European Monitoring Centre
for Drugs and Drug Addiction

DRAFT

Technical report on *N*-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide (ADB-CHMINACA)

Parts of this technical report were prepared under contract from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Given the time frame stipulated in the Council Decision, additional data presented and discussed during the preparatory meeting for the risk assessment and the risk assessment meeting have not yet been incorporated into the technical report. In addition, this technical report has not been formally edited by the EMCDDA. As such, this report should be regarded as a draft document until such time that the final version is produced by the EMCDDA which will incorporate the additional data and which will be formally edited. The EMCDDA may not be held responsible for the use of the information contained herein without prior consultation. The *Risk assessment report on a new psychoactive substance: N*-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide (ADB-CHMINACA) to which this report is annexed, was produced by the extended Scientific Committee of the EMCDDA and shall be regarded as the authoritative document.

3 November 2017

Annex 1 to the *Risk Assessment Report on* N-*(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H-*indazole-3-carboxamide (ADB-CHMINACA)*.

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Introduction

Synthetic cannabinoid receptor agonists (synthetic cannabinoids), such as ADB-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* (CB_1 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 CB_1 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-3,3-dimethyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide (ADB-CHMINACA) on the basis of data reported by the Member States through 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 with Article 6 of the Council Decision, on 14 September 2017, the Council of the European Union requested that a risk assessment on ADB-CHMINACA should be carried out by the extended Scientific Committee of the EMCDDA.

In order to prepare for the risk assessment, 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

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([1]) (–)-*trans*-Δ^9-tetrahydrocannabinol.

([2]) The endocannabinoid system helps regulate a large number functions in the body. It consists of the cannabinoid CB_1 and CB_2 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.

a technical report. This technical report has been prepared for the risk assessment of ADB-CHMINACA that will be held at the EMCDDA premises in Lisbon on Tuesday 7 November 2017.

Some of the sections in this report were prepared under EMCDDA contracts (ref. CT.17.SAT.0084.1.0 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 ADB-CHMINACA.

Search strategy

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

Chemical structure-based searches were done in SciFinder® (American Chemical Society, Chemical Abstract Service) and Reaxys® (Elsevier) databases using both the exact structure of ADB-CHMINACA and a similarity search. Structural and text-based searches in the SureChEMBL patent database retrieved no relevant hits.

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 terms used were: 'ADB-CHMINACA' and 'MAB-CHMINACA'.

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.

Cursory, though repeated, inspections of Internet forums covered Bluelight, Drugs-forum, ecstasydata.org, Erowid, Eve&Rave, Reddit and The Vespiary.

Additionally, the scientific networks of the authors were contacted to obtain information.

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 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 ADB-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.

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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-3,3-dimethyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide, also known as ADB-CHMINACA and MAB-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 dimethylaminobutanone linked group (ADB), a cyclohexylmethyl tail (CHM), an indazole core (INA) and a carboxamide linker (CA).

ADB-CHMINACA contains a stereogenic centre and therefore two possible enantiomers may exist, (*R*)- and (*S*)-ADB-CHMINACA. (*S*)-ADB-CHMINACA was originally described in a patent application by Pfizer Inc. and published in 2009 (compound 13) (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 ADB-CHMINACA detected within the European Union.

ADB-CHMINACA was first reported to the EMCDDA in 2014.

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 the valinamide analogue of ADB-CHMINACA called AB-CHMINACA ([13]) (EMCDDA, 2017d), 5F-MDMB-PINACA (5F-ADB) ([14]) (EMCDDA, 2017e), and CUMYL-4CN-BINACA ([15]) (EMCDDA, 2017f) have also been the subjects of EMCDDA–Europol Joint Reports.

([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]) 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.

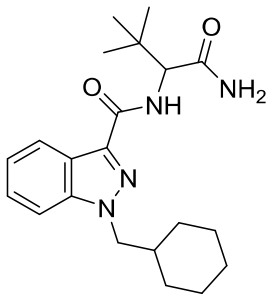
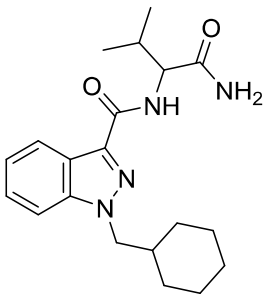
([11]) 5F-APINACA: *N*-(Adamantan-1-yl)-1-(5-fluoropentyl)-1*H*-indazole-3-carboxamide.

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

([13]) AB-CHMINACA: *N*-[(2*S*)-1-amino-3-methyl-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.

	
$C_{21}H_{30}N_4O_2$	$C_{20}H_{28}N_4O_2$
370.50 g/mol	356.47 g/mol
Figure 1. The molecular structure, molecular formula and molecular mass of ADB-CHMINACA (left) and AB-CHMINACA (right).	

Names and other identifiers

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

N-(1-Amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide.

Chemical Abstract name:

1*H*-Indazole-3-carboxamide, *N*-[(1*S*)-1-(aminocarbonyl)-2,2-dimethylpropyl]-1-(cyclohexylmethyl)-

1*H*-Indazole-3-carboxamide, *N*-[1-(aminocarbonyl)-2,2-dimethylpropyl]-1-(cyclohexylmethyl)-

Other names:

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

N-(1-Carbamoyl-2,2-dimethyl-propyl)-1-(cyclohexylmethyl)indazole-3-carboxamide;

N-(1-Amino-3,3-dimethyl-1-oxo-2-butanyl)-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide;

N-(1-Amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide;

N-[(2*S*)-1-amino-3,3-dimethyl-1-oxobutan-2-yl]-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide ((*S*)-enantiomer);

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

*N*α-[1-(Cyclohexylmethyl)-1*H*-indazole-3-yl-carbonyl]-3-methyl-L-valinamide.

Chemical Abstract Service Registry Numbers (CAS RNs) ([16])

1863065-92-2: racemate

1185887-13-1: ((S)-enantiomer)

PubChem SID:

68894304 ((*S*)-enantiomer) ([17])

IUPAC International Chemical Identifier Key (InCHI Key) ([18]):

ZWCCSIUBHCZKOY-UHFFFAOYSA-N (racemate)

ZWCCSIUBHCZKOY-GOSISDBHSA-N ((*S*)-enantiomer);

SMILES ([19]):

CC(C)(C)C(C(=O)N)NC(=O)c1c2ccccc2n(n1)CC3CCCCC3 (racemate);

CC(C)(C)[C@H](NC(=O)c1nn(CC2CCCCC2)c3ccccc13)C(N)=O ((S)-enantiomer)

Common names: ADB-CHMINACA, MAB-CHMINACA.

Street names:

ADB-CHMINACA; MAB-CHMINACA; 'Spice'; 'K2', 'legal weed', 'synthetic cannabis', 'herbal incense'.

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

ADB-CHMINACA has been described as a white powder (SWGDRUG, 2016), crystalline solid (Cayman Chemical Company, 2014) and neat solid (Cayman Chemical Company, 2016). It is soluble in dichloromethane (DCM), methanol (MeOH) and is poorly soluble in water (Slovenian National Forensic Laboratory, 2016). Its solubility has also been described as follows: ~0.5 mg/mL in 1:1 dimethyl sulfoxide:phosphate-buffered saline (pH 7.2); ~1 mg/mL in ethanol; ~10 mg/ml in dimethyl sulfoxide and ~5 mg/mL in *N*,*N*-dimethylformamide (Cayman Chemical Company, 2014). The reported melting point for

([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.

([17]) https://pubchem.ncbi.nlm.nih.gov/compound/68894304

([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.

ADB-CHMINACA is 141.5 °C (SWGDRUG, 2016). ADB-CHMINACA has been typically seized in 'herbal' material and in powder form. A more detailed description of seizures and collected samples reported to the EMCDDA can be found in Section C.

ADB-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 due to the use of the reagent L-*tert*-leucinamide in its preparation. 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 may affect its biological activity, including activity on the 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).*

Chemical stability and typical reactions

For long-term storage it is recommended that ADB-CHMINACA, supplied as a solid, is stored at -20 °C (Cayman Chemical Company, 2016). In the case of the AB-CHMINACA analogue, it has been reported that hydrolysis of the terminal amide function can occur as a consequence of smoking but also following deposition on human hair (Franz et al., 2016a), which suggested that this degradation was not reserved solely for a metabolic transformation. It seems conceivable that a similar phenomenon, i.e. formation of the carboxylic acid derivative, might be observable for ADB-CHMINACA as well. A study assessing the freeze/thaw stability (3 cycles, at least 20 h freezing and one hour thawing at room temperature) in serum revealed that ADB-CHMINACA degraded only 3.6%. A long-term storage stability study in serum showed that ADB-CHMINACA was stable for at least 31 days at -20 °C (decomposition occurred at/after 105 days), 31 days at 4 °C (but unstable at 105 days), and over 315 days at room temperature (stability criterion: measured degradation below 20%) (Hess et al., 2016).

Analytical profile

Analytical data for ADB-CHMINACA is abundantly available and several studies have explored its characterization and detection in various matrices such as 'herbal mixtures', powders and biofluids (Table 1). The analysis of biological samples requires sensitive methods of analysis, e.g. liquid chromatography coupled to tandem mass spectrometry approaches, especially when blood-derived samples are involved. The detection of synthetic cannabinoid metabolites is a frequently chosen method for urine analysis although there are examples where the parent synthetic cannabinoid species has been targeted quantitative analysis in this particular matrix (Minakata et al., 2017).

Table 1. Studies associated with the detection and chemical analysis of ADB-CHMINACA (amongst other substances) published in the scientific literature.

Techniques [a]	**Comment**	**Reference**
^{1}H-NMR, API-MS	Synthesis and characterization.	Buchler et al. (2009)
GC-MS; LC-MS/MS	Intoxication cases and analysis of biofluids.	Franz et al. (2015)
LC-QqQ-MS/MS	Detection of ADB-CHMINACA in biofluids and tissue samples obtained from a fatal intoxication.	Hasegawa et al. (2015a)
LC-QTOF-MS	Detection of ADB-CHMINACA in	Kasper et al. (2015)

	serum samples.	
Not reported.	Detection of ADB-CHMINACA in biofluids.	Trecki et al. (2015)
GC-MS, LC-QqQ-MS/MS	Detection of ADB-CHMINACA in 'herbal mixture'.	Wurita et al. (2015)
LC-QqQ-MS/MS	Analysis of blood samples obtained from two intoxication cases.	Adamowicz and Gieron (2016)
GC-MS, LC-TOF-MS	Characterization of reference material.	Akamatsu and Yoshida (2016)
Not reported	Detection of ADB-CHMINACA in fatal intoxication cases.	Babel et al. (2016)
LC-QTOF-MS	Blood analysis involving fatal intoxication.	Bottei et al. (2016)
Immunoanalysis, LC-MS/MS	Evaluation of immunoassays using authentic urine samples.	Franz et al. (2016b)
LC-MS/MS	Analysis of urine and serum samples obtained from an intoxication case.	Hermanns-Clausen et al. (2016)
LC-QTRAP-MS/MS	Stability studies in human plasma.	Hess et al. (2016)
GC-MS	Identification in samples obtained from dealer.	Kaizaki-Mitsumoto et al. (2016)
LC-MS	Analysis of serum samples collected from 11 acute intoxication cases.	Katz et al. (2016)
GC-TOF-MS, GC-EI-MS, NMR, LC-MS/MS, IR, UV	Identification in 'herbal mixtures' collected from Internet retailers.	Langer et al. (2016)
GC-MS, LC-TOF-MS, ATR-FTIR, GC-MS, GC-IR, IC	Characterization of test purchase sample.	Slovenian National Forensic Laboratory (2016)
Melting point, ^{1}H-NMR, GC-MS, ATR-FTIR	Characterization of reference material.	SWGDRUG (2016)
LC-Q-Orbitrap-MS/MS	Metabolism study using ten-donor-pooled cryopreserved human hepatocytes.	Carlier et al. (2017a)
LC-MS/MS	Analysis of human urine sample obtained from autopsy and quantitation of two metabolites.	Hasegawa et al. (2017)
LC-MS/MS	Analysis of serum and urine samples collected from intoxication cases.	Hermanns-Clausen et al. (2017)
Not reported	Review of cases associated with motor vehicle collisions in Japan between 2012 and 2014.	Kaneko (2017)

GC-MS	Analysis of blood and urine specimen involved in intoxications between July 2015 and July 2016.	Mazer-Amirshahi et al. (2017)
LC-QTRAP-MS/MS	Analysis of urine samples obtained from autopsies.	Minakata et al. (2017)
LC-MS/MS	Detection in biofluids associated with intoxication cases.	Moosmann et al. (2017)
GC-MS	Analysis of products obtained from Internet retailers.	Müller et al. (2017)
LC-QqQ-MS/MS	Analysis of blood samples collected between March and December 2015.	Tynon et al. (2017)
LC-MS/MS, CB receptor activation assay using NanoLuc luciferase	Receptor assay development and analysis of authentic urine samples.	Cannaert et al. (2017)

[a] NMR: nuclear magnetic resonance spectroscopy; API: atmospheric pressure ionization; LC: liquid chromatography (various forms); GC: gas chromatography; MS: mass spectrometry; MS/MS: tandem mass spectrometry; QqQ: triple quadrupole; QTOF: quadrupole time-of-flight; EI: electron ionization; IR: infrared spectroscopy; UV: ultraviolet spectroscopy; ATR: attenuated total reflectance; FT: Fourier transform; IC: ion chromatography.

Methods and chemical precursors used for the manufacture

Synthesis

Information about the methods used for the synthesis of the ADB-CHMINACA that has been detected on the drug market in Europe has not been reported to the EMCDDA. However, it seems likely that the methods described in the work published by Pfizer Inc. (compound 13) might have been used for the manufacturing of this substance destined for the drug market. The specific conditions for the ADB-CHMINACA synthesis have not been disclosed, but the preparation of the synthetic cannabinoids covered followed the scheme shown in Figure 2. The final reaction step (c) involves the coupling of the acid intermediate (3) with L-*tert*-leucinamide, which yields the (*S*)-enantiomer of ADB-CHMINACA as disclosed by Buchler et al. (2009). Although not explicitly mentioned in the work published by these authors, employing D-*tert*-leucinamide or the D,L-racemate should theoretically give the (*R*)- and racemic form of ADB-CHMINACA. L-*tert*-Leucinamide can be prepared from L-*tert*-leucine (Banister et al., 2015, Buchler et al., 2009). If this intermediate were more readily available and less expensive than D-*tert*-leucine then one would expect this to have an impact on the manufacturing process, thus, potentially favouring the production of the (*S*)-form as originally disclosed by Pfizer Inc. A recent investigation on the isolation from another *tert*-leucine derived synthetic cannabinoid (MDMB-CHMICA) used in herbal smoking mixtures revealed that the compound was indeed showing the (*S*)-configuration (Andernach et al., 2016).

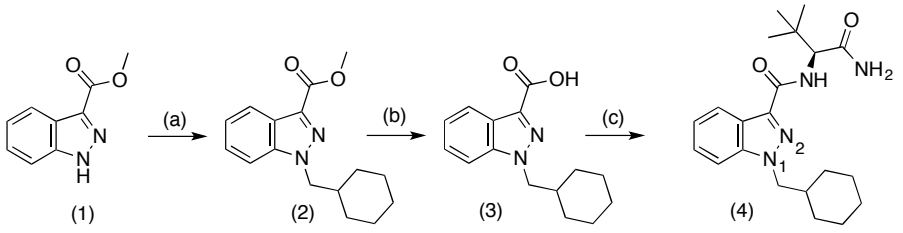


Figure 2. Synthesis route for ADB-CHMINACA ((*S*)-enantiomer) starting from methyl 1*H*-indazole-3-carboxylate

(which might also be prepared) (1). Reagents: (a) base (e.g. sodium hydride, potassium *tert*-butoxide, sodium hexamethyldisilazide, or potassium carbonate) and (X-methyl)cyclohexane (X = leaving group; e.g. halogen, mesilate, or tosylate) provide (2); (b) saponification with aqueous base (e.g. sodium hydroxide, potassium hydroxide, or lithium hydroxide) yields (3); (c) amide bond coupling with L-*tert*-leucinamide using a carboxyl group activating reagent provides (4) (e.g. *N,N´*-dicyclohexylcarbodiimide (DCC) or 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC), either alone or in combination with 1-hydroxybenzotriazole (HOBt) and uronium reagents such as *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), *O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), or *O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU)). The two nitrogen atoms found in the indazole ring of ADB-CHMINACA (4) have been numbered indicate the site of alkylation ([20]).

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 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 analysis of an ADB-CHMINACA sample purchased from an Internet retailer was reported to contain an unidentified impurity (Slovenian National Forensic Laboratory, 2016). It was commented that the impurity might have been related to an impurity detected in a test purchased APP-CHMINACA product ([21]). In this case, the reported impurity was characterized by the presence of a second cyclohexylmethyl substituent on the molecule (Slovenian National Forensic Laboratory, 2015), which might be consistent with dialkylation. Although not documented, the N1-alkylation can be carried out on the indazolyl *tert*-leucinamide derivative as the last step under conditions described for serotonin receptor antagonists (Furlotti et al., 2012; Schaus et al., 1998) and, recently, for the preparation of a metabolite of the synthetic cannabinoid receptor agonist AKB-48 (Wallgren et al., 2017). In addition, it has been reported that the preparation of various indazole-based synthetic cannabinoids can result in the formation of another regioisomer that is alkylated at the N2-position, which was shown to depend on the base used for the alkylation reaction (Buchler et al., 2009, Longworth et al., 2016). However, reports on the detection of these synthesis by-products could not be identified.

A1.2. Physical/pharmaceutical form

Data from seizures and collected samples reported to the EMCDDA have revealed that ADB-CHMINACA has typically been detected in plant/herbal material (herbal smoking mixtures) and powders. A small number of other forms have also been encountered, which included blotters, 'agglomerated material' containing other synthetic cannabinoids and substances such as caffeine, a 'slab' mixed with another synthetic cannabinoid (MDMB-CHMICA) and a 'lump' containing various additional synthetic

([20]) The detection of a 'dicyclohexylmethylated' contaminant in ADB-CHMINACA samples (Slovenian National Forensic Laboratory, 2016; see also next paragraph) suggests an alternative production method in which a cyclohexylmethyl derivative alkylating agent is reacted with the *N*-indazolyl-*tert*-leucinamide (*N*-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1*H*-indazole-3-carboxamide). Overalkylation could, in theory, take place not only at the indazole *N*-atom but also at the nitrogen – or even of the oxygen – atom of the amide group(s).

([21]) APP-CHMINACA (PX3): *N*-[(2*S*)-1-Amino-1-oxo-3-phenylpropan-2-yl]-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide.

cannabinoids apart from ADB-CHMINACA (AB-FUBINACA ([22]), 5F-ADB-PINACA ([23]) and FUB-APINACA ([24])) (EMCDDA, 2017c). The Pfizer Inc. patent also refers to 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

The most common route of administration for synthetic cannabinoids is smoking ready-to-use or self-prepared 'herbal mixtures' as a joint or utilizing a vaporizer, 'bong' or pipe. Because these ready-to-use products rarely state the ingredients, most users may be unaware that they are using ADB-CHMINACA.

In addition, and, unknown to users, the concentrations of synthetic cannabinoids found in smoking mixtures can vary dramatically, which may range from low mg/g to hundreds of mg/g, depending on the potency of the substance and manufacturing practices involved (e.g. Ernst et al., 2017; Frinculescu et al., 2017; Langer et al., 2014; Langer et al., 2016; Moosmann et al., 2015) (Section D3.4).

Dosage

Limited information is available regarding the dose and the dose regimens of ADB-CHMINACA. User reports specifically about ADB-CHMINACA were not particularly revealing and it is not possible to discern the 'typical' dosages administered by users.

One website lists the following dosage information for the valinamide analogue AB-CHMINACA (smoking): 'light': 50–100 µg; 'common': 100–250 µg; 'strong': 250–400 µg; 'heavy': 400+ µg (Tripsit, 2017). As already highlighted in the introduction, the assessment of such reports is problematic not least because users cannot confirm the actual substance used. Information about the extent to which this can be translated to ADB-CHMINACA could not be identified.

A2. Pharmacology, including pharmacodynamics and pharmacokinetics

Pharmacologically, ADB-CHMINACA is a cannabinoid receptor agonist.

Pharmacodynamics

The limited available data suggest that ADB-CHMINACA binds to and activates the cannabinoid CB_1 receptor. For example, ADB-CHMINACA was reported to bind to the human CB_1 receptor expressed and prepared from human embryonic kidney cells with a K_i value of 0.289 nM (radioligand [^{3}H]CP-55,940) ([25]), which compared to a K_i value of 0.519 nM for AB-CHMINACA (Buchler et al., 2009). The United States Drug Enforcement Administration reported a K_i value of 0.49 nM (experimental details not provided

([22]) AB-FUBINACA: *N*-[(2*S*)-1-Amino-3-methyl-1-oxobutan-2-yl]-1-[(4-fluorophenyl)methyl]-1*H*-indazole-3-carboxamide.

([23]) 5F-ADB-PINACA: *N*-[(2*S*)-1-Amino-3,3-dimethyl-1-oxobutan-2-yl]-1-(5-fluoropentyl)-1*H*-indazole-3-carboxamide.

([24]) FUB-APINACA: *N*-(Adamantan-1-yl)-1-[(4-fluorophenyl)methyl]-1*H*-indazole-3-carboxamide.

([25]) K_i represents the equilibrium inhibition constant for the test drug displacing the radioligand.

including information about the absolute configuration) (US DEA, 2014). When using the *in vitro* [^{35}S]GTPγS binding assay (receptors expressed in Chinese hamster ovary cells), the EC_{50} value reported for ADB-CHMINACA was 0.620 nM ([26]), which suggests that this compound was a potent agonist although efficacy information was not reported. In comparison, the EC_{50} value reported for AB-CHMINACA was 2.55 nM, indicating that ADB-CHMINACA was 4 times more potent than its valinamide counterpart (Buchler et al., 2009). A comparison between efficacies could not be made since these data were not reported. Functional activity studies using the same assay (details not reported) produced via the DEA-VA Interagency Agreement revealed an EC_{50} value of 0.214 nM (US DEA, 2014), similarly indicating that ADB-CHMINACA displays potency values in the sub-nanogram range. The reason as to why the patent published by Pfizer only explicitly featured the (*S*)-enantiomers (Buchler et al., 2009) has not been disclosed and it is not known whether the (*R*)-forms showed reduced biological activity ([27]). A recent study exploring the differences in functional activity (*in vitro* [^{35}S]GTPγS binding assay) between five pairs of enantiomeric synthetic cannabinoids, namely AB-FUBINACA (2-fluorobenzyl isomer) ([28]), APP-CHMINACA ([29]), EMB-FUBINACA ([30]), 5F-EMB-PINACA, and MDMB-FUBICA ([31]), revealed that agonist activity at CB_1 and CB_2 receptors was retained in most of the (*R*)-enantiomers. A drop in potency was determined at CB_1 but not always at the CB_2 receptor. (*R*)-MDMB-FUBICA, however, was reported to have lost activity at the CB_1 receptor (Doi et al., 2017).

A recent study reported $CB_{1/2}$ receptor EC_{50} values and activation efficiency data (via β-arrestin 2 recruitment), for a range of synthetic cannabinoids, including ADB-CHMINACA, and some hydroxylated urinary metabolites (Cannaert et al., 2017). In the case of ADB-CHMINACA, the respective EC_{50} values for the CB_1 and CB_2 receptor are 1.49 and 2.2 nM in this assay system. For JWH-018, which was one of the comparative drugs, the respective EC_{50} values for the CB_1 and CB_2 receptor were 23.9 and 6.8 nM, which suggested a 16-fold (CB_1) and 3.1-fold (CB_2) increase in potency compared to JWH-018. $CB_{1/2}$-mediated receptor activation data relative to JWH-018 (concentration of all test drugs 10 µM) have also been investigated and summarized in Table 2 below, which revealed that ADB-CHMINACA was almost two times more effective than JWH-018 in activating the CB_1 receptor. In comparison, CB_2 receptor activation induced by ADB-CHMINACA was observed to reach the 82% level. 4-HO-AB-CHMINACA, one of the three metabolites investigated, was capable of inducing a slightly stronger CB_1 receptor activation than JWH-018. The extent to which these metabolites contribute to psychoactive effects *in vivo* remains to be investigated. The effect of ADB-CHMINACA on pharmacological or biochemical targets other than the cannabinoid receptors has not been studied.

Table 2. Receptor activation efficacy of ADB-CHMINACA and three of its metabolites ± SEM (number of replicates) relative to JWH-018 (modified from Canneart et al., 2017).

([26]) EC_{50} represents the half maximal effective concentration.

([27]) The chiral amino acid precursor (*S*)-L-tert-Leucine is widely used for the manufacture of antiviral medicines (such as the HIV protease inhibitor atanazavir or the hepatitis C virus protease inhibitors asunaprevir, bocepvir, grazoprevir, faldaprevir, narlaprevir, telaprevir, vaniprevir). (*S*)-L-*tert*-Leucine is produced mainly in China in large, multi-ton quantities. This may explain the choice of this precursor for the synthesis of ADB-CHMINACA and other related synthetic cannabinoids including MDMB-CHMICA (EMCDDA, 2017g) that have been reported to the EMCDDA through the EU Early Warning System

([28]) AB-FUBINACA (2-fluorobenzyl isomer): *N*-[1-Amino-3-methyl-1-oxobutan-2-yl]-1-[(2-fluorophenyl)methyl]-1*H*-indazole-3-carboxamide.

([29]) APP-CHMINACA (PX3): *N*-[1-Amino-1-oxo-3-phenylpropan-2-yl]-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide.

([30]) EMB-FUBINACA: Ethyl 2-({1-[(4-fluorophenyl)methyl]-1*H*-indazole-3-carbonyl}amino)-3-methylbutanoate.

([31]) MDMB-FUBICA: Methyl 2-({1-[(4-fluorophenyl)methyl]-1*H*-indole-3-carbonyl}amino)-3,3-dimethylbutanoate.

Drug/metabolite	Relative efficacy of CB_1 activation at 10 µM	Relative efficacy of CB_2 activation at 10 µM
JWH-018	100 ± 4.6 (4)	100 ± 19.9 (4)
ADB-CHMINACA	194.3 ± 13.7 (4)	82.1 ± 10.6 (4)
4-OH-ADB-CHMINACA (M1) ([32])	110.5 ± 6.0 (4)	62.1 ± 8.67 (4)
tert-Leucine-ADB-CHMINACA (M2) ([33])	56.9 ± 4.3 (4)	85.7 ± 12.8 (4)
tert-Leucine-4-OH-ADB-CHMINACA (M3) ([34])	36.4 ± 4.3 (4)	70.9 ± 11.6 (4)

Animal studies

Information derived from animal studies could not be identified, although it seems conceivable that ADB-CHMINACA would display activity in assays that probe for Δ^9-THC-like properties such as drug discrimination or mouse tetrad tests similar to what has been demonstrated with AB-CHMINACA. In the tetrad test battery that evaluates drug-induced changes in spontaneous motor activity, antinociception, ring immobility, and body temperature, AB-CHMINACA (i.p. administration) was shown to be 11- to 58 times more potent than Δ^9-THC (Wiley et al., 2015).

Pharmacokinetics

An incubation study with ten-donor-pooled cryopreserved human hepatocytes (10 µmol/L ADB-CHMINACA, 3 h) identified ten major phase I metabolites (Figure 3). Key reactions included oxidation of the cyclohexylmethyl substituent into hydroxylated (A4–A6, A8 and A9) or ketone (A7) species; *tert*-butyl hydroxylation (A10), and dihydroxylation (A1, A2, A3) also occurred to some extent. Interestingly, transformations at the indazole core, the carboxamide linker, or the dimethylbutanamide side chain (including hydrolysis of the terminal amide) were not observed (Carlier et al., 2017a). Correspondingly, the ADB-CHMINACA species hydroxylated at the cyclohexylmethyl substituent have been recommended as compound-specific analytical targets.

([32]) 4-OH-ADB-CHMINACA (M1): *N*-[(2*S*)-1-Amino-3,3-dimethyl-1-oxobutan-2-yl]-1-[(4-hydroxycyclohexyl)methyl]-1*H*-indazole-3-carboxamide.

([33]) *tert*-Leucine-ADB-CHMINACA (M2): (2*S*)-2-{[1-(Cyclohexylmethyl)-1*H*-indazole-3-carbonyl]amino]}-3,3-dimethylbutanoic acid.

([34]) *tert*-Leucine-4-OH-ADB-CHMINACA (M3): (2*S*)-2-({1-[(4-Hydroxycyclohexyl)methyl]-1*H*-indazole-3-carbonyl}amino)-3,3-dimethylbutanoic acid.

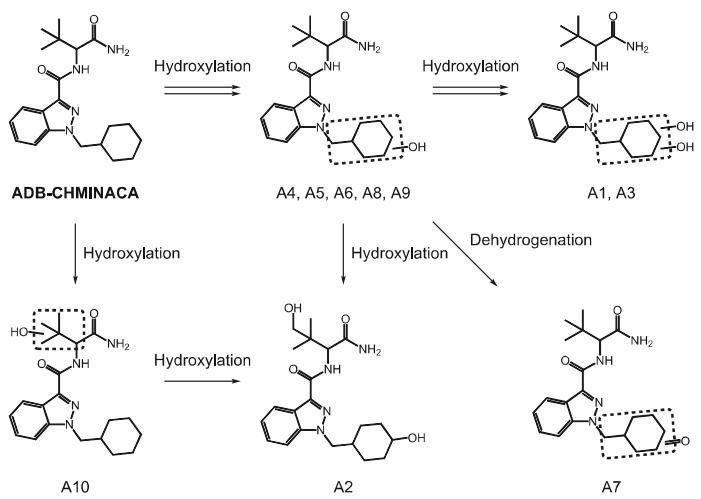


Figure 3. Proposed metabolic pathway of ADB-CHMINACA. Dominant pathways are indicated by double arrows (Carlier et al., 2017a).

Interestingly, no phase II reaction products have been observed and amide hydrolysis resulting in the formation of the carboxylic function has also not been detected under the conditions studied, which deviated from incubation studies carried out with the L-*tert*-leucinamide derivative ADB-FUBINACA ([35]) where more extensive biotransformations (23 metabolites) were observed (Carlier et al., 2017b). In the case of ADB-FUBINACA, the cyclohexylmethyl substituent found in ADB-CHMINACA is replaced by a (4-fluorophenyl)methyl moiety. An investigation into the quantitation of ADB-CHMINACA metabolites in authentic urine specimen collected from an autopsy case performed in 2014 has recently been reported. Two hydroxylated metabolites were investigated, namely the (4-hydroxycyclohexyl)methyl derivative of ADB-CHMINACA (2.17 ng/mL) and its *tert*-butyl hydroxylated derivative (10.2 ng/mL) (Hasegawa et al., 2017), which would reflect the metabolites A4 and A2 reported by Carlier et al. (Carlier et al., 2017a) (Figure 3). The parent molecule ADB-CHMINACA has been shown to be still detectable in authentic urine samples at a concentration of 229 pg/mL (Minakata et al., 2017).

A number of ADB-CHMINACA metabolites have been detected in authentic human urine samples (unpublished observations): the (4-hydroxycyclohexyl)methyl metabolite (M1) ([36]) and its regioisomeric alcohol (hydroxylation site is not specified); the hydrolysed terminal amide species (M2), and the 4-hydroxycyclohexyl)methyl analogue of the hydrolysed terminal amide (M3) and four M3 isomers (Table 2) (Cannaert et al., 2017).

Additional information on the pharmacokinetic properties of ADB-CHMINACA could not be identified.

Relevant user reports on the Internet about ADB-CHMINACA's effect profile are limited.

([35]) ADB-FUBINACA: *N*-[(2*S*)-1-Amino-3,3-dimethyl-1-oxobutan-2-yl]-1-[(4-fluorophenyl)methyl]-1*H*-indazole-3-carboxamide.

([36]) The designations M1–M3 were based on the reference materials offered by the Chemical Company, Ann Arbor, M, USA.

Based on an *in vitro* assay evaluating the changes of membrane potentials following G-protein activation, it was found that the transition from a L-valinamide to L-*tert*-leucinamide moiety led to an increase in potency at the CB_1 receptor, at least in some cases (Banister et al., 2016, Banister et al., 2015). However, it is not known how this would translate to ADB-CHMINACA despite structural similarity.

Inter-individual genetic variability in metabolising enzymes

No information specifically for ADB-CHMINACA has been identified.

Interactions with other substances and other interactions

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

Effects on ability to drive and operate machines

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

A3. Psychological and behavioural effects

While there is limited data, the psychological and behavioural effects of ADB-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

ADB-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 ADB-CHMINACA is used for other legitimate purposes.

There are no reported uses of ADB-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 returned no results.

There is no marketing authorisation (existing, on-going or suspended) for ADB-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 ADB-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 ADB-CHMINACA is currently used in the manufacture of a medicinal product.

Section B. Dependence and abuse potential

B1. Animal data

No studies were identified that have investigated the dependence and/or abuse potential of ADB-CHMINACA in animal models.

B2. Human data

No studies were identified that have investigated the dependence and/or abuse potential of ADB-CHMINACA in humans. However, it has been suggested that consumption of synthetic cannabinoids can produce tolerance and withdrawal symptoms when use is abruptly discontinued following a regular use (Cooper, 2016, Macfarlane and Christie, 2015, Van Hout and Hearne, 2017).

Section C. Prevalence of use

Information from seizures, collected and biological samples

ADB-CHMINACA was formally notified on 24 September 2014 by the EMCDDA on behalf of the Hungarian National Focal Point, in accordance with Article 4 of the Council Decision. The Reporting Form details a seizure of 2.07 grams of light brown powder that was seized in August 2014 by Hungarian Police in Hajós. The identification and analytical characterisation was based on GC-MS, FT-IR and NMR analysis.

Since then, a total of 17 Member States (Belgium, Croatia, Estonia, Finland, France, Germany, Greece, Hungary, Latvia, Lithuania, the Netherlands, Poland, Romania, Slovenia, Spain, Sweden and the United Kingdom), Turkey and Norway have reported detections of ADB-CHMINACA (EMCDDA, 2017c).

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

Information from seizures

A total of 19 countries reported seizures ([37]) of ADB-CHMINACA to the EMCDDA and/or Europol ([38]).

Information reported to the EMCDDA and Europol indicates that 3794 seizures of ADB-CHMINACA have been reported by: Belgium (16), Croatia (2), Estonia (2), Finland (10), France (3), Germany (2), Greece (1), Hungary (75), Latvia (33), Lithuania (1), the Netherlands (1), Norway (2), Poland (233), Romania (1), Slovenia (1), Spain (1), Sweden (83), Turkey (3162) and the United Kingdom (165).

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

([37]) 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 EWS progress and final reports) and from individual Reporting forms submitted on an ad hoc basis.

([38]) The United Kingdom reported additional seizures of ADB-CHMINACA after the production of the Joint Report.

The most commonly seized physical forms were herbal (plant) materials and powders. A small number of seizures of blotters and other physical forms were also reported.

Physical forms seized included: herbal material (485 seizures; amounting to a total weight of 11 kg), powders (76; 9.8 grams) and blotters (41; 25.35 grams and 2 blotters). Other physical forms were encountered in 22 of the cases (258.8 grams).

No quantitative information on the purity of ADB-CHMINACA in seized samples was provided to the EMCDDA.

Herbal material

485 seizures of ADB-CHMINACA in herbal material were reported by 13 countries: Croatia, Estonia, Germany, Greece, Hungary, Latvia, Lithuania, Norway, Poland, Romania, Slovenia, Sweden and the United Kingdom, amounting to nearly 11 kg seized.

Turkey reported around 3160 seizures of herbal material amounting to almost 128 kg which have not been included in the total count ([39]).

The largest single seizure of ADB-CHMINACA in herbal material was reported by Germany; 1.66 kg of a mixture containing ADB-CHMINACA, 5F-AMB-PICA, EMB-FUBINACA, 5F-APP-PINACA, THC and cannabidiol.

Greece reported a seizure of nine bags of herbal material, found to contain just over 1 kg of ADB-CHMINACA mixed with 5F-AMB. The seizure was made during a raid on a tobacco store in Drama, where a number of products containing other synthetic cannabinoids were seized.

In just over 30% of all cases involving herbal material, ADB-CHMINACA was often found mixed with other synthetic cannabinoids.

Powders

A total of 76 seizures of powders were reported by 10 countries: Belgium, Finland, France, Hungary, Latvia, the Netherlands, Poland, Spain, Sweden and Turkey, amounting to a total of 9.8 kg.

In just over 90% of all cases involving powders, ADB-CHMINACA was the only substance detected.

The largest single seizure of ADB-CHMINACA in powder form was 3 kg that was reported by Belgium. The consignment was seized by customs. It originated in China and was in transit to Austria and Romania.

Turkey reported 2 large seizures of powders:

- 1.84 kg, containing ADB-CHMINACA, FUBIMINA, FUB-AKB, AMB-FUBINACA and NEP;
- 1 kg, containing ADB-CHMINACA mixed with THC, cannabinol and cannabidiol.

([39]) Minimum estimate provided by the Turkish national focal point for 2016.

Blotters

Seizures of blotters containing ADB-CHMINACA were reported by Poland (40 cases; 25.35 g) and Sweden (1 case; 2 blotters).

Other physical forms

Poland reported 19 seizures of 'agglomerated material' containing ADB-CHMINACA mixed with either caffeine (14 cases) or 5F-AKB48 (5), amounting to a total of over 235 g of substance.

One seizure of a 'slab' containing ADB-CHMINACA mixed with MDMB-CHMICA was reported by Estonia (13.4 g); one case of a 'lump' containing ADB-CHMINACA, AB-FUBINACA, 5F-ADB-PINACA and FUB-APINACA was reported by Norway (9.7 g) and one seizure of a 'paste-like substance' was reported by Finland (0.7 g).

Information from collected samples

Two collected samples of ADB-CHMINACA were reported to the EMCDDA by:

- Slovenia, 5 g of white powder purchased online as '5F-AEB' from China, and;
- Germany, ADB-CHMINACA identified as one of many substances in a number of powder samples collected from a scene of a death.

Information from biological samples

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

Additionally, a total of 28 analytically confirmed detections of ADB-CHMINACA in biological samples were reported by two Member States ([40]). Briefly these were:

- 22 cases related to drug abuse (consumption), intoxication or non-fatal intoxication, with no further details provided, Hungary (16 cases), Poland (6).
- 6 cases related to persons suspected of driving under the influence of drugs, all reported by Hungary.

Availability, supply, price

Information on production

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

Information on trafficking

([40]) Turkey reported 181 biological samples (blood, hair and urine) which may contain duplicates and therefore have not been included in the total count.

Information related to trafficking routes is limited. In cases reported to the EMCDDA, China was indicated as a source country in a customs seizure made in Belgium and collected sample reported by Slovenia. In addition, in two cases that were reported to Europol, one involved a courier seizure in Estonia that reportedly originated in Russia, and the second involved the interception of a postal package intercepted by customs in Bulgaria that arrived from Spain.

Availability from Internet vendors

The available data suggests that ADB-CHMINACA is sold openly online under its own name as powder and in herbal smoking mixtures (where the ingredients/composition is sometimes not stated). A structured search of online vendors on the surface web by the EMCDDA ([41]) found that the substance is available online in small and wholesale amounts as a 'research chemical' and as 'aroma blends', a common reference to 'legal-high' type products containing synthetic cannabinoids.

On the websites identified, ADB-CHMINACA powders were available in amounts ranging from 1 gram to 3 kg. Prices varied according to the amounts on sale and ranged from EUR 1.43 per gram to EUR 42.5 per gram.

The availability of ADB-CHMINACA on the darknet is not currently known.

Prevalence of use

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

Similar to other synthetic cannabinoids, ADB-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 ADB-CHMINACA and its prevalence of use. Overall, the available information does not suggest widespread use of the substance.

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 ADB-CHMINACA. As a result, the prevalence of use of ADB-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

([41]) The search for online vendors of ADB-CHMINACA on the surface web was performed in October 2017. The search identified 5 vendors that appeared to be based in, and/or claim to have presence in China (n=2; 1 of which in Hong Kong), Hungary (n=1) and Sweden (n=1); the remaining website did not list a location. Three websites listed quantities and prices for ADB-CHMINACA. The remaining sites only provided prices on request.

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

Data on the acute toxicity, abuse liability or dependence producing potential of ADB-CHMINACA could not be identified.

D1.2. Human data

No clinical studies were identified that have examined the acute health effects of ADB-CHMINACA and/or its metabolites in humans. Data from serious adverse events associated with ADB-CHMINACA are discussed below. In general, the acute health risks associated with ADB-CHMINACA appear to be similar to those found with other synthetic cannabinoids.

As synthetic cannabinoids activate the CB_1 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), rapid loss of consciousness/coma, respiratory depression, seizures and convulsions, hyperemesis, delirium, agitation, psychosis, and aggressive and violent behaviour (Adams et al., 2017; Brenneman et al., 2016; Capron, 2016; Ford et al., 2017, Hermanns-Clausen et al., 2013; EMCDDA, 2017c, EMCDDA, 2017d, EMCDDA, 2017e; 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 3 acute intoxications with confirmed exposure to ADB-CHMINACA were reported by the United Kingdom ([42]). The cases occurred during 2016. In 1 case, no other substances were detected. In the remaining 2 cases, another synthetic cannabinoid was detected. All the cases included clinical features of poisoning similar to those reported for other synthetic cannabinoids.

Acute intoxications identified from other sources

Table 4 provides a summary of non-fatal intoxications and cases of suspected driving under the influence of drugs identified in the literature involving confirmed exposure to ADB-CHMINACA. Where reported, the range of ADB-CHMINACA concentration in serum ranged from 0.22 to 31 ng/mL. The clinical features of poisoning were similar to those reported for other synthetic cannabinoids.

([42]) In addition, Germany reported 8 acute intoxications with possible exposure to ADB-CHMINACA and Sweden reported 2 acute intoxications with suspected exposure to ADB-CHMINACA. These cases are not discussed further in this report.

Table 4. Non-fatal intoxications and driving under the influence cases associated with confirmed exposure to ADB-CHMINACA

Type of event	Number of cases	Country	Age	Gender	ADB-CHMINACA analytical confirmation	Other drugs present	Reported symptoms	Treatment provided	Additional information	Reference
Non-fatal intoxication	1	Poland	17	female	Concentration of MAB-CHMINACA in blood: 5.2 ng/mL	diazepam (155 ng/mL) and nordiazepam (12 ng/mL) present in blood sample (patient received diazepam in the hospital). The blood analyses did not reveal any other substance (including alcohol, classic drugs as well as other NPS).	Vomiting, unresponsive, seizures, unnaturally twisted limbs. On admission to the hospital unconscious or with periodic losses of consciousness, verbally incoherent. Acute respiratory failure, wheezing and muscle tremors were observed. After regaining consciousness: aggression, agitation, slurred speech, enlarged pupils, poorly responsive to light were observed	diazepam	Patient had a history of NPS abuse. Patient smoked mixture of tobacco with a white powdered substance from a package labelled ‘‘AM-2201’’.	Adamowicz & Gieron (2016)
Non-fatal intoxication	1	Poland	17	female	Concentration of MAB-CHMINACA in blood: 1.3 ng/mL	The blood analyses did not reveal any other substance (including alcohol, classic drugs as well as other NPS).	On admission to the hospital unconscious or with periodic losses of consciousness, verbally incoherent.		Patient had a history of NPS abuse. Patient smoked mixture of tobacco with a	Adamowicz & Gieron (2016)

							Acute respiratory failure, wheezing and muscle tremors were observed. After regaining consciousness: aggression, agitation, slurred speech, enlarged pupils, poorly responsive to light were observed		white powdered substance from a package labelled ‘‘AM-2201’’.	
Non-fatal intoxication	1	Poland	15	male	Concentration of MAB-CHMINACA in blood: 1.7 ng/mL	The blood analyses did not reveal any other substance (including alcohol, classic drugs as well as other NPS).	On admission to the hospital unconscious or with periodic losses of consciousness, verbally incoherent. Acute respiratory failure, wheezing, muscle tremors and blood pressure spikes were observed. After regaining consciousness: aggression, agitation, slurred speech, enlarged pupils, poorly responsive to light were observed		Patient had a history of NPS abuse. Patient smoked mixture of tobacco with a white powdered substance from a package labelled ‘‘AM-2201’’.	Adamowicz & Gieron (2016)
Non-fatal intoxication	1	Poland	18	male	Concentration of MAB-CHMINACA in blood: 14.6 ng/mL	Diazepam (1205 ng/mL), nordiazepam (16 ng/mL) and temazepam (6 ng/mL) were present in blood	Vomiting, unresponsive, seizures, unnaturally twisted limbs. On admission to the hospital unconscious or with periodic	diazepam	Patient had a history of NPS abuse. Patient smoked mixture of tobacco with a white	Adamowicz & Gieron (2016)

						(patient received diazepam in the hospital). The blood analyses did not reveal any other substance (including alcohol, classic drugs as well as other NPS).	losses of consciousness, verbally incoherent. Acute respiratory failure, wheezing and muscle tremors were observed. After regaining consciousness: aggression, agitation, slurred speech, enlarged pupils, poorly responsive to light were observed		powdered substance from a package labelled ‘‘AM-2201’’.	
Non-fatal intoxication	>125	US	n/a	n/a	Positive result				Cluster of cases of adverse health effects or severe toxic effects. Oct 2014, Baton Rouge, LA	DHSL (2014)
Non-fatal intoxication	>41	US	n/a	n/a	11 out of 12 available samples were positive for ADB-CHMINACA				Cluster of cases of adverse health effects or severe toxic effects. Nov 2014, Bryan, TX	Trecki et al. (2015)
Non-fatal intoxication	>62	US	n/a	n/a	9 available samples were positive for ADB-CHMINACA	AB-PINACA ADB-PINACA			Cluster of cases of adverse health effects or severe toxic effects. Dec.	Trecki et al. (2015)

									2014–Jan 2015, Beaumont, TX	
Non-fatal intoxication	3	US	n/a	n/a					Cluster of cases of adverse health effects or severe toxic effects. Dec. 2014–Jan 2015, Salina, KS	Trecki et al. (2015)
Non-fatal intoxication	6	US	n/a	n/a					Cluster of cases of adverse health effects or severe toxic effects. Apr 2015, Philadelphia, MS	Trecki et al. (2015)
Non-fatal intoxication	7	US	n/a	n/a					Cluster of cases of adverse health effects or severe toxic effects. Apr 2015, Hampton, VA	Trecki et al. (2015)
Non-fatal intoxication	9	US	n/a	n/a					Cluster of cases of adverse health effects or severe toxic effects. Apr	Trecki et al. (2015)

									2015, Hagerstown, MD	
Non-fatal intoxication	19	US	n/a	n/a					Cluster of cases of adverse health effects or severe toxic effects. Apr 2015, Jackson, MS	Trecki et al. (2015)
Non-fatal intoxication	2	US	n/a	n/a					Dec 2014, Salina, KS	Trecki et al. (2015)
Non-fatal intoxication	14	Germany	17-46	12 male, 2 female	ADB-CHMINACA was identified in 13 (10) serum (urine) samples. Concentration in serum varied from 0.22 to 31 ng/mL (median 0.49 ng/mL).	In 7 cases more than one SC was found (4 times in urine samples only). Amphetamine derivatives were detected in 6 cases.	Ten patients reported panic attacks. Clinical features included tachycardia (n ¼ 9), recurrent vomiting (n ¼ 7), agitation (n ¼ 7), somnolence, disorientation, aggressiveness and shivering (each 6),dyspnea (n ¼ 5), seizures (n ¼ 2), bradycardia (n ¼ 2), double vision (n ¼ 1), and psychosis (n ¼ 1). Elevation of creatine kinase (CK, n ¼ 6) and of creatinine (n ¼ 4), hyperkalemia (n ¼ 2), and hypoglycemia		All patients recovered.	Hermanns-Clausen et al. (2017)

							(47 mg/dL, n ¼ 1) were also recorded. One patient developed posterior reversible encephalopathic syndrome (PRES), with recovery after 4 days. Extreme agitation and rioting was followed by muscle hematomas, rhabdomyolysis (maximum CK 166,000 U/L) and renal impairment (creatinine 1.7 mg/dL) in one case. A 25-year-old required mechanical ventilation after aspiration.			
Non-fatal intoxication	1	Germany	20	male	ADB-CHMINACA was identified in serum (31 ng/mL), and in urine.	Ketamine, which was therapeutically applied, was also found in serum (240 ng/mL).	Vomiting, restlessness, severe headache, disorientation, somnolence, impaired coordination, posterior reversible leucencephalopathy syndrome, fever, rhabdomyolysis			Hermanns-Clausen et al. (2017)
Non-fatal intoxication	14	US	n/a	n/a	Analytically confirmed				Patients who presented to two academic EDs in	Mazer-Amirshahi et al.

									Washington with reported SC exposure from July 2015 to July 2016	(2017)
Non-fatal intoxication	10	US	n/a	n/a	Serum specimens positive for ADB-CHMINACA or its metabolite				Apr 2015, Jackson Mississippi	Kasper et al. (2015)[§]
Non-fatal intoxication	1	US	18	male	Serum specimens positive for ADB-CHMINACA	Urine: caffeine	Unresponsiveness, agitation, tachycardia,	Sedative for agitation	Patient smoked 'K2'	Katz et al. (2016)
Non-fatal intoxication	1	US	28	male	Serum specimens positive for ADB-CHMINACA	Urine: Caffeine, morphine, midazolam, lorazepam	Unresponsiveness, hallucinations, tachycardia,	Sedative for agitation; endotracheal intubation	History of substance abuse and hepatitis. Patient developed aspiration pneumonia.	Katz et al. (2016)
Non-fatal intoxication	1	US	17	female	Serum specimens positive for ADB-CHMINACA	Urine: Lorazepam	Agitation, delirium, tachycardia	Sedative for agitation (benzodiazepines)		Katz et al. (2016)
Non-fatal intoxication	1	US	14	male	Serum specimens positive for	Urine: norfentanyl	Unresponsiveness, agitation	Sedative for agitation; endotracheal	Patient smoked 'K2'	Katz et al. (2016)

					ADB-CHMINACA			intubation		
Non-fatal intoxication	1	US	13	female	Serum specimens positive for ADB-CHMINACA	Urine: phenylephrine, midazolam, fentanyl, norfentanyl, diphenhydramine, cotinine	Patient was found Intermittently responsive, combative. Tachycardia	Sedative for agitation (benzodiazepines); endotracheal intubation	History of marijuana abuse	Katz et al. (2016)
Non-fatal intoxication	1	US	13	male	Serum specimens positive for ADB-CHMINACA	Urine: lorazepam, hydroxymidazolam	Unresponsiveness, agitation, combativeness	Sedative for agitation; endotracheal intubation	Patient developed aspiration pneumonia.	Katz et al. (2016)
Non-fatal intoxication	1	US	50	male	Serum specimens positive for ADB-CHMINACA	Urine: ethanol, naloxone, metoprolol, caffeine	Unresponsiveness, apnea, cyanosis,	Sedative for agitation; endotracheal intubation	History of polysubstance abuse	Katz et al. (2016)
Non-fatal intoxication	1	US	40	female	Serum specimens positive for ADB-CHMINACA	Urine: acetaminophen	Seizure, tachycardia	Sedative for agitation (benzodiazepines); endotracheal intubation	History of bipolar disorder	Katz et al. (2016)
Non-fatal intoxication	1	US	19	female	Serum specimens positive for ADB-CHMINACA	Urine: morphine, norfentanyl, cocaine, amphetamine, methamphetamine, codeine, midazolam, lorazepam	Seizure, arrhythmia, unresponsiveness,	Sedative for agitation; endotracheal intubation	History of epilepsy, bipolar disorder and substance abuse.	Katz et al. (2016)

Non-fatal intoxication	1	US	14	male	Serum specimens positive for ADB-CHMINACA	Urine: sertraline	Agitation, bradycardia, periods of unresponsiveness, combativeness	Sedative for agitation; endotracheal intubation	History of substance abuse	Katz et al. (2016)
Non-fatal intoxication	4	US	n/a	n/a	Positive result				Oct 2014, Shreveport, Louisiana	US DEA (2015)
Non-fatal intoxication	13	US	n/a	n/a	6 available samples positive for ADB-CHMINACA				Apr 2015, Philadelphia, Mississippi	US DEA (2015)[§]
Non-fatal intoxication	15	US	n/a	n/a	7 available samples positive for ADB-CHMINACA				Apr 2015, Hampton, Virginia	US DEA (2015)[§]
Non-fatal intoxication	15	US	n/a	n/a	9 available samples positive for ADB-CHMINACA				Apr 2015, Hagerstown, Maryland	US DEA (2015)[§]
Non-fatal intoxication	2	US	n/a	n/a	positive				Dec 2014, Salina, Kansas	US DEA (2015)[§]
Non-fatal intoxication	1	US	n/a	n/a	Positive				Dec 2014/Jan 2015, Salina Kansas	US DEA (2015)[§]
Non-fatal	>10	US	n/a	n/a	10 samples				Apr/ May 2015,	US DEA

intoxication					positive				Mississippi	(2015)[§]
Non-fatal intoxication	1	Germany	46	male		Cocaine, methadone	Panic, dyspnea, tachycardia, nausea, somnolence			Franz et al. (2015)
Non-fatal intoxication	2	Germany	n/a	n/a						Franz et al. (2015)[*]
DUI	3	Hungary	n/a	n/a	Concentration in blood: 2.48–25.9 ng/ml					Institóris et al. (2017)
Non-fatal intoxication	3	UK	n/a	n/a	positive			One patient required intubation and ventilation		Hill et al. (2017)
Non-fatal intoxication	1	US	1 > (10 months)	male	Serum analysis confirmed the presence of ADB-CHMINACA and its metabolite		Patient was unresponsive, moaning, and rigid on arrival. Bradycardia, apnea hypothermia.	endotracheal intubation	Analysis of the substance ingested revealed the presence of the synthetic cannabinoid MAB-CHMINACA	Hawkins et al. (2015)
Non-fatal intoxication	1	US	47	female	positive		somnolence			DeGeorge et al. (2017)
Non-fatal intoxication	1	US	21	male	positive		somnolence			DeGeorge et al. (2017)
Non-fatal intoxication	1	US	59	male	positive		somnolence			DeGeorge et al.

										(2017)
Non-fatal intoxication	1	US	53	male	positive		somnolence			DeGeorge et al. (2017)
Non-fatal intoxication	1	US	31	female	positive		agitation			DeGeorge et al. (2017)
Non-fatal intoxication	1	US	34	male	positive		agitation			DeGeorge et al. (2017)
Non-fatal intoxication	1	US	34	male	positive		somnolence			DeGeorge et al. (2017)
Non-fatal intoxication	1	US	45	male	positive		Awake and alert			DeGeorge et al. (2017)
Non-fatal intoxication	1	US	33	male	positive	AB-CHMINACA 3 methyl	Awake and alert			DeGeorge et al. (2017)
Non-fatal intoxication	1	US	42	male	positive	AB-CHMINACA 3 methyl	Awake and alert			DeGeorge et al. (2017)
Non-fatal intoxication	1	US	50	female	positive	AB-CHMINACA 3 methyl	somnolence			DeGeorge et al. (2017)
Non-fatal intoxication	1	US	67	male	positive	AB-CHMINACA 3 methyl	Awake and alert			DeGeorge et al. (2017)

Non-fatal intoxication	1	US	34	male	positive	AB-CHMINACA 3 methyl	somnolence			DeGeorge et al. (2017)
Non-fatal intoxication	1	US	35	male	positive	AB-CHMINACA	somnolence			DeGeorge et al. (2017)
Non-fatal intoxication	1	US	34	male	positive	AB-CHMINACA 3 methyl; AB-CHMINACA	somnolence			DeGeorge et al. (2017)
[§] Potential duplicates with those reported by Trecki et al., (2015). [*] Potential duplicates with those reported by Hermanns-Clausen et al., (2017).										

Deaths reported by the Member States

Deaths

A total of 13 deaths were reported by 3 Member States: Germany (6), Sweden (5) and Hungary (2). In all cases, exposure to ADB-CHMINACA was analytically confirmed from post-mortem samples.

The German deaths occurred between January 2015 and September 2016. Those in Hungary occurred in 2016 and October 2014. Four of the five deaths in Sweden occurred between February and July 2015, with the remainder occurring in October 2016.

Demographic data were available for all but one death and involved only males. The mean age was 28 years (median 28) and ranged from 17 to 38 years.

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. Where described, the deceased had been sleeping, had vomited or had become 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). 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 all but one case, and, in at least 9 deaths, ADB-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 11 cases. ADB-CHMINACA was the only drug present in 1 death where additional toxicological information was known.

ADB-CHMINACA was quantified in 12 cases. Post-mortem blood concentrations between 0.7 and 16 ng/mL (median 1.1 ng/mL) and between 5 and 30 ng/g blood were recorded (median 10 ng/g blood). With ng/g being approximately equivalent to ng/mL, an inclusive range of 0.7 to 30 and median of 5.9 ng/mL in blood (~ng/g) across all 12 cases. 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, cocaine, antidepressants, antipsychotics, synthetic cathinones, diphenidines, opioids (buprenorphine and methadone) and benzodiazepines. Other synthetic cannabinoid receptor agonists were detected in 3 of the deaths; 5F-AKB-48, AKB-48, 5F-PB-22, FUB-AKB48 (FUB-APINACA), FUB-AMB, AB-CHMINACA. In one of these cases, 5 other synthetic cannabinoids were detected in addition to ADB-CHMINACA.

Overall, whilst other substances may have contributed some toxicity, the potent nature of ADB-CHMINACA means the primary toxic contribution could be attributed to the drug and death may not have occurred if ADB-CHMINACA had not been used. However, in the 3 cases where multiple synthetic cannabinoids were present, it is not possible or appropriate to identify ADB-CHMINACA as the primary synthetic cannabinoid that may have produced toxicity but a synergistic effect is likely nonetheless. Sufficient case data were available in all 13 deaths and an assessment of the toxicological significance score (TSS) (Elliott, Sedefov, & Evans-Brown, 2017) incorporating the above considerations in the deaths, showed that ADB-CHMINACA had a TSS value of 3 (high) in all 13 deaths (where it was cited as the cause of death or is likely to have contributed to death).

Deaths identified from other sources

Table 5 provides a summary of deaths identified in the literature involving confirmed exposure to ADB-CHMINACA. The majority of cases occurred in United States in the period towards the end of 2014 and beginning of 2015. In cases where the demographic of subjects was provided, young male patients were involved (reported ages: 18, 20, and 30). In two cases the blood concentration of ADB-CHMINACA was reported (6.05 ng/ml and 2.7 ng/mL) and in once case ADB-CHMINACA was quantified in urine (229 pg/mL).

Table 5. Deaths associated with confirmed exposure to ADB-CHMINACA

Number of cases	Country	Age	Gender	ADB-CHMINACA analytical confirmation	Other drugs present	Reported symptoms	Reported cause of death	Treatment provided	Additional information	Reference
1	Japan	n/a	male	Concentration of MAB-CHMINACA in urine: 229 pg/mL	Concentration of 5F-ADB in urine: 19 pg/mL				Three silver - colored packages containing herbal blend mixtures were found close to the body.	Minakata et al. (2017) [§]
2	US	n/a	n/a						Cluster of cases of adverse health effects or severe toxic effects. Nov 2014, Bryan, TX	Trecki et al (2015)
1	US	n/a	n/a	Positive result	AB-CHMINACA, AB-PINACA, ADB-PINACA				Oct 2014, Austin, TX	Trecki et al (2015)
1	Japan	30	male	MAB-CHMINACA was detected in body fluids, and solid tissues. Concentration in Femoral vein blood 6.05 ng/ml. The highest concentration in the liver: 156	5F-ADB was detected in the stomach contents and nine solid tissues (the highest concentration in adipose tissue- 7.95 ng/g). Routine analysis of blood alcohol showed a low level of alcohol. Drug		Direct cause of death: asphyxia; the indirect cause appeared to be synthetic cannabinoid poisoning.		Three opened, silver-colored herbal blend packages with brand names ‘‘AL 37’’ ‘‘AP 31’’ and ‘‘GM sapphire’’ were found near the body. In the	Hasegawa et al. (2015a) Hasegawa et al. (2015b) Hasegawa et al. (2017)

				ng/g. Two metabolites of MAB-CHMINACA were detected in urine: M1 (2.17 ng/ml) and M11 (10.2 ng/ml)	screening for urine specimens showed a positive result for barbiturate drugs. Analysis of blood revealed the presence of a low level of quetiapine and a nicotine metabolite.				subsequent analysis MAB-CHMINACA was detected in ‘‘GM sapphire’’ and 5F-ADB was detected in ‘‘AL 37’’ and ‘‘AP 31’’	
1	US	18	male	Concentration of MAB-CHMINACA in blood 2.7 ng/mL	Blood: N-methyl-2-aminoindane 95.4 ng/mL Urine: UR-144 metabolites, N-(4-hydroxypentyl)1.7 ng/mL – N-pentanoic acid 2.6 ng/mL. Standard forensic drug screen on whole blood was negative for 129 pharmaceuticals and chemicals.	Vomiting, coughing up blood, Diffuse alveolar hemorrhage (DAH)	Whether the DAH was caused by the synthetic cannabinoid or the aminoindane is unknown.			Bottei et al. (2016)
1	US	20	male	Serum specimens positive for ADB-CHMINACA	Urine: sertraline	Unresponsiveness, hyperthermia, tachycardia, decorticate posturing, rhabdomyolysis, acute renal failure, anoxic brain injury		Sedative for agitation; endotracheal intubation		Katz et al. (2016)
1	US	n/a	n/a	Positive result					Nov 2014, Navasota, Texas	US DEA (2015)

2	US	n/a	n/a	Positive					Dec 2014/Jan 2015, Salina Kansas	US DEA (2015)
[§] Potential duplicate with those reported by Hasegawa et al., (2015a), Hasegawa et al., (2015b) , and Hasegawa et al., (2017).										

D2. Chronic health effects

D2.1. Animal data

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

D2.2. Human data

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

D3. Factors affecting public health risks

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

ADB-CHMINACA is 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 ADB-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 ADB-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 ADB-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 ADB-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; Zaurova 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 ADB-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 CB_1 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 smoked (and, to a lesser degree, vaped) 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 ADB-CHMINACA (DHSL, 2014; Trecki 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 ADB-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 ADB-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 ADB-CHMINACA (Section C and Section D1.2.1). The available data suggests that ADB-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 ADB-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 ADB-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 ADB-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 ADB-CHMINACA on society as a whole.

E4. Economic costs

There are no data on the effects of ADB-CHMINACA in respect to its health and social costs.

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

There is no specific data on the possible effects of ADB-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 ADB-CHMINACA to specific user groups, it is reasonable to assume ADB-CHMINACA may be sought by those looking for 'legal' substitutes for cannabis. This includes individuals subject to drug testing (such as drivers, prisoners, and those in drug treatment).

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 ADB-CHMINACA.

In the cases where the origin of the seizures reported to Europol was known, the country of origin indicated was: Spain (1) and Russia (1). Bulgaria reported 1 seizure which was en-route from Spain. Bulgaria also reported an additional seizure in 2016 which was reported to have been intended for distribution within the country and was offered for sale via the internet. Estonia reported 1 seizure of ADB-CHMINACA from a courier, which was en-route from Russia.

In the cases where the origin of seizures reported to the EMCDDA was known, the country of origin indicated was China (1). Belgian customs reported the largest single seizure of ADB-CHMINACA in powder form, which amounted to 3 kg. The seizure was en-route from China and destined for Austria and Romania.

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 ADB-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 ADB-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 ADB-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 ADB-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 ADB-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 ADB-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 ADB-CHMINACA.

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Annex 2. List of participants at the risk assessment meetings of *N*-(1-Amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide (ADB-CHMINACA)

7-8 November 2017

A. Extended Scientific Committee

Dr Anne Line BRETTEVILLE-JENSEN
Norwegian Institute for Alcohol and Drug Research, Oslo
Chair of the Scientific Committee

Professor Dr Gerhard BUEHRINGER
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B. Invited Experts

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Dr Robert KRONSTRAND
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Professor Dr Bela SZABO
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