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AB-CHMINACA

EMCDDA–Europol Joint Report on a new psychoactive substance: *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide (AB-CHMINACA)

In accordance with Article 5 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances

About this series

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

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

EUROPOL

EMCDDA–Europol
joint publication

Contents

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- the Early Warning System (EWS) correspondents of the Reitox national focal points (NFPs) and experts from their national EWS networks;
- the Europol National Units (ENUs) and Europol Project Synergy;
- the national competent authorities responsible for human and veterinary medicinal products in the Member States, Norway and Iceland;
- the European Medicines Agency (EMA) and the European Commission;
- the World Health Organization.

Project team: Anabela Almeida, Rachel Christie, Helgi Valur Danielsson, Michael Evans-Brown, Ana Gallegos, Rita Jorge, Roumen Sedefov (EMCDDA) and Werner Verbruggen (Europol).

1. Introduction

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

In March 2017, the EMCDDA and Europol examined the available information on the new psychoactive substance *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide, commonly known as AB-CHMINACA, through a joint assessment based upon the following criteria:

1. the amount of the material seized;
2. evidence of organised crime involvement;
3. evidence of international trafficking;
4. analogy with better-studied compounds;
5. evidence of the potential for further (rapid) spread; and,
6. evidence of cases of serious intoxication or fatalities.

The EMCDDA and Europol agreed that the information collected on AB-CHMINACA satisfied criteria 1, 4 and 6. The two agencies therefore concluded that sufficient information had been accumulated to merit the production of a Joint Report on AB-CHMINACA as stipulated by Article 5.1 of the Council Decision.

2. Information collection process

In compliance with the provisions of the Council Decision, on 25 April 2017 the EMCDDA and Europol launched a procedure for the collection of information on AB-CHMINACA, in order to prepare the Joint Report. The information was collected mainly through the Reitox national focal points in the Member States, Turkey and Norway as well as the Europol National Units. In addition, the EMA collected information through the national competent authorities responsible for human and veterinary medicinal products in the Member States as well as in Norway, Iceland and Liechtenstein. The EMA also provided information as relevant to the centralised procedure for authorising medicinal products. The information collection process was largely concluded by 6 June 2017.

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

Information collected by Europol

Europol asked the Europol National Units to provide information on:

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

Europol received responses from 15 Member States ([2]).

Information collected by the EMA

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

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

Twenty-three countries provided a response to the EMA's request regarding human and/or veterinary medicinal products ([3]). The EMA also provided information as relevant to the centralised procedure for authorising human and veterinary medicinal products.

Furthermore, in anticipation of Article 7.3 of the Council Decision in relation to the manufacturing of medicinal products in the European Union, the EMA also requested

([2]) In alphabetical order: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Finland, Germany, Greece, Latvia, Lithuania, Luxembourg, Romania, Slovakia and Slovenia.

([3]) Austria, Belgium, Denmark, Estonia, Finland, Germany, Greece, Ireland, Latvia, Norway, Poland, Spain, Sweden and the United Kingdom provided a response in relation to human and veterinary medicinal products. Croatia, Czech Republic, Hungary, Italy and the Netherlands provided a response in relation to human medicinal products. France, Portugal, Slovakia and Slovenia provided a response in relation to veterinary medicinal products.

information on whether the new psychoactive substance AB-CHMINACA is used to manufacture a medicinal product:

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

Twenty-three countries ([4]) provided a response to the EMA's request in this regard. The EMA also provided information as relevant to the centralised procedure for authorising human and veterinary medicinal products.

Information collected by the EMCDDA

The EMCDDA collected information through:

- a structured questionnaire to the Reitox national focal points. The EMCDDA received replies from 27 Member States ([5]), as well as Turkey and Norway;
- reports previously provided to the European Union Early Warning System, including EMCDDA–Europol Reporting Forms and Progress Reports and Final Reports;
- routine monitoring of open source information;
- a specific information request to the World Health Organization on whether or not AB-CHMINACA is under assessment by the United Nations system;
- a search of open source information conducted specifically for the production of the Joint Report which included: scientific and medical literature, official reports, grey literature, internet drug discussion forums and related websites (hereafter, 'user websites'), and, online vendors selling AB-CHMINACA.

Thus, the information included in sections 3.2.1 and 3.3 of the Joint Report was provided by Europol, while the EMCDDA provided information included in sections 3.1, 3.2.2, 3.4, 3.5, 3.6, 3.7, 3.8.1, 3.8.2 and 3.8.3 (in part). The information included in sections 3.8.3 (in part) and 4 was provided by the EMA. Images of the seizures and collected samples reported to the EMCDDA and Europol are provided in Annex 1 and Annex 2, respectively.

3. Information required by Article 5.2 of the Council Decision

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

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

Chemical description and names

N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide is commonly referred to as AB-CHMINACA ([6]).

AB-CHMINACA is a synthetic cannabinoid receptor agonist. It has an indazole core, which is a common structural feature in many of the synthetic cannabinoids monitored by the EMCDDA.

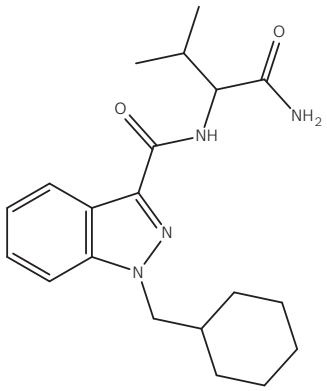
Two synthetic cannabinoid receptor agonists have been recently controlled under Schedule II of the United Nations Convention on Psychotropic Substances of 1971: JWH-018 ([7]) and AM-2201 ([8]). In addition, MDMB-CHMICA, 5F-APINACA (5F-AKB48) and XLR-11 will be included in the same schedule.

The molecular structure, molecular formula and molecular mass of AB-CHMINACA are provided in in Figure 1.

([4]) Austria, Belgium, Denmark, Estonia, Finland, Germany, Greece, Ireland, Latvia, Norway, Poland, Spain, Sweden and the United Kingdom provided a response in relation to human and veterinary medicinal products. Croatia, Czech Republic, Hungary, Italy and the Netherlands provided a response in relation to human medicinal products. France, Portugal, Slovakia and Slovenia provided a response in relation to veterinary medicinal products.
([5]) A reply was not received from Slovakia.

([6]) The common name for the substance is derived after its structural features. Different naming systems exist and are used for applying short/code names to synthetic cannabinoids.
([7]) Naphthalen-1-yl(1-pentyl-1*H*-indol-3-yl)methanone
([8]) 1-(5-Fluoropentyl)-1*H*-indol-3-yl]-(naphthalen-1-yl)methanone

FIGURE 1
Molecular structure, molecular formula and molecular mass of AB-CHMINACA



	AB-CHMINACA
Molecular formula	$C_{20}H_{28}N_4O_2$
Molecular mass	356.47

AB-CHMINACA has a positional isomer, where the cyclohexylmethyl tail is attached to the nitrogen at position 2 of the indazole, which has been identified in products in Japan (Longworth et al., 2016) ([9]). It is unknown whether this regiosiomer represents a manufacturing impurity or was intentionally synthesised. Both isomers have the same molecular formula and molecular weight which result in very similar mass spectra. However, they can be differentiated based on their retention time and it would be expected that the infrared (IR) and nuclear magnetic resonance spectra (NMR) would be different. AB-CHMINACA contains a stereocentre thus allowing for the existence of a pair of enantiomers ([10]), (*R*)- and (*S*)-AB-CHMINACA. The synthesis of (*S*)-AB-CHMINACA was first described in the patent literature in 2009 (Buchler et al., 2009). Based on the literature and the most likely precursors to be used, an (*S*)-configuration of the stereocentre could be expected.

There is no representative information on the enantiomeric composition of the samples of AB-CHMINACA detected within the European Union, which in part may reflect the fact that stereochemical analysis is not routinely undertaken in forensic laboratories. Differentiation of enantiomers is possible using the following techniques: chiral chromatography, vibrational circular dichroism (VCD) spectroscopy and/or electronic circular dichroism (ECD) spectroscopy.

Commonly used names:
AB-CHMINACA

Systematic (IUPAC) name:
N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide

Chemical Abstracts names:
N-[1-(aminocarbonyl)-2-methylpropyl]-1-(cyclohexylmethyl)- 1*H*-indazole-3-carboxamide;
N-[(1*S*)-1-(aminocarbonyl)-2-methylpropyl]-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide (*S* enantiomer)

Other chemical names:
N-(1-carbamoyl-2-methyl-propyl)-1-(cyclohexylmethyl) indazole-3-carboxamide;
N-[(1*S*)-1-carbamoyl-2-methyl-propyl]-1-(cyclohexylmethyl) indazole-3-carboxamide (*S* enantiomer);
N-[1-(aminokarbonyl)-2-metylpropyl]-1-(cyclohexylmetyl)-1*H*-indazol-3-karboxamid (Swedish)

Chemical Abstracts Service (CAS) registry numbers ([11]):

1805788-79-7	AB-CHMINACA racemate
1185887-21-1	(*S*)-AB-CHMINACA

IUPAC International Chemical Identifier Key (InCHI Key) ([12]):

KJNZIEGLNLCWTQ-UHFFFAOYSA-N	AB-CHMINACA racemate
KJNZIEGLNLCWTQ-KRWDZBQOSA-N	(*S*)-AB-CHMINACA

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

Physical description

In its pure form AB-CHMINACA is a white crystalline solid (Longworth et al., 2016). AB-CHMINACA is soluble in organic solvents such as ethanol, dimethyl sulfoxide (DMSO) and dimethyl formamide (DMF). The solubility of AB-CHMINACA in these solvents is approximately 3, 10 and 5 mg/ml respectively. AB-CHMINACA is also soluble in deuterated chloroform (CDCl3) (Slovenian National Forensic Laboratory, 2015). AB-CHMINACA is sparingly soluble in aqueous buffers (Cayman Chemical Company).

The measured melting point for AB-CHMINACA is 88.5-92.5ºC (Longworth et al., 2016).

AB-CHMINACA has been typically seized as herbal material and in powder form. It has also been detected in liquids and

([9]) The positional isomer of AB-CHMINACA is referred to as 'AB-CHMINACA 2-isomer' by Longworth et al.
([10]) Optical isomers (or enantiomers) have the same physico-chemical characteristics, differing only in their interaction with plane polarized light.

([11]) The Chemical Abstract Service Registry Number (CAS RN) is a unique numeric identifier assigned by the Chemical Abstract Service Division of the American Chemical Society to a specific, single chemical substance.
([12]) InChI Key is a unique, non-proprietary stuctural identifier of chemical substances useful in electronic sources.

blotters. A more detailed description of seizures and collected samples can be found in section 3.2.1 and section 3.2.2.

Chemical stability and typical reactions

For long term storage it is recommended that AB-CHMINACA, supplied as a crystalline solid, is stored at -20ºC (Cayman Chemical Company).

Storage in solution or under non-ideal conditions (e.g. high humidity or elevated temperatures) can lead to hydrolysis of the carboxylic ester function. Ester hydrolysis can be expected to occur during smoking as it was observed by analysis of smoke condensates of AB-CHMINACA (Auwärter 2017). Most of the known free carboxylic acids formed by hydrolysis of similar compounds are not active or are poorly active at the CB_1-receptor (Buchler, 2009 and 2011).

Detection and analysis

Reference materials are claimed to be available for (*S*)-AB-CHMINACA ([13]).

Literature on the analytical identification of AB-CHMINACA includes:

- gas chromatography–mass spectrometry (GC-MS), Fourier transform infrared spectroscopy attenuated total reflectance (FTIR-ATR), high performance liquid chromatography time-of-flight (HPLC-TOF) and nuclear magnetic resonance spectroscopy (NMR) (Slovenian National Forensic Laboratory, 2015);
- GC-MS (Akamatsu and Yoshida, 2016, Dronova et al., 2016, Langer et al., 2016, Uchiyama et al., 2015);
- liquid chromatography – mass spectrometry (LC-MS) (Dronova et al., 2016, Uchiyama et al., 2015);
- FTIR (Langer et al., 2016 and Longworth et al., 2016);
- NMR (Buchler et al., 2009, Langer et al., 2016 and Longworth et al., 2016), ultraviolet-visible spectroscopy (UV-VIS) (Langer et al., 2016);
- low resolution – mass spectrometry (LRMS) and high resolution mass spectrometry (HRMS) (Longworth et al., 2016);
- direct analysis in real time (DART-MS) and liquid chromatography/electrospray ionization quadrupole time-of-flight mass spectrometry (LC/QTOFMS) (Nie et al., 2016).

([13]) http://shop.chiron.no/main.aspx?page=article&artno=C10464.20-100-ME&gid=&gidlevel=&pid=; https://www.caymanchem.com/product/15434; https://www.trc-canada.com/product-detail/?CatNum=A105960&-CAS=1185887-21-1&Chemical_Name=AB-CHMINACA&Mol_Formula=C%E2%82%82%E2%82%80H%E2%82%82%E2%82%88N%E2%82%84O%E2%82%82

Quantification of AB-CHMINACA in products can be carried out according to the general procedure described by the (UNODC, 2013).

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

The data reported to Europol discussed in section 3.2.1 may overlap with the data reported to the EMCDDA discussed in section 3.2.2.

3.2.1 Information provided to Europol

Europol received replies from 15 Member States (Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Finland, Germany, Greece, Latvia, Lithuania, Luxembourg, Romania, Slovakia and Slovenia).

Six countries reported that they have no available information on AB-CHMINACA (Belgium, Cyprus, Czech Republic, Greece, Luxembourg and Slovenia).

The remaining nine countries provided limited information on AB-CHMINACA (Austria, Bulgaria, Croatia, Finland, Germany, Latvia, Lithuania, Romania and Slovakia).

The level of production

No information was received in relation to the production of AB-CHMINACA.

The level of distribution

At least 271 seizures were reported by 10 Member States: Austria (2), Bulgaria (3), Croatia (30), Czech Republic (2), Finland (minor seizures in 2014, 2015 and 2016, exact number unspecified), Germany (152), Latvia (62), Lithuania (6), Romania (2) and Slovakia (9).

- Austria: 2 small seizures of herbal material, containing other synthetic cannabinoids. The packages were labelled 'Red Dub Herbal Blend'.
- Bulgaria: 3 seizures amounting to 37 g, which were delivered from Spain to Bulgaria and from the Netherlands to Bulgaria. At least one of the packages was labelled 'MMB CHMINACA – 2g Legal Research Chemical Reagent Use Only'.
- Croatia: seizures of herbal material were reported in 2015 (30 seizures, amounting to almost 1 kg), 2016 (7, 19.26 g)

and 2017 (1, 0.66 g). In most cases the seizures contained other synthetic cannabinoids.
- Finland: unspecified number of seizures made in 2014, 2015 and 2016.
- Germany: 144 small seizures of herbal smoking mixtures made in 2016, one of the seizures amounted to 284 g; and 8 seizures in 2017, most of which were in the form of herbal material, which amounted to 57 g.
- Latvia: reported 62 seizures, among which there was one seizure amounting to 495 g.
- Lithuania: 6 seizures made in 2017, which amounted to 8.578 g. Lithuania reported that 'AB-CHMINACA is one of the most frequently seized synthetic cannabinoids, but in general the distribution level of NPS is not very high within the country'.
- Romania: 2 seizures amounting to 9.4 kg and 5.7 kg.
- Slovakia: a total of 9 small seizures in various physical forms were reported. Seizures were made in 2014 (3), 2015 (5) and 2016 (1). See Annex 2 for more details.

The level of trafficking

Information related to trafficking routes is limited to the seizures reported above.

3.2.2 Information provided to the EMCDDA

The EMCDDA received responses from 27 Member States ([5]), as well as from Turkey and Norway. Of these, 24 Member States ([14]), Turkey and Norway reported detections of AB-CHMINACA ([15]).

It is important to note that detections of AB-CHMINACA may be under-reported since the substance is not routinely screened for. Three Member States (Austria, Slovenia and Sweden) and Norway reported that AB-CHMINACA is part of routine screening in some (but not all) of their laboratories.

Seizures

In total, 6 422 seizures of AB-CHMINACA were reported to the EMCDDA by 24 Member States, Norway and Turkey, as follows: Austria (10 seizures), Belgium (24), Bulgaria (17), Croatia (45), Denmark (2), Estonia (18), Finland (114), France (26), Germany (2), Greece (3), Hungary (1 723), Italy (1), Latvia (221), Lithuania (62), Luxembourg (4), the Netherlands (7), Norway (9), Poland (1 793), Portugal (3), Romania (3), Slovakia (6), Slovenia (2), Spain (7), Sweden (121), Turkey (1 801) and the United Kingdom (398). The majority of the seizures comprise police and customs cases, with additional seizures taking place in custodial settings.

Seizures included herbal materials, powders, liquids, blotters and unspecified physical forms. A summary is provided below.

Herbal material
- 4 066 seizures of AB-CHMINACA in herbal material were reported by 24 countries: Austria, Bulgaria, Croatia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Luxembourg, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the United Kingdom, amounting to over 40 kg, plus more than 145 000 packages of commercially labelled herbal smoking mixtures ([16]) weighing 1-3 g each. In addition, Turkey reported 1 757 seizures of herbal material amounting to almost 150 kg ([17]).
- The largest single seizure of AB-CHMINACA in herbal material was reported by Spain. In the frame of 'Operation Alimaya', a large-scale operation carried out in Alicante in March 2016, a total of 145 157 packages (of 1-3 g each, containing also AMB-FUB and AB-FUBINACA) and 2 bags (of 2 kg each, containing also AMB-FUB) were seized.
- Other large single seizures of herbal materials were reported by Lithuania (3.9 kg in the form of briquettes with Euro signs, seized by Police) and Bulgaria (2 kg, no further information).
- Hungary reported around 1 700 seizures of herbal material amounting to 16 kg.
- In herbal material, AB-CHMINACA was commonly found mixed with other synthetic cannabinoids. In 15 seizures, samples contained stimulants: Hungary (8 cases; amphetamine, pentedrone, clephedrone) and Poland (7 cases; amphetamine, alpha-POP and clephedrone).

Powder
- 281 seizures of powder were reported by 22 countries: Austria, Belgium, Bulgaria, Denmark, Estonia, Finland, France, Germany, Hungary, Latvia, Lithuania, Luxembourg, the Netherlands, Norway, Poland, Romania, Slovakia, Slovenia, Spain, Sweden, Turkey and the United Kingdom, amounting to a total of more than 43.8 kg.
- The largest single seizures of AB-CHMINACA in powder form were reported by: Luxembourg (4.8 kg seized by customs in a FedEx delivery), France (3.5 kg of white powder seized at Roissy Airport, coming from China and headed to Austria) and Spain (2 kg of powder seized at Madrid-Barajas Airport, coming from China and headed to France).

([14]) Four Member States (Czech Republic, Cyprus, Ireland and Malta) reported no detections of AB-CHMINACA.
([15]) 'Detections' is an all-encompassing term and may include seizures and/or collected and/or biological samples that are analytically confirmed. 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.).

([16]) Products seized include: 'Aromatic Pot Pourri', 'Jamaican Gold Supreme', 'Jamaican Gold Extreme', 'Yama', 'Bonzai Summer Boost', 'Bonzai Winter Boost', 'Bonzai Citrus', 'Blaze', 'Bubblegum', 'Manga Xtreme', 'Manga XXL', 'V.I.P.', 'Love', 'R&B', and 'King Size Slim Rolling Papers'.
([17]) Minimum estimate provided by the Turkish national focal point for 2016.

Liquid

- Sweden (4 cases) and Finland (3) reported seizures of AB-CHMINACA in liquid form, amounting to a total of 293 ml. The largest seizure was reported by Finland and consisted of 50 bottles (225 ml) of "e-liquid" for vaping (concentration 3.5 mg/ml).

Other physical forms

- 178 seizures of AB-CHMINACA in blotter form were reported by Poland, amounting to 193.9 g.
- Additionally, 2 seizures were reported by Lithuania amounting to more than 20 kg where no information on the physical form was available.

Lithuania provided quantitative information on the purity of AB-CHMINACA in eight analysed samples of herbal material and one sample where the physical form was not specified. The purity of AB-CHMINACA in the samples was in the range of 0.15–4.3 % (mean: 1.97 %, median: 2.0 %).

Collected samples

Two collected samples of AB-CHMINACA were reported to the EMCDDA from Belgium (1 case) and Poland (1). The case from Belgium involved a patient requiring medical treatment at a hospital in Antwerp, following ingestion of AB-CHMINACA. A sample of white powder collected from the patient was found to contain AB-CHMINACA. The sample from Poland consisted of a bag of herbal material which also contained alpha-PVP.

Biological samples

Serious adverse events with confirmed exposure to AB-CHMINACA from biological samples are discussed in section 3.4.2.

In addition to these, 551 detections where AB-CHMINACA was analytically confirmed in biological samples were reported by three Member States: Hungary (537 cases), Sweden (10) and Poland (4) ([18]). Detections include:

- 52 cases related to persons suspected of driving under the influence of drugs (including 10 traffic accidents), all reported by Hungary;
- 484 cases were reported in relation to drug abuse (consumption), intoxication or non-fatal intoxication, with no further details provided;
- 15 cases, where the type of event was not specified.

([18]) In addition, Turkey reported 902 samples (blood, hair and urine) which may contain duplicates and therefore have not been included in the total count.

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

No information concerning the involvement of organised crime in the manufacture and/or trafficking of the AB-CHMINACA was provided.

Money laundering aspects

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

Violence in connection with production, wholesale and distribution

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

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

3.4.1 Health risks

Pharmacology and toxicology

Limited data suggests that AB-CHMINACA is a CB_1 receptor agonist (Longworth, et al., 2016; Moosmann et al., 2017; Wiley et al., 2015 ([19])) that shares some similarities with the major psychoactive constituent of cannabis (–)-*trans*-Δ^9-tetrahydrocannabinol (THC) and synthetic cannabinoids such as JWH-018 and MDMB-CHMICA (EMCDDA, 2017; Järbe and Raghav, 2017; Pertwee, 2014; Reggio, 2009).

The acute effects of THC (and consequently cannabis) include: relaxation, euphoria, lethargy, depersonalisation, distorted perception of time, impaired motor performance, hallucinations, paranoia, confusion, fear, anxiety, dry mouth, reddening of the conjunctivae of the eyes, tachycardia, and, nausea and vomiting. THC also has an abuse liability and dependence potential (Pertwee, 2014; Wiley et al., 2016). Similar effects to cannabis have been reported for synthetic cannabinoids such as AB-CHMINACA. In some cases, the effects are reported to be more pronounced/severe (EMCDDA, 2017).

([19]) Where reported the (*S*) enantiomer was studied.

Compared to cannabis, severe and fatal poisoning appears to be more common with synthetic cannabinoids (EMCDDA, 2017; Tait et al., 2016). Poisoning may include rapid loss of consciousness/coma, cardiovascular effects (such as hypertension, tachycardia, bradycardia, chest pain, myocardial infarction and stroke), seizures and convulsions, vomiting/hyperemesis, delirium, agitation, psychosis, and, aggressive and violent behaviour. Sudden death has also been reported. The mechanisms of this toxicity are poorly understood (Tai and Fantegrossi, 2016), but factors that are likely to play an important role are the potency of the substances and the doses that users are exposed to. In addition, some of the effects of poisoning — such as loss of consciousness or behavioural effects — may place users at additional risks such as choking on vomitus, drowning, or self-harm.

There is no antidote to poisoning caused by synthetic cannabinoids.

In general, the use of herbal smoking mixtures containing synthetic cannabinoids appears to pose a high risk of poisoning. This is because manufacturers guess the amount of cannabinoid (s) to add to the herbal material and the manufacturing process makes it difficult to dilute them sufficiently and distribute them consistently throughout the material. This can result in mixtures that contain a large amount of highly potent cannabinoid, as well as 'hot pockets' where the cannabinoid is highly concentrated within parts of the herbal material (e.g. Schäper, 2016). Together, this makes it difficult for users to control the dose that they are exposed to. As these mixtures are typically smoked as cigarettes ('joints'), users can inadvertently administer a toxic dose; in some cases, a small number of puffs from a cigarette have been sufficient to cause severe poisoning. Reflecting these risks, smoking mixtures have caused a large number of outbreaks of mass poisonings in recent years (Adams et al., 2017; Kasper et al., 2015; Schwartz et al., 2015; Shevyrin et al., 2015; Trecki et al., 2015; Tyndall et al., 2015).

While there is limited data for AB-CHMINACA, the chronic health risks might share similarities to cannabis and other synthetic cannabinoids. This may include dependence.

3.4.2 Serious adverse events

Acute intoxications

A total of seven acute intoxications with confirmed exposure to AB-CHMINACA were reported by Belgium (1 case), France (1), Hungary (3) and the United Kingdom (2). The cases occurred between 2014 and 2016. No further details are available on the cases from Hungary.

In two out of the remaining four cases, no other substances were detected. In the other two cases other substances detected included synthetic cannabinoids and an opioid. In all four cases, the clinical features of the poisoning were typical of those reported for synthetic cannabinoids.

Deaths

A total of 31 deaths with confirmed exposure to AB-CHMINACA were reported by Croatia (1 case), Germany (4), Hungary (11), Poland (2), Sweden (5) and the United Kingdom (8). The cases occurred between 2014 and 2017.

Of the deaths, 24 were male (77 %), one was female (3 %); the data was missing for six cases (20 %). The males were aged between 16 and 66 years (n=23; mean 29.7, median 26.5); the female was aged 38. In six cases, no other substances were detected. In two cases, it was unknown if other substances were detected. In the remaining cases, other substances were detected including central nervous system depressants (such as alcohol, synthetic cannabinoids, opioids and benzodiazepines). Where known, many of the cases were found dead; in at least some cases the individuals were in a home environment or prison. In at least seven cases, AB-CHMINACA was the cause of death or contributed to the death.

3.4.3 Characteristics of users

Similar to other synthetic cannabinoids, AB-CHMINACA is sold and used as a 'legal' substitute for cannabis (EMCDDA, 2009; EMCDDA, 2017). The most common way of using it is by smoking a cigarette of herbal mixture that has been laced with the substance. Because these products rarely state the ingredients, most users will be unaware that they are using AB-CHMINACA.

People who use AB-CHMINACA may include recreational users, high-risk drug users and groups who experiment with the substance (such as psychonauts). This may also include individuals who are subject to drug testing (such as people in drug treatment, prisoners and drivers) because some drug tests/screens will be unable to detect AB-CHMINACA. In the past few years, synthetic cannabinoids have become increasingly used by vulnerable groups (such as the homeless and prisoners).

3.4.4 Social risks

While there is limited data for AB-CHMINACA, the social risks might share some similarities with cannabis and other synthetic cannabinoids.

Of particular note is that synthetic cannabinoids are increasingly used by vulnerable groups, such as the homeless and prisoners. Reports suggest that this has caused new health and social problems as well as exacerbated existing ones for these groups. For example, in prisons, alongside the adverse health effects, the market in synthetic cannabinoids has been linked to an increase in aggression, violence, bullying and debt. In some cases this has caused a serious threat to the overall safety and security of the prison environment (Blackman and Bradley, 2017; HMIP, 2015; Ralphs et al., 2017; User Voice, 2016).

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

The World Health Organization is the specialised United Nations agency designated for the evaluation of the medical, scientific and public health aspects of psychoactive substances under the Single Convention on Narcotic Drugs, 1961 and the Convention on Psychotropic Substances, 1971.

On 1 May 2017, the World Health Organization informed the EMCDDA that AB-CHMINACA is currently not under assessment and has not been under assessment by the UN system.

On 12 May 2017, the WHO informed the EMCDDA that AB-CHMINACA will be reviewed at the 39th meeting of the WHO Expert Committee on Drug Dependence (ECDD) that will be held on 16–20 November 2017. At the time of writing this report neither a critical review nor a written recommendation had been published.

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

The first official EMCDDA–Europol notification of AB-CHMINACA dates from 10 April 2014 from the Latvian national focal point. The Reporting Form details a seizure of eight plastic bags containing herbal material amounting to 3.81 g that were seized in February 2014 by the Municipal Police in Riga. The substance was analytically identified by the Forensic Service Department of the State Police by GC-MS and the Latvian Institute of Organic Synthesis confirmed the structure using NMR.

AB-CHMINACA was added to the list of new psychoactive substances monitored by the EMCDDA and Europol through the European Union Early Warning System. A profile of the substance was created on the European Database on New Drugs (EDND). Since then, analytical details and other information, including a public health alert, have been exchanged between the EMCDDA, Europol, and the Member States, Turkey and Norway, on an ad hoc basis; the European Commission and the EMA have been kept duly informed.

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

Sixteen Member States (Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Estonia, Finland, France, Germany, Hungary, Italy, Latvia, Lithuania, Luxembourg, Slovenia and Sweden) and Turkey reported that AB-CHMINACA is controlled under drug control legislation. Information previously reported by Slovakia on the control status of AB-CHMINACA indicates that the substance is controlled under drug control legislation.

Two Member States (Austria and Poland) reported that AB-CHMINACA is controlled under specific new psychoactive substances control legislation.

Nine Member States (Denmark, Greece, Ireland, Malta, the Netherlands, Portugal, Romania, Spain and the United Kingdom) reported that AB-CHMINACA is not subject to control measures at the national level.

Norway reported that AB-CHMINACA is controlled under medicinal products legislation.

3.8 Further information (Article 5.2(h) of the Council Decision)

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

No information was reported by the Member States, Turkey, or Norway, about the chemical precursors or manufacturing methods used to make the AB-CHMINACA which has been detected within Europe.

The synthesis of (*S*)-AB-CHMINACA was first described in a 2009 patent (Buchler et al., 2009). More recently, the

synthesis of (*S*)-AB-CHMINACA has been described by Longworth et al. (Longworth et al., 2016).

The synthesis of (*S*)-AB-CHMINACA described by Longworth et al., started with 1*H*-indazole-3-carboxylic acid, which was subjected to Fischer esterification to give the corresponding methyl ester (methyl 1*H*-indazole-3-carboxylate). Alkylation of the ester with the appropriate bromoalkane ((bromomethyl) cyclohexane), in the presence of potassium *tert*-butoxide produced methyl 1-(cyclohexylmethyl)-1*H*-indazole-3-carboxylate. Saponification of the ester gave the acid 1-(cyclohexylmethyl)-1*H*-indazole-3-carboxylic acid, which was then reacted with L-valinamide to produce (*S*)-AB-CHMINACA (Longworth et al., 2016).

(*R*)-AB-CHMINACA could also be synthesised under identical conditions, using D-valinamide instead of L-valinamide. Using valinamide would produce racemic AB-CHMINACA (Moosmann et al., 2017).

According to Buchler et al. (Buchler at al., 2009) the starting compound methyl 1*H*-indazole-3-carboxylate, which is commercially available, can be prepared from 1*H*-indole-2,3-dione (Johnson and Rodgers, 2005).

In summary, potential precursors of AB-CHMINACA are 1*H*-indole-2,3-dione ([20]), 1*H*-indazole-3-carboxylic acid, methyl 1*H*-indazole-3-carboxylate, L-valinamide (for the synthesis of the (*S*)-enantiomer), valinamide for the racemic AB-CHMINACA and (bromomethyl)cyclohexane.

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

No studies were identified that have examined the mode and scope of established or expected use of AB-CHMINACA. Given the limited information currently available, the relevant information has been included in the previous sections.

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

No information was provided by the Member States, Turkey or Norway that indicated that AB-CHMINACA had any other use apart from in analytical reference materials and scientific research.

From the available information, it does not appear that AB-CHMINACA is used in the manufacture of a medicinal product in the European Union. However, the data collection is incomplete and some countries indicated that this information is not known. It is understood that the collection of such information is a challenge in the absence of a database on the synthetic route of all medicinal products.

Eleven countries (Austria, Belgium, Croatia, Denmark, Finland, Greece, Italy, the Netherlands, Poland, Spain and the United Kingdom) reported that AB-CHMINACA is not used to manufacture a medicinal product for human use. Eight countries (Czech Republic, Estonia, Germany, Hungary, Ireland, Latvia, Norway and Sweden) reported that it was unknown if AB-CHMINACA is used to manufacture a medicinal product for human use.

In addition, the EMA reported that it is not known if AB-CHMINACA is used in the manufacture of medicinal products for human use and which are centrally authorised within the European Union.

Eleven countries (Austria, Belgium, Denmark, Finland, France, Greece, Latvia, Poland, Slovakia, Spain and the United Kingdom) provided information that AB-CHMINACA is not used to manufacture a medicinal product for veterinary use. Seven countries (Estonia, Germany, Ireland, Norway, Portugal, Slovenia and Sweden) reported that it was unknown if AB-CHMINACA is used to manufacture a medicinal product for veterinary use.

In addition, the EMA reported that it is not known if AB-CHMINACA is used in the manufacture of medicinal products for veterinary use and which are centrally authorised within the European Union.

([20]) A pre-precursor.

4. Information from the EMA (Article 5.3 of the Council Decision)

Nineteen countries (Austria, Belgium, Croatia, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Hungary, Ireland, Italy, Latvia, the Netherlands, Norway, Poland, Spain, Sweden and the United Kingdom) reported that:

- AB-CHMINACA has not been granted a marketing authorisation as a medicinal product for human use;
- AB-CHMINACA is not the subject of an application for a marketing authorisation as a medicinal product for human use;
- there had been no cases of suspended marketing authorisation in respect to AB-CHMINACA as a human medicine.

Eighteen countries (Austria, Belgium, Denmark, Estonia, Finland, France, Germany, Greece, Ireland, Latvia, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden and the United Kingdom) reported that:

- AB-CHMINACA has not been granted a marketing authorisation as a medicinal product for veterinary use;
- AB-CHMINACA is not the subject of an application for a marketing authorisation as a medicinal product for veterinary use;
- there had been no cases of suspended marketing authorisation in respect to AB-CHMINACA as a veterinary medicine.

The EMA also reported that AB-CHMINACA:

- has not been granted a marketing authorisation as a medicinal product for neither human nor veterinary use through the centralised procedure;
- is not the subject of an application for a marketing authorisation for neither human nor veterinary use through the centralised procedure;

is not the subject of a suspended marketing authorisation for neither human nor veterinary use through the centralised procedure.

5. Conclusion

AB-CHMINACA is a synthetic cannabinoid and a CB_1 receptor agonist. It shares some pharmacological similarities with Δ^9-tetrahydrocannabinol (THC), which is responsible for the major psychoactive effects of cannabis. In humans, AB-CHMINACA appears to cause effects that resemble those of cannabis and other synthetic cannabinoids.

AB-CHMINACA has been available in the European Union since at least February 2014. It has been detected in 24 Member States, Turkey and Norway. More than 4 000 seizures have been made within the European Union, which includes 43 kg of powder and 40 kg of herbal material which has been laced with AB-CHMINACA. This herbal material is typically sold as smoking mixtures; the products are marketed as 'legal' replacements to cannabis. Due to the way that these products are produced, it appears that users are at risk of serious poisoning. There are indications that the AB-CHMINACA available on the market was synthesised by chemical companies based in China.

Thirty-one deaths with confirmed exposure to AB-CHMINACA have been reported by six Member States. In at least seven of the deaths, AB-CHMINACA was the cause of death or contributed to the death.

AB-CHMINACA is under assessment within the United Nations system. It will be assessed at the 39th meeting of the WHO Expert Committee on Drug Dependence (ECDD) that will be held in November 2017. Currently, neither a critical review nor a written recommendation had been published.
AB-CHMINACA is not subject to control measures in nine Member States.

We conclude that the health and social risks caused by the manufacture, trafficking and use of AB-CHMINACA and the involvement of organised crime and possible consequences of control measures, could be thoroughly assessed through a risk assessment procedure in accordance with Article 6 of Council Decision 2005/387/JHA.

The EMCDDA and Europol will continue to intensively monitor AB-CHMINACA in order to ensure that new information is provided to the Member States, the EMA and the Commission via the information exchange of the European Union Early Warning System.

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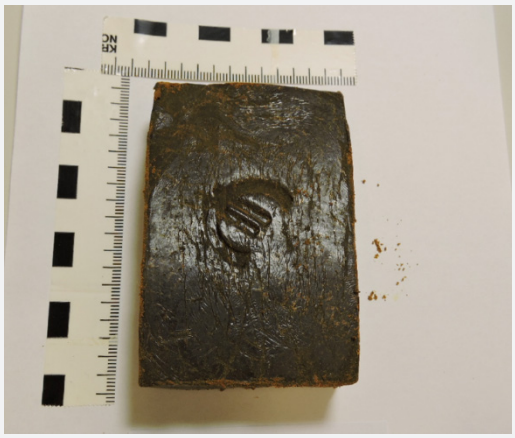
Annex 1

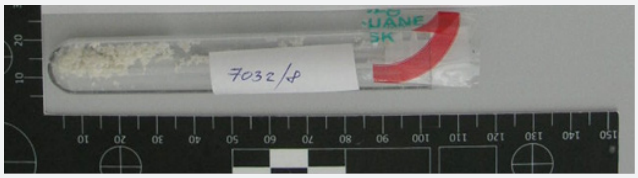
Images from seizures and collected samples provided to the EMCDDA

Country	Image	Description
Slovakia		**Seizure, 12 May 2014** Green herbal particles, seized at Dunajská Streda Seizing authority: Police
United Kingdom		**Collected sample, 19 May 2014** White powder Collecting authority: WEDINOS
Finland	 	**Seizures, from 11 September 2014 to 16 December 2014** Hashish-like material, seized at Helsinki Seizing authority: Police

Country	Image	Description
Italy	 	**Seizure, May 2015** Green herbal mixture, seized at Genova Seizing authority: Police
Finland		**Seizure, 29 September 2016** Clear viscous liquid ("e-liquid"), seized at Turku Seizing authority: Police

Annex 2

Images from seizures provided to Europol

Country	Image	Description
Slovakia		**Seizure, 4 March 2014** White crystal, seized at Bratislava Seizing authority: Police
Slovakia		**Seizure, 12 May 2014** Green herbal particles, seized at Dunajská Streda Seizing authority: Police
Slovakia		**Seizure, 7 August 2014** Green herbal particles, seized at Saky Seizing authority: Police
Slovakia		**Seizure, 22 September 2014** Green herbal particles, seized at Nitra Seizing authority: Police

Country	Image	Description
Italy	 	**Seizure, May 2015** Green herbal mixture, seized at Genova Seizing authority: Police
Finland		**Seizure, 29 September 2016** Clear viscous liquid ("e-liquid"), seized at Turku Seizing authority: Police

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The Joint Report represents a legal document, prepared in cooperation with the Council, EMA, and Commission and is published in the original version that has not been edited.

About the EMCDDA

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is the central source and confirmed authority on drug-related issues in Europe. For over 20 years, it has been collecting, analysing and disseminating scientifically sound information on drugs and drug addiction and their consequences, providing its audiences with an evidence-based picture of the drug phenomenon at European level.

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

Related publications and websites

EMCDDA

- *European Drug Report 2017: Trends and developments*, 2017

EMCDDA and Europol

- *EMCDDA–Europol 2016 Annual Report on the implementation of Council Decision 2005/387/JHA*, Implementation reports, 2017

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