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Critical Review Report:  
4F-MDMB-BICA

Expert Committee on Drug Dependence  
Forty-fourth Meeting  
Geneva, 11-15 October 2021

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## Contents

<b>Executive Summary .....</b>	<b>5</b>
<b>1. Substance identification.....</b>	<b>6</b>
A. International Nonproprietary Name (INN) .....	6
B. Chemical Abstract Service (CAS) Registry Number.....	6
C. Other Chemical Names.....	6
D. Trade Names .....	6
E. Street Names.....	6
F. Physical Appearance.....	7
G. WHO Review History .....	7
<b>2. Chemistry.....</b>	<b>7</b>
A. Chemical Name .....	7
B. Chemical Structure.....	7
C. Stereoisomers.....	7
D. Methods and Ease of Illicit Manufacturing .....	8
E. Chemical Properties.....	8
F. Identification and Analysis.....	9
<b>3. Ease of Convertibility Into Controlled Substances.....</b>	<b>9</b>
<b>4. General Pharmacology.....</b>	<b>10</b>
A. Routes of administration and dosage.....	10
B. Pharmacokinetics .....	10
C. Pharmacodynamics .....	10
<b>5. Toxicology.....</b>	<b>11</b>
<b>6. Adverse Reactions in Humans .....</b>	<b>11</b>
<b>7. Dependence Potential.....</b>	<b>12</b>
A. Animal Studies.....	12
B. Human Studies.....	12
<b>8. Abuse Potential.....</b>	<b>12</b>
A. Animal Studies.....	12
B. Human Studies.....	12
<b>9. Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use.....</b>	<b>12</b>
<b>10. Listing on the WHO Model List of Essential Medicines.....</b>	<b>12</b>
<b>11. Marketing Authorizations (as a Medicinal Product).....</b>	<b>12</b>
<b>12. Industrial Use.....</b>	<b>12</b>
<b>13. Non-Medical Use, Abuse and Dependence.....</b>	<b>13</b>
<b>14. Nature and Magnitude of Public Health Problems Related to Misuse, Abuse and Dependence.....</b>	<b>13</b>

<i>15. Licit Production, Consumption and International Trade.....</i>	<i>13</i>
<i>16. Illicit Manufacture and Traffic and Related Information.....</i>	<i>13</i>
<i>17. Current International Controls and Their Impact.....</i>	<i>14</i>
<i>18. Current and Past National Controls.....</i>	<i>14</i>
<i>19. Other Medical and Scientific Matters Relevant for a Recommendation on the Scheduling of the Substance.....</i>	<i>14</i>
References.....	15
Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances.....	17

## Executive Summary

4F-MDMB-BICA (CAS: not available), methyl (S)-2-(1-(4-fluorobutyl)-1H-indole-3-carboxamido)-3,3-dimethylbutanoate, is a synthetic cannabinoid that first appeared on the drug market in March 2020 in Belgium. To date, seizures have occurred in Europe and in the United States. The compound is not under international control, but it is regulated by drug or medicines control legislation in thirteen Member States.

Scant information is available in the scientific literature concerning 4F-MDMB-BICA. User forum posts suggest that its primary route of administration is inhalation via smoking or vaping after the chemical has been sprayed onto herbal material or solubilized in vehicle for vaping, respectively. It is metabolized extensively, with the most prominent metabolite and primary biomarker being the ester hydrolysis metabolite. The bioactivity of this metabolite is unknown. The mechanism of action for 4F-MDMB-BICA's psychoactive effects is presumed to be activation of the CB<sub>1</sub> receptor, although its binding affinity and canonical activation of this receptor have not been assessed. It has been shown to activate two of the receptor's noncanonical signaling pathways. In the  $\beta$ -arrestin-2 recruitment assay, 4F-MDMB-BICA exhibits an EC<sub>50</sub> = 121 nM and E<sub>max</sub> = 253% (the latter as a percentage of JWH-018 as a control) whereas in a calcium flux assay in CHO cells expressing the CB<sub>1</sub> receptor, it has similar potency and efficacy (EC<sub>50</sub>=37.7 nM, E<sub>max</sub>=129%) to JWH-018. The relationship between activation of these non-canonical pathways, activation of the canonical pathway of the CB<sub>1</sub> receptor, and in vivo potency has not been fully established.

The use of 4F-MDMB-BICA has been associated with 21 deaths in Hungary and an undetermined number of deaths in other countries, including Germany and the United States. Hospitalizations and driving under the influence cases have also been reported in the UK and in the United States. In most cases, however, causality for these adverse effects could not be definitively assigned to 4F-MDMB-BICA, as toxicology results often showed use of more than one substance, including mixtures of synthetic cannabinoids. Products containing 4F-MDMB-BICA have been seized by law enforcement in prisons (11 seizures), suggesting that it is being smuggled in and used by incarcerated persons.

The primary source of information about its psychological effects is unverified information from user forums, where analytical confirmation of the substance used is not available. The reported effects from these forums include include dissociation, "stoned" feeling, blurry vision, sleepiness, and random muscle twitches.

## 1. Substance identification

### A. *International Nonproprietary Name (INN)*

Not available.

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

Not yet assigned at the time of this writing.

### C. *Other Chemical Names*

Methyl 2-{{[1-(4-fluorobutyl)-1H-indole-3-carbonyl]amino}-3,3-dimethylbutanoate  
Methyl 3,3-dimethyl-2-[1-(4-fluorobutyl)-1H-indole-3-carboxamido]butanoate  
Methyl 3-methyl-N-[1-(4-fluorobutyl)-1H-indole-3-carbonyl]valinate  
Methyl 3,3-dimethyl-2-{{[1-(4-fluorobutyl)-1H-indol-3-yl]formamido}butanoate  
Methyl N-{{[1-(4-fluorobutyl)-1H-indole-3-yl]carbonyl}-3-methylvalinate  
Methyl 2-[1-(4-fluorobutyl)-1H-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)-1H-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)-1H-indole-3-  
carboxamide

MDMB-4F-BICA  
4F-MDMB-2201  
MDMB-4F-BUTICA  
4F-MDMB-BUTICA  
4-Fluoro MDMB-BICA  
4-Fluoro MDMB-BUTICA  
4FBC  
4FBCA  
MDMB-073-F.

### D. *Trade Names*

(S)-enantiomer (Methyl (S)-2-(1-(4-fluorobutyl)-1H-indole-3-carboxamido)-3,3-dimethylbutanoate) is sell by Cayman chemicals as analytical standard under the trade name "4-fluoro MDMB-BUTICA" (Cayman, 2021a).

### E. *Street Names*

'Bika' (in Hungary, meaning 'bull') (Rompos et al., 2021). In one case, a seized smoking mixture branded as a 'legal-high' product called 'Pico Bello' was found to contain 4F-MDMB-BICA (EMCDDA, 2020).

**F. Physical Appearance**

Seized quantities of street version have been formulated as a white, off-white, brown or orange powder (EMCDDA, 2020a)

4F-MDMB-BICA has also been identified in herbal blends, vaping solutions, and infused onto paper (EMCDDA, 2020a)

Available as a crystalline solid from Cayman Chemicals (Cayman Chemical, 2021)

**G. WHO Review History**

4F-MDMB-BICA has not been formally reviewed by WHO and is not currently under international control. Information was brought to WHO's attention that this substance is manufactured clandestinely, poses a risk to public health and has no recognized therapeutic use.

## 2. Chemistry

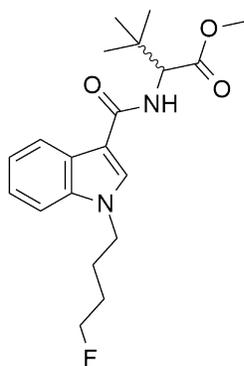
**A. Chemical Name**

**IUPAC Name:** ~~1-(1,3-benzodioxol-5-yl)-2-(ethylamino)butan-1-one~~

**CA Index Name:** Not yet available at the time of this writing.

**B. Chemical Structure**

Free base:



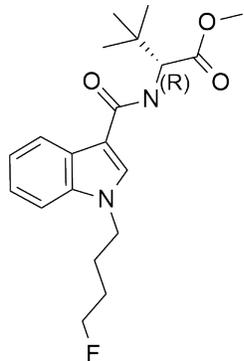
**Molecular Formula:** C<sub>20</sub>H<sub>27</sub>FN<sub>2</sub>O<sub>3</sub>

**Molecular Weight:** 363.44 g/mol

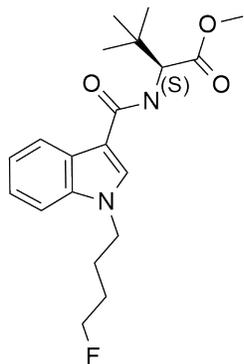
**Monoisotopic mass:** 362.2006

**C. Stereoisomers**

The presence of an asymmetric carbon atom gives rise to the (*R*)- and (*S*)-enantiomers of 4F-MDMB-BICA. Although structurally related synthetic SCRA typically show the (*S*)-configuration, it cannot be ruled out that the same substance with either (*R*)-configuration or the racemic mixture can be present in seized samples (EMCDDA, 2020).



~~Methyl (R)-2-(1-(4-fluorobutyl)-1H-indole-3-carboxamido)-3,3-dimethylbutanoate~~  
((*R*)-4F-MDMB-BICA).



~~Methyl (S)-2-(1-(4-fluorobutyl)-1H-indole-3-carboxamido)-3,3-dimethylbutanoate~~  
((*S*)-4F-MDMB-BICA).

#### D. *Methods and Ease of Illicit Manufacturing*

Information on the manufacturing of 4F-MDMB-BICA seized or collected from the market is not available. The preparation of this substance is however straightforward and follows standard procedures using cheap and readily available reagents. One example could include the procedure for the synthesis of (*S*)-4F-MDMB-BICA described by Annelies Cannart et al., which includes three steps starting from indole (Cannaert et al., 2020). The process, although simple, requires the equipment of a chemical synthetic laboratory and qualified personnel.

#### E. *Chemical Properties*

##### Melting point

The melting point of (*S*)-enantiomer has been reported as 86–88 °C (Cannaert et al., 2020).

#### Boiling point

No information could be identified.

#### Solubility

No information could be identified.

### ***F. Identification and Analysis***

Synthetic 4F-MDMB-BICA was characterized and <sup>1</sup>H NMR, <sup>13</sup>C NMR and IR properties (Cannaert et al., 2020) are reported. (*S*)-4F-MDMB-BICA is available as reference material from commercial suppliers to assist with the implementation of routine methods of analysis associated with forensic and clinical investigations (Cayman, 2021a, Cayman, 2021b).

Analytical methodologies for the identification and quantification of 4F-MDMB-BICA in seized and biological sample matrices have recently published and include various chromatographic, spectroscopic and mass spectrometric methods (EMCDDA, 2021).

Analysis for identification of 4F-MDMB-BICA in powders were conducted employing gas chromatography-mass spectrometry (GC-MS); infrared spectroscopy (IR); liquid chromatography- mass spectrometry (LC-MS); ion chromatography (IC); nuclear magnetic resonance spectroscopy (NMR) (HIFS, 2020, NFL, 2020).

Analysis for identification of 4F-MDMB-BICA in seized paper impregnated samples were conducted employing ion mobility spectrometry (IMS) (Norman et al., 2021).

Analysis for identification and quantification of 4F-MDMB-BICA and its major metabolites were conducted in zebrafish exposed to 4F-MDMB-BICA, human liver microsome, human urine and blood samples by means of liquid chromatography coupled with quadrupole time-of-flight mass spectrometry (LC-QTOF), ultra-high performance liquid chromatography coupled to quadrupole-Orbitrap high-resolution mass spectrometry (UHPLC–HRMS) or liquid chromatography coupled to triple-quadrupole mass spectrometry (QqQ-MS) (Kleis et al., 2021, Yue et al., 2021, Körmöczi et al., 2021).

No information about the enantiomeric composition of 4F-MDMB-BICA has been reported as stereochemical analysis is not usually undertaken, but it would seem likely that the 4F-MDMB-BICA available on the market exists as the (*S*)-enantiomer similar to most other closely related synthetic cannabinoids. The explicit identification of the (*S*)-enantiomer has not been confirmed in association with the identification of 4F-MDMB-BICA. Until reference material for the *s*-enantiomer is available, the existence of the (*R*)-enantiomer (including its presence as an impurity) cannot be excluded (EMCDDA, 2021).

### **3. Ease of Convertibility Into Controlled Substances**

It is not known from the literature that 4F-MDMB-BICA can be converted into a controlled substance.

## 4. General Pharmacology

### A. *Routes of administration and dosage*

Postings on online user forums indicate that 4F-MDMB-BICA is usually inhaled via smoking or vaping after the chemical has been sprayed onto herbal material or solubilized in vehicle for vaping, respectively (Reddit, 2020, 2021). Further, the presence of 4F-MDMB-BICA has been confirmed in seizures of various products: herbal mixtures designed for smoking, liquids formulated for vaping, paper infused with the chemical (primarily used to smuggle material into controlled environments such as prisons), and powders for user-formulation and product making (EMCDDA and Europol, 2020). Dosage required for intoxication is uncertain.

### B. *Pharmacokinetics*

Information on the absorption and distribution of 4F-MDMB-BICA is not available. A few studies have specifically examined its phase I metabolism, with emphasis on the identification of biomarker(s) that could serve in forensic investigations as indicators of use. One study investigated the effects of 4F-MDMB-BICA in a pooled human liver microsome assay, with follow up analysis of five authentic urine samples and two blood samples from human users (Körmöczy et al., 2021) whereas another study examined the metabolism of 4F-MDMB-BICA in zebrafish (Yue et al., 2021). A third study mentioned detection of the parent compound and hydrolysis metabolite(s) in serum or urine samples (Kleis et al., 2021). While the authors of this study noted that the presence of hydrolysis metabolites served to extend the window of opportunity for detection of 4F-MDMB-BICA in biological samples, they did not provide further information on metabolite identification. The first (and most comprehensive) study reported that, like many other synthetic cannabinoids, 4F-MDMB-BICA is extensively metabolized, with the parent compound identified in only one (of five) authentic urine samples evaluated (Körmöczy et al., 2021). Thirty putative metabolites were observed in the pooled human liver microsomes, twenty were identified in authentic urine samples, and thirteen were identified in blood. Of these, the ester hydrolysis metabolite (identified in urine and blood) was suggested as the primary biomarker for 4F-MDMB-BICA and the mono-hydroxylation and ester hydrolysis + dehydrogenation metabolites products in the urine and blood, respectively, were suggested as secondary markers.

While time course information is not published in the scientific literature, one user reports that the effects of vaped 4F-MDMB-BICA lasted 40 min to 1 h whereas another user reported time course of a smoked blend containing 4F-MDMB-BICA lasted approximately 1 h and 45 min (Reddit, 2021). However, this information should be considered anecdotal, as verification of the identify of chemicals contained in the products was not available.

### C. *Pharmacodynamics*

Very little information is available on the pharmacodynamic effects of 4F-MDMB-BICA. Given the cannabinoid subjective effects reported in online user forums (Reddit, 2021), CB<sub>1</sub> receptor binding would be suspected, but has not been confirmed by empirical

studies. Examination of 4F-MDMB-BICA in a  $\beta$ -arrestin-2 recruitment assay has shown that it activates this signaling pathway (that has been associated with the CB<sub>1</sub> receptor), with an EC<sub>50</sub> = 121 nM and E<sub>max</sub> = 253% (Cannaert et al., 2020). In the same assay and lab, the potency of 4F-MDMB-BICA was ~5-6 times lower than that of JWH-104 (EC<sub>50</sub> = 21.4 nM) with higher efficacy (253% of JWH-018 as standard), although 4F-MDMB-BICA was reported to have similar potency and efficacy (EC<sub>50</sub>=37.7 nM, E<sub>max</sub>=129%) to JWH-018 at the CB<sub>1</sub> receptor expressed in CHO cells using an aequorin-based assay measuring calcium flow (EMCDDA and Europol, 2020, Persson et al., 2020). The relationship between activation of these non-canonical pathways, activation of the canonical pathway of the CB<sub>1</sub> receptor, and in vivo potency has not been fully established. At the time of this report, investigation of the effects of 4F-MDMB-BICA on the canonical pathway has not been done and its CB<sub>1</sub> receptor binding affinity has not been reported.

## 5. Toxicology

Preclinical toxicology studies on 4F-MDMB-BICA have not been conducted.

## 6. Adverse Reactions in Humans

Between May and August 2020 there were 21 reported deaths related to confirmed use of 4F-MDMB-BICA (EMCDDA, 2020b). Causes of death included cardiac arrest/failure (14 cases), traumatic shock (2 cases), strangulation (1 case), brain edema (1 case), and asphyxiation after aspiration of vomit (1 case) (EMCDDA, 2020b). Ante-mortem symptoms, when known, were similar to those reported for overdose with other synthetic cannabinoids, including loss of consciousness, chest pain, respiratory difficulty, seizures, and somnolence (EMCDDA, 2020b, EMCDDA and Europol, 2020). However, a causal relationship between 4F-MDMB-BICA exposure and mortality cannot be firmly established, as in most cases additional substances (e.g., other synthetic cannabinoids, benzodiazepines, stimulants, THC) were detected through post-mortem toxicological screening of femoral blood or urine (EMCDDA, 2020b).

Other fatal cases involving use of 4F-MDMB-BICA have been implied in the published literature; however, details are not available. For example, in an analysis of biological samples provided by law enforcement in Germany, exposure to 4F-MDMB-BICA was confirmed in femoral blood (a typical medium for autopsy samples) (Kleis et al., 2021). In New Zealand, 4F-MDMB-BICA has been associated with two deaths (Ministry of Health NZ, 2021). In the United States, identification of 4F-MDMB-BICA occurred in 26 blood samples from autopsies or driving under the influence cases (Center for Forensic Science Research and Education, 2021a). Nonfatal cases involving hospitalization with life threatening symptoms similar to those reported with other synthetic cannabinoids were reported in the UK (EMCDDA and Europol, 2020); however, other substances were also detected in all cases. One serious hospitalization has also been reported in New Zealand (Ministry of Health NZ, 2021).

While information on 4F-MDMB-BICA is rather scant on user forums, several posts to the sub-Reddit sites (r/noids) reported adverse effects from 4F-MDMB-BICA use. For example,

a user stated that he smoked “pure chemical” placed in a cigar and on plant material and passed out after each incident (Reddit, 2020). A second user reported considerable anxiety after inhaling a “normal hit” and holding it in while a third reported observing seizures in companions who used the substance (Reddit, 2021). Other subjective effects following purported use of 4F-MDMB-BICA included dissociation followed by “feeling stoned,” blurry vision, sleepiness, and random muscle twitches (Reddit, 2021). These user posts should be considered anecdotal reports, as analytical confirmation of sole use of 4F-MDMB-BICA was not obtained.

## 7. Dependence Potential

### A. *Animal Studies*

Animal studies to evaluate the dependence potential of 4F-MDMB-BICA have not been conducted.

### B. *Human Studies*

Human studies to evaluate the dependence potential of 4F-MDMB-BICA have not been done.

## 8. Abuse Potential

### A. *Animal Studies*

Animal studies to evaluate the abuse potential of 4F-MDMB-BICA have not been done.

### B. *Human Studies*

Human studies to evaluate the abuse potential of 4F-MDMB-BICA have not been conducted.

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

4F-MDMB-BICA does not have any known therapeutic applications and is not used medically.

## 10. Listing on the WHO Model List of Essential Medicines

4F-MDMB-BICA is not listed on the WHO Model List of Essential Medicines.

## 11. Marketing Authorizations (as a Medicinal Product)

No known marketing authorizations.

## 12. Industrial Use

No known industrial use.

### **13. Non-Medical Use, Abuse and Dependence**

4F-MDMB-BICA appeared on the European drug market in March 2020 in a seizure by Belgian authorities (EMCDDA and Europol, 2020). The substance was identified in the United States in May 2020 and was listed in toxicology trend reports issued by the Center for Forensic Science, Research, and Education from the third quarter of 2020 to the latest report from the second quarter of 2021 (Center for Forensic Science Research and Education, 2021b). By November 2020, 111 seizures had occurred in 12 Member States of the European Union, with the bulk of the total amount confiscated occurring in Belgium (EMCDDA and Europol, 2020). In Europe, seizures by law enforcement or customs occurred in the following Member States (with number of seizures in parentheses): Hungary (72), 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). Seizures included pure powder as well as e-liquids, plant material mixtures, and paper blotters infused with the chemical. Toxicology reports found that other synthetic cannabinoids were frequently used in conjunction with 4F-MDMB-BICA (Center for Forensic Science Research and Education, 2021b, EMCDDA and Europol, 2020).

The prevalence of chronic use and dependence of 4F-MDMB-BICA has not been reported.

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

At least 21 deaths in which 4F-MDMB-BICA was present in postmortem toxicology results have occurred in Hungary (EMCDDA, 2020b). While deaths in other locations most likely have also occurred (see Section 6), detailed information on the number of deaths and their circumstances was not available. In addition, five hospitalizations resulting from acute poisoning with 4F-MDMB-BICA combined with other substances occurred in the UK (EMCDDA and Europol, 2020) and one hospitalization with serious symptoms was reported in New Zealand (Ministry of Health NZ, 2021). Driving under the influence has also been documented in the United States (Center for Forensic Science Research and Education, 2021b). Eleven seizures of 4F-MDMB-BICA infused on paper blotters has occurred in prisons, suggesting that the chemical has infiltrated into the incarcerated population (EMCDDA, 2020b, EMCDDA and Europol, 2020).

### **15. Licit Production, Consumption and International Trade**

No licit production.

### **16. Illicit Manufacture and Traffic and Related Information**

Based upon the number of seizures and quantity of each, early distribution efforts appear to have been focused on Hungary and northern Europe (e.g., Belgium, the Netherlands, Finland) (EMCDDA and Europol, 2020). Its first documented seizure in Europe was in March

2020 in Belgium. The chemical quickly moved to the United States, showing up in at least 26 toxicology reports by July 2020 (Center for Forensic Science Research and Education, 2021b).

#### **17. Current International Controls and Their Impact**

Currently, there are no international controls specifically related to 4F-MDMB-BICA.

#### **18. Current and Past National Controls**

Thirteen Member States of the EU have issued control regulations for 4F-MDMB-BICA, either under drug control or medicines legislation (EMCDDA and Europol, 2020). These nations include Austria, Belgium, Croatia, Cyprus, France, Germany, Hungary, Italy, Latvia, Luxembourg, Norway, Poland, Turkey, and the United Kingdom. Presence of 4F-MDMB-BICA has also been confirmed in New Zealand (Ministry of Health NZ, 2021). The United States has not yet scheduled 4F-MDMB-BICA, but recently issued a notice and request for comments concerning the substance in the Federal Register as a prelude to possible scheduling (Food and Drug Administration, 2021).

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

No other relevant medical or scientific matters.

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## Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances

Data were obtained from 98 Member States (12 African Region, 12 Eastern Mediterranean Region, 37 European Region, 14 Region of the Americas, 7 South-East Asia Region and 16 Western Pacific Region) for the WHO Questionnaires for the Review of Psychoactive Substances. The total number of countries opting out of participation in the questionnaire was 9 (1 African Region, 2 Eastern Mediterranean Region, 2 European Region, 2 Region of the Americas, 1 South-East Asia Region and 1 Western Pacific Region), leaving 89 countries that agreed to provide data.

Of the 89 countries who agreed to provide data, 30 countries had information on 4F-MDMB-BICA (Table 1).

Table 1. Numbers of countries providing information on 4F-MDMB-BICA

Region	Number of countries without information	Number of countries with information on substance
African	8	0
Eastern Mediterranean	7	1
European	11	20
Region of the Americas	9	3
South-East Asia	2	2
Western Pacific	9	4
Total (76)	46	30

### APPROVED MEDICAL, SCIENTIFIC OR INDUSTRIAL USE

One country (European Region) reported approved human medical products and veterinary products containing 4F-MDMB-BICA.

No countries reported approved therapeutic indications for 4F-MDMB-BICA.

No countries reported 4F-MDMB-BICA was being currently used in medical or scientific research (excluding use as an analytical standard) in their country (such as in clinical trials for any human or veterinary indication).

No countries reported that 4F-MDMB-BICA was being used for industrial purposes.

## EPIDEMIOLOGY OF NON-MEDICAL USE

Fifteen countries (12 European, 1 Eastern European, 1 Region of the Americas and 1 Western Pacific) reported that there is evidence of the use of 4F-MDMB-BICA for non-medical use (use outside of the medical, industrial or scientific context). This evidence was primarily seizure/customs data (n=9).

### Routes of administration and formulations

The most common route of administration reported was smoking, followed by oral and inhalation (Table 2).

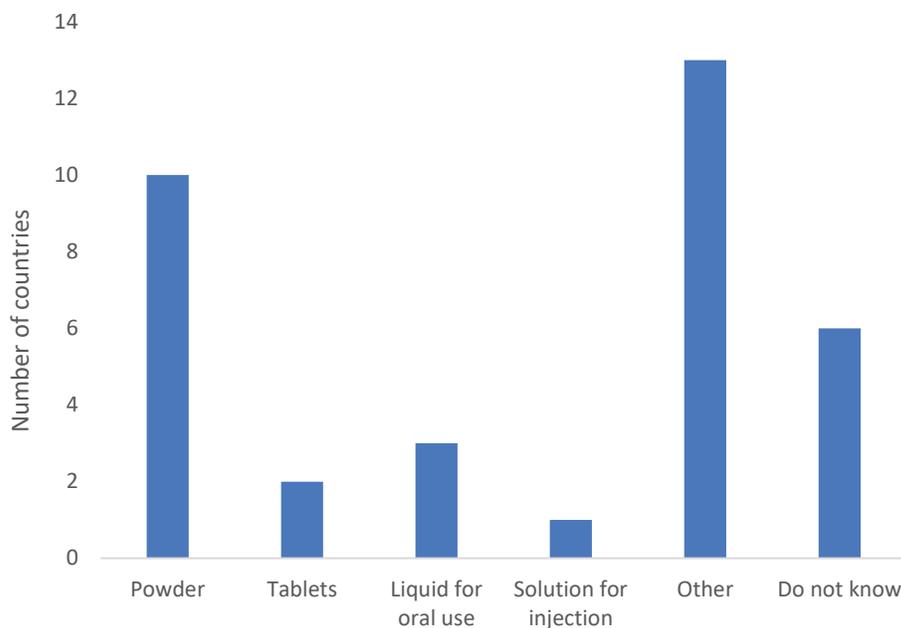
Table 2. Reported routes of 4F-MDMB-BICA administration

Route of administration	Number of countries
Smoking	14
Oral	5
Inhalation	2
Sniffing	0
Injection	0
Other*	2
Do not know	10

\* Other routes of administration for 4F-MDMB-BICA included vaping (n=1) and "oral, but accidental" (n=1).

The most common known formulations of 4F-MDMB-BICA reported was powder and as a part of an herbal mixture (Figure 1).

Figure 1. Formulations of 4F-MDMB-BICA



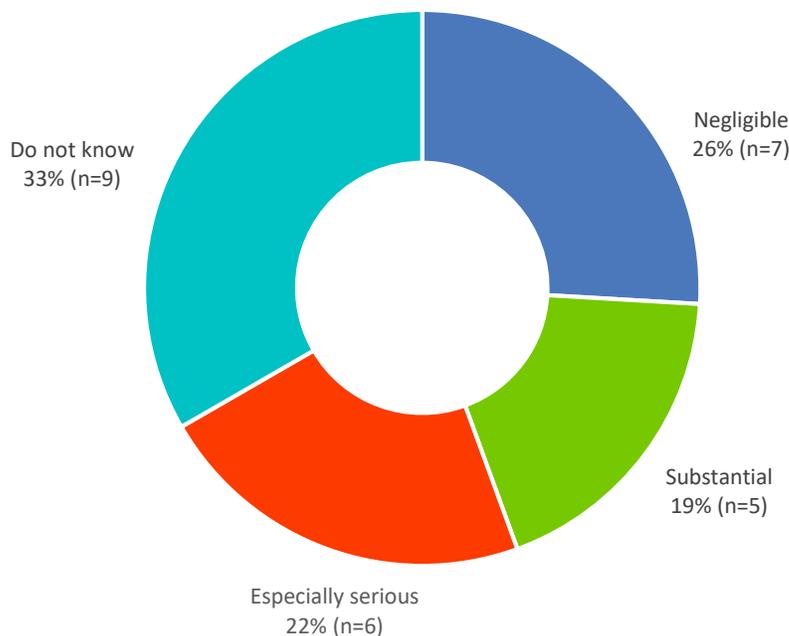
\* Other formulations for 4F-MDMB-BICA most commonly referenced an herbal mixture/plant material (n=11) and blotters/paper (n=2).

### Perceived negative health impact

Eleven countries (6 European, 2 Western Pacific, 1 Eastern Mediterranean, 1 Region of the Americas, 1 South-East Asia) reported the level of negative health impact due to 4F-MDMB-BICA's non-medical consumption as "especially serious" or "substantial" (Figure 2).

Four countries (European Region) noted seizures of 4F-MDMB-BICA. Four countries (2 European Region, 1 Eastern Mediterranean, 1 South-East Asia) described negative health impacts such as psychological dependency, hallucinations, mood disorders, paranoia, aggression, chest pain, respiratory problems, tremor and seizures. An additional country (Region of the Americas) noted 4F-MDMB-BICA had been positively identified in over 26 toxicology cases.

Figure 2. Negative health impact of the non-medical consumption of 4F-MDMB-BICA



### Emergency Department visits

Four countries (3 European Region, 1 South-East Asia) were aware of emergency room/department (ED) visits related to 4F-MDMB-BICA. One European country described an ED visit involving a non-fatal accidental poisoning of a 13-month-old child. One European country described eight ED presentations where 4F-MDMB-BICA was consumed with other substances; a wide range of symptoms were reported, most commonly reduced consciousness (seven of the eight cases), and increased ALT/AST (suggesting abnormal liver function; five cases). One South-

East Asian country described confusion and memory loss as adverse effects experienced by ED patients.

### Deaths

Three countries (2 European Region, 1 Region of the Americas) reported a total of 9541 4F-MDMB-BICA-related deaths over the years 2018 to 2020. More specifically, one country (European Region) reported 501 deaths where it was the only drug involved for the year 2018, and 9015 deaths where there was another drug involved in the year 2019. Another country (European Region) reported 3 4F-MDMB-BICA-related deaths where another substance was also involved in 2020. One country (Region of the Americas) reported 22 4F-MDMB-BICA-related deaths where another substance was also involved in 2020.

### Drug Dependence

Two countries (1 European region, 1 Eastern Mediterranean) reported they were aware of people presenting to drug dependence treatment in their country due to use of 4F-MDMB-BICA.

## **CURRENT DRUG CONTROL**

Twenty-five countries (17 European, 4 Western Pacific, 2 Region of the Americas, 1 Eastern Mediterranean, 1 South East Asia) responded 4F-MDMB-BICA is currently controlled under national legislation to regulate its availability. Table 3 shows the main reported activities involving 4F-MDMB-BICA.

Table 3. Reported activities involving 4F-MDMB-BICA for purposes other than medical, scientific or industrial use.

Activity	Number of countries
Smuggling (from other countries)	10
Trafficking	6
Internet sales (from abroad to buyers in respondent's country)	7
Internet sales (other or location of sellers and website unknown)	5
Internet sales (seller or website located in respondent's country)	3
Manufacture of the substance by chemical synthesis	2
Direct sales	2
Production of consumer products containing the substance	1
Manufacture of the substance by extraction from other products	1
Diversion	1
Do not know	9
Other*	3

\*Other includes "As there has been seizures of this substance, we know there must be activities going on, but we do not know the source", "seizures by customs" and "use for recreational purposes".

Seizures

Six countries (3 European, 1 Western Pacific, 1 South-East Asia) reported seizures in 2021. Seizure number per country ranged from 3-185 and seizure amounts ranged from 7.75 grams to 19 kilograms (Table 4).

Eleven countries (8 European, 1 Western Pacific, 1 South-East Asia, 1 Region of the Americas) reported seizures in 2020. Seizure number per country ranged from 1-254 and seizure amounts ranged from 0.155 grams to 23 tonnes.

Table 4. Reported seizures of 4F-MDMB-BICA

Year	Number of countries reporting seizures	Number of seizures
2021	7	247
2020	11	537

Twenty-two countries (18 European, 3 Western Pacific, 2 South East Asia, 1 Eastern Mediterranean, 1 Region of the Americas) have the forensic laboratory capacity to analyze 4F-MDMB-BICA.