European Monitoring Centre
for Drugs and Drug Addiction

Risk Assessment Report
of a new psychoactive substance:

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

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

1. Introduction

This *Risk Assessment Report* presents the summary findings and the conclusions of the risk assessment carried out by the extended Scientific Committee of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) on the new psychoactive substance 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 presenting a summary of the information considered during the detailed analysis of the scientific and law enforcement data available at this time. The conclusion section of the report summarises the main issues addressed and reflects the opinions held by the members of the 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 establishes a mechanism for the rapid exchange of information on new psychoactive substances (hereafter 'Early Warning System' ([3])) that may pose public health and social threats, including the involvement of organised crime. Thus, it allows the institutions of the European Union and the Member States to act on all new narcotic and psychotropic substances ([4]) that appear on the European Union drug market. The Council Decision also provides for an assessment of the risks associated with these new psychoactive substances so that, if necessary, control measures can be applied in the Member States for narcotic and psychotropic substances ([5]).

AH-7921 was first identified in a sample purchased from an Internet retailer in July 2012 and formally notified to the Early Warning System in August 2012 by the United Kingdom. Following

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([1]) EMCDDA (2009), *Risk assessment of new psychoactive substances: operating guidelines*, The Publications Office of the European Union, Luxembourg. Available at: http://www.emcdda.europa.eu/html.cfm/index100978EN.html

([2]) OJ L 127, 20.5.2005, p. 32.

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

([4]) According to the definition provided by the Council Decision, a '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 Schedule I, II or IV; 'new psychotropic drug' means a substance in pure form or in a preparation that has not been scheduled under the 1971 United Nations Convention on Psychotropic Substances, and that may pose a threat to public health comparable to the substances listed in Schedule I, II, III or IV.

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

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 to the Council of the European Union, the European Commission and the European Medicines Agency (EMA) a *Joint Report* on AH-7921 ([6]).Taking into account the conclusion of the *Joint Report*, and in accordance with Article 6 of the Council Decision, on 29 January 2014, the Council formally requested that 'the risk assessment should be carried out by the extended Scientific Committee of the EMCDDA and be submitted to the Commission and the Council within twelve weeks from the date of this notification'.

In accordance with Article 6.2, the meeting to assess the risks of 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 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, as well as the list of participants attending the risk assessment meeting is annexed to this report (Annex 1).

For the risk assessment, the extended Scientific Committee considered the following information resources:

(i) *Technical Report on 3,4-dichloro*-N-*{[1-(dimethylamino)cyclohexyl]methyl}benzamide (AH-7921)* (Annex 2);

(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, grey literature, Internet drug discussion forums and related websites (hereafter, 'user websites');

(iv) Data from EMCDDA Internet monitoring of suppliers (that typically appear to be manufacturers and/or wholesalers) and retailers selling AH-7921;

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

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([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)*, EMCDDA, Lisbon. Available at: http://www.emcdda.europa.eu/publications/joint-report/AH-7921

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

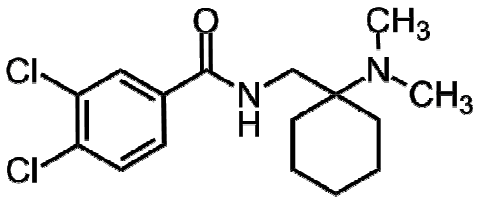
Finally, it is important to note that this *Risk Assessment Report* contains a discussion of the available information on non-fatal intoxications and deaths associated with new psychoactive substances that are critical to the identification of emerging toxicological problems within the European Union.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

2. Physical, chemical and pharmacological description of 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.

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



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

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

Another name of 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’ — sometimes abbreviated also as ‘doxylam’ — which is the International Nonproprietary Name (INN) of a widely used and chemically different

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

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 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.

There have been several model studies in animals and experiments *in vitro* which 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

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([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.).

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. Since 1989, no studies with AH-7921 have been published. 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 nor in the Member States that responded to the information request by the EMA that was launched under Article 5 of the Council Decision. There is no information 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.

3. 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. 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.

4. 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, as well as 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 (LD_{50}) 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 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 as well as 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 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 as well as other information provided thereon, which is sometimes incorrect or contradictory.

([12]) A 'Material Safety Data Sheet' of a fine chemicals company offering AH-7921 (free amine) for sale in 2014 lists acute oral LD_{50} values of 300 mg/kg in the mouse and 980 mg/kg in the rat. However, the MSDS is not a peer-reviewed document.

There have been 6 non-fatal intoxications associated with AH-7921 that were reported by Sweden to the Early Warning System; 5 of these have been analytically confirmed; the clinical symptoms reported included hypertension, tachycardia and seizures. The routes of administration were reported as peroral, nasal, smoking. No further information is available to allow interpretation of these cases.

There have been 15 deaths associated with AH-7921 reported to the Early Warning System: Sweden (10 deaths), the United Kingdom (3) and Norway (2). 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. Of note is that in five deaths one or more internationally controlled or non-controlled benzodiazepines were detected; while in only one of the deaths was another opioid (buprenorphine) detected. Notably, no heroin, or 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 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 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 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 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 2 of the 15 European deaths associated with AH-7921 involved this route of administration. As such, sharing of needles and syringes carries the risk of transmission blood-borne viruses. People who experimented with the drug often reported repeated intake of AH-7921 to maintain its effects for six to twelve 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

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

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 as well as deaths reported to the Early Warning System suggests that AH-7921 is used in the home environment.

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

5. 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.

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

AH-7921 was first identified in a collected sample purchased form 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 reported seizures ranging from 0.02 to 500 g.

There is no information that suggests 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 nor 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.

7. 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 will be subject to evaluation at the thirty-sixth meeting of the Expert Committee on Drug Dependence, which will be held in June 2014.

Article 7.1 of Council Decision states:

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

The risk assessment has been carried out on the understanding that AH-7921 is not at an advanced stage of assessment within the United Nations system.

8. 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, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, 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, Netherlands, Poland, Romania and Spain) and Norway use other legislative measures to control AH-7921:

In Finland medicines legislation is used to control AH-7921. In the Netherlands medicines legislation is used 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 is penalized 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 which, if necessary, is fully applicable. In Norway medicines legislation is used to control AH-7921.

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

Under Article 9.1 of the Council Decision, the option for control that is available at 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 of the European Union.

- A 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, which may in themselves have public health consequences.

- It is not possible to gauge to what extent this control is likely to impact on current and future research by research/academic institutes, pharmaceutical or chemical industries.

- This control option could create an illicit drug market in AH-7921 with 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.

10. Conclusions

AH-7921 is a structurally unique synthetic opioid analgesic which was first identified in a collected sample purchased from an Internet retailer in July 2012 and formally notified to the Early Warning System in August 2012 by the United Kingdom. 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 are 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 6 non-fatal intoxications. There have been 15 deaths associated with AH-7921 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 as well as a risk of respiratory depression that 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 dependence potential similar to morphine.

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.

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 States controls AH-7921 under drug control legislation. Five Member States and Norway control AH-7921 under other legislation. 22 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 would be 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 this drug has potential positive consequences in terms of reducing availability and therefore the adverse health and social consequences arising from the use of AH-7921. 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.

11. List of annexes

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

Annex 2: Technical Report on 3,4-dichloro-*N*-{[1-(dimethylamino)cyclohexyl]methyl}benzamide (AH-7921).

European Monitoring Centre for Drugs and Drug Addiction

Annex 1. List of participants at the Risk Assessment meeting on AH-7921, 1 April 2014

A. Extended Scientific Committee

Scientific Committee Members

Dr. Anne-Line BRETTEVILLE JENSEN
Norwegian Institute for Alcohol and Drug Research, Oslo

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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

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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, Krakow

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LINC, Leuven Institute of Criminology, University of Leuven Faculty of Law, Leuven

Dr. Fernando RODRIGUEZ de FONSECA
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Institute of Psychopharmacology, Central Institute of Mental Health, Mannheim

Additional Experts to the Scientific Committee

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Belgian Early Warning System on Drugs, DO Public Health&Surveillance, Substance use & related disorders (SURD), Brussels

Dr. Simon BRANDT
School of Pharmacy & Biomolecular Sciences, Liverpool John Moores University, Liverpool

Prof. Desmond CORRIGAN
The School of Pharmacy & Pharmaceutical Sciences, Trinity College, Dublin

Prof. Gaetano DI CHIARA
Cagliari University, Biomedical Sciences Department, Cagliari

Dr. Daríusz ZUBA
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Institutional Representatives

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Fabiano RENIERO
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European Medicines Agency (EMA)
Jean-Marc VIDAL
Scientific Support and Projects, Non-clinical Safety, Human Medicines Evaluation Division, London

Europol
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Project SYNERGY, Europol, The Hague

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B. Invited Experts

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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

European Monitoring Centre
for Drugs and Drug Addiction

Annex 2. Technical report on 3,4-dichloro-N-{[1-(dimethylamino)cyclohexyl]methyl}benzamide (AH-7921)

Prepared by: Dr István Ujváry

iKem BT, Budapest, Hungary

EMCDDA contract code: CC.14.SAT.003

Table of contents

Summary

AH-7921 is a synthetic opioid analgesic with a unique chemical structure containing an aminocyclohexane ring to which a 3,4-dichlorobenzamide moiety is appended. Its systematic name is 3,4-dichloro-*N*-{[1-(dimethylamino)cyclohexyl]methyl}benzamide. It was invented and patented by the London-based company Allen & Hanburys Limited in the mid-1970s. AH-7921 can be manufactured from commercially available starting materials in three steps.

The pharmacological, especially analgesic, properties of AH-7921 were studied in non-clinical trials in the 1970s, but the drug was not developed into a medicine. AH-7921 has no current known legitimate industrial, agrochemical, cosmetic, human or veterinary medical use.

AH-7921 has appeared recently on the illicit drug market typically as a white powder. AH-7921 was first identified in a collected sample purchased from the Internet in the United Kingdom in July 2012 and reported to EU Early Warning System in August 2012. The structural characterisation of this novel substance required GC-MS as well as NMR spectroscopy. Subsequently in September 2012, the substance was also identified in small seized samples in Sweden and Finland in October. Between January 2013 and March 2014, a further five Member States (Austria, Belgium, Denmark, France and Germany) and Norway reported several seizures of small samples ranging from 0.02 to 11.8 g. In 2013, larger seizures by customs were reported by France and Sweden (500 g and 103.86 g, respectively).

There is no information on the prevalence of use of AH-7921 as there are currently no co-ordinated national or European population surveys on its use.

According to user reports posted on Internet drug forums, AH-7921 appears to have been sold online since 2011. It is advertised as a ‘research chemical’ or a legal opioid. The amounts typically offered range from 250 mg to several grams, but bulk quantities can also be ordered. According to Internet searches for ‘AH-7921’, the opioid-like analgesic properties of the substance have been discussed from March 2010 followed by user reports from 2011.

From information available from self-reports posted on Internet user forums, many of the users of AH-7921 are experimenting or self-medicating with this new opioid. These types of users have been considered by some to be innovators, early-adopters or so-called ‘psychonauts’. These self-reports indicate that the substance has been used orally, by nasal insufflation, rectally and by intravenous injection; smoking or inhalation of the vapours of the free amine form of the drug has also been mentioned. The typical doses range from 40 to 150 mg.

There are no studies on the subjective effects of AH-7921 in humans. According to self-reports available on Internet forums, the effects of AH-7921 resemble those of other opioids with the feeling of mild euphoria and relaxation; nausea has been mentioned as an adverse effect. Some users self-medicate with this new drug to relieve pain, others to alleviate withdrawal symptoms due to cessation of the use of another opioid.

While the number of reported non-fatal acute AH-7921 poisoning cases is relatively low, Member States and Norway have reported 15 deaths associated with AH-7921 over a period of 15 months, clustered between December 2012 and March 2014. For all but one cases the presence of AH-7921 in biological samples was analytically confirmed. In most of these cases forensic analysis detected other psychoactive substances, including alcohol, prescription only medicines and/or new psychoactive substances. While it is not possible to determine with certainty the role of AH-7921 in these fatalities, in some cases it has been specifically noted in the cause of death.

There are limited data on the pharmacokinetics of AH-7921. Recent forensic studies related to poisoning cases identified two *N*-desmethyl metabolites that may be 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.

There have been several animal models and studies *in vitro* which have investigated the pharmacodynamics, including 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 peptide receptor agonist with some effect on the κ-opioid peptide receptor as well. The opioid receptor antagonist naloxone appears to counteract the effect of AH-7921. In various animal models, AH-7921 was nearly as active an analgesic as morphine and several times more potent than codeine. In experiments with mice, the opioid adverse effect profile of AH-7921 was similar to that of morphine and, remarkably, AH-7921 was a 1.6-fold more potent respiratory inhibitor than morphine in this animal. The involvement of other pharmacological targets, such as receptors, enzymes or transport proteins, in the biological activity, including toxicity, of AH-7921 has not been studied. The acute toxicity of AH-7921 in animals has not been properly established.

Based on studies involving animal models of dependence, AH-7921 could be classified as a narcotic analgesic having dependence liability. While no studies have 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.

In conclusion, AH-7921 is a recently emerged synthetic opioid analgesic with an unusual chemical structure. The known pharmacological properties of AH-7921 are qualitatively and quantitatively similar to morphine. The substance appears to have a limited use in EU Member States and Norway. Between September 2012 and March 2014, AH-7921 was seized in eight Member States and Norway. Between December 2012 and March 2014, AH-7921 has been detected in number of non-fatal poisoning cases and there have been 15 deaths reported that are associated with AH-7921.

Section A. Physical, chemical, pharmaceutical and pharmacological information

A1. Physical, chemical and pharmaceutical information

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

Chemical description and names

AH-7921 is a structurally unprecedented synthetic analgesic invented four decades ago. Chemically, it is a derivative of dimethylaminocyclohexane to which a 3,4-dichlorobenzamide group is appended (Figure 1). The pharmacology of AH-7921 has been studied by industrial and academic laboratories in the 1970s and 1980s but the development of the compound was apparently abandoned. Only a handful of publications, including patents, describe its chemical and pharmacological properties.

In the commonly used name AH-7921, 'AH' refers to 'Allen & Hanburys', the pharmaceutical company that patented and investigated the drug in the 1970s ([1]).

The systematic (International Union of Pure and Applied Chemistry, IUPAC) name:

3,4-dichloro-*N*-{[1-(dimethylamino)cyclohexyl]methyl}benzamide

Additional chemical synonyms have been reported:

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

Another name encountered in the non-scientific literature is 'doxylam' ([2]). 'Doxylam' should not be confused with 'doxylamine' – sometimes abbreviated also as 'doxylam' – which is the International Nonproprietary Name (INN) of a chemically different and widely used antihistaminic medicine with sedative-hypnotic properties (for example, it is used in non-prescription medicines for the treatment of allergies and assisting sleep) ([3]) ([4]) ([5]). It is of concern that taking AH-7921, mislabelled as 'Doxylam', instead of the sleep-aid 'Doxylamine' could lead to unintentional adverse events related to AH-7921 toxicity. Furthermore, 'Doxylan' is a (seldom used) trade name of the semisynthetic tetracycline antibiotic doxycycline (INN).

The Chemical Abstract Service Registry Numbers (CAS RNs) for AH-7921:

([1]) A wholly owned subsidiary of Glaxo Laboratories Ltd. from 1961, Allen & Hanburys Ltd had already launched 'salbutamol' (1968), one of the most important asthma medicines used today.

([2]) See, for example, http://forum.opiophile.org/shothread.php?45627-AH-7921-(Doxylam)

([3]) http://www.drugs.com/mtm/doxylamine.html

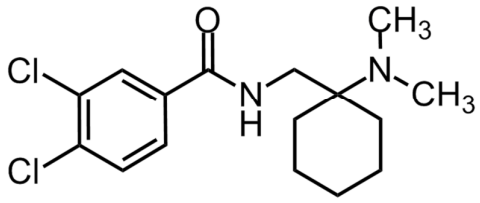
([4]) http://www.chemspider.com/Chemical-Structure.3050

([5]) http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=3162

55154-30-8 free amine
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.

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



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

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

Identification and analytical profile

According to a Material Safety Data Sheet (MSDS) available from a supplier of analytical standards ([6]), AH-7921, as a free amine, is soluble in ethanol at ~11 mg/ml, in DMSO at ~3 mg/ml, and in dimethyl formamide at ~10 mg/ml; it is sparingly soluble in water; it has an approximate solubility of 0.5 mg/ml in a 1:1 mixture of ethanol and aqueous phosphate buffer (pH 7.2).

Analysis using gas chromatography (GC) coupled with mass spectrometry (MS) is straightforward ([7]) (see also, Uchiyama et al., 2013; Soh and Elliott, 2014; Vorce et al., 2014). The electron impact mass spectrum of AH-7921 contains the following characteristic fragments (m/z): 328 and 326 $[M-1]^+$, 175 and 173, 147 and 145, 127 and 126 (base peak), 109, 96, 84, 70, 58 and 44. Due to the natural co-occurrence of chlorine-35 and chlorine-37 isotopes, chlorine-containing fragments appear as a group of distinct peaks of which two are clearly observable in the mass spectrum of AH-7921.

The ultraviolet and visible spectrum of AH-7921 has λ_{max} values at 205 and 237 nm ([8]).

The Fourier Transform infrared spectrum of the HCl salt of AH-7921 contains the following characteristic bands: 677, 710, 769, 800, 852, 877, 903, 1032, 1084, 1130, 1142, 1250, 1306,

([6]) http://www.caymanchem.com/catalog/12036

([7]) http://www.swgdrug.org/Monographs/AH-7921.pdf

([8]) http://www.caymanchem.com/catalog/12036

1464, 1533, 1653, 2563, 2854, 2937, and 3230 cm^{-1} ([9]).

The proton and ^{13}C nuclear magnetic resonance (NMR) spectra used for the structure identification in the first detection the substance are available (see ([10])). In July 2012, a supplier of AH-7921 also uploaded on its Internet site the NMR spectra of a batch of the substance ([11]).

There is no information on presumptive colour tests with AH-7921.

As of March 2014, there is no immunoassay field test for AH-7921. Reportedly, urinary AH-7921 did not show cross-reactivity in immunoassay kits developed for 6-acetylmorphine, amphetamine, barbiturates, benzodiazepines, cannabinoids, cocaine, MDMA, opiates, oxycodone, or phencyclidine (Vorce et al., 2014; see also Kronstrand and Thelander, 2013).

To estimate the ability of AH-7921 to be transported through biomembranes, including the blood-brain barrier (Kelder et al., 1999), the polar surface area (PSA) was calculated using a freely accessible software tool ([12]). The topological PSA was calculated to be 32.34 $Å^2$, which is in the range found for drugs acting on the centrally nervous system (<60–70 $Å^2$; drugs with a PSA >120 $Å^2$ are hardly absorbed when taken orally). For comparison, the PSA values for amphetamine, dronabinol (THC), loperamide, alprazolam, caffeine, morphine and aspirin are 23.63, 28.71, 40.75, 44.90, 58.75, 59.05 and 65.01 $Å^2$, respectively (Vieth et al., 2004).

Physical description

The hydrochloride salt of AH-7921 is a solid with a melting point of 215–216 ºC (colourless microneedles from EtOH-Et_2O) (Harper et al., 1974). The free amine of AH-7921 is also reported to be a solid at room temperature but the melting point is unknown ([13]).

An Internet search conducted by the EMCDDA has found that AH-7921 is being offered for sale as the free base and the hydrochloride salt form (EMCDDA–Europol, 2014). Nevertheless, suppliers giving the structural formula and the CAS RN of the free base of AH-7921 may actually sell a salt of the substance, and vice versa.

Information provided from seizures and collected samples have usually noted the presence of AH-7921 in white or off-white powder form; whether the sample was the free amine or a salt has not been reported. A detailed description of AH-7921 seizures and collected samples that have been encountered can be found in Table 2 (Section C).

([9]) http://www.swgdrug.org/Monographs/AH-7921.pdf

([10]) http://www.swgdrug.org/Monographs/AH-7921.pdf

([11]) https://www.bcr-finechemicals.com/ah-7921-analysis-batch2

([12]) http://molinspiration.com/cgi-bin/properties Note that PSA is just one of the simple quantitative measures used to predict blood-brain barrier permeation and it considers passive transport only.

([13]) http://www.caymanchem.com/catalog/12036

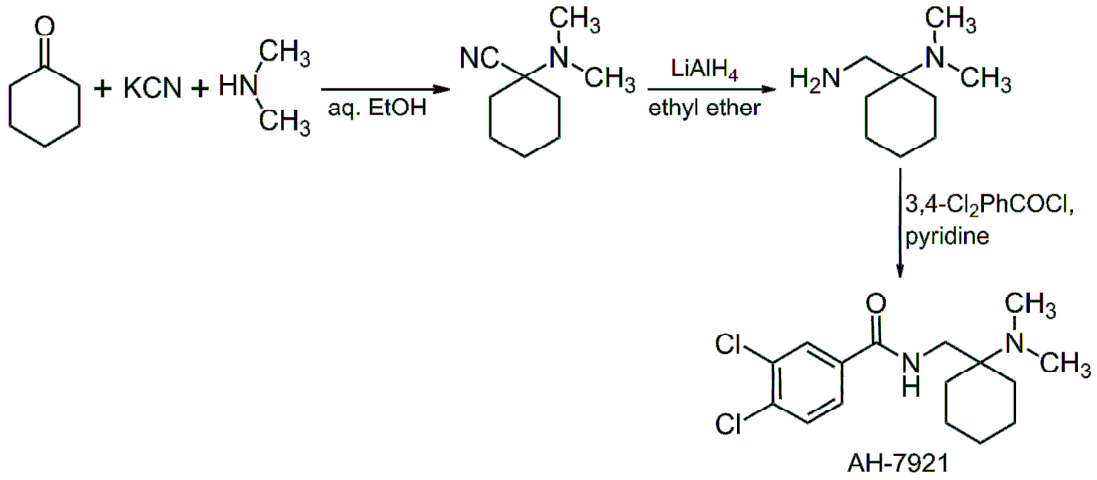
Certified reference materials, including deuterium-labeled AH-7921 suitable for forensic analysis, are commercially available ([14]).

Methods and chemical precursors used for the manufacture of AH-7921

There is no information regarding the manufacturing sites, the precursors or the synthetic methods used for AH-7921 found in seizures or collected samples.

Only one common synthetic route to AH-7921 and its analogues has been published in the scientific and patent literature (Harper et al., 1974; Harper and Veitch, 1976; Caulfield et al., 2001) (Figure 2). Briefly, heating an equimolar amount of cyclohexanone, potassium cyanide ([15]) and the hydrochloride salt of dimethylamine in aqueous ethanol affords the α-aminonitrile adduct ([16]) (Strecker synthesis). Reduction of the cyano group of the product with $LiAlH_4$ in anhydrous ether affords the corresponding primary amine, that is 1-(aminomethyl)-*N*,*N*-dimethylcyclohexanamine. This 1,2-diamine, in turn, is then acylated with 3,4-dichlorobenzoyl chloride in pyridine to give AH-7921 isolated as the hydrochloride salt. The reduction of the α-aminonitrile can also be accomplished by catalytic hydrogenation (Reihlen et al, 1932; Granger and Técher, 1960).

Figure 2. The synthesis of AH-7921.



The above synthesis of AH-7921 uses readily available starting materials, requires conventional equipment and no special chemical expertise is needed for the production of the

([14]) For example, http://www.caymanchem.com, http://www.lipomed.com or http://www.cerilliant.com

([15]) Potassium cyanide is a highly toxic substance! Special permit is required for its manufacture, trade and use. Other cyanides might serve as alternative cyanide sources. However, a cyanide-free method for the preparation of the 1,2-diamine precursor could also be feasible (Nomura et al., 1964; Robiette et al., 2010).

([16]) This α-aminonitrile can also be used in the synthesis of phencyclidine and some of its analogues.

substance.

It must, however, be noted that there is no information regarding the manufacturing sites or the synthetic methods used for AH-7921 detected in the European Union and Norway. Suppliers that advertise AH-7921 might not necessarily be the manufacturers of the chemical.

Typical impurities encountered in seized samples

There is currently no information available on impurities arising from the synthesis of AH-7921 in the analysed products. For seizures and collected samples reported to the EMCDDA and Europol, the concentrations of the contents have not been provided.

Except for caffeine detected in two out of ten seizures in Sweden, no other substances have been reported to be present. (For further details on seized and collected samples, see Section C).

During forensic analysis of a range of products purchased in Japan between July 2012 and January 2013, the co-occurrence of AH-7921 with a synthetic cathinone (α-PBP ([17])) and a synthetic cannabinoid (EAM-2201 ([18])) in a herbal mixture was noticed (Uchiyama et al., 2013).

A1.2. Physical/pharmaceutical form

As noted above, information provided from seizures and collected samples have usually reported the presence of AH-7921 in powder form. A detailed description of AH-7921 seizures and collected samples that have been encountered can be found in Table 2 (Section C). Since no systematic analysis has been done, it is not known that the drug traded under the name 'AH-7921' or 'doxylam' is the free amine or the hydrochloride salt of the chemical.

A1.3. Route of administration and dosage

Information provided by the Member States and obtained from Internet drug discussion forums suggests that the route of administration for AH-7921 include inhalation, nasal insufflation, oral ('bombing' or drinking) or sublingual intake, as well as intravenous injection and rectal administration. For intravenous administration, an injectable aqueous solution has to prepared from the powdery product (see Section D1.2.1). Self-reported information from drug discussion forums indicates typical single acute doses ranging from 40 mg to 150 mg (for examples, see Section D1.2; Drugs-Forum, 2013; Erowid, 2013a; Google, 2013a,b,c; Bluelight, 2014).

Information from user websites suggests that AH-7921 may be used on its own as well as in combination with other psychoactive substances, including new psychoactive substances and/or controlled drugs (Drugs-Forum, 2013; Erowid, 2013; Google, 2013b,c). It must be noted that in several of the deaths reported by the Member States and Norway, AH-7921 was

([17]) 1-phenyl-2-(pyrrolidin-1-yl)butan-1-one

([18]) (4-ethylnaphthalen-1-yl)[1-(5-fluoropentyl)-1*H*-indol-3-yl]methanone

detected along with other new psychoactive substances and/or controlled drugs in biological samples (see Section D1.2.3 and Table 3).

A2. Pharmacology, including pharmacodynamics and pharmacokinetics

Pharmacokinetics

There are no data available from animal studies in the literature on the pharmacokinetics of AH-7921.

In a recent death associated with AH-7921, two putative metabolites of AH-7921, namely *N*-desmethyl-AH-7921 (nor-AH-7921) and *N*,*N*-didesmethyl-AH-7921 (dinor-AH-7921) ([19]), were reported to be present in the urine and blood of the deceased persons (Soh and Elliott, 2013; Vorce et al., 2014) (see Section D.1.2.3). The biological activity of these demethylated metabolites is not known.

Self-reported information from drug discussion forums indicate that the opioid-like effects become apparent at about 30 min after oral intake of a single dose of, for example, 50 mg of AH-7921 and last for about 1.5 h; re-dosing is frequently reported (see Section D1.2.1).

Pharmacodynamics

Inspired by the analgesic and other therapeutically valuable properties of substances structurally related to fentanyl and phencyclidine, a series of benzamide derivatives with an aminocyclohexane moiety were invented in the early 1970s (Harper and Veitch, 1976; Harper et al., 1974). In animal pain models, one of the most active compounds in the series was AH-7921 (Figure 1). Further 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 1989, no studies with AH-7921 or its close analogues appear to have been published in the scientific literature.

Of the 57 aminocyclohexane derivatives synthesised, the 3,4-dichlorobenzamide (AH-7921), the 2-chlorobenzamide and the 4-fluorobenzamide derivatives as well as a non-acylated pyrrolidine amine analogue showed significant analgesic properties (Harper et al., 1974). Detailed studies with AH-7921 revealed that, on a weight basis, this simple compound is nearly as active as morphine and several times more potent than codeine in several pain models. The analgesic potencies reported for morphine, codeine and AH-7921 in the initial studies with mice and rats are given in Table 1 (Brittain et al., 1973; Harper et al., 1974; Tyers, 1980). Because of its higher molecular mass, AH-7921 is somewhat more active than morphine on a

([19]) The systematic names of the two metabolites are 3,4-dichloro-*N*-{[1-(methylamino)cyclohexyl]methyl}benzamide and *N*-[(1-aminocyclohexyl)methyl]-3,4-dichlorobenzamide, respectively.

molar basis in some assays ([20]).

Table 1. Antinociceptive potencies (ED_{50} values in mg/kg) of morphine, codeine and AH-7921 (representative data). Abbreviation: s.c.: subcutaneous. Key: a: Brittain et al., 1973, and Harper et al., 1974; b: Tyers, 1980.

Compound	Hot-plate test mouse, s.c.	Tail-flick test 55°C, rat, s.c.	Phenylquinone test, mouse, oral	Acetylcholine-induced writhing, mouse, s.c.	Inflamed paw pressure, rat, s.c.
morphine	2.8[a]; 1.7[b]	0.6[b]	1.1[a]	0.45[b]	0.43[b]
codeine	17.0[a]	16.1[b]	5.8[a]	5.0[b]	2.1[b]
AH-7921	2.5[a]; 1.8[b]	0.8[b]	0.85[a]	0.59[b]	0.57[b]

In rhesus monkeys, the minimal oral antinociceptive doses of AH-7921, codeine and morphine to suppress pain evoked by electric stimulation of the dental pulp were 13.8, 11.3 and ≤5.0 mg/kg, respectively (Brittain et al., 1973). In a similar test using dogs, morphine and AH-7921 proved to be equipotent on a weight basis with a minimal effective antinociceptive oral dose of 1.25 mg/kg for each, while the corresponding analgesic dose for codeine was 3.5 mg/kg. Antinociceptive doses of AH-7921 caused no overt behavioural effects in the test animals; at the high oral dose of 50 mg/kg, however, “central nervous system depression” was noted (Brittain et al., 1973).

Sewell and Spencer (1974) studied the action of intracerebroventricularly (ICV) injected serotonin and noradrenaline on the analgesics effect of several drugs in the mouse tail-flick test. Importantly, it was found that serotonin increased (prolonged) the antinociceptive effects of subcutaneously injected morphine and AH-7921. Conversely, ICV administration of noradrenaline attenuated the antinociceptive effects of the analgesics. Based on these results, potential *in vivo* drug interactions between AH-7921 and brain-penetrable serotonergic and adrenergic drugs or medicines may be assumed.

Comparative pharmacological evaluation in rodents indicated that AH-7921, like morphine, is a μ opioid peptide (MOP) receptor agonist, while its analgesic effect against chemically-induced pain suggests the involvement of κ opioid peptide (KOP) receptors as well (Table 1) (Tyers, 1980). These observations were confirmed in subsequent studies *in vitro* with guinea pig brain preparations in which AH-7921 showed reasonable selectivity towards MOP receptors over KOP receptors (K_i = 10 nM versus 150 nM) ([21]) (Loew et al., 1988, 1989). Hayes and Tyers

([20]) For example, the respective molar ED_{50} values for morphine and AH-7921 are 6.0 and 5.5 μmol/kg in the mouse hot-plate test, 2.1 and 2.4 μmol/kg in the tail-flick test, and 3.8 and 2.6 μmol/kg in the phenylquinone test.

([21]) Analogues of AH-7921 with high selectivity towards the KOP receptor have been developed (Loew et al., 1988,1989). In fact, similar 1,2-diamines containing the characteristic 3,4-dichlorophenyl moiety were developed of which U50,488, i.e.,

(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 or adverse effects (e.g., motor impairment as measured by the 'rotarod test' ([22]), inhibition of gut propulsion as well as changes in pupil diameter and 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.).

From a toxicological point of view, it is noteworthy that the dose-response curves for AH-7921 were rather steep and doses that produced adverse effects were close to those producing analgesia (Hayes and Tyers, 1983; see also, Sewell and Spencer, 1974; Tyers, 1980). 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. Morphine was found to have a greater margin of safety (two-fold), having ED_{50} values for respiratory depression and analgesia of 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. It is expected, and indeed is supported by user reports, that, as a MOP receptor agonist, AH-7921 produces relaxation, euphoria, hypertension, nausea, hypothermia and respiratory depression. It is, however, difficult to estimate the role of KOP receptor agonism in the overall physiological and psychological effects of AH-7921 in humans.

In addition to close analogues of AH-7921 described in the original publications, several series of related substances were described in subsequent patents (Harper and Veitch, 1977; Lednicer and Szmuszkovicz, 1980; Lednicer, 1982). Limited biological data are available for these newer analogues.

With exception of the already mentioned ICV injection experiments studying the effect of noradrenaline and serotonin on the analgesic activity of AH-7921 (Sewell and Spencer, 1974), no other study has examined drug interactions related to AH-7921. As such, there are no data on the interaction of AH-7921 with medicinal products (including oral contraceptives) and other forms of interactions. Based on the mode of action of AH-7921, however, it is likely that tolerance towards this synthetic analgesic could develop and this might extend to other opioid receptor agonists used in pain management.

A3. Psychological and behavioural effects

As described in Section A2, animal studies only characterised the narcotic-analgesic effects of AH-7921. There is no information on the behavioural effects of AH-7921 in animals (for

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2-(3,4-dichlorophenyl)-*N*-methyl-*N*-[2-(pyrrolidin-1-yl)cyclohexyl]acetamide and U69,593, i.e., *N*-methyl-2-phenyl-*N*-[(5*R*,7*S*,8*S*)-7-(pyrrolidin-1-yl)-1-oxaspiro[4.5]dec-8-yl]acetamide became prototypical KOP receptor agonists widely used in pain and addiction research (Szmuszkovicz and vonVoigtlander, 1982; http://www.iuphar-db.org/DATABASE/ObjectDisplayForward?0objectId=318).

([22]) The 'rotarod' is a standard rodent test of motor impairment, sedation or fatigue. It measures the animal's ability to remain on a rotating horizontal rod.

dependence liability assessment, see Section B1).

There are no published formal studies assessing the psychological and/or behavioural effects of AH-7921 in humans. (For effects described in selected self-reports by users, see Section D1.2.1)

A4. Legitimate uses of the product

No information was provided by any Member State indicating industrial, agrochemical, cosmetic, veterinary or human medical use. The legitimate use of AH-7921 is currently restricted to scientific research and as an analytical reference standard.

There is no information that AH-7921 is currently used in the manufacture of a medicinal product in the European Union. However, in the absence of a European Union database on the synthetic routes of all medicinal products this information cannot be verified. There is no marketing authorisation (existing, ongoing or suspended) for AH-7921 in the European Union nor in the 24 Member States, Norway and Iceland that provided responses to the request for information from the European Medicines Agency (EMCDDA–Europol, 2014).

A literature search ([23]) has indicated that the [(aminocyclohexyl)methyl]benzamide core structure present in AH-7921 is a rarely used, unique template in medicinal chemistry.

([23]) A literature search in SciFinder® (CAS, American Chemical Society) using the complete AH-7921 molecule as substructure retrieved not only the parent drug but also two patents (Lednicer, 1982; Strupczewski and Gardner, 1984) and a scientific publication (Cioffi et al., 2013; see also Caulfield et al., 2001) that describe such compounds as potential analgesics or antipsychotics. The query also retrieved another patent (Collins et al., 1984) but this appears to be erroneously referenced in the database. A broader substructure search found distant analogues possessing either serotonergic (Yang et al., 1996), analgesic (McClure et al., 2011) or fungicidal activity (Komori et al., 2010).

Section B. Dependence and abuse potential

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

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' akin to that observable for morphine using a similar dose schedule. Nalorphine, another opioid receptor antagonist, precipitated 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 the drug "would be classed as a narcotic analgesic having high addictive liability".

An already cited study (Loew et al., 1988, 1989; see Section A2) examining *in vitro* the receptor selectivity of AH-7921 and a series of related dichlorophenyl-containing aminocyclohexanes, including U50,488 and its analogues, found that AH-7921 had 15-fold preference to MOP over KOP receptors. Since MOP receptor agonism is largely responsible for the abuse and dependence potential of opioid analgesics ([24]), this would indicate that AH-7921 has addictive liability. The data from *in vitro* experiments are in agreement with animal studies described in the previous paragraph. However, the full characterisation of the receptor profile of AH-7921 extending to other molecular targets involved in drug-seeking behaviour is lacking.

No animal self-administration studies appear to have been published. Tolerance, cross-tolerance and sensitisation studies are also lacking.

B2. Human data

No studies were identified that have examined the dependence and/or abuse potential of AH-7921 in humans. There are no published cases in the scientific or grey literature describing the potential for dependence or abuse potential for AH-7921. Additionally, there have been no formal studies investigating the dependence and/or 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 (Drugs-Forum, 2013; Google, 2013b,c). A comment from another user report is instructive: "The bag is empty, and I think im done with this chem, its lovely but the thinkin of Wds, is makin me quit" (Bluelight, 2014). 'Wds' potentially referring to withdrawal symptoms here.

No reports have been made to the EMCDDA from local, regional or national drug treatment agencies relating to AH-7921 dependence.

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

Section C. Prevalence of use

Information from seizures, collected and biological samples

AH-7921 was first detected in a collected sample purchased from the Internet in the United Kingdom in July 2012 with formal notification to the EU Early Warning System on 1 August 2012. By March 2014, an additional seven Member States: Austria, Belgium, Denmark, Finland, France, Germany and Sweden, as well as Norway, have reported the detection ([25]) of AH-7921 either in one or more seizures, collected samples or biological samples. The details of seizures, indicating year, number, amount and seizing authority, by Member States and Norway are listed in Table 2. AH-7921 has without exception been seized in powder form; the colour is typically not reported. In one case, the presence of AH-7921 was confirmed in a sample that was taken from a syringe found at the scene of a death.

Table 2 Details of seizures and collected samples of AH-7921 reported to the EMCDDA and Europol.

Country	Amount and details of the seizure / collected sample
Austria	
2013	Two small seizures (0.9 and 1.9 g) made by police.
Belgium	
2014	Detected in a powdery sample obtained from a user and tested by a 'pill testing' service.
Denmark	
2013	One seizure of 0.87 g by the police.
Finland	
2012	Three small seizures (0.5, 0.5 and 2 g) by customs.
2013	Two small seizures (0.9 and 1 g) by customs and one seizure of 0.1 g by the police
France	
2013	One seizure of 500 grams of powder seized by customs
Germany	

([25]) '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.).

Country	Amount and details of the seizure / collected sample
2013	Four seizures (2.8, 2.9, 4.52 and 9.81 g) by the police
Sweden	
2012	One seizure of 12.9 g by the police, one seizure of 0.98 g by customs.
2013	Four seizures (0.02, 2.15, 3.46, and 6.61 g) by the police, four seizures (0.2, 9,99, 59.79 and 103.86 g) by customs.
United Kingdom	
2012	A powdery sample of 0.25 g obtained as a test purchase (July 2012) on the Internet proved to be AH-7921. The price of the product was GBP10.00.
Norway	
2012	Small amount of white powdery residue in a ziplock bag and a syringe both containing AH-7921 was recovered at the scene of a death.
2013	Three seizures (0.23, 1 and 1 g) by the police

The drug has recently been encountered in Japan (Uchiyama et al., 2013) and in a death in the USA (Vorce et al., 2014; see also ([26])).

Availability from Internet retailers

According to Internet searches for 'AH-7921' conducted several times from late-2013 to March 2014, the effects of the substance have been discussed from March 2010 ([27]). Experience reports followed from 2011 (Erowid, 2013a; Google, 2013a,b,c; Bluelight, 2014). According to 'Google Trends' ([28]), searches for the term 'AH-7921' appeared first in the spring of 2012. The first peak of the relative search frequency for 'AH-7921' emerged in August 2012 coinciding with the detection of the substance in the United Kingdom and following its notification to EMCDDA.

As noted, the first detection of AH-7921 reported to the EMCDDA was a collected sample of 250 milligrams of white powder purchased in July 2012 for GBP10 (EUR12) from an Internet retailer selling 'research chemicals' ([29]). By March 2014, AH-7921 was placed at this site in the category of 'Rare Chemicals' 'available only by application or invite' to members of the 'Intermediate Customer Group'.

A search of google.com using the search string "buy "AH-7921"" conducted in December 2013

([26]) J. Scherbenske referred to the detection of AH-7921 in the USA during a recent webinar dated May 13, 2013. Available at https://www.nttac.org/media/trainingCenter/89/Saving Our Youth from Alcohol_Drugs PowerPoint.pdf

([27]) Wikipedia (2010) http://en.wikipedia.org/w/index.php?title=AH-7921&action=history

([28]) http://www.google.com/trends

([29]) Purchased from http://www.buyresearchchemicals.co.uk; current URL: www.brc-finechemicals.com

for the Joint Report on AH-7921 (EMCDDA–Europol, 2014) 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'. Repeating the search in March 2014 gave similar results ([30]). It was noted that the web address of some of the retailers changed though the original URL redirected the web browser to the new URL. In addition to offers on a multigram scale, an anonymous request for custom synthesis for 10 kg quantity was also noted ([31]).

Prevalence of use

There are currently no co-ordinated national or European general population surveys on AH-7921 use. Further, neither the European school survey project on alcohol and other drugs (ESPAD) nor other school/college/university surveys have investigated or reported on AH-7921 use. No prevalence surveys were identified that have examined the use of AH-7921 in the general population or in targeted populations.

([30]) A recent unconfirmed report posted on the Internet on 16 March 2014 asserts that "AH-7921 has been banned in China where it is commonly produced. … we were told that [vendors] are in talks with an European vendor however it could be over 2 weeks until they can produce it at levels which allow them to sell it for the same price as the Chinese version" (http://the-tripreport.com/site/news/ah-7921-ban). As of 17 March, 2014, another supplier indicated that AH-7921 is "OUT OF STOCK. Small quantity of stock available to existing customers. New European sourced stock due approx. 3-4 weeks." (http://chemsupply.eu/shop/index.php?main_page=index&cPath=32) At this supplier, the representative prices of 250 mg and 5 g of AH-7921 were GBP18 and GBP135, respectively.

([31]) http://sourcing.alibaba.com/buying-request/hot-products/ah--7921.html

Section D. Health risks

D1. Acute health effects

D1.1. Animal data

The already cited rodent study by Hayes and Tyers (1983) noted that the dose-response curves for AH-7921 were steep and that the dose required for analgesia was close to that producing adverse effects (see Section A2). For example, the margin of safety, calculated from the ED_{50} values for respiratory depression ([32]) and analgesia, for AH-7921 was 4.5, while for morphine it was 9.3. Furthermore, the ED_{50} values morphine, codeine and AH-7921 were 4.2, 35.7 and 2.5 mg/kg, respectively, indicating that AH-7921 is more than 1.6 times more potent than morphine at inhibiting respiration in the mouse.

Nevertheless, there are insufficient data to fully establish the acute toxicity associated with AH-7921. The LD_{50} value, that is the dosage causing death in 50% of the exposed animals, of AH-7921 has not been reported in the scientific literature. It can be inferred from the study by Harper et al. (1974) that the intravenous LD_{50} of AH-7921 is higher than 10 mg/kg in the mouse ([33]) ([34]). In this study, the LD_{50} values for the unsubstituted benzamide and the 2-chloro-substituted benzamide analogues of AH-7921 were 45 and 10 mg/kg, respectively.

An Internet search for AH-7921 retrieved an MSDS ([35]) giving the following acute oral LD_{50} values for the free amine form of the substance: 300 mg/kg in the mouse; 980 mg/kg in the rat; 3200 mg/kg in the rabbit. For comparison, a toxicological database ([36]) gives the following oral LD_{50} values for morphine: 524 mg/kg in the mouse and 335 mg/kg in the rat. (Note: because pharmacokinetics, including absorption and liver metabolism, can markedly affect the toxicity of a drug upon oral exposure, the LD_{50} values for AH-7921 and morphine should not be directly compared.) In the same MSDS, the eye irritation for 100 mg of AH-7921 is rated ‘moderate’ in the Draize-test in rabbit eye ([37]).

Apart from respiratory depression (see above), there is insufficient information available to determine the clinical features of acute toxicity associated with AH-7921 alone.

D1.2. Human data

([32]) The ED_{50} value is the dose of the test drug capable of depressing the respiratory rate of the untreated control group by 25%.

([33]) The publication by Harper et al. (1974) provides analgesic activity data for 35 compounds in a supplementary table, which does not specify the experimental animal species used. It is implied that toxicity data refer to mouse experiments, as that was the rodent mentioned in the main body of the paper.

([34]) For comparison, LD_{50} values of morphine range between 225 to 318 mg/kg (mouse, i.v.) or 64 to 223 mg/kg (rat, i.v.) depending upon experimental conditions, which salt of the drug and which strain of rat is used (Buchwald and Eadie, 1941; Finnegan et al., 1948; Niemegeers et al., 1976; Strandberg et al., 2006).

([35]) http://www.clearsynth.com/docs/MSD-CS-T-1162.pdf. Note: this is a non-peer reviewed document.

([36]) http://toxnet.nlm.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+DOCNO+2134

([37]) The controversial Draize-test involves the administration of a single dose of a solution of a chemical to one eye of a rabbit with the other serving as control; after a certain time, damage to ocular tissue is scored (OECD, 2012).

No studies were identified that have examined the toxicity of AH-7921 in humans.

D1.2.1. User reports

No clinical studies were identified that have examined the psychological or physiological effects of AH-7921 in humans.

There are few user reports discussing the subjective effects of AH-7921. The section below is mainly based on Internet drug discussion forums and related websites and include self-reports. As such it is important to note that it is not possible to confirm the specific substance(s) used, nor the purity, dose or whether or not other substances have been taken. 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, as well as vary over different geographical areas and time. Furthermore, the users' physical characteristics and health status are rarely reported. The limitations of self-reports, including the fact that users may be unaware or misinformed about the substance they have consumed, should be borne in mind when interpreting these reports. As such, users may have taken other substances which may account for some or all of the described effects.

In addition, the information on user websites should be regarded as illustrative only and not taken as representative of users of AH-7921 in general. Consequently, these reports need to be interpreted with caution.

Belgium:

A user who ingested approximate dosages of 0.25 g and 0.5 g of a drug reported nausea, vomiting, hyperthermia, headache, anxiety, aggressiveness and insomnia. While these symptoms are akin to those typically observed for stimulants, the powdery material was analysed and confirmed to contain AH-7921; however, there was no analysis of biological samples to exclude the use of other substances nor confirm the presence of AH-7921 ([38]).

Drugs Forum:

In August 2012, a polydrug user reported on a near fatal overdose caused by the simultaneous oral intake ('bombing') of 150 mg of AH-7921, 4 mg of etizolam, and 50–100 mg ethylphenidate followed by another 'bomb' containing 200 mg of AH-7921 and 8–10 mg of etizolam four hours later, followed by nasal insufflation of about 500 mg ethylphenidate; during this time he was also smoking joints containing the synthetic cannabinoid UR-144. Finally, inhalation of the vapours of some 50 mg of AH-7921 triggered the loss of consciousness requiring intensive care in the hospital (Drugs-Forum, 2012).

This website also contains a collection of reports with mixed opinions on the uses and effects

([38]) The sample was collected by the pill testing service 'Modus Vivendi' and analysed by the Medicines Laboratory of the Belgian Scientific Institute for Public Health (WIC-ISP) in Brussels.

of AH-7921 (Drugs-Forum, 2013). In a comment posted in April 2012, a total dose of 70 mg of AH-7921 (10 mg insufflated + 60 mg orally) failed to alleviate cold symptoms; the mild and transient relieving effects felt 40 min after administration were overshadowed by nausea; the same forum participant reported in August 2012 that oral doses of 80–120 mg had provided "subtle mood lift", accompanied by slight nausea, lasting for about 90 min. A comment posted in July 2012 reported that an oral dose of 50 mg of AH-7921 could mitigate opioid withdrawal symptoms; however, a reply by another commentator mentioned the lack of effects at doses of AH-7921 as high as 120 mg. In January 2013, an ex-heroin user reported the intravenous injection of 100–150 mg of a solution ([39]) of AH-7921 that produced "a lovely smack-like high… complete with nod, decent euphoria and all 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'). In February 2013, An opioid-naïve commenter, who took butylone beforehand, described euphoria, "unimpaired cognition" as the main outcome of a rectal administration of 40 mg of AH-7921 which, after 2 h, was followed by another 30 mg of the drug (also rectally); the effect lasted for about 8 hr after the first dose with tiredness and itching being the side effects reported.

Bluelight:

Since December 2011, user reports have appeared on Bluelight.org, some of which are noted below (Bluelight, 2014). A user mentioned that "50 mg oral produced no effects in a fairly opiate tolerant person", while another reported that injecting a solution of 70 mg AH-7921 caused "nice warm rush" and "[n]ot itching … feels on a par with a medium dose of oxy". 'Oxy' in this context may relate to the synthetic opioid, oxycodone. Another user reported that during the day, repeated oral doses of 50–100 mg of AH-7921 were needed to relieve withdrawal symptoms that had manifested 14 h after the last tramadol intake; compared to tramadol, which the user called a "get-you-high" drug, AH-7921 was rather a "calm-you down" drug. It was also mentioned in one of the comments that after a 50 or 70 mg dose of the drug "i get weird flu like symptoms the next day, as well as stomach discomfort, though i have no current medical issue in that department". (These might be symptoms of AH-7921 withdrawal.) A combination of 100 mg of AH-7921 and 5 mg of flubromazepam taken orally for a lasting and relaxing 'high' was also mentioned. The nose-irritating property upon nasal insufflation of powdery AH-7921 was often mentioned in self-reports on this forum.

Erowid:

A report described the inhalation of the vapours of a total of 40 mg of the free amine (free base) of AH-7921 powder; the peak-effects lasted for 1.5 h 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 (corresponding

([39]) Noting the poor aqueous solubility of the substance lead to speculation that the sample in hand was the free amine. Injectable solution could be made by dissolving 100 mg of the substance in one ml of a mixture of 'Propylene Glycol', citric acid and 'warm water'.

to 40 mg of the drug), total amounts of about 145 and 155 mg of AH-7921 were consumed during an 11 h session by the users (redosing 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 myosis was noted three hours after the first dose (Erowid, 2013c).

D.1.2.2. Clinical acute AH-7921 toxicity

AH-7921 has been detected in six non-fatal intoxications and two drug-related offences in Sweden.

Non-fatal intoxications reported by Sweden:

Between December 2012 and March 2013, the Swedish Poison Information Centre reported six non-fatal intoxications associated with AH-7921 use. The presence of AH-7921 was analytically confirmed in five of these cases. No information was provided on whether AH-7921 was quantified in these five cases. The clinical symptoms mentioned in these cases include hypertension, tachycardia and seizures.

In an additional two cases reported in April 2013, AH-7921 was detected in the urine of the intoxicated patients who were suspected of committing minor criminal offences; no quantification was done.

D1.2.3. AH-7921 related deaths

Since December 2012, when the first death associated with AH-7921 use was reported by Norway, a total of 15 deaths where AH-7921 was detected have been reported from two Member States (Sweden and the United Kingdom) and Norway.

The deaths reported to the EMCDDA associated with AH-7921 are summarised below and tabulated in Table 3.

Norway:

Norway reported two deaths associated with AH-7921.

The first fatality related to AH-7921 use happened in late November or early December 2012 (exact date is not reported to the EWS): in this case AH-7921 was not analytically confirmed during post-mortem but was suspected due to the circumstances of the death (although details of a case analysed in Sweden may in fact relate to this death – see below). During the investigation the police found a bag with small amounts of a white powder and a used syringe with dried blood close to the deceased. AH-7921 was identified in both the powder and a sample taken from the syringe. Etizolam and phenazepam were also found at the scene.

Another fatality associated with this substance was reported by Norway on 20 August, 2013. In this case the peripheral blood of the overdosed 23-year-old male contained AH-7921 (0.428 μg/ml), as well as 2-FMA (6.86 ng/ml), 3-MMC (2.13 ng/ml), codeine (0.419 μg/ml) and paracetamol (18.75 μg/ml).

Additional details were provided about a death associated with AH-7921 that occurred in Norway, but was analysed in Sweden. AH-7921 was detected in femoral blood and quantified at a concentration of 0.34 μg/ml; etizolam was also detected and quantified at 0.27 μg/ml. 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.

Sweden:

Sweden reported 10 deaths associated with AH-7921 that occurred between January 2013 and September 2013. All of these cases were analytically confirmed. In nine of the cases, the concentration of AH-7921 in post-mortem femoral 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, nordiazepam, pyrazolam) and other medicines (zopiclone, paroxetine, bupropione, mirtazapine, pregabalin, gabapentin, aripiprazole). 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.

Initial results of some of these cases were reported by Kronstrand and Thelander (2013) who reported, in the first half of 2013, several deaths associated with AH-7921 in Sweden. Details of one of the overdose cases were available for a 27-year-old male injecting drug user. The femoral blood contained 0.81 μg/g of AH-7921 and ca. 10 μg/g gabapentin. No ethanol or other drugs could be detected. Preliminary forensic analyses of blood samples of another four cases revealed the presence of 0.03, 0.20, 0.34 and 0.99 μg/g of AH-7921 ([40]). All cases covered in this paper are included in the total mentioned in the previous paragraph.

United Kingdom:

The United Kingdom reported three deaths associated with AH-7921 that were thought to have occurred between February 2013 and August 2013. All of these cases were analytically confirmed (Soh and Elliott, 2013; Elliott and Evans, 2014).

([40]) For comparison, in fatal heroin or morphine poisoning cases the reported blood concentrations of morphine range from 0.04 to 3.0 mg/L (Darke et al., 1997, Musshoff et al., 2004; Moffatt et al., 2011; Häkkinen et al., 2012).

Case 1 (February 2013): AH-7921 was detected in post-mortem femoral blood with a concentration of 0.58 mg/L. The deceased was found dead at home along with various packets of labelled powders that were identified as 5F-AKB48, a synthetic cannabinoid ([41]), AH-7921, 3,4-dichloromethylphenidate, 4-iodo-2,5-dimethoxyamphetamine (DOI) and etaqualone. In addition to AH-7921, 4-methylethcathinone (4-MEC), pentedrone, mephedrone, diphenylprolinol (D2PM) ([42]), etizolam and etaqualone were also detected in post-mortem urine. Only a low concentration of 4-MEC and/or pentedrone metabolites was detected in femoral blood, therefore AH-7921 was the predominant compound present in the blood.

Case 2 (July 2013): AH-7921 was detected in post-mortem femoral blood with a concentration of 0.05 mg/L. The deceased was found dead with a bag over the head containing chloroform. Chloroform and ethanol were also detected in the blood.

Case 3 (August 2013): AH-7921 was detected in post-mortem femoral blood with a concentration of 4.46 mg/L. The victim was found unresponsive at home and died later in hospital. The anxiolytic clobazam and a codeine metabolite were detected in the urine along with the sedative-hypnotic doxylamine and the antidepressant mirtazapine that were both also present in the blood at a low concentration.

([41]) *N*-(1-adamantyl)-1-(5-fluoropentyl)-1*H*-indazole-3-carboxamide

([42]) diphenyl-2-pyrrolidinylmethanol or diphenyl(pyrrolidin-2-yl)methanol

Table 3. Deaths associated with AH-7921 as reported to EMCDDA ([a]).

	Country	Date of death (gender, age)	Biological sample ([b])	AH-7921 result ([c])	Results for other substances ([d])	Notes
1	Sweden	08-01-2013 (M, 28)	Femoral blood	0.81 µg/g	10 µg/g gabapentin	Cause of death reported as 'unintentional overdose'
2	Sweden	04-02-2013 (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	22-02-2013	Femoral blood	0.03 µg/g	0.03 µg/g paroxetine	Cause of death reported as 'not decided yet'
4	Sweden	08-04-2013	Femoral blood	0.2 µg/g	pyrazolam, diazepam	Cause of death reported as 'overdose of benzo-diazepines and opiates'
5	Sweden	03-05-2013	Femoral blood	0.3 µg/g	pyrazolam, alprazolam, zopiclone	Cause of death reported as 'overdose of AH-7921'
6	Sweden	15-04-2013	Femoral blood	0.08 µg/g	0.01 µg/g *N*-ethylnorketamine, alcohol	Cause of death reported as 'unclear'
7	Sweden	16-06-2013	Femoral blood	0.16 µg/g	0.04 µg/g amphetamine	Cause of death reported as 'not decided yet'
8	Sweden	19-06-2013	Femoral blood	0.35 µg/g	3-methylmethcatinone	Cause of death reported as 'overdose of AH-7921'
9	Sweden	09-07-2013	Femoral blood	0.43 µg/g	12 µg/g pregabalin, 0.53 µg/g nor-bupropion, 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'

	Country	Date of death (gender, age)	Biological sample ([b])	AH-7921 result ([c])	Results for other substances ([d])	Notes
10	Sweden	05-09-2013	Hair	+	3-methylmethcatinone, 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	07-08-2013 (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.

Cases reported in the literature

Vorce et al. (2014) reported the death associated with AH-7921 of a 19-year old male who was found dead in bed by a friend. The friend indicated that the deceased had purchased two drug-containing vials two nights earlier and used them on the night of and the night prior to his death. Autopsy revealed pulmonary congestion, oedema of the lungs; enlargement of the liver and the spleen were also observed. Analysis of the content of the vials found at the scene identified AH-7921 in one of the vials, and '4-methyl-α-pyrrolidinohexanophenone' (MPHP) ([43]) in the other. Dextromethorphan, MPHP and AH-7921 were found in the post-mortem urine, with only AH-7921 found in the post-mortem blood. The concentrations of AH-7921 in various fluids and organs were as follows ([44]): heart blood 3.9 mg/L, "peripheral blood" 9.1 mg/L, urine 6.0 mg/L, liver 26 mg/kg, kidney 7.2 mg/kg, spleen 8.0 mg/kg, heart 5.1 mg/kg, lung 21 mg/kg, brain 7.7 mg/kg and bile 18 mg/kg. The submitted stomach content of 125 ml contained a total of 120 mg of AH-7921; this amount, based on user reports (see Section D1.2.1), constitutes an excessive ingestion. The cause of death was attributed to opioid, that is AH-7921 intoxication.

The study by Vorce at al., (2014) also reported two *N*-demethylated derivatives of AH-7921, as putative metabolites (see Section A2). Due to the lack of analytical standards, these were not quantified.

D2. Chronic health effects

D2.1. Animal data

There is no animal data in the scientific or grey literature on the chronic health effects of AH-7921.

There are no data on the neurotoxicity or carcinogenicity of AH-7921 *in vitro*.

D2.2. Human data

No studies were identified in the scientific literature investigating the chronic health effects of AH-7921 in humans.

D3. Factors affecting public health risks

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

AH-7921 is offered for sale on gram scale as well as in bulk (kg) quantities on the Internet by several suppliers (see also Section C). The purity of these products has not been ascertained. Recently, AH-7921 has become commercially available as an analytical standard or experimental research chemical from several fine chemical suppliers.

([43]) 1-(4-methylphenyl)-2-(pyrrolidin-1-yl)hexan-1-one

([44]) For comparison, in fatal heroin or morphine poisoning cases the blood concentrations ranged from 0.04 to 3.0 mg/L (Musshoff et al., 2004; Moffatt et al., 2011; Häkkinen et al., 2012).

Analyses of seizures and collected samples indicate that adulterants are not typically present in the powdery products (although they may have been present but either not detected or not reported). The exceptions are two samples (0.2 g and 59.79 g) in Sweden in which caffeine was detected in powders seized by customs.

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

There is relatively limited information on drug discussion forums regarding the effects and potential health / adverse effects related to the use of AH-7921. On some discussion forums the use of AH-7921 as a drug in its own right has been discussed. Nevertheless, it is likely that the information, degree of knowledge, and perceptions amongst users concerning AH-7921 and its effects are likely to be limited (see Section D1.2.1).

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

There are no surveys relating to the characteristics of users or the pattern of AH-7921 use. The available reports, mostly self-reports originating from Internet drug discussion forums, indicate that AH-7921 is typically used in a home environment. Current information suggests some users are experimenting with this new synthetic opioid, while others have used it to relieve pain or the withdrawal symptoms arising from the cessation of the use of other licit or illicit opioids.

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

The very limited information on the acute health effects of AH-7921 in humans has been discussed in Section D1.2. Based on animal model experiments discussed in Section A2, it may, however, be assumed that the acute behavioural effects of AH-7921 on operating machinery and driving are similar to those caused by other opioid-type narcotic-analgesics.

There is insufficient information in the reported fatalities where AH-7921 has been detected to discuss in detail the circumstances of these deaths. However, from the information available, it does not appear that any of these were related to work or road traffic accidents.

D3.5. Long-term consequences of use

As discussed in Sections D2.1 and D2.2, there are no animal or human data on the chronic health effects of AH-7921 use. In particular, there have been no long-term follow up studies to determine whether AH-7921 users are at greater risk of health deterioration later in life, or of developing chronic or life-threatening medical conditions.

D3.6. Conditions under which the new psychoactive substance is obtained and used, including context-related effects and risks

Based on user reports and Internet searches, AH-7921, being a substance that is not

controlled under drug legislation in most Member States, is openly advertised as a ‘new research chemical’. The amounts typically offered in the Internet range from 250 mg to several grams, but bulk quantities can also be requested (see also Section C).

Section E. Social risks

E1. Individual social risks

There are no published data to be able to determine the impact of AH-7921 in this area. In particular, there is no data on the effects of AH-7921 on fertility, pregnancy and lactation.

E2. Possible effects on direct social environment

There are no published data to be able to determine the impact of AH-7921 in this area.

E3. Possible effects on society as a whole

There are no published data to be able to determine the impact of AH-7921 in this area.

E4. Economic costs

Given the lack of data available on acute health emergencies and healthcare utilisation related to the use of AH-7921, it is not possible at this time to estimate whether this substance is associated with greater healthcare costs than other opioid drugs.

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

There is no specific data in relation to use in marginalised groups, however, it is possible that AH-7921 may be used by those individuals who use other opioids, including injecting users.

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

At this time, there does not seem to be any particular appeal related to the use of AH-7921 within the general population, or even within sub-populations that are usually associated with higher levels of drug use or the use of new psychoactive substances.

Section F. Involvement of organised crime

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

There is no information that criminal groups are systematically involved in the production, trafficking and/or distribution of AH-7921 for financial gain (EMCDDA–Europol, 2014).

There is no information indicating the production of AH-7921 in any of the Member States ([45]).

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

There is nothing to suggest that distribution networks established for heroin or other opioids are being used. Based on the information available to ECMDDA and Europol, the production, trafficking and distribution of AH-7921 does not appear to have any impact on other existing psychoactive substances or new psychoactive substances.

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

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 additional information available in this area.

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

No information has been received by Europol on incidents of violence in connection with AH-7921.

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

No information has been received by Europol on incidents of money-laundering in connection with AH-7921.

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

([45]) A recent unconfirmed report posted on the Internet on 16 March 2014 asserts that "AH-7921 has been banned in China where it is commonly produced. … we were told that [vendors] are in talks with an European vendor however it could be over 2 weeks until they can produce it at levels which allow them to sell it for the same price as the Chinese version" (http://the-tripreport.com/site/news/ah-7921-ban). As of 17 March, 2014, another supplier indicated that AH-7921 is "OUT OF STOCK. Small quantity of stock available to existing customers. New European sourced stock due approx. 3-4 weeks." (http://chemsupply.eu/shop/index.php?main_page=index&cPath=32).

There are no published data to be able to determine the impact of AH-7921 in this area.

F7. Use of violence between or within criminal groups

There are no published data to be able to determine the impact of AH-7921 in this area.

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

There are no published data to be able to determine the impact of AH-7921 in this area.

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