European Monitoring Centre for Drugs and Drug Addiction

EUROPOL

EMCDDA–Europol Joint Report on a new psychoactive substance: methoxetamine (2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone)

In accordance with Article 5 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances

Contents

1. Introduction

Article 5.1 of Council Decision 2005/387/JHA ([1]) (hereinafter referred to as the 'Decision') stipulates that *'Where Europol and the EMCDDA, or the Council, acting by a majority of its members, consider that the information provided by the Member State on a new psychoactive substance merits the collection of further information, this information shall be collated and presented by Europol and the EMCDDA in the form of a Joint Report (hereinafter the 'Joint Report').'* The Joint Report shall be submitted to the Council, the European Medicines Agency (EMA) and the European Commission.

At the end of September 2013, the EMCDDA and Europol examined the available information on a new psychoactive substance 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone, commonly known by the short name 'methoxetamine', through a joint assessment based upon the following criteria:

1. the amount of the material seized;
2. evidence of organised crime involvement;
3. evidence of international trafficking;
4. analogy with better-studied compounds;
5. evidence of the potential for further (rapid) spread; and,
6. evidence of cases of serious intoxication or fatalities.

The EMCDDA and Europol agreed that the information collected on methoxetamine satisfied criteria 1, 3, 4 and 6. The two organisations therefore concluded that sufficient information had been accumulated to merit the production of a Joint Report on methoxetamine as stipulated by Article 5.1 of the Decision.

2. Information collection process

In compliance with the provisions of the Decision, on 7 October 2013 the EMCDDA and Europol launched a procedure for the collection of information on methoxetamine, in order to prepare the Joint Report. The information was collected mainly through the Reitox National Focal Points in the Member States, Turkey and Norway as well as the Europol National Units. In addition, the EMA collected information through the national competent authorities responsible for human and veterinary medicinal products in the Member States as well as in Norway and Iceland. The information collection process was largely concluded by 18 November 2013; however, additional information and clarifications from some countries were received up to four weeks after this date.

([1]) OJ L 127, 20.5.2005, p. 32.

Europol asked the Europol National Units to provide information on:

- the level of production of methoxetamine in their country;
- the level of distribution of methoxetamine in their country;
- the level of trafficking of methoxetamine in their country, both for internal, transit or export purposes;
- the number of seizures of methoxetamine in their country, the total amount of the seizures, country of origin, details on the physical forms (including photos);
- the role of organised crime, or criminal groups, in the production, distribution and trafficking of methoxetamine in their country; and,
- any known aspect of violence and/or money laundering relating to the production and trafficking of methoxetamine.

Europol received responses from 15 Member States.

According to Article 5.3 of the Decision, the EMA asked national competent authorities responsible for human and veterinary medicinal products in the Member States as well as Norway and Iceland to provide information on whether:

- the new psychoactive substance methoxetamine has obtained a marketing authorisation;
- the new psychoactive substance methoxetamine is the subject of an application for a marketing authorisation; and,
- a marketing authorisation that had been granted in respect of the new psychoactive substance methoxetamine has been suspended.

Twenty-four Member States ([2]), Norway and Iceland replied to the EMA's request regarding human and/or veterinary medicinal products. The EMA also provided information as relevant to the central authorisation procedure.

Furthermore, in anticipation of Article 7.3 of the Decision in relation to the manufacturing of medicinal products in the European Union, the EMA also requested whether the new psychoactive substance methoxetamine is used to manufacture a medicinal product:

- which has been granted a marketing authorisation;
- for which an application has been made for a marketing authorisation; and,

([2]) Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Malta, Netherlands, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom.

- for which a marketing authorisation has been suspended by a competent authority.

Twenty-three Member States ([3]), Norway and Iceland replied to the EMA's request in this regard. The EMA also provided information as relevant to the central authorisation procedure.

The EMCDDA collected data through:

1. a structured questionnaire from the Reitox National Focal Points. The EMCDDA received replies from 28 Member States as well as from Turkey and Norway;

2. data previously provided to the EU Early Warning System in EMCDDA-Europol Reporting Forms, EWS Progress and Final Reports;

3. a specific information request to the World Health Organization on whether or not methoxetamine is under assessment by the United Nations system (see section 3.5), and;

4. a structured search of the scientific literature and of relevant Internet sites.

Thus, information included in sections 3.2.1 and 3.3 of the Joint Report was provided by Europol, while the EMCDDA provided information included in sections 3.1, 3.2.2, 3.4, 3.5, 3.6, 3.7, 3.8.1, 3.8.2 and 3.8.3 (in part). The information included in sections 3.8.3 (in part), 4.1, 4.2 and 4.3 was provided by the EMA. The conclusion of the Joint Report were prepared and agreed by the two organisations responsible — the EMCDDA and Europol. Further details of the seizures and collected samples (including images where available) reported to the EMCDDA are provided in Annex 1. The details of non-fatal intoxications and deaths associated with methoxetamine that have been reported to the EMCDDA are provided in Annex 2.

3. Information required by Article 5.2 of the Decision

The order and titles of subsections 3.1 to 3.8 and section 4 below are as they appear in Article 5.2(a) to (h) and Article 5.3(a) to (c) of the Decision; all sections are cross-referenced with those set down in the Decision.

([3]) Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Malta, Netherlands, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom.

3.1 Chemical and physical description, including the names under which the new psychoactive substance is known — Article 5.2(a) of the Decision

Chemical description and names

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 (Figure 1).

The systematic chemical name for methoxetamine is (*RS*)2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone.

Additional chemical synonyms reported are:

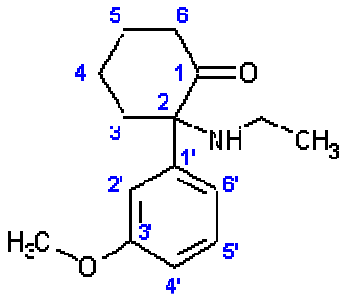
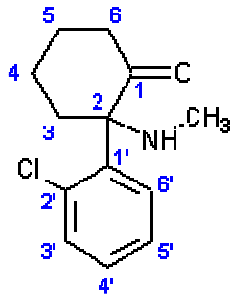
2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone;
2-(3-methoxy-phenyl)-2-(ethylamino)-ciklohexanone;
2-(ethylamino)-2-(3-methoxyphenyl)cyclohexan-1-one;
(2-(ethylamino)-2(3-methoxyphenyl)cyclohexan-1-one);
(*RS*)2-(3-metoksifenyyli)-2-(etyyliamino)sykloheksanoni (Finnish);
methoxyphenylethylamino-ketocyclohexane.

Common names or codenames that have also been reported are: 3-MeO-2-Oxo-PCE, MXE, MXE100 and metoksetamiini (Finnish).

The following street names have also been reported: ‘MXE’, ‘Mexxy’, ‘M-ket’, ‘MEX’, ‘Kmax’, ‘Special M’, ‘MA’, ‘legal ketamine’, ‘Minx’, ‘Jipper’ and ‘Roflcoptr’.

Finally, the following ‘legal high’ product names have been associated with methoxetamine: ‘Kwasqik’, ‘Hypnotic’, ‘Panoramix’, ‘Magic’, ‘Lotus’, ‘Special K’ and ‘X’.

Figure 1. The numbered molecular structure, formula, weight and monoisotopic mass of methoxetamine. The molecular structure for ketamine is provided for comparison.

	
Methoxetamine	Ketamine

Molecular formula:	$C_{15}H_{21}NO_2$
Molecular weight:	247.33
Monoisotopic mass:	247.157

Chemical Abstract Service registry numbers (CAS RN)

1239943-76-0	free base
1239908-48-5	hydrochloride salt

The REACH registered substances database hosted by the European Chemicals Agency (ECHA) was searched using the CAS registry numbers listed above. The search returned no results.

Physical description

The hydrochloride salt of methoxetamine is a crystalline powder at room temperature. A physical description of the freebase form could not be found in readily accessible literature. An Internet search conducted by the EMCDDA reported that methoxetamine is offered for sale in free base and hydrochloride salt forms. The forms in which methoxetamine have been encountered in seizures and collected samples have not been specified by any country.

Information provided from seizures and collected samples have noted the presence of methoxetamine in powders, powder-filled capsules, tablets, liquids and plant material.

A more detailed description of methoxetamine seizures and collected samples that have been reported can be found in subsections 3.2.1 and 3.2.2 below.

3.2 Information on the frequency, circumstances and/or quantities in which a new psychoactive substance is encountered, and information on the means and methods of manufacture of the new psychoactive substance — Article 5.2(b) of the Decision

3.2.1 Information provided to Europol

Europol received replies from 15 Member States (Belgium, Bulgaria, Croatia, Cyprus, Denmark, Estonia, Finland, Hungary, Italy, Latvia, Lithuania, Luxembourg, Poland, Slovakia and Slovenia). Of these, seven countries had no data relating to methoxetamine (Bulgaria, Cyprus, Estonia, Italy, Latvia, Luxembourg, and Slovenia). The remaining eight countries (Belgium, Croatia, Finland, Germany, Hungary, Lithuania, Poland and Slovakia) reported the following information.

The level of production, distribution and trafficking

Belgium reported that methoxetamine had been seized on two occasions: once in 2012, when the substance came from China and was destined to Italy (510 grams labelled as ZEOLITE; and once in 2013, when methoxetamine came from China again and was destined for Spain, 93 grams labelled as ULTRAVIOLET.

Croatia provided information that methoxetamine appeared in three cases (2 grams in total).

Finland reported 35 seizures in powder form (323.8 g in total). They also noted that as the use of ketamine in Finland is at a very low level there is limited demand for substitutes like methoxetamine.

Germany reported 41 seizures that were made between December 2011 to July 2013. The seizures ranged from 0.06 grams to 39.10 grams. The information provided indicated that either methoxetamine was identified as a single product or as mixture with other substances: MDPV, AM-2201, 4-fluoramphetamine and 3-FMC. In 2013, methoxetamine was identified in mixtures with caffeine, taurine, methiopropamine and camfetamine. In some seizures methoxetamine was labelled with different names: “Xtreme White”, "methoxyphenylethylamino-ketocyclohexane" - "Warning: Research Use Only", "NOT FOR HUMAN CONSUMPTION", 2-Naphthoxyacetic Acid, "Sodium Formate", "N-Ethyl-Ketamin" and "Methoxydin".

Germany also reported details of an investigation that focused on online shop operators, which resulted in the seizure of more than 30 kg of new psychoactive substances with 39 different active agents identified. The methoxetamine that was identified among these active ingredients was labelled as methoxetamine and N-Ethyl-Ketamine. Moreover, as part of this investigation police seized two capsule filling machines, 2500 empty capsules, cannabis, cash and several new psychoactive substances. Further checks have revealed that suspects ordered several new psychoactive substances via the Internet from Switzerland. These include:

methoxetamine, MDPV, 2C-E, 2C-P, 2-DPMP, 2-FA, 3,4-DMMC, 4-AcO-DiPT, 4-HO-MIPT and 4-MEC.

Hungary reported that seizures of methoxetamine had been made in tablet and powder form since 2011. Significant seizures of methoxetamine tablets (1890 in total) were reported in 2011.

Lithuania recorded one seizure of 0.133 grams of methoxetamine in 2012.

Poland reported three seizures of methoxetamine all in the form of a white powder (0.25 grams to 1.07 grams).

Slovakia reported seven seizures as white or beige powder as well as capsules. The seizures ranged from 1.27 g to 643.91 g. The capsules have been reported in three seizures and had two different names: “Magic Hypnotic” (two of the seizures) and “PANORAMIX”.

No reports were received that indicated licit or illicit production of methoxetamine in any of these countries.

3.2.2 Information provided to the EMCDDA

Twenty-two Member States (Austria, Belgium, Bulgaria, Croatia, Cyprus, Denmark, Estonia, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, the Netherlands, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom) and Turkey and Norway, reported detections of methoxetamine ([4]).

Methoxetamine has been typically encountered in powder form. In most cases, it is reported as the only active substance present. In approximately 15 % of detections it was found in combination with other compounds, including phenethylamines (e.g. 4-fluoroamphetamine in 20 cases), other synthetic cathinones (e.g. 4-MEC and/or MDPV in about 20 cases; mephedrone and/or methylone in 9 cases; 3,4-DMMC in 6 cases; 4-FMC in 5 cases), synthetic cannabinoids (e.g. AM-2201, 4 cases; JWH-018, 2 cases), other substances (e.g. 6-APB in 4 cases; 2-DPMP, 4 cases; methiopropamine/MPA, 3 cases; 3-MeO-PCP, 3 cases), benzodiazepines, methylphenidate, tryptamines, etc. It has been also encountered with ketamine and internationally controlled substances such as amphetamine, methamphetamine, MDMA, cannabis, morphine and heroin. In some of the samples, caffeine was also present.

([4]) ‘Detections’ is an all-encompassing term and may include seizures and/or collected and/or biological samples. Seizure means a substance available (seized) through law enforcement activities (police, customs, border guards, etc.). Collected samples are those that are actively collected by drug monitoring systems (such as test purchases) for monitoring and research purposes. Biological samples are those from human body fluids (urine, blood, etc.) and/or specimens (tissues, hair, etc.)

The available information strongly suggests that methoxetamine is sold both as a 'legal' replacement for ketamine and on the illicit drug market as ketamine. In the latter case, users are unlikely to be aware of this.

Seizures

Twenty-two Member States (Austria, Belgium, Bulgaria, Croatia, Cyprus, Denmark, Estonia, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, the Netherlands, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom) and Turkey and Norway reported seizures of methoxetamine. Eight countries reported more than 40 seizures of methoxetamine: United Kingdom (640 seizures), Finland (252), Spain (76), Hungary (74), Norway (50), Poland (46), Germany (45) and France (43). In most of the countries, a large proportion of the seizures were small amounts of powder.

Methoxetamine has typically been seized as a powder. Quantities of powders seized ranged from 0.01 grams to 15.5 kilograms (Hungary). In 2011, Hungarian customs reported four single seizures above 5 kilograms each, amounting to a total of more than 40 kilograms, and Italy reported one seizure above 4 kilograms from June 2011. There are also over 50 reports of seizures of tablets (about 10 % of cases, up to 2800 units, Norway), twelve seizures of capsules containing powder (up to 173 units, Germany) and four seizures of liquids (up to 10 ml, United Kingdom). Methoxetamine was detected on injecting equipment in 13 occasions in Hungary (2011), and twice in Poland; in these cases, methoxetamine or traces of it were typically detected in combination with opioids or synthetic cathinones.

In the United Kingdom, aggregated data on methoxetamine seizures ([5]) indicate that over 14 kilograms of methoxetamine powder have been seized since 2011. Finland (customs, 242 seizures; police, 10 seizures) reported most of the seizures in powder form (from 0.01 to 248.7 grams), amounting to a total of 810 grams, since December 2010. Spain reported 76 seizures of powder amounting to a total of 1.4 kilograms. Hungary reported two thirds of the seizures in powder (amounting to a total of 41.8 kilograms) and one third of seizures of tablets (from 1 to 500 units). Of the tablets, 80% contained 3- or 4-fluoroamphetamine alone or in combination mostly with synthetic cathinones (pentedrone, 4-FMC, 4-MEC, MDPV, methylone), synthetic cannabinoids (AM-2201) or 6-APB. Norway reported 50 seizures, including 6 seizures of capsules containing powder (from 1 to 200 units) and 9 seizures of tablets (from 1 to 2800 units) since September 2011. Poland reported small seizures of powder (from 0.05 to 62.5 grams), three seizures of tablets (from 2 to 10 units), and 1 capsule containing powder (5 units). In two cases, traces of methoxetamine were found in a metal spoon in combination with other substances, including morphine, papaverine, codeine, and thebaine in one case, and morphine, heroin,

([5]) Many 'seizures' relate to individual case-level data, however, some data provided to the EMCDDA are aggregated at the country level. Some of the data from the United Kingdom are reported as 'records', where several records may have come from the same case. Data is drawn from the Joint report questionnaires and data provided in the bi-annual data gathering and from individual reporting forms submitted on an ad hoc basis.

acetylcodeine and 6-MAM in the other case. In Germany, a seizure of 173 capsules and a range of powders seized in small quantities (from 0.63 to 39.1 grams) were reported, including products seized from an online shop labeled as 'methoxetamine' and 'N-Ethyl-Ketamin'. In France, small quantities of powder were seized, including a single seizure of 500 grams of methoxetamine seized by customs at the Roissy airport (Paris).

Six countries reported between 5 and 20 seizures of methoxetamine: Netherlands (18), Sweden (17, with the biggest single seizures amounting to 289 grams of powder and 72 tablets), Italy (13, one of which was 4.36 kilograms), Austria and Denmark (9 small seizures of powder each), Slovakia (7, the two biggest ones consisting of 330 and 643 grams). A small number of seizures were reported in Bulgaria, Croatia, Cyprus, Estonia, Ireland, Latvia, Portugal and Slovenia. Belgium reported two seizures from customs at Bierset airport (Liége), one of which from China; Turkey reported one seizure in the form of light green plants, which also contained the synthetic cannabinoids JWH-122 and AM-2021.

Biological samples

Eight Member States reported biological detections of methoxetamine.

Four countries (Belgium, France, Italy and Sweden) reported a total of 54 analytically confirmed non-fatal intoxications (Belgium, 1 case; France, 3; Italy, 12; Sweden, 38). Not all of these were analytically confirmed.

Six Member States reported a total of 20 deaths: Austria (1 case), Finland (1), France (1), Poland (1), Sweden (1) and the United Kingdom (15).

Sweden reported 17 detections (5 in blood; 12 in urine) related to individuals suspected of committing a minor criminal offence. The United Kingdom reported one detection related to a case of suspected driving under the influence of drugs.

See section 3.4.1 and Annex 2 for further details of the non-fatal intoxications and deaths associated with methoxetamine.

Collected samples

In addition to the detections of methoxetamine in seizures and biological samples, eight Member States (Austria, Belgium, France, Hungary, Italy, the Netherlands, Slovakia, the United Kingdom) also reported collected samples of methoxetamine.

In Austria, between July 2012 and February 2013 the 'pill'-testing project run by 'ChEckiT!' detected methoxetamine in samples collected in Vienna. There were 4 tablets (containing between 19 to 73 mg of methoxetamine) and six samples of powder (with methoxetamine concentration ranging from 7 mg/g to 980 mg/g). The samples were sold at user level as methoxetamine (4 cases), ecstasy (4), MDMA (1)

and speed (1). In one of the samples, amphetamine (66 mg/g) and caffeine (179 mg/g) were also detected.

Belgium reported the analysis of one gram of powder related to the non-fatal intoxication described below which was found on the patient.

France reported 21 samples of powder collected from different venues by the SINTES surveillance system (16 samples collected between July 2011 and July 2013) and the Observatoire Français des Drogues et des Toxicomanies (OFDT) (5 samples collected in 2013) ([6]). In about half of the samples collected by SINTES the methoxetamine had been sold as ketamine. No quantitative information is available for any of the 21 samples.

Hungary reported a sample of powder collected for the purpose of analysis which was found to contain methoxetamine.

Italy reported three samples of powder ranging in weight from 0.63 grams to 5 grams (sample related to a non-fatal intoxication described in Section 3.4.1) and one sample of liquid ([7]). No other substances were detected in addition to methoxetamine.

In the Netherlands, the Drugs Information and Monitoring System (DIMS) detected methoxetamine tablets in two cases in 2011 ([7]) and powders in 21 cases in 2012 and in seven cases in 2013. In all the cases it was sold as either methoxetamine or ketamine.

Slovakia reported three 'legal high' products offered online as capsules or powder and branded 'Hypnotic', 'Panoramix' and 'Magic'.

The United Kingdom reported a sample of methoxetamine purchased from an Internet retailer (buyresearchchemical.co.uk) in September 2010. The product, labelled 'Methoxetamine', contained 250 mg of white powder which was found to be high purity methoxetamine. This sample formed the basis of the first notification of detection of methoxetamine in the European Union (see section 3.6).

Further details of these collected samples, including information on the product labels, are provided in Annex 1.

([6]) Subjective effects reported include: ketamine-like but more aggressive at the same dose; teeth pain when using sublingual route of administration; one convulsion followed by coma and hospitalisation for 96 hours and psychological effects including paranoia, panic attack, black out and depression.

([7]) Data reported in EMCDDA-Europol Reporting Forms and biannual EWS progress and final reports.

3.3 Information on the involvement of organised crime in the manufacture or trafficking of the new psychoactive substance — Article 5.2(c) of the Decision

Germany reported that there are no links to suggest the involvement of organised crime groups in the production, trafficking and/or distribution of methoxetamine. They also noted that it should be borne in mind that easy access to substances in and outside of the European Union (also in big amounts) via Internet shops indicates at least a certain level of organisation. In addition, the interest and presence of organised crime groups in the phenomenon of new psychoactive substances can be easily concluded from enormous attainable financial profits they can obtain from this type of criminal activities.

Money laundering aspects

No information was received on money laundering connected to the production and/or trafficking of methoxetamine.

Violence in connection with production, wholesale and distribution

No information was received on incidents of violence in connection with the production, wholesale and/or trafficking of methoxetamine.

3.4 A first indication of the risks associated with the new psychoactive substance, including the health and social risks, and of the characteristics of users — Article 5.2(d) of the Decision

3.4.1 First indication of health risks

A total of 110 non-fatal intoxications and 20 deaths associated with methoxetamine were reported by eight Member States (Austria, Belgium, Finland, France, Italy, Poland, Sweden and the United Kingdom). Not all of these cases have been analytically confirmed.

Non-fatal intoxications

Belgium

Belgium reported two non-fatal intoxications. The first case occurred in October 2011. The patient contacted the Belgian Poison Centre and complained about dizziness after taking methoxetamine. This case was not analytically confirmed. In the second case, from October 2013, the patient reported experiencing hallucinations and dissociation after taking an unspecified amount of powder sold as ‘Special K’ (a street name for ketamine). The presence of methoxetamine was analytically confirmed in a urine sample as well as in a sample of the powder that had been consumed by the patient. Reported symptoms were: mydriasis, black outs,

confusion, vertigo, insomnia, lowered consciousness, and cardiac and respiratory depression.

France

France reported three non-fatal intoxications. In one case the methoxetamine was quantified as 30 µg/L in plasma and 408 µg/L in urine; in another the methoxetamine was quantified as 136 ng/mL in plasma (cannabis and acetaminophen were also detected); while in a third case methoxetamine was detected in a sample of hair. No further details are available at this time ([8]).

Italy

Italy provided detailed reports for 14 non-fatal intoxications which occurred between March 2011 and July 2013 (1 case in 2011; 9 in 2012; and, 4 in 2013). Twelve of the cases were analytically confirmed. The first case, which was not analytically confirmed is described as an example. The patient reported having ordered ketamine via the Internet and then instead of the expected substance, a package of powder labelled as methoxetamine arrived. The patient dissolved the powder in water and injected the solution and then 'experienced panic, anxiety, hallucinations and feelings clearly different from those expected … with the use of ketamine', so then called the emergency service to be taken to hospital. In the other case without analytical confirmation, the patient reported being given methoxetamine powder by a friend which was taken nasally. The remaining cases were all confirmed analytically and further details are provided in Annex 2. The levels of methoxetamine are provided for three of the cases. Where information is provided on the substance taken, five of the patients reported having taken ketamine which was detected in just two of those cases. In two further cases, the patients reported having taken methoxetamine. Two patients reported taking an unknown powder. In six cases the patients had attended dance or rave parties.

All analyses conducted revealed the presence of methoxetamine with other substances in the following frequencies: alcohol (5 cases), cannabis (finding of THC) (5), amphetamines (4), MDMA (4), cocaine (3), ketamine (2), APB ([9]) isomers (2), levamisole (2), opiates (1), MDA ([10]) (1), methorphan (1), buprenorphine (1) and methadone (1).

Adverse observed effects included: agitation (7 cases), confusion (5), hallucinations (4), amnesia (3), dissociation (1), anxiety (1), disorientation (1), violence (1). Furthermore, physiological symptoms were reported: mydriasis (4 cases), mild

([8]) France also reported nine cases through the Centres d'Evaluation et d'information sur la Pharmacodépendance (CEIP) on the unique basis on patient's interview. These nine patients had requested medical support after using what they thought to be methoxetamine but its presence was not analytically confirmed, either in blood sample neither in a drug sample. In some cases the methoxetamine had been purchased from the Internet.

([9]) (Aminopropyl)benzofuran

([10]) 3,4-Methylenedioxyamphetamine

hypertension (4), tachycardia (4), unresponsive (2) stupor (2, one of which was catatonic at times), oxygen saturation of 90% (1) coma (1), chest pain (1), elevated creatine phosphokinase (CPK) (1) and tremors (1). Several of the case reports mentioned the absence of elevated temperature.

Sweden

Sweden reported 91 non-fatal intoxications between March 2011 and January 2013. Further information was provided for 38 cases that were analytically confirmed that were part of a larger case series of 71 cases of suspected methoxetamine intoxication (see Section 3.4.2 and Annex 2 for further details).

Methoxetamine was the only substance detected in 11 of these cases. In these cases, the following symptoms were noted: hypertension (4), tachycardia (4), hallucinations (3), nystagmus (3), CNS-depression (3), mydriasis (3), anxiety (3), muscular symptoms (2) and agitation/restlessness (1). The Poison Severity Scores (Persson et al., 1998) reported for these cases were PSS 1-mild (7 cases), PSS 2-moderate (2) and PSS 3-severe (2).The two cases of severe poisoning presented unconscious, one of them with respiratory depression. A mixed poisoning in the latter case, cannot be ruled out as a urine sample was not available. (Östberg et al, 2013).

Deaths

Austria

Austria reported one death that occurred in August 2012. The cause of death was reported as central circulatory failure due to methoxetamine overdose. No further details were provided.

Finland

Finland reported one death that occurred in August 2012. The case related to a drowning. Methoxetamine was detected in blood at a concentration of 5200 mg/mL. Other substances detected were olanzapine (0.24 mg/mL); citalopram (0.20 mg/mL) and clozapine (0.13 mg/mL).

France

France reported one death that occurred in February 2013. The deceased was found dead at home. The cause of death was reported as asphyxia. Methoxetamine was detected in blood at a concentration of 9.48 µg/mL. The drug was in a powder form and the route of administration was oral or nasal. The results of toxicological analysis for other substances detected only benzodiazepines that are believed to be from hospital treatment.

Poland

Poland reported one death that occurred in July 2012. The cause of death was reported as acute poisoning as a result of methoxetamine and amphetamine. The methoxetamine had been bought via the Internet. It was taken nasally. It was believed that '2-CB' (1 "stamp" saturated with 100-120 µg), amphetamine and 'hashish' had also been taken. Toxicological analyses revealed methoxetamine in blood (0.32 µg/mL) and urine (4.36 µg/mL). No methoxetamine was detected in the hair. Amphetamine was present in blood (0.06 µg/mL), urine (0.27 µg/mL) and hair (0.19 µg/g). The patient was taken to hospital in a very poor general condition. He was in a deep coma, with clinical and biochemical features of acute respiratory failure, hyperthermia (>39°C) and generalized seizures. Laboratory tests showed elevated leukocytosis, signs of massive rhabdomyolysis and acute renal and hepatic failure. Despite intensive therapy the patient died 28 days later as a result of multiple organ failure.

Sweden

Sweden reported one death which occurred in February 2012. Methoxetamine was detected in post-mortem femoral blood at a concentration of 8.6 µg/g. The synthetic cannabinoids AM-694, AM-2201, and JWH-018, cannabis and venlafaxine were also detected. The cause of death was suspected to be acute intoxication with methoxetamine although the presence of the three synthetic cannabinoids may have contributed to the death (Wikström et al., 2012).

United Kingdom

The United Kingdom reported a total of 15 deaths that occurred between 2011 (month not reported) and January 2013 (2 cases in 2011, 12 in 2012 and 1 in 2013). In one of the cases from 2011, the deceased was found decomposed at home and the cause of death was not provided. Additional substances that were detected post-mortem were fluoromethcathinone, MDMA, methylone, MDAI ([11]), 5-IAI ([12]), MDPV, and AMT ([13]). The causes of death were provided for eight cases as: acute intoxication (4 deaths), drowning (3), natural causes (1). In the cases of acute intoxication, methoxetamine was not the only substance detected. One case involved 6-APB ([14]), another methylthienylpropamine (MPA), in another case methadone, mirtazapine were implicated in the death and the final case of mixed drug toxicity also contained cocaine, ecstasy, amitriptyline and diazepam. In one of the cases of drowning and two of the acute intoxications the concentrations of methoxetamine were reported (see Annex 2). In the remaining six cases no cause of death was reported.

([11]) 5,6-Methylenedioxy-2-aminoindane
([12]) 5-Iodo-2-aminoindane
([13]) Alpha-methyltryptamine
([14]) 6-(2-Aminopropyl)benzofuran

Additional details of the deaths associated with methoxetamine are provided in Annex 2.

Pharmacology and mode of action

Roth et al., (2013) examined the neuropharmacological profile of methoxetamine *in vitro*. Information was not provided on the enantiomeric composition of the methoxetamine that was used. The data suggests that methoxetamine has a sub-micromolar affinity for the N-methyl-D-aspartate (NMDA) receptor that is comparable to or greater than ketamine. The specific NDMA receptor subtype was not distinguished. In addition methoxetamine appears to have a sub-micromolar affinity for SERT (the serotonin transporter) (Table 1). This is a property that methoxetamine shares with phencyclidine (PCP) but not ketamine (Roth et al., 2013). Metabolites of methoxetamine were not studied.

Data on the possible metabolites and metabolic pathways for methoxetamine have been reported by Meyer et al., (2012) and Menzies et al., (2013).

No studies were identified that have examined the pharmacology and mode of action of methoxetamine in humans.

Table 1. Representative pKi values for methoxetamine, ketamine and phencyclidine. Key: "—" indicate that compounds failed the Primary Screen criterion of >50% inhibition at 10 mM. Abbreviations: NMDA (N-methyl-D-aspartate receptor); SERT (serotonin transporter); NET (norepinephrine transporter). Adapted from Roth et al., (2013).

Compound	NMDA pKi ± SD (Ki, nM)	SERT pKi ± SD (Ki, nM)	NET pKi ± SD (Ki, nM)	$Sigma_1$ pKi ± SD (Ki, nM)	$Sigma_2$ pKi ± SD (Ki, nM)
Ketamine	6.18±0.07 (659)	—	—	—	—
Methoxetamine	6.59±0.06 (259)	6.32±0.05 (481)	—	—	—
Phencyclidine	7.23±0.07 (59)	5.65±0.05 (2234)	—	—	6.82±0.09 (136)

Toxicology

No studies were identified that have examined the toxicity of methoxetamine *in vitro*. No studies were identified that have examined the acute toxicity of methoxetamine in animals. One study was identified that examined the potential for chronic toxicity of methoxetamine on the renal system and bladder of mice (Wood et al., 2012d; Yew et al., 2012). The study was undertaken to examine the claim made by retailers that methoxetamine is a 'bladder friendly' alternative to ketamine. Chronic use of ketamine is associated with serious toxicity of the renal system and bladder (Advisory Council on the Misuse of Drugs, 2013; Li et al., 2013; Morgan et al., 2012). Two-month-old Institute of Cancer Research (ICR) mice were administered either 30

mg/kilograms of methoxetamine per day (n=5) or saline control (n=3) by intraperitoneal injection for three months. Hydropic degeneration in both the proximal and distal convoluted tubules of the kidney and inflammatory cell infiltration of the kidneys was seen in all the mice administered methoxetamine; glomerular atrophy was seen in three of these mice. Mononuclear cell infiltration in the submucosal layer and in the muscle layer of bladder was seen in all of the mice administered methoxetamine. None of the above histological changes were seen in mice administered the saline control. No studies were identified that have examined the toxicity of methoxetamine in humans.

The clinical features of acute toxicity associated with methoxetamine use as reported by the Member States are provided in section 3.4.1 'non-fatal intoxications' and Annex 2 ([15]). These include a number of analytically confirmed cases and in a subset of these methoxetamine was the only substance detected in the toxicology screen. Two case series from the United Kingdom were also identified in the literature which reports the details of a total of six analytically confirmed cases of acute intoxication associated with methoxetamine use (Shields et al., 2012; Wood et al., 2012b). The clinical features were similar to some of those reported by the Member States. These included ketamine-like dissociation and activation of the sympathetic nervous system. In addition, in three of the six cases the patients developed acute cerebellar toxicity (Shields et al., 2012). In these three cases, methoxetamine was the only substance detected in the toxicology screen.

Methods for the toxicological screening for methoxetamine have been reported by De Paoli et al., (2013).

Dependence and abuse potential

No studies were identified that have examined the dependence and abuse potential of methoxetamine *in vitro*, in animals or in humans.

Some self-reported experiences on user websites suggest compulsive re-dosing of methoxetamine as well as the unintentional consumption of more than was initially planned (e.g. Erowid, 2013a,b).

3.4.2 Characteristics of users

The section below includes a discussion of the characteristics of users which include self-reported use (including drug regimens and effects) from Internet drug discussion forums and related websites (hereafter 'user websites'). This includes a phenomenological study by Kjellgren & Jonsson (2013) that draws on self-reported experiences on user websites. As such it is important to note that it is not possible to confirm the specific substance(s) used, nor the purity, dose, etc. Analysis of products

([15]) The study by Hill et al., (2013) provides additional information on the clinical characteristics and patterns of enquiries related to acute toxicity associated with methoxetamine that were reported to the National Poisons Information Service in the United Kingdom. These cases were not necessarily analytically confirmed.

containing new psychoactive substances that are sold on the drug market have shown that the composition can differ between that claimed by the retailer, as well as differ over different geographical areas and time. In addition, the information provided by patients in case reports/series as well as that provided on user websites should be regarded as illustrative only and not taken as representative of users of methoxetamine in general. Finally, information from seizures and collected samples and user websites suggest that methoxetamine has been commonly sold as a 'legal' replacement for ketamine or sold as ketamine directly on the illicit drug market. In the latter case users may be unaware that they are using methoxetamine. Additional research is required in order to examine to what extent, if any, the characteristics of methoxetamine users overlap and/or reflect those who use ketamine.

Route of administration, dose and drug regimens

Information provided by the Member States, as well as from patients in case reports/series, and self-reports from user websites suggest the route of administration for methoxetamine include nasal insufflation ('sniffing' or 'snorting'), oral (swallowed either as a solid, such as through 'bombing', or dissolved into a solution), rectal, intramuscular injection, and intravenous injection (Erowid, 2013; Google, 2013a; Google, 2013b; Kjellgren & Jonsson, 2013; Östberg et al., 2013; Sein et al., 2012; Shields et al., 2012; Westwell et al., 2013; Wood et al., 2012b). In one case series of 71 patients, half of which were aged under 26 years old, that were hospitalised after suspected methoxetamine intake, and in which 38 patients the use of methoxetamine was analytically confirmed in urine and/or serum, the route of administration was reported as oral (38%), nasal (37%), intramuscular/intravenous injection (7%), sublingual (4%), rectal (1%), unknown (13%) (Östberg et al., 2013).

Kjellgren & Jonsson (2013) analysed 33 self-reported experiences of methoxetamine use from drug user sites where methoxetamine was the only substance (excluding tobacco) reported to be used (32 male; 1 female) found that the most common route of administration was nasal insufflation (64%), intramuscular injection (15%), sub-lingual (12%) and oral (9%). Methoxetamine has also been detected in samples recovered from injecting equipment on 13 occasions in Hungary during 2011 and two occasions in Poland during once in 2012 (the date in the second case was not specified). In these cases methoxetamine was typically detected in combination with opioids or synthetic cathinones.

An analysis of the 33 self-reported experiences of methoxetamine use from user websites, where methoxetamine was the only drug reported to be used at the time, found that the total amount of methoxetamine taken during the experiences ranged from 10 mg to 200 mg (n=29 reports; mean dose=88 mg). The amount taken by route of administration was not provided; Table 2 provides an indication of these (Kjellgren & Jonsson, 2013). Other information from user websites appear to be consistent with these doses although there is considerable variation therein depending on the length of the experience, route of administration, other drugs used, etc. (Erowid, 2013; Google 2013a; Google 2013b).

In respect of the doses reported by patients of non-fatal intoxications, Westwell et al., (2013) in their case report of a non-fatal intoxication from the United Kingdom reported that their patient initially insufflated 25 mg, a further 25 mg half an hour later, and 'pleased with the initial effects' approximately 950 mg. Wood et al., (2012b) in their case series of three non-fatal intoxications from the United Kingdom report that in one case the patient had snorted 0.5 g of methoxetamine, 0.75 g of "benzofury" and had drunk approximately 1.5 L of beer; while another patient had drunk approximately 200 mg of 'methoxetamine powder' which had been dissolved in water. Information was not provided in the third case.

Information from user websites and case report/series suggest that methoxetamine may be used on its own as well as in combination with other new psychoactive substances and/or controlled drugs (Erowid, 2013; Google 2013a; Google 2013b; Kjellgren & Jonsson, 2013; Shields et al., 2012; Wood et al., 2012b). In addition in some of the cases of non-fatal intoxications and deaths provided by the Member States other new psychoactive substances and/or controlled drugs were detected in biological samples.

Subjective effects

No clinical trials were identified that have examined the subjective effects of methoxetamine in humans; information is largely limited to that provided in case reports/series and self-reported experiences from user websites (Erowid, 2013; Google 2013a; Google 2013b; Kjellgren & Jonsson, 2013; Shields et al., 2012; Ward et al., 2011; Westwell et al., 2012). These include dissociative (including depersonalization), hallucinogenic and stimulant-type effects. In some cases the dissociative effects of methoxetamine are described as being ketamine-like although user reports suggest they may last for a longer period of time (up to 24 hours) (Erowid, 2013; Google 2013a; Google 2013b). Table 2 provides an indication of the dosages, subjective effects and duration of effects based on an unspecified number of user reports from a user website (Erowid). (Kjellgren & Jonsson, 2013).

Table 2. Comparison of dose, duration and effects between methoxetamine and ketamine based on user reports from Erowid. Details on the number of cases included were not provided. Adapted from Kjellgren & Jonsson (2013).

	Methoxetamine	**Ketamine**
Common dosage (recreational use)	20–60 mg insufflated 40–60 mg oral 15–30 mg intramuscular	30–75 mg insufflated 75–300 mg oral 25–50 mg intramuscular
Duration	150–240 min insufflated 180–300 min oral 120–180 h intramuscular	45–60 min insufflated 60–120 min oral 30–60 min intramuscular
Positive effects	euphoria sense of calm and serenity	euphoria sense of calm and serenity
Neutral effects	distortion or loss of sensory perception	distortion or loss of sensory perception

	Methoxetamine	Ketamine
Negative effects	severe dissociation, depersonalization, loss of consciousness, nausea, vomiting	severe dissociation, depersonalization, loss of consciousness, nausea, vomiting

Availability and supply

Internet monitoring of online shops selling new psychoactive substances to consumers (conducted by the EMCCDA) as well as information from user websites suggest that while methoxetamine is sold, bought and used as a drug in its own right it is marketed as a 'legal' and 'bladder friendly' alternative to ketamine. In some cases it is used as a substitute for ketamine (EMCDDA 2011; EMCDDA 2012; Kjellgren & Jonsson, 2013; Morris, 2011). Reflecting this, analysis of products sold as 'legal highs' and analytically confirmed as containing methoxetamine have in some cases been branded using the same street names used for ketamine such as 'Special K' (EMCDDA, 2002; Wood et al., 2012a). Information provided by the Member States from collected samples supports this finding; in some cases methoxetamine has been sold to users directly on the illicit drugs market as ketamine as well as mescaline, ecstasy, MDMA, and 'speed'.

The Internet monitoring exercise also identified 14 online shops offering methoxetamine in January 2011, 58 in July 2011, and 68 in January 2012. The price in 2011 for 10 g ranged from 145 to 195EUR (EMCDDA, 2011; EMCCDA, 2012). It is important to note that the online sale of methoxetamine may have changed substantially between the date of the last data collection on methoxetamine in January 2012 and the time of writing the Joint Report in December 2013. In part this may reflect responses of retailers to national control measures that have been put in place in some countries. A search of google.com using the search string "buy "methoxetamine" OR "mxe"" conducted in December 2013 for the Joint Report identified a number of online shops offering methoxetamine for sale in both retail and wholesale quantities (Google, 2013c).

Prevalence of use

Data from prevalence surveys

No prevalence surveys were identified that have examined the use of methoxetamine in the general population. Five targeted surveys were identified that have included questions on the use of methoxetamine. Four surveys examined use in the United Kingdom. One study examined use in the Netherlands; data from this study is not included here as the results are currently embargoed. Among other possible methodological limitations, targeted surveys tend to use non-probabilistic sampling. As such the findings cannot be generalised to other populations. In addition it is important to note that two of the surveys from the United Kingdom, reported by the 2012 Global Drug Survey and Wood et al., (2012c), and some of the fieldwork for the survey conducted by Measham et al., (2012), were undertaken before methoxetamine was subject to a temporary control measure on 5 April 2012 making

it unlawful to supply, possess with intent to supply, produce, and import or export methoxetamine except under licence. Possession for personal use was lawful at this time until methoxetamine was brought under permanent control in the United Kingdom on 26 February 2013 ([16]).

Wood et al., (2012c) surveyed a total of 315 individuals attending gay-friendly night clubs in South East London in July 2011 on their use of novel psychoactive substances, cocaine, MDMA/ecstasy. The majority were men 262 (82%), reflecting that the night clubs catered for the gay community, 45 (15%) were women and 3 (1%) trans-gender (data only available for 310 participants). The mean age of respondents was 29.7 years (range: 18–59 years). 206 out of 313 (65.8%) individuals reported having previously used a 'legal high'. Of these, 6.4% reported life-time use of methoxetamine; 1.9% reported use in the last month; 1.6% reported use on the night of the survey or planned to use it later that night.

The online 2012 Global Drug Survey conducted in November 2011 reported that out of 7700 respondents from the United Kingdom, 4.2% reported using methoxetamine in the last year (6% of clubbers and 3% of non-clubbers) and 2.4% reported using methoxetamine in the previous month (4% of clubbers and 1% of non-clubbers). For comparison, 24.5% and 9.3% reported using ketamine in the previous year and previous month respectively (Advisory Council on the Misuse of Drugs, 2012; Rogers, 2012).

A survey conducted in ten nightclubs on six fieldwork nights in March, April and June 2012 by Measham et al., (2012) reported that out of 343 respondents, 3% had ever used methoxetamine, with 3% reporting use in the last year, 2% in the past month and 1% in the past week. It is unclear from this survey whether all the respondents reporting methoxetamine use had done so during the period when the majority of fieldwork was conducted in March 2012 and hence before methoxetamine was subject to temporary control measures on 5 April 2012.

The online 2013 Global Drug Survey conducted towards the end of 2012 reported that the lifetime use of methoxetamine by clubbers in the United Kingdom was less than 3%. For comparison, 50.6% reported lifetime use ketamine (Mixmag, 2013). No further details on the sample size, etc., are available. The survey appears to have been conducted during the period that methoxetamine was subject to temporary control measures in the United Kingdom.

Information from a range of sources suggests that methoxetamine is being sold as a 'legal' replacement to ketamine and directly on the illicit drug market as ketamine. As such it may be relevant to consider the prevalence of ketamine use. Data from the 2012/2013 Crime Survey for England and Wales (United Kingdom) reported that 0.4% of adults aged 16 to 59 and 0.8% of young adults aged 16 to 24 reported use of ketamine in the last year (Home Office, 2013).

([16]) For further details see: https://www.gov.uk/government/publications/change-to-the-misuse-of-drugs-act-1971

Data from pooled urine samples

Archer et al., (2013) analysed samples of pooled urine collected from 12 portable urinals located in the City of Westminster, a borough in central London, United Kingdom. The borough had a variety of night-time economy venues including bars, late night cafes and nightclubs. The urinals were available for use by the general public over a 12 hour period between 18:00 and 06:00 on a Saturday night and Sunday morning in March 2012. The urinals were designed for men. Use of the urinals was anonymous. Methoxetamine and metabolites were detected in a sample taken from one urinal. For comparison, ketamine and metabolites were detected in a sample taken from six urinals.

3.5 Information on whether or not the new substance is currently under assessment, or has been under assessment, by the UN system — Article 5.2(e) of the Decision

The World Health Organization is the specialised United Nations agency designated for the evaluation of the medical, scientific and public health aspects of psychoactive substances under the Single Convention on Narcotic Drugs, 1961 and the Convention on Psychotropic Substances, 1971. On 10 October 2013, the World Health Organization informed the EMCDDA that methoxetamine is currently under assessment and *'the critical review report will be published only early next year (probably April)'*.

Article 7.1 of Council Decision states that '*no risk assessment shall be carried out in the absence of a Europol/EMCDDA Joint Report. Nor shall a risk assessment be carried out where the new psychoactive substance concerned is at an advanced stage of assessment within the United Nations system, namely once the WHO expert committee on drug dependence has published its critical review together with a written recommendation, except where there is significant new information that is relevant in the framework of this Decision*'.

This Joint Report has been produced on the understanding that methoxetamine is not at an advanced stage of assessment within the United Nations system.

3.6 The date of notification on the Reporting Form of the new psychoactive substance to the EMCDDA or to Europol — Article 5.2(f) of the Decision

The first official EMCDDA–Europol notification of methoxetamine dates from November 2010 from the United Kingdom National Focal Point. The Reporting Form details a collected sample purchased from the internet ([17]) on 30 September 2010. The collected sample comprised a packet labelled 'Methoxetamine' containing 250 milligrams of white powder. The report notes that it 'appeared to be of high purity'.

([17]) Purchased from http://www.buyresearchchemical.co.uk

The identification was based on the analytical techniques of GC-MS ([18]) and NMR ([19]).

Methoxetamine was added to the list of new psychoactive substances monitored by the EMCDDA and Europol through the European Union Early Warning System and a profile of the substance was created in the EMCDDA European Database on New Drugs (EDND). Analytical details and background information have been exchanged on various occasions between EMCDDA, Europol and the Member States. The European Commission and the EMA were kept duly informed.

3.7 Information on whether or not the new psychoactive substance is already subject to control measures at national level in a Member State — Article 5.2(g) of the Decision

Eight Member States (Cyprus, Denmark, France, Germany, Italy, Slovenia, Sweden, and the United Kingdom) and Turkey reported that methoxetamine is subject to control under drug control legislation.

In Cyprus, methoxetamine was listed as covered by Cypriot drug control law by name in 2012. In Denmark methoxetamine is covered by the Executive Order on Euphoriant Substances. In France methoxetamine is added on the controlled narcotic substance list by the ordinance of 5 August 2013. In Germany methoxetamine is included in the list covered by the Narcotic Substance Law since 17 July 2013. In Italy methoxetamine is addressed by Ministerial Decree of 24 October 2012. In Slovenia methoxetamine was included by the Decree amending the Decree on classification of illicit drugs, Official Gazette of RS No. 62/2013. In Sweden methoxetamine comes under the Narcotic drugs control Act (SFS 1992-860) and the Narcotic drugs control Ordinance (SFS 1994:1554). In the United Kingdom methoxetamine is controlled under the Misuse of Drugs Act 1971. In Turkey methoxetamine is listed in the Law on Control of Narcotics no. 2313.

Six Member States (Austria, Hungary, Poland, Portugal, Romania and Slovakia) reported that methoxetamine is controlled under legislation prohibiting the unauthorised supply of defined or qualifying new psychoactive substances. In Austria methoxetamine is listed as controlled by the New Psychoactive Substances Act. In Hungary methoxetamine is listed in Schedule C of Government Decree 66/2012. In Poland, methoxetamine falls under the definition of a “substitution drug” under the Act amending the Act on counteracting drug addiction and the Act on State Sanitary Inspection, 2010 and as such its marketing and production is penalized with a fine (administrative sanctions). In Portugal, methoxetamine is listed as controlled under Decree-Law 54/2013. In Romania the Law 194/2011 subjects to control any psychoactive substance that qualifies by conforming to certain criteria (all substances with psychoactive potential are subject to control until proven harmless by a special designated commission). In Slovakia, methoxetamine is in the List of risk substances

([18]) Gas chromatography-mass spectrometry
([19]) Nuclear magnetic resonance spectroscopy

published in a Ministry of Health Regulation No 298/2013 Coll., which came into force on 1 October 2013.

Two Member States (Finland and the Netherlands) and Norway reported that methoxetamine is subject to control measures under medicines legislation. In Finland methoxetamine has been controlled under the Medicines Act (395/87) since 9 December 2011. In the Netherlands, the sale of methoxetamine in consumer amounts it is treated as being a medicinal product and must comply with medicines legislation (and general product safety legislation). In Norway, methoxetamine is regulated by the Medicines Act and a prescription would be required to receive it.

Eleven Member States (Belgium, Bulgaria, Croatia, Czech Republic, Estonia, Greece, Ireland, Lithuania, Luxembourg, Latvia and Malta) reported that methoxetamine is not subject to control measures.

No information was provided regarding the control status of methoxetamine in Spain.

3.8 Further information — Article 5.2(h) of the Decision

3.8.1 The chemical precursors that are known to have been used for the manufacture of the substance

No information was reported about the chemical precursors or manufacturing methods used to make methoxetamine.

Methods for the production of methoxetamine are documented in the scientific literature.

3.8.2 The mode and scope of the established or expected use of the new substance

Methoxetamine has been marketed and sold through online shops as a legal and 'bladder friendly' alternative to ketamine (Beaumont-Thomas, 2012; EMCDDA, 2011; Miller, 2012; Morris, 2011; Google, 2013a,b) both as branded 'legal highs' (Wood et al., 2012) as well as a 'research chemical'. It is important to note in this respect that information from the Member States (such as seizures, collected samples, non-fatal intoxications) and user websites suggest that methoxetamine may be commonly sold as a 'legal' replacement for ketamine or sold as ketamine directly on the illicit drug market (20). As a result, the mode and scope of use of methoxetamine may, in part, overlap and/or reflect the mode and scope of use of ketamine. Additional research is required in order to examine to what extent, if any, the mode and scope of methoxetamine use overlap and/or reflect those of ketamine.

Settings of use

([20]) Along with ketamine, methoxetamine has also been sold as controlled substances such as MDMA and amphetamine.

The online 2012 Global Drug Survey that was conducted in November 2011 reported that out of 7700 respondents from the United Kingdom, 4.2% reported using methoxetamine in the last year (6% of clubbers and 3% of non-clubbers) and 2.4% reported using methoxetamine in the previous month (4% of clubbers and 1% of non-clubbers). Wood et al., (2012c) in their study of use of novel psychoactive substances by patrons of gay friendly night clubs in South London reported that 1.6% of individuals reported use of methoxetamine on the night of the survey or planned to use it later that night. Six of the non-fatal intoxications reported by Italy noted that use of methoxetamine was in the context of dance or rave parties. Details from case series in the literature also suggest use in the night-time environment (Wood et al., 2012c) as well as in the home environment (Westwell et al., 2012; Wood et al., 2012c).

Price

Internet monitoring of the surface web conducted by the EMCDDA identified 14 online shops offering methoxetamine in January 2011, 58 in July 2011, and 68 in January 2012. The price in 2011 for 10 g ranged from 145 to 195EUR (EMCDDA, 2011; EMCCDA, 2012). It is important to note that the online sale of methoxetamine may have changed substantially between January 2012 and the time of writing the Joint Report in December 2013. In part this may reflect responses of retailers to national control measures that have been put in place in some countries. A search of google.com using the search string “buy "methoxetamine" OR “mxe"" conducted in December 2013 for the Joint Report identified a number of online shops offering methoxetamine for sale in both retail and wholesale quantities (Google, 2013c).

3.8.3 Other use of the new psychoactive substance and the extent of such use, the risks associated with this use of the new psychoactive substance, including the health and social risks

No information was provided by the Member States, Norway or Turkey that indicated that methoxetamine had any other use apart from in legitimate scientific research and as an analytical reference standard.

From the available information it does not appear that methoxetamine is used in the manufacture of a medicinal product in the European Union. However, the collection of information cannot be considered exhaustive in the absence of an European Union database on the synthetic routes of all medicinal products ([21]).

([21]) i.e. products that have been granted a marketing authorisation, or where an application for a marketing authorisation has been made, or where the marketing authorisation has been suspended.

4. Information from the EMA as requested by Article 5.3 of the Decision

4.1 Marketing authorisation

Twenty-four Member States, Norway and Iceland responded to the EMA's information request (see section 2) reported that the new psychoactive substance methoxetamine has not obtained a marketing authorisation ([22]).The EMA also reported that the new psychoactive substance methoxetamine has not obtained a marketing authorisation through the central authorisation procedure.

4.2 Application for a marketing authorisation

Twenty-four Member States, Norway and Iceland responded to the EMA's information request (see section 2) reported that the new psychoactive substance methoxetamine is not the subject of an application for a marketing authorisation ([22]). The EMA also reported that the new psychoactive substance methoxetamine is not the subject of an application for a marketing authorisation through the central authorisation procedure.

4.3 Suspended marketing authorisation

Twenty-four Member States, Norway and Iceland responded to the EMA's information request (see section 2) reported that there had been no cases of a suspended marketing authorisation that had been granted in respect of the new psychoactive substance methoxetamine ([22]). The EMA also reported that the new psychoactive substance methoxetamine is not the subject of a suspended marketing authorisation through the central authorisation procedure.

5. Conclusion

Methoxetamine is an arylcyclohexamine, closely related in many respects to ketamine. It has been available on the European Union drug market since at least September 2010 and has been detected in 22 Member States, Turkey and Norway. Multi-kilogram quantities of the substance in powder form have been seized. One hundred and ten non-fatal intoxications and 20 deaths associated with the substance have been reported. As methoxetamine is marketed as a legal and 'bladder-friendly' alternative to ketamine and at the same time being sold directly on the illicit drug market as ketamine, a key concern is that these may play a role in the further spread of the substance. We conclude that the health and social risks caused by the manufacture, trafficking and use of methoxetamine, as well as the involvement of

([22]) Austria, Belgium, Croatia, Czech Republic, Denmark, Estonia, Germany, Greece, Hungary, Iceland, Ireland, Netherlands, Norway, Portugal, Slovenia, Spain, Sweden and the United Kingdom provided responses in relation to both human and veterinary medicinal products. Cyprus, Italy, Lithuania, Malta and Slovakia provided responses in relation to human medicinal products. France, Latvia and Poland provided responses in relation to veterinary medicinal products. In addition the EMA provided information in relation to both human and veterinary medicinal products in respect to the central authorisation procedure.

organised crime and possible consequences of control measures, could be thoroughly assessed through a risk assessment procedure in accordance with Article 6 of Council Decision 2005/387/JHA.

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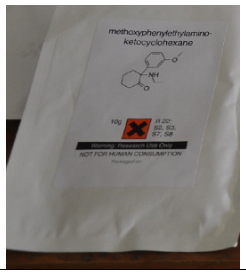
European Monitoring Centre for Drugs and Drug Addiction

EUROPOL

Annex 1

EMCDDA–Europol Joint Report on a new psychoactive substance: Methoxetamine

Images of Methoxetamine from seizures and collected samples

Country	Image	Description
Croatia		**Seizure, February 2012** 4 green tablets. Seizing authority: police
Hungary		**Seizure, April 2011** 2 white tablets, seized in Pest county. Contents: Methoxetamine, 4-FMC and MDPV Seizing authority: police
Italy		**Seizure, 2011** 6,713g of white powder contained in 1 polyethylene bag, seized in Como province. Seizing authority: police

Annex 2 — Deaths and non-fatal intoxications associated with methoxetamine

Deaths

	Country	Date of death (gender, age)	Biological sample	Methoxetamine result	Results for other substances	Notes
1	**Austria**	Aug 2012	Not reported	+	None reported	Cause of death reported as central circulatory failure due to methoxetamine overdose
2	**Finland**	Aug 2012	Blood	5200 mg/mL	Olanzapine (0.24 mg/L) Citalopram (0.20 mg/L) Clozapine (0.13 mg/L)	Death by drowning. Medico-legal status not determined
3	**France**	Feb 2013 (M, 38)	Blood	9.48 µg/mL	Benzodiazepines (from hospital treatment)	Found dead at home. Cause of death reported as asphyxia
4	**Poland**	Jul 2012 (M, 31)	Blood Urine Hair	0.32 µg/mL 4.36 µg/mL Negative	Amphetamine (0.06 µg/ml in blood, 0.27 µg/ml in urine and 0.19 µg/g in hair)	Cause of death reported as acute poisoning as a result of methoxetamine and amphetamine.
5	**Sweden**	Feb 2012	Femoral blood	8.6 µg/g	AM-694 (+) AM-2201 (+) JWH-018 (+) cannabis (+) venlafaxine (+)	The cause of death reported as suspected acute intoxication with methoxetamine although the presence of the three synthetic cannabinoids may have contributed to the death.
6	**United Kingdom**	Aug 2011 (M, 29)	Blood	+	Methadone (645µg/L EDDP in blood, also present in urine) and mirtazepine (69 µg/L in blood, also present in urine)	Cause of death was reported as drug overdose

	Country	Date of death (gender, age)	Biological sample	Methoxetamine result	Results for other substances	Notes
7	**United Kingdom**	2011 (month not specified)	Blood	+	Fluoromethcathinone (+) MDMA (+) Methylone (+) MDAI (+) MDPV (+) 5-IAI (+) AMT (+)	Deceased was found decomposed at home
8	**United Kingdom**	Jan 2012 (M, 25)	Blood, urine & vitreous humour	+	Alcohol (80 mg/100 ml in blood, 146 mg/100 mL in urine, 155 mg/100 mL in vitreous humour) and dihydrocodeine (+)	Cause of death was reported as drowning, with methoxetamine ingestion noted as a contributory factor.
9	**United Kingdom**	Jan 2012 (M, 17)	Blood, urine & vitreous humour	+	Alcohol (80 mg/100 ml in blood, 146 mg/100 mL in urine, 109 mg/100 mL in vitreous humour)	Cause of death was reported as drowning, with methoxetamine ingestion noted as a contributory factor.
10	**United Kingdom**	Jan 2012 (M, 43)	Blood	0.89 mg/L (unpreserved) 1.1 mg/L (preserved)	Methiopropamine (2.8 mg/L in unpreserved blood)	Case of death was reported as methoxetamine and methypropamine toxicity [sic]
11	**United Kingdom**	Mar 2012 (M, 20)	Not reported	0.22 mg/L	None reported	Cause of death was reported as drowning
12	**United Kingdom**	Sep 2012 (F, 27)	Blood	+	6-APB (2460 ng/mL)	Case of death was reported as ingestion of 6-APB (benzofury) and methoxetamine

	Country	Date of death (gender, age)	Biological sample	Methoxetamine result	Results for other substances	Notes
13	**United Kingdom**	Sep 2012 (M, 41)	Blood & urine	+ (in urine)	Methiopropamine (1.74 mg/L in blood and present in urine), MDA (0.18 mg/L in blood and present in urine) and Alcohol (7 mg/100 ml in blood and 16 mg/100ml in urine)	Cause of death was reported as natural causes (ischaemic heart disease and coronary artery atheroma)
14-19	**United Kingdom**	2012 (months unspecified)	Not reported	+	None reported	6 deaths
20	**United Kingdom**	Jan 2013 (M, 27)	Blood, urine, gastric and nasal swabs	0.03 mg/L in blood, present in gastric and nasal swab samples	Amitriptyline (0.13 mg/L in blood and present in gastric sample) Cocaine (0.44 mg/L in blood and present on nasal swabs) Diazepam (4.27 mg/l in blood, 9 mg in gastric sample) and metabolites MDMA (0.20 mg/L in blood, 3 mg in gastric sample and present on nasal swabs) MDA (present in blood)	Case of death was reported as mixed drug toxicity

Non-fatal intoxications

Country	Date of death (gender, age)	Biological sample	Methoxetamine results	Results for other substances	Notes
Belgium	Oct 2013	Urine	+	Not detected	Powder (confirmed to contain methoxetamine) marketed as 'Special K'. Most prominent symptoms: euphoria, hallucinations and dissociation. Supportive and symptomatic treatment.
France	Dec 2011	Blood and urine	30µg/L (plasma) 408µg/L (urine)	Negative	No further details reported.
France	Jun 2012	Hair	+	Not reported	No further details reported.
France	2012	Blood	136ng/mL	Cannabis (+) Paracetamol (+)	No further details reported.
Italy	Feb 2012 (M, 27)	Blood and urine	0.0002 mg/mL (serum) 0.167 mg/mL (urine)	Methorphan (present in urine)	Powder, nasally insufflated. At admission to hospital the patient was tachycardic (HR 120 bpm), confused, hallucinated and severely agitated. Treatment: IV diazepam; the day after admission, a treatment with midazolam 15 mg/day, delorazepam 7 mg/day and valproic acid 400 mg/day was started: subsequently, the delorazepam dosage was increased up to 20 mg/day and haloperidol was added.
Italy	Jun 2012 (M, 38)	Blood and urine	167 ng/mL (blood) 7400 ng/mL (urine)	APB-isomers (164 ng/mL) Amphetamines (+) MDMA (traces)	A man coming from a rave was admitted to the emergency room accompanied by the police in a serious state of agitation and violent behavior. At admission the patient was mydriatic, stuporous (sometimes catatonic), normothermic (T 36°C), hypertensive (150/90 mmHg) and normo-frequent (78 bpm). The blood alcohol content, performed on site, was found to be 2.3 g/L. The patient was treated with fluids and has left against medical advice after about 8 hours of observation.

Country	Date of death (gender, age)	Biological sample	Methoxetamine results	Results for other substances	Notes
Italy	Jul 2012 (M, 17)	Blood and urine	198 ng/mL (blood) 9000 ng/ml (urine)	Amphetamine (1000 ng/mL) MDMA (500 ng/mL) THC (141 ng/mL) Ketamine/norketamine (+) MDA (+)	Severe psychomotor agitation status associated with hallucinations. Acute intoxication.
Italy	Oct 2012 (M, 24)	Urine	+	Alcohol (2.7 g/L) Methadone (+) Cocaine (+) Amphetamines (+) MDMA (+). APB-isomers (+) Levamisole (+)	Severe agitation associated with stupor, mydriasis, slight rise in blood pressure (130/80 mmHg) and significant tachycardia (150 bpm) without hyperthermia. The patient left the hospital voluntarily after 8 hours of observation.
Italy	Oct 2012 (M, 23)	Urine	+	THC Cocaine (+) Opiates (+) Levamisole (+)	Intoxication after the consumption of '3 red cylinders' and alcohol. The patient was rescued in confused state. At admission to the emergency room the patient was slowed, sometimes somnolent, normothermic, normotensive and normo-frequent, without abnormal rhythms of the ECG.
Italy	Nov 2012 (M, 23)	Urine	+	Alcohol (2.2 g/L in blood) THC (+) Ketamine and norketamine (+)	At admission to the emergency room the patient was in coma, with normal vital parameters except for peripheral oxygen saturation (Sat O2 90%).
Italy	Nov 2012 (M, 22)	Urine	+	THC (+) Ketamine and norketamine (+)	At admission to the emergency room the patient presented mydriasis and severe psychomotor agitation associated with hallucinations/dissociative state.
Italy	Nov 2012 (F, 16)	Urine	+	THC (+)	At admission to the emergency room the patient was confused, agitated and sometimes amnesic for the events that happened during the night.

Country	Date of death (gender, age)	Biological sample	Methoxetamine results	Results for other substances	Notes
Italy	Nov 2012 (F, 17)	Urine	+	THC (+) Ketamine and norketamine (+)	At admission to the emergency room the patient appeared miotic, confused, disoriented, agitated and sometimes amnesic for the events that happened during the night.
Italy	Jan 2013 (F, 22)	Urine	+	Cocaine (+) Opiates (+) Buprenorphine (+) Levamisole (+)	At admission to the emergency room, the patient was unresponsive, with response to painful stimuli, with open eyes and pupils of medium size reactive to light, with no signs of venipuncture, normothermic, BP of 140/100 mmHg, mild tachycardia (100 bpm) with no other alterations of the rhythm.
Italy	Jan 2013 (M, 23)	Urine	+	Amphetamine (+) Cocaine (+) MDMA (+) Levamisole (+)	At admission to the emergency department, the patient was unresponsive, with eyes open and pupils of medium size and reactive to light, vertical nystagmus, somnolent, normothermic, with normal blood pressure, heart rate of 98 bpm with no other abnormal rhythms. There was alcohol halitosis. The patient was treated with naloxone, leading to slight clinical improvement. Blood tests showed slightly elevated CPK (390 IU/L).
Italy	Feb 2013 (F, 22)	Urine	+	Negative	Sniffing At admission to the emergency department the patient was awake, lucid, and referred chest pain, diffuse pain sensation and tremors.
Sweden	Mar 2011 – Oct 2012	Blood and Urine	+	None	11 cases. Symptoms were hypertension (36%), tachycardia (36%), hallucinations (27%), nystagmus (27%), CNS-depression (27%), mydriasis (27%), anxiety (18%), muscular symptoms (18%), agitation/restlessness (9%) Poisoning severity scores were mild (7 cases), moderate (2) and severe (2). See Östberg et al., (2011) for further details.

Country	Date of death (gender, age)	Biological sample	Methoxetamine results	Results for other substances	Notes
Sweden	Mar 2011 – Oct 2012	Blood and Urine	+	5-IT ([23]) (+) Amphetamine (+) Benzodiazepines (+) Buprenorphine (+) Ethanol (+) MDPV (+) Morphine (+) 4-OHMET ([24]) (+) Cannabis/THC (+) Tramadol (+)	27 cases. Symptoms were hypertension (48%), CNS-depression (44%), tachycardia (44%), agitation/restlessness (33%), mydriasis (30%), nystagmus (26%), hallucinations (22%), anxiety (19%) and muscular symptoms (11%) Poisoning severity scores were mild (11 cases), moderate (10), severe (3) and unknown (3). The results for other substances detected were not provided for each case. See Östberg et al., (2011) for further details.

([23]) 5-(2-Aminopropyl)indole
([24]) 4-Hydroxy-methylethyltryptamine