

ADVANCED RELEASE

EMCDDA technical report on the new psychoactive substance methyl 3,3-dimethyl-2-[[1-(pent-4-en-1-yl)-1*H*-indazole-3-carbonyl]amino]butanoate (MDMB-4en-PINACA)

Note: In the interests of public health protection the EMCDDA is releasing this report before formal page layout in the EMCDDA house style. The final report will be available on the EMCDDA website in due course.

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Purpose

The purpose of this technical report is to provide an analysis of the available information on methyl 3,3-dimethyl-2-[[1-(pent-4-en-1-yl)-1*H*-indazole-3-carbonyl]amino]butanoate — also known as methyl 3,3-dimethyl-2-[1-(pent-4-en-1-yl)-1*H*-indazole-3-carboxamido]butanoate — (MDMB-4en-PINACA), a synthetic cannabinoid receptor agonist (synthetic cannabinoid) that has recently emerged on the drug market in Europe, in order to support the risk assessment of the substance which has been requested by the European Commission in accordance with Article 5c of Regulation (EC) No 1920/2006 (as amended).

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Statement regarding the United Kingdom

The reference period for this technical report includes 2020 (up to 24 November 2020). The United Kingdom left the European Union as of 1 February 2020. However, during the transitional period, the United Kingdom continues to participate in the European Union Early Warning System on new psychoactive substances. Unless stated otherwise, for the purpose of this report, the term 'Member States' shall include the United Kingdom.

Information sources

The information in this technical report is derived from:

- Information reported by the Member States, Turkey, and Norway to the EMCDDA and Europol in accordance with the requirements of Article 5a and Article 5b of Regulation (EC) No 1920/2006 (as amended)
- Information reported by the European Medicines Agency (EMA), the European Chemicals Agency (ECHA), the European Centre for Disease Prevention and Control (ECDC), and the European Food Safety Authority (EFSA) to the EMCDDA in accordance with the requirements of Article 5b of Regulation (EC) No 1920/2006 (as amended)
- Information collected by the EMCDDA through searches of open source information, including the scientific and medical literature, patents, official reports, grey literature, online drug discussion forums and related websites, and online vendors selling MDMB-4en-PINACA.

Search strategy

Literature searches used both chemical structure and textual queries in online databases; searches were conducted in October 2020. The retrieved publications were then scanned for additional relevant references (snowballing technique).

SciFinder[®] and Reaxys were searched by exact structure-based search. PubMed, Web of Science and Google Scholar were searched for 'MDMB-4en-PINACA', IUPAC names, and

the various other code names stated in this document. The references were screened for relevance and included in the review where appropriate.

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

Terminology and definitions

The terminology and definitions used in this technical report are based on those used for the operation of the EU Early Warning System on new psychoactive substances, including those related to relevant internal EMCDDA processes. They can be accessed at:

<http://www.emcdda.europa.eu/system/files/publications/12213/downloads/Guidance%20Not%20e%201-%20Terminology%20and%20definitions.pdf> (EMCDDA, 2019).

Unless otherwise indicated, the terms and definitions are for operational use only and do not have legal meaning. They may differ from those used in other settings and by other organisations (EMCDDA, 2019).

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1. Summary

Synthetic cannabinoid receptor agonists (synthetic cannabinoids), such as MDMB-4en-PINACA, are a group of substances that mimic the effects of tetrahydrocannabinol (THC), which is a substance found in cannabis ⁽¹⁾. THC is responsible for many of the psychoactive effects of cannabis which are dose-dependent and include relaxation, euphoria, distorted perception of time and impaired motor performance (the feeling of being 'stoned' or 'high'), as well as confusion, anxiety, occasional hallucinations and paranoia, dry mouth, bloodshot eyes, and cardiovascular effects (Gaoni and Mechoulam, 1964; Huestis et al., 2001; Pertwee, 2014). THC causes these effects by activating a receptor in the brain called the cannabinoid receptor type 1 (CB₁ receptor) (Huestis et al., 2001; Pertwee, 2005a). This receptor is part of a signalling system in the body called the endocannabinoid system, which helps regulate, among other things, behaviour, mood, pain, appetite, sleep, and the immune system (Pertwee, 2015) ⁽²⁾. Because synthetic cannabinoids activate the CB₁ receptor in a similar way to THC, some of their effects appear to be similar to cannabis. Most prominently, they are able to create a feeling of being 'stoned'.

Synthetic cannabinoids were originally developed to study the endocannabinoid system, as well as provide insights into disease states, and to help develop new medicines (Pertwee, 2005a; Pertwee, 2005b; Pertwee, 2015; Reggio, 2009). In around 2006, some of these substances began to appear in Europe in products called 'Spice' that were sold as 'legal' replacements to cannabis (Auwärter et al., 2009; EMCDDA, 2009; Jack, 2009). In these products, synthetic cannabinoids were found to be mixed with plant (herbal) material which could then be smoked as cigarettes ('joints') (Auwärter et al., 2009; EMCDDA, 2009; EMCDDA, 2017; Jack, 2009). Such products have been referred to by a variety of names that depend on the country, region, product type, brand names, and user groups. Names include: 'smoking mixtures', 'herbal incense', 'synthetic cannabis', 'legal weed', and 'K2'. A common name used in Hungary is 'magic tobacco'; in France 'chimique'; in Turkey, 'Bonsai'; whereas in Birmingham, United Kingdom, the name 'Black Mamba' or simply 'Mamba' is used. Since 2008, more than 200 synthetic cannabinoids have been identified on the drug market in hundreds of different products. They are the largest group of substances that are monitored by the EMCDDA through the European Union Early Warning System on New Psychoactive Substances (EU Early Warning System). In recent years, alongside smoking mixtures, new dosage forms, including e-liquids for vaping using electronic cigarettes, as well as paper (including blotters) impregnated with synthetic

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

⁽²⁾ The endocannabinoid system helps regulate a large number functions in the body. It consists of the cannabinoid CB₁ and CB₂ receptors, the endocannabinoids (such as anandamide) which act as endogenous agonists for these receptors, and the processes responsible for endocannabinoid biosynthesis, cellular uptake, and metabolism. Important exogenous agonists for the cannabinoid receptors are (-)-*trans*- Δ^9 -tetrahydrocannabinol (THC) which is the major active substance in cannabis, and the synthetic cannabinoids found in herbal mixtures smoked like cannabis. Data from laboratory studies suggests that the endocannabinoid system is involved in important biological processes many of which await exploration. For example, in response to some diseases, the body increases the amount of endocannabinoids it produces which can reduce unwanted symptoms or slow disease progression (Pertwee, 2005a; Pertwee, 2005b; Pertwee, 2015). It has also been recognized that endocannabinoids, as well as the structurally distinct phytocannabinoids and synthetic cannabinoids, which show an astonishing structural diversity, affect other neurotransmitter systems, such as the dopaminergic, glutamatergic, and GABAergic systems.

cannabinoids, have appeared on the drug market.

In Europe, MDMB-4en-PINACA is monitored as a new psychoactive substance by the EMCDDA in accordance with Council Framework Decision 2004/757/JHA (as amended) and Regulation (EC) No 1920/2006 (as amended) (EMCDDA, 2020b). The substance has been available on the drug market in Europe since at least 2017. There is limited information on the substance, in particular formal epidemiological studies have not been conducted which limits understanding of the use and patterns of use of MDMB-4en-PINACA.

It is important to note that the presence of MDMB-4en-PINACA on the market and the extent of its involvement in serious adverse events (such as from acute poisonings presenting to hospital emergency rooms and medico-legal death investigations) may be undetected since the substance is not routinely screened for in some laboratories. It is also important to note that, in some settings, the ongoing COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (ECDC, 2020; EMCDDA, 2020d; WHO, 2020b) may have reduced the capacity of early warning systems, including forensic science and toxicology laboratories, to detect and report events involving MDMB-4en-PINACA.

As of November 2020, MDMB-4en-PINACA has been identified in twenty-one Member States as well as Norway and Turkey; 770 seizures have been reported, which include approximately 47 kg of powder and 4.7 kg of smoking mixtures. Although MDMB-4en-PINACA was first identified on the drug market in 2017, it was only in 2019 that a large number of first identifications in Member States were reported. In addition, it was during 2020 that there was a large increase in the quantity of MDMB-4en-PINACA seized by customs, with approximately 99% of the total amount of powder seized by customs (44 kg) having occurred during the year.

Although MDMB-4en-PINACA has not been formally studied in humans, limited information suggests that MDMB-4en-PINACA is a potent CB₁ receptor agonist and, as such, shares some pharmacological similarities with THC and other synthetic cannabinoids. Compared to cannabis, severe and fatal poisoning appears to be more common with synthetic cannabinoids. Poisoning may include rapid loss of consciousness/coma, cardiovascular effects (such as hypertension, tachycardia, bradycardia, chest pain, myocardial infarction, and stroke), seizures and convulsions, vomiting (including hyperemesis), delirium, agitation, psychosis, and, aggressive and violent behaviour. Sudden death has also been reported. There is no known antidote to poisoning caused by synthetic cannabinoids and thus the treatment of an overdose is the same as that of cannabis toxicity: supportive treatment and serial reassessment of the airway and neurological signs. Because of their high potency and the unintentionally high doses that users may be exposed to, synthetic cannabinoids can pose a high risk of severe poisoning, which in some cases can be life-threatening or even fatal. These factors can also be responsible for the outbreaks of mass poisonings seen with synthetic cannabinoids. Such outbreaks have the potential to overwhelm local healthcare systems, which is of particular concern given the ongoing COVID-19 pandemic and the additional burden already on healthcare systems.

There is no information on the chronic health effects of MDMB-4en-PINACA. The chronic

health risks might share some similarities to those seen with cannabis and other synthetic cannabinoids; this may include dependence.

A total of eleven acute non-fatal poisonings with confirmed exposure to MDMB-4en-PINACA have been reported to the EMCDDA by one Member State, the United Kingdom. All the cases included clinical features of poisoning similar to those reported for synthetic cannabinoids. In all cases other substances were identified, including other synthetic cannabinoids. In ten of the cases, the poisoning was considered life-threatening and required hospitalisation of the patient.

A total of twelve deaths with confirmed exposure to MDMB-4en-PINACA have been reported to the EMCDDA by three Member States: Hungary, Sweden, and the United Kingdom. The deaths occurred between January 2019 and August 2020. In some of the cases, MDMB-4en-PINACA was reported to be the cause of death or contributed to the death.

The available information suggests that MDMB-4en-PINACA is manufactured by chemical companies based in China. It is imported into Europe as bulk powders and then sold and distributed in wholesale and retail amounts within Europe either as a powder for processing into products or finished consumers products. There are three main types of products containing MDMB-4en-PINACA that are available on the drug market:

- smoking mixtures, where MDMB-4en-PINACA is mixed with herbal plant material or tobacco that is then smoked or inhaled from a vaporiser (similar to herbal cannabis, the mixture is usually prepared for smoking as a hand-rolled cigarette ('joint'));
- e-liquids, where a solution of MDMB-4en-PINACA is prepared by mixing it with a solvent, which is then inhaled using an e-cigarette; and
- paper impregnated with MDMB-4en-PINACA which can then be smoked or vaped. This is a commonly used approach to smuggle synthetic cannabinoids into prison in some countries.

To a lesser extent, users may prepare their own similar products using MDMB-4en-PINACA purchased from a vendor or dealer.

The available information suggests that MDMB-4en-PINACA may be used by cannabis users, by those who are regularly subjected to drug testing procedures (including those in prison), and by people who self-experiment with a range of psychoactive substances (so-called 'psychonauts'). The substance may also be used by high risk drug users and other marginalised groups, such as people experiencing homelessness and prisoners, as synthetic cannabinoids are typically readily available, and have gained a reputation for causing profound intoxication while being comparatively cheaper to other drugs. Although limited, there is some information to suggest a recent increase in vaping of synthetic cannabinoids using electronic cigarettes by young people, including teenagers, in some Member States; in some cases, the users believed that they were using cannabidiol (CBD) or THC.

There is no information whether or not criminal groups are involved in the manufacture, trafficking, and distribution of MDMB-4en-PINACA within Europe (EMCDDA, 2020b).

The effect of the ongoing COVID-19 pandemic (ECDC, 2020; EMCDDA, 2020d; WHO, 2020b) on the manufacture, trafficking, distribution, and use of MDMB-4en-PINACA is currently unknown. However, seizures of bulk powders by European national customs agencies during the pandemic suggests that it continues to be imported into and distributed within Europe. It is possible, that in case of a reduced availability of cannabis and other synthetic cannabinoids in Europe, criminal groups, as well as drug users, may use a range of replacement substances, including MDMB-4en-PINACA.

There is no information on the social harms that may be caused by MDMB-4en-PINACA. Despite this, it is likely that some of the risks are similar to those associated with the use of cannabis and other synthetic cannabinoids. For example, in prisons, alongside the adverse health effects, such as acute poisonings, the market in synthetic cannabinoids has been linked to an increase in bullying and debt, as well as aggression and violence. In some cases this has caused a serious threat to the overall safety and security of the prison environment. As such, it is a concern given that six Member States reported seizures of MDMB-4en-PINACA in prisons and other custodial settings, and, that overall, approximately 15 % of all the seizures of MDMB-4en-PINACA made by police occurred in these settings.

Based on the available information, it appears that MDMB-4en-PINACA is not an active substance in a medicinal product for human use or in a veterinary medicinal product in Europe. However, although unlikely, the use of MDMB-4en-PINACA as an active substance in medicinal products prepared extemporaneously or in investigational medicinal products cannot be excluded in some Member States (EMCDDA, 2020b). There is currently no information that suggests MDMB-4en-PINACA is used for legitimate purposes other than research or forensic application (EMCDDA, 2020b).

MDMB-4en-PINACA is not controlled under the United Nations Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol, nor the Convention on Psychotropic Substances of 1971 ('United Nations system') (UNODC, 2020a; UNODC, 2020b). MDMB-4en-PINACA was assessed at the 43rd meeting of the WHO Expert Committee on Drug Dependence (ECDD) that was held in October 2020 (WHO, 2020a).

MDMB-4en-PINACA is subject to restrictive measures in fifteen Member States:

- in Croatia, Cyprus, Finland, France, Italy, Latvia, Luxembourg, Poland, Sweden, and the United Kingdom the substance is controlled under drug control legislation;
- in Lithuania it is controlled under medicines legislation;
- in the Austria, Belgium, Germany, and Hungary it is controlled by new psychoactive substance legislation.

In addition, MDMB-4en-PINACA is controlled under medicines legislation in Norway and

under drug control legislation in Turkey. It is unknown if MDMB-4en-PINACA is controlled in China, where at least some of the substance on the European market appears to have been sourced from (EMCDDA, 2020b).

2. Chemical and physical properties, methods and the precursors used for manufacture or extraction

2.1 Background

Methyl 3,3-dimethyl-2-[[1-(pent-4-en-1-yl)-1*H*-indazole-3-carbonyl]amino]butanoate (MDMB-4en-PINACA) ⁽³⁾ – also known as methyl 3,3-dimethyl-2-[1-(pent-4-en-1-yl)-1*H*-indazole-3-carboxamido]butanoate (Figure 1) – is a synthetic cannabinoid which does not appear to have a history in the scientific literature. It is structurally related to compounds of the indazole-3-carboxamide class that feature pendant amino acid esters (methyl *L*-*tert*-leucinate) developed by Pfizer Inc. and published in a 2009 patent (e.g. compounds 125-130; Buchler et al., 2009). The substances described in the patent literature make reference to compounds that only show the (*S*)-configuration (Buchler et al., 2009). As far as it is known, synthetic cannabinoids available on the drug market have generally been found to retain the (*S*)-configuration although the presence of (*R*)-enantiomers or racemic mixtures cannot be excluded. According to information received by EMCDDA, MDMB-4en-PINACA has been available on the European drug market at least since 2017 although there has been a significant increase in the number of Member States identifying the substance for the first time since 2019 (EMCDDA, 2020b; EMCDDA, 2020c).

MDMB-4en-PINACA is structurally related to 5F-MDMB-PINACA (5F-ADB) (Figure 1) ⁽⁴⁾. 5F-MDMB-PINACA was formally notified in January 2015 and underwent EMCDDA risk assessment in November 2017 following reports of increasing availability and serious harms in Europe, including 28 deaths (EMCDDA, 2018). In March 2018, it was placed in Schedule II of the 1971 United Nations Single Convention on Psychotropic Substances (INCB, 2019) after undergoing a critical review by the World Health Organization's (WHO) Expert Committee on Drug Dependence (ECDD) in November 2017 (WHO, 2017). In October 2020, MDMB-4en-PINACA underwent a Critical Review by WHO's ECDD (WHO, 2020a).

MDMB-4en-PINACA is also structurally related to 4F-MDMB-BICA ⁽⁵⁾, MDMB-PINACA ⁽⁶⁾, 4F-MDMB-BINACA ⁽⁷⁾, and 5F-MDMB-PICA (5F-MDMB-2201) ⁽⁸⁾. The latter two substances were placed in Schedule II of the 1971 United Nations Single Convention on Psychotropic Substances (CND, 2020) after undergoing a critical review by the WHO's ECDD in October

⁽³⁾ MDMB-4en-PINACA and many other synthetic cannabinoid receptor agonists described in this report contain one asymmetric carbon atom which gives rise to (*S*)- and (*R*)-enantiomers. The code names described in this report do not include the designated, absolute configuration since the available data were not consistently available to EMCDDA.

⁽⁴⁾ 5F-MDMB-PINACA IUPAC name: methyl 2-[[1-(5-fluoropentyl)-1*H*-indazole-3-carbonyl]amino]-3,3-dimethylbutanoate

⁽⁵⁾ 4F-MDMB-BICA IUPAC name: methyl 2-[[1-(4-fluorobutyl)-1*H*-indole-3-carbonyl]amino]-3,3-dimethylbutanoate

⁽⁶⁾ MDMB-PINACA IUPAC name: methyl 3,3-dimethyl-2-[[1-pentyl-1*H*-indazole-3-carbonyl]amino]butanoate

⁽⁷⁾ 4F-MDMB-BINACA IUPAC name: methyl 2-[[1-(4-fluorobutyl)-1*H*-indazole-3-carbonyl]amino]-3,3-dimethylbutanoate

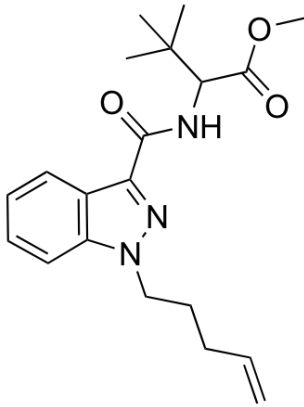
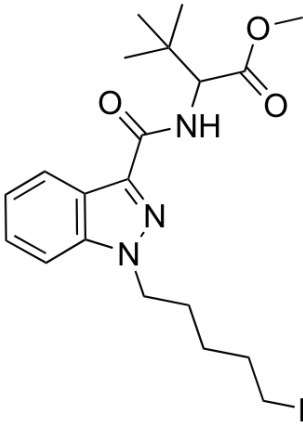
⁽⁸⁾ 5F-MDMB-PICA IUPAC name: methyl 2-[[1-(5-fluoropentyl)-1*H*-indole-3-carbonyl]amino]-3,3-dimethylbutanoate

2019 (WHO, 2019a; WHO, 2019b). In 2020, the EMCDDA also launched an initial report on 4F-MDMB-BICA (⁵) in accordance with Article 5b of Regulation (EC) No 1920/2006 (as amended) (EMCDDA, 2020a).

2.2 Names and chemical structure

MDMB-4en-PINACA is a synthetic cannabinoid. The MDMB-4en-PINACA code name for the substance is derived from its structural features: a methyl 3,3-dimethylbutanoate linked group (MDMB), a terminal alkene (4en), a modified *N*-pentyl tail (P), an indazole core (INA), and a carboxamide linker (CA).

Figure 1. Chemical structure and molecular information of MDMB-4en-PINACA and 5F-MDMB-PINACA (5F-ADB)

MDMB-4en-PINACA	5F-MDMB-PINACA (5F-ADB)
	
Molecular formula: C ₂₀ H ₂₇ N ₃ O ₃	Molecular formula: C ₂₀ H ₂₈ FN ₃ O ₃
Molecular weight: 357.45	Molecular weight: 377.45
Monoisotopic mass: 357.2052	Monoisotopic mass: 377.2115

Common name:

MDMB-4en-PINACA

Systematic (IUPAC) name:

Methyl 3,3-dimethyl-2-[[1-(pent-4-en-1-yl)-1*H*-indazole-3-carbonyl]amino]butanoate

Other chemical names:

Methyl 3,3-dimethyl-2-[1-(pent-4-en-1-yl)-1*H*-indazole-3-carboxamido]butanoate

Methyl 3-methyl-*N*-[1-(pent-4-en-1-yl)-1*H*-indazole-3-carbonyl]valinate

Methyl 3-methyl-*N*-[1-(pent-4-en-1-yl)-1*H*-indazole-3-carbonyl]-*L*-valinate ((*S*)-enantiomer);

Methyl 3-methyl-*N*-[1-(pent-4-en-1-yl)-1*H*-indazole-3-carbonyl]-*D*-valinate ((*R*)-enantiomer);

Methyl 3,3-dimethyl-2-[[1-(pent-4-en-1-yl)-1*H*-indazol-3-yl]formamido]butanoate

Methyl *N*-[[1-(pent-4-en-1-yl)-1*H*-indazole-3-yl]carbonyl]-3-methylvalinate;

Methyl 2-[1-(pent-4-en-1-yl)-1*H*-indazole-3-carboxamido]-3,3-dimethylbutanoate;

N-(1-methoxy-3,3-dimethyl-1-oxobutan-2-yl)-1-(pent-4-en-1-yl)-1*H*-indazole-3-carboxamide;

Other names:

MDMB-4en-PINACA

(4-en) ABD-PINACA

ADB-PINACA-A

(Pentyl-4-en) MDMB-PINACA

MDMB-PENINACA

MDMB-PINACA *N*1-pentyl-4-en isomer

5-CL-ADB-A [*sic*]⁽⁹⁾

At least historically, a common slang name for smoking mixtures containing synthetic cannabinoids in some countries 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. Many other names are now used and depend on the country, region, product type, brand names, and user groups. These include: 'smoking mixtures', 'herbal smoking mixtures', 'herbal incense', 'synthetic cannabis', 'legal weed', and 'K2'. A common name used in Hungary is 'magic

⁽⁹⁾ Potentially confusing code name though it appears to be advertised as MDMB-4en-PINACA by some Internet retailers. The IUPAC name for 5Cl-ADB (5Cl-MDMB-PINACA) is methyl 2-[[1-(5-chloropentyl)-1*H*-indazole-3-carbonyl]amino]-3,3-dimethylbutanoate. It is the chloro analogue of 5F-MDMB-PINACA (5F-ADB) (Figure 1). The exact meaning or purpose of the '-A' suffix in '5-CL-ADB-A' is unclear though one suggestion advertised by some retailers included 'amylene' (2-methylbut-2-ene). It does not exactly capture the structural nature of the tail group but '5-CL-ADB-A' appears to be used synonymously for MDMB-4en-PINACA in some cases.

tobacco'; in France 'chimique'; in Turkey, 'Bonsai'; whereas in Birmingham, United Kingdom, the name 'Black Mamba 'or simply 'Mamba 'is used.

In France, liquids containing synthetic cannabinoids may be sold under the street name 'PTC '(from the French, 'pète ton crâne'). At least one such sample containing MDMB-4en-PINACA was reported. Two additional collected samples of unknown physical form (also containing 5F-MDMB-PICA ⁽⁸⁾) were sold as 'Chimique'.

In Germany, 'legal high 'products brands containing MDMB-4en-PINACA included 'Pico Bello Extra Strong '(seized in 2017, containing 5F-ADB and 5F-ADB-PINACA), 'Pico Bello Made In Holland '(3 seizures, containing also 5F-MDMB-PICA ⁽⁸⁾). One sample was purchased as '5CL-ADB-A '(⁹). One seized sample determined to be MDMB-4en-PINACA was labelled incorrectly as '5F-MDMB-2201 '(5F-MDMB-PICA).

In the United States, MDMB-4en-PINACA has been detected in a product labelled as 'Heavy Weight (WHO 2020a).

Product names cannot be considered a reliable source of information regarding the actual substances present in such products since the compositions of such products might be subject to significant variations in contents (e.g. Moosmann et al., 2015; Frinculescu et al., 2017).

Chemical Abstracts Service (CAS) registry numbers:

2504100-70-1 ((S)-enantiomer)

2504100-73-4 ((R)-enantiomer)

IUPAC International Chemical Identifier Key (InCHI Key):

LWOCBHBFWNGPGM-UHFFFAOYSA-N

Simplified Molecular-Input Line-Entry System (SMILES):

CC(C(C(=O)OC)NC(=O)C1=NN(C2=CC=CC=C12)CCCC=C)(C)C ⁽¹⁰⁾

2.3 Physical properties

In its pure form MDMB-4en-PINACA has been described as a neat solid (Cayman Chemical Company, 2020b), a powder (NFL Ljubljana, 2018), and a white powder (Watanabe et al., 2019). It has also been described as a tan and yellow/brown powder (WHO, 2020a). Seized and collected samples determined to contain MDMB-4en-PINACA have been described as white, beige, yellow and orange powders (EMCDDA, 2020a; EMCDDA, 2020b).

⁽¹⁰⁾ Generated from IUPAC name by OPSIN: Open Parser for Systematic IUPAC nomenclature (<http://opsin.ch.cam.ac.uk>) (Lowe et al., 2011).

Information available on the lipophilicity, melting and boiling points or other physico-chemical properties of MDMB-4en-PINACA, with the exception of its solubility, could not be identified. It has been reported to be soluble in dichloromethane, methanol, and partially in water (Krotulski et al., 2019; NFL Ljubljana, 2018; Norman et al., 2020b) but also deuterated chloroform (Antonides et al., 2020; Norman et al., 2020a; Norman et al., 2020b). (*S*)-MDMB-4en-PINACA has also been described as a colourless oil (Stove and Banister, personal communication) ⁽¹¹⁾.

Information involving the analysis of seized and collected samples received by EMCDDA suggests that MDMB-4en-PINACA has been detected in e-liquids for use electronic cigarettes, powders, smoking mixtures, and impregnated papers and cards (including blotters) (EMCDDA, 2020b).

2.4 Methods and chemical precursors used for the manufacture or extraction

No information was reported by the Member States, Norway, or Turkey about the chemical precursors or manufacturing methods used to make the MDMB-4en-PINACA which has been identified within Europe. However, the synthesis of both (*S*)- and (*R*)-MDMB-4en-PINACA enantiomers has been recently described (Antonides et al., 2020) (Stove and Banister, personal communication ⁽¹⁰⁾), following previously established procedures (e.g. Banister et al., 2016; Buchler et al., 2009) (Figure 2).

Methyl 1*H*-indazole-3-carboxylate (available commercially or might be prepared from various precursors) (1) undergoes *N*-alkylation with 5-bromopent-1-ene and followed by hydrolysis to the carboxylic acid intermediate (3). Coupling with methyl *L*-*tert*-leucinate (methyl (2*S*)-2-amino-3,3-dimethylbutanoate) ⁽¹²⁾ gives (*S*)-MDMB-4en-PINACA (4) (Figure 2). Coupling with methyl *D*-*tert*-leucinate yields (*R*)-MDMB-4en-PINACA.

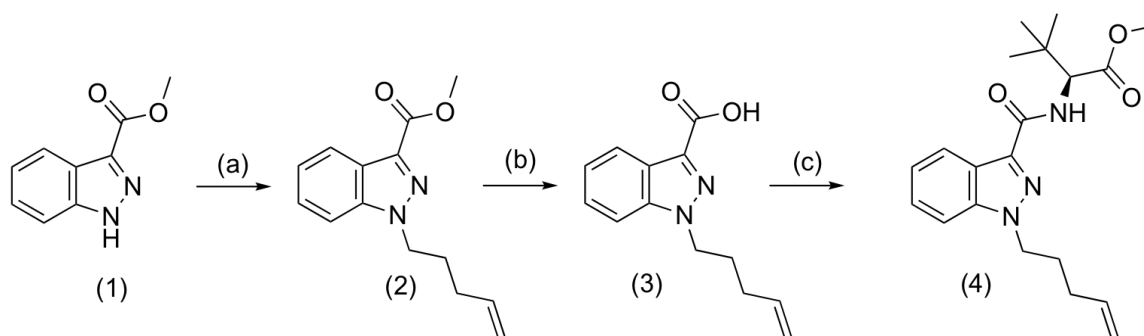


Figure 2. Synthesis route for MDMB-4en-PINACA ((*S*)-enantiomer) starting from methyl 1*H*-indazole-3-carboxylate (Antonides et al., 2020) and Stove and Banister (personal communication ⁽¹¹⁾). Reagents: (a) *tert*-butoxide or NaH, THF or DMF, 5-bromopent-1-ene; (b) 1 M aq. NaOH, MeOH, reflux or room temperature; (c) methyl *L*-*tert*-leucinate, EDC·HCl, HOBt, DIPEA, DMSO or EDC·HCl, HOBt·H₂O, Et₃N, DMF at room temperature. For the preparation of the (*R*)-enantiomer (Antonides et al. 2020), the coupling reaction involves the

⁽¹¹⁾ Cannaert et al., 2020

⁽¹²⁾ (*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-4en-PINACA and other related synthetic cannabinoids that have been reported to the EU Early Warning System.

use of methyl D-*tert*-leucinate instead.

2.5 Methods for identification and analysis

Analytical data for MDMB-4en-PINACA and methods for its identification have been published in the scientific literature and are in the public domain (Table 1). The analysis of biological samples requires the use of sensitive analytical methods, e.g. liquid chromatography coupled to (tandem) mass spectrometry approaches (high and low resolution). (S)-MDMB-4en-PINACA is available as reference material from commercial suppliers. The EMCDDA has not received information about the enantiomeric composition of MDMB-4en-PINACA-containing products, although the presence of the (S)-enantiomer, similar to most other closely related synthetic cannabinoid receptor agonists available on the market, seems likely. However, the presence of the (R)-enantiomer or the racemic mixture cannot not be excluded in the absence of further information. Chiral profiling analyses carried out on paper samples seized in three Scottish prisons confirmed the presence of the (S)-enantiomer (McKenzie, 2020).

In some biological specimens, the parent molecule might not always be detectable due to ester hydrolysis which gives rise to the formation of an acidic transformation product (¹³), a phenomenon described for other synthetic cannabinoids with such ester moieties (e.g. Ong et al. 2020). However, the detection of this metabolite/degradation product alone might not be sufficient for unambiguous identification as it might also arise from various other ester and amide analogues (see, for example, Diao and Huestis, 2019).

Table 1. Detections and analytical data associated with the detection and chemical analysis of MDMB-4en-PINACA (amongst other substances) available in the scientific literature and public domain		
Techniques ^a	Comment	Reference
GC-MS; IR; NMR	Analysis of test purchased material	NFL Ljubljana (2018)
EI-MS; LC-MS	Analysis of reference material and blood samples	Krotulski et al. (2019)
LC-MS	<i>In vitro</i> metabolism study and analysis of a case sample	Watanabe et al. (2019)
GC-MS; NMR; LC-UV-MS	Analysis of synthesised (S)- and (R)-MDMB-4en-PINACA	Antonides et al. (2020)
GC-MS	Analysis of reference material	Cayman Chemical Company (2020a)

¹³) Ester hydrolysis product IUPAC name: 3,3-dimethyl-2-[[1-(pent-4-en-1-yl)-1H-indazole-3-carbonyl]amino]butanoic acid

LC-MS	Analysis of case samples	Krotulski et al. (2020a)
GC-MS; NMR; LC-UV-MS	Analysis of seized samples (impregnated papers) and analysis of synthesised (S)- and (R)-MDMB-4en-PINACA	Norman et al. (2020b)
IMS	Analysis of seized samples paper impregnated samples in prison	Norman et al. (2020a)
LC-MS	Analysis of post-mortem blood samples	Rice et al. (2020)
NMR	Analysis of 'unknown' substance	Tomažič (2020)
LC-MS	<i>In vitro</i> metabolism study and analysis of a case sample	Yeter et al. (2020)
LC-MS; LC-UV; IR; NMR	Analysis of synthesised material	Stove and Banister, personal communication ⁽¹⁾
<p>^a GC: gas chromatography; MS: mass spectrometry; LC: liquid chromatography; IR: infrared spectroscopy; NMR: nuclear magnetic resonance spectroscopy; EI: electron ionisation; HR: high resolution; IMS: ion mobility spectrometry; UV: ultraviolet spectroscopy; LC-MS and ESI-MS: might involve single, tandem, low, or high resolution methods of analysis.</p>		

2.6 Dosage regimens

Information on the dose and dosage regimens⁽¹⁴⁾ for MDMB-4en-PINACA is limited. Products containing synthetic cannabinoids such as MDMB-4en-PINACA rarely state the correct ingredients and concentrations, as such, people who use such products will be unaware that they are using this substance and will be unable to obtain accurate dosage information.

In addition, in respect to smoking mixtures, the process for mixing the synthetic cannabinoids with the plant material to make the smoking mixture can lead to dangerous amounts of the substances in the products. This is because producers have to guess the amount of substances to be added, while the mixing process makes it difficult to dilute them sufficiently and distribute them consistently throughout the plant material. This can result both in products that contain toxic amounts of the substances in general (Ernst et al. 2017;

⁽¹⁴⁾ Dosage regimen: is information on the formulation (dosage form), route of exposure, as well as the schedule of doses of a new psychoactive substance, including the amount taken each time, time between doses, and the duration of use.

Frinculescu et al. 2017; Langer et al. 2014; Langer et al. 2016), as well as in products where the solid particles of synthetic cannabinoids are clumped together, forming highly concentrated pockets within the plant material (Frinculescu et al. 2016; Moosmann et al. 2015; Schäper et al. 2016). In fact, in the latter case, simply tapping a packet containing a smoking mixture can dislodge the substances from the plant material. In addition, paper (such as blotters and cards) impregnated with synthetic cannabinoids can pose a similar high risk of poisoning because the amount of synthetic cannabinoid can be unevenly distributed in different parts of the paper, sometimes forming highly concentrated sections on the paper (Norman, et al., 2020). These issues are made worse because the products are smoked or vaped, allowing the substances to be rapidly absorbed into the bloodstream and to reach the central nervous system and other parts of the body to cause their effects. Accounts from patients and people who witness poisonings suggest that in some cases a small number of puffs from a cigarette ('joint') have been sufficient to cause severe and fatal poisoning.

Together, these factors, coupled to the typically high potency of synthetic cannabinoids, makes it difficult for users to control the dose that they are exposed to. This can lead them to unintentionally administer a toxic dose.

Reports posted on Internet forums that involve information of dosage regimens of MDMB-4en-PINACA are limited. MDMB-4en-PINACA can be inhaled by smoking and it is expected that similar to related synthetic cannabinoids, that MDMB-4en-PINACA might also be inhaled by vaporising e-liquid solutions ('vaping'), for example by using electronic cigarettes, and administered orally or sublingually (Reddit, 2020).

The concentration of MDMB-4en-PINACA in products seized by law enforcement or from collected samples in Europe is currently limited (see below). The composition of products is likely to vary over time and place, as well as based on the specific location in the drug supply chain in which the sample is obtained from (for example, from the manufacturer, wholesaler, retailer, or at street-level markets).

In reports to the EMCDDA, MDMB-4en-PINACA has been predominantly encountered in the form of smoking mixtures. Other forms included powders, liquids (including e-liquids), impregnated papers and cards (including blotters). Some reports did not specify the physical form encountered (EMCDDA, 2020b).

According to reports received by EMCDDA, MDMB-4en-PINACA has been detected in combination with other synthetic cannabinoids including: 5F-MDMB-PICA⁽⁸⁾, 4F-MDMB-BICA⁽⁵⁾, 4F-MDMB-BINACA⁽⁷⁾, 5CI-AB-PINACA⁽⁹⁾, 5F-EMB-PICA⁽¹⁵⁾, AMB-FUBINACA⁽¹⁶⁾, AB-FUBINACA⁽¹⁷⁾, Cumyl-PeGaClone⁽¹⁸⁾, CUMYL-4CN-BINACA⁽¹⁹⁾, Cumyl-5F-

⁽¹⁵⁾ 5F-EMB-PICA IUPAC name: ethyl 2-([1-(5-fluoropentyl)-1H-indole-3-carbonyl]amino)-3-methylbutanoate

⁽¹⁶⁾ AMB-FUBINACA IUPAC name: methyl 2-([1-(4-fluorophenyl)methyl]-1H-indazole-3-carbonyl)amino)-3-methylbutanoate

⁽¹⁷⁾ AB-FUBINACA IUPAC name: N-[1-amino-3-methyl-1-oxobutan-2-yl]-1-[(4-fluorophenyl)methyl]-1H-indazole-3-carboxamide

⁽¹⁸⁾ Cumyl-PeGaClone IUPAC name: 5-pentyl-2-(2-phenylpropan-2-yl)-2,5-dihydro-1H-pyrido[4,3-b]indol-1-one

⁽¹⁹⁾ CUMYL-4CN-BINACA IUPAC name: 1-(4-cyanobutyl)-N-(2-phenylpropan-2-yl)-1H-indazole-3-carboxamide

PINACA (²⁰) and JWH-210 (²¹).

In a seizure of three 'Spice' samples reported by the United Kingdom and that were made in July 2020 in Manchester, MDMB-4en-PINACA was identified in a ratio 'per plant material of 1.56% to 2.09% w/w'. The report noted that this was 1.5 to 2 times the ratio of MDMB-4en-PINACA found in seized samples tested in June 2020. For comparison, herbal cannabis samples typically contain roughly 8–12% THC w/w (Freeman et al., 2020).

During the analysis of 360 individual seized paper samples (168 seizures) from 3 Scottish prisons between 1 June 2018 and 27 September 2019, 146 samples (41%) were found to contain at least one synthetic cannabinoid receptor agonist. For MDMB-4en-PINACA, the reported concentration range in 22 samples was <0.07–0.58 mg/cm² (Norman, 2020b). As of 18 September 2020, MDMB-4en-PINACA has been detected in 97 separate seizures of synthetic cannabinoid impregnated papers submitted for analysis (McKenzie, 2020). MDMB-4en-PINACA has been detected in papers in isolation but is also commonly detected with 4F-MDMB-BINACA (⁷) as well as 5F-MDMB-PICA (⁸), both 4F-MDMB-BINACA and 5F-MDMB-PICA, and more recently with 5F-EMB-PICA (¹⁵) (McKenzie, 2020).

Analysis of drug samples submitted to the Welsh Emerging Drugs & Identification of Novel Substances Project (WEDINOS) found that MDMB-4en-PINACA was identified in e-liquids purchased as THC (WEDINOS, 2020). WEDINOS also reported the identification of MDMB-4en-PINACA and flubromazolam in tablets sold as alprazolam (WEDINOS, 2020). Eighty-four samples containing MDMB-4en-PINACA were submitted to WEDINOS between August 2019 and September 2020. Of these, 76 samples (90%) were submitted in 2020. Fifty-seven of the samples (68%) submitted to WEDINOS were smoking mixtures (EMCDDA, 2020b; WEDINOS, 2020).

Drug-checking services operating in Switzerland reported that MDMB-4en-PINACA was identified with CBD in 37 samples (between May and September 2020) sold as 'THC cannabis' or 'THC hashish'. Nineteen samples contained other synthetic cannabinoids such as 5F-MDMB-PICA (⁸), 4F-MDMB-BINACA (⁷), 5F-ADBICA-A, 4F-MDMB-BICA (⁵) and THJ-018 (²²) (EMCDDA, 2020b; Rave it Safe, 2020; Saferparty.ch, 2020). An additional 45 samples (²³) submitted as herbal cannabis or cannabis resin ('hashish') tested in Switzerland were found to contain MDMB-4en-PINACA and other synthetic cannabinoids, according to the website DrugsData.org, Erowid's anonymous drug analysis programme. According to the same source, three powdered samples submitted to drug testing (at least one of which sold as heroin) from the Boston area (Massachusetts, United States) identified MDMB-4en-PINACA in combination with fentanyl, lidocaine, caffeine, and traces of 4-ANPP in two of the samples, and MDMB-4en-PINACA in combination with fentanyl and lidocaine in the other

⁽²⁰⁾ Cumyl-5F-PINACA IUPAC name: 1-(5-fluoropentyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide

⁽²¹⁾ JWH-210 IUPAC name: (4-ethylnaphthalen-1-yl)(1-pentyl-1*H*-indol-3-yl)methanone

⁽²²⁾ THJ-018 IUPAC name: (naphthalen-1-yl)(1-pentyl-1*H*-indazol-3-yl)methanone

⁽²³⁾ As of 22 November 2020

sample⁽²⁴⁾ (DrugsData.org, 2020).

Whilst formal epidemiological studies have not been performed, the small number of anecdotal self-reported experiences on user websites suggest, that, similar to other synthetic cannabinoids, the dosage regimens used for MDMB-4en-PINACA can differ within and between individuals. Reported doses included 0.02–0.1 mg ('vaping') and 0.1–0.6 mg (sublingual) (Reddit, 2020), but it is not possible to discern typical dosage regimens. These also depend on the tolerance of the user, the use of other drugs, and the desired effects. Furthermore, the purity, amount and/or composition of the substance ingested are not typically known by the user. In addition, the actual composition of the substance may differ over time and place.

3. Legitimate use

3.1 Summary

Based on the available information, it appears that MDMB-4en-PINACA is not an active substance in a medicinal product for human use or in a veterinary medicinal product in Europe.

However, although highly unlikely, the use of MDMB-4en-PINACA as an active substance in medicinal products prepared extemporaneously or in investigational medicinal products cannot be excluded in some Member States (EMCDDA, 2020b). There is currently no information that suggests MDMB-4en-PINACA is used for legitimate purposes other than research or forensic application.

3.2 Medical use

Based on information from the European Medicines Agency for the initial report (EMCDDA, 2020b), it appears that MDMB-4en-PINACA is not an active substance in:

- a medicinal product for human use or in a veterinary medicinal product that has obtained a marketing authorisation in accordance with Directive 2001/83/ EC of the European Parliament and of the Council, Directive 2001/82/EC of the European Parliament and of the Council or Regulation (EC) No 726/2004 of the European Parliament and of the Council;
- a medicinal product for human use or in a veterinary medicinal product that is the subject of an application for a marketing authorisation;
- a medicinal product for human use or in a veterinary medicinal product whose marketing authorisation has been suspended by the competent authority.

⁽²⁴⁾ 4-ANPP: 4-anilino-*N*-phenethylpiperidine (IUPAC name: *N*-phenyl-1-(2-phenylethyl)18piperidine-4-amine); an intermediate used for the synthesis of fentanyl analogues.

In addition, it appears that MDMB-4en-PINACA is not an active substance in the following, although the information, especially in relation to use in extemporaneously prepared products, is unknown in some cases:

- an unauthorised medicinal product for human use in accordance with Article 5 of Directive 2001/83/ EC or in a veterinary medicinal product prepared extemporaneously by a person authorised to do so under national law in accordance with point (c) of Article 10(1) of Directive 2001/82/EC;
- an investigational medicinal product as defined in point (d) of Article 2 of Directive 2001/20/EC of the European Parliament and of the Council.

3.3 Industrial, commercial, and scientific use

MDMB-4en-PINACA is used as an analytical reference material in clinical and forensic case work as well as scientific research. There is currently no information that suggests MDMB-4en-PINACA is used for other legitimate purposes.

As part of the initial report process, the European Chemical Agency (ECHA) and European Food Safety Authority (EFSA) reported to the EMCDDA that MDMB-4en-PINACA did not retrieve any results in their information systems (EMCDDA, 2020b).

According to the recent critical review of MDMB-4en-PINACA published by the World Health Organization (WHO, 2020a), China reported that the substance is 'being used in industrial or other non-medical or non-scientific use'.

4. Pharmacological and toxicological properties

4.1 Summary

MDMB-4en-PINACA has been shown to act as a potent, low to sub-nanomolar full agonist at the cannabinoid type 1 (CB₁) receptor when investigated assays *in vitro*. When investigated under identical conditions, the ester hydrolysis product (an important metabolite) was found to show a 233-fold drop in binding affinity compared to the parent molecule. The evaluation of (*R*)-MDMB-4en-PINACA also revealed a large drop in potency when compared to (*S*)-MDMB-4en-PINACA. Data on the pharmacokinetics of MDMB-4en-PINACA in humans are limited to the identification of metabolites and *in vitro* data on metabolic stability. No studies were identified that have investigated the pharmacodynamics of MDMB-4en-PINACA on pharmacological targets other than cannabinoid receptor type 1 (CB₁). Initial data obtained from *in vivo* studies suggest that the effects induced MDMB-4en-PINACA appear to be consistent with those observed for other synthetic cannabinoids.

Although not formally studied, the psychological and behavioural effects of MDMB-4en-PINACA are likely to share some similarities with those commonly reported for other synthetic cannabinoids, including: relaxation, euphoria, lethargy, confusion, anxiety, fear, distorted perception of time, depersonalisation, hallucinations, paranoid inclusions, as well

as dry mouth, bloodshot eyes, cardiovascular effects, nausea, vomiting and impaired motor performance.

Information on the toxicological properties of MDMB-4en-PINACA could not be identified. Compared to cannabis, severe and fatal poisoning appears to be more common with synthetic cannabinoids. Poisoning symptoms may include rapid loss of consciousness/coma, cardiovascular effects (such as hypertension, tachycardia, bradycardia, chest pain, myocardial infarction, and stroke), seizures and convulsions, vomiting (including hyperemesis), delirium, agitation, psychosis, and, aggressive and violent behaviour. Sudden death has also been reported. There is no known antidote to poisoning caused by this substance and thus the treatment of an overdose is the same as that of cannabis toxicity: supportive treatment and serial reassessment of the airway and neurological signs. Effects reported by people who used a substance believed to be MDMB-4en-PINACA included stimulation, sensations of feeling 'really stoned', craving for food, depersonalisation, anxiety, paranoia, sedation, and dissociation. Anecdotal reports indicated that the threshold dose for MDMB-4en-PINACA when inhaled by 'vaping' might be below the 0.1 mg level, which suggests it is similar to other highly potent synthetic cannabinoids. The development of rapid tolerance has been reported and duration of effects have been described to last between 15–45 min when inhaled by 'vaping', depending on the extent of tolerance. The assessment of such reports is problematic not least because users cannot confirm the actual substance or the amount used. In general, given the difficulties of collecting accurate self-reported data, it should be interpreted with caution.

The abuse liability and dependence producing potential of MDMB-4en-PINACA have not been studied. However, it has been suggested that consumption of synthetic cannabinoids can produce tolerance and withdrawal-like symptoms when use is discontinued following a regular use.

4.2 Pharmacodynamics

4.2.1 *In vitro* data

Though limited, current available information from *in vitro* studies suggests that MDMB-4en-PINACA binds to and activates the cannabinoid type 1 (CB₁) receptor (Table 2) ⁽²⁵⁾. MDMB-4en-PINACA has also been confirmed to act as a potent, full agonist in two separate assay systems with activity in the low to sub-nanomolar range. Another comparison with JWH-018 ⁽²⁶⁾ revealed that MDMB-4en-PINACA activated the CB₁ receptor with slightly higher potency (~1.6-fold) (Vikingsson and Gréen, 2020) (Table 2). The closely related 5F-MDMB-PINACA (5F-ADB) was shown to show comparable properties (EMCDDA, 2018; WHO, 2017). For comparison, MDMB-PINACA, the saturated analogue of MDMB-4en-PINACA, was more potent than THC but less efficacious than 5F-MDMB-PINACA with respective EC₅₀ values of

⁽²⁵⁾ K_i represents the equilibrium inhibition constant for the test drug displacing the radioligand; EC₅₀ represents the half maximal effective concentration for a given substance.

⁽²⁶⁾ JWH-018 IUPAC name: (naphthalen-1-yl)(1-pentyl-1*H*-indol-3-yl)methanone

1.4, 171 and 0.59 nM (Banister et al., 2016).

Table 2. *In vitro* binding and activation data at the hCB₁ receptor reported for enantiopure MDMB-4en-PINACA

Enantiomer	K _i (nM)	EC ₅₀ (nM)	E _{max} (%)	Reference
Not described (presumably (S)-MDMB-4en-PINACA))	3.26 ^a	0.33 ^b	112.7	Janowski, cited in WHO (2020a)
(S)-MDMB-4en-PINACA	–	2.47 ^c	239 ^d	Krotulski et al. (2020a)
(S)-MDMB-4en-PINACA	–	1.11 ^c	229 ^d	Antonides et al. (2020)
(S)-MDMB-4en-PINACA	–	2.33 ^c	299 ^e	Stove and Banister, personal communication (¹⁰)
(R)-MDMB-4en-PINACA	–	229 ^c	197 ^d	Antonides et al (2020)
(S)-MDMB-4en-PINACA	–	16.7 ^f	109 ^g	Vikingsson and Gréen (2020)

^a HEK cells
^b Forskolin-stimulated accumulation of cyclic adenosine monophosphate (cAMP) assay
^c HEK cells; β-Arrestin 2 recruitment assay
^d Relative to JWH-018 (E_{max} = 100%; EC₅₀ = 14.2 nM)
^e Relative to JWH-018 (E_{max} = 100%; EC₅₀ = 21.4 nM)
^f Aquerin base system; CHO cells
^g Relative to JWH-018 (E_{max} = 100%; EC₅₀ = 27.2 nM)

Under the same assay conditions shown in Table 2 (Antonides et al., 2020; Krotulski et al., 2020a), (S)-5F-ADB was also shown to display high potencies in the same range: EC₅₀ = 1.78 nM (E_{max} = 331%) (Antonides et al., 2019); EC₅₀ = 0.84 nM (E_{max} = 319%) (Wouters et al., 2019); (EC₅₀ = 0.18 nM; E_{max} = 250%) (Antonides et al., 2020; Wouters et al., 2020). On the other hand, (R)-5F-ADB showed a ~74-fold drop in potency (EC₅₀ = 131 nM; E_{max} = 180%) compared to its (S)-counterpart (Antonides et al., 2019). The reduction in potency observed for (R)-MDMB-4en-PINACA (EC₅₀ = 229 nM; E_{max} = 197%) was 206-fold (Table 2). The ester hydrolysis product of (S)-MDMB-4en-PINACA (11) was found to result in a 233-fold drop in potency regarding receptor activation (EC₅₀ = 576 nM; E_{max} = 265%, relative to

JWH-018) (Krotulski et al., 2020a). As shown in Section 4.5, the acidic hydrolysis product has also been found to be an important metabolite that might be targeted for analysis. It is not known whether MDMB-4en-PINACA affects other pharmacological targets, such as receptors, enzymes or transport processes.

4.2.2 *In vivo* data

Detailed information on the *in vivo* effects of MDMB-4en-PINACA could not be identified. Unpublished information provided to the World Health Organization for the critical review of MDMB-4en-PINACA (WHO, 2020a) refers to a study using 6 male ICR mice by Wiley and Marusich from RTI International (North Carolina, USA) and states that:

'In this experiment, MDMB-4en-PINACA (0.1, 1 or 10 mg/kg) was injected intraperitoneally. Rectal temperature was measured at 30, 45 and 60 minutes post-injection and overt behaviour was observed over the same period. Whereas the dose of 0.1 mg/kg did not reduce temperature at any time point, 1 and 10 mg/kg decreased temperature, with maximal decreases of -4.6 ± 0.62 °C and -8.15 ± 0.41 °C, respectively. In addition, some mice that received either 1 or 10 mg/kg were lethargic and exhibited seizures upon handling. At 1 mg/kg, cage behaviour normalized within 2 hours; however, at 10 mg/kg, mice were still lethargic at 5 hours post-injection. The 10 mg/kg dose also led to gasping and aggression in some mice. These effects had worn off by 3 hours post-injection.'

These results suggest that MDMB-4en-PINACA shares similar properties to other synthetic cannabinoids. Cannabimimetic (i.e. Δ^9 -THC-like) effects commonly reported for such substances include hypolocomotion, antinociception, hypothermia, and catalepsy (e.g. Lefever et al., 2017; Wiley et al., 2017); these effects are similar to but not entirely identical with those observed for MDMB-4en-PINACA.

4.3 Psychological and behavioural effects

Information on the study of psychological and behavioural effects of MDMB-4en-PINACA in humans could not be identified. Based on the limited information on the pharmacological properties of MDMB-4en-PINACA, as well information from previous observations involving closely related synthetic cannabinoids such as 5F-MDMB-PINACA (⁴), it is likely that the effects of MDMB-4en-PINACA share some similarities with those commonly reported for cannabis but also other synthetic cannabinoids, including: relaxation, euphoria, lethargy, confusion, anxiety, fear, distorted perception of time, depersonalisation, hallucinations, paranoid delusions, as well as dry mouth, bloodshot eyes, cardiovascular effects, nausea, vomiting and impaired motor performance. These dose-dependent effects appear to be much more pronounced and severe when compared to cannabis (Ford et al., 2017; Zaurava et al. 2016). Specifically, psychotic episodes, confusion, paranoia, as well as aggressive and violent behaviour, have been reported for 5F-MDMB-PINACA (EMCDDA, 2018; WHO, 2017).

Effects reported by people who used a substance they believed to be MDMB-4en-PINACA included stimulation, sensations of feeling 'really stoned', craving for food, depersonalisation,

anxiety, paranoia, sedation, and dissociation (Reddit, 2020). The self-reported effects from users submitting samples containing MDMB-4en-PINACA were consistent with those reported for other synthetic cannabinoids, and included euphoria, relaxation, chest pains, irregular heartbeat, vomiting, confusion, agitation, auditory and visual hallucinations, and paranoia (WEDINOS, 2020).

4.4 Safety pharmacology

Detailed information on the safety pharmacology (ICH, 2000) of MDMB-4en-PINACA could not be identified. However, the available data described in this section suggest that this substance is a potent, full CB₁ receptor agonist and that it shows mechanistic similarities with THC and other synthetic cannabinoids receptor agonists *in vivo*.

Based on the currently information on the pharmacological properties of MDMB-4en-PINACA and other closely related synthetic cannabinoids such as 5F-MDMB-PINACA, adverse effects from overdosing MDMB-4en-PINACA might include gastrointestinal (e.g. nausea, and vomiting (including hyperemesis)), neurological (e.g. hallucination, agitation, anxiety, paranoia, confusion, delusions, catatonia, lethargy, psychosis especially in susceptible individuals) and severe central nervous system depression (such as rapid loss of consciousness/coma), cardiovascular (e.g. tachycardia, hypertension, acute myocardial infarction and sudden cardiac death) and renal (e.g. acute kidney failure) clinical features (Ford et al., 2017; Hermanns-Clausen et al., 2013; Ozturk et al., 2019; Pacher et al., 2018; Tait et al., 2016). These effects appear to be much more pronounced and severe when compared to cannabis (Ford et al., 2017; Zaurova et al., 2016).

4.5 Pharmacokinetics

The biotransformation of MDMB-4en-PINACA has recently been investigated following incubation with human hepatocytes and human liver microsomes (HLM). Thirty-two metabolites were detected, with 11 metabolites being detected in hepatocyte samples, and 31 in HLM. The detected metabolites were suggested to involve butanoic acid formation via terminal oxidation of the alkenyl chain, carboxylation, dehydrogenation, dihydrodiol formation, ester hydrolysis, hydrogenation, hydroxylation, and glucuronidation either alone or in combination (Figure 3) (Watanabe et al., 2019). The three most abundant metabolites were M8 (ester hydrolysis and dihydrodiol), M30 (ester hydrolysis) ⁽¹³⁾, and M20 (ester hydrolysis and hydroxylation) for a 5 h hepatocyte incubation and M7 (ester hydrolysis, dihydrodiol, and dehydrogenation), M8 (ester hydrolysis and dihydrodiol), and M3 (ester hydrolysis, dihydrodiol, hydroxylation, and dehydrogenation) for HLM incubation (Figure 3). The analysis of an authentic blood and urine sample confirmed the detection of the parent MDMB-4en-PINACA. Two metabolites were detected in hydrolysed urine (M8, ester hydrolysis and dihydrodiol; M30, ester hydrolysis), whereas one metabolite was detected in blood and non-hydrolysed urine (M30 and M8). The ester hydrolysis metabolite M8 was considered more abundant in hydrolysed urine (Watanabe et al., 2019).

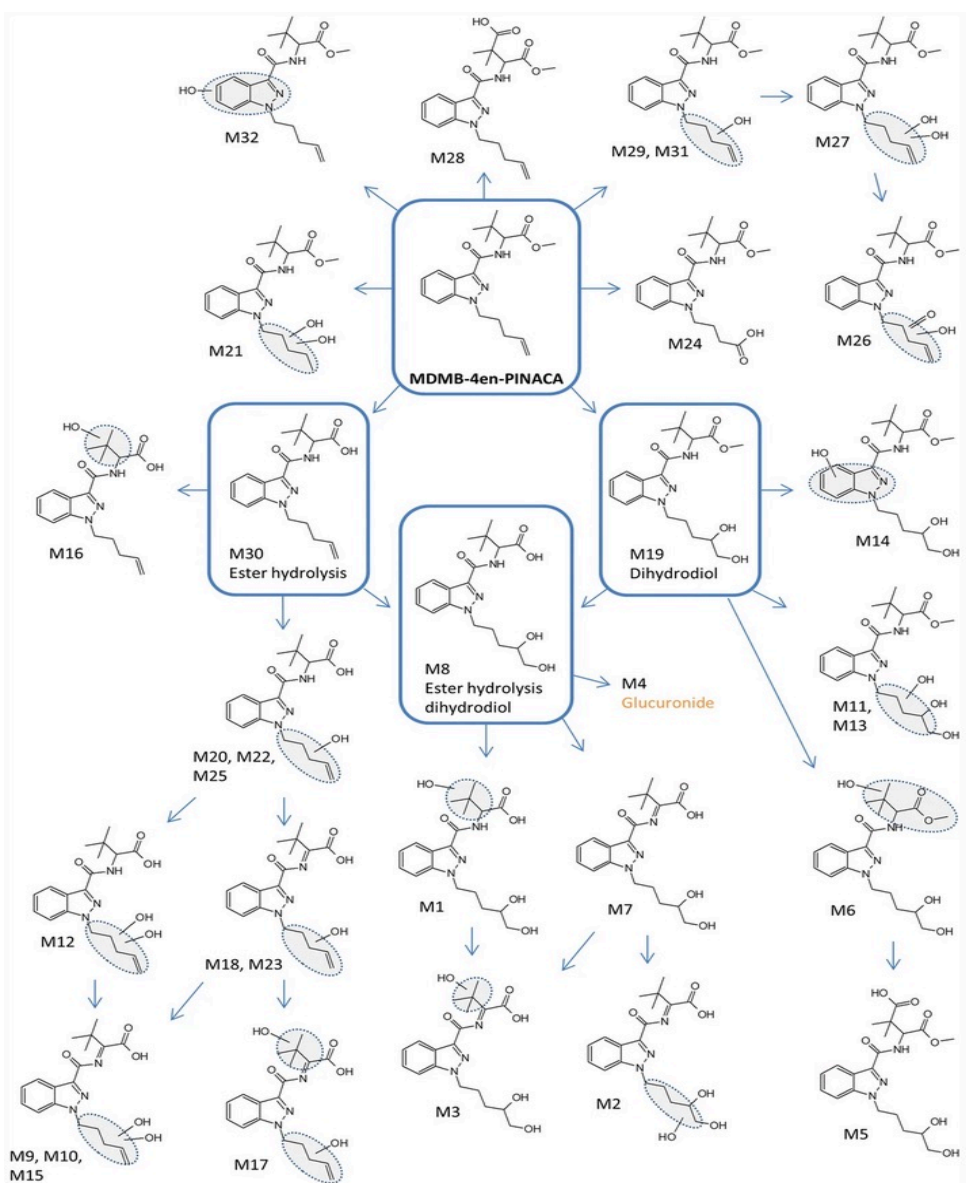


Figure 3. Proposed metabolic pathways of MDMB-4en-PINACA (Watanabe et al., 2019).

A separate study involving the incubation of MDMB-4en-PINACA with pooled HLMs reported the detection of 14 metabolites, thought to be formed *via* double bond oxidation, ester hydrolysis, *N*-dealkylation, hydroxylation, dehydrogenation and further oxidation to *N*-pentanoic acid or combinations thereof (Yeter and Yeter, 2020). MDMB-4en-PINACA was detected as the parent drug in 10 of 22 authentic urine samples chosen for investigations (MDMB-4en-PINACA detected in 56/2150 case samples). Three of the identified main metabolites (double bond oxidation in combination with ester hydrolysis and hydroxylation reactions) were suggested as suitable urinary markers, including the ester hydrolysis product (¹³) (Yeter and Yeter, 2020). The parent molecule and its ester hydrolysis product have also been used as targets during the analysis of authentic blood and urine specimen involving post-mortem, clinical and driving under the influence of drugs cases (Krotulski et al., 2020a). The detection of MDMB-4en-PINACA and metabolites (not specified) has also

been reported during the analysis of post-mortem sample material by Rice et al. (2020).

The pharmacological activity, if any, of the possible metabolites of MDMB-4en-PINACA is not known, except for the activity at the CB₁ receptor of the ester hydrolysis product.

The lipophilic nature of synthetic cannabinoids such as (S)-MDMB-4en-PINACA is reflected in significant plasma protein binding (99%). The intrinsic metabolic stability of (S)-MDMB-4en-PINACA has been determined in human liver microsomes and human hepatocytes. *In vitro* half-life, microsomal clearance (CL_{int micr}) and intrinsic clearance (CL_{int}) with predicted *in vivo* hepatic clearance (CL_H) and hepatic extraction ratio (E_H) for pooled human liver microsome incubations were as follows: T_{1/2} = 5.3 min; C_{Lint micr} = 0.261 mL min⁻¹ mg microsomal protein⁻¹; CL_{int} = 353 mL min⁻¹ kg⁻¹; CL_H = 3.02 mL min⁻¹ kg⁻¹; E_H = 0.14. *In vitro* half-life and intrinsic clearance (CL_{int}) with predicted *in vivo* hepatic clearance (CL_H) and hepatic extraction ratio (E_H) for pooled cryopreserved human hepatocyte incubations were determined as follows: T_{1/2} = 9.1 min; CL_{int} = 843 mL min⁻¹ kg⁻¹; CL_H = 6.01 mL min⁻¹ kg⁻¹; E_H = 0.29 (McKenzie, 2020).

Information about the duration of effects recorded during human studies could not be identified. Anecdotal reports from people who used a substance they believed to be MDMB-4en-PINACA suggest that the psychoactive effects might range between 15–45 min when inhaled by 'vaping' depending on the administered dose and whether tolerance developed (Reddit, 2020).

4.6 Toxicology

Information on the toxicological properties (including pre-clinical safety data) of MDMB-4en-PINACA could not be identified.

Though relevant information is lacking, the involvement of other, non-cannabinoid toxicological targets or unexpected drug-drug interactions in the overall pharmacotoxicological effects of MDMB-4en-PINACA cannot be excluded.

There is no known antidote to poisoning caused by synthetic cannabinoids. Treatment in poisoning cases should be symptomatic.

4.7 Abuse liability and dependence producing potential

Unpublished work involving drug discrimination studies (Wiley and Marusich; RTI International (North Carolina, USA)) presented in the Critical Review report on MDMB-4en-PINACA published by WHO described 'that intraperitoneal MDMB-4en-PINACA substituted for Δ⁹-tetrahydrocannabinol (THC) in male (n = 8) and female (n = 2) C57/Bl6 mice trained to discriminate 5.6 mg/kg THC (intraperitoneal) from vehicle in a two nose-poke drug discrimination procedure. Substitution was dose-dependent, with maximal substitution (97% THC-aperture responding) occurring at 0.1 mg/kg and was not accompanied by effects on response rates. The ED₅₀ for THC-like discriminative stimulus effects for MDMB-4en-PINACA was 0.071 μmol/kg (WHO, 2020a). These findings are consistent with other

synthetic cannabinoids that have shown THC-like discriminative stimulus effects in mice (Wiley et al., 2018).

Further information on the abuse liability and dependence producing potential of MDMB-4en-PINACA could not be identified. It has been suggested that consumption of synthetic cannabinoids can produce tolerance and withdrawal-like symptoms when regular use is discontinued. These include: anxiety, unstable mood, crying fits, feeling of inner emptiness, spatial disorientation, hyperacusis (increased sensitivity to ordinary environmental sounds), somatic pain, shortness of breath, hyperventilation, intense sweating and sensations of motor and inner restlessness.

Anecdotal reports from people who used a substance they believed to be MDMB-4en-PINACA suggest that tolerance develops quickly when vaped (Reddit, 2020). Given what is currently known about the pharmacology of synthetic cannabinoids in general, including the closely related 5F-MDMB-PINACA (⁴) (and some similarities to THC), it is reasonable to consider that the substance may have both a potential for abuse and dependence (EMCDDA, 2018). The THC-like discriminative stimulus effects of MDMB-4en-PINACA together with high potency binding to and activation of CB₁ receptors (Section 4.2.1) are in alignment with anecdotal reports on the psychoactive effects of MDMB-4en-PINACA (Reddit, 2020), which supports the hypothesis that MDMB-4en-PINACA shows abuse liability similar to other synthetic cannabinoids under international and European control.

5. Extent and patterns of use, availability, and potential for diffusion

5.1 Summary

There is limited information on the extent and patterns of use, availability, and potential for diffusion of MDMB-4en-PINACA in Europe.

MDMB-4en-PINACA has been available on the drug market in Europe since at least 2017. As of November 2020, MDMB-4en-PINACA has been identified in twenty-one Member States as well as Norway and Turkey; 770 seizures have been reported, which include approximately 47 kg of powder and 4.7 kg of smoking mixtures. Although MDMB-4en-PINACA was first identified on the drug market in 2017, it was only in 2019 that a large number of first identifications in Member States occurred. In addition, in 2020 there was a large increase in the quantity of MDMB-4en-PINACA seized by customs, with approximately 99% of the total amount of powder seized by customs (44 kg) having occurred during the year.

The available information suggests that MDMB-4en-PINACA is manufactured by chemical companies based in China. It is imported into Europe as bulk powders and then sold and distributed in wholesale and retail amounts within Europe either as a powder for processing into products or finished consumers products. There are three main types of products containing MDMB-4en-PINACA that are available on the drug market:

- smoking mixtures, where MDMB-4en-PINACA is mixed with plant material or tobacco that

is then smoked or inhaled from a vaporiser (similar to herbal cannabis, the mixture is usually prepared for smoking as a hand-rolled cigarette ('joint'));

- e-liquids, where a solution of MDMB-4en-PINACA is prepared by mixing it with a solvent, which is then inhaled using an e-cigarette;
- paper impregnated with MDMB-4en-PINACA, which can then be smoked or vaped. This is a commonly used approach to smuggle synthetic cannabinoids into prison in some countries.

To a lesser extent, users may prepare similar formulations on their own using MDMB-4en-PINACA purchased from a vendor or dealer.

Although MDMB-4en-PINACA may be deliberately sought after by some users, in most cases, such as those that purchase it at street-level and/or in prison, they are likely to be unaware that they are using the substance which presents an inherent risk to the individuals.

Detections of MDMB-4en-PINACA may be undetected, since the substance may not be routinely screened for in forensic and toxicology laboratories. Therefore, the presence of MDMB-4en-PINACA on the European drug market may be undetected in some areas, including in law enforcement seizures as well as in biological samples related to serious adverse events. It is also important to note that, because of differences in reporting practices across Europe, identifications of MDMB-4en-PINACA may be unreported to the Reitox national focal points and as a consequence to the EMCDDA.

It is also important to note that, in some settings, the ongoing COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (ECDC, 2020; EMCDDA, 2020d; WHO, 2020b) may have reduced the capacity of early warning systems, including forensic science and toxicology laboratories, to detect and report events involving MDMB-4en-PINACA.

The effect of the ongoing COVID-19 pandemic (ECDC, 2020; EMCDDA, 2020d; WHO, 2020b) on the manufacture, trafficking, distribution, and use of MDMB-4en-PINACA is currently unknown. However, seizures of bulk powders by European national customs agencies during the pandemic suggests that it continues to be imported into and distributed within Europe. It is conceivable that should there be a reduced availability of cannabis and other synthetic cannabinoids in Europe, criminal groups as well as people who use drugs, may use a range of replacement substances, including MDMB-4en-PINACA.

5.2 Information from seizures

In total, 770 seizures of MDMB-4en-PINACA, which include approximately 47 kg of powder and 4.7 kg of smoking mixtures, were reported to the EMCDDA by 21 Member States and Norway, as follows: the United Kingdom (380 seizures), Hungary (223), Germany (40), France (35), Sweden (20), Belgium (12), Poland (11), Bulgaria (10), Latvia (7), Lithuania (7), Slovakia (5), Slovenia (5), Spain (3), Austria (2), Cyprus (2), Romania (2), Croatia (1),

Greece (1), the Netherlands (1), Portugal (1), Italy (1) and Norway (1). In addition, Turkey reported 663 additional cases that may contain duplicates and have not been included in the count.

The majority of the seizures comprise police cases (732), with 109 (15%) of the seizures taking place in prisons and other custodial settings. There were 38 customs cases reported.

Seizures included smoking mixtures, powders, liquids, and papers impregnated with the substance (including blotters). Some reports did not specify physical forms. A summary is provided below.

5.2.1 Customs seizures

A total of 38 customs seizures of MDMB-4en-PINACA were reported by France (13), Belgium (12), Poland (4), Germany (3), Sweden (2), Bulgaria (1), Lithuania (1), the Netherlands (1), and Norway (1). When reported, the seizures occurred between May 2019 and September 2020. In the majority of cases (36) no other substances were reported in the seizures.

In customs seizures, MDMB-4en-PINACA was detected in powders, and smoking mixtures. A summary is provided below.

Powders

In total, 22 customs seizures, amounting to 44.5 kg were in powder form. Overall, most of powders were seized in 2020 (44.36 kg; 99.7%), while only 115 grams were seized in 2019.

In total, Belgium reported 11 seizures of MDMB-4en-PINACA amounting to 44.3 kg of powder. These included two single seizures amounting to 16 kg each. All the seizures reported by Belgium originated in China and the destinations were reported as: Turkey (for each of the 16 kg seizures); the United Kingdom (for 3 seizures amounting to 7.2 kg); Israel (2, 2.7 kg); Reunion (France) (1, 500 grams); Netherlands (1, 1.5 kg); Belgium (1, 300 grams); and Romania (1, 100 grams). No other substances were reported as identified in any of the seizures.

Lithuania reported a shipment originating from Spain of MDMB-4en-PINACA in a package labelled '5CL'.

Smoking mixtures

Four seizures of smoking mixtures were reported, amounting to 287 g, In 2 of them 5F-MDMB-PICA was also detected.

Other

For 12 seizures no physical form was specified and/or known. These amounted to approximately 2.6 kg.

5.2.2 Police seizures

A total of 732 seizures made by police were reported by 19 Member States, as follows: the United Kingdom (380 seizures), Hungary (223), Germany (37), France (22), Sweden (18), Bulgaria (9), Latvia (7), Poland (7), Lithuania (6), Slovakia (5), Slovenia (5), Spain (3), Austria (2), Cyprus (2), Romania (2), Croatia (1), Greece (1), Portugal (1), and Italy (1).

Seizures occurred between 2017 and September 2020. Where known, seizures occurred in 2017 (1), 2018 (14), 2019 (325), and 2020 (390). The police seizures amounted to approximately 16 kg. In terms of quantity, material containing MDMB-4en-PINACA was seized mainly in 2020 (9.7 kg) and 2019 (6.2 kg).

Out of the 732 police seizures, 109 seizures occurred in prisons, including correction houses and were reported by: the United Kingdom (98), Slovenia (5), Lithuania (3), Cyprus (1), France (1) and Germany (1). The seizures occurred between June 2019 and August 2020. In 100 cases, the seizures were in blotter form, including all cases reported by the United Kingdom, and amounted to 135 blotters. In 5 seizures, reported by Slovenia, MDMB-4en-PINACA was detected in herbal material amounting to 11.51 grams. Other synthetic cannabinoids were detected in 11 of the seizures; these included: 5F-MDMB-PICA (9), 4F-MDMB-BICA (4), 4F-MDMB-BINACA (3), and others. In the case reported by Cyprus, 14 impregnated sheets of A4 sized paper which had been concealed inside a television were seized in a delivery of a package to a prison.

The remaining 623 seizures reported by the police were detected in smoking mixtures, powders, blotters, and liquids. A summary is provided below (excluding seizures made in prison).

Smoking mixtures

A total of 301 seizures of smoking mixtures amounting to 4.5 kg were reported by: Hungary (194), the United Kingdom (49), Germany (32), Latvia (7), Sweden (7), Slovakia (5), Poland (3), Lithuania (2), Greece (1), and Croatia (1). Seizures occurred between 2017 and September 2020.

In 67 cases, other synthetic cannabinoids were detected: mainly 5F-MDMB-PICA (39), 4F-MDMB-BICA (11), and 4F-MDMB-BINACA (11). In 3 cases reported by the United Kingdom, cannabis and THC were detected. In 4 cases reported by the United Kingdom, nicotine was detected.

Most of the seizures (260) were under 10 grams, but seizures ranged from 0.03 grams to 842 grams. Germany reported MDMB-4en-PINACA in branded 'legal-high' type products: 'Pico Bello Extra Strong' (seized in 2017, containing 5-ADB and 5-ADB-PINACA), 'Pico Bello Made In Holland' (3 seizures, containing also 5F-MDMB-PICA). Mixtures were also found in joints, in small non-branded grip-seal clear bags and inside paper wrappers.

Powders

In total, 46 seizures of powder amounting to 2.6 kg were reported by: Hungary (17), Sweden (11), the United Kingdom (5), Germany (3), Spain (3), Poland (2), Cyprus (1), Lithuania (1), Portugal (1), Romania (1), and Italy (1). Most of the seizures (29) were under 10 g, but seizures ranged from 0.01 grams to approximately 1 kg.

Only three seizures were reported to contain other substances: dimethyl sulfone (1) ⁽²⁷⁾; 4F-MDMB-BINACA (1), and 5F-MDMB-2201 (1). In a seizure reported by Italy, MDMB-4en-PINACA was labelled incorrectly as 5F-MDMB-2201.

Impregnated papers, including blotters

A total of 42 seizures amounting to 150 blotters were reported by 3 Member States: the United Kingdom (30), Hungary (11), and Germany (1). In 11 cases, other synthetic cannabinoids were also detected, 5F-MDMB-PICA (9 cases), 4F-MDMB-BINACA (2) and AMB-FUBINACA (1).

Liquids

In total, 15 seizures of liquid amounting to 39 ml were reported by 3 Member States: France (11), the United Kingdom (3) and Hungary (1). Of these, in 11 seizures other psychoactive substances were detected including mainly synthetic cannabinoids. The liquids were found in most cases in vials, as e-liquids for vaping (10 cases), and in one case in an e-cigarette with a half empty cartridge.

Other

For 219 seizures amounting to close to 8.8 kg the physical form was not specified, reported as 'other' or unknown. These included 5 single seizures amounting to close to 1 kg each, reported by the United Kingdom, which occurred in February 2020.

5.3 Information from collected samples

A total of 15 collected samples were reported by 6 Member States: France (5 samples), Poland (3), Germany (2), the Netherlands (2), Slovenia (2), and Belgium (1). Of these, 7 samples were in powder form, 4 samples were in liquid form, 1 sample was a smoking mixture, 1 sample was reported as 'resin', and for the remaining 2 samples the form was reported as 'other'.

Powders were collected as beige or yellow solids. In one case reported by Slovenia MDMB-4en-PINACA was purchased from an internet website as '5-CL-ADB-A' for the price of 21 dollars per gram.

⁽²⁷⁾ Dimethyl sulfone or methylsulfonylmethane (MSM) is a crystalline solid occasionally used in dietary supplements or as a cutting agent in illicit psychostimulants. It also occurs in nature.

All the cases where MDMB-4en-PINACA was detected in liquid form were recovered from poisoning cases. They were reported by France (3) and Belgium (1),.

The 3 liquid samples reported by France were collected between September 2019 and January 2020 and were collected from young patients which were taken ill with acute non-fatal poisonings.

- In one case, the sample was sold under the street name 'PTC' (from the French, 'pète ton crâne') and was associated to the poisonings with probable exposure to MDMB-4en-PINACA of two males, aged 16.
- In another case, a commercially available bottle of a common (legal) e-liquid ('Born to DYI') was re-filled with a liquid containing MDMB-4en-PINACA and 4F-MDMB-BINACA. The substance was distributed among a network of 6th form students.
- In the remaining case, a liquid containing MDMB-4en-PINACA and 4F-MDMB-BINACA was collected from a 17-year-old patient who had taken it with a younger friend.

The sample reported by Belgium was in an e-liquid for vaping found on a poisoned patient. Along with MDMB-4en-PINACA, the sample contained five other cannabinoids and benzylone (28). The case occurred in July 2020.

The Netherlands reported one herbal cannabis and one cannabis resin sample that were submitted for analysis at one of the drug checking services after users experienced strong negative side effects. Samples were purchased from street dealers in October 2020. Both samples contained MDMB-4en-PINACA together with THC.

Two additional samples reported by France, which also contained 5F-MDMB-PICA, were collected in the overseas department and region of Mayotte and sold as 'Chimique'.

5.4 Information from biological samples

Serious adverse events with confirmed exposure to MDMB-4en-PINACA from biological samples are discussed in sections 6.2.1. and 6.2.2.

Sixty-four detections of MDMB-4en-PINACA in biological samples were reported by Turkey (36) and Hungary (28) ⁽²⁹⁾. Detections included (EMCDDA 2020b):

- 3 samples associated with non-fatal intoxications, reported by Hungary;
- 4 cases of persons suspected of driving under the influence of drugs (including two traffic

⁽²⁸⁾ Benzylone, or BMDP, is a cathinone derivative. IUPAC name: 1-(2*H*-1,3-benzodioxol-5-yl)-2-(benzylamino)propan-1-one.

⁽²⁹⁾ In addition, Turkey reported 101 samples associated with non-fatal intoxications which may contain duplicates and therefore have not been included in the total count.

accidents), reported by Hungary;

- 11 cases of drug consumption, reported by Hungary;
- 10 cases of drug dependence, reported by Hungary (in all of the cases other substances were detected);
- 36 samples taken by the law enforcement agencies, reported by Turkey.

In addition to information from biological samples reported by the Member States, the following information was identified from Germany, Turkey, and the United States.

Germany

As shown in Table 3, the number of identifications of MDMB-4en-PINACA in authentic urine samples at the Institute of Forensic Medicine, Medical Centre, University of Freiburg, Germany, increased in the period between the third quarter of 2019 and third quarter of 2020. These detections predominantly reflected results from routine screenings involving abstinence control cases within correctional and psychiatric facilities but not poisonings.

Table 3. Detections of MDMB-4en-PINACA in authentic urine samples at the Institute of Forensic Medicine, Medical Centre, University of Freiburg, Germany ^a					
	Q3 2019	Q4 2019	Q1 2020	Q2 2020	Q3 2020
Number of samples	1720	1027	1062	873	1123
Number of samples positive for synthetic cannabinoids	227 (13%)	239 (23%)	235 (22%)	198 (23%)	268 (24%)
Number of samples positive for MDMB-4en-PINACA	8 (3.5%)	26 (11%)	20 (9%)	76 (38%)	179 (67%)
^a Courtesy of Prof. Volker Auwärter					

Turkey

Between April and August 2019, researchers in Turkey confirmed the detection of 56 MDMB-4en-PINACA-positive out of 2150 urine samples although case details were not included. The authors stated that 'the number of MDMB-4en-PINACA-positive cases increased significantly compared to other months' (Yeter and Yeter, 2020).

United States

In the United States of America, MDMB-4en-PINACA was stated to have been identified in

at least 51 toxicology specimens ⁽³⁰⁾ associated with post-mortem death investigations (34), driving under the influence of drugs investigations, and clinical investigations. Details about the cases and the proportion of positive findings out of the total number of drug tests were not reported (Krotulski et al. 2020b). Whether these cases included the detections reported in Section 6 (Krotulski et al. 2020a) was not stated.

6. Health risks

6.1 Summary

Data from studies in animals or humans featuring the acute and chronic health effects of MDMB-4en-PINACA use could not be identified. However, it appears likely that the clinical features of poisonings caused by MDMB-4en-PINACA will be similar to those reported from other synthetic cannabinoid receptor agonist NPS resulting in gastrointestinal, neurological, cardiovascular, renal clinical features. These effects appear to be much more pronounced and severe when compared to cannabis. Similar to other synthetic cannabinoids, the use of MDMB-4en-PINACA with other drugs, especially central nervous system depressants (such as alcohol, opioids, and sedative/hypnotics) is likely to increase the risk of life-threatening poisoning.

A total of eleven acute non-fatal poisonings with confirmed exposure to MDMB-4en-PINACA have been reported to the EMCDDA by one Member State, the United Kingdom. Exposure to other substances was reported in most cases, including other synthetic cannabinoids. At least some of the clinical features of the poisonings were consistent with exposure to synthetic cannabinoids. In ten of the cases, the poisoning was reported to be life-threatening and required hospitalisation of the patient.

A total of twelve deaths with confirmed exposure to MDMB-4en-PINACA have been reported to the EMCDDA by three Member States, Hungary (8 cases), the United Kingdom (3 cases), and Sweden (1 case). In some of the cases, MDMB-4en-PINACA was reported to be the cause of death or to have contributed to the death.

In the United States of America, analyses of 16 post-mortem blood samples identified MDMB-4en-PINACA (and/or its ester hydrolysis metabolite ⁽¹³⁾) as the only synthetic cannabinoid in five cases with ethanol being also detected in two cases. The authors stated that the results from toxicology testing paired with case history showed the potential for MDMB-4en-PINACA to cause or contribute to impairment or death.

There is no information on the chronic health effects of MDMB-4en-PINACA, including abuse liability and dependence production potential. The chronic health risks might share some similarities to those seen with other synthetic cannabinoids. This may include dependence.

⁽³⁰⁾ As of October 2020.

6.2 Acute health effects

Specific information about MDMB-4en-PINACA could not be identified. Based on the available information on the pharmacological properties of MDMB-4en-PINACA and other closely related synthetic cannabinoids such as 5F-MDMB-PINACA, adverse effects from overdosing MDMB-4en-PINACA might include gastrointestinal (e.g. nausea and vomiting (including hyperemesis)), neurological (e.g. hallucination, agitation, anxiety, paranoia, confusion, delusions, catatonia, lethargy, psychosis (including in susceptible individuals) and severe central nervous system depression (such as rapid loss of consciousness/coma)), cardiovascular (e.g. tachycardia, hypertension, acute myocardial infarction and sudden cardiac death) and renal (e.g. acute kidney failure) clinical features (Ford et al., 2017; Hermanns-Clausen et al., 2013; Ozturk et al., 2019; Pacher et al., 2018; Skryabin and Vinnikova, 2018; Tait et al., 2016). These effects appear to be much more pronounced and severe when compared to cannabis (Ford et al., 2017; Zaurova et al., 2016).

As discussed in section 2.6, due to the typically high potency of synthetic cannabinoids and inadvertent high dose users may be exposed to from products, it is difficult for users to control the dose that they are exposed to. This can lead them to unintentionally administer a toxic dose.

Some individuals may use MDMB-4en-PINACA in combination with other drugs (either intentionally or unintentionally) and are unlikely to be aware of the substance(s) being ingested and doses used (by whatever route). Similar to other synthetic cannabinoids, the use of MDMB-4en-PINACA with other drugs, especially central nervous system depressants (such as alcohol, opioids, and sedative/hypnotics) is likely to increase the risk of life-threatening poisoning.

Some of the features of poisoning — particularly loss of consciousness, respiratory depression, and behavioural effects — may place users at additional risks, such as choking on/aspirating vomit, drowning, falling, hypothermia as a result of falling unconscious outside in cold weather, and self-inflicted violence/injury (e.g. EMCDDA; 2017; Tait et al., 2016; Yeter, 2017).

6.2.1 Acute poisonings

Acute poisoning reported by the Member States

A total of 11 acute non-fatal poisonings with confirmed exposure to MDMB-4en-PINACA were reported by one Member State, the United Kingdom ⁽³¹⁾⁽³²⁾. The cases occurred between January and August 2020. Of the cases, nine were male and two were female. The males were aged between 19 and 60 (mean 36; median 32.5). The females were aged 31 and 35.

⁽³¹⁾ In addition, France reported two acute intoxications with probable exposure to MDMB-4en-PINACA. These cases are not discussed further in this report.

⁽³²⁾ In addition, Germany reported one intoxication involving MDMB-4en-PINACA. This case is not discussed further in this report.

All cases included clinical features of poisoning similar to those reported for other synthetic cannabinoids, such as confusion, tachycardia, respiratory insufficiency, reduced conscious level, seizures, abnormal sweating, agitation, aggression. However, in all cases other substances were also identified in the biological samples taken from the patients, including one or more other synthetic cannabinoids, which may account, at least in part, for the observed effects. Other substances identified in the patients, include:

- other synthetic cannabinoids: 4F-MDMB-BICA (5 cases), 5F-EMB-PICA (3 cases), 4F-MDMB-BINACA (3 cases), 5F-MDMB-PICA (2 cases), AB-FUBINACA (1 case);
- benzodiazepines: diazepam (8 cases), temazepam (5 cases), oxazepam (4 cases), flubromazolam (3 cases), etizolam (2 cases), flualprazolam (1 case), clonazolam (1 case), chlordiazepoxide (1 case);
- opioids: methadone (6 cases), morphine (4 cases), codeine (3 cases), alfentanil (1 case);
- other drugs: pregabalin (6 cases), THC (6 cases), cocaine/ benzoylecgonine (4 cases), ketamine (2 cases), methamphetamine (1 case).

In ten of the cases, the poisoning was considered life threatening and required hospitalisation of the patients.

Acute poisonings identified from other sources

In the United States of America, a summary involving the qualitative detection of MDMB-4en-PINACA and/or its ester hydrolysis metabolite⁽¹³⁾ was published with details summarised in Table 4 (Krotulski et al., 2020a). Eight cases from suspected clinical toxicology investigations revealed the detection of the MDMB-4en-PINACA ester hydrolysis metabolite in urine samples. No further information about the cases was reported and in seven of these cases other synthetic cannabinoid receptor agonist metabolites could be detected although it was unclear whether the suggested parent molecules could have also arisen from substances other than methyl esters (Table 4).

6.2.2 Deaths

Deaths reported by the Member States

A total of 12 deaths with confirmed exposure to MDMB-4en-PINACA were reported by three Member States: Hungary (8), the United Kingdom (3), and Sweden (1)⁽³³⁾. The cases occurred between January 2019 and August 2020. Of the deaths, ten were male and two were female. The males were aged between 20 and 41 (mean 28; median 27.5); the females were aged 31.

⁽³³⁾ In addition, Germany reported four deaths involving MDMB-4en-PINACA. These cases are not discussed further in this report.

In all cases other substances were identified, including:

- other synthetic cannabinoids: 4F-MDMB-BICA (8 cases); 5F-MDMB-PICA (4 cases); 'fluoro'-MDMB-PICA (1 case)
- benzodiazepines: clonazepam metabolite (1 case), midazolam metabolite(1 case), flualprazolam (1 case); diazepam (1 case); oxazepam (1 case); temazepam (1 case);
- opioids: morphine (1 case); codeine (1 case);
- other drugs and alcohol: THC (2 cases); alcohol (2 cases); ethylhexedrone (1 case); methylphenidate (1 case); ritalinic acid (1 case); alpha-PiHP (1 case); bupropion (1 case); cocaine (1 case); pregabalin (1 case).

Four of the cases were found dead, in one case the individual fell from a balcony. In some of the cases it was reported that the individuals collapsed and/or had seizure before the death. A cause of death was reported in all cases:

- in the cases reported by Hungary, the reported causes of death were: cardiac arrest due to substance overdose (4 cases), acute heart failure (3 cases), and asphyxiation following aspirating vomit (1 case);
- in the cases reported by the United Kingdom, the reported causes of death were: synthetic cannabinoid (MDMB-4en-PINACA) and alcohol toxicity (1 case), synthetic cannabinoid use (1 case) and mixed drug toxicity (1 case);
- in the case reported by Sweden, the cause of death was trauma from a fall where the contribution from drugs present could not be determined.

Deaths identified from other sources

United Kingdom

A case report published in the medical literature from the United Kingdom involved the death of a 40-year old female known to use drugs, including synthetic cannabinoid products ('Mamba') who was found dead. Analysis of biological samples from the decedent identified (unpreserved blood) of methadone (711 ng/mL), methadone metabolite (EDDP, (67 ng/mL), pregabalin (7.9 mg/L), mirtazapine (3229 ng/mL), 4F-MDMB-BINACA (⁷) metabolites, along with MDMB-4en-PINACA and metabolites. The cause of death was ruled mixed drug toxicity (Rice et al., 2020).

United States of America

The detection of MDMB-4en-PINACA in two blood samples obtained from post-mortem cases (no details available) has been reported (Krotulski et al., 2019). A follow-up summary involving the detection of MDMB-4en-PINACA and/or its ester hydrolysis metabolite (¹³) has

been published (Krotulski et al., 2020a). The results from the analysis of 25 biofluid samples (16 x post-mortem, 8 x clinical, 1 x DUID⁽³⁴⁾) are summarised in Table 4 which shows that 16 out of 25 forensic were post-mortem investigations (Table 4). The average age was 36 years (SD 11 years; range 21–57 years). Twelve individuals were female, seven were male, and the gender was not reported in six cases.

In four post-mortem samples, MDMB-4en-PINACA (or its ester hydrolysis metabolite⁽¹³⁾) was the only synthetic cannabinoid receptor agonist/metabolite detected. One case involved a death in custody where the manner of death was ruled accidental (no details reported); the only additional finding was caffeine. One case states a history of lupus with a history of heavy ethanol and ‘Kush’ use; the individual was found unresponsive after drinking ethanol (ethanol concentration not reported). In the third case, no other information was reported.

In two additional cases, ethanol was also detected in femoral blood samples together with the MDMB-4en-PINACA ester hydrolysis metabolite. In one case, the person was found in a jail cell with a bottle of green liquid (caffeine and phenytoin also detected) whereas the other involved the use of a suspected synthetic cannabinoid receptor agonist-containing product, as well as ‘an illicit substance’ prior to death; ethanol was stated as the only toxicological finding. In the remaining 11 post-mortem samples, either MDMB-4en-PINACA (and/or its ester hydrolysis metabolite) was detected with other controlled substances (e.g. amphetamine, methamphetamine, and fentanyl) or it was detected in conjunction with other synthetic cannabinoids and/or metabolites and controlled substances (Table 4). The authors stated that the results from toxicology testing paired with case history showed the potential for MDMB-4en-PINACA to cause or contribute to impairment or death (Krotulski et al., 2020a).

Table 4. Cases involving detections of MDMB-4en-PINACA and other substances (modified from Krotulski et al. (2020a))

Date Received	Case Type	Age	Sex	US State	Matrix	Toxicology Results	Case History
21 May 2019	Clinical	50	F	UT	Urine	MDMB-4en-PINACA 3,3-dimethylbutanoic acid, 4F-MDMB-BINACA 3,3-dimethylbutanoic acid, MMB-FUBINACA 3-methylbutanoic acid, 5F-MDMB-PINACA 3,3-dimethylbutanoic acid	N/A
24 May	Clinical	50	F	UT	Urine	MDMB-4en-PINACA 3,3-	N/A

⁽³⁴⁾ DUID: driving under the influence of drugs

2019	al					dimethylbutanoic acid	
23 July 2019	PM	45	M	IN	Peripheral Blood	MDMB-4en-PINACA, caffeine	Death in custody; manner of death: accidental
07 Aug 2019	PM	31	F	IN	Blood	MDMB-4en-PINACA, 5F-MDMB-PICA, BZE (<100 ng/mL), caffeine, cotinine	Pedestrian in motor vehicle accident
27 Aug 2019	PM	46	F	TX	Heart Blood	MDMB-4en-PINACA	History of lupus; history of heavy ethanol and 'Kush' use; found unresponsive after drinking ethanol
17 Sep 2019	PM	42	F	OH	Blood	MDMB-4en-PINACA, 5F-MDMB-PICA	Undetermined death
28 Sep 2019	Clinical	23	F	UT	Urine	MDMB-4en-PINACA 3,3-dimethylbutanoic acid, 5F-MDMB-PICA 3,3-dimethylbutanoic acid	N/A
04 Oct 2019	Clinical	36	F	UT	Urine	MDMB-4en-PINACA 3,3-dimethylbutanoic acid, 4F-MDMB-BINACA 3,3-dimethylbutanoic acid, 5F-MDMB-PICA 3,3-dimethylbutanoic acid	N/A
05 Oct 2019	Clinical	30	F	UT	Urine	MDMB-4en-PINACA 3,3-dimethylbutanoic acid, 4F-MDMB-BINACA 3,3-dimethylbutanoic acid, 5F-MDMB-PICA 3,3-dimethylbutanoic acid	N/A
12 Oct 2019	Clinical	21	F	MI	Urine	MDMB-4en-PINACA 3,3-dimethylbutanoic acid, 5F-MDMB-PICA 3,3-dimethylbutanoic acid	N/A

12 Oct 2019	Clinical	21	M	MI	Urine	MDMB-4en-PINACA 3,3-dimethylbutanoic acid	N/A
17 Oct 2019	Clinical	24	M	UT	Urine	MDMB-4en-PINACA 3,3-dimethylbutanoic acid, 4F-MDMB-BINACA 3,3-dimethylbutanoic acid, 5F-MDMB-PICA 3,3-dimethylbutanoic acid	N/A
17 Oct 2019	PM	44	M	TX	Femoral Blood	MDMB-4en-PINACA 3,3-dimethylbutanoic acid, ethanol (50 mg/dL), caffeine, phenytoin	Found in jail cell with a bottle of green liquid
08 Nov 2019	PM	31	M	AR	Cardiac Blood	MDMB-4en-PINACA, MDMB-4en-PINACA 3,3-dimethylbutanoic acid, ethanol (48 mg/dL), methamphetamine (630 ng/mL), amphetamine (83 ng/mL), nicotine	Suspected drug overdose; history of synthetic drug use
13 Nov 2019	PM	43	M	WI	Iliac Blood	MDMB-4en-PINACA, MDMB-4en-PINACA 3,3-dimethylbutanoic acid, THC (2.3 ng/mL), fentanyl (48 ng/mL), nicotine	Found unresponsive at residence; undetermined death
03 Dec 2019	PM	N/A	N/A	FL	Heart Blood	MDMB-4en-PINACA, MDMB-4en-PINACA 3,3-dimethylbutanoic acid, 4F-MDMB-BINACA, 5F-MDMB-PICA	N/A
10 Dec 2019	PM	32	F	TX	Heart Blood	MDMB-4en-PINACA, 4F-MDMB-BINACA, 5F-MDMB-PICA	Homeless individual; history of 'Kush' use
08 Jan 2020	PM	57	M	CO	Femoral Blood	MDMB-4en-PINACA 3,3-dimethylbutanoic acid, ethanol (84 mg/dL)	Possible illicit drug abuse; possible 'Black Mamba' use

08 Jan 2020	DUID	N/A	N/A	TX	Blood	MDMB-4en-PINACA, MDMB-4en-PINACA 3,3-dimethylbutanoic acid, 4F-MDMB-BINACA, 5F-MDMB-PICA, 5-OH-MDMB-PICA, 5F-MDMB-PICA 3,3-dimethylbutanoic acid	Driving while intoxicated; suspected synthetic cannabinoid use
08 Jan 2020	PM	N/A	N/A	PA	Femoral Blood	MDMB-4en-PINACA, 4F-MDMB-BINACA	N/A
10 Jan 2020	PM	27	M	LA	Blood	MDMB-4en-PINACA, 4F-MDMB-BINACA, 4OH-MDMB-BINACA, 5F-MDMB-PICA, 5-OH-MDMB-PICA, cotinine	Suspected drug overdose; possible 'Mojo' use; history of diabetes
15 Jan 2020	PM	N/A	N/A	AL	Femoral Blood	MDMB-4en-PINACA, 4F-MDMB-BINACA, 4-OH-MDMB-BINACA	N/A
15 Jan 2020	PM	N/A	N/A	AL	Femoral Blood	MDMB-4en-PINACA, MMB-FUBINACA 3-methylbutanoic acid	N/A
17 Jan 2020	PM	N/A	N/A	DC	Heart Blood	MDMB-4en-PINACA	N/A
20 Jan 2020	PM	33	F	IN	Blood	MDMB-4en-PINACA, 4F-MDMB-BINACA, fentanyl (11 ng/mL), xylazine (6.1 ng/mL), diazepam (29 ng/mL), morphine (53 ng/mL), naloxone, cotinine	N/A

PM: post-mortem; DUID: driving under the influence of drugs; N/A: not available; F: female; M: male; BZE: benzoylecgonine; THC: Δ^9 -THC; (-)-*trans*- Δ^9 -tetrahydrocannabinol; 4F-MDMB-BINACA: methyl (2-{{1-(4-fluorobutyl)-1*H*-indazole-3-carbonyl}amino}-3,3-dimethylbutanoate; MMB-FUBINACA (AMB-FUBINACA, FUB-AMB): methyl 2-{{1-[(4-fluorophenyl)methyl]-1*H*-indazole-3-carbonyl}amino)-3-methylbutanoate; 5F-MDMB-PINACA (5F-ADB): methyl 2-{{1-(5-fluoropentyl)-1*H*-indazole-3-carbonyl}amino}-3,3-dimethylbutanoate; 5F-MDMB-PICA (5F-MDMB-2201): methyl 2-{{1-(5-fluoropentyl)-1*H*-indole-3-carbonyl}amino}-3,3-dimethylbutanoate

6.2.3 Driving and operating machinery under influence

Hungary reported 4 identifications of MDMB-4en-PINACA in biological samples reported as suspected driving under the influence of drugs (including two traffic accidents).

The results from the analysis of one blood sample taken from a person suspected to be driving while intoxicated in the United States of America identified MDMB-4en-PINACA and its ester hydrolysis metabolite but also other synthetic cannabinoids and metabolites (Table 4) (Krotulski et al., 2020a). Further details were not available.

Driving while under the influence of synthetic cannabinoids places people who use these substances and others at risk of injury (Capron, 2016; Kaneko, 2017; Karinen et al., 2015; Musshoff et al., 2014). The extent of impairment in cases involving motor vehicle accidents was considered severe for a range of different synthetic cannabinoids: examples from reports included: loss of consciousness, lane travel, causing collisions, erratic driving, speeding, poor coordination and focus, confusion, aggressiveness, slow response to questioning, incoherent speech, excited states such as agitation, shouting, and stereotyped behaviours (Capron, 2016; Kaneko, 2017). Similarly, the operation of machinery while under the influence of synthetic cannabinoids may place the people who use these substances and others at risk of injury.

6.3 Chronic health effects

Specific information about MDMB-4en-PINACA could not be identified. Similar to other synthetic cannabinoids, chronic use has been associated with greater risks for developing mental health disorder than cannabis (Cohen and Weinstein, 2018; Skryabin and Vinnikova, 2018), which may include dependence. Acute and chronic use of synthetic cannabinoids has also been associated with cases displaying detrimental cardiovascular health (Ozturk et al., 2019; Pacher et al., 2018).

7. Social risks

Whilst there is limited information for MDMB-4en-PINACA, the social risks might share some similarities with cannabis and other synthetic cannabinoids. Of particular note is that synthetic cannabinoids are increasingly used by vulnerable groups, such as prisoners and people experiencing homelessness. Reports suggest that this has caused new health and social problems as well as exacerbated existing ones for these groups. For example, in

prisons, alongside the adverse health effects, such as acute poisonings, the market in synthetic cannabinoids has been linked to an increase in bullying and debt, as well as aggression and violence. In some cases this has caused a serious threat to the overall safety and security of the prison environment (Blackman and Bradley, 2017; HMIP, 2015; Ralphs et al., 2017; User Voice, 2016). As such, it is a concern that MDMB-4en-PINACA has been seized in prisons and other custodial settings in at least 6 Member States and, that overall, approximately 15 % of all the seizures of MDMB-4en-PINACA made by police occurred in these settings.

7.1 Individual social risks

While there is no specific information on whether the use of MDMB-4en-PINACA causes individual social risks, any such risks may have some similarities with those associated with cannabis and other synthetic cannabinoids. These may impact on education or career, family or other personal and social relationships and may result in marginalisation.

7.2 Possible effects on direct social environment

While there is no specific information on the possible effects of MDMB-4en-PINACA on the direct social environment, the behavioural effects of synthetic cannabinoids include reports of aggressive and violent behaviour. This may place users and others at risk of injury.

7.3 Possible effects on society as a whole

While there is no specific information on the possible effects of MDMB-4en-PINACA on society as a whole, as noted, the behavioural effects of synthetic cannabinoids include reports of aggressive and violent behaviour. In particular, concern was expressed in this regard to use in certain environments such as prisons and psychiatric institutions.

In prisons, alongside the adverse health effects, the market in synthetic cannabinoids has been linked to an increase in aggression, violence, bullying, and debt. In some cases this has caused a serious threat to the overall safety and security of the prison environment.

Due to the lack of data, it is not possible at this time to estimate the social risk associated with the trafficking and distribution of MDMB-4en-PINACA.

7.4 Economic costs

There is no information on the health and social costs related to MDMB-4en-PINACA. As MDMB-4en-PINACA is a synthetic cannabinoid, any such costs may have some similarities with those associated with the use of cannabis and other synthetic cannabinoids.

7.5 Possible effects related to the cultural context, for example marginalisation

There is no information on the possible effects of MDMB-4en-PINACA related to the cultural context. As MDMB-4en-PINACA is a synthetic cannabinoid, any such effects may have some similarities with those associated with the use of cannabis and other synthetic

cannabinoids.

7.6 Possible appeal to specific population groups within the general population

There is limited information on the possible appeal to specific population groups. As MDMB-4en-PINACA is a synthetic cannabinoid, it could be expected that suppliers as well as users who are looking for 'legal' substitutes for cannabis and replacements for controlled synthetic cannabinoids, may be interested in MDMB-4en-PINACA. This may include individuals subject to drug testing (such as drivers, prisoners, those in drug treatment, and those subject to workplace drug testing), as commonly used drug tests may be unable to detect the compounds.

In addition, reports suggest that in some areas, high risk drug users and other vulnerable groups, such as prisoners and people experiencing homelessness, may specifically seek out synthetic cannabinoids as they are readily available and have gained a reputation for causing profound intoxication while being comparatively cheaper to other drugs. In addition, synthetic cannabinoids, particularly when impregnated on to paper, can be easy to smuggle into prison and other custodial settings. Investigations involving the analysis of impregnated papers and cards seized in three Scottish prisons suggested that MDMB-4en-PINACA (first identification in June 2019) is currently the most prevalent synthetic cannabinoid receptor agonist MDMB-4en-PINACA (McKenzie, 2020).

Although limited, there is some information to suggest a recent increase in vaping of synthetic cannabinoids using electronic cigarettes by young people, including teenagers, in some Member States; in some cases, the users believe that they were using cannabidiol (CBD) or THC.

Similar to other new psychoactive substances, it also appears that there is interest in MDMB-4en-PINACA by people who experiment with a range of substances (so-called psychonauts).

7.7 Involvement of criminal groups in the manufacture, distribution and distribution methods, and trafficking

There is no information whether or not criminal groups are involved in the manufacture, trafficking, and distribution of MDMB-4en-PINACA within Europe (EMCDDA, 2020b). The effect of the ongoing COVID-19 pandemic (ECDC, 2020; EMCDDA, 2020d; WHO, 2020b) on the manufacture, trafficking, distribution, and use of MDMB-4en-PINACA is currently unknown. However, seizures of bulk powders by European national customs agencies during the pandemic suggests that it continues to be imported into and distributed within Europe. It is possible, that in case of a reduced availability of cannabis and other synthetic cannabinoids in Europe, criminal groups, as well as drug users, may use a range of replacement substances, including MDMB-4en-PINACA.

8. Other relevant information

8.1 Information on restrictive measures

8.1.1 International restrictive measures

At international level, MDMB-4en-PINACA is not controlled under the United Nations Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol, or the Convention on Psychotropic Substances of 1971 ('United Nations system') (UNODC, 2020a; UNODC,2020b). MDMB-4en-PINACA was assessed at the 43rd meeting of the WHO Expert Committee on Drug Dependence (ECDD) that was held on 12–16 October 2020 (WHO, 2020a).

8.1.2 National restrictive measures

Thirteen Member States (Bulgaria, Czechia, Denmark, Estonia, Greece, Ireland, Malta, the Netherlands, Portugal, Romania, Slovakia, Slovenia, and Spain) reported that MDMB-4en-PINACA is not subject to restrictive measures at national level (EMCDDA, 2020b).

MDMB-4en-PINACA is subject to restrictive measures in fifteen Member States:

- in Croatia, Cyprus, Finland, France, Italy, Latvia, Luxembourg, Poland, Sweden, and the United Kingdom the substance is controlled under drug control legislation;
- in Lithuania it is controlled under medicines legislation;
- in Austria, Belgium, Germany, and Hungary it is controlled by new psychoactive substance legislation.

In addition, MDMB-4en-PINACA is controlled under medicines legislation in Norway and under drug control legislation in Turkey (EMCDDA, 2020b).

It is unknown if MDMB-4en-PINACA is controlled in China, where at least some of the substance on the European market has been sourced from.

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