N-ethylhexedrone was reported by the UNODC-EWA to be the most persistent and most prevalent NPS seized. In China, the Global SMART Programme reported N-ethylhexedrone was the 5th most frequently reported NPS. In 2018, N-ethylhexedrone was the second most common drug of the cathinone class to be identified by US DEA-DOJ.

N-ethylhexedrone is a derivative of hexedrone, in which the methyl group attached to the nitrogen atom is substituted by an ethyl group and is structurally similar to pentedrone, and also α -pyrrolidinohexiophenone (α -PHP), from which it differs by the substitution of a pyrrolidine group with an N-ethyl group. Patterns of use and pharmacological effects appear similar to other cathinones. Doses in the range of 10-250 mg N-ethylhexedrone are most often insufflated but may also be administered by other methods.

Pharmacological effects of N-ethylhexedrone are proposed to begin 2 min after intranasal administration and peak around 20-25 min or begin 20-25 min after oral administration and peak around 50-60 min. N-ethylhexedrone has been reported to produce euphoria, stimulation, empathy, an enhanced sense of well-being, increased talkativeness, sociability, insomnia, and sensory enhancement. This description is similar to descriptions of some of the effects produced by other cathinones. Limited pharmacokinetic and pharmacodynamics data are available; however it appears that N-ethylhexedrone has high preference for the dopamine transporter and fully substitutes for both cocaine and (+) methamphetamine in preclinical studies.

The adverse effects of N-ethylhexedrone administration resemble patterns observed for other cathinones such as toxicity of the sympathomimetic system such as hypertension, pains in the chest, and tachycardia. Only a few toxicological reports and one fatality have emerged in the published literature, but as the compound was just reported in 2016-2018 in various countries, it is likely more data will become available in the near future. The population likely to abuse N-ethylhexedrone intersects with the population using other cathinones and stimulants as evidenced by self-reports and toxicological case reports.

Very few countries have scheduled N-ethylhexedrone at the present time. In summary, 4-ethylhexedrone is one of the latest cathinone derivatives to be sold and used in a similar manner to other licit and illicit stimulants. At present, the most distinguishing feature for N-ethylhexedrone is its recent and rapid emergence on the NPS market.

1. Substance identification

A. *International Nonproprietary Name (INN)*

N-ethylhexedrone

B. *Chemical Abstract Service (CAS) Registry Number*

802857-66-5

C. *Other Chemical Names*

1-Hexanone, 2-(ethylamino)-1-phenyl

2-(Ethylamino)-1-phenyl-1-hexanon

2-(Ethylamino)-1-phenyl-1-hexanone

2-(Éthylamino)-1-phényl-1-hexanone

2-(Ethylamino)-1-phenylhexan-1-one

N-Ethylhexedrone

N-ethylnorhexedrone

α -ethylaminocaprophenone

a-ethylaminocaprophenone

N-ethylamino-Hexanophenone

N-ethyl Hexedrone

Hexanophenone, 2-(ethylamino) - (8CI)

D. *Trade Names*

There are no trade names for N-ethylhexedrone.

E. *Street Names*

Ethyl-hexedrone, Ethyl-hex, Hexen, HEX-EN, NEH, Henio, Henryk

F. *Physical Appearance*

White, grey or yellow powder; white, fine crystalline solid. Conflicting users reports on internet sites describe N-ethylhexedrone as both odorless or an unpleasant smell; as both tasteless or as an unpleasant chemical taste with a bitter aftertaste.

G. *WHO Review History*

N-ethylhexedrone has not been previously reviewed by WHO.

2. Chemistry

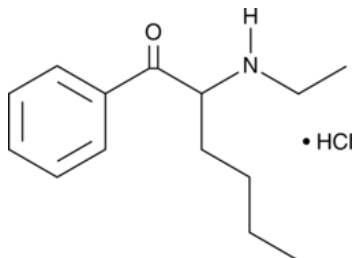
A. *Chemical Name*

IUPAC Name: 2-(Ethylamino)-1-phenyl-1-hexanone

CA Index Name: 1-Hexanone, 2-(ethylamino)-1-phenyl-

B. Chemical Structure

Free base:



Molecular Formula: $C_{14}H_{21}NO$; $C_{14}H_{21}NO \cdot HCl$

Molecular Weight: $219.328 \text{ g}\cdot\text{mol}^{-1}$

C. Stereoisomers

R- and S-enantiomers

D. Methods and Ease of Illicit Manufacturing

N-Ethylhexedrone was first mentioned and the synthesis described, together with other derivatives of aminoketone, in a patent by Boehringer Ingelheim in Germany in 1964 and then in the US in 1971 (Koppe et al., 1971). The basic patent describes compounds with active ingredients of a racemic mixture of a 1-phenyl-2-(lower alkyl-amino)-lower alkanone with a range of different R1 and R2 groups prepared from forty relatively convenient and efficient known chemical methods.

E. Chemical Properties

Flash point (Melting point not available)

$110.5 \pm 23.3 \text{ }^\circ\text{C}$

Boiling point

$322.3 \pm 25.0 \text{ }^\circ\text{C}$ at 760 mmHg

Solubility

Sparingly Soluble (0.79 g/L) Temp: $25 \text{ }^\circ\text{C}$

F. Identification and Analysis

Recent identification and analyses of N-ethylhexedrone have used ultra-high-performance liquid chromatography-quadrupole time-of-flight-mass spectrometry (UHPLC-QTOF-MS), gas chromatography-mass spectrometry (GC-MS), and nuclear magnetic resonance (NMR) spectroscopy (Liu et al., 2016). To develop an enantioseparation method for N-ethylhexedrone, as well as other novel psychoactive substances, a high-performance liquid chromatography separation method in normal-phase mode under isocratic conditions using ultraviolet detection and using cellulose tris(3,5-dichlorophenylcarbamate) as a chiral

selector (i.e., Lux® i-Cellulose-5 column as CSP by HPLC–UV) was applied (Kadkhodaei et al., 2018). In addition, liquid chromatography quadrupole time-of-flight mass spectrometry (LC-QTOF-MS) (Krotulski et al., 2019) and LC-QToF-MS, LC-QqQ-MS methods (Mikołajczyk et al., 2017) were developed, validated, and implemented for forensic toxicology testing of N-ethylhexedrone.

The authors of these analysis papers report the identification of cathinones such as N-ethylhexedrone is problematic due to its structural similarity to other cathinones. For example, N-ethylhexedrone can easily be confused with its isomer, i.e., n-ethyl-4'-methyl norpentedrone (4-MeaP). Assuming that N-ethylhexedrone is metabolized through N-dealkylation and/or reduction of the carbonyl group followed by N-dealkylation, it is likely some of N-ethylhexedrone metabolites will be isomers of other cathinones present on the drug market such as pentedrone, 4-ethylmethcathinone, 3-ethylmethcathinone, 3,4-dimethylmethcathinone, or 4-methylbuphedrone. Therefore, multiple analytical techniques such as LC-QToF-MS, LC-LiTMS, LC-QqQ-MS, and GC-MS and keen analysis of the mass spectra are suggested in the analytical process of N-ethylhexedrone (Mikołajczyk et al., 2017).

In other identifications, N-ethylhexedrone was identified in extracts initially designated for designer benzodiazepine and opioid confirmation; and found in conjunction with diclazepam, etizolam, fentanyl, and FIBF. In addition, N-ethylhexedrone was also found in combination with 4Cl- α -PVP (Krotulski et al., 2019).

3. Ease of Convertibility into Controlled Substances

No information was found on the ease of convertibility of N-ethylhexedrone into controlled substances.

4. General Pharmacology

A. *Routes of administration and dosage*

Internet searches and self-reports from case studies reveal that N-ethylhexedrone is most often insufflated (strongest effects) or vapor inhaled (weaker and short-acting effects) but may also be administered orally, rectally, intravenously, smoked in e-cigarettes, or by 'hot rails', i.e., inhaling through the nose by way of a heated glass tube (Mikołajczyk et al., 2017). A dose range of 10 – 250 mg N-ethylhexedrone has been reported (Mikołajczyk et al., 2017; Dunlop et al., 2019; Kovács et al., 2019). N-ethylhexedrone doses of 10–20 mg and 30–40 mg are reported as threshold or low doses while 50–60 mg and 70–90 mg are reported as typical and high dose respectively. Very high doses of 100-250 mg N-ethylhexedrone have also been reported including a series of repeated doses totaling up to 350 mg in a short episode.

B. Pharmacokinetics

There are no published reports on the pharmacokinetics of N-ethylhexedrone. However, based on the structure and assuming that N-ethylhexedrone is metabolized similarly to other cathinones (Helfer et al., 2015; Lewin et al., 2014), this compound is likely metabolized through N-dealkylation and/or reduction of the carbonyl group followed by N-dealkylation (Mikołajczyk et al., 2017). Again, there are no published reports on absorption or distribution. However, user reports of short-lived psychoactive effects suggest that N-ethylhexedrone is absorbed, distributed, and metabolized relatively quickly. The effects of N-ethylhexedrone are proposed to begin 2 min after intranasal administration. The greatest effects were observed after about 20–25 min and last up 2–3 h while the effects are diminished by ~4–8 h. The effects of N-ethylhexedrone are proposed to begin 20–25 min after oral administration. The greatest effects after oral dosing were observed after ~ 50–60 min (Mikołajczyk et al., 2017).

C. Pharmacodynamics

In HEK cells expressing cDNA for the human dopamine transporter (HEK-hDAT cells), N-ethylhexedrone inhibited ($[^{125}\text{I}]\text{RTI-55}$) radioligand binding with a $K_i \pm \text{SEM}$ of $0.171 \pm 0.038 \mu\text{M}$ and inhibited $[^3\text{H}]\text{dopamine}$ uptake with an $\text{IC}_{50} \pm \text{SEM}$ of $0.0467 \pm 0.0040 \mu\text{M}$. In HEK cells expressing cDNA for the human serotonin transporter (HEK-hSERT cells), N-ethylhexedrone inhibited radioligand ($[^{125}\text{I}]\text{RTI-55}$) binding with a $K_i \pm \text{SEM}$ of $11.4 \pm 1.8 \mu\text{M}$ and inhibited $[^3\text{H}]\text{serotonin}$ uptake with an $\text{IC}_{50} \pm \text{SEM}$ of $4.88 \pm 0.47 \mu\text{M}$. Finally, in HEK cells expressing cDNA for the human norepinephrine transporter (HEK-hNET cells), N-ethylhexedrone inhibited radioligand ($[^{125}\text{I}]\text{RTI-55}$) binding with a $K_i \pm \text{SEM}$ of $1.259 \pm 0.043 \mu\text{M}$ and $[^3\text{H}]\text{norepinephrine}$ uptake with an $\text{IC}_{50} \pm \text{SEM}$ of $0.0978 \pm 0.0083 \mu\text{M}$. The ratio of DAT/SERT was 100-fold indicating that N-ethylhexedrone has high preference for the hDAT (Eshleman et al., 2019).

5. Toxicology

At the time of the report, there were no acute or chronic preclinical toxicology studies found in animals. However, a toxicology screen was developed to examine five cathinones, 4-FMC, 4-MEC, buphedrone, methedrone, and N-ethylhexedrone using two models: yeast *S. cerevisiae* and differentiated SH-SY5Y cells. In these two assays, concentrations of 0, 25, 50, 75, and 100 mM for each cathinone were tested. N-ethylhexedrone was the most toxic cathinone tested in differentiated SH-SY5Y cells and the second most toxic cathinone in yeast *S. cerevisiae* (Ferreira et al., 2019).

6. Adverse Reactions in Humans

Forensic and case reports indicate adverse reactions in humans, although often N-ethylhexedrone is administered in combination with other substances so the specific adverse effects are difficult to separate from the other substances. Generally, in summary of observations and self-reports of users from internet sites, N-ethylhexedrone produces adverse effects similar to other cathinones such as hypertension, trembling hands, convulsions, chest pains, tachycardia, dysrhythmia, hypopnea, limb numbness, circulatory

problems in the extremities, vasoconstriction, elevated temperature, dehydration, sweating, dry mouth, lack of emotion, depression, paranoia, nausea, lack of appetite, visual disturbances, involuntary mouth movements, teeth grinding, jaw cramps, and nasal mucosa burning when snorted (Mikołajczyk et al., 2017; Kovács et al., 2019).

According to the UNODC.org/tox portal, two clinical admissions were reported: in France of a 25-44 year old male with N-ethylhexedrone and α -pyrrolidinopentiophenone in urine samples; and, in Germany of a 15-24 year old male with N-ethylhexedrone in the urine sample. These were reported in 2019 and 2018, respectively (UNODC EWA Tox-Portal, 2019). In a case report from the United Kingdom, a 56-year-old man was brought to the Emergency Department with symptoms of visual hallucinations, reduced level of consciousness, diaphoresis, tachycardia, hypertension, hyperthermia, and vertical nystagmus after consumption of N-ethylhexedrone (100 mg dose), 3-hydroxyphenylidine (patient guessed 10 mg), and cough syrup. Based on the symptoms and time course of the toxicity, the authors suggested that the 3-hydroxyphenylidine was likely the predominate cause of the severe toxicity in this patient with some minor contribution from N-ethylhexedrone (Dunlop et al., 2019).

7. Dependence Potential

A. *Animal Studies*

At the time of this report, there were no animal studies of dependence potential in the literature for N-ethylhexedrone.

B. *Human Studies*

There are no published studies on human dependence potential of N-ethylhexedrone. The data on trends of administration and doses from the internet forums suggest a potential for dependence similarly to other cathinones. In a case report, a 56-year-old man reported that he had purchased 25 g of N-ethylhexedrone from an internet supplier. He claimed that after using N-ethylhexedrone every day for 3 months by nasal insufflation and/or rectal insertion, he developed a 'psychological addiction' to it (Dunlop et al., 2019). However, this statement is a single self-report in a case study.

8. Abuse Potential

A. *Animal Studies*

In mouse locomotor studies, N-ethylhexedrone resulted in time- and dose-dependent stimulation of locomotor activity following doses of 10 to 50 mg/kg, i.p. The locomotor stimulating effects of 10 and 25 mg/kg occurred within 10 min following injection and lasted 120-240 min. An ED₅₀ of 7.7 mg/kg was calculated for N-ethylhexedrone. In comparison to the locomotor stimulating effects of cocaine and methamphetamine, N-ethylhexedrone produced 108% and 91% of the maximal stimulant effect, respectively (Sumien et al., 2018).

In rat drug discrimination studies, N-ethylhexedrone fully substituted for the discriminative stimulus effects of 10 mg/kg cocaine, i.p., with an ED₅₀ of 3.42 mg/kg. The response rates were increased to 131% of the vehicle control response rates following a dose of 5 mg/kg N-ethylhexedrone (Forester et al. 2019a). Similarly, N-ethylhexedrone i.p. fully substituted for the discriminative stimulus effects of 1 mg/kg i.p. fully (+)-methamphetamine i.p., with an ED₅₀ value of 1.44 mg/kg. The response rates after N-ethylhexedrone were not significantly changed from vehicle control response rates at the doses that were tested (0.25 to 2.5 mg/kg) (Forester, 2019b).

No conditioned place preference or self-administration studies of N-ethylhexedrone were published at the time of this report.

B. Human Studies

The data on trends and doses from the internet and forums suggest a potential for abuse similarly to other cathinones. For example, the descriptions on the internet forums describe euphoria, stimulation, empathy and enhanced sense of well-being, increased talkativeness, sociability, insomnia, increased creativity, increased libido, increased concentration, thought acceleration, sensory enhancement and altered perception of music which are similar to descriptions of some of the effects produced by other cathinones and MDMA. These forums also describe an unpleasant so-called “comedown” in which the user experiences strong feelings of fatigue and discouragement, dejection, depressive states, anxiety, irritability, insomnia, delusions, auditory and visual hallucinations (Mikołajczyk et al., 2017).

In a case report, a 56-year-old man reported that he had purchased 25 g of N-ethylhexedrone from an internet supplier. In a pattern suggestive of abuse potential, he claimed that after using N-ethylhexedrone every day for 3 months by nasal insufflation and/or rectal insertion, he developed a ‘psychological addiction’ to it (Dunlop et al., 2019). This is a single report from a case study.

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

There are currently no therapeutic applications or recorded medical use at this time.

10. Listing on the WHO Model List of Essential Medicines

N-ethylhexedrone is not listed on the WHO Model List of Essential Medicines.

11. Marketing Authorizations (as a Medicinal Product)

No evidence is available that N-ethylhexedrone is being pursued as a medicinal product in any country. Furthermore, N-ethylhexedrone has not been granted a marketing authorization as a medicinal product for human use or veterinary use, has not been the subject of an application for marketing authorization as a medicinal product for human use

or veterinary, or has not had a case of suspended marketing authorization as a human or animal medicine in any country.

12. Industrial Use

No potential industrial use was detected for N-ethylhexedrone besides as an analytical reference standard for scientific research and forensic applications. N-ethylhexedrone currently is available for purchase synthesized by various chemical companies available in wholesale amounts and in consumer amounts.

13. Non-Medical Use, Abuse and Dependence

At the time of this report, there were no formal epidemiology reports published on the prevalence, abuse, or dependence of N-ethylhexedrone. Only the case reports described above and two toxicology reports from France and Germany were available despite the fact that N-ethylhexedrone was one of the most frequently seized cathinones in 2017 (Mikołajczyk et al., 2017; Dunlop et al., 2019; Kovács et al., 2019; UNODC EWA Tox-Portal, 2019). Other indications of the non-medical use and abuse of N-ethylhexedrone are the number and percentage of syringes detected with traces of N-ethylhexedrone in monitored sentinel cities. In 2017, the European Syringe Collection and Analysis Project Enterprise reported identifying N-ethylhexedrone in used syringes in four of six sentinel cities: Amsterdam, Budapest, Helsinki, and Lausanne. Further, they indicated 171 counts or ~76% of the samples collected in Budapest contained N-ethylhexedrone (EMCDDA, 2019a). The Department of Forensic Toxicology of the Hungarian Institute for Forensic Sciences collected and analyzed 1006 blood samples of living subjects in 2017. Fourteen were positive for N-ethylhexedrone. The concentration varied between 10.2 and 83.9 ng/ml, with an average of 28.3 ng/ml. Seven of these samples contained N-ethylhexedrone alone [10.2–37.8 ng/ml] (as reported in Kovács et al., 2019). Therefore, N-ethylhexedrone has recently been part of the illicit market for cathinones, and it has been found in syringes and in blood, but reports of the pattern or extent of abuse and dependence are currently not available.

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

Toxicological case reports have indicated that N-ethylhexedrone is a substance involved in nonfatal intoxication including emergency department visits (Dunlop et al., 2019; UNODC EWA Tox-Portal, 2019), driving under the influence, and in fatalities including overdoses and traffic accidents (Mikołajczyk et al., 2017; Kovács et al., 2019). In two separate cases involving motor vehicles, an 18-year-old man and a 25-year old man were suspected of driving vehicles under the influence of intoxicating substances which turned out to be concentrations of 8 and 34 ng/mL N-ethylhexedrone, respectively. In a third case, a 27-year-old man died as a result of injuries from a road accident and N-ethylhexedrone was detected at a concentration of 37 ng/mL with 3-fluorophenmetrazine in a concentration of 9 ng/mL in post mortem blood samples (Mikołajczyk et al., 2017).

One toxicological report indicated interactions of N-ethylhexedrone with a synthetic cannabinoid as likely producing additive adverse effects that contributed to a fatality in the UK. A 23-year-old male regular drug user died a few hours after N-ethylhexedrone and ADB-FUBINACA consumption, likely oral administration. Postmortem blood levels of N-ethylhexedrone were 285 ng/ml, along with 0.08 ng/ml ADB-FUBINACA and five ADB-FUBINACA metabolites. Autopsy results found evidence consistent with coronary vasoconstriction such as contraction band necrosis and cardiomyocyte hypercontraction in addition to pulmonary edema, alveolar hemorrhage, enlarged kidneys and acute tubular necrosis. The deceased had a medical history of arrhythmias in childhood, some seizures, and obesity. Based on the blood concentrations of N-ethylhexedrone measured in other suspected drug users (≤ 83.9 ng/ml), the authors hypothesized that N-ethylhexedrone intoxication was the cause of death, with the co-factors of heart disease and a minor synthetic cannabinoid effect (Kovács et al., 2019).

15. Licit Production, Consumption and International Trade

There is currently no licit production, consumption, or trade for N-ethylhexedrone.

16. Illicit Manufacture and Traffic and Related Information

Between August 2016 and September 2018, 233 reports of N-ethylhexedrone appeared in 22 states of the US (USDOJ DEA, 2018). The Customs and Borders Protection office encountered 73 shipments of products some of which contained N-ethylhexedrone from 2014-2017. The Special Testing and Research Laboratory's Emerging Trends Program compiled the data and reported 29 identifications of archived seizure and analysis information from drug evidence of N-ethylhexedrone in 2018 and 3 identifications in the first half of 2019 (Emerging Threat Report Annual 2018, 2019).

In 2017, N-ethylhexedrone was one of the top UNODC EWA substances reported as the most persistent and most prevalent novel psychoactive substances seized (Tetty, 2017). N-ethylhexedrone was reported in Europe for the first time on 16 February 2016 from Hungary (European Monitoring Centre for Drugs and Drug Addiction, 2017).

IONICS, a free communication platform contributing to the real-time communication of suspicious shipments, trafficking, manufacture or production of novel psychoactive substances provided the following information on N-ethylhexedrone in August 2019: 13 total incidents were reported. For N-ethylhexedrone, 2 incidents took place in 2016, 4 incidents in 2017, 3 incidents in 2018, and 4 incidents in 2019. Broken down by country, 6 incidents were reported from the United Kingdom (4 in 2017 and 2 in 2019), 2 from Belgium (1 each in 2018 and 2019), 1 from the Netherlands (2017), 1 from Spain (2016), 1 from Japan (2018) and 1 from Mexico (2018). As countries of origin for N-ethylhexedrone, China was identified in 6 incidents, Netherlands in 2 incidents, Hong Kong SAR of China in 1 incident, Czechia in 1 incident, Germany in 1 incident and Spain in 1 incident. In one incident of N-ethylhexedrone, the origin was unknown (IONICS, 2019).

According to the Hungarian Institute for Forensic Sciences, cathinones in general represented nearly 10% of seized material between September 2016 and August 2017 and in this country, N-ethylhexedrone represented 40–60% of the seizures (as reported in Kovács et al., 2019). In China, N-ethylhexedrone was the 5th most commonly identified novel psychoactive substance according to the NPS Monitoring Programme in 2017 (Global SMART, 2019).

17. Current International Controls and Their Impact

At the current time, there are no international controls for N-ethylhexedrone.

18. Current and Past National Controls

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and Europol added N-ethylhexedrone to the list of new psychoactive substances to be monitored through the European Union Early Warning System and a profile of the substance was created on the European Database on New Drugs in November 2016 (EMCDDA–Europol 2016).

The legal status for N-ethylhexedrone is Schedule 1 controlled drug in Canada, Class B in the UK, and temporarily Schedule 1 in the US (US DEA DOJ, 2019). Recently, Japan and Sweden’s public health agencies classified N-ethylhexedrone as an illegal narcotic and in Hungary, N-ethylhexedrone has been controlled as a new psychoactive substance.

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

Because users of N-ethylhexedrone obtain this substances through unregulated sources, the identity, purity, and potency are uncertain, posing significant adverse health risks to the purchaser. Limited pharmacological data and toxicological information are available for N-ethylhexedrone, increasing the risk for harmful adverse events.

References

1. Dunlop LC, Wood D, Archer J, Hudson S, Dargan P. Severe Toxicity to the New Psychoactive Substances 3-Hydroxyphencyclidine and N-Ethylhexedrone: an Analytically Confirmed Case Report. *J Med Toxicol*. 2019 Sep 3. doi: 10.1007/s13181-019-00734-x.
2. EMCDDA–Europol 2015 Annual Report on the implementation of Council Decision 2005/387/JHA, July 2016. N-ethylhexedrone (NEH) (2-(ethylamino)-1-phenylhexan-1-one). Available at: <http://www.emcdda.europa.eu/publications/implementation-reports/2015>
3. Emerging Threat Report Annual 2018. The Special Testing and Research Laboratory's Emerging Trends Program. Available at: <https://ndews.umd.edu/sites/ndews.umd.edu/files/Emerging-Threat-Report-2018-Annual.pdf>
4. Emerging Threat Report Mid-Year 2019. The Special Testing and Research Laboratory's Emerging Trends Program. Available at: <https://ndews.umd.edu/sites/ndews.umd.edu/files/Emerging-Threat-Report-2019-Mid-Year.pdf>
5. Eshleman AJ, Nagarajan S, Wolfrum KM, Reed JF, Swanson TL, Nilsen A, Janowsky A. Structure-activity relationships of bath salt components: substituted cathinones and benzofurans at biogenic amine transporters. *Psychopharmacology (Berl)*. 2019 Mar;236(3):939-952. doi: 10.1007/s00213-018-5059-5.
6. European Monitoring Centre for Drugs and Drug Addiction, European Drug Report 2017: Trends and Developments, Publications Office of the European Union, Luxembourg, 2017.
7. European Monitoring Centre for Drugs and Drug Addiction. Drugs in syringes from six European cities: results from the ESCAPE project 2017, Publications Office of the European Union, Luxembourg, 2019a.
8. European Monitoring Centre for Drugs and Drug Addiction, European Drug Report 2019: Trends and Developments, Publications Office of the European Union, Luxembourg, 2019b.
9. Ferreira C, Vaz AR, Florindo PR, Lopes Á, Brites D, Quintas A. Development of a high throughput methodology to screen cathinones' toxicological impact. *Forensic Sci Int*. 2019 May;298:1-9. doi: 10.1016/j.forsciint.2019.02.022.
10. Forster MJ, Gatch MB, Taylor CM (2018a) Test of substitution for the discriminative stimulus effects of cocaine. N01DA--18-8936 (HHSN271201800031) University of North Texas Health Science Center at Fort Worth and National Institute on Drug Abuse, 2019a.

11. Forster MJ, Gatch MB, Tourigny, A.A. Test of substitution for the discriminative stimulus effects of (+)-methamphetamine. N01DA-18-8936 (HHSN271201800031) University of North Texas Health Science Center at Fort Worth and National Institute on Drug Abuse, 2019b.
12. Global SMART Programme . Synthetic Drugs in East and South-East Asia. A Report from Global SMART Programme. March 2019. Trends and Patterns of Amphetamine-type Stimulants and New Psychoactive Substances. Research and Trend Analysis Branch, Division for Policy Analysis and Public Affairs, United Nations Office on Drugs and Crime, 2019.
13. Helfer AG, Turcant A, Boels D, Ferec S, Lelièvre B, Welter J, Meyer MR, Maurer HH. Elucidation of the metabolites of the novel psychoactive substance 4-methyl-N-ethyl-cathinone (4-MEC) in human urine and pooled liver microsomes by GC-MS and LC-HR-MS/MS techniques and of its detectability by GC-MS or LC-MS(n) standard screening approaches. *Drug Test Anal.* 2015 May;7(5):368-75. doi: 10.1002/dta.1682.
14. IONICS Narcotic Control and Estimates Section. International Narcotic Control Board Secretariat (INCB). United Nations Office on Drugs and Crime (UNODC). <http://www.incb.org/>
15. Kadkhodaei K, Forcher L, Schmid MG. Separation of enantiomers of new psychoactive substances by high-performance liquid chromatography. *Journal of Separation Science* (2018), 41(6), 1274-1286. doi: 10.1002/jssc.201701239.
16. Koppe H, Ludwig G, Zeille K. α -Aminoketone derivatives. 1971, US 3622675, Boehringer Ingelheim GmbH, Germany. (German Patent: GB1069797, 1964)
17. Kovács K, Kereszty É, Berkecz R, Tizslavicz L, Sija É, Körmöczi T, Jenei N, Révész-Schmehl H, Instítóris L. Fatal intoxication of a regular drug user following N-ethyl-hexedrone and ADB-FUBINACA consumption. *J Forensic Leg Med.* 2019 Jul;65:92-100. doi: 10.1016/j.jflm.2019.04.012.
18. Krotulski AJ, Varnum SJ, Logan BK. Sample Mining and Data Mining: Combined Real-Time and Retrospective Approaches for the Identification of Emerging Novel Psychoactive Substances. *J Forensic Sci.* 2019 Sep 9. doi: 10.1111/1556-4029.14184.
19. Lewin AH, Seltzman HH, Carroll FI, Mascarella SW, Reddy PA. Emergence and properties of spice and bath salts: a medicinal chemistry perspective. *Life Sci.* 2014 Feb 27;97(1):9-19. doi: 10.1016/j.lfs.2013.09.026.
20. Liu C, Jia W, Li T, Hua Z, Qian Z. Identification and analytical characterization of nine synthetic cathinone derivatives N-ethylhexedrone, 4-Cl-pentedrone, 4-Cl- α -EAPP,

propylone, N-ethylnorpentylone, 6-MeO-bk-MDMA, α -PiHP, 4-Cl- α -PHP, and 4-F- α -PHP. Drug Test Anal. 2017 Aug;9(8):1162-1171. doi: 10.1002/dta.2136.

21. Mikołajczyk A, Adamowicz P, Tokarczyk B, Sekuła K, Gieroń J, WrzeSień W, Stanaszek R. Determination of N-ethylhexedrone, a new cathinone derivative, in blood collected from drivers – analysis of three cases. Probl Forensic Sci.2017;109:53–63.
22. Sumien N, Shetty RA, and Forster MJ. Time-course (8-h) mouse locomotor activity test vs cocaine and (+)-Methamphetamine time courses. N01DA-13-8908 (HHSN271201300001) University of North Texas Health Science Center at Fort Worth and National Institute on Drug Abuse
23. Tettey J. Update on emerging substances of abuse. Reconvened Sixtieth Session of the Commission of Narcotics Drugs, 8 December 2017, Vienna, Austria
24. UNODC Early Warning Advisory (EWA) Tox-Portal. N-ethylhexedrone. Accessed September 20, 2019. <https://www.unodc.org/tox/#/admin/search/detailed/%7B%22textQuery%22:%22N-ethylhexedrone%22%7D>
25. US Drug Enforcement Administration – Department of Justice (2019). Schedules of Controlled Substances: Temporary Placement of N-ethylhexedrone, α -PHP, 4-MEAP, MPHP, PV8, and 4-Chloro- α -PVP into Schedule I. Federal Register Volume 84, Number 138 (Thursday, July 18, 2019)] [Proposed Rules] [Pages 34291-34297]

Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances

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