



AH-7921

Report on the risk assessment of 3,4-dichloro-*N*-{[1-(dimethylamino)cyclohexyl]methyl} benzamide (AH-7921) 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.

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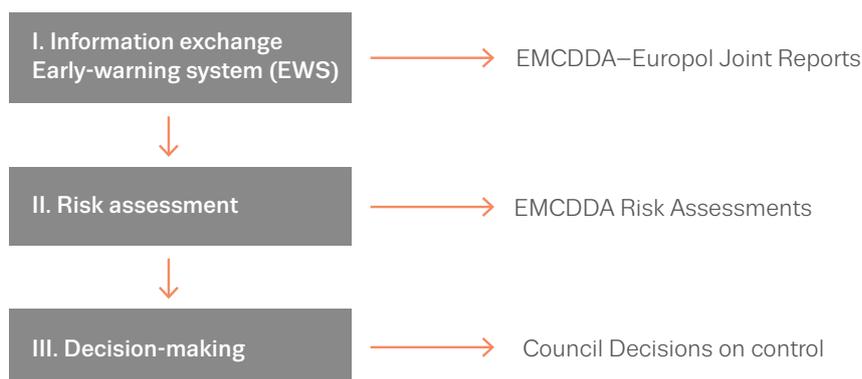
EMCDDA actions on monitoring and responding to new drugs

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 AH-7921 (3,4-dichloro-*N*-{[1-(dimethylamino)cyclohexyl]methyl} benzamide) — a summary

EMCDDA–Europol Joint Report on a new psychoactive substance: 3,4-dichloro-*N*-{[1-(dimethylamino)cyclohexyl]methyl}benzamide — in accordance with Article 5 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances

At the end of September 2013, the EMCDDA and Europol examined the available information on a new psychoactive substance 3,4-dichloro-*N*-{[1-(dimethylamino)cyclohexyl]methyl}benzamide, commonly known by the abbreviation 'AH-7921', 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 AH-7921 satisfied criteria 4, 5 and 6. The two organisations therefore concluded that sufficient information has been accumulated to merit the production of a Joint Report on AH-7921 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 AH-7921 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 AH-7921, 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/AH-7921

Risk Assessment Report of a new psychoactive substance: 3,4-dichloro-N-[[1-(dimethylamino)cyclohexyl]methyl]benzamide (AH-7921)

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 3,4-dichloro-N-[[1-(dimethylamino)cyclohexyl]methyl]benzamide (AH-7921). 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 Committee. A list of the information resources considered by the Scientific Committee, including a detailed Technical report on AH-7921, 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⁾ (hereafter 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. 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 ⁽⁵⁾.

AH-7921 was first identified in a sample purchased from an Internet retailer in July 2012 and the United Kingdom formally notified the Early Warning System in August 2012. Following an assessment of the available information on AH-7921, and in accordance with Article 5 of the Council Decision, on 16 December 2013 the EMCDDA and Europol submitted a Joint Report on AH-7921 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 AH-7921 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

⁽¹⁾ EMCDDA (2009), *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 definition provided by the Council Decision, 'new psychoactive substance' means 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: AH-7921 (3,4-dichloro-N-[[1-(dimethylamino)cyclohexyl]methyl]benzamide)*, Lisbon.

Scientific Committee, and whose contribution was necessary for a balanced and adequate assessment of the possible risks of AH-7921, 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 during the risk assessment:

- (i) Technical report on 3,4-dichloro-*N*-{[1-(dimethylamino)cyclohexyl]methyl}benzamide (AH-7921) (Annex 1);
- (ii) *EMCDDA–Europol Joint Report on a new psychoactive substance: AH-7921 (3,4-dichloro-*N*-{[1-(dimethylamino)cyclohexyl]methyl}benzamide)*;
- (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 AH-7921;
- (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 new psychoactive substances. Such information is critical to the identification of emerging toxicological problems 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 AH-7921 and its mechanism of action, including its medical value

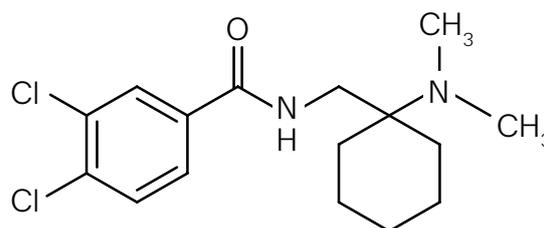
AH-7921 is a structurally atypical synthetic opioid analgesic invented in the mid-1970s. Chemically, it is a derivative of dimethylaminocyclohexane, to which a 3,4-dichlorobenzamide moiety is appended (Figure 1). The systematic (International Union of Pure and Applied Chemistry, IUPAC) name is 3,4-dichloro-*N*-{[1-(dimethylamino)cyclohexyl]methyl}benzamide.

The hydrochloride salt of AH-7921 is a white solid; the free amine of AH-7921 is reported to be a solid. Seizures and collected samples have usually noted the presence of AH-7921 in powder form; it is not known whether the salt or the free amine was present.

Another name for AH-7921 ⁽⁷⁾, used by Internet suppliers/retailers selling the substance, user websites and in the popular media, is ‘doxylam’. It is important to note that ‘doxylam’ can easily be confused with ‘doxylamine’ — also sometimes abbreviated as ‘doxylam’ — which is the International Nonproprietary Name (INN) of a widely used and chemically different antihistaminic medicine with sedative-hypnotic properties, and as such is present in non-prescription medicines for the treatment of allergies and as a hypnotic. It is of concern that taking AH-7921, mislabelled as ‘Doxylam’, instead of ‘doxylamine’ could lead to unintentional overdoses.

The detection ⁽⁸⁾ of AH-7921 by gas chromatography and liquid chromatography coupled with mass spectrometry is

FIGURE 1
The molecular structure, formula and weight of AH-7921



Molecular formula: C₁₆H₂₂Cl₂N₂O
Molecular weights: 329.26 (base);
365.72 (HCl salt)

⁽⁷⁾ In the commonly used name AH-7921, ‘AH’ refers to Allen & Hanburys, the pharmaceutical company that invented the drug.

⁽⁸⁾ ‘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.).

straightforward. Infrared spectroscopy can also be used for the analysis of AH-7921 in bulk samples. The recent availability of analytical reference materials facilitates the quantification of AH-7921 in biological samples.

Several model studies in animals and experiments *in vitro* have investigated the pharmacodynamics (i.e. the analgesic mode of action) of AH-7921. These studies established AH-7921 to be a morphine-like analgesic acting mainly as a μ -opioid (MOP) receptor agonist. AH-7921 also acts on the κ -opioid (KOP) receptor but to a lesser degree. Opioid receptor antagonists, such as naloxone, appear to counteract the effect of AH-7921; this observation could be important in the management of AH-7921 overdose in humans. In various animal models, AH-7921 has been found to be an analgesic several times more potent than codeine and in some tests it was as at least as active as morphine. During these studies it was also noted that doses producing analgesia were close to those producing side effects, including respiratory depression.

In experiments with mice, the side effect profile of AH-7921 was similar to that of morphine. However, AH-7921 was a 1.6 times more potent respiratory inhibitor than morphine in this animal model. Nevertheless, neither the acute nor the chronic toxicity of AH-7921 have been adequately characterised in animals.

Based on a single study that examined the effect of intracerebroventricularly injected noradrenaline and serotonin on the analgesic activity of AH-7921 in the mouse, *in vivo* interactions between AH-7921 and other substances, such as adrenergic and serotonergic drugs or medicines that can penetrate the central nervous system, can be assumed. The activity of AH-7921 at pharmacological targets other than the opioid system has not been studied. No studies were identified that examined the (psycho)pharmacological effects of AH-7921 in humans. The self-reported subjective effects of AH-7921 from user websites are discussed below.

Limited forensic data from recent deaths associated with AH-7921 indicate the formation of two *N*-desmethyl metabolites formed by sequential *N*-demethylation of the *N,N*-dimethylamino moiety of the parent drug. There are no data available on the biological activity of these metabolites.

The development of AH-7921 into a medicine was abandoned for unknown reason. No studies with AH-7921 have been published since 1989. Nevertheless, the unique structural features of AH-7921 provided impetus for the development of receptor ligands with high KOP receptor-selectivity that are now widely used in pain and addiction research.

AH-7921 is available as analytical reference materials 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 AH-7921 as an industrial, agricultural or cosmetic compound. According to information provided by EMA, there is no known human or veterinary medical use of AH-7921 in the European Union. There is no marketing authorisation (existing, ongoing or suspended) for AH-7921 at 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 to suggest that AH-7921 is used for the manufacture of a medicinal product or an active pharmaceutical ingredient 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.

Chemical precursors that are used for the manufacture of AH-7921

Only one common synthetic route to AH-7921 and its analogues has been published in the scientific and patent literature. Briefly, heating an equimolar amount of cyclohexanone, potassium cyanide⁽⁹⁾ and the hydrochloride salt of dimethylamine in aqueous ethanol affords an α -aminonitrile adduct⁽¹⁰⁾. The cyano group of this product is then reduced by either LiAlH_4 or catalytic hydrogenation to afford 1-(aminomethyl)-*N,N*-dimethylcyclohexanamine. Acylation of this primary amine with 3,4-dichlorobenzoyl chloride in an appropriate solvent gives AH-7921 that can be directly isolated as hydrochloride salt or obtained as free amine.

Precursors and other chemicals needed for the manufacture of AH-7921 are inexpensive and, with the exception of potassium cyanide or other cyanides, are readily available⁽¹¹⁾. These reactions are feasible in an amateur laboratory setting and do not require sophisticated equipment.

There is no information regarding the manufacturing sites, the precursors or the synthetic methods used for AH-7921 detected in Member States and Norway. As such, the impurities and side-products are also unknown.

⁽⁹⁾ Potassium cyanide is a highly toxic substance and is typically controlled under poisons legislation. A special permit is required for its manufacture, trade and use. Other cyanides might also be used as alternative cyanide sources.

⁽¹⁰⁾ This α -aminonitrile can also be used in the synthesis of phencyclidine and its analogues.

⁽¹¹⁾ Alternate manufacturing methods avoiding the use of toxic cyanides may exist.

Health risks associated with AH-7921

Individual health risks

The assessment of individual health risks includes consideration of the acute and chronic toxicity of AH-7921, its abuse liability and dependence potential and its similarities to and differences from other chemically or pharmacologically related substances.

The acute toxicity of AH-7921 in animals has not been properly established. A preliminary acute toxicity study at Allen & Hanburys in the 1970s indicated that the median lethal dose (LD₅₀) of AH-7921 in the mouse is higher than 10 mg/kg upon intravenous administration⁽¹²⁾. Animal studies on the adverse effects of AH-7921 indicate a steep dose–response relationship, and that the risk of respiratory depression is at least equivalent to morphine. On the basis of reports on the route of administration in animal models and self-reported experience in humans, AH-7921 appears to be effective by the oral route, suggesting good oral bioavailability.

The name ‘Doxylam’ is used by Internet retailers as an alternative name for AH-7921. There is therefore a concern that individuals looking to obtain the unrelated hypnotic ‘Doxylamine’ may accidentally purchase AH-7921, mislabelled as ‘Doxylam’, which could lead to unintentional overdoses.

Based on the limited information available from user websites and deaths reported by the Member States, the typical route of administration of AH-7921 is oral or intravenous injection, although users have reported that the apparently poor solubility of the substance in water may cause difficulties in producing a solution suitable for injection. As reported on user websites, the acute doses range from 40 mg to 150 mg; re-dosing has been reported.

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.

Information from user websites suggests that (potential) users rely on experiential self-reports from users of AH-7921

and other information provided thereon, which is sometimes incorrect or contradictory.

Six non-fatal intoxications associated with AH-7921 have been reported by Sweden to the Early Warning System; five of these have been analytically confirmed. The clinical symptoms reported included hypertension, tachycardia and seizures. The routes of administration were reported as peroral, nasal and smoking. No further information is available to allow interpretation of these cases.

Fifteen deaths associated with AH-7921 have been reported to the Early Warning System: Sweden (10 deaths), the United Kingdom (three) and Norway (two). In 14 of these deaths AH-7921 was detected in post-mortem toxicological screening; in the remaining death, AH-7921 was detected in a collected sample recovered from the scene of death. All the deaths occurred within a 10-month period between December 2012 and September 2013. Taking into consideration the relatively small number of detections reported by the Member States and the perceived low levels of use, it is of note that 15 deaths occurred within a short period of time.

In the 14 deaths that had analytical confirmation from biological samples, one or more pharmacologically active substances, most of which can be classed as psychoactive, were also detected in addition to AH-7921. These included controlled drugs, medicines, new psychoactive substances and alcohol. It is notable that at least one internationally controlled or non-controlled benzodiazepine was detected in five of the deaths, while another opioid (buprenorphine) was detected in only one of the deaths. Notably, no heroin, methadone or their metabolites were detected. In some cases stimulant drugs such as phenethylamines and cathinones were detected.

The cause of death was provided for six cases: ‘toxic effect of AH-7921’; ‘overdose of AH-7921’; ‘unintentional overdose’; ‘overdose of benzodiazepines and opiates’; ‘intoxication with opioids among others’; and ‘pneumonia caused by aspiration’. In one case the cause of death was reported as ‘unclear’.

Overall, there are insufficient details from the deaths reported by the Member States to allow the clinical profile of acute toxicity to be delineated. However, given the known pharmacology of AH-7921, it is expected to be associated with opioid-type adverse effects.

Based on studies involving animal models of dependence, AH-7921 could be classed as a narcotic analgesic having a dependence potential similar to morphine. In rats and monkeys receiving repeated (chronic) doses of AH-7921, opioid receptor antagonists precipitated abstinence or withdrawal symptoms similar to those seen with morphine. Furthermore, in an animal

⁽¹²⁾ A Material Safety Data Sheet of a fine chemicals company offering AH-7921 (free amine) for sale in 2014 lists acute oral LD₅₀ values of 300 mg/kg in the mouse and 980 mg/kg in the rat. However, the MSDS is not a peer-reviewed document.

model (rhesus monkeys) a single dose of AH-7921 alleviated the abstinence syndrome occurring after withdrawing morphine treatment. No self-administration studies in animals appear to have been published.

While no studies examined the abuse liability and dependence potential of AH-7921 in humans, self-reported user experiences suggest the development of tolerance and withdrawal-like symptoms. Since the principal mode of action of AH-7921 is opioid receptor agonism, and since MOP receptor agonism is largely responsible for the abuse and dependence potential of opioid analgesics⁽¹³⁾, this would indicate that AH-7921 may have an abuse liability and dependence potential.

There are no data on the interaction of AH-7921 with psychoactive substances or medicinal products (including oral contraceptives). In this context, it is worth noting that the sedative effects of morphine (opioid analgesics) are enhanced when used with anti-psychotics as well as central nervous system depressants including hypnotics, anxiolytics, tricyclic antidepressants and sedating antihistamines.

No studies have been published on neurotoxicity, reproductive toxicity, genotoxicity or the carcinogenic potential of AH-7921. No studies have examined the chronic toxicity of AH-7921 in animals or humans.

There is no information on the psychosocial consequences of chronic AH-7921 use, such as the effects on psychological development and the interaction with the social environment.

Public health risks

The public health risks associated with AH-7921 may be categorised in terms of: patterns of use (extent, frequency, route of administration, etc.); availability and quality of the drug; availability and degree of information relevant to the effect of the drug amongst users; and negative health consequences.

According to self-reported experiences on user websites, AH-7921 appears to have been sold by Internet retailers since as early as 2011. It is advertised as a 'research chemical' or a 'legal opioid'. EMCDDA monitoring of Internet suppliers and retailers selling AH-7921 (conducted in the month prior to the risk assessment) identified more than twenty companies that may be based within the European Union and China, offering

up to multi-kilogram quantities of the substance. The preferred route of administration appears to be oral. Injection has also been reported, and at least two of the 15 European deaths associated with AH-7921 involved this route of administration. Injection, which could include the sharing of needles and syringes, carries the risk of transmission of blood-borne viruses. People who experimented with the drug often reported repeated intake of AH-7921 to maintain its effects for 6–12 hours.

There are no prevalence data on the use of AH-7921. In addition, there are no surveys that have examined the characteristics of users or the patterns of AH-7921 use. The available information suggests that some users are experimenting with AH-7921, while others may have used it to self-treat pain or the withdrawal symptoms arising from the use of other opioids. Information from user websites and from deaths reported to the Early Warning System suggests that AH-7921 is used in the home environment.

The availability of AH-7921 coupled with its pharmacological similarities to morphine raises the possibility that opioid users could use AH-7921 as a (temporary) replacement for established controlled opioids.

Social risks associated with AH-7921

There is limited information on the social risks associated with AH-7921.

There is no information on whether the use of AH-7921 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 (e.g. sedative) effects of AH-7921 on operating machinery and driving are similar to those caused by other opioid-type narcotic-analgesics.

One Member State reported the detection of AH-7921 in biological samples from two individuals suspected to have committed minor criminal offences. Additional information on these cases is not available to allow further analysis.

There is no information on the social risks associated with the distribution and trafficking of AH-7921.

Due to lack of data, it is not possible at this time to estimate whether the use of AH-7921 is associated with greater healthcare costs (on a case by case basis) than other opioid drugs.

⁽¹³⁾ Pure KOP receptor agonists produce dysphoria and, as mentioned earlier, are devoid of the respiratory depression, cardiovascular and reinforcing behaviour effects of morphine.

Information on the level of involvement of organised crime, seizures and/or detections by the authorities, and the manufacture of AH-7921

AH-7921 was first identified in a collected sample purchased from an Internet retailer in the United Kingdom in July 2012 and reported to the Early Warning System in August 2012. Since then, a further seven Member States and Norway have reported seizures ranging from 0.02 g to 500 g.

There is no information to suggest the involvement of organised crime or criminal groups in the manufacture, distribution (trafficking) and supply of AH-7921.

There is no information regarding the manufacturing sites or the methods used to synthesize AH-7921 detected in the Member States and Norway. Suppliers that advertise AH-7921 on the Internet, including in bulk amounts, might not necessarily be the manufacturers of the chemical.

Information on any assessment of AH-7921 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 AH-7921 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 AH-7921 is not at an advanced stage of assessment within the United Nations system.

Description of the control measures that are applicable to AH-7921 in the Member States

AH-7921 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').

One Member State (Sweden) controls AH-7921 under legislation by virtue of its obligations under the UN drug conventions.

Twenty-seven Member States (Austria, Belgium, Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain and the United Kingdom), Turkey and Norway do not control AH-7921 by virtue of their obligations under the UN drug conventions.

Of these 27 Member States, five (Finland, the Netherlands, Poland, Romania and Spain) and Norway use other legislative measures to control AH-7921. Finland and the Netherlands use medicines legislation to control AH-7921. In Poland, AH-7921 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 are penalised with a fine (administrative sanctions). 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). Spain reported that although there is no current specific legislation controlling production, commerce, imports, exports or use/consumption of AH-7921, 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. Norway uses medicines legislation to control AH-7921.

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 at the European Union level is for the Member States to submit the new psychoactive substance AH-7921 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 AH-7921. 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 AH-7921 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 the European Union.
- A positive health consequence that may result from this control is the benefit brought about by the presumed reduction of availability and use.
- This control option could facilitate the detection, seizure and monitoring of AH-7921 related to its unlawful manufacture, distribution and use by facilitating cooperation between the judicial authorities and law enforcement agencies across 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 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 research/academic institutes, pharmaceutical or chemical industries.
- This control option could create an illicit drug market in AH-7921, with an 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 AH-7921 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 AH-7921 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.

Conclusions

AH-7921 is a structurally unique synthetic opioid analgesic that was first identified in a collected sample purchased from an Internet retailer in July 2012, and the United Kingdom formally notified the Early Warning System in August 2012. It was invented and patented by the London-based company Allen & Hanburys Limited in the mid-1970s but was not developed into a medicine. AH-7921 is typically encountered as a powder. AH-7921 has emerged on the 'legal highs' market where it is sold openly as an 'opioid' research chemical and discussed on user websites as a 'legal opioid'. It appears to be sold mostly through Internet retailers. In general, analyses of seized samples have found AH-7921 to be the sole psychoactive substance present.

A total of eight Member States and Norway have reported detections of AH-7921, typically as small seizures. EMCDDA monitoring of Internet suppliers and retailers selling AH-7921 identified more than twenty companies that may be based within the European Union and China, offering up to multi-kilogram quantities of the substance.

There are no prevalence data on the use of AH-7921, but the information that is available does not suggest it has been widely used. It appears that some users are experimenting with AH-7921, while others may have used it to self-treat pain or the withdrawal symptoms arising from the use of other opioids. There is limited information on the environments in which AH-7921 has been used; there is some evidence to suggest that it is used in the home. Further information on the size and demand, and the characteristics of users, is not available. There is no specific information on the social risks that may be related to AH-7921.

The limited information available suggests that the reported routes of administration of AH-7921 may be oral and, to a lesser extent, injection. Limited studies in animals have established that AH-7921 is an opioid analgesic with potency similar to that of morphine. The biological activity of AH-7921 in humans has not been studied.

AH-7921 has been detected in six non-fatal intoxications. Fifteen deaths associated with AH-7921 have been reported to the Early Warning System; in 14 of these deaths AH-7921 has been detected in post-mortem biological samples. In all cases AH-7921 was found in combination with at least one other psychoactive substance. The cause of death was provided for six cases: 'toxic effect of AH-7921'; 'overdose of AH-7921'; 'unintentional overdose'; 'overdose of benzodiazepines and opiates'; 'intoxication with opioids among others'; and 'pneumonia caused by aspiration'. In one case the cause of death was reported as 'unclear'. All 15 deaths occurred within a 10-month period between December 2012 and September 2013.

There is insufficient information on the clinical presentation of acute toxicity related to AH-7921. Limited animal models indicate that the adverse effect profile of AH-7921 is expected to be similar to opioid narcotic-analgesics, such as morphine. Animal studies on the adverse effects of AH-7921 indicate a steep dose–response relationship, and that the risk of respiratory depression is at least equivalent to morphine. Animal studies also suggest that opioid receptor antagonists, such as naloxone, could be used as an antidote to counteract the effect of AH-7921 in humans. The use of other psychoactive drugs with depressant properties, such as opioids, alcohol and benzodiazepines, would be expected to increase the risk of respiratory depression. Based on studies involving animal models of dependence, AH-7921 could be classified as a narcotic analgesic having a dependence potential similar to morphine.

Internet retailers use the name 'Doxylam' as an alternative name for AH-7921. There is therefore a concern that individuals looking to obtain the unrelated hypnotic 'Doxylamine' may accidentally purchase AH-7921, mislabelled as 'Doxylam', which could lead to unintentional overdoses.

There is no information to suggest the involvement of organised crime in the manufacture, distribution (trafficking) and supply of AH-7921. There is no information to suggest that AH-7921 is currently manufactured in any of the Member States. The chemical precursors and the synthetic routes used to manufacture the AH-7921 detected in Member States and Norway are unknown. The starting materials used in the documented synthetic route are commercially available and not under international control. However, sales of the highly toxic potassium cyanide used in the first step of the published synthesis of AH-7921 are restricted.

The substance has no established or acknowledged medical (human or veterinary) use in the European Union. There are no indications that AH-7921 may be used for any other purpose aside from in analytical reference materials and in scientific research.

AH-7921 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. AH-7921 is currently undergoing assessment by the United Nations system. One Member State controls AH-7921 under drug control legislation. Five Member States and Norway control AH-7921 under other legislation. Twenty-two Member States and Turkey do not currently control AH-7921.

Many of the questions posed by the lack of evidence on the health and social risks of AH-7921, as for any new psychoactive substance, could be answered through further research. Areas where additional information is important include: prevalence and patterns of use (including targeted studies that examine user groups and risk behaviours); market studies; chemical profiling studies; receptor binding and functional activity studies; metabolic pathway studies; behavioural studies; clinical patterns of acute and chronic toxicity in humans; the potential interaction between AH-7921 and other substances; the dependence and abuse potential in humans; and the social risks associated with its use.

The Committee notes that a decision to control AH-7921 has potential positive consequences in terms of reducing availability and therefore the adverse health and social consequences arising from its use. The Committee also notes the number of deaths associated with AH-7921 with the relatively small number of detections reported by the Member States and the perceived low levels of 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 AH-7921, with the associated risk of criminal activity, and lead to the manufacture, availability and use of other synthetic opioid substances. 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 AH-7921 to users and to relevant professionals.

ANNEX 1

Technical report on 3,4-dichloro-*N*-**{[1-(dimethylamino)cyclohexyl]methyl}** benzamide (AH-7921)

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 3,4-dichloro-*N*-**{[1-(dimethylamino)cyclohexyl]methyl}**benzamide (AH-7921), 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 3,4-dichloro-*N*-**{[1-(dimethylamino)cyclohexyl]methyl}**benzamide (AH-7921)*, EMCDDA, Lisbon, April 2014.

The full text of the Technical report on 3,4-dichloro-*N*-**{[1-(dimethylamino)cyclohexyl]methyl}**benzamide (AH-7921) can be accessed under the following link:
www.emcdda.europa.eu/publications/risk-assessment/AH-7921/annex1

Table on deaths reported to the EWS, in which AH-7921 was analytically confirmed, has been extracted from the Technical report and is presented in the following pages.

TABLE 3 FROM THE TECHNICAL REPORT

Deaths associated with AH-7921 as reported to the EMCDDA ^(a)

Case number	Country	Date of death (gender, age)	Biological sample ^(b)	AH-7921 result ^(c)	Results for other substances ^(d)	Notes
1	Sweden	8 Jan 2013 (M, 28)	Femoral blood	0.81 µg/g	10 µg/g gabapentin	Cause of death reported as 'unintentional overdose'.
2	Sweden	4 Feb 2013 (M, 25)	Femoral blood	0.99 µg/g	4.7 µg/g amphetamine, aripiprazol	Cause of death reported as 'pneumonia caused by aspiration'.
3	Sweden	22 Feb 2013	Femoral blood	0.03 µg/g	0.03 µg/g paroxetine	Cause of death reported as 'not decided yet'.
4	Sweden	8 Apr 2013	Femoral blood	0.2 µg/g	pyrazolam, diazepam	Cause of death reported as 'overdose of benzodiazepines and opiates'.
5	Sweden	3 May 2013	Femoral blood	0.3 µg/g	pyrazolam, alprazolam, zopiclone	Cause of death reported as 'overdose of AH-7921'.
6	Sweden	15 Apr 2013	Femoral blood	0.08 µg/g	0.01 µg/g N-ethylnoreketamine, alcohol	Cause of death reported as 'unclear'.
7	Sweden	16 Jun 2013	Femoral blood	0.16 µg/g	0.04 µg/g amphetamine	Cause of death reported as 'not decided yet'.
8	Sweden	19 Jun 2013	Femoral blood	0.35 µg/g	3-methylmethcathinone	Cause of death reported as 'overdose of AH-7921'.
9	Sweden	9 Jul 2013	Femoral blood	0.43 µg/g	12 µg/g pregabalin, 0.53 µg/g norbupropion, 0.40 µg/g bupropion, 0.17 µg/g nordiazepam, 0.12 µg/g diazepam, mirtazapine and desmethylmirtazapin	Cause of death reported as 'intoxication with opioids among others'.
10	Sweden	5 Sep 2013	Hair	+	3-methylmethcathinone, buprenorphine	Deceased was treated in intensive care.
11	United Kingdom	Jan–Nov 2013	Blood; urine	0.05 mg/L	chloroform and ethanol were also detected in the blood	Deceased was found dead with chloroform-containing bag over the head.
12	United Kingdom	Jan–Nov 2013	Blood; urine	0.58 mg/L	4-MEC, pentedrone, mephedrone, D2PM, etizolam, etaqualone	Deceased was found dead at home with powders.
13	United Kingdom	Jan–Nov 2013	Peripheral blood	4.46 mg/L	clobazam, doxylamine, mirtazapine	Subject was unresponsive at home; died in hospital.
14	Norway	7 Aug 2013 (M, 23)	Peripheral blood	1.3 µmol/L (0.43 mg/L)	2-FMA (0.041 µmol/L), 3-MMC (0.012 µmol/L), codeine (1.4 µmol/L) and paracetamol (124 µmol/L)	There was information that the deceased had bought drugs on the internet.
15	Norway	Dec 2012	—	—	—	Not analytically confirmed. White powder and a used syringe with dried blood were found close to the deceased. AH-7921 was detected in both the powder and the syringe.

^(a) Sweden reported a death that occurred in Norway where the post-mortem biological sample were analysed by the Swedish National Laboratory of Forensic Medicine. AH-7921 was detected in femoral blood and quantified at 0.34 µg/g; etizolam was also detected and quantified at 0.27 µg/g. Information provided by Norway suggests that is most likely relates to the first death as the first case reported from Norway (above). It has not been included in the total number of deaths reported by Sweden nor treated as a separate case from Norway. As such it has not been listed in the table.

^(b) For the first 14 deaths in this table, the analytical confirmation of AH-7921 was in post mortem samples.

^(c) A '+' in this column indicates that AH-7921 was detected but no quantification was provided.

^(d) 4-MEC is 4-methylmethcathinone; D2PM is diphenyl-2-pyrrolidinylmethanol; 2-FMA is 2-fluoromethamphetamine; 3-MMC is 3-methylmethcathinone.

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-methylenedioxypropylvalerone (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-methylenedioxypropylvalerone (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-methylenedioxypropylvalerone (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

Scientific Committee members

- | **Dr Anne-Line Bretteville Jensen**, Norwegian Institute for Alcohol and Drug Research, Oslo
- | **Prof. Dr Gerhard Bühringer**, Addiction Research Unit, Dep. of Clinical Psychology and Psychotherapy, Technische Universität Dresden, Institut für Therapieforschung (IFT), Munich, Vice-Chair of the Scientific Committee
- | **Dr Catherine Comiskey**, Director, Centre for Practice and Healthcare Innovation, Trinity College Dublin, School of Nursing and Midwifery, Dublin
- | **Dr Paul Dargan**, Clinical Toxicology, St Thomas' Hospital, Guy's and St Thomas' NHS Foundation Trust, London
- | **Prof. Gabriele Fischer**, Medical University Vienna, Center of Public Health, Department of Psychiatry and Psychotherapy, Vienna
- | **Prof. Dr Henk Garretsen**, Faculty of Social and Behavioural Sciences, Tilburg University, LE Tilburg
- | **Prof. Dr Matthew Hickman**, Social Medicine, Bristol
- | **Prof. Dr Dirk J. Korf**, Universiteit of Amsterdam, Law Faculty, Amsterdam
- | **Prof. Dr Krzysztof Krajewski**, Department of Criminology, Jagiellonian University, Kraków
- | **Prof. Letizia Paoli**, LINC, Leuven Institute of Criminology, University of Leuven Faculty of Law, Leuven
- | **Dr Fernando Rodriguez de Fonseca**, Fundación IMABIS, Hospital Carlos Haya, Málaga
- | **Prof. Dr Brice De Ruyver**, Department of Criminal Law and Criminology, Faculty of Law, Universiteit Gent
- | **Prof. Dr Rainer Spanagel**, Institute of Psychopharmacology, Central Institute of Mental Health, Mannheim

Advisers to the Scientific Committee

- | **Dr Peter Blanckaert**, Belgian Early Warning System on Drugs, DO Public Health and Surveillance, Substance use and related disorders (SURD), Brussels
- | **Dr Simon Brandt**, School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Liverpool
- | **Prof. Desmond Corrigan**, The School of Pharmacy and Pharmaceutical Sciences, Trinity College, Dublin
- | **Prof. Gaetano Di Chiara**, Cagliari University, Biomedical Sciences Department, Cagliari
- | **Dr Dariusz Zuba**, Institute of Forensic Research, Kraków

Representatives of the institutions

European Commission

- | **Elsa Maia**, Anti-Drugs Policy Unit, European Commission, Brussels
- | **Fabiano Reniero**, Joint Research Centre, Institute for Health and Consumer Protection (IHCP), Brussels

European Medicines Agency (EMA)

- | **Jean-Marc Vidal**, Scientific Support and Projects, Non-clinical Safety, Human Medicines Evaluation Division, London

Europol

- | **Daniel Dudek**, Project SYNERGY, Europol, The Hague

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

EMCDDA staff present

- | **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
- | **Anabela Almeida**, Project assistant, Action on new drugs, Supply reduction and new trends unit
- | **Isabelle Giraudon**, Scientific analyst, Health consequences, Prevalence, consequences and data management unit

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European Monitoring Centre for Drugs and Drug Addiction (2014), *Report on the risk assessment of 3,4-dichloro-N-[[1-(dimethylamino)cyclohexyl]methyl]benzamide (AH-7921) in the framework of the Council Decision on new psychoactive substances*, Risk Assessments, Publications Office of the European Union, Luxembourg.

About the EMCDDA

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.

The EMCDDA's publications are a prime source of information for a wide range of audiences including: policymakers and their advisors; professionals and researchers working in the drugs field; and, more broadly, the media and general public. Based in Lisbon, the EMCDDA is one of the decentralised agencies of the European Union.

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: AH-7921, 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

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EMCDDA, Praça Europa 1, Cais do Sodré, 1249-289 Lisbon, Portugal
Tel. (351) 211 21 02 00 | info@emcdda.europa.eu
emcdda.europa.eu | twitter.com/emcdda | facebook.com/emcdda

