ACMD

Advisory Council on the Misuse of Drugs

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Norman Baker MP, Minister for Crime Prevention
Home Office
2 Marsham Street
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10 June 2014

Dear Minister,

RE: ACMD's recommendation on the synthetic opiate AH-7921

The Advisory Council on the Misuse of Drugs (ACMD) is reviewing the synthetic opiates as part of your commissioning on revising generic definitions under the Misuse of Drugs Act 1971 to control new and emerging novel psychoactive substances (NPS).

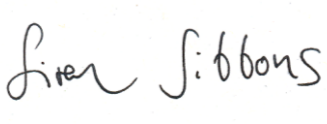
Following a report from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) earlier this year on the potency and toxicity of a particular synthetic opiate, referred to as AH-7921, the ACMD has been compelled to prioritise the review of this substance in its ongoing work on synthetic opiates. Although the ACMD has reviewed the existing evidence in the UK and found little evidence of misuse, the Advisory Council strongly recommends the permanent control of this opiate – mainly based on its potential to cause harm, its potency, fatalities widely reported in other European countries, and its highly addictive potential. AH-7921 has a similar pharmacological profile to morphine, which itself is controlled under the Misuse of Drugs Act 1971 as a Class A substance. The ACMD is not aware of any legitimate use for this compound.

I attach with this letter the ACMD's review of AH-7921 (Annex A), along with an associated report from the European database on new drugs (Annex B) and a joint risk assessment from EMCDDA/Europol (Annex C).

The ACMD recommends that AH-7921 be controlled under the Misuse of Drugs Act 1971- specifically named as a **Class A** substance and scheduled under **Schedule 1** of the Misuse of Drugs Regulations 2001 (as amended).

The ACMD's NPS committee will continue to monitor synthetic opiates as a priority under this review and expects to report again by the end of 2014.

Yours sincerely,



Professor Les Iversen

ACMD Chair

Professor Simon Gibbons

Chair of the ACMD's NPS Committee

CC: Rt Hon Theresa May MP, Home Secretary

Annex A: ACMD's review of AH-7921

Background

AH-7921 (synonym "doxylam") is a potent synthetic analgesic developed by Allen & Hanburys' pharmaceutical company in the UK more than 40 years ago. The compound was not developed further, presumably because animal studies revealed a high addictive potential. The synthetic drug has recently become available as a legal product; it was first detected in Europe in July 2012 (EMCDDA, 2014). Since then a number drug-related deaths have been reported, detailed in the EMCDDA/Europol report published recently (EMCDDA, 2014).

Prevalence in the UK

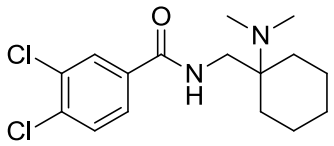
As of 3 March 2014, the Home Office's 'drugs early warning system' (DEWS) had not reported any confirmed cases of deaths related to AH-7921. AH-7921 has yet to be identified by the Home Office's Forensic Early Warning System (FEWS).

Chemistry

AH-7921 is an *N*-substituted cyclohexylmethylbenzamide. The name AH-7921 refers to its origin as a research chemical; in the Allen & Hanburys' pharmaceutical company in the UK in the 1970's, another name less commonly used is "doxylam".

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

Figure 1: The molecular structure of AH-7921:



AH-7921

Chemists at Allen & Hanburys reported the synthesis of 56 *N*-substituted cyclohexlyamines, of which AH-7921 was the most potent analgesic in an animal test (ACh induced writhing in mice) (Harper et al, 1974).

Pharmacology

In another study reported by Allen & Hanburys' AH-7921 was the most potent analgesic in a series of synthetic *N*-substituted cyclohexylmethylbenzamides in two animal tests (ACh induced writhing and a hot plate test in mice) with a potency

comparable to that of morphine. AH-7921 was chosen for more detailed studies in animal models of drug dependence. After treatment with AH-7921 orally three times a day in escalating doses of up to 20 mg/kg, mice demonstrated a typical opiate withdrawal behavioural syndrome when challenged with the opiate antagonist naloxone. Tests for dependence in rhesus monkeys were also positive (Brittain et al, 1973). The authors concluded that:

"AH-7921 could be classed as a narcotic analgesic having high addictive potential".

Further studies by Allen & Hanburys' scientists confirmed the potent analgesic effects of AH-7921 in a range of animal models (mouse abdominal pain, mouse hot plate, rat tail immersion, rat paw pressure), (Tyers, 1980). A comparison of the analgesic doses of AH-7921 with those causing adverse side effects (e.g. inhibition of respiration, inhibition of gut propulsion, mouse Straub tail) demonstrated that AH-7921 resembled morphine in having a relatively narrow therapeutic window between wanted and unwanted effects (Hayes & Tyers, 1983).

The reported pharmacology clearly indicates that AH-7921 is a selective μ-agonist at mammalian opiate receptors, with a potency comparable to that of morphine. Like morphine, AH-7921 has a high addictive liability.

Misuse of AH-7921

AH-7921 is available for sale on the Internet. It is available both as the free base and the hydrochloride salt in quantities ranging from a few milligrams to kilogram amounts (the latter from Chinese suppliers).

User forums report doses of 30-50 mg rectally, or sublingually (bitter taste). There are some reports of insufflation but accompanied by painful irritant effect and oral doses seem less effective, requiring >100 mg dose.

Toxicology

The ACMD is not aware of any acute toxicity reports in the UK.

The National Programme on Substance Abuse Deaths (NPSAD) in the UK reported three deaths involving AH-7921 in 2013.

Table 1- Results of three deaths in the UK involving AH-7921

Biological sample	**AH-7921 result**	**Results for other substances in blood**	**Cause of death**
Blood and urine	4.46 mg/L	Clobazam	Accidental overdose
		Doxylamine	
		Mirtazapine	
Blood and urine	0.58 mg/L	4-MEC	Unknown

		Pentedrone	
		Mephedrone	
		D2PM	
		Etizolam	
		Etaqualone	
Blood	0.05 mg/L	Ethanol	Chloroform, alcohol, AH-7921 and Methqualone-like substance toxicity
		Unidentified methqualone-like compound	
		Chloroform	

A recent EMCDDA/Europol report listed a further ten deaths associated with AH-7921 in Sweden and two deaths in Norway. Internationally, Austria, Denmark, Finland, France, Germany, Sweden and Norway also reported detections of AH-7921 to the EMCDDA (see Annex C).

References

Brittain, R.T., Kellett, D.N., Neat, M .L., Stables, R.(1973) Anti-nociceptive effects of *N*–substituted cyclohexylmethylbenzamides. Br. J. Pharmacol. 49: 158-159P.

EMCDDA (2014) European Monitoring Centre for Drugs and Drug Addiction – EUROPOL “Joint report on a new psychoactive substance: AH-7921”.

Hayes, A.G. and Tyers, M.B. (1983) Determination of receptor that mediate opiate side effects in the mouse. Br. J. Pharmacol. 79:731-736.

Harper, N.J., Veitch,G.B.A., Wibberley, D.G. (1974) 1-(3,4-Dichlorobenzamdmethyl)cyclohexydimethylamine and related compounds as potential analgesics. J. Med. Chem. 17:1188-1193.

Tyers, M.B. (1980) A classification of opiate receptor that mediate antinociception I animals. Br. J. Pharmacol. 69: 503-512.

Annex B - Reports received by the European Database on New Drugs

Country	Date of report	Report
Germany	26 November 2013	German FP reported a seizure of 2,9 gram of AH-7921 seized in September 2013 by the police in Ravensburg. The substance was seized together with 11,85g white powder of W-15 and several herbal mixtures (bulk) laced with synthetic cannabinoids (AM-2201 and JWH-210).
	18 June 2013	German NFP reported a seizure of 4,52g white powder seized on 15/02/13 by the police at Munich.
Norway	22 August 2013	Norwegian FP reported that: "A 23-year old boy was found dead, forensic autopsy was performed and peripheral blood revealed AH-7921 (1,3 micromol per litre), 2-FMA (0,041 micromol per litre), 3-MMC (0,012 micromol per litre). Other findings were codeine (1,4 micromol per litre) and paracetamol (124 micromol per litre). There was information that the deceased had bought drugs on the internet".
	25 February 2013	Norwegian NFP reported a seizure of 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 on 03/12/12 by the police at Alstahaug. The seizure was done in connection with one death, where overdose caused by AH -7921 is suspected (the compound was also identified in a syringe which have been used by the person).
Denmark	4 July 2013	Danish NFP reported a seizure of 0,9g powder seized on 21/05/2013 by the police at Varde, Southern Jutland.
Sweden	25 June 2013	Swedish NFP sent additional information from National Board of forensic medicine. They have had one case labelled as a mixed intoxication and one case described as an overdose of AH-7921 since last reported. They have no additional information to give regarding these cases at the moment.
	20 February 2013	Swedish NFP reported 2 post-mortem examinations from femoral blood. One death where it is assessed that the cause of death is AH-7921 (accidental poisoning). This person (male, born 1985) was reported to have taken AH 7921 and 0.81 µg/g post-mortem femoral blood was found. The coroner has described some sort of powerful anaphylactic reaction, which is common in opiate poisonings. Another unfinished case (male, born 1987) where it was detected 0.99 µg/g post-mortem femoral blood, which is a high concentration.
	12 October 2012	Swedish NFP reported a seizure of 1,0g white powder seized on 14/09/12 by the Customs at Stockholm. The substance was identified by the National Laboratory of Forensic Science (SKL) using GC-MS (M+ is very weak but present) and NMR.
Finland	3 December 2012	Finnish NFP reported a seizure of 0,5g white powder seized on 15/10/2012 by the Customs at Helsinki incoming mail from UK.
UK	1 August 2012	NFP reported a collected sample of 250mg white powder. Test purchase (250 mg, £10.00) from Buy Research Chemicals UK at http://www.buyresearchchemicals.co.uk/ , July 2012. Analytical characterization, by GC-MS, 1H and DEPTQ NMR, carried out by Roland Archer (States Analyst's Laboratory, Guernsey) and Simon D. Brandt, Liverpool John Moores University. Note: The GC-MS peaks at 6.646 and 9.260 min are internal standards, quinoline and triplennamine, respectively.

Annex C: Joint EMCDDA/Europol risk assessment of 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

1. Introduction

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

At the end of September 2013, the EMCDDA and Europol examined the available information on a new psychoactive substance 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;

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

- the level of trafficking of AH-7921 in their country, both 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:

- which 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.

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).

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

[3] With the exception of France

Thus, information included in sections 3.2.1 and 3.3 of the Joint Report was provided by Europol, while the EMCDDA provided information included in sections 3.1, 3.2.2, 3.4, 3.5, 3.6, 3.7, 3.8.1, 3.8.2 and 3.8.3 (in part). The information included in sections 3.8.3 (in part), 4.1, 4.2 and 4.3 was provided by the EMA. The conclusion of the Joint Report was 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 (of the EMCDDA report). The details of deaths associated with AH-7921 that have been reported to the EMCDDA are provided in Annex 2 (of the EMCDDA report).

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.

3.1 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 codenames have also been reported: doxylam and CN 2924 29 98.

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