ADVANCED RELEASE

EMCDDA technical report on the new psychoactive substance methyl 2-{[1-(4-fluorobutyl)-1*H*-indole-3-carbonyl]amino}-3,3-dimethylbutanoate (4F-MDMB-BICA)

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 2-{[1-(4-fluorobutyl)-1*H*-indole-3-carbonyl]amino}-3,3-dimethylbutanoate (4F-MDMB-BICA), a synthetic receptor cannabinoid agonist 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).

Parts of this report were prepared under an EMCDDA contract (ref. CT.20.SAS.0108.1.0).

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 4F-MDMB-BICA.

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 '4F-MDMB-BICA', 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%20Note%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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- the European Medicines Agency (EMA), the European Chemicals Agency (ECHA), the European Centre for Disease Prevention and Control (ECDC), the European Food Safety Authority (EFSA), and the European Commission;
- Public Health Agency of Sweden (PHA) and National Board of Forensic Medicine (NBFM), Sweden;
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- Prof. Volker Auwärter, University of Freiburg, Germany;
- Dr István Ujváry, iKem BT, Budapest, Hungary.

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1. Summary

Synthetic cannabinoid receptor agonists (synthetic cannabinoids), such as 4F-MDMB-BICA, 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 (CB_1 receptor) (Huestis et al., 2001; Pertwee, 2005a). This receptor is part of a signalling system in the body called the endocannabinoid system, which helps regulate, among other things, behaviour, mood, pain, appetite, sleep, and the immune system (Pertwee, 2015) ([2]). Because synthetic cannabinoids activate the CB_1 receptor, 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 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 cannabinoids, have appeared

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

([2]) The endocannabinoid system helps regulate a large number functions in the body. It consists of the cannabinoid CB_1 and CB_2 receptors, the endocannabinoids (such as anandamide) which act as endogenous agonists for these receptors, and the processes responsible for endocannabinoid biosynthesis, cellular uptake, and metabolism. Important exogenous agonists for the cannabinoid receptors are (–)-*trans*-Δ^9-tetrahydrocannabinol (THC) which is the major active substance in cannabis, and the synthetic cannabinoids found in 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.

on the drug market.

In Europe, 4F-MDMB-BICA 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, 2020a). The substance has been available on the drug market in Europe since at least March 2020. As 4F-MDMB-BICA has only recently emerged on the drug market, there is limited information on the substance. Formal epidemiological studies have not been conducted, which limits understanding of the use and patterns of use of 4F-MDMB-BICA. In addition, it is important to note that the presence of 4F-MDMB-BICA on the market and as the cause of 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 on-going COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (ECDC, 2020; EMCDDA, 2020e; WHO, 2020b) may have reduced the capacity of early warning systems, including forensic and toxicology laboratories, to detect and report events involving 4F-MDMB-BICA.

As of November 2020, 4F-MDMB-BICA has been identified in twelve Member States; 111 seizures have been reported, which include 5.6 kg of powder and 0.6 kg of smoking mixtures. Of particular note are four large scale seizures of 4F-MDMB-BICA powder reported by Belgian customs amounting to approximately 5.5 kg and eleven seizures that occurred in prisons in five Member States. The most recent identifications of 4F-MDMB-BICA reported to the EMCDDA are from seizures made by police in Cyprus and customs in Finland in September 2020.

Although 4F-MDMB-BICA has not been formally studied in humans, limited information suggests that 4F-MDMB-BICA is a potent CB_1 receptor agonist and, as such, shares some pharmacological similarities with Δ^9-tetrahydrocannabinol (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. Cases of sudden death have 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 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 on-going COVID-19 pandemic and the additional burden already on healthcare systems.

There is no information on the chronic health effects of 4F-MDMB-BICA. The chronic health risks might share some similarities to those seen with cannabis and other synthetic

cannabinoids; this may include dependence.

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

A total of twenty-one deaths with confirmed exposure to 4F-MDMB-BICA have been reported to the EMCCDA by one Member State, Hungary. The deaths occurred over relatively short period of time, between May and August 2020. In all cases other substances were identified, including other synthetic cannabinoids.

The available information suggests that 4F-MDMB-BICA 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 consumer products. There are three main types of products containing 4F-MDMB-BICA that are available on the drug market: smoking mixtures, where 4F-MDMB-BICA is mixed with herbal plant material or tobacco that is then smoked (similar to herbal cannabis, the mixture is usually prepared for smoking as a hand-rolled cigarette ('joint')) or inhaled using a vaporiser; e-liquids, where a solution of 4F-MDMB-BICA is prepared by mixing it with a solvent, which is then inhaled ('vaped') using an e-cigarette; in addition, 4F-MDMB-BICA is also impregnated on to paper which can then be smoked or vaped. The latter is a commonly used approach to smuggle synthetic cannabinoids into prison in some countries. To a lesser extent, people who are using these substances may also prepare their own products using powdered 4F-MDMB-BICA purchased from a vendor or dealer.

The available information suggests that 4F-MDMB-BICA 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 4F-MDMB-BICA within Europe (EMCDDA, 2020b). The effect of the on-going COVID-19 pandemic (ECDC, 2020; EMCDDA, 2020e; WHO, 2020b) on the manufacture, trafficking, distribution, and use of 4F-MDMB-BICA 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 4F-MDMB-BICA.

There is no information on the social harms that may be caused by 4F-MDMB-BICA. 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. This is a concern given the reports of seizures of 4F-MDMB-BICA in prisons and other custodial settings in at least five Member States.

Based on the available information, it appears that 4F-MDMB-BICA 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 4F-MDMB-BICA 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 4F-MDMB-BICA is used for legitimate purposes other than research or forensic application (EMCDDA, 2020b).

4F-MDMB-BICA 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). 4F-MDMB-BICA has not been subject to assessment nor is it currently under assessment by the United Nations system (EMCDDA, 2020b).

4F-MDMB-BICA is subject to restrictive measures in thirteen Member States: in Croatia, Cyprus, France, Italy, Latvia, Luxembourg, Poland, 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, 4F-MDMB-BICA is controlled under medicines legislation in Norway and under drug control legislation in Turkey. It is unknown if 4F-MDMB-BICA 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 2-{[1-(4-fluorobutyl)-1*H*-indole-3-carbonyl]amino}-3,3-dimethylbutanoate (4F-MDMB-

BICA) ([3]) – also known as methyl 2-({[1-(4-fluorobutyl)-1*H*-indol-3-yl]carbonyl}amino)-3,3-dimethylbutanoate – (Figure 1), is a synthetic cannabinoid receptor agonist which does not appear to have a history in the scientific literature. However, it is structurally related to compounds of the indazole-3-carboxamide class that feature pendant amino acid esters (methyl L-tert-leucinate) previously developed by Pfizer Inc. and published in 2009 (e.g. compounds 125-130; Buchler et al., 2009). The switch to an indole core not covered by the Pfizer patent reflects an example of scaffold hopping (Banister and Connor, 2018). The substances described in the patent literature make reference to compounds that only show the (*S*)-configuration (e.g. 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 reported to the EMCDDA, 4F-MDMB-BICA has been available on the European drug market at least since March 2020 (EMCDDA, 2020d).

4F-MDMB-BICA is structurally related to 4F-MDMB-BINACA ([4]) (indazole instead of indole core) and 5F-MDMB-PICA (5F-MDMB-2201) ([5]) (homologue) (Figure 1). In 2020, these two synthetic cannabinoids were placed in Schedule II of the 1971 United Nations Single Convention on Psychotropic Substances (CND, 2020) after undergoing a critical review by the World Health Organization's Expert Committee on Drug Dependence in October 2019 (WHO, 2019a; WHO, 2019b).

4F-MDMB-BICA is also structurally related to 5F-MDMB-PINACA (5F-ADB) ([6]). 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 2018, 5F-MDMB-PINACA was placed in Schedule II of the 1971 United Nations Single Convention on Psychotropic Substances (INCB, 2019) after undergoing a critical review by the WHO's ECDD in November 2017 (WHO, 2017). In 2020, the EMCDDA also launched an initial report on MDMB-4en-BINACA ([7]) in accordance with Article 5b of Regulation (EC) No 1920/2006 (as amended) (EMCDDA, 2020c). MDMB-4en-BINACA was also critically reviewed by the WHO's ECDD in October 2020 (WHO, 2020a).

2.2 Names and chemical structure

4F-MDMB-BICA is a synthetic cannabinoid receptor agonist (synthetic cannabinoid). The 4F-MDMB-BICA code name used for the substance is derived from its structural features: a methyl 3,3-dimethylbutanoate linked group (MDMB), a 4-fluorobutyl tail (4F and B) attached to

([3]) 4F-MDMB-BICA and many other synthetic cannabinoids 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]) 4F-MDMB-BINACA IUPAC name: methyl 2-{[1-(4-fluorobutyl)-1*H*-indazole-3-carbonyl]amino}-3,3-dimethylbutanoate

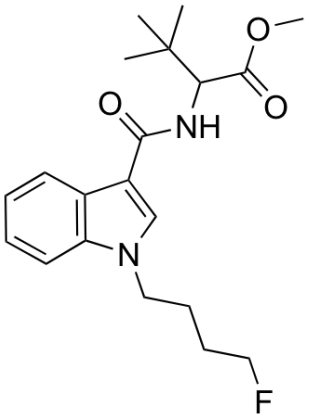
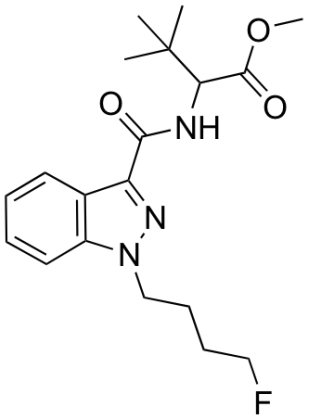
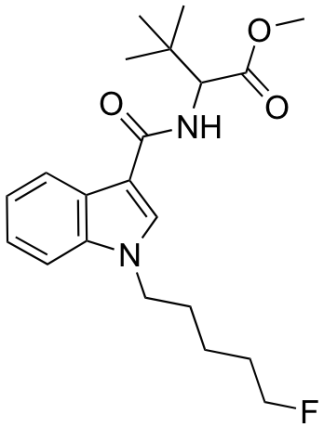
([5]) 5F-MDMB-PICA IUPAC name: methyl 2-{[1-(5-fluoropentyl)-1*H*-indole-3-carbonyl]amino}-3,3-dimethylbutanoate

([6]) 5F-MDMB-PINACA IUPAC name: methyl 2-{[1-(5-fluoropentyl)-1*H*-indazole-3-carbonyl]amino}-3,3-dimethylbutanoate

([7]) MDMB-4en-PINACA IUPAC name: methyl 3,3-dimethyl-2-{[1-(pent-4-en-1-yl)-1*H*-indazole-3-carbonyl]amino}butanoate

the indole nitrogen atom of an indole core (I), and a carboxamide linker (CA).

Figure 1. Chemical structures and molecular information of 4F-MDMB-BICA, 4F-MDMB-BINACA, and 5F-MDMB-PICA.

4F-MDMB-BICA	4F-MDMB-BINACA	5F-MDMB-PICA
		
Molecular formula: $C_{20}H_{27}FN_2O_3$	Molecular formula: $C_{19}H_{26}FN_3O_3$	Molecular formula: $C_{21}H_{29}FN_2O_3$
Molecular weight: 362.44	Molecular weight: 363.43	Molecular weight: 376.47
Monoisotopic mass: 362.2006	Monoisotopic mass: 363.1958	Monoisotopic mass: 376.2162

Common name:

4F-MDMB-BICA

Systematic (IUPAC) name:

Methyl 2-{[1-(4-fluorobutyl)-1*H*-indole-3-carbonyl]amino}-3,3-dimethylbutanoate

Other chemical names:

Methyl 3,3-dimethyl-2-[1-(4-fluorobutyl)-1*H*-indole-3-carboxamido]butanoate

Methyl 3-methyl-*N*-[1-(4-fluorobutyl)-1*H*-indole-3-carbonyl]valinate

Methyl 3,3-dimethyl-2-{[1-(4-fluorobutyl)-1*H*-indol-3-yl]formamido}butanoate

Methyl *N*-{[1-(4-fluorobutyl)-1*H*-indole-3-yl]carbonyl}-3-methylvalinate

Methyl 2-[1-(4-fluorobutyl)-1*H*-indole-3-carboxamido]-3,3-dimethylbutanoate

Methyl 2-{[1-(4-fluorobutyl)indol-3-yl]formamido}-3,3-dimethylbutanoate

Methyl 2-{[1-(4-fluorobutyl)indole-3-carbonyl]amino}-3,3-dimethyl-butanoate

Methyl *N*-{[1-(4-fluorobutyl)-1*H*-indol-3-yl]carbonyl}-3-methylvalinate

Methyl 2-{[1-(4-fluorobutyl)indol-3-yl]formamido}-3,3-dimethylbutanoate

N-(1-methoxy-3,3-dimethyl-1-oxobutan-2-yl)-1-(4-fluorobutyl)-1*H*-indole-3-carboxamide

Other names:

MDMB-4F-BICA

4F-MDMB-BICA

4F-MDMB-2201

MDMB-4F-BUTICA

4F-MDMB-BUTICA

4-Fluoro MDMB-BICA

4-Fluoro MDMB-BUTICA

4FBC

4FBCA

MDMB-073-F

Street names:

'Bika' (in Hungary, meaning 'bull') (Tihanyi et al., 2020)

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 tobacco'; in France 'chimique'; in Turkey, 'Bonsai'; whereas in Birmingham, United Kingdom, the name 'Black Mamba 'or simply 'Mamba 'is used. In one case reported to EMCDDA, a

seized smoking mixture branded as a 'legal-high' product called 'Pico Bello' was found to contain 4F-MDMB-BICA.

Smoking mixtures were also found to contain other synthetic cannabinoids (MDMB-4en-PINACA ([7]), 5F-MDMB-PICA ([5]), and 5F-EMB-PICA ([8])). 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). Three seized samples determined to be 4F-MDMB-BICA were labelled incorrectly as '5F-MDMB-2201' (5F-MDMB-PICA; two cases) (EMCDDA, 2020b) and 4F-MDMB-BINACA (one case).

Chemical Abstracts Service (CAS) registry numbers:

Not yet listed (as of 15 Nov 2020)

IUPAC International Chemical Identifier Key (InCHI Key):

QIKHYQCWGUGFBB-UHFFFAOYSA-N

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

FCCCCN1C=C(C2=CC=CC=C12)C(=O)NC(C(=O)OC)C(C)(C)C ([9])

2.3 Physical properties

In its pure form 4F-MDMB-BICA has been described as a crystalline solid (Cayman Chemical Company, 2020a; Cayman Chemical Company, 2020b). Seized powder samples containing 4F-MDMB-BICA have been described as white, brown-off-white, beige-brown, orange, rose-red crystal-like (EMCDDA, 2020a; EMCDDA, 2020b), and as an orange coloured amorphous solid material (HIFS, 2020). The pure material has been described as a white solid with a melting point of 86–88 °C (Stove and Banister, personal communication) ([10]). Based on seizures and collected samples reported to the EMCDDA, 4F-MDMB-BICA has been detected in smoking mixtures, powders, paper impregnated with the substance (including blotters), liquids, and e-liquids contained in a vape cartridge, In addition, on one occasion, powdered 'nuggets' of 4F-MDMB-BICA were found in a mixture with tobacco and on another occasion, 4F-MDMB-BICA was identified in a liquid that was reported to be in a bottle of nail varnish remover (EMCDDA, 2020b).

([8]) 5F-EMB-PICA IUPAC name: ethyl 2-{[1-(5-fluoropentyl)-1*H*-indole-3-carbonyl]amino}-3-methylbutanoate
([9]) Generated from IUPAC name by OPSIN: Open Parser for Systematic IUPAC nomenclature (http://opsin.ch.cam.ac.uk) (Lowe et al., 2011).
([10]) Cannaert et al. 2020

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 4F-MDMB-BICA which has been identified within Europe.

The synthesis of (*S*)-4F-MDMB-BICA has been described (Stove and Banister, personal communication) ([10]) following previously established procedures (Banister et al., 2016; Banister et al., 2019) (Figure 2). Indole (1) undergoes *N*-alkylation with 1-bromo-4-fluorobutane and acylation with trifluoroacetic anhydride to give the 2,2,2-trifluoro-1-[1-(4-fluorobutyl)-1*H*-indol-3-yl]ethanone intermediate (2). Hydrolysis under alkaline conditions produces the carboxylic acid intermediate 1-(4-fluorobutyl)-1*H*-indole-3-carboxylic acid (3). Coupling with methyl L-*tert*-leucinate (methyl (2*S*)-2-amino-3,3-dimethylbutanoate) ([11]) gives (*S*)-4F-MDMB-BICA (4) (Figure 2).

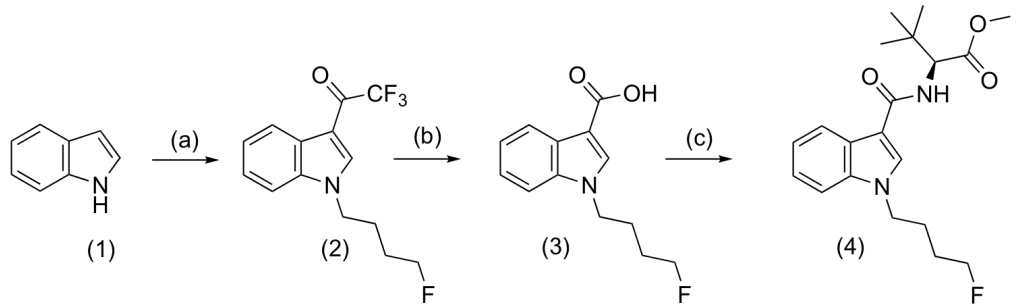


Figure 2. Synthesis route for (*S*)-4F-MDMB-BICA starting from indole (1) (Stove and Banister, personal communication) ([10]). (a) (i) NaH, DMF, 1-bromo-4-fluorobutane; 0 °C–rt, 1 h; (ii) $(CF_3CO)_2O$, 0 °C–rt, 2 h; (b) KOH, MeOH, PhMe, reflux, 2 h; c) methyl L-*tert*-leucinate, EDC·HCl, HOBt·H_2O, Et_3N, DMF, rt, 18 h. For the preparation of the (*R*)-enantiomer, the coupling reaction would involve the use of methyl D-*tert*-leucinate instead.

2.5 Methods for identification and analysis

Analytical data for 4F-MDMB-BICA and methods for its detection have been published in the scientific literature and public domain (Table 1). The analysis of biological specimen requires sensitive methods of analysis, e.g. liquid chromatography coupled to (tandem) mass spectrometry approaches (high and low resolution). (*S*)-4F-MDMB-BICA is available as reference material from commercial suppliers. EMCDDA have not yet received any information about the enantiomeric composition of 4F-MDMB-BICA-containing products although the presence of the (*S*)-enantiomer, similar to most other closely related synthetic cannabinoids available on the market, seems likely. However, the presence of the (*R*)-enantiomer in seized samples or the racemic mixture cannot not be excluded in the absence of further information. In some biological specimen, the parent molecule might not always be detectable directly as a consequence of ester hydrolysis which gives rise to the formation of an acidic transformation

(11) (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 4F-MDMB-BICA and other related synthetic cannabinoids that have been reported to the EU Early Warning System.

product ([12]), 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 4F-MDMB-BICA (amongst other substances) available in the scientific literature and public domain

Techniques [a]	**Comment**	**Reference**
GC-MS; LC-MS	Analysis of seized material	Krotulski et al. (2020)
GC-MS; LC-MS; IR; Raman; NMR	Analysis of herbal mixture and orange solid	ADEBAR Project (2020)
MP; LC-MS; LC-UV; IR; NMR	Analysis of synthesised material	Stove and Banister, personal communication ([10])
GC-MS, UV	Analysis of synthetic reference material	Cayman Chemical Company (2020a, 2020c)
GC-MS; IR; NMR	Analysis of orange, amorphous solid	HIFS (2020)
GC-MS; IR; LC-MS; IC; NMR	Analysis of test purchased powder	NFL Ljubljana (2020)
IMS, ESI-MS	Analysis of seized paper impregnated samples in prisons	Norman et al. (2020)

[a] GC: gas chromatography; MS: mass spectrometry; LC: liquid chromatography; IR: infrared spectroscopy; Raman: Raman spectroscopy; NMR: nuclear magnetic resonance spectroscopy; MP: melting point; UV: ultraviolet spectroscopy; IC: ion chromatography; IMS: ion mobility spectrometry; ESI: electrospray ionisation. LC-MS and ESI-MS: might involve single, tandem, low, or high-resolution methods of analysis.

(12) Ester hydrolysis product IUPAC name: 3,3-dimethyl-2-{[1-(4-fluorobutyl)-1H-indole-3-carbonyl]amino}butanoic acid

2.6 Dosage regimens

Information on the dose and dosage regimens ([13]) for 4F-MDMB-BICA is limited. Products containing synthetic cannabinoids such as 4F-MDMB-BICA 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 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; 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 4F-MDMB-BICA are currently very limited. 4F-MDMB-BICA can be inhaled by smoking and it is expected that similar to related synthetic cannabinoids, that 4F-MDMB-BICA 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 4F-MDMB-BICA in products seized by law enforcement or from collected

([13]) 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.

samples in Europe has not been reported ([14]). 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).

Information involving the analysis of seized and collected samples reported to the EMCDDA notes that 4F-MDMB-BICA has been encountered in the form of smoking mixtures, powders, papers (including blotters) impregnated with the substance, and liquids (EMCDDA, 2020b).

Papers, including blotters and cards, impregnated with 4F-MDMB-BICA were seized in prisons and other custodial settings in Cyprus, Hungary, Lithuania, and the United Kingdom (EMCDDA, 2020b). In the latter case, seizures were made Scottish prisons during 2020, with the first seizure made in May 2020 (McKenzie, 2020; Norman et al., 2020).

Drug-checking services operating in Switzerland have reported two cannabis samples adulterated with 4F-MDMB-BICA. In addition to cannabidiol and traces of THC ([15]), one of the samples revealed the presence of 4F-MDMB-BICA and MDMB-4en-PINACA ([7]), whereas the other sample contained 4F-MDMB-BICA, 5F-MDMB-PICA ([5]) and MDMB-4en-PINACA ([7]) (Erowid, 2020; Rave it Safe, 2020; Saferparty.ch, 2020).

In the United States of America (USA), the Centre for Forensic Science Research and Education (CFSRE) reported its first identification of 4F-MDMB-BICA in July 2020. The report was related to the analysis plant-like material seized in May 2020 (Krotulski et al., 2020).

Formal epidemiological studies have not been performed to examine the use and patterns of use of 4F-MDMB-BICA, however in many cases these are likely to share some similarities with other synthetic cannabinoids. Anecdotal reports on internet drug discussion forums and related websites from people who used a substance believed to be 4F-MDMB-BICA are very limited. One report involving the inhalation (‘vaping’) of pure 4F-MDMB-BICA powder, estimated to represent a dose of approximately 50 µg, was considered by the user to be intoxicating (Reddit, 2020). However, it is not possible to currently 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 product containing the substance may differ over time and place.

3. Legitimate use

3.1 Summary

Based on the available information, it appears that 4F-MDMB-BICA is not an active substance

[14] Slovenia reported a test-purchase of 4F-MDMB-BICA made by the EU-funded project RESPONSE; the substance was identified in 5 grams of beige-brown powder contained in a zip-lock plastic bag. The purity of the sample was over 95%.
[15]

in a medicinal product for human use or in a veterinary medicinal product in Europe.

However, although highly unlikely, the use of 4F-MDMB-BICA 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 4F-MDMB-BICA is used for legitimate purposes other than research or forensic applications in Europe.

3.2 Medical use

Based on information from the European Medicines Agency for the initial report (EMCDDA, 2020b), it appears that 4F-MDMB-BICA 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.

In addition, it appears that 4F-MDMB-BICA 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

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

As part of the initial report process, the European Chemical Agency (ECHA) and European Food Standard Authority (EFSA) reported to the EMCDDA that 4F-MDMB-BICA did not

retrieve any results in their information systems (EMCDDA, 2020b).

4. Pharmacological and toxicological properties

4.1 Summary

(*S*)-4F-MDMB-BICA has been shown to act as a potent, full agonist at the cannabinoid type 1 (CB_1) receptor when investigated under *in vitro* conditions. When studied under identical assay conditions, the homologue (*S*)-5F-MDMB-PICA ([5]) was found to be ~37- and ~57-times more potent. The indazole counterpart (*S*)-4F-MDMB-BINACA ([4]) was determined to be ~16- and ~44 times more potent than (*S*)-4F-MDMB-BICA. A comparison with another synthetic cannabinoid under international control (JWH-018, ([16])) revealed that it activated the CB_1 receptor with comparable potency. Information on the pharmacokinetics of 4F-MDMB-BICA could not be identified but it is expected to be comparable to closely related substances such as 5F-MDMB-PICA and 4F-MDMB-BINACA. No studies were identified that have investigated the pharmacodynamics of 4F-MDMB-BICA on pharmacological targets other than the CB_1 receptor.

Although not formally studied, the psychological and behavioural effects of 4F-MDMB-BICA are likely to share similarities with those commonly reported for other synthetic cannabinoids, including: relaxation, euphoria, lethargy, confusion, anxiety, fear, distorted perception of time, depersonalisation, hallucinations, paranoia, as well as dry mouth, bloodshot eyes, cardiovascular effects, nausea, vomiting and impaired motor performance.

In vivo studies and information on toxicological properties of 4F-MDMB-BICA could not be identified. 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.

The information shared online by people who used a substance they believed to be 4F-MDMB-BICA is very limited. Reported adverse effects included anxiety, visual alterations, loss of consciousness, increased heart rate, and derealisation. 4F-MDMB-BICA was considered a potent substance when inhaled by ‘vaping’, with effects lasting around 40–60 min, according to one anecdotal report; the perceived high potency of 4F-MDMB-BICA required adjustments to be made relating to the number and extent of inhalations (‘hits’). It should be noted that the assessment of such reports is problematic not least because typically users cannot confirm the substance they were actually using or the amount used. In general, given the difficulties of collecting accurate self-reported data, it should be interpreted with caution.

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

The abuse liability and dependence producing potential of 4F-MDMB-BICA 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, currently available information from *in vitro* studies suggests that 4F-MDMB-BICA binds to and activates the cannabinoids type 1 (CB_1) receptor as a full agonist (Table 2). Compared to another synthetic cannabinoids under international control (JWH-018) ([14]) used as a positive control, its efficacy was found to increase to E_{max} = 253% (Stove and Banister, personal communication) ([10]). The potency of 4F-MDMB-BICA (EC_{50} = 121 nM; ([17])) was considerable although it dropped by a factor of ~16 and ~44 compared to its indazole counterparts 4F-MDMB-BINACA ([4]) (Table 2). Similarly, the homologue 5F-MDMB-PICA ([5]) was also shown to be ~37- and ~57-times more potent than 4F-MDMB-BICA. Another comparison with JWH-018 revealed that it activated the CB_1 receptor with comparable potency (Persson et al., 2020) (Table 2).

Table 2. *In vitro* activation data at the hCB_1 receptor reported for enantiopure 4F-MDMB-BICA in comparison with 4F-MDMB-BINACA and 5F-MDMB-PICA under identical assay conditions. [a]

Compound	EC_{50} (nM)	E_{max} (%)	Reference
4F-MDMB-BICA	121	253	(Stove and Banister, personal communication) ([10]).
4F-MDMB-BINACA	7.39	378	(Stove and Banister, personal communication) ([10]).
	2.78	255	Antonides et al. (2020)
5F-MDMB-PICA	3.26	331	Noble et al. (2019)
	2.13	289	Antonides et al. (2020)
4F-MDMB-BICA	37.7	129	Persson et al. (2020) [b]

([17]) EC_{50} represents the half maximal effective concentration for a given substance.

[a] HEK cells; β-arrestin 2 recruitment assay; relative to JWH-018 (E_{max} = 100%); EC_{50} = 14,2 nM; data are for the (*S*)-enantiomers. Reductions in potency were determined for the (*R*)-enantiomers: 4F-MDMB-BINACA (EC_{50} = 1076 nM; E_{max} = 128%); 5F-MDMB-PICA (EC_{50} = 224 nM; E_{max} = 121%) (Antonides et al. 2020).
[b] Aquerin base system; CB_1 receptor expressed in CHO cells; relative to JWH-018 (E_{max} = 100%); EC_{50} = 51.9 nM.

It is not known whether 4F-MDMB-BICA affects other pharmacological targets, such as receptors, enzymes or transport processes.

4.2.2 In vivo data

Information on the *in vivo* effects of 4F-MDMB-BICA could not be identified. Based on the available information obtained from investigations carried out so far *in vitro* (Table 2), it is likely that 4F-MDMB-BICA will also share similar properties compared to other synthetic cannabinoids. For example, cannabimimetic (i.e. THC-like) effects expected to be induced by 4F-MDMB-BICA in mice may include hypolocomotion, antinociception, hypothermia, and catalepsy (Wiley et al., 2017) and THC-like discriminative stimulus effects (Wiley et al., 2018; Wiley et al., 2019). However, the reported comparatively low potency *in vitro* of 4F-MDMB-BICA (EC50 = 121 nM; Table 2) alone fails to explain the local outbreak of serious adverse events, including death cases, where post-mortem analysis detected (see also Section 6).

4.3 Psychological and behavioural effects

Information on the study of psychological and behavioural effects of 4F-MDMB-BICA in humans could not be identified. Based on the limited information on the pharmacological properties of 4F-MDMB-BICA, as well information from previous observations involving closely related synthetic cannabinoids such as 4F-MDMB-BINACA ([4]) and 5F-MDMB-PICA ([5]) (WHO, 2019b; WHO, 2019a), it is likely that the effects of 4F-MDMB-BICA 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 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; Zaurova et al., 2016). In addition, psychotic episodes, confusion, paranoia, as well as aggressive and violent behaviour, have also been reported (EMCDDA, 2018; Yalçın et al., 2018). Effects reported by people who used a substance believed to be 4F-MDMB-BICA included anxiety, visual alterations, loss of consciousness, and derealisation (Reddit, 2020).

A case series of three individuals suspected of committing a road traffic offence and with confirmed exposure to the homologue 5F-MDMB-PICA ([5]) but no other toxicological findings noted the following physical effects: balance deficiencies and ocular effects such as reddened conjunctivae, glassy eyes and delayed or unresponsive pupil light reactions. Observed mental and behavioural effects were predominantly changing moods, aggression, confusion, erratic

behaviour, mental leaps, disorientation, slowed reaction, and slurred speech (Kleis et al., 2020).

4.4 Safety pharmacology

Detailed information on the safety pharmacology (ICH, 2000) of 4F-MDMB-BICA could not be identified. However, the available data suggest that this substance is a reasonably potent, full CB_1 receptor agonist *in vitro*. Based on the currently available information on the pharmacological properties of 4F-MDMB-BICA, as well as information from previous observations involving closely related synthetic cannabinoids such as 4F-MDMB-BINACA ([4]) and 5F-MDMB-PICA ([5]) (WHO, 2019b; WHO, 2019a), adverse effects from overdosing 4F-MDMB-BICA might include gastrointestinal (e.g. nausea, vomiting (including hyperemesis)), neurological (e.g. hallucination, agitation, anxiety, paranoia, confusion, delusions, catatonia, lethargy, psychosis (including 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). Effects reported by people who used a substance believed to be 4F-MDMB-BICA included anxiety, loss of consciousness, and visual alterations (Reddit, 2020).

4.5 Pharmacokinetics

Information on the biotransformation and pharmacokinetic parameters of 4F-MDMB-BICA could not be identified. The structural similarity to 4F-MDMB-BINACA ([4]) suggests that similar metabolic conversions might be involved, for example ester hydrolysis (+ detection of glucuronidation products in urine), oxidative defluorination, formation of butanoic acid substituent (tail), hydroxylations of aromatic and alkyl moieties, dehydrogenation, lactone formation, *N*-dealkylation and a combination of those metabolic reactions (Diao and Huestis, 2019; Haschimi et al., 2019; Krotulski et al., 2019; Wagmann et al., 2020). Correspondingly, the metabolic steps thought to be involved in humans following ingestion of the homologue 5F-MDMB-PICA ([5]) (e.g. mono-hydroxylation, oxidative defluorination, dehydrogenation, amide, and ester hydrolysis, as well as combinations of these metabolic modifications) (Kleis et al., 2020; Mogler et al., 2018) are likely to apply to 4F-MDMB-BICA as well.

The pharmacological activity, if any, of the possible metabolites of 4F-MDMB-BICA is not known.

Information about the duration of effects recorded during human studies could not be identified. An anecdotal report from a person who used a substance believed to be 4F-MDMB-BICA suggested a duration of effects around 40–60 min when inhaled in the form of a ‘c-liquid’; the perceived high potency of 4F-MDMB-BICA required adjustments to be made relating to the number and extent of inhalations (‘hits’) (Reddit, 2020).

4.6 Toxicology

Information on the toxicological properties (including pre-clinical safety data) of 4F-MDMB-BICA 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 pharmaco-toxicological effects of 4F-MDMB-BICA 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

Information on the abuse liability and dependence producing potential of 4F-MDMB-BICA could not be identified. It has been suggested that consumption of synthetic cannabinoids can produce tolerance and withdrawal-like symptoms when use is discontinued following a regular use. Withdrawal-like symptoms following cessation of synthetic cannabinoids have been described in the literature. These include: anxiety, unstable mood, crying fits, feeling of inner emptiness, spatial disorientation, hyperacusis (increased sensitivity to ordinary environmental sounds), somatic pain, shortness of breath, hyperventilation, intense sweating and sensations of motor and inner restlessness (Cooper, 2016; Macfarlane and Christie, 2015; Van Hout and Hearne, 2017; Zimmermann et al., 2009). Given what is currently known about the pharmacology of synthetic cannabinoids in general, including the closely related 5F-MDMB-PINACA ([6]) (and some similarities to THC), it is reasonable to consider that 4F-MDMB-BICA has a potential for abuse and dependence (EMCDDA, 2018).

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 4F-MDMB-BICA in Europe.

4F-MDMB-BICA has been available on the drug market in Europe since at least March 2020, when it was seized by customs in Belgium. As of November 2020, 4F-MDMB-BICA has been identified in twelve Member States; 111 seizures have been reported, which include 5.6 kg of powder and 0.6 kg of smoking mixtures. Of particular note are four large scale seizures of 4F-MDMB-BICA powder reported by Belgian customs and eleven seizures that occurred in prisons. The most recent identifications of 4F-MDMB-BICA reported to the EMCDDA are from seizures made by police in Cyprus and customs in Finland in September 2020.

The available information suggests that 4F-MDMB-BICA 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 consumer products. There are three main types of products containing 4F-MDMB-BICA that are available on the drug market:

- smoking mixtures, where 4F-MDMB-BICA is mixed with herbal material or tobacco that is then smoked or inhaled, for example using 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 4F-MDMB-BICA is prepared by mixing it with a solvent, which is then inhaled using an e-cigarette; and

- impregnated on to paper 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, people who are using these substances may also prepare their own products using powdered 4F-MDMB-BICA purchased from a vendor or dealer.

Although 4F-MDMB-BICA 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.

As 4F-MDMB-BICA has only recently emerged on the drug market in Europe, it is important to note that its presence on the market and as the cause of 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 on-going COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (ECDC, 2020; EMCDDA, 2020e; WHO, 2020b) may have reduced the capacity of early warning systems, including forensic science and toxicology laboratories, to detect and report events involving 4F-MDMB-BICA.

The effect of the on-going COVID-19 pandemic (ECDD, 2020; EMCDDA, 2020e; WHO, 2020b) on the manufacture, trafficking, distribution, and use of 4F-MDMB-BICA 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 4F-MDMB-BICA.

5.2 Information from seizures

Law enforcement seizures of 4F-MDMB-BICA have been reported by 12 Member States: Hungary (72 seizures), the United Kingdom (17), Belgium (4), Slovenia (4), Cyprus (3), Finland (3), Germany (2), Lithuania (2), Croatia (1), Poland (1), Italy (1), and Sweden (1).

In total, 111 seizures were reported. These included: 8 seizures by customs and 103 seizures

by police; 11 of the police seizures occurred in prisons. Where reported, seizures took place between March and September 2020.

Seizures included smoking mixtures (32 cases), powders (20), blotters and other types of paper impregnated with the substance (7), and liquids (3). For 49 of the seizures reported by Hungary no details were provided.

5.2.1 Customs seizures

A total of 8 seizures were made by customs and amounted to 5.58 kg. These were reported by: Belgium (4), Finland (3), and Sweden (1). All the seizures were in powder form, and occurred between March and September 2020.

The seizures reported by Belgium accounted for 99.9% of the powders seized by customs (3 kg, 1.5 kg, and 2 seizures of approximately 0.5 kg each). The seizure that led to the formal notification of 4F-MDMB-BICA, made at Liège Airport, was reported as a case of large-scale international trafficking; the parcel originated from China and was *en route* to the Netherlands. The destination for all the seizures reported by Belgium was the Netherlands.

The three seizures reported by Finland originated from the Netherlands (2) and Spain (1). One of the seizures was labelled as '5F-MDMB-2201'.

Sweden reported a seizure of 4F-MDMB-BICA powder amounting to 9.82 g in a package labelled '5F-MDMB-2201'.

No other substances were typically reported in seizures made by customs. In one seizure reported by Belgium, the precursor ethylamine (ethanamine) was identified at approximately 4% (w/w %) along with other minor impurities (section 3.2.3).

The available information suggests that at least some powders of 4F-MDMB-BICA are sourced from China and imported to Europe via Belgium to the Netherlands.

5.2.2 Police seizures

A total of 103 seizures made by police were reported by Hungary (72 seizures), the United Kingdom (17), Slovenia (4), Cyprus (3), Germany (2), Lithuania (2), Croatia (1), Poland (1), and Italy (1). These seizures occurred between April and September 2020.

Out of the 103 police seizures, 11 seizures occurred in prisons, and were reported by Slovenia (4), the United Kingdom (3), Lithuania (2), Cyprus (1), and Hungary (1).

4F-MDMB-BICA was detected in smoking mixtures, powders, paper impregnated with the substance (including blotters), and liquids. All the seizures of impregnated papers and blotters occurred in prisons. A summary is provided below.

Smoking mixtures

In total, 32 seizures of smoking mixtures containing 4F-MDMB-BICA were reported by Police. These amounted to 612.66 g and were reported by Hungary (12 cases), the United Kingdom (12), Slovenia (4), Cyprus (2), Croatia (1), and Germany (1).

There is no information on the concentration of 4F-MDMB-BICA in the smoking mixtures. In 15 cases, no substances other than 4F-MDMB-BICA were reported. In the remaining17 cases, alongside the identification of 4F-MDMB-BICA, 1 other synthetic cannabinoid (10 cases), 2 (2), 3 (3), 4 (1) and 7 other cannabinoids (1) were also identified.

All four seizures reported by Slovenia occurred in prisons. The samples also contained MDMB-4en-PINACA, 5F-MDMB-PICA and 5F-EMB-PICA. One of the seizures contained a total of 8 different synthetic cannabinoids.

In one case reported by Germany, the mixtures were found in a branded 'legal-high' product ('Pico Bello'); in another case the mixture was found in aluminium bag.

Powders

In total, 12 seizures of powder containing 4F-MDMB-BICA were reported by 4 Member States: Hungary (9), Germany (1), Poland (1) and Italy (1). The seizures reported by Germany, Poland, and Italy amounted to 12.78 grams.

Powders were described as white, off-white, brown, and orange. Appearance as rose-red crystals was also reported. No other substances were reported to be detected in the powders.

In one case reported by Hungary, powder 'nuggets' were found in a mixture with tobacco at the scene of a death. It is not clear whether the mixture was supplied as such to the deceased or whether it was homemade.

Impregnated papers, including blotters

In total, 7 seizures of paper impregnated with 4F-MDMB-BICA were reported to the EMCDDA. These were reported by the United Kingdom (3), Lithuania (2), Cyprus (1) and Hungary (1). All the seizures occurred in prisons and other custodial settings.

Other synthetic cannabinoids were detected in 3 of the seizures, predominantly MDMB-4en-PINACA ([7]) (identified in 3 cases), and 5F-MDMB-PICA (2) ([5]).

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.

Liquids

A total of 3 seizures containing 4F-MDMB-BICA in liquid form were reported by two Member States: the United Kingdom (2) and Hungary (1).

In the 2 seizures reported by the United Kingdom, 4F-MDMB-BICA was detected in an e-liquid

contained within a vaping cartridge. The seizures were of 0.8 and 563 mL. The seizure of 0.8 mL also contained 4F-MDMB-BINACA ([4]).

In the seizure reported by Hungary, 4F-MDMB-BICA was identified in a liquid that was reported to be in a bottle of nail varnish remover.

Other

For 49 seizures reported by Hungary no details were provided.

5.3 Information from collected samples

Slovenia reported a test-purchase of 4F-MDMB-BICA made by the EU-funded project RESPONSE; the substance was identified in 5 grams of beige-brown powder contained in a zip-lock plastic bag. The purity of the sample was over 95%.

5.4 Information from biological samples

Serious adverse events with confirmed exposure to 4F-MDMB-BICA from biological samples are discussed in section 6.2.12 and 6.2.2.

Hungary reported 126 cases where exposure to 4F-MDMB-BICA was analytically confirmed in biological samples. All detections were reported as cases due to police arrest. It was reported that in the majority of the cases other substances, mostly synthetic cannabinoids, in particular 5F-MDMB-PICA ([5]) were also identified. Where reported, the cases occurred between May and August 2020 (71 cases).

In addition to information from biological samples reported by the Member States, Table 3 shows the number of identifications of 4F-MDMB-BICA in authentic urine samples analysed by the Institute of Forensic Medicine, Medical Centre, University of Freiburg, Germany, between the third quarter of 2019 and the third quarter of 2020. As can be seen, 4F-MDMB-BICA has only recently been detected in biological samples, i.e. from the second quarter of 2020 onwards. These detections predominantly reflected results from routine screenings involving abstinence control cases within correctional and psychiatric facilities but not poisoning cases.

Table 3. Detections of 4F-MDMB-BICA 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 4F-MDMB-BICA	0	0	0	1 (0.5%)	35 (13%)
[a] Courtesy of Prof. Volker Auwärter					

6. Health risks

6.1 Summary

Data from studies in animals or humans featuring the acute and chronic health effects of 4F-MDMB-BICA use could not be identified. However, it appears likely that the clinical features of poisonings caused by 4F-MDMB-BICA will be similar to those reported from other synthetic cannabinoids resulting in gastrointestinal, neurological, cardiovascular, and 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 4F-MDMB-BICA with other drugs, especially central nervous system depressants (such as alcohol, opiates/opioids, and sedative/hypnotics) is likely to increase the risk of life-threatening poisoning.

A total of 21 deaths with confirmed exposure to 4F-MDMB-BICA have been reported to the EMCDDA by Hungary. The deaths occurred between May and August 2020. It was reported that in some of the deaths other synthetic cannabinoids, particularly 5F-MDMB-PICA ([5]) were detected in biological samples. Reported ante-mortem symptoms and clinical features included chest pain, respiratory problems, tremor, and seizures.

A total of five acute poisonings with confirmed exposure to 4F-MDMB-BICA have been reported to the EMCDDA by 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. In all of the cases, the poisoning was considered life threatening and required hospitalisation of the patient.

There is no information on the chronic health effects of 4F-MDMB-BICA, 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.

6.2 Acute health effects

Specific information about 4F-MDMB-BICA could not be identified. Based on the currently available information on the pharmacological properties of 4F-MDMB-BICA and other closely

related synthetic cannabinoids such as 4F-MDMB-BINACA ([4]) and 5F-MDMB-PICA ([5]) (WHO, 2019b; WHO, 2019a), adverse effects from poisoning with 4F-MDMB-BICA might include gastrointestinal (e.g. nausea and vomiting (including hyperemesis)), neurological (e.g. hallucination, agitation, anxiety, paranoia, confusion, delusions, catatonia, lethargy, psychosis (including 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). Effects reported by people who used a substance they believed to be 4F-MDMB-BICA included anxiety, loss of consciousness, visual alterations. In one case, 'vaping' pure powder (approximately 50 µg with no tolerance) was considered 'too much', with effects including derealisation and an increase in heart rate from 70 to 120 beats per minute (Reddit, 2020).

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 4F-MDMB-BICA 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 4F-MDMB-BICA 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 reported for synthetic cannabinoids — 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 five acute non-fatal poisonings with confirmed exposure to 4F-MDMB-BICA were reported to the EMCDDA by the United Kingdom. All cases occurred between June and July 2020. Of the cases, four were male and one was female. The males were aged between 27 and 53 (mean 38; median 36). The female was 31 years old.

All cases included clinical features of poisoning similar to those reported for synthetic cannabinoids, such as confusion, tachycardia, respiratory insufficiency, reduced conscious level, abnormal sweating, and agitation. However, in all cases other substances were also

identified in the biological samples take from the patients, including one or more other synthetic cannabinoid, which may account, at least in part, for the observed effects. Other substances identified in the patients, include:

- other synthetic cannabinoids: MDMB-4en-PINACA (in all cases), 5F-EMB-PICA ([8]) (3 cases), 4F-MDMB-BINACA ([4]) (1 case), AB-FUBINACA ([18]) (1 case);
- benzodiazepines: diazepam (in all cases), flubromazolam (3 cases), etizolam (2 cases), temazepam (2 cases), flualprazolam (1 case), oxazepam (1 case);
- opioids: methadone (in all cases), morphine (3 cases), codeine (3 cases);
- other drugs: pregabalin (4 cases), cocaine (3 cases), THC (3 cases), ketamine (1 case)

In all cases the poisoning was considered to be life-threatening and required hospitalisation of the patient.

Acute poisonings identified from other sources

Information about acute poisoning associated with 4F-MDMB-BICA resulting in non-fatal poisonings from other sources could not be identified.

6.2.2 Deaths

Deaths reported in Europe

A total of 21 deaths with confirmed exposure to 4F-MDMB-BICA were reported to the EMCDDA by Hungary. The cases occurred between May and August 2020. Further details are available on 20 cases and are summarised below.

Of the 20 death cases, all involved males aged between 19 and 42 (mean 28.5; median 28). In 19 cases other substances were identified, including:

- other synthetic cannabinoids: 5F-MDMB-PICA (10 cases); MDMB-4en-PINACA (8 cases);
- benzodiazepines: alprazolam (2 cases); clonazepam metabolite (1 case), midazolam metabolite (1 case);
- other drugs and alcohol: THC (3 cases); alcohol (3 cases); ethylhexedrone (3 cases); ethylheptedrone (2 cases); MDMA (2 cases); ketamine (1 case); carbamazepine (1 case); clomipramine (1 case); tiapride (1 case).

Reported ante-mortem symptoms and clinical features included loss of consciousness, chest pain, respiratory problems, tremor, seizures, somnolence, aggressive behaviour, and foaming

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

at the mouth. Three of the cases were found dead. At least some of the individuals were known drug users. One case involved prisoner and one case a person experiencing homelessness.

A cause of death was reported in 19 cases. The reported causes of death were: cardiac arrest due to substance overdose (7 cases; 37%), acute heart failure (7 cases; 37%), traumatic shock (2 cases; 11%), strangulation (1 case; 5%), brain oedema (1 case; 5%), and asphyxiation following aspirating vomit (1 case; 5%).

In some cases, 4F-MDMB-BICA appears to be supplied to people who are using these substances in a mixture with one or more other synthetic cannabinoids, including 5F-MDMB-PICA and MDMB-4en-PINACA (7) (also subject to an EMCDDA initial report (EMCDDA, 2020c)). It is unknown whether producers add these substances deliberately or accidentally. In addition, it is unknown what effect such mixtures may have in humans.

Evaluating the toxicological significance of synthetic cannabinoids involved in death cases requires a case-by-case approach. This has been recommended to include evaluations of patterns of use (e.g. occasional versus chronic) and tolerance, but also a multi-disciplinary evaluation of clinical, circumstantial, toxicological, and autoptic data (Giorgetti et al., 2020).

Deaths identified from other sources

Information about deaths associated with 4F-MDMB-BICA from other sources could not be identified.

6.2.3 Driving and operating machinery under influence

Specific information related to 4F-MDMB-BICA could not be identified. However, 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, and examples from reports include: 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, confusion, and continuous 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 4F-MDMB-BICA 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 detrimental cardiovascular health (Ozturk et al., 2019; Pacher et al., 2018).

7. Social risks

Whilst there is limited information for 4F-MDMB-BICA, 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 4F-MDMB-BICA has been seized in prisons and other custodial settings in at least 5 Member States during 2020.

7.1 Individual social risks

While there is no specific information on whether the use of 4F-MDMB-BICA 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 4F-MDMB-BICA 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 4F-MDMB-BICA on society as a whole, 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, 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.

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

7.4 Economic costs

There is no information on the health and social costs related to 4F-MDMB-BICA. As 4F-MDMB-BICA 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 4F-MDMB-BICA related to the cultural context. As 4F-MDMB-BICA 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 4F-MDMB-BICA 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 4F-MDMB-BICA. 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.

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.

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.

Similar to other new psychoactive substances, it also appears that there is interest in 4F-MDMB-BICA by people who experiment with a range of psychoactive 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 4F-MDMB-BICA within Europe (EMCDDA, 2020b).

The effect of the on-going COVID-19 pandemic (ECDD, 2020; EMCDDA, 2020e; WHO, 2020b) on the manufacture, trafficking, distribution, and use of 4F-MDMB-BICA is currently unknown. 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 4F-MDMB-BICA.

8. Other relevant information

8.1 Information on restrictive measures

8.1.1 International restrictive measures

At international level, 4F-MDMB-BICA 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). 4F-MDMB-BICA has not been subject to assessment nor is it currently under assessment by the United Nations system (EMCDDA, 2020b).

8.1.2 National restrictive measures

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

4F-MDMB-BICA is subject to restrictive measures in thirteen Member States: in Croatia, Cyprus, France, Italy, Latvia, Luxembourg, Poland, 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, 4F-MDMB-BICA is controlled under medicines legislation in Norway and under drug control legislation in Turkey (EMCDDA, 2020b).

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

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