

Methoxetamine

Critical Review Report

Agenda item 4.22

Expert Committee on Drug Dependence
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**World Health
Organization**

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Summary

Methoxetamine (2-(3-methoxyphenyl)-2(*N*-ethylamino)-cyclohexanone) is a new synthetic drug derived from ketamine and belongs to the arylcyclohexylamine class, which is used for its recreational and psychedelic effects. The mechanism of action is not demonstrated but is likely to share the mechanism of action of ketamine through N-methyl D-aspartate (NMDA) receptor antagonism and the inhibition of dopamine reuptake (Corazza, Schifano et al 2011). It is described to show longer lasting and more powerful effects than ketamine but with weaker analgesic and anesthetic effects.

Since 2010, methoxetamine has been sold over the Internet as a white powder under street names such as “M-ket”, “Mexxy”, “Kmax” and often labeled as “research chemicals” or “legal highs”. It has been detected in 22 EU Member States, Turkey and Norway.

Main effects of methoxetamine are hallucinations, depersonalization, dissociation of the physical body as well as antidepressant and recreational effects [1]. Side effects after methoxetamine consumption are vomiting, nausea, diarrhea and tachycardia as well as reduced consciousness and disturbances in mental health. Several people have died or been hospitalized after methoxetamine usage (often in combination with other drugs).

No toxicity studies on humans have been performed using methoxetamine and the few animal studies on long-term toxicity displays the similar effects as ketamine.

1. Substance identification

- A. International Nonproprietary Name (INN)**
Not available.
- B. Chemical Abstract Service (CAS) Registry Number**
1239943-76-0 free base
1239908-48-5 hydrochloride salt
- C. Other chemical names**
MXE
3-MeO-2-Oxo-PCE
2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone;
2-(3-methoxy-phenyl)-2-(ethylamino)-ciklohexanone;
2-(ethylamino)-2-(3-methoxyphenyl)cyclohexan-1-one;
(2-(ethylamino)-2(3-methoxyphenyl)cyclohexan-1-one);
(RS)2-(3-metoksifenyyli)-2-(etyyliamino)sykloheksanoni (Finnish);
methoxyphenylethylamino-ketocyclohexane.
Common names or codenames that have also been reported are: 3-MeO-2-Oxo-PCE, MXE, MXE100 and metoksetamiini (Finnish).
- D. Trade Names**
'Kwasqik', 'Hypnotic', 'Panoramix', 'Magic', 'Lotus', 'Special K', 'Ultraviolet', 'Zeolite' and 'X'.
- E. Street names**
'MXE', 'Mexxy', 'M-ket', 'MEX', 'Kmax', 'Special M', 'MA', 'legal Ketamine', 'Minx', 'Jipper' and 'Roflcoptr'
- F. Physical properties**
The hydrochloride salt of methoxetamine is a white, odourless crystalline powder at room temperature. A physical description of the freebase form could not be found in readily accessible literature.
- G. WHO Review History**
Methoxetamine was not previously pre reviewed or critically reviewed. A direct critical review is proposed based on information brought to WHO's attention that methoxetamine 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

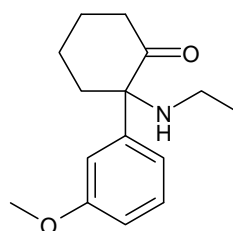
A. *Chemical Name*

IUPAC Name: (RS)-2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone

CA Index Name: N/A

B. *Chemical Structure*

Free base:



Molecular Formula: C₁₅H₂₁NO₂

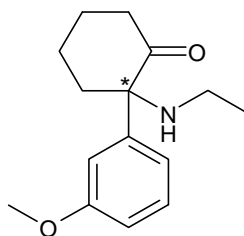
Molecular Weight: 247.33 g/mol (Monoisotopic mass: 247.157)

Melting point: 227-233 °C (hydrochloride salt)

Boiling point: 389,084°C at 760 mm Hg

C. *Stereoisomer*

Two enantiomers, the chiral center is marked with a star below. Methoxetamine is commonly available as the racemic mixture.



D. *Synthesis*

The synthesis of methoxetamine was achieved by 4 steps through simple reactions involving an aromatic nitrile, a Grignard reagent, bromination, imine formation through reaction with a suitable amine, followed by the application of heat to the product to allow ring expansion of 1-[(ethylimino)(3-methoxyphenyl)methyl]-1-cyclopentanol [2].

This process is presumably readily applicable to analogues of methoxetamine by substitution of starting aromatic nitrile and selected amine to afford the desired N-substituted derivative analogues of methoxetamine [3].

E. Chemical description

Methoxetamine is an arylcyclohexylamine substance which shares some structural similarities to the dissociative anaesthetic drug ketamine. In methoxetamine, the 2-chloro group on the phenyl ring and the N-methylamino group of ketamine have been replaced by a 3-methoxy and N-ethylamino groups respectively.

F. Chemical properties

Methoxetamine hydrochloride (salt) is soluble in organic solvents like ethanol (10 mg/mL) at 25° C, DMSO (14 mg/mL) and dimethyl formamide (5 mg/mL) and in aqueous, nonorganic solvents like PBS (5 mg/mL).

G. Chemical identification

Identification and analytical profile (GC-MS, LC-MS, LC-MS/MS) provided by LGC Forensics Ltd. has been reported [4]. Analysis by HPLC-DAD and NMR, IR and GC-MS has been reported in an analytical monograph provided by LGC standards [5]. Liquid chromatography-mass spectrometry (LC-MS) can be used for identification of methoxetamine [6].

3. Ease of convertibility into controlled substances

Methoxetamine is not readily converted into other controlled substances.

4. General Pharmacology

Described in this section are studies that have examined the pharmacological actions of methoxetamine. In research examining the pharmacological profile, data suggests that methoxetamine has affinity for the N-methyl-D-aspartate (NMDA) receptor and acts as an antagonist, similar to the related ketamine. In addition similarly to ketamine, methoxetamine also involves dopamine and serotonin reuptake inhibition. No studies have been performed examining the pharmacology and mode of action of methoxetamine in humans.

4.1. Pharmacodynamics

At present, very little is known about methoxetamine due to the lack of information on methoxetamine in the scientific literature. Methoxetamine is not formally profiled but is classified as a dissociative anaesthetic, an arylcyclohexamine, resembling the toxicological and side effects of ketamine. That suggested that use of methoxetamine will cause euphoria, sensory loss, catatonia and analgesia in addition to amnesia. The side-effects following methoxetamine consumption are vomiting, nausea, diarrhea, hypertension and tachycardia [1, 7-12].

4.2. Routes of administration and dosage

Methoxetamine is generally administered by insufflation, orally or injected (both intramuscular and intravenously). The dosage is ranging from 20–100 mg insufflated, 40–100 mg orally and 10–80 mg when injected intramuscularly. Effects may not be apparent for 30 to 90 minutes after the drug is insufflated, which may cause users to repeat dosing or consumption of a different substance, possibly resulting to synergistic adverse effects. When methoxetamine is injected, effects may emerge within 5 minutes. Rectal and sublingual administration has also been reported [13].

4.3 Pharmacokinetics

The duration of effect of methoxetamine is generally longer than for ketamine, up to 5 to 7 hours but as little as 1-2 hours when injected [14]. In animal studies, the metabolites detected proposes that the enzymes CYP2B6 and CYP3A4 were mainly involved in the initial metabolic steps. The metabolite N-deethyl methoxetamine was suggested to be the most significant in humans [15].

5. Toxicology

Toxicity in Animals

No studies were identified that have examined the acute toxicity of methoxetamine in animals. One mice study investigating chronic toxicity shows that chronic administration of methoxetamine results in renal and cystic inflammation similar to that of ketamine [16, 17]. The study was undertaken to investigate whether methoxetamine, which is said to be a ‘bladder friendly’ alternative to ketamine, was causing the same damage to the renal system and bladder as ketamine does [18, 19]. Two-month-old Institute of Cancer Research (ICR) mice were administered either 30mg/kilograms of methoxetamine per day (n=5) or saline control (n=3) by intraperitoneal injection for three months. In all the mice which were administered methoxetamine, degeneration in both the proximal and distal convoluted tubules of the kidney and inflammatory cell infiltration of the kidneys was observed. Mononuclear cell infiltration in the submucosal layer and in the muscle layer of bladder was also observed. None of the above histological changes were seen in mice administered the saline control concluding that methoxetamine is not a ‘bladder friendly’ alternative to ketamine.

Toxicity in Humans

No studies were identified that have examined the toxicity of methoxetamine in humans. However, a few analytically confirmed cases of acute toxicity following recreational use of methoxetamine have been reported [20, 21].

6. Adverse reactions in humans

Table 1 Cases of methoxetamine intoxication in humans - non-fatal Cases Reported Hospital Admissions

Case No.	Patient Details	Country [Reference]	Clinical Presentation	Comments
1		Belgium[22]	Euphoria, hallucinations and dissociation.	Powder markets as 'Special K'.
2	24yrs M	Italy [22]	Severe agitation associated with stupor, mydriasis, slight rise in blood pressure and tachycardia.	Other substances also ingested, unknown doses.
3	23yrs, M	Italy [22]	The patient was confused, slowed, sometimes somnolent.	Consumption of '3 red cylinders' and alcohol. Co-ingestion of MXE with THC, cocaine, opiates and levamisole
4	23yrs, M	Italy [22]	Low oxygen saturation at admission and in coma.	Co-ingestion of alcohol, THC and ketamine/norketamine
5	22yrs, M	Italy [22]	Mydriasis and severe psychomotor agitation associated with hallucinations.	Co-ingestion with THC and ketamine/norketamine
6	17yrs, F	Italy [22]	Confused, agitated and amnesic.	Co-ingestion with THC and ketamine/norketamine
7	17yrs, F	Italy [22]	Miotic, confused, disoriented, agitated and amnesic.	Co-ingestion with THC and ketamine/norketamine
8	22yrs, F	Italy [22]	Unresponsive, with response to painful stimuli, with open eyes and pupils of medium size reactive to light, mild tachycardia.	Co-ingestion with THC, cocaine, opiates, buprenorphine and levamisole
9	23yrs, M	Italy [22]	Unresponsive, somnolent with open eyes and pupils of medium size reactive to light.	Co-ingestion with amphetamine, cocaine, MDMA and levamisole
10	22yrs, M	Italy [22]	Lucid with chest pain, diffuse pain sensation and tremors.	Sniffing
11-21		Sweden [22]	Symptoms were hypertension, tachycardia, hallucinations, nystagmus, CNS-depression, mydriasis, anxiety, muscular symptoms and agitation/restlessness.	11 cases, see [23] for further details.
22-48		Sweden [22]	Symptoms were hypertension, CNS-depression, tachycardia, agitation/restlessness, mydriasis, nystagmus, hallucinations, anxiety and muscular symptoms	27 cases, co-ingestion with 5-IT, amphetamine, benzodiazepines, buprenorphine, ethanol, MDPV, morphine, 4-OHMET, cannabis/THC and tramadol

Table 2 Methoxetamine concentration detected in biological fluid (Reference 22)

Case No.	Patient Details	Drugs detected	Methoxetamine (MXE) conc	Comments
1		MXE	Urine: 408 µg/l Plasma: 30 µg/l	
2		MXE + cannabis + paracetamol	Blood: 136 ng/ml	
3	27yrs M	MXE + methorphan	Urine: 0,167 mg/ml Serum: 0.0002 mg/ml	Powder, nasally insufflated Possible overdose of MXE
4	38yrs M	MXE + APB-isomers + amphetamines + MDMA (traces)	Urine: 7400 ng/ml Blood: 167 ng/ml	Rave, violent behaviour
5	17yrs M	MXE + amphetamine + MDMA + THC + ketamine/norketamine + MDA	Urine: 9000 ng/ml Blood: 198 ng/ml	Acute intoxication
6	27yrs M	MXE + THC + AM694 + AM2201 + venlafaxine	Blood: 8,6 µg/g	Intoxication

Table 3 Fatalities Involving methoxetamine (Reference 22)

Case No.	Patient Details	Drugs detected	Concentration(s)	Comments
1		MXE + olanzapine + citalopram + clozapine	Blood MXE: 5200 mg/ml Blood olanzapine: 0,24 mg/ml Blood citalopram: 0,20 mg/ml Blood clozapine: 0,13 mg/ml	Death by drowning.
2	38yrs, M	MXE	Blood MXE: 9,48 µg/ml	Found dead at home. Cause of death asphyxia.
3	31yrs, M	MXE + amphetamine	Blood MXE: 0,32 µg/ml Urine MXE: 4,36 µg/ml Blood amphetamine: 0,06 µg/ml Urine amphetamine: 0,27 µg/ml Hair amphetamine: 0,19 µg/ml	Cause of death reported as acute poisoning of the two drugs.
4		MXE + AM-694 + AM-2201 + JWH-018 + cannabis + venlafaxine	Blood MXE: 8,6 µg/ml	Cause of death reported as acute intoxication with MXE although the presence of the three synthetic cannabinoids may have contributed to the death.
5	29yrs, M	MXE + methadone + mirtazepine	Blood methadone: 645 µg/l Blood mirtazepine: 69 µg/l	Cause of death reported as drug overdose.
6		MXE + fluoromethcathinone + MDMA + methylone + MDAI + MDPV + 5-IAI + AMT		Deceased was found decomposed at home
7	25yrs, M	MXE + alcohol	Blood alcohol: 80 mg/100 ml Urine alcohol: 146 mg/100 ml	Death by drowning.
8	17yrs, M	MXE + alcohol	Blood alcohol: 80 mg/100 ml Urine alcohol: 146 mg/100 ml	Death by drowning.
9	43yrs, M	MXE + methiopropamine	Blood MXE: 0,89 mg/l Blood methiopropamine: 2,8 mg/l	Cause of death was reported as MXE and methiopropamine toxicity.
10	20yrs, M	MXE	Blood MXE: 0,22 mg/l	Death by drowning.
11	27yrs, F	MXE + 6-APB	Blood 6-APB: 2460 ng/ml	Ingestion of MXE and 6-APB
12	41yrs, M	MXE + methiopropamine + MDA + alcohol	Blood methiopropamine: 1,74 mg/l Blood MDA: 0,18 mg/l Blood alcohol: 7 mg/100 ml Urine alcohol: 16 mg/100 ml	Cause of death was reported as natural causes.
13	27yrs, M	MXE + amitriptyline + cocaine + diazepam + MDMA + MDA	Blood MXE: 0,03 mg/l Blood amitriptyline: 0,13 mg/l Blood cocaine: 0,44 mg/l Blood diazepam: 4,27 mg/l Blood MDMA: 0,20 mg/l	Cause of death was reported as mixed drug toxicity.

7. Dependence potential

Animal Studies

No studies were identified that have examined the dependence potential of methoxetamine in animals.

Human Studies

No studies were identified that have examined the dependence potential of methoxetamine in humans.

Self-reported experiences on user websites suggest compulsive re-dosing as well as the unintentional consumption of more than was initially planned [25]. A possible explanation for this behavior is that methoxetamine has a longer delay in onset than ketamine which might lead to a high risk of re-dose.

8. Abuse potential

Animal Studies

No studies were identified that have examined the abuse potential of methoxetamine in animals.

Human Studies

No studies were identified that have examined the abuse potential of methoxetamine in humans.

However, it is believed that since methoxetamine shares many similarities with ketamine regarding effects and chemical structure, it might have a similar abuse potential [1, 26, 27].

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

No evidence has been found that methoxetamine has been therapeutically used.

10. Listing on the WHO Model List of Essential Medicines

Methoxetamine is not found on the WHO Model List of Essential Medicines.

11. Marketing authorizations (as a medicine)

None known.

12. Industrial use

No evidence has been found that methoxetamine has any legitimate industrial use.

13. Non-medical use, abuse, dependence

Dependence and various, mostly psychological adverse effects may result following the use of methoxetamine. The reported cases of abuse have resulted in hospital admissions and deaths. The cases have mainly been reported in Europe and the US. In Europe, a total of 110 non-fatal intoxications and 20 deaths associated with methoxetamine, although not all analytically confirmed. In cases analytically determined, the presence of other substances was revealed, e.g. alcohol, cannabis, amphetamines, MDMA, cocaine. Patients who experience methoxetamine toxicity and require treatment will primarily be managed by supportive care and pharmacological treatment by benzodiazepines.

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

14. The nature and magnitude of public health problems related to misuse, abuse and dependence

The global emergence of NPS reported in December 2013 the following countries highlighted methoxetamine: Austria, Norway, Canada, Russian Federation, Estonia, Singapore, Finland, Spain, France, Ukraine, Italy, United Kingdom, Netherlands and the United States.

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

15. Licit production, consumption and international trade

Not applicable. Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

16. Illicit manufacture and traffic and related information

The seizures of methoxetamine reported, from countries worldwide, have typically encountered the substance in powder form and the amounts are normally in milligram quantities. In total, multi-kilogram amounts of methoxetamine in powder form have been seized. In addition, methoxetamine in tablet form have been seized in several countries and includes preparations of methoxetamine alone and in combination with a wide variety of other drug substances, e.g. synthetic cathinones, cannabinoids and opioids.

The distribution and trafficking mainly occurs through the Internet. In a few cases, methoxetamine seized in Europe have originated from China. In addition, a seizure in January 2014 in the US originated from Spain. No specific reports on the licit and illicit production are available.

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances

17. Current international controls and their impact

Methoxetamine is not controlled under the United Nations conventions.

18. Current and past national controls

Methoxetamine is subject to control under drug legislation in nine European countries (Cyprus, Denmark, France, Germany, Italy, Slovenia, Sweden, Turkey and the United Kingdom). In addition, six European countries (Austria, Hungary, Poland, Portugal, Romania and Slovakia) have methoxetamine under legislation prohibiting the unauthorized supply of defined or qualifying new psychoactive substances. In Finland, Norway and the Netherlands, methoxetamine is subject to control measures under medicines legislations. Furthermore, methoxetamine is a controlled substance in Japan, Switzerland and Russia.

In the United States, methoxetamine is not controlled under the Controlled Substances Act (CSA). However, may be considered as a controlled substance analogue of eticyclidine (PCE) under the CSA if intended for human consumption.

Also refer 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

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Annex 1:

Report on WHO Questionnaire for Review of Psychoactive Substances for the 36th ECDD: Evaluation of Methoxetamine

Data were obtained from 72 WHO Member States (18 AFR, 13 AMR, 5 EMR, 29 EUR, 3 SEAR, 4 WPR).

A total of 63 Member States answered the questionnaire for methoxetamine. Of these, only 28 respondents (AMR 4, EUR 21, WPR 3) had information on this substance.

LEGITIMATE USE

None reported that Methoxetamine was currently authorized or in the process of being authorized/registered as a medical product in their country. Four respondents stated that this substance was used in research or as analytical reference standard. There was no stated use for animal/veterinary care

HARMFUL USE

Twenty respondents confirmed that there was recreational/harmful use of methoxetamine; 6 stated the common route of administration was oral, 4 oral/injection/inhaling/sniffing, 3 inhaling/sniffing and 2 oral/ inhaling/sniffing. Thirteen respondents stated this was obtained via trafficking and one each via clandestine manufacturing and via trafficking plus clandestine manufacturing. Methoxetamine was reported as available in powder form by 14, powder and tablet forms by two and powder and liquid forms by one. Three respondents stated that it was only used by the general population and two only in clubs and one respondent stated use in clubs and among general population. Three respondents each report one death due to Methoxetamine in 2012. Two respondents provide data on emergency room visits with 1 and 54 visits respectively in 2012. The same respondent reporting 54 visits in 2012 stated that there were 2 visits in 2013. Four respondents reported withdrawal, tolerance and other adverse effects or medical illnesses caused by methoxetamine. These included dissociative feeling, bladder pain, euphoria, giddiness, drowsiness, memory lapse, black out, agitation, rapid heart rate, hypertension and hallucinations. It has been reported that the methoxetamine-induced effects lasts longer than and with a greater duration than those of ketamine.

CONTROL

Of those with information on this substance, 21 reported that methoxetamine was controlled under legislation that was intended to regulate its availability - 12 under “controlled substance act”, 4 under “medicines law”, 1 under “analogue legislation” and 2 under “other” laws. Only 3 respondents stated that there were challenges with the implementation of this legislation. On illicit activities involving methoxetamine, one respondent reported clandestine manufacture and none the synthesis of the product itself. One respondent reported processing into the consumer product, 11 reported trafficking, 3 reported diversion and 12 an internet market.

Details on seizures are presented below.

	2011 (number of respondents)	2012 (number of respondents)
Total number of seizures	103 (8)	460 (12)
Total quantity seized (kg)	2.40 (4)	3.04 (9)
Total quantity seized (tablets/pills)	1,543 (2)	130 (4)

IMPACT OF SCHEDULING

Twenty-five respondents reported that if Methoxetamine was placed under international control, they would have the laboratory capacity to identify the substance. It has no reported medical use