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Subject:	Risk Assessment Report on the new psychoactive substance methoxetamine (2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone)

Following the Council's request to conduct a Risk Assessment on methoxetamine (2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone), the EMCDDA hereby presents the above-mentioned Risk Assessment Report drawn up by its Scientific Committee pursuant to Article 6 of Council Decision 2005/387/JHA on information exchange, risk assessment and control of new psychoactive substances.



European Monitoring Centre
for Drugs and Drug Addiction

**Risk Assessment Report
of a new psychoactive substance:**

2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone (methoxetamine)

In accordance with Article 6 of Council Decision 2005/387/JHA on information exchange,
risk assessment and control of new psychoactive substances

1. Introduction

This *Risk Assessment Report* presents the summary findings and the conclusions of the risk assessment carried out by the extended Scientific Committee of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) on the new psychoactive substance 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone (*methoxetamine*). The report has been prepared and drafted in accordance with the conceptual framework and the procedure set out in the *Risk assessment of new psychoactive substances: Operating guidelines* ⁽¹⁾. It is written as a stand-alone document which presents a summary of the information considered during the detailed analysis of the scientific and law enforcement data available at this time. The conclusion section of the report summarises the main issues addressed and reflects the opinions held by the members of the Scientific Committee. A list of the information resources considered by the Scientific Committee, including a detailed *Technical Report* on methoxetamine, is provided below.

The risk assessment has been undertaken in compliance with Article 6 of Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk assessment and control of new psychoactive substances ⁽²⁾ (the 'Council Decision'). The Council Decision establishes a mechanism for the rapid exchange of information on new psychoactive substances (hereafter 'Early Warning System' ⁽³⁾) that may pose public-health and social threats, including the involvement of organised crime. Thus, it allows the institutions of the European Union and the Member States to act on all new narcotic and psychotropic substances ⁽⁴⁾ that appear on the European Union drug market. The Council Decision also provides for an assessment of the risks associated with these new psychoactive substances so that, if necessary, control measures can be applied in the Member States for narcotic and psychotropic substances ⁽⁵⁾.

⁽¹⁾ EMCDDA, (2010), *Risk assessment of new psychoactive substances: Operating guidelines*, Publications Office of the European Union, Luxembourg. Available at: <http://www.emcdda.europa.eu/html.cfm/index100978EN.html>

⁽²⁾ OJ L 127, 20.5.2005, p. 32.

⁽³⁾ The information exchange mechanism laid down by the Council Decision is operationalized as the *European Union Early Warning System on New psychoactive Substances ('Early Warning System')*. It is operated by the EMCDDA and Europol in partnership with the Retiox National Focal Points in the Member States, the European Commission and the European Medicines Agency.

⁽⁴⁾ According to the Council Decision, a 'new psychoactive substance' is defined as 'a new narcotic drug or a new psychotropic drug in pure form or in a preparation; 'new narcotic drug' means a substance in pure form or in a preparation that has not been scheduled under the 1961 United Nations Single Convention on Narcotic Drugs, and that may pose a threat to public health comparable to the substances listed in Schedule I, II or IV; 'new psychotropic drug' means a substance in pure form or in a preparation that has not been scheduled under the 1971 United Nations Convention on Psychotropic Substances, and that may pose a threat to public health comparable to the substances listed in Schedule I, II, III or IV'.

⁽⁵⁾ In compliance with the provisions of the 1961 United Nations Single Convention on Narcotic Drugs and the 1971 United Nations Convention on Psychotropic Substances.

Methoxetamine was first identified in a sample purchased from an Internet retailer in September 2010 and formally notified to Early Warning System in November 2010 by the United Kingdom. Following an assessment of the available information on methoxetamine, and in accordance with Article 5 of the Council Decision, on 16 December 2013, the EMCDDA and Europol submitted to the Council of the European Union, the European Commission and the European Medicines Agency (EMA) a *Joint Report* on methoxetamine ⁽⁶⁾. Taking into account the conclusion of the *Joint Report* and in accordance with Article 6 of the Council Decision, on 29 January 2014, the Council formally requested that ‘the risk assessment should be carried out by the extended Scientific Committee of the EMCDDA and be submitted to the Commission and the Council within twelve weeks from the date of this notification’.

In accordance with Article 6.2, the meeting to assess the risks of methoxetamine was convened under the auspices of the Scientific Committee of the EMCDDA with the participation of five additional experts designated by the Director of the EMCDDA, acting on the advice of the Chairperson of the Scientific Committee, chosen from a panel proposed by Member States and approved by the Management Board of the EMCDDA. The additional experts were from scientific fields that were either not represented, or not sufficiently represented on the Scientific Committee, and whose contribution was necessary for a balanced and adequate assessment of the possible risks of methoxetamine, including health and social risks. Furthermore, two experts from the Commission, one expert from Europol and one expert from the EMA participated in the risk assessment. The meeting took place on 1 and 2 April 2014 at the EMCDDA in Lisbon. The risk assessment was carried out on the basis of information provided to the Scientific Committee by the Member States, the EMCDDA, Europol and the EMA. A list of the extended Scientific Committee, as well as the other participants attending the risk assessment meeting is annexed to this report (Annex 1).

The extended Scientific Committee considered the following information resources for the risk assessment:

- (i) *Technical Report on 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone (methoxetamine)* (Annex 2);
- (ii) *EMCDDA–Europol Joint Report on a new psychoactive substance: methoxetamine (2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone)*;
- (iii) Scientific articles, official reports, grey literature, Internet drug discussion forums and related websites (hereafter, ‘user websites’);
- (iv) Data from EMCDDA Internet monitoring of suppliers (that typically appear to be

⁽⁶⁾ EMCDDA and Europol (2014), EMCDDA–Europol Joint Report on a new psychoactive substance: methoxetamine (2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone), EMCDDA, Lisbon. Available at: <http://www.emcdda.europa.eu/publications/joint-report/methoxetamine>

manufacturers and/or wholesalers) and retailers selling methoxetamine;

(v) *Risk assessment of new psychoactive substances: Operating guidelines*; and,

(vi) *Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk assessment and control of new psychoactive substances.*

Finally, it is important to note that this *Risk Assessment Report* contains a discussion of the available information on non-fatal intoxications and deaths associated with methoxetamine. Such information is critical to the identification of emerging toxicological problems associated with new psychoactive substances within the European Union. In this context, it is important to recognise that the capacity to detect, identify and report these events differs both within and between the Member States. In the past few years, programmes have been introduced in some Member States to strengthen these capacities. As a result, more information is available; however, it is likely that serious adverse events remain under-detected.

2. Physical, chemical and pharmacological description of methoxetamine and its mechanism of action, including its medical value

Methoxetamine is an arylcyclohexylamine substance (Figure 1). The systematic (International Union of Pure and Applied Chemistry, IUPAC) name for methoxetamine is (*RS*)-2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone. Methoxetamine contains one asymmetric carbon atom and thus is a chiral molecule (Figure 1). There are no details available on the enantiomeric form detected⁽⁷⁾. It is structurally similar to ketamine⁽⁸⁾ and the internationally control substance phencyclidine⁽⁹⁾. There are a number of other arylcyclohexylamine substances that have been notified to the Early Warning System, including: 2-methoxyketamine, *N*-ethylorketamine, 3-MeO-PCE and 4-MeO-PCP⁽¹⁰⁾.

The name 'methoxetamine' was reported to have been coined as a contraction of methoxyketamine. The Chemical Abstract Service (CAS) Registry Numbers for methoxetamine are 1239943-76-0 (base) and 1239908-48-5 (hydrochloride salt).

Figure 1. The molecular structure, formula and weight of methoxetamine (the asterisk

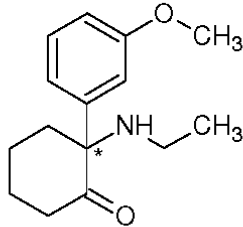
⁽⁷⁾ 'Detections' is an all-encompassing term and may include seizures and/or collected and/or biological samples. Seizure means a substance available (seized) through law enforcement activities (police, customs, border guards, etc.). Collected samples are those that are actively collected by drug monitoring 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.).

⁽⁸⁾ Report on the risk assessment of ketamine (2-(2-chlorophenyl)-2-(methylaminocyclohexanone) in the framework of the joint action on new synthetic drugs EMCDDA, Lisbon, June 2002.

⁽⁹⁾ Phencyclidine is also known as PCP and chemically as 1-(1-phenylcyclohexyl)piperidine.

⁽¹⁰⁾ 2-methoxyketamine is 2-(2-methoxyphenyl)-2-(methylamino)cyclohexanone, *N*-ethylorketamine is 2-(2-chlorophenyl)-2-(ethylamino)cyclohexanone, 3-MeO-PCE is *N*-Ethyl-1-(3-methoxyphenyl)cyclohexylamine and 4-MeO-PCP is 1-[1-(4-methoxyphenyl)cyclohexyl]-piperidine

indicates the asymmetric carbon).



Molecular formula: C₁₅H₂₁NO₂

Molecular weight: 247.33 g/mol

The physico-chemical properties of methoxetamine have not been described in the scientific literature. It has been mostly encountered in seized or collected samples as a white crystalline powder. There are also reports of it being seized as 'off white', beige or yellow powder. It appears to be commonly sold in powder form; it is also available in tablets, capsules and liquid form. Common routes of administration are nasal insufflation and oral ingestion. Methoxetamine (salt) is soluble in water and the powder can be dissolved for oral use or intravenous/intramuscular injection.

Methods have been developed for the analysis of methoxetamine and some of its metabolites, including liquid-chromatography coupled with mass-spectrometry (LC-MS), gas-chromatography coupled with mass-spectrometry (GC-MS) and high-performance liquid chromatography coupled with ultraviolet detection (HPLC-UV).

There is one published *in vitro* study investigating the pharmacodynamics of methoxetamine, which suggests that it has an affinity for the NMDA (*N*-methyl-D-aspartate) receptor similar to ketamine. However, unlike ketamine, methoxetamine also has affinity for the serotonin transporter.

No animal studies were identified that investigated the median lethal dose (LD₅₀) of methoxetamine.

No animal studies were identified that investigated the potential for self-administration of methoxetamine.

There are no studies in the scientific literature that have assessed the psychological and/or behavioural effects of methoxetamine in humans. In addition, there are no animal studies on which to base an extrapolation of potential effects. However, self-reported experiences from user websites suggest that the desired psychological and behavioural effects of methoxetamine are broadly comparable to those reported for ketamine, which is a

dissociative ⁽¹¹⁾ anaesthetic. These include: euphoria, empathy, pleasant intensification of sensory experiences, mild to strong sense of dissociation from the physical body, derealisation, "coziness", improved social interaction, distorted sense of reality, vivid hallucinations, introspection and brief antidepressant effects.

According to information from user websites, methoxetamine appears to be used in single doses of between 10–200 mg, although some reports suggest that initial doses should not exceed 50 mg. The onset of desired effects is typically seen within 30–90 minutes of nasal insufflation, 90 minutes after oral ingestion and 5 minutes after intramuscular injection. Users report that the desired effects last approximately 1–7 hours depending on route of administration.

There have only been two studies that have investigated the pharmacokinetics of methoxetamine, both of which have investigated its metabolism; no studies have assessed other pharmacokinetic parameters such as absorption, distribution or excretion.

The five most abundant phase I and two most abundant phase II metabolites found in the *in vitro* studies were due to demethylation, reduction, oxidation and glucuronidation. No data are available on the biological activity of the metabolites.

Methoxetamine is used in analytical reference materials and scientific research investigating its chemistry, pharmacology and toxicology as a result of its emergence on the drug market. There are currently no known uses of methoxetamine as an industrial, agricultural or cosmetic compound. However, the name 'methoxetamine' has been registered as a trade mark in a Member State (December 2010); the significance of this trade mark application is unknown.

According to information provided by EMA, there are no known human or veterinary medical uses of methoxetamine in the European Union. There is no marketing authorisation (existing, on-going or suspended) for methoxetamine at the European Union level nor in the Member States that responded to the information request by the EMA that was launched under Article 5 of the Council Decision. There is no information that methoxetamine is used for the manufacture of a medicinal product in the European Union. However, it should be noted that there is no European Union database on the synthetic routes of all registered medicinal products. There remains a theoretical possibility that methoxetamine could in the future be developed for use as an antidepressant due to its actions at the NMDA receptor; to date there has been no formal evaluation of such a potential application.

⁽¹¹⁾ The term 'dissociative' has two meanings: firstly, it refers to an effect on the brain, inducing a lack of responsive awareness, not only to pain but also to the general environment; secondly, it refers to a feeling of dissociation of the mind from the body ('out-of-body experience').

Methoxetamine is sold openly from Internet suppliers and retailers where it can be purchased in bulk and retail quantities. It is also available from bricks and mortar head shops and street level drug dealers.

3. Chemical precursors that are used for the manufacture of methoxetamine

The method based on the patent on the synthesis of aminoketones from 1966 requires four steps. A Grignard reagent made from cyclopentyl bromide is reacted with 3-methoxybenzotrile to form 3-methoxyphenyl cyclopentyl ketone, which is then brominated. The resulting α -bromo ketone is reacted with ethylamine and the product undergoes rearrangement to form methoxetamine upon heating.

There is currently no information regarding manufacturing sites, the chemical precursors or the synthetic routes used for methoxetamine that has been detected on the drug market. Precursors and other chemicals needed for the manufacture of methoxetamine are inexpensive and are readily available. These reactions are feasible in an amateur laboratory setting and do not require sophisticated equipment.

There is no information on the purity of methoxetamine that is present on the drug market. Analysis of seized products has found both methoxetamine on its own and in combination with pharmacologically active substances (e.g. lidocaine, phenacetin, chlordiazepoxide and caffeine) and/or other psychoactive substances (e.g. cocaine, ketamine, MDPV, 4-MEC, AM-2201, 4-HO-MET, 5-MeO-DiPT, and 6-APB).

4. Health risks associated with methoxetamine

Individual health risks

The assessment of individual health risks includes a consideration of the acute and chronic toxicity of methoxetamine, as well as its dependence potential, and its similarities to and differences from other chemically-related substances.

The structural similarities and the available information on the *in vitro* and *in vivo* properties of methoxetamine would suggest a pharmacological and toxicological profile similar to ketamine, and, to a certain extent, PCP, although additional studies are needed to confirm this.

As noted, information on the acute toxicity associated with methoxetamine is not collected uniformly across the European Union.

There have been 120 non-fatal intoxications associated with methoxetamine that have been reported by five Member States: Belgium (2 cases), France (3), Germany (9), Italy (15), and Sweden (91); analytical confirmation of methoxetamine from biological samples has been reported in 55 of these cases: Belgium (1), France (3), Italy (13), and Sweden (38). In

addition, 15 clinical case reports ⁽¹²⁾ relating to non-fatal intoxications associated with methoxetamine have been reported in the scientific literature; of these, analytical confirmation was reported in 11 cases: Poland (2), United Kingdom (7), Switzerland (1) and US (1).

Data from these reports, along with information from self-reported user experiences, suggest that individuals present with adverse effects similar to ketamine intoxication. These include: nausea and severe vomiting, diarrhoea, slow and/or irregular heart rates, blackouts/loss of consciousness, sweating, distorted vision, buzzing / ringing in ears, difficulty breathing, headaches, seizures, tremor, disorientation, post-use depression, mental slowing, anxiety, difficulty speaking or moving limbs, catatonia, confusion, agitation, aggression, hallucinations, paranoia and psychosis. In addition, acute methoxetamine intoxications include stimulant effects (e.g. agitation, tachycardia and hypertension) and cerebellar features (e.g. ataxia and nystagmus) that would not be expected with acute ketamine intoxication.

Methoxetamine may be used on its own or in combination with other substances. Analysis of various products has shown that the composition of the products can differ and that the user is unlikely to be aware of the exact dose or compound(s) present. There is the potential therefore that in such cases, some or all of the reported symptoms may be due to other substances or a combination of them, rather than methoxetamine itself.

There have been 20 deaths associated with methoxetamine reported to the Early Warning System by six Member States where the substance has been detected in post mortem biological samples: Austria (1 death), Finland (1), France (1), Poland (1), Sweden (1) and the United Kingdom (15). In 8 of the cases, methoxetamine was the only psychoactive substance reported. It should be noted that in the remaining cases it is possible that other pharmacologically active substances (such as controlled drugs and medicines) and/or other medical conditions or trauma may have contributed to and/or been responsible for death. It was also noted that 4 of the 20 deaths mentioned drowning as the cause of death.

Methoxetamine has been marketed to users as a 'bladder friendly' alternative to ketamine. Since methoxetamine has only been reported to be available and used for a relatively short period of time compared to ketamine, there is currently no human data to support or refute these claims. Using an established animal model of ketamine toxicity, there has been one published study which showed that three months of intraperitoneal methoxetamine administration in mice was associated with similar bladder and renal tract toxicity that has been seen in similar animal models of chronic ketamine administration. There is currently no data from animal or human studies to be able to determine whether chronic methoxetamine use may be associated with the other patterns of chronic toxicity seen with ketamine use.

⁽¹²⁾ The term 'clinical case reports' is used to denote both clinical case reports and case series published in the scientific literature.

There are no data on the potential for interactions between methoxetamine and other drugs, medicinal products, and other forms of interaction including inhibitors or inducers of drug metabolism. In this context, it is worth noting, however, that the use of ketamine with other CNS depressants, e.g. alcohol, can potentiate CNS depression and/or increase the risk of developing respiratory depression. Concurrent use of diazepam or other benzodiazepines will increase plasma levels and reduce the clearance rate of ketamine.

There are no published animal or human studies that have investigated the potential for neurotoxicity, reproductive toxicity, genotoxicity and carcinogenic potential of methoxetamine.

There are no published studies on the abuse liability or dependence potential of methoxetamine. There has been one self-reported experience of methoxetamine 'addiction' on a user website.

There is no information on the psychosocial consequences of chronic methoxetamine use such as effects on psychological development and the interaction with the social environment.

Public health risks

The public health risks associated with methoxetamine may be categorised in terms of patterns of use (extent, frequency, route of administration, etc.); availability and quality of the drug; information, availability and levels of knowledge amongst users; and, negative health consequences.

There are reports to the EMCDDA of detections of methoxetamine in 23 Member states, Turkey and Norway since November 2010.

Methoxetamine is sold and used as a substance in its own right; it is also sold as ketamine on the illicit drug market. EMCDDA monitoring of Internet suppliers and retailers selling methoxetamine (conducted in the month prior to the risk assessment) identified more than ten companies, which may be based within the European Union and China, offering up to multi-kilogram quantities of the substance. This availability coupled with evidence of its sale as ketamine raises the possibility that methoxetamine could be supplied and used as a (temporary) replacement for ketamine. In some seizures and detections, methoxetamine has been reported to be the only psychoactive substance identified; in other cases it has been found in combination with other psychoactive substances including ketamine. Similar to other drugs, users may combine methoxetamine with stimulants, hallucinogens and/or depressants including alcohol and medicines. However, some users may have taken methoxetamine unknowingly along with or instead of other substances, particularly when they may have intended to use ketamine.

The main routes of administration of methoxetamine appear to be nasal insufflation and oral ingestion. Intramuscular and intravenous injection has also been reported; sharing of injecting equipment carries the risk of bacterial infections and transmission of blood-borne viruses.

There are limited data available on the characteristics and behaviour of users. These are likely to overlap with users of ketamine and/or users of other new psychoactive substances. Information from clinical case reports suggests that methoxetamine may be used in a range of settings, including the home environment and recreational settings. In the latter case this includes informal settings (such as 'house parties') as well organised events (such as music festivals).

There are currently no coordinated national or European population surveys on methoxetamine use. There are data available from non-representative studies in the Netherlands and the United Kingdom.

One non-representative Internet survey open to respondents across the world, found that from 7,700 United Kingdom-based respondents (including 'clubbers'), both life-time (4.9 %) and last year (4.2%) use of methoxetamine was lower than ketamine (47.5 % and 24.5 % respectively). Data was reported on four different reasons as to why respondents used methoxetamine: i) easier to get hold of – 73 %; ii) better value for money – 20 %; iii) curious or it was sold as ketamine – 20 %; less damaging to liver / kidneys – 18 %.

In a survey of 313 individuals attending 'gay friendly' nightclubs in South East London in July 2011, self-reported use of methoxetamine was considerably lower than ketamine for life-time (6.1 % vs. 60.3 %), last year (4.8 % vs. 48.7 %) and last month (1.9 % vs. 34.9 %) use. Only 1.6 % reported use or planned use of methoxetamine on the night of the survey compared to 41.0 % for mephedrone and 16.7 % for cocaine. When the surveys were repeated in July 2012 there had been a significant increase in self-reported use of methoxetamine: i) life-time use 2012: 21.0 % vs. 2011: 6.1 %; ii) last year use 2012: 19.2 % vs. 2011: 4.8 %; and iii) last month use 2012: 10.1 % vs. 2011: 1.9 %. Although there was no significant change in life-time and last year use of ketamine between the two surveys, there was a reduction in last month use of ketamine (2012: 24.4 % vs. 2011: 34.9 %).

A web survey among frequent visitors to parties, festivals and clubs was undertaken in the Netherlands in 2013. There was limited information on the survey population in this report and no information on the number of individuals surveyed. The lifetime, last year and last month prevalence of methoxetamine were lower than the rates reported for ketamine (3.0 % vs. 19.3 %, 2.3 % vs. 12.8 % and 0.3 % vs. 5.0 % respectively).

As noted, information from a range of sources suggests that methoxetamine is being sold as a 'legal' replacement to ketamine and is also sold as ketamine on the illicit drug market. As such it may be relevant to consider the prevalence of ketamine use in the general population. 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.

5. Social risks associated with methoxetamine

There is limited information on the social risks associated with methoxetamine.

There is no information on whether the use of methoxetamine affects education or career, family or other personal or social relationships, including marginalisation.

Although there are no relevant studies, it may be assumed that the acute behavioural effects of methoxetamine on operating machinery and driving are similar to those caused by other dissociative substances. There are currently no reports of methoxetamine detection in either fatal or non-fatal road traffic accidents. However, two cases were reported by Germany of driving under the influence of drugs that were associated with methoxetamine; in addition two cases from the United Kingdom were reported where methoxetamine was detected in biological samples from individuals suspected of driving under the influence of drugs and/or alcohol. The available information does not permit comment on the extent to which driving is impaired.

One Member State (Sweden) reported 17 detections of methoxetamine in biological samples related to individuals suspected of committing a minor drug offence. Additional information on these cases are not available to allow further comment.

There are some healthcare costs associated with cases of acute methoxetamine toxicity presenting to hospitals. Most of these involve short assessments within the emergency department; however a minority of individuals have had more prolonged symptoms over a few days or have required admission to psychiatric facilities due to ongoing symptoms.

There is no information on the social risks associated with the distribution and trafficking of methoxetamine.

There are no systematic studies available on the characteristics and behaviour of those who use methoxetamine. It is likely that these will be similar to those using other dissociative drugs such as ketamine and/or experimenting with new psychoactive substances.

6. Information on the level of involvement of organised crime and information on seizures and/or detections by the authorities, and the manufacture of methoxetamine

There is no information to suggest the involvement of organised crime or criminal groups in the manufacture, distribution (trafficking) and supply of methoxetamine. However, there have been reports of tablets with markings that would normally be associated with other recreational drugs (e.g. 'ecstasy').

7. Information on any assessment of methoxetamine in the United Nations system

The World Health Organization is the specialised agency of the United Nations designated for the evaluation of the medical, scientific and public health aspects of psychoactive substances under the 1961 United Nations Single Convention on Narcotic Drugs, and the 1971 United Nations Convention on Psychotropic Substances.

The World Health Organization informed the EMCDDA that methoxetamine will be subject to evaluation at the thirty-sixth meeting of the Expert Committee on Drug Dependence, which will be held in June 2014.

Article 7.1 of Council Decision states:

'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'.

The risk assessment has been carried out on the understanding that methoxetamine is not at an advanced stage of assessment within the United Nations system.

8. Description of the control measures that are applicable to methoxetamine in the Member States

Methoxetamine is not listed for control in the 1961 United Nations Single Convention on Narcotic Drugs or in the 1971 United Nations Convention on Psychotropic Substances (together 'UN drug conventions').

Nine Member States (Cyprus, Denmark, France, Germany, Italy, Lithuania, Slovenia, Sweden, and the United Kingdom) and Turkey control methoxetamine under legislation by virtue of their obligations under the UN drug conventions.

Nineteen Member States (Austria, Belgium, Bulgaria, Croatia, Czech Republic, Estonia, Finland, Greece, Hungary, Ireland, Luxembourg, Latvia, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, and Spain) and Norway do not control methoxetamine by virtue of their obligations under the UN drug conventions.

Of these nineteen Member States, nine (Austria, Finland, Hungary, Netherlands, Poland, Portugal, Romania, Slovakia and Spain) and Norway use other legislative measures to control methoxetamine:

In Austria methoxetamine is listed as controlled by the New Psychoactive Substances Act. In Finland methoxetamine has been controlled under the Medicines Act (395/87) since 9 December 2011. In Hungary methoxetamine is listed in Schedule C of Government Decree 66/2012. 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 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 penalised 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

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subject to control until proven harmless by a special designated commission). In Slovakia, methoxetamine is in the List of risk substances published in a Ministry of Health Regulation No 298/2013 Coll., which came into force on 1 October 2013. Spain reported that although there is no current specific legislation controlling production, commerce, imports, exports or use/consumption of methoxetamine, given that it may cause harmful effects to users there is general (administrative and criminal) legislation on health protection which, if necessary, is fully applicable. In Norway, methoxetamine is regulated by the Medicines Act and a prescription would be required to receive it.

9. Options for control and the possible consequences of the control measures

Under Article 9.1 of the Council Decision, the option for control that is available is for the Member States to submit the new psychoactive substance methoxetamine to control measures and criminal penalties, as provided for under their legislation, by virtue of their obligations under the UN drug conventions. There are no studies on the possible consequences of such control measures on methoxetamine. If this option of control is pursued, the Committee considers that the following consequences are possible. Some of these may apply to any new psychoactive substance.

- This control option could be expected to limit the availability of methoxetamine and hence the further expansion of the current open trade in this substance. However, this may have little impact on the manufacturers and suppliers based outside of the European Union.
- A health consequence that may result from this control option is the benefit brought about by the presumed reduction in availability and use of methoxetamine.
- This control option could facilitate the detection, seizure and monitoring of methoxetamine related to its unlawful manufacture, trafficking and use. In so doing, it could facilitate cooperation between the judicial authorities and law enforcement agencies within the European Union.
- This control option would imply additional costs for the criminal justice system, including forensic services, law enforcement and the courts.
- This control option could lead to replacement with structurally related or other (established or new) psychoactive substances which may in themselves have public health consequences.
- It is not possible to gauge to what extent this control is likely to impact on current and future research by academic institutes, the pharmaceutical or chemical industries.
- This control option could create an illicit market in methoxetamine with the increased risk of associated criminal activity, including organised crime.
- It is a concern that a common technique used by Internet retailers within the European Union is to offer price discounts or other promotions in order to dispose of remaining

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stocks of new psychoactive substances when control measures are impending. Therefore, this control option could lower the price of any methoxetamine that is still available on the market and temporarily increase its availability. The extent to which this will impact on public health, criminality or levels of use is difficult to predict.

In order to examine the consequences of control, the Committee wishes to note that should this option be pursued it will be important to monitor for the presence of methoxetamine on the market post-control.

Aside from the option for control under those stipulated in Article 9.1 of the Council Decision, other options for control may be available to Member States. These may include medicines legislation or restricting the importation and supply of the substance using other legislative options.

10. Conclusion

Methoxetamine is an arylcyclohexylamine substance which is chemically similar to ketamine and PCP and in common with these, has dissociative properties. Methoxetamine was first identified in a collected sample purchased from an Internet retailer in September 2010 and formally notified to the Early Warning System in November 2010 by the United Kingdom.

Methoxetamine has emerged on the 'legal highs' market where it is sold as a 'research chemical' and advertised as a 'legal' replacement for ketamine by Internet retailers, brick and mortar head shops and street-level drug dealers; it is also sold as ketamine. It has been mostly found as a powder but also as tablets and in liquid form.

Methoxetamine has been detected in 23 Member States, Turkey and Norway. EMCDDA monitoring of Internet suppliers and retailers selling methoxetamine has identified more than ten companies, which may be based within the European Union and China, offering up to multi-kilogram quantities of the substance. Data on prevalence are limited to non-representative studies in the United Kingdom and the Netherlands. These data suggest that the lifetime, last year and last month prevalence of the use of methoxetamine is lower than ketamine. Given that some ketamine users have reported the use of methoxetamine, it is likely that there is an overlap between these groups and/or users of other new psychoactive substances. However, detailed information on the characteristics of methoxetamine users is not available. There is no specific information on the social risks that may be related to methoxetamine.

The main routes of administration appear to be nasal insufflation and oral ingestion; intramuscular and intravenous injection has also been reported. The subjective effects reported by methoxetamine users are similar to ketamine. There are no published studies assessing the psychological and/or behavioural effects of methoxetamine neither in animals nor in humans.

Methoxetamine either alone or in combination with one or more substances has been detected in 120 non-fatal intoxications in five Member States reported to the Early Warning System; an additional 15 clinical case reports (Poland (3), United Kingdom (8), Switzerland

(1) and US (3)) have been published in the scientific literature. There have been 20 deaths associated with methoxetamine in six Member States. It is not possible to determine the significance of the detection of methoxetamine in most of these deaths.

It appears that the effect profile and clinical presentations of acute methoxetamine toxicity share some features seen with ketamine, but that there is the potential for additional effects such as stimulant and cerebellar features. The current data does not allow an accurate assessment to be made on the extent to which methoxetamine users are likely to experience health problems. There is currently no data from either animal studies or human users of methoxetamine to determine its abuse liability and dependence potential.

There is only one animal study that has examined the potential for chronic health effects of methoxetamine. This study suggests that methoxetamine may be associated with similar renal and lower urinary tract effects to ketamine; however there is no data in humans to substantiate this. No studies have been published investigating the potential for neurotoxicity, reproductive toxicity, genotoxicity and carcinogenic potential of methoxetamine use.

Multi-kilogram quantities of methoxetamine in powder form have been seized within the European Union but there is no information on the involvement of organised crime. Precursors and other chemicals needed for the manufacture of methoxetamine are inexpensive and are readily available. These reactions are feasible in an amateur laboratory setting and do not require sophisticated equipment.

Methoxetamine is used in analytical reference materials and in scientific research. It has no established or acknowledged medical value or use (human or veterinary) in the European Union. There are no indications that methoxetamine may be used for any other purposes.

Methoxetamine is not listed for control in the 1961 United Nations Single Convention on Narcotic Drugs nor in the 1971 United Nations Convention on Psychotropic Substances. Methoxetamine is currently undergoing assessment by the United Nations system. Nine Member States and Turkey control methoxetamine under legislation by virtue of their obligations under the UN drug conventions. Nine of the remaining Member States and Norway use other legislative measures to control the substance.

Many of the questions posed by the lack of evidence on the health and social risks of methoxetamine, as for any new psychoactive substance, could be answered through further research. Areas where additional information would be important include: receptor binding and functional activity studies; metabolic pathway studies; behavioural studies; clinical patterns of acute and chronic toxicity in humans; the potential interaction between methoxetamine and other substances; prevalence and patterns of use (including targeted studies that examine user groups and risk behaviours); market studies; chemical profiling studies; studies on the abuse liability and dependence potential; and, studies on the social risks associated with its use.

The Committee notes that a decision to control this drug has potential positive consequences in terms of reducing availability and therefore the adverse health and social

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consequences arising from the use of methoxetamine. It is important, however, to anticipate and minimise where possible any potential negative consequences of control. Control measures could extend an illegal market in methoxetamine with the associated risk of criminal activity. The implementation of control measures may also lead to the criminalisation of those who continue to use this substance with the possible attendant risks of socio-economic stigmatisation and marginalisation. Finally, control should not inhibit the gathering and dissemination of accurate information on methoxetamine to users and to relevant professionals.

11. List of annexes

Annex 1: List of participants attending the risk assessment meeting.

Annex 2: *Technical Report on 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone (methoxetamine).*



Annex 1. List of participants at the Risk Assessment meeting on methoxetamine, 1 April 2014

A. Extended Scientific Committee

Scientific Committee Members

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Annex 2. Technical Report on 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone (methoxetamine)

Prepared by Dr David M Wood and Dr Paul I Dargan

Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom

Note: This Technical Report includes a discussion of the characteristics of users of methoxetamine. This includes information from Internet drug discussion forums and related websites (hereafter 'user website(s)') and includes self-reported use of methoxetamine, the drug regimens used and the subjective effects experienced. It is important to note that in these cases it is not possible to confirm the specific substance(s) used, nor the purity, dose, etc. Analysis of products 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 may not necessarily be 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.

This Technical Report was prepared under EMCDDA contract. Given the time frame stipulated in the Council Decision, it has not been formally edited by the EMCDDA. As a result, while the scientific data presented has been verified to the extent possible, minor changes may be introduced at a later date when the report is officially published. The EMCDDA may not be held responsible for the use of the information contained herein without prior consultation. The Risk Assessment Report on 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone (methoxetamine), to which this report is annexed was produced by the Scientific Committee of the EMCDDA and shall be regarded as the authoritative document.

Suggested citation: Technical Report on 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone (methoxetamine). EMCDDA, Lisbon, April 2014.

Summary

Methoxetamine is an arylcyclohexylamine substance (Figure 1) with dissociative properties. Apart from its use as an analytical reference standard and its use in scientific research investigating its chemistry, pharmacology and toxicology, methoxetamine has no known legitimate uses as a research, industrial, cosmetic or medicinal compound. There has been evidence of the availability of methoxetamine in Europe since 2010, with detections ⁽¹⁾ reported in 23 Member States, Turkey and Norway. Methoxetamine was first detected within the European Union in 2010 with formal notification to the European Union Early Warning System (hereafter 'EU Early Warning System') in November 2010 by the United Kingdom National Focal Point. The number and size of methoxetamine seizures has increased year on year. Most of the detections were in 2012 and 2013, but there are reports from Finland, Spain and the United Kingdom of detections since 2010.

Methoxetamine is structurally related to both phencyclidine ("PCP", 1-(1-phenylcyclohexyl)piperidine) and ketamine (2-(2-chlorophenyl)-2-(methylaminocyclohexanone). There are a number of other arylcyclohexamine derivatives that have been notified to the Early Warning System. These include: 2-methoxyketamine, N-ethylorketamine, 3-MeO-PCE, and 3-MeO-PCP. ⁽²⁾

There appear to be no co-ordinated national or European population surveys on the prevalence of methoxetamine use. There are reports from targeted surveys in clubbers in both the Netherlands and the United Kingdom. These reports suggest that the life-time, last-year and last-month use of methoxetamine is lower than ketamine.

Methoxetamine is typically supplied as a white powder; there are also reports of its supply in tablet, capsule and liquid form. It is used predominantly by nasal insufflation and oral ingestion, there are also reports of its use by intramuscular or intravenous injection. Single use doses of methoxetamine are typically 10–200 mg, although users report that initial doses should not exceed 50 mg. There are reports that some individuals use repeated doses during a single use session.

Methoxetamine has and/or is currently available from bricks and mortar head shops, Internet retailers and street level drug dealers; in the 2011 and 2012 EMCDDA Internet snapshot studies methoxetamine was available in 5–10 % of the web sites that were selling new psychoactive substances.

(1) '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.).

(2) 2-methoxyketamine is 2-(2-methoxyphenyl)-2-(methylamino)cyclohexanone, N-ethylorketamine is 2-(2-chlorophenyl)-2-(ethylamino)cyclohexanone, 3-MeO-PCE is N-Ethyl-1-(3-methoxyphenyl)cyclohexylamine and 4-MeO-PCP is 1-[1-(4-methoxyphenyl)cyclohexyl]-piperidine

There is one published *in vitro* study investigating the pharmacodynamics of methoxetamine, which suggests that methoxetamine has an affinity for the *N*-methyl-D-aspartate (NMDA) receptor that is comparable to ketamine. However, unlike ketamine, methoxetamine also has affinity for the serotonin transporter. Data on the pharmacokinetics of methoxetamine is limited to two studies with data on the likely metabolites of methoxetamine. There are no animal or human studies reporting on its pharmacokinetics or pharmacodynamics. Information from user self-reports and clinical data on individuals presenting to hospital with acute methoxetamine toxicity (non-fatal intoxications) suggest that the desired effects of methoxetamine are similar to those seen with ketamine, but also include stimulant effects and cerebellar features that would not be expected with acute ketamine intoxication.

There have been 120 non-fatal intoxications reported by the Member States to the Early Warning System: Belgium (2 cases), France (3), Germany (9), Italy (15), and Sweden (91); analytical confirmation of methoxetamine from biological samples has been reported in 55 of these cases: Belgium (1 case), France (3), Italy (13), and Sweden (38). Data from these cases, along with information from case reports in the scientific and medical literature from Europe and the United States, as well as self-reported information from users, suggest that individuals typically present with 'ketamine-like' effects including agitation, aggression, hallucinations, paranoia and psychosis. There are reports of additional acute adverse health effects, including stimulant features (significant tachycardia, significant hypertension, palpitations), cerebellar toxicity (nystagmus, ataxia, tremor) and seizures. Since experience on the toxicological profile of methoxetamine is currently limited to only tens of cases, it is difficult to be sure that rare, but clinically significant, severe effects are not associated with methoxetamine use.

There is one user report on a user website of self-reported "addiction" to methoxetamine. There are no other data from animal or human studies on the dependence liability of methoxetamine.

There have been 20 deaths reported by the Member States to the Early Warning System where methoxetamine has been detected in post mortem biological samples and/or implicated as the cause of death: Austria (1 death), Finland (1), France (1), Poland (1), Sweden (1) and the United Kingdom (15). It should be noted that in some of these deaths it is likely that other pharmacologically active substances (such as controlled drugs) and/or other medical conditions or trauma may have contributed to and/or been responsible for death. Drowning was the cause of death in 4 of the 20 cases.

Methoxetamine has been marketed to users as a "bladder friendly" alternative to ketamine. Since methoxetamine has only been reported to be available and used for a relatively short period of time compared to ketamine, there is currently no human data to support or refute these claims. Using an established animal model of ketamine toxicity, chronic methoxetamine administration has been demonstrated to cause bladder and renal tract toxicity similar to ketamine.

There have been no reports of anti-social behaviour related to the use of methoxetamine. There have been a small number of cases of detection of methoxetamine in cases of other types of crimes (e.g. driving under the influence of drugs).

In conclusion, methoxetamine is an arylcyclohexylamine substance which is chemically similar to ketamine, which is used for its ketamine-like dissociative effects. There is increasing evidence of its use and availability within the European Union. There are numerous reports of acute toxicity associated with methoxetamine, including presentations to emergency departments (ED), within the European Union and elsewhere and it has been detected in 20 deaths. In addition, one animal model suggests that there is the potential for significant chronic toxicity associated with methoxetamine that is similar to the chronic toxicity seen with ketamine use. Given the reports of significant acute health effects, emerging reports of detection in fatalities and potential for chronic toxicity, there is a risk of increasing acute toxicity, chronic morbidity and mortality related to methoxetamine use within the European Union, with associated health care utilisation and social costs. In addition, based on data from animal models that chronic methoxetamine use is likely to have similar bladder and renal toxicity as seen in chronic ketamine use, there is the potential that long-term use of methoxetamine could be associated with significant clinical risks of long-term harm.

Section A. Physical, chemical, pharmaceutical and pharmacological information

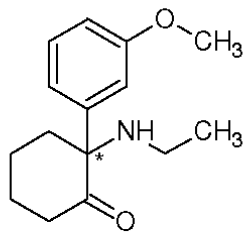
A1. Physical, chemical and pharmaceutical information

A1.1. Physical and chemical description (including methods of synthesis, precursors, impurities if known – type and level)

The systematic (International Union of Pure and Applied Chemistry, IUPAC) name for methoxetamine is (*RS*)-2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone. Methoxetamine contains one asymmetric carbon atom (marked with an asterisk on Figure 1), thus it is a chiral molecule. There are no details available on the enantiomeric form detected. The Chemical Abstract Service (CAS) Registry Numbers for methoxetamine are 1239943-76-0 (methoxetamine base) and 1239908-48-5 (methoxetamine hydrochloride salt). Another abbreviated name for methoxetamine is 3-MeO-2-oxo-PCE. There are no official synonyms or non-proprietary names methoxetamine.

Methoxetamine is an arylcyclohexylamine substance (Figure 1), structurally similar to ketamine (2-(2-chlorophenyl)-2-(methylaminocyclohexanone) ⁽³⁾) and phencyclidine ('PCP', 1-(1-phenylcyclohexyl)piperidine). The name 'methoxetamine' was reported to have been coined as a contraction of methoxy-ketamine [Morris and Wallace, 2014]. The molecular formula for methoxetamine is C₁₅H₂₁NO₂, equating to a molecular weight of 247.33 g/mol.

Figure 1. The chemical structure of methoxetamine (the asterisk indicates the asymmetric carbon).



The method based on the patent on the synthesis of aminoketones from 1966 requires four steps [Stevens, 1966]. A Grignard reagent made from cyclopentyl bromide is reacted with 3-methoxybenzoyl chloride to form 3-methoxyphenyl cyclopentyl ketone, which is then brominated. The resulting α -bromo ketone is converted to the Schiff's base with ethyl amine, which is then heated to form methoxetamine [Hays, 2012].

This route would also apply to the synthesis of methoxetamine analogues.

⁽³⁾ Report on the risk assessment of ketamine in the framework of the joint action on new synthetic drugs. EMCDDA, Lisbon, June 2002.

Common street names for methoxetamine include 'MXE', 'Mexxy', 'Roflicopter', '3-MeO-2-Oxo-PCE' 'M-ket', 'Kmax', 'Special M', 'legal ketamine', 'Minx' and 'Jipper' [Erowid Vault; MixMag 2012].

There are a number of other arylcyclohexylamine derivatives that have been formally notified to the Early Warning System. These are:

2-methoxyketamine (IUPAC: 2-(2-methoxyphenyl)-2-(methylamino)cyclohexanone)

N-ethyl-norketamine (IUPAC: 2-(2-chlorophenyl)-2-(ethylamino)cyclohexan-1-one)

3-MeO-PCE (IUPAC: 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexane)

3-MeO-PCP (IUPAC: 1-[1-(3-methoxyphenyl)cyclohexyl]-piperidine)

4-MeO-PCP (IUPAC: 1-[1-(4-methoxyphenyl)cyclohexyl]-piperidine)

Methoxetamine brominated derivative (IUPAC: 2-(2-bromo-5-methoxyphenyl)-2-(ethylamino)cyclohexanone)

A number of publications describe well-developed analytical techniques for methoxetamine. The techniques employed include: liquid-chromatography with mass-spectrometry (LC-MS), gas-chromatography with mass-spectrometry (GC-MS) and high-performance liquid chromatography with ultraviolet detection (HPLC-UV) [Al-Saffar 2013, De Paoli G 2013, Elie MP 2013, Abe E 2012, Soh YN 2013]. One study has shown that methoxetamine is stable for at least 21 days in blood and plasma samples [Soh YN 2013].

A1.2. Physical/pharmaceutical form (i.e. powder, capsules, tablets, liquids, injectables, cigarettes. Any distinctive markings, logos, etc., to be noted)

The physico-chemical properties of methoxetamine have not been described in the scientific literature. It has been mostly encountered as a white crystalline powder. There are also reports of it being seized as 'off white', beige or yellow powder. It appears to be commonly sold in powder form; it is also available in tablets, capsules and liquid form. Common routes of administration are nasal insufflation and oral ingestion. Methoxetamine (the salt form) is soluble in water and the powder can be dissolved for oral use or intravenous/intramuscular injection.

In addition, as summarised in Section C, there are also reports of detections of white, yellow, pink, blue, green and turquoise tablets, capsules, 'light green plant material' and liquids all found to contain methoxetamine. In addition, there are also reports of plastic sample tubes found to contain methoxetamine. Some methoxetamine tablets have had a variety of markings on them, which include 'LV', Puma, Android, Playboy logos and cherries or a smiley face. It is not possible at this time to determine if any of these logos are distinctive markings for methoxetamine, however many have been previously found on 'ecstasy' tablets. There is one report from 2011 of methoxetamine being detected in the United

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Kingdom in a product that was marketed using the 'Special K' logo, which is the logo and trade name for a legitimate breakfast cereal [Wood DM 2011]. This name has specific relevance to the link between ketamine and methoxetamine.

A1.3. Route of administration and dosage (e.g. oral, inhalation, intravenous etc)

Methoxetamine is used by the oral and/or buccal route, nasal insufflation, intramuscular injection and intravenous injection [Westwell AD 2012; Wood DM 2012; Shields JE 2012; Hofer KE 2011; Ward J 2011; Sein Anand J 2012; Wilde JM 2012]. The majority of cases of acute toxicity discussed in Section D (below) have related to nasal insufflation or intramuscular injection [Westwell AD 2012; Wood DM 2012; Shields JE 2012; Hofer KE 2011; Sein Anand J 2012]. Reported oral use includes ingestion of tablets, capsules and liquid methoxetamine, dissolving methoxetamine powder in water prior to drinking or dipping a wet finger into methoxetamine powder and then licking the finger [Wood DM 2012; Wilde JM 2012]. Similarly, a review of 33 self-reports of use of methoxetamine on three different user websites (www.erowid.org, www.bluelight.ru and www.flashback.org), suggests that the most common route of administration was nasal insufflation (21 reports), followed by intramuscular injection (5), sublingual administration (4) and oral ingestion (3) [Kjellgren A 2013].

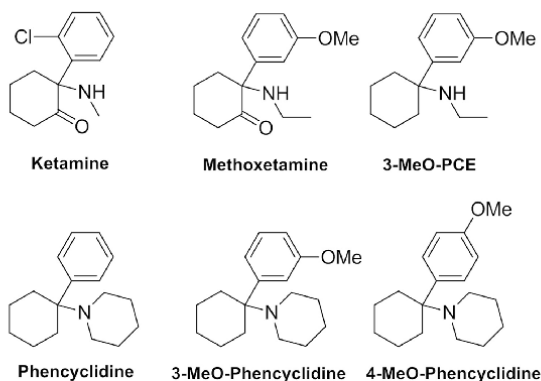
Single use doses of methoxetamine reported by users on user websites are reported to be 10–200 mg, with users reporting that initial doses should not exceed 50 mg [Kjellgren A 2013; Corazza O 2012]. Doses appear to vary between route of administration: 20–60mg for nasal insufflation; 20–100 mg for oral administration; 10–30 mg for intramuscular injection [Kjellgren A 2013; Corazza O 2012]. There are anecdotal reports on some user websites of individuals redosing during a single use session, and also reporting the desire to use more methoxetamine the next day due to the pleasurable effects experienced whilst using methoxetamine [Kjellgren A 2013].

A2. Pharmacology, including pharmacodynamics and pharmacokinetics

Pharmacodynamics

One study has investigated the mode of action of methoxetamine. This was an *in vitro* study that used the resources of the United States National Institute of Mental Health Psychoactive Drug Screening Program (NIMH-PDSP) to obtain neurochemical profiles of methoxetamine and novel PCP analogues and compare these to ketamine and phencyclidine (PCP) [Roth BL 2013]. In addition to methoxetamine, ketamine and PCP, the other substances studied were 3-MeO-PCP, 3-MeO-PCE and 4-MeO-PCP.

Figure 3. Substances studied in the NIMH-PDSP studies of methoxetamine.



These substances were each screened four times at a fixed concentration of 10 μM . K_i (inhibition constant) determination, receptor binding profiles and functional assays were undertaken using the NIMH-PDSP [UNC Assay Protocol]. Substances which yielded inhibition of binding of greater than 50 % were then further studied to determine K_i via 12-point concentration response studies in triplicate. A total of 57 molecular targets were screened. In addition, a dose response curve for the representative K_i determination for methoxetamine in the NMDA receptor assay was prepared against the non-competitive NMDA receptor antagonist dizocilpine (MK-801).

The representative K_i and pK_i values are shown in Table 1. This shows that methoxetamine is an NMDA receptor antagonist and has an affinity for the NMDA receptor that is comparable or higher than ketamine. The most potent of the analogues at the NMDA receptor was 3-MeO-PCP. Methoxetamine had additional activity at the serotonin transporter which was not observed with ketamine.

Table 1: Representative K_i and pK_i in the NIMH-PDSP studies of methoxetamine and its analogues.

(NMDA: *N*-methyl-D-aspartate receptor; SERT: serotonin transporter; NET: norepinephrine transporter; - indicates that the substance failed the primary screen of greater than 50 % inhibition at 10 μM)

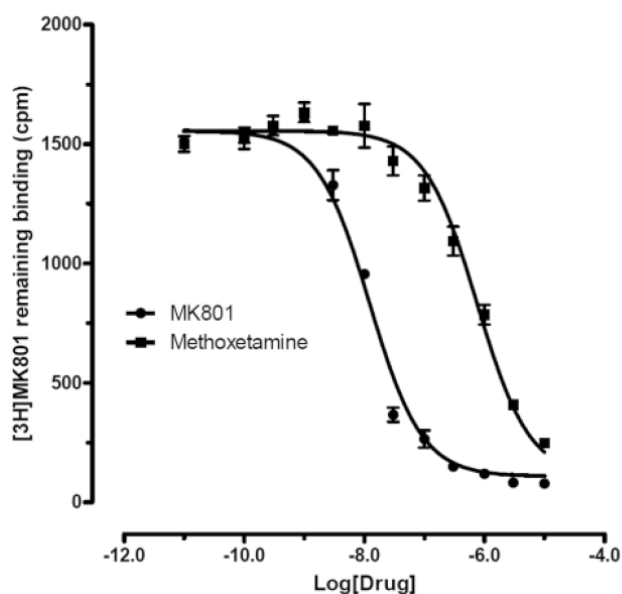
	NMDA $pK_i \pm$ SD (K_i , nM)	SERT $pK_i \pm$ SD (K_i , nM)	NET $pK_i \pm$ SD (K_i , nM)	Sigma ₁ $pK_i \pm$ SD (K_i , nM)	Sigma ₂ $pK_i \pm$ SD (K_i , nM)
Methoxetamine	6.59 ± 0.06 (259)	6.32 ± 0.05 (481)	-	-	-
Ketamine	6.18 ± 0.07	-	-	-	-

	(659)				
Phencyclidine	7.23 ± 0.07 (59)	5.65 ± 0.05 (2234)	-	-	6.82 ± 0.09 (136)
4-MeO-PCP	6.39 ± 0.06 (404)	6.07 ± 0.05 (844)	6.1 ± 0.01 (713)	6.5 ± 0.1 (296)	7.93 ± 0.08 (143)
3-MeO-PCP	7.69 ± 0.08 (20)	6.7 ± 0.1 (216)	-	7.4 ± 0.1 (42)	-
3-MeO-PCE	7.22 ± 0.88 (61)	6.9 ± 0.06 (115)	-	5.3 ± 0.1 (4519)	6.31 ± 0.1 (525)

It would appear that there is a relationship between chemical structure and pharmacological activity. Methoxetamine is ketamine without the 2-chloro group but with a 3-methoxy substituent on the phenyl ring (and with an *N*-ethyl rather than an *N*-methyl substitute). The addition of the 3-methoxy group appears to increase affinity for SERT.

The dose response curve for methoxetamine compared to the non-competitive NMDA receptor antagonist dizocilpine is shown in Figure 4. Methoxetamine and dizocilpine K_i values were both determined in three separate experiments: K_i 337 ± 76nM and 5.7 ± 0.57 nM respectively.

Figure 4: K_i for methoxetamine in the NMDA receptor assay compared with dizocilpine.



Pharmacokinetics

There have only been two studies that have investigated the pharmacokinetics of methoxetamine, both of which have investigated methoxetamine metabolism [Menzies EL 2013, Meyer MM 2013]; no studies have assessed other pharmacokinetic parameters such as absorption, distribution or excretion.

In the first of these studies, phase I and phase II metabolites of methoxetamine were identified and characterised by examining the concordance of data gathered from analysis of microsomal incubates using human liver microsomal cell preparations, with that from the analysis of urine specimens from three individuals with analytically confirmed acute methoxetamine toxicity [Menzies EL 2013]. Analysis was undertaken with ultra high-performance liquid chromatography-high resolution mass spectrometry. The five most abundant Phase I and two most abundant Phase II metabolites found in the *in vitro* studies were:

Phase I: *N*-desethyl(nor)methoxetamine, *O*-desmethylnormethoxetamine, hydroxy-normethoxetamine, *O*-desmethylnormethoxetamine, dihydro-normethoxetamine.

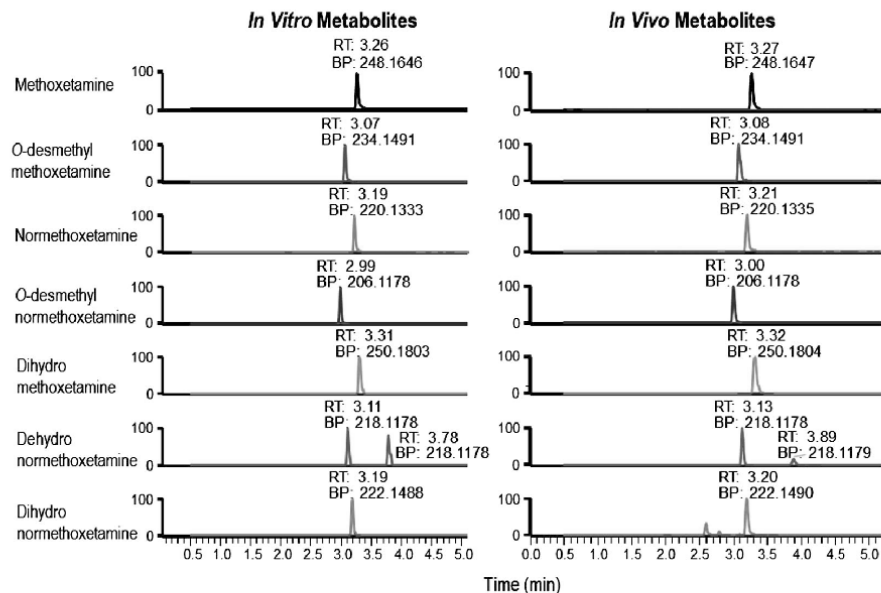
Phase II: *O*-desmethylnormethoxetamine glucuronide, *O*-desmethylnormethoxetamine glucuronide

The *N*-desethyl(nor)methoxetamine metabolite was the most abundant with a response relative to methoxetamine of 100%; *O*-desmethylnormethoxetamine and hydroxy-nor-

methoxetamine were present with a response relative to methoxetamine of 73 % and 14 % respectively. The other metabolites all had relative responses of less than 1 %.

Figure 5 shows the extracted ion chromatographs for the major Phase I metabolites identified both in the *in vitro* incubates and the *in vivo* urine samples from patients with analytically confirmed acute methoxetamine toxicity. One major difference was the absence of the *O*-desmethylhydroxynormmethoxetamine metabolite in all three of the patient urine samples. This may be due to the Phase I metabolite being conjugated or to other factors such as the timing of the urine collection relative to methoxetamine use. As noted above, *N*-desethyl(nor)methoxetamine (or normethoxetamine) was the most abundant metabolite in the *in vitro* incubates; this was also the most abundant metabolite in two of the human urine samples based on its signal intensity. In the third human urine sample the most abundant metabolite based on signal intensity was dihydromethoxetamine, this was followed by normethoxetamine.

Figure 5: Extracted ion chromatograms of selected Phase I metabolites from *in vitro* microsomal incubates and an *in vivo* urine sample



There was also concordance in the Phase II metabolites between the *in vitro* and *in vivo* samples with detection of *O*-desmethylmethoxetamine glucuronide, *O*-desmethylnormmethoxetamine glucuronide and *O*-desmethylhydroxymethoxetamine glucuronide in all samples. In the *in vitro* incubates and all three urine sample *O*-desmethylmethoxetamine was the most abundant Phase II metabolite based on its signal intensity.

In the second study, Phase I and Phase II metabolites were identified gas-chromatography-mass spectrometry (GC-MS) and liquid chromatography-high-resolution-mass spectrometry (LC-(HR)-MSⁿ) [Meyer MM 2013]. Pooled urine samples were collected over a 24 hour period from male Wistar rats after administration of 20 mg/kg methoxetamine by gastric intubation. Human samples were also analysed, these were from forensic cases in which there was a suspicion of methoxetamine use.

A total of eight metabolites were identified in rat and human urine samples and based on this it was postulated (similar to the above study by Menzies et al) that the following metabolic pathways were involved: *N*-deethylation, *O*-demethylation, hydroxylation as well as glucuronidation and sulphation. This study also confirmed that the *N*-deethyl enzyme kinetic studies showed that *N*-deethylation, the initial metabolism of methoxetamine in humans, is catalysed by the cytochrome P450 isoenzymes CYP2B6 and CYP3A4. The K_M values were 171µM for CYP2B6 and 93 µM for CYP3A4 and V_{max} were 1.4µg/pmol/min for CYP2B6 and 1.9 µg/pmol/min for CYP3A4. In addition to *N*-deethylation, CYP2B6 also catalysed *O*-desmethylation and hydroxylation.

The pharmacological or toxicological properties of the most abundant metabolites have not been investigated. However, based on structure-activity relationships established for phencyclidine analogues, it is likely that the *O*-desmethyl compound would be of particular interest in this regard.

In the absence of formal pharmacokinetic data, the only information available on the likely onset and duration of effects of methoxetamine comes from user reports. The onset of action is reported to be within 30–90 minutes following nasal insufflation, 5 minutes after intramuscular injection and around 90 minutes following oral ingestion [Corazza O 2012; Corazza 2013]. The duration of action of methoxetamine is reported to be 2.5–7 hours after nasal insufflation, 3–5 hours after oral ingestion and 1–3 hours after intramuscular injection [Kjellgren A 2013; Corazza O 2012; Corazza O 2013].

Interaction with other drugs, medicinal products and other forms of interaction

There are no data on the potential for interactions between methoxetamine and other drugs, medicinal products, and other forms of interaction.

A3. Psychological and behavioural effects

There are no published formal studies assessing the psychological and/or behavioural effects of methoxetamine in humans. In addition, there are no animal studies on which to base an extrapolation of potential effects. Therefore, the psychological and behavioural effects related to methoxetamine use are based on users' reports and clinical reports of acute methoxetamine toxicity. The latter are summarised in Section D1.2.

The desired psychological and behavioural effects reported by users on user websites include: euphoria, empathy, pleasant intensification of sensory experiences, mild to strong sense of dissociation from the physical body, derealisation, "coziness", improved social

interaction, distorted sense of reality, vivid hallucinations, introspection and brief antidepressant effects [Corazza O 2013; Kjellgren A 2012; Corazza O 2012].

Undesired psychological and behavioural effects reported by users include catatonia, dissociate haze, disorientation, paranoia, post-use depression, mental slowing, anxiety, difficulty speaking and confusion [Erowid Health Effects 1-4; Corazza O 2012; Kjellgren A 2013]. It should be noted that a significant proportion of these individuals had used one or more other pharmacologically active substance, including controlled drugs, new psychoactive substances and/or alcohol which may in part have explained their reported symptoms. It appears from the user reports that the unwanted psychological and behavioural effects occur at similar doses (10–100 mg) to those reported to be used for the desired effects.

A4. Legitimate uses of the product

Methoxetamine is available as an analytical reference standard and is used in scientific research investigating its chemistry, pharmacology and toxicology as a result of its emergence on the drug market. There are currently no known uses of methoxetamine as an industrial, agricultural or cosmetic compound. Methoxetamine is currently not a recognised medicinal product in its own right and it is not used for the synthesis of any other medicinal products or active pharmaceutical ingredients. However the collection of information cannot be considered exhaustive in the absence of a European Union database on the synthetic routes of all medicinal products.

RChem UK Limited, London, United Kingdom applied for a Trade Mark for methoxetamine to the UK Intellectual Property Office in September 2010 and the trade mark was registered on 17 December 2010 (Trade Mark Number UK00002558985) [RChem UK Trade Mark]. There is no further information on the significance of this Trade Mark application.

It has been suggested that due to its actions at NMDA receptors that methoxetamine may have a role as a possible rapid acting antidepressant [Coppola M 2012]. There is a single case report, published in abstract form only, of a 29 year old male who self-treated with 5–10 mg methoxetamine every four hours as an analgesic for chronic foot pain [Wilde JM Clin Tox 2012]. In addition, there is one report on the user website Erowid of a 22 year old male with self-reported bipolar disorder who describes self-treatment with methoxetamine. This individual notes that he developed the following symptoms: "with this illness I became anxious around people, couldn't concentrate in school, depressed and couldn't get out of bed"; he notes that when he started using methoxetamine, he "began to soar!" and "my brain felt clear, I could read, write, draw, play, the way I used to as a child" [Erowid Analgesia Report]. None of these claims about potential medicinal role(s) for methoxetamine have been formally evaluated.

Section B. Dependence and abuse potential

B1. Animal *in vivo* and *in vitro* data

There are no published animal *in vivo* or *in vitro* studies (such as *in vitro* receptor binding studies) that have investigated the dependence potential or abuse potential of methoxetamine.

B2. Human data

There have been no formal studies investigating the dependence potential or abuse potential of methoxetamine in humans. There are no published reports in the medical literature of individuals with suspected or proven dependency on and/or abuse of methoxetamine.

There is one single report on Erowid, from 2012, of an 18 year old male with an extensive drug-using history from the age of 15, who self-reported 'addiction' to methoxetamine [Erowid Abuse Report]. This individual was sent a free 250 mg sample of methoxetamine when he purchased '2-CP' ⁽⁴⁾. Following initial pleasurable experiences ("state of dissociation and opiate-like euphoria") with low doses of methoxetamine (25–40 mg per line), he started craving the drug and started using increasing amounts of up to 1 g of methoxetamine per week "doing it all day, low doses in the morning and afternoon culminating into intense trips in the evening" and needing at least 50 mg of methoxetamine to get "threshold effects". When he stopped regular use of methoxetamine, he described feeling "detached and sad". From the information provided in the report there does not appear to have been physical withdrawal symptoms after cessation.

(4) Presumably 2C-P (2-(2,5-dimethoxy-4-(n)-propyl-phenyl)ethanamine).

Section C. Prevalence of use

Methoxetamine was first detected within the European Union in 2010 with formal notification to the Early Warning System in November 2010 by the United Kingdom National Focal Point. There have been detections ⁽⁵⁾ of methoxetamine in 23 Member States, Turkey and Norway. Multi-kilogram quantities of the substance in powder form have been seized. Table 2 provides a summary of the seizures and collected samples reported by the Member States.

Table 2: Summary of seizures and collected samples reported by the Member States to the Early Warning System

Country	Amount and details of the seizure or collected sample
Austria	<p>2011: One customs seizure of powder (amount and colour not reported) containing methoxetamine. One police seizure of powder (amount and colour not reported) containing methoxetamine</p> <p>2012: One police seizure of 1.6 g of powder (colour not reported) containing methoxetamine. Four powder samples from venues analysed through Checkit! Project found to contain methoxetamine (980 mg/g, 980 mg/g, 940 mg/g and 947 mg/g)</p> <p>2013: One customs seizure of powder (amount and colour not reported) containing methoxetamine. Five police seizures of powder (colour not reported) totalling 11.6 g. Samples analysed from venues through Checkit! Project: i) powder sold as speed containing methoxetamine (7 mg/g) and amphetamine; ii) powder sold as MDMA containing methoxetamine (153 mg/g); iii) turquoise tablet with unknown logo sold as XTC containing methoxetamine (19 mg) and caffeine (10 mg); iv) white tablet with smiley logo sold as XTC containing methoxetamine (62 mg); v) white tablet with unknown logo sold as XTC containing methoxetamine (72 mg); vi) white tablet with smiley logo sold as XTC containing methoxetamine (25 mg)</p>
Belgium	<p>2012: One customs seizure of 0.2 g of powder (colour not reported) containing methoxetamine.</p> <p>2013: One customs seizure of 10 g of powder (colour not reported) containing methoxetamine. Seizure made at the Airport,</p>

(5) '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.).

	in transit from China
Bulgaria	2011: One border and customs seizure of capsules (number and/or weight not reported) containing methoxetamine..
Croatia	2012: One police seizure of 4 green tablets, marketed as 'XXXX' by www.diablo-pills.com , containing methoxetamine. One police seizure of 0.36 g of powder (colour not reported) containing methoxetamine 2013: One police seizure of a capsule with 0.22 g of powder (colour not reported) containing methoxetamine
Cyprus	2013: One seizure of 93.8 g of white powder containing methoxetamine
Czech Republic	No reported seizures
Denmark	2012: One border and customs seizure of 10 g of white powder containing methoxetamine. Three customs seizures of powder (light beige 0.55 g, white 1.1 g and white 2.3 g) in International post all containing methoxetamine. Two police seizures of white powder (0.19 g and 0.14 g) containing methoxetamine 2013: Two police seizures of white powder (0.43 g and 0.45 g) containing methoxetamine
Estonia	2013: Two police seizures of 0.2 g and 1.09 g white powder containing methoxetamine. One border and customs seizure of 9.94 g of white powder containing methoxetamine
Finland	2010: One customs seizure of 1.0 g white powder containing methoxetamine 2011: Eighty-three customs seizures of powder totalling 232.2 g containing methoxetamine. 2012: 111 customs seizures of powder totalling 229.3 g containing methoxetamine. Seven police seizures of a total of nine powders totalling 8.21 g all containing methoxetamine 2013: Forty-seven customs seizures of powder totalling 340.9 g containing methoxetamine. Four police seizure of a total of four powders totalling 1.6 g containing methoxetamine
France	Date not recorded: Five police seizures: i) three powders (colour and amount not reported) containing methoxetamine; ii) one liquid (amount not reported) containing methoxetamine; and iii) one

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	<p>powder (colour and amount not reported) containing methoxetamine and MBDB</p> <p>2011: Four police seizures of powder (colour and amount not recorded) containing methoxetamine (2) and methoxetamine with methiopropamine (2). Two powder samples from hospitals containing methoxetamine and 5-Me-O-DALT and methoxetamine and benzodiazepines</p> <p>2012: The French SINTES study identified one powder sample of methoxetamine. Eight police seizures of powder (colour and amount not reported) containing: i) methoxetamine (5); ii) methoxetamine with 4-methylethylcathinone (1); iii) methoxetamine with 4-MEC and MDVP (1); and methoxetamine with pentylone (1). One police seizure of liquid (amount not reported) containing methoxetamine, gamma-butyrolactone and 4-MEC</p> <p>2013: Eighteen customs seizures from express freight of powder totalling 678 g (weight not reported in five seizures) containing methoxetamine. Seven police seizures of powder (colour and amount not reported) containing: i) methoxetamine (4); ii) methoxetamine with ketamine (1); iii) methoxetamine with pentedrone (1); and iv) methoxetamine with 3,4-methylenedioxy-N-methylcathinone (methylone) and dimethylone (1). Five samples of powder (colour and amount not reported) collected from venues containing methoxetamine. Seven powder samples from hospitals containing: i) methoxetamine; ii) methoxetamine and mephedrone (20 g); and iii) methoxetamine with NRG-3 (10 g)</p>
Germany	<p>2012: One police seizure of 8.59 g containing methoxetamine. Not specified if powder, capsule or tablet.</p> <p>2013: Forty-three police seizures totalling 486.1 g; majority (32) not reported as to nature of seizure; ten powders, one capsule. 36 seizures contained methoxetamine only; the substances detected included: 3,4-DMMC (1), MDPV and AM-2201 (1), MDPV, para-fluoramphetamine & AM-2201 (1), MDPV & 3-FMC (1), 3-MeO-PCP (1), caffeine & taurine (1) and methiopropamine & amfetamine (1)</p>
Greece	No reported seizures
Hungary	2011: One seizure of 2 white tablets with 'LV' marking containing methoxetamine with 4-FMC and MDPV. Twenty-nine police seizures of powder totalling 62.25 g; Sixteen methoxetamine

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	<p>alone; 4-MEC, FMC, JWH-210, lidocaine, MDPV, methylone & methoxetamine (1), JWH-018 & methoxetamine (2), amphetamine, fluoroamphetamine, caffeine & cocaine (1) and MDPV & methoxetamine (1); 4-MEC (2); 4-APB, 4-MEC, 6-APB, caffeine & methoxetamine (1); 3,4-DMMC, mephedrone & methoxetamine (1); 4-FMC, 4-MEC, MDPV & methoxetamine (2); 3,4-DMMC, 4-FMC, 4-MEC, MDPV & methoxetamine (1); and 4-FA, 4-MEC, MDPV & methoxetamine (1). Nineteen police seizures of a total of 1490 tablets: i) 1072.5 yellow tablets with Puma logo containing methoxetamine and 4-FA; ii) 339 beige/yellow tablets with seahorse markings containing methoxetamine and 4-FA; iii) 17 yellow tablets with Puma logo containing 4-MEC and methylone; iv) 1.5 yellow tablets with Android logo containing methoxetamine, 4-MEC, caffeine, methylone; v) 34 white tablets with 'LV' logo containing methoxetamine, 4-FMC and MDPV; vi) 2 white tablets with 'LV' logo containing methoxetamine, 4-FA, 4-FMC, 4-MEC, caffeine and MDPV; vi) 8 yellow tablets with Playboy logo containing methoxetamine, 4-FA, 4-MEC, 6-APB, caffeine, MDPV, mephedrone, methylone; 4 pink tablets with Playboy logo containing methoxetamine, 4-FA, 4-MEC, 6-APB, caffeine, MDPV, methylone; vii) 3 pink tablets with Playboy logo containing methoxetamine, 4-FA, 4-MEC, 6-APB, MDPV, methylone. Five customs seizures of powder totalling 41,809.3 g containing methoxetamine</p> <p>2012: Eleven police seizures of powder totalling 18.0314 g; nine methoxetamine alone; one methoxetamine with 3,4-DMMC, MDMA and mephedrone; one methoxetamine with pentedrone. Six police seizures of a total of 56 tablets: i) 33 yellow tablets with Puma logo, methoxetamine with 4-FA; ii) 20 light green tablets with no markings, methoxetamine alone; iii) 3 yellow tablets with cherries marking containing methoxetamine with 3-FA and pentedrone</p> <p>2013: Four police seizures of powder totalling 1.6828 g. Two lone methoxetamine, one methoxetamine with AM-2201 and one methoxetamine with 4-FA and methylone.</p>
Ireland	2012: One police seizure of 'off white' powder containing methoxetamine (amount not reported)
Italy	2011: One police seizure of 4360 g powder (colour not reported) containing methoxetamine. One sample of 6.713 g of powder containing methoxetamine collected from a shop

	<p>2012: Five police seizures of powder (colour not reported) totalling 15.936 g containing methoxetamine. One sample of 5 g of powder (colour not reported) from the Internet containing methoxetamine</p> <p>2013: Seven police seizures of powder (colour not reported) totalling 96.6104 g containing methoxetamine. One police seizure of 0.1733 g of powder (colour not reported) containing methoxetamine and ketamine (38.22 %)</p>
Latvia	<p>2012: One seizure of 0.1654 g of white powder containing methoxetamine, MDPV, mephedrone and caffeine.</p> <p>2013: Three police seizures (0.1654 g, 0.2133 g and 55.4008 g) of white powder in small foil packages, all found to contain methoxetamine, MDPV, mephedrone and caffeine</p>
Lithuania	2012: One border and customs seizure of 1.0895 g of white powder containing methoxetamine
Luxembourg	No reported seizures
Malta	No reported seizures
Netherlands	<p>2012: 3 customs seizures of white powder totalling 0.1 kg containing methoxetamine. Samples analysed by the Netherlands Forensic Institute: i) ten samples of white powder totalling 95.8 g containing methoxetamine; ii) one tablet (colour and markings not reported) containing methoxetamine and MDMA; and iii) one sample of 0.7 g powder (colour not reported) containing methoxetamine, MDMA, ketamine, lidocaine, methamphetamine and ephedrine. Twenty-one powder samples (colour not reported) sold to users as methoxetamine or ketamine containing methoxetamine analysed by Drugs Information and Monitoring System (DIMS).</p> <p>2013: 2 customs seizures of white powder totalling 0.018 kg containing methoxetamine. One sample of 32.9 g of powder (colour not reported) analysed by the Netherlands Forensic Institute containing methoxetamine. Seven powder samples (colour not reported) sold to users as methoxetamine or ketamine containing methoxetamine analysed by Drugs Information and monitoring system (DIMS).</p>
Poland	Date not recorded: Eight police seizures of white powder totalling 0.82 g: i) methoxetamine alone (2); ii) methoxetamine with 4-HO-MET (1); iii) methoxetamine with 4-HO-MIPT, 5-MeO-DIPT (1); iv)

	<p>methoxetamine with psilocin, 4-HO-MET, 4-HO-MiPT (1); v) methoxetamine with 5-MeO-NiPT, 5-MeO-DiPT (1); vi) methoxetamine with 4-MEC, 2C-E, MDPV, buphedrone, mephedrone (1); vii) methoxetamine with caffeine and 2-DPMP. One police seizure of five yellow capsules (each weighing 0.12 g) containing methoxetamine, 2-DPMP, caffeine and piracetam. One police seizure of "a dark substance on a metal spoon" containing methoxetamine, morphine, heroin, acetylcodeine and 6-MAM. One police seizure of powder in a white-green capsule (weighing 0.52 g) containing methoxetamine and piracetam. One police seizure of five vials containing traces of methoxetamine, ethylphenidate, methylphenidate, MDPV, 2-DPMP and lidocaine.</p> <p>2010: One police seizure of 0.06 g of white powder containing methoxetamine</p> <p>2011: One police seizure of 5 white pentagonal tablets (each tablet weighing 0.55 g) containing methoxetamine. Four police seizures of white powder totalling 77.28 g containing methoxetamine</p> <p>2012: Two police seizures of a total of 12 pentagonal white tablets (each weighing 0.45-0.53 g) containing methoxetamine. One police seizure of "traces of a dark substance on two metal spoons" containing methoxetamine, morphine, codeine and papaverine. Eight police seizures of white powder totalling 63.35 g containing: i) methoxetamine (6); ii) methoxetamine, 2-DPMP, caffeine, buphedrone, piracetam (1); iii) methoxetamine, ethcathinone, 3,4-DMMC, ethylphenidate, lidocaine, phenacetin, caffeine (1). Eight customs seizures of white powder totalling 16.52g containing methoxetamine</p> <p>2013: Eight customs seizures of white powder totalling 8.8g containing methoxetamine. One police seizure of 14 'Eppendorf' vials with traces of methoxetamine and ethylphenidate, methylphenidate, 3,4-DMMC, ethcathinone, 4-MEC, caffeine, methylone. Seven police seizures of powder (4 recorded as white, 4 with no further details recorded) totalling 13.73g containing methoxetamine</p>
Portugal	<p>2011: One police seizure of 2.258g powder containing methoxetamine</p> <p>2012: One seizure of nine capsules containing methoxetamine (weight not specified)</p>

Romania	No reported seizures
Slovenia	2012: One police seizure of 2.6g white powder and one police seizure of 4x10g white powder, all containing methoxetamine 2013: One police seizure of 0.04g of white powder containing methoxetamine
Slovakia	2012: Police seizures: Three white powder (1.97g, 643.91g, 330.96g); 14 packets of light beige powder totalling 17.28g and three sets of capsules (8 "Magic Hypnotic" – 4.996g; 2 "Panoramix" – 1.27g; 15 "Magic Hypnotic" – 9.612g). All seizures only containing methoxetamine
Spain	2010: Methoxetamine detected, but no details on nature or amount of sample analysed, nor source of sample(s) 2012: Seizures through the Centre of Intelligence Against Organised Crime: i) 39 cases totalling 21g of powder containing methoxetamine; ii) 16 cases totalling 419g of powder containing methoxetamine with other substances (not specified) 2013. Seizures from unspecified source: i) 19 cases totalling 1025g of powder containing methoxetamine; ii) 2 cases of powder totalling 2.25g containing methoxetamine with other substances (not specified)
Sweden	2011: One police seizure of 0.06g white powder containing methoxetamine. One police seizure of 53 tablets (colour and markings not reported) containing methoxetamine. One customs seizure of 289g of powder (colour not reported) containing methoxetamine. 2012: One police seizure of 128.73g of powder containing methoxetamine. One police seizure of 24 tablets (colour and markings not reported) containing methoxetamine. One police seizure of 0.1g of a sample described as "other" containing methoxetamine. One customs seizure of 164.62g of powder (colour not reported) containing methoxetamine. One customs seizure of 72 tablets (colour and markings not reported) containing methoxetamine. 2013: Three police seizures of powder (colour not reported) totalling 30.26g containing methoxetamine. One police seizure of 10 tablets (colour and markings not reported) containing methoxetamine. One police seizure of 17.3g of a sample described as "other" containing methoxetamine. One police

	<p>seizure of 10ml of liquid containing methoxetamine. One customs seizure of 15 tablets (colour and markings not reported) containing methoxetamine. Nine customs seizures of powder (7 white, 2 not reported) totalling 92.18g containing: i) methoxetamine (6); ii) methoxetamine and 3-MeO-PCP (3)</p>
United Kingdom	<p>2010: One packet purchased from an Internet supplier and labelled 'methoxetamine' containing 250mg white powder confirmed to be 'high purity' methoxetamine.</p> <p>2011: Eighteen law enforcement seizures of powder (colour not reported) totalling 1076.99g containing methoxetamine. One law enforcement seizure of 2 capsules containing methoxetamine. One law enforcement seizure of 23 blue tablets with no specific markings containing methoxetamine</p> <p>2012: Two police seizures totalling 8 capsules (4 white, 4 not reported) containing methoxetamine. One police seizure of 2ml of liquid containing methoxetamine. Seventeen law enforcement seizures of tablets totalling 1013 tablets (153 blue and marked 'Matrix Fury'; no details for remaining tablets) containing methoxetamine. 390 law enforcement seizures of powder totalling 7353.0133g containing: i) methoxetamine (388); ii) methoxetamine and 4-MMC (1); methoxetamine with chlordiazepoxide and THC (1). 158 law enforcement seizures totalling 1015.2g containing methoxetamine (nature of seizures not reported)</p> <p>2013: Twenty-six law enforcement seizures of powder (colour not reported) totalling 2512.078g containing methoxetamine. Twenty-four law enforcement seizures (nature of seizures not reported) totalling 842.03g containing methoxetamine</p>
Norway	<p>2011: Four police seizures of powder (3 white, 1 yellow) totalling 2.07g containing methoxetamine.</p> <p>2012: Six police seizures totalling 250 capsules containing methoxetamine. Six police seizures totalling 3872 tablets (1024 brown, 2814 not specified, 34 white) containing methoxetamine. Twenty-four police seizures of white or yellowish-white powder totalling 120.382g containing methoxetamine</p> <p>2013: Nine police seizures of white or yellowish-white powder totalling 37.96g containing methoxetamine (8) or methoxetamine and 3-methoxy-PCP (1). One police seizure of one cylinder shaped tablet containing methoxetamine and one police seizure</p>

	of 50 brown tablets containing methoxetamine
Turkey	2012: One seizure of 0.1g of 'light green plant' containing methoxetamine with JWH-122 and AM-2201

The EMCDDA Internet snapshot studies conducted in 2011 and 2012 found that methoxetamine was available from a number of sites selling to the European Union. These results are discussed in Section D3.1. 'Availability and quality of the new psychoactive substance on the market'

In October 2011, the Observatoire Français des Drogues et des Toxicomanies, (OFTD, French Monitoring Centre for Drugs and Drug Addiction), identified thirteen Internet sites that were selling methoxetamine using a "non-exhaustive search". They stated for two of these sites, prices had decreased by 15–25 % in the month prior to the study [OFTD 2011]. The amounts of methoxetamine available on these sites varied from 250 mg to 5 kg, with a price of 16 EUR per gram.

The price of methoxetamine reported to the EMCDDA varies across Europe, some examples of reported prices are: Belgium 25 EUR per gram, France 16–30 EUR per gram, Italy 21 EUR per gram, Poland 14–18 EUR per gram, Spain 20–60 EUR per gram and the Netherlands 20–30 EUR per gram. In the 2011 EMCDDA snapshot of Internet retailers selling new psychoactive substances, the reported price for 10 g of methoxetamine was 145–195 EUR [EMCDDA Snapshot 2011].

There appear to be no co-ordinated national or European population surveys on methoxetamine use. Despite there being no population level surveys looking at the scale of methoxetamine use, it is likely based on the seizure data/surveys summarised above and the health risks discussed in Section D1.2 that methoxetamine is present in drug markets across most of the European Union.

In the annual non-representative 2011–2012 Global Drugs Survey, previously more commonly known as the "MixMag" survey, of the 7,700 United Kingdom based respondents, both life-time (4.9 %) and last year (4.2%) use of methoxetamine was considerably lower than ketamine (47.5 % and 24.5 % respectively) [MixMag 2012]. In those defined as "regular United Kingdom clubbers" the last year use of methoxetamine was lower than that of ketamine (6 % compared to 40 %). Data was reported on four different reasons as to why respondents used methoxetamine: i) easier to get hold of – 73 %; ii) better value for money – 20 %; iii) curious or it was sold as ketamine – 20 %; less damaging to liver / kidneys – 18 %. It is not clear as to whether these were pre-defined categories respondents could select, or whether other reasons for use were stated by respondents. ⁽⁶⁾

(6) Information on methoxetamine use from the 2012–2013 Global Drug Survey is limited to: 'Drugs that didn't make it into the top 20 (tried by less than 3% of UK clubbers) included Benzo Fury, methoxetamine, anabolic steroids, mescaline, heroin and GBL/GHB' [MixMag 2013].

In a survey of 343 respondents in ten nightclubs in Lancashire, UK conducted over six fieldwork nights in March, April and June 2012, life-time, last year, last month and last week use of methoxetamine was 3 %, 3 %, 2 % and 1 % respectively [Measham 2012]. It is not clear from this report as to how many of the respondents were surveyed before and after the UK temporary control measures for methoxetamine were introduced on the 5 April 2014.

The Netherlands National Focal Point reported data from a web survey among frequent visitors to parties, festivals and clubs undertaken by Goossens *et al* in 2013. There was limited information on the survey population in this report and no information on the number of individuals surveyed. The lifetime, last year and last month prevalence of methoxetamine were 3.0 %, 2.3 % and 0.3 % respectively. This was considerably lower than the rates reported for ketamine: lifetime – 19.3 %; last year – 12.8 %; and last month – 5.0 %.

In a survey of 313 individuals attending 'gay friendly' nightclubs in South East London in July 2011, self-reported use of methoxetamine was considerably lower than ketamine for life-time (6.1 % vs. 60.3 %), last year (4.8 % vs. 48.7 %) and last month (1.9 % vs. 34.9 %) use [Wood QJM 2012; Wood NACCT abstract 197 Clin Tox 2013]. Only 1.6 % reported use or planned use of methoxetamine on the night of the survey compared to 41.0 % for mephedrone and 16.7 % for cocaine [Wood QJM 2012]. In March 2012, methoxetamine was controlled in the United Kingdom under a Temporary Class Drug Order (TCDO) [ACMD TCDO methoxetamine]. When the surveys were repeated in July 2012, 33.1 % of the 330 individuals surveyed had heard of methoxetamine compared to 97 % for ketamine (data was not available for 2011 on this for comparison) [Wood Clin Tox abstract 2013]. There had been a significant increase in self-reported use of methoxetamine between the 2011 and 2012 surveys: i) life-time use 2011: 6.1 % vs. 2012: 21.0 %; ii) last year use 2011: 4.8 % vs. 19.2 %; and iii) last month use 2011: 1.9 % vs. 2012: 10.1 %. Interestingly although there was no significant change in life-time and last year use of ketamine between the two surveys, there was a reduction in last month use of ketamine (2011: 34.9 % vs. 2012: 24.4 %).

The analysis of pooled anonymous urine samples from portable stand-alone male urinals in the night-time economy and at festivals can be used to detect and monitor the use of both classical recreational drugs and new psychoactive substances [Archer JRH QJM 2013; Archer JRH Clin Tox 2014; Archer JRH Current Drug Review 2013; Archer JSU 2013]. Methoxetamine was not detected in a pooled urine sample from a 'gay friendly' night-club in a South East London in July 2011 [Archer JSU 2013]. However, in a single collection on one Saturday night in March 2012 from urinals in twelve different locations in and around the City of Westminster, London (an area with a large number of night-time economy venues), methoxetamine was detected in one of the urinals, whereas ketamine and mephedrone were both detected in 6 urinals [Archer JRH QJM 2013]. When the study was repeated collecting and analysing urine from the first Saturday night of each month between July to December 2012, methoxetamine was not detected in any of the urinals in the study period, compared to ketamine in 4–8 urinals per month and mephedrone in 2–8 urinals per month [Archer JRH Clin Tox 2014].

Section D. Health Risks

D1. Acute health effects

D1.1. Animal data

There is no animal data in the scientific literature on the acute health effects of methoxetamine.

D1.2. Human data

D1.2.1 User reports

By February 2014, there were 26 reports on the user website Erowid relating to unwanted effects from the self-reported use of methoxetamine [Erowid Health Effects 1; Erowid Health Effects 2; Erowid Health Effects 3; Erowid Health Effects 4]. Of these, 18 related to lone methoxetamine use and 8 related to the use of methoxetamine in combination with at least one other pharmacologically active substance, including controlled drugs or new psychoactive substances (for example: methadone, cannabis, 25I-NBOMe, GHB, AM-2201, 6-APB, MDMA, nitrous oxide, benzodiazepines, alcohol and 4-AcO-DMT). Four individuals reported needing medical attention or review in an ED in relation to the unwanted symptoms that they experienced.

There are numerous symptoms reported including catatonia, nausea and severe vomiting, slow and/or irregular heart rates, 'dissociate haze', diarrhoea, distorted vision, disorientation, paranoia, post-use depression, mental slowing, anxiety, black outs/loss of consciousness, difficulty speaking, buzzing/ringing in the ears, difficulty breathing, sweating, headaches, confusion and difficulty moving/co-ordinating limbs.

It is not possible to estimate the prevalence of these symptoms based on the user reports available and it is important to note that these are unconfirmed anecdotal reports from users.

D1.2.2. Non-fatal intoxications associated with methoxetamine

Non-fatal intoxications reported by the Member States

A total of 120 non-fatal intoxications were reported by the Member States to the Early Warning System: Belgium (2 cases), France (3), Germany (9), Italy (15), and Sweden (91); of these, analytical confirmation of the presence of methoxetamine in biological samples was reported in 55 cases: Belgium (1), France (3), Italy (13), and Sweden (38) (Table 4 provides a summary of the 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 paracetamol were also detected); while in a third case methoxetamine was detected in a sample of hair. No further details are available at this time ⁽⁷⁾.

Germany

Germany reported 9 non-fatal intoxications associated with methoxetamine. No further details are available on these cases.

Italy

Italy reported 15 non-fatal intoxications which occurred between March 2011 and July 2013 (1 case in 2011; 9 in 2012; and, 5 in 2013). Thirteen of these cases were analytically confirmed.

Sweden

Sweden reported 91 non-fatal intoxications that occurred 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 [Lovisa Ostberg Clin Tox 2013]. Of these 38 analytically confirmed cases, 11 were lone methoxetamine and 27 were "mixed poisonings" involving one or more additional co-used substance (exact frequency of detection of other substances was not provided)⁽⁸⁾. The frequency of symptoms for both groups is shown in Table 3 below; there was no definition provided for the clinical features reported, nor whether these were pre-defined and therefore other clinical features were not recorded. Poisoning severity scores for the 11 methoxetamine only cases were mild (7 cases), moderate (2) and severe (2) and for the 27

(7) 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.

(8) See Table 3 for a summary of these cases.

mixed methoxetamine / other drug cases were mild (11 cases), moderate (10), severe (3) and unknown (3).

Table 3: Clinical features reported in the 38 analytically confirmed non-fatal intoxications reported by Sweden [Lovisa Ostberg Clin Tox 2013].

Symptom	Methoxetamine only cases (n=11)	Mixed methoxetamine / other drug cases (n=27)
Hypertension	36%	48%
Tachycardia	36%	44%
Hallucinations	27%	22%
Nystagmus	27%	26%
CNS depression	27%	44%
Mydriasis	27%	30%
Anxiety	18%	19%
Muscular symptoms	18%	11%
Agitation / restlessness	9%	33%

Table 4: Non-fatal intoxications reported by the Member States to the Early Warning System in which methoxetamine was analytically confirmed in biological samples.

Country	Date of non-fatal intoxication (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	30 µg/L (plasma) 408 µg/L (urine)	Negative	Case from Lyon, France. No further details or clinical information reported.
France	Jun 2012	Hair	+	Not reported	Case from Toulouse, France. No further details or clinical information reported.
France	2012	Blood	136 ng/mL	Cannabis (+) Paracetamol (+)	Case from Garches, France. No further details or clinical information reported.

Country	Date of non-fatal intoxication (gender, age)	Biological sample	Methoxetamine results	Results for other substances	Notes
Italy	Feb 2012 (M, 27)	Blood and urine	0.0002 mg/mL (serum) 0.167 mg/mL (urine)	Methorphan (present in urine)	He reported that he had "snorted half a package" of methoxetamine (2-(3-Methoxyphenyl)-2-(ethylamino)cyclohexanone) purchased on the Internet and also ingested an undefined amount of dextromethorphan. On admission to the emergency room he was tachycardic (HR 120 bpm), confused, hallucinating and "severely agitated". He required treatment with intravenous benzodiazepines (diazepam) initially. By the following day he was being treated with midazolam 15 mg/day, delorazepam 7 mg/day and valproic acid 400 mg/day; subsequently, the delorazepam dosage was increased up to 20 mg/day and haloperidol was added. Although a methoxetamine analytical standard was not available, by use of the product residue, it was estimated that the urine and serum concentrations were 167 microgram/ml and 0.2 microgram/ml respectively.
Italy	Jun 2012 (M, 38)	Blood and urine	167 ng/mL (blood) 7400 ng/mL (urine)	APB-isomers (164 ng/mL) Amphetamines (+) MDMA (traces) blood alcohol content 2.3 g/L	Admitted from a rave accompanied by the police with serious agitation and violent behavior. On admission he was mydriatic, stuporous, sometimes catatonic, hypertensive (150/90 mmHg) with a normal heart rate (78 bpm) and normothermic (36°C). The patient was treated with intravenous fluids and left hospital against medical advice after about 8 hours of observation.

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Country	Date of non-fatal intoxication (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 (+)	Acute intoxication following attendance at a 'rave party'. On admission to the ED, he had severe psychomotor agitation associated with hallucinations.
Italy	Oct 2012 (M, 24)	Urine	+	Alcohol (2.7 g/L) Methadone (+) Cocaine (+) Amphetamines (+) MDMA (+). APB-isomers (+) Levamisole (+)	Admitted to the ED with severe agitation, stupor, mydriasis, mild hypertension (130/80 mmHg) and significant tachycardia (150 bpm); "no 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 with a normal heart rate. ECG was normal.
Italy	Nov 2012 (M, 23)	Urine	+	Alcohol (2.2 g/L in blood) THC (+) Ketamine and norketamine (+)	Reported using ketamine and cannabis at a disco and presented to the emergency room in a coma, with normal vital parameters except for peripheral oxygen saturation (Sat O ₂ 90%).

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Country	Date of non-fatal intoxication (gender, age)	Biological sample	Methoxetamine results	Results for other substances	Notes
Italy	Nov 2012 (M, 22)	Urine	+	THC (+) Ketamine and norketamine (+)	Reported using ketamine and THC at a disco and presented to the emergency room with mydriasis, severe psychomotor agitation, hallucinations and in a dissociative state.
Italy	Nov 2012 (F, 16)	Urine	+	THC (+)	Reported to have consumed alcohol and other unspecified substances at a rave party. She presented to the emergency room confused, agitated with some amnesia for the events that happened during the night.
Italy	Nov 2012 (F, 17)	Urine	+	THC (+) Ketamine and norketamine (+) Blood alcohol content 35 mg/dL	Reported to have consumed alcohol and other unspecified substances at a rave party. She presented to the emergency room confused, disoriented, agitated with some amnesia for the events that happened during the night.
Italy	Jan 2013 (F, 22)	Urine	+	Cocaine and metabolites (+) Opiates (+) Buprenorphine (+) Levamisole (+)	22 year old female reported using ketamine, heroin and alcohol at a New Year's celebration and presented to the emergency room unresponsive with response to painful stimuli only. She was normothermic with a mild hypertension (140/100 mmHg) and mild tachycardia (100 bpm) with no other alterations of the rhythm. It was reported that there was "only slight clinical response to naloxone"; the dose / route of administration were not specified.

Country	Date of non-fatal intoxication (gender, age)	Biological sample	Methoxetamine results	Results for other substances	Notes
Italy	Jan 2013 (M, 23)	Urine	+	Amphetamine (+) Cocaine and metabolites (+) MDMA (+) Levamisole (+)	Reported using ketamine at a New Year's celebration and presented to the emergency room unresponsive with response to painful stimuli only. On examination he had normal size pupils, vertical nystagmus, was normothermic, with a normal blood pressure and heart rate (98 bpm). There was alcohol halitosis. The patient was treated with naloxone, leading to slight clinical improvement. Blood tests showed slightly elevated CPK (390 IUL).
Italy	Feb 2013 (F, 22)	Urine	+	Negative	Admitted to the emergency room with chest pain, diffuse pain sensation and tremors having reported that he used both ketamine and LSD.
Italy	Sept 2013 (M, 24)	Urine	+	Negative	Admitted unconscious to the emergency room following use of alcohol and methoxetamine.
Sweden	Mar 2011 – Oct 2012	Blood and Urine	+	None	11 cases identified from the Swedish Poisons Information Service. See main text for further discussion of these cases.

Country	Date of non-fatal intoxication (gender, age)	Biological sample	Methoxetamine results	Results for other substances	Notes
Sweden	Mar 2011 – Oct 2012	Blood and Urine	+	5-IT ⁽⁹⁾ (+) Amphetamine (+) Benzodiazepines (+) Buprenorphine (+) Ethanol (+) MDPV (+) Morphine (+) 4-OHMET ⁽¹⁰⁾ (+) Cannabis/THC (+) Tramadol (+)	27 cases identified from the Swedish Poisons Information Service. See main text for further discussion of these cases.

(9) 5-(2-Aminopropyl)indole

(10) 4-Hydroxy-methylethyltryptamine

Non-fatal intoxications published in the literature

In addition to the non-fatal intoxications reported by the Member States, 15 non-fatal intoxications were identified in the scientific and medical literature. These cases were from Poland (3 cases), United Kingdom (8), Switzerland (1), and the US (3); of these, analytical confirmation of methoxetamine in a biological sample was reported in 11 cases: Poland (2), United Kingdom (7), Switzerland (1), and the US (1). In one case from the United Kingdom, a collected sample of the substance used by the patient was analysed and found to contain methoxetamine. These cases are summarised below.

Case reports from within the European Union with analytical confirmation of biological samples

In a report from Poland, a patient (age not specified) presented to hospital with confusion, hallucinations, tachycardia (120 bpm) but normal blood pressure (130/80 mmHg); no further clinical details were provided [Łukasik-Głębocka M *Przegl Lek.* 2013]. Methoxetamine was detected in serum (270 ng/mL) and urine (660 ng/mL).

A 24 year old male was admitted to a toxicology clinic in Poland with suspicion of use of a new psychoactive substance [Hydzek P *Prob Forens Sci* 2012]. He had taken methoxetamine (50–100 mg intranasally) for several days prior to hospitalisation. He had become confused, developed mobility problems and lost consciousness. On arrival at the ED he was conscious with slowed psychomotor performance, having occasional hallucinations; heart rate was up to 120 bpm and blood pressure up to 140/90 mmHg. He was observed for “several hours” and his clinical features settled. Methoxetamine was detected in his urine (7200 ng/mL) and serum (450 ng/mL).

A 30 year old man presented to an ED in the United Kingdom with agitation, confusion and hallucinations following use of methoxetamine after heavy alcohol consumption [Hamilton EJ 2012]. On examination the clinical findings of note were that he was hypertensive (155/99 mmHg) with a normal heart rate (80 bpm), pyrexial (37.9°C) with dilated reactive pupils. His symptoms settled with supportive care, and he did not require benzodiazepines or other treatment for his agitation. A urine immunoassay screen was “negative for all drugs of abuse”, but subsequent gas-chromatography mass-spectrometry (GC-MS) of the sample detected an unknown compound that was consistent with methoxetamine.

There is a small case series of three patients who presented to an ED in the United Kingdom following the use of methoxetamine [Wood DM *EJCP* 2011].

Case One: A 42 year old male presented with reduced level of consciousness (GCS 6/15), tachycardia (135 bpm), hypertension (187/83 mmHg), pyrexia (38.2°C) with a normal neurological examination following nasal insufflation of a “white powder”. He was admitted for observation and treated with oral benzodiazepines (diazepam). Once he had recovered, he admitted drinking three pints of beer and to nasal insufflation of 0.75g of “benzofury” and 0.5g of methoxetamine both sourced from an Internet supplier of research chemicals. Serum methoxetamine concentration was 0.12 mg/L; the only other drug detected was 5-APB or 6-APB.

Case Two: A 29 year old male was found "catatonic" with tremor, visual hallucinations, confusion and dilated pupils. He presented to the ED with confusion, hypertension (201/104 mmHg), tachycardia (121 bpm) with a normal neurological examination. He was admitted for observation overnight and treated with oral benzodiazepines (diazepam). The following day he admitted he had purchased 2g of methoxetamine from an Internet supplier, of which he diluted 200mg in water and then ingested orally. Serum methoxetamine concentration was 0.09 mg/L; other drugs detected were diphenhydramine and venlafaxine.

Case Three: A 28 year old male presented with collapse, agitation and aggression with white powder visible around his nostrils, suggesting nasal insufflation. On examination he was drowsy (GCS 10), confused, agitated, tachycardic (113 bpm), hypertensive (198/78 mmHg) and had dilated pupils. He was treated with intramuscular benzodiazepines (midazolam) and his symptoms rapidly settled. He subsequently admitted purchasing methoxetamine from a brick and mortar headshop. Serum methoxetamine concentration was 0.2 mg/L; other drug detected was midazolam (the sample was taken after midazolam administration in the ED).

There is one further small case series of three patients who presented to the ED in the United Kingdom following the use of methoxetamine [Shields JE Clin Tox 2012].

Case One: A 19 year old male presented with severe incoordination and dysarthria 4-5 hours after nasal insufflation of what he believed to be ketamine. On examination he was drowsy (GCS 13), disorientated with severe cerebellar ataxia, coarse nystagmus and slurred speech. He was tachycardic (107 bpm) and hypertensive (194/110 mmHg). His haemodynamic changes settled within 2-3 hours, but his cerebellar toxicity was more prolonged and settled over the next four days. Serum methoxetamine concentration was 0.24 mg/L in a sample taken four hours after use.

Case Two: A 17 year old male presented with severely impaired consciousness and loss of consciousness following nasal insufflation of methoxetamine supplied by a friend. On presentation he was comatose (GCS 7) with mild hypertension (148/104 mmHg) and a normal heart rate (72 bpm). As his level of consciousness improved he was noted to have severe truncal ataxia, dysarthria, dysdiadochokinesia, incoordination and horizontal nystagmus. These symptoms settled over the next 16 hours with no specific treatment. Serum methoxetamine concentration was 0.45 mg/L in a sample taken two hours after use.

Case Three: An 18 year old male presented to the ED with severe limb incoordination and imbalance 30 minutes after nasal insufflation of methoxetamine. He was noted to be drowsy (GCS 10), with mild hypertension (151/112 mmHg) and normal heart rate (67 bpm). He had slurred speech, horizontal nystagmus, impaired upper limb co-ordination and truncal ataxia. His symptoms also resolved within 16 hours of use. Serum methoxetamine concentration was 0.16 mg/L in a sample taken two hours after use.

Case reports from within the European Union with analytical confirmation from a drug sample collected from the patient

A 35 year old male, with underlying bipolar disorder and non-compliant with lithium treatment, presented to an ED in the United Kingdom having been found unresponsive with

bleeding from his left nostril following insufflation of a white powder [Westwell AD DTA 2012]. An empty packet found with the patient was labelled 'methoxyphenyl-2-(ethylamine) cyclo-hexanone' with the chemical structure displayed. On arrival in the ED he was drowsy and incoherent (he described "being in contact with both heaven and hell and in the spirit of his dead father"). On examination he was hypertensive (167/110 mmHg) but not tachycardic, normothermic and had a normal neurological examination apart from bilateral papillary mydriasis. After he had recovered, he was admitted for on-going psychiatric assessment and discharged "several days later". He admitted to having purchased the powder from the Internet; initially he nasally insufflated 25 mg of this powder, followed 30 minutes later by nasal insufflation of a further 25 mg as he was "pleased" with the initial effects. He used the remaining 950 mg in one go by nasal insufflation. Analysis of the powder residue confirmed it contained methoxetamine. There was no analysis of biological samples to confirm that he had used this powder or to exclude use of any other drugs.

Case reports from outside the European Union with analytical confirmation of biological samples

A 19 year old male with underlying drug abuse, psychosis, depression and attention-deficit hyperactivity disorder presented to an ED in Switzerland after intravenous injection of an unknown amount of methoxetamine [Hofer KE 2011]. He had extreme agitation, ataxia and a reduced level of consciousness. On examination he was hypertensive (168/77 mmHg), tachycardic (134 bpm), pyrexial (37.6°C) with dilated pupils and nystagmus. He was treated with intravenous benzodiazepines (midazolam and diazepam) with some resolution of his symptoms; he was then treated with chlorprothixene for on-going insomnia. The following day he was transferred to an inpatient psychiatric facility for on-going irritation and mild agitation. It should be noted that two days prior to this episode, he had been admitted following intravenous injection of 2g of MDMA with similar symptoms. Screening of a serum sample taken 5 hours after injection of the methoxetamine was positive for methoxetamine, MDMA, hydroxybupropion, aripiprazole, midazolam, diazepam and chlorprothixene. It is therefore not possible to determine whether the clinical features on the second admission were due to methoxetamine, MDMA or a combination of the two.

In Massachusetts, USA, a male driver (age not specified), was stopped for driving his car around with a flat front tyre [Elian AA J Forensic Sci 2014]. When examined by a drug recognition expert, he had a thick, slurred, and deliberate speech, his eyes were red, watery, and bloodshot. His eyelids were droopy, then wide open when spoken to and he had a blank, vacant expression. His movements were slow and deliberate, and his motor skills appeared to be diminished. It was reported that he had "twitching", uncontrolled movements, lack of smooth pursuit in both left and right eyes and bilateral nystagmus. Based on this the officer was concerned that the driver was driving under the influence of drugs. The driver admitted taking "bath salts" and several other drugs including MDMA and Klonopin (clonazepam); he also admitted that he had a bag of 4-hydroxy-N-methyl-N-ethyltryptamine in the car. He was taken to a local hospital – no clinical details are reported regarding his assessment in the hospital. A blood sample was taken and in addition to methoxetamine (10 ng/mL), clonazepam, 7-aminoclonazepam, carboxy-THC, diphenhydramine and MDMA were detected.

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Case reports from within the European Union with no analytical confirmation

A 25 year old male presented to an ED in Poland with a coma following use of methoxetamine [Sein Anand J 2012]. He had a history of ethanol and codeine abuse, and had been using methoxetamine for approximately one year to reduce the agitation, excitement and nervousness he experienced after using codeine (usually 100mg of methoxetamine injected 3 hours prior to use of codeine). On this occasion, he reported injecting 750mg of methoxetamine intramuscularly into his right buttock three hours prior to his usual 80 tablets of NeoAzarine (10 mg codeine phosphate per tablet). One hour later (four hours after injection of the methoxetamine) he became unconscious. After presentation to the ED he became increasingly agitated requiring pharmacological (benzodiazepine) and physical restraint. He developed tachycardia and hypertension during the periods of agitation, although his neurological examination remained normal. There was no analysis of biological samples from the patient to confirm methoxetamine use or to determine the concentrations of codeine (or other drugs) which may have explained some or all of his symptoms.

Case reports from outside the European Union with no analytical confirmation

The first published case of methoxetamine toxicity was from the US of a 32 year old male who presented to the ED with agitation following intramuscular injection of an unknown amount of methoxetamine [Ward J Clin Tox 2011]. On examination he was tachycardic (heart rate 105 bpm) with a blood pressure of 140/95 mmHg, dilated reactive pupils (6mm) and bilateral rotatory nystagmus. After eight hours observations, his clinical symptoms settled and prior to discharge he was able to confirm that he had purchased the methoxetamine from the Internet. There was no analysis of biological samples from the patient to confirm methoxetamine use, and there was no remaining powder to analyse.

There is one further case published in abstract only of a 29 year old individual in the US who developed altered mental status and agitation following self-medicated use of methoxetamine for analgesia for chronic foot pain [Wilde JM Clin Tox 2012]. He had previously used 5–10 mg every four hours five days a week for analgesia and 100 mg by nasal insufflation for recreational use. On this occasion, he sampled a new bag of 'MXE' by dipping a wet finger into the powder and then licking it; this is the only time that he reported an 'abnormal reaction' to methoxetamine.

Other information published in the literature

The United Kingdom National Poisons Information Service has reported the pattern of calls and access to the online TOXBASE service before and after the introduction of a temporary control measure (known as a Temporary Class Drug Order, which made it unlawful to supply, possess with intent to supply, produce, and import or export methoxetamine except under licence) for methoxetamine on 5 April 2012, along with description of the clinical characteristics of toxicity from cases reported by telephone to the National Poisons Information Service [Hill SL EMJ 2012]. Data from poisons information services on frequency of toxicity and patterns of clinical symptoms needs to be interpreted with caution, as they are

not contacted about all cases of toxicity with a particular compound and not all symptoms may be reported during the telephone call or follow-up. There were no enquiries to the National Poisons Information Service concerning methoxetamine prior to October 2010. The number of enquires subsequently increased in late 2011 and early 2012, but reduced from April 2012. There were 151 TOXBASE accesses in the 3 months prior to the introduction of the temporary control measure in the United Kingdom on 5 April 2012, which reduced by 79 % in the three months after to 32. Similarly telephone calls to the National Poisons Information Service fell by 80 % from 15 in the 3 months prior to the introduction of the temporary control measure to 3 after its introduction. There are a number of potential explanations for the decline in enquiries to the National Poisons Information Service regarding methoxetamine toxicity since the introduction of the temporary control measure, not simply that this reflects a reduction in use due to the introduction of the temporary control measure. These include an actual reduction in the number of presentations to hospital with acute methoxetamine toxicity; increased awareness amongst clinicians about methoxetamine and its associated toxicity/management (and therefore a decrease in their use of National Poisons Information Service for support in the management of cases of methoxetamine toxicity); or a reduction in the use of methoxetamine. It is not possible to determine to what extent these and/or other factors have contributed to the decline in NPIS enquiries concerning methoxetamine toxicity.

Of the total 47 telephone enquiries to the National Poisons Information Service, 35 (74 %) related to males, with an overall median age of 24 years (range 16 to 49 years). 38 (81 %) cases were reported to be lone methoxetamine ingestions; in the remaining 9 cases, reported co-ingested substances were ibuprofen, alcohol, dextromethorphan, 'NRG-3', etizolam, 5-IAI, co-codamol, cannabinoids and other unknown recreational drugs. There were no reported fatalities in these patients. Clinical symptoms were grouped into six different toxidromes and the frequency of these clinical features is outlined in Table 5.

Table 5: Clinical symptoms / features reported in telephone enquiries to the United Kingdom National Poisons Information Service relating to methoxetamine.

Toxidrome	Reported Terms	% of total (95% CI)
Stimulant	Tachycardia, hypertension, mydriasis, palpitation, increased sweating	36 (24 to 50)
Acute mental health disturbance	Agitation, confusion, euphoria, aggression, hallucination, paranoia, hysteria, manic reaction, psychosis	43 (30 to 57)
Dissociative	Catatonia, dystonia, hypertonia, tetany	11 (5 to 23)
Cerebellar	Nystagmus, tremor	6 (2 to 17)
Reduced	Reduced consciousness level, stupor, somnolence,	17 (9 to 30)

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consciousness	coma	
Seizures	Seizures	2.1 (0 to 11)

D1.2.3. Deaths associated with methoxetamine

Deaths reported by the Member States

There have been 20 deaths reported by the Member States to the Early Warning System in which there was analytical confirmation of methoxetamine in post-mortem biological samples: Austria (1 death), Finland (1), France (1), Poland (1), Sweden (1) and the United Kingdom (15).

Data on deaths associated with methoxetamine needs, like all data on drug related deaths, to be interpreted carefully. Detection of a drug in post-mortem samples does not necessarily mean that this drug is responsible for, or has contributed to, death. There is also the potential that methoxetamine associated deaths in other countries may not have been detected because methoxetamine was not screened for in post-mortem samples or samples were not taken for toxicological analysis.

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 involving a 26 year old male with underlying depression treated with venlafaxine and a history of drug abuse was found lying in his flat surround by several 'red line' plastic bags; one was labelled "2-(3-methoxyphenyl)-2-(ethylamino)-cyclohexanone" and another "Haze". At autopsy pulmonary oedema was found. Analysis of a post-mortem femoral blood sample detected methoxetamine (8.6 µg/gram), venlafaxine (0.3 µg/gram), O-desmethylvenlafaxine (0.4 µg/gram) and tetrahydrocannabinol (0.001 µg/gram). In addition three synthetic cannabinoid receptor agonists were detected: AM-694 (0.00009 µg/gram), AM-2201 (0.003 µg/gram) and JWH-018 (0.00005 µg/gram). There is no formal coroner or equivalent decision on the cause of death, although the authors postulate that the cause of death was an unintentional acute intoxication related to methoxetamine [Wikstrom M JAT 2012].

United Kingdom

The United Kingdom reported a total of 15 deaths associated with methoxetamine 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

(11) 5,6-Methylenedioxy-2-aminoindane

(12) 5-Iodo-2-aminoindane

(13) Alpha-methyltryptamine

(14) 6-(2-Aminopropyl)benzofuran

intoxications the concentrations of methoxetamine were reported (see Annex 2). In the remaining six cases no cause of death was reported.

Table 6: Deaths reported by the Member States to the Early Warning System in which methoxetamine was analytical confirmed in post-mortem biological samples.

	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.

	Country	Date of death (gender, age)	Biological sample	Methoxetamine result	Results for other substances	Notes
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. ⁽¹⁵⁾
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

(15) Further details of this death have been published in the literature [Wikstrom M JAT 2012] and is discussed in more detail above.

	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 methiopropamine toxicity [sic]

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	Country	Date of death (gender, age)	Biological sample	Methoxetamine result	Results for other substances	Notes
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
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

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	Country	Date of death (gender, age)	Biological sample	Methoxetamine result	Results for other substances	Notes
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	<p>Amitriptyline (0.13 mg/L in blood and present in gastric sample)</p> <p>Cocaine (0.44 mg/L in blood and present on nasal swabs)</p> <p>Diazepam (4.27 mg/l in blood, 9 mg in gastric sample) and metabolites</p> <p>MDMA (0.20 mg/L in blood, 3 mg in gastric sample and present on nasal swabs)</p> <p>MDA (present in blood)</p>	Case of death was reported as mixed drug toxicity

D2. Chronic Health Effects

D2.1. Animal Data and *In Vitro* Studies

There have been no *in vitro* studies investigating the potential for chronic toxicity associated with methoxetamine.

There has been only one animal study which has investigated the potential for chronic renal and bladder toxicity associated with methoxetamine [Dargan PI 2014]. This study used a mouse model that has previously been used to investigate the chronic renal tract toxicity associated with ketamine [Yeung LY 2009, Wai MS 2012, Tan S 2011]. This is important because methoxetamine has been marketed to users as a 'bladder friendly' alternative to ketamine [Morris H 2011].

In this study, eight Institute of Cancer Research mice were divided into control (n=3) and methoxetamine-treated (n=5) groups. Methoxetamine-treated mice received 30 mg/kg methoxetamine hydrochloride dissolved in 20 mL saline intraperitoneally daily for three months; control animals had a daily intraperitoneal injection of 20 mL saline for three months. At the end of the three month period, the animals were sacrificed and histological examination, immunocytochemistry using polyclonal anti-CD4 antibodies and sirius-red staining for collagen were performed.

Histopathological examination revealed numerous changes within both the tubules and glomeruli of the kidneys of the methoxetamine-treated mice. These included inflammatory cell infiltration, tubular cell necrosis, tubular colloidal casts, cystic vacuolation of the tubules and glomerular damage. The percentage of shrunken glomeruli (defined as having a size that was half or less than normal) was $1.9 \pm 0.3\%$ in control mice and $9.8 \pm 0.8\%$ in methoxetamine-treated mice ($p < 0.0001$); the proportion of abnormal glomeruli in the methoxetamine treated mice ($23.5 \pm 2.9\%$) was greater than in the control mice ($10.2 \pm 2.6\%$), ($p < 0.01$). There was a greater proportion of proximal tubular cell degeneration in the methoxetamine-treated mice ($20.4 \pm 1.1\%$) than in the control mice ($2.9 \pm 0.3\%$) ($p < 0.0001$).

Significant changes were also seen in the bladder of methoxetamine-treated mice with infiltration of fibroblasts, lymphocytes and macrophages in the lamina propria and submucosal layers. There was a greater density of mononuclear cells in the bladder lamina propria and submucosa in methoxetamine-treated (43.0 ± 2.1 per $250 \mu\text{m} \times 250 \mu\text{m}$ under 100x magnification) than control mice (7.1 ± 1.2 per $250 \mu\text{m} \times 250 \mu\text{m}$ under 100x magnification), $p < 0.001$. In two of the five methoxetamine-treated animals, there was halo-like degeneration of the muscle layer of the bladder. There was an increase in sirius-red positive sites for collagen in the sub-mucosal layers and in between muscular bundles of the bladder in all methoxetamine-treated mice compared to control mice. CD4 positive staining by immunocytochemistry was seen in the submucosa and lamina propria of the bladder of all methoxetamine-treated mice and muscle layer of two methoxetamine-treated mice. None of these Sirius-red or CD-4 positive changes were seen in the control mice.

In summary, this study demonstrated that three months of daily 30mg/kg intra-peritoneal methoxetamine resulted in significant bladder and renal toxicity in mice. Changes in the kidney were seen at both a tubular and glomerular level and the bladder changes included inflammatory changes with subsequent fibrosis. These changes are similar to those that were seen in comparable animal models of chronic ketamine administration [Yeung LY 2009, Wai MS 2012, Tan S 2011]. Further work is required to determine the time course of the onset of these effects, the dose threshold for bladder and renal toxicity, and whether the effects are reversible with methoxetamine cessation. The potential that metabolites of methoxetamine may be involved in the chronic toxicity of the drug also deserves further study.

D2.2. Human Data

To date there have been no reported studies investigating chronic physical health effects associated with methoxetamine use. However there is the potential for long-term physical harm as a direct result of acute methoxetamine toxicity (e.g. prolonged seizures resulting in cerebral hypoxia). In addition, in view of the data from the animal model demonstrating that chronic methoxetamine exposure is associated with renal tract and bladder toxicity, it is likely that long-term methoxetamine use will be associated with similar bladder toxicity as seen with long-term ketamine use [ACMD Ketamine report 2013; Chu 2007; Chu 2007; Cottrell 2008; Cottrell 2008].

D3. Factors affecting public health risks

D3.1. Availability and quality of the new psychoactive substance on the market (purity, adulterants etc)

Information from collected samples, Internet monitoring of online retailers selling new psychoactive substances (discussed further below), as well as from case reports of non-fatal intoxications suggest that in some cases methoxetamine is sourced from Internet retailers. There have also been reports methoxetamine being sold in bricks and mortar headshops and through street level drug dealers. Some user reports have suggested that methoxetamine is qualitatively of 'high purity'.

In the 2011 EMCDDA snapshot studies that assessed the online availability of new psychoactive substances in Europe in January and July 2011 data was available on the number of online sites selling methoxetamine [EMCDDA Snapshot 2011]. The snapshots were carried out on metacrawler.com, Google and an additional specific national search engine relevant to each country. The July 2011 was multilingual and included 18 languages spoken in the European Union (spoken as the primary language by 97% of the EU population). In January 2011 314 online sites selling new psychoactive substances were identified; this increased to 631 in July 2011. Methoxetamine was available from 14 (4.5%) sites in January 2011 and 58 (9.2%) sites in July 2011. The January 2012 EMCDDA snapshot was reported in the EMCDDA 2012 Annual Report, this snapshot was carried out using the same methodology in 20 European languages. Methoxetamine was available in 68 (9.8%) of the 693 sites selling new psychoactive substances [EMCDDA 2012].

Analysis of the seizures and collected samples in Section C, suggests that methoxetamine is sold both as methoxetamine alone or in combination with classical recreational drugs, other new psychoactive substances and/or other medicines. It is not possible to determine from these reports whether this was due to either adulteration of methoxetamine by the other detected substances or methoxetamine adulteration of one or more other NPS. Therefore, there is insufficient data to estimate the prevalence of adulteration of methoxetamine at this time.

As noted in Section 1.2, there is one report from 2011 of methoxetamine being detected in the United Kingdom in a product that was marketed using the 'Special K' logo, which is the logo and trade name for a legitimate breakfast cereal [Wood DM 2011]. Products with this branding containing methoxetamine are thought to be no longer available.

D3.2. Availability of the information, degree of knowledge and perceptions amongst users concerning the psychoactive substance and its effects

There is no published information on the degree of knowledge and perceptions amongst users concerning methoxetamine and its effects, other than that which is available on user websites (summarised in Section D.1.2.1).

In the 2non-representative 2011–2012 annual Global Drugs Survey, previously more commonly known as the "MixMag" survey, data was reported on those who had previously used methoxetamine, their reasons for use: i) 73% reported that it was easier to get hold of ii) 20% reported that it was better value for money; iii) 20% reported they were curious or it was sold as ketamine; 18% reported that it was less damaging to liver/kidneys. It is not clear from this report as to whether these were the only pre-defined categories respondents could select, or whether other reasons for use were stated by respondents.

D3.3. Characteristics and behaviour of users (including risk factors, vulnerability, etc.)

It is likely that the characteristics and behaviours of those using methoxetamine will be similar to those ketamine and/or other new psychoactive substances. In the 2011–2012 Global Drug Survey of 7,700 United Kingdom based respondents life-time (4.9 %) and last year (4.2 %) use of methoxetamine was considerably lower than ketamine (47.5 % and 24.5 % respectively) [MixMag 2012]. In surveys of individuals attending 'gay friendly' nightclubs in South East London there was a significant increase in self-reported use of methoxetamine between the 2011 (313 individuals) and 2012 (330 individuals) surveys: i) life-time use 2011: 6.1 % vs. 2012: 21.0 %, $p < 0.001$; ii) last year use 2011: 4.8 % vs. 19.2 %, $p < 0.001$; and iii) last month use 2011: 1.9 % vs. 2012: 10.1 %, $p < 0.0001$ [Wood DM 2013; Wood DM 2013].

D3.4. Nature and extent of health consequence (e.g. acute emergencies, road traffic accidents)

The acute health effects of methoxetamine have been discussed in Section D1.2. Currently there are no data to suggest that the impact of these acute health effects would be any different to that from other similar drugs such as ketamine.

There are currently no reports of methoxetamine being detected in either non-fatal or fatal road traffic accidents.

Germany reported two cases of driving under the influence of drugs involving methoxetamine. In addition, the United Kingdom reported two cases where methoxetamine was detected in biological samples taken for analysis for suspected driving under the influence of drugs and/or alcohol (concentrations 0.05 mg/L and 0.47 mg/L). No further information of these cases was provided so it is not possible to comment on the extent of impairment.

D3.5 Long-term consequences of use (e.g. irreversible toxicity leading to deterioration of health in later life)

As discussed in Section D2.1 there are data from an animal study demonstrating that long-term methoxetamine use is associated with similar bladder and renal tract pathology as seen with ketamine in these animal models. There is currently no human data on the chronic health effects of methoxetamine and in particular, there have been no long-term follow up studies to determine whether methoxetamine users are at greater risk of health deterioration later in life, or of developing chronic or life-threatening medical conditions.

D3.6. Conditions under which the new psychoactive substance is obtained and used, including context-related effects and risks (e.g. continuous dancing in hot environments, other substances used)

As noted in Sections D.1.2.2 and D.1.2.3, reports of methoxetamine exposure have occurred in individuals who have purchased or intended to use ketamine. Therefore it is likely that methoxetamine can be obtained from the same sources as ketamine. In addition, in Section C, there are reports of analysis of collected samples purchases from Internet retailers, which were positive for methoxetamine, suggesting that similar to other new psychoactive substances methoxetamine can be obtained from Internet suppliers. As discussed in more detail in Section D., the EMCDDA Internet snapshot studies have shown that methoxetamine was available in 5–10% of online sites that were identified in these snapshots to be selling new psychoactive substances in Europe.

There is limited data available on where methoxetamine is used, although it is likely that it is used in the same environments as ketamine and other similar drugs are used. This would be within home environments, bars / pubs, discotheques / nightclubs and at outdoor music festivals.

Section E. Social risks

E1. Individual social risks

There are no published data to be able to determine the impact of methoxetamine in this area; in particular there are no data on the effects of methoxetamine on fertility, pregnancy and lactation.

E2. Possible effects on direct social environment

There are no published data to be able to determine the impact of methoxetamine in this area.

E3. Possible effects on society as a whole

To date there are no specific reports of acquisitive crime related to methoxetamine use.

Sweden reported 17 ⁽¹⁶⁾ cases where methoxetamine alone or in combination with one or more other substance was detected in blood or urine from individuals suspected of committing a minor criminal offence. Urine analyses in 2011: methoxetamine with 6-APB and PMA (1 case); methoxetamine with cannabis (1). Blood analyses in 2012: i) methoxetamine alone (1); ii) methoxetamine with AM-2201 (2); iii) methoxetamine with AM-2201 and cannabis (1); iv) methoxetamine with cannabis (1). Urine results from 2012: i) methoxetamine alone (1); methoxetamine with cannabis (2); methoxetamine with oxazepam (1); methoxetamine with 2-fluorometamphetamine (1); methoxetamine with "benzos", 2-DPMP and 4-MEC (1). Urine analyses in 2013: methoxetamine with cocaine (1); methoxetamine with 3-methylmetcatinone (1); methoxetamine with 4-fluoramphetamine (1); methoxetamine with 4-APB, ethylphenidate and "benzos" (1). No further information is available on these cases.

There are no data available on the effects of methoxetamine on the ability to drive or operate machinery, other than one report from the USA (detailed in D1.2.2) of an individual who was driving and was apprehended by the police with significant impairment related to methoxetamine (blood concentration 10 mg/L); however other drugs were also detected (clonazepam, 7-aminoclonazepam, carboxy-THC, didphenhydramine, and MDMA) and so it is not possible to determine the role of methoxetamine in this case [Elian AA J Forensic Sci 2014].

(16) It is possible that four of these cases are the same as those reported by Wikstrom, M. et al (2013). Here, it was reported that methoxetamine was detected in four cases of "petty drug offence" where the police requested screens for "Internet drugs". The methoxetamine concentrations detected ranged from 0.13 microgram/gram to 0.49 microgram/gram whole blood; other drugs were detected in three samples – AM-2201/THC, AM-2201 alone; carboxy-THC alone. Three of the cases had no information regarding the case provided; in the fourth case the individual was reported to have been found unresponsive at home with a bag labelled "2-(3-methoxyphenyl)-2-(ethylamino)-cyclohexanone". There is no data on the number of petty drug offence cases that were screened, or how these samples were identified for screening. In addition, there was no information provided on the exact offence.

E4. Economic costs

As noted in Section D1.2 there are reports of acute health effects relating to methoxetamine use. These appear to involve short assessments within the ED; however some individuals have had more prolonged symptoms over a few days or have required admission to psychiatric facilities due to ongoing symptoms. In some of these reports, it is difficult to determine whether these admissions are due to underlying mental health illness for which the patient is poorly compliant with prior management/treatment.

E5. Possible effects related to the cultural context, for example marginalisation

There are no specific data in relation to use in marginalised groups, and it is likely that methoxetamine will be used by those individuals who use ketamine.

E6. Possible appeal of the new psychoactive substance to specific population groups within the general population

Methoxetamine has been marketed to potential users as a “bladder friendly” alternative to ketamine. It is possible that this marketing may appeal to existing ketamine users who are aware of the potential long-term renal tract and bladder toxicity associated with chronic ketamine use. There is no conclusive data to suggest that this marketing has lead to a switch from ketamine use to methoxetamine use in those individuals who previously used ketamine.

Section F. Involvement of organised crime

F1. Evidence that criminal groups are systematically involved in production, trafficking and distribution for financial gain

Europol reported that no information has been received to suggest the production, trafficking and/or distribution of methoxetamine by criminal gangs [EMCDDA-Europol Joint Report]. In Section C, there have been reports of tablets with markings that would normally be associated with other recreational drugs such those seen on 'ecstasy tablets'. It is possible, therefore, that criminal groups may be involved in the production of methoxetamine tablets.

F2. Impact on the production, trafficking and distribution of other substances, including existing psychoactive substances as well as new psychoactive substances

As noted in Section C, methoxetamine has been detected in both police and border seizures in combination with a range of new psychoactive substances and/or controlled drugs. It is not possible to determine whether this was intentional adulteration of methoxetamine with these substances or the adulteration of these substances with methoxetamine. In addition, it possible that in some circumstances the mixing with other substances could have been done by the end user.

F3. Evidence of the same groups of people being involved in different types of crime

There is no published data to be able to determine the impact of methoxetamine in this area.

F4. Impact of violence from criminal groups on society as a whole or on social groups or local communities (public order and safety)

Europol reported that no information has been received on incidents of violence in connection with the production, wholesale and/or trafficking of methoxetamine [EMCDDA-Europol Joint Report].

F5. Evidence of money laundering practices, or impact of organised crime on other socioeconomic factors in society

Europol reported that no information has been received related to money laundering in connection with the production, wholesale and/or distribution of methoxetamine [EMCDDA-Europol Joint Report].

F6. Economic costs and consequences (evasion of taxes or duties, costs to the judicial system)

There is no published data to be able to determine the impact of methoxetamine in this area.

F7. Use of violence between or within criminal groups

Europol reported that no information has been received related to violence in connection with the production and/or distribution of methoxetamine [EMCDDA-Europol Joint Report].

F8. Evidence of strategies to prevent prosecution, for example through corruption or intimidation

There is no published data to be able to determine the impact of methoxetamine in this area.

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