



European Monitoring Centre
for Drugs and Drug Addiction

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Risk assessment report on a new psychoactive substance: Methyl 2-[[1-(5-fluoropentyl)-1H-indazole-3-carbonyl]amino]-3,3-dimethylbutanoate (5F-MDMB-PINACA; 5F-ADB)

In accordance with Article 6 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances

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(5F-MDMB-PINACA; 5F-ADB)**

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1. Introduction

This risk assessment report presents the summary findings and the conclusion of the risk assessment carried out by the extended Scientific Committee of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) on the new psychoactive substance methyl 2-[[1-(5-fluoropentyl)-1*H*-indazole-3-carbonyl]amino]-3,3-dimethylbutanoate (commonly known as 5F-MDMB-PINACA). The report is intended for policy makers and decision makers in the institutions of the European Union.

The report has been prepared and drafted in accordance with the conceptual framework and the procedure set out in the risk assessment operating guidelines ⁽¹⁾. It is written as a stand-alone document, which presents a summary of the information considered during the detailed analysis of the scientific and law enforcement data available at this time. The conclusion section of the report summarises the main issues addressed and reflects the opinions held by the members of the Scientific Committee. A list of the information resources considered by the Scientific Committee, including a detailed technical report on 5F-MDMB-PINACA, is provided below.

The risk assessment has been undertaken in compliance with Article 6 of Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk assessment and control of new psychoactive substances ⁽²⁾ (hereafter ‘Council Decision’). The Council Decision establishes a mechanism for the rapid exchange of information on new psychoactive substances (hereafter ‘EU Early Warning System’ ⁽³⁾) that may pose public health and social threats, including those related to the involvement of organised crime. Thus, it allows the institutions of the European Union and the Member States to act on all new narcotic and psychotropic substances ⁽⁴⁾ that appear on the European Union drug market. The Council Decision also provides for an assessment of the risks associated with these new psychoactive substances so that, if necessary, control measures can be applied in the Member States for narcotic and psychotropic substances ⁽⁵⁾.

5F-MDMB-PINACA was formally notified on 8 January 2015 by the EMCDDA on behalf of the Hungarian National Focal Point, in accordance with Article 4 of the Council Decision. The notification related to the seizure of 0.79 grams of white powder seized in September 2014 by customs. Following an assessment of the available information on 5F-MDMB-PINACA, and, in accordance with Article 5 of the Council Decision, on 3 July 2017 the EMCDDA and Europol submitted a *Joint Report* on 5F-MDMB-PINACA ⁽⁶⁾ to

⁽¹⁾ EMCDDA (2010), Risk assessment of new psychoactive substances: Operating guidelines, Publications Office of the European Union, Luxembourg. Available at: <http://www.emcdda.europa.eu/html.cfm/index100978EN.html>

⁽²⁾ OJ L 127, 20.5.2005, p. 32.

⁽³⁾ The information exchange mechanism laid down by the Council Decision is operationalized as the European Union Early Warning System on New Psychoactive Substances (‘EU Early Warning System’). It is operated by the EMCDDA and Europol in partnership with the Reitox National Focal Points and Europol National Units in the Member States, the European Commission, and the European Medicines Agency.

⁽⁴⁾ According to the definition provided by the Council Decision, a ‘new psychoactive substance’ means a new narcotic drug or a new psychotropic drug in pure form or in a preparation; ‘new narcotic drug’ means a substance in pure form or in a preparation that has not been scheduled under the 1961 United Nations Single Convention on Narcotic Drugs, and that may pose a threat to public health comparable to the substances listed in Schedule I, II or IV; ‘new psychotropic drug’ means a substance in pure form or in a preparation that has not been scheduled under the 1971 United Nations Convention on Psychotropic Substances, and that may pose a threat to public health comparable to the substances listed in Schedule I, II, III or IV.

⁽⁵⁾ In compliance with the provisions of the United Nations Single Convention on Narcotic Drugs, 1961, and the United Nations Convention on Psychotropic Substances, 1971.

⁽⁶⁾ EMCDDA (2017), EMCDDA–Europol Joint Report on a new psychoactive substance methyl 2-[[1-(5-fluoropentyl)-1*H*-indazole-3-carbonyl]amino]-3,3-dimethylbutanoate (5F-MDMB-PINACA), EMCDDA, Lisbon. Available at: <http://emcdda.europa.eu/publications/joint-reports/5F-MDMB-PINACA>

the Council of the European Union, the European Commission, and the European Medicines Agency (EMA). Taking into account the conclusion of the *Joint Report*, and, in accordance with Article 6 of the Council Decision, on 14 September 2017 the Council formally requested that ‘the risk assessment should be carried out by the extended Scientific Committee of the EMCDDA and be submitted to the Commission and the Council within twelve weeks from the date of this notification’.

In accordance with Article 6.2, the meeting to assess the risks of 5F-MDMB-PINACA was convened under the auspices of the Scientific Committee of the EMCDDA with the participation of four additional experts designated by the Director of the EMCDDA, acting on the advice of the Chairperson of the Scientific Committee, chosen from a panel proposed by Member States and approved by the Management Board of the EMCDDA. The additional experts were from scientific fields that were either not represented, or not sufficiently represented on the Scientific Committee, and whose contribution was necessary for a balanced and adequate assessment of the possible risks of 5F-MDMB-PINACA, including health and social risks. A further four experts participated in the risk assessment: two experts from the Commission, one expert from Europol, and one expert from the European Medicines Agency (EMA). The meeting took place on 7 and 8 November 2017 at the EMCDDA in Lisbon. The risk assessment was carried out on the basis of information provided to the Scientific Committee by the Member States, the EMCDDA, Europol, and the EMA. A list of the extended Scientific Committee, as well as the list of other participants attending the risk assessment meeting, is annexed to this report (Annex 2).

For the risk assessment, the extended Scientific Committee considered the following information resources:

- Technical report on Methyl 2-{{1-(5-fluoropentyl)-1*H*-indazole-3-carbonyl}amino}-3,3-dimethylbutanoate (5F-MDMB-PINACA) (Annex 1);
- EMCDDA–Europol Joint Report on a new psychoactive substance: methyl 2-{{1-(5-fluoropentyl)-1*H*-indazole-3-carbonyl}amino}-3,3-dimethylbutanoate (5F-MDMB-PINACA) ⁽⁶⁾;
- Open source information including scientific articles, official reports, grey literature, internet drug discussion forums and related websites (hereafter ‘user websites’);
- Additional information provided during the course of the risk assessment meeting by the participants;
- The EMCDDA operating guidelines for the risk assessment of new psychoactive substances ⁽¹⁾; and,
- Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk assessment and control of new psychoactive substances ⁽²⁾.

Finally, it is important to note that this risk assessment report contains a discussion of the available information on serious adverse events such as acute intoxications (typically presenting to hospital emergency departments) and deaths associated with 5F-MDMB-PINACA. Such information is critical to the identification of emerging toxicological problems associated with new psychoactive substances within the European Union. In this context, it is important to recognise that the capacity to detect, identify, and report these events differ both within and between Member States. In the past few years, programmes have been introduced in some Member States to strengthen these capacities. The EMCDDA’s toxicovigilance system, which is a central component of the EU Early Warning System, has also been strengthened resulting in more information being available regarding serious adverse events associated with new psychoactive substances. Nonetheless, it is likely that these events remain under-detected and under-reported.

2. Physical, chemical and pharmacological description

Methyl 2-[[1-(5-fluoropentyl)-1*H*-indazole-3-carbonyl]amino]-3,3-dimethylbutanoate, also known as 5F-MDMB-PINACA, is an indazole-based synthetic cannabinoid receptor agonist (synthetic cannabinoid). The common name for the substance is derived after its structural features ⁽⁷⁾: a fluoro moiety at the position 5 of the *N*-pentyl chain (5F), a dimethyl methyl butanoate linked group (MDMB), a pentyl tail (P), an indazole core (INA) and a carboxamide linker (CA).

5F-MDMB-PINACA contains a stereogenic centre thus allowing for the existence of a pair of enantiomers, (*S*)-5F-MDMB-PINACA and (*R*)-5F-MDMB-PINACA. Neither 5F-MDMB-PINACA nor any of its enantiomers had been described in the scientific or patent literature prior to its first appearance on the European drug market. No information is available on whether the 5F-MDMB-PINACA found in the European drug market corresponds to the (*R*)- or (*S*)- enantiomer, or a mixture of both.

Synthetic cannabinoids such as 5F-MDMB-PINACA are functionally similar to Δ^9 -tetrahydrocannabinol (THC), the major psychoactive principle of cannabis. Like THC, they bind to and activate the CB₁ and CB₂ cannabinoid receptors which form part of the endocannabinoid system — a system that helps regulate a large number of physiological functions in the body such as behaviour, mood, pain, appetite, sleep, the immune system, and the cardiovascular system. Many synthetic cannabinoids were first developed to study the endocannabinoid system as well as to explore their potential as therapeutic agents to treat a number of diseases and their symptoms (such as neurodegenerative diseases, drug dependence, pain disorders, and cancer).

Since around 2006, 'legal high' products containing synthetic cannabinoids have been sold in Europe as 'herbal smoking mixtures' and marketed as 'legal' replacements for cannabis. These products are made by dissolving the synthetic cannabinoids in solvents such as acetone or methanol and then mixing them with, or, spraying them on, plant material such as the herbs Damiana (*Turnera diffusa*) and Lamiaceae (such as *Melissa*, *Mentha* and *Thymus*). Such products are generally referred to by a variety of names in Europe, including 'Spice' ⁽⁸⁾, 'herbal smoking mixtures', 'herbal incense', and 'synthetic cannabis'. Manufacturers of smoking mixtures frequently change the synthetic cannabinoids in the products, which means that product names are not a reliable source of information regarding the actual substances that are present. Almost 180 synthetic cannabinoids, in hundreds of different products, have been identified on the European drug market since 2008. They are the largest group of substances that are monitored by the EMCDDA through the EU Early Warning System.

A number of cannabinoids are controlled under the United Nations Convention on Psychotropic Substances, 1971 (Schedule II). These are: the major active principle of cannabis, delta-9-tetrahydrocannabinol (Δ^9 -THC) ⁽⁹⁾, as well as the synthetic cannabinoids JWH-018 ⁽¹⁰⁾, AM-2201 ⁽¹¹⁾,

⁽⁷⁾ Different naming systems exist and are used for applying short/code names to synthetic cannabinoids. <http://www.emcdda.europa.eu/topics/pods/synthetic-cannabinoids>

⁽⁸⁾ Which is a reference to the most common brand name used for these types of products when they first appeared on the European market.

⁽⁹⁾ Including some of its named isomers and their stereochemical variants.

⁽¹⁰⁾ JWH-018: Naphthalen-1-yl(1-pentyl-1*H*-indol-3-yl)methanone.

⁽¹¹⁾ AM-2201: 1-(5-Fluoropentyl)-1*H*-indol-3-yl]-(naphthalen-1-yl)-methanone.

MDMB-CHMICA (¹²), 5F-APINACA (5F-AKB-48) (¹³), and XLR-11 (¹⁴).

In its pure form 5F-MDMB-PINACA has been described as a white solid. It is poorly soluble in water.

Information provided from seizures and collected samples reported to the EMCDDA have noted that 5F-MDMB-PINACA is typically found in herbal/plant material (including as commercially-branded 'legal high' products) and as a powder. To a lesser extent, other forms, such as liquids and blotters, have also been reported.

The analytical identification of 5F-MDMB-PINACA in physical and biological samples is possible using standard analytical techniques. These include chromatographic and mass spectrometric methods.

Analytical reference material is important for correct identification and for facilitating the quantification of 5F-MDMB-PINACA in physical and biological samples. Such material is commercially available.

Route of administration and dosage

The most common way of using synthetic cannabinoids such as 5F-MDMB-PINACA is by smoking either ready-to-use or homemade 'smoking mixtures' as a cigarette ('joint') or by using a vaporizer, 'bong', or pipe. Some synthetic cannabinoids, including 5F-MDMB-PINACA, have also been offered in the form of e-liquids for vaping in e-cigarettes. Additionally, users might also prepare 5F-MDMB-PINACA containing e-liquids at home. To a lesser extent, other routes of administration for synthetic cannabinoids have been reported; these include oral and rectal.

Limited information is available regarding the dose and the dose regimens of 5F-MDMB-PINACA. User reports specifically about 5F-MDMB-PINACA were not particularly revealing. It is not possible to discern the 'typical' dosages administered as most individuals use herbal smoking mixtures. Nonetheless, based on data from the analysis of some of these products, a gram of herbal material could contain more than 100 mg of 5F-MDMB-PINACA (and potentially other synthetic cannabinoids). These compounds may be active at less than 1 mg.

Pharmacology

Data on the pharmacodynamic effects of 5F-MDMB-PINACA show that it is a potent and full agonist at the CB₁ receptor (i.e. activates the receptor) of the endocannabinoid system. These data show that 5F-MDMB-PINACA is more potent than MDMB-CHMICA, which is a full agonist under international control. 5F-MDMB-PINACA is also a potent and full agonist at the CB₂ receptor.

Data on the pharmacokinetics of 5F-MDMB-PINACA are limited to the identification of metabolites. So far, a number of metabolites have been identified in humans. The pharmacological effects of these metabolites have not been investigated.

(¹²) MDMB-CHMICA: methyl (2S)-2-([1-(cyclohexylmethyl)-1H-indole-3-carbonyl]amino)-3,3-dimethylbutanoate. MDMB-CHMICA was risk assessed by the Scientific Committee of the EMCDDA in July 2016.

(¹³) 5F-APINACA: *N*-(adamantan-1-yl)-1-(5-fluoropentyl)-1H-indazole-3-carboxamide.

(¹⁴) XLR-11: [1-(5-fluoropentyl)-1H-indole-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone.

No studies were identified that have investigated the pharmacodynamics of 5F-MDMB-PINACA on other pharmacological targets.

User reports on the Internet regarding time of onset and duration of effects of structurally related synthetic cannabinoids usually describe an onset of 1 to 5 minutes after smoking and effect duration of 1 to 2 hours. In some cases effects have been described to last over 10 to 15 hours. The assessment of such reports is problematic not least because users cannot confirm the actual substance or the amount used. In general, given the difficulties of collecting accurate self-reported data, it should be interpreted with caution.

Interactions with other substances, medicines, and other forms of interactions

No studies were identified that have investigated the potential interactions of 5F-MDMB-PINACA.

Psychological and behavioural effects

While there is limited data, the psychological and behavioural effects of 5F-MDMB-PINACA appear to share some similarities with cannabis, THC, and other synthetic cannabinoids. This includes: relaxation, euphoria, lethargy, confusion, anxiety, and fear, distorted perception of time, depersonalisation, hallucinations, paranoia, as well as dry mouth, bloodshot eyes, tachycardia, nausea, vomiting, and impaired motor performance. These effects appear to be much more pronounced and severe when compared to cannabis. In addition, psychotic episodes, as well as aggressive and violent behaviour, have also been reported.

Legitimate uses

5F-MDMB-PINACA is used as an analytical reference material in clinical and forensic case work/investigations as well as scientific research. There is currently no information that suggests 5F-MDMB-PINACA is used for other legitimate purposes.

There are no reported uses of 5F-MDMB-PINACA as a component in industrial, cosmetic, or agricultural products. In addition, a search of the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) registered substances database hosted by the European Chemicals Agency (ECHA) using the available CAS Registry Numbers returned no hits.

There is no marketing authorisation (existing, on-going, or suspended) for 5F-MDMB-PINACA in the European Union or in the Member States that responded to the request for information, that was undertaken as part of the Joint Report process ⁽⁶⁾.

There is no information to suggest that 5F-MDMB-PINACA is currently used in the manufacture of a medicinal product in the European Union ⁽⁶⁾. However, in the absence of a database on the synthetic routes of all medicinal products it is not possible to confirm whether or not 5F-MDMB-PINACA is currently used in the manufacture of a medicinal product.

3. Chemical precursors that are used for the manufacture

The chemical precursors and the synthetic routes used to manufacture 5F-MDMB-PINACA are known from the literature. The potential precursors of 5F-MDMB-PINACA are: 1*H*-indole-2,3-dione, 1*H*-indazole-

3-carboxylic acid, methyl 1*H*-indazole-3-carboxylate, methyl L-*tert*-leucinate (for synthesis of the (S)-enantiomer), and 1-bromo-5-fluoropentane. Some of these are commercially available.

Commercially available domestic or industrial products which could be used for synthesis of 5F-MDMB-PINACA may contain potentially toxic substances, including heavy metals and organic solvents. Use of such products as reagents may result in serious toxic effects if the resultant impure product is consumed. The herbal material which is used as a basis for smoking mixtures may also contain toxicologically relevant substances (such as pesticides that could potentially be present in the plant material).

4. Health risks

Individual health risks

The assessment of individual health risks includes consideration of the acute and chronic toxicity of 5F-MDMB-PINACA, as well as its abuse liability and dependence potential. Similarities to, and, differences from, other chemically or pharmacologically related substances should also be considered.

It is important to note that when interpreting information from acute intoxications and deaths as well as information from user websites, individuals may have used other pharmacologically active substances in addition to 5F-MDMB-PINACA. The presence of and/or interaction with other substances or pre-existing health conditions may account for some of the effects reported.

Some individuals may use 5F-MDMB-PINACA in combination with other drugs (either intentionally or unintentionally). 5F-MDMB-PINACA is typically encountered in combination with other substances in commercially branded 'legal high' products, and, in particular, with other synthetic cannabinoids. Analyses of various seized products have shown that the composition can vary significantly over geographical areas and time. Therefore, the users are unlikely to be aware of the substance(s) being ingested and doses used (by whatever route). This presents an inherent risk to the individual.

As synthetic cannabinoids such as 5F-MDMB-PINACA mimic the effects of THC, their effects appear to have some similarities with cannabis. This includes: relaxation, euphoria, lethargy, confusion, anxiety, and fear, distorted perception of time, depersonalisation, hallucinations, paranoia, as well as dry mouth, bloodshot eyes, tachycardia, nausea, vomiting, and impaired motor performance. In some cases, these effects appear to be much more pronounced and severe when compared to cannabis.

Severe and fatal poisonings have occurred with synthetic cannabinoids. This can include severe cardiovascular toxicity (including sudden death), severe central nervous system depression (such as rapid loss of consciousness/coma), respiratory depression, seizures and convulsions, hyperemesis, delirium, agitation, psychotic episodes, and aggressive and violent behaviour.

In addition, some of the features of poisoning—particularly loss of consciousness, respiratory depression, and behavioural effects—may place users at additional risks, such as choking on/aspirating vomit, drowning, falling, hypothermia as a result of falling unconscious outside in cold weather, and self-inflicted violence/injury. The aggressive and violent behaviours reported with synthetic cannabinoids may also place others at risk of injury.

The reasons for these more pronounced and severe effects, as well as severe and fatal poisoning, are poorly understood, but at least two factors are likely to be important: the high potency of the substances and the unintentionally high doses that users are exposed to.

Firstly, studies have found that many of the synthetic cannabinoids, including 5F-MDMB-PINACA, which are sold on the drug market, are much more potent and active, typically behaving as full agonist as compared to THC. This means that even at very small doses they can activate the CB₁ receptor much more strongly than THC.

Secondly, the process for making smoking mixtures (which are the most common way of using these substances) can lead to dangerous amounts of the substances in the products. This is because producers have to guess the amount of cannabinoids(s) to add, while the mixing process makes it difficult to dilute the substances sufficiently and distribute them consistently throughout the plant material. This can result both in products that contain toxic amounts of the substances in general, as well as products where the cannabinoids are clumped together forming highly concentrated pockets within the plant material. These issues are made worse as the products are typically smoked allowing the substances to be rapidly absorbed into the systemic circulation (bloodstream) and to reach the brain.

The combination of these two factors makes it difficult for users to control the dose that they are exposed to and can lead them to rapidly administer a toxic dose unintentionally. Accounts from patients and people who witness poisonings involving smoking mixtures suggest that in some cases a small number of puffs from a cigarette have been sufficient to cause severe and fatal acute poisoning.

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

Overall, poisoning with synthetic cannabinoids may be made worse when other drugs, especially central nervous system depressants (such as alcohol, opioids, and sedative/hypnotics), are used at the same time.

Acute toxicity

The acute toxicity of 5F-MDMB-PINACA and/or its metabolites have not been studied in non-clinical and clinical studies. In addition to the acute intoxications and deaths reported to the EMCDDA (discussed below), cases of acute intoxications and deaths have also been reported in the literature. In general, the available data suggests that intoxication/poisoning with 5F-MDMB-PINACA appears to be similar to other synthetic cannabinoids.

Acute intoxications

A total of 35 acute intoxications with confirmed exposure to 5F-MDMB-PINACA were reported by Hungary (1 case) and the United Kingdom (34 cases). The cases occurred during 2016. No further details are available on the case from Hungary.

In 6 of the cases from the United Kingdom, no other substances were detected. In the remaining cases, other synthetic cannabinoids (detected in 20 cases) and opioids (with methadone detected in 19 cases) were typically detected. Overall, in many of the cases the clinical features of poisoning appeared to be similar to those reported for other synthetic cannabinoids.

Deaths

A total of 28 deaths were reported by 2 Member States: Germany (16) and the United Kingdom (12). In all cases, exposure to 5F-MDMB-PINACA or associated metabolites were analytically confirmed from post-mortem samples.

The deaths in Germany occurred between December 2015 (1) and December 2016 (15). Those in the United Kingdom occurred between January 2016 and February 2017. Demographic data were available for all but one death and involved 26 males and 1 female. The mean age was 34 years (median 33) and ranged from 19 to 49 years.

Cause of death and toxicological significance

A cause of death was reported in all but three cases and in at least 20 deaths, 5F-MDMB-PINACA was either the cause of death or is likely to have contributed to death (even in presence of other substances); other substances were detected in 23 cases. 5F-MDMB-PINACA was the only drug present in 5 deaths based on additional toxicological information.

5F-MDMB-PINACA was quantified in 13 cases. Post-mortem blood concentrations between <0.1 and 1.2 ng/mL (median ~0.28 ng/mL) were recorded. However, post-mortem blood concentrations cannot necessarily be used to determine a “fatal” concentration. In the majority of circumstances involving synthetic cannabinoids, the mere presence of the drug is of significance whether concentration has been determined or not, especially in situations of poly-drug use and the varying circumstances in which they are used.

A range of other substances were detected in the deaths, including: alcohol, cannabinoids, antidepressants, amphetamines (amphetamine, MDMA), zopiclone, paracetamol, synthetic cathinones, opiates (morphine, codeine, noscapine) and benzodiazepines. Other synthetic cannabinoids and/or metabolites were detected in 7 of the deaths, including: MDMB-CHMICA, MDMB-CHMCZCA, 5F-PB-22, 5F-CUMYL-PINACA, and AB-FUBINACA.

Overall, whilst other substances may have contributed some toxicity, the potent nature of 5F-MDMB-PINACA means the primary toxic contribution could be attributed to the drug and death may not have occurred if 5F-MDMB-PINACA had not been used. However, in the cases where multiple synthetic cannabinoids were present, it is not necessarily possible or appropriate to identify 5F-MDMB-PINACA as the primary synthetic cannabinoid that may have produced toxicity but a synergistic effect is likely nonetheless. Sufficient case data were available in 27 of the 28 deaths and an assessment of the toxicological significance score (TSS) ⁽¹⁵⁾ incorporating the above considerations in the deaths, showed that 5F-MDMB-PINACA had a TSS value of 3 (high) in 23 out of 27 of the deaths (where it was cited as the cause of death or is likely to have contributed to death). In the remaining deaths, 2 had an alternative cause of death — drowning and hanging (TSS value of 1, low), with 2 deaths being assessed as having a TSS value of 2 (medium). One of these deaths involved morphine toxicity and in the other case, while drowning was the likely manner of death, it was possible that use of 5F-MDMB-PINACA could have contributed to the situation/cause.

Circumstances of death

There was a lack of information regarding any symptoms experienced by the deceased prior to death in the majority of cases but where described the deceased had collapsed, had vomited or had become unconscious. Where information was known, in the majority of instances the individuals were found dead, predominantly in a home environment (either their own or a friend's), or outside with 2 deaths in prison.

⁽¹⁵⁾ Elliott, S., Sedefov, R. and Evans-Brown, M. (2017), 'Assessing the toxicological significance of new psychoactive substances in fatalities', *Drug Testing and Analysis*. <https://doi.org/10.1002/dta.2225>

Consequently, it was not possible to identify or evaluate ante-mortem symptoms (especially in relation to acute intoxication) in these cases.

Ability to operate machinery and drive

No studies of the effects of 5F-MDMB-PINACA on the ability to drive and operate machines have been performed. However, it has been reported that intoxications caused by a range of synthetic cannabinoids, including 5F-MDMB-PINACA, significantly impair the mental and physical ability that is required to drive and operate machines.

Chronic toxicity

No studies were identified that investigated the chronic health effects of 5F-MDMB-PINACA and/or its metabolites.

Abuse liability and dependence potential

There have been no studies that have investigated the abuse liability and dependence potential of 5F-MDMB-PINACA. Given what is currently known about the pharmacology of 5F-MDMB-PINACA, including some similarities to THC, it is reasonable to consider that the substance may have both a potential for abuse and dependence. Further research will be required in order to determine such effects.

Public health risks

The public health risks associated with 5F-MDMB-PINACA may be categorised in terms of patterns of use (extent, frequency, route of administration, etc.); availability and quality of the drug; information, availability and levels of knowledge amongst users; and, negative health consequences. Detailed information, including data on sporadic versus chronic use, that allow for a determination of public health risks associated with 5F-MDMB-PINACA are unavailable.

Extent, frequency, and patterns of use

The available data suggest that 5F-MDMB-PINACA is typically sold as commercial branded 'legal high' smoking mixtures in head shops as well as on the Internet as 'legal' replacements for cannabis. It may also be sold directly on the illicit drug market. Overall, the available information does not suggest widespread use of the substance.

No surveys were identified that have investigated the prevalence of 5F-MDMB-PINACA use in the general population or in specific user groups.

Because of the variability in the composition of smoking mixtures, and the fact that the ingredients are not typically disclosed, most users will be unaware that they are using 5F-MDMB-PINACA. As a result, the prevalence of use should be considered in the wider context of the prevalence of use of herbal smoking mixtures (sometimes referred to as 'spice').

The use of herbal smoking mixtures has been studied in some European countries in general population surveys and in specific populations such as students, 'clubbers' and/or internet users. The results of these surveys are not comparable as they use different methodology and samples, but, overall, they indicate generally low prevalence levels in these groups.

It is reasonable to assume that 5F-MDMB-PINACA may be sought by those looking for 'legal' substitutes for cannabis. This includes 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 the homeless and prisoners, may specifically seek out synthetic cannabinoids because they have a reputation for causing profound intoxication, they can be cheap, and are easy to smuggle.

Availability and quality on the market

Since September 2014, when it was detected first in Hungary, 5F-MDMB-PINACA has been detected in 25 Member States, Norway, and Turkey. As the substance is not routinely screened for, detections of 5F-MDMB-PINACA may be under-reported.

5F-MDMB-PINACA is sold online either as commercial 'legal high' smoking mixtures or as a powder. The presence of 5F-MDMB-PINACA (or any other synthetic cannabinoid) is not typically disclosed on the packaging/advertising of smoking mixtures.

Due to the high potency of some synthetic cannabinoids, the amount of powder needed for each packet can be in the order of tens of milligrams. This means that each kilogram of bulk powder may produce thousands of packets of 'legal highs' (Section 6).

Detailed information with regards to route-specific by-products produced during the synthesis of 5F-MDMB-PINACA is not available. Quantitative information on 5F-MDMB-PINACA in the seized samples is limited. In herbal material, 5F-MDMB-PINACA was frequently found with other substances, and, in particular, synthetic cannabinoids.

As discussed above, in general, smoking mixtures appear to pose a high risk of poisoning/acute toxicity because of the high potency of synthetic cannabinoids, the manufacturing process used, and the route of administration.

Characteristics and behaviour of users

Information on the characteristics and behaviour of users of 5F-MDMB-PINACA is limited.

'Legal high' products containing 5F-MDMB-PINACA are marketed as 'legal' replacements to cannabis. It is therefore likely that a range of different cannabis users would be interested in these products. The available data suggests that 5F-MDMB-PINACA is used by cannabis users, including those who are regularly subjected to drug testing procedures. To a lesser degree it is also used by psychonaut-type users.

In addition, and, of particular note, is that in some settings, synthetic cannabinoids are increasingly used by high risk drug users and other vulnerable groups, such as the homeless and prisoners. In at least some cases, these users are specifically seeking out synthetic cannabinoids because the substances have developed a reputation for causing profound intoxication, they can be cheap, and are easy to smuggle.

In most cases, it appears that 5F-MDMB-PINACA is not specifically sought after by users who will typically purchase it unknowingly as part of a smoking mixture product.

Nature and extent of health consequences

Information on the nature and extent of health consequences are mostly limited to those discussed in relation to individual health risks.

The high potency of the synthetic cannabinoids, coupled to the unintentionally high doses that users are exposed to, is also responsible for outbreaks of mass poisonings involving smoking mixtures. Such outbreaks have ranged in size from four or five to over 800 victims, including deaths. While many of the outbreaks that have been reported so far are from the United States, they have also occurred in Russia and Europe. Mass poisonings can rapidly overwhelm emergency responders and other local healthcare systems.

Unknown to users, synthetic cannabinoids have also been sold as ecstasy/MDMA and other illicit drugs. In some cases, this has led to severe poisoning. Opioids have also been identified in smoking mixtures; while the overall number of detections appears to be relatively small, it could pose a risk of severe opioid poisoning, including life-threatening respiratory depression, especially in individuals with no tolerance to opioids. Users of smoking mixtures will be unaware of this risk.

Long-term consequences of use

While there is limited data for 5F-MDMB-PINACA, the long-term consequences of use might share similarities to cannabis and other synthetic cannabinoids. This may include dependence.

Conditions under which the substance is obtained and used

There is limited data on the conditions under which 5F-MDMB-PINACA is obtained and used. Sources appear to include internet retailers, physical shops, friends and other acquaintances, and street-level drug dealers. As highlighted, most users will be unaware that they have sourced and used 5F-MDMB-PINACA as they will be using smoking mixtures. The available data suggests that 5F-MDMB-PINACA is used in similar environments to cannabis, including the home, other recreational settings, and prisons.

5. Social risks

The available data suggests that the acute behavioural effects of 5F-MDMB-PINACA bear some similarities to cannabis but are more pronounced and severe.

In addition, and, of particular note, is that in some settings, synthetic cannabinoids are increasingly used by high risk drug users and other vulnerable groups, such as the homeless and prisoners. In at least some cases, these users are specifically seeking out synthetic cannabinoids because the substances have developed a reputation for causing profound intoxication, they can be cheap, and are easy to smuggle. Reports suggest that this has exacerbated existing health and social problems for these vulnerable groups, as well as creating new ones.

Individual social risks

While there is no specific information on whether the use of 5F-MDMB-PINACA causes individual social risks, any such risks may have some similarities with those associated with cannabis and other synthetic cannabinoids. These may impact on education or career, family or other personal and social relationships and may result in marginalisation.

Possible effects on direct social environment (e.g. neglect of family, violence)

While there is no specific information on the possible effects of 5F-MDMB-PINACA on the direct social environment, the behavioural effects of synthetic cannabinoids include reports of aggressive and violent behaviour. This may place users and others at risk of injury.

Possible effects on society as a whole (public order and safety, acquisitive crime)

While there is no specific information on the possible effects of 5F-MDMB-PINACA on society as a whole, as noted, the behavioural effects of synthetic cannabinoids include reports of aggressive and violent behaviour. In particular, concern was expressed in this regard to use in certain environments such as prisons and psychiatric institutions. In addition, the detection of 5F-MDMB-PINACA in cases of suspected driving under the influence of drugs indicates a potential for a wider risk to public safety.

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

Due to the lack of data, it is not possible at this time to estimate the social risk associated with the trafficking and distribution of 5F-MDMB-PINACA.

Economic costs

Due to the lack of data, it is not possible at this time to estimate whether 5F-MDMB-PINACA is associated with greater healthcare costs than other drugs.

Possible appeal to specific population groups

While no specific examples are available on the possible appeal of 5F-MDMB-PINACA to specific user groups, it is reasonable to assume 5F-MDMB-PINACA may be sought after by those looking for 'legal' substitutes for cannabis. This includes 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 the homeless and prisoners, may specifically seek out synthetic cannabinoids because they have a reputation for causing profound intoxication, they can be cheap, and are easy to smuggle.

6. Information on manufacturing, trafficking, distribution, and the level of involvement of organised crime

There is no specific information to suggest the involvement of organised crime or established criminal groups in the manufacture, distribution, and supply of 5F-MDMB-PINACA.

No information has been received by Europol indicating synthesis of 5F-MDMB-PINACA within the European Union. Information reported to the EMCDDA and Europol indicates that chemical companies based in China may be one source of 5F-MDMB-PINACA, as well as of other synthetic cannabinoids. Seizures, particularly of bulk powders of synthetic cannabinoids are frequently reported to have occurred at international European airports and to have been shipped by such companies.

For 5F-MDMB-PINACA, single seizures of powders in excess of 1 kg were reported by Belgium, Bulgaria, France, and the Netherlands. Whilst the majority of these seizures were made by customs at international airports the origin and destination of the packages was not reported.

Powders of synthetic cannabinoids, including 5F-MDMB-PINACA, are imported into the European Union where they are either processed and packaged into commercial smoking mixtures or sold as powder. There are indications of a significant internet retail trade in synthetic cannabinoid products within Europe, with customs and police making regular seizures of such products, including herbal smoking products containing 5F-MDMB-PINACA.

5F-MDMB-PINACA has been available on the European drug market since at least September 2014. A total of 25 Member States (Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Romania, Slovenia, Spain, Sweden, the United Kingdom), Turkey, and Norway, have reported detections of 5F-MDMB-PINACA. Information reported to the EMCDDA and Europol indicates that 5F-MDMB-PINACA has been seized as herbal material (approximately 100 kg; 74 kg of which reported by Turkey) or powder form (approximately 13 kg).

The available data suggests that herbal smoking mixtures containing 5F-MDMB-PINACA are being sold directly on the illicit market. The United Kingdom reported 129 seizures of 5F-MDMB-PINACA (amounting to 3 kg) that occurred in prisons or other custodial setting. The majority of the seizures were in herbal form and often in combination with other synthetic cannabinoids.

7. Information on any assessment in the United Nations system

The World Health Organization (WHO) 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. In May 2017, the WHO informed the EMCDDA that 5F-MDMB-PINACA will be reviewed at the 39th meeting of the WHO Expert Committee on Drug Dependence (ECDD) that will be held in November 2017.

8. Description of the control measures that are applicable in the Member States

Fourteen Member States (Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Latvia, Lithuania, Luxembourg, Sweden, and the United Kingdom) reported that 5F-MDMB-PINACA is controlled under drug control legislation.

- In Bulgaria, 5F-MDMB-PINACA was controlled in 2017 according to the 'Regulation on the classification of plants and substances as narcotics'.
- In Croatia, 5F-MDMB-PINACA is controlled within the 'List of drugs, psychotropic substances, plants used to produce drugs and substances that can be used in the production of drugs', Official Gazette no. 10/16.
- In Cyprus, 5F-MDMB-PINACA is controlled as a Class B drug within the Narcotic Drugs and Psychotropic Substances Law 1977.
- In the Czech Republic, 5F-MDMB-PINACA is controlled since March 2017.

- In Denmark, 5F-MDMB-PINACA is controlled as of 15 June 2017 by an amendment of the Executive Order on Controlled Substances.
- In Estonia, 5F-MDMB-PINACA is controlled as of 15 September 2016.
- In Finland, 5F-MDMB-PINACA is controlled as a 'psychoactive substance banned from the consumer market'.
- In France, 5F-MDMB-PINACA is controlled since 31 March 2017.
- In Germany, 5F-MDMB-PINACA is included in schedule II 'narcotics eligible for trade but not for medical prescription'.
- In Latvia, 5F-MDMB-PINACA is included in the Cabinet Regulation N 847 'Regulations regarding Narcotic Substances, Psychotropic Substances and Precursors to be Controlled in Latvia' and the law 'On the Procedures for the Coming into force and Application of the Criminal Law'.
- In Lithuania, 5F-MDMB-PINACA is subjected to control measures by The Republic of Lithuania Minister of Health Order No V-1062 (21/09/2015) 'On the amendment of the Ministry of Health of the Republic of Lithuania Order No. 5 of 6 January 2000'.
- In Luxembourg, 5F-MDMB-PINACA is controlled by way of generic definition by the Grand-ducal decree of 20/04/2009.
- In Sweden, 5F-MDMB-PINACA is regulated under the Act on the Prohibition of Certain Goods Dangerous to Health, as of 24 March 2015.
- In the United Kingdom, 5F-MDMB-PINACA is controlled by way of generic definition under the 1971 Misuse of Drugs Act.

Four Member States (Austria, Belgium, Hungary, and Poland) and Turkey reported that 5F-MDMB-PINACA is controlled under specific new psychoactive substances control legislation.

- In Austria, 5F-MDMB-PINACA is covered by the Austrian Act on New Psychoactive substances.
- In Belgium, 5F-MDMB-PINACA is controlled by way of generic definition.
- In Hungary, 5F-MDMB-PINACA is controlled under specific NPS control legislation. No additional details were provided.
- In Poland, 5F-MDMB-PINACA is controlled according to the general definition of the 'substitute drug' (Act of 8 October 2010 amending the Act on counteracting drug addiction and the Act on State Sanitary Inspection, Journal of Laws "Dz.U." No. 213, item 1396). Pursuant to Article 44b of the Act on counteracting drug addiction, it is prohibited to manufacture and introduce substitute drugs to trade.
- In Turkey, 5F-MDMB-PINACA is controlled by way of generic definition under specific new psychoactive substances control legislation.

Norway reported that 5F-MDMB-PINACA is controlled under medicinal products legislation.

Nine Member States (Greece, Ireland, Italy, Malta, the Netherlands, Portugal, Romania, Slovenia, and Spain), reported that 5F-MDMB-PINACA is not subject to control measures at the national level.

Slovakia did not provide information on the control status of 5F-MDMB-PINACA.

9. Options for control and the possible consequences of the control measures

Under Article 9.1 of the Council Decision, the option for control that is available at European Union level is for the Member States to submit the new psychoactive substance 5F-MDMB-PINACA to control measures and criminal penalties, as provided for under their legislation, by virtue of their obligations under the Convention on Psychotropic Substances, 1971.

There are no studies on the possible consequences of such control measures on 5F-MDMB-PINACA. If this option of control is pursued, the Committee considers that the following consequences are possible. Some of these may apply to any new psychoactive substance.

- This control option could be expected to limit the availability of 5F-MDMB-PINACA and hence the further expansion of the current open trade in this substance.
- A health consequence that might result from this control option is the benefit brought about by the presumed reduction in availability and use.
- This control option could facilitate the detection, seizure and monitoring of 5F-MDMB-PINACA related to its unlawful manufacture, trafficking and use. In so doing, it could facilitate cooperation between the judicial authorities and law enforcement agencies across the European Union.
- This control option would imply additional costs for the criminal justice system, including forensic services, law enforcement, and the courts.
- This control option could lead to replacement with other (established or new) psychoactive substances, which may in themselves have public health consequences and social risks.
- This control option could create an illicit market in 5F-MDMB-PINACA with the increased risk of associated criminal activity, including the involvement of organised crime.
- This control option could impact on both the quality/purity and price of any 5F-MDMB-PINACA still available on the illicit market. The extent to which this will impact on public health, criminality, or levels of use, is difficult to predict.
- It is difficult to predict the impact of this control option on current or future research by the pharmaceutical or chemical industries.
- In order to examine the consequences of control, the Committee wishes to note that it will be important to monitor for the presence of 5F-MDMB-PINACA on the market post-control, should this control option be pursued.

- Aside from the option for control under those stipulated in Article 9.1 of the Council Decision, other options for control may be available to Member States. These may include restricting the importation and supply of the substance as some Member States have already done.

10. Conclusion

Methyl 2-[[1-(5-fluoropentyl)-1*H*-indazole-3-carbonyl]amino]-3,3-dimethylbutanoate (5F-MDMB-PINACA) is an indazole-based synthetic cannabinoid receptor agonist. Information on the pharmacology of 5F-MDMB-PINACA suggests that it is a potent and full agonist at the CB₁ receptor and CB₂ receptor. It shows similar effects to THC but with additional life-threatening toxicity. The high potency of 5F-MDMB-PINACA and the large and variable content of the substance in smoking mixtures constitute a high risk of poisoning.

5F-MDMB-PINACA is often sold as a 'legal' replacement for cannabis. It is typically administered by smoking a herbal mixture that is either from a ready-to-use commercial 'legal high' product, or, less commonly, that is self-prepared. Similar to herbal cannabis, the mixture is usually prepared for smoking as a hand-rolled cigarette ('joint') but it may also be smoked in a pipe or 'bong'. 5F-MDMB-PINACA can also be inhaled using an e-cigarette or other vaporisation device.

5F-MDMB-PINACA has been available on the drug market in the European Union since at least September 2014 and has been detected in 25 Member States, Turkey, and Norway. It is sold online as commercially branded 'legal high' products and powders. It may also be sold directly on the illicit drug market.

The available data suggests that 5F-MDMB-PINACA is used by cannabis users, by those who are regularly subjected to drug testing procedures (including those in prison), and by 'psychonauts'. It may also be used by high risk drug users and other marginalised groups (such as prisoners) as synthetic cannabinoids have gained a reputation for causing profound intoxication, they can be cheap, and are easy to smuggle. However, no further information on the size and demand and the characteristics of these groups of people is available.

Thirty-five acute intoxications with confirmed exposure to 5F-MDMB- have been reported by 2 Member States. Where known, the features of the poisoning were similar to those found with other synthetic cannabinoids.

Twenty eight deaths with confirmed exposure to 5F-MDMB-PINACA have been reported by 2 Member States. In at least 20 of these cases, 5F-MDMB-PINACA was either the cause of death or is likely to have contributed to the death.

Due to the nature of 5F-MDMB-PINACA, both non-fatal intoxications and deaths are likely to be under-detected and under-reported.

There is no approved antidote to poisoning caused by synthetic cannabinoids such as 5F-MDMB-PINACA.

Reports suggest a possibility for violence and aggression following use of synthetic cannabinoids. In particular, concern was expressed in this regard to use in certain environments, such as prisons and psychiatric institutions. In addition, the detection of 5F-MDMB-PINACA in cases of suspected driving under the influence of drugs indicates a potential for a wider risk to public safety.

There is no specific information on the involvement of organised crime in the manufacture, distribution (trafficking), and supply within the European Union. There is limited information on the chemical precursors and the synthetic routes used to manufacture the 5F-MDMB-PINACA detected within the European Union. The largest single seizure of 5F-MDMB-PINACA was in France in 2017, when approximately 2.3 kg of powder was seized by customs. During 2017, 5F-MDMB-PINACA continued to be regularly seized by law enforcement within the European Union.

5F-MDMB-PINACA has no recognized human or veterinary medical use in the European Union, nor, it appears, elsewhere. There are no indications that 5F-MDMB-PINACA may be used for any other purpose aside from as an analytical reference standard and in scientific research.

5F-MDMB-PINACA is not listed for control in the Single Convention on Narcotic Drugs, 1961, nor in the Convention on Psychotropic Substances, 1971. 5F-MDMB-PINACA is currently under assessment by the United Nations system.

Fourteen Member States control 5F-MDMB-PINACA under drug control legislation. Four Member States, Turkey, and Norway control 5F-MDMB-PINACA under other legislation.

As for any new psychoactive substance, many of the questions related to 5F-MDMB-PINACA that are posed by the lack of data on the risks to individual health, risks to public health, and social risks, could be answered through further research. Areas where additional information would be important include studies on: rationale for use, prevalence and patterns of use (including targeted studies that examine user groups and risk behaviours); the market; chemical profiling; complete pharmacological profiling; metabolic pathways; behavioural effects; acute and chronic toxicity; the potential interaction between 5F-MDMB-PINACA and other substances; the dependence and abuse potential; and the public health risks associated with its use.

The Committee notes that a decision to control 5F-MDMB-PINACA has the potential to bring with it both intended and unintended consequences. Potential intended consequences include reduced levels of availability and ultimately use. This may reduce the health and social risks arising from the use of 5F-MDMB-PINACA. It is important to recognise that a potential unintended consequence of control may be the manufacture and availability of other substances. Indeed, pharmacologically analogous substances that may replace 5F-MDMB-PINACA are already being sold on the drug market. The implementation of control measures may also lead to the criminalisation of those who continue to use this substance with the possible attendant risks of socio-economic stigmatisation and marginalisation. Should control measures be adopted, they should be accompanied by the gathering and dissemination of accurate information on 5F-MDMB-PINACA to users, practitioners, policy makers, and decision makers.

11. List of annexes

Annex 1: Technical report on Methyl 2-[[1-(5-fluoropentyl)-1*H*-indazole-3-carbonyl]amino]-3,3-dimethylbutanoate (5F-MDMB-PINACA).

Annex 2: List of participants at the risk assessment meeting of Methyl 2-[[1-(5-fluoropentyl)-1*H*-indazole-3-carbonyl]amino]-3,3-dimethylbutanoate (5F-MDMB-PINACA).



DRAFT

Technical report on methyl 2-[[1-(5-fluoropentyl)-1H-indazole-3-carbonyl]amino]-3,3-dimethylbutanoate (5F-MDMB-PINACA; 5F-ADB)

Parts of this technical report were prepared under contract from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Given the time frame stipulated in the Council Decision, additional data presented and discussed during the preparatory meeting for the risk assessment and the risk assessment meeting have not yet been incorporated into the technical report. In addition, this technical report has not been formally edited by the EMCDDA. As such, this report should be regarded as a draft document until such time that the final version is produced by the EMCDDA which will incorporate the additional data and which will be formally edited. The EMCDDA may not be held responsible for the use of the information contained herein without prior consultation. The *Risk assessment report on a new psychoactive substance: 2-(1-(5-fluoropentyl)-1H-indazole-3-carboxamido)-3,3-dimethylbutanoate (5F-MDMB-PINACA; 5F-ADB)*, to which this report is annexed, was produced by the extended Scientific Committee of the EMCDDA and shall be regarded as the authoritative document.

3 November 2017

Annex 1 to the *Risk Assessment Report on 2-(1-(5-fluoropentyl)-1H-indazole-3-carboxamido)-3,3-dimethylbutanoate (5F-MDMB-PINACA; 5F-ADB)*.

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Introduction

Synthetic cannabinoid receptor agonists (synthetic cannabinoids), such as 5F-MDMB-PINACA, are a group of substances that mimic the effects of tetrahydrocannabinol (THC), which is a substance found in cannabis ⁽¹⁾. THC is responsible for many of the psychoactive effects of cannabis which give that feeling of being 'stoned' (or 'high') (Gaoni et al, 1964; Huestis et al., 2001; Pertwee, 2014). THC causes these effects by activating a receptor in the brain called the *cannabinoid receptor type 1* (CB₁ receptor) (Huestis et al., 2001; Pertwee, 2005a). This receptor is part of a signalling system in the body called the endocannabinoid system, which helps regulate, among other things, behaviour, mood, pain, appetite, sleep, and the immune system (Pertwee, 2015) ⁽²⁾. Because synthetic cannabinoids activate the CB₁ receptor in a similar way to THC, some of their effects appear to be similar to cannabis. Most prominently, they are able to create a feeling of being 'stoned'.

Synthetic cannabinoids were originally developed by scientists to study the endocannabinoid system, as well as provide insights into disease, and to help make new medicines (Pertwee, 2005a; Pertwee, 2005b; Pertwee, 2015; Reggio, 2009). From around 2006, they began to appear in Europe in products called 'Spice' that were sold as 'legal' replacements to cannabis (Auwärter et al., 2009; EMCDDA, 2009; Jack, 2009). In these products, synthetic cannabinoids had been mixed with plant (herbal) material which could then be smoked as cigarettes ('joints') (Auwärter et al., 2009 ; EMCDDA, 2009; EMCDDA, 2017a; Jack, 2009). Such products have been referred to by a variety of names, including 'herbal smoking mixtures', 'herbal incense', 'Spice', 'K2', and 'synthetic cannabis'. Since 2008, almost 180 synthetic cannabinoids have been identified on the drug market in hundreds of different products. They are the largest group of substances that are monitored by the EMCDDA through the European Union Early Warning System on New Psychoactive Substances (EU Early Warning System) (EMCDDA, 2017b).

In accordance with Article 5 of the *Council Decision 2005/387/JHA on the information exchange, risk-assessment and control of new psychoactive substances* ⁽³⁾ on 25 April 2017, the EMCDDA and Europol launched the Joint Report procedure for methyl 2-[[1-(5-fluoropentyl)-1H-indazole-3-carbonyl]amino]-3,3-dimethylbutanoate (5F-MDMB-PINACA; 5F-ADB) on the basis of data reported by the Member States to the EU Early Warning System in accordance with Article 4 of the Council Decision. The information collection process for the Joint Report was completed in June 2017. The report was submitted to the Institutions of the European Union in July 2017 (EMCDDA, 2017c). In accordance with Article 6 of the Council Decision, on 14 September 2017, the Council of the European Union requested that a risk assessment on 5F-MDMB-PINACA should be carried out by the extended Scientific Committee of the EMCDDA.

In order to prepare for a risk assessment that has been convened under the Council Decision, and, to facilitate the risk assessment process, the EMCDDA is responsible for the collection and analysis of data on the substance to be assessed as well as drafting a technical report. This technical report has been prepared for the risk assessment of 5F-MDMB-PINACA that will be held at the EMCDDA premises in Lisbon on 8 November 2017.

⁽¹⁾ (–)-*trans*-Δ⁹-tetrahydrocannabinol.

⁽²⁾ The endocannabinoid system helps regulate a large number functions in the body. It consists of the cannabinoid CB₁ and CB₂ receptors, the endocannabinoids (such as anandamide) which act as endogenous agonists for these receptors, and the processes responsible for endocannabinoid biosynthesis, cellular uptake, and metabolism. Important exogenous agonists for the cannabinoid receptors are (–)-*trans*-Δ⁹-tetrahydrocannabinol (THC) which is the major active substance in cannabis, and the synthetic cannabinoids found in legal high-type smoking mixtures. Data from laboratory studies suggests that the endocannabinoid system plays an important protective role. For example, in response to some diseases the body increases the amount of endocannabinoids it produces which can reduce unwanted symptoms or slow disease progression (Pertwee, 2005a; Pertwee, 2005b; Pertwee, 2015).

⁽³⁾ OJ L 127, 20.5.2005, p. 32.

Some of the sections in this report were prepared under EMCDDA contracts (ref. CT.16.SAT.0101.1.0 and CT.17.SAT.0110.1.0).

Data sources

The information in this technical report is derived from:

- data reported by the Member States, Turkey and Norway to the EMCDDA and Europol in accordance with the Council Decision (EMCDDA, 2017c); and,
- data collected through systematic searches of open source information, including the scientific and medical literature, patents, official reports, grey literature, Internet drug discussion forums and related websites, and online vendors selling 5F-MDMB-PINACA.

Search strategy

Literature searches used both chemical structure and text queries in online databases; searches were conducted in August 2017. The retrieved publications were then reviewed for additional relevant references (snowballing technique).

Textual searches were conducted online in *PubMed* (National Center for Biotechnology Information), Web of Science™ (Thomson Reuters), and in popular English-language drug forums. The search terms used were: '5F-MDMB-PINACA' and '5F-ADB'. Medline and Google Scholar were searched for '5F-MDMB-PINACA', '5F-ADB', 'MDMB-PINACA-5F', '5-fluoro MDMB-PINACA', '5-fluoro ADB' (with and without hyphen) and the IUPAC names of this compound stated in this document. In addition, exact chemical structure-based searches were done in SciFinder (American Chemical Society, Chemical Abstract Service) and Reaxys (Elsevier). Google and specific drug user discussion forums and related websites (such as Bluelight, Eve and Rave, and Erowid) were searched for the terms: '5F-MDMB-PINACA', '5F-ADB', 'MDMB-PINACA-5F', '5-Fluoro-MDMB-PINACA', alone or in combination with 'buy', 'shop', 'research chemical', 'synthetic cannabinoid', 'dosing', 'intoxication', 'kaufen', 'räuchermischung', 'powder', 'synthesis'. Additionally, colleagues within the scientific network of the authors were contacted to obtain information.

The REACH registered substances database hosted by the European Chemicals Agency (ECHA) was searched using the CAS registry numbers listed below. The searches returned no hits.

Note

It is important to note that when interpreting the information on self-reported user experiences in this report, it is not possible to confirm the specific substance(s) that have been claimed to be used; similarly it is also not possible to confirm the strength, purity, dose/amount, etc., used. Moreover, the actual composition of the substance/product claimed to be used may differ over time and different geographical areas. In addition, the information provided on user websites may not necessarily be representative of other users of 5F-MDMB-PINACA and should be regarded as illustrative only. In general, given the difficulties of collecting accurate self-reported data, it should be interpreted with caution.

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Section A. Physical, chemical, pharmaceutical and pharmacological information

A1. Physical, chemical, and pharmaceutical information

A1.1. Physical and chemical description

Chemical description and names

Methyl 2-[[1-(5-fluoropentyl)-1*H*-indazole-3-carbonyl]amino]-3,3-dimethylbutanoate, also known as 5F-MDMB-PINACA (Figure 1) is a synthetic cannabinoid receptor agonist (synthetic cannabinoid). The common name for the substance is derived after its structural features ⁽⁷⁾: a fluoro moiety at the position 5 of the *N*-pentyl chain (5F), a dimethyl methyl butanoate linked group (MDMB), a pentyl tail (P), an indazole core (INA) and a carboxamide linker (CA).

5F-MDMB-PINACA contains a stereogenic centre and therefore two possible enantiomers may exist, (*R*)- and (*S*)-5F-MDMB-PINACA. Neither 5F-MDMB-PINACA nor its enantiomers had been described in the scientific or patent literature prior to its first appearance on the European drug market around September 2014 (Section C).

5F-MDMB-PINACA contains an indazole core, which is a common structural feature in many of the synthetic cannabinoids monitored by the EMCDDA, such as AB-CHMINACA and ADB-CHMINACA. Five synthetic cannabinoid receptor agonists have been recently controlled under Schedule II of the United Nations Convention on Psychotropic Substances, 1971: JWH-018 ⁽⁸⁾, AM-2201 ⁽⁹⁾, MDMB-CHMICA ⁽¹⁰⁾, 5F-APINACA (5F-AKB-48) ⁽¹¹⁾ and XLR-11 ⁽¹²⁾. Other synthetic cannabinoids, including AB-CHMINACA ⁽¹³⁾ (EMCDDA, 2017d), ADB-CHMINACA ⁽¹⁴⁾ (EMCDDA, 2017e), and CUMYL-4CN-BINACA ⁽¹⁵⁾ (EMCDDA, 2017f), have also been the subjects of Joint Reports by the EMCDDA and Europol.

⁽⁷⁾ The common name for the substance is derived after its structural features. Different naming systems exist and are used for applying short/code names to synthetic cannabinoids.

⁽⁸⁾ JWH-018: (Naphthalen-1-yl)(1-pentyl-1*H*-indol-3-yl)methanone.

⁽⁹⁾ AM-2201: [1-(5-Fluoropentyl)-1*H*-indole-3-yl](naphthalen-1-yl)methanone.

⁽¹⁰⁾ MDMB-CHMICA: Methyl (2*S*)-2-[[1-(cyclohexylmethyl)-1*H*-indole-3-carbonyl]amino]-3,3-dimethylbutanoate.

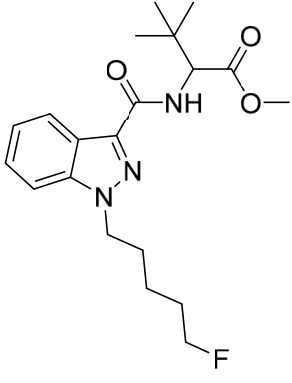
⁽¹¹⁾ 5F-APINACA: *N*-(Adamantan-1-yl)-1-(5-fluoropentyl)-1*H*-indazole-3-carboxamide.

⁽¹²⁾ XLR-11: [1-(5-Fluoropentyl)-1*H*-indole-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone.

⁽¹³⁾ AB-CHMINACA: *N*-(1-Amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide

⁽¹⁴⁾ ADB-CHMINACA: *N*-[1-Amino-3,3-dimethyl-1-oxobutan-2-yl]-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide.

⁽¹⁵⁾ CUMYL-4CN-BINACA: 1-(4-Cyanobutyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide.


$C_{20}H_{28}FN_3O_3$
377.46 g/mol
Figure 1. The molecular structure, molecular formula and molecular mass of 5F-MDMB-PINACA.

Names and other identifiers

Systematic International Union of Pure and Applied Chemistry (IUPAC) names:

Methyl 2-[[1-(5-fluoropentyl)-1*H*-indazole-3-carbonyl]amino]-3,3-dimethylbutanoate

Chemical Abstract name:

Valine, *N*-[[1-(5-fluoropentyl)-1*H*-indazol-3-yl]carbonyl]-3-methyl-, methyl ester

Other names:

Methyl 2-[[1-(5-fluoropentyl)-1*H*-indazole-3-yl]carbonyl]amino)-3,3-dimethylbutanoate;

Methyl 2-[[1-(5-fluoropentyl)-1*H*-indazole-3-yl]formamido]-3,3-dimethylbutanoate;

Methyl *N*-[[1-(5-fluoropentyl)-1*H*-indazole-3-yl]carbonyl]-3-methylvalinate;

Methyl-[2-(1-(5-fluoropentyl)-1*H*-indazole-3-carboxamido)-3,3-dimethylbutanoate];

N-(1-methoxy-3,3-dimethyl-1-oxobutan-2-yl)-1-(5-fluoropentyl)-1*H*-indazole-3-carboxamide;

L-Valine, *N*-[[1-(5-fluoropentyl)-1*H*-indazol-3-yl]carbonyl]-3-methyl-, methyl ester ((*S*)-enantiomer);

D-valine, *N*-[[1-(5-fluoropentyl)-1*H*-indazole-3-yl]carbonyl]-3-methyl-, methyl ester ((*R*)-enantiomer);

Methyl (*S*)-2-(1-(5-fluoropentyl)-1*H*-indazole-3-carboxamido)-3,3-dimethylbutanoate ((*S*)-enantiomer);

Methyl (2*S*)-2-[[1-(5-fluoropentyl)-1*H*-indazole-3-carbonyl]amino]-3,3-dimethylbutanoate ((*S*)-enantiomer).

Methyl *N*-[[1-(5-fluoropentyl)-1*H*-indazole-3-yl]carbonyl]-3-methyl-D-valinate ((*R*)-enantiomer);

Methyl (*R*)-2-(1-(5-fluoropentyl)-1*H*-indazole-3-carboxamido)-3,3-dimethylbutanoate ((*R*)-enantiomer);

N-[[1-(5-fluoropentyl)-1*H*-indazole-3-yl]carbonyl]-3-methyl-D-valine, methyl ester ((*R*)-enantiomer);

Methyl (2*R*)-2-[[1-(5-fluoropentyl)-1*H*-indazole-3-carbonyl]amino]-3,3-dimethylbutanoate ((*R*)-enantiomer)

Chemical Abstract Service Registry Numbers (CAS RNs) ⁽¹⁶⁾:

1715016-75-3: racemate

1838134-16-9: ((*R*)-enantiomer)

1971007-89-2: ((*S*)-enantiomer)

PubChem SID:

101895417 (racemate) ⁽¹⁷⁾

IUPAC International Chemical Identifier Key (InChI Key) ⁽¹⁸⁾:

PWEKNGSNNAKWBL-UHFFFAOYSA-N (racemate)

PWEKNGSNNAKWBL-KRWDZBQOSA-N ((*R*)-enantiomer)

PWEKNGSNNAKWBL-QGZVFWFLSA-N ((*S*)-enantiomer)

SMILES ⁽¹⁹⁾:

CC(C)(C)C(=O)OCNC(=O)c1c2ccccc2n(n1)CCCCCF (racemate)

[H][C@](C(=O)OC)(C(C)(C)C)NC(=O)c1c2ccccc2n(n1)CCCCCF ((*R*)-enantiomer)

FCCCC[N]2C1=CC=CC=C1C(=N2)C(=O)N[C@H](C(=O)OC)C(C)(C)C ((*S*)-enantiomer)

Common names:

5F-MDMB-PINACA, 5F-ADB

Other names:

5F-methyl-AMB, 5-fluoro-MAMB; 5-fluoro ADB; MDMB(*N*)-2201; 5-fluoro-ADB

Street names:

⁽¹⁶⁾ The Chemical Abstract Service Registry Number (CAS RN) is a unique numeric identifier assigned by the Chemical Abstract Service Division of the American Chemical Society to a specific, single chemical substance.

⁽¹⁷⁾ <https://pubchem.ncbi.nlm.nih.gov/compound/101895417>

⁽¹⁸⁾ InChI Key is a unique, non-proprietary structural identifier of chemical substances useful in electronic sources.

⁽¹⁹⁾ The simplified molecular-input line-entry system (SMILES) is a unique, non-proprietary structural identifier of chemical substances useful in electronic sources.

'Spice', 'K2', 'legal weed', 'synthetic cannabis', 'herbal incense'

5F-MDMB-PINACA has been detected in herbal smoking mixtures bought from vendors on the surface web as part of the EU project 'SPICE Profiling' project (JUST/2013/ISEC/DRUGS/AG/6421) (Moosmann et al., 2017).

These products bore invented names such as: 4g für ein Halleluja – Hausmarke, Abyss Regeneration, Alien, Armata, Bakus vip, Berlin, Black Afghan, Black Diamonds, Black Sun, Blu3 Moon, Bonzai Winterboost, Brain Bad, Brennstoff, Bubble Gum, Bubble Trouble, Candy Rush, Citrus Bomb, Citrus Bomb, Citrus Monster, C-Liquid 5F-MDMB-PINACA Ice Methol, C-Liquid 5F-MDMB-PINACA Lemon, C-Liquid 5F-MDMB-PINACA Rhubarb&Custard, C-Liquid 5F-MDMB-PINACA Skittles, C-Liquid 5F-MDMB-PINACA Tobacco, Couch Trip, Cracker, Crazy, Crazy Monkees *2*, Dark Night, Dreamcatcher, Fear and Loathing, Galaxy *2*, Ganja Style, Global Bäääm blue, Gold, Hexenmeister, Honey Cognac Bronze, Hydro, Incense, Incense Extreme, Insomnia Fantasy, Jamaican Bird, Jamaican Gold Extreme, Kraftstoff, Jamaican Lion, Lollipop Bronze, Lollipop Gold, Lollipop Silver, Made in Holland, Mandala, Moroccan Caramello, MEX - Herbal Incense, Miami Spice, Natural Born Chiller, New Maya *deluxe*, New Spice, No Kangaroo Inside, Platin, Play Hard, Psycho, Russian Elite, Shiva Passion, Spice Girls, Spongebob Smoke Weed, Strawberry Kiss Bronze, Strong Smerf Vip, The Light, The New Warning, The Orion, The Pope, Trank, Up In the Sky, Vanilla Ice Summer, V.I.P. M.G., Viva la Revolution/ CHE Lemon, Viva la Revolution/ CHE Watermelon, Weired Chocolate Bronze (Angerer et al., 2016).

Other street names reported to the EMCDDA are: ANNIHILATION, BLACK MAMBA ULTRA, Blueberry Blitz, CHERRY BOMB, Dutchy, EXODUS FORMULA 6-A, Sky High, Spike 99 ULTRA, and Vanilla Ice.

Manufacturers of herbal smoking mixtures frequently change the synthetic cannabinoids in the products, which means that product names are not a reliable source of information regarding the actual substances that are present (e.g. Frinculescu et al., 2017, Moosmann et al., 2015).

Identification and analytical profile

Physical description

In its pure form 5F-MDMB-PINACA is a white solid (Banister et al., 2016). It is soluble up to approximately 25 mg/mL in ethanol, DMSO and DMF (Cayman Chemical Company, 2017). The substance is sparingly soluble in aqueous buffers (Cayman Chemical Company, 2017).

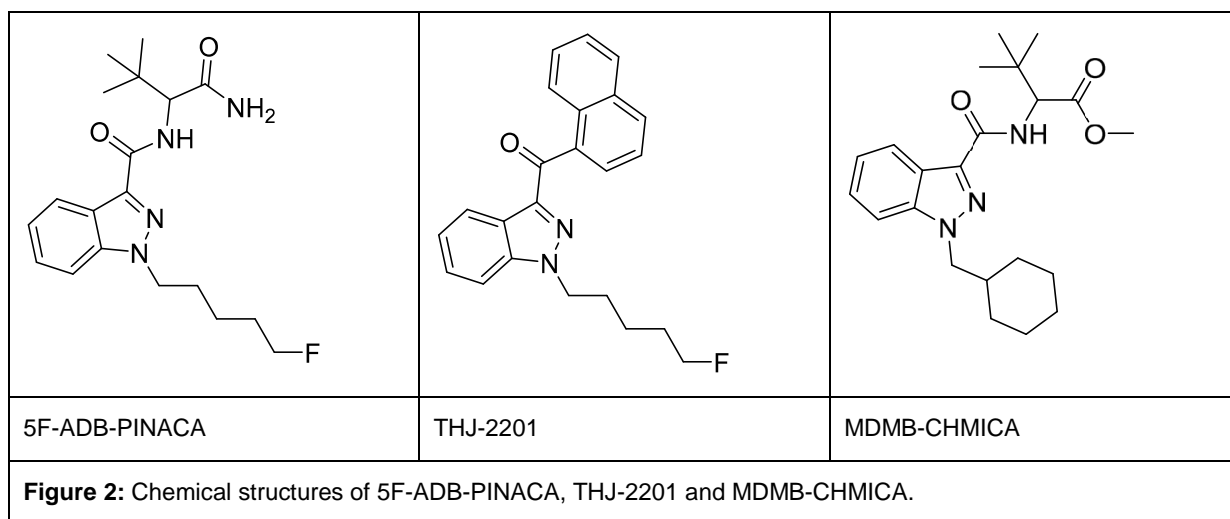
The melting point is 64–66°C (Banister et al., 2016). The boiling point is not available in the literature; it can be estimated to be below 350°C according to its retention time in GC-MS analysis (Moosmann et al., 2017).

5F-MDMB-PINACA carries one asymmetric carbon atom. Based on the patent literature of similar compounds that exclusively mention the activity of (*S*)-enantiomers (Buchler et al., 2009; Buchler et al., 2011) and the most likely precursors, the (*S*)-configuration might be considered likely. However, the reference material supplier *Cayman Chemical Company* lists the compound as the (*R*)-enantiomer ⁽²⁰⁾. The absolute configuration of the structurally similar synthetic cannabinoid MDMB-CHMICA has recently been described in the literature which confirmed the (*S*)-configuration in samples from the drug market (including a seizure of a powder as well as 'legal high' type herbal smoking mixtures) (Andernach et al., 2016). The preparation of the (*S*)-enantiomer requires the

⁽²⁰⁾ <https://www.caymanchem.com/product/16603>

availability/preparation of methyl L-tert-leucinate⁽²¹⁾ (see *Methods and chemical precursors used for the manufacture*, below). Reagent prices and access to the relevant precursor might be expected to be the driving force (methyl D-tert-leucinate would give rise to the (*R*)-enantiomer)

5F-MDMB-PINACA shares structural elements with other synthetic cannabinoids like 5F-ADB-PINACA, THJ-2201 and MDMB-CHMICA which have been described in the patent literature and/or are offered on the drug market (Figure 2) (Buchler et al., 2009 and 2011). MDMB-CHMICA was risk-assessed in 2016 (EMCDDA, 2017g), and subjected to control measures across the European Union. It has also been controlled under Schedule II of the United Nations Convention on Psychotropic Substances, 1971.



Chemical stability and typical reactions

Storage in solution or under non-ideal conditions (e.g. high humidity or elevated temperatures) can lead to hydrolysis of the carboxylic ester function. Ester hydrolysis can be expected to occur during smoking as it was observed by analysis of smoke condensates of structural related compounds like AB-CHMINACA and MDMB-CHMICA⁽²²⁾. Most of the known free carboxylic acids formed by hydrolysis of similar compounds are either not active or only poorly active at the CB₁ receptor (Buchler et al., 2009 and 2011). Therefore, the hydrolysis product(s) of 5F-MDMB-PINACA might be expected to be inactive at cannabinoid receptor.

In the presence of ethanol, transesterification of 5F-MDMB-PINACA can lead to the ethyl ester derivative, which most probably retains binding affinity towards the CB₁ receptor. Reaction with other alcohols could lead to corresponding ester compounds.

The amide bond of 5F-MDMB-PINACA may be cleaved chemically or enzymatically.

Hess et al., investigated freeze/thaw stability as well as long term stability of synthetic cannabinoids in human serum samples (Hess et al., 2016). They showed that 5F-MDMB-PINACA was relatively

⁽²¹⁾ The chiral amino acid precursor (*S*)-L-tert-leucine is widely used for the manufacture of antiviral medicines (such as the HIV protease inhibitor atazanavir or the hepatitis C virus protease inhibitors asunaprevir, boceprevir, grazoprevir, faldaprevir, narlaprevir, telaprevir, vaniprevir). (*S*)-L-tert-leucine is produced mainly in China in large, multi-ton quantities. This may explain the choice of this precursor for the synthesis of 5F-MDMB-PINACA and other related synthetic cannabinoids including MDMB-CHMICA (EMCDDA, 2017g) that have been reported to the EU Early Warning System.

⁽²²⁾ Personal communication from Volker Auwärter.

stable with degradation in serum below 10% when exposed to three freeze/thaw cycles (at least 20 h freezing and one hour thawing at room temperature). 5F-MDMB-PINACA's long term stability in serum was determined for at least 105 days at -20 °C, 105 days at 4 °C and over 315 days at room temperature (stability criterion: measured degradation below 20%).

There are no data available in the literature regarding the post-mortem stability of 5F-MDMB-PINACA. However, it has been observed that structurally similar synthetic cannabinoids undergo hydrolysis most likely during the post-mortem interval⁽²³⁾. Consequently, analytical methods solely covering the parent compounds (as it is the case for most serum/blood screening methods) might miss exposure of 5F-MDMB-PINACA in case of a long post-mortem interval or if the samples have been stored for a longer period of time prior to analysis.

Analytical profile

The analytical profile of 5F-MDMB-PINACA has been described in a publication utilizing NMR, LRMS, HRMS, IR and UV-VIS detection (Langer et al., 2016).

The UV maxima of 5F-MDMB-PINACA were reported at 208 and 302 nm in methanol.

IR data are as follows: wavenumber (cm⁻¹): 3419 (w), 2959 (m), 2871 (w), 1737 (s), 1670 (s), 1523 (s), 1491 (s), 1332 (m), 1214 (m), 1165 (s), 1038 (w), 1004 (w), 992 (w), 835 (w), 751 (s), 544 (m).

The mass spectrometric fragmentation pattern of 5F-MDMB-PINACA was described in four publications (Langer et al., 2016; Akamatsu and Yoshida, 2016; Shevyrin et al., 2015; Hasegawa et al., 2015). GC-MS and IR data have been published in the public domain⁽²⁴⁾.

Quantification of 5F-MDMB-PINACA in products can be carried out according to the general procedure described by the UNODC, e.g. by HPLC-DAD analysis (UNODC, 2013).

For blood serum analysis the parent compound is the main analytical target. Quantification of 110 authentic serum samples positive for 5F-MDMB-PINACA showed that concentrations detected were typically in the sub-ng/mL range (range < 0.1 – 15 ng/mL, mean: 1.1 ng/mL, median: 0.4 ng/mL) in a non-representative collective of forensic samples⁽²⁵⁾. Due to its high sensitivity LC-MS/MS instrumentation can be regarded as the gold standard for analysis, particularly in abstinence control settings. Two methods for the detection of 5F-MDMB-PINACA in serum samples have been published in the literature so far, all of them utilizing LC-MS/MS (Hasegawa et al., 2015; Hess et al., 2017).

For urine analysis, the identification of the main *in vivo* metabolites is recommended prior to setting up a method, as the detection of very low 5F-MDMB-PINACA levels excreted unchanged in urine might be challenging. However, a recent report involving a death and detection of 5F-MDMB-PINACA (19 pg/mL) and ADB-CHMINACA (229 pg/mL) in urine suggested that traces of the parent molecule are detectable in this particular matrix (Minakata et al., 2017). The detection of what appears to be parent 5F-MDMB-PINACA has also been reported in samples obtained from public street urinals (May 2016) in central London (Archer et al., 2017).

Based on the analysis and evaluation of authentic urine samples from different individuals, the carboxylic acid ester hydrolysis product and the product of hydrolytic defluorination (5-hydroxy-pentyl

⁽²³⁾ Personal communication from Volker Auwärter.

⁽²⁴⁾ http://www.policija.si/apps/nfl_response_web/0_Analytical_Reports_final/5F-MDMB-PINACA-ID-1652-16_rpt170916.pdf

⁽²⁵⁾ Personal communication from Volker Auwärter.

metabolite) seem to be the most suitable targets for a reliable detection of 5F-MDMB-PINACA exposure (Moosmann et al., 2017)).

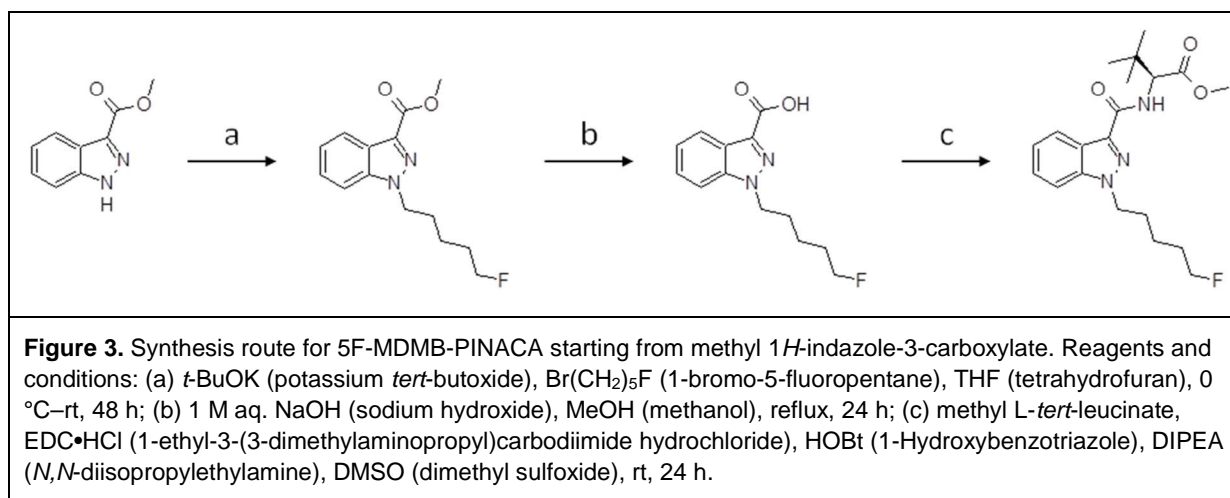
For all metabolites having undergone ester hydrolysis it has to be noted that they can also be formed following exposure to the synthetic cannabinoid 5F-ADB-PINACA (Figure 2), and, consequently, when detected alone do not unequivocally prove exposure to 5F-MDMB-PINACA. For all metabolites having undergone hydrolytic defluorination it should be noted that they can also be formed after exposure to the synthetic cannabinoid MDMB-PINACA (= ADB) (methyl 3-methyl-*N*-[(1-pentyl-1*H*-indazole-3-yl)carbonyl]valinate), and, consequently, when detected alone do not unequivocally prove exposure to 5F-MDMB-PINACA.

Similar to structurally related synthetic cannabinoids (e.g. AB-CHMINACA or MDMB-CHMICA), it can be expected that two 5F-MDMB-PINACA metabolites may be formed thermolytically during smoking, which could bias the detected metabolic profile.

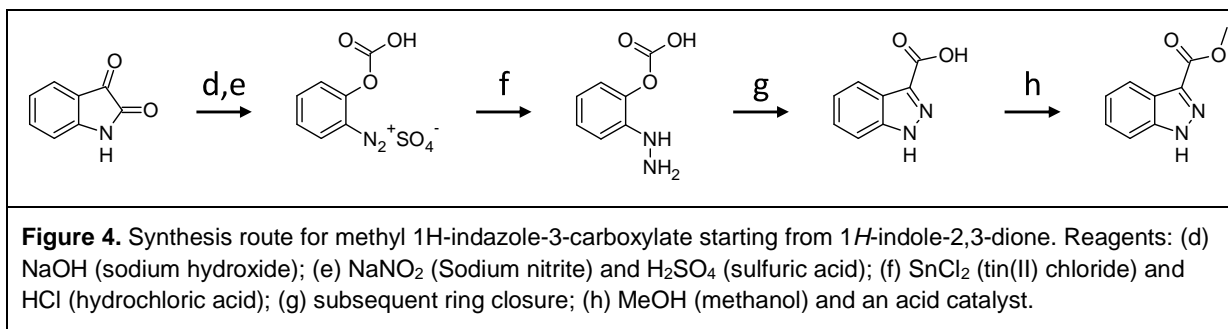
Methods and chemical precursors used for the manufacture

Synthesis

The synthesis of the 5F-MDMB-PINACA (*S*)-enantiomer was described by Banister et al., (compound 13), starting from the commercially available methyl 1*H*-indazole-3-carboxylate (Figure 3) (Banister et al., 2016). Other 1*H*-indazole-3-carboxylic acid esters might be suitable as alternative starting material. The respective (*R*)-enantiomer might be synthesized under identical conditions using methyl *D*-*tert*-leucinate instead of methyl *L*-*tert*-leucinate in reaction step (c). Using racemic methyl *tert*-leucinate in this reaction step would lead to a racemic 5F-MDMB-PINACA. The reported synthesis route is comparable to the way Buchler et al., described the synthesis of other structurally related indazole derivatives (Buchler et al., 2009).



According to Buchler et al., (2009) the starting compound methyl 1*H*-indazole-3-carboxylate can be prepared from 1*H*-indole-2,3-dione using the procedure of Johnson and Rodgers (2005), as shown in Figure 4. The product of reaction step (g) (1*H*-indazole-3-carboxylic acid) is also commercially available and might be used as starting compound for synthesis of 5F-MDMB-PINACA after esterification (reaction step h).



According to the synthesis routes described in Figure 3 and Figure 4, potential precursors of 5F-MDMB-PINACA are: 1H-indole-2,3-dione, 1H-indazole-3-carboxylic acid, methyl 1H-indazole-3-carboxylate, methyl L-*tert*-leucinate (for synthesis of the (S)-enantiomer), and 1-bromo-5-fluoropentane.

Although not documented, the N1-alkylation can be carried out on the indazolyl *tert*-leucinamide derivative as the last step under conditions described for serotonin receptor antagonists (Furlotti et al., 2012; Schaus et al., 1998) and, recently, for a metabolite of the synthetic cannabinoid AKB-48 (Wallgren et al., 2017).

Commercially available domestic or industrial products which could be used for synthesis may contain potentially toxic substances, including heavy metals and organic solvents. Use of such products as reagents may result in serious toxic effects if the resultant impure product is consumed. The herbal material which is used as a basis for the smoking mixtures may also contain toxicologically relevant substances like e.g. pesticides potentially present in the plant material.

Typical impurities encountered in seized and collected samples

Systematic studies that report the formation of impurities in 5F-MDMB-PINACA powders available on the drug market are not available.

In principle, reaction step (a) (Figure 3) can also produce the N2-alkylated regioisomer (methyl 2-(5-fluoropentyl)-2H-indazole-3-carboxylate) as a by-product, depending on the base and alkylating agent used. The described synthesis route of Banister et al., using t-BuOK (potassium tert-butoxide) was stated to be regioselective for the 1H-isomer under the chosen conditions (Banister et al., 2016). It was also shown for structural related compounds (e.g. 5F-AB-PINACA and AB-CHMINACA) that the use of K₂CO₃ (potassium carbonate) instead of t-BuOK in reaction step (a) lowered the regioselectivity and produced higher amounts of the N2-alkylated by-product (Longworth et al., 2016). These 2H-regioisomers were observed to be significantly less active at the CB₁ and CB₂ receptors and might not contribute to the cannabimimetic effects. Nevertheless, the toxicological properties of these by-products have not yet been evaluated. Further variations of the reagents, conditions and synthesis procedures may cause additional, possibly toxic impurities.

A1.2. Physical/pharmaceutical form

Data from seizures and collected samples reported to the EMCDDA show that 5F-MDMB-PINACA has typically been detected in herbal/plant material. Other forms have also been encountered, including powders, and, to a lesser degree, liquids, blotters and unspecified forms (Section C).

For the production of smoking mixtures, the substance is dissolved in an organic solvent (e.g. acetone) and applied to the plant material—such as damiana (*Turnera diffusa*) or marshmallow (*Althaea officinalis*)—either via spraying or soaking and subsequent evaporation of the solvent (EMCDDA, 2017a).

A1.3. Route of administration and dosage

5F-MDMB-PINACA is offered by online retailers either as powder ('research chemical') or in the form of herbal smoking mixtures. The presence of 5F-MDMB-PINACA or any other particular synthetic cannabinoid is not usually disclosed in these latter products. Some synthetic cannabinoids, including 5F-MDMB-PINACA, have also been offered in the form of e-liquids for vaping. Additionally, consumers might also prepare 5F-MDMB-PINACA containing e-liquids at home by dissolving the powdered form in propylene glycol.

The most common route of administration for synthetic cannabinoids is smoking either ready-to-use or self-prepared 'herbal mixtures' as a joint or utilizing a vaporizer, 'bong' or pipe. Oral consumption of synthetic cannabinoids has also been described. In the case of oral consumption a strong first-pass-effect can be expected. Additionally, the bioavailability can possibly be further reduced due to limited solubility and absorption or efflux pumps (e.g. multidrug resistance protein 1).

Based on a limited number of self-reported experiences posted on Internet discussion forums, dosages of 5F-MDMB-PINACA were lower than for MDMB-CHMICA, which were reported in the sub-milligram range.

When consuming smoking mixtures, users will be unaware of the dose they are exposed to. Studies have found that many of these products are inhomogeneous with respect to the content of active ingredients (Logan et al., 2012; Zuba and Byrska, 2013; Moosman et al., 2015; Kikura-Hanajiri, 2013). Both high intra- as well as inter-package variability was observed for many synthetic cannabinoids (Moosman et al., 2015). (Section D.3.4.)

5F-MDMB-PINACA content was analysed by Langer and co-workers in four products. The products contained 81 mg/g, 71 mg/g, 120 mg/g and 44 mg/g 5F-MDMB-PINACA; none of the products contained other active ingredients (Langer et al., 2016).

Additionally, the 5F-MDMB-PINACA content was analysed in eight products. In five of them 5F-MDMB-PINACA was the only ingredient. The contents varied from 0.7% (w/w) to 10.6% (w/w) with a median of 3.0% (w/w) and a mean of 4.1% (w/w) (Moosmann et al., 2017). In order to estimate the dose consumed under realistic conditions, no homogenisation was carried out prior to analysis.

A powdered sample found to contain 5F-MDMB-PINACA was obtained from a vendor of psychoactive substances in August 2014 (Kaizaki-Mitsumoto et al., 2016).

Continuous market monitoring within the EU 'SPICE' projects included the analysis of 776 'herbal mixtures' between January 2015 and June 2017. 5F-MDMB-PINACA was detected in 72 samples (9.3%), with 61% containing 5F-MDMB-PINACA only, 18% containing 5F-MDMB-PINACA and one additional synthetic cannabinoid, and 21% containing 5F-MDMB-PINACA and two or more (up to 5) additional synthetic cannabinoids (Moosmann et al., 2017). Within the Welsh drug checking project WEDINOS, 5F-MDMB-PINACA was detected in 20 herbal mixtures and in four powders sent for analysis between November 2015 and March 2017 (WEDINOS, 2017).

Data from law enforcement seizures as well as studies have shown that it is relatively common for more than one synthetic cannabinoid to be added to smoking mixtures (Moosman et al., 2015). In Japan, Kikura-Hanajiri et al., (2013) detected an average number of 2.6 synthetic cannabinoids per product. The maximum number of synthetic cannabinoids detected in one mixture by these authors was ten.

A2. Pharmacology, including pharmacodynamics and pharmacokinetics

Pharmacologically, 5F-MDMB-PINACA is a cannabinoid receptor agonist.

Pharmacodynamics

In an *in vitro* hyperpolarization assay probing for G-protein-gated inwardly rectifying potassium channels (GIRKs), 5F-MDMB-PINACA was shown to be a highly potent full agonist at the cloned human CB₁ and CB₂ receptor. The (S)-enantiomer of 5F-MDMB-PINACA showed an EC₅₀ approximately 290 times lower than the EC₅₀ of Δ⁹-THC, and e.g. a 17-fold lower EC₅₀ than MDMB-CHMICA (Banister et al., 2016). 5F-MDMB-PINACA is also a full agonist at the CB₂ receptor. The EC₅₀ of the (S)-enantiomer of 5F-MDMB-PINACA was approximately 9-fold lower than the EC₅₀ of CP-55,940 and also 9-fold lower than the EC₅₀ of MDMB-CHMICA (Table 1). The CB₁ selectivity of 5F-MDMB-PINACA was 12.7 (ratio EC₅₀ CB₁/EC₅₀ CB₂) (Banister et al., 2016). In contrast to CB₁ receptors, CB₂ receptors are mainly expressed on cells of the immune system and are believed to be involved in modulations of the immune system.

Of all the synthetic cannabinoids tested, 5F-MDMB-PINACA was the second most potent compound (5F-MDMB-PICA being the most potent). A summary of selected results from these experiments are listed in Table 1.

Table 1. Half maximal effective concentration (EC ₅₀) of 5F-MDMB-PINACA and efficacy relative to the full agonist CP-55,940 (E _{max}) and other synthetic cannabinoids, as assessed by a fluorometric based hyperpolarization assay (Banister et al., 2016).					
Compound	hCB₁ EC₅₀ [nM]	E_{max} (% CP-55,940)	hCB₂ EC₅₀ [nM]	E_{max} (% CP-55,940)	CB₁ selectivity*
Δ ⁹ -THC	171	50%	Inactive	20% (10 μM)	NA
CP-55,940	42	100%	68	100%	1.6
5F-MDMB-PICA	0.45	110%	7.4	94	16.4
5F-MDMB-PINACA	0.59	108%	7.5	94	12.7
MDMB-CHMICA	10	112%	71	103	7.1

*CB₁ selectivity expressed as the ratio of EC₅₀ (CB₁) to EC₅₀ (CB₂).

As it has been shown for 'first generation' synthetic cannabinoids (e.g. JWH-018, JWH-073) (Brents et al., 2011; Brents et al., 2012) and for the THC metabolite 11-hydroxy-THC, it is likely that some of the mono-hydroxylated metabolites of 5F-MDMB-PINACA retain activity at the CB₁ receptor. They might therefore contribute to the pharmacological profile of the compound. Based on the properties of structurally related compounds like MDMB-CHMINACA or ADB-CHMINACA, it can be assumed that the ester cleavage product (a free carboxylic acid) does not show relevant affinity towards the CB₁ receptor (Buchler et al., 2009).

Asaoka and co-workers described that 5F-MDMB-PINACA increased the spontaneous activity of midbrain dopaminergic neurons through activation of CB₁ receptors. An activation of serotonergic neurons was not observed (Asaoka et al., 2016). There are no further data available on the effects of 5F-MDMB-PINACA on other pharmacological (receptor or enzyme) targets. The biological properties of its metabolites are also unknown. Assessment of 'first-generation' synthetic cannabinoids (e.g. JWH-018, AM-2201, JWH-081) showed that binding to non-cannabinoid receptors was absent or weak for these compounds (Wiley et al., 2016a).

Animal studies

Information derived from animal studies could not be identified, although it seems conceivable that 5F-MDMB-PINACA would display activity in assays that probe for Δ^9 -THC-like properties such as drug discrimination or mouse tetrad tests similar to what has been demonstrated with AB-CHMINACA (Wiley et al., 2015).

Pharmacokinetics

5F-MDMB-PINACA undergoes extensive metabolism in the human body. Like most synthetic cannabinoids it is not excreted unchanged in urine to a relevant extent. The main metabolic phase I reactions comprise hydrolysis of the carboxylic ester function and hydrolytic defluorination (Kusano et al., 2017). It is very likely that these phase I metabolites undergo extensive conjugation prior to renal excretion, similar to what has been reported for other synthetic cannabinoids.

No additional data on the pharmacokinetics of 5F-MDMB-PINACA are available in the literature. User reports on the Internet regarding time of onset and duration of effects of structurally related synthetic cannabinoids usually describe an onset of 1 to 5 minutes after smoking and effect duration of 1 to 2 hours. In some cases effects have been described to last over 10 to 15 hours. As highlighted in the introduction, the assessment of such reports is problematic not least because users cannot confirm the actual substance used.

Toxicology

No studies were identified that have examined the toxicity of 5F-MDMB-PINACA.

Inter-individual genetic variability in metabolising enzymes

No studies were identified that have examined the inter-individual genetic variability in metabolising enzymes for 5F-MDMB-PINACA.

Interactions with other substances and other interactions

No studies were identified that have examined the interaction of 5F-MDMB-PINACA with other substances, including medicinal products.

Effects on ability to drive and operate machines

No studies of the effects of 5F-MDMB-PINACA on the ability to drive and operate machines have been performed. However, it has been reported that intoxications caused by a range of synthetic cannabinoids, including 5F-MDMB-PINACA, significantly impair the mental and physical ability that is required to drive and operate machines (Section D1.2) (Capron, 2016; Griffiths and Griffin, 2016; Kaneko, 2017; Karinen et al., 2015; Musshoff et al., 2014; Peterson and Couper, 2015).

In a recent case series of 36 drivers suspected of driving under the influence of drugs in Washington, United States, where 5F-MDMB-PINACA was the predominate psychoactive substance identified, 50% of the drivers were found unconscious and 28% has been involved in collisions with single/multiple cars (Capron, 2016).

A3. Psychological and behavioural effects

While there is limited data, the psychological and behavioural effects of 5F-MDMB-PINACA appear to share some similarities with cannabis, THC, and other synthetic cannabinoids (e.g. Griffiths and Griffin, 2016; Peterson and Couper, 2015; See also Section D). This includes: relaxation, euphoria, lethargy, confusion, anxiety, fear, distorted perception of time, depersonalisation, hallucinations,

paranoid inclusions, as well as dry mouth, bloodshot eyes, tachycardia, nausea, vomiting and impaired motor performance. These effects appear to be much more pronounced and severe when compared to cannabis (Ford et al., 2017; Zaurova et al., 2016). In addition, psychotic episodes, as well as aggressive and violent behaviour, have also been reported. (See also Section D1 and Section D3.4.)

A4. Legitimate uses of the product

5F-MDMB-PINACA is used as an analytical reference material in clinical and forensic case work/investigations as well as scientific research. There is currently no information that suggests 5F-MDMB-PINACA is used for other legitimate purposes.

There are no reported uses of 5F-MDMB-PINACA as a component in industrial, cosmetic or agricultural products. In addition, a search of the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) registered substances database hosted by the European Chemicals Agency (ECHA) using the CAS Registry Numbers listed above returned no results.

There is no marketing authorisation (existing, on-going or suspended) for 5F-MDMB-PINACA neither in the European Union nor in the Member States that responded to the request for information from the European Medicines Agency, which was undertaken as part of the Joint Report process (EMCDDA 2017c).

There is no information to suggest that 5F-MDMB-PINACA is currently used in the manufacture of a medicinal product in the European Union. However, in the absence of a database on the synthetic routes of all medicinal products it is not possible to confirm whether or not 5F-MDMB-PINACA is currently used in the manufacture of a medicinal product.

Section B. Dependence and abuse potential

B1. Animal data

No studies were identified that have investigated the dependence and/or abuse potential of 5F-MDMB-PINACA in animals.

Studies conducted with JWH-018 and JWH-073 in rats and monkeys suggest cannabinoid-like effects in the drug discrimination paradigm (Ginsburg et al., 2012; Järbe et al., 2010; Järbe et al., 2011). As a consequence, 5F-MDMB-PINACA might show similar properties. Further behavioural studies are needed to assess the extent to which this translates into abuse liability in humans (Wiley et al., 2016b).

B2. Human data

No studies were identified that have investigated the dependence and/or abuse potential of 5F-MDMB-PINACA in humans.

It has been suggested that consumption of synthetic cannabinoids can produce tolerance and withdrawal-like symptoms when use is discontinued following a regular use (Cooper, 2016, Macfarlane and Christie, 2015, Van Hout and Hearne, 2017; Zimmermann et al., 2009).

Withdrawal-like symptoms following cessation of synthetic cannabinoids have been described in the literature. These include: anxiety, unstable mood, crying fits, feeling of inner emptiness, spatial disorientation, hyperacusis (increased sensitivity to ordinary environmental sounds), somatic pain, shortness of breath, hyperventilation, intense sweating and sensations of motor and inner restlessness (Hermanns-Clausen et al., 2012; Hermanns-Clausen et al., 2013).

Section C. Prevalence of use

Information from seizures, collected and biological samples

5F-MDMB-PINACA was formally notified on 8 January 2015 by the EMCDDA on behalf of Hungary, in accordance with Article 4 of the Council Decision. The Reporting Form details a seizure of 0.79 grams of white powder that was seized in September 2014 by the National Tax and Customs Administration Airport Directorate Nr.1, in Budapest. The substance was analytically confirmed by GC-MS and Fourier transform infrared spectroscopy (FT-IR).

Since then, a total of 25⁽²⁶⁾ Member States, Norway, and Turkey have reported detections ⁽²⁷⁾ of 5F-MDMB-PINACA (EMCDDA, 2017c).

Quantitative information on the purity of 5F-MDMB-PINACA in the seized samples is limited to two samples of powder, which are discussed below. In herbal smoking mixtures, 5F-MDMB-PINACA was frequently found with other substances.

It is important to note that detections of 5F-MDMB-PINACA may be under-reported since the substance is not routinely screened for. Three Member States (Austria, Slovenia and Sweden) and Norway reported that 5F-MDMB-PINACA is part of routine screening in some (but not all) of their laboratories.

Information from seizures

A total of 1986 seizures of 5F-MDMB-PINACA were reported by 23 countries to the EMCDDA and/or Europol: Austria (1 seizure), Belgium (9), Bulgaria (11), Czech Republic (1), Denmark (1), Estonia (1), Finland (8), France (16), Germany (1), Greece (3), Hungary (252), Ireland (36), Lithuania (27), Latvia (1), Malta (3), the Netherlands (1), Poland (58), Romania (3), Spain (8), Sweden (71), the United Kingdom (1252), Norway (13) and Turkey (209) ⁽²⁸⁾.

The majority of the seizures comprised police and customs cases, with a considerable amount of seizures taking place in custodial settings.

Seizures included herbal materials, powders, liquids, blotters and unspecified physical forms.

Herbal material

Herbal materials for smoking were the most frequently encountered physical form of 5F-MDMB-PINACA. A total of 1485 seizures of 5F-MDMB-PINACA in herbal material were reported by 16 countries: Bulgaria, Germany, Greece, Finland, France, Hungary, Ireland, Lithuania, Latvia, Malta,

⁽²⁶⁾ Cyprus reported the first identification of the substance in the country after the Joint Report was prepared. This case is not discussed further in this report.

⁽²⁷⁾ Detections' is an all-encompassing term and may include seizures and/or collected and/or biological samples that are analytically confirmed. Seizure means a substance available (seized) through law enforcement activities (police, customs, border guards, etc.). Collected samples are those that are actively collected by drug monitoring systems (such as test purchases) for monitoring and research purposes. Biological samples are those from human body fluids (urine, blood, etc.) and/or specimens (tissues, hair, etc.)

⁽²⁸⁾ This is a minimum estimate provided by the Turkish National Focal Point.

Norway, Poland, Romania, Spain, Sweden, and the United Kingdom, amounting to 26 kg seized ⁽²⁹⁾. In addition, Turkey reported 209 seizures of herbal material amounting to nearly 74 kg ⁽²⁾.

The largest single seizures of 5F-MDMB-PINACA in herbal material were reported by:

- Romania (2.9 kg which also contained MDMB-CHMICA) and;
- the United Kingdom (2.4 kg, with no other substance detected).

In 2 large seizures reported by the Scottish Police (UK) , a total of 7669 sealed foil packages (~10 kg), of commercially labelled herbal materials were seized. The seizure comprised the following:

- 'Exodus Damnation 1G' (5198 packages),
- 'Exodus Damnation 3G' (1106 packages),
- 'Exodus Nightshade 1G' (1197 packages),
- 'Exodus Nightshade 3G' (168 packages),
- 'Vertex Space Cadet Edition 1G' (20 packages).

A small number of samples of each product were analysed and were found to contain 5F-MDMB-PINACA, mixed with 5F-AMB-PICA (not confirmed analytically).

In the herbal materials seized, 5F-MDMB-PINACA was frequently found mixed with other synthetic cannabinoids. In two cases reported by the United Kingdom, the synthetic opioid U-47,700 was also detected in herbal materials mixed with 5F-MDMB-PINACA.

The United Kingdom reported 129 seizures of 5F-MDMB-PINACA that took place in a prison or other custodial setting, amounting to a total of 3 kg of mostly herbal material and often found in combination with other synthetic cannabinoids.

Powders

A total of 77 seizures of powder were reported by 12 countries (Belgium, Bulgaria, Czech Republic, Finland, France, Hungary, Ireland, Lithuania, the Netherlands, Poland, Sweden and the United Kingdom) amounting to a total of more than 13.4 kg.

The largest single seizures of 5F-MDMB-PINACA in powder form were reported by:

- Bulgaria (2 kg of white powder, seized in April 2016 by customs at Sofia Airport),
- France (2 seizures over 2 kg, one of which was 2.3 kg of brown powder seized by customs in March 2017 at Roissy airport) and,
- the Netherlands (2 kg seized by customs).

Four additional customs seizures of powders, weighing more than 1 kg each, were reported by Belgium (2 seizures) and France (2). The seizures were all carried out at international airports.

⁽²⁹⁾ No amounts were reported for 686 detections reported by the United Kingdom for the year 2016, so the total amount is likely to be higher.

Quantitative information on purity of 5F-MDMB-PINACA in seized samples was reported by Lithuania for two samples of powder: 96 % purity (for a sample of 141.01 g) and 91 % (sample of 0.9835 g).

Liquids

Six countries reported a total of 9 seizures of 5F-MDMB-PINACA in liquid form: Denmark (1 seizure), Estonia (1), Finland (1), Norway (3), Sweden (1) and the United Kingdom (2), amounting to a total 309.2 g and 94 ml seized.

In a 274 g seizure reported by the UK, the liquid (clear and yellow) was also found to contain the synthetic opioid U-47,700.

Two bottles (of 5 ml each) of 'C-liquid' for vaping were seized by customs in Denmark. The bottles originated in Spain, with Denmark as the final destination.

Two bottles (7 ml each) of a pink liquid named "SKITTLES" were seized by Norwegian customs.

Other physical forms

Small amounts of 5F-MDMB-PINACA in blotter form were reported by Poland (2 seizures) and Lithuania (1).

Additionally, in 287 cases, amounting to more than 3.5 kg, the physical form was unspecified.

Information from collected samples

A total of 9 collected samples were reported to the EMCDDA by 5 Member States: Germany (4 cases), Italy (1), Luxembourg (1), Slovenia (1) and the United Kingdom (2). Some of the collected samples were linked to biological detections including serious adverse events, whereas other detections involved test purchases from online vendors.

The sample reported by Slovenia consisted of 5 g of white powder purchased as the synthetic cannabinoid '5F-NPB-22' and shipped from Germany.

The United Kingdom reported a test purchase of a product named 'K2 Black edition', purchased from a domestic website.

Information from biological samples

Serious adverse events (deaths and acute intoxications) with confirmed exposure to 5F-MDMB-PINACA from biological samples are discussed in section D.

In addition to these, 84 detections where 5F-MDMB-PINACA was analytically confirmed in biological samples were reported by two Member States: Hungary (83) and Sweden (1). The detections related to persons suspected of driving under the influence of drugs (including traffic accidents), persons suspected of having committed minor offences or crimes and other aggregated data associated with forensic case work.

Availability, supply, price

The available data suggests that 5F-MDMB-PINACA is typically sold in commercial branded 'legal-high' products both in physical and in virtual (online) shops. It is also possible that some of these products are sold directly on the illicit market. Similarly to what occurs with other synthetic

cannabinoid products, preparations containing 5F-MDMB-PINACA are marketed as 'legal' replacements to cannabis. The composition of the mixtures is typically not stated in the packages.

Information on production

No information was received in relation to the production of 5F-MDMB-PINACA. Based on the limited information reported to the EMCDDA and Europol related to seizures by customs, some of the 5F-MDMB-PINACA seized in Europe originated from China, where it may have been produced.

Information on trafficking

Information related to trafficking routes is limited to the seizures reported above.

Limited information reported to Europol indicates that China may be one source of the substance with some seizures having originated in China. Additionally, Spain was the origin of a number of seizures made in Denmark, Bulgaria, and Estonia.

Availability from Internet vendors

The available data suggests that 5F-MDMB-PINACA is openly sold online under its own name in powders and in branded herbal smoking mixtures where the composition is sometimes not stated. A structured search of online vendors on the surface web by the EMCDDA ⁽³⁰⁾ found that the substance is available online in small and wholesale amounts as a 'research chemical' and as 'herbal blends' with various brand names, a common reference to 'legal-high' type products.

On the websites identified, 5F-MDMB-PINACA powders were available in amounts ranging from 1 g to 5 kg. Prices varied according to the amounts on sale and ranged from EUR 1.11 per gram to EUR 19.99 per gram. Herbal smoking mixtures containing 5F-MDMB-PINACA were available in two websites, in amounts ranging from 1 gram to 1 kg. Prices also varied according to the amounts on sale and ranged from EUR 0.60 per gram to EUR 10 per gram. Liquids containing 5F-MDMB-PINACA were advertised in 1 website. Here, a 7 mL bottle was being sold for EUR 25. In some websites, products containing 5F-MDMB-PINACA were listed as "out-of-stock"

Prevalence of use

No studies were identified that have investigated the prevalence of use of 5F-MDMB-PINACA in the general population.

Similar to other synthetic cannabinoids, 5F-MDMB-PINACA is often sold and used as a 'legal' substitute for cannabis, typically as herbal smoking mixtures (EMCDDA, 2009; EMCDDA, 2017a). The composition of these products varies over time, with substances being changed in response to, or, in anticipation of, the introduction of control measures. This may have implications on the availability of 5F-MDMB-PINACA and its prevalence of use. Overall, the available information does not suggest widespread use of the substance.

Because of the variability in the composition of smoking mixtures, and the fact that the ingredients are not typically disclosed, most users will be unaware that they are using 5F-MDMB-PINACA. As a

⁽³⁰⁾ The search for online vendors of 5F-MDMB-PINACA on the surface web was performed on 20/07/2017 using previously established methodology (EMCDDA, 2017c). The search identified 23 vendors that appeared to be based in, and/or claim to have presence in China (n=6), USA (n=4), Turkey (n=1) and Ukraine (n=1); the remaining websites appeared to be based in Europe but a specific location was not listed although some websites appeared to ship from Spain. Four websites only provided prices for 5F-MDMB-PINACA products on request. The remaining sites provided prices and quantities.

result, the prevalence of use of 5F-MDMB-PINACA should be considered in the wider context of the prevalence of use of herbal smoking mixtures, commonly referred to as 'spice'.

The use of 'spice'-like products has been studied in some European countries in general population surveys or in specific populations such as students, 'clubbers' and/or internet users. The results of these surveys are not comparable as they use different methodology and samples but overall they indicate generally low prevalence levels in these groups (EMCDDA, 2017a).

There is evidence that in some groups, such as high risk drug users and other marginalised groups, the prevalence of use of synthetic cannabinoids, particularly as smoking mixtures, may be higher. This includes individuals who are subject to drug testing (such as people in drug treatment, prisoners, and drivers) because some drug tests/screens will be unable to detect synthetic cannabinoids. In addition some vulnerable populations, such as the homeless and prisoners, specifically seek out synthetic cannabinoids because they have a reputation for causing profound intoxication, they can be cheap and are easy to smuggle (EMCDDA, 2017a; Blackman and Bradley, 2017; HMIP, 2015; Ralphs et al., 2017; User Voice, 2016).

Section D. Health risks

D1. Acute health effects

D1.1. Animal data

No animal data were identified that have examined the acute health effects of 5F-MDMB-PINACA in animals.

D1.2. Human data

No clinical studies were identified that have examined the acute health effects of 5F-MDMB-PINACA and/or its metabolites in humans. Data from serious adverse events associated with 5F-MDMB-PINACA are discussed below. In general, the acute health risks associated with 5F-MDMB-PINACA appear to be similar to those found with other synthetic cannabinoids.

As synthetic cannabinoids activate the CB₁ receptor in a similar way to THC, their effects appear to have some similarities with cannabis (Auwärter et al., 2009). This includes: relaxation, euphoria, lethargy, confusion, anxiety, fear, distorted perception of time, depersonalisation, hallucinations, paranoid inclusions, as well as dry mouth, bloodshot eyes, tachycardia, nausea, vomiting and impaired motor performance. These effects appear to be much more pronounced and severe when compared to cannabis (Ford et al., 2017; Winstock et al., 2013; Zaurova et al., 2016).

Severe and fatal poisoning also appears to be more common with synthetic cannabinoids as compared to cannabis. This can include severe cardiovascular toxicity (including sudden death), severe central nervous system depression (such as rapid loss of consciousness/coma), respiratory depression, seizures and convulsions, hyperemesis, delirium, agitation, psychosis, and aggressive and violent behaviour (Adams et al., 2017; Brennehan et al., 2016; Capron, 2016; Ford et al., 2017, Hermanns-Clausen et al., 2013; EMCDDA, 2017c, EMCDDA, 2017d, EMCDDA, 2017e; EMCDDA, 2017f; EMCDDA, 2017g; Kasper et al., 2015; Pap, 2016; Schwartz et al., 2015; Shevyrin et al., 2015; Springer et al., 2016; Tait et al., 2016; Trecki et al., 2015; Tyndall et al., 2015; Waugh et al., 2016; Winstock et al., 2013; Zaurova et al., 2016). (See Section D3.4.)

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

aggressive and violent behaviours reported with synthetic cannabinoids may also place others at risk of injury.

Overall, poisoning with synthetic cannabinoids may be made worse when other drugs, especially central nervous system depressants (such as alcohol, opioids, and sedative/hypnotics), are used at the same time.

There is no approved antidote to poisoning caused by synthetic cannabinoids.

Acute intoxications reported by the Member States

A total of 35 acute intoxications with confirmed exposure to 5F-MDMB-PINACA were reported by Hungary (1 case) and the United Kingdom (34 cases)⁽³¹⁾. The cases occurred during 2016. No further details are available on the case from Hungary.

In 6 of the cases from the United Kingdom, no other substances were detected. In the remaining cases, other synthetic cannabinoids (detected in 20 cases) and opioids (with methadone detected in 19 cases) were typically detected. Overall, many of the cases included clinical features of poisoning similar to those reported for synthetic cannabinoids.

Acute intoxications identified from other sources

Seven acute intoxications (3 mono-intoxications and 4 mixed intoxications), with confirmed exposure to 5F-MDMB-PINACA were reported to the Poisons Information Centre Freiburg (Hermanns-Clausen et al., 2017)). Compared to intoxications with other synthetic cannabinoids, the range and severity of symptoms after use of 5F-MDMB-PINACA seem to be similar.

A case series consisting of 5 non-fatal intoxications and acute toxicity occurred in Spain has also recently been described. Four teenagers and one young adult presented at the Emergency Department after having smoked an herbal product. Three patients presented with psychomotor agitation, confusion, anxiety and psychosis and tachycardia; one patient experienced an “altered consciousness” and headaches and was hypoactive, but reactive to stimuli. The neurologic examination showed a tendency to stupor. The fifth patient presented with vomiting, agitation, altered language, bradypsychia and mydriasis. All patients recovered. The analysis of urine suggested the ingestion of 5F-MDMB-PINACA based on the qualitative identification of the *N*-(5-hydroxypentyl) metabolite and the ester hydrolysis product 5F-MDMB-PINACA-COOH. In one urine sample, another metabolite, namely “MMB-2201 amide/ester hydrolysis product”, was detected (Barceló et al., 2017a, Barceló et al., 2017b).

Fourteen cases (10 male, age range 18–47, median 32 years) involving the smoking ($n = 12$) of 5F-MDMB-PINACA containing products were identified in 2016 as part of the UK IONA study. Clinical features most commonly recorded included confusion (5/8 and 4/6), paranoid ideation (4/8 and 4/6), reduced level of consciousness (7/8 and 3/6), convulsions (1/8 and 3/6), hallucinations (2/8 and 2/6), bradycardia (2/8 and 2/6), tachycardia (2/8 and 2/6), chest pain (1/8 and 2/6), agitation (4/8 and 2/6) and raised plasma lactate (1/8 and 2/6). All patients recovered within 10 h without specific treatment (Elamin et al., 2017).

A review of cases related to motor vehicle collisions involving the use of synthetic cannabinoids mentions 2 cases from 2014 in Japan where 5F-MDMB-PINACA was detected in biological samples. In one case, a 30-year old male experienced a memory loss following the smoking of a herbal

⁽³¹⁾ In addition, Germany reported 5 acute intoxications with possible exposure to ADB-CHMINACA and Italy reported 1 acute intoxication with possible exposure to ADB-CHMINACA. These cases are not discussed further in this report.

mixture, which subsequently resulted in loss of consciousness and a car crash. His heart rate was 106 beats/min with tachypnea 13 min after the crash. 5F-MDMB-PINACA was detected in urine, saliva and hair and 4F- α -PHPP was detected in blood (Kaneko, 2017).

Deaths reported by the Member States

A total of 28 deaths were reported by 2 Member States: Germany (16) and the United Kingdom (12). In all cases, exposure to 5F-MDMB-PINACA or associated metabolites were analytically confirmed from post-mortem samples.

The German deaths occurred between December 2015 (1 case) and December 2016 (15). Those in the United Kingdom occurred between January 2016 and February 2017.

Demographic data were available for all but one death and involved 26 males and 1 female. The mean age was 34 years (median 33) and ranged from 19 to 49 years.

Circumstances and cause of death

There was a lack of information regarding any symptoms experienced by the deceased prior to death in the majority of cases, but, where described, the deceased had collapsed, had vomited or had become unconscious. Where information was known, in the majority of instances the individuals were found dead, predominantly in a home environment (either their own or a friend's), or outside with 2 deaths in prison. Consequently, it was not possible to identify or evaluate ante-mortem symptoms (especially in relation to acute intoxication) in these cases.

A cause of death was reported in all but three cases, and, in at least 20 deaths, 5F-MDMB-PINACA was either the cause of death or is likely to have contributed to death (even in presence of other substances); other substances were detected in 23 cases. 5F-MDMB-PINACA was the only drug present in 5 deaths based on additional toxicological information.

5F-MDMB-PINACA was quantified in 13 cases. Post-mortem blood concentrations between <0.1 and 1.2 ng/mL (median ~0.28 ng/mL) were recorded. Due to the toxicity of potent synthetic cannabinoids, a post-mortem blood concentration cannot necessarily be used to determine a "fatal" concentration. In the majority of circumstances involving synthetic cannabinoids, the mere presence of the drug is of significance whether concentration has been determined or not, especially in situations of poly-drug use and the varying circumstances in which they are used.

A range of other substances were detected in the deaths, including: alcohol, cannabinoids, antidepressants, amphetamines (amphetamine, MDMA), zopiclone, paracetamol, synthetic cathinones, opiates (morphine, codeine, noscapine) and benzodiazepines. Other synthetic cannabinoids and/or metabolites were detected in 7 of the deaths, including; MDMB-CHMICA, MDMB-CHMCZCA, 5F-PB-22, 5F-CUMYL-PINACA, AB-FUBINACA.

Overall, whilst other substances may have contributed some toxicity, the potent nature of 5F-MDMB-PINACA means the primary toxic contribution could be attributed to the drug and death may not have occurred if 5F-MDMB-PINACA had not been used. However, in the cases where multiple synthetic cannabinoids were present, it is not necessarily possible or appropriate to identify 5F-MDMB-PINACA as the primary synthetic cannabinoid that may have produced toxicity, but a synergistic effect is likely nonetheless. Sufficient case data were available in 27 of the 28 deaths and an assessment of the toxicological significance score (TSS) incorporating the above considerations in the deaths, showed that 5F-MDMB-PINACA had a TSS value of 3 (high) in 23 out of 27 of the deaths (where it was cited as the cause of death or is likely to have contributed to death). In the remaining deaths, 2 had an alternative cause of death—drowning and hanging (TSS value of 1, low), with 2 deaths being assessed as having a TSS value of 2 (medium). One of these deaths involved morphine

toxicity and the other, whilst drowning was the likely manner of death, it was possible that use of 5F-MDMB-PINACA could have contributed to the situation/cause.

Deaths identified from other sources

There is only limited information published in the scientific literature regarding deaths involving confirmed exposure to 5F-MDMB-PINACA.

Hasegawa et al., reported that 10 deaths occurred in Japan since September 2014 and described a death of a 34-year-old man (Hasegawa et al., 2015) ⁽³²⁾. The deceased was grasping a small handmade aluminium foil pipe in his right hand. Around his nostrils and mouth vomit debris were attached. Under the pillow of the deceased three opened packages of different brands of herbal blends were found. Medical examination at the scene revealed no injuries on the body surface and there were no serious injuries explaining death. Autopsy found the trachea filled with a large amount of stomach contents, which reached the tracheal bifurcation, thus completely occluding the airway. The direct cause of death was stated asphyxia with the indirect cause appearing to be synthetic cannabinoid poisoning. The deceased had a history of admissions to a psychiatric hospital because of heavy dependence on synthetic cannabinoids for about 3 months in 2013 and 2014. Discharge in 2014 was a few days before death. 5F-MDMB-PINACA was detected in the three herbal mixtures at concentrations of 49.2 mg/g, 12.2 µg/g and 0.766 µg/g. Additionally, 5F-MDMB-PINACA was detected in stomach contents, brain, lung, heart muscle, liver, spleen, kidney, pancreas, skeletal muscle and adipose tissue. The drug screening also detected low levels of quetiapine.

Kusano et al., reported a death with 5F-MDMB-PINACA and diphenidine. A 53 year-old male was found dead in his apartment; next to him an open package of an herbal blend ('Heart Shot BLACK') and several pipes were found. The herbal blend only contained 5F-MDMB-PINACA. At autopsy no specific injuries or internal findings were observed. 5F-MDMB-PINACA could be detected in heart blood at a concentration of 0.19 ± 0.04 ng/mL. Diphenidine was detected at a concentration of 12 ± 2.6 ng/mL (Kusano et al., 2017).

D2. Chronic health effects

While there is limited data for 5F-MDMB-PINACA, the chronic health risks might share similarities to cannabis and other synthetic cannabinoids. This may include dependence.

D2.1. Animal data

No studies were identified that have investigated the chronic health effects of 5F-MDMB-PINACA in animals.

D2.2. Human data

No studies were identified that have investigated the chronic health effects of 5F-MDMB-PINACA in humans.

D3. Factors affecting public health risks

D3.1. Availability and quantity of the new psychoactive substance on the market

⁽³²⁾ It is unknown if this is the same case as reported by Minakata (2017) which involved the detection of 5F-MDMB-PINACA (19 pg/mL) and ADB-CHMINACA (229 pg/mL) in urine. A male in his thirties was found dead at home and a handmade aluminium foil pipe was held in one of his hands. Further details were not reported (Minakata, 2017).

5F-MDMB-PINACA is sold on the surface web as a powder and in 'legal-high' type products such as herbal smoking mixtures. The substance is available in small and wholesale amounts. In herbal smoking mixtures it is not frequently stated if the product contains 5F-MDMB-PINACA or any other synthetic cannabinoid. As a result, many users will not be aware that they are using the substance.

Limited information also suggests that 5F-MDMB-PINACA is being sold in the illicit drug market, including in prisons and in other custodial settings.

Data from seizures reported to the EMCDDA and to Europol indicate that bulk quantities of 5F-MDMB-PINACA in powder have been imported into the European Union from China (EMCDDA, 2017c). As noted, these can potentially be used to produce large amounts of 'spice-like' herbal smoking mixtures, as often only small quantities are used in individual packages (in the orders of the tens of milligrams).

D3.2. Availability of the information, degree of knowledge and perceptions amongst users concerning the psychoactive substance and its effects

The availability of information, degree of knowledge and perceptions amongst users concerning 5F-MDMB-PINACA and its effects are limited. There is considerable variability both within and between different batches of synthetic cannabinoid products, in terms of both the substances and the amount present.

Unknown to users, synthetic cannabinoids have also been sold as ecstasy/MDMA and other illicit drugs. In some cases, this has led to severe poisoning (Allibe et al., 2016; Brenneman et al., 2016; Pap, 2016). For that reason, most individuals will be unaware that they are using 5F-MDMB-PINACA.

Opioids (such as U-47,700 and furanyl/fentanyl) have also been identified in smoking mixtures/plant material. Users will be unaware of this, and the use of such opioid-containing products could pose a risk of life-threatening respiratory depression. This risk will be especially high in individuals with no tolerance to opioids (Coopman et al., 2017; EMCDDA, 2017h).

D3.3. Characteristics and behaviour of users

No studies were identified that have examined the characteristics and behaviour of users of 5F-MDMB-PINACA.

Synthetic cannabinoids are sold and used as a 'legal' replacement for cannabis (EMCDDA, 2009; EMCDDA, 2017a). In addition some users specifically seek out synthetic cannabinoids because they have a reputation for causing profound intoxication, they can be cheap and are easy to smuggle. In most cases they are smoked using a cigarette of plant material that has been mixed with one or more of the cannabinoids. Because these products rarely state the ingredients, most users will be unaware that they are using synthetic cannabinoids.

People who use synthetic cannabinoids may include recreational users (including cannabis users), high-risk drug users, and groups who experiment with the substances (such as psychonauts). They may also include individuals who are subject to drug testing (such as people in drug treatment, prisoners, and drivers) because some drug tests/screens will be unable to detect some of the cannabinoids (especially those that are relatively new to the drug market). In the past few years, synthetic cannabinoids have become increasingly used by vulnerable groups (such as the homeless and prisoners).

D3.4. Nature and extent of health consequences

The limited information available on the pharmacology, dependence and abuse potential, and acute health effects of 5F-MDMB-PINACA have been discussed above (Section A2, Section B, Section D1 and Section D2).

Compared to cannabis, more pronounced effects as well as severe and fatal poisoning appear to be more common with synthetic cannabinoids (EMCDDA, 2017c; EMCDDA, 2017d, EMCDDA, 2017e, EMCDDA, 2017f, EMCDDA, 2017g; Tait et al., 2016; Waugh et al., 2016; Winstock et al., 2013; Zourova et al., 2016). The reasons for this are poorly understood, but at least two factors are likely to be important: the high potency of the substances and the unintentionally high doses that users are exposed to.

Firstly, studies have found that many of the cannabinoids, including 5F-MDMB-PINACA, which are sold on the drug market, are much more potent and active, typically behaving as full agonists, as compared to THC. This means that even at very small doses they can activate the CB₁ receptor much more strongly than THC (Banister et al., 2016; Ford et al., 2017; Reggio, 2009; Tai and Fantegrossi, 2017).

Secondly, the process for mixing the synthetic cannabinoids with the plant material (which are the most common way of using these substances) can lead to dangerous amounts of the substances in the products. This is because producers have to guess the amount of cannabinoids(s) to add, while the mixing process makes it difficult to dilute the substances sufficiently and distribute them consistently throughout the plant material. This can result both in products that contain toxic amounts of the substances in general (Ernst et al., 2017; Frinculescu et al., 2016; Langer et al., 2014; Langer et al., 2016), as well as products where the cannabinoids are clumped together forming highly concentrated pockets within the plant material (Frinculescu et al., 2016; Moosmann et al., 2015; Schäper et al., 2016). These issues are made worse as the products are typically smoked allowing the substances to be rapidly absorbed into the systemic circulation (bloodstream) and to reach the brain.

The combination of these two factors makes it difficult for users to control the dose that they are exposed to. This can lead them to rapidly administer a toxic dose unintentionally. Accounts from patients and people who witness poisonings suggest that in some cases a small number of puffs from a cigarette have been sufficient to cause severe and fatal acute poisoning.

These two factors are also responsible for outbreaks of mass poisonings caused by smoking mixtures, which have ranged in size from four or five victims to over 800. Mass poisonings can overwhelm emergency responders and other local healthcare systems. Many of the outbreaks that have been reported so far are from the United States, but they have also occurred in Russia and Europe (Adams et al., 2017; Kasper et al., 2015; Schwartz et al., 2015; Shevyrin et al., 2015; Springer et al., 2016; Trecki et al., 2015; Tyndall et al., 2015).

Driving while under the influence of synthetic cannabinoids places users and others at risk of injury (Capron, 2016; Kaneko, 2017; Karinen et al., 2015; Musshoff et al., 2014). In a recent case series of 36 drivers suspected of driving under the influence of drugs in Washington, United States, where 5F-MDMB-PINACA was the predominate psychoactive substance identified, 50% of the drivers were found unconscious and 28% has been involved in collisions with single/multiple cars (Capron, 2016). Similarly, the operation of machinery while under the influence of synthetic cannabinoids may place the user and others at risk of injury.

D3.5. Long-term consequences of use

While there is limited data for 5F-MDMB-PINACA, the long-term consequences of use might share similarities to cannabis and other synthetic cannabinoids. This may include dependence.

D3.6. Conditions under which the new psychoactive substance is obtained and used, including context-related effects and risks

There is very limited data on the conditions which 5F-MDMB-PINACA is obtained and used.

Sources appear to include internet retailers, physical shops, friends and other acquaintances, and street level drug dealers (Section D3.1). In addition, the available data also supports the premise that some users are unaware that they have sourced and used 5F-MDMB-PINACA (Section C and Section D1.2.1). The available data suggests that 5F-MDMB-PINACA is used in the same environments as cannabis. Based on a limited dataset from serious adverse events, the substance is used at home and to a lesser extent in recreational settings.

Section E. Social Risks

The available data suggests that the acute behavioural effects of 5F-MDMB-PINACA bear some similarities to cannabis but are more pronounced and severe.

In addition, and, of particular note, is that in some settings, synthetic cannabinoids are increasingly used by high risk drug users and other vulnerable groups, such as the homeless and prisoners. In at least some cases, these users are specifically seeking out synthetic cannabinoids because the substances have developed a reputation for causing profound intoxication, they can be cheap and are easy to smuggle. Reports suggest that this has exacerbated existing health and social problems for these vulnerable groups, as well as creating new ones.

E1. Individual social risks

There is no information on the individual social risks that may be associated with the use of 5F-MDMB-PINACA.

E2. Possible effects on direct social environment

While there is no specific information on the possible effects of 5F-MDMB-PINACA on the direct social environment, the behavioural effects of synthetic cannabinoids include reports of aggressive and violent behaviour. This may place users and others at risk of injury.

E3. Possible effects on society as a whole

There is no specific information on the possible effects of 5F-MDMB-PINACA on society as a whole.

E4. Economic costs

There are no data on the effects of 5F-MDMB-PINACA on economic costs.

E5. Possible effects related to the cultural context, for example marginalisation

There are no data on the possible effects of 5F-MDMB-PINACA related to the cultural context.

E6. Possible appeal of the new psychoactive substance to specific population groups within the general population

While no specific examples are available on the possible appeal of 5F-MDMB-PINACA to specific user groups, it is reasonable to assume 5F-MDMB-PINACA may be sought by those looking for 'legal' substitutes for cannabis (Section D3.3.).

In addition, and, of particular note, is that synthetic cannabinoids are increasingly used by high risk drug users and other vulnerable groups, such as the homeless and prisoners. In at least some cases, these users are specifically seeking out synthetic cannabinoids because they have a reputation for causing profound intoxication, they can be cheap and are easy to smuggle. Reports suggest that this has exacerbated existing health and social problems as well as creating new 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 et al., 2017; HMIP, 2015; Ralphs et al., 2017; User Voice, 2016).

Section F. Involvement of organised crime

F1. Evidence that criminal groups are systematically involved in production, trafficking and distribution for financial gain

There is no specific information to suggest the involvement of organised crime or established criminal groups in the manufacture, distribution, and supply of 5F-MDMB-PINACA.

In the cases where the origin of the seizures reported to Europol was known, the country of origin indicated was: Spain (1) and China (1). Austria reported 3 seizures from China and Bulgaria reported 1 seizure from Spain. The Czech Republic reported 2 seizures where the final destination was Israel and 1 of the seizures occurred in Israel.

Slovenia reported a collected sample to Europol and the EMCDDA where the country of origin indicated was Germany.

Denmark reported to the EMCDDA a seizure where the country of origin was indicated as Spain.

The United Kingdom reported to the EMCDDA, 129 seizures of 5F-MDMB-PINACA which occurred in a prison or other custodial setting, amounting to a total of 3 kg. The majority of the seizures were in herbal form and often in combination with other synthetic cannabinoids.

F2. Impact on the production, trafficking and distribution of other substances, including existing psychoactive substances as well as new psychoactive substances

No information was reported nor identified concerning the impact of 5F-MDMB-PINACA on the production, trafficking and distribution of other substances, including existing psychoactive substances as well as new psychoactive substances.

F3. Evidence of the same groups of people being involved in different types of crime

No information was reported nor identified concerning evidence of the same groups of people being involved in different types of crime related to the availability of 5F-MDMB-PINACA.

F4. Impact of violence from criminal groups on society as a whole or on social groups or local communities (public order and safety)

No information was reported nor identified concerning incidents of violence related to the availability of 5F-MDMB-PINACA.

F5. Evidence of money laundering practices, or impact of organised crime on other socioeconomic factors in society

No information was reported nor identified concerning evidence of money laundering practices, or impact of organised crime on other socioeconomic factors in society related to the availability of 5F-MDMB-PINACA.

F6. Economic costs and consequences (evasion of taxes or duties, costs to the judicial system)

No information was reported nor identified concerning the economic costs and consequences related to the availability of 5F-MDMB-PINACA.

F7. Use of violence between or within criminal groups

No information was reported nor identified concerning the use of violence between or within criminal groups related to the availability of 5F-MDMB-PINACA.

F8. Evidence of strategies to prevent prosecution, for example through corruption or intimidation

No information was reported nor identified concerning evidence of strategies to prevent prosecution related to the availability of 5F-MDMB-PINACA.

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>
- Akamatsu, S., Yoshida, M. (2016), 'Fragmentation of synthetic cannabinoids with an isopropyl group or a tert-butyl group ionized by electron impact and electrospray', *Journal of Mass Spectrometry*, 51(1), pp.28–32.
- Allibe, N., Richeval, C., Willeman, T., Humbert, L., Allorge, D., Maignan, M., Eysseric-Guerin, H., Stanke-Labesque, F. and Gaulier, J-M. (2016), 'Case reports: Four concomitant non-fatal intoxications with AB-FUBINACA and MDMA', *Toxicologie Analytique et Clinique*, 29(1), pp. 101–110. <https://doi.org/10.1016/j.toxac.2016.12.006>
- Andernach, L., Pusch, S., Weber, C., Schollmeyer, D., Münster-Müller, S., Pütz, M. et al., (2016), 'Absolute configuration of the synthetic cannabinoid MDMB-CHMICA with its chemical characteristics in illegal products', *Forensic Toxicology*, 34(2), pp. 344–352.
- Angerer, V., Bisel, P., Moosmann, B., et al., (2016), 'Separation and structural characterization of the new synthetic cannabinoid JWH-018 cyclohexyl methyl derivative "NE-CHMIMO" using flash chromatography, GC-MS, IR and NMR spectroscopy', *Forensic Science International*, 266, pp. e93–e98.
- Archer, J. R. H., Hudson, S., Abouchedid, R., et al., (2017), 'Synthetic cannabinoid receptor agonist (SCRA) detection from pooled urine samples in central London', *Clinical Toxicology*, 55(5), p 451.
- Asaoka, N., Kawai, H., Nishitani, N., Kinoshita, H., Shibui, N., Nagayasu, K., et al., (2016), 'A new designer drug 5F-ADB activates midbrain dopaminergic neurons but not serotonergic neurons', *The Journal of Toxicological Sciences*, 41(6), pp. 813–816.
- Auwärter, V., Dresen, S., Weinmann, W., Müller, M., Pütz, M., and Ferreirós, N. (2009), "'Spice' and other herbal blends: harmless incense or cannabinoid designer drugs? ', *Journal of Mass Spectrometry*, 44(5), pp. 832–837. <https://doi.org/10.1002/jms.1558>
- 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.
- Barceló, B., Gomila, I., Pellegrini, M., et al., (2017a), 'Acute effects after consumption of the novel synthetic cannabinoids 5F-ADB', *Clinical Toxicology*, 55(5), p 439.
- Barceló, B., Pichini, S., López-Corominas, V., Gomila, I., et al., (2017b), 'Acute intoxication caused by synthetic cannabinoids 5F-ADB and MMB-2201: A case series', *Forensic Science International*, 273, pp. e10–e14.
- Brents, L. K., Gallus-Zawada, A., Radomska-Pandya, A., Vasiljevik, T., Prisinzano, T. E., Fantegrossi, W. E., et al., (2012), 'Monohydroxylated metabolites of the K2 synthetic cannabinoid JWH-073 retain intermediate to high cannabinoid 1 receptor (CB1R) affinity and exhibit neutral antagonist to partial agonist activity', *Biochemical Pharmacology*, 83(7), pp. 952–961.
- Blackman, S. and Bradley, R. (2017), 'From niche to stigma-Headshops to prison: Exploring the rise and fall of synthetic cannabinoid use among young adults', *International Journal on Drug Policy*, 40, pp. 70–77.

Brenneman, R., Papsun, D. M., Logan, B. K., Neavyn, M. J. (2016), 'A death-like slumber, toxic outbreak of AB-FUBINACA', *Journal of Medical Toxicology*, 12(1), 3–47, p 39.
<https://doi.org/10.1007/s13181-016-0538-8> and
http://www.acmt.net/_Library/2016_ASM_Posters/Abstract_108.pdf

Brents, L. K., Reichard, E. E., Zimmerman, S. M., Moran, J. H., Fantegrossi, W. E., Prather, P. L. (2011) 'Phase I hydroxylated metabolites of the K2 synthetic cannabinoid JWH-018 retain *in vitro* and *in vivo* cannabinoid 1 receptor affinity and activity', *PLoS ONE*, 6(7), pp. e21917.

Buchler, I. P., Hayes, M. J., Hegde, S. G., Hockerman, S. L., Jones, D. E., Kortum, S. W., et al., (2009); Assignee: Pfizer. Indazole derivatives. International patent WO2009106980.

Buchler, I. P., Hayes, M. J., Hegde, S. G., Hockerman, S. L., Jones, D. E., Kortum, S. W., et al., (2011), Assignee: Pfizer. Indazole derivatives. United States patent US 20110028447A1.

Capron, B. (2016), '5F-ADB drivers in the State of Washington', *ToxTalk*, 40(2), pp. 23–26.
http://www.soft-tox.org/files/toxtalk/SOFT_ToxTalk_v40-2_0.pdf

Cayman Chemical Company (2017), '5-fluoro-ADB product information'. Cayman Chemical Company, Ann Arbor, M, USA. Available at: <https://www.caymanchem.com/product/16603>

Cooper, Z. D. (2016), 'Adverse effects of synthetic cannabinoids: management of acute toxicity and withdrawal', *Current Psychiatry Reports*, 18(5), p 52.

Coopman, V. and Cordonnier J. (2017), 'Spice-like' herbal incense laced with the synthetic opioid U-47700', *Toxicologie Analytique et Clinique*. <https://doi.org/10.1016/j.toxac.2017.07.004>

Drug Enforcement Administration (2012). Schedules of Controlled Substances: Placement of 1-Butyl-3-(1-naphthoyl)indole (JWH-073), 1-pentyl-3-(1-naphthoyl)indole (JWH-018), 1-[2-(4-morpholinyl)ethyl]-3-(1-naphthoyl)indole (JWH-200), 5-(1,1-dimethylheptyl)-2-(3-hydroxycyclohexyl)-phenol (CP-47,497), and 5-(1,1-dimethyloctyl)-2-(3-hydroxycyclohexyl)-phenol (cannabicyclohexanol and CP-47,497 C8 homologue) into Schedule I Background, Data and Analysis: Eight Factors Determinative of Control and Findings Pursuant to 21 U.S.C. 812(b). Available at <https://www.regulations.gov/document?D=DEA-2012-0001-0002>

Elamin, M., Dunn, M., Dargan, P. I., et al., (2017), 'Clinical features following analytically confirmed use of 5F-ADB, a synthetic cannabinoid receptor agonist. A report from the UK IONA study', *Clinical Toxicology*, 55(5), pp. 443–444.

EMCDDA (2009). Understanding the 'Spice' phenomenon. Luxembourg: Publications Office of the European Union. <http://www.emcdda.europa.eu/system/files/publications/537/Spice-Thematic-paper-final-version.pdf>

EMCDDA (2016). EU Early Warning System Alert: '5 deaths and 4 acute intoxications associated with synthetic cannabinoid 5F-MDMB-PINACA (5F-ADB)', 07 July 2016. Accessible via the European Database on New Drugs (EDND) of the EMCDDA. Accessed: 30 June 2017.

EMCDDA (2017a). Synthetic cannabinoids in Europe, perspectives on drugs.
<http://www.emcdda.europa.eu/topics/pods/synthetic-cannabinoids>

EMCDDA (2017b). EMCDDA–Europol 2016 Annual Report on the implementation of Council Decision 2005/387/JHA. In accordance with Article 10 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances, Publications Office of the European Union, Luxembourg. <http://www.emcdda.europa.eu/publications/implementation-reports/2016>

EMCDDA (2017c). Joint Report on a new psychoactive substance: methyl 2-[[1-(5-fluoropentyl)-1*H*-indazole-3-carbonyl]amino]-3,3-dimethylbutanoate (5F-MDMB-PINACA; 5F-ADB). In accordance with Article 5 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances, EMCDDA-Europol. Lisbon, Portugal.

EMCDDA (2017d). Joint Report on a new psychoactive substance: *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide (AB-CHMINACA). In accordance with Article 5 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances, EMCDDA-Europol. Lisbon, Portugal.

EMCDDA (2017e). Joint Report on a new psychoactive substance: *N*-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide (ADB-CHMINACA). In accordance with Article 5 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances, EMCDDA-Europol. Lisbon, Portugal.

EMCDDA (2017f). Joint Report on a new psychoactive substance: 1-(4-cyanobutyl)-*N*-(2-phenylpropan-2-yl)indazole-3-carboxamide (CUMYL-4CN-BINACA). In accordance with Article 5 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances, EMCDDA-Europol. Lisbon, Portugal.

EMCDDA (2017g). 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, EMCDDA-Europol. Lisbon, Portugal. Available at: http://www.emcdda.europa.eu/system/files/publications/4093/TDAK16002ENN_PDFWEB.pdf_en

EMCDDA (2017h). Joint report on a new psychoactive substance: *N*-phenyl-*N*-1-(2-phenylethyl)piperidin-4-yl-furan-2-carboxamide (furanylfentanyl), Publications Office of the European Union, Luxembourg. <https://doi.org/10.2810/83192>

Ernst, L., Brandhorst, K., Papke, U., et al., (2017), 'Identification and quantification of synthetic cannabinoids in 'spice-like' herbal mixtures: Update of the German situation in early 2017', *Forensic Science International*, 277, pp. 51–58.

Ferk, F., Gminski, R., Al-Serori, H., Mišák, M., Nersesyan, A., Koller, V. J., et al., (2016), 'Genotoxic properties of XLR-11, a widely consumed synthetic cannabinoid, and of the benzoyl indole RCS-4', *Archives of Toxicology*, 90(12), pp. 3111–3123.

Ford, B. M., Tai, S., Fantegrossi, W. E., et al., (2017), 'Synthetic pot: not your grandfather's marijuana', *Trends in Pharmacological Sciences*, 38(3), pp. 257–276.

Frinculescu, A., Lyall, C. L., Ramsey, J., et al., (2017), 'Variation in commercial smoking mixtures containing third-generation synthetic cannabinoids', *Drug Testing and Analysis*, 9(2), pp. 327–333.

Furlotti, G., Alisi, M. A., Apicella, C., Capezzone de Joannon, A., Cazzolla, N., et al., (2012), 'Discovery and pharmacological profile of new 1*H*-indazole-3-carboxamide and 2*H*-pyrrolo[3,4-*c*]quinoline derivatives as selective serotonin 4 receptor ligands', *Journal of Medicinal Chemistry*, 55(22), pp. 9446–9466.

Gaoni, Y. and Mechoulam, R. (1964), 'Isolation, structure, and partial synthesis of an active constituent of hashish', *Journal of the American Chemical Society*, 86(8), pp. 1646–1647. <https://doi.org/10.1021/ja01062a046>

Ginsburg, B. C., Schulze, D. R., Hrubá, L., McMahon, L. R. (2012), 'JWH-018 and JWH-073: Delta(9)-tetrahydrocannabinol-like discriminative stimulus effects in monkeys', *Journal of Pharmacology and Experimental Therapeutics*, 340(1), pp. 37–45.

Hasegawa, K., Wurita, A., Minakata, K., Gonmori, K., Yamagishi, I., Nozawa, H., et al., (2015), 'Identification and quantitation of 5-fluoro-ADB, one of the most dangerous synthetic cannabinoids, in the stomach contents and solid tissues of a human cadaver and in some herbal products', *Forensic Toxicology*, 33(1), pp. 112–121.

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/hmiprison/wp-content/uploads/sites/4/2015/12/Substance-misuse-web-2015.pdf>

Hermanns-Clausen, M., Kneisel, S., Hutter, M., Szabo, B., Auwärter, V. (2013), 'Acute intoxication by synthetic cannabinoids - Four case reports', *Drug Testing and Analysis*, 5(9-10), pp. 790–794.

Hermanns-Clausen, M., Kithinji, J., Spehl, M., Angerer, V., Franz, F., Eyer, F., et al., (2016), 'Adverse effects after the use of JWH-210—a case series from the EU Spice II plus project', *Drug Testing and Analysis*, 8(10), pp. 1030–1038.

Hermanns-Clausen, M., Kneisel, S., Szabo, B., et al., (2013), 'Acute toxicity due to the confirmed consumption of synthetic cannabinoids: clinical and laboratory findings', *Addiction*, 108(3), pp. 534–544.

Hess, C., Krueger, L., Unger, M., Madea, B. (2016a), 'Freeze thaw stability and long term stability of 84 synthetic cannabinoids in serum', *Drug Testing and Analysis*, 9(10), pp. 1506–1511.
<https://doi.org/10.1002/dta.2133>

Hess, C., Murach, J., Krueger, L., Scharrenbroch, L., Unger, M., Madea, B., et al., (2017), 'Simultaneous detection of 93 synthetic cannabinoids by liquid chromatography-tandem mass spectrometry and retrospective application to real forensic samples', *Drug Testing and Analysis*, 9(5), pp. 721–733.

Hrubá, L., Ginsburg, B. C., McMahon, L. R. (2012), 'Apparent inverse relationship between cannabinoid agonist efficacy and tolerance/cross-tolerance produced by Δ^9 -tetrahydrocannabinol treatment in rhesus monkeys', *Journal of Pharmacology and Experimental Therapeutics*, 342(3), pp. 843–849.

Huestis, M. A., Gorelick, D. A., Heishman, S. J., Preston, K. L., Nelson, R. A., Moolchan, E. T. and Frank, R. A. (2001), 'Blockade of effects of smoked marijuana by the CB1-selective cannabinoid receptor antagonist SR141716', *Archives of General Psychiatry*, 58(4), pp. 322–328.
<https://doi.org/10.1001/archpsyc.58.4.322>

Jack, A., (2009), 'The Story of Spice', Financial Times. <https://www.ft.com/content/1721e2da-f8a0-11dd-aae8-000077b07658?mhq5j=e5>

Johnson, B. L., Rodgers, J. D. (2005), 'Practical synthesis of 3-carboxyindazoles', *Synthetic Communications*, 35(20), pp. 2681–2684.

Järbe, T. U., Deng, H., Vadivel, S. K., Makriyannis, A. (2011), 'Cannabinergic aminoalkylindoles, including AM678=JWH018 found in 'Spice', examined using drug (Δ^9 -tetrahydrocannabinol) discrimination for rats', *Behavioural Pharmacology*, 22(5-6), pp. 498–982.

Järbe, T. U., Li, C., Vadivel, S. K., Makriyannis, A. (2010), 'Discriminative stimulus functions of methanandamide and Δ^9 -THC in rats: tests with aminoalkylindoles (WIN55,212-2 and AM678) and ethanol', *Psychopharmacology*, 208(1), pp. 87–98.

Kaizaki-Mitsumoto, A., Noguchi, N., Yamaguchi, S., et al., (2016), 'Three 25-NBOMe-type drugs, three other phenethylamine-type drugs (25I-NBMD, RH34, and escaline), eight cathinone derivatives, and a phencyclidine analog MMXE, newly identified in ingredients of drug products before they were sold on the drug market', *Forensic Toxicology*, 34(1), pp. 108–114.

Kaneko, S. (2017), 'Motor vehicle collisions caused by the 'super-strength' synthetic cannabinoids, MAM-2201, 5F-PB-22, 5F-AB-PINACA, 5F-AMB and 5F-ADB in Japan experienced from 2012 to 2014', *Forensic Toxicology*, 35(2), pp. 244–251.

Karinen, R., Tuv, S. S., Øiestad, E. L., Vindenes V. (2015), 'Concentrations of APINACA, 5F-APINACA, UR-144 and its degradant product in blood samples from six impaired drivers compared to previous reported concentrations of other synthetic cannabinoids', *Forensic Science International*, 246, pp. 98–103. <https://doi.org/10.1016/j.forsciint.2014.11.012>

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>

Kikura-Hanajiri, R., Uchiyama, N., Kawamura, M., Goda, Y. (2013), 'Changes in the prevalence of synthetic cannabinoids and cathinone derivatives in Japan until early 2012', *Forensic Toxicology*, 31(1), pp. 44–53.

Koller, V., Zlabinger, G., Auwärter, V., Fuchs, S., Knasmüller, S. (2013), 'Toxicological profiles of selected synthetic cannabinoids showing high binding affinities to the cannabinoid receptor subtype CB1', *Archives of Toxicology*, 87(7), pp. 1287–1297. (Erratum: *idem ibid*, 87(7), p. 1299.)

Koller, V., Auwärter, V., Grummt, T., Moosmann, B., Mišík, M., Knasmüller, S. (2014), 'Investigation of the in vitro toxicological properties of the synthetic cannabimimetic drug CP-47,497-C8', *Toxicology and Applied Pharmacology*, 277(2), pp. 164–171.

Koller, V., Ferk, F., Al-Serori, H., Mišík, M., Nersesyan, A., Auwärter, V., et al., (2015), 'Genotoxic properties of representatives of alkylindazoles and aminoalkyl-indoles which are consumed as synthetic cannabinoids', *Food and Chemical Toxicology*, 80, pp. 130–136.

Kusano, M., Zaitso, K., Taki, K., Hisatsune, K., Nakajima, J., Moriyasu, T., et al., (2017), 'Fatal intoxication by 5F-ADB and diphenidine: detection, quantification, and investigation of their main metabolic pathways in human by LC/MS/MS and LC/Q-TOFMS', *Drug Testing and Analysis*, DOI: 10.1002/dta.2215

Langer, N., Lindigkeit, R., Schiebel, H. M., et al., (2014), 'Identification and quantification of synthetic cannabinoids in 'spice-like' herbal mixtures: a snapshot of the German situation in the autumn of 2012', *Drug Testing and Analysis*, 6(1-2), pp. 59–71.

Langer, N., Lindigkeit, R., Schiebel, H-M., Papke, U., Ernst, L., Beuerle, T. (2016), 'Identification and quantification of synthetic cannabinoids in "spice-like" herbal mixtures: Update of the German situation for the spring of 2016', *Forensic Science International*, 269, pp. 31–41.

Logan, B. K., Reinhold, L. E., Xu, A., Diamond, F. X. (2012), 'Identification of synthetic cannabinoids in herbal incense blends in the United States', *Journal of Forensic Sciences*, 57(5), pp. 1168–80.

Longworth, M., Banister, S. D., Mack, J. B., Glass, M., Connor, M., Kassiou, M. (2016), 'The 2-alkyl-2H-indazole regioisomers of synthetic cannabinoids AB-CHMINACA, AB-FUBINACA, AB-PINACA, and 5F-AB-PINACA are possible manufacturing impurities with cannabimimetic activities', *Forensic Toxicology*, 34(2), pp. 286–303.

- Macfarlane, V. and Christie, G. (2015), 'Synthetic cannabinoid withdrawal: a new demand on detoxification services', *Drug and Alcohol Review*, 34(2), pp. 147–153.
- Minakata, K., Yamagishi, I., Nozawa, H., et al., (2017), 'Sensitive identification and quantitation of parent forms of six synthetic cannabinoids in urine samples of human cadavers by liquid chromatography–tandem mass spectrometry', *Forensic Toxicology*, 35(2), pp. 275–283.
- Moosmann, B., Angerer, V., Auwärter, V. (2015), 'Inhomogeneities in herbal mixtures: a serious risk for consumers', *Forensic Toxicology*, 33(1), pp. 54–60.
- Moosmann, B., Franz, F., Angerer, V., Auwärter, V (2017), Technical review on [2-(1-(5-fluoropentyl)-1H-indazole-3-carboxamido)-3,3-dimethylbutanoate] 5F-MDMB-PINACA. Prepared under EMCDDA contract CT.16.SAT.0101.1.0.
- Musshoff, F., Madea, B., Kernbach-Wighton, G., Bicker, W., Kneisel, S., Hutter, M. and Auwärter, V. (2014), 'Driving under the influence of synthetic cannabinoids ("Spice"): a case series', *International Journal of Legal Medicine*, 128(1), pp. 59–64. <https://doi.org/10.1007/s00414-013-0864-1>
- Pant, S., Deshmukh, A., Dholaria, B., Kaur, V., Ramavaram, S., Ukor, M., et al., (2012), 'Spicy seizure', *American Journal of the Medical Sciences*, 344(1), pp. 67–68.
- Pap, C. (2016), 'ADB-Fubinaca in the real world: a case series of 15 poisonings', *Clinical Toxicology (Philadelphia)*, 54(4), p 384.
- Papanti, D., Schifano, F., Botteon, G., Bertossi, F., Mannix, J., Vidoni, D., et al., (2013), '"Spiceophrenia": a systematic overview of "Spice"-related psychopathological issues and a case report', *Human Psychopharmacology*, 28(4), pp. 379–389.
- Pertwee RG (ed). (2005a), 'Cannabinoids. Handbook of Experimental Pharmacology.' Berlin: Springer-Verlag. <https://link.springer.com/book/10.1007/b137831>
- Pertwee, R. G. (2005b), 'The therapeutic potential of drugs that target cannabinoid receptors or modulate the tissue levels or actions of endocannabinoids.', *AAPS Journal*, 7(3), pp. E625–E654. <https://doi.org/10.1208/aapsj070364>
- Pertwee, R. G., (Ed). (2014), 'Handbook of cannabis', Oxford University Press, Oxford.
- Pertwee, R. G., (Ed). (2015), 'Endocannabinoids. Handbook of Experimental Pharmacology. Springer-Verlag Berlin', <https://10.1007/978-3-319-20825-1>
- Peterson, B. L. and Couper, F. J. (2015), 'Concentrations of AB-CHMINACA and AB-PINACA and driving behavior in suspected impaired driving cases', *Journal of Analytical Toxicology*, 39(8), pp. 642–647.
- Ralphs, R., Williams, L., Askew, R., et al., (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.
- Reggio, P. H. (Ed). (2009), 'The cannabinoids receptors.', Humana Press, New York, <https://doi.org/10.1007/978-1-59745-503-9>
- Schäper, J. (2016), 'Wirkstoffgehalte und inhomogene Verteilungdes Wirkstoffs MDMB-CHMICA in Kräutermischungen', *Toxichem Krimtech*, 83(2), pp. 112–114. https://www.gtfc.org/cms/images/stories/media/tk/tk83_2/Schaeper_et_al_2016.pdf

Schaus, J. M., Thompson, D. C., Bloomquist, W. E., Susemichel, A. D., Calligaro, D. O., Cohen, M. L. (1998), 'Synthesis and structure-activity relationships of potent and orally active 5-HT₄ receptor antagonists: indazole and benzimidazolone derivatives', *Journal of Medicinal Chemistry*, 41(11), pp. 1943–1955.

Schwartz, M. D., Trecki, J., Edison, L. A., Steck, A. R., Arnold, J. and 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., et al., (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.

Slovenian National Forensic Laboratory (2016) '5F-MDMB-PINACA'. Analytical report. Available at http://www.policija.si/apps/nfl_response_web/0_Analytical_Reports_final/5F-MDMB-PINACA-ID-1652-16_rpt170916.pdf

Springer, Y. P., Gerona, R., Scheunemann, E., Shafer, S. L., Lin, T., Banister, S. D., Cooper, M. P., Castrodale, L. J., Levy, M., Butler, J. C. and McLaughlin, J. B. (2016), 'Increase in adverse reactions associated with use of synthetic cannabinoids - Anchorage, Alaska, 2015–2016', *MMWR Morbidity and Mortality Weekly Report*, 65(40), pp. 1108–1111. <https://doi.org/10.15585/mmwr.mm6540a4>

Tai, S. and Fantegrossi, W. E. (2017), 'Pharmacological and toxicological effects of synthetic cannabinoids and their metabolites', *Current Topics in Behavioral Neurosciences*, 32, pp. 249–262. <https://doi.org/10.1007/7854201660>

Tait, R. J., Caldicott, D., Mountain, D., et al., (2016), 'A systematic review of adverse events arising from the use of synthetic cannabinoids and their associated treatment', *Clinical Toxicology*, 54(1), pp. 1–13.

Trecki, J., Gerona, R. R., and 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>

United Nations Office on Drugs and Crime (UNODC) (2013). *Recommended methods for the Identification and Analysis of Synthetic Cannabinoid Agonists in Seized Materials*. UNODC, Vienna.

User Voice. (2016), 'Spice: the bird killer — what prisoners think about the use of spice and other legal highs in prison'. <http://www.uservoice.org/wp-content/uploads/2016/05/User-Voice-Spice-The-Bird-Killer-Report-Low-Res.pdf>

Vandrey, R., Dunn, K. E., Fry, J. A., Girling, E. R. (2012), 'A survey study to characterize use of Spice products (synthetic cannabinoids) ', *Drug and Alcohol Dependence*, 120(1), pp. 238–241.

Wallgren, J., Vikingsson, S., Johansson, A., Josefsson, F., Green, H., et al., (2017), 'Synthesis and identification of an important metabolite of AKB-48 with a secondary hydroxyl group on the adamantyl ring', *Tetrahedron Letters*, 58(15), pp. 1456–1458.

Waugh, J., Najafi, J., Hawkins, L., Hill, S. L., Eddleston, M., Vale, J. A., Thompson, J. P., and Thomas, S. H. (2016), 'Epidemiology and clinical features of toxicity following recreational use of synthetic cannabinoid receptor agonists: a report from the United Kingdom National Poisons Information Service', *Clinical Toxicology (Philadelphia)*, 54(6), pp. 512–518. <https://doi.org/10.3109/15563650.2016.1171329>

WEDINOS (2017). Welsh Emerging Drugs & Identification of Novel Substances Project. 30 June 2017. Available from: <http://www.wedinos.org/>

Wiley, J. L., Marusich, J. A., Lefever, T. W., et al., (2015), 'AB-CHMINACA, AB-PINACA, and FUBIMINA: affinity and potency of novel synthetic cannabinoids in producing Δ^9 -tetrahydrocannabinol-like effects in mice', *The Journal of Pharmacology and Experimental Therapeutics*, 354(3), pp. 328–339.

Wiley, J. L., Lefever, T.W., Marusich, J.A., Grabenauer, M., Moore, K.N., Huffman, J.W., et al., (2016a), 'Evaluation of first generation synthetic cannabinoids on binding at non-cannabinoid receptors and in a battery of in vivo assays in mice', *Neuropharmacology*, 110, pp.143–153.

Wiley, J. L., Owens, R. A., Lichtman, A. H. (2016b), 'Discriminative stimulus properties of phytocannabinoids, endocannabinoids, and synthetic cannabinoids', *Current Topics in Behavioral Neurosciences*, doi: 10.1007/7854_2016_1024

Winstock, A. R. and Barratt M. J. (2013), 'Synthetic cannabis: a comparison of patterns of use and effect profile with natural cannabis in a large global sample', *Drug and Alcohol Dependence*, 131(1–2), pp. 106–111. <https://doi.org/10.1016/j.drugalcdep.2012.12.011>

Yeter, O. (2017), 'Identification of the synthetic cannabinoid 1-(4-cyanobutyl)-N-(2-phenylpropan-2-yl)-1H-indazole-3-carboxamide (CUMYL-4CN-BINACA) in plant material and quantification in post-mortem blood samples', *Journal of Analytical Toxicology*, doi: 10.1093/jat/bkx1061

Zaurova, M., Hoffman, R. S., Vlahov, D. and Manini, A. F. (2016), 'Clinical effects of synthetic cannabinoid receptor agonists compared with marijuana in emergency department patients with acute drug overdose', *Journal of Medical Toxicology*, 12(4), pp. 335–340. <https://doi.org/10.1007/s13181-016-0558-4>

Zimmermann, U. S., Winkelmann, P. R., Pilhatsch, M., Nees, J. A., Spanagel, R., Schulz, K. (2009), 'Withdrawal phenomena and dependence syndrome after the consumption of "Spice Gold"', *Deutsches Ärzteblatt International*, 106(27), pp. 464–467.

Zuba, D., Byrska, B. (2013), 'Analysis of the prevalence and coexistence of synthetic cannabinoids in 'herbal high' products in Poland', *Forensic Toxicology*, 31(1), pp. 21–30.



Annex 2. List of participants at the risk assessment meetings of Methyl 2-[[1-(5-fluoropentyl)-1*H*-indazole-3-carbonyl]amino]-3,3-dimethylbutanoate (5F-MDMB-PINACA)

7-8 November 2017

A. Extended Scientific Committee

Dr Anne Line BRETTEVILLE-JENSEN

Norwegian Institute for Alcohol and Drug Research, Oslo
Chair of the Scientific Committee

Professor Dr Gerhard BUEHRINGER

Addiction Research Unit, Department of Clinical Psychology and Psychotherapy, Technische Universität Dresden, Institut für Therapieforschung (IFT), Munich

Professor Dr Paul DARGAN

Clinical Toxicology, St Thomas' Hospital, Guy's and St Thomas' NHS Foundation Trust, London

Dr Marina DAVOLI

Department of Epidemiology, Lazio Regional Health Service, Rome

Professor Dr Gabriele FISCHER

Medical University Vienna, Center of Public Health, Vienna

Professor Dr Henk GARRETSEN

Faculty of Social and Behavioural Sciences, Tilburg University, Tilburg

Professor Dr Krzysztof KRAJEWSKI

Department of Criminology, Jagiellonian University, Krakow

Dr Fernando RODRÍGUEZ de FONSECA

Fundación IMABIS, Hospital Universitario Carlos Haya de Málaga, Málaga

Professor Dr Rainer SPANAGEL

Institute of Psychopharmacology, Central Institute of Mental Health, Mannheim

Dr Wim BEST

Utrecht University, Faculty of Science, Freudenthal Institute, Utrecht

Dr Simon BRANDT

School of Pharmacy & Biomolecular Sciences, Liverpool John Moores University, Liverpool

Professor Dr Gaetano Di CHIARA

Biomedical Sciences Department, University of Cagliari, Cagliari

Professor Dr Éva KELLER

Semmelweis University, Department of Forensic and Insurance Medicine, Budapest

Dr Claude GUILLOU

Directorate F – Health, Consumers and Reference Materials, DG Joint Research Centre, European Commission

Edith HOFER

Organised Crime and Drugs Policy Unit, DG HOME, European Commission

Dr Leon Van Aerts

Section Pharmacology, Toxicology and Biotechnology, College ter Beoordeling van Geneesmiddelen, Medicines Evaluation Board, Utrecht, on behalf of European Medicines Agency

Werner VERBRUGGEN

Europol's Drug Unit, Europol

Paul GRIFFITHS

Scientific Director, EMCDDA

Dr Roumen SEDEFOV

Head of Unit, Supply reduction and new drugs unit, EMCDDA

B. Invited Experts

Professor Dr Volker AUWÄRTER

Freiburg University, Institute of Forensic Medicine, Freiburg

Dr Robert KRONSTRAND

Dep. Forensic Genetics and Toxicology, Swedish National Board of Forensic Medicine, Linköping

Professor Dr Bela SZABO

Institute of Experimental and Clinical Pharmacology and Toxicology, Freiburg

Dr István UJVÁRY

Budapest University of Technology and Economics, Budapest

C. EMCDDA Staff

Anabela ALMEIDA

Action on new drugs sector, Supply reduction and new drugs unit

Rachel CHRISTIE

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