World Health Organization

Critical Review Report:

5F-MDMB-PICA

Expert Committee on Drug Dependence

Forty-second Meeting

Geneva, 21-25 October 2019

This report contains the views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization

Contents

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Executive Summary

Substance identification

The identification of 5F-MDMB-PICA (5F-MDMB-2201) (IUPAC name: methyl (2*S*)-2-{[1-(5-fluoropentyl)-1*H*-indole-3-carbonyl]amino}-3,3-dimethylbutanoate) has been described first in 2016. Information obtained from seizures and collections suggests that it has been encountered in powdered form and as a synthetic constituent in herbal plant mixtures most commonly distributed for the purpose of smoking and/or vaping. It is the indole analogue of 5F-ADB (5F-MDMB-PINACA) that is listed in Schedule II of the Convention on Psychotropic Substances of 1971.

WHO Review History

5F-MDMB-PICA has not been previously pre-reviewed or critically reviewed.

Chemistry

There is no specific information available about the routes of synthesis employed for seized 5F-MDMB-PICA products circulating on the drug market but straightforward methods for its preparation exist without requiring access to precursors that are controlled internationally. The presence of an asymmetric carbon atom gives rise to the (*R*)- and (*S*)-enantiomer and it seems likely for 5F-MDMB-PICA to be most commonly available as the (*S*)-enantiomer.

Ease of convertibility into controlled substances

There is no specific information available but it appears unlikely that 5F-MDMB-PICA is converted into a substance currently listed in any of the international drug conventions.

Similarity to known substances / Effects on the central nervous system

The information currently available suggests that 5F-MDMB-PICA functions as a synthetic cannabinoid receptor agonist (SCRA). Information about effects induced *in vivo* is currently not available but the existing data suggest that 5F-MDMB-PICA will likely exhibit a profile shared by other SCRAs controlled internationally (potent full agonists at cannabinoid receptors) such as 5F-ADB.

General pharmacology

5F-MDMB-PICA, in its pure form but mostly as a synthetic constituent added to a plant matrix, is primarily smoked (or vaped) although reliable data about dosage are unavailable. A small number of *in vitro* studies are currently available and the data indicate that 5F-MDMB-PICA binds to and activates human CB_1 and CB_2 receptors at low nanomolar concentrations. 5F-MDMB-PICA acted as a full agonist at both receptor subtypes with significantly higher potency than Δ^9-THC which has also been observed with other SCRAs that are listed in the Convention on Psychotropic Substances of 1971. Data collected from *in vitro* metabolism studies and detections in biological specimens revealed that the biotransformation observed included mono-hydroxylation, oxidative defluorination, dehydrogenation, amide, and ester hydrolysis, as well as combinations thereof. Glucuronidation products have also been detected.

Toxicology
Information could not be identified.

Adverse reactions in humans
Detailed information about the clinical features associated with the consumption of 5F-MDMB-PICA specifically is not available. However, “mass-overdose” cases were described in Connecticut (United States of America (USA)) that have been associated with the detection of 5F-MDMB-PICA and other SCRAs and fentanyl. Clinical features reported included decreased mental status, agitated delirium, and seizures. Within a 6-day period in September 2018, 244 overdose cases (details not reported) have been identified in Washington, DC, (USA) that also included the detection of 5F-ADB and other SCRAs. Data collected from intoxication cases with other SCRAs suggest that clinical features might include a range of adverse effects on gastrointestinal, neurological, and cardiovascular systems.

Dependence potential
No studies carried out in humans or animals could be identified.

Abuse potential
Studies specifically linked to 5F-MDMB-PICA could not be identified.

Therapeutic applications / usefulness
5F-MDMB-PICA is not known to have any therapeutic uses.

Listing on WHO Model List of Essential Medicines
5F-MDMB-PICA is not listed.

Marketing authorizations
5F-MDMB-PICA is not known to have any marketing authorisations.

Industrial use
5F-MDMB-PICA is not known to have any agricultural, industrial or cosmetic uses.

Non-medical use
The mode of use may involve the combinational use (intentionally or unintentionally) of other drugs and users may be unaware of the exact dose or compound being ingested (by whatever route). Household or subpopulation surveys that specifically probe for prevalence of 5F-MDMB-PICA could not be identified. People who use SCRAs in general include recreational users, high-risk substance users but also individuals who are subject to drug testing such as people in drug treatment, prisoners, abstinence control programs and drivers.

Nature and magnitude of public health problems
Products sold as herbal smoking mixtures frequently change in drug composition and quantity, often without indications on product labels, which results in challenges to unambiguously correlate harms to public health with a specific drug such as 5F-MDMB-PICA. People who use these drugs are most likely not aware of the identity of the constituent and the quantity. The

consumption of these products might be attractive to a variety of users, such as regular users of cannabis and those who believe that SCRA use might help with avoiding a positive finding in drug-testing procedures. There are indications that socially vulnerable and stigmatised substance users, for example found in homeless and prison populations, are increasingly associated with problematic use of SCRA products. Heavy use of SCRAs has been associated with problematic withdrawal symptoms and further research is needed to evaluate the underlying mechanisms.

Licit production, consumption, and international trade

5F-MDMB-PICA is available as standard reference material and produced for scientific research by a number of commercial suppliers. Other uses could not be identified.

Illicit manufacture and traffic

5F-MDMB-PICA began to emerge at the end 2016 both in Europe and the USA. In general, SCRAs are often imported in their pure form and converted into herbal forms on the domestic level. In recent years it has emerged that SCRAs have been smuggled into prisons in the form of impregnated papers (e.g. letters) and textiles and this extended to the detection of 5F-MDMB-PICA.

Current international controls and their impact

5F-MDMB-PICA is not controlled under the 1961, 1971 or 1988 United Nations Conventions.

Current and past national controls

5F-MDMB-PICA is controlled in some UN Member States.

1. Substance identification

A. International Nonproprietary Name (INN)

Not available.

B. Chemical Abstract Service (CAS) Registry Number

1971007-88-1 ((*S*)-enantiomer)

C. Other Chemical Names

Methyl (*S*)-2-(1-(5-fluoropentyl)-1*H*-indole-3-carboxamido)-3,3-dimethylbutanoate

Methyl (2*S*)-2-{[1-(5-fluoropentyl)-1*H*-indole-3-carbonyl]amino}-3,3-dimethylbutanoate

N-[[1-(5-Fluoropentyl)-1*H*-indol-3-yl]carbonyl]-3-methyl-L-valine, methyl ester

D. Trade Names

Not available.

E. Street Names

5F-MDMB-PICA
5F-MDMB-2201
5-Fluoro-MDMB-PICA
5-Fluoro-MDMB-2201

5F-MDMB-PICA has also been detected in a number of seized branded herbal smoking mixtures and product names included 'Mind Trip', 'Devil', 'Armageddon', 'Trippy Top', 'Tropical High', 'Astro', 'Red Russian', 'Supernova', 'AK-47', 'Dead Man Walking', and 'Joker' *(1)*. However, products associated with the sale of synthetic cannabinoid receptor agonists rarely retain the same composition and will frequently change over time.

F. Physical Appearance

5F-MDMB-PICA has been described as a white solid *(2)* and crystalline solid *(3)*.

G. WHO Review History

5F-MDMB-PICA has not been previously pre-reviewed or critically reviewed. A direct critical review is proposed based on information brought to WHO's attention that 5F-MDMB-PICA clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any party. Preliminary data collected from literature and different countries indicated that this substance may cause substantial harm and that it has no medical use.

2. Chemistry

A. Chemical Name

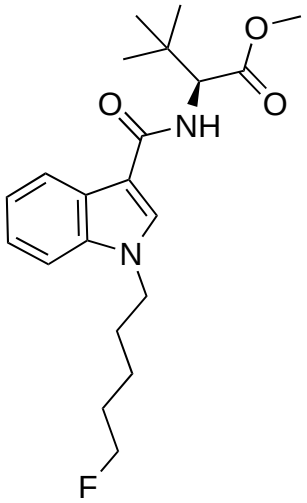
IUPAC Name: Methyl (2*S*)-2-{[1-(5-fluoropentyl)-1*H*-indole-3-carbonyl]amino}-3,3-dimethylbutanoate

Methyl *N*-[1-(5-fluoropentyl)-1*H*-indole-3-carbonyl]-3-methyl-L-valinate

CA Index Name: L-Valine, *N*-[[1-(5-fluoropentyl)-1*H*-indol-3-yl]carbonyl]-3-methyl-, methyl ester

B. Chemical Structure

Free base:



Molecular Formula: $C_{21}H_{29}FN_2O_3$
Molecular Weight: 376.47 g/mol

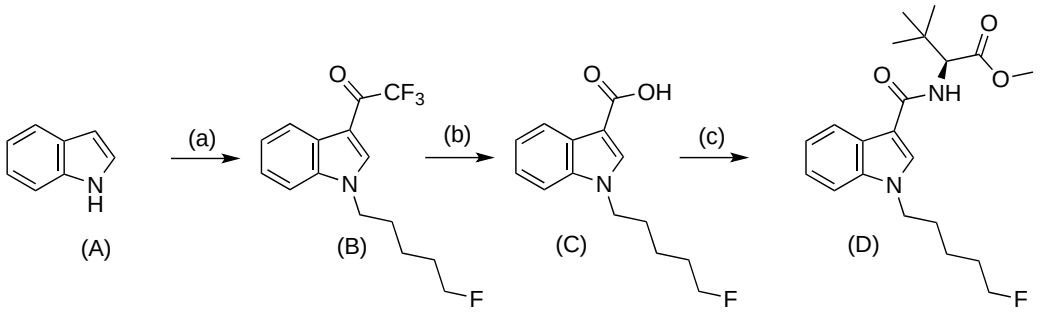
C. Stereoisomers

The presence of an asymmetric carbon atom gives rise to the (*R*)- and (*S*)-enantiomer of 5F-MDMB-PICA. Historically, structurally related synthetic cannabinoid receptor agonists (SCRAs) that feature such chiral centres have typically shown the (*S*)-configuration. It is currently not known whether 5F-MDMB-PICA has been exclusively found on the market with the absolute (*S*)-configuration although it appears very likely to be the case. Similar to other closely related SCRAs, it seems conceivable that the (*R*)-enantiomer might be detectable *(*e.g. *4, 5)*.

D. *Methods and Ease of Illicit Manufacturing*

Information on the manufacturing of 5F-MDMB-PICA seized or collected from the market is not available. Its preparation is straightforward and follows standard procedures using cheap reagents. One option used for the synthesis of 5F-MDMB-

PICA is shown in the Scheme below *(2)*. Using a one-pot procedure, indole (A) was subjected to *N*-alkylation and conversion to the trifluoroacetylindole analogue (B). Hydrolysis gave the carboxylic acid intermediate (C) that then underwent coupling with L-*tert*-Leucine methyl ester to afford 5F-MDMB-PICA (D).



Reagents and conditions: (a) (i) NaH, 1-bromo-5-fluoropentane, DMF, 0 °C–rt, 1 h; (ii) $(CF_3CO)_2O$, DMF, 0 °C–rt, 1 h; (b) 1 M aq. NaOH, MeOH, reflux, 24 h; (c) methyl L-*tert*-leucinate, EDC·HCl, HOBt, DIPEA, DMSO, rt, 24 h *(2)*.

E. Chemical Properties

Melting point: 82–84 °C *(2)*.

Boiling point: Information could not be identified.

Solubility: A sample obtained from a test purchase was reported to be soluble in dichloromethane and methanol and partially soluble in water *(6)*.

F. Identification and Analysis

Data and analytical methodologies that facilitate the identification of 5F-MDMB-PICA in various sample matrices are available and include physical characteristics (melting point), chromatographic, spectroscopic, and mass spectrometric methods (Annex 2).

Analytical reference standards are accessible to assist with the implementation of routine methods of analysis associated with forensic and clinical investigations. The analytical determination of synthetic cannabinoid receptor agonists such as 5F-MDMB-PICA in biological fluids can be a challenge, for example in cases where analytical methodologies are not specifically designed to detect these substances. In some instances (e.g. analysis of urine), the detection of metabolites may be the preferred approach. The explicit identification of the (*S*)-enantiomer has not been confirmed in the reports associated with the identification of 5F-MDMB-PICA but it appears conceivable that the 5F-MDMB-PICA available on the market predominantly exists as the (*S*)-enantiomer. However, until further information is available, one cannot exclude the existence of the (*R*)-enantiomer and the

differentiation between the two might present challenges in routine forensic laboratories unless more specific approaches are employed to facilitate chiral analysis. The implementation of immunoassays for the analysis of human authentic urine samples containing 5F-MDMB-PICA metabolites was shown to be unreliable *(1)*.

3. Ease of Convertibility Into Controlled Substances

No information could be identified.

4. General Pharmacology

A. Routes of administration and dosage

5F-MDMB-PICA, in its pure form but mostly as a synthetic constituent added to a plant matrix, is primarily smoked (or vaped) although reliable data about dosage are unavailable. The variations in drug composition and quantities frequently observed with many smoking mixtures make such estimation impossible for users despite the information displayed on a product label (e.g. *(7, 8)*). It has been suggested that the amide and ester hydrolysis products might be expected to form during pyrolysis *(1)* though these might not retain psychoactive properties. Ten samples seized in New Zealand in 2017 were reported to contain 5F-MDMB-PICA with an average concentration of 9 g/kg (range 3–16 g/kg, RSD = 13%)) *(9)*.

B. Pharmacokinetics

Information from clinical studies in humans is not available. A recent study investigated the metabolic fate of 5F-MDMB-PICA in an *in vitro* assay using pooled human liver microsomes *(1, 10)*. The identified phase I metabolites were then compared with metabolites obtained from authentic human urine samples *(1)*. In this matrix, 12 phase I metabolites of 5F-MDMB-PICA were detected and assigned to 9 different biotransformations, including mono-hydroxylation, oxidative defluorination, dehydrogenation, amide, and ester hydrolysis, as well as combinations thereof. Eleven of the 12 metabolites were also detected *in vitro*. The four most abundant metabolites were 1) the methyl ester hydrolysis product, 2) the indole-*N*-propionic acid derivative, 3) a hydroxylated indole species, and 4) the hydroxylated (*N*-alkyl chain) methyl ester hydrolysis product. Numbers 1) and 3) were also considered suitable biomarkers for consumption of 5F-MDMB-PICA. Two of the main phase I metabolites were also identified as glucuronidation products *(1)*.

In a more recent investigation, 22 metabolites were detected following hepatocyte incubations and analysis of authentic human urine samples. Metabolites were formed via carboxylation or hydroxylation on the aliphatic chain or aromatic ring followed by glucuronidation; *N*-dealkylation followed by hydroxylation on the aromatic ring; oxidative defluorination followed by conversion to pentanoic acid; oxidative defluorination with conversion to propionic acid. Oxidative defluorination pathway also subsequently underwent hydroxylation on the aromatic ring followed by *N*-dealkylation or glucuronidation. The ester hydrolysis metabolite was further

metabolized via hydroxylation, glucuronidation, or dehydrogenation followed by *N*-dealkylation, or ester hydrolysis with oxidative defluorination followed by dehydrogenation, or conversion to pentanoic acid. The two most abundant metabolites after the 5 h incubation with hepatocytes were ester hydrolysis and ester hydrolysis with oxidative defluorination *(11)*.

A. Pharmacodynamics

Data currently available from some *in vitro* studies indicate that 5F-MDMB-PICA functions like a synthetic cannabinoid receptor agonist (SCRA) as it has been found to bind and activate CB_1 and CB_2 receptors (Table 1).

Although the binding affinity ([^{3}H]CP-55,940, HEK cells) was slightly lower (K_i = 5.4 nM) compared to Δ^9-THC (K_i = 2.5 nM) *(12)*, the various functional assays employed revealed that 5F-MBMD-PICA was significantly more potent than Δ^9-THC and other SCRAs used as positive controls. The available information also suggests that 5F-MDMB-PICA is a potent agonist at both receptor subtypes (Table 1). At the time of writing, information on the *in vivo* effects of 5F-MDMB-PICA could not be identified.

Table 1. 5F-MDMB *in-vitro* data	Reference
Functional activity and efficacy: [a] 5F-MDMB-PICA at hCB_1: EC_{50} = 0.45 nM (E_{max} = 110%); hCB_2: EC_{50} = 7.4 nM (E_{max} = 94%) Δ^9-THC at hCB_1: EC_{50} = 171 nM (E_{max} = 50%); hCB_2: EC_{50} not determined; too low (E_{max} = 20% at 10,000 nM) CP-55,490 at hCB_1: EC_{50} = 42 nM (E_{max} = 100%); hCB_2: EC_{50} = 68 nM (E_{max} = 100%) 5F-ADB at hCB_1: EC_{50} = 0.59 nM (E_{max} = 108%); hCB_2: EC_{50} = 7.5 nM (E_{max} = 94%)	*(2)*
Receptor binding: [b] 5F-MDMB-PICA at CB_1: K_i = 5.4 nM (*R*)-(+)-WIN-55,212-2 at CB_1: K_i = 21.4 nM Δ^9-THC at hCB_1: K_i = 2.46 nM Functional activity: [c] 5F-MDMB-PICA, EC_{50} = 0.21 nM (E_{max} = 92.5%) (-)CP-55,940, EC_{50} = 0.53 nM (E_{max} = 102.3%) Δ^9-THC, EC_{50} = 25.9 nM (E_{max} = 78.5%)	*(12)*
Functional activity and efficacy: [d] Operational efficacy tau at CB_1: 5F-MDMB-PICA (314), CP-55,490 (91), WIN-55,212-2 (24), Δ^9-THC (1.3). Functional affinity pK_A at CB_1: 5F-MDMB-PICA (6.55), CP-55,490 (5.37), WIN-55,212-2 (5.27), Δ^9-THC (5.65). Log (tau/K_A): 5F-MDMB-PICA (9.12), CP-55,490 (7.53), WIN-55,212-2 (6.79), Δ^9-THC (6.18).	*(13)*
Functional activity and efficacy: [e] 5F-MDMB-PICA at hCB_1: EC_{50} = 3.26 nM (E_{max} = 331%); hCB_2: EC_{50} = 0.87 nM (E_{max} = 244%) JWH-018 at hCB_1: EC_{50} = 41 nM (E_{max} = 99.3%); hCB_2: EC_{50} = 12.3 nM (E_{max} = 104%)	*(14)*
Functional activity (hCB_1): [f] 5F-MDMB-PICA, EC_{50} = 27.6 nM (E_{max} = 83%, 129%) 5F-MDMB-PINACA (5F-ADB), EC_{50} = 15.7 nM (E_{max} = 88%, 136%) JWH-018, EC_{50} = 36.6 nM (E_{max} not reported, 100%)	*(11)*

[a] Ref *(2)*: murine AtT20-FlpIn neuroblastoma cells stably expressing human CB_1 or CB_2 receptors; activation of CB receptors resulted in opening of endogenous G protein-gated inwardly rectifying potassium channels (GIRKs) that produced a hyperpolarisation of cells resulting in a decrease in fluorescence of a proprietary membrane potential dye. Comparison of test drugs was normalized against CP-55,940 response (set at 100% efficacy).

[b] Ref *(12)*: HEK cells; [^{3}H]CP-55,940 (~1.3 nM) used as radioligand.

[c] Ref *(12)*: Adenylate cyclase assay using cyclic AMP ELISA kit. Basal cAMP subtracted from all values; CB_1 receptor agonists inhibit forskolin-stimulated cAMP formation with maximal inhibition defined using 1 µM (-)CP-55,940.

[d] Ref *(13)*: GIRK assay, see also [a]. Irreversible CB_1 antagonist AM6544 used to deplete 94% of receptor reserve followed by measurement of efficacy to generate CB_1-dependent hyperpolarization in GIRK assay. *tau* parameter in the control state used to measure the CB_1 agonist efficacy, representing the inverse of the number of receptors that need to be occupied by an agonist to produce a response 50% of the system maximum.

[e] Ref *(14)*: HEK cells; assay based on NanoLuc Binary Technology via recruitment of β-arrestin 2 (βarr2). Efficacy normalized to JWH-018 response.

[f] Ref *(11)*: AequoScreen recombinant CHO-K1 cell lines (hCB_1); digitonin used as a positive control for coelenterazine cell loading and blank wells with no drug used as negative controls. Activation was determined using a Tecan Spark™ microplate reader and compared to digitonin and JWH-018.

5. Toxicology

Information could not be identified.

6. Adverse Reactions in Humans

Available reports associated with the detection of 5F-MDMB-PICA in biofluids are included in Appendix 2 though information about any clinical features associated with the detection of this drug *(e.g. 1, 15)*, was not documented. The published information related to intoxications and adverse reactions are available in an aggregated form only which means that causal links with 5F-MDMB-PICA specifically cannot be identified based on the available information alone.

"Mass-overdose" cases were described in New Haven, Connecticut (USA) that occurred in August 2018 where intoxicated patients presented to emergency departments (EDs) *(16)*. Detailed information related to 5F-MDMB-PICA specifically was not reported. The information from the published abstract revealed the following: fifty-two patients presented over 109 ED visits (range 1–13 visits per patient); 49 of these visits occurred

within a 10 h period on 15 August 2018. Symptoms described to vary significantly between visits (including patients with multiple visits) and included decreased mental status (51/109), agitated delirium (13/109), and seizures (5/109). Naloxone use was documented in 13/109 visits, with mixed responses. Two patients were intubated for decreased mental status. Urine samples from 21 patients were found to contain 5F-MDMB-PICA (5/21), 5F-ADB and FUB-AMB metabolites (20/21), and fentanyl (4/21). Unstructured interviews with patients revealed that products containing SCRAs may have been given away freely or very cheaply by multiple dealers targeting methadone users in a competitive open-air market on the town green *(16)*.

The Background Information and Evaluation of 'Three Factor Analysis' (Factors 4, 5, and 6) for Temporary Scheduling document linked to the temporary placement of 5F-MDMB-PICA (among other SCRAs) into Schedule I of the United States Controlled Substances Act provided a summary of the number of exposure calls received by US poison control centres (Table 2). It has been stated that "the misuse of 5F-EDMB-PINACA, 5F-MDMB-PICA, FUB-AKB48, 5F-CUMYL-PINACA and FUB- 144 has been associated with law enforcement seizures, overdoses requiring emergency medical intervention, or both" but without providing further details *(17)*.

Table 2. Exposure cases of synthetic cannabinoids as reported to poison centres [a,b,c]

Year	Number of cases
2011	6,968
2012	5,230
2013	2,668
2014	3,682
2015	7,797
2016	2,706
2017	1,959
2018 (up to 30 September 2018)	1,627

[a] Adapted from reference *(17)*

[b] American Association of Poison Control Centers (AAPCC), 23 October 2018

[c] Summary of exposure calls related to SCRAs in general. 5F-MDMB-PICA identified in the USA first in October 2016 *(17)* and number of cases related to 5F-MDMB-PICA specifically, however, cannot be extracted from this table.

The document announcing the temporary placement of 5F-MDMB-PICA (and 5F-EDMB-PINACA, FUB-AKB48, 5F-CUMYL-PINACA, and FUB-144) into Schedule I of the US Controlled Substances Act *(18)* also states that "In August 2018, in New Haven, Connecticut, in excess of 47 overdoses were reported following the use of a synthetic cannabinoid product. Analysis of drug evidence from the overdose event confirmed the presence of the synthetic cannabinoids 5F-ADB, FUB-AMB and 5F-MDMB-PICA" (see also above, reference *(16)* and Appendix 2). Furthermore, "from September 10 to 16, 2018, in Washington, DC, at least 244 overdoses were reported following use of a synthetic cannabinoid product.

Analysis of drug evidence from the overdose event confirmed the presence of the synthetic cannabinoids FUB-AMB and 5F-MDMB-PICA" *(18)*. More specific information related to 5F-MDMB-PICA could not be identified.

Reported adverse drug reactions associated with a range SCRAs frequently include gastrointestinal (e.g. nausea/hyperemesis), neurological (e.g. hallucination, agitation, anxiety, paranoia, confusion, delusions, catatonia, lethargy, psychosis (including susceptible individuals)), cardiovascular (e.g. tachycardia, hypertension) and renal (e.g. acute kidney failure) clinical features (e.g. *(19-22)*).

In a recent UNODC communication to the ECDD secretariat, data from the UNODC's ToxPortal that collects death and clinical cases contained 13 cases related to 5F-MDMB-PICA *(23)*. One incident was reported from the USA in 2018, one from Germany in 2018, and 10 from New Zealand 2018/2019. In 4 cases the contribution could not be determined, while it was rated low in 2, medium in 1 and high in another 6 cases. In an updated report provided by the UNODC that includes data obtained from the UNODC's ToxPortal, a total number of 33 case reports involving the detection of 5F-MDMB-PICA were recorded *(24)*. More detailed case level information was not provided (Table 3):

Table 3. Toxicology reports according to data provided by the UNODC's ToxPortal *(24)*

Case reports	Reporting country	Type of cases	Comments
2017 (3) 2018 (12) 2019 (18)	New Zealand (21) Singapore (8) Germany (2) USA (2)	Post-mortem (17)	15/17 poly-drug cases. NPS and controlled substances detected in 8 cases and medicines in 3.
		Clinical admission (15)	12/15 poly-drug cases. NPS and/or metabolites detected in 10 cases and controlled substances in 2 cases.
		Other cases (1)	–

5F-MDMB-PICA was detected in biological specimens collected from two post-mortem cases *(11)*. In case 1, a 47-year-old male (history of drug abuse and diagnosed with type I diabetes) was found dead. Examination revealed pulmonary edema, fatty liver and underweight. Toxicological analysis showed no ethanol but 0.45 part per thousand of acetone in femoral blood as well as 0.60 part per thousand in urine. Vitreous glucose was 78.4 mmol/L and the femoral blood had an elevated BHB at >1000 µg/g. The only exogenous compound found was 0.28 ng/g 5F-MDMB-PICA in femoral blood. The investigation concluded that the cause of death was diabetic ketoacidosis. In case 2, a 49-year-old male (history of alcohol and drug abuse) was found dead. Examination was unremarkable without underlying pathology. The toxicological analysis revealed no ethanol but 0.13 part per thousand of acetone in femoral blood as well as 0.74 part per thousand in urine. Glucose was negative but the femoral blood had an elevated BHB at >1000 µg/g.

The only exogenous compound found was 0.32 ng 5F-MDMB-PICA/g femoral blood. The cause of death was considered due to ketoacidosis possibly with a contribution from drug use *(11)*.

7. Dependence Potential

A. Animal Studies

Information could not be identified.

B. Human Studies

Information could not be identified.

8. Abuse Potential

A. Animal Studies

Information could not be identified.

B. Human Studies

Information could not be identified.

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

5F-MDMB-PICA is not known to have any therapeutic applications.

10. Listing on the WHO Model List of Essential Medicines

5F-MDMB-PICA is not listed on the WHO Model List of Essential Medicines.

11. Marketing Authorizations (as a Medicinal Product)

5F-MDMB-PICA is not marketed as a medicinal product

12. Industrial Use

5F-MDMB-PICA has no reported industrial use.

13. Non-Medical Use, Abuse and Dependence

Household or subpopulation surveys that specifically probe for prevalence of 5F-MDMB-PICA could not be identified in the currently available literature. Epidemiological data, such as prevalence of use, abuse and dependence information, are not available specifically for 5F-MDMB-PICA. The Monitoring the Future (MTF), a national cross-sectional survey in the United States of America that queries use of SCRAs among high-school attending

adolescents revealed a decrease in past-year use from 11.86% in 2011 to 4.75% in 2015. It was however found that the decrease was slower for some subgroups, predominantly those with high socioeconomic status and those who are frequent marijuana users. Across time, risk factors for use also include older adolescents, adolescents who identify as Hispanic/mixed race, and cigarette/other substance users *(25)*.

Heavy use of synthetic cannabinoid receptor agonists has been associated with problematic withdrawal symptoms (e.g. *(26, 27)*) and further research is needed to investigate the underlying mechanisms. As highlighted by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), people who use SCRAs include recreational users, high-risk drug users but also individuals who are subject to drug testing such as people in drug treatment, prisoners and drivers *(28, 29)*.

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

The majority of available SCRA products (including those containing 5F-MDMB-PICA) is sold in the form of herbal mixtures, and designed for smoking purposes and vaping (for example in the form of e-liquids). It is common for retailers to purchase bulk quantities of the synthetic substance and to add the synthetic material to a variety of vegetable matter as the plant base. Products sold as herbal smoking mixtures frequently change in drug composition and quantity, often without indications on product labels, which results in challenges to unambiguously correlate harms to public health with a specific drug such as 5F-MDMB-PICA. The consumption of these products might be attractive to a variety of users, such as regular users of cannabis and those who believe that SCRA use might help with avoiding positive findings in drug-testing procedures. Ease of access, and perceived lack of legislative control might equally be of interest to some users. However, people who use these drugs are most likely not aware of the constituent and the quantity. The high potency associated with many SCRAs carries the risk of accidental overdose and potentially severe adverse events but information specific to 5F-MDMB-PICA is limited. Cases of impaired driving and motor vehicle collisions have been reported with closely related SCRAs such as the indazole analogue 5F-ADB *(30)*. There are indications that socially vulnerable and stigmatised substance users, for example found in homeless and prison populations, are increasingly associated with problematic use of SCRA products *(31-34)*. SCRA use in prisons has been associated with increase in aggression, violence, bullying and debt but also serious threats to safety and security of the prison environment *(28, 29)*. The detections of 5F-MDMB-PICA in biological specimens (Section 16) confirm that this substance is consumed either intentionally or unintentionally though detailed information on the extent of use and circumstances is not available.

A number of trend reports published in the USA have also featured the detection of 5F-MDMB-PICA in various biological samples or sample extracts. In total, cases were submitted from 24 US States and the District of Colombia (Table 4).

Table 4. Trend reports that feature the detection of 5F-MDMB-PICA.[a]			
Time frame	Positive findings	5F-ADB	Reference
Jan–Aug 2018	13 out of 1,037 specimens Metabolites: NR[b] Combinations: 6	100 out of 1,037 specimens Metabolites: 61 Combinations: 10	*(35)*
Oct–Dec 2018	27 out of 964 specimens Metabolites: 4 Combinations: 8	32 out of 964 specimens Metabolites: 31 Combinations: 11	*(36)*
Jan–Mar 2019	52 out of 1,533 specimens Metabolites: 23 Combinations: 13	8 out of 1,533 specimens Metabolites: 19 Combinations: 3	*(37)*
Apr–June 2019	64 out of 1,328 specimens Metabolites: 9 Combinations: 10	None reported.	*(38)*
[a] 5F-ADB (SCRA reviewed during 39th ECDD, *(30)*) results included for comparison. [b] NR: not reported.			

15. Licit Production, Consumption and International Trade

5F-MDMB-PICA is available as standard reference material and produced for scientific research by a number of commercial suppliers. Other uses could not be identified.

16. Illicit Manufacture and Traffic and Related Information

EMCDDA received reports that 5F-MDMB-PICA (detection first notified in September 2016 *(39)*) was encountered in seizures and collected specimens (herbal mixtures or powders) in Germany, Belgium, France, Denmark, Cyprus, Turkey, Sweden, Romania, Slovenia, Lithuania, Croatia, United Kingdom, and Serbia *(40)*. SCRAs are typically imported from Chinese suppliers and prepared locally for distribution in their herbal form *(28)*.

5F-MDMB-PICA was first identified in the United States of America (USA) in October 2016 *(17)*.

The National Forensic Laboratory Information System (NFLIS), which is dedicated to the collection of drug cases submitted by State and local laboratories in the USA, registered two reports in 2016, 84 in 2017, and 29 in 2018 (query date 25 July 2018) *(17)*. At the same time of querying STRIDE and STARLiMS databases, no reports related to 5F-MDMB-PICA could be identified *(17)*. The temporary scheduling order (USA, Controlled Substances Act) document stated that 5F-MDMB-PICA was identified in 381 NFLIS reports from 22 US States, since 2016 and 32 STRIDE/STARLiMS reports from seven US States and the District of Columbia, since 2017 *(18)*. According to information received by the secretariat of the ECDD the total number of drug reports (NFLIS and federal forensic labs) (NFLIS data still pending for 2017-2018) was 849. In the period January 2018–June 2018, 197 reports related to 5F-MDMB-PICA were registered by NFLIS compared to 4,135 for 5F-ADB and 2,972 for FUB-AMB *(41)*.

Detections of 5F-MDMB-PICA have also been reported to UNODC's Early Warning Advisory on New Psychoactive Substances *(42)*. Detections of 5F-MDMB-PICA were reported by 6 countries in 2016, 14 countries in 2017, and 10 countries in 2018 (as of 25 July 2019).

UNODC's evaluation of NPS emergence data (2015–2018) revealed the detection of 5FMDMB-PICA in 20 countries: 7 reports in 2016, 14 reports in 2017, and 9 reports in 2018, respectively *(24)*.

The US National DRUG Early Warning System (NDEWS) hosted at the University of Maryland (USA) publishes Emerging Threat Reports based on the US Drug Enforcement Administration's Special Testing and Research Laboratory's Emerging Trend Program. For the first quarter of 2019, the report featured 9 out of 30 identifications *(43)*.

In recent years it has emerged that SCRAs have been smuggled into prisons in the form of impregnated papers (e.g. letters) and textiles *(29, 44, 45)* including 5F-MDMB-PICA *(46)*.

In a drug-monitoring pilot programme covering three Scottish prisons in the United Kingdom, suspected SCRA-infused paper samples were seized for analytical evaluation in the period between 01 June 2018 and 01 July 2019. In this period, 257 individual paper samples obtained from 116 seizures were analysed which revealed the detection of at least one SCRA in 108 samples (42%). 5F-MDMB-PICA began to emerge in November 2018 and became one of the most commonly detected SCRAs (36.7%, n = 106 in total), thereby replacing 5F-ADB, and FUB-AMB as the most commonly detected compounds in infused papers until that time *(47)*.

17. Current International Controls and Their Impact

5F-MDMB-PICA is not controlled under the 1961 (as amended by the 1972 Protocol), 1971 or 1988 United Nation Conventions.

18. Current and Past National Controls

Refer to Annex 1: Report on WHO questionnaire for review of psychoactive substances.

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

No further comments.

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

Refer to separate Annex 1: Report on WHO questionnaire for review of psychoactive substances

Annex 2: Investigations associated with the chemical analysis of 5F-MDMB-PICA (amongst other substances) including those reported in the published scientific literature

Techniques [a,b]	Comment	Reference
MP, TLC, NMR, ESI-MS, IR	Analysis of synthesised sample for pharmacological testing	*(1)*
GC-MS	Analysis of reference material	*(2)*
IR, GC, EI-MS, NMR	Analysis of seized sample	*(3)*
EI-MS, IR, ESI-MS, IC	Analysis of collected sample	*(4)*
GC-MS, LC-PDA, LC-MS, ESI-MS, NMR	Analysis of seized sample	*(5)*
NR	Analysis of seized samples	*(6)*
GC-MS, LC-MS, NMR	Analysis of seized samples and biological specimens	*(7, 8)*
GC-MS, LC-MS, IM	Analysis of seized samples, biological specimens and metabolism study	*(9)*
LC-MS	Analysis of hair samples	*(10)*
LC-MS	Elucidation of structure-metabolism relationships using pooled human liver microsomes	*(11)*
LC-MS	Analysis of biological specimens and seized samples	*(12)*
LC-MS	Analysis of biological specimens	*(13)*
LC-MS, FC, NMR	Analysis of seized MDMB-CHMICA[c] samples and identification of 5F-MDMB-PICA as a contaminant	*(14)*
IM, LC-MS	Analysis of biological specimens related to “mass overdose” cases.	*(15)*
Raman	Analysis of seized/collected samples	*(16)*
IR, GC-MS, GC-FID	Analysis of seized samples in New Zealand in 2017	*(17)*
LC-MS	In vitro metabolism assay and analysis of biological specimens	*(18)*
LC-MS	Analysis of biological specimens	*(19)*
LC-MS	Analysis of biological specimens, identification metabolites and *in vitro* hCB_1 receptor activation	*(20)*

[a] As of July 2019.

[b] MP: melting point; TLC: thin-layer chromatography; NMR: nuclear magnetic resonance spectroscopy; ESI: electrospray ionisation; MS: mass spectrometry (may involve high or low resolution approaches); IR: infrared spectroscopy; GC: gas chromatography; EI: electron ionisation; IC: ion chromatography; LC: liquid chromatography (various forms); PDA: photo diode array detection; FC: flash chromatography; IM: immunoanalysis; NR: details not reported; FID: flame ionisation detection.

[c] MDMB-CHMICA: methyl (2*S*)-2-{[1-(cyclohexylmethyl)-1*H*-indole-3-carbonyl]amino}-3,3-dimethylbutanoate, a synthetic cannabinoid receptor agonist.

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