European Monitoring Centre
for Drugs and Drug Addiction

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

In accordance with Article 5b of Regulation (EC) No 1920/2006 (as amended)

Contents

Statement regarding the United Kingdom

The reference period for this report includes 2020 (up to the moment of writing). The United Kingdom left the European Union as of 1 February 2020. However, during the transitional period, the UK 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.

Acknowledgements

The EMCDDA would like to thank the following for their contribution in producing this publication:

- the Early Warning System (EWS) correspondents of the Reitox national focal points (NFPs) and experts from their national EWS networks;
- the Europol national units (ENUs) and Europol Project Synergy;
- the national competent authorities responsible for human and veterinary medicinal products in the Member States, Norway, Iceland and Liechtenstein;
- 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; and,
- the World Health Organization.

In addition, the EMCDDA would also like to express their thanks and appreciation to the Public Health Agency of Sweden and the National Board of Forensic Medicine, Sweden, for providing information on the pharmacology of 4F-MDMB-BICA used in this initial report.

1. Introduction

Methyl 2-({[1-(4-fluorobutyl)-1*H*-indol-3-yl]carbonyl}amino)-3,3-dimethylbutanoate (4F-MDMB-BICA) is a synthetic cannabinoid receptor agonist. Similar to other synthetic cannabinoids, it is sold as a 'legal' replacement for cannabis. Because of their high potency, synthetic cannabinoids can pose a high risk of severe poisoning, which in some cases can be fatal.

In Europe, 4F-MDMB-BICA is monitored by the EMCDDA as a new psychoactive substance ([1]) through the European Union Early Warning System (EWS) in accordance with Article 5a of Regulation (EC) No 1920/2006 (as amended) ([2,3]).

4F-MDMB-BICA was formally notified as a new psychoactive substance ([4,5]) by the EMCDDA on behalf of Belgium on 2 July 2020. The notification was based on the identification of the substance in 1.5 kilograms of white powder seized by Belgian Customs at Bierset Airport, Belgium, on 31 March 2020. The seizure originated from China and was en route to the Netherlands.

Since the formal notification, information on 4F-MDMB-BICA has been exchanged between the EMCDDA and the European Union EWS Network (EMCDDA, Europol, Reitox national focal points, and the Commission); the EMA have been kept duly informed.

On 14 August 2020, the EMCDDA issued a public health alert to the Network highlighting an outbreak of 11 deaths ([6]) associated with 4F-MDMB-BICA in Hungary between May and August 2020.

On 8 September 2020, the EMCDDA informed the EWS Network that based on potential public health risks, the EMCDDA had added 4F-MDMB-BICA to the list of new psychoactive substances under intensive monitoring ([7]) and requested that the Network expedite reporting of any event involving 4F-MDMB-BICA to the EMCDDA until further notice.

Article 5b of Regulation (EC) No 1920/2006 (as amended) requires that '*Where the Centre, the Commission or a majority of the Member States considers that information shared on a*

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[1] As defined in point 4 of Article 1 of Council Framework Decision 2004/757/JHA of 25 October 2004 laying down minimum provisions on the constituent elements of criminal acts and penalties in the field of illicit drug trafficking (OJ L 335, 11.11.2004, p. 8).
[2] Regulation (EC) No 1920/2006 of the European Parliament and of the Council of 12 December 2006 on the European Monitoring Centre for Drugs and Drug Addiction (recast) (O J L 376, 27.12.2006, p.1-13).
[3] Regulation (EU) 2017/2101 of the European Parliament and of the Council of 15 November 2017 amending Regulation (EC) No 1920/2006 as regards information exchange on, and an early warning system and risk assessment procedure for, new psychoactive substances (O J L 305, 21.11.2017, p.1-7).
[4] EMCDDA (2019), EMCDDA operating guidelines for the European Union Early Warning System on new psychoactive substances, European Monitoring Centre for Drugs and Drug Addiction, Publications Office of the European Union, Luxembourg. https://www.emcdda.europa.eu/publications/guidelines/operating-guidelines-for-the-european-union-early-warning-system-on-new-psychoactive-substances_en
[5] EMCDDA (2019), EMCDDA operating guidelines for the European Union Early Warning System on new psychoactive substances, Guidance note 2. Formal notification of a new psychoactive substance. https://www.emcdda.europa.eu/system/files/publications/12213/downloads/Guidance%20Note%202-%20Formal%20notification%20of%20a%20new%20psychoactive%20substance.pdf
[6] At the time the alert was issued, Hungary reported 11 deaths in which 4F-MDMB-BICA had been identified in biological samples. Since then, Hungary has reported an additional ten deaths, bringing the total number of deaths reported to 21 as of 8 October 2020.
[7] EMCDDA (2019), EMCDDA operating guidelines for the European Union Early Warning System on new psychoactive substances, Guidance note 6. Intensive monitoring. https://www.emcdda.europa.eu/system/files/publications/12213/downloads/Guidance%20Note%207-%20Substances%20of%20high%20concern.pdf

new psychoactive substance collected pursuant to Article 5a in one or more Member States gives rise to concerns that the new psychoactive substance may pose health or social risks at Union level, the Centre shall draw up an initial report on the new psychoactive substance'.

The initial report is submitted to the Commission and the Member States. The purpose of the initial report is to provide scientific evidence to the Commission to allow it to make an informed decision regarding whether or not there is a need to request a risk assessment on a new psychoactive substance as set out in Article 5c of Regulation (EC) No 1920/2006 (as amended).

Based on the information reported by the Network, on 2 September 2020, the EMCDDA assessed the existing information ([8,9]) on 4F-MDMB-BICA, based on the following criteria:

- reports of health problems;
- reports of social problems;
- reports of seized material;
- pharmacological and toxicological properties and analogy with better-studied substances; and,
- potential for further spread.

The EMCDDA concluded that the assessment gave rise to concerns that 4F-MDMB-BICA may pose health or social risks at Union level, and, consequently, determined that an initial report should be produced.

2. Information collection process

In accordance with the requirements of Article 5b of the Regulation, on 9 September 2020, the EMCDDA launched a procedure for the collection of additional information on 4F-MDMB-BICA in order to support the production of the initial report.

The EMCDDA collected information through:

- a structured reporting form to the Reitox national focal points in the Member States, Turkey, and Norway (Article 5b(4));
- routine monitoring of open source information;
- a search of open source information conducted specifically for the production of the initial report which included: scientific and medical literature, official reports, grey literature, internet drug discussion forums and related websites (hereafter, 'user websites'), and online vendors.

[8] EMCDDA (2019), EMCDDA operating guidelines for the European Union Early Warning System on new psychoactive substances, European Monitoring Centre for Drugs and Drug Addiction, Publications Office of the European Union, Luxembourg. https://www.emcdda.europa.eu/publications/guidelines/operating-guidelines-for-the-european-union-early-warning-system-on-new-psychoactive-substances_en

[9] This included information reported to the EMCDDA through the Early Warning System, including case reports and aggregated datasets.

In addition, the EMCDDA also submitted requests to:

- The World Health Organization (WHO) in order to determine if 4F-MDMB-BICA is under assessment or has been under assessment within the system established by the 1961 Single Convention on Narcotic Drugs, as amended by the 1972 Protocol, and the 1971 Convention on Psychotropic Substances ('United Nations system').

- The European Medicines Agency (EMA) in order to determine if 4F-MDMB-BICA is used as an active substance in a medicinal product for human or veterinary use at Union or national level (Article 5b(5)). Specifically, the EMA was asked if 4F-MDMB-BICA is an active substance in:

    a. 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 ([10]), Directive 2001/82/EC of the European Parliament and of the Council ([11]) or Regulation (EC) No 726/2004 of the European Parliament and of the Council ([12]);

    b. a medicinal product for human use or in a veterinary medicinal product that is the subject of an application for a marketing authorisation;

    c. a medicinal product for human use or in a veterinary medicinal product whose marketing authorisation has been suspended by the competent authority;

    d. 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;

    e. 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 ([13]).

- Europol in order to provide information on the involvement of criminal groups in the manufacture, distribution and distribution methods, and trafficking of 4F-MDMB-BICA, and in any use of 4F-MDMB-BICA (Article 5b(6)).

- The European Chemicals Agency (ECHA), the European Centre for Disease Prevention and Control (ECDC) and the European Food Safety Authority (EFSA) in order to provide the information and data at their disposal on 4F-MDMB-BICA (Article 5b(7)).

[10] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67).
[11] Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products (OJ L 311, 28.11.2001, p. 1).
[12] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30.4.2004, p. 1).
[13] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (OJ L 121, 1.5.2001, p. 34).

The information collection process was concluded on 7 October 2020. The EMCDDA received responses from all 28 Member States, Turkey, and Norway. In addition, the EMCDDA received responses from WHO, EMA, Europol, ECHA, ECDC, and EFSA.

3. Information required by Article 5b(2) of the Regulation

The order and titles of subsections 3.1 to 3.9, below, are as they appear in Article 5b(2) of Regulation (EC) No 1920/2006 (as amended); sections 3.1 to 3.4 are cross-referenced with the headings of Article 5b(2a) to Article 5b(2d) of the Regulation.

3.1. Nature, number and scale of incidents showing health and social problems in which the new psychoactive substance may potentially be involved, and the patterns of use of the new psychoactive substance

As 4F-MDMB-BICA has only been on the drug market for a short period of time, it may not be part of drug screening in many forensic and toxicology laboratories. Therefore, the presence of 4F-MDMB-BICA 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, due to differences in reporting practices across Europe, identifications of 4F-MDMB-BICA may be unreported to the Reitox national focal points and as a consequence to the EMCDDA.

3.1.1. Information from seizures, collected and biological samples

As of 8 October 2020, 4F-MDMB-BICA has been identified in a total of 256 detections in ten Member States: Hungary (219 detections), the United Kingdom (17), Belgium (4), Slovenia (4), Cyprus (3), Finland (3), Germany (2), Lithuania (2), Croatia (1) and Poland (1). These relate to 108 seizures, of which 101 were reported by the police, and 7 by customs; 1 collected sample; and 147 biological samples (of which 21 were associated with deaths). All detections occurred in 2020. In addition, two detections were reported by Slovenia ([14]) and by Italy ([15]) after the data submission deadline, which have not been included in the dataset.

Information from seizures

Law enforcement seizures of 4F-MDMB-BICA have been reported by 10 Member States: Hungary (72 seizures), the United Kingdom (17), Belgium (4), Cyprus (3), Finland (3), Slovenia (3), Germany (2), Lithuania (2), Croatia (1) and Poland (1).

In total, 108 seizures were reported. These included: 101 seizures by the police, and 7 by customs. Ten of the police seizures occurred in prisons. Where reported, seizures took place between March and September 2020.

[14] Slovenia reported a seizure made by police in prison, of 6.31 grams of herbal material containing also MDMB-4en-PINACA, 5F-MDMB-PICA, 5F-EMB-PICA and traces of JWH-210.
[15] Italy reported a seizure of a padded postal envelope containing two packages, one of which contained 4F-MDMB-BICA (labelled as 4F-MDMB-BINACA). The seizure occurred in July 2020.

Seizures included smoking mixtures (31 cases), powders (18), pieces of paper impregnated with the substance (7) (including blotters), and liquids (3). For 49 seizures reported by Hungary no details were provided.

Customs seizures

A total of 7 seizures made by customs amounting to 5.57 kg were reported by: Belgium (4) and Finland (3). All the seizures were in powder form, and occurred between March and September 2020.

The seizures reported by Belgian customs accounted for 99.9% of the powders seized (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 Bierset 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 seizures reported by Finnish customs ranged from 0.4 mg to 1.3 grams. They originated from the Netherlands (2) and Spain (1). One of the seizures was labelled as '5F-MDMB-2201'.

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

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

Police seizures

A total of 101 seizures by the police were reported by Hungary (72 seizures), the United Kingdom (17), Cyprus (3), Slovenia (3), Germany (2), Lithuania (2), Croatia (1) and Poland (1). The seizures occurred between April and September 2020.

Out of the 101 police seizures, 10 seizures occurred in prisons and other custodial settings, and were reported by Slovenia (3), the United Kingdom (3), Lithuania (2), Cyprus (1), and Hungary (1).

4F-MDMB-BICA was detected in smoking mixtures, powders, pieces of 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, 31 police seizures of smoking mixtures amounting to 606.35 grams and containing 4F-MDMB-BICA were reported by Hungary (12 cases), the United Kingdom (12 cases), Slovenia (3), Cyprus (2), Croatia (1), and Germany (1).

There is no indication 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 remaining cases, 1 other synthetic cannabinoid (10 cases), 2 (2 cases), 3 (3 cases), and 7 other cannabinoids (1 case) were also identified.

The three seizures reported by Slovenia occurred in prisons. All the seizures reported contained also 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, 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, 11 seizures of powder containing 4F-MDMB-BICA were reported by 3 Member States: Hungary (9), Germany (1), and Poland (1). The seizures reported by Germany and Poland amounted to 10.78 grams.

Powders were described as white, off-white, brown and orange. 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, including in 13 blotters (5 of the seizures) were reported. 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 (identified in 3 cases), and 5F-MDMB-PICA (2).

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 vape cartridge. The seizures were of 0.8 and 563 ml. The seizure of 0.8 ml also contained 4F-MDMB-BINACA.

In the seizure reported by Hungary, 4F-MDMB-BICA was identified in nail varnish remover.

- *Other*

For 49 seizures reported by Hungary no details were provided.

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%.

Information from biological samples

Serious adverse events with confirmed exposure to 4F-MDMB-BICA from biological samples (21 cases reported by Hungary) are discussed in section 3.1.2.

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

3.1.2. Health problems

As 4F-MDMB-BICA is a synthetic cannabinoid, the health risks may have some similarities with those associated with other synthetic cannabinoids.

Hungary reported 21 deaths in which 4F-MDMB-BICA was identified in biological samples. The deaths occurred between May and August 2020. It was reported that in some of the deaths other synthetic cannabinoids, particularly 5F-MDMB-PICA, were also identified in biological samples. The reported symptoms and clinical features included chest pain, respiratory problems, tremor, and seizures. Further information on the role of 4F-MDMB-BICA in the deaths are currently unavailable.

In some cases, 4F-MDMB-BICA appears to be supplied to users in a mixture with one or more other synthetic cannabinoid, including 5F-MDMB-PICA as well as MDMB-4en-PINACA (also currently subject to an EMCDDA initial report). It is unknown whether these substances are added deliberately or accidentally by producers. In addition, it is also unknown what effect such mixtures may have in humans.

ECDC reported that currently they do not have any information on 4F-MDMB-BICA.

3.1.3. Social problems

While there is limited data 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, the market in synthetic cannabinoids has been linked to an increase in aggression, violence, bullying, and debt. In some cases this has caused a serious threat to the overall safety and security of the prison environment (Blackman and Bradley, 2017; HMIP, 2015; Ralphs et al., 2017; User Voice, 2016). 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.

3.1.4. Patterns of use

There is limited information on the patterns of use of 4F-MDMB-BICA. 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.

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.

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.

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

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

There are three main types of products containing 4F-MDMB-BICA that are sold on the drug market. The most common products are smoking mixtures, where 4F-MDMB-BICA 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’)). There are also e-liquids, where a solution of 4F-MDMB-BICA is prepared by mixing it with a solvent, which is then vaped using an electronic 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, users may prepare their own similar products using 4F-MDMB-BICA purchased from a vendor or dealer.

3.2. Chemical and physical description of the new psychoactive substance and the methods and precursors used for its manufacture or extraction

3.2.1. Chemical description and names

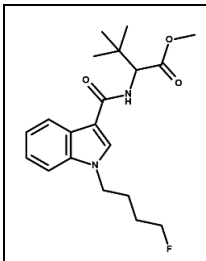
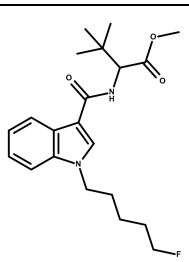
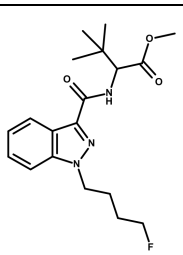
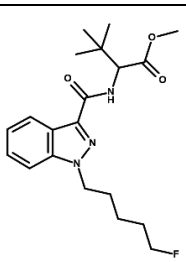
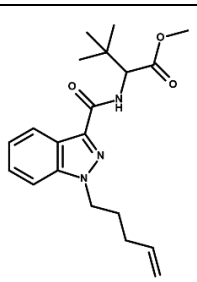
4F-MDMB-BICA is a synthetic cannabinoid receptor agonist. It contains an indole core, a common structural feature in many of the synthetic cannabinoids monitored by the EMCDDA, a carboxamide link, a dimethyl methyl butanoate linked group, and a 4-fluorobutyl tail.

4F-MDMB-BICA appears not to have been described in the scientific or patent literature prior to the first detection on the drug market in Europe in March 2020.

4F-MDMB-BICA shares structural features with a number of substances, including: 5F-MDMB-PICA ([16]), 4F-MDMB-BINACA ([16]), 5F-MDMB-PINACA ([17]) and MDMB-4en-PINACA ([18]). Structurally, 4F-MDMB-BICA differs in the tail (5-fluoropentyl) from 5F-MDMB-PICA; in the core (indazole) from 4F-MDMB-BINACA; in the core (indazole) and in the tail (5-fluoropentyl) from 5F-MDMB-PINACA; and in the core (indazole) and tail (pent-4-ene moiety) from MDMB-4en-PINACA.

The molecular structure, molecular formula and molecular mass of 4F-MDMB-BICA are provided in Figure 1.

Figure 1. Molecular structure, molecular formula, and molecular mass of 4F-MDMB-BICA. Information on 5F-MDMB-PICA, 4F-MDMB-BINACA, 5F-MDMB-PINACA and MDMB-4en-PINACA is provided for comparison.

					
	4F-MDMB-BICA	5F-MDMB-PICA ([19])	4F-MDMB-BINACA ([20])	5F-MDMB-PINACA ([21])	MDMB-4en-PINACA ([22])
Molecular formula	$C_{20}H_{27}FN_2O_3$	$C_{21}H_{29}FN_2O_3$	$C_{19}H_{26}FN_3O_3$	$C_{20}H_{28}FN_3O_3$	$C_{20}H_{27}N_3O_3$
Molecular mass	362.44	376.47	363.43	377.453	357.45

Common name:

4F-MDMB-BICA

Systematic (IUPAC) name:

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

[16] 5F-MDMB-PICA and 4F-MDMB-BINACA were critically reviewed by the WHO's Expert Committee on Drug Dependence (ECDD) in 2019 and have been added to Schedule II of the 1971 United Nations Single Convention on Psychotropic Substances, which will come into force on 3 November 2020.
[17] 5F-MDMB-PINACA was critically reviewed by ECDD in 2017 and is internationally controlled under Schedule II of the 1971 United Nations Single Convention on Psychotropic Substances.
[18] MDMB-4en-PINACA is currently under review by ECDD and is the subject of an EMCDDA initial report.
[19] Methyl 2-[[1-(5-fluoropentyl)indole-3-carbonyl]amino]-3,3-dimethyl-butanoate
[20] Methyl 2-(1-(4-fluorobutyl)-1*H*-indazole-3-carboxamido)-3,3-dimethylbutanoate
[21] Methyl 2-[[1-(5-fluoropentyl)indazole-3-carbonyl]amino]-3,3-dimethyl-butanoate
[22] Methyl 3,3-dimethyl-2-(1-(pent-4-en-1-yl)-1*H*-indazole-3-carboxamido)butanoate

Other chemical names:

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

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

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

Other names:

MDMB-4F-BICA

4F-MDMB-BUTICA

MDMB-4F-BUTICA

4-Fluoro MDMB-BICA

4-Fluoro MDMB-BUTICA

4FBC

4FBCA

MDMB-073-F

4F-MDMB-2201

Chemical Abstracts Service (CAS) registry numbers:

Not registered

IUPAC International Chemical Identifier Key (InCHI Key):

QIKHYQCWGUGFBB-UHFFFAOYSA-N

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

O=C(OC)C(NC(=O)c1cn(CCCCF)c2ccccc21)C(C)(C)C

3.2.2. Physical description

There is no information available on the solubility, lipophilicity, melting and boiling points or other physico-chemical properties of 4F-MDMB-BICA.

Due to its similarity to 5F-MDMB-PINACA, 4F-MDMB-BICA is expected to be soluble in ethanol (EtOH), methanol (MeOH), dimethyl sulfoxide (DMSO) and partially soluble in water.

To date, seizures and collected samples containing 4F-MDMB-BICA reported to the EMCDDA have been in white, brown and orange powders and in herbal material. 4F-MDMB-

BICA has also been identified in blotters, papers impregnated with the substance and in liquids contained in vape cartridges.

4F-MDMB-BICA has been identified in combination with other synthetic cannabinoids including: 5F-MDMB-PICA, MDMB-4en-PINACA, 5F-EMB-PICA, 5F-MDMB-PINACA, 4F-MDMB-BINACA, CUMYL-5FPINACA, CUMYL-PeGACLONE.

In at least some of the detections, the free base of 4F-MDMB-BICA was identified.

A more detailed description of seizures and collected samples can be found in section 3.1.1.

3.2.3. 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 4F-MDMB-BICA has not been reported in the literature. However, it may be carried out in analogy to the synthesis of its higher homologue 5F-MDMB-PICA, described by Banister *et al*., starting with indole which was reacted with methyl L-*tert*-leucinate, yielding (*S*)-5F-MDMB-PICA (Banister et al., 2016). The (*R*)-enantiomer may be synthesised under identical conditions using methyl D-*tert*-leucinate instead of methyl L-*tert*-leucinate. Using methyl *tert*-leucinate as a racemate would lead to the production of the racemic substance.

Potential precursors of 4F-MDMB-BICA are indole-3-carboxylic acid, indole-3-carboxylic acid methyl ester, indole, L-*tert*-leucine methyl ester (for the synthesis of the (*S*) enantiomer) and 1-bromo-4-fluorobutane.

There is no information on the actual manufacturing methods used to make the 4F-MDMB-BICA which has been identified in Europe. However, impurities identified may provide some indication of the synthetic route utilised. In one of the samples of powder seized by Belgian customs, the precursor ethanamine (commonly known as ethylamine) was identified in the sample at approximately 4% (w/w %), along with other minor impurities. In another seizure, triethylamine salt and dimethylformamide were reported as impurities.

3.2.4. Detection and analysis

Methods documented in the literature for the identification of 4F-MDMB-BICA in physical samples include: gas chromatography–mass spectrometry (GC-MS) (NPS Discovery, 2020; Cayman Chemical, 2020; RESPONSE, 2020; Norman et al., 2020a); Fourier transform infrared spectroscopy (FTIR), high-performance liquid chromatography (HPLC) and ^{1}H, ^{13}C and ^{19}F nuclear magnetic resonance spectroscopy (NMR) (RESPONSE 2020); ultraviolet spectroscopy (Cayman Chemical, 2020); liquid chromatography-mass spectrometry (LC-MS) (NPS Discovery, 2020); ultra-performance liquid chromatography-photodiode detector-quadrupole/time of flight-mass spectrometry (UPLC-PDA-Q/TOF-MS) and Ion mobility spectrometry (IMS) (Norman et al., 2020a; Norman et al. 2020b).

No methods documenting the detection of 4F-MDMB-BICA in biological samples were identified in the literature.

Quantification of 4F-MDMB-BICA in products can be carried out according to the general procedure described by the UNODC (UNODC, 2013).

4F-MDMB-BICA contains a stereocentre thus allowing for the existence of a pair of enantiomers, (*R*)- and (*S*)-4F-MDMB-BICA. The S-enantiomer of 4F-MDMB-BICA is available as a reference standard, in the form of a crystalline solid ([23]).

There is no representative information on the enantiomeric composition of the samples of 4F-MDMB-BICA detected within the European Union, which in part may reflect the fact that stereochemical analysis is not routinely undertaken in forensic laboratories. Based on the literature of similar compounds (Banister 2016) and the most likely precursors to be used, an (*S*)-configuration of the stereocentre could be expected.

Differentiation of enantiomers is possible using the following techniques: chiral chromatography, vibrational circular dichroism (VCD) spectroscopy and/or electronic circular dichroism (ECD) spectroscopy.

4F-MDMB-BICA and 5F-AMB-PICA ([24]) are isomers therefore it is important to note that GC-MS analysis of these substances will result in very similar mass spectrometry fragmentation patterns. The ability to distinguish between isomers requires the use of analytical reference standards, access to reference spectra for both substances, and/or additional analytical methods ([25]).

Norman et al., highlighted that although 4F-MDMB-BICA is not currently included in Ion Trap Mobility Spectroscopy (ITMS) instrument libraries, the substance produced a 'system "spice" alarm' as a result of structural similarities with synthetic cannabinoids used to set up the alarms, which then allowed for the provisional identification of 4F-MDMB-BICA (Norman et al, 2020b).

4F-MDMB-BICA is currently screened for in some, but not all, forensic and toxicology laboratories in Europe. As a result, some cases of 4F-MDMB-BICA are likely to be undetected and under reported, leading to incomplete data regarding detections of 4F-MDMB-BICA in Europe.

3.3. Pharmacological and toxicological description of the new psychoactive substance

4F-MDMB-BICA is a synthetic cannabinoid receptor agonist. Limited data suggests that 4F-MDMB-BICA is a CB_1 receptor agonist (NBFM and PHA, 2020) that shares some similarities with the major psychoactive constituent of cannabis Δ^9-tetrahydrocannabinol (THC) and other synthetic cannabinoids, such as JWH-018.

The acute effects of THC (and consequently cannabis) include: relaxation, euphoria, lethargy, depersonalisation, distorted perception of time, impaired motor performance, hallucinations, paranoia, confusion, fear, anxiety, dry mouth, reddening of the conjunctivae of the eyes, tachycardia, and, nausea and vomiting. THC also has an abuse liability and

[23] https://www.caymanchem.com/product/31075/4-fluoro-mdmb-butica
[24] Methyl 2-[[1-(5-fluoropentyl)indole-3-carbonyl]amino]-3-methyl-butanoate
[25] Reference standard material for 5F-AMB-PICA is available: https://www.caymanchem.com/product/15971/mmb2201

dependence potential (Pertwee, 2014; Wiley et al., 2016). Similar effects to cannabis have been reported for synthetic cannabinoids such as 4F-MDMB-BICA. In some cases, the effects are reported to be more pronounced/severe (EMCDDA, 2017).

Compared to cannabis, severe and fatal poisoning appears to be more common with synthetic cannabinoids (EMCDDA, 2017; Tait et al., 2016). 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/hyperemesis, delirium, agitation, psychosis, and, aggressive and violent behaviour. Sudden death has also been reported. The mechanisms of this toxicity are poorly understood (Tai and Fantegrossi, 2016), but factors that are likely to play an important role are the potency of the substances and the doses that users are exposed to. In addition, some of the effects of poisoning — such as loss of consciousness or behavioural effects — may place users at additional risks such as choking on vomitus, drowning, or self-harm.

Considering its chemical structure, 4F-MDMB-BICA might pose similar health risks as 4F-MDMB-BINACA and 5F-MDMB-PICA. Both 4F-MDMB-BINACA and 5F-MDMB-PICA have been associated with serious adverse events, including deaths (ECDD 2019a; ECDD 2019b; Krotulski et al.,2019; Kleis et al., 2020).

Currently there is no antidote to poisoning caused by synthetic cannabinoids.

In general, the use of smoking mixtures containing synthetic cannabinoids appears to pose a high risk of poisoning. This is because manufacturers guess the amount of cannabinoids(s) to add to the herbal material, and the manufacturing process makes it difficult to dilute them sufficiently and distribute them consistently throughout the material. This can result in mixtures that contain a large amount of highly potent cannabinoid, as well as ‘hot pockets’ where the cannabinoid is highly concentrated within parts of the herbal material (Schäper, 2016). Together, this makes it difficult for users to control the dose that they are exposed to. As these mixtures are typically smoked as cigarettes ('joints'), users can inadvertently administer a toxic dose; in some cases, a small number of puffs from a cigarette have been sufficient to cause severe poisoning. Reflecting these risks, smoking mixtures have caused a large number of outbreaks of mass poisonings in recent years (Adams et al., 2017; Kasper et al., 2015; Schwartz et al., 2015; Shevyrin et al., 2015; Trecki et al., 2015; Tyndall et al., 2015). Such outbreaks have the potential to overwhelm local healthcare systems, which is of particular concern considering the ongoing COVID-19 pandemic.

While there is limited data for 4F-MDMB-BICA, the chronic health risks might share similarities to cannabis and other synthetic cannabinoids. This may include dependence.

ECHA reported to the EMCDDA that they do not currently have any information on 4F-MDMB-BICA at their disposal, in particular any data on its toxicological properties. EFSA reported to the EMCDDA that they do not currently have any information on 4F-MDMB-BICA, including both describing the hazard and concerning human exposure.

3.4. Involvement of criminal groups in the manufacture or distribution of the new psychoactive substance.

Europol received replies from 19 Member States: Belgium, Bulgaria, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Latvia, Lithuania, Luxembourg, Romania, Portugal, Slovakia, Slovenia, Spain, and the United Kingdom.

Replies were also received from the United States Drug Enforcement Administration (DEA) ([26]) and New Zealand ([27]).

No information was received on the involvement of criminal groups in the manufacture or distribution of 4F-MDMB-BICA.

All seizures of 4F-MDMB-BICA reported to Europol occurred in 2020, with the majority reported to have taken place between April and September 2020.

Belgium reported 4 seizures of between 0.001 and 3 kilograms of 4F-MDMB-BICA, between April and July 2020. 4F-MDMB-BICA was labelled as 'Ion Exchange Resin' in two of these seizures. The substance was en-route from China to the Netherlands in 3 of the seizures. Belgium remarked that they are a transit country for 4F-MDMB-BICA from China to other EU Member States, such as Hungary, the Netherlands, Romania, and the United Kingdom.

Slovakia ([28]) reported that 4F-MDMB-BICA was identified with MDMB-4en-PINACA and A-CHMINACA ([29]) in yellow crystalline material, contained in 2 plastic tubes, seized in postal consignments en-route from the Netherlands to Hong Kong, in September 2020.

4F-MDMB-BICA was also identified in 5 grams of herbal material seized in a prison in Slovenia in September 2020,

4F-MDMB-BICA has also been identified in seizures in Finland and Romania ([30]) in 2020.

3.5. Information on the human and veterinary medical use of the new psychoactive substance, including as an active substance in a medicinal product for human use or in a veterinary medicinal product

Based on the reported information from the EMA ([31]), it appears that 4F-MDMB-BICA is not an active substance in:

a. 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;

[26] The U.S. DEA did not report any seizures of 4F-MDMB-BICA.
[27] New Zealand did not report any seizure of 4F-MDMB-BICA.
[28] Slovakia had not reported this seizure of 4F-MDMB-BICA to the EMCDDA
[29] *N*-(1-adamantyl)-1-(cyclohexylmethyl)indazole-3-carboxamide
[30] Romania had not reported this seizure of 4F-MDMB-BICA to the EMCDDA
[31] 26 Member States, as well as Norway and Iceland provided a response to the EMA's request regarding human and/or veterinary medicinal products.

b. a medicinal product for human use or in a veterinary medicinal product that is the subject of an application for a marketing authorisation;

c. 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:

d. 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;

e. 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.

3.6. Information on the commercial and industrial use of the new psychoactive substance, the extent of such use, as well as its use for scientific research and development purposes

4F-MDMB-BICA 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 4F-MDMB-BICA is used for other legitimate purposes.

ECHA and EFSA reported that 4F-MDMB-BICA did not retrieve any results in their databases.

3.7. Information on whether the new psychoactive substance is subject to any restrictive measures in the Member States

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

Drug control legislation

Seven Member States (Croatia, Cyprus, France, Latvia, Luxembourg, Poland, and the United Kingdom) and Turkey reported that 4F-MDMB-BICA is controlled under drug control legislation.

- Croatia reported that 4F-MDMB-BICA is controlled within the List of drugs, psychotropic substances and plants used to produce drugs, and substances that can be used for the production of drugs (OG 13/19) since 2016.

- Cyprus reported that 4F-MDMB-BICA is controlled under drug control legislation (generic legislation) since 15 June 2018.

- France reported that 4F-MDMB-BICA is controlled under drug control legislation (NOR: AFSP1710288A) since 31 March 2017.

- Latvia reported that 4F-MDMB-BICA is controlled under drug control legislation (the Law on Procedures for the Coming into force and Application of the Criminal Law) since 2013.

- Luxembourg reported that 4F-MDMB-BICA is controlled under drug control legislation (RGD du 20 avril 2009 modifiant le RGD modifié du 20 mars 1974 concernant certaines substances psychotropes) since 2009.

- Poland reported that 4F-MDMB-BICA is covered by generic definition of synthetic cannabinoids (Regulation of the Minister of Health on Regulation of the Minister of Health on list of psychotropic drugs, psychoactive substances and new psychoactive substances; main act: Act on Counteracting Drug Addiction) since July 2018.

- United Kingdom reported that 4F-MDMB-BICA is controlled under the Misuse of Drugs Act 1971 since 2 December 2016.

- Turkey reported that 4F-MDMB-BICA is included in Law on Drug Control No. 2313 (taken automatically under legal control with the generic legislation as the NPS detected in the country) as of March 2019.

New psychoactive substance legislation

Four Member States (Austria, Belgium, Germany, and Hungary) reported that 4F-MDMB-BICA is controlled under specific new psychoactive substances control legislation.

- Austria reported that 4F-MDMB-BICA is covered by the Austrian Act on New Psychoactive Substances.

- Belgium reported that 4F-MDMB-BICA is controlled under Belgian Generic Legislation, active since September 2017.

- Germany reported that 4F-MDMB-BICA is covered by the New Psychoactive Substances Act (NpSG).

- Hungary reported that 4F-MDMB-BICA is controlled under specific NPS control legislation (Regulation 55/2014 (XII.30) of the Ministry of Human Capacities).

Medicines legislation

Lithuania and Norway reported that 4F-MDMB-BICA is controlled under medicines legislation.

- Lithuania reported that 4F-MDMB-BICA is controlled under medicines legislation (falls under the definition of the generic group of synthetic cannabinoids) since 21 September 2015.

- Norway reported that 4F-MDMB-BICA is controlled under the Norwegian Law of Medicines.

3.8. Information on whether the new psychoactive substance is currently or has been under assessment within the system established by the 1961 Single Convention on Narcotic Drugs, as amended by the 1972 Protocol, and the 1971 Convention on Psychotropic Substances

The World Health Organization is the specialised United Nations agency designated for the evaluation of the medical, scientific, and public health aspects of psychoactive substances under the Single Convention on Narcotic Drugs, 1961, and the Convention on Psychotropic Substances, 1971.

On 1 October 2020, the World Health Organization informed the EMCDDA that 4F-MDMB-BICA is not currently under assessment nor has it been under assessment by the United Nations system.

3.9. Other relevant information

Switzerland

In June and July 2020, the drug checking service Saferparty reported two samples of cannabis adulterated with 4F-MDMB-BICA. Both samples contained other synthetic cannabinoids: MDMB-4en-PINACA and 5F-MDMB-PICA (Saferparty, 2020).

United States

In the United States, 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 detection of 4F-MDMB-BICA in plant-like material seized in May 2020 (NPS Discovery, 2020).

4. Analysis and assessment

Methyl 2-({[1-(4-fluorobutyl)-1*H*-indol-3-yl]carbonyl}amino)-3,3-dimethylbutanoate (4F-MDMB-BICA) is a synthetic cannabinoid receptor agonist monitored by the EMCDDA as a new psychoactive substance in accordance with Regulation (EC) No 1920/2006 (as amended).

4F-MDMB-BICA has been available on the drug market in Europe since at least March 2020. The substance is sold as a 'legal' replacement for cannabis and other controlled synthetic cannabinoids. 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), which is responsible for the major psychoactive effects of cannabis, and other synthetic cannabinoids, such as JWH-018, which are under international control.

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 consumers products. There are three main types of products containing 4F-MDMB-BICA that are sold on the drug market: smoking mixtures, where 4F-

MDMB-BICA 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 4F-MDMB-BICA is prepared by mixing it with a solvent, which is then inhaled 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, users may prepare their own similar products using 4F-MDMB-BICA purchased from a vendor or dealer.

As of October 2020, 4F-MDMB-BICA has been identified in ten Member States; 108 seizures have been reported, which include 5.6 kg of powder and 0.6 kg of smoking mixtures.

A total of twenty one deaths with confirmed exposure to 4F-MDMB-BICA have been reported by one Member State, Hungary. The deaths occurred over relatively short period of time, between May and August 2020. Further information of the role of 4F-MDMB-BICA in the deaths is currently unavailable.

It is important to note that the presence of 4F-MDMB-BICA on the drug market and in serious adverse events may be undetected in Europe since the substance is not routinely screened for in some laboratories.

The available data 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. In addition, synthetic cannabinoids, particularly when impregnated on to paper, can be easy to smuggle into the prisons 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.

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 ongoing COVID-19 pandemic and the additional burden already on healthcare systems. There is no antidote to poisoning caused by synthetic cannabinoids.

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. As such, it is a concern given the reports of seizures of 4F-MDMB-BICA in prisons and other custodial settings in at least five Member States.

There is no information whether or not criminal groups are involved in the manufacture, trafficking, and distribution of 4F-MDMB-BICA within Europe. The effect of the ongoing

COVID-19 pandemic 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 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.

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, 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 due to a lack of information. Aside from limited use as an analytical reference standard and in scientific research, there is currently no information that suggests 4F-MDMB-BICA is used for other legitimate purposes.

4F-MDMB-BICA is subject to restrictive measures in twelve Member States, Turkey, and Norway. 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. 4F-MDMB-BICA has not been subject to assessment nor is currently under assessment by the United Nations system.

Based on the information reported to the EMCDDA, there are indications that 4F-MDMB-BICA has the potential to spread rapidly in Europe. Of note is that the appearance of 4F-MDMB-BICA on the market appears to coincide with the recent decision to internationally control two closely related synthetic cannabinoids commonly found on the drug market in Europe, 4F-MDMB-BINACA and 5F-MDMB-PICA. As such, it is possible that 4F-MDMB-BICA will be a replacement for these substances.

The EMCDDA will continue to intensively monitor 4F-MDMB-BICA in order to ensure that new information is provided to the Member States, Europol, the Commission, and the EMA through the European Union Early Warning System in a timely manner in order to strengthen situational awareness as well as to continue to inform preparedness and response measures at both national and EU level in order to protect public health.

Based on the analysis of the available information, the EMCDDA considers that there are indications that 4F-MDMB-BICA may pose health or social risks at Union level. We conclude that the potential health and social risks posed by the use, manufacture, distribution and the involvement of criminal groups, could be thoroughly assessed through a risk assessment procedure in accordance with Article 5c of Regulation (EC) No 1920/2006 (as amended).

5. References

Adams, A. J., Banister, S. D., Irizarry, L., Trecki, J., Schwartz, M., Gerona, R., (2017), '"Zombie" outbreak caused by the synthetic cannabinoid AMB-FUBINACA in New York', New England Journal of Medicine, 376(3), pp. 235–242. https://doi.org/10.1056/NEJMoa1610300

Banister, S. D., Longworth, M., Kevin, R., Sachdev, S., Santiago, M., Stuart, J., et al., (2016), 'Pharmacology of valinate and tert-leucinate synthetic cannabinoids 5F-AMBICA, 5F-AMB, 5F-ADB, AMB-FUBINACA, MDMB-FUBINACA, MDMB-CHMICA, and their

analogues', American Chemical Society Chemical Neuroscience, 7(9), pp. 1241–1254. https://doi.org/10.1021/acschemneuro.6b00137

Blackman, S., Bradley, R. (2017), 'From niche to stigma-Headshops to prison: Exploring the rise and fall of synthetic cannabinoid use among young adults', International Journal of Drug Policy, 40, pp. 70–77. https://doi.org/10.1016/j.drugpo.2016.10.015

Cayman Chemical (2020), 'Product Information: 4-fluoro MDMB-BUTICA', https://www.caymanchem.com/product/31075/4-fluoro-mdmb-butica

ECDD (2019a), Expert Committee on Drug Dependence, Critical Review Report: 4F-MDMB-BINACA. Forty-second Meeting, Geneva, 21–25 October 2019. https://www.who.int/medicines/access/controlled-substances/Final_4F-MDMB-BINACA.PDF?ua=1

ECDD (2019b), Expert Committee on Drug Dependence, Critical Review Report: 5F-MDMB-PICA. Forty-second Meeting, Geneva, 21–25 October 2019. https://www.who.int/medicines/access/controlled-substances/Final_5F-MDMB-PICA.PDF?ua=1

EMCDDA (2017), Report on the risk assessment of methyl 2-[[1-(cyclohexylmethyl)-1*H*-indole-3-carbonyl]amino]-3,3-dimethylbutanoate (MDMB-CHMICA) in the framework of the Council Decision on new psychoactive substances, European Monitoring Centre for Drugs and Drug Addiction, Publications Office of the European Union, Luxembourg. http://www.emcdda.europa.eu/publications/risk-assessments/mdmb-chmica

Her Majesty's Inspectorate of Prisons (HMIP) (2015), 'Changing patterns of substance misuse in adult prisons and service responses', Her Majesty's Inspectorate of Prisons, London. https://www.justiceinspectorates.gov.uk/hmiprisons/wp-content/uploads/sites/4/2015/12/Substance-misuse-web-2015.pdf

Kasper, A. M., Ridpath, A. D., Arnold, J. K., Chatham-Stephens, K., Morrison, M., Olayinka, O. et al., (2015), 'Severe illness associated with reported use of synthetic cannabinoids—Mississippi, April 2015', MMWR Morbidity and Mortality Weekly Report, 64(39), pp. 1121–1122. https://doi.org/10.15585/mmwr.mm6439a7

Kleis, J., Germerott, T., Halter, S., Héroux, V., Roehrich, J., Schwarz, C.S., Hess, C., (2020), 'The synthetic cannabinoid 5F-MDMB-PICA: A case series', Forensic Science International, 314, 110410. https://doi.org/10.1016/j.forsciint.2020.110410

Krotulski, A.J., Mohr, A.L., Kacinko, S.L., Fogarty, M.F., Shuda, S.A., Diamond, F.X., Kinney, W.A., Menendez, M., Logan, B.K., (2019), '4F-MDMB-BINACA: a new synthetic cannabinoid widely implicated in forensic casework', Journal of Forensic Sciences, 64(5), pp. 1451–1461. https://doi.org/10.1111/1556-4029.14101

National Board of Forensic Medicine (NBFM) and Public Health Agency of Sweden (PHA), (2020), English summary of receptor activation for 4-fluoro MDMB-BUTICA.

Norman, C., Walker, G., McKirdy, B., McDonald, C., Fletcher, D., Antonides, L.H., Sutcliffe, O.B., Nic Daéid, N., McKenzie, C. (2020a), 'Detection and quantitation of synthetic

cannabinoid receptor agonists in infused papers from prisons in a constantly evolving illicit market', Drug Testing and Analysis,12(4), pp. 538–554. https://doi.org/10.1002/dta.2767

Norman, C., McKirdy, B., Walker, G., Dugard, P., NicDaéid, N., McKenzie, C. (2020b), (under review), 'Large-scale evaluation of ion mobility spectrometry for the rapid detection of synthetic cannabinoid receptor agonists in infused papers in prisons', Drug Testing and Analysis.

NPS Discovery (2020), '4F-MDMB-BICA', Center for Forensic Science Research and Education (CFSRE). https://www.npsdiscovery.org/wp-content/uploads/2020/06/4F-MDMB-BICA_070120_NMSLabs_Report.pdf

Pertwee, R. G., (ed). (2014), 'Handbook of Cannabis', Oxford University Press, Oxford.

Ralphs, R., Williams, L., Askew, R., Norton, A. (2017), 'Adding Spice to the Porridge: The development of a synthetic cannabinoid market in an English prison', International Journal of Drug Policy, 40, pp. 57–69. https://doi.org/10.1016/j.drugpo.2016.10.003

Saferparty. https://www.saferparty.ch/warnungen.html

Schäper, J., (2016), 'Wirkstoffgehalte und inhomogene Verteilung des Wirkstoffs MDMB-CHMICA in Kräutermischungen', Toxichem Krimtech, 83(2), pp. 112–114. https://www.gtfch.org/cms/images/stories/media/tk/tk83_2/Schaeper_et_al_2016.pdf

Schwartz, M. D., Trecki, J., Edison, L. A., Steck, A. R., Arnold, J., Gerona, R. R., (2015), 'A common source outbreak of severe delirium associated with exposure to the novel synthetic cannabinoid ADB-PINACA', Journal of Emergency Medicine, 48(5), pp. 573–580. https://doi.org/10.1016/j.jemermed.2014.12.038

Shevyrin, V., Melkozerov, V., Nevero, A., Eltsov, O., Shafran, Y., Morzherin, Y., Lebedev, A. T. (2015), 'Identification and analytical characteristics of synthetic cannabinoids with an indazole-3-carboxamide structure bearing a *N*-1-methoxycarbonylalkyl group', Analytical and Bioanalytical Chemistry, 407(21), pp. 6301–6315. https://doi.org/10.1007/s00216-015-8612-7

Slovenian National Forensic Laboratory, (2020), 'Analytical report 5F-MDMB-PINACA (C20H27FN2O3) methyl 2-{[1-(4-fluorobutyl)indol-3-yl]formamido}-3,3-dimethylbutanoate; Methyl 2-(1-(4-fluorobutyl)-1*H*-indole3-carboxamido)-3,3-dimethylbutanoate', NPS and related compounds – analytical reports. European project RESPONSE 2 to challenges in forensic drugs analyses. https://www.policija.si/apps/nfl_response_web/0_Analytical_Reports_final/4F-MDMB-BICA-ID-2189-20_report.pdf

Tai, S., Fantegrossi, W. E., (2016), 'Pharmacological and toxicological effects of synthetic cannabinoids and their metabolites', Current Topics in Behavioral Neurosciences, 32, pp. 249–262. https://doi.org/10.1007/7854_2016_60

Tait, R. J., Caldicott, D., Mountain, D., Hill, S. L., Lenton, S. (2016), 'A systematic review of adverse events arising from the use of synthetic cannabinoids and their associated treatment', Clinical Toxicology (Philadelphia), 54(1), pp. 1–13. https://doi.org/10.3109/15563650.2015.1110590

Trecki, J., Gerona, R. R., Schwartz, M. D., (2015), 'Synthetic cannabinoid-related illnesses and deaths', New England Journal of Medicine, 373(2), pp. 103–107. https://doi.org/10.1056/NEJMp1505328

Tyndall, J. A., Gerona, R., De Portu, G., Trecki, J., Elie, M. C., Lucas, J., Slish, J, et al. (2015), 'An outbreak of acute delirium from exposure to the synthetic cannabinoid AB-CHMINACA', Clinical Toxicology (Philadelphia), 53(10), pp. 950–956. https://doi.org/10.3109/15563650.2015.1100306

UNODC (2013), Recommended methods for the identification and analysis of synthetic cannabinoid receptor agonists in seized materials, United Nations Office on Drugs and Crime, Vienna. https://www.unodc.org/documents/scientific/STNAR48_Synthetic_Cannabinoids_ENG.pdf

User Voice (2016), 'Spice: the bird killer — what prisoners think about the use of spice and other legal highs in prison'. https://www.uservoice.org/wp-content/uploads/2020/07/User-Voice-Spice-The-Bird-Killer-Report-compressed.pdf

Wiley, J.L., Owens, R. A., Lichtman, A. H. (2016), 'Discriminative stimulus properties of phytocannabinoids, endocannabinoids, and synthetic cannabinoids', Current Topics in Behavioral Neurosciences, pp. 153–173. https://doi.org/10.1007/7854_2016_24