



AB-CHMINACA

Report on the risk assessment of *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide in the framework of the Council Decision on new psychoactive substances

About this series

EMCDDA Risk Assessments are publications examining the health and social risks of individual new psychoactive substances.

The Risk Assessment Report consists of an analysis of the scientific and law enforcement information available on the new psychoactive substance under scrutiny and the implications of placing it under control. It is the outcome of a meeting convened under the auspices of the EMCDDA Scientific Committee.

This process is part of a three-step procedure involving information exchange/early warning, risk assessment and decision-making in the framework of Council Decision 2005/387/JHA.

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Foreword

This publication presents the data and findings of the risk assessment on the new psychoactive substance AB-CHMINACA (*N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide), carried out by the extended Scientific Committee of the EMCDDA on 7 and 8 November 2017.

The Risk Assessment Report, which was submitted to the European Commission and the Council of the European Union on 14 November 2017, examines the health and social risks of the substance, information on international trafficking and the involvement of organised crime, as well as a consideration of the potential implications of subjecting the substance to control measures. AB-CHMINACA is the fifteenth new psychoactive substance to be risk assessed under the terms of Council Decision 2005/387/JHA.

On the basis of the Risk Assessment Report on a new psychoactive substance, and, on the initiative of the European Commission, the Council may decide that the substance should be subject to control measures across the Member States. This decision is adopted in the final stage of the three-step process — early warning, risk assessment and control of new psychoactive substances — established by the Council Decision 2005/387/JHA. This legal framework allows the EU institutions and Member States to act on all new and potentially threatening narcotic and psychotropic drugs which appear on the European drug scene, with the EMCDDA and Europol, in collaboration with their respective networks, playing a central role in the early detection of such substances as well as the harms caused by their use — information that underpins risk assessment, and, ultimately, decision-making.

In March 2018, at its 61st regular session, the Commission on Narcotic Drugs (CND) decided to place AB-CHMINACA in Schedule II of the Convention on Psychotropic Substances of 1971 based on a recommendation by the World Health Organization. This recommendation was substantially supported by European data provided by the EMCDDA.

In this respect we would like to acknowledge the excellent work done by the networks of the EMCDDA and Europol, as well as those of the EMA — the Reitox national focal points, Europol national units and the national competent authorities responsible for medicinal products — who played an essential role in collecting and providing national data.

Finally, we would like to thank all the participants in the risk assessment process for the high quality of work carried out. The resulting report is a valuable contribution at European level, which gives clear support to political decision-making.

Dr Anne Line Bretteville-Jensen

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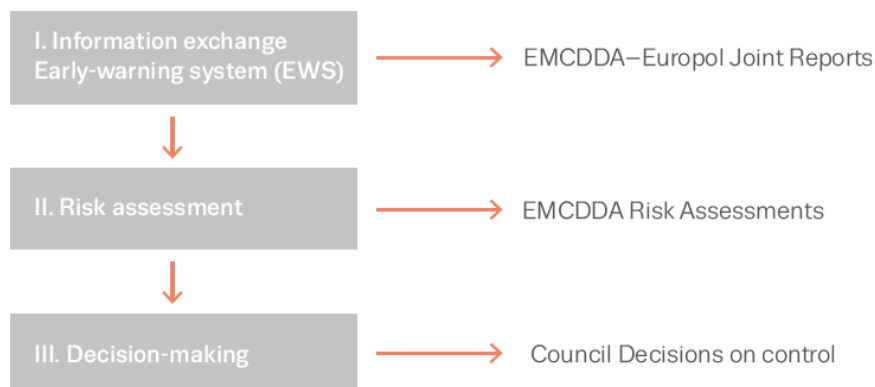
EMCDDA actions on monitoring and responding to new drugs

The EMCDDA has been assigned a key role in the detection and assessment of new drugs in the European Union under the terms of a Council Decision 2005/387/JHA on the information exchange, risk-assessment and control of new psychoactive substances.

It establishes a mechanism for the rapid exchange of information on new psychoactive substances and provides for an assessment of the risks associated with them in order to permit the measures applicable in the Member States for the control of narcotic and psychotropic substances to be applied also to new psychoactive substances.

The three-step process involves information exchange/early warning, risk assessment and decision-making (see below). More detailed information can be found in the section 'Action on new drugs' of the EMCDDA's website: www.emcdda.europa.eu/activities/action-on-new-drugs

Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk-assessment and control of new psychoactive substances:



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

Europol–EMCDDA Joint Report on a new psychoactive substance: *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide — in accordance with Article 5 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances

In March 2017, the EMCDDA and Europol examined the available information on a new psychoactive substance *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide, commonly known by the abbreviation '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 available on AB-CHMINACA satisfied criteria 1, 4 and 6. The two organisations therefore concluded that sufficient information has been accumulated to merit the production of a Joint Report on AB-CHMINACA as stipulated by Article 5.1 of the Decision. Accordingly, the NFPs, the Europol national units (ENUs), the EMA and the World Health Organization (WHO) were formally asked to provide the relevant information within six weeks from the date of the request, i.e. by 6 June 2017.

The resulting Joint Report on AB-CHMINACA was submitted to the Council, the Commission and the EMA on 3 July 2017. The report concluded that the health and social risks, caused by the use of, the manufacture of, and traffic in AB-CHMINACA, as well as the involvement of organised crime and possible consequences of control measures, could be thoroughly assessed through a risk assessment procedure as foreseen by Article 6 of Council Decision 2005/387/JHA.

The full text of the Joint Report can be found at:
www.emcdda.europa.eu/publications/joint-reports/ab-chminaca

Risk Assessment Report on a new psychoactive substance: *N*-(1-Amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide (AB-CHMINACA)

Introduction

This Risk Assessment Report presents the summary findings and the conclusion 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 *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide (commonly known as AB-CHMINACA). The report is intended for policy makers and decision makers in the institutions of the European Union.

The report has been prepared and drafted in accordance with the conceptual framework and the procedure set out in the risk assessment operating guidelines ⁽¹⁾. It is written as a stand-alone document, which presents 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 Scientific Committee. A list of the information resources considered by the Scientific Committee, including a detailed technical report on AB-CHMINACA, 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 'Council Decision'). The Council Decision establishes a mechanism for the rapid exchange of information on new psychoactive substances (hereafter 'EU Early Warning System' ⁽³⁾) that may pose public health and social threats, including those related to 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

⁽¹⁾ EMCDDA (2010), *Risk assessment of new psychoactive substances: Operating guidelines*, 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 ('EU Early Warning System')*. It is operated by the EMCDDA and Europol in partnership with the Reitox national focal points and Europol national units 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.

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⁾.

AB-CHMINACA was formally notified on 10 April 2014 by the EMCDDA on behalf of the Latvian national focal point, in accordance with Article 4 of the Council Decision. The notification related to the seizure of 8 bags of herbal material with a total weight of 3.81 grams seized in February 2014 by police. Following an assessment of the available information on AB-CHMINACA, and, in accordance with Article 5 of the Council Decision, on 3 July 2017 the EMCDDA and Europol submitted a *Joint Report* on AB-CHMINACA ⁽⁶⁾ to the Council of the European Union, the European Commission, and the European Medicines Agency (EMA). Taking into account the conclusion of the *Joint Report*, and, in accordance with Article 6 of the Council Decision, on 14 September 2017 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 AB-CHMINACA was convened under the auspices of the Scientific Committee of the EMCDDA with the participation of four 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 AB-CHMINACA, including health and social risks. A further four experts participated in the risk assessment: two experts from the Commission, one expert from Europol, and one expert from the European Medicines Agency (EMA). The meeting took place on 7 and 8 November 2017 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 other participants attending the risk assessment meeting, is annexed to this report (page 65).

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

- i. Technical report on *N*-(1-Amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide (AB-CHMINACA) (Annex 1);
- ii. 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) ⁽⁶⁾;
- iii. Open source information including scientific articles, official reports, grey literature, internet drug discussion forums and related websites (hereafter ‘user websites’);
- iv. Additional information provided during the course of the risk assessment meeting by the participants;
- v. The EMCDDA operating guidelines for the risk assessment of new psychoactive substances ⁽¹⁾; and,

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

⁽⁶⁾ EMCDDA (2017), 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), EMCDDA, Lisbon. Available at: <http://emcdda.europa.eu/publications/joint-reports/ab-chminaca>

- vi. Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk assessment and control of new psychoactive substances ⁽²⁾.

Finally, it is important to note that this risk assessment report contains a discussion of the available information on serious adverse events such as acute intoxications (typically presenting to hospital emergency departments) and deaths associated with AB-CHMINACA. Such information is critical to the identification of emerging toxicological problems associated with new psychoactive substances within the European Union. In this context, it is important to recognise that the capacity to detect, identify, and report these events differ both within and between Member States. In the past few years, programmes have been introduced in some Member States to strengthen these capacities. The EMCDDA's toxicovigilance system, which is a central component of the EU Early Warning System, has also been strengthened resulting in more information being available regarding serious adverse events associated with new psychoactive substances. Nonetheless, it is likely that these events remain under-detected and under-reported.

Physical, chemical and pharmacological description

N-(1-Amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide, also known as AB-CHMINACA, is an indazole-based synthetic cannabinoid receptor agonist (synthetic cannabinoid). The common name for the substance is derived after its structural features ⁽⁷⁾: a methyl amino butanone linked group (AB), a cyclohexylmethyl tail (CHM), an indazole core (INA) and a carboxamide linker (CA).

AB-CHMINACA contains a stereogenic centre and therefore two possible enantiomers may exist, (*R*)- and (*S*)-AB-CHMINACA. (*S*)-AB-CHMINACA was originally described in a patent application by Pfizer Inc., and published in 2009. No information is available on whether the AB-CHMINACA detected in the European drug market corresponds to the (*R*)- or (*S*)- enantiomer, or a mixture of both. Based on the literature and the precursors that are most likely to be used, an (*S*)-configuration of the stereocentre could be expected.

Synthetic cannabinoids such as AB-CHMINACA are functionally similar to Δ^9 -tetrahydrocannabinol (THC), the major psychoactive principle of cannabis. Like THC, they bind to and activate the CB₁ and CB₂ cannabinoid receptors which form part of the endocannabinoid system — a system that helps regulate a large number of physiological functions in the body such as behaviour, mood, pain, appetite, sleep, the immune system, and the cardiovascular system. Many synthetic cannabinoids were first developed to study the endocannabinoid system as well as to explore their potential as therapeutic agents to treat a number of diseases and their symptoms (such as neurodegenerative diseases, drug dependence, pain disorders, and cancer).

Since around 2006, 'legal high' products containing synthetic cannabinoids have been sold in Europe as 'herbal smoking mixtures' and marketed as 'legal' replacements for cannabis. These products are made by dissolving the synthetic cannabinoids in solvents such as acetone or methanol and then mixing them with, or, spraying them on, plant material such as the herbs Damiana (*Turnera diffusa*) and Lamiaceae (such as *Melissa*, *Mentha* and *Thymus*). Such products are generally referred to by a variety of names in Europe, including 'Spice' ⁽⁸⁾, 'herbal smoking mixtures', 'herbal incense', and 'synthetic cannabis'. Manufacturers of smoking mixtures frequently change the synthetic cannabinoids

⁽⁷⁾ Different naming systems exist and are used for applying short/code names to synthetic cannabinoids. <http://www.emcdda.europa.eu/topics/pods/synthetic-cannabinoids>

⁽⁸⁾ Which is a reference to the most common brand name used for these types of products when they first appeared on the European market.

in the products, which means that product names are not a reliable source of information regarding the actual substances that are present. Almost 180 synthetic cannabinoids, in hundreds of different products, have been identified on the European drug market since 2008. They are the largest group of substances that are monitored by the EMCDDA through the EU Early Warning System.

A number of cannabinoids are controlled under the United Nations Convention on Psychotropic Substances, 1971 (Schedule II). These are: the major active principle of cannabis, delta-9-tetrahydrocannabinol (Δ^9 -THC) ⁽⁹⁾, as well as the synthetic cannabinoids JWH-018 ⁽¹⁰⁾, AM-2201 ⁽¹¹⁾, MDMB-CHMICA ⁽¹²⁾, 5F-APINACA (5F-AKB-48) ⁽¹³⁾, and XLR-11 ⁽¹⁴⁾.

In its pure form AB-CHMINACA has been described as a white to off-white crystalline powder. It is poorly soluble in water.

Information provided from seizures and collected samples reported to the EMCDDA have noted that AB-CHMINACA is typically found in herbal/plant material (including as commercially-branded 'legal high' products) and as a powder. To a lesser extent, other forms, such as liquids and blotters, have also been reported.

The analytical identification of AB-CHMINACA in physical and biological samples is possible using standard analytical techniques. These include chromatographic and mass spectrometric methods.

Analytical reference material is important for correct identification and for facilitating the quantification of AB-CHMINACA in physical and biological samples. Such material is commercially available.

Route of administration and dosage

The most common way of using synthetic cannabinoids such as AB-CHMINACA is by smoking either ready-to-use or homemade 'smoking mixtures' as a cigarette ('joint') or by using a vaporizer, 'bong', or pipe. Some synthetic cannabinoids, including AB-CHMINACA, have also been offered in the form of e-liquids for vaping in e-cigarettes. Additionally, users might also prepare AB-CHMINACA containing e-liquids at home. To a lesser extent, other routes of administration for synthetic cannabinoids have been reported; these include oral and rectal.

Limited information is available regarding the dose and the dose regimens of AB-CHMINACA. User reports specifically about AB-CHMINACA were not particularly revealing. It is not possible to discern the 'typical' dosages administered as most individuals use herbal smoking mixtures. Nonetheless, based on data from the analysis of some of these products, a gram of herbal material could contain more than 100 mg of AB-CHMINACA (and potentially other synthetic cannabinoids). These compounds may be active at less than 1 mg.

⁽⁹⁾ Including some of its named isomers and their stereochemical variants.

⁽¹⁰⁾ JWH-018: naphthalen-1-yl(1-pentyl-1*H*-indol-3-yl)methanone.

⁽¹¹⁾ AM-2201: 1-(5-fluoropentyl)-1*H*-indol-3-yl]-(naphthalen-1-yl)-methanone.

⁽¹²⁾ MDMB-CHMICA: methyl (2*S*)-2-[[1-(cyclohexylmethyl)-1*H*-indole-3-carbonyl]amino-3,3-dimethylbutanoate. MDMB-CHMICA was risk assessed by the Scientific Committee of the EMCDDA in July 2016.

⁽¹³⁾ 5F-APINACA: *N*-(adamantan-1-yl)-1-(5-fluoropentyl)-1*H*-indazole-3-carboxamide.

⁽¹⁴⁾ XLR-11: [1-(5-fluoropentyl)-1*H*-indole-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone.

Pharmacology

Data on the pharmacodynamic effects of AB-CHMINACA show that it is a potent and full agonist at the CB₁ receptor (i.e. activates the receptor) of the endocannabinoid system. These data show that AB-CHMINACA is 4 times more potent than JWH-018, which is a full agonist under international control. In addition, AB-CHMINACA can produce cannabinoid/THC-like effects at doses much lower than THC, which is a partial agonist. So far AB-CHMINACA has been identified as a partial agonist at the CB₂ receptor.

Data on the pharmacokinetics of AB-CHMINACA are limited to the identification of metabolites. So far, over 10 metabolites have been identified in humans. The pharmacological effects of these metabolites have not been investigated.

No studies were identified that have investigated the pharmacodynamics of AB-CHMINACA on other pharmacological targets.

Information from self-reported user experiences on the Internet have described an onset time of 1 to 5 minutes after smoking with duration of the effect for 1 to 2 hours. The assessment of such reports is problematic not least because users cannot confirm the actual substance or the amount used. In general, given the difficulties of collecting accurate self-reported data, it should be interpreted with caution.

Interactions with other substances, medicines, and other forms of interactions

No studies were identified that have investigated the potential interactions of AB-CHMINACA.

Psychological and behavioural effects

While there is limited data, the psychological and behavioural effects of AB-CHMINACA appear to share some similarities with cannabis, THC, and other synthetic cannabinoids. This includes: relaxation, euphoria, lethargy, confusion, anxiety, and fear, distorted perception of time, depersonalisation, hallucinations, paranoia, as well as dry mouth, bloodshot eyes, tachycardia, nausea, vomiting, and impaired motor performance. These effects appear to be much more pronounced and severe when compared to cannabis. In addition, psychotic episodes, as well as aggressive and violent behaviour, have also been reported.

Legitimate uses

AB-CHMINACA is used as an analytical reference material in clinical and forensic case work/investigations as well as scientific research. There is currently no information that suggests AB-CHMINACA is used for other legitimate purposes.

There are no reported uses of AB-CHMINACA as a component in industrial, cosmetic, or agricultural products. In addition, a search of the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) registered substances database hosted by the European Chemicals Agency (ECHA) using the available CAS Registry Numbers returned no hits.

There is no marketing authorisation (existing, on-going, or suspended) for AB-CHMINACA in the European Union or in the Member States that responded to the request for information, that was undertaken as part of the Joint Report process ⁽⁶⁾.

There is no information to suggest that AB-CHMINACA is currently used in the manufacture of a medicinal product in the European Union ⁽⁶⁾. However, in the absence of a database on the synthetic routes of all medicinal products it is not possible to confirm whether or not AB-CHMINACA is currently used in the manufacture of a medicinal product.

Chemical precursors that are used for the manufacture

The chemical precursors and the synthetic routes used to manufacture AB-CHMINACA are known from the literature. The potential precursors of AB-CHMINACA are: 1*H*-indole-2,3-dione, 1*H*-indazole-3-carboxylic acid, methyl or other alkyl 1*H*-indazole-3-carboxylic acid esters, L-valinamide (for synthesis of the (*S*)-enantiomer), and (bromomethyl)cyclohexane. Some of these are commercially available. It is important to note that L-valinamide is derived from inexpensive natural sources or produced by industrial fermentation. Since this reagent is used for the synthesis of the (*S*)-enantiomer, it can be speculated that this will be the form of AB-CHMINACA most likely to be encountered on the European market.

Commercially available domestic or industrial products which could be used for synthesis of AB-CHMINACA may contain potentially toxic substances, including heavy metals and organic solvents. Use of such products as reagents may result in serious toxic effects if the resultant impure product is consumed. The herbal material which is used as a basis for smoking mixtures may also contain toxicologically relevant substances (such as pesticides that could potentially be present in the plant material).

Health risks

Individual health risks

The assessment of individual health risks includes consideration of the acute and chronic toxicity of AB-CHMINACA, as well as its abuse liability and dependence potential. Similarities to, and differences from, other chemically or pharmacologically related substances should also be considered.

It is important to note that when interpreting information from acute intoxications and deaths as well as information from user websites, individuals may have used other pharmacologically active substances in addition to AB-CHMINACA. The presence of and/or interaction with other substances or pre-existing health conditions may account for some of the effects reported.

Some individuals may use AB-CHMINACA in combination with other drugs (either intentionally or unintentionally). AB-CHMINACA is typically encountered in combination with other substances in commercially branded 'legal high' products, and, in particular, with other synthetic cannabinoids. Analyses of various seized products have shown that the composition can vary significantly over geographical areas and time. Therefore, the users are unlikely to be aware of the substance(s) being ingested and doses used (by whatever route). This presents an inherent risk to the individual.

As synthetic cannabinoids such as AB-CHMINACA mimic the effects of THC, their effects appear to have some similarities with cannabis. This includes: relaxation, euphoria, lethargy, confusion, anxiety, and fear, distorted perception of time, depersonalisation, hallucinations, paranoia, as well as dry mouth, bloodshot eyes, tachycardia, nausea, vomiting, and impaired motor performance. In some cases, these effects appear to be much more pronounced and severe when compared to cannabis.

Severe and fatal poisonings have occurred with synthetic cannabinoids. This can include severe cardiovascular toxicity (including sudden death), severe central nervous system depression (such as rapid loss of consciousness/coma), respiratory depression, seizures and convulsions, hyperemesis, delirium, agitation, psychotic episodes, and aggressive and violent behaviour.

In addition, some of the features of poisoning—particularly loss of consciousness, respiratory depression, and behavioural effects—may place users at additional risks, such as choking on/aspirating vomit, drowning, falling, hypothermia as a result of falling unconscious outside in cold weather, and self-inflicted violence/injury. The aggressive and violent behaviours reported with synthetic cannabinoids may also place others at risk of injury.

The reasons for these more pronounced and severe effects, as well as severe and fatal poisoning, are poorly understood, but at least two factors are likely to be important: the high potency of the substances and the unintentionally high doses that users are exposed to.

Firstly, studies have found that many of the synthetic cannabinoids, including AB-CHMINACA, which are sold on the drug market, are much more potent and active, typically behaving as full agonist as compared to THC. This means that even at very small doses they can activate the CB₁ receptor much more strongly than THC.

Secondly, the process for making smoking mixtures (which are the most common way of using these substances) can lead to dangerous amounts of the substances in the products. This is because producers have to guess the amount of cannabinoids(s) to add, while the mixing process makes it difficult to dilute the substances sufficiently and distribute them consistently throughout the plant material. This can result both in products that contain toxic amounts of the substances in general, as well as products where the cannabinoids are clumped together forming highly concentrated pockets within the plant material. These issues are made worse as the products are typically smoked allowing the substances to be rapidly absorbed into the systemic circulation (bloodstream) and to reach the brain.

The combination of these two factors makes it difficult for users to control the dose that they are exposed to and can lead them to rapidly administer a toxic dose unintentionally. Accounts from patients and people who witness poisonings involving smoking mixtures suggest that in some cases a small number of puffs from a cigarette have been sufficient to cause severe and fatal acute poisoning.

Currently there is no approved antidote to poisoning caused by synthetic cannabinoids.

Overall, poisoning with synthetic cannabinoids may be made worse when other drugs, especially central nervous system depressants (such as alcohol, opioids, and sedative/hypnotics), are used at the same time.

Acute toxicity

The acute toxicity of AB-CHMINACA and/or its metabolites have not been studied in non-clinical and clinical studies. In addition to the acute intoxications and deaths reported to the EMCDDA (discussed below), cases of acute intoxications and deaths have also been reported in the literature. In general, the available data suggests that intoxication/poisoning with AB-CHMINACA appears to be similar to other synthetic cannabinoids.

Acute intoxications

A total of 7 acute intoxications with confirmed exposure to AB-CHMINACA were reported to the EMCDDA 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 2 out of the remaining 4 cases, no other substances were detected. In the other 2 cases other substances detected included synthetic cannabinoids and an opioid. In all 4 cases, the clinical features of poisoning appeared to be similar to those reported for other synthetic cannabinoids.

Deaths

A total of 31 deaths with confirmed exposure to AB-CHMINACA were reported to the EMCDDA by Croatia (1 case), Germany (4), Hungary (11), Poland (2), Sweden (5), and the United Kingdom (8). In all cases, exposure to AB-CHMINACA (or an associated metabolite in one case) was analytically confirmed from post-mortem samples.

The deaths occurred between 2014 and 2017. Demographic data were available for all but 6 deaths and involved 24 males (77%) and 1 female (3%). The mean age of the males was 30 years (median 27) and ranged from 16 to 66 years. The female was 38 years old.

Cause of death and toxicological significance

A cause of death was reported in 22 cases, and, in at least 9 deaths, AB-CHMINACA was either the cause of death or is likely to have contributed to death (even in presence of other substances); other substances were detected in 25 cases. AB-CHMINACA was the only drug present in 6 deaths based on additional toxicological information, where available.

AB-CHMINACA was quantified in 11 cases. Post-mortem blood concentrations between 0.32 and 12 ng/mL (median 3.70 ng/mL), or equivalent, were recorded. However, post-mortem blood concentrations cannot necessarily be used to determine a "fatal" concentration. In the majority of circumstances involving synthetic cannabinoids, the mere presence of the drug is of significance whether concentration has been determined or not, especially in situations of poly-drug use and the varying circumstances in which they are used.

A range of other substances were detected in the deaths, including: alcohol, cannabinoids, antidepressants, antipsychotics, cocaine, zopiclone, synthetic cathinones, opiates/opioids (morphine, buprenorphine, acetylfentanyl, tramadol, methadone, codeine) and benzodiazepines. Other synthetic cannabinoids and/or metabolites were detected in 6 of the deaths, including: MDMB-CHMICA, 5F-MDMB-PINACA, ADB-CHMINACA, FUB-AKB-48, 5F-PB-22, and UR-144.

Overall, while other substances may have contributed some toxicity, the potent nature of AB-CHMINACA means the primary toxic contribution could be attributed to the drug and death may not

have occurred if AB-CHMINACA had not been used. However, in the cases where multiple synthetic cannabinoids were present, it is not necessarily possible or appropriate to identify AB-CHMINACA as the primary synthetic cannabinoid that may have produced toxicity, but a synergistic effect is likely nonetheless. Sufficient case data were available in 29 of the 31 deaths. An assessment of the toxicological significance score (TSS) ⁽¹⁵⁾ incorporating the above considerations in the deaths, showed that AB-CHMINACA had a TSS value of 3 (high) in 18 deaths (where it was cited as the cause of death or is likely to have contributed to death following assessment). In the remaining 11 deaths, there was an alternative cause of death (such as hanging, drowning, stabbing, other drug overdose, or other physiological cause) (TSS value of 1, low). However, there is a possibility that use of AB-CHMINACA could have contributed to some of these situations/causes but there was insufficient circumstance and other information to allow this attribution.

Circumstances of death

There was a lack of information regarding any symptoms experienced by the deceased prior to death in the majority of cases, but, in one case, the deceased was described to have vomited and became hypothermic and unconscious. Where information was known, in the majority of instances the individuals were found dead, predominantly in a home environment (either their own or a friend's), or outside; 2 of the deaths occurred in prison. Consequently, it was not possible to identify or evaluate ante-mortem symptoms (especially in relation to acute intoxication) in these cases.

Ability to operate machinery and drive

No studies of the effects of AB-CHMINACA on the ability to drive and operate machines have been performed. However, it has been reported that intoxications caused by a range of synthetic cannabinoids, including AB-CHMINACA, significantly impair the mental and physical ability that is required to drive and operate machines.

Chronic toxicity

No studies were identified that investigated the chronic health effects of AB-CHMINACA and/or its metabolites.

Abuse liability and dependence potential

There have been no studies that have investigated the abuse liability and dependence potential of AB-CHMINACA. Given what is currently known about the pharmacology of AB-CHMINACA, including some similarities to THC, it is reasonable to consider that the substance may have both a potential for abuse and dependence. Further research will be required in order to determine such effects.

Public health risks

The public health risks associated with AB-CHMINACA may be categorised in terms of patterns of use (extent, frequency, route of administration, etc.); availability and quality of the drug; information, availability, and levels of knowledge amongst users; and, negative health consequences. Detailed information, including data on sporadic versus chronic use, that allow for a determination of public health risks associated with AB-CHMINACA are unavailable.

⁽¹⁵⁾ Elliott, S., Sedefov, R. and Evans-Brown, M. (2017), 'Assessing the toxicological significance of new psychoactive substances in fatalities', *Drug Testing and Analysis*. <https://doi.org/10.1002/dta.2225>

Extent, frequency, and patterns of use

The available data suggest that AB-CHMINACA is typically sold as commercial branded 'legal high' smoking mixtures in head shops as well as on the Internet as 'legal' replacements for cannabis. It may also be sold directly on the illicit drug market. Overall, the available information does not suggest widespread use of the substance.

No surveys were identified that have investigated the prevalence of AB-CHMINACA use in the general population or in specific user groups.

Because of the variability in the composition of smoking mixtures, and the fact that the ingredients are not typically disclosed, most users will be unaware that they are using AB-CHMINACA. As a result, the prevalence of use should be considered in the wider context of the prevalence of use of herbal smoking mixtures (sometimes referred to as 'spice').

The use of herbal smoking mixtures has been studied in some European countries in general population surveys and in specific populations such as students, 'clubbers' and/or internet users. The results of these surveys are not comparable as they use different methodology and samples, but, overall, they indicate generally low prevalence levels in these groups.

It is reasonable to assume that AB-CHMINACA may be sought by those looking for 'legal' substitutes for cannabis. This includes individuals subject to drug testing (such as drivers, prisoners, those in drug treatment, and those subject to workplace drug testing), as commonly used drug tests may be unable to detect the compounds.

In addition, reports suggest that in some areas, high risk drug users and other vulnerable groups, such as the homeless and prisoners, may specifically seek out synthetic cannabinoids because they have a reputation for causing profound intoxication, they can be cheap, and are easy to smuggle.

Availability and quality on the market

Since February 2014, when it was detected first in Latvia, AB-CHMINACA has been detected in a total of 24 Member States, as well as Turkey and Norway. As the substance is not routinely screened for, detections of AB-CHMINACA may be under-reported.

AB-CHMINACA is sold online either as commercial 'legal high' smoking mixtures or as a powder. The presence of AB-CHMINACA (or any other synthetic cannabinoid) is not typically disclosed on the packaging/advertising of smoking mixtures.

Due to the high potency of some synthetic cannabinoids, the amount of powder needed for each packet can be in the order of tens of milligrams. This means that each kilogram of bulk powder may produce thousands of packets of 'legal highs' (Section 6).

Detailed information with regards to route-specific by-products produced during the synthesis of AB-CHMINACA is not available. Quantitative information on the AB-CHMINACA in the seized samples is limited. In herbal material, AB-CHMINACA was frequently found with other substances, and, in particular, synthetic cannabinoids.

As discussed above, in general, smoking mixtures appear to pose a high risk of poisoning/acute toxicity because of the high potency of synthetic cannabinoids, the manufacturing process used, and the route of administration.

Characteristics and behaviour of users

Information on the characteristics and behaviour of users of AB-CHMINACA is limited.

'Legal high' products containing AB-CHMINACA are marketed as 'legal' replacements to cannabis. It is therefore likely that a range of different cannabis users would be interested in these products. The available data suggests that AB-CHMINACA is used by cannabis users, including those who are regularly subjected to drug testing procedures. To a lesser degree it is also used by psychonaut-type users.

In addition, and, of particular note, is that in some settings, synthetic cannabinoids are increasingly used by high risk drug users and other vulnerable groups, such as the homeless and prisoners. In at least some cases, these users are specifically seeking out synthetic cannabinoids because the substances have developed a reputation for causing profound intoxication, they can be cheap, and are easy to smuggle.

In most cases, it appears that AB-CHMINACA is not specifically sought after by users who will typically purchase it unknowingly as part of a smoking mixture product.

Nature and extent of health consequences

Information on the nature and extent of health consequences are mostly limited to those discussed in relation to individual health risks.

The high potency of the synthetic cannabinoids, coupled to the unintentionally high doses that users are exposed to, is also responsible for outbreaks of mass poisonings involving smoking mixtures. Such outbreaks have ranged in size from four or five to over 800 victims, including deaths. While many of the outbreaks that have been reported so far are from the United States, they have also occurred in Russia and Europe. AB-CHMINACA has been involved in a number of outbreaks in the United States. Mass poisonings can rapidly overwhelm emergency responders and other local healthcare systems.

Unknown to users, synthetic cannabinoids have also been sold as ecstasy/MDMA and other illicit drugs. In some cases, this has led to severe poisoning. Opioids have also been identified in smoking mixtures. While the overall number of detections appears to be relatively small, it could pose a risk of severe opioid poisoning, including life-threatening respiratory depression especially in individuals with no tolerance to opioids. Users of smoking mixtures will be unaware of this risk.

Long-term consequences of use

While there is limited data for AB-CHMINACA, the long-term consequences of use might share similarities to cannabis and other synthetic cannabinoids. This may include dependence.

Conditions under which the substance is obtained and used

There is limited data on the conditions under which AB-CHMINACA is obtained and used. Sources appear to include internet retailers, physical shops, friends and other acquaintances, and street-level drug dealers. As highlighted, most users will be unaware that they have sourced and used AB-CHMINACA as they will be using smoking mixtures. The available data suggests that AB-CHMINACA is used in similar environments to cannabis, including the home, other recreational settings, and prisons.

Social risks

The available data suggests that the acute behavioural effects of AB-CHMINACA bear some similarities to cannabis but are more pronounced and severe.

In addition, and, of particular note, is that in some settings, synthetic cannabinoids are increasingly used by high risk drug users and other vulnerable groups, such as the homeless and prisoners. In at least some cases, these users are specifically seeking out synthetic cannabinoids because the substances have developed a reputation for causing profound intoxication, they can be cheap and are easy to smuggle. Reports suggest that this has exacerbated existing health and social problems for these vulnerable groups, as well as creating new ones.

Individual social risks

While there is no specific information on whether the use of AB-CHMINACA causes individual social risks, any such risks may have some similarities with those associated with cannabis and other synthetic cannabinoids. These may impact on education or career, family or other personal and social relationships, and may result in marginalisation.

Possible effects on direct social environment (e.g. neglect of family, violence)

While there is no specific information on the possible effects of AB-CHMINACA on the direct social environment, the behavioural effects of synthetic cannabinoids include reports of aggressive and violent behaviour. This may place users and others at risk of injury.

Possible effects on society as a whole (public order and safety, acquisitive crime)

While there is no specific information on the possible effects of AB-CHMINACA on society as a whole, as noted, the behavioural effects of synthetic cannabinoids include reports of aggressive and violent behaviour. In particular, concern was expressed in this regard to use in certain environments such as prisons and psychiatric institutions. In addition, the detection of AB-CHMINACA in cases of suspected driving under the influence of drugs indicates a potential for a wider risk to public safety.

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.

Due to the lack of data, it is not possible at this time to estimate the social risk associated with the trafficking and distribution of AB-CHMINACA.

Economic costs

Due to the lack of data, it is not possible at this time to estimate whether AB-CHMINACA is associated with greater healthcare costs than other drugs.

Possible appeal to specific population groups

While no specific examples are available on the possible appeal of AB-CHMINACA to specific user groups, it is reasonable to assume AB-CHMINACA may be sought after by those looking for 'legal'

substitutes for cannabis. This includes individuals subject to drug testing (such as drivers, prisoners, those in drug treatment, and those subject to workplace drug testing), as commonly used drug tests may be unable to detect the compounds.

In addition, reports suggest that in some areas, high risk drug users and other vulnerable groups, such as the homeless and prisoners, may specifically seek out synthetic cannabinoids because they have a reputation for causing profound intoxication, they can be cheap, and are easy to smuggle.

Information on manufacturing, trafficking, distribution, and the level of involvement of organised crime

There is no specific information to suggest the involvement of organised crime or established criminal groups in the manufacture, distribution, and supply of AB-CHMINACA.

No information has been received by Europol indicating synthesis of AB-CHMINACA within the European Union. Information reported to the EMCDDA and Europol indicates that chemical companies based in China may be one source of AB-CHMINACA, as well as of other synthetic cannabinoids. Seizures, particularly of bulk powders of synthetic cannabinoids are frequently reported to have occurred at international European airports and to have been shipped by such companies.

For AB-CHMINACA, single seizures of powders in excess of 1 kg were reported by Luxembourg, France and Spain. When known, the country of origin indicated was China. In a seizure made at Roissy Airport in France, the origin of the seizure was reported as China and the final destination was Austria. In a seizure made at Madrid-Barajas Airport in Spain, the origin was also reported as China and the final destination was France.

Powders of synthetic cannabinoids, including AB-CHMINACA, are imported into the European Union where they are typically processed and packaged into commercial smoking mixtures or sold as powder. There are indications of a significant trade in synthetic cannabinoid products within Europe, with customs and police in many countries making regular seizures of such products, including herbal smoking products containing AB-CHMINACA.

The largest single seizure of AB-CHMINACA in herbal material was reported by Spain, as part of a law enforcement operation. This large-scale operation was carried out in Alicante in March 2016. A total of 145,157 packages each containing between 1 and 3 grams of herbal material (that also contained the synthetic cannabinoids AMB-FUB and AB-FUBINACA) and 2 bags (of 2 kg each, that also contained AMB-FUB) were seized.

AB-CHMINACA has been available on the European drug market since at least February 2014. A total of 24 Member States (Austria, Belgium, Bulgaria, Croatia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Luxembourg, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom), Turkey, and Norway, have reported detections of AB-CHMINACA. Information reported to the EMCDDA and Europol indicates that AB-CHMINACA has been typically seized as herbal material (approximately 190 kg; 150 kg of which reported by Turkey) and powder form (approximately 44 kg).

The available data suggests that herbal smoking mixtures containing AB-CHMINACA are being sold directly on the illicit market. The United Kingdom and Lithuania reported seizures of AB-CHMINACA which occurred in prisons or other custodial settings.

Information on any assessment in the United Nations system

The World Health Organization (WHO) 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. In 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 in November 2017.

Description of the control measures that are applicable in the Member States

Eighteen Member States (Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Italy, Latvia, Lithuania, Luxembourg, Slovakia, Slovenia, Sweden, and the United Kingdom) and Turkey reported that AB-CHMINACA is controlled under drug control legislation.

- In Bulgaria, AB-CHMINACA was controlled in 2016 according to the 'Regulation on the classification of plants and substances as narcotics'.
- In Croatia, AB-CHMINACA is controlled within the 'List of drugs, psychotropic substances, plants used to produce drugs and substances that can be used in the production of drugs', Official Gazette no. 10/16.
- In Cyprus, AB-CHMINACA is controlled by a generic legislation, implemented since 2012 in the 'Existing Law on Narcotic Drugs and Psychotropic Substances'.
- In the Czech Republic, AB-CHMINACA is controlled since March 2017.
- In Denmark, AB-CHMINACA is controlled as of 15 June 2017 by an amendment of the Executive Order on Controlled Substances.
- In Estonia, AB-CHMINACA is controlled as of 15 December 2014.
- In Finland, AB-CHMINACA is controlled as a narcotic drug since 28 September 2015.
- In France, AB-CHMINACA is controlled since 31 March 2017.
- In Germany, AB-CHMINACA is included since 22 May 2015 in schedule II 'narcotics eligible for trade but not for medical prescription'.
- In Hungary, AB-CHMINACA is included, as of 1 January 2015, in Schedule A of Act XXV on Medicinal Products of 1998 and on Schedule B of Government Decree 66/2012.
- In Italy, AB-CHMINACA is included in Table 1 of the Ministerial Decree 309/90 of 1 August 2016.
- In Latvia, AB-CHMINACA is included in the Cabinet Regulation N 847 'Regulations regarding Narcotic Substances, Psychotropic Substances and Precursors to be Controlled in Latvia' and the law 'On the Procedures for the Coming into force and Application of the Criminal Law'.

- In Lithuania, AB-CHMINACA is subjected to control measures by The Republic of Lithuania Minister of Health Order No V-267 (21/02/2014) 'On the amendment of the Ministry of Health of the Republic of Lithuania Order No. 5 of 6 January 2000'.
- In Luxembourg, AB-CHMINACA is controlled by way of generic definition by the Grand-ducal decree of 20/04/2009.
- In Slovakia, AB-CHMINACA is included in Regulation no.121/2015 Coll. as of 1 October 2015.
- In Slovenia, AB-CHMINACA is included the 'Decree on the Scheduling of Illicit Drugs' that was published in Official Gazette No. 22/2016, on 25 March 2016.
- In Sweden, AB-CHMINACA is regulated under the Act on the Prohibition of Certain Goods Dangerous to Health, as of 27 May 2014.
- In the United Kingdom, AB-CHMINACA is controlled by way of generic definition under the 1971 Misuse of Drugs Act.
- In Turkey, AB-CHMINACA was included in Law No.2313 on the Control of Drugs, which was published in the Official Gazette on 2 October 2014.

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

- In Austria, AB-CHMINACA is covered by the Austrian Act on New Psychoactive substances.
- In Belgium, AB-CHMINACA is controlled by way of generic definition.
- In Poland, AB-CHMINACA is included in the regulation of the Minister of Health on the list of new psychoactive substances. Article 44b of the Act of counteracting drug addiction bans manufacturing or introducing new psychoactive substances to trade.

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

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

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 AB-CHMINACA to control measures and criminal penalties, as provided for under their legislation, by virtue of their obligations under the Convention on Psychotropic Substances, 1971.

AB-CHMINACA was controlled in China in January 2015. This control measure may at least deter the open manufacture and sale of this substance by chemical companies in this country, which are linked to the supply of the substance in Europe.

There are no studies on the possible consequences of such control measures on AB-CHMINACA. 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 AB-CHMINACA and hence the further expansion of the current open trade in this substance.
- A health consequence that might result from this control option is the benefit brought about by the presumed reduction in availability and use.
- This control option could facilitate the detection, seizure and monitoring of AB-CHMINACA related to its unlawful manufacture, trafficking and use. In so doing, it could facilitate 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 and social risks.
- This control option could create an illicit market in AB-CHMINACA with the increased risk of associated criminal activity, including the involvement of organised crime.
- This control option could impact on both the quality/purity and price of any AB-CHMINACA still available on the illicit market. The extent to which this will impact on public health, criminality, or levels of use, is difficult to predict.
- It is difficult to predict the impact of this control option on current or future research by the pharmaceutical or chemical industries.
- In order to examine the consequences of control, the Committee wishes to note that it will be important to monitor for the presence of AB-CHMINACA on the market post-control, should this control option be pursued.
- 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 restricting the importation and supply of the substance as some Member States have already done.

Conclusion

N-(1-Amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide (AB-CHMINACA) is an indazole-based synthetic cannabinoid receptor agonist. Information on the pharmacology of AB-CHMINACA suggests that it is a potent and full agonist at the CB₁ receptor. It shows similar effects to THC, but with additional life-threatening toxicity. The high potency of AB-CHMINACA and the large and variable content of the substance in smoking mixtures constitute a high risk of poisoning.

AB-CHMINACA is often sold as a 'legal' replacement for cannabis. It is typically administered by smoking a herbal mixture that is either from a ready-to-use commercial 'legal high' product, or, less commonly, that is self-prepared. Similar to herbal cannabis, the mixture is usually prepared for smoking as a hand-rolled cigarette ('joint') but it may also be smoked in a pipe or 'bong'. AB-CHMINACA can also be inhaled using an e-cigarette or other vaporisation device.

AB-CHMINACA has been available on the drug market in the European Union since at least February 2014 and has been detected in 24 Member States, Turkey, and Norway. It is sold online as commercially branded 'legal high' products and powders. It may also be sold directly on the illicit drug market.

The available data suggests that AB-CHMINACA is used by cannabis users, by those who are regularly subjected to drug testing procedures (including those in prison), and by 'psychonauts'. It may also be used by high risk drug users and other marginalised groups (such as prisoners), as synthetic cannabinoids have gained a reputation for causing profound intoxication, they can be cheap, and are easy to smuggle. However, no further information on the size and demand and the characteristics of these groups of people is available.

Seven acute intoxications with confirmed exposure to AB-CHMINACA have been reported by 4 Member States. Where known, the features of the poisoning were similar to those found with other synthetic cannabinoids.

Thirty-one deaths with confirmed exposure to AB-CHMINACA have been reported by 6 Member States. In at least 9 of these cases, AB-CHMINACA was either the cause of death or is likely to have contributed to the death.

Due to the nature of AB-CHMINACA, both non-fatal intoxications and deaths are likely to be under-detected and under-reported.

There is currently no approved antidote to poisoning caused by synthetic cannabinoids such as AB-CHMINACA.

Reports suggest a possibility for violence and aggression following use of synthetic cannabinoids. In particular, concern was expressed in this regard to use in certain environments, such as prisons and psychiatric institutions. In addition, the detection of AB-CHMINACA in cases of suspected driving under the influence of drugs indicates a potential for a wider risk to public safety.

There is no specific information on the involvement of organised crime in the manufacture, distribution (trafficking), and supply within the European Union. There is limited information on the chemical precursors and the synthetic routes used to manufacture the AB-CHMINACA detected within the European Union. The largest single seizure of AB-CHMINACA was in Luxembourg in 2015, when 4.8

kg of powder that was in transit was seized by customs. During 2017, AB-CHMINACA continued to be seized by law enforcement within the European Union.

AB-CHMINACA has no recognized human or veterinary medical use in the European Union, nor, it appears, elsewhere. There are no indications that AB-CHMINACA may be used for any other purpose aside from as an analytical reference standard and in scientific research.

AB-CHMINACA is not listed for control in the Single Convention on Narcotic Drugs, 1961, nor in the Convention on Psychotropic Substances, 1971. AB-CHMINACA is currently under assessment by the United Nations system.

Eighteen Member States and Turkey control AB-CHMINACA under drug control legislation. Three Member States and Norway control AB-CHMINACA under other legislation.

As for any new psychoactive substance, many of the questions related to AB-CHMINACA that are posed by the lack of data on the risks to individual health, risks to public health, and social risks, could be answered through further research. Areas where additional information would be important include studies on: rationale for use, prevalence and patterns of use (including targeted studies that examine user groups and risk behaviours); the market; chemical profiling; complete pharmacological profiling; metabolic pathways; behavioural effects; acute and chronic toxicity; the potential interaction between AB-CHMINACA and other substances; dependence and abuse potential; and the public health risks associated with its use.

The Committee notes that a decision to control AB-CHMINACA has the potential to bring with it both intended and unintended consequences. Potential intended consequences include reduced levels of availability and ultimately use. This may reduce the health and social risks arising from the use of AB-CHMINACA. It is important to recognise that a potential unintended consequence of control may be the manufacture and availability of other substances. Indeed, pharmacologically analogous substances that may replace AB-CHMINACA are already being sold on the drug market. 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. Should control measures be adopted, they should be accompanied by the gathering and dissemination of accurate information on AB-CHMINACA to users, practitioners, policy makers, and decision makers.

ANNEX 1

Technical report on *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide (AB-CHMINACA)

Introduction

Synthetic cannabinoid receptor agonists (synthetic cannabinoids), such as AB-CHMINACA, are a group of substances that mimic the effects of tetrahydrocannabinol (THC), which is a substance found in cannabis ⁽¹⁾. THC is responsible for many of the psychoactive effects of cannabis which give that feeling of being 'stoned' (or 'high') (Gaoni et al, 1964; Huestis et al., 2001; Pertwee, 2014). THC causes these effects by activating a receptor in the brain called the *cannabinoid receptor type 1* (CB₁ receptor) (Huestis et al., 2001; Pertwee, 2005a). This receptor is part of a signalling system in the body called the endocannabinoid system, which helps regulate, among other things, behaviour, mood, pain, appetite, sleep, and the immune system (Pertwee, 2015) ⁽²⁾. Because synthetic cannabinoids activate the CB₁ receptor in a similar way to THC, some of their effects appear to be similar to cannabis. Most prominently, they are able to create a feeling of being 'stoned'.

Synthetic cannabinoids were originally developed by scientists to study the endocannabinoid system, as well as provide insights into disease, and to help make new medicines (Pertwee, 2005a; Pertwee, 2005b; Pertwee, 2015; Reggio, 2009). From around 2006, they began to appear in Europe in products called 'Spice' that were sold as 'legal' replacements to cannabis (Auwärter et al., 2009; EMCDDA, 2009; Jack, 2009). In these products, synthetic cannabinoids had been mixed with plant (herbal) material which could then be smoked as cigarettes ('joints') (Auwärter et al., 2009; EMCDDA, 2009; EMCDDA, 2017a; Jack, 2009). Such products have been referred to by a variety of names, including 'herbal smoking mixtures', 'herbal incense', 'Spice', 'K2', and 'synthetic cannabis'. Since 2008, almost 180 synthetic cannabinoids have been identified on the drug market in hundreds of different products. They are the largest group of substances that are monitored by the EMCDDA through the European Union Early Warning System on New Psychoactive Substances (EU Early Warning System) (EMCDDA, 2017b).

In accordance with Article 5 of the *Council Decision 2005/387/JHA on the information exchange, risk-assessment and control of new psychoactive substances* ⁽³⁾, on 25 April 2017, the EMCDDA and Europol launched the Joint Report procedure for *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide (AB-CHMINACA) on the basis of data reported by the Member States to the EU Early Warning System in accordance with Article 4 of the Council Decision. The information collection process for the Joint Report was completed in June 2017. The report was submitted to the Institutions of the European Union in July 2017 (EMCDDA, 2017c). In accordance

⁽¹⁾ (-)-*trans*- Δ^9 -tetrahydrocannabinol.

⁽²⁾ The endocannabinoid system helps regulate a large number functions in the body. It consists of the cannabinoid CB₁ and CB₂ receptors, the endocannabinoids (such as anandamide) which act as endogenous agonists for these receptors, and the processes responsible for endocannabinoid biosynthesis, cellular uptake, and metabolism. Important exogenous agonists for the cannabinoid receptors are (-)-*trans*- Δ^9 -tetrahydrocannabinol (THC) which is the major active substance in cannabis, and the synthetic cannabinoids found in legal high-type smoking mixtures. Data from laboratory studies suggests that the endocannabinoid system plays an important protective role. For example, in response to some diseases the body increases the amount of endocannabinoids it produces which can reduce unwanted symptoms or slow disease progression (Pertwee, 2005a; Pertwee, 2005b; Pertwee, 2015).

⁽³⁾ OJ L 127, 20.5.2005, p. 32.

with Article 6 of the Council Decision, on 14 September 2017, the Council of the European Union requested that a risk assessment on AB-CHMINACA should be carried out by the extended Scientific Committee of the EMCDDA.

In order to prepare for a risk assessment that has been convened under the Council Decision and to facilitate the risk assessment process, the EMCDDA is responsible for the collection and analysis of data on the substance to be assessed as well as drafting a technical report. This technical report has been prepared for the risk assessment AB-CHMINACA that will be held at the EMCDDA premises in Lisbon on 7 November 2017.

Some of the sections in this report were prepared under EMCDDA contracts (ref. CT.16.SAT.0101.1.0 and CT.17.SAT.0110.1.0).

Data sources

The information in this technical report is derived from:

- data reported by the Member States, Turkey and Norway to the EMCDDA and Europol in accordance with the Council Decision (EMCDDA, 2017c); and,
- data collected through systematic searches of open source information, including the scientific and medical literature, patents, official reports, grey literature, Internet drug discussion forums and related websites, and online vendors selling AB-CHMINACA.

Search strategy

Literature searches used both chemical structure and text queries in online databases; searches were conducted in August 2017. The retrieved publications were then reviewed for additional relevant references (snowballing technique).

Textual searches were conducted online in *PubMed* (National Center for Biotechnology Information), Web of Science™ (Thomson Reuters), and in popular English-language drug forums. The search term used was: 'AB-CHMINACA'. Medline and Google Scholar were searched for 'AB-CHMINACA' (with and without hyphen) and the IUPAC names of this compound stated in this document. In addition, exact chemical structure-based searches were done in SciFinder (American Chemical Society, Chemical Abstract Service) and Reaxys (Elsevier). Google and specific drug user discussion forums and related websites (such as Bluelight, Eve and Rave, and Erowid) were searched for the terms: 'AB-CHMINACA' alone or in combination with 'buy', 'shop', 'research chemical', 'synthetic cannabinoid', 'dosing', 'intoxication', 'kaufen', 'räuchermischung', 'powder', 'synthesis'. Additionally, colleagues within the scientific network of the authors were contacted to obtain information.

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

Note

It is important to note that when interpreting the information on self-reported user experiences in this report, it is not possible to confirm the specific substance(s) that have been claimed to be used; similarly it is also not possible to confirm the strength, purity, dose/amount, etc., used. Moreover, the actual composition of the substance/product claimed to be used may differ over time and different geographical areas. In addition, the information provided on user websites may not necessarily be representative of other users of AB-CHMINACA and should be regarded as illustrative only. In

general, given the difficulties of collecting accurate self-reported data, it should be interpreted with caution.

Report prepared by

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Section A. Physical, chemical, pharmaceutical and pharmacological information

A1. Physical, chemical, and pharmaceutical information

A1.1. Physical and chemical description

Chemical description and names

N-(1-Amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide, also known as AB-CHMINACA (Figure 1) is a synthetic cannabinoid receptor agonist (synthetic cannabinoid). The common name for the substance is derived after its structural features ⁽⁷⁾: a methyl amino butanone linked group (AB), a cyclohexylmethyl tail (CHM), an indazole core (INA) and a carboxamide linker (CA).

AB-CHMINACA contains a stereogenic centre and therefore two possible enantiomers may exist, (*R*)- and (*S*)-AB-CHMINACA. (*S*)-AB-CHMINACA was originally described in a patent application by Pfizer Inc. and published in 2009 (compound 21) (Buchler et al., 2009). It is worth noting that the compounds described in the patent literature only show the (*S*)-configuration (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. However, there is no representative information on the enantiomeric composition of the samples of AB-CHMINACA detected within the European Union.

AB-CHMINACA was first reported to the EMCDDA in 2014 (Section C).

AB-CHMINACA contains an indazole core, which is a common structural feature in many of the synthetic cannabinoids monitored by the EMCDDA, such as ADB-CHMINACA (Figure 1). Five synthetic cannabinoids have been recently controlled under Schedule II of the United Nations Convention on Psychotropic Substances, 1971: JWH-018 ⁽⁸⁾, AM-2201 ⁽⁹⁾, MDMB-CHMICA ⁽¹⁰⁾, 5F-APINACA (5F-AKB-48) ⁽¹¹⁾ and XLR-11 ⁽¹²⁾. Other synthetic cannabinoids, including ADB-CHMINACA ⁽¹³⁾ (EMCDDA, 2017d), 5F-MDMB-PINACA (5F-ADB) ⁽¹⁴⁾ (EMCDDA, 2017e), and CUMYL-4CN-BINACA ⁽¹⁵⁾ (EMCDDA, 2017f) (Figure 1), have also been the subjects of Joint Reports by the EMCDDA and Europol.

⁽⁷⁾ 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.

⁽⁸⁾ JWH-018: (Naphthalen-1-yl)(1-pentyl-1*H*-indol-3-yl)methanone.

⁽⁹⁾ AM-2201: [1-(5-Fluoropentyl)-1*H*-indole-3-yl](naphthalen-1-yl)methanone.

⁽¹⁰⁾ MDMB-CHMICA: Methyl (2*S*)-2-[[1-(cyclohexylmethyl)-1*H*-indole-3-carbonyl]amino]-3,3-dimethylbutanoate.

⁽¹¹⁾ 5F-APINACA: *N*-(adamantan-1-yl)-1-(5-fluoropentyl)-1*H*-indazole-3-carboxamide.

⁽¹²⁾ XLR-11: [1-(5-Fluoropentyl)-1*H*-indole-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone.

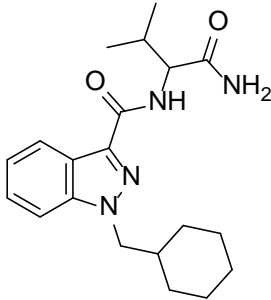
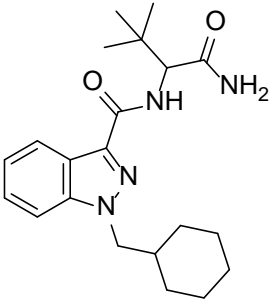
⁽¹³⁾ ADB-CHMINACA: *N*-[1-Amino-3,3-dimethyl-1-oxobutan-2-yl]-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide.

⁽¹⁴⁾ 5F-MDMB-PINACA (5F-ADB): Methyl (2*S*)-2-[[1-(5-fluoropentyl)-1*H*-indazole-3-carbonyl]amino]-3,3-dimethylbutanoate.

⁽¹⁵⁾ CUMYL-4CN-BINACA: 1-(4-Cyanobutyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide.

FIGURE 1

The molecular structure, molecular formula and molecular mass of AB-CHMINACA (left) and ADB-CHMINACA (right).

	
C ₂₀ H ₂₈ N ₄ O ₂	C ₂₁ H ₃₀ N ₄ O ₂
356.47 g/mol	370.50 g/mol

Names and other identifiers

Systematic International Union of Pure and Applied Chemistry (IUPAC) names:

N-(1-Amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide (racemate)

Chemical Abstract name:

N-[1-(Aminocarbonyl)-2-methylpropyl]-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide (racemate);

N-[(2*S*)-1-Amino-3-methyl-1-oxobutan-2-yl]-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide ((*S*)-enantiomer);

N-[(1*S*)-1-(Aminocarbonyl)-2-methylpropyl]-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide ((*S*)-enantiomer)

Other names:

N-[(2*S*)-1-Amino-3-methyl-1-oxo-2-butanyl]-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide ((*S*)-enantiomer)

Chemical Abstract Service Registry Numbers (CAS RNs) ⁽¹⁶⁾:

1805788-79-7: racemate

1185887-21-1: ((*S*)-enantiomer)

⁽¹⁶⁾ 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.

*PubChem SID:*70969900 (racemate) ⁽¹⁷⁾*IUPAC International Chemical Identifier Key (InChI Key)*⁽¹⁸⁾:

KJNZIEGLNLCWTQ-UHFFFAOYSA-N (racemate)

KJNZIEGLNLCWTQ-QGZVFWFLSA-N ((R)-enantiomer)

KJNZIEGLNLCWTQ-KRWDZBQOSA-N ((S)-enantiomer);

SMILES ⁽¹⁹⁾:CC(C)C(C(=O)N)NC(=O)c1c2ccccc2n(n1)CC3CCCCC3 (racemate)[H][C@@](C(C)C)(C(=O)N)NC(=O)c1c2ccccc2n(n1)CC3CCCCC3 ((R)-enantiomer)CC(C)[C@H](NC(=O)c1nn(CC2CCCCC2)c3ccccc13)C(N)=O ((S)-enantiomer)*Common names:*

AB-CHMINACA

Street names:

'Spice', 'K2', 'legal weed', 'synthetic cannabis', 'herbal incense'

AB-CHMINACA has been detected in herbal smoking mixtures bought from vendors on the surface web as part of the EU project 'SPICE Profiling' project (JUST/2013/ISEC/DRUGS/AG/6421) (Moosmann et al., 2017).

These products bore invented names such as: 2012, After Party, AK 47, 24 Karat Gold, AK-47 Gelb, Aliens, Armageddon, Astro, Aura Core, Aura Sniper, Bad Monkey, Barely legal, Be Happy, Beach Party, Big Party, Bionic Sphere, Black Diamonds, Blaze, Bonzai, Bonzai 2.0, Bonzai Banana, Bonzai Cherry, Bonzai Citrus, Bonzai DNS, Bonzai Summerboost, Bonzai Winterboost neu, Bonzai Winterboost, Brazil Gold, British Blend, Buzzooka, Caramba, Cherry-Apple, Citrus Bomb, Citrus Monster, Couchtrip, Couchtrip Strawberry, Dark Night, Denim, Desert, Dimension 8, Dragon Fire, E-Liquid Apfel, E-Liquid Vanille, Explosion, Flight Risk, G20, Galaxy, Galaxy "2", Gangsta, Geeked up, Gorby Mix, Green Giant, Green Leaves, Hafnium, Hammer Head, Hard Play, Hausmarke, Head Crash, Head Trip "Premium-Produkt", Herbal Tank, Hexen Meister, High School, Holy Shit, Jamaican Gold Extreme, Jamaican Gold Extrime, Joker, Kidz, Magic, Mandala, Maui, Moonlight, Namifu, New Bonzai Citrus, New Yama, Nexus Blue, Nexus Extreme, Nexus Extreme Blueberry, Nexus Extreme Chocolate, Nexus Extreme Strawberry, Nexus Extreme Vanilla, Nexus Red, Night Angels, Panic, Play Hard, Pure Sin, Red Russian, Shiva Passion, SHOOP, Spice 2.0, Springbang, Supernova, SWEED classic, SWEED Gold, SWEED Platin, Toxic Snake "Legal Hash", Vulkan, WTF.

⁽¹⁷⁾ <https://pubchem.ncbi.nlm.nih.gov/compound/70969900>

⁽¹⁸⁾ InChI Key is a unique, non-proprietary structural identifier of chemical substances useful in electronic sources.

⁽¹⁹⁾ The simplified molecular-input line-entry system (SMILES) is a unique, non-proprietary structural identifier of chemical substances useful in electronic sources.

Other street names reported to the EMCDDA are: 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, King Size Slim Rolling Papers, Vertex Ultra Extreme Incense Pirate Edition, Mary Jean, Waldemar Uszkiewicz Taak, Vertex Pirate Edition Ultra Extreme Incense, Galaxy Herbal Incense: *Althea officinalis*, Matt Hardener, Aura mystic Bulc.

Manufacturers of herbal smoking mixtures frequently change the synthetic cannabinoids in the products, which means that product names are not a reliable source of information regarding the actual substances that are present (e.g. Frinculescu et al., 2017, Moosmann et al., 2015).

Identification and analytical profile

Physical description

In its pure form AB-CHMINACA is a white to off-white crystalline powder (Lipomed, 2017). It is soluble in ethanol, DMSO and DMF (dimethyl formamide) to approximately 3, 10 and 5 mg/mL, respectively. The substance is sparingly soluble in aqueous buffers (Cayman Chemical Company, 2017).

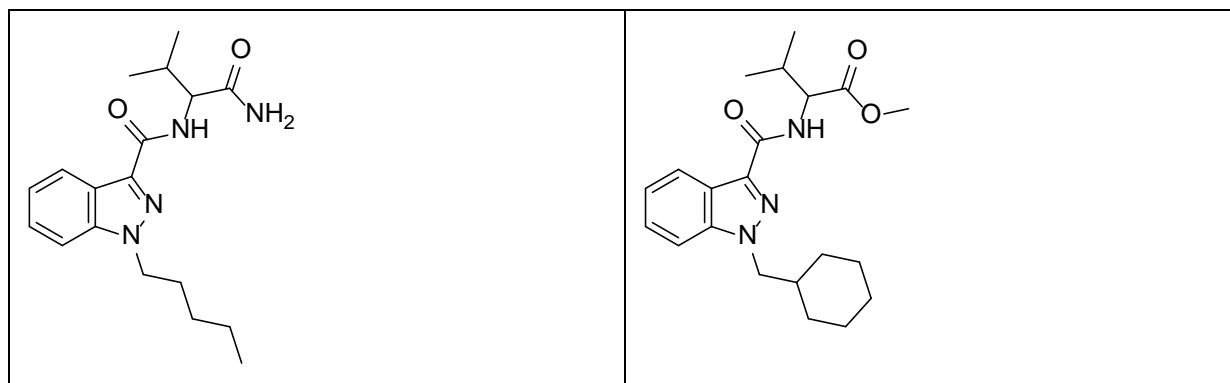
The melting point is 85 ± 5 °C (Lipomed, 2017). The boiling point is not available in the literature. However, the boiling point can be estimated to be below 350 °C according to the retention time of AB-CHMINACA in GC-MS analysis (Moosmann et al., 2017).

AB-CHMINACA carries one asymmetric carbon atom. Based on the patent literature and the most likely precursors, an (*S*)-configuration of the stereocentre can be assumed, possibly because one of the reagents used in its preparation (L-valinamide, see below) is derived from inexpensive natural sources or produced by industrial fermentation. The biological evaluation of the compounds described in the Pfizer patents exclusively report on compounds with the (*S*)-configuration and since data on the (*R*)-form were not included, it is not known how the stereochemistry affects activity on cannabinoid receptors. The absolute configuration of the structurally similar synthetic cannabinoid MDMB-CHMICA has recently been described in the literature which confirmed the (*S*)-configuration in samples from the drug market (including a seizure of a powder as well as 'legal high' type herbal smoking mixtures) (Andernach et al., 2016).

AB-CHMINACA shares structural features with other synthetic cannabinoids such as AB-PINACA and MA-CHMINACA or AMB-CHMINACA which have been described in the patent literature and/or are offered on the drug market (Figure 2) (Buchler et al., 2009).

FIGURE 2

Chemical structures of AB-PINACA and MA-CHMINACA (AMB-CHMINACA)



AB-PINACA	MA-CHMINACA (AMB-CHMINACA)
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Chemical stability and typical reactions

The terminal and the secondary amide bonds of AB-CHMINACA may be cleaved chemically or enzymatically.

Hydrolysis of the amide functions can be expected to occur during smoking as it was observed by analysis of smoke condensates (Franz et al., 2016). Most of the known free carboxylic acids formed by hydrolysis of similar compounds are not active at the CB₁ receptor (Buchler et al., 2009 and 2011). Therefore, the hydrolysis product of AB-CHMINACA might also not be active.

Hess et al., investigated the freeze/thaw stability as well as long term stability of synthetic cannabinoids in human serum samples (Hess et al., 2016a). They showed that AB-CHMINACA degraded less than 10% in serum during three freeze/thaw cycles (at least 20 h freezing and one hour thawing at room temperature). The long term stability of AB-CHMINACA in serum was given for at least 105 days at -20 °C, 105 days at 4 °C and over 315 days at room temperature (stability criterion: measured degradation below 20%).

Analytical profile

The analytical profile of AB-CHMINACA has been described in a publication utilizing EI-MS, ESI-EPI-MS/MS, IR and UV-VIS detection (Langer et al., 2016).

The UV maxima of AB-CHMINACA were reported at 303 nm in methanol.

IR data are as follows: wavenumber (cm⁻¹): 3331 (w), 3193 (w), 2926 (m), 2852 (w), 1649 (s), 1527 (s), 1491 (m), 1368 (w), 1303 (w), 1175 (m), 749 (s), 603 (m), 568 (m). Additionally, an FTIR spectrum has been published by Veress and Nagy (2015).

NMR data have been reported by Buchler et al., (2009) and Uchiyama et al., (2014).

The mass spectrometric fragmentation patterns of AB-CHMINACA was reported in publications of Akamatsu et al., (2016), Uchiyama et al., (2014) and Langer et al., (2016). Additionally, a GC-PI-MS spectrum was published by Akutsu et al., (2017), a paperspray HRMS method by Kennedy et al., (2016) and GC-EI-MS, positive and negative GC-CI-MS spectra were published by Umebachi et al., (2017). Analytical data for AB-CHMINACA have also been published (Slovenian National Forensic Laboratory, 2015; LaGory et al., 2014).

A voltammetric determination method of indole and indazole synthetic cannabinds, including AB-CHMINACA, has also been described (Dronova et al., 2016).

Quantification of AB-CHMINACA in herbal smoking mixtures can be carried out according to the general procedure described by the UNODC, e.g. by HPLC-DAD analysis (UNODC, 2013). Additionally, quantification of AB-CHMINACA in herbal material has been carried out using NMR analysis by Dunne et al., (2017) and by DART-MS by Nie et al., (2016).

For blood serum analysis, the parent compound is the main analytical target. Quantification of 137 authentic serum samples positive for AB-CHMINACA showed that concentrations detected are often

in the sub-ng/mL range (mean: 7.7 ng/mL, median: 2.6 ng/mL, range 0.1 – 81 ng/mL) (Moosmann et al., 2017). Taking into account an anticipated serum/blood ratio slightly below 1 (Schaefer et al., 2015), this concentration range is in accordance with the data Peterson et al., obtained from analysing whole blood samples (1 to >10 ng/g) (Peterson and Couper, 2015). LC-MS/MS instrumentation can be regarded as the gold standard for analysis of serum/blood samples due to its high sensitivity which is particularly useful when applied in abstinence control settings. A fully validated method for the detection of AB-CHMINACA in serum samples has been published using LC-MS/MS (detected in 9 samples: < 0.66 – 21.3 ng/mL) by Hess et al., (2017). In addition, two LC-MS/MS methods for the detection of AB-CHMINACA in whole blood were published, also applying LC-MS/MS (Peterson and Couper, 2015; Tynon et al., 2017). A semiquantitative approach was employed to estimate the concentration of AB-CHMINACA in serum samples collected from three acute intoxication cases involving this compound (1.8 ng/mL, 0.28 ng/mL and 0.05 ng/mL) (Abouchedid et al., 2017).

For urine analysis, the identification of the main *in vivo* metabolites is recommended prior to setting up an analytical method as AB-CHMINACA is not excreted unchanged in urine to a relevant extent, which can make its detection in this matrix challenging. However, the detection of the parent molecule in a human urine sample collected from a fatal intoxication has been reported with a concentration of 239 pg/mL (Minakata et al., 2017).

Based on the analysis and evaluation of authentic urine samples, metabolites formed by mono-hydroxylation (at the cyclohexyl moiety) and hydrolysis of the terminal amide function seem to be the most suitable targets for a reliable detection of exposure to AB-CHMINACA ⁽²⁰⁾. Two articles on the identification of AB-CHMINACA metabolites in authentic human urine samples have been published (Erratico et al., 2015; Wurita et al., 2016), confirming these findings. AB-CHMINACA and its 'carboxy' metabolite (presumably the terminal amide hydrolysis product) have been detected in urine samples obtained from users (Brajković et al., 2015).

For all metabolites having undergone hydrolysis of the terminal amide function it has to be noted that they may also be formed after exposure to the synthetic cannabinoid MA-CHMINACA (Figure 2), and, consequently, when detected alone do not unequivocally prove exposure to AB-CHMINACA.

Another aspect which has to be taken into account is the thermolytic formation of two AB-CHMINACA metabolites during smoking which could bias the detected metabolic profile (Franz et al., 2016). A GC-MS analysis of stomach content collected from an acute intoxication case revealed the presence of AB-CHMINACA, AB-FUBINACA, α -PHP, α -PVP, diazepam, and quetiapine (Klavž et al., 2016)

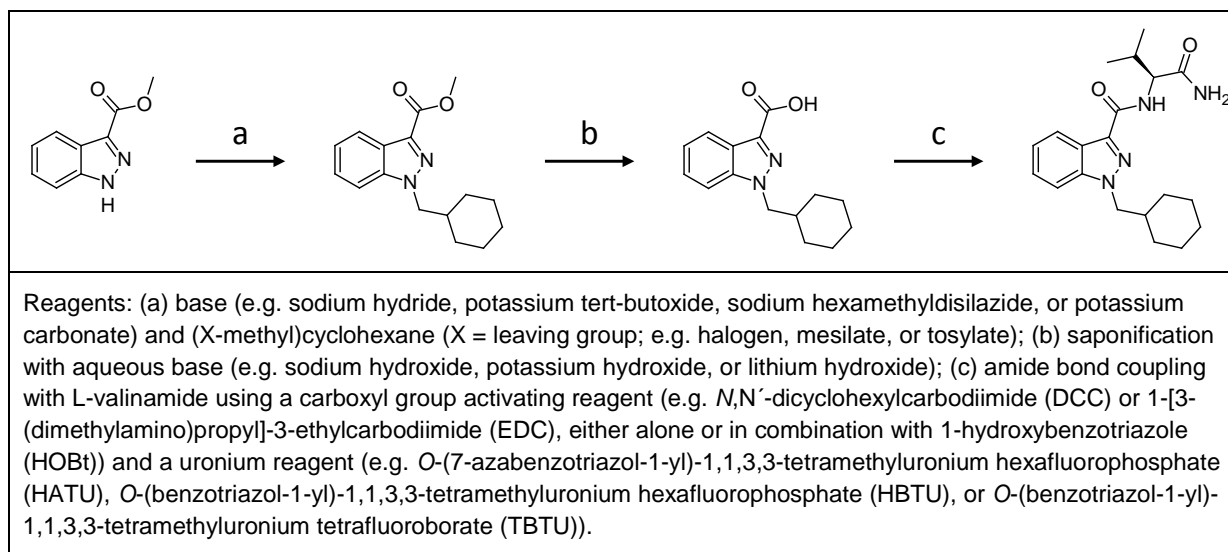
Methods and chemical precursors used for the manufacture

Synthesis

Information about the methods used for the synthesis of the AB-CHMINACA that has been detected on the drug market in Europe has not been reported to the EMCDDA. The synthesis of the AB-CHMINACA (S)-enantiomer was first published in a patent application of Buchler et al., (compound 21) starting from methyl 1*H*-indazole-3-carboxylate as shown in Figure 3 (Buchler et al., 2009). It is possible that the methods described therein might have been used to manufacture the AB-CHMINACA that has been detected in Europe.

⁽²⁰⁾ Institute of Forensic Medicine, Forensic Toxicology, Medical Center – University of Freiburg, Germany.

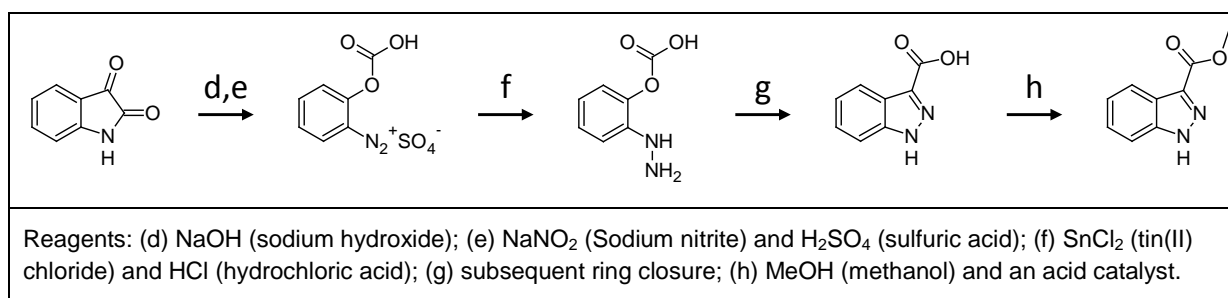
FIGURE 3
Synthesis route for AB-CHMINACA starting from methyl 1*H*-indazole-3-carboxylate.



The respective (*R*)-enantiomer might be synthesized under identical conditions using D-valinamide instead of L-valinamide in reaction step (c). Using valinamide as a racemate in reaction step (c) would lead to racemic AB-CHMINACA.

It was also described that the starting compound methyl 1*H*-indazole-3-carboxylate can be prepared from 1*H*-indole-2,3-dione using the procedure of Johnson and Rodgers (2005) as shown in Figure 4.

FIGURE 4
Synthesis route for methyl 1*H*-indazole-3-carboxylate starting from 1*H*-indole-2,3-dione.



In principle, reaction step (a) can also produce the N2-alkylated 2*H*-regioisomer (IUPAC: methyl 2-(cyclohexylmethyl)-2*H*-indazole-3-carboxylate) as a by-product, depending on the base and alkylating agent used. Longworth and co-workers published an evaluation of the reaction conditions regarding regioselectivity of the alkylation step, starting the synthesis from 1*H*-indazole-3-carboxylic acid. (Longworth et al., 2016). The use of potassium tert-butoxide in the alkylation step affords mainly the N1-cyclohexylmethyl derivative, while a substantial amount of the N2 alkylated regioisomer is formed if potassium carbonate is used.

According to the synthesis routes described in Figure 3 and Figure 4 potential precursors of AB-CHMINACA are 1*H*-indole-2,3-dione, 1*H*-indazole-3-carboxylic acid, methyl 1*H*-indazole-3-carboxylate, L-valinamide (for synthesis of the (*S*)-enantiomer), and (bromomethyl)cyclohexane. Other 1*H*-indazole-3-carboxylic acid esters might be suitable as alternative starting material.

Although not documented, the N1-alkylation can be carried out on the indazolyl valinamide derivative as the last step under conditions as described for serotonin receptor antagonists (Furlotti et al., 2012; Schaus et al., 1998) and, recently, a metabolite of the synthetic cannabinoid receptor agonist AKB-48 (Wallgren et al., 2017).

Commercially available domestic or industrial products which could be used for synthesis may contain potentially toxic substances, including heavy metals and organic solvents. Use of such products as reagents may result in serious toxic effects if the resultant impure product is consumed. The herbal material which is used as a basis for the smoking mixtures may also contain toxicologically relevant substances like e.g. pesticides potentially present in the plant material as well.

Typical impurities encountered in seized and collected samples

There are no quantitative data available on the impurities detected in seized and collected samples reported to the EMCDDA. However, the 2*H*-analogue, that is the N2-alkylated regioisomer, of AB-CHMINACA has been identified in a 'herbal mixture' obtained from the Internet in Japan (Uchiyama et al., 2015). The N2-regioisomer of AB-CHMINACA was observed to be significantly less active at the CB₁ and CB₂ receptors and might not contribute to the cannabimimetic effects (Longworth et al., 2016). Nevertheless, the toxicological properties of this by-product have not been evaluated. Further variations of the reagents, conditions and synthesis procedures may cause additional, possibly, toxic impurities.

A1.2. Physical/pharmaceutical form

Data from seizures and collected samples reported to the EMCDDA show that AB-CHMINACA has typically been detected in herbal/plant material. Other forms have also been encountered, including powders. The Pfizer Inc. patent also included the use of synthetic cannabinoids in a range of pharmaceutical compositions depending on the methods used for administration (Buchler et al., 2009).

For the production of smoking mixtures, the substance is dissolved in an organic solvent (e.g. acetone) and applied to the plant material—such as damiana (*Turnera diffusa*) or marshmallow (*Althaea officinalis*)—either via spraying or soaking and subsequent evaporation of the solvent (EMCDDA, 2017a).

A1.3. Route of administration and dosage

AB-CHMINACA is offered by online retailers either as powder ('research chemical') or in the form of herbal smoking mixtures. The presence of AB-CHMINACA or any other particular synthetic cannabinoid is not usually disclosed in these latter products. Some synthetic cannabinoids, including AB-CHMINACA, have also been offered in the form of e-liquids for vaping (Kennedy et al., 2016). Additionally, consumers might also prepare AB-CHMINACA containing e-liquids at home by dissolving the powdered form in propylene glycol.

The most common route of administration for synthetic cannabinoids is smoking either ready-to-use or self-prepared 'herbal mixtures' as a joint or utilizing a vaporizer, 'bong' or pipe. Oral consumption of synthetic cannabinoids has also been described. In the case of oral consumption a strong first-pass-effect can be expected. Additionally, the bioavailability can possibly be further reduced due to limited solubility and absorption or efflux pumps (e.g. multidrug resistance protein 1).

Lefever et al., (2017) developed a model of e-cigarette use in mice to compare the differences in pharmacological effects after intraperitoneal injection and aerosol inhalation of AB-CHMINACA and other synthetic cannabinoids. They demonstrated that AB-CHMINACA showed a full cannabinoid profile in three bioassays after both application routes. The time course for hypothermia after AB-CHMINACA exposure caused a faster onset and shorter duration after inhalation compared to injection. Since the time course of hypothermia is linked to the action of the synthetic cannabinoid, the authors stated that 'one particular concern with quick-onset and short-acting synthetic cannabinoids is that users will smoke or vape more frequently to maintain their high, thereby also exposing themselves to greater potential for toxicities of these compounds'. Similar observations were noted for locomotor activity where AB-CHMINACA and CP 55,940 showed similar dose–response curves upon aerosol inhalation exposure but AB-CHMINACA was about tenfold less active upon injection; the difference in the antinociceptive activity of these two cannabinoids were less marked though CP 55,940 was more active upon injection.

Based on a limited number of self-reported experiences posted on Internet discussion forums ⁽²¹⁾, dosages of AB-CHMINACA range from 0.1 to 0.4 mg. When consuming smoking mixtures, users will be unaware of the dose they are exposed to. Studies have found that many of these products are inhomogeneous with respect to the content of active ingredients (Logan et al., 2012; Zuba and Byrska, 2013; Moosman et al., 2015; Kikura-Hanajiri, 2013). Both high intra- as well as inter-package variability was observed for many synthetic cannabinoids (Moosman et al., 2015). (Section D.3.4.)

The content of AB-CHMINACA was analysed by Langer et al., in three products. The products contained 63 mg/g, 87 mg/g, and 92 mg/g AB-CHMINACA. None of the products contained other active ingredients (Langer et al., 2016).

In addition, the content of AB-CHMINACA was also analysed in 33 products received within the product monitoring performed in the Institute of Forensic Medicine Freiburg, Germany. The concentrations ranged from 0.1% (w/w) to 16.4% (w/w), the median was 3.2% (w/w) and the mean 5.2% (w/w) (Moosmann et al., 2017). In this study no homogenisation was carried out prior to analysis in order estimate the doses that users could be exposed to under real world use (Langer et al., 2016).

Kennedy et al., (2016) detected AB-CHMINACA in one e-cigarette liquid, next to three additional synthetic cannabinoids.

Seizure data as well as studies have shown that it is relatively common for more than one synthetic cannabinoid to be added to 'herbal mixtures' (Moosman et al., 2015). In Japan, Kikura-Hanajiri et al., (2013) detected an average number of 2.6 synthetic cannabinoids per product. The maximum number of synthetic cannabinoids detected in one mixture by these authors was ten.

Continuous market monitoring within the EU 'SPICE' projects included the analysis of 975 smoking mixtures between August 2014 and June 2017. AB-CHMINACA was detected in 148 samples (15%), with 72% containing AB-CHMINACA only, 19% containing AB-CHMINACA and one additional synthetic cannabinoid, and 9% containing AB-CHMINACA and two or more (up to 6) additional synthetic cannabinoids (Moosmann et al., 2017). Within the Welsh drug checking project WEDINOS, AB-CHMINACA was detected in six herbal mixtures and in five powders sent for analysis between May 2014 and October 2015 (WEDINOS, 2017).

⁽²¹⁾ <http://drugs.tripsit.me/ab-chminaca>. Accessed: 07.10.2017

A2. Pharmacology, including pharmacodynamics and pharmacokinetics

Pharmacologically, AB-CHMINACA is a cannabinoid receptor agonist.

Pharmacodynamics

AB-CHMINACA is a highly potent full agonist at the CB₁ receptor of the endocannabinoid system. In the patent application by Pfizer Inc. a K_i value at the human CB₁ receptor of 0.519 nM and EC₅₀ of 2.55 nM (GTPγS assay) is reported (Buchler et al., 2009). Wiley et al., (2015) report a K_i of 0.78 nM ([³H]CP-55,940) for hCB₁ and an EC₅₀ of 7.4 nM (GTPγS assay) (Table 1). Other EC₅₀ values (GTPγS assay) reported for AB-CHMINACA for hCB₁ were 0.226 nM (CP-55,940 EC₅₀ = 0.417 nM) and 0.152 nM (CP-55,940 EC₅₀ = 0.272 nM) for hCB₂ (Inomata et al., 2017). Cannaert and co-workers, when employing an *in vitro* hCB₁ and hCB₂ receptor activation assay that included β-arrestin recruitment, determined a higher potency for AB-CHMINACA (hCB₁ EC₅₀ = 6.1 nM; hCB₂ EC₅₀ = 3.7 nM) than JWH-018 (hCB₁ EC₅₀ = 23.9 nM; hCB₂ EC₅₀ = 6.8 nM) (Cannaert et al., 2017). Franz et al., measured a CB₁ receptor-mediated EC₅₀ value of 0.278 nM (cAMP-Assay) for AB-CHMINACA in comparison to JWH-018 and MDMB-CHMICA with EC₅₀ values of 1.132 and 0.142, respectively (Franz et al., 2017).

TABLE 1

Binding affinity (K_i), half maximal effective concentration (EC₅₀) and efficacy (E_{max}) of AB-CHMINACA and other synthetic cannabinoids as assessed with a GTPγS assay (data shown for CB₁ receptor) (Wiley et al., 2015).

Compound	CB ₁ K _i [nM]	EC ₅₀ [nM]	E _{max} *
CP-55,490	0.59	23.3	124
AB-CHMINACA	0.78	7.4	205
AB-PINACA	2.87	71	108

* Values represent percentage of maximal increase for [³⁵S]GTPγS binding over basal at CB₁ receptor

As noted in Section A.1.1, the AB-CHMINACA that has been detected on the drug market might be contaminated with its N2-cyclohexylmethyl regioisomer. According to a recent comparative functional study with cloned human CB₁ receptor preparation, AB-CHMINACA (that is the N1-alkylated isomer) is a full agonist and about 500-times more active than the partial agonist N1-alkylated isomer: the respective EC₅₀ values are 7.8 and 4080 nM (Longworth et al., 2016).

As it has been shown for 'first generation' synthetic cannabinoids (e.g. JWH-018, JWH-073) (Breits et al., 2011 and 2012) and for the THC metabolite 11-hydroxy-THC, it is likely that some of the mono-hydroxylated metabolites of AB-CHMINACA retain activity at the CB₁ receptor, which suggests that they might contribute to the pharmacological profile of the compound. Cannaert et al., (2017) determined in an *in vitro* receptor activity screen, using authentic human urine specimen confirmed to contain AB-CHMINACA metabolites that several metabolites retained the ability to activate cannabinoid receptors albeit at lower potency. However, in the case of CB₁ receptor activity, it is unclear if the metabolites are able to cross the blood-brain-barrier and reach effective concentrations levels in the brain. For example, the amide cleavage product (a free carboxylic acid) shows only a low affinity towards the CB₁ receptor (K_i: 380 nM) (Buchler et al., 2009).

AB-CHMINACA is also a partial agonist at the CB₂ receptor. Despite a high binding affinity (K_i: 0.45 nM) the EC₅₀ is rather low (232 nM) (Table 2) (Wiley et al., 2015). In contrast to CB₁ receptors, CB₂

receptors are mainly expressed on cells of the immune system and do not appear to contribute to psychoactivity.

TABLE 2

Binding affinity (K_i), half maximal effective concentration (EC_{50}) and efficacy (E_{max}) of AB-CHMINACA and other synthetic cannabinoids as assessed with a GTP γ S assay (data shown for CB_2 receptor) (Wiley et al., 2015).

Compound	CB_2 K_i [nM]	EC_{50} [nM]	E_{max} *
CP-55,490	0.30	2.1	63%
AB-CHMINACA	0.45	232.4	35%
AB-PINACA	0.88	14.9	41%

* Values represent percentage of maximal increase for [35 S] GTP γ S binding over basal at CB_2 receptor

There are no data available on the effect of AB-CHMINACA on other pharmacological (receptor or enzyme) targets. The biological properties of its metabolites are also unknown. Assessment of ‘first-generation’ synthetic cannabinoids (e.g. JWH-018, AM-2201, JWH-081) showed that binding to non-cannabinoid receptors was weak or even absent for these compounds (Wiley et al., 2016).

Pharmacokinetics

AB-CHMINACA undergoes extensive metabolism in the human body. Like most synthetic cannabinoids it is not excreted unchanged in urine to a relevant extent. The main metabolic phase I reactions comprise mono-hydroxylations (e.g. at the cyclohexyl methyl moiety) and hydrolysis of the terminal amide function. Erratico et al., (2015) published a detailed investigation on the *in vitro* and *in vivo* metabolism of AB-CHMINACA. They identified several phase I metabolites formed by mono- and di-hydroxylation, desalkylation, as well as hydrolysis of the terminal and secondary amide function. Two glucuronidated forms of the metabolite formed by hydrolysis of the terminal amide function were detected in human urine. Wurita et al., (2016) reported quantitative data on the 4-hydroxy-cyclohexyl methyl metabolite (52.8 ± 3.44 ng/mL) and the hydrolysis product of the terminal amide function (41.3 ± 5.04 ng/mL) in human urine. AB-CHMINACA (2.2 to 1512.0 (mean = 299.2 pg/mg, median = 133.6 pg/mg) could be identified in hair samples obtained from users and both primary and secondary amide hydrolysis products were also detectable in some of the hair samples (Sim et al., 2017). A single hydroxylated metabolite and its glucuronide conjugate were detected in mouse urine following intraperitoneal administration (3 mg/kg) of AB-CHMINACA (Wiley et al., 2015). AB-CHMINACA (7.61 ng/mL) and the two hydrolysed metabolites (terminal amide: 56.73 ng/mL and secondary amide moiety: 2.29 ng/mL) were detected in blood samples taken from a fatal intoxication (Maeda et al., 2017). Thirteen metabolites have been tentatively identified during the analysis of plasma, serum and urine samples that originated from 35 intoxication cases. The suggested biotransformations were hydroxylation of the cyclohexyl ring, hydrolysis of the terminal amide, hydrolysis of the secondary (“internal”) amide and hydroxylation/oxidation of the isopropyl group (Tyndall et al., 2015). The terminal carboxylic acid metabolite has also been detected in the urine of AB-FUBINACA users (Brajković et al., 2015).

No further data on the pharmacokinetics of AB-CHMINACA are available in the literature. Self-reported user experiences on the Internet have described an onset time of 1 to 5 minutes after

smoking with duration of the effect for 1 to 2 hours⁽²²⁾. As highlighted in the introduction, the assessment of such reports is problematic not least because users cannot confirm the actual substance used.

Toxicology

No studies were identified that have examined the toxicity of AB-CHMINACA.

Data on cytotoxicity and genotoxicity of the structurally unrelated synthetic cannabinoids JWH-018, JWH-073, JWH-122, JWH-210, AM-694, AM-2201, UR-144, AKB-48-5F, AM-2201-IC, XLR-11 and RCS-4 have been published (Ferk et al., 2016; Koller et al., 2013, 2014 and 2015). Transferability of the results from other synthetic cannabinoids is very limited as individual compounds can show distinct toxicological profiles.

Inter-individual genetic variability in metabolising enzymes

No information specifically for AB-CHMINACA has been identified.

Interactions with other substances and other interactions

No studies were identified that have examined the interaction of AB-CHMINACA with other substances, including medicinal products.

Effects on ability to drive and operate machines

No studies of the effects of AB-CHMINACA on the ability to drive and operate machines have been performed. However, it has been reported that intoxications caused by a range of synthetic cannabinoids, including AB-CHMINACA, significantly impair the mental and physical ability that is required to drive and operate machines (Section D1.2) (Capron, 2016; Griffiths and Griffin, 2016; Kaneko, 2017; Karinen et al., 2015; Musshoff et al., 2014; Peterson and Couper, 2015).

Griffiths and Griffin report on 25 cases of suspected impaired driving in Queensland, Australia, in which AB-CHMINACA was detected in the blood samples of the drivers. The concentration in whole blood ranged from 2.4 to > 80 ng/g and in most of the cases AB-CHMINACA was the only drug consumed. The most commonly recorded symptoms of impairment were lane divergence, drowsiness, slurred speech, bloodshot eyes, confusion, impaired answers to questions and uncoordinated movement (Griffiths and Griffin, 2016).

Peterson and Couper report on 33 suspected driving under the influence cases and drug recognition expert (DRE) cases in which AB-CHMINACA was detected in the blood samples. In 23 of these samples no further drug was detected. Drug recognition expert findings of impairment were reported in 10 of the 33 cases. The most common finding was extreme lane travel with near collisions and in nine cases the driver was found unconscious or slumped over the wheel. Horizontal gaze nystagmus was detected in 50 % and lack of convergence was observed in 30% of the DRE cases (Peterson and Couper, 2015).

Analysis by UHPLC–MS/MS of the blood and/or urine of 1252 suspected drivers driving under the influence of drugs in 2014 and 2015 found that AB-CHMINACA was the most common synthetic cannabinoid (46 cases) with blood and urinary concentrations in the range of 0.27–22.6 and 0.5–3.79 n/mL, respectively, when quantified (n = 10) (Institoris et al., 2017).

⁽²²⁾ <http://drugs.tripsit.me/>. Accessed: 30.06.2017

A3. Psychological and behavioural effects

Animal *in vivo* and *in vitro* data

Consistent with cannabinoid receptor activation under *in vitro* conditions, AB-CHMINACA was also found to induce cannabinoid/ Δ^9 -THC-like properties *in vivo*. Wiley et al., (2015) confirmed that AB-CHMINACA more potently (11- to 58-fold) induced rimobanant-reversible activity in the mouse tetrad test battery, i.e. leading to reduction in locomotor activity ($ED_{50} = 1.8 \mu\text{mol/kg}$; Δ^9 -THC $ED_{50} = 104 \mu\text{mol/kg}$); antinociception ($ED_{50} = 2.0 \mu\text{mol/kg}$; Δ^9 -THC $ED_{50} = 34 \mu\text{mol/kg}$); hypothermia ($ED_{50} = 1.1 \mu\text{mol/kg}$; Δ^9 -THC $ED_{50} = 30 \mu\text{mol/kg}$), and catalepsy ($ED_{50} = 2.7 \mu\text{mol/kg}$; Δ^9 -THC $ED_{50} = 30 \mu\text{mol/kg}$). Furthermore, AB-CHMINACA also fully substituted for Δ^9 -THC (training dose 5.6 mg/kg) in the drug discrimination assay (C57/BL6J mice), where AB-CHMINACA was determined to be ~17-fold more potent than Δ^9 -THC ($ED_{50} = 0.34 \mu\text{mol/kg}$; Δ^9 -THC $ED_{50} = 5.5 \mu\text{mol/kg}$) (Wiley et al., 2015).

Human data

While there is limited data, the psychological and behavioural effects of AB-CHMINACA appear to share some similarities with cannabis, THC, and other synthetic cannabinoids (e.g. Griffiths and Griffin, 2016; Peterson and Couper, 2015; See also Section D). This includes: relaxation, euphoria, lethargy, confusion, anxiety, fear, distorted perception of time, depersonalisation, hallucinations, paranoid inclusions, as well as dry mouth, bloodshot eyes, tachycardia, nausea, vomiting and impaired motor performance. These effects appear to be much more pronounced and severe when compared to cannabis (Ford et al., 2017; Zaurova et al., 2016). In addition, psychotic episodes, as well as aggressive and violent behaviour, have also been reported. (See also Section D1 and Section D3.4.)

A4. Legitimate uses of the product

AB-CHMINACA is used as an analytical reference material in clinical and forensic case work/investigations as well as scientific research. There is currently no information that suggests AB-CHMINACA is used for other legitimate purposes.

There are no reported uses of AB-CHMINACA as a component in industrial, cosmetic or agricultural products. In addition, a search of the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) registered substances database hosted by the European Chemicals Agency (ECHA) using the CAS Registry Number listed in Section A1.1 returned no results.

There is no marketing authorisation (existing, on-going or suspended) for AB-CHMINACA neither in the European Union nor in the Member States that responded to the request for information from the European Medicines Agency, which was undertaken as part of the Joint Report process (EMCDDA, 2017c).

There is no information to suggest that AB-CHMINACA is currently used in the manufacture of a medicinal product in the European Union. However, in the absence of a database on the synthetic routes of all medicinal products it is not possible to confirm whether or not AB-CHMINACA is currently used in the manufacture of a medicinal product.

Section B. Dependence and abuse potential

B1. Animal data

No data from animal studies regarding AB-CHMINACA are available in the literature in respect to dependence potential. Studies conducted with JWH-018 and JWH-073 in rats and monkeys suggest cannabinoid-like effects in the drug discrimination paradigm (Ginsburg et al., 2012; Järbe et al., 2010 and 2011). Though no specific data exist for AB-CHMINACA, it is possible that the substance might show similar properties. As noted above, AB-CHMINACA more potently induced Δ^9 -THC-like responses in the mouse tetrad assays, and fully substituted for Δ^9 -THC in a drug discrimination assay. This suggests an overlap in the mechanism of action (Wiley et al., 2015), and, thus, AB-CHMINACA might show potential for abuse liability.

B2. Human data

No studies were identified that have investigated the dependence and/or abuse potential of AB-CHMINACA in humans.

It has been suggested that consumption of synthetic cannabinoids can produce tolerance and withdrawal-like symptoms when use is discontinued following a regular use (Cooper, 2016, Macfarlane and Christie, 2015, Van Hout and Hearne, 2017; Zimmermann et al., 2009).

Two cases of withdrawal-like symptoms following use of AB-CHMINACA have been reported to the Poisons Information Centre Freiburg, Germany ⁽²³⁾.

Withdrawal-like symptoms following cessation of synthetic cannabinoid have been described in the literature. These include: anxiety, unstable mood, crying fits, feeling of inner emptiness, spatial disorientation, hyperacusis (increased sensitivity to ordinary environmental sounds), somatic pain, shortness of breath, hyperventilation, intense sweating and sensations of motor and inner restlessness (Hermanns-Clausen et al., 2012; Hermanns-Clausen et al., 2013).

Section C. Prevalence of use

Information from seizures, collected and biological samples

AB-CHMINACA was formally notified 10 April 2014 by the EMCDDA on behalf of Latvia, in accordance with Article 4 of the Council Decision. The Reporting Form details a seizure of 8 bags of herbal material with a total weight of 3.81 grams, seized in February 2014 by the Municipal Police. The identification was initially based on GC-MS analysis performed by the Forensic Service of the State Police, followed by NMR confirmation performed at the Latvian Institute of Organic Synthesis.

Since then, a total of 24 Member States, Norway, and Turkey have reported detections of AB-CHMINACA ⁽²⁴⁾ (EMCDDA, 2017c).

⁽²³⁾ Personal communication to Volker Auwärter.

⁽²⁴⁾ '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

Detections of AB-CHMINACA may well 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.

Information from seizures

A total of 26 countries reported seizures ⁽²⁵⁾ of AB-CHMINACA to the EMCDDA and/or Europol.

Information reported to the EMCDDA and Europol indicates that 6422 seizures of AB-CHMINACA have been reported by: Austria (10 seizures), Belgium (24), Bulgaria (17), Croatia (45), Denmark (2), Estonia (18), Finland (114), France (26), Germany (2), Greece (3), Hungary (1723), Italy (1), Latvia (221), Lithuania (62), Luxembourg (4), the Netherlands (7), Poland (1793), Portugal (3), Romania (3), Slovakia (6), Slovenia (2), Spain (7), Sweden (121), the United Kingdom (398), Turkey (1801), and Norway (9).

Physical forms seized were typically herbal/plant materials. There were also notable large seizures of powders. To a lesser extent, liquids and blotters were also seized.

The majority of the seizures comprise police and customs cases, with additional seizures taking place in custodial settings.

Herbal material

4066 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, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, the United Kingdom, and Norway. These amounted to over 40 kg as well as more than 145,000 packages of commercially labelled herbal smoking mixtures ⁽²⁶⁾ that weighed 1–3 g each. In addition, Turkey reported 1757 seizures of herbal material amounting to almost 150 kg ⁽²⁷⁾.

The largest single seizure of AB-CHMINACA in herbal material was reported by Spain, as part of the law enforcement operation codenamed 'Operation Alimaya'. This large-scale operation was carried out in Alicante in March 2016. A total of 145,157 packages (of 1–3 g each, also containing the synthetic cannabinoids 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 1700 seizures of herbal material amounting to 16 kg.

In herbal material, AB-CHMINACA was commonly found mixed with other synthetic cannabinoids. In 15 seizures, stimulants were also detected: Hungary (8 cases; amphetamine, pentedrone, clephedrone) and Poland (7 cases; amphetamine, α -POP and clephedrone).

purchases) for monitoring and research purposes. Biological samples are those from human body fluids (urine, blood, etc.) and/or specimens (tissues, hair, etc.)

⁽²⁵⁾ Many 'seizures' relate to individual case-level data, however, some data provided to the EMCDDA are aggregated at the country level. Data is drawn from the Joint Report Questionnaires and data provided in the bi-annual data gathering (EU Early Warning System progress and final reports) and from individual Reporting forms submitted on an ad hoc basis.

⁽²⁶⁾ 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'.

⁽²⁷⁾ Minimum estimate provided by the Turkish national focal point for 2016.

Quantitative information on the purity of AB-CHMINACA in 8 analysed samples of herbal material was provided by Lithuania and in one sample where the physical form was not specified. The concentration of AB-CHMINACA in the samples was in the range of 0.15–4.3 % (mean: 1.97 %, median: 2.0 %).

Powders

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.

A number of large single customs seizures of AB-CHMINACA in powder form were reported, such as:

- i. 4.8 kg of powder seized by customs in a FedEx delivery, reported by Luxembourg;
- ii. 3.5 kg of white powder seized at Roissy Airport, France (originating from China and destined for Austria); and,
- iii. 2 kg of powder seized at Madrid-Barajas Airport, Spain (originating from China and destined for France).

Liquids

Seizures of AB-CHMINACA in liquid form were reported by Sweden (4 cases) and Finland (3), 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, with a reported concentration of 3.5 mg/ml).

Blotters

178 seizures (193.9 g) of AB-CHMINACA in blotter form were reported by Poland.

Other physical forms

Lithuania reported 2 seizures, amounting to more than 20 kg where no information on the physical form was available.

Information from collected samples

Two collected samples of AB-CHMINACA were reported to the EMCDDA from Belgium and Poland. The case from Belgium involved a sample of white powder found to contain AB-CHMINACA, collected from a patient who had used the substance and subsequently required medical treatment at hospital. A bag of herbal material containing AB-CHMINACA was reported by Poland, with the synthetic cathinone α -PVP also detected in the sample.

Information from biological samples

Serious adverse events (deaths and acute intoxications) with confirmed exposure to AB-CHMINACA from biological samples are discussed in Section D.

Additionally, a total of 551 analytically confirmed detections of AB-CHMINACA in biological samples were reported ⁽²⁸⁾ by three Member States: Hungary (537 cases), Sweden (10) and Poland (4).

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

Availability, supply, price

Information on production

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

Information on trafficking

Information related to trafficking routes is limited to the seizures reported above. Large shipments containing AB-CHMINACA in powder form, that were intercepted by customs officials in France and Spain, originated in China. Information reported to Europol is limited to seizures made by Bulgarian customs of shipments containing AB-CHMINACA arriving from Spain and the Netherlands.

Availability from Internet vendors

Table 3 provides the results of an search for online shops on the surface web selling research chemicals in various countries (Belgium, Czech Republic, Germany, Hungary, The Netherlands, Poland, Portugal, Spain, Sweden, United Kingdom, Canada, United States, and, China; allocation based on entries at reddit.com). Fifty-seven shops were screened for their product portfolio. Seven of the shops listed AB-CHMINACA on their website. The compound was listed as 'out of stock' in six of these shops. The table also lists the price range for the compound depending on the order quantity.

TABLE 3

Prices of AB-CHMINACA depending on the order quantity from 7 surface web vendors.

	1 g	10 g	100 g	1000 g
Number of products	5	4	4	1
Range	9.38–21.99 EUR	130–159 EUR	790–912 EUR	N/A
Median	21.99 EUR	154 EUR	859 EUR	N/A
Mean	21.99 EUR	150.20 EUR	855.8 EUR	5127 EUR

It is important to note that AB-CHMINACA has been controlled in China since October 2015. While some of the vendors that appear to be based in China still list AB-CHMINACA on their websites, they usually do not ship the compound to Germany ⁽²⁹⁾.

⁽²⁸⁾ Turkey reported 902 detections of AB-CHMINACA in biological samples (blood, hair and urine) which may contain duplicates and therefore have not been included in the total count above.

⁽²⁹⁾ Observations based on test purchases from such sites. Personal Communication from Volker Auwärter.

Prevalence of use

No studies were identified that have investigated the prevalence of use of AB-CHMINACA in the general population.

Similar to other synthetic cannabinoids, AB-CHMINACA is often sold and used as a 'legal' substitute for cannabis, typically as herbal smoking mixtures (EMCDDA, 2009; EMCDDA, 2017a). The composition of these products varies over time, with substances being changed in response to, or, in anticipation of, the introduction of control measures. This may have implications on the availability of AB-CHMINACA and its prevalence of use. Overall, the available information does not suggest widespread use of the substance ⁽³⁰⁾.

Because of the variability in the composition of smoking mixtures, and the fact that the ingredients are not typically disclosed, most users will be unaware that they are using AB-CHMINACA. As a result, the prevalence of use of AB-CHMINACA should be considered in the wider context of the prevalence of use of herbal smoking mixtures, commonly referred to as 'spice'.

The use of 'spice'-like products has been studied in some European countries in general population surveys or in specific populations such as students, 'clubbers' and/or internet users. The results of these surveys are not comparable as they use different methodology and samples but overall they indicate generally low prevalence levels in these groups (EMCDDA, 2017a).

There is evidence that in some groups, such as high risk drug users and other marginalised groups, the prevalence of use of synthetic cannabinoids, particularly as smoking mixtures, may be higher. This includes 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 synthetic cannabinoids. In addition some vulnerable populations, such as the homeless and prisoners, specifically seek out synthetic cannabinoids because they have a reputation for causing profound intoxication, they can be cheap and are easy to smuggle (EMCDDA, 2017a; Blackman and Bradley, 2017; HMIP, 2015; Ralphs et al., 2017; User Voice, 2016).

Section D. Health risks

D1. Acute health effects

D1.1. Animal data

With the exception of the data published by Wiley et al., (2015) that demonstrated that AB-CHMINACA can induce cannabinoid/ Δ^9 -THC-like properties *in vivo*, no other animal data were identified that have examined the acute health effects of the substance.

D1.2. Human data

No clinical studies were identified that have examined the acute health effects of AB-CHMINACA and/or its metabolites in humans. Data from serious adverse events associated with AB-CHMINACA

⁽³⁰⁾ Based on the product monitoring within the EU-projects 'SPICE II Plus' and 'SPICE Profiling' and the results from serum and urine analysis conducted at the Institute of Forensic Medicine Freiburg, Germany, it appears that the prevalence of AB-CHMINACA in Germany increased in the last quarter of 2014, reached its maximum in the first half of 2015 and decreased since the third quarter of 2015. In the first half of 2015 AB-CHMINACA was detected in 30% of all 'legal high' products analysed (n = 217). AB-CHMINACA was detected in 36% of all serum samples positive for synthetic cannabinoids (n = 186, total number of samples analysed n = 634) in the same time period.

are discussed below. In general, the acute health risks associated with AB-CHMINACA appear to be similar to those found with other synthetic cannabinoids.

As synthetic cannabinoids activate the CB₁ receptor in a similar way to THC, their effects appear to have some similarities with cannabis (Auwärter et al., 2009). This includes: relaxation, euphoria, lethargy, confusion, anxiety, fear, distorted perception of time, depersonalisation, hallucinations, paranoid inclusions, as well as dry mouth, bloodshot eyes, tachycardia, nausea, vomiting and impaired motor performance. These effects appear to be much more pronounced and severe when compared to cannabis (Ford et al., 2017; Winstock et al., 2013; Zaurova et al., 2016).

Severe and fatal poisoning also appears to be more common with synthetic cannabinoids as compared to cannabis. This can include severe cardiovascular toxicity (including sudden death), severe central nervous system depression (such as rapid loss of consciousness/coma), respiratory depression, seizures and convulsions, hyperemesis, delirium, agitation, psychosis, and aggressive and violent behaviour (Adams et al., 2017; Brennehan et al., 2016; Capron, 2016; Ford et al., 2017; Hermanns-Clausen et al., 2013; EMCDDA, 2017c, EMCDDA, 2017d, EMCDDA, 2017e; EMCDDA, 2017f; EMCDDA, 2017g; Kasper et al., 2015; Pap, 2016; Schwartz et al., 2015; Shevyrin et al., 2015; Springer et al., 2016; Tait et al., 2016; Trecki et al., 2015; Tyndall et al., 2015; Waugh et al., 2016; Winstock et al., 2013; Zaurova et al., 2016). (See Section D3.4.)

In addition, some of the features of poisoning—particularly loss of consciousness, respiratory depression, and behavioural effects—may place users at additional risks, such as choking on/aspirating vomit, drowning, falling, hypothermia as a result of falling unconscious outside in cold weather, and self-inflicted violence/injury (EMCDDA, 2017g; Tait et al., 2016; Yeter, 2017). The aggressive and violent behaviours reported with synthetic cannabinoids may also place others at risk of injury.

Overall, poisoning with synthetic cannabinoids may be made worse when other drugs, especially central nervous system depressants (such as alcohol, opioids, and sedative/hypnotics), are used at the same time.

There is no approved antidote to poisoning caused by synthetic cannabinoids.

Acute intoxications reported by the Member States

A total of 7 acute intoxications with confirmed exposure to AB-CHMINACA were reported to the EMCDDA 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 2 out of the remaining 4 cases, no other substances were detected. In the other 2 cases other substances detected included synthetic cannabinoids and an opioid. In all 4 cases, the clinical features of the poisoning were typical of those reported for synthetic cannabinoids.

Acute intoxications identified from other sources

Angerer et al., have reported a case in which AB-CHMINACA and MDMB-CHMICA was detected in the serum samples (0.28 ng/mL & 0.45 ng/mL, respectively) and the patient did not show any symptoms (Angerer et al., 2016).

In an observational study of 18 patients with analytically confirmed synthetic cannabinoid toxicity in London, United Kingdom, seizures and agitation were mentioned as clinical features observed in

three acute intoxication cases shown to involve exposure to AB-CHMINACA (Abouchedid et al., 2017). In one of these cases, AB-CHMINACA was the only substance detected. The male patient (29 years) suffered from agitation and seizures; admission observation: heart rate 123 bpm; Glasgow Coma Score 13; temperature 34.6 °C. The patient's length of stay was 14.8 h (Abouchedid et al., 2017).

A series of acute delirium (n = 24) and seizures (n = 14) was encountered in 35 patients between 28 May 2014 and 8 June 2014 in Florida, United States, (median age was 34.6 years (range, 14–58); 31 male, 4 female) reported symptoms included altered mental status (61%, n = 24), hallucinations (6%, n = 2), and seizures (40%, n = 14). None of the patients were hyperthermic. Clinical presentations: patients requiring intubation (14.3%, n = 5), seizures (40%, n = 14), intensive care unit submission (20%, n = 7), initial tachycardia (heart rate >100) (45.7%, n = 16), initial hypertension (systolic >150 or diastolic >90) (17.1%, n = 6), altered mental status (Glasgow Coma Score ≤14) (54.3%, n = 19). Forty-five samples from 26 cases were available for analysis and 15 cases were confirmed AB-CHMINACA exposures. In some instances, plasma, serum and urine samples were available (Tyndall et al., 2015).

Other cases of intoxications associated with AB-CHMINACA occurring in various other cities in the United States have been reported. No specific details on these cases were reported (Trecki, Gerona and Schwartz, 2015).

In a prospective study of patients treated in emergency departments after use of synthetic cannabinoids in Germany, AB-CHMINACA was identified in 20 serum samples and in 21 urine samples (Hermanns-Clausen et al., 2017). Concentration in serum varied from trace amounts (0.1 ng/mL) up to 27 ng/mL. The most frequent clinical symptoms were central nervous system depression (in 13 out of 20 patients), tachycardia (in 10 out of 20 patients) and disorientation (in 9 out of 20 patients). No correlation between serum level of AB-CHMINACA and the severity of poisoning was observed.

Deaths reported by the Member States

A total of 31 deaths with confirmed exposure to AB-CHMINACA were reported to the EMCDDA by Croatia (1 case), Germany (4), Hungary (11), Poland (2), Sweden (5), and the United Kingdom (8). In all cases, exposure to AB-CHMINACA (or an associated metabolite in one case) was analytically confirmed from post-mortem samples.

The deaths occurred between 2014 and 2017.

Demographic data were available for all but 6 deaths and involved 24 males (77%) and 1 female (3%). The mean age of the males was 30 years (median 27) and ranged from 16 to 66 years. The female was 38 years old.

Circumstances and cause of death

There was a lack of information regarding any symptoms experienced by the deceased prior to death in the majority of cases, but, in one case, the deceased was described to have vomited and became hypothermic and unconscious. Where information was known, in the majority of instances the individuals were found dead, predominantly in a home environment (either their own or a friend's), or outside; 2 of the deaths occurred in prison. Consequently, it was not possible to identify or evaluate ante-mortem symptoms (especially in relation to acute intoxication) in these cases.

A cause of death was reported in 22 cases, and, in at least 9 deaths, AB-CHMINACA was either the cause of death or is likely to have contributed to death (even in presence of other substances); other substances were detected in 25 cases. AB-CHMINACA was the only drug present in 6 deaths based on additional toxicological information, where available.

AB-CHMINACA was quantified in 11 cases. Post-mortem blood concentrations between 0.32 and 12 ng/mL (median 3.70 ng/mL), or equivalent, were recorded. Due to the toxicity of potent synthetic cannabinoids, a post-mortem blood concentration cannot necessarily be used to determine a “fatal” concentration. In the majority of circumstances involving synthetic cannabinoids, the mere presence of the drug is of significance whether concentration has been determined or not, especially in situations of poly-drug use and the varying circumstances in which they are used.

A range of other substances were detected in the deaths, including: alcohol, cannabinoids, antidepressants, antipsychotics, cocaine, zopiclone, synthetic cathinones, opiates/opioids (morphine, buprenorphine, acetylfentanyl, tramadol, methadone, codeine) and benzodiazepines. Other synthetic cannabinoids and/or metabolites were detected in 6 of the deaths, including; MDMB-CHMICA, 5F-MDMB-PINACA, ADB-CHMINACA, FUB-AKB-48, 5F-PB-22, UR-144.

Overall, whilst other substances may have contributed some toxicity, the potent nature of AB-CHMINACA means the primary toxic contribution could be attributed to the drug and death may not have occurred if AB-CHMINACA had not been used. However, in the cases where multiple synthetic cannabinoids were present, it is not necessarily possible or appropriate to identify AB-CHMINACA as the primary synthetic cannabinoid that may have produced toxicity but a synergistic effect is likely nonetheless. Sufficient case data were available in 29 of the 31 deaths. An assessment of the toxicological significance score (TSS) (Elliott, Sedefov, and Evans-Brown, 2017) incorporating the above considerations in the deaths, showed that AB-CHMINACA had a TSS value of 3 (high) in 18 deaths (where it was cited as the cause of death or is likely to have contributed to death following assessment). In the remaining 11 deaths, there was an alternative cause of death (such as hanging, drowning, stabbing, other drug overdose, or other physiological cause) (TSS value of 1, low). However, there is a possibility that use of AB-CHMINACA could have contributed to some of these situations/causes but there was insufficient circumstance and other information to allow this attribution.

Deaths identified from other sources

There are only limited data published in the scientific literature regarding fatalities following confirmed exposure to AB-CHMINACA.

Hess et al., reported a death where AB-CHMINACA was detected in femoral blood along with ten other synthetic cannabinoids. The cause of death was determined to be diabetic ketoacidosis and the authors state that the death could have been induced by skipping of insulin doses due to the intoxicated state or by the synthetic cannabinoids, which were described to be able to produce hyperglycaemia themselves (Hess et al., 2015).

Hasegawa et al., report on a death involving the synthetic cannabinoids AB-CHMINACA and 5F-AMB, as well as the NMDA receptor channel blocker diphenidine. The deceased was found in a prone position in a car with a lighter in his hand and an opened package of herbal blend (later confirmed to contain diphenidine) lying below his chest and a second package (later confirmed to contain AB-CHMINACA and 5F-AMB) on the backseat. Based on the high concentrations of diphenidine in the post-mortem tissue the authors suggested that this drug played a major role in the cause of death.

AB-CHMINACA was detected in multiple tissues and 5F-AMB was only detected in the adipose tissue in this case (Hasegawa et al., 2014).

Maeda et al., reported a case of sudden death linked to non-cardiogenic severe pulmonary oedema and hypoxia. AB-CHMINACA (7.61 ng/mL) and the terminally and internally hydrolysed carboxylic acid metabolites (56.73 and 2.29 ng/mL, respectively) were detected in blood; AB-FUBINACA (0.11 ng/mL), FUB-PB22, and 5F-AMB (both below the limit of quantitation) were also detected (Maeda et al., 2017).

A male in his thirties was found dead in his car parked at a supermarket parking lot. AB-CHMINACA was detected in urine (232 pg/mL) (Minakata et al., 2017).

There are no data available in the literature regarding the post-mortem stability of AB-CHMINACA. However, it has been observed that structurally similar synthetic cannabinoids might undergo hydrolysis during the post-mortem interval (Moosmann et al., 2017). Consequently, analytical methods solely targeting the parent compounds (as it is the case for most serum/blood screening methods) might miss AB-CHMINACA detection in cases where a long post-mortem interval is involved or if the samples are stored for a longer period of time prior to analysis.

D2. Chronic health effects

D2.1. Animal data

No studies were identified that have investigated the chronic health effects of AB-CHMINACA in animals.

D2.2. Human data

No studies were identified that have investigated the chronic health effects of AB-CHMINACA in humans.

D3. Factors affecting public health risks

D3.1. Availability and quality of the new psychoactive substance on the market

AB-CHMINACA has been sold on the surface web as a powder and in 'legal-high' type products such as herbal smoking mixtures. The substance is available in small and wholesale amounts. Herbal smoking mixtures do not commonly state the presence of synthetic cannabinoids. As a result, many users will not be aware that they are using such substances.

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

The availability of information, degree of knowledge and perceptions amongst users concerning AB-CHMINACA and its effects are limited. There is considerable variability both within and between different batches of synthetic cannabinoid products, in terms of both the substances and the amount present. For that reason, most individuals will be unaware that they are using AB-CHMINACA.

Unknown to users, synthetic cannabinoids have also been sold as ecstasy/MDMA and other illicit drugs. In some cases, this has led to severe poisoning (Allibe et al., 2016; Brenneman et al., 2016; Pap, 2016).

Opioids (such as U-47,700 and furanylfentanyl) have also been identified in smoking mixtures/plant material. Users will be unaware of this, and the use of such opioid-containing products could pose a risk of life-threatening respiratory depression. This risk will be especially high in individuals with no tolerance to opioids (Coopman et al., 2017; EMCDDA, 2017h).

D3.3. Characteristics and behaviour of users

No studies were identified that have examined the characteristics and behaviour of users of AB-CHMINACA.

Synthetic cannabinoids are sold and used as a 'legal' replacement for cannabis (EMCDDA, 2009; EMCDDA, 2017a). In addition some users specifically seek out synthetic cannabinoids because they have a reputation for causing profound intoxication, they can be cheap and are easy to smuggle. In most cases they are smoked using a cigarette of plant material that has been mixed with one or more of the cannabinoids. Because these products rarely state the ingredients, most users will be unaware that they are using synthetic cannabinoids.

People who use synthetic cannabinoids may include recreational users (including cannabis users), high-risk drug users, and groups who experiment with the substances (such as psychonauts). They 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 some of the cannabinoids (especially those that are relatively new to the drug market). In the past few years, synthetic cannabinoids have become increasingly used by vulnerable groups (such as the homeless and prisoners).

D3.4. Nature and extent of health consequences

The limited information available on the pharmacology, dependence and abuse potential, and acute health effects of AB-CHMINACA have been discussed above (Section A2, Section B, Section D1 and Section D2).

Compared to cannabis, more pronounced effects as well as severe and fatal poisoning appear to be more common with synthetic cannabinoids (EMCDDA, 2017c; EMCDDA, 2017d, EMCDDA, 2017e, EMCDDA, 2017f, EMCDDA, 2017g; Tait et al., 2016; Waugh et al., 2016; Winstock et al., 2013; Zourova et al., 2016). The reasons for this are poorly understood, but at least two factors are likely to be important: the high potency of the substances and the unintentionally high doses that users are exposed to.

Firstly, studies have found that many of the cannabinoids, including AB-CHMINACA, which are sold on the drug market, are much more potent and active, typically behaving as full agonists, as compared to THC. This means that even at very small doses they can activate the CB₁ receptor much more strongly than THC (Banister et al., 2016; Ford et al., 2017; Reggio, 2009; Tai and Fantegrossi, 2017).

Secondly, the process for mixing the synthetic cannabinoids with the herbal/plant material (which are the most common way of using these substances) can lead to dangerous amounts of the substances in the products. This is because producers have to guess the amount of cannabinoids(s) to add, while the mixing process makes it difficult to dilute the substances sufficiently and distribute them consistently throughout the plant material. This can result both in products that contain toxic amounts of the substances in general (Ernst et al., 2017; Frinculescu et al., 2016; Langer et al., 2014; Langer et al., 2016), as well as products where the cannabinoids are clumped together forming highly

concentrated pockets within the plant material (Frinculescu et al., 2016; Moosmann et al., 2015; Schäper et al., 2016). These issues are made worse as the products are typically smoked allowing the substances to be rapidly absorbed into the systemic circulation (bloodstream) and to reach the brain.

The combination of these two factors makes it difficult for users to control the dose that they are exposed to and can lead them to rapidly administer a toxic dose unintentionally. Accounts from patients and people who witness poisonings suggest that in some cases a small number of puffs from a cigarette have been sufficient to cause severe and fatal acute poisoning.

These two factors are also responsible for outbreaks of mass poisonings caused by smoking mixtures, which have ranged in size from four or five victims to over 800. Mass poisonings can overwhelm emergency responders and other local healthcare systems. Many of the outbreaks that have been reported so far are from the United States, but they have also occurred in Russia and Europe (Adams et al., 2017; Kasper et al., 2015; Schwartz et al., 2015; Shevyrin et al., 2015; Springer et al., 2016; Trecki et al., 2015; Tyndall et al., 2015). Such types of outbreaks have been reported for AB-CHMINACA (Trecki et al., 2015; Tyndall et al., 2015).

Driving while under the influence of synthetic cannabinoids places users and others at risk of injury (Capron, 2016; Kaneko, 2017; Karinen et al., 2015; Musshoff et al., 2014; Peterson and Couper, 2015). In a recent case series of 36 drivers suspected of driving under the influence of drugs in Washington, United States, where 5F-MDMB-PINACA was the predominate psychoactive substance identified, 50% of the drivers were found unconscious and 28% has been involved in collisions with single/multiple cars (Capron, 2016). Similarly, the operation of machinery while under the influence of synthetic cannabinoids may place the user and others at risk of injury.

D3.5. Long-term consequences of use

While there is limited data for AB-CHMINACA, the long-term consequences of use might share similarities to cannabis and other synthetic cannabinoids. This may include dependence.

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

There is limited data on the conditions which AB-CHMINACA is obtained and used.

Sources appear to include internet retailers, physical shops, friends and other acquaintances, and street-level drug dealers (Section D3.1). In addition, most users will be unaware that they have sourced and used AB-CHMINACA (Section C and Section D1.2.1). The available data suggests that AB-CHMINACA is used in the same environments as cannabis, including the home, and, to a lesser extent, in recreational settings.

Section E. Social risks

The available data suggests that the acute behavioural effects of AB-CHMINACA bear some similarities to cannabis but are more pronounced and severe.

In addition, and, of particular note, is that in some settings, synthetic cannabinoids are increasingly used by high risk drug users and other vulnerable groups, such as the homeless and prisoners. In at least some cases, these users are specifically seeking out synthetic cannabinoids because the

substances have developed a reputation for causing profound intoxication, they can be cheap and are easy to smuggle. Reports suggest that this has exacerbated existing health and social problems for these vulnerable groups, as well as creating new ones.

E1. Individual social risks

There is no information on whether the use of AB-CHMINACA causes individual social risks; however, they may have some similarities with those associated with other synthetic cannabinoids. These may impact on education or career, family or other personal and social relationships and may result in marginalisation.

E2. Possible effects on direct social environment

While there is no specific information on the possible effects of AB-CHMINACA on the direct social environment, the behavioural effects of synthetic cannabinoids include reports of aggressive and violent behaviour. This may place users and others at risk of injury.

E3. Possible effects on society as a whole

There is no specific information on the possible effects of AB-CHMINACA on society as a whole.

E4. Economic costs

There are no data on the effects of AB-CHMINACA on economic costs.

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

There is no specific data on the possible effects of AB-CHMINACA related to the cultural context.

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).

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

While no specific examples are available on the possible appeal of AB-CHMINACA to specific user groups, it is reasonable to assume AB-CHMINACA may be sought by those looking for 'legal' substitutes for cannabis. This includes individuals subject to drug testing (such as drivers, prisoners, those in drug treatment, and those subject to workplace drug testing), as commonly used drug tests may be unable to detect the compounds (Gunderson et al., 2014; Vandrey et al., 2012).

In addition, and, of particular note, is that synthetic cannabinoids are increasingly used by high risk drug users and other vulnerable groups, such as the homeless and prisoners. In at least some cases,

these users are specifically seeking out synthetic cannabinoids because they have developed a reputation for causing profound intoxication, they can be cheap and are easy to smuggle. Reports suggest that this has exacerbated existing health and social problems as well as creating new 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 et al., 2017; HMIP, 2015; Ralphs et al., 2017; User Voice, 2016).

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 specific information to suggest the involvement of organised crime or established criminal groups in the manufacture, distribution and supply of AB-CHMINACA.

In the cases where the origin of the seizures reported to Europol was known, the country of origin indicated was: Spain (1) and the Netherlands (1). Bulgaria reported 3 seizures that were en-route from Spain (1) and the Netherlands (1). The Czech Republic also reported 2 seizures, for which the final destination was Israel and 1 of the seizures occurred in Israel.

In the cases where the origin of the seizures reported to the EMCDDA was known, the country of origin indicated was China (2). In a seizure made at Roissy Airport in France, the origin of the seizure was reported as China and the final destination was Austria. In a seizure made at Madrid-Barajas Airport in Spain, the origin was also reported as China and the final destination was France.

The largest single seizure of AB-CHMINACA, which was in herbal form, was reported to the EMCDDA by Spain. In March 2016, in the frame of 'Operation Alimaya', a large scale operation carried out in Alicante, 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.

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

No information was reported nor identified concerning the impact of AB-CHMINACA on the production, trafficking and distribution of other substances, including existing psychoactive substances as well as new psychoactive substances.

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

No information was reported nor identified concerning evidence of the same groups of people being involved in different types of crime related to the availability of AB-CHMINACA.

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 was reported nor identified concerning incidents of violence related to the availability of AB-CHMINACA.

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

No information was reported nor identified concerning evidence of money laundering practices, or impact of organised crime on other socioeconomic factors in society related to the availability of AB-CHMINACA.

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

No information was reported nor identified concerning the economic costs and consequences related to the availability of AB-CHMINACA.

F7. Use of violence between or within criminal groups

No information was reported nor identified concerning the use of violence between or within criminal groups related to the availability of AB-CHMINACA.

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

No information was reported nor identified concerning evidence of strategies to prevent prosecution related to the availability of AB-CHMINACA.

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Edith HOFER

Organised Crime and Drugs Policy Unit, DG HOME, European Commission

Dr Leon Van Aerts

Section Pharmacology, Toxicology and Biotechnology, College ter Beoordeling van Geneesmiddelen, Medicines Evaluation Board, Utrecht, on behalf of European Medicines Agency

Werner VERBRUGGEN

Europol's Drug Unit, Europol

Paul GRIFFITHS

Scientific Director, EMCDDA

Dr Roumen SEDEFOV

Head of Unit, Supply reduction and new drugs unit, EMCDDA

Invited external experts

Professor Dr Volker AUWÄRTER

Freiburg University, Institute of Forensic Medicine, Freiburg

Dr Robert KRONSTRAND

Dep. Forensic Genetics and Toxicology, Swedish National Board of Forensic Medicine, Linköping

Professor Dr Bela SZABO

Institute of Experimental and Clinical Pharmacology and Toxicology, Freiburg

Dr István UJVÁRY

Budapest University of Technology and Economics, Budapest

EMCDDA staff present

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Action on new drugs sector, Supply reduction and new drugs unit

Rachel CHRISTIE

Action on new drugs sector, Supply reduction and new drugs unit

Michael EVANS-BROWN

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The risk assessment report and technical annex of the publication are published in the original version that has not been edited.

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

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

Related publications and websites**EMCDDA**

| Risk assessment of new psychoactive substances — operating guidelines, 2010
www.emcdda.europa.eu/html.cfm/index100978EN.html

EMCDDA and Europol

| EMCDDA-Europol Joint Report on a new psychoactive substance N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1H-indazole-3-carboxamide (AB-CHMINACA), 2017
www.emcdda.europa.eu/publications/joint-reports/ab-chminaca

| EMCDDA–Europol 2016 Annual Report on the implementation of Council Decision 2005/387/JHA, Implementation reports, 2017 www.emcdda.europa.eu/publications/implementation-reports/2016

| EMCDDA–Europol Early-warning system on new psychoactive substances — operating guidelines, 2007
www.emcdda.europa.eu/html.cfm/index52448EN.html

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

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