

MDMB-CHMICA
Critical Review Report
Agenda Item 4.9

Expert Committee on Drug Dependence
Thirty-eighth Meeting
Geneva, 14-18 November 2016

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Summary

MDMB-CHMICA is an indole-3-carboxamide derivative used as an active ingredient of products sold as cannabis substitutes or research chemicals. Structurally, MDMB-CHMICA shares some similarities with JWH-018 and AM-2201, indole core derivatives that are controlled as a Schedule II substance under the U.N.1971 Convention on Psychotropic Substances. MDMB-CHMICA has no known approved medical or industrial use. MDMB-CHMICA has been detected in seized materials in several countries including Europe and USA. In Europe, it was first detected in 2014.

MDMB-CHMICA is being used for non-medical use in several countries. The most common route of administration is smoking. MDMB-CHMICA is an endocannabinoid agonist with higher potency compared to delta-9-tetrahydrocannabinol (THC) and possibly to JWH-018. Use of MDMB-CHMICA has been associated with cannabimimetic effects in doses lower than the doses of delta-9-tetrahydrocannabinol (THC) needed to produce effects of similar strength. Use of MDMB-CHMICA has been associated with acute toxicities and serious adverse events including respiratory acidosis, hypothermia, loss of consciousness, severe behavioural and psychological effects. Twenty nine deaths have been associated with MDMB-CHMICA in Europe alone.

Regarding abuse and dependence potential of MDMB-CHMICA, controlled scientific studies in both human and animals are lacking. However, testimonials from user websites and case reports suggest potential possibilities for abuse and physical dependence. Chronic toxicity effects have not been evaluated including documented studies on prevalence of its use. Due to its harmful effects and increased risk of abuse, over 14 countries have brought MDMB-CHMICA under regulatory control. MDMB-CHMICA is a full agonist at the CB1-receptor. Because of lack of clear dosages in the contents of the products sold containing MDMB-CHMICA, users are at risk of experiencing life threatening side effects associated with MDMB-CHMICA.

1. Substance identification

A. *International Nonproprietary Name (INN)*

Not applicable

B. *Chemical Abstract Service (CAS) Registry Number*

1863065-84-2

(1715016-78-6 has been referred on the Internet and used in Chinese regulation).¹

C. *Other Chemical Names*

Methyl 2-[[1-(cyclohexylmethyl)indole-3-carbonyl]amino]-3,3-dimethylbutanoate
[IUPAC Name]

Methyl 2-{{1-(cyclohexylmethyl)-1H-indole-3-yl}carbonyl}amino-3,3-dimethylbutanoate

Methyl 2-{{1-(cyclohexylmethyl)-1H-indole-3-yl}formamido}-3,3-dimethylbutanoate

Methyl 2-(1-(cyclohexylmethyl)-1H-indole-3-carboxamido)-3,3-dimethylbutanoate
N-(1-methoxy-3,3-dimethyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1H-indole-3-carboxamide

D. *Trade Names*

None

E. *Street Names*

‘Spice’, ‘K2’, ‘legal weed’, ‘synthetic cannabis’, ‘herbal incense.

MDMB-CHMICA was found as an additive in over 80 brands of herbal mixture products including ‘Sweet Leaf’, ‘Pandora Reborn’, ‘Vertex’, ‘Black Mamba’, ‘Old Spice’, ‘AK47 loaded’, ‘Manga Hot’, ‘Cloud 9-second generation-Mad Hatters-incense’, ‘Black Diamond’, ‘Damiana’, ‘Sky High’, ‘Godfather’, ‘CUSH cotton Candy’, ‘KUSH Second Generation’, ‘KUSH herbal incense’, ‘Ninja’ and ‘Critical haze’.^{2,3}

Different batches of a herbal product sold under a specific brand name do not necessarily contain the same ingredients. For example, MDMB-CHMICA has also been sold on the internet as MMB-CHIMINACA.

F. *Physical Appearance*

MDMB-CHMICA is an odourless white crystalline solid (in pure form). It has been seized in powder, tablet and herbal mixtures form. MDMB-CHMICA has been detected in seized herbal mixtures of green/brown color.⁴

G. *WHO Review History*

MDMB-CHMICA has not been previously pre-reviewed or critically reviewed. A direct critical review is proposed based on information brought to WHO's attention that MDMB-CHMICA is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any party. Preliminary data collected from literature and different countries indicated that this substance may cause substantial harm and that it has no medical use.

2. Chemistry

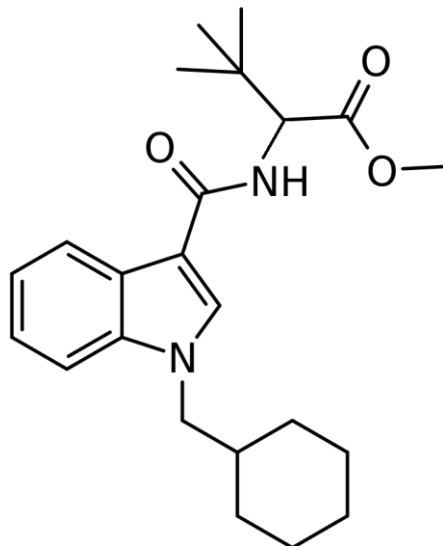
A. Chemical Name

IUPAC Name: methyl 2-[[1-(cyclohexylmethyl)indole-3-carbonyl]amino]-3,3-dimethylbutanoate

CA Index Name: L-Valine, N-[[1-(cyclohexylmethyl)-1H-indol-3-yl]-3-methyl-, methyl ester

B. Chemical Structure

Free base:



Molecular Formula: C₂₃H₃₂N₂O₃

Molecular Weight: 384.52

C. Stereoisomers

MDMB-CHMICA has a chiral carbon in the butanoic chain. Therefore, two stereoisomers exist: (S)-MDMB-CHMICA and (R)-MDMB-CHMICA. The S-isomer has been found in analyzed samples of seized materials⁵ and has been listed by some reference material suppliers.^{6,7}

D. Methods and Ease of Illicit Manufacturing

Published scientific literature could not be retrieved regarding the details of chemical precursors or specific routes and manufacturing methods used to make MDMB-CHMICA.

The synthesis of MDMB-CHMICA is assumed to follow the same pathway as that of MDMB-CHMINACA, the indazole analogue of MDMB-CHMICA, or in analogy to the synthesis of other similar compounds.^{8,9,11} Banister et al. has described a pathway to include N-alkylation of the indole with an alkyl bromide and trifluoroacetic anhydride, base-mediated hydrolysis of the trifluoroacetylindole for the formation of the carboxylic acid, and an amide bond formation through a reaction with HOBt/EDC coupled with a methyl *tert*-leucinate in specified environmental conditions.

E. Chemical Properties

Melting point: The melting point is stated to be 133-134 °C. High humidity, elevated temperatures and storage in solution can lead to hydrolysis of the carboxylic ester.

Solubility: MDMB-CHMICA is poorly soluble in water. It is soluble in dimethylformamide (DMF) and in dimethylsulfoxide (DMSO) at 20mg/ml and 5mg/ml.⁶

Boiling point: The boiling point is stated to be 576.6 ± 30.0 °C at 760 mm Hg.²⁷

F. Identification and Analysis

The analytical profile of MDMB-CHMICA has been described by Langer et al. using a number of methods such as NMR, LC-HRMS, IR and UV-VIS.¹² Detection in biological samples could be identified and quantified using liquid chromatographic tandem mass spectrometric (LC-MS/MS) analyzed in serum^{15, 16 17, 25} targeting MDMB-CHMICA. In urine samples, the main metabolites are the analytical targets.^{13, 14} Franz et al. reported that some of the MDMB-CHMICA metabolites may also be formed after exposure to other synthetic cannabinoid receptor agonists.¹³

MDMB-CHMICA is not detected using the standard set of immunoassay urine screening tests for drugs of abuse. Reference standard materials suppliers of the enantiomer for analytical methodologies are commercially available.^{6, 7} However, there is no commercial reference material available for the MDMB-CHMICA metabolites.⁴

3. Ease of Convertibility Into Controlled Substances

There were no published data regarding ease of convertibility of MDMB-CHMICA to other controlled substances. MDMB-CHMICA belongs to the group of Synthetic Cannabinoid Receptor Agonists (SCRA's). MDMB-CHMICA contains a carboxamide linkage and an ester linkage. The carboxamide linkage can be hydrolyzed in strong acid and strong base (under heating). The ester linkage can be easily hydrolyzed in mild base. Therefore, it can be expected that MDMB-CHMICA can be converted into other SCRA's. However, replacement of the group attached to the carboxamide is not an easy chemical process.

At present, JWH-018 and AM-2201 are the only SCRA's scheduled, i.e., under the 1971 Convention on Psychotropic Substances. These two substances do not contain a carboxamide linkage. Therefore, the conversion of MDMB-CHMICA into AM-2201 or JWH-018 is not possible and MDMB-CHMICA cannot be considered an immediate precursor of any internationally controlled substance.¹⁸

4. General Pharmacology

A. Routes of administration and dosage

MDMB-CHMICA is mainly offered on the Internet either in the form of 'herbal mixtures', where the chemical has been sprayed on plant material, or as a powder. The most common route of administration is inhalation either by smoking a self-prepared herbal mixture in form of a joint or utilizing a vaporizer, bong or pipe, or as a ready to use brand of legal high. Hill et al. reported smoking as the most common route of administration in six of the seven

males presenting in participating hospitals in the United Kingdom with clinical data and analytically confirmed exposure to MDMB-CHMICA.¹⁹

Likewise, the EMCDDA-Europol joint report showed that out of the 25 acute intoxications associated with MDMB-CHMICA, 21 persons had presumably smoked or inhaled the substance.⁴ Based on user reports from discussion forums, prepared solutions of MDMB-CHMICA are available for inhaling with an e-cigarette or a vaporization device. Users have also described oral and rectal routes of administration when consuming MDMB-CHMICA.^{20, 21}

It has been considered that many of the herbal mixtures are highly variable in terms of composition of active ingredients and dosages. Furthermore, quite often more than one synthetic cannabinoid is added to the herbal mixture.¹² Dose or amount, purity and strength of MDMB-CHMICA are not straightforwardly known to users and most users wouldn't know that they are consuming MDMB-CHMICA sold as legal high. Based on information posted at internet drug discussion forums, common dosages of up to 15 mg have been documented, with dosages less than 0.1 mg producing subjective effects.^{20, 21, 22, 26}

B. Pharmacokinetic

Literature search in Pubmed, Medline and Ovid resulted in a limited number of published reports on pharmacokinetic studies of MDMB-CHMICA in humans. There were no studies that examined the interaction of MDMB-CHMICA with other substances including medicinal products.

Grigoryev et al. was the first study to examine drug-intoxicated urine samples and the presence of the MDMB-CHMICA metabolites in human urine.¹⁴ In another metabolite study, Franz et al. analyzed 10 urine samples from 10 different individuals who reportedly had consumed MDMB-CHMICA. A total of 31 metabolites were identified *in vivo* as a result of several metabolic steps including amide hydrolysis, ester hydrolysis, dehydrogenation, mono and dihydroxylation of parent compound, dehydrogenation, and mono and dihydroxylation of the ester hydrolysis compound. However, four metabolites were found to be predominant. Franz et al. have reported on MDMB-CHMICA specific metabolites resulting from cyclohexylmethyl hydroxylated products proposed as common biomarkers.¹³

C. Pharmacodynamics

There is limited information on the pharmacodynamics of MDMB-CHMICA from the published literature. At the time of the review, *in vivo* studies on pharmacodynamics of MDMB-CHMICA have not been published, including data on pharmacological effects of its metabolites or the effects of MDMB-CHMICA on other pharmacological targets.

MDMB-CHMICA has been shown to activate CB1 and CB2 receptors with preference for CB1 receptors over CB2 receptors. Banister et al. also found MDMB-CHMICA to be a highly efficacious compound with full agonist properties at the CB1 receptor of the endocannabinoid system and with a greater potency (EC₅₀ 10nM) than Δ9-THC (EC₅₀ 171nM).¹⁰

Furthermore, other studies have shown that MDMB-CHMICA may be more potent than JWH-018 using functional assay (cAMP) accumulation studies.¹³ The CB1 receptor mediated potency (EC₅₀) of MDMB-CHMICA in relation to the EC₅₀ values of other synthetic cannabinoids such as JWH-018, AB-CHMINACA and AB-FUBINACA showed an EC₅₀ of 0.14 nM for MDMB-CHMICA compared to 1.13 nM for JWH-018 and 0.28 nM for AB-CHMINACA (approximately 8 times lower than that of JWH-018 and 2 fold lower than AB-CHMINACA) indicating a higher potency. The structural features of MDMB-CHMICA such as the indole core, a *tert*-butyl moiety and a carboxamide methyl ester have been proposed to be associated with the higher activity at the CB1 receptor via structural activity relationship studies.^{9, 23}

5. Toxicology

There are no preclinical studies that have examined the acute toxicity or chronic health effects of MDMB-CHMICA or its metabolites in animals.

6. Adverse Reactions in Humans

There is no data of systematic controlled studies available for MDMB-CHMICA in the scientific literature that examined acute or chronic health effects of MDMB-CHMICA or its metabolites in humans or animals.

In February 2016, a European risk assessment was conducted by EMCDDA and Europol on MDMB-CHMICA. During the period 2014 – 2015, MDMB-CHMICA was detected (analytical confirmed) in 29 deaths and 35 non-fatal intoxications (25 of which confirmed by urine/blood analysis and 10 by epidemiological link) in countries in Europe. In 14 of the deaths, MDMB-CHMICA was either reported as a cause of death or contributing to the death.⁴

Of the 25 non-fatal acute intoxications (with analytically confirmed biological samples) reported by EMCDDA joint report, 22 were detected with MDMB-CHMICA along with other substances such as THC and its metabolites, other new psychoactive substances, ethanol or other medications. Adverse effects described include confusion, aggression, changes in mood, hallucinations, dilated pupils, hyperemesis and unresponsiveness in those cases with only MDMB-CHMICA identified in the analytical samples.⁴

Data based from published scientific literature in the form of case series and case reports indicated that deaths associated with MDMB-CHMICA was found either alone or in combination with at least one other psychoactive substance including psychoactive medications.^{15, 17, 24}

Hill et al. reported on acute intoxication symptoms of seven MDMB-CHMICA positive patients presented at admission to Emergency Department hospitals in UK within a four-month period. The age of the victims ranged from 16 to 57 years. The clinical features observed included acidosis (respiratory or metabolic), reduced level of consciousness, mydriasis, bradycardia, tonic-clonic seizures and agitation that required short-stay hospitalization of less than 24 hours, except for one case where the patient was hospitalized for up to 9 days.¹⁹

Bläckberg and colleagues from the Swedish Poison Information Centre (STRIDA project) reported on acute intoxication symptoms in 9 patients, associated with MDMB-CHMICA (analytical confirmed). Eight of these patients had a Poison Severity Score of 2 or 3, and presented with clinical features including seizures and loss of consciousness. Majority of these patients (5 of the 9) required monitoring in the intensive care unit.²⁸ Clinical features such as coma, seizures, bradycardia and respiratory failure have been documented in other cases associated with MDMB-CHMICA use, confirmed by blood analysis.²⁹

Seywright et al. described nine cases of acute intoxications with analytical confirmed uptake of MDMB-CHMICA who presented at the Emergency Department hospitals.²⁴ Their age ranged from 15 to 41 years of age. Clinical symptoms included syncope, vomiting, altered mental state, serotonin like toxicity features, hypothermia (range 33-38.5°C) and hypoglycemia. Of the 9 cases, 2 (15 year old and 21 year old) had only MDMB-CHMICA identified in the serum (the two cases are described below).

First case describes a 15-year old male estimated to have consumed a branded product named “Red Exodus” about an hour prior to sampling. Patient’s temperature was 36 °C (hypothermia) on presentation. Glucose level was 4.3 mmol/L, heart rate 54 bpm (sinus bradycardia), BP 100/57, persistent vomiting and syncope that required hospitalization for 22 hours. In this patient, the MDMB-CHMICA concentration in the blood sample was less than 2 ng/mL.

Second case describes a 21-year old male estimated to have consumed a legal high product more than 24 hours prior to time of sampling. In this case, patient presented with acute behavioral disturbances, aggression, thought disorder, spontaneous urinating/defecating, temperature 38.5, tachycardia (HR 150bpm), and hypertension (BP 148 /91). The concentration of MDMB-CHMICA was found to be less than 1 ng/mL. Seywright et al. found that concentrations of MDMB-CHMICA in blood of less than 1 or 2 ng/ml could be associated with serious adverse events and death.²⁴ In both studies (Hill et al. and Seywright et al.), hypothermia was observed in about 50% of the cases. No positive correlation was found between MDMB-CHMICA concentration in blood and toxicity features displayed by cases in that study. Other case reports have documented non-fatal toxicities associated with doses less than 1 ng/mL.¹⁶

Self-reported user experiences from internet discussion forums describes MDMB-CHMICA as a potent compound, with higher intensity of euphoria compared to cannabis and variable duration of onset of action and effects ranging from minutes to several hours. Some users have also described re-dosing several times per day given the short duration of action. Symptoms described by users included nausea, vomiting, increased appetite, increased heart rate, shivering, inability to move, changes in mood, confusion, disorientation, tiredness, poor concentration and behavioural/psychological disturbances such as agitation, dissociation, aggressive and violent behaviour, visual and auditory hallucinations, psychosis, anxiety, and panic attacks.^{20,21,22,26}

7. Dependence Potential

A. Animal Studies

There were no published studies that show physical dependence (withdrawal or tolerance) like features of MDMB-CHMICA in animals.

B. Human Studies

There were no published scientific literatures on signs or symptoms of physical dependence including high or chronic use of MDMB-CHMICA from clinical studies. Nevertheless, withdrawal like symptoms from abstinence of MDMB-CHMICA such as numbing of skin, cravings, mental fog, depressed mood, nausea and abdominal pain have been reported on user websites and by poison information centers. However, in such circumstances information on duration of use, pattern and amount consumed overtime was not described.²⁶ Other case reports have also documented high serum concentration of (91 ng/mL) without any symptoms.¹⁶

8. Abuse Potential

A. Animal Studies

There were no published scientific controlled preclinical studies involving drug discrimination, self-administration or conditioned place preference that indicated abuse liability of MDMB-CHMICA.

B. Human Studies

Published scientific controlled clinical studies on abuse liability in humans could not be found.

9. Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use

There are no known approved therapeutic applications for MDMB-CHMICA.

10. Listing on the WHO Model List of Essential Medicines

MDMB-CHMICA is not listed on the WHO Model List of Essential Medicines.

11. Marketing Authorizations (as a Medicinal Product)

There was no information available indicating that MDMB-CHMICA has been authorized as a medicinal product. A survey conducted by the EMA through a centralized procedure has shown that, twenty two EU member states including Norway reported that MDMB-CHMICA had not obtained a market authorization for human use, nor had one been applied for.⁴

12. Industrial Use

Information searched from various databases including ECHA database, FDA, Australian Therapeutic Goods Administration and Japan PMDA and information based on EMCDDA-Europol joint report⁴ could not reveal that MDMB-CHMICA has any known legitimate industrial, cosmetic, agricultural or veterinary use.

13. Non-Medical Use, Abuse and Dependence

Epidemiology of non-medical use, abuse and dependence

Published epidemiological data from general population or targeted surveys on prevalent use of MDMB-CHMICA as of September 9th 2016 could not be found. This is consistent with the findings in the EMCDDA-Europol joint report on MDMB-CHMICA. This report mentions that there is no information on the prevalence of its use.

Available data is based on seizure reports, internet vendors and biological samples. MDMB-CHMICA was first detected as a legal high in the European Union in September 2014.⁴ Over 3600 seizures or detections of MDMB-CHMICA were reported during the EMCDDA-Europol Survey in February 2016. A total of 19 European countries namely Austria, Belgium, Bulgaria, Croatia, Denmark, Estonia, France, Finland, Greece, Germany, Hungary, Latvia, Lithuania, Luxembourg, Poland, Romania, Sweden, Slovakia, UK, Norway and Turkey provided information on the seizures. About 54 kg of herbal materials and 43 kg of powder containing MDMB-CHMICA were reported in various sizes and amounts.

MDMB-CHMICA was either detected alone or in combination with other synthetic cannabinoids including AB-CHIMINACA, 5F-AMBICA, 5F-AMB (5F-AMB-PINACA), 5F-AKB48, 5F-AMB-PINACA and AB-FUBINACA. These additives bear potential health risks on their own or potentiate the risks of MDMB-CHMICA. In the EMCDDA-Europol survey described above, a total of 306 biological sample detections (analytically confirmed) from Austria, Estonia, Germany, Hungary, Poland, Sweden, United Kingdom and Norway were associated with 53 serious adverse events including 28 deaths.

Authentic urine samples (n= 5717) analyzed for the purpose of abstinence control in the time period of October 2014 to November 2015 in Germany resulted in 818 (14%) cases of proven MDMB-CHMICA consumption.¹³ Overall, the percentage of urine samples positive for MDMB-CHMICA metabolites in relation to the total number of synthetic cannabinoid positive samples (n= 1345) was 61% with relative prevalence increasing over time.

MDMB-CHMICA is easily purchased on the internet (sold online) as a commercial branded legal high or as a research chemical in various countries in Europe, Canada, USA and China. The legal-high product is usually not stated to contain MDMB-CHMICA, so users may not necessarily know what they are taking as the smoking mixtures are marketed as a legal replacement to cannabis or compounds are listed as MMB-CHIMINACA.⁴ From searches on user websites it appears that MDMB-CHMICA is used as a recreational drug by a variety of users, including users with experience with other synthetic cannabinoids.^{20, 21, 22}

Other information regarding toxicities and mortalities associated with MDMB-CHMICA use is described in section 6.

Also see Annex 1: Report on WHO questionnaire for review of psychoactive substances.

14. Nature and Magnitude of Public Health Problems Related to Misuse, Abuse and Dependence

Information related to abuse and dependence potential as well as acute toxicities and serious adverse events have been described in section 6, 7 and 8.

The joint EMCDDA-Europol report mentions a total of 100 cases of MDMB-CHMICA use (analytical confirmed) that were related to unlawful acts including driving under the influence and violent public behaviour. In addition, 8 cases of persons suspected of driving under the influence (including one traffic accident) were reported.⁴ Furthermore, the nature of behavioural effects exhibited by MDMB-CHMICA during operating machinery may be comparable to those induced by either THC or by other synthetic cannabinoids. Published scientific data on individual social risks, society risks and impacts, co-morbidities, injecting practices and evidence of harm to others could not be found.

Also see Annex 1: Report on WHO questionnaire for review of psychoactive substances.

15. Licit Production, Consumption and International Trade

No information on licit production of MDMB-CHMICA from any country was obtained from the literature search, apart from its legitimate scientific research and production in analytical reference materials.⁴

16. Illicit Manufacture and Traffic and Related Information

Based on the information available as of February 2016, EMCDDA and Europol did not receive information on the production of MDMB-CHMICA within the EU. However, some European countries may serve as hubs for receiving MDMB-CHMICA from source countries such as China or other Asian countries in bulks and processed for final destination to other countries in Europe. For example it was documented that a total of 40 kg MDMB-CHMICA in powder form was seized in Luxembourg in 2014 originated from China en-route to Spain. "This seizure is reported to be one of the largest seizures of synthetic cannabinoids in Europe".³⁰ Furthermore, easy access of MDMB-CHMICA via 95 online shops sold as "research chemicals" has also been documented.⁴

Also see Annex 1: Report on WHO questionnaire for review of psychoactive substances.

17. Current International Controls and Their Impact

MDMB-CHMICA is not controlled under the 1961, 1971 or 1988 United Nation Conventions.

18. Current and Past National Controls

A joint report by the EMCDDA and Europol reported the following regarding national controls of MDMB-CHMICA in Europe.⁴

- a) Fourteen European countries (Belgium, Bulgaria, Czech Republic, France, Italy, Ireland, Malta, Portugal, Romania, Slovakia, Slovenia, Spain and the United Kingdom) reported that MDMB-CHMICA was not under national control.
- b) Croatia had placed MDMB-CHMICA as part of list of drugs, psychoactive substances and plants used for drug production as well as precursors. It falls under generic definition of 'JWH-018 and its structural analogues'.
- c) Denmark controlled MDMB-CHMICA under drug control legislation.
- d) Estonia controlled MDMB-CHMICA since June 2015 under drug control legislation.
- e) Finland added MDMB-CHMICA to drug control legislation since 28th September 2015.
- f) Germany reported that MDMB-CHMICA is a controlled narcotic drug (30. Betaubungsmittelrechts-Anderungsverordnung, BtMAndV; in force since 21st November 2015) controlled under schedule I of the German Narcotics Act.
- g) Greece placed MDMB-CHMICA in the Table C of the Law 4139/2013.
- h) Hungary had reported that MDMB-CHMICA is under drug control legislation since 22nd July 2015 through Government Decree 66/2012 (IV.2).
- i) Latvia had reported that MDMB-CHMICA was included in the list of the Cabinet Regulation N847 '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'.
- j) Lithuania has placed MDMB-CHMICA under control based on Republic of Lithuania Minister of Health Order No.V-1062 (21/09/2009) and amendment of the Ministry of Health of the Republic of Lithuania Order No. 5 of 6th January 2000.
- k) Luxembourg controlled MDMB-CHMICA by the Grand Ducale Decree of 04/05/2009.
- l) In Turkey, MDMB-CHMICA is legally controlled using Generic Classification (Provisions of the Law on Control of Drugs numbered 2313).
- m) Austria had MDMB-CHMICA regulated under the Australian Act on new psychoactive substances (Neue-Psychoaktive-Substanzen-Gesetz, NPSG).
- n) Poland controlled MDMB-CHMICA under the Act on counteracting drug addiction and the Act on State Sanitary Inspection (Journal of Laws 'Dz.U' No.213, item 1396) whose Article 44b bans manufacturing or introducing substitute drugs to trade.

- o) Sweden reported that MDMB-CHMICA is controlled under the Act on Prohibition of Certain Goods Dangerous to Health (SFS1999:42).
- p) Norway controlled the importation and trade of MDMB-CHMICA using Medicinal Products Legislation.

MDMB-CHMICA is also controlled in China under national drug control legislation.¹
In Canada, MDMB-CHMICA falls under synthetic cannabinoids legislation in schedule II.³¹
In Louisiana (USA), MDMB-CHMICA is a controlled substance.³²

Also see Annex 1: Report on WHO questionnaire for review of psychoactive substances.

19. Other Medical and Scientific Matters Relevant for a Recommendation on the Scheduling of the Substance

No data

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Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances for the 38th ECDD: Evaluation of MDMB-CHMICA

Data was obtained from 47 Member States (6 AFR, 2 EMR, 26 EUR, 7 PAH, 1 SEAR and 5 WPR).

A total of 41 Member States (3 AFR, 2 EMR, 22 EUR, 7 PAH, 1 SEAR and 6 WPR) answered the questionnaire for MDMB-CHMICA. Of these, 25 respondents (19 EUR, 3 PAH and 3 WPR) had information on this substance.

LEGITIMATE USE

There were 24 countries that reported no approved medical products containing MDMB-CHMICA for human or veterinarian indications. There was no reported industrial use in 18 countries.

MDMB-CHMICA is currently being used in medical or scientific research in one country for metabolism and abuse potential research. Importation and domestic manufacturing is the origin/source of MDMB-CHMICA when used for legitimate non-medical/non-scientific use.

MDMB-CHMICA was not reported to be used for any cultural, religious or ceremonial purposes in 20 countries.

EPIDEMIOLOGY OF NON-MEDICAL/NON-SCIENTIFIC USE – USE FOR PSYCHOACTIVE PURPOSES OR RECREATIONAL DRUG USE

There were 17 countries that reported MDMB-CHMICA as being misused for its psychoactive properties (as a recreational drug). Common routes of administration for non-medical/non-scientific purposes are smoking (13 countries), oral (3 countries), inhalation (3 countries) and sniffing (1 country). The main route of administration for MDMB-CHMICA was reported as smoking (8 countries) and oral (2 countries).

The most common formulation reported for non-medical/non-scientific purposes was powder (9 countries), tablets (2 countries) and liquid or solution for oral administration/use (1 country). There were 14 countries which reported plant material impregnated with the MDMB-CHMICA being used as a formulation. One country mentioned that it was prepared in this way to resemble cannabis. Another country commented that MDMB-CHMICA is also used as an e-liquid for vaping.

Illegal manufacturing (1 country) and smuggling from other countries (12 countries) were reported as the sources of MDMB-CHMICA for non-medical/non-scientific use.

There were 5 countries which specified subpopulations known to misuse MDMB-CHMICA. These populations include the homeless, prison population, cannabis users, young people, schools, known drug consumers and party goers.

The level of negative health-impact originating from this substance's non-medical consumption was reported as either negligible (1 country), substantial (6 countries) or serious (6 countries). For the countries that indicated a substantial or serious level of negative health-impact, they specified that it was due to the association of MDMB-CHMICA with adverse events (including hospitalisations and

intoxications) and fatalities. It is also described as a potent cannabinoid. One country commented that the serious level was as a result of people believing they were smoking a substance that they had previously smoked (same brand name as another psychoactive that was previously legal), however, the psychoactive substance was very different resulting in adverse effects.

Six countries reported emergency room/department visits related to the non-medical use of MDMB-CHMICA. Two countries had a total of 21 hospitalisation cases in 2015. Another country had 37 non-fatal intoxications between September 2014 and February 2016. A further 12 cases (November and December 2014) of intoxication were reported by another separate country.

The adverse effects which presented for MDMB-CHMICA at the emergency room/department included nausea, dyspnoea, somnolence, emesis, coma, seizure, tongue-cramp, bradycardia, tachycardia, cyanosis, sweating, pyrexia, inability to move, disorientation, confusion, acute psychoses, hallucinations and delusions. MDMB-CHMICA also resulted in violent acts and aggressive behaviour.

In regards to the mortality rate, data was provided by 2 countries. The rate where only MDMB-CHMICA was involved included 2 cases in 2014 and 2015. Another country had 2 cases in 2015 to 2016 where only MDMB-CHMICA was involved.

The rate which included involvement of other substances was reported to be 4 cases in 2015. Finally the rate, where it was unknown if other substances were involved was 4 cases in 2016. Another country commented that there may be a higher number of cases because in their country there is no reporting obligation by hospitals, poison centers etc.

One country reported that people presented to drug dependence treatment centers due to the use of MDMB-CHMICA, however, they were unsure if was specifically for this psychoactive substance, rather it is for synthetic cannabinoids generally.

STATUS OF NATIONAL CONTROL AND POTENTIAL IMPACT OF INTERNATIONAL CONTROL

There were 21 countries reported that MDMB-CHMICA was under national control. The legislation the control is based upon included Medicines Act (4 countries), Controlled Substances Act (13 countries), Criminal Law Act (2 countries) and other specific legislation (2 countries stated that it was specific legislation for new psychoactive substances). In one country the control is a temporary provision since 2016, however, they noted that it is likely to become permanent after that. There were no challenges to implementing controls for MDMB-CHMICA reported.

The scope of the controls includes production (16 countries), manufacturing (18 countries), exporting (17 countries), importing (19 countries), distribution (19 countries), use (13 countries) and possession (16 countries).

Reported illicit activities involving MDMB-CHMICA include manufacture of the substance by chemical synthesis (1 country), production of consumer products (4 countries), trafficking (12 countries), smuggling (1 country), diversion (1 country), domestic internet sales (4 countries), internet sales from abroad (8 countries), internet sales from unknown locations (5 countries) and finally sales to people who use this substance (8 countries).

There were 16 countries which completed the section on the number of seizures. The combined number of seizures was 401 (2014), 1303 (2015) and 299 (2016 to date). One country commented that they had noticed a decline of cases as soon as the substance was placed under control by national legislation.

If MDMB-CHMICA was placed under international control, 24 countries responded that they would have the capacity to enforce the control at the national level. There were 24 countries which responded that they would have the forensic laboratory capacity to analyse the substance.