Council of the
European Union

Brussels, 28 July 2016
(OR. en)

11521/16

CORDROGUE 43
SAN 303
ENFOPOL 246

NOTE

From:	EMCDDA
To:	Delegations
No. prev. doc.:	14785/15
Subject:	Risk assessment report on a new psychoactive substance: methyl 2-[[1-(cyclohexylmethyl)-1H-indole-3-carbonyl]amino]-3,3-dimethylbutanoate (MDMB-CHMICA)

Following the Council's request to conduct a Risk Assessment on a new psychoactive substance, methyl 2-[[1-(cyclohexylmethyl)-1H-indole-3-carbonyl]amino]-3,3-dimethylbutanoate (MDMB-CHMICA), the EMCDDA hereby presents the above-mentioned Risk Assessment Report drawn up by its Scientific Committee pursuant to Article 6 of Council Decision 2005/387/JHA on information exchange, risk assessment and control of new psychoactive substances.

ANNEX

Risk assessment report on a new psychoactive substance:
methyl 2-[[1-(cyclohexylmethyl)-1*H-indole*-3-carbonyl]amino]-3,3-dimethylbutanoate
(MDMB-CHMICA)

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

Contents

1. Introduction

This risk assessment report presents the summary findings and the conclusion of the risk assessment carried out by the extended Scientific Committee of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) on the new psychoactive substance methyl 2-[[1-(cyclohexylmethyl)-1*H*-indole-3-carbonyl]amino]-3,3-dimethylbutanoate, commonly abbreviated to MDMB-CHMICA. The report is intended for policy makers and decision makers in the institutions of the European Union.

The report has been prepared and drafted in accordance with the conceptual framework and the procedure set out in the risk assessment operating guidelines[1]. It is written as a stand-alone document, which presents a summary of the information considered during the detailed analysis of the scientific and law enforcement data available at this time. The conclusion section of the report summarises the main issues addressed and reflects the opinions held by the members of the Scientific Committee. A list of the information resources considered by the Scientific Committee, including a detailed technical report on MDMB-CHMICA, is provided below.

[1] EMCDDA. (2010), *Risk assessment of new psychoactive substances: Operating guidelines*, Publications Office of the European Union, Luxembourg. Available at: http://www.emcdda.europa.eu/html.cfm/index100978EN.html

The risk assessment has been undertaken in compliance with Article 6 of Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk assessment and control of new psychoactive substances[2] (hereafter 'Council Decision'). The Council Decision establishes a mechanism for the rapid exchange of information on new psychoactive substances (hereafter 'EU Early Warning System'[3]) that may pose public health and social threats, including those related to the involvement of organised crime. Thus, it allows the institutions of the European Union and the Member States to act on all new narcotic and psychotropic substances[4] that appear on the European Union drug market. The Council Decision also provides for an assessment of the risks associated with these new psychoactive substances so that, if necessary, control measures can be applied in the Member States for narcotic and psychotropic substances[5].

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2 OJ L 127, 20.5.2005, p. 32.

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

4 According to the definition provided by the Council Decision, a 'new psychoactive substance' means a new narcotic drug or a new psychotropic drug in pure form or in a preparation; 'new narcotic drug' means a substance in pure form or in a preparation that has not been scheduled under the 1961 United Nations Single Convention on Narcotic Drugs, and that may pose a threat to public health comparable to the substances listed in Schedule I, II or IV; 'new psychotropic drug' means a substance in pure form or in a preparation that has not been scheduled under the 1971 United Nations Convention on Psychotropic Substances, and that may pose a threat to public health comparable to the substances listed in Schedule I, II, III or IV.

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

MDMB-CHMICA was formally notified to the EMCDDA through the EU Early Warning System in September 2014 by the Hungarian National Focal Point, in accordance with Article 4 of the Council Decision. The notification related to the seizure of 0.19 grams of green/brown herbal product that was seized in August 2014 by police in Ács, Hungary. Following an assessment of the available information on MDMB-CHMICA, and in accordance with Article 5 of the Council Decision, on 14 April 2016 the EMCDDA and Europol submitted a *Joint Report* on MDMB-CHMICA[6] to the Council of the European Union, the European Commission, and the European Medicines Agency (EMA). Taking into account the conclusion of the *Joint Report*, and in accordance with Article 6 of the Council Decision on 26 May 2016, the Council formally requested that 'the risk assessment should be carried out by the extended Scientific Committee of the EMCDDA and be submitted to the Commission and the Council within twelve weeks from the date of this notification'.

In accordance with Article 6.2, the meeting to assess the risks of MDMB-CHMICA was convened under the auspices of the Scientific Committee of the EMCDDA with the participation of four additional experts designated by the Director of the EMCDDA, acting on the advice of the Chairperson of the Scientific Committee, chosen from a panel proposed by Member States and approved by the Management Board of the EMCDDA. The additional experts were from scientific fields that were either not represented, or not sufficiently represented on the Scientific Committee, and whose contribution was necessary for a balanced and adequate assessment of the possible risks of MDMB-CHMICA, including health and social risks. A further four experts participated in the risk assessment: two experts from the Commission, one expert from Europol, and one expert from the European Medicines Agency (EMA). The meeting took place on 22 July 2016 at the EMCDDA in Lisbon. The risk assessment was carried out on the basis of information provided to the Scientific Committee by the Member States, the EMCDDA, Europol and the EMA. A list of the extended Scientific Committee, as well as the list of other participants attending the risk assessment meeting, is annexed to this report (Annex 2).

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6 EMCDDA and Europol. (2016), EMCDDA–Europol joint report on a new psychoactive substance: methyl 2-[[1-(cyclohexylmethyl)-1*H*-indole-3-carbonyl]amino]-3,3-dimethylbutanoate (MDMB-CHMICA), EMCDDA, Lisbon. Available at: http://www.emcdda.europa.eu/publications/joint-reports

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

i. Technical report on methyl 2-[[1-(cyclohexylmethyl)-1*H*-indole-3-carbonyl]amino]-3,3-dimethylbutanoate (MDMB-CHMICA) (Annex 1);

ii. EMCDDA–Europol Joint Report on a new psychoactive substance: methyl 2-[[1-(cyclohexylmethyl)-1*H*-indole-3-carbonyl]amino]-3,3-dimethylbutanoate (MDMB-CHMICA) ([6]);

iii. Open source information including scientific articles, official reports, grey literature, internet drug discussion forums and related websites (hereafter 'user websites');

iv. Additional information provided during the course of the risk assessment meeting by the participants;

v. The EMCDDA operating guidelines for the risk assessment of new psychoactive substances ([1]); and,

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

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

2. Physical, chemical and pharmacological description

Methyl 2-[[1-(cyclohexylmethyl)-1*H*-indole-3-carbonyl]amino]-3,3-dimethylbutanoate (MDMB-CHMICA) is an *N*-cyclohexylmethyl indole-3-carboxamide (Figure 1). This substance is classed as a synthetic cannabinoid receptor agonist, a chemically diverse group of substances also referred to as synthetic cannabinoids [7].

Synthetic cannabinoid receptor agonists are functionally similar to Δ^9-tetrahydrocannabinol (THC), the major psychoactive principle of cannabis. Like THC, they bind to and activate the CB_1 and CB_2 cannabinoid receptors which form part of the endocannabinoid system — a system that helps regulate a large number of physiological functions in the body such as behaviour, mood, pain, appetite, sleep, the immune system, and the cardiovascular system. Many synthetic cannabinoids were first developed to study the endocannabinoid system as well as to explore their potential as therapeutic agents to treat a number of diseases and their symptoms — such as neurodegenerative diseases, drug dependence, pain disorders, and cancer. However, among other limitations, it has so far often proved difficult to separate the desired medicinal properties from unwanted effects.

[7] For the purposes of monitoring within the framework of the EU Early Warning System, the term 'synthetic cannabinoids' is used to include: the large number of synthetic cannabinoid (CB_1 and CB_2) receptor agonists that have been detected on the European drug market; a much smaller number of allosteric modulators (such as Org 27569) that change the structure of the cannabinoid receptors leading to altered activity when a ligand binds to the receptors; and substances that act as inhibitors of fatty-acid amide hydrolase (FAAH), which is the enzyme responsible for breaking down the endocannabinoid anandamide (such as URB597).

Since the mid-2000s, commercial 'legal high' products containing synthetic cannabinoid receptor agonists have been sold in Europe as 'herbal smoking mixtures' and marketed as 'legal' replacements for cannabis. Most of the synthetic cannabinoid receptor agonists that are used in these products are manufactured by chemical companies based in China. They are shipped as bulk powders to Europe using express mail and courier companies; larger amounts may be shipped by air or sea cargo. Once in Europe, the retail products are put together. The herbs Damiana (*Turnera diffusa*) and Lamiaceae (such as *Melissa*, *Mentha* and *Thymus*) are commonly used as the plant base for the smoking mixtures. The synthetic cannabinoid receptor agonists are mixed with or sprayed onto the plant material, on an large scale using solvents such as acetone or methanol to dissolve the powders; equipment like cement mixers are then used to mix the ingredients together. The mixture is then dried and packaged. They are then sold on the internet by 'legal high' retailers and in bricks-and-mortar head shops under a large number of brand names. A common blanket name (or slang name) for these herbal smoking mixtures in Europe is 'Spice' — which is a reference to the most common brand name used for these types of products when they first appeared on the market.

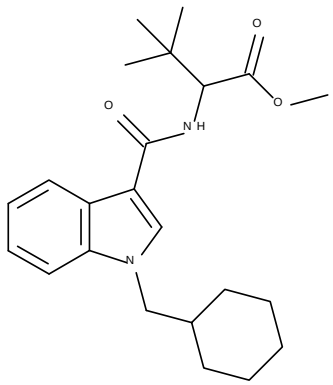
Cannabinoid receptor agonists controlled under the 1971 United Nations Convention on Psychotropic Substances (Schedule II) are: the major active principle of cannabis, delta-9-tetrahydrocannabinol (Δ^9-THC)[8] and two aminoalkylindole synthetic cannabinoid receptor agonists: JWH-018[9] and AM-2201[10].

[8] And some of its named isomers and their stereochemical variants

[9] Naphthalen-1-yl(1-pentyl-1*H*-indol-3-yl)methanone

[10] 1-(5-Fluoropentyl)-1*H*-indol-3-yl]-(naphthalen-1-yl)-methanone

Figure 1: The molecular structure, molecular formula and molecular mass of MDMB-CHMICA.



MDMB-CHMICA
Molecular formula: $C_{23}H_{32}N_2O_3$ Molecular weight: 384.5118 g/mol Monoisotopic mass: 384.2413

In its pure form MDMB-CHMICA is an odourless, white and crystalline solid. It is poorly soluble in water.

Information provided from seizures and collected samples reported by the Member States have noted that MDMB-CHMICA is typically found added to herbal material and as a powder. In the former case this includes a large number of commercially-branded 'legal high' products. The detection of MDMB-CHMICA in liquid form, tablets or capsules has not been reported to the EMCDDA.

MDMB-CHMICA contains a stereogenic centre thus allowing for the existence of a pair of enantiomers, (*S*)-MDMB-CHMICA and (*R*)-MDMB-CHMICA[11]. The limited information available suggests that MDMB-CHMICA may be found in the European drug market as the (*S)* enantiomer, although it is not possible to exclude the presence of the (*R)* enantiomer.

[11] Enantiomers are pairs of molecules that are mirror images of each other and therefore not superimposable. Although they have the same two dimensional molecular structure, enantiomers can exhibit marked differences in biological activity including pharmacological effects.

The analytical identification of MDMB-CHMICA in physical and biological samples is possible using several analytical techniques (Annex 1). The availability of analytical reference material is important for correct identification and for facilitating the quantification of MDMB-CHMICA in physical and biological samples; such reference materials are commercially available.

Route of administration and dosage

MDMB-CHMICA is typically administered by smoking a herbal mixture that is either from a ready-to-use commercial 'legal high' product, or, less commonly, that is self-prepared. Similar to herbal cannabis, the mixture is usually prepared for smoking as a hand-rolled cigarette ('joint') but it may also be smoked in a pipe or 'bong'. Psychonaut-type users [12] also report preparing solutions of MDMB-CHMICA which are then inhaled using an e-cigarette or other vaporisation device; oral administration and rectal administration has also been reported by this group.

Typically the synthetic cannabinoid receptor agonists in commercial herbal mixtures are frequently changed and rarely declared on the packaging. Therefore it is reasonable to assume that many individuals exposed to MDMB-CHMICA will be unaware that they are using the substance. In addition these consumers will be unaware of the dose they are consuming.

Limited information from self-reported experiences of psychonaut-type users suggests that a range of doses (0.1–15 mg) may be used in respect to self-prepared preparations. Doses above 1 mg have been generally described as 'strong' or 'very strong'.

Pharmacology

Data on the pharmacodynamic effects of MDMB-CHMICA are limited to very recent *in vitro* studies which have investigated the functional activity of the substance on the cannabinoid CB_1 and CB_2 receptors. These data show that the (*S*) enantiomer of MDMB-CHMICA is a potent and full agonist at the CB_1 receptor (i.e. activates the receptor), and is approximately 10 times more potent than JWH-018 (which is a full agonist already under international control). (*S*)-MDMB-CHMICA has also been shown to be an agonist at the CB_2 receptor. MDMB-CHMICA has some selectivity for the CB_1 receptor over the CB_2 receptor.

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12 Defined by O'Brien et al., (2015) as 'individuals who are motivated by a desire to explore drug effects, to document and share drug experiences with like-minded individuals'. O'Brien, K., Chatwin, C., Jenkins, C., Measham, F. (2015), 'New psychoactive substances and British drug policy: A view from the cyber-psychonauts', *Drugs: Education, Prevention and Policy*, 22(3), pp. 217–223.

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

Data on the pharmacokinetics of MDMB-CHMICA are limited to the identification of metabolites. So far, over 30 metabolites of MDMB-CHMICA have been identified in humans. The four most abundant metabolites detected were either products of the mono-hydroxylation of the cyclohexyl moiety or products of the hydrolysis of the carboxylic ester function with associated glucuronide conjugates. No studies were identified that have investigated the pharmacology of these metabolites.

Information from self-reported experiences on user websites typically suggest that time of onset from smoking a herbal mixture containing MDMB-CHMICA is around 1 minute, with the duration of effects lasting around 120 minutes. In some cases the effects were reported to last longer.

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

No studies were identified that have investigated the potential interactions of MDMB-CHMICA. Although no data exist at the moment, it is expected that the highly lipophilic MDMB-CHMICA is oxidatively metabolised by cytochrome P450 enzymes. If so, interaction with the metabolism of many drugs and medicines may occur.

Psychological and behavioural effects

Information on the psychological and behavioural effects of MDMB-CHMICA are limited to data provided in serious adverse events reported to the EMCDDA and in the scientific literature, as well as self-reported experiences from user websites.

Some users report that the effects of smoking herbal mixtures containing MDMB-CHMICA are more pronounced in comparison to cannabis. A review of 36 user experiences on user websites found that the most commonly self-reported effects were euphoria, visual hallucinations, anxiety, paranoia, amnesia, sense of doom, and auditory hallucinations (in decreasing order). Other effects that have been reported include: feeling of warmth, laughing, changes in mood, disorientation, confusion, lack of concentration, vertigo, agitation, fear/panic, psychosis, dissociation, violent behaviour, aggression and ‘acute behavioural disturbances’. These are similar to psychological and behavioural effects reported for other synthetic cannabinoid receptor agonists. Many of the effects mentioned relate to neuropsychiatric symptoms.

Legitimate uses

There is currently no indication that MDMB-CHMICA may be used, in Europe or elsewhere, for legitimate purposes aside from in scientific research and as analytical reference materials as a result of its appearance on the drug market.

There are no reported uses of MDMB-CHMICA as a component in industrial, cosmetic or agricultural products. A search of the REACH registered substances database hosted by the European Chemicals Agency (ECHA) using the CAS Registry Number returned no results.

MDMB-CHMICA does not appear to have an established or acknowledged medical value or use (human or veterinary) in the European Union. There is no marketing authorisation (existing, ongoing or suspended) for MDMB-CHMICA in the European Union or in the Member States that responded to the information request by the EMA that was launched under Article 5 of the Council Decision[6]. In addition, there is no information that MDMB-CHMICA is used for the manufacture of a medicinal product or an active pharmaceutical ingredient of a medicinal product in the European Union. It is important to note that the data collection is incomplete and some countries indicated that this information is unknown. It should also be noted that there is no European Union database on the synthetic routes of all registered medicinal products.

3. Chemical precursors that are used for the manufacture

There is some information regarding the chemical precursors and the synthetic routes used to manufacture MDMB-CHMICA that has been detected within the European Union.

Methods for the production of MDMB-CHMICA are documented in the scientific literature and extensively studied in an EU funded project. According to the synthetic routes described, potential precursors of MDMB-CHMICA are indole, indole-3-carboxylic acid, indole-3-carboxylic acid methyl ester, indole-3-carbaldehyde, cyclohexylmethyl bromide and *L-tert*-leucine methyl ester (for synthesis of the (*S*) enantiomer). (*S)-L-tert*-Leucine is widely used for the manufacture of antiviral medicines and is produced mainly in China in large quantities. This may explain the choice of this precursor for the synthesis of MDMB-CHMICA and other related synthetic cannabinoids that have been reported to the EU Early Warning System.

4. Health risks

Individual health risks

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

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

The mode of use of MDMB-CHMICA may involve the combined use of other drugs (either intentionally or unintentionally). MDMB-CHMICA may be encountered in combination with other substances in commercially branded 'legal high' products. Analyses of various seized products have shown that the composition of commercial 'legal-high' type products containing synthetic cannabinoids that are sold on the drug market can vary significantly over geographical areas and time. Therefore, the users are unlikely to be aware of the exact dose or substance(s) being ingested (by whatever route). This presents an inherent risk to the individual.

It should be noted that the manufacturing process used to make smoking mixtures can lead to an uneven distribution of the synthetic cannabinoid receptor agonists within the herbal material. Inter-package and intra-package content of synthetic cannabinoid receptor agonists may vary significantly resulting in different amounts of the active substance. This may result in some products containing 'hot pockets' where the cannabinoid is highly concentrated, leading to doses that increase the risk of acute toxicity.

Acute toxicity

No non-clinical or clinical studies were identified that have investigated the acute toxicity of MDMB-CHMICA and/or its metabolites.

Acute intoxications

Forty-two acute intoxications associated with MDMB-CHMICA were reported to the EMCDDA by 7 Member States: Austria (7 cases), France (2), Germany (7), Poland (3), Spain (2), Sweden (10), and, the United Kingdom (11). These typically related to acute non-fatal presentations to hospital emergency departments. They occurred during 2014 and 2015. In 25 of the 42 cases, MDMB-CHMICA was analytically confirmed in one or more biological samples taken from the patient at or around the time of intoxication: Austria (7 cases), Germany (3), Sweden (6) and the United Kingdom (9). In the remaining 17 cases, MDMB-CHMICA was only detected in a sample of the product/drug used or thought to have been used by the patient; these cases are not discussed further. The discussion below therefore relates to the findings in the 25 cases which were analytically confirmed through biological samples.

Data on the seriousness of the intoxication were reported for 13 out of the 25 cases. The seriousness of the intoxication was classified as: life threatening in 8 out of the 13 cases; non-life-threatening in 3 cases; and, 'requiring treatment in hospital' for 2 cases.

Of the 25 cases, 17 (68%) were male; 6 (24%) were female; in 2 (8%) of the cases the gender of the patient was unknown. The mean age of the male cases for which an age was known was 26 years (median 21); for the female cases the mean age was 25 years (median 20). For all cases, the ages ranged between 15 and 50 years.

In 6 of the 25 cases, MDMB-CHMICA was the only substance identified in the biological samples taken from the patients. In the remaining 19 cases other substances were detected along with MDMB-CHMICA. Typically these were other cannabinoids (including THC and its metabolites) (17 out of 25 cases) and/or ethanol (6/25). Other substances that were detected included: methamphetamine (4/25); amphetamine (3/25); benzodiazepines (3/25); morphine (1/25); and, buprenorphine (1/25).

Information on the length of hospital stay (including treatment in the emergency room only) was available for 9 out of 25 cases. The hospitalisation period varied between 3 hours to 24 hours (mean: 12 hours; median: 8 hours).

Data on clinical features reported in the 25 cases were consistent with those associated with acute intoxication by MDMB-CHMICA that have been reported in the literature and with intoxications with other synthetic cannabinoid receptor agonists. Coma and unconsciousness were the most prevalent features, having been reported for 10 out of 25 cases. Other clinical features include: tachycardia (7 cases), syncope (6), hyperemesis and/or nausea (4), mydriasis (3), seizures and convulsions (2), bradycardia (2), somnolence (2), serotonin toxicity (2), urinary and faecal incontinence (1), respiratory acidosis (1) and metabolic acidosis (1). In 4 out of 25 cases the patients were described as exhibiting aggression and/or severe disturbance of behaviour, some of which resulted in police intervention and/or transfers to psychiatric units.

Data on the route of administration was available for 14 out of 25 cases. In all of them, the substance was either smoked or presumed to have been smoked or inhaled. In 8 cases MDMB-CHMICA was consumed as a herbal product (information not available for the other cases).

Data on the psychological and behavioural effects associated with MDMB-CHMICA, including neuropsychiatric symptoms are discussed in Section 2 of this report.

Deaths

A total of 29 deaths associated with MDMB-CHMICA were reported by 5 Member States and Norway: Germany (5 cases), Hungary (3), Poland (1), Sweden (9), the United Kingdom (10), and Norway (1).

In 28 cases, MDMB-CHMICA was analytically confirmed in one or more biological samples taken from the decedents. In the remaining case, MDMB-CHMICA was only confirmed from a sample of the product/drug believed to have been consumed by the deceased; this case has not been considered further.

Of the 28 cases, 24 were male (85.7%), 3 were female (10.7%), and, the gender was not reported for one death (3.6 %). The decedents' ages ranged from 17 to 52 years. The mean age of the male decedents was 32 years (median 33); the mean age of the female decedents was 31 years (median 30). In 6 cases the deaths occurred in 2014; 20 deaths occurred in 2015; and, 1 death occurred in 2016. The year of death was not known for 1 case.

Information regarding the circumstances of death was reported for 18 out of 28 cases. In 72% of those cases, the individuals were found comatose or dead (at home or outside). In at least 2 of these cases smoking mixtures and smoking paraphernalia were found next to the body.

In 12 deaths MDMB-CHMICA was reported either as the cause of death or as contributing to death (even in the presence of other substances); in 3 of these deaths MDMB-CHMICA was the sole drug present. In 10 deaths MDMB-CHMICA may have contributed to death but other substances were present that may have been more toxicologically significant. An alternative cause of death was recorded in 4 cases. In the cases where other substances were found these included, alcohol, benzodiazepines, opiates/opioids, antipsychotics, anticonvulsants, antidepressants, and other new psychoactive substances including synthetic cannabinoids.

Ability to operate machinery and drive

The behavioural effects of MDMB-CHMICA may limit the ability to operate machinery and drive safely.

Chronic toxicity

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

Abuse liability and dependence potential

No studies were identified that have investigated the abuse liability and dependence potential of MDMB-CHMICA in animals or in humans. *In vitro* data show that MDMB-CHMICA affects the same molecular target as THC (specifically the CB_1 receptor), it is therefore reasonable to consider that MDMB-CHMICA may have an abuse liability and dependence potential, however demonstrating this would require additional data from experimental studies.

Data from user websites and serious adverse events suggest that MDMB-CHMICA may have an abuse liability.

A case series of 4 patients seeking medical treatment with withdrawal-like symptoms who had consumed MDMB-CHMICA has been reported. A small number of user experiences posted on user websites include apparent tolerance and withdrawal-like symptoms indicate that the substance may have dependence and abuse potential.

Public health risks

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

Extent, frequency, and patterns of use

The available data suggest that MDMB-CHMICA is sold typically as commercial branded 'legal high' products in head shops as well as on the Internet as a 'legal' replacement for cannabis. Similar to other synthetic cannabinoid receptor agonists, it is reasonable to assume that many individuals are unaware that they are consuming MDMB-CHMICA.

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

Information on the extent to which products containing synthetic cannabinoid receptor agonists are used is limited. From the information that is available, it would appear that the prevalence of their use in the general population is low in Europe. A number of surveys aimed at examining the prevalence of use of 'Spice'-like products[13] have been launched but their coverage and representativeness remains limited.

[13] 'Spice' is a common blanket name used for 'legal high' products containing synthetic cannabinoid receptor agonists (Section 2).

In the United Kingdom last year, the reported lifetime use of 'Spice' in household surveys (age 16–64) was 0.2 % (2010/2011) and 0.1 % (2011/2012). In Spain, in 2012, a national survey on drug use among students (age 14–18) also identified low levels of use of 'Spice' products, with prevalence rates of 1.4 % for lifetime use, 1.0 % for last year use and 0.6 % for last month use, which indicated a small increase from the previous survey results from 2010 (1.1 %; 0.8 %; and 0.5 % respectively). In France in 2014 a survey of adults (18–64) with a question about the use of 'synthetic cannabinoids' reported lifetime use of 1.7 %. Another survey in France, among young people aged 17, reported that 1.7 % of them have previously used a synthetic cannabinoid. The German city of Frankfurt has studied the use of smoking mixtures and 'Spice' among students aged 15–18. They reported lifetime levels of use of 7 % in 2009; 9 % in 2010; 7 % in 2011 and 2012; 5 % in 2013; and 6 % in 2014. Studies with non-probabilistic samples have identified higher levels of synthetic cannabinoid receptor agonist use than among the general population. The 2012 Global Drug Survey, for example, reported last year prevalence levels of 3.3 % among all respondents from the United Kingdom and 5.0 % among regular clubbers from the United Kingdom.

Availability and quality on the market

Since August 2014, when it was detected first in Hungary, MDMB-CHMICA has been detected in 23 Member States (Austria, Belgium, Bulgaria, Croatia, Cyprus, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Latvia, Lithuania, Luxembourg, Netherlands, Poland, Romania, Slovenia, Spain, Sweden, Slovakia, and the United Kingdom), Turkey and Norway.

MDMB-CHMICA is sold online either as commercial 'legal high' 'herbal mixtures' or as a powder. In commercial products it is usually not stated if the product contains MDMB-CHMICA or any other synthetic cannabinoid receptor agonist. Furthermore, Germany reported to Europol, that, in addition to being sold online, MDMB-CHMICA is well known among drug users and is often offered by drug dealers in addition to being available to purchase online.

Due to the high potency of some synthetic cannabinoid receptor agonists, the amount of powder needed for each packet can be in the order of a few tens of milligrams. This means that each kilogram of bulk powder may produce thousands of packets of 'legal highs' (Section 6). For example, 1 kg of powder can be used to produce 1 million doses each containing 1 mg of active substance.

Detailed information available with regards to route-specific by-products produced during the synthesis of MDMB-CHMICA is currently not available. There are no quantitative data available on the impurities detected in seized and collected samples reported to the EMCDDA by the Member States.

The manufacturing process used to make smoking mixtures can lead to an uneven distribution of the synthetic cannabinoid receptor agonists within the herbal material. There is often a large variation in the amount of synthetic cannabinoid receptor agonists present both between different packages of products and within an individual product. This can result in some products containing large amounts of synthetic cannabinoid receptor agonists as well as 'hot pockets' where the cannabinoid is highly concentrated on certain parts of an individual product, leading to higher doses in that region increasing the risk of acute toxicity and outbreaks of mass poisonings.

Characteristics and behaviour of users

Information on the characteristics and behaviour of users of MDMB-CHMICA is limited.

'Legal high' products containing MDMB-CHMICA are marketed as 'legal' replacements to cannabis. It is therefore likely that a range of different cannabis users would be interested in these products.

The available data suggests that MDMB-CHMICA is used by cannabis users including those who are regularly subjected to drug testing procedures such as prisoners. It is also used by psychonaut-type users.

In most cases, it appears that MDMB-CHMICA is not specifically sought after by users, who may purchase it unknowingly. Commercial branded 'legal high' products are known to be highly variable in terms of composition and dosage and therefore users are unlikely to know that they are consuming MDMB-CHMICA.

Nature and extent of health consequences

Data on the health consequences of MDMB-CHMICA are mostly limited to the acute intoxications and deaths which are discussed above.

Long-term consequences of use

There is no information on the long-term consequences of MDMB-CHMICA use.

Conditions under which the substance is obtained and used

There is limited data on the conditions which MDMB-CHMICA is obtained and used.

1. Sources appear to include internet retailers, bricks-and-mortar shops, friends and other acquaintances, as well as street-level drug dealers. The available data suggests that many users are likely to be unaware that they have sourced and used MDMB-CHMICA.

2. Based on the available data, and given that MDMB-CHMICA is typically sold as a 'legal' replacement to cannabis, it seems reasonable to consider that MDMB-CHMICA will be used in the same environments as cannabis.

5. Social risks

While there have been no studies of the effects of MDMB-CHMICA in animals or in humans, data from acute intoxications, deaths, and, self-reported user experiences, suggest that the acute behavioural effects of MDMB-CHMICA might, at least, bear some similarities to cannabis.

Individual social risks

There is no information on whether the use of MDMB-CHMICA affects education or career, family or other personal or social relationships, including marginalisation.

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

While there is no specific information on the possible effects of MDMB-CHMICA on the direct social environment, multiple reports have indicated a possibility for violence and aggression.

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

While there is no specific information on the possible effects of MDMB-CHMICA on society as a whole, multiple reports have indicated a possibility for violence and aggression. In particular, concern was expressed with regard this in certain circumstances e.g. prisons and psychiatric institutions. In addition, the detection of MDMB-CHMICA in cases of suspected driving under the influence indicated a potential for a wider risk to public safety.

Data related to the social risk associated with the trafficking and distribution of MDMB-CHMICA is limited.

Economic costs (demands on healthcare)

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

Possible appeal to specific population groups

There is no detailed data on the possible appeal of MDMB-CHMICA to specific user groups. However, the available data suggests that those using MDMB-CHMICA include: cannabis users; people who experiment with any drug that is new and readily available (such as 'psychonauts'); and, by individuals who are subjected to drug testing procedures (including those in prison).

The extent of the possible appeal of synthetic cannabinoid receptor agonists to cannabis users may be compounded by different factors, as they are a heterogeneous group. They may include those wanting a 'legal' alternative to illicit drugs, or drug users wishing to pass successfully an employment/other drug testing procedure aimed at detecting illicit drug use. This may be an important issue for any setting where drug abstinence control is obligatory (e.g. specific psychiatry or prison settings, driving liability testing, etc.).

Overall, the extent of the possible appeal of MDMB-CHMICA to users is unknown.

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

Although Hungary and Romania provided information in relation to the involvement of criminal groups in the processing, trafficking and distribution of MDMB-CHMICA, limited information is available in relation to the involvement of organised crime in the manufacture and/or trafficking.

MDMB-CHMICA has been available on the European Union drug market since at least August 2014. Data from seizures reported to the EMCDDA and to Europol suggest that bulk powders of MDMB-CHMICA have been produced by chemical companies based in China. They are imported into the EU where they are either processed and packaged into commercial smoking mixtures or sold as powder. No information has been received by Europol indicating production of MDMB-CHMICA within the EU.

It is important to note that in October 2015 the People's Republic of China controlled MDMB-CHMICA under national drug control legislation.

MDMB-CHMICA has been detected in 23 Member States (Austria, Belgium, Bulgaria, Croatia, Cyprus, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Latvia, Lithuania, Luxembourg, Netherlands, Poland, Romania, Slovenia, Spain, Sweden, Slovakia and the United Kingdom), Turkey and Norway.

Information reported to the EMCDDA and Europol indicates that over 120 kg of MDMB-CHMICA has been seized, as herbal material (approximately 67 kg) or powder form (approximately 46 kg). The largest single bulk seizure reported to the EMCDDA was 40 kg of highly pure MDMB-CHMICA in powder form by Luxembourg, in December of 2014. The powder was contained in forty 1 kg packages and was seized at Luxembourg airport where it was in transit from China (Shanghai) with Spain (Madrid). Single seizures in excess of 1 kg were reported by five other countries: Germany, Spain, Lithuania, Romania, and the Netherlands.

There are indications of a significant internet retail trade within Europe, with customs and police making regular seizures of small quantities of these products.

Germany reported details on an investigation that led to the dismantling of a processing site, where herbal mixtures containing MDMB-CHMICA were prepared. Tablets mimicking ecstasy but containing different NPS were also detected during this investigation. German authorities stated that no direct links with organised crime groups (OCG) have been identified.

7. Information on any assessment in the United Nations system

The World Health Organization is the specialised United Nations agency designated for the evaluation of the medical, scientific and public health aspects of psychoactive substances under the Single Convention on Narcotic Drugs of 1961 and the Convention on Psychotropic Substances of 1971. At the time that the Joint Report was prepared ([6]), the World Health Organization informed the EMCDDA that MDMB-CHMICA was not currently under assessment nor had it been under assessment by the United Nations system.

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

Ten Member States (Croatia, Denmark, Estonia, Finland, Germany, Greece, Hungary, Latvia, Lithuania, and Luxembourg) and Turkey reported that MDMB-CHMICA is controlled under drug control legislation.

- In Croatia, MDMB-CHMICA is part of the list of drugs, psychoactive substances and plants used for drug production, as well as precursors (OG 10/16). MDMB-CHMICA is covered with generic definition 'JWH-018 and its structural analogues'.

- In Denmark, MDMB-CHMICA is controlled under drug control legislation.

- In Estonia, MDMB-CHMICA has been added to drug control legislation since 8 June 2015.

- In Finland, MDMB-CHMICA has been added to drug control legislation since 28 September 2015.

- In Germany, by adoption of the 30th Amending Regulation on Narcotic Drugs (30. Betäubungsmittelrechts-Änderungsverordnung, BtMÄndV) MDMB-CHMICA is controlled under schedule I (narcotics not eligible for trade and medical prescription) of the German Narcotics Act (Betäubungsmittelgesetz, BtMG). The legislation has been published on November 11th 2015 in the Federal Gazette, and entered into force on 21 November 2015.

- In Greece, MDMB-CHMICA is classified as an isomer of Zipeprol[14]. Zipeprol and its isomers are classified in the Table C of the Law 4139/2013.

- In Hungary, MDMB-CHMICA is under drug control legislation from 22/07/2015 through Government Decree 66/2012 (IV. 2.).

- In Latvia, MDMB-CHMICA is included in the first list of the Cabinet Regulation N 847 'Regulations regarding Narcotic Substances, Psychotropic Substances and Precursors to be Controlled in Latvia' and the law 'On the Procedures for the Coming into force and Application of the Criminal Law'. Control of MDMB-CHMICA is introduced by the generic approach.

[14] Systematic name: 1- methoxy-3-[4- β –methoxyphenethyl)-piperazin-1-yl]-1-phenylpropan-2-ol

- In Lithuania, MDMB-CHMICA has been placed under control, according to the Republic of Lithuania Minister of Health Order No V-1062 (21/09/2015) 'On the amendment of the Ministry of Health of the Republic of Lithuania Order No. 5 of 6 January 2000.

- In Luxembourg, MDMB-CHMICA is controlled by the Grand Ducale Decree of 04/05/2009.

- In Turkey, MDMB-CHMICA is under legal control via the Generic Classification which was deliberated by the council of Ministers on 26/01/2015 and published in the official gazette on 6 February 2015 the annexed list subject to the provisions of the Law on Control of Drugs numbered 2313; according to the 19th article of the said Law. Generic Classification text is updated and adopted to the said law on 16/02/2016 by the council of Ministers.

Four Member States (Austria, Cyprus, Poland, and the United Kingdom) reported that MDMB-CHMICA is controlled under specific new psychoactive substances control legislation.

- In Austria, MDMB-CHMICA is controlled under the Austrian Act on new psychoactive substances (Neue-Psychoaktive-Substanzen-Gesetz, NPSG).
- In Cyprus, MDMB-CHMICA is controlled as a category B drug under a generic legislation since March 2016.
- In Poland, MDMB-CHMICA is controlled according to the general definition of 'substitute drug' which has been included to the Act of 8 October 2010 amending the Act on counteracting drug addiction and the Act on State Sanitary Inspection (Journal of Laws 'Dz.U.' No. 213, item 1396). Article 44b of the above mentioned Act bans manufacturing or introducing substitute drugs to trade.

- In the United Kingdom, MDMB-CHMICA is not controlled under the Misuse of Drugs Act 1971 but might be captured under the Psychoactive Substances Act 2016.

One Member State (Sweden) and Norway reported that MDMB-CHMICA is controlled under other types of legislation:

- In Sweden, MDMB-CHMICA is controlled Act on the Prohibition of Certain Goods Dangerous to Health (SFS 1999:42).
- In Norway, the import of and trade in MDMB-CHMICA is controlled by Medicinal Products Legislation.

Thirteen Member States (Belgium, Bulgaria, Czech Republic[15], France, Italy, Ireland, Malta, the Netherlands, Portugal, Romania, Slovakia, Slovenia and Spain) reported that MDMB-CHMICA is not subject to control measures at the national level.

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

Under Article 9.1 of the Council Decision, the option for control that is available at European Union level is for the Member States to submit the new psychoactive substance MDMB-CHMICA to control measures and criminal penalties, as provided for under their legislation, by virtue of their obligations under the Convention on Psychotropic Substances of 1971. There are no studies on the possible consequences of such control measures on MDMB-CHMICA. If this option of control is pursued, the Committee considers that the following consequences are possible. Some of these may apply to any new psychoactive substance.

- This control option could be expected to limit the availability of MDMB-CHMICA and hence the further expansion of the current open trade in this substance.
- A health consequence that might result from this control option is the benefit brought about by the presumed reduction in availability and use. In this respect it is noteworthy that the People's Republic of China placed MDMB-CHMICA under national drug control legislation in October 2015.
- This control option could facilitate the detection, seizure and monitoring of MDMB-CHMICA related to its unlawful manufacture, trafficking and use. In so doing, it could facilitate cooperation between the judicial authorities and law enforcement agencies across the European Union.

[15] The Czech Republic reported that an amendment of the Government Regulation No. 463/2013 Coll., on the lists of addictive substances is currently being prepared. MDMB-CHMICA is one of the 33 substances proposed to place under control.

- This control option would imply additional costs for the criminal justice system, including forensic services, law enforcement, and the courts.

- This control option could lead to replacement with other (established or new) psychoactive substances, which may in themselves have public health consequences and social risks.

- This control option could create an illicit market in MDMB-CHMICA with the increased risk of associated criminal activity, including the involvement of organised crime.

- This control option could impact on both the quality/purity and price of any MDMB-CHMICA still available on the illicit market. The extent to which this will impact on public health, criminality, or levels of use, is difficult to predict.

- It is difficult to predict the impact of this control option on current or future research by the pharmaceutical or chemical industries.

- In order to examine the consequences of control, the Committee wishes to note that it will be important to monitor for the presence of MDMB-CHMICA on the market post-control, should this control option be pursued.

- Aside from the option for control under those stipulated in Article 9.1 of the Council Decision, other options for control may be available to Member States. These may include restricting the importation and supply of the substance as some Member States have already done.

10. Conclusion

The new psychoactive substance methyl 2-[[1-(cyclohexylmethyl)-1*H*-indole-3-carbonyl]amino]-3,3-dimethylbutanoate (MDMB-CHMICA) is a novel indole-3-carboxamide derivative. It is classed as a synthetic cannabinoid receptor agonist. Information on the pharmacology of MDMB-CHMICA is limited to *in vitro* data, which suggest that MDMB-CHMICA is a potent and full agonist at the CB_1 receptor. It also acts as an agonist at the CB_2 receptor.

The high potency of MDMB-CHMICA and the highly variable amounts of the substance in 'legal high' products constitute a high risk of acute toxicity.

MDMB-CHMICA has been available on the drug market in the European Union since at least August 2014 and has been detected in 23 Member States, Turkey and Norway. It is sold either as powder or commercially branded 'legal high' products by chemical companies and by online retail shops.

MDMB-CHMICA is typically sold as a 'legal' replacement for cannabis.

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

The available data suggests that MDMB-CHMICA is used by cannabis users; 'psychonauts'; and by those who are regularly subjected to drug testing procedures (including those in prison). However, no further information on the size and demand and the characteristics of these groups of people is available.

Twenty-five acute intoxications have been reported where MDMB-CHMICA was detected in biological samples taken from the patients by 4 Member States. Clinical features were generally consistent with cannabis-like toxicity but included life threatening conditions.

Twenty-eight deaths have been reported where MDMB-CHMICA was detected post-mortem. In 12 (43%) of these cases MDMB-CHMICA was reported as either the cause of death or that it likely contributed to the death; in 3 of these cases MDMB-CHMICA was the only substance detected.

Multiple reports have indicated a possibility for violence and aggression. In particular, concern was expressed with regard this in certain circumstances e.g. prisons and psychiatric institutions. In addition, the detection of MDMB-CHMICA in cases of suspected driving under the influence indicated a potential for a wider risk to public safety.

There is limited information to suggest the potential involvement of organised crime in the manufacture, distribution (trafficking) and supply within the European Union. There is limited information on the chemical precursors and the synthetic routes used to manufacture the MDMB-CHMICA detected within the European Union. The largest single seizure of MDMB-CHMICA was in Luxembourg in December 2014, when 40 kg of powder seized en-route from China to Madrid.

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

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

Ten Member States and Turkey control MDMB-CHMICA under drug control legislation and five Member States and Norway control MDMB-CHMICA under other legislation.

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

The Committee notes that a decision to control MDMB-CHMICA has the potential to bring with it both intended and unintended consequences. Potential intended consequences include reduced levels of availability and ultimately use. This may reduce the health and social risks and consequences arising from the use of MDMB-CHMICA. It is important to recognise that a potential unintended consequence of control may be the manufacture and availability of other substances. Indeed, chemically analogous substances that may replace MDMB-CHMICA are already being sold on the drug market. The implementation of control measures may also lead to the criminalisation of those who continue to use this substance with the possible attendant risks of socio-economic stigmatisation and marginalisation. Should control measures be adopted, they should be accompanied by the gathering and dissemination of accurate information on MDMB-CHMICA to users, practitioners, policy makers, and decision makers.

11. List of annexes

Annex 1: Technical report on methyl 2-[[1-(cyclohexylmethyl)-1*H*-indole-3-carbonyl]amino]-3,3-dimethylbutanoate (MDMB-CHMICA).

Annex 2: List of participants at the risk assessment meeting of methyl 2-[[1-(cyclohexylmethyl)-1*H*-indole-3-carbonyl]amino]-3,3-dimethylbutanoate (MDMB-CHMICA).

Technical report on methyl 2-[[1-(cyclohexylmethyl)-1*H*-indole-3-carbonyl]amino]-3,3-dimethylbutanoate (MDMB-CHMICA)

Annex 1 to the *Risk assessment report on a new psychoactive substance: methyl 2-[[1-(cyclohexylmethyl)-1H-indole-3-carbonyl]amino]-3,3-dimethylbutanoate (MDMB-CHMICA)*

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EMCDDA contract: CT.16.SAT.0012.1.0

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: methyl 2-[[1-(cyclohexylmethyl)-1H-indole-3-carbonyl]amino]-3,3-dimethylbutanoate (MDMB-CHMICA)* to which this report is annexed, was produced by the extended Scientific Committee of the EMCDDA and shall be regarded as the authoritative document.

Acknowledgement

The authors would like to thank Michael Pütz and Sascha Münster-Müller (BKA, Wiesbaden, Germany), Verena Angerer and Florian Franz (Institute of Forensic Medicine Freiburg, Germany), Dr. Bernd Schwarze (Institute of Forensic Medicine Nürnberg, Germany), Dr. Maren Hermanns-Clausen (Poison Information Center Freiburg, Germany) and Dean Acreman (WEDINOS, Wales) for their support.

The authors would like to thank Dr. István Ujváry (hon. associate professor, Budapest University of Technology & Economics; hon. associate professor, University of Szeged; iKem BT, Budapest, Hungary) for reviewing the document.

Data sources

The information in this technical report is derived from:

- data reported by the Member States to the EMCDDA and Europol in accordance with Council Decision 2005/387/JHA on the information exchange, risk-assessment and control of new psychoactive substances[1]; 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 MDMB-CHMICA.

Search strategy

Medline and Google Scholar were searched for 'MDMB-CHMICA', 'MMB-CHMINACA', and the IUPAC names of this compound stated in this document.

Exact chemical structure-based searches were done in *SciFinder* (American Chemical Society, Chemical Abstract Service) and *Reaxys* (Elsevier).

Google, Internet drug user forums (such as Erowid, Bluelight, Reddit and Eve and Rave) were searched for the terms: 'MDMB-CHMICA', 'MMB-CHMINACA', alone or in combination with 'buy', 'shop', 'research chemical', 'synthetic cannabinoid', 'dosing', 'intoxication', 'kaufen', 'räuchermischung', 'powder', 'synthesis'.

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

Note

It is important to note that when interpreting the data on self-reported user experiences that is provided in this report, it is not possible to confirm the specific substance(s) used; similarly it is also not possible to confirm the strength, purity, dose/amount, etc., used. In addition, the information provided on user websites and from specific user groups may not necessarily be representative of other users of MDMB-CHMICA and should be regarded as illustrative only.

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

Contents

Section A. Physical, chemical, pharmaceutical and pharmacological information

A1. Physical, chemical, and pharmaceutical information

A1.1. Physical and chemical description

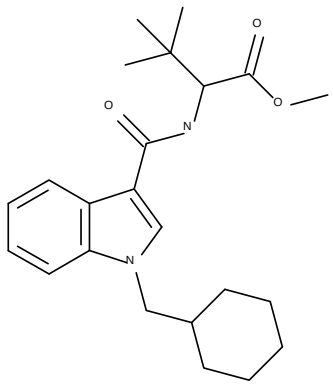
Chemical description and names

Methyl 2-[[1-(cyclohexylmethyl)indole-3-carbonyl]amino]-3,3-dimethylbutanoate (MDMB-CHMICA) is an *N*-cyclohexylmethyl indole-3-carboxamide (Figure 1). This substance is classified as a synthetic cannabinoid receptor agonist, a chemically diverse group of substances also referred to as synthetic cannabinoids[2].

Synthetic cannabinoid receptor agonists are a large family of chemically unrelated structures functionally similar to Δ^9-tetrahydrocannabinol (THC), the active principle of cannabis. Like THC, they bind to the same cannabinoid receptors in the brain and other organs. They were developed over the past 40 years as potential pharmaceutical agents, often intended for pain management.

[2] For the purposes of monitoring within the framework of the EU Early Warning System, the term 'synthetic cannabinoids' is used to include: the large number of synthetic cannabinoid (CB_1 and CB_2) receptor agonists that have been detected on the European drug market; a much smaller number of allosteric modulators (such as Org 27569) that change the structure of the cannabinoid receptors leading to altered activity when a ligand binds to the receptors; and substances that act as inhibitors of fatty-acid amide hydrolase (FAAH), which is the enzyme responsible for breaking down the endocannabinoid anandamide (such as URB597).

Figure 1: The molecular structure, molecular formula and molecular mass of MDMB-CHMICA.



MDMB-CHMICA
Molecular formula: $C_{23}H_{32}N_2O_3$
Molecular weight: 384.5118 g/mol
Monoisotopic mass : 384.2413

Cannabinoid receptor agonists controlled under the 1971 United Nations Convention on Psychotropic Substances (Schedule II) are: the major active principle of cannabis, delta-9-tetrahydrocannabinol (Δ^9-THC) and its stereochemical variants[3] and two aminoalkylindole synthetic cannabinoid receptor agonists: JWH-018[4] (Commission on Narcotic Drugs, 2015a) and AM-2201[5] (Commission on Narcotic Drugs, 2015b). JWH-018 was the first synthetic cannabinoid reported to the EU Early Warning System (EU EWS)[6] (EMCDDA, 2009) and AM-2201 is the 5-fluoropentyl analogue of JWH-018 (Figure 2). The controls on JWH-018 and AM-2201 entered into force in November 2015.

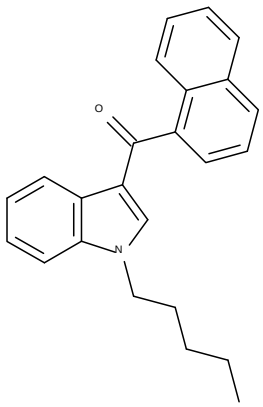
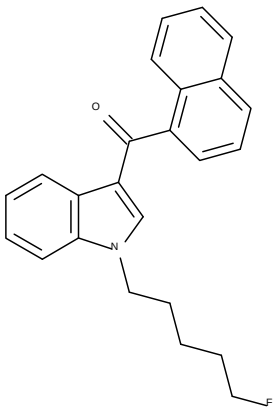
[3] Also controlled are the following isomers: Δ^6a(10a), Δ^6a(7), Δ7, Δ8, Δ10, Δ9(11) and their stereochemical variants.

[4] Naphthalen-1-yl(1-pentyl-1*H*-indol-3-yl)methanone

[5] 1-(5-Fluoropentyl)-1*H*-indol-3-yl]-naphthalen-1-ylmethanone

[6] Forensic investigators in Germany and Austria detected the synthetic cannabinoid JWH-018 in a product sold under the brand name 'Spice'.

Figure 2: The molecular structure, molecular formula and molecular mass of JWH-018 and AM-2201.

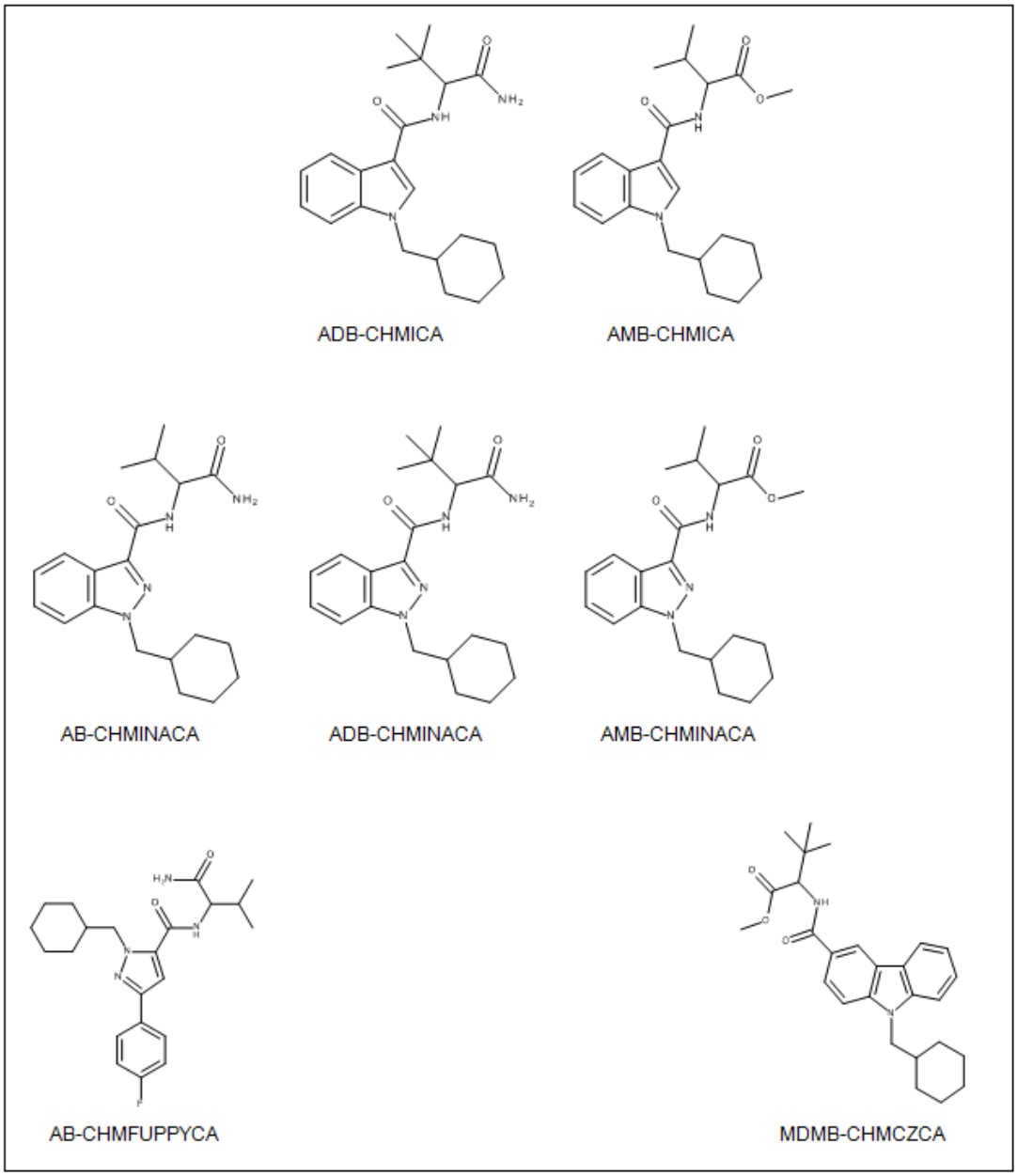
	
JWH-018	**AM-2201**
Molecular formula: $C_{24}H_{23}NO$ Molecular weight: 341.4455 g/mol Monoisotopic mass: 341.1780	Molecular formula: $C_{24}H_{22}FNO$ Molecular weight: 359.4360 g/mol Monoisotopic mass: 359.1685

The abbreviation used for MDMB-CHMICA is derived from its chemical name (EMCDDA, 2016): 'MDMB' stands for **m**ethyl**d**i**m**ethyl**b**utanoate; 'CHM' stands for **c**yclo**h**exyl**m**ethyl; 'I' stands for **i**ndole; and 'CA' stands for **c**arbox**a**mide. MDMB-CHMICA was first advertised as 'MMB-CHMINACA', which would falsely imply an indazole core structure. Online shops continue to offer this substance under the name 'MMB-CHMINACA'.

Examples of structurally related synthetic cannabinoid receptor agonists currently monitored by the EMCDDA, which also contain a cyclohexylmethyl and a carboxamide moiety are given in Figure 3, where abbreviations have been used.

ADB-CHMICA and AMB-CHMICA have an indole core in common with MDMB-CHMICA. AB-CHMINACA, ADB-CHMINACA and AMB-CHMINACA have an indazole core instead; AB-CHMFUPPYCA has a pyrazole core; and MDMB-CHMCZCA has a carbazole core.

Figure 3: Chemical structures of ADB-CHMICA, AMB-CHMICA, AB-CHMINACA, ADB-CHMINACA, AMB-CHMINACA, AB-CHMFUPPYCA and MDMB-CHMCZCA.



Systematic names for MDMB-CHMICA compatible with the IUPAC (International Union of Pure and Applied Chemistry) nomenclature:

methyl 2-({[1-(cyclohexylmethyl)-1*H*-indol-3-yl]carbonyl}amino)-3,3-dimethylbutanoate or

methyl 2-{[1-(cyclohexylmethyl)-1*H*-indol-3-yl]formamido}-3,3-dimethylbutanoate or

methyl *N*-{[1-(cyclohexylmethyl)-1*H*-indol-3-yl]carbonyl}-3-methylvalinate

N-(1-methoxy-3,3-dimethyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indole-3-carboxamide (name used in the Chinese regulation published in 2015[7])

IUPAC International Chemical Identifier (InChI)

InChI=1S/C23H32N2O3/c1-23(2,3)20(22(27)28-4)24-21(26)18-15-25(14-16-10-6-5-7-11-16)19-13-9-8-12-17(18)19/h8-9,12-13,15-16,20H,5-7,10-11,14H2,1-4H3,(H,24,26)

Standard InChI Key:

SRJKCVHWIDFUBO-UHFFFAOYSA-N

Simplified Molecular-Input Line-Entry System (SMILES)

SMILES: C1(CCCCC1)CN1C=C(C2=CC=CC=C12)C(=O)NC(C(=O)OC)C(C)(C)C

Chemical Abstract Service Registry Number (CAS RN):

International CAS RN: 1863065-84-2

'CAS RN' referenced on the Internet and used in the Chinese regulation ([7])[8]: 1715016-78-6.

Other names:

MMB-CHMINACA

Street names:

Some of the street names used commonly for products containing synthetic cannabinoid receptor agonists are: 'Spice', 'K2', 'legal weed', 'synthetic cannabis', 'herbal incense'.

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7 China Food and Drug Administration (CFDA), 2015. Available at: http://www.sfda.gov.cn/WS01/CL0056/130753.html.

8 A search of this CAS number in pubchem.ncbi.nlm.nih.gov returns the indazole analogue of MDMB-CHMICA, incorrectly labelled as 'MDMB-CHMICA'. See: https://pubchem.ncbi.nlm.nih.gov/compound/119058045

A list of street names reported for products containing MDMB-CHMICA purchased online in as part of the EU-funded projects 'SPICE II Plus'[9] and 'SPICE Profiling' [10] are provided in Appendix 1. It should be noted that there can be considerable variability both within and between different batches of products sold under specific brand names, in terms of both the substances and the amount present.

Other street names reported to the EMCDDA are: Godfather, CUSHCottonCandy, KUSHSecondGereration, KUSHherbal incense, Ninja, Sirius, SKIHIGH, CRITICAL haze.

Stereochemistry

MDMB-CHMICA contains a stereogenic centre thus allowing for the existence of a pair of enantiomers, (*S*)-MDMB-CHMICA and (*R*)-MDMB-CHMICA. There is no representative information on the isomeric composition of the samples of MDMB-CHMICA detected within the European Union, which in part may reflect the fact that stereochemical analysis is not routinely undertaken in forensic laboratories.

In an article by Andernach et al., the isomeric composition and the optical purity of five samples of herbal products containing MDMB-CHMICA have been analysed (Andernach et al., 2016). In addition, a sample from a 40 kg seizure made by customs in Luxembourg in December 2014 (Section C) was analysed in the same study. All the samples were found to contain the (*S*) isomer and to be of very high optical purity.

Some reference material suppliers such as Cayman Chemical (Cayman Chemical Company, 2015) and Toronto Research Chemicals (Toronto Research Chemicals, 2016) list the (*S*)-enantiomer for sale. Other suppliers (Cerilliant, 2016; LGC Standards, 2016) do not indicate which is the stereoisomeric form sold as a reference material.

Identification and analytical profile

MDMB-CHMICA was first identified in a seizure made in Hungary in August 2014. There is no information published in the scientific or patent literature prior to this first detection.

[9] JUST/2011/DPIP/AG/3597
[10] JUST/2013/ISEC/DRUGS/AG/6421

The analytical profile of MDMB-CHMICA has been described in a publication using NMR, LC-HRMS, IR and UV-VIS detection (Langer et al., 2016). The UV maxima of MDMB-CHMICA are reported at 216 and 290 nm in methanol and IR data as follows: wavenumber (cm^{-1}): 3325 (w), 3105 (w), 2926 (m), 2852 (w), 1738 (m), 1616 (s), 1536 (s), 1511 (s), 1464 (m), 1395 (m), 1217 (m), 1196 (m), 1157 (s), 1129 (m), 1014 (m), 776 (m), 742 (s), 618 (m), 549 (m) (Langer et al., 2016).

A recent study described the fragmentation patterns of MDMB-CHMICA (Akamatsu and Yoshida, 2016).

A full analytical profile is also available from the Slovenian National Forensic Laboratory, which analyses test-purchased products within the EU-funded project *Response to challenges in forensic drug analysis* ([11]).

Quantification of MDMB-CHMICA in products can be carried out according to the general procedure described by UNODC, e.g. by HPLC-DAD analysis (United Nations Office on Drugs and Crime, 2013).

Detection of MDMB-CHMICA in biological samples

In the analysis of serum samples, the main analytical target is the parent compound. In an unpublished study by the authors (Moosmann and Auwärter, 2016, unpublished), the concentration of MDMB-CHMICA was quantified in 225 serum samples positive for the substance. The concentrations were in the range of ng/ml (mean: 2.9 ng/ml, median: 0.5 ng/ml, range <0.1 – 91 ng/ml, n=225). Therefore, due to its high sensitivity, LC-MS/MS is the most appropriate technique for quantifying the substance. Three methods for the detection of MDMB-CHMICA in serum samples have been published in the literature so far, all of them using LC-MS/MS (Adamowicz, 2016; Angerer et al., 2016; Westin et al., 2016).

11 Analytical profile available at: http://www.policija.si/apps/nfl_response_web/0_Analytical_Reports_final/MDMB-CHMICA-ID-1190-15-report_final.pdf

In the analysis of urine, the main metabolites need to be identified prior to setting up a method, as MDMB-CHMICA is not excreted unchanged in urine to a relevant extent. Based on the analysis and evaluation of ten urine samples from different individuals (Moosmann and Auwärter, 2016, unpublished), three mono-hydroxylated (hydroxylation at the cyclohexyl moiety) and the carboxylic acid ester hydrolysis product appear to be the most suitable targets for the detection of MDMB-CHMICA exposure.

When interpreting analytical findings it should be noted that some of the substances in which MDMB-CHMICA is metabolised into may be also formed after exposure to other synthetic cannabinoid receptor agonists.

For example, the metabolites that undergo ester hydrolysis are also formed after exposure to ADB-CHMICA. Additionally, one minor metabolite of MDMB-CHMICA (hydrolysis of the amide) is identical with one of the major metabolites of the synthetic cannabinoid BB-22 (QUCHIC)[12] [13]. Since no commercial reference material is available for the metabolites, misidentification could occur due to the fact that MDMB-CHMICA and BB-22 have identical nominal masses and show very similar fragmentation patterns.

Another aspect which has to be considered is the thermolytic formation of two MDMB-CHMICA metabolites during smoking which could bias the detected metabolic profile.

Physical description

In its pure form MDMB-CHMICA is an odourless, white and crystalline solid. It is soluble up to approximately 20 mg/ml in dimethylformamide and 5 mg/ml in dimethyl sulfoxide (Cayman Chemical Company, 2015). The substance is expected to be poorly soluble in water.

The melting point is stated to be 133-134°C (Toronto Research Chemicals, 2016).

The boiling point is not available in the literature; however, it can be estimated to be below 350°C according to its retention time in GC-MS analysis.

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12 Quinolin-8-yl 1-(cyclohexylmethyl)-1H-indole-3-carboxilate

13 More information on the pharmacodynamics and pharmacokinetics of this substance is available in Section A2.

Chemical stability and typical reactions

Storage in solution or under non-ideal conditions (e.g. high humidity or elevated temperatures) can lead to hydrolysis of the carboxylic ester. Ester hydrolysis was shown to occur during smoking by analysis of smoke condensates (Moosmann and Auwärter, 2016, unpublished). Most of the known free carboxylic acids formed by hydrolysis of similar compounds are not active at the CB_1-receptor (Buchler et al., 2009; Buchler et al., 2011). Therefore, the hydrolysis product of MDMB-CHMICA might not be active as a cannabinoid.

In the presence of ethanol, transesterification can lead to the formation of the ethyl ester derivative, which may bind to the CB_1-receptor. Reaction with other alcohols could lead to corresponding ester compounds.

The amide bond may be cleaved chemically or enzymatically.

Methods and chemical precursors used for the manufacture of MDMB-CHMICA

No information was reported to the EMCDDA about the chemical precursors or manufacturing methods used to make the MDMB-CHMICA which has been detected on the drug market in Europe.

Detailed information available with regards to route-specific by-products produced during the synthesis of MDMB-CHMICA is currently not available.

Synthesis

The synthesis of MDMB-CHMICA may be carried out similarly to the synthesis of its indazole analogue, MDMB-CHMINACA, which has been described in a patent application (Buchler et al., 2009; Buchler et al., 2011) or in analogy to similar compounds, as described by Banister (Banister *et al., 2015*) and Adam (Adam et al., 2010). Possible synthetic routes are available in Appendix 2 of the Technical report.

According to the synthetic routes described in Appendix 2, potential precursors of MDMB-CHMICA are L-*tert*-leucine methyl ester (for synthesis of the (*S*) enantiomer), indole-3-carboxylic acid, indole-3-carboxylic acid methyl ester, indole and cyclohexylmethyl bromide.

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.

Impurities identified in powders containing MDMB-CHMICA analysed by the Federal Criminal Police Office of Germany (in German, *Bundeskriminalamt*) are: 'MDMB-CHMICA-2-Cl-analogue'[14] '*tert*-leucine-MDMB-CHMICA'[15] and CHMICA-*N,N*-dimethyl-analogue[16] (Moosmann & Auwärter, 2016).

Commercially available products which could be used for synthesis of MDMB-CHMICA may contain other 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 such as heavy metals and pesticides potentially present in the plant material.

A1.2. Physical/pharmaceutical form

Data from seizures and collected samples reported to the EMCDDA have noted that MDMB-CHMICA has typically been detected in the form of herbal material (Section C). Over 90% of the total number of seizures reported by countries where MDMB-CHMICA has been detected have been of herbal material (EMCDDA and Europol, 2016). This includes the seizure of a number of commercial branded 'legal high' products. MDMB-CHMICA has also been detected in powder form.

MDMB-CHMICA is sold by Internet retailers either as commercial branded 'legal high' products in the form of herbal material or as a powder, typically advertised as 'research chemicals'.

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14 IUPAC name: methyl *N*-({1-[(2-chlorocyclohexyl)methyl]-1*H*-indol-3-yl}carbonyl)-3-methylvalinate)

15 IUPAC name: methyl *N*-{[1-(cyclohexylmethyl)-1*H*-indol-3-yl]carbonyl}-3-methylvalyl-3-methylvalinate

16 IUPAC name: 1-(cyclohexylmethyl)-*N*,*N*-dimethyl-1*H*-indole-3-carboxamide

For the production of 'herbal mixtures' the synthetic cannabinoid(s) is mixed with or sprayed/soaked onto the plant material – mostly damiana (*Turnera diffusa*) or marshmallow (*Althaea officinalis*) – using solvents such as acetone or methanol to dissolve the powders. Once mixed, the mixtures are then dried and solvent is evaporated. Typically this is done on a large scale, using equipment like cement mixers to mix the ingredients together.

A case reported to Europol by German police indicates that MDMB-CHMICA has been impregnated on writing paper along with other cannabinoids to writing paper and was used by prisoners. The prisoners cut the writing paper into pieces and smoked them mixed with tobacco (one unit of administration estimated as a 2x2 cm piece of paper).

Some countries have reported finding other synthetic cannabinoid receptor agonists in products that look like cannabis resin, either in branded 'legal high' products or simply passed off as cannabis resin on the illicit market. In a small number of cases, the presence of synthetic cannabinoid receptor agonists has been detected in what appear to be ecstasy tablets or capsules. Another recent development has been the discovery of synthetic cannabinoid receptor agonists in the liquid-filled cartridges for use in electronic cigarettes; this most likely reflects the recent popularity of 'vaping' among young people.

The detection of MDMB-CHMICA in liquid form, tablets or capsules has not been reported to the EMCDDA.

A1.3. Route of administration and dosage

Route of administration

The most common route of administration for synthetic cannabinoid receptor agonists, including MDMB-CHMICA, is smoking either ready-to-use commercial branded 'legal high' products or self-prepared herbal mixtures as a joint or utilizing a vaporizer, 'bong' or pipe. Oral administration of other synthetic cannabinoid receptor agonists has also been described. In the case of oral administration a strong first-pass-effect can be expected.

See Section D.1.2.2 for more information on route of administration reported for individuals with had serious adverse events associated with the use of MDMB-CHMICA.

Some synthetic cannabinoid receptor agonists (e.g. 5F-cumyl-PINACA, AKB-48-5F) are also offered in the form of e-liquids for administration in an electronic cigarette, but no such products containing MDMB-CHMICA have been reported so far (EMCDDA and Europol, 2016). However, reports on the Internet state that some users prepare MDMB-CHMICA containing e-liquids at home by dissolving in propylene glycol.

Dosage

It is important to note that when interpreting the data on self-reported user experiences that it is not possible to confirm the specific substance(s) used; similarly it is also not possible to confirm the strength, purity, dose/amount, etc., used. In addition, the information provided on user websites and from specific user groups may not necessarily be representative of other users of MDMB-CHMICA and should be regarded as illustrative only.

Self-reported user experiences posted in Internet drug discussion forums (Bluelight, 2016; Erowid, 2016; Reddit, 2016), have reported doses of MDMB-CHMICA that range from 120 µg to 15 mg (Appendix 3). Doses above 1 mg have been generally described as ‘strong’ or ‘very strong’. Doses above 5 mg have been reported by non-naïve users.

The doses by route of administration reported by users are given in Table 1 (source: systematic review that analyses 36 reports from MDMB-CHMICA users on internet discussion forums, Dargan et al., 2016b, unpublished).

Table 1. Routes of administration of MDMB-CHMICA, dose and duration of effects by number of reports (source: Dargan et al., 2016b, unpublished).

Route of Administration	**No. of reports (%)**	**Dose**			**Time to Onset**			**Duration of Symptoms**		
	N=38	n	Median (mg)	IQR	n	Median (mins)	IQR	n	Median (mins)	IQR
Smoked	24 (63.2)	9	5	5 - 8	12	1	1 - 1	12	120	60 - 172.5
E-cigarette inhalation	5 (13.2)	1	0.5	-	1	30	-	2	120	120 - 120
Oral ingestion	4 (10.5)	2	12	8 - 16	3	120	61.5 - 120	1	180	-
Rectal insertion	1 (2.6)	1	0.12	-	1	15	-	1	180	-
Not Reported	3 (7.9)									

A2. Pharmacology, including pharmacodynamics and pharmacokinetics

THC and other cannabinoids (endogenous or synthetic) mediate their actions by binding to the cannabinoid receptors of which there are at least two types, classed as CB_1 and CB_2 found in mammalian tissues (Pertwee, 2004). The CB_1 receptors are located primarily in central and peripheral neurons whilst CB_2 receptors are primarily expressed outside of the central nervous system and play a role with the immune system. Although there is some conflicting evidence in the literature, it is believed that activation of CB_1 receptors by endogenous cannabinoids is said to play a role in neuronal signalling involved dopamine, glutamate and GABA (Pertwee, 2004; Seely et al., 2012).

Activation of CB_1 receptors by THC – the major active principle in cannabis – results in sedative, analgesic, psychedelic and anxiolytic effects (Ashton, 2001). It is also more commonly associated with a euphoric effect of being "high" with colours appearing brighter, music more appealing and changes in emotion (Ashton, 2001). Cannabis can also induce a tachycardia and another symbolic effect of a reddening of the conjunctivae (Paton et Pertwee, 1973). Reaction times and motor skills can also be reduced.

THC has partial agonist activity at the CB_1 receptor in certain neuronal areas (Seely et al., 2012; Wiley et al., 2015).

Pharmacodynamics

Published data on the pharmacodynamics of MDMB-CHMICA are limited to *in vitro* studies.

Indole and indazole synthetic cannabinoid receptor agonists (SCs) were synthesized and assessed for cannabimimetic activity *in vitro* and *in vivo* by Banister et al. (Banister et al., 2016), using a fluorometric assay of membrane potential. The (*S*) enantiomer of MDMB-CHMICA was synthetised and studied in this paper. All the compounds studied, including (*S*)-MDMB-CHMICA, activated CB_1 and CB_2 receptors , displaying greater potency (10 nM for (*S*)-MDMB-CHMICA) than either Δ^9-THC (171 nM) or CP 55,940 (42 nM) for CB_1 receptor-mediated activation of G protein-coupled inwardly-rectifying potassium channels (GIRK). Most of the studied compounds, including (*S*)-MDMB-CHMICA, had a similar maximal effect to CP 55,940 at CB_1 and CB_2 receptors, suggesting that these SCs are also high efficacy agonists. (*S*)-MDMB-CHMICA showed a preference for CB_1 receptors over CB_2 receptors (7.1).

Table 2. Functional activity of Δ^9-THC, CP 55,490 and (*S*)-MDMB-CHMICA at CB_1 and CB_2 receptors.

Compound	hCB_1	hCB_1	hCB_2	hCB_2	CB_1 sel
	pEC_{50} ± SEM (EC_{50}, nM)	Max ± SEM (% CP 55,940	pEC_{50} ± SEM (EC_{50}, nM)	Max ± SEM (% CP 55,940	Expressed as the ratio of CB_1 EC_{50} to CB_2 EC_{50}
Δ^9-THC	6.77 ± 0.05 (171)	50 ± 11	-	20 ± 3 at 10 µM	-
CP 55,490	7.47 ± 0.05 (42)	-	7.17 ± 0.07 (68)	-	1.6
(*S*)-MDMB-CHMICA	8.00 ± 0.05 (10)	112 ± 3	7.16 ± 0.05 (71)	103 ± 3	7.1

Although specific data are not presented, a study evaluating the binding affinity of 54 newly-emerged synthetic cannabinoid receptor agonists at the cannabinoid CB_1 and CB_2 receptors revealed that most of the substances had almost the same or higher CB_1 and CB_2 receptor binding affinities as compared to JWH-018 and that MDMB-CHMICA 'was one of the substances with the highest binding affinities at the CB_1 receptor' in the study (Kikura-Hanajiri, 2015). At present, no further details are available, since this publication is available in abstract form only.

The available data suggests that MDMB-CHMICA is a potent efficaceous agonist at the CB_1 receptor of the endocannabinoid system. Using a cAMP assay, MDMB-CHMICA showed an EC_{50} approximately 8 times lower than the EC_{50} of JWH-018, and a twofold lower EC_{50} than AB-CHMINACA[17] [18] (Table 3) (Moosmann and Auwärter, 2016, unpublished).

[17] The EC_{50} is the concentration of a drug which produces 50% of the maximum possible response in a dose response curve. The lower the EC_{50} value is indicative of a higher potency.

[18] Systematic name: *N*-[(1*S*)-1-(aminocarbonyl)-2-methylpropyl]-1-(cyclohexylmethyl)-1H-indazole-3-carboxamide.

Table 3: Half maximal effective concentration (EC_{50}) and efficacy as compared to the full agonist CP 55,940 (E_{max}) of MDMB-CHMICA and other synthetic cannabinoids as assessed using a cAMP assay (CB_1 receptor, DiscoverX) (Moosmann and Auwärter, 2016, unpublished).

Compound	**EC_{50} [nM]**	**E_{max}**
MDMB-CHMICA	0.14	94%
AB-CHMINACA	0.27	94%
AB-FUBINACA	0.89	97%
JWH-018	1.13	97%

Structure activity relationship (SAR) studies comparing different synthetic cannabinoid receptor agonists have been published (see information below). MDMB-CHMICA appears to have some of the structural features (i.e. an indole core, a *tert*-butyl moiety, and a carboxamide methyl ester) that have been associated with low CB_1 values (higher activity at the CB_1 receptor).

Structure activity relationships show that the substitution of the indole core with an indazole core is expected to lead to a significant reduction of the activity at the CB_1 receptor. This is observed in the case of APICA [19] (indole core) and APINACA[20] (indazole core) (IC_{50}: 175 nM vs. 824 nM) (Uchiyama et al., 2012) and in the case of AM-2201 (indole core) and THJ-2201 (indazole core) (EC_{50}: 0.45 nM vs. 1.68 nM) (Moosmann and Auwärter, 2016, unpublished).

The introduction of a *tert*-butyl moiety (e.g. ADB-CHMINACA[21]) is expected to lead to an increase in affinity towards the CB_1 receptor as compared to compounds that carry an isopropyl moiety (e.g. AB-CHMINACA) (ADB-CHMINACA K_i: 0.289 nM; EC_{50}:IC_{50} 0.62 nM vs. AB-CHMINACA K_i: 0.519 nM; EC_{50}:IC_{50} 2.55 nM) (Moosmann and Auwärter, 2016, unpublished).

19 Systematic name: *N*-(1-adamantyl)-1-pentyl-1H-indole-3-carboxamide.

20 Systematic name: *N*-(1-adamantyl)-1-pentyl-1H-indazole-3-carboxamide.

21 Systematic name: *N*-[1-(aminocarbonyl)-2,2-dimethylpropyl]-1-(cyclohexylmethyl)-1H-indazole-3-carboxamide.

Furthermore, a carboxamide linker (e.g. ADB-CHMINACA) is related to a decrease in activity as compared with its methyl ester analogue (e.g. MDMB-CHMINACA) (ADB-CHMINACA K_i: 0.289 nM; EC_{50}:IC_{50} 0.62 nM vs. MDMB-CHMINACA K_i: 0.094 nM; EC_{50}:IC_{50} 0.330 nM) (Buchler et al., 2009; Bluchler et al., 2011; Banister et al., 2015).

There are no data available on the effect of MDMB-CHMICA on other pharmacological targets.

The pharmacological properties of the metabolites of MDMB-CHMICA are not known. It has been previously shown that the mono-hydroxylated metabolites of cannabinoids such as JWH-018, JWH-073 and THC have activity at the CB_1 receptor. It is therefore possible that the mono-hydroxylated metabolites of MDMB-CHMICA may contribute to the pharmacological profile of the compound. It should be noted, however, that it is unclear if these metabolites will be able to cross the blood-brain-barrier and reach effective concentrations levels in the central nervous system.

Pharmacokinetics

There is limited information in the literature concerning the pharmacokinetics of MDMB-CHMICA.

MDMB-CHMICA is expected to undergo extensive metabolism in the human body. Similar to other synthetic cannabinoid receptor agonists which have been previously studied (Erratico et al., 2015, Hegstad et al., 2015), it is not excreted unchanged in urine to a relevant extent.

A study by Moosmann and co-workers (Moosmann and Auwärter, 2016, unpublished) has identified a total of 31 metabolites of MDMB-CHMICA *in vivo.* The four most abundant metabolites detected were either products of the mono-hydroxylation of the cyclohexyl moiety or products of the hydrolysis of the carboxylic ester function. Given the metabolites found, it is thought that the main metabolic reactions comprise mono-hydroxylations and hydrolysis of the carboxylic ester function (similarly to what occurs for AB-CHMINACA).

A second study by Dobos and co-workers (Dobos et al., 2015) has identified the carboxylate derivative formed by ester de-methylation as the main metabolite of MDMB-CHMICA in human urine.

Metabolites specific to MDMB-CHMICA have been identified. A study by Franz and co-workers (Franz et al., 2015) suggests that the cyclohexyl-methyl hydroxylated product of MDMB-CHMICA is a potential target for the identification of the compound in human urine samples.

Interactions with other drugs or medicines

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

A3. Psychological and behavioural effects

Information on the psychological and behavioural effects of MDMB-CHMICA is limited to serious adverse events reported to the EMCDDA, case reports published in the scientific literature and self-reported user experiences published in Internet drug discussion forums and related websites.

Some users report that the effects of MDMB-CHMICA are comparable to the effects of cannabis, with a more pronounced euphoria. In summary, reported psychological and behavioural effects after use of MDMB-CHMICA include: increased appetite, nausea and vomiting, tachycardia, inability to move, numbness of extremities, shivering, feeling of warmth, laughing, changes in mood (for example alternating crying and singing), disorientation, confusion, lack of concentration and short-term memory, vertigo, tiredness, visual and auditory hallucinations, agitation, severe anxiety and fear/panic, psychosis, dissociation, violent behaviour, aggression and 'acute behavioural disturbances'. These effects are consistent with known psychological and behavioural effects of synthetic cannabinoid receptor agonist use (Tait et al., 2016; Kronstrand et al., 2013) and it has been suggested that they may be connected to alterations in dopaminergic transmission (Seywright et al., 2016) (see Section D1.2.1 and Section D3.3).

The most common psychological effect reported by users was euphoria (11; 30.6%), followed by visual hallucinations (6; 16.7%) (source: systematic review that analyses 36 reports from MDMB-CHMICA users on internet discussion forums, Dargan et al., 2016b, unpublished) (see Section D1.2.1).

A4. Legitimate uses of the product

As a result of its appearance on the drug market, MDMB-CHMICA and its (*S*) enantiomer are used in scientific research as well as analytical reference materials in clinical and forensic case work/investigations. There is currently no other information that suggests MDMB-CHMICA may be used for other legitimate purposes.

There are no reported uses of MDMB-CHMICA as a component in industrial, cosmetic or agricultural products. In addition, a search of the REACH registered substances database hosted by the European Chemicals Agency (ECHA) using the CAS Registry Numbers returned no results.

There is no marketing authorisation (existing, ongoing or suspended) for MDMB-CHMICA 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 and Europol, 2015).

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

The dependence potential of two other synthetic cannabinoid receptor agonists have been studied in animals by Ginsburg and co-workers (Ginsburg et al., 2012) and can provide some insight into the dependence and abuse potential of MDMB-CHIMICA. According to the study, 'the relatively short duration of action of JWH-018 and JWH-073 [relative to Δ^9-THC] may lead to a more frequent use, which could strengthen habitual use by increasing the frequency of stimulus outcome pairings'. This, coupled with the possible greater efficacy of JWH-018 at CB1 receptors, could be associated with a greater dependence liability for these synthetic cannabinoid receptor agonists when compared to Δ^9-THC.

In rhesus monkeys, cross-tolerance was observed after 3 days of Δ^9-THC treatment for Δ^9-THC but not for JWH-018 (Hruba et al., 2012). The greater loss of sensitivity to Δ^9-THC relative to JWH-018 suggests that differences in CB1 receptor agonist efficacy are important in vivo and might underlie differences in the dependence liability and adverse effects of synthetic cannabinoid receptor agonists versus cannabis.

B2. Human data

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

The available information comes from:

- A small case series of patients seeking medical treatment due to withdrawal symptoms following MDMB-CHMICA consumption;
- Self-reported user experiences published in Internet drug discussion forums;
- Comparison to studies regarding other synthetic cannabinoids.

Four cases of patients seeking medical treatment due to withdrawal symptoms following MDMB-CHMICA consumption were reported to the Poison Information Centre in Freiburg, Germany (Moosmann and Auwärter, 2016, unpublished). In all 4 cases consumption of MDMB-CHMICA was analytically confirmed, but other substances were also detected (including THC-COOH, other synthetic cannabinoid receptor agonists, antidepressants and antipsychotic drugs). In one of the cases, the withdrawal symptoms were reported by a patient with a daily use of 3 grams of a commercial branded herbal mixture containing synthetic cannabinoid receptor agonists which included MDMB-CHMICA. In two of the cases, withdrawal symptoms were reported following 'regular' consumption of herbal mixtures containing MDMB-CHMICA, which motivated the patients to seek medical help 1 to 2 weeks after the last use. The duration and extent of use was not reported for one case. A description of the withdrawal symptoms experienced by the patients was not reported.

A limited number of self-reported user experiences published in Internet drug user forums further suggest the substance may have dependence and abuse potential. These should to be interpreted with caution as it is not possible to confirm the specific substance(s) used, nor the purity, nor the dose/amount in respect to self-reported cases. Analyses of new psychoactive substances and the products containing them that are sold on the drug market have shown that the composition can differ between that claimed by the retailer, as well as vary over geographical areas and time. Furthermore, the users' physical characteristics and health status are rarely reported. For these reasons, the information on user websites should be regarded as illustrative only and not taken as representative of users of MDMB-CHMICA in general.

Some users reported the existence of withdrawal effects from abstinence of MDMB-CHMICA. In one case, a user mentioned experiencing '[bad] cravings' and reported a 'numbing of the skin', depression, anger and nausea[22]. Other users report withdrawal symptoms which seem to last for longer periods ('whole body went numb for 5 days') than expected with other synthetic cannabinoid receptor agonists (Castaneto et al., 2014). 'Addiction' to MDMB-CHMICA was reported by a user after consumption of 'a couple of grams' over 'a few weeks' (consumption 'every two hours').

Other synthetic cannabinoid receptor agonists have been previously found to produce withdrawal symptoms in humans. The literature in this regard has been systematically reviewed previously by Castaneto et al. (Castaneto et al., 2014). The authors found that whilst it was difficult to directly compare synthetic cannabinoid and cannabis, many of the symptoms are the same.

[22] Available at: https://drugs-forum.com/forum/showthread.php?t=253270, accessed 13/06/2016

Section C. Prevalence of use

Information from seizures, collected and biological samples

The formal notification of MDMB-CHMICA to the European Union Early Warning System (EU EWS) was in September 2014 by the Hungarian National Focal Point. The Reporting Form details a seizure of 0.19 grams of green/brown herbal product that was seized in August 2014 by police in Ács, Hungary. Since then, the substance has been detected in 23 Member States, Turkey and Norway[23] (EMCDDA and Europol, 2016).

Information from seizures

- At the time of writing this report, 22 Member States (Austria, Belgium, Bulgaria, Croatia, Cyprus, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Latvia, Lithuania, Luxembourg, Netherlands, Poland, Romania, Spain, Sweden, Slovakia and the United Kingdom), Turkey and Norway had reported seizures ([24]) of MDMB-CHMICA to the EMCDDA and/or Europol.

- Information reported to the EMCDDA and Europol indicates that over 120 kg of MDMB-CHMICA has been seized, as either herbal material or powder form.

- Over 90% of the total number of seizures reported to the EMCDDA were in the form of herbal material (EMCDDA and Europol, 2016). This includes the seizure of a large number of commercial branded 'legal high' products.

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[23] 'Detections' is an all-encompassing term and may include seizures and/or collected and/or biological samples that are analytically confirmed. Seizure means a substance available (seized) through law enforcement activities (police, customs, border guards, etc.). Collected samples are those that are actively collected by drug monitoring systems (such as test purchases) for monitoring and research purposes. Biological samples are those from human body fluids (urine, blood, etc.) and/or specimens (tissues, hair, etc.)

([24]) 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.

- The largest single bulk seizure reported to the EMCDDA was 40 kg of MDMB-CHMICA in powder form by Luxembourg, in December of 2014. The powder was contained in forty 1 kg packages and was seized at Luxembourg airport where it was in transit from Shanghai, China to Madrid, Spain (final destination).

- Single seizures in excess of 1 kg were reported by five other countries: Germany (9.6 kg, herbal material containing also ADB-CHMINACA; 3.4 kg, herbal material containing only MDMB-CHMICA); Spain (4.8 kg, undefined physical form); Lithuania (4 kg, undefined physical form, purity 0.2%); Romania (2.9 kg, herbal material containing also 5F-MDMB-PINACA); and the Netherlands (over 1 kg of powder).

Information reported to Europol and the EMCDDA suggests that bulk powders of MDMB-CHMICA are imported from chemical companies based in China. These powders are then used to produce smoking mixtures within Europe.

Due to the high potency of some synthetic cannabinoid receptor agonists, the amount of powder needed for each packet can be in the order of a few tens of milligrams. This means that each kilogram of bulk powder may produce thousands of packets of 'legal highs'.

The discovery of a large seizure suggests the involvement of organised crime in the distribution process. There are also indications of a significant internet retail trade within Europe, with customs and police making regular seizures of small quantities of these products.

Information from collected samples

- A total of 4 Member States reported 60 samples that contained MDMB-CHMICA collected from users and purchased from bricks-and-mortar shops and online shops: Spain (3), France (2), Slovenia (2), and the United Kingdom (53). Some of the collected samples from users were linked to biological detections including serious adverse events (EMCDDA and Europol, 2016).

Information from biological samples

- A total of 306 detections where MDMB-CHMICA was analytically confirmed in biological samples were reported by 7 Member States (Austria, Germany, Estonia, Hungary, Poland, Sweden, and the United Kingdom) and Norway. These include 53 serious adverse events (25 acute intoxications and 28 deaths). The remaining detections related to: intoxications reported to the Poisons Information Centres, persons suspected of driving under the influence of drugs, and persons suspected of having committed minor offences or crimes.

Availability, supply, price

Data from seizures, collected samples and acute intoxications reported to the EMCDDA, as well as data from the EU 'SPICE' project (Moosmann and Auwärter, 2016) suggest that MDMB-CHMICA is sold typically as commercial branded 'legal high' products in head shops as well as on the Internet. 'Legal high' products containing MDMB-CHMICA are marketed as 'legal' replacements to cannabis. As already mentioned, it is usually not stated if the 'legal high' product contains MDMB-CHMICA or any other particular synthetic cannabinoid therefore, it is reasonable to assume that the vast majority of users consume MDMB-CHMICA unknowingly.

MDMB-CHMICA is sold by online retailers either as commercial branded legal high products or as a powder which is advertised as a 'research chemical'. In 'legal high' products it is not usually stated if the product contains MDMB-CHMICA or any other particular synthetic cannabinoid receptor agonist.

Monitoring of online shops selling products containing synthetic cannabinoid receptor agonists provides some insight into the range of smoking mixtures available for purchase. Such monitoring, when combined with test purchasing of products for sale, is also a way of both keeping track of how the substances contained in a product change over time.

Detection in commercial branded 'legal high' products

Data obtained through the EU-funded projects 'SPICE II Plus' and 'SPICE Profiling'[25] suggests that MDMB-CHMICA was commonly found in Germany in 'legal high' products being sold on the market, even though the representatively of the samples analysed cannot be commented on (Moosmann and Auwärter, 2016, unpublished).

In the analysis of 532 products purchased on the Internet (Pütz et al., 2016), MDMB-CHMICA was the most commonly detected synthetic cannabinoid receptor agonist being detected in 31% of all products (166 products). MDMB-CHMICA was detected in 22% of all the herbal mixture products analysed between April 2015 and April 2016 (116 products out of 532 test-purchased from the internet) (Pütz et al., 2016).

Test purchase analysis of herbal mixture products has been conducted within EU-funded projects 'SPICE II Plus' and 'SPICE Profiling'. In 2015, 427 'herbal mixtures' were analysed, of which 186 samples (44%) contained MDMB-CHMICA. Of these 186 samples, 82% contained solely MDMB-CHMICA, 14% contained MDMB-CHMICA and one additional synthetic cannabinoid, and 4% contained MDMB-CHMICA and two additional synthetic cannabinoid receptor agonists (Moosmann and Auwärter, 2016, unpublished).

Within the Public Health Wales drug checking project WEDINOS[26], MDMB-CHMICA was detected in 36 herbal mixtures and in one powder sent for analysis (Moosmann & Auwärter, 2016; monitoring results between September 2014 and February 2016) (see Section D1.2.1).

Detection in biological samples

See also sections D1.2.2 and D1.2.3.

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25 EU funded research project (2010 – 2012), continued by the "Spice II Plus" project aimed at ensuring a scientific knowledge base (including analytical libraries) on synthetic cannabinoid receptor agonists and other new psychoactive substances

26 Welsh Emerging Drugs and Identification of Novel Substances

Between September 2014 and August 2015, MDMB-CHMICA was detected in 14% of all serum samples tested in routine forensic work by the Institute of Forensic Medicine in Freiburg (Germany) (n=140 of a total of 1,046 samples analysed) (Angerer et al., 2016).

The IONA[27] project analysed samples of suspected NPS users who were at least 16 years of age presenting to participating hospitals in the United Kingdom with at least one defined feature of severe toxicity (Seywright et al., 2016). Out of 49 participants presenting in 7 hospital emergency departments, 7 individuals (14%) tested positive for MDMB-CHMICA.

A prospective observational cohort study (Abouchedid et al., 2016) enrolling adult patients who presented with acute recreational drug toxicity to the emergency department of 1 hospital in London (United Kingdom) found MDMB-CHMICA in 4% (n=7) of all recruited cases (n=149). Synthetic cannabinoid exposures represented 12% (n=18) of the total caseload (n=149).

Finally, the EU-funded project Euro-DEN Plus analysed 10,956 presentations to 16 sentinel centres in 10 European countries in a two year period (October 2013 – September 2015). MDMB-CHMICA was found in only one case (in Munich, Germany). Synthetic cannabinoid receptor agonists were found for in less than 1% of all presentations (104 out of 10,956). Euro-DEN data are collected based on self-report, with analytical screening being carried out in approximately 15% of the cases (with methods varying according to the centre in question).

Availability from Internet vendors

Table 4 lists the results of an Internet search for online shops selling research chemicals in various countries (Belgium, Czech Republic, Germany, Hungary, The Netherlands, Poland, Spain, Sweden, United Kingdom, Canada, USA, China) which was conducted in March 2016 (Moosmann and Auwärter, 2016, unpublished). 95 shops were screened for their product portfolio. 28 shops had MDMB-CHMICA listed on their website, of which two shops advertised the substance ‘MDMB-CHMICA’ and 26 shops named it ‘MMB-CHMINACA’. In 6 of the 28 shops the compound was listed as ‘out of stock’. The table also lists the price range for the compound depending on the quantity ordered.

[27] Identification of Novel psychoActive Substances

Table 4: Online prices of MDMB-CHMICA depending on the order quantity[28]

	1 g	**10 g**	**100 g**	**1,000 g**
Number of products	16	20	19	16
Range	8.50 – 23.40 €	60.00 – 203.40 €	405 – 770 €	1,620 – 6,100 €
Median	13.90 €	97.50 €	545 €	3,600 €
Mean	14.93 €	98.43 €	556 €	3,505 €
Mean (per gram)	14,93 €	9,84 €	5,56 €	3,50 €

MDMB-CHMICA was controlled in the People's Republic of China in October 2015 and although some Chinese vendors still list MDMB-CHMICA on their webpage, it has been reported that this compound is generally not shipped any longer (Moosmann & Auwärter, 2016).

Prevalence of use

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

Prevalence of use of products containing synthetic cannabinoid receptor agonists

Information on the extent to which synthetic cannabinoid products are used is limited; however, knowledge of the situation is improving as more countries incorporate questions about their use in general population surveys. From the information that is available, it would appear that the prevalence of their use in the general population is low in Europe. A number of surveys aimed at examining the prevalence of use of 'Spice'-like products have been launched but their coverage and representativeness remains limited (EMCDDA, 2016).

A number of surveys in European countries report on the use of synthetic cannabinoid receptor agonists, although they are not comparable as they use different methods, sampling frames and terminology. Overall, these studies indicate very low prevalence levels.

[28] Exchange rates used for calculation in €: 1 GBP = 1.30 €; 1 USD = 0.90 €, 1 PLN = 0.23 €

The United Kingdom (England and Wales) asked about the use of 'Spice' in two consecutive household surveys and reported lifetime prevalence levels for adults (16–64) at 0.2 % in 2010/2011 and 0.1 % in 2011/2012 (Smith and Flatley, 2011;Office for National Statistics, 2012). In the latest British Crime Survey for England and Wales covering 2014/2015 a total of 0.9 % of adults (16–59) had used new psychoactive substances in the last year, of which 61 % had used a herbal smoking mixture (Home Office, 2015). The question was not repeated in subsequent years due to the low prevalence rate.

In Spain a 2012 national survey on drug use among students aged 14–18 with a sample of 27 503 also identified low levels of use of 'Spice' products, with prevalence rates of 1.4 % for lifetime use, 1.0 % for last year use and 0.6 % for last month use, which indicated a small increase from the previous survey results from 2010 (1.1 %; 0.8 %; and 0.5 % respectively) (Spanish Observatory on Drugs, 2012). This compares with 0.5 %, 0.1 % and 0 % in a more general Spanish survey of 15- to 64-year-olds conducted in 2013 (Spanish Observatory on Drugs, 2013).

In France in 2014 a survey of adults (18–64) with a question about the use of 'synthetic cannabinoids' reported lifetime use of 1.7 %. First-time users of these new synthetic products are mostly males (2.3 % vs. 1.2 % of females) and from the youngest generation (under 35 years): 4.0 % of 18- to 34-year-olds had tried synthetic cannabinoid compared to 0.6 % of 35- to 64-year-olds (Beck et al., 2015). Another survey in France, among young people aged 17, reported that 1.7 % of them have previously used a synthetic cannabinoid (Spilka et al., 2015).

The German city of Frankfurt has studied the use of smoking mixtures and 'Spice' among students aged 15–18. They reported lifetime levels of use of 7 % in 2009; 9 % in 2010; and 7 % in 2011 and 2012 (Werse et al., 2011; Werse et al., 2012; Bernard et al., 2013). In 2013 lifetime use of smoking mixtures fell to 5 %, and although it increased to 6 % in 2014 it was still below the values from 2009–12 (Werse et al., 2014; Werse et al., 2015). Students reporting the consumption of 'Spice' were, for the most part, experienced cannabis consumers.

Finally, a number of studies among particular groups (clubbers, internet users, etc.) with non-probabilistic samples have generally identified higher levels of synthetic cannabinoid use than among the general population. The 2012 Global Drug Survey, for example, reported last year prevalence levels of 3.3 % among all UK respondents (not representative of the general population) and 5.0 % among UK regular clubbers (Guardian/Mixmag Survey, 2012).

There are notable differences between the prevalence of use of synthetic cannabinoid products between the European and US drug markets. The 2014 US Monitoring the Future survey of students suggests use is declining, with last year prevalence for 17- to 18-year-olds of 5.8 % in 2014, down from 7.9 % in 2013 and 11.3 % in 2012 (National Institute on Drug Abuse, 2014).

Section D. Health risks

D1. Acute health effects

D1.1. Animal data

No studies were identified examining the acute toxicity of MDMB-CHMICA and/or its metabolites in animals.

D1.2. Human data

No clinical studies were identified that have examined the acute health effects of MDMB-CHMICA and/or its metabolites in humans.

In vitro data on cytotoxicity and genotoxicity is available for other synthetic cannabinoid receptor agonists (Koller et al., 2013a; Koller et al., 2013b; Koller et al., 2015; Ferk et al., 2016).

Data from serious adverse events associated with MDMB-CHMICA are discussed in section D.1.2.2. Based on the data reported, the clinical features presented in cases of intoxication involving MDMB-CHMICA appear to be broadly similar to those found with other synthetic cannabinoid receptor agonists (Hermanns-Clausen et al., 2013; Pant et al., 2012; Papanti et al., 2013). These include: tachycardia, agitation, hallucinations, vomiting, chest pain, seizures, myoclonus, extreme anxiety leading to panic attacks and acute psychosis.

D1.2.1. User reports

There are limited user reports discussing MDMB-CHMICA in Internet drug discussion forums. It is likely that this is because MDMB-CHMICA is sold mostly as commercial branded ‘legal-high’ products with little or no indication of the ingredients and therefore users may be unaware that they are taking MDMB-CHMICA. The few available user reports should be interpreted with caution, as discussed in section B2.

Self-reported users of MDMB-CHMICA describe it as a 'potent' compound. Several describe their experience with MDMB-CHMICA as unpleasant, and some mention having to resort to medical emergency services following consumption.

Some users report that the effects of MDMB-CHMICA are comparable to the effects of cannabis, with a more pronounced euphoria (see Section A3).

The most common effects reported by users in a systematic review that analyses 36 reports from MDMB-CHMICA users on internet discussion forums (Dargan et al., 2016b, unpublished) are presented in Table 5.

Table 5 Most commonly reported effects related to use of MDMB-CHMICA (Dargan et al., 2016b, unpublished).

Theme	Effect	Number of Reports	%
Total Number of Reports		36	
Physiological	Palpitations	11	30.6%
	Nausea & Vomiting	9	25.0%
	Loss of Consciousness	6	16.7%
	Chest Pain	5	13.9%
	Sedation	4	11.1%
	Red Eyes	2	5.6%
Mental State	Euphoria	11	30.6%
	Visual hallucinations	6	16.7%
	Anxiety	5	13.9%
	Paranoia	4	11.1%
	Retrograde amnesia	3	8.3%
	Sense of Doom	2	5.6%
	Auditory Hallucinations	2	5.6%
Drug-related	Tolerance	3	8.3%
Withdrawal Related	Numbness	4	11.1%
	Vomiting	2	5.6%
	Depression	2	5.6%
	Anorexia	2	5.6%
	Insomnia	2	5.6%

Some users report difficulties in dosing their consumption of MDMB-CHMICA, in that frequently the user may only realise that a 'large' dose was taken after the first effects are felt. When mentioned, onset is reported to occur between 0 to 3 minutes and last between 1 hour to 4 hours. This is in agreement with data presented in section D1.2.2. which suggests an average onset of action at 2.6 minutes and an average duration of effects of 2.6 hours.

In more than one case, longer term effects were described. One user reported 'terrible dissociation, panic attacks and severe concentration issues over weeks' and another one experienced withdrawal symptoms where the 'whole body went numb for 5 days, I thought I was having a stroke'. These statements are consistent with data from serious adverse events where some individuals where kept in hospital care for up to 9 days following MDMB-CHMICA exposure (section D.1.2.2.).

Doses are described from 0.1 mg to 15 mg of MDMB-CHMICA typically mixed in herbal media and 2 mg to 20 mg of pre-prepared herbal material. In most cases the dose is described as 'too much', even for users who describe themselves as 'tolerant' (see Section A1.3).

D1.2.2. MDMB-CHMICA associated acute toxicity

Acute intoxications reported by the Member States

42 acute intoxications associated with MDMB-CHMICA were reported by 7 countries: Austria (7 cases), France (2), Germany (7), Poland (3), Spain (2), Sweden (10), and the United Kingdom (11). These typically relate to acute non-fatal presentations to hospital emergency departments. The acute intoxications occurred during 2014 and 2015.

In 25 of the 42 cases, MDMB-CHMICA was analytically confirmed in one or more biological samples taken from the patient at or around the time of intoxication: Austria (7 cases), Germany (3), Sweden (6) and the United Kingdom (9). The remaining 17 cases were excluded from the analysis[29].

[29] In the remaining cases confirmation was either not obtained, not reported or made through an epidemiologically linked sample (for example, a sample collected from the patient found to contain MDMB-CHMICA).

Demographics

Of the 25 analytically confirmed acute intoxications, 17 (68%) were male; 6 (24%) were female; in 2 (8%) of the cases the gender of the patient was unknown. The mean age of the male cases for which an age was known was 26 years (median 21); for the female cases the mean age was 25 years (median 20). For all cases, the ages ranged between 15 and 50 years old.

Substances analytically identified in biological samples

In 6 of the 25 analytically confirmed cases, MDMB-CHMICA was the only substance identified. In the remaining 19 cases MDMB-CHMICA was detected along with other substances[30]. These were typically other cannabinoids (including THC and its metabolites) (17 out of 25 cases) and/or ethanol (6/25). Other substances detected included methamphetamine (4/25), amphetamine (3/25) benzodiazepines (3/25)[31], morphine (1/25), and buprenorphine (1/25).

Seriousness of the intoxications

Data on the seriousness of the intoxication were reported for 13 out of the 25 analytically confirmed acute intoxications:

- In 8 out of the 13 cases the seriousness of the intoxication was classified as life threatening. In all 8 cases MDMB-CHMICA was not the only substance found. At least 4 of those cases were treated in hospital (no information on hospitalisation for the remaining 4 individuals);
- In 3 out of the 13 cases the intoxication was classified as non-life threatening but required treatment in hospital;
- In 2 out of the 13 cases no information was reported on whether the intoxication was life-threatening but both patients were found unconscious and required treatment in hospital.

30 In section 3.4.1 of the EMCDDA-Europol Joint Report on MDMB-CHMICA information is provided on 25 analytically confirmed acute intoxications, 3 of which were mono-intoxications. Since the drafting of the Joint Report, further reporting has clarified that MDMB-CHMICA was the only substance found in a further 3 cases.

31 In all 3 cases, no benzodiazepines were prescribed or used in the treatment of these individuals. The benzodiazepines found were considered to be due to illicit consumption.

Information on the length of hospital stay was available for 9 out of 25 cases. The hospitalisation period varied between 3 hours to 24 hours (mean: 12 hours; median: 8 hours). In the work published by Hill and co-workers (Hill et al., 2016) the length of hospital stay of patients exposed to MDMB-CHMICA varied between 5 hours to 22 hours[32] (n=6; mean: 14 hours; median: 15 hours).

Clinical features

Data on clinical features related to the 25 acute intoxications (including the 6 cases where MDMB-CHMICA was the only substance detected) were generally consistent with those associated with intoxication by MDMB-CHMICA reported in the literature (Hill et al., 2016; Seywright et al., 2016; Angerer et. al, 2016)[33] and with intoxication by other synthetic cannabinoid receptor agonists (Tait et. al, 2016).

Coma and unconsciousness was the most prevalent feature, having been reported for 10 out of 25 cases. Other clinical features reported were: tachycardia (7 cases), syncope (6), hyperemesis and/or nausea (4), mydriasis (3), seizures and convulsions (2), bradycardia (2), somnolence (2), serotonin toxicity (2), urinary and faecal incontinence (1), respiratory acidosis (1), metabolic acidosis (1). These included (but are not limited to): confusion, agitation, aggressiveness, changes in mood, hallucinations, tachycardia, mydriasis, hyperemesis, and unresponsiveness.

In 4 out of 25 cases the patients were described as exhibiting aggression and/or severe disturbance of behaviour, some of which resulted in police intervention and/or transfers to psychiatric units.

Route of administration and physical form of the substance/product

Data on the route of administration was available for 14 out of 25 cases. In all of them, the substance was smoked, presumably smoked or inhaled. The substance was consumed as a herbal product in all cases (8 cases) for which information about the physical form of the substance was available.

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32 One (atypical) case was not included in this analysis. The patient in question had been exposed to MDMB-CHMICA and methiopropamine and the hospitalisation was prolonged for 189 hours (ca. 8 days).

33 The 9 reports of acute intoxications with MDMB-CHMICA published by Seywright and co-workers (Seywright et al., 2016) may be duplicates of cases reported to the EMCDDA.

Acute intoxications identified from open source information and other sources

30 cases of individuals seeking medical assistance following consumption of MDMB-CHMICA were registered by the Poisons Information Centre in Freiburg, Germany, between 2014 and 2015 (Moosmann and Auwärter, 2016, unpublished)[34]. All cases were analytically confirmed from biological samples taken from the patients. 12 out of 30 cases were considered mono-intoxications because all other serum findings were considered either not relevant (e.g. low levels of THC-COOH) or resulting from hospital treatment (e.g. benzodiazepines). The clinical features reported for the cases of mono-intoxications were in agreement with the data already discussed and included: drowsiness or somnolence, tachycardia, vomiting and nausea, seizures, syncope and behavioural disturbances such as aggression, panic, agitation and disorientation.

Two case series of patients exposed to MDMB-CHMICA presenting to hospital with acute intoxications were published by **Hill** et al. (Hill et al., 2016; n=7) and **Seywright** et al. (Seywright et al., 2016; n=9)[35]. Clinical features of acute intoxications from these datasets appear to be similar with the clinical features of the cases reported to the EMCDDA. The demographic data of both cohorts was also comparable to the case-level data reported to the EMCDDA (n=16, 87.5% males, 12.5% females, ages between 15 and 57 years old). Duration of the hospitalization ranged from 3 to 24 hours (mean: 13h, median: 17h, n=15). Recovery occurred within 24 hours except one case (Hill et al., 2016), where methiopropamine was also detected, in which the patient was discharged after 9 days[36].

Both studies collected information on a number of clinical features which included body temperature. Hypothermia was observed in at least 50% of the cases (n=8 out of 16), which is 'believed to be reflective of the action of MDMB-CHMICA in the body' (Seywright et al., 2016).

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34 It is possible that some cases may be duplicates of cases published by Angerer and co-workers (Angerer et al., 2016), as well as with data reported to the EMCDDA.

35 As has been mentioned before, the 9 reports of acute intoxications with MDMB-CHMICA published by Seywright and co-workers (Seywright et al., 2016) may be duplicates of cases reported to the EMCDDA by the United Kingdom.

36 This case has not been included in the analysis of duration of hospitalization.

Hypoglycaemia was also discussed as resulting from exposure to MDMB-CHMICA. In one study (Seywright et al., 2016), 75% of the cases (n=7 out of 9) exhibited blood glucose concentrations indicative of fasting. Poor self-care from the users is admitted as a confounding factor but the association between MDMB-CHMICA exposure and hypoglycaemia is further supported by details of one of the cases. Here, a patient suffered from episodes of acute hypoglycaemia following consumption of the substance whilst in hospital and whilst being treated with a dextrose infusion. Previous studies with synthetic cannabinoid receptor agonists have linked exposure to the substances to hyperglycaemia rather than hypoglyceamia (Seely et al., 2011; Hess et al., 2015).

In the 3 cases analysed by Hill and co-workers (Hill et al., 2016) where MDMB-CHMICA was the only substance found, respiratory acidosis and respiratory depression evidenced by hypercapnia was reported. All the individuals for which information is available (5 out of 7) reported smoking as a route of administration.

Where measured (Seywright et al., 2016), concentration of MDMB-CHMICA in blood ranged from less than 1 to 22 ng/ml (mean: 5 ng/ml, median: 2 ng/ml, n=9). No positive correlation was found between MDMB-CHMICA concentration and toxicity features displayed by the patients.

Recent work by **Angerer** et al. (Angerer et al., 2016) further suggests that the 'severity of intoxication cannot be directly correlated with serum concentrations' of MDMB-CHMICA. In a case series of 7 individuals with positive serum findings of MDMB-CHMICA[37], higher serum concentration was not associated with more severe symptoms. Furthermore, high serum concentrations can be expected in frequent users without necessarily leading to acute toxicity.

The series comprised of:

- 3 acute (mono) intoxications which required hospitalisation[38] where MDMB-CHMICA serum concentrations varied between 0.1 ng/mL to 2.0 ng/mL;
- 2 cases of driving under the influence of drugs where MDMB-CHMICA serum concentration were 1.0 ng/mL and 2.0 ng/mL;

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37 It is possible that some cases may be duplicates of cases published by Moosmann and Auwärter (Moosmann and Auwärter, 2016, unpublished), as well as with data reported to the EMCDDA.

38 The 3 reports of acute intoxications with MDMB-CHMICA published by Angerer and co-workers (Angerer et al., 2016) overlap with data reported to the EMCDDA by Germany.

- 1 case for which no which no clinical features were reported and which did not required hospitalisation where MDMB-CHMICA serum concentration was 0.45 ng/mL; and
- 1 case of police arrest for which no clinical features were reported and which did not required hospitalisation but displayed the highest MDMB-CHMICA serum concentration of the case series (91 ng/mL).

A prospective observational cohort study of adult patients presenting to an emergency department in London during a period of 6 months in 2015 (**Abouchedid** et al., 2016) found that at least 7 patients had been exposed to MDMB-CHMICA (80 – 8,000 pg/mL in blood) prior to being treated by emergency services. No further details are given about the cases.

1 case of acute monointoxication with MDMB-CHMICA was reported by **Dargan** et al. (Dargan et al., 2016) as part of the EURO-Den project. The individual in question (male, 30 years old) presented at a hospital in Germany following consumption of MDMB-CHMICA, which was analytically confirmed (serum: 0.94 ng/mL). He was agitated, psychotic and aggressive with hallucinations and had destroyed a room in his house; there was also a history of pre-hospital seizures. On arrival in the Emergency Department he was drowsy and tachycardic but other observations were normal including temperature (37.9 ºC) and blood pressure (118/61 mmHg). He was admitted to intensive care and was sedated and intubated for ongoing agitation and aspiration pneumonia. He was in hospital for 9.5 days before discharging himself.

Lastly, **WEDINOS** has registered 14 cases of acute intoxications following exposure to MDMB-CHMICA. These were analytically confirmed from samples of the products used or believed to be used by the patients but not from biological samples. The cases were comprised of 71% males and 29% females (n=14) with ages between 19 and 38. All the individuals who reported a route of administration (13 out of 14) smoked MDMB-CHMICA as an herbal mixture (purchased as 5F-AKB48 in 2 out of 14 cases). Onset of adverse effects was reported to happen between 10 seconds and 5 minutes (n=10; mean: 2.6 minutes, median: 3.0 minutes) and duration of effects were self-reported between 45 minutes to 10 hours (n=6; mean: 2.6 hours; median: 55 minutes).

D1.2.3. MDMB-CHMICA associated deaths

Deaths reported by the Member States

Case-level data for 29 deaths associated with MDMB-CHMICA were reported by 5 Member States and Norway: Germany (5 cases), Hungary (3), Poland (1), Sweden (9), the United Kingdom (10), and Norway (1).

In 28 cases, MDMB-CHMICA was analytically confirmed in one or more biological samples taken from the decedents. In the remaining case MDMB-CHMICA was confirmed from a sample of the product believed to be used by the deceased, and this case has been excluded from the analysis.

Demographics

Of the 28 deaths, 24 were male (86%), 3 were female (11%) and the gender was not reported for one death (4 %). The decedent's ages ranged from 17 to 52 years old. The mean age of the male decedents was 32 years (median 33); the mean age of the female decedents was 31 years (median 30).

Number of deaths by year

6 deaths occurred in 2014; 20 deaths occurred in 2015 and 1 death occurred in 2016. The year of death was not known for 1 case.

Cause of death reported by the Member States

A review of the causes of death, which were reported for 23 out of the 28 fatalities, found that:

- In 1 case MDMB-CHMICA was reported to be the cause of death;
- In 4 cases the information provided on the cause of death suggested that it was probably or possibly caused by MDMB-CHMICA;
- In 6 cases MDMB-CHMICA was reported to have contributed to the cause of death;
- In 2 cases the information provided on the cause of death suggested that MDMB-CHMICA probably or possibly contributed to the cause of death
- In 2 cases the cause of death was reported as drug overdose or mixed intoxication;
- In 8 cases an alternative cause of death was reported.

Circumstances of death

Information regarding the circumstances of death was reported for 18 out of 28 cases. For 72% of the cases, the individuals were found comatose or dead (at home or outside). In at least 2 of these cases smoking mixtures and smoking paraphernalia were found next to the body.

Deaths identified from open source information and other sources

10 deaths associated with MDMB-CHMICA exposure were identified in published scientific studies (Kronstrand et al., 2015; Westin et al.; 2015; Adamowic et al., 2016; Seywright et al, 2016). All cases are duplicates of the cases reported to the EMCDDA by Member States.

The circumstances for a case series of 10 deaths which may be duplicates of cases reported to the EMCDDA that occurred between 2014 and 2015 (Moosmann and Auwärter, 2016, unpublished) are given below.

In one case MDMB-CHMICA was reported as the cause of death; in 3 other the substance was found to have contributed to the death. The remaining cases included mixed intoxications (with contribution from synthetic cannabinoid receptor agonists) (3 cases) or were attributed to other causes (3 cases).

In 6 out of 10 cases the decedents were found dead next to smoking paraphernalia. In these cases, the descriptions of the circumstances surrounding the decedent (location, position of the body, etc.) suggest that the deaths may have occurred shortly and suddenly after consumption of the substance.

In one case, it is reported that the decedent smoked 1 cigarette containing a herbal mixture after which he complained about nausea, began to gasp, and was not responsive to resuscitation attempts. MDMB-CHMICA and THC metabolites were found in the individual's urine. This suggests the symptoms of intoxication were felt in a sudden manner.

Violent behaviour was reported in 1 case from this series.

As noted in section D1.2.2, correlation between the concentration of MDMB-CHMICA in biological samples and the severity of intoxication cannot be made. Some of the case reports show that the concentration of substance measured in asymptomatic users does not differ significantly from the concentration measured in cases of acute intoxications and/or deaths (Kronstrand et al., 2015). Angerer et al. (Angerer et al., 2016) emphasise that evaluation of death cases after use of synthetic cannabinoid receptor agonists should take into account all available information, including medical history, use of other drugs, preanalytical issues like post-mortem redistribution and possible tolerance.

D2. Chronic health effects

D2.1. Animal data

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

D2.2. Human data

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

D3. Factors affecting public health risks

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

MDMB-CHMICA is offered via the Internet either as powder (‘research chemical’) or in the form of ‘herbal mixtures’. In ‘herbal mixtures’ it is usually not stated if the product contains MDMB-CHMICA or any other synthetic cannabinoid. Furthermore, Germany reported to Europol that information from case reports associated with MDMB-CHMICA, indicates that this substance is well known among drug users and is quite often offered by drug dealers in addition to being available to purchase online (EMCDDA and Europol, 2016).

Data from seizures reported to the EMCDDA and to Europol indicate that bulk quantities of MDMB-CHMICA in powder have been imported into the EU from China (EMCDDA and Europol, 2016). In this respect, it is important to note that in October 2015 the People's Republic of China controlled MDMB-CHMICA under national drug control legislation.

Information reported to the EMCDDA indicates that where MDMB-CHMICA has been detected with other substances, it has almost exclusively been detected in combination with other synthetic cannabinoid receptor agonists such as: ADB-CHMINACA, 5F-MDMB-PINACA, 5F-AMB (5F-AMB-PINACA), 5F-AMBICA, AB-CHMINACA, 5F-AKB48, 5F-AMB-PINACA, and AB-FUBINACA (EMCDDA and Europol, 2016).

- Information reported to Europol by Hungary regarding seizures of MDMB-CHMICA (EMCDDA and Europol, 2016) stated that in 31% of all reported seizures (n=1257), MDMB-CHMICA was detected with other substances (EMCDDA and Europol, 2016) (see section A1.1). They reported that NPS frequently detected together with MDMB-CHMICA include: 5F-AMBICA (10% of seizures), 5F-AMB[39] (5% of seizures) and AB-CHMINACA (4% of seizures). Furthermore, the purity of powder samples in five cases forensically analysed revealed very high concentrations of 95% or more of MDMB-CHMICA. Generally, the concentration of MDMB-CHMICA in herbal mixtures analysed in Hungary was established as ranging for 1 to 8%.

- Additionally, Lithuania reported to Europol that the purity of a single seizure of 4 kg of MDMB-CHMICA was determined as 0.2%

Regular market monitoring within the EU 'SPICE' projects including the analysis of 427 'herbal mixtures' in 2015 came to the result that 186 samples (44%) contained MDMB-CHMICA. Of these positive samples, 82% contained solely MDMB-CHMICA, 14% MDMB-CHMICA and one additional synthetic cannabinoid, 4% MDMB-CHMICA and two additional synthetic cannabinoid receptor agonists (Moosmann and Auwärter, 2016, unpublished) (see Section C).

In the analysis of 532 products purchased on the Internet between April 2015 and April 2016 (Pütz et al., 2016), MDMB-CHMICA was the cannabinoid most commonly found (detected in 166 products, 31%). 81% of the total number of herbal mixtures analysed (n=390) contained one substance, 16% contained two or more substances, and 3% contained no psychoactive substance. For the research chemicals analysed in the same study (n=60), in 65% of the products, labelling of the product was correct; in 6% of the products, labelling was partially correct; and in 29% of the cases labelling was wrong.

[39] 5F-AMB is also known as 5F-AMB-PINACA (Methyl 2-({[1-(5-fluoropentyl)-1H-indazol-3-yl]carbonyl}amino)-3-methylbutanoate)

Within the Welsh drug checking project WEDINOS, MDMB-CHMICA was detected in 36 herbal mixtures and in one powder sent for analysis (Moosmann & Auwärter, 2016; monitoring results between September 2014 and February 2016).

It should be noted that there can be considerable variability both within and between different batches of products sold under specific brand names, in terms of both the substances and the amount present, as it has been shown by various authors (Logan et al., 2012; Zuba and Byrska, 2013; Langer et al., 2014). Both high intra- as well as inter-package variabilities were observed for many synthetic cannabinoids (Choi et al., 2013).

MDMB-CHMICA content was analysed by Langer *et al*. in two products. One product contained 82 mg/g MDMB-CHMICA and no further active ingredient. The second product contained 12 mg/g MDMB-CHMICA, 89 mg/g AB-PINACA-5F and 66 mg/g AMB-5F (8).

Analysis of 79 herbal mixtures containing MDMB-CHMICA as the only active ingredient showed a range of content from 0.1% (w/w) to 11.1% (w/w). The median was 4.5% (w/w) and the mean 5.3% (w/w) (Moosmann and Auwärter, 2016, unpublished). It has to be noted that no homogenization was carried out prior to analysis to get an estimate of the doses actually consumed under realistic conditions (Pütz et al., 2016) (see Section C).

It should be noted that the manufacturing process can lead to an uneven distribution of the substances within the plant material. This may result in some products containing ‘hot pockets’ where the cannabinoid is highly concentrated, leading to doses that are higher than intended and increasing the risk of acute toxicity.

Furthermore, quite often more than one synthetic cannabinoid is added to ‘herbal mixtures’ (Moosmann et al., 2015). In this study, both interpackage and intrapackage content of synthetic cannabinoid receptor agonists variation were investigated by sampling without prior homogenization. The results showed that two joints of herbal mixture prepared from the same package could contain significantly different amounts of the active substance.

In Japan, Kikura-Hanajiri *et al.* (Kikura-Hanajiri et al., 2013*)* detected an average number of 2.6 synthetic cannabinoid receptor agonists per product (Kikura-Hanajiri et al., 2013). The maximum number of synthetic cannabinoid receptor agonists detected in one mixture by these authors was ten.

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

There is limited information on Internet drug discussion forums regarding the effects and potential health/adverse effects related to the use of MDMB-CHMICA (Section D1.2.1).

D3.3. Characteristics and behaviour of users

Information on the characteristics and behaviour of users of MDMB-CHMICA is limited.

'Legal high' products containing MDMB-CHMICA are marketed as 'legal' replacements to cannabis. It is therefore likely that a range of different cannabis users would be interested in these products.

The available data suggests that MDMB-CHMICA is used by recreational users; by people who experiment with any drug that is new and readily available (such as 'psychonauts'); and by those who are regularly subjected to drug testing procedures (including those in prison).

MDMB-CHMICA might not be directly sought by users. Commercial branded legal high products are known to be highly variable in terms of composition and dosage and therefore users might not necessarily know that they are consuming MDMB-CHMICA.

D3.4. Nature and extent of health consequences

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

Based on the available data, as well as self-reports and acute intoxications, the acute behavioural effects of MDMB-CHMICA, including effects on the ability to operate machinery and drive might bear some similarities to those induced by THC and by other synthetic cannabinoid receptor agonists such as JWH-018 and AM-2201.

Data related to cases of suspected driving under the influence of drugs were reported to the EMCDDA. There are insufficient data available to discuss the circumstances of these cases.

D3.5. Long-term consequences of use

There is no data regarding the long term consequences of using MDMB-CHMICA.

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

There is very limited data on the conditions which MDMB-CHMICA is obtained and used.

Sources appear to include internet retailers, bricks-and-mortar shops, friends and other acquaintances, and street level drug dealers (Section D3.1). In addition, the available data also supports the premise that some users are unaware that they have sourced and used MDMB-CHMICA (Section C and Section D1.2.1).

The substance appears to be sourced by individuals that are seeking a replacement for cannabis (including users that need to pass drug-screening tests), by experimental drug users or 'psychonauts' that attempting to source the drug itself as well as others who seek synthetic cannabinoid legal-high type mixtures in a more generic sense, rather than individual compositions (Section D3.3, Section E6).

Based on the available data, it seems reasonable to consider that MDMB-CHMICA is used in the same environments as cannabis. Based on a limited dataset from serious adverse events, MDMB-CHMICA is used at home and to a lesser extent in recreational settings.

Section E. Social Risks

E1. Individual social risks

There is no data on the effects of MDMB-CHMICA on individual social risks.

E2. Possible effects on direct social environment

There is no data on the possible effects of MDMB-CHMICA on the direct social environment.

E3. Possible effects on society as a whole

There is no specific data on the possible effects of MDMB-CHMICA on society as a whole.

E4. Economic costs

There is no data on the effects of MDMB-CHMICA on economic costs.

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

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

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

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

There is no specific data on the possible appeal of MDMB-CHMICA to specific population groups.

The available data suggests that MDMB-CHMICA is used by cannabis users. The extent of the possible appeal of synthetic cannabinoid receptor agonists to this group of users may be compounded by different factors, as users seem to be a heterogeneous group. They may include those wanting a legal alternative to illegal drugs, or drug users wishing to pass successfully an employment/other drug testing procedure aimed at detecting illicit drug use. This may be an important issue for any setting where drug abstinence control is obligatory (e.g. specific psychiatry or prison settings, driving liability testing, etc.).

Section F. Involvement of organised crime

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

No information has been received by Europol indicating production of MDMB-CHMICA within the EU.

Germany reported details on an investigation that led to the dismantling of a processing site, where herbal mixtures containing MDMB-CHMICA were prepared. Tablets mimicking ecstasy but containing different NPS were also detected during this investigation. In November 2015, German police seized over 17 kilograms of herbal mixtures during a house search. Several small plastic bags containing different powders and tablets were also seized along with ingredients required for tableting: caffeine, other binding agents, coloured dyes, vitamin preparations and packaging units. An individual involved in the processing stated that he mixed the herbal material with the synthetic cannabinoid 'MMB-CHMINACA' (MDMB-CHMICA) and then sold the mixtures via the internet.

Forensic analysis conducted as part of this investigation resulted in the following findings, specifically in relation to MDMB-CHMICA [40]:

- 365.62 gram of herbal mixture: MDMB-CHMICA
- 9612 gram of herbal mixture: MDMB-CHMICA and ADB-CHMINACA

German authorities stated that no direct links with organised crime groups (OCG) have been identified. However, they also state that easy access to MDMB-CHMICA in smaller amounts via online vendors in and outside of the EU combined with access to bulk amounts via the Internet - mostly from wholesalers in China or other Asian countries, indicate at least a certain degree of organisation.

Hungary and Romania provided information in relation to the involvement of criminal groups in the processing, trafficking and distribution of MDMB-CHMICA.

[40] Other NPS were also detected as part of this investigation into a processing site in Germany, including: synthetic cathinones i.e. 4-CMC, buphedrone; arylalkylamines i.e. EAPB; and other synthetic cannabinoid receptor agonists i.e. ADB-CHMINACA.

Hungary and Romania indicated that criminal syndicates operating in their countries are responsible for tableting and/or processing sites (involving mixing and packaging), where NPS imported from China are prepared for final distribution via the Internet and/or through shipping companies. In one particular case investigated by the Romanian authorities, a criminal group imported NPS from China to Romania via the Czech Republic and Hungary. Members of this criminal organization were reported to be Hungarian nationals of Croatian origin.

Investigations conducted in the Member States and supported by Europol suggest that some Member States may be emerging as European hubs for receiving new psychoactive substances from source countries.

Information provided by Spain regarding a seizure of almost 5 kilograms of MDMB-CHMICA, where the final destination of this shipment was another unspecified EU Member State, may be noteworthy in this context. Additionally, the largest single seizure of MDMB-CHMICA reported in Europe [41], had originated in China (Shanghai) but was actually en-route to Spain as the final destination.

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

Based on the information available to the EMCDDA and Europol it does not appear that the production, trafficking and distribution of MDMB-CHMICA impacts on other existing psychoactive substances or new psychoactive substances.

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

No information has been received by Europol of evidence of the same groups of people being involved in different types of crime in connection with MDMB-CHMICA.

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

No specific information has been received by Europol on incidents of violence in connection with MDMB-CHMICA. However, Germany reported that use of MDMB-CHMICA has led to reported acts of violence and aggressive behaviour.

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41 40 kilograms in powder form seized in Luxembourg in 2014

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

No specific information has been received by Europol on incidents of money laundering or impact of organised crime on other socio economic factors in society in connection with MDMB-CHMICA.

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

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

F7. Use of violence between or within criminal groups

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

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

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

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Appendix 1

List of street names reported for products containing MDMB-CHMICA. The products were purchased online in the frame of the EU-funded projects ‘SPICE II Plus’ (JUST/2011/DPIP/AG/3597) and ‘SPICE Profiling’ (JUST/2013/ISEC/DRUGS/AG/6421).

AK 47, 24 Karat Gold
Blueberry WTF
Flight Risk
Game Over
Pure Sin
Strawberry WTF
4g für ein Halleluja – Hausmarke
5G
5G Monster
7H
ABYSS Erdbeer
AK47
AK47 - Free sample
AK47 reloaded
Aliens XL
Alpha Club Black 2015
Alpha Club Gold
Amnesia
Annihilation
Armageddon
BcG 2013
Bizarro
Black Afghan – Räucherhash
Black Jack "Diamant Deluxe"
Black Jack Diamond

Black Sun

Blue Beary

Bomb Marley

Bomb Marley - Happy Blueberry

Bonzai

Bonzai Citrus

Bonzai NEU

Bonzai New

Bonzai Winterspice

Brain Bad

Brain Jump

Brazil Gold Extreme

Budabar Gold

Buffalo Soldier

Butterfly

Call of Herbal

Callofherbal

Candy Rush

Crazy Monkees 2

Cuba Libre

Dead Man Walking

Desert

Don't lose your Mind

Druid

Enjoy your summer

Freak Show

Full Moon

Full Moon Mix

GALAXY DELUXE

Global BÄÄÄM

Glory

Glory - Free sample

Goa Party

Green Explosion

Green Giant

Green Leaves

Happy Halloween

Happy New Year

Hausmarke - 1 g

Hausmarke - 3g

Hausmarke - Teufels Rausch

Hausmarke Kiwi

Hausmix - Check your Taste

Haze

Hexenmeister

Hexensabbat

High School

Hot Apple

Hulk

I Love Amsterdam

Jackpot 777 Platinum

Jamaican Extrime neu, Jamaican Gold Extreme

Jamaican Gold Extrim

Jamaican Gold Extrime

Jamaican Gold Extrime neu

Joker

Kamasutra

Kraut

Kush Pineapple

Lion Taste

Love IT

M.I.G

Mango Sun

MAYA

Maya XL

Miami Beach

Millenium "Platinum Deluxe"

Millenium Gold

Millenium Platinum

Millenium Platinum – Sample

Mr. Nice Guy

Mr. Nice Guy ShamRocks

Namifu

New "Spice"

New Bonzai "Winter"

New Bonzai Citrus

New MAYA "Deluxe"

NISCHA

Nischa "The Original"

OMG Extreme

Orange

Orangen Bomber

Orgazmo

Panoramix

Pink Bull

Rauchfreunde Bubblegum

Rauchfreunde Citrus

Rauchfreunde Citrus – Sample

Rauchfreunde Extreme

Rauchfreunde Extreme – Sample

Rauchfreunde Extreme Mango – Sample

Red Mind

Red Russian

Royal Overkill

Scooby Snax

Scooby Snax Potpourri

Shaman

Simply Bob

Sniper

Soulfire

Space

Spice

Spice Girls

Spice Gold

Spice New

Spicies BLUEBERRY

Springbang

Strawberry Dream Supernova

Supernova – Free sample

Supersoft

Sweet Leaf

Teufelszeug

The Black Hole

Tropic Thunder

Unicorn Magic Dust (black Edition)

Waldmeister AHOY!

Winterdream

Wolf Queen

Appendix 2

Possible synthetic routes of MDMB-CHMICA

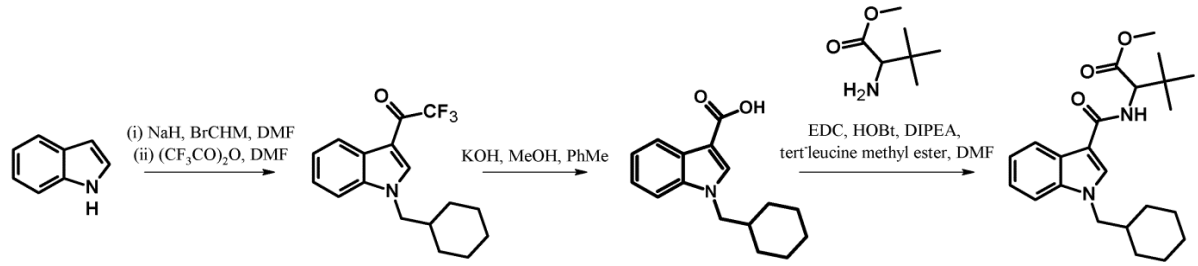

Figure 1: Possible synthetic route for MDMB-CHMICA starting from 1*H*-indole (BrCHM: cyclohexylmethyl bromide, EDC: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, DIPEA: N,N-diisopropylethylamine) – variant I

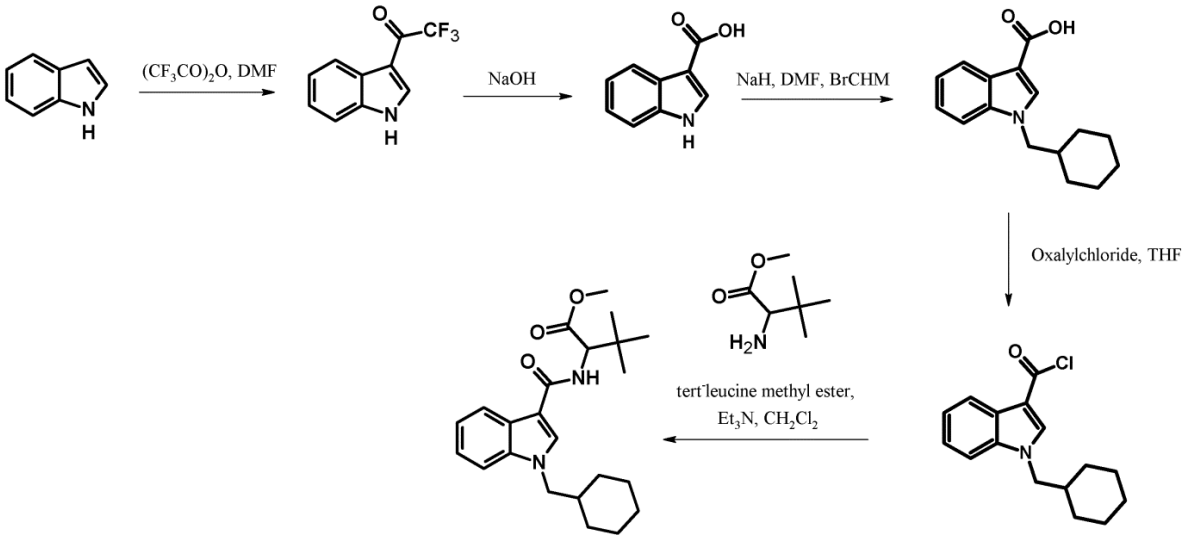

Figure 2: Possible synthetic route for MDMB-CHMICA starting from 1*H*-indole – variant II

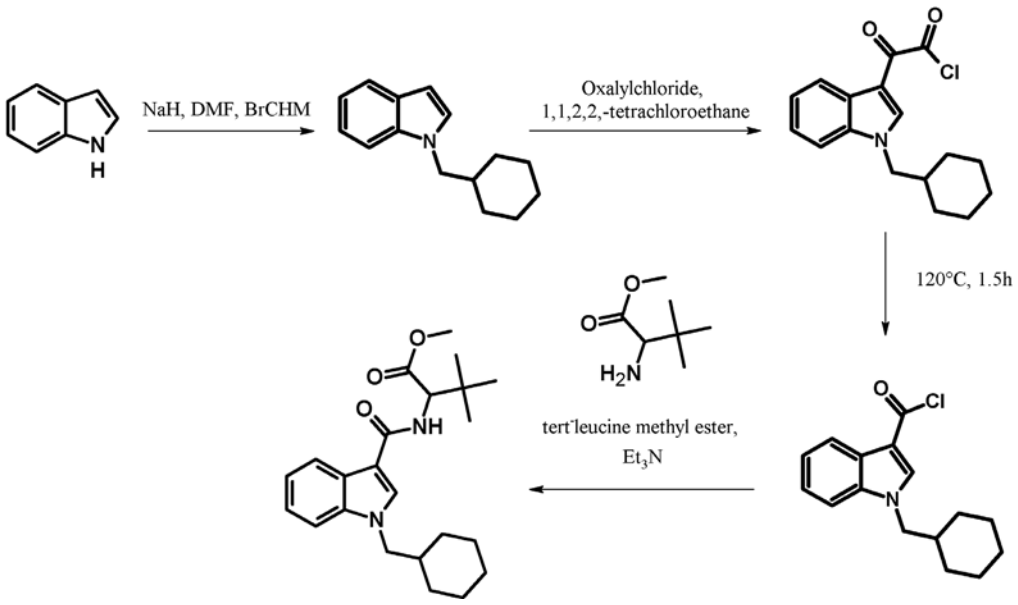

Figure 3: Possible synthetic route for MDMB-CHMICA starting from 1*H*-indole – variant III

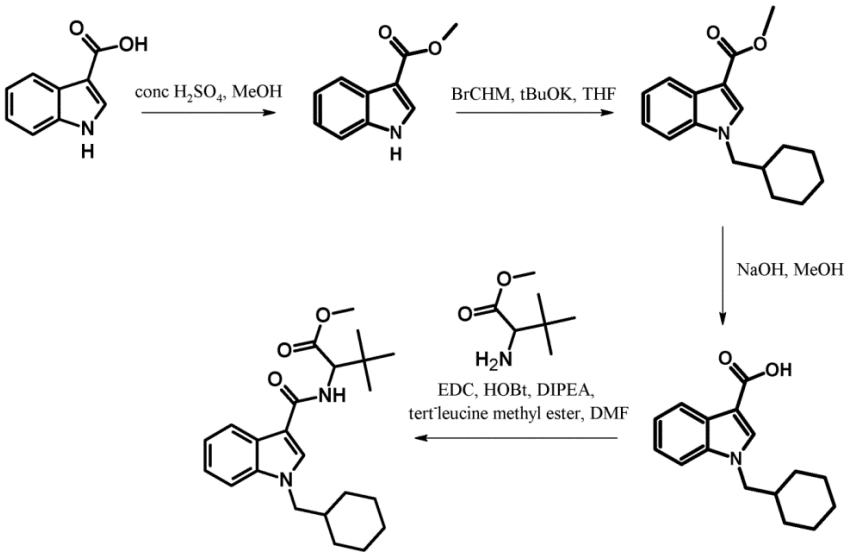

Figure 4: Possible synthetic route for MDMB-CHMICA starting from 1*H*-indole-3-carboxylic acid

Appendix 3

Extracts of reports from Internet fora

Erowid:

1.) Dissolved 1 mg acetone and dipped cigarette in it

Smoked a tiny hit – felt nothing – finished the cigarette – dipped a second cigarette in a higher concentration – felt good and stoned – did not inhale much.

Later, 20 mg herbal material and 1-5 mg MDMB-CHMICA –smoked it –immediately felt like marijuana – a little bit more euphoria – after three minutes it got stronger – felt a little uncomfortable – after 5 minutes – suddenly delirious – felt like I was lost – got extremely sick – trying to vomit – gagging – couldn't move – felt like being in a video game – mother called ambulance – confusion - Seeing patterns and colors - blacking in and out - heart beat: 160 bpm.

After 3 hours finally started to come back but was still high as shit. Left hospital after 4 hours.

Lasted for about 15 hours total.

It was a terrible experience, the worst I ever had.

Bluelight:

1.) Strong. Very strong.

Small joint caused a massive increase in heart rate, severe anxiety & fear/panic along with closed eye visual hallucinations - could not move - rode it out for I'd say 30-60 minutes.

Smoked approximately 20mg of herbal mixture

Additional uptake of 10mg diazepam

This was not a pleasant experience at all.

2.) 10-15mg of this stuff in herbal mixture - very very high.

3.) 0.5-1mg - totally floored and that was with tolerance.
It needs to be dissolved and dosed in micrograms.
The high was not pleasant (strong synthetic trippy high with a lot of sedation and increased heart rate) but I overdosed so I can't really say much about it yet.
0.5mg of MDMB-CHMICA equals roughly 5mg of AB-FUBINACA

4.) Smoked a little bit less that other synthetic cannabinoids – gained consciousness in an ambulance – thinks he was violent – threatened the medic – went back in his house – woke up handcuffed – taken to hospital – got home from hospital – smoked another joint containing MDMB-CHMICA (1/3 of the first does, barely substance in the cigarette) – regained consciousness at hospital.

5.) Put MDMB-CHMICA powder on the scale until it flickered between 0-1mg – quartered the dose – eyeballed 0.25 mg of powder in tobacco – smoked half of the cigarette - noticed shivering - arms slightly shaking – went to bed - very pronounced straight high but with something missing - no nice fuzziness like with marijuana – dose was to too high even though only half cigarette smoked
In bed – shivering - unable to properly control – coordination - expecting a seizure - after 85 minutes the episode was fading - still shivering - slept.
Next day at work - felt cold and slightly hollow and ill from the experience of the night before - felt nauseous.
MDMB-CHMICA is so strong that it's difficult to measure a minimal dose. You need to use less than you originally think. As soon as you start to feel it coming on, you've had enough.

6.) Previous synthetic cannabinoids use: about an ounce of powder a month.
After withdrawal. Smoked 2 grams over a few weeks - noticed usual poor sleeping patterns and tremors - withdrawing: .whole body went numb for 5 days, I thought I was having a stroke at first! Extreme muscle weakness, could barely flex my muscles. Withdrawal seemed to take about 3 times longer than normal synthetic cannabinoids.

7.) Potency of MDMB-CHMICA is possibly being overstated. Produces strong effects at doses at 1mg for non-tolerant people and up to 10-15mg for tolerant. Statements of microgram doses are exaggerated.
Effects are very sedating. Red eyes last forever. Lasts a few hours. It will knock you out.
Onset: about 3 min. You could finish a joint before you realize you did too much.

8.) Tolerance:
Common effects include clear and loud auditory hallucination, buzzing, deep thoughts and increased interest in anything leading to pointless starring on a plant or the desktop for minutes.

9.) After smoking herbal mixture – tried it pure. Eyeballing a bit more than the tiniest amount I could pick up with my nail file - went well - repeated the next days leading to constant stonedness, numbed mind and increased tiredness to the point of falling asleep by accident. No euphoria or giggling under the influence.
One time clot with the diameter of a pupil - barely finished the bowl and already knew it was too much - strong buzz, tinnitus and white noise - tried to concentrate on breathing and not vomiting - the act became my whole existence - closed eyes -became a thunderbolt, moving up and down probably to the intervals of my breathing, feeling incredibly awful - continued for several minutes, minutes like eternities, in which I just wanted to stop this existence.
After a while I came back, but fell into the hole again for unspecified time.
For the next weeks: terrible dissociation, panic attacks and severe concentration issues. Due to addiction to the cannabinoid - repeated consumption of lower amounts - felt nothing but sick every time, yet couldn't quit that easily.

Forum 3 (German, translated)

1.) 0.1 mg – 1mg as initial dose – as low as possible
Extremely potent, easily leads to severe overdose; seems almost impossible for inexperienced user not to cause an overdose.
Symptoms of overdose: Complete disorientation, vomiting, heart problems, tremor, numbness of extremities and more.
Most of the times symptoms are over after 1 – 1.5 hours.

2.) Psychedelic

cev's and oev's

effects almost directly after smoking

high potency

3.) Symptoms:

Euphoria, felling of warmth, laughing, increases appetite, mouth dryness, severe disorientation, lack of concentration and short-term memory, everything is vibrating, restlessness, hallucinations, vertigo, tremor in legs, tiredness at a later stage

Duration: approx. 1hour

Dose: < 1 mg

Potent cannabinoid, little psychedelic action

Annex 2. List of participants at the risk assessment meeting on methyl 2-[[1-(cyclohexylmethyl)-1H-indole-3-carbonyl]amino]-3,3-dimethylbutanoate (MDMB-CHMICA)
22 July 2016

A. Extended Scientific Committee

Professor Dr Henk GARRETSEN
Faculty of Social and Behavioural Sciences, Tilburg University, Tilburg
Co-chair of the risk assessment meeting

Dr Fernando RODRIGUEZ de FONSECA
Fundación IMABIS, Hosp. Univ. Carlos Haya de Málaga
Co-chair of the risk assessment meeting

Professor Catherine COMISKEY
Director, Centre for Practice and Healthcare Innovation, Trinity College Dublin

Dr Marina DAVOLI
Department of Epidemiology, Lazio Regional Health Service, Rome

Professor Dr Gabriele FISCHER
Medical University Vienna, Center of Public Health, Vienna

Professor Dr Brice De RUYVER
Ghent University, Faculty of Law, Department of Criminal Law and Criminology, Ghent

Dr Simon BRANDT

School of Pharmacy & Biomolecular Sciences, Liverpool John Moores University, Liverpool

Professor Félix CARVALHO

Faculty of Pharmacy, University of Porto, Porto

Professor Gaetano Di CHIARA

Dpt. Biomedical Sciences, University of Cagliari, Cagliari

Professor Éva KELLER

Semmelweis University, Department of Forensic and Insurance Medicine, Budapest

Ute STIEGEL

DG HOME – Anti drugs policy unit, European Commission, Brussels

Fabiano RENIERO

Directorate General Joint Research Centre, Directorate F – Health, Consumers and Reference Materials, European Commission, Ispra

Dr Leon Van AERTS

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

Daniel DUDEK

Serious and Organised Crime Unit - Europol, The Hague

Michael EVANS-BROWN

Scientific analyst, Action on new drugs, Supply reduction and new drugs unit

Ana GALLEGOS

Head of Sector, Action on new drugs, Supply reduction and new drugs unit

B. Invited Experts

Professor Dr Volker AUWÄRTER

Forensic Toxicologist, Freiburg University, Institute of Forensic Medicine, Freiburg

Dr Simon ELLIOTT

(ROAR) Forensics Ltd, Worcestershire

Dr Michael PÜTZ

Federal Criminal Police Office, Forensic Science Institute, Wiesbaden

Professor Dr Bela SZABO

Institute of Experimental and Clinical Pharmacology and Toxicology, Freiburg

Dr István UJVÁRY

Budapest University of Technology and Economics, Budapest

C. EMCDDA Staff

Alexis GOOSDEEL

Director

Andrew CUNNINGHAM

Head of Sector, Markets, Crime and supply reduction, Supply reduction and new drugs unit

Thomas Le RUEZ

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

Manuel RUIZ

Observer

D. Other Participants

Helgi DANIELSSON

Observer