European Monitoring Centre
for Drugs and Drug Addiction

RISK ASSESSMENTS 15

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Methoxetamine

Report on the risk assessment of 2-(3-methoxyphenyl)-2-(ethylamino) cyclohexanone (methoxetamine) in the framework of the Council Decision on new psychoactive substances

About this series

EMCDDA Risk Assessments are publications examining the health and social risks of individual new psychoactive substances.

The Risk Assessment Report consists of an analysis of the scientific and law enforcement information available on the new psychoactive substance under scrutiny and the implications of placing it under control. It is the outcome of a meeting convened under the auspices of the EMCDDA Scientific Committee.

This process is part of a three-step procedure involving information exchange/early warning, risk assessment and decision-making in the framework of Council Decision 2005/387/JHA.

Contents

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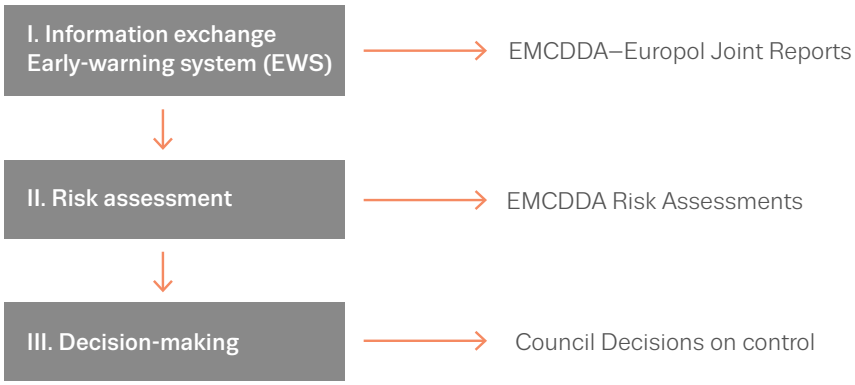
EMCDDA project leaders: Michael Evans-Brown, Andrew Cunningham, Ana Gallegos and Roumen Sedefov

EMCDDA actions on monitoring and responding to new drugs

The EMCDDA has been assigned a key role in the detection and assessment of new drugs in the European Union under the terms of a Council Decision 2005/387/JHA on the information exchange, risk-assessment and control of new psychoactive substances. It establishes a mechanism for the rapid exchange of information on new psychoactive substances and provides for an assessment of the risks associated with them in order to permit the measures applicable in the Member States for the control of narcotic and psychotropic substances to be applied also to new psychoactive substances.

The three-step process involves information exchange/early warning, risk assessment and decision-making (see below). More detailed information can be found in the section 'Action on new drugs' of the EMCDDA's website: www.emcdda.europa.eu/activities/action-on-new-drugs

Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk-assessment and control of new psychoactive substances



EMCDDA–Europol Joint Report on methoxetamine (2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone) — a summary

EMCDDA–Europol Joint Report on a new psychoactive substance: 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone — in accordance with Article 5 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances

available information on a new psychoactive substance 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone, commonly known by the abbreviation 'methoxetamine', through a joint assessment based upon the following criteria: (1) the amount of the material seized; (2) evidence of organised crime involvement; (3) evidence of international trafficking; (4) analogy with better-studied compounds; (5) evidence of the potential for further (rapid) spread; and (6) evidence of cases of serious intoxication or fatalities.

The EMCDDA and Europol agreed that the information available on methoxetamine satisfied criteria 1, 3, 4 and 6. The two organisations therefore concluded that sufficient information has been accumulated to merit the production of a Joint Report on methoxetamine as stipulated by Article 5.1 of the Decision. Accordingly, the NFPs, the Europol national units (ENUs), the EMA and the World Health Organization (WHO) were formally asked to provide the relevant information within six weeks from the date of the request, i.e. by 18 November 2013.

The resulting Joint Report on methoxetamine was submitted to the Council, the Commission and the EMA on 16 December 2013. The report concluded that the health and social risks, caused by the use of, the manufacture of, and traffic in methoxetamine, as well as the involvement of organised crime and possible consequences of control measures, could be thoroughly assessed through a risk assessment procedure as foreseen by Article 6 of Council Decision 2005/387/JHA.

The full text of the Joint Report can be found at:

www.emcdda.europa.eu/publications/joint-report/methoxetamine

Risk Assessment Report of a new psychoactive substance: 2-(3-methoxyphenyl)-2-(ethylamino) cyclohexanone (methoxetamine)

Introduction

This Risk Assessment Report presents the summary findings and 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 that presents a summary of the information considered during the detailed analysis of the scientific and law enforcement data available at this time. The conclusion 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 established a mechanism for the rapid exchange of information on new psychoactive substances (hereafter 'Early Warning System' ([3])) that may pose a threat to public health and create social problems, including the involvement of organised crime. The Council Decision therefore 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 ([5]).

Methoxetamine was first identified in a sample purchased from an Internet retailer in September 2010, and the United Kingdom formally notified the Early Warning System in November 2010. 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 a Joint Report on methoxetamine to the Council of the European Union, the European Commission and the European Medicines Agency (EMA) ([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 12 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

([1]) EMCDDA (2010), *Risk assessment of new psychoactive substances: operating guidelines*, Publications Office of the European Union, Luxembourg.
([2]) OJ L 127, 20.5.2005, p. 32.
([3]) The information exchange mechanism laid down by the Council Decision is operationalised 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 Reitox national focal points in the Member States, the European Commission and the European Medicines Agency.
([4]) According to the Council Decision, '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 Schedules 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 Schedules 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.
([6]) EMCDDA and Europol (2014), *EMCDDA–Europol Joint Report on a new psychoactive substance: methoxetamine (2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone)*, Lisbon.

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 and the other participants attending the risk assessment meeting is included at the end of this publication.

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 1);
(ii) *EMCDDA–Europol Joint Report on a new psychoactive substance: methoxetamine (2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone*;
(iii) scientific articles, official reports and grey literature, and Internet drug discussion forums and related websites (hereafter 'user websites');
(iv) data from EMCDDA monitoring of Internet suppliers (which typically appear to be 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.

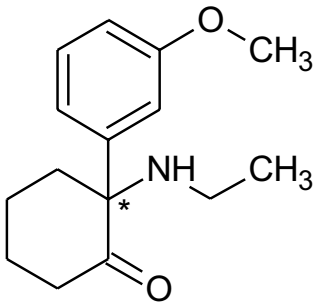
Finally, it is important to note that this Risk Assessment Report contains a discussion of the available information on non-fatal intoxications and deaths associated with methoxetamine. Such information is critical to the identification of emerging toxicological problems associated with new psychoactive 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. Some Member States have introduced programmes in the past few years to strengthen these capacities. As a result, more information is available; however, it is likely that serious adverse events remain under-detected.

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*-ethylnorketamine, 3-MeO-PCE and 4-MeO-PCP ([10]).

The name 'methoxetamine' was reported to have been created as a contraction of methoxy-ketamine. 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 indicates the asymmetric carbon)



Molecular formula: $C_{15}H_{21}NO_2$
Molecular weight: 247.33 g/mol

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

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, although 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 (LD_{50}) of methoxetamine.

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

No studies in the scientific literature 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.

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

Users report that the desired effects last approximately 1–7 hours depending on the route of administration.

Only two studies have investigated the pharmacokinetics of methoxetamine, both of which 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 or 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.

Internet suppliers and retailers openly sell methoxetamine in bulk and retail quantities. It is also available from bricks and mortar head shops and street-level drug dealers.

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 3methoxybenzonitrile 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 methoxetamine on its own, and also 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).

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, 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.

A total of 120 non-fatal intoxications associated with methoxetamine have been reported by five Member States: Belgium (two cases), France (three), Germany (nine), Italy (15) and Sweden (91); analytical confirmation of methoxetamine from biological samples has been reported in 55 of these cases: Belgium (one case), France (three), 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 (two cases), the United Kingdom (seven), Switzerland (one) and the United States (one).

Data from these reports, together 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 to methoxetamine itself.

Twenty deaths associated with methoxetamine have been reported to the Early Warning System by six Member States where the substance has been detected in post mortem biological samples: Austria (one death), Finland (one), France (one), Poland (one), Sweden (one) and the United Kingdom (15). In eight 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 is also notable that four 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, one published study showed that three months of intraperitoneal methoxetamine administration in mice was associated with similar bladder and renal tract toxicity that have been seen in similar animal models of chronic ketamine administration.

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

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.

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.

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

No studies have been published 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 its 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.

Detections of methoxetamine have been reported to the EMCDDA 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 injection and intravenous injection have also been reported; sharing of injecting equipment carries the additional risks of bacterial infections and transmission of blood-borne viruses.

There are limited data available on the characteristics and behaviour of users. Users are likely to overlap with people who use ketamine and/or 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') and 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 lifetime (4.9 %) and last year (4.2 %) use of methoxetamine was lower than for ketamine (47.5 % and 24.5 % respectively). Data was reported on four different reasons as to why respondents used methoxetamine: easier to get hold of (73 %); better value for money (20 %); 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 lifetime (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 survey was repeated in July 2012 there had been a significant increase in self-reported use of methoxetamine: lifetime use was 21.0 % in 2012 compared to 6.1 % in 2011; last year use was 19.2 % compared to 4.8 %; and last month use was 10.1 % compared to 1.9 %. Although there was no significant change in lifetime and last year use of ketamine between the two surveys, there was a reduction in last month use of ketamine (24.4 % in 2012, down from 34.9 % in 2011).

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 prevalence rates of methoxetamine use were lower than the rates reported for ketamine at 3.0 % (methoxetamine) and 19.3 % (ketamine) for lifetime use; 2.3 % and 12.8 % for last year use; and 0.3 % and 5.0 % for last month use.

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. 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 16–59 and 0.8 % of young adults aged 16–24 reported use of ketamine in the last year.

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 is 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.

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

Information on the level of involvement of organised crime, 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').

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 would be subject to evaluation at the 36th meeting of the Expert Committee on Drug Dependence 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.

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, the Czech Republic, Estonia, Finland, Greece, Hungary, Ireland, Luxembourg, Latvia, Malta, the 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, the 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 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 that, if necessary, is fully applicable. In Norway methoxetamine is regulated by the Medicines Act and a prescription would be required to receive it.

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 positive 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 that may also 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 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.

Conclusion

Methoxetamine is an arylcyclohexylamine substance that 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 the United Kingdom formally notified to the Early Warning System in November 2010.

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 injection and intravenous injection have 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 in animals or 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 that reported to the Early Warning System; an additional 15 clinical case reports — Poland (three cases), the United Kingdom (eight), Switzerland (one) and the United States (three) — 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 or 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 methoxetamine has potential positive consequences in terms of reducing its availability and therefore the adverse health and social consequences arising from its use. 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.

ANNEX 1

Technical report on 2-(3-methoxyphenyl)-2-(ethylamino) cyclohexanone (methoxetamine)

This Technical report was prepared under EMCDDA contract and, while the scientific data presented has been verified to the extent possible, it has not been formally edited by the EMCDDA. The Risk Assessment Report of 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.

The full text of the Technical report on 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone (methoxetamine) can be accessed under the following link: www.emcdda.europa.eu/publications/risk-assessment/methoxetamine/annex1

Tables on non-fatal intoxications and deaths, in which methoxetamine was analytically confirmed, have been extracted from the Technical report and are presented in the following pages.

TABLE 4 FROM THE TECHNICAL REPORT

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.
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 (36ºC). The patient was treated with intravenous fluids and left hospital against medical advice after about 8 hours of observation.
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.

Country	Date of non-fatal intoxication (gender, age)	Biological sample	Methoxetamine results	Results for other substances	Notes
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 O2 90%).
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.
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 IU/L).
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	Sep 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.
Sweden	Mar 2011 – Oct 2012	Blood and Urine	+	5-IT [1] (+) Amphetamine (+) Benzodiazepines (+) Buprenorphine (+) Ethanol (+) MDPV (+) Morphine (+) 4-OHMET [2] (+) Cannabis/THC (+) Tramadol (+)	27 cases identified from the Swedish Poisons Information Service. See main text for further discussion of these cases.

[1] 5-(2-Aminopropyl)indole.
[2] 4-Hydroxy-methylethyltryptamine.

TABLE 6 FROM THE TECHNICAL REPORT

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

Case number	Country	Date of death (gender, age)	Biological sample	Methoxetamine result	Results for other substances	Notes
1	**Austria**	Aug 2012	Not reported	+	None reported	Cause of death reported as central circulatory failure due to methoxetamine overdose.
2	**Finland**	Aug 2012	Blood	5200 mg/mL	Olanzapine (0.24 mg/L) Citalopram (0.20 mg/L) Clozapine (0.13 mg/L)	Death by drowning. Medico-legal status not determined.
3	**France**	Feb 2013 (M, 38)	Blood	9.48 µg/mL	Benzodiazepines (from hospital treatment)	Found dead at home. Cause of death reported as asphyxia.
4	**Poland**	Jul 2012 (M, 31)	Blood Urine Hair	0.32 µg/mL 4.36 µg/mL Negative	Amphetamine (0.06 µg/ml in blood, 0.27 µg/ml in urine and 0.19 µg/g in hair)	Cause of death reported as acute poisoning as a result of methoxetamine and amphetamine.
5	**Sweden**	Feb 2012	Femoral blood	8.6 µg/g	AM-694 (+) AM-2201 (+) JWH-018 (+) cannabis (+) venlafaxine (+)	The cause of death reported as suspected acute intoxication with methoxetamine although the presence of the three synthetic cannabinoids may have contributed to the death (1).
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.
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 and 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 and vitreous humour	+	Alcohol (80 mg/100 ml in blood, 146 mg/100 mL in urine, 109 mg/100 mL in vitreous humour)	Cause of death was reported as drowning, with methoxetamine ingestion noted as a contributory factor.
10	**United Kingdom**	Jan 2012 (M, 43)	Blood	0.89 mg/L (unpreserved) 1.1 mg/L (preserved)	Methiopropamine (2.8 mg/L in unpreserved blood)	Case of death was reported as methoxetamine and methypropamine toxicity [sic].
11	**United Kingdom**	Mar 2012 (M, 20)	Not reported	0.22 mg/L	None reported	Cause of death was reported as drowning.
12	**United Kingdom**	Sep 2012 (F, 27)	Blood	+	6-APB (2460 ng/mL)	Case of death was reported as ingestion of 6-APB (benzofury) and methoxetamine.
13	**United Kingdom**	Sep 2012 (M, 41)	Blood and 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).

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

Case number	Country	Date of death (gender, age)	Biological sample	Methoxetamine result	Results for other substances	Notes
14-19	**United Kingdom**	2012 (months unspecified)	Not reported	+	None reported	6 deaths.
20	**United Kingdom**	Jan 2013 (M, 27)	Blood, urine, gastric and nasal swabs	0.03 mg/L in blood, present in gastric and nasal swab samples	Amitriptyline (0.13 mg/L in blood and present in gastric sample) Cocaine (0.44 mg/L in blood and present on nasal swabs) Diazepam (4.27 mg/l in blood, 9 mg in gastric sample) and metabolites MDMA (0.20 mg/L in blood, 3 mg in gastric sample and present on nasal swabs) MDA (present in blood)	Case of death was reported as mixed drug toxicity.

Council Decision

COUNCIL IMPLEMENTING DECISION of 25 September 2014 on subjecting 4-iodo-2,5-dimethoxy-N-(2-methoxybenzyl)phenethylamine (25I-NBOMe), 3,4-dichloro-N-[[1-(dimethylamino)cyclohexyl]methyl]benzamide (AH-7921), 3,4-methylenedioxypyrovalerone (MDPV) and 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone (methoxetamine) to control measures (2014/688/EU)

THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk-assessment and control of new psychoactive substances ([1]), and in particular Article 8(3) thereof,

Having regard to the proposal from the European Commission,

Whereas:

(1) Risk assessment reports on the new psychoactive substances 4-iodo-2,5-dimethoxy-N-(2-methoxybenzyl) phenethylamine (25I-NBOMe), 3,4-dichloro-N-[[1-(dimethylamino) cyclohexyl]methyl]benzamide (AH-7921), 3,4-methylenedioxypyrovalerone (MDPV) and 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone (methoxetamine) were drawn up in compliance with Decision 2005/387/JHA by a special session of the extended Scientific Committee of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), and were subsequently submitted to the Commission and to the Council on 23 April 2014.

(2) 25I-NBOMe, AH-7921, MDPV and methoxetamine had not been under assessment at the United Nations' level by the time the risk assessment was requested at Union level, but they were evaluated in June 2014 by the Expert Committee on Drug Dependence of the World Health Organization.

(3) 25I-NBOMe, AH-7921, MDPV and methoxetamine have no established or acknowledged medical use (human or veterinary). Apart from their use in analytical reference materials, and in scientific research investigating their chemistry, pharmacology and toxicology as a result of their emergence on the drug market — and, in the case of 25I-NBOMe, also in the field of neurochemistry — there is no indication that they are being used for other purposes.

(4) 25I-NBOMe is a potent synthetic derivative of 2,5-dimethoxy-4-iodophenethylamine (2C-I), a classical serotonergic hallucinogen, which was subject to risk assessment and to control measures and criminal sanctions at Union level from 2003 by Council Decision 2003/847/JHA ([2]).

(5) The specific physical effects of 25I-NBOMe are difficult to determine because there are no published studies assessing its acute and chronic toxicity, its psychological and behavioural effects, and dependence potential, and because of the limited information and data available.

([1]) OJ L 127, 20.5.2005, p. 32.
([2]) Council Decision 2003/847/JHA of 27 November 2003 concerning control measures and criminal sanctions in respect of the new synthetic drugs 2C-I, 2C-T-2, 2C-T-7 and TMA-2 (OJ L 321, 6.12.2003, p. 64).

Clinical observations of individuals who have used this substance suggest that it has hallucinogenic effects and has the potential for inducing severe agitation, confusion, intense auditory and visual hallucinations, aggression, violent accidents and self-induced trauma.

(6) There have been four deaths associated with 25I-NBOMe registered in three Member States. Severe toxicity associated with its use has been reported in four Member States, which notified 32 non-fatal intoxications. If this new psychoactive substance were to become more widely available and used, the implications for individual and public health could be significant. There is no information available on the social risks associated with 25I-NBOMe.

(7) 22 Member States and Norway have reported to the EMCDDA and European Police Office (Europol) that they detected 25I-NBOMe. No prevalence data is available on the use of 25I-NBOMe, but the limited information that exists suggests that it may be consumed in a wide range of settings, such as at home, in bars, nightclubs and at music festivals.

(8) 25I-NBOMe is openly marketed and sold on the internet as a 'research chemical' and information from seizures, collected samples, user websites and internet retailers suggests that it is being sold as a drug in its own right and also marketed as a 'legal' replacement for LSD. EMCDDA identified more than 15 internet retailers selling this substance, who may be based within the Union and China.

(9) The risk assessment report reveals that there is limited scientific evidence available on 25I-NBOMe and points out that further research would be needed to determine the health and social risks that it poses. However, the available evidence and information provides sufficient ground for subjecting 25I-NBOMe to control measures across the Union. As a result of the health risks that it poses, as documented by its detection in several reported fatalities, of the fact that users may unknowingly consume it and of the lack of medical value or use of the substance, 25I-NBOMe should be subjected to control measures across the Union.

(10) Since six Member States control 25I-NBOMe under national legislation complying with the obligations of the 1971 United Nations Convention on Psychotropic Substances, and seven Member States use other legislative measures to control it, subjecting this substance to control measures across the Union would help avoid the emergence of obstacles to cross-border law enforcement and judicial cooperation, and would help protect against the risks that its availability and use can pose.

(11) AH-7921 is a structurally atypical synthetic opioid analgesic commonly known by internet suppliers, user websites and media as 'doxylam'. It can be easily confused with 'doxylamine', an antihistaminic medicine with sedative-hypnotic properties, which could lead to unintentional overdoses.

(12) The specific physical effects of AH-7921 are difficult to determine because there are no published studies assessing its acute and chronic toxicity, its psychological, behavioural effects, and dependence potential, as well as the limited information and data available. Based on user reports, the effects of AH-7921 appear to resemble those of classical opioids with the feeling of mild euphoria, itchiness and relaxation; nausea appears to be a typical adverse effect. In addition to self-experimentation with AH-7921, as well as 'recreational use', some of the users report self-medicating with this new drug to relieve pain, others to alleviate withdrawal symptoms due to cessation of the use of other opioids. This may indicate a potential of AH-7921 to spread among the injecting opioid population.

(13) There is no prevalence data on the use of AH-7921, but the information available suggests that it is not widely used, and that when it is used, that use is in the home environment.

(14) 15 fatalities were recorded in three Member States between December 2012 and September 2013 where AH-7921, alone or in combination with other substances, was detected in post-mortem samples. While it is not possible to determine with certainty the role of AH-7921 in all of those fatalities, in some cases it has been specifically noted in the cause of death. One Member State reported six non-fatal intoxications associated with AH-7921. If this new psychoactive substance were to become more widely available and used, the implications for individual and public health could be significant. There is no information available on the social risks associated with AH-7921.

(15) The risk assessment report reveals that there is limited scientific evidence available on AH-7921 and points out that further research would be needed to determine the health and social risks that it poses. However, the available evidence and information provides sufficient ground for subjecting AH-7921 to control measures across the Union. As a result of the health risks that it poses, as documented by its detection in several reported fatalities, of the fact that users may unknowingly consume it, and of the lack of medical value or use of the substance, AH-7921 should be subjected to control measures across the Union.

(16) Since one Member State controls AH-7921 under national legislation complying with the obligations of the 1971 United Nations Convention on Psychotropic Substances and five Member States use other legislative measures to control it, subjecting this substance to control measures across the Union would help avoid the emergence of obstacles in cross-border law enforcement and judicial cooperation, and would help protect against the risks that its availability and use can pose.

(17) MDPV is a ring-substituted synthetic derivative of cathinone chemically related to pyrovalerone, which are both subject to control under the 1971 United Nations Convention on Psychotropic Substances.

(18) Information on the chronic and acute toxicity associated with MDPV, as well as on psychological and behavioural effects, and on dependence potential, is not collected uniformly across the Union. Information from published studies, confirmed by clinical cases, suggests that the psychopharmacological profile observed for MDPV is similar to that for cocaine and methamphetamine, albeit more potent and longer lasting. Furthermore, MDPV was found to be 10 times more potent in its ability to induce locomotor activation, tachycardia and hypertension.

(19) Users' websites indicate that its acute toxicity can provoke adverse effects on humans, similar to those associated with other stimulants. These include paranoid psychosis, tachycardia, hypertension, diaphoresis, breathing problems, severe agitation, auditory and visual hallucinations, profound anxiety, hyperthermia, violent outbursts and multiple organ dysfunctions.

(20) 108 fatalities were registered in eight Member States and Norway between September 2009 and August 2013, where MDPV has been detected in post-mortem biological samples or implicated in the cause of death. A total of 525 non-fatal intoxications associated with MDPV have been reported by eight Member States. If this new psychoactive substance were to become more widely available and used, the implications for individual and public health could be significant.

(21) The detection of MDPV has also been reported in biological samples related to fatal and non-fatal road traffic accidents, or driving under the influence of drugs, in four Member States since 2009.

(22) MDPV has been present in the Union drug market since November 2008 and 27 Member States, Norway and Turkey reported multi-kilogram seizures of the substance. MDPV is being sold as a substance in its own right, but it has also been detected in combination with other substances. It is widely available from internet suppliers and retailers, 'head shops' and street-level dealers. There are some indications that suggest a degree of organisation in the tableting and distribution of this substance in the Union.

(23) The risk assessment report reveals that further research would be needed to determine the health and social risks posed by MDPV. However, the available evidence and information provides sufficient ground for subjecting MDPV to control measures across the Union. As a result of the health risks that it poses, as documented by its detection in several reported fatalities, of the fact that users may unknowingly consume it, and of the lack of medical value or use of the substance, MDPV should be subjected to control measures across the Union.

(24) Since 21 Member States control MDPV under national legislation complying with the obligations of the 1971 United Nations Convention on Psychotropic Substances and four Member States use other legislative measures to control it, subjecting this substance to control measures across the Union would help avoid the emergence of obstacles in cross-border law enforcement and judicial cooperation, and would protect against the risks that its availability and use can pose.

(25) Methoxetamine is an arylcyclohexylamine substance which is chemically similar to ketamine and the internationally controlled substance phencyclidine (PCP). Like ketamine and PCP, it has dissociative properties.

(26) There are no studies assessing the chronic and acute toxicity associated with methoxetamine, as well as its psychological and behavioural effects, and dependence potential. Self-reported experiences from user websites suggest adverse effects similar to ketamine intoxication. These include nausea and severe vomiting, difficulty in breathing, seizures, disorientation, anxiety, catatonia, aggression, hallucination, paranoia and psychosis. In addition, acute methoxetamine intoxications may include stimulant effects (agitation, tachycardia and hypertension) and cerebral features, which are not expectable with acute ketamine intoxication.

(27) Twenty deaths associated with methoxetamine were reported by six Member States that detected the substance in post-mortem samples. Used alone or in combination with other substances, methoxetamine was detected in 20 non-fatal intoxications reported by five Member States. If this new psychoactive substance were to become more widely available and used, the implications for individual and public health could be significant.

(28) 23 Member States, Turkey and Norway have reported that they detected methoxetamine, since November 2010. Information suggests that it is sold and used as a substance in its own right, but it is also sold as a 'legal' replacement for ketamine by internet retailers, 'head shops' and street-level drug dealers.

(29) Multi-kilogram quantities in powder form were seized within the Union, but there is no information on the possible involvement of organised crime. The manufacture of methoxetamine does not require sophisticated equipment.

(30) Prevalence data are limited to non-representative studies in two Member States. Those studies suggest that the prevalence of the use of methoxetamine is lower than that

of ketamine. The available information suggests that it may be consumed in a wide range of settings, including at home, in bars, nightclubs and at music festivals.

(31) The risk assessment report reveals that further research would be needed to determine the health and social risks posed by methoxetamine. However, the available evidence and information provides sufficient grounds for subjecting methoxetamine to control measures across the Union. As a result of the health risks that it poses, as documented by its detection in several reported fatalities, of the fact that users may unknowingly consume it, and of the lack of medical value or use, methoxetamine should be subjected to control measures across the Union.

(32) Since nine Member States control methoxetamine under national legislation complying with the obligations of the 1971 United Nations Convention on Psychotropic Substances and nine Member States use other legislative measures to control it, subjecting this substance to control measures across the Union would help avoid the emergence of obstacles in cross-border law enforcement and judicial cooperation, and would protect against the risks that its availability and use can pose.

(33) Decision 2005/387/JHA reserves to the Council implementing powers with a view to giving a quick and expertise-based response at the Union level to the emergence of new psychoactive substances detected and reported by the Member States, by submitting those substances to control measures across the Union. As the conditions and procedure for triggering the exercise of such implementing powers have been met, an implementing decision should be adopted in order to put 25I-NBOMe, AH-7921, MDPV and methoxetamine under control across the Union,

HAS ADOPTED THIS DECISION:

Article 1

The following new psychoactive substances shall be subjected to control measures across the Union:

(a) 4-iodo-2,5-dimethoxy-N-(2-methoxybenzyl) phenethylamine(25I-NBOMe);
(b) 3,4-dichloro-N-[[1-dimethylamino) cyclohexyl]methyl] benzamide (AH-7921);
(c) 3,4-methylenedioxypyrovalerone (MDPV);
(d) 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone (methoxetamine).

Article 2

By 2 October 2015, Member States shall subject in accordance with their national legislation, the new psychoactive substances referred to in Article 1 to control measures and criminal penalties, as provided for under their legislation complying with their obligations under the 1971 United Nations Convention on Psychotropic Substances.

Article 3

This Decision shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.

Done at Brussels, 25 September 2014.

For the Council
The President
F. Guidi

Participants of the risk assessment meeting, 1 April 2014

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EMCDDA

- **Paul Griffiths,** Scientific Director, EMCDDA, Lisbon
- **Roumen Sedefov,** Head of unit, Supply reduction and new trends unit, EMCDDA, Lisbon

Invited external experts

- **Dr Simon Elliott,** (ROAR) Forensics Ltd, Worcestershire
- **Dr István Ujváry,** Budapest University of Technology and Economics, Budapest
- **Dr David Wood,** Clinical Toxicology, St Thomas' Hospital, Guy's and St Thomas' NHS Foundation Trust, London

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- **Ana Gallegos,** Head of Sector, Action on new drugs, Supply reduction and new trends unit
- **Andrew Cunningham,** Scientific analyst, Action on new drugs, Supply reduction and new trends unit
- **Michael Evans-Brown,** Scientific analyst, Action on new drugs, Supply reduction and new trends unit
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The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is the central source and confirmed authority on drug-related issues in Europe. For over 20 years, it has been collecting, analysing and disseminating scientifically sound information on drugs and drug addiction and their consequences, providing its audiences with an evidence-based picture of the drug phenomenon at European level.

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Related publications and websites

EMCDDA

- Risk assessment of new psychoactive substances — operating guidelines, 2010

EMCDDA and Europol

- EMCDDA–Europol Joint Report on a new psychoactive substance: methoxetamine, 2014
- EMCDDA–Europol 2013 Annual Report on the implementation of Council Decision 2005/387/JHA, 2014
- EMCDDA–Europol Early-warning system on new psychoactive substances — operating guidelines, 2007

These and all other EMCDDA publications are available from emcdda.europa.eu/publications

- EMCDDA Action on new drugs website: www.emcdda.europa.eu/drug-situation/new-drugs

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