European Monitoring Centre
for Drugs and Drug Addiction

JOINT REPORTS

ISSN 1977-7868

AH-7921

EMCDDA–Europol Joint Report on a new psychoactive substance: AH-7921 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

About this series

EMCDDA–Europol Joint Report publications examine the detailed information provided by the EU Member States on individual new psychoactive substances. Information is collected from the Reitox network, the Europol national units and the national competent authorities of the European Medicines Agency.

Each Joint Report serves as the basis upon which the decision to conduct a risk assessment of the new psychoactive substance is taken. It is part of the three-step procedure involving information exchange, risk assessment and decision-making in the framework of the Council Decision 2005/387/JHA.

EUROPOL

EMCDDA–Europol
joint publication

Contents

3 1. Introduction

3 2. Information collection process

4 3. Information required by Article 5.2 of the Decision
4 3.1 Chemical and physical description, including the names under which the new psychoactive substance is known — Article 5.2(a) of the Decision
5 3.2. Information on the frequency, circumstances and/or quantities in which a new psychoactive substance is encountered, and information on the means and methods of manufacture of the new psychoactive substance — Article 5.2(b) of the Decision
5 3.2.1. Information provided to Europol
5 3.2.2. Information provided to the EMCDDA
6 3.3. Information on the involvement of organised crime in the manufacture or trafficking of the new psychoactive substance — Article 5.2(c) of the Decision...
6 3.4. A first indication of the risks associated with the new psychoactive substance, including the health and social risks, and of the characteristics of users — Article 5.2(d) of the Decision
6 3.4.1. First indication of health risks
8 3.4.2. Characteristics of users
9 3.5. Information on whether or not the new substance is currently under assessment, or has been under assessment, by the UN system — Article 5.2(e) of the Decision
9 3.6. The date of notification on the Reporting Form of the new psychoactive substance to the EMCDDA or to Europol — Article 5.2(f) of the Decision
10 3.7. Information on whether or not the new psychoactive substance is already subject to control measures at national level in a Member State — Article 5.2(g) of the Decision
10 3.8. Further information — Article 5.2(h) of the Decision
10 3.8.1. The chemical precursors that are known to have been used for the manufacture of the substance
10 3.8.2. The mode and scope of the established or expected use of the new substance
10 3.8.3. Other use of the new psychoactive substance and the extent of such use, the risks associated with this use of the new psychoactive substance, including the health and social risks

11 4. Information from the EMA as requested by Article 5.3 of the Decision
11 4.1 Marketing authorisation
11 4.2 Application for a marketing authorisation
11 4.3 Suspended marketing authorisation

11 5. Conclusions

12 References

13 Annexes

Acknowledgements

The EMCDDA would like to thank the following for their contribution in producing this publication:

- the Early-warning system (EWS) correspondents of the Reitox national focal points (NFPs) and experts from their national EWS networks;
- the Europol national units (ENUs) and Europol Project Synergy;
- the national competent authorities responsible for human and veterinary medicinal products in the Member States, Norway and Iceland;
- the European Medicines Agency (EMA) and the European Commission;
- the World Health Organization;
- Dr István Ujváry for preparing a technical review on AH-7921;
- EMCDDA staff: Brendan Hughes, Isabelle Giraudon, Athanasios Stamos, Marta Rychert and Katarzyna Natoniewska.

Project team: Roumen Sedefov, Michael Evans-Brown, Andrew Cunningham, Ana Gallegos, Anabela Almeida (EMCDDA) and Daniel Dudek (Europol).

1. Introduction

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

At the end of September 2013, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and Europol examined the available information on a new psychoactive substance 3,4-dichloro-N-[[1-(dimethylamino)cyclohexyl] methyl]benzamide, commonly abbreviated as 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 collected on AH-7921 satisfied criteria 4, 5 and 6. The two organisations therefore concluded that sufficient information had been accumulated to merit the production of a Joint Report on AH-7921 as stipulated by Article 5.1 of the Decision.

2. Information collection process

In compliance with the provisions of the Decision, on 7 October 2013 the EMCDDA and Europol launched a procedure for the collection of information on AH-7921, in order to prepare the Joint Report. The information was collected mainly through the Reitox national focal points in the Member States, Turkey and Norway as well as the Europol National Units. In addition, the EMA collected information through the national competent authorities responsible for human and veterinary medicinal products in the Member States as well as in Norway and Iceland. The information collection process was largely concluded by 18 November 2013; additional information and clarifications from some countries were received up to four weeks after this date.

Europol asked the Europol National Units to provide information on:

- the level of production of AH-7921 in their country;
- the level of distribution of AH-7921 in their country;
- the level of trafficking of AH-7921 in their country, for internal, transit or export purposes;
- the number of seizures of AH-7921 in their country, the total amount of the seizures, country of origin, details on the physical forms (including photos);
- the role of organised crime, or criminal groups, in the production, distribution and trafficking of AH-7921 in their country; and,
- any known aspect of violence and/or money laundering relating to the production and trafficking of AH-7921.

Europol received responses from 15 Member States.

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

- the new psychoactive substance AH-7921 has obtained a marketing authorisation;
- the new psychoactive substance AH-7921 is the subject of an application for a marketing authorisation; and,
- a marketing authorisation that had been granted in respect of the new psychoactive substance AH-7921 has been suspended.

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

Furthermore, in anticipation of Article 7.3 of the Decision in relation to the manufacturing of medicinal products in the European Union, the EMA also requested information on whether the new psychoactive substance AH-7921 is used to manufacture a medicinal product:

- that has been granted a marketing authorisation;
- for which an application has been made for a marketing authorisation; and,
- for which a marketing authorisation has been suspended by a competent authority.

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

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

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

The EMCDDA collected data through:

1. a structured questionnaire from the Reitox national focal points. The EMCDDA received replies from 28 Member States as well as Norway and Turkey;
2. data previously provided to the EU early-warning system in EMCDDA–Europol Reporting Forms, EWS Progress and Final Reports;
3. a specific information request to the World Health Organization on whether or not AH-7921 is under assessment by the United Nations system (see section 3.5); and,
4. a structured search of the scientific literature and of relevant Internet sites.

In addition, some sections of the Joint Report ([4]) have been adapted from a review commissioned by the EMCDDA (Ujváry, 2013).

Thus, information included in sections 3.2.1 and 3.3 of the Joint Report was provided by Europol, while the EMCDDA provided information included in sections 3.1, 3.2.2, 3.4, 3.5, 3.6, 3.7, 3.8.1, 3.8.2 and 3.8.3 (in part). The information included in sections 3.8.3 (in part), 4.1, 4.2 and 4.3 was provided by the EMA. The conclusions of the Joint Report were prepared and agreed by the two organisations responsible — the EMCDDA and Europol. Further details of the seizures and collected samples (including images where available) reported to the EMCDDA are provided in Annex 1. The details of deaths associated with AH-7921 that have been reported to the EMCDDA are provided in Annex 2.

3. Information required by Article 5.2 of the Decision

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

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

([4]) Notably, information on the pharmacology and mode of action, toxicology, dependence and abuse potential, and the subjective effects of AH-7921.

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

Chemical description and names

AH-7921 is an *N*-substituted cyclohexylmethylbenzamide, where the benzamide moiety is dichlorinated at positions 3 and 4 of the ring and the aminocyclohexane moiety is *N,N*-dimethylated.

In the commonly used name AH-7921, 'AH' refers to 'Allen & Hanburys', the company that patented the drug. Another name used is doxylam; this may be easily confused with 'doxylamine', which is the International Nonproprietary Name (INN) of a chemically different and widely used antihistaminic medicine with sedative-hypnotic properties.

The systematic IUPAC name for AH-7921 is 3,4-dichloro-*N*-{[1-(dimethylamino)cyclohexyl]methyl}benzamide.

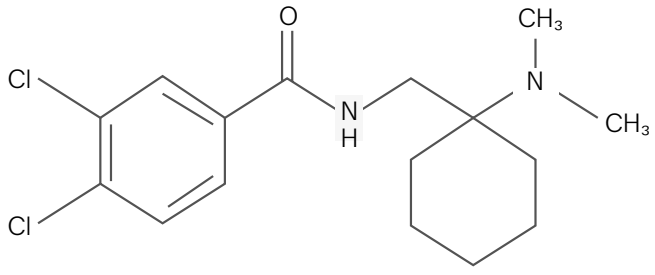
Additional chemical synonyms have been reported:

3,4-dichloro-N-[[1-(dimethylamino)cyklohexyl]methyl] bensamid
3,4-dikloori-N-[(1-dimetyyliamino)sykloheksyyli-metyyli] bentsamidi (Finnish)
1-(3,4-dichlorobenzamidomethyl)cyclohexyldimethylamine

Furthermore, common names or code names have also been reported: doxylam and CN 2924 29 98.

Finally, the following street names have been reported: 'AH-7921' and 'doxylan'.

FIGURE 1
The molecular structure of AH-7921



Molecular formula: $C_{16}H_{22}Cl_2N_2O$
Molecular weight: 329.26

Chemical Abstract Service registry numbers

55154-30-8 free base
41804-96-0 hydrochloride salt

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

Physical description

The free base form of AH-7921 is a solid; its melting point is not known. The hydrochloride salt, also a solid, has been documented to have a melting point of 215–216°C.

An Internet search conducted by the EMCDDA found that AH-7921 is being offered for sale in free base and hydrochloride salt forms.

Information provided from seizures and collected samples has usually noted the presence of AH-7921 in powder form. In one case it was also detected in a sample taken from a syringe that was recovered from the scene of a death.

A detailed description of AH-7921 seizures and collected samples that have been encountered can be found in subsections 3.2.1 and 3.2.2 below.

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

3.2.1. Information provided to Europol

Europol received replies from 15 Member States (Belgium, Bulgaria, Croatia, Cyprus, Estonia, Finland, Germany, Hungary, Italy, Latvia, Lithuania, Luxembourg, Poland, Slovakia and Slovenia). Of these, Finland and Germany provided information relating to AH-7921.

The level of production, distribution and trafficking

Finland reported three seizures of AH-7921 totalling 3.1 g of powder.

Germany reported four seizures of AH-7921, which ranged from 2.8 g to 9.81 g. All seizures were made in 2013.

No reports were received that indicated licit or illicit production of AH-7921 in Finland or Germany.

3.2.2. Information provided to the EMCDDA

Seven Member States (Austria, Denmark, Finland, France, Germany, Sweden and the United Kingdom) and Norway reported detections of AH-7921 ([5]).

Seizures

Six Member States and Norway reported seizures of AH-7921: Austria (two seizures); Denmark (one); Finland (six); France (one); Germany (four); Sweden (10); and, Norway (four).

AH-7921 has usually been seized in powder form. In one case it was also detected in a sample taken from a syringe found at the scene of a death.

Where information has been provided, quantities of powder ranged from 0.02 g (Sweden) to 500 g (France). Caffeine was the only additional substance to have been reported in two seizures reported by Sweden.

Austria reported two seizures of powder of 0.9 g and 1.9 g, seized by the police in August and September 2013.

Denmark reported a seizure of 0.87 g of powder, seized by the police on 21 May 2013.

Finland reported five seizures made by customs authorities at Helsinki Airport (freight) and one seizure by the police, between October 2012 and October 2013. Quantities seized were small, ranging from 0.1 g to 2 g.

France reported one seizure of 500 g of powder, seized by customs authorities in freight at Roissy Airport (Paris) in October 2013.

Germany reported four seizures of powder, weighing from 2.8 g to 9.81 g, seized in February and October 2013.

Sweden reported a total of 10 seizures made during 2012 and 2013. Five were made by the police (from 0.02 g to 12.94 g) and five by customs authorities (from 0.2 g to 103.86 g). Caffeine was also detected in two of the samples seized by customs.

Norway reported four seizures made by police. The quantities seized ranged from 0.23 g to 1 g. The first seizure was made in December 2012. In this case, a ziplock bag containing a white

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

powder along with a used syringe, both of which contained AH-7921, were recovered from the scene of a death (see details in section 3.4.1).

Biological samples

Two Member States (Sweden and the United Kingdom) and Norway reported detections of AH-7921 in biological samples.

Sweden reported five non-fatal intoxications between December 2012 and 30 March 2013 where AH-7921 was detected.

Sweden, the United Kingdom and Norway reported a total of 15 deaths where AH-7921 was detected (Sweden, 10 deaths ([6]); the United Kingdom, three; Norway, two) (see section 3.4.1 and Annex 2 for further details).

Sweden reported two detections of AH-7921 in the urine of two people suspected of committing minor criminal offences.

Collected samples

The United Kingdom reported a collected sample of AH-7921 purchased from an Internet retailer in July 2012 ([7]). This sample formed the basis of the first notification of detection of AH-7921 in the European Union (see section 2.6 for further details). The product was supplied in a ziplock bag as a white powder and cost GBP 10 (approximately EUR 11.93) for 250 mg. Further details of this sample are provided in Annex 1.

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

Germany reported that no links have been identified between organised crime groups and the production, trafficking and/or distribution of AH-7921. They also noted that it should be borne in mind that given the easy access to substances (which can be in large amounts) via Internet retailers it cannot be excluded that a certain level of organisation may exist. In addition, the interest and presence of organised crime groups in the phenomenon of new psychoactive substances can be easily concluded from the substantial profits that can be obtained from this type of activity.

Money laundering aspects

No information was received on money laundering in connection with the production and/or trafficking of AH-7921.

Violence in connection with production, wholesale and distribution

No information was received on incidents of violence in connection with the production, wholesale and/or trafficking of AH-7921.

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

3.4.1. First indication of health risks

A total of six non-fatal intoxications and 15 deaths associated with AH-7921 were reported by Sweden, the United Kingdom and Norway. Not all of these cases have been analytically confirmed. See Annex 2 for further details on the deaths.

Non-fatal intoxications

Sweden

Sweden reported six non-fatal intoxications associated with AH-7921 reported by the Swedish Poison Information Centre between December 2012 and 30 March 2013. The presence of AH-7921 was analytically confirmed in five of the six cases. No information was provided on whether the AH-7921 was quantified in these five cases. No further details are currently available for these cases.

Deaths

Sweden

Sweden reported 10 deaths associated with AH-7921 that occurred between January 2013 and September 2013 ([8]). All of these cases were analytically confirmed. In nine of the cases, the concentration of AH-7921 in post-mortem femoral

([6]) Sweden also reported one death that occurred in Norway where the post-mortem biological sample was analysed by the Swedish National Laboratory of Forensic Medicine. At this time it is not clear if this case relates to one of the deaths reported by Norway (below) or is an additional death.

([7]) Purchased from buyresearchchemicals.co.uk

([8]) As noted in section 3.2.2, 'biological detections', Sweden also reported one 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 femoral blood; etizolam was also detected and quantified at 0.27 µg. At this time it is not clear if this case relates to one of the deaths reported by Norway or is an additional death.

blood ranged from 0.03 to 0.99 µg/g; in the remaining case AH-7921 was detected in post-mortem hair but was not quantified. In all 10 cases AH-7921 was found in combination with at least one other psychoactive substance. These included: amphetamine (two cases); 3-methylmethcathinone (two cases); a metabolite of ketamine; alcohol; buprenorphine; benzodiazepines (alprazolam, diazepam, nordazepam, pyrazolam) and other medicines (zopiclone, paroxetine, bupropion, mirtazapine, pregabalin, gabapentin, aripiprzol). 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'. In two cases the cause of death remains to be determined. In one death no further information was provided.

United Kingdom

The United Kingdom reported three deaths associated with AH-7921. The dates of death were not reported, but they are thought to have occurred between January and November 2013. All of these cases were analytically confirmed.

In the first case, AH-7921 was detected in blood with a concentration of 0.58 mg/L. The deceased was found dead at home. 4-MEC ([9]), pentedrone, mephedrone, D2PM ([10]), etizolam and etaqualone were also detected in post-mortem blood.

In the second case, AH-7921 was detected in blood with a concentration of 0.05 mg/L. The deceased was found dead with bag over the head, and chloroform was also involved.

In the third case, AH-7921 was detected in blood with a concentration of 4.46 mg/L. The victim was found unresponsive at home and died in hospital. Clobazam, doxylamine and mirtazapine were also detected in post-mortem blood.

Norway

Norway reported two deaths associated with AH-7921. The first death occurred in December 2012, the second in August 2013.

In the first case AH-7921 was not analytically confirmed but was suspected due to the circumstances of the death. During the investigation the police found a bag with small amounts of white powder and a used syringe with dried blood close to the deceased. AH-7921 was detected in both the powder and a sample taken from the syringe. Etizolam and phenazepam were also found at the scene.

In the second case the presence of AH-7921 was analytically confirmed. The level of AH-7921 was quantified at 1.3 µmol/L. Other substances were also present: 2-fluoromethamphetamine (0.041 µmol/L), 3-methylmethcathinone (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.

See Annex 2 for further details of these cases.

Pharmacology and mode of action

In the early 1970s a series of benzamide derivatives with an aminocyclohexane moiety were invented, inspired by the analgesic and other therapeutically valuable properties of substances structurally related to fentanyl and phencyclidine (Harper and Veitch, 1976; Harper et al., 1974). The most active compound in the series was AH-7921 (Figure 1). Laboratory experiments with animals established AH-7921 to be an opioid receptor agonist with analgesic potency similar to that of morphine. However, the development of the substance was abandoned and only limited information on its biological properties is available. Since 1988, no studies with AH-7921 or its analogues appear to have been published in the scientific literature.

Of the 57 cyclohexyl derivatives tested, AH-7921 showed significant analgesic properties, being nearly as active as morphine in several pain models. The analgesic potencies found for morphine and AH-7921 in the initial studies with mice and rats are given in Table 1 (Tyers, 1980; Harper et al., 1974; Brittain et al., 1973).

In rhesus monkeys, the minimal antinociceptive doses of morphine and AH-7921 to suppress pain evoked by electric stimulation of the dental pulp were <5.0 and 13.8±1.2 mg/kg, respectively (Brittain et al., 1973).

Comparative pharmacological evaluation with rodents indicated that AH-7921, like morphine, is a µ opioid peptide (MOP) receptor agonist. Its analgesic effect against chemically induced pain indicates the involvement of κ opioid peptide (KOP) receptors as well (Tyers, 1980), which was confirmed in subsequent studies in vitro with guinea pig brain preparations in which AH-7921 showed moderate selectivity towards MOP receptors over KOP receptors (Ki = 10 nM versus 150 nM) (Loew et al., 1988). Hayes and Tyers (1983) studied in the mouse the role of opioid receptor types in the various side effects produced by selected opioid receptor agonists, including AH-7921, applied subcutaneously. In general, the side effects (e.g., changes in pupil diameter and

([9]) 4-Methylethcathinone.
([10]) Diphenylprolinol.

TABLE 1

Analgesic potencies (ED_{50} values in mg/kg) of morphine and AH-7921 in rodents (representative data). Abbreviations: s.c.: subcutaneous.

Compound	Hot-plate test, mouse, s.c.	Tail-flick test, 55ºC, rat, s.c.	Phenylquinone test, mouse, oral	Acetylcholine-induced writhing, mouse, s.c.	Inflamed paw pressure, rat, s.c.
Morphine	1.7	0.6	1.1	0.45	0.43
AH-7921	1.8	0.8	0.85	0.59	0.57

respiratory rate) for AH-7921 and morphine were similar, indicating a shared mode of action at the receptor level. All the effects produced by the drugs were reduced significantly by simultaneous administration of the opioid receptor antagonist naloxone (1 mg/kg s.c.). It is noteworthy that the dose-response curves for AH-7921 were rather steep: doses that produced side effects were close to those producing analgesia (see also Sewell and Spencer, 1974). For example, the ED_{50} value for respiratory depression, that is the dose of the drug capable of depressing the respiratory rate of the control group by 25 %, was 2.5 mg/kg, for analgesia the ED_{50} value was 0.55 mg/kg; in the case of morphine the ED_{50} values for respiratory depression and analgesia were 4.2 and 0.45 mg/kg, respectively. No studies were identified that have examined the pharmacology and mode of action of AH-7921 in humans.

Toxicology

The study by Harper et al. (1974) implies that the LD_{50} of AH-7921 is higher than 10 mg/kg upon intravenous administration in the rat ([11]). No studies were identified that have examined the toxicity of AH-7921 in humans.

Insufficient information is available to determine the clinical features of acute toxicity associated with AH-7921.

Dependence and abuse potential

Brittain et al. (1973) assessed the dependence liability of AH-7921 in the rat and rhesus monkey. Naloxone treatment of rats that had received repeated doses of AH-7921 (5–20 mg/kg orally, three times a day for five days) showed 'abstinence syndrome' similar to that observable for morphine using a similar dose schedule. Nalorphine, another opioid receptor antagonist, evoked withdrawal symptoms in rhesus monkeys that had received repeated doses of AH-7921 (7.5–30 mg/kg s.c., twice daily for 30 days). Furthermore, single doses of AH-7921 (5–10 mg/kg s.c.) completely alleviated the abstinence syndrome in morphine-dependent rhesus monkeys. The study concluded that AH-7921 'would be classified as a narcotic analgesic having high addictive liability'. No studies were identified that have examined the dependence and abuse potential of AH-7921 in humans.

Some self-reported user experiences suggest development of tolerance, taking more than was planned and withdrawal-like symptoms (Google, 2013a, 2013b, 2013c).

3.4.2. Characteristics of users

No studies were identified that examined the characteristics of users of AH-7921. The section below includes a discussion of the characteristics of users, which include self-reported use from Internet drug discussion forums and related websites (hereafter 'user websites'). As such it is important to note that it is not possible to confirm the specific substance(s) used, nor the purity, dose, etc. Analyses of products containing new psychoactive substances that are sold on the drug market have shown that the composition can differ between that claimed by the retailer, and also over different geographical areas and time. In addition, the information provided on user websites should be regarded as illustrative only and not taken as representative of users of AH-7921 in general.

Route of administration, dose and drug regimens

Information provided by the Member States and from user websites suggests that the routes of administration for AH-7921 include nasal, oral or sublingual intake, as well as intravenous injection and rectal administration. Information from user websites suggests a range of doses are used; see 'subjective effects', below, for examples (Erowid, 2013a; Google, 2013a, 2013b, 2013c).

Information from user websites suggests that AH-7921 may be used on its own and in combination with other psychoactive substances, including new psychoactive substances and/or controlled drugs (Erowid, 2013a, 2013b, 2013c; Google, 2013a, 2013b, 2013c). In some of the deaths reported by the Member States and Norway new psychoactive substances and/or controlled drugs were detected in biological samples (Section 3.4.1 and Annex 2).

([11]) For comparison, LD_{50} values of morphine (rat, i.v.) range between 64 mg/kg and 223 mg/kg, depending upon which salt of the drug and which strain of rat are used (Strandberg et al., 2006; Niemegeers et al., 1976. Finnegan et al., 1948).

Subjective effects

No studies were identified that have examined the subjective effects of AH-7921 in humans; information is limited to self-reported experiences ('trip reports') on user websites (Erowid, 2013a; Google, 2013a, 2013b, 2013c).

In January 2012 an ex-heroin user reported the intravenous injection of 100–150 mg of a solution of AH-7921 that produced 'a lovely smack-like high…complete with nod, decent euphoria and the hallmarks of a quality Morphine/bordering Diamorphine high'; development of tolerance was noted after repeated use of AH-7921 alone and in combination with ethylphenidate ('speedballing') (Drugs-Forum, 2013). A separate report described the inhalation of the vapours of a total of 40 mg of the free amine (free base) of AH-7921 (powdery crystal). The peak effects lasted for 1.5 hours and were described as 'like a relaxed morphine effect' (Erowid, 2013b). Another report described the experiences of two users who sublingually applied a solution made from 1 g of the powdery crystal (the CAS registration number provided by the vendor indicated the HCl salt form), lemon juice (10 ml) and warm water (40 ml). After the initial sublingual doses of 2 ml of the solution (containing 40 mg of the drug), total amounts of about 145 mg and 155 mg of the drug were consumed during an 11 hour session by the users (re-dosing was done in 60 to 120 minutes intervals). In addition to analgesia, relaxation, euphoria, 'opiate glow' and alertness, occasional itching, nausea and, toward the end of the session, tremors were experienced. Slight miosis was noted three hours after the first dose (Erowid, 2013c). No serious adverse events were mentioned in these three reports.

Availability and supply

A search of google.com using the search string 'buy "AH-7921"' conducted in December 2013 for the Joint Report identified a number of Internet retailers offering AH-7921 for sale in both retail and wholesale quantities (Google, 2013d). In the former case AH-7921 appears to be usually sold as a 'research chemical'. As noted, the first detection of AH-7921 reported to the EMCDDA was a collected sample of 250 mg of white powder purchased in July 2012 for GBP 10 (EUR 11.98) from an Internet retailer selling 'research chemicals' ([12]).

Prevalence of use

Data from prevalence surveys

No prevalence surveys were identified that have examined the use of AH-7921 in the general population or in targeted populations.

([12]) Purchased from http://www.buyresearchchemicals.co.uk

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

The World Health Organization is the specialised United Nations agency designated for the evaluation of the medical, scientific and public health aspects of psychoactive substances under the Single Convention on Narcotic Drugs, 1961 and the Convention on Psychotropic Substances, 1971. On 10 October 2013 the World Health Organization informed the EMCDDA that AH-7921 is currently under assessment and 'the critical review report will be published only early next year (probably April)'.

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

The Joint Report has been produced on the understanding that AH-7921 is not at an advanced stage of assessment within the United Nations system.

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

The first official EMCDDA–Europol notification of AH-7921 dates from August 2012 from the United Kingdom National Focal Point. The Reporting Form details a collected sample of 250 mg of white powder purchased in July 2012 from an Internet retailer ([13]) at a cost of GBP 10 (EUR 11.98). It was sold as AH-7921 and was received in packaging with a label indicating that it was for use as a 'laboratory reagent only'. Other details included the full chemical name and hazard warning codes. The identification and analytical characterisation was based on GC-MS ([14]), ^{1}H NMR ([15]) and DEPTQ NMR ([16]).

AH-7921 was added to the list of new psychoactive substances monitored by the EMCDDA and Europol through

([13]) Purchased from http://www.buyresearchchemicals.co.uk
([14]) Gas chromatography-mass spectrometry.
([15]) Proton nuclear magnetic resonance spectroscopy.
([16]) Distortionless enhancement by polarisation transfer with quaternary carbons NMR.

the European Union early-warning system, and a profile of the substance was created in the EMCDDA European Database on New Drugs (EDND). Since then, analytical details, background information and public health alerts have been exchanged between EMCDDA, Europol and the Member States on an ad hoc basis. The European Commission and the EMA were kept duly informed.

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

Sweden reported that AH-7921 is a controlled under the Narcotic Drugs Control Act (SFS 1992-860) and the Narcotic Drugs Control Ordinance (SFS 1994-1554).

Two Member States (Poland and Romania) reported that AH-7921 is controlled under legislation prohibiting the unauthorised supply of defined or qualifying new psychoactive substances. 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 is penalised with a fine (administrative sanctions). In Romania, 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).

Two Member States (Finland and the Netherlands) and Norway reported that AH-7921 is subject to control measures under medicine legislation. In Finland AH-7921 has been controlled under the Medicines Act (395/87) since 15 March 2013. In the Netherlands, the sale of AH-7921 in consumer amounts is treated as being a medicinal product and must comply with medicines legislation (and general product safety legislation). In Norway AH-7921 is regulated by the Medicines Act and a prescription would be required to receive it.

Twenty-two Member States (Austria, Belgium, Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, France, Germany ([17]), Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Portugal, Slovakia, Slovenia and the United Kingdom) and Turkey reported that AH-7921 is not subject to control measures at the national level.

No information was provided regarding the control status of AH-7921 in Spain.

([17]) Germany reported an intention to introduce national control measures for AH-7921.

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

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

No information was reported about the chemical precursors or manufacturing methods used to make AH-7921. Methods for the production of AH-7921 are documented in the scientific literature.

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

No studies were identified that have examined the mode and scope of established or expected use of AH-7921. Given the limited information currently available, the relevant information on the mode and scope of established or expected use of AH-7921 that has been reported by the Member States as well as that from user websites has been included in the previous sections.

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

No information was provided by any Member State that indicated that AH-7921 had any other use apart from in legitimate scientific research and as an analytical reference standard.

From the available information it does not appear that AH-7921 is used in the manufacture of a medicinal product in the European Union. However, the collection of information cannot be considered exhaustive in the absence of a European Union database on the synthetic routes of all medicinal products ([18]).

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

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

4.1. Marketing authorisation

Twenty-four Member States, Norway and Iceland responded to the EMA's information request (see section 2). They reported that the new psychoactive substance AH-7921 has not obtained a marketing authorisation ([19]). The EMA also reported that the new psychoactive substance AH-7921 has not obtained a marketing authorisation through the central authorisation procedure.

4.2. Application for a marketing authorisation

Twenty-four Member States, Norway and Iceland responded to the EMA's information request (see section 2). They reported that the new psychoactive substance AH-7921 is not the subject of an application for a marketing authorisation ([19]). The EMA also reported that the new psychoactive substance AH-7921 is not the subject of an application for a marketing authorisation through the central authorisation procedure.

4.3. Suspended marketing authorisation

Twenty-four Member States, Norway and Iceland responded to the EMA's information request (see section 2). They reported that there had been no cases of a suspended marketing authorisation that had been granted in respect of the new psychoactive substance AH-7921 ([19]). The EMA also reported that the new psychoactive substance AH-7921 is not the subject of a suspended marketing authorisation through the central authorisation procedure.

5. Conclusions

AH-7921 is a synthetic opioid. It has been available in the European Union since at least July 2012 and has been detected in seven EU Member States and Norway. In most cases it has been seized in small quantities as a powder. Over a short period of time it has been associated with six non-fatal intoxications and 15 deaths in three countries. The similarity of AH-7921 to morphine in terms of pharmacology is a key concern. This may play an important role in the further spread of AH-7921 by opioid users, including the injecting population. We conclude that the health and social risks caused by the manufacture, trafficking and use of 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 in accordance with Article 6 of Council Decision 2005/387/JHA.

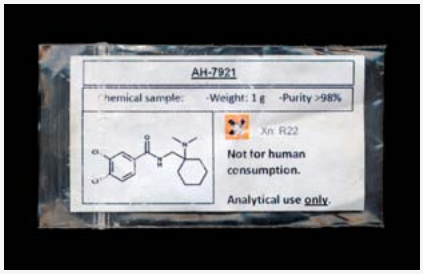
([19]) Austria, Belgium, Croatia, the Czech Republic, Denmark, Estonia, Germany, Greece, Hungary, Iceland, Ireland, the Netherlands, Norway, Portugal, Slovenia, Spain, Sweden and the United Kingdom provided responses in relation to both human and veterinary medicinal products. Cyprus, Italy, Lithuania,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

References

- Brittain, R. T., Kellett, D. N., Neat, M. L. and Stables, R. (1973), 'Anti-nociceptive effects in N-substituted cyclohexylmethylbenzamides', *British Journal of Pharmacology*, 49, pp. 158–159.
- Drugs-Forum (2013). http://www.drugs-forum.com/forum/showthread.php?t=182016
- Erowid (2013a), AH-7921 reports. http://www.erowid.org/experiences/subs/exp_AH7921.shtml
- Erowid (2013b). http://erowid.org/experiences/exp.php?ID=93949
- Erowid (2013c). http://erowid.org/experiences/exp.php?ID=100939
- Finnegan, J. K., Haag, H. B., Larson, P. S. and Dreyfuss, M. L. (1948), 'Observations on the comparative pharmacologic actions of 6-dimethylamino-4,4-diphenyl-3-heptanone (amidone) and morphine', *Journal of Pharmacology and Experimental Therapeutics*, 92, pp. 269–276.
- Google (2013a). https://www.google.com/search?q=site:drugs-forum.com+AH-7921&ie=UTF-8&oe=UTF-8
- Google (2013b). https://www.google.com/search?q=site:bluelight.ru+AH-7921&ie=UTF-8&oe=UTF-8
- Google (2013c). https://www.google.com/search?q=site:forum.opiophile.org+AH-7921&ie=UTF-8&oe=UTF-8
- Google (2013d). https://www.google.com/search?q=buy+"AH-7921"&ie=UTF-8&oe=UTF-8
- Harper, N. J. and Veitch, G. B. A. (1976), '1-(3,4-Dichlorobenzamidomethyl)-cyclohexyldimethylamine', US Patent 3,975,443 (17 August 1976) assigned to Allen & Hanburys Limited, 20 pages.
- Harper, N. J., Veitch, G. B. A. and Wibberley, D. G. (1974), '1-(3,4-Dichlorobenzamidomethyl) cyclohexyldimethylamine and related compounds as potential analgesics', *Journal of Medicinal Chemistry*, 17, pp. 1188–1193, plus supplementary material.
- Hayes, A. G. and Tyers, M. B. (1983), 'Determination of receptors that mediate opiate side effects in the mouse', *British Journal of Pharmacology*, 79, pp. 731–736.
- Loew, G., Lawson, J., Toll, L., Frenking, G., Berzetei-Gurske, I. and Polgar, W. (1988), 'Structure activity studies of two classes of beta-amino-amides: the search for kappa-selective opioids', in Harris, L. S. (ed.), *Problems of Drug Dependence*, NIDA Research Monograph, 90, pp. 144–151, U.S. Department of Health and Human Services, Rockville, Maryland.
- Niemegeers, C. J. E., Schellekens, K. H. L., Van Bever, W. F. M. and Janssen, P. A. J. (1976), 'Sufentanil, a very potent and extremely safe intravenous morphine-like compound in mice, rats and dogs', *Arzneimittelforschung*, 26, pp. 1551–1556.
- Sewell, R. D. E. and Spencer, P. S. J. (1974), 'Biogenic amines and the anti-nociceptive activity of agents with a non-opiate structure', *Journal of Pharmacy and Pharmacology*, 26 (Supplement), pp. 92–93.
- Strandberg, J. J., Kugelberg, F. C., Alkass, K., Gustavsson, A., Zahlsen, K., Spigset, O. and Druid, H. (2006), 'Toxicological analysis in rats subjected to heroin and morphine overdose', *Toxicology Letters*, 166, pp. 11–18.
- Tyers, M. B. (1980), 'A classification of opiate receptors that mediate antinociception in animals', *British Journal of Pharmacology*, 69, pp. 503–512.
- Ujváry, I. (2013), 'Review on synthetic opioids with special emphasis on ODT, AH-7921, (iso)butyryl fentanyl, (iso)butyryl α-methylfentanyl and carfentanil (CC.13.SAT.014)', Lisbon, EMCDDA.

Annex 1

Images of AH-7921 from seizures and collected samples

Country	Image	Description
Norway		Seizure: December 2012 One ziplock bag with trace amounts of white powder, and one used syringe with deposits of red/brown material (assumed to be dried blood), seized in Alstahaug. Seizing authority: police
United Kingdom	 	Collected sample, analysed in July 2012 250 mg white powder, test purchase (250 mg, GBP 10.00) from Buy Research Chemicals Collecting authority: States Analyst's Laboratory, Guernsey and Liverpool John Moores University

Annex 2
Deaths associated with AH-7921 ([20])

	Country	Date of death (gender, age)	Biological sample ([21])	AH-7921 result ([22])	Results for other substances ([23])	Notes
1	Sweden	8 Jan 2013 (M, 28)	Femoral blood	0.81 µg/g	10 µg gabapentin	Cause of death reported as 'unintentional overdose'.
2	Sweden	4 Feb 2013 (M, 25)	Femoral blood	0.99 µg/g	4.7 µg amphetamine, aripiprzol	Cause of death reported as 'pneumonia caused by aspiration'.
3	Sweden	22 Mar 2013	Femoral blood	0.03 µg/g	0.03 µg 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 N-ethylnorketamine, alcohol	Cause of death reported as 'unclear'.
7	Sweden	16 June 2013	Femoral blood	0.16 µg/g	0.04 µg amphetamine	Cause of death reported as 'not decided yet'.
8	Sweden	19 June 2013	Femoral blood	0.35 µg/g	3-methylmethcatinone	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-methylmethcatinone, buprenorphine	Deceased was treated in intensive care.
11	United Kingdom	Jan–Nov 2013	Blood; urine	0.05 mg/L		Deceased was found dead with bag over head and chloroform.
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	Blood; urine	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	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 ([24])	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.

([20]) 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 femoral blood; etizolam was also detected and quantified at 0.27 µg. At this time it is not clear if this case relates to one of this deaths reported by Norway or is an additional death. As such it has not been listed in the table.
([21]) For the first 14 deaths in this table, the analytical confirmation of AH-7921 was in post-mortem samples.
([22]) A '+' in this column indicates AH-7921 was detected but no quantification was provided.
([23]) 4-MEC is 4-methylmethcathinone.
D2PM is diphenyl-2-pyrrolidin-2-yl-methanol.
2-FMA is 2-fluoromethamphetamine.
3-MMC is 3-methylmethcathinone.
([24]) This death was not analytically confirmed. It has been included because a white powder and a used syringe with dried blood were recovered from close to the deceased and AH-7921 was detected in both the powder and the syringe.

TD-AS-14-004-EN-N

Recommended citation:

European Monitoring Centre for Drugs and Drug Addiction (2014), *EMCDDA–Europol Joint Report on a new psychoactive substance: AH-7921 3,4-dichloro-N-{[1-(dimethylamino) cyclohexyl]methyl}benzamide*, Joint Reports, Publications Office of the European Union, Luxembourg.

About the EMCDDA

The European Monitoring Centre for Drugs and Drug Addiction is the hub of drug-related information in Europe. Its mission is to provide the European Union and its Member States with 'factual, objective, reliable and comparable information' on drugs and drug addiction and their consequences. Established in 1993, it opened its doors in Lisbon in 1995, and is one of the European Union's decentralised agencies. The Centre offers policymakers the evidence base they need for drawing up drug laws and strategies. It also helps professionals and researchers pinpoint best practice and new areas for analysis.

Related publications and websites

EMCDDA

- *European Drug Report 2013: Trends and developments*, 2013

EMCDDA and Europol

- *EMCDDA–Europol 2012 Annual Report on the implementation of Council Decision 2005/387/JHA (New drugs in Europe, 2012),* Implementation reports, 2013

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

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

Luxembourg: Publications Office of the European Union
doi: 10.2810/2846 | ISBN 978-92-9168-685-8

This publication is only available in electronic format.

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

Publications Office