European Monitoring Centre
for Drugs and Drug Addiction

TECHNICAL REPORT

# Synthetic cannabinoids in Europe – a review

## About this report

This report provides a technical review of the current body of knowledge regarding synthetic cannabinoids that are monitored by the the EU Early Warning System. The aim of this report is to strengthen situational awareness of synthetic cannabinoids in Europe and to help stakeholders prepare for, and respond to, public health and social threats caused by such substances.

## About the EMCDDA

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is the central source and confirmed authority on drug-related issues in Europe. For over 25 years, it has been collecting, analysing and disseminating scientifically sound information on drugs and drug addiction and their consequences, providing its audiences with an evidence-based picture of the drug phenomenon at European level.

The EMCDDA's publications are a prime source of information for a wide range of audiences including: policymakers and their advisors; professionals and researchers working in the drugs field; and, more broadly, the media and general public. Based in Lisbon, the EMCDDA is one of the decentralised agencies of the European Union.

European Monitoring Centre
for Drugs and Drug Addiction

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**Statement on the United Kingdom**

The United Kingdom left the European Union on 1 February 2020. For the purpose of this report, the United Kingdom is not included in the term 'Member States'.

# Contents

## Methods and information sources

In the context of this report, 'synthetic cannabinoids' are defined as new psychoactive substances that mimic the effects of tetrahydrocannabinol, the major psychoactive substance in cannabis. Another common name for this group of substances is 'synthetic cannabinoid receptor agonists'.

The terms 'synthetic cannabinoid receptor agonists', 'spice' and 'synthetic cannabinoid' were searched in Medline, Google Scholar and PubMed. Literature searches used both the chemical structure and text queries in online databases; searches were conducted in August 2019. The publications retrieved were then reviewed for additional relevant references (the snowball technique). Searches of the websites of selected medical specialty societies and international, national and local government agencies were conducted to identify position statements and reports. Search strings were introduced in Google and Google Scholar, and the first 100 hits were screened to find additional relevant content. Although the systematic searches were conducted in 2018, information from thematic scientific papers and reports published in 2019 and 2020 was also included in this report.

English-language articles were selected from a search of PubMed (National Center for Biotechnology Information), Web of Science (Thomson Reuters), Medline and Google Scholar. The search terms used were 'synthetic cannabinoid receptor agonists', 'spice' and 'synthetic cannabinoid'. Textual searches were also conducted in popular English-language drug forums.

In addition, exact chemical structure-based searches were done in SciFinder (American Chemical Society, Chemical Abstract Service) and Reaxys (Elsevier). As part of the report, the individual profiles of selected synthetic cannabinoids were developed. The substances were identified by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) based on reports of high availability in Europe and/or reports of serious adverse events. Google and specific drug user discussion forums and related websites (such as Bluelight, Eve and Rave, and Erowid) were searched for the terms 'CUMYL-PeGACLONE', 'AMB-FUBINACA', 'AB-FUBINACA', 'CUMYL-5F-P7AICA' and '5F-MDMB-PICA', alone or in combination with 'buy', 'shop', 'research chemical', 'synthetic cannabinoid', 'dosing', 'poisoning', 'kaufen', 'räuchermischung', 'powder' or 'synthesis'. In addition, colleagues within the authors' scientific networks were contacted to obtain information.

Searches of open source information, including scientific articles, official reports, grey literature, internet drug discussion forums and related websites, were also included.

Information from the European Union Early Warning System on NPS (EWS), operated by the EMCDDA, has been included, as relevant. The EWS is composed of a multiagency and multidisciplinary network, which includes the EMCDDA, 29 national early warning systems (27 EU Member States, Turkey, and Norway), Europol and its law enforcement networks, the European Medicines Agency (EMA), the European Commission and other partners. Information from United Nations agencies (the United Nations Office on Drugs and Crime and the World Health Organization) as well as from third countries such as Canada, Russia, the United Kingdom, and the United States has also been included, as relevant.

# 1. Executive summary

Synthetic cannabinoids are functionally similar to $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC), the major psychoactive substance in cannabis. They bind to the same cannabinoid receptors in the brain and other organs as THC. They were originally developed by scientists to study the body's endocannabinoid system, as well as to provide insights into disease and to help develop new medicines. Around the mid-2000s, they began to appear in Europe in products called 'Spice' that were sold as 'legal' replacements for cannabis. In these products, synthetic cannabinoids were mixed with plant material, which could then be smoked as cigarettes ('joints'). In recent years, alongside these smoking mixtures, new products, including e-liquids for vaping using electronic cigarettes and paper impregnated with synthetic cannabinoids, have been sold on the drug market. Unknown to users, synthetic cannabinoids have also been mis-sold or used to adulterate cannabidiol (CBD) and THC e-liquids, as well as other illicit drugs, such as opioids. Another concerning development is the recent adulteration of cannabis products with synthetic cannabinoids in Europe. Typically, these adulterated products are low-THC herbal material or resins. In terms of look, smell and flavour, these adulterated products would be very difficult to distinguish from 'genuine' illicit cannabis products and, as a result, users may be unaware that they are using synthetic cannabinoids. As synthetic cannabinoids are highly potent substances, people who use these products could be at high risk of poisoning.

Synthetic cannabinoids activate the same cannabinoid receptors in the body as THC. The behavioural and physiological effects that have been reported with synthetic cannabinoids include relaxation, euphoria, lethargy, depersonalisation, distorted perception of time, impaired motor performance, hallucinations, paranoia, confusion, fear, anxiety, dry mouth, bloodshot eyes, tachycardia, nausea, and vomiting.

Despite similarities, however, synthetic cannabinoids can cause more profound intoxication than cannabis. Severe poisonings are also more common, and fatalities linked to the consumption of these substances have been recorded. There have been case reports of serious cardiovascular toxicity (including sudden death), rapid loss of consciousness/coma, respiratory depression, seizures and convulsions, hyperemesis, delirium, agitation, psychosis, and aggressive and violent behaviour. It appears that, at least in part, these effects are due to the high potency of synthetic cannabinoids and the unintentionally high doses that users may be exposed to. Firstly, laboratory studies have found that many of the cannabinoids sold on the drug market are much more potent than THC and act as full agonists at the cannabinoid receptors (THC, in contrast, is a partial agonist). This means that, even at very small doses, synthetic cannabinoids can activate the cannabinoid receptors much more strongly than THC. Secondly, products containing synthetic cannabinoids often contain high doses of the substances. 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. These factors are also responsible for the outbreaks of mass poisonings seen with synthetic cannabinoids, which have ranged from a handful of people to hundreds, some of whom have died. While many of the outbreaks reported so far have been in the United States, they have also occurred in Russia, Canada

and Europe. Outbreaks due to synthetic cannabinoids being mis-sold or used to adulterate cannabis products, as well as other illicit drugs, such as opioids, are increasingly common. Such outbreaks can rapidly overwhelm the capacity of emergency responders and hospital emergency departments, which is of particular concern given the ongoing COVID-19 pandemic and the additional burden already placed on healthcare systems. There is no approved antidote to poisoning caused by synthetic cannabinoids. The effects on health from the chronic use of synthetic cannabinoids are largely unknown; however, regular use has been linked to problems such as dependence and withdrawal symptoms.

Synthetic cannabinoids are used by a range of people, including those who use cannabis, those who are regularly subjected to drug-testing procedures (such as prisoners) and people who experiment with a range of substances (so called 'psychonauts'). Increasingly, synthetic cannabinoids are also used by some high-risk drug users and other vulnerable groups (such as prisoners and people experiencing homelessness), as they have gained a reputation for causing profound intoxication, they can be cheaper than other drugs and they are easy to smuggle.

In Europe, synthetic cannabinoids are monitored as new psychoactive substances by the European Union Early Warning System. They are the largest group of substances monitored by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), with 209 reported between 1 January 2008 and 31 December 2020. Since 2015, there has been a decrease in the number of synthetic cannabinoids appearing for the first time each year on the drug market and an overall decrease in seizures of synthetic cannabinoids by law enforcement. In part, these changes appear to be related to a disruption in the 'legal high' trade, which for a period saw new psychoactive substances being sold openly on the high street in many countries in Europe. More generally, broader policy responses designed to restrict the availability of new psychoactive substances are also likely to have had an effect. Despite this, the market in synthetic cannabinoids, once the epitome of the 'legal highs' phenomenon, continues to evolve and pose a threat to health security. During 2020, signals related to two synthetic cannabinoids, MDMB-4en-PINACA and 4F-MDMB-BICA, led the EMCDDA to launch initial reports on the substances because of concerns of potential public health and social threats to Europe. Both MDMB-4en-PINACA and 4F-MDMB-BICA were formally risk assessed by the EMCDDA in December 2020. Based on the risk assessment reports, in March 2021 the European Commission proposed that MDMB-4en-PINACA and 4F-MDMB-BICA be controlled in Europe. Since 2016, a total of seven synthetic cannabinoids have been formally risk assessed by the EMCDDA (i.e. MDMB-CHMICA (2016), 5F-MDMB-PINACA, AB-CHMINACA, ADB-CHMINACA, CUMYL-4CN-BINACA (2017), 4F-MDMB-BICA and MDMB-4en-PINACA (2020)).

Despite measures intended to reduce the availability of synthetic cannabinoids on the drug market, data reported to the EMCDDA through the EU Early Warning System show that synthetic cannabinoids continue to be widely available across Europe. As noted, the relatively low cost, easy availability and high potency of synthetic cannabinoids appear to have resulted in increased use among marginalised groups such as people experiencing homelessness and prisoners. This development has been associated with an increase in reports of serious harms. For example, in prisons, alongside the adverse health effects, the

market in and use of 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.

In the future, it can be expected that synthetic cannabinoids with high potency and that are easy to synthesise will continue to be introduced into the market.

The ongoing COVID-19 pandemic and the related response measures may affect the existing synthetic cannabinoid drug markets in unpredictable ways. Such effects may extend to changes in use and patterns of use of synthetic cannabinoids. Seizures of bulk powders by European national customs agencies during the pandemic suggest that synthetic cannabinoids continue to be imported into and distributed within Europe. It is possible that, in the case of a reduced availability of cannabis and other illicit drugs in Europe, criminal groups, as well as drug users, may use a range of replacement substances, including synthetic cannabinoids.

This report provides a technical review of the current body of knowledge regarding synthetic cannabinoids that are monitored by the EMCDDA. The aim of this report is to strengthen situational awareness of synthetic cannabinoids in Europe and to help stakeholders prepare for and respond to public health and social threats caused by such substances.

## 2. Background

### 2.1. History of the development of synthetic cannabinoids

The first synthetic analogues of $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC; the major psychoactive substance in cannabis) were synthesised by Mechoulam (Mechoulam and Carlini, 1978) shortly after the first total synthesis of $\Delta^9$-THC was published (Mechoulam and Gaoni, 1965). Their chemical structure was similar to the structure of $\Delta^9$-THC (e.g. nabilone and A-41988). After the identification and cloning of the $CB_1$ and $CB_2$ cannabinoid receptors (Matsuda et al., 1990; Munro et al., 1993), a variety of chemicals with diverse structures were screened for the ability to bind to these receptors. This led to the discovery of several classes of substances that could bind to and activate the cannabinoid receptors (Huffman and Padgett, 2005; Makriyannis and Deng, 2007). Subsequently, a large body of literature on the subject emerged, focused on the development of synthetic cannabinoids as medicines. Cannabis was recognised as potentially useful for the treatment of conditions such as pain, anorexia, wasting syndrome, muscle spasms and glaucoma (Compton et al.,1992; Melvin et al., 1984), and new drug candidates were developed, focusing on easy to synthesise synthetic cannabinoids with fewer psychotropic side effects than cannabis. Simultaneously, other groups were also investigating the structure–activity relationships of this new class of substances (Aung et al., 2000; Huffman et al., 2005; Melvin et al., 1993; Wiley et al., 2014).

### 2.2. Legitimate uses of synthetic cannabinoids

Synthetic cannabinoids have been the subject of extensive pharmacological and toxicological research. Some were developed as drug candidates. Nabilone (Cesamet®), for example, is used as an orally administered medicine for the treatment of nausea and vomiting induced by cancer chemotherapy in patients receiving a wide variety of chemotherapy regimens, or to treat cachexia under HIV treatment for patients who have failed to respond adequately to conventional antiemetic treatments. Owing to its side effects and potential for abuse, which are very similar to those of THC, nabilone is not a first-choice therapy. In addition, synthetic cannabinoids are widely used in scientific research and in analytical reference material in clinical and forensic case work.

### 2.3. International control measures

The following synthetic cannabinoids are included in the list of substances in Schedule II of the United Nations Convention on Psychotropic Substances of 1971 (INCB, 2020):

— AM-2201 (JWH-2201) and JWH-018 (AM-678) (since 2015),

— 5F-AKB-48 (5F-APINACA), MDMB-CHMICA and XLR-11 (5F-UR-144) (since 2017),

— AB-CHMINACA, AB-PINACA, 5F-MDMB-PINACA (5F-ADB), AM-2201 carboxylate analogue quinolinyl derivative (5F-PB-22) and UR-144 (since 2018),

— ADB-FUBINACA, AMB-FUBINACA (FUB-AMB), CUMYL-4CN-BINACA and ADB-CHMINACA (since 2019),

— AB-FUBINACA, 5F-AMB (5F-AMB-PINACA), 5F-MDMB-PICA and 4F-MDMB-BINACA (since 2020).

In 2020, MDMB-4en-PINACA (WHO, 2020a) and CUMYL-PeGACLONE (WHO, 2020b) were assessed at the 43rd meeting of the WHO Expert Committee on Drug Dependence and were recommended to be included in Schedule II of the 1971 Convention on Psychotropic Substances (WHO, 2020c).

# 3. Synthetic cannabinoids in Europe

## 3.1. Emergence as new psychoactive substances

A product called 'Spice', containing synthetic cannabinoids, appears to have emerged around 2004 as a legal alternative to cannabis and started to gain popularity in European countries. By 2008, these products were gaining wider popularity and were associated with numerous poisonings. Towards the end of 2008, the active substances in these Spice products were identified as JWH-018 and CP-47,497-C8, two synthetic cannabinoids developed decades ago in the context of research on the endocannabinoid system (Auwärter et al., 2009; Uchiyama et al., 2009). These products were found to contain synthetic cannabinoids mixed with plant (herbal) material, which could then be smoked as cigarettes ('joints') (Auwärter et al., 2009; EMCDDA, 2009, 2017; Jack, 2009). Such smoking mixtures have been referred to by a variety of names, depending on the country, region, product type, brand name and user group. Names associated with these products include 'smoking mixtures', 'herbal smoking mixtures', 'herbal incense', 'synthetic cannabis', 'legal weed' and 'K2'. Common street names used include 'magic tobacco' in Hungary, 'chimique' in France, 'Bonsai' in Turkey and, in Birmingham (United Kingdom), 'Black Mamba' or simply 'Mamba'. 'Legal high' products containing synthetic cannabinoids have been subject to innovative marketing approaches and are widely and openly available on the web. During the first few years of the phenomenon, similar products were also available in some countries in bricks-and-mortar ('head' and 'smart') shops.

Owing to the number and variety of synthetic cannabinoids emerging on the drug market, one of the challenges associated with their appearance is their naming. As the structures of most synthetic cannabinoids can be broken down into four components – tail, core, linker and linked group – the EMCDDA has introduced a semi-systematic approach to assigning common names to them (EMCDDA, 2017). Each component of the structure is assigned a code name, and the ordered combination of code names for the linked group, tail, core and linker allows the chemical structure of the substance to be ciphered.

## 3.2. Availability and size of the market

Synthetic cannabinoids are the largest group of new psychoactive substances monitored by the EMCDDA through the EU Early Warning System, with 209 identified on the drug market over the 13 years between 1 January 2008 and 31 December 2020. This includes 11 that were identified for the first time in 2020. An average of 27 cannabinoids appeared each year in Europe between 2011 and 2015, but since 2016 the annual number has dropped to around 10 (Figure 1).

FIGURE 1

**Number of synthetic cannabinoids formally notified to the EU Early Warning System for the first time, 2008–2020**



In 2019, over 18 700 seizures of synthetic cannabinoids were reported to the EU Early Warning System, which represents around 54 % of the total number of seizures reported during that year (29 % in the Member States). In the European Union, most synthetic cannabinoids seized were in the form of herbal plant material (5 208 cases, 112 kg) or powders (684 cases, 78 kg) (Figure 2). The number of seizures is unevenly distributed across Europe, with Turkey accounting for the large majority of the seizures of synthetic cannabinoids reported in 2019 (65 %).

FIGURE 2

**Seizures of synthetic cannabinoids reported to the EU Early Warning System: trends in (a) the number of seizures of synthetic cannabinoids and (b) the quantity seized, in weight (kg), 2005–2019 (all forms including powders and herbal smoking mixtures – EU-27 and EU-27 + 2)**

a)
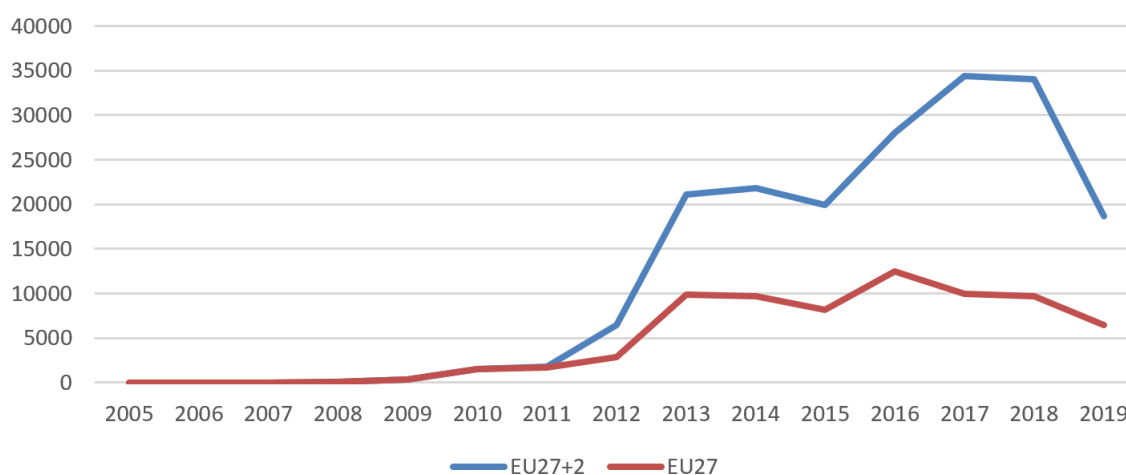


b)
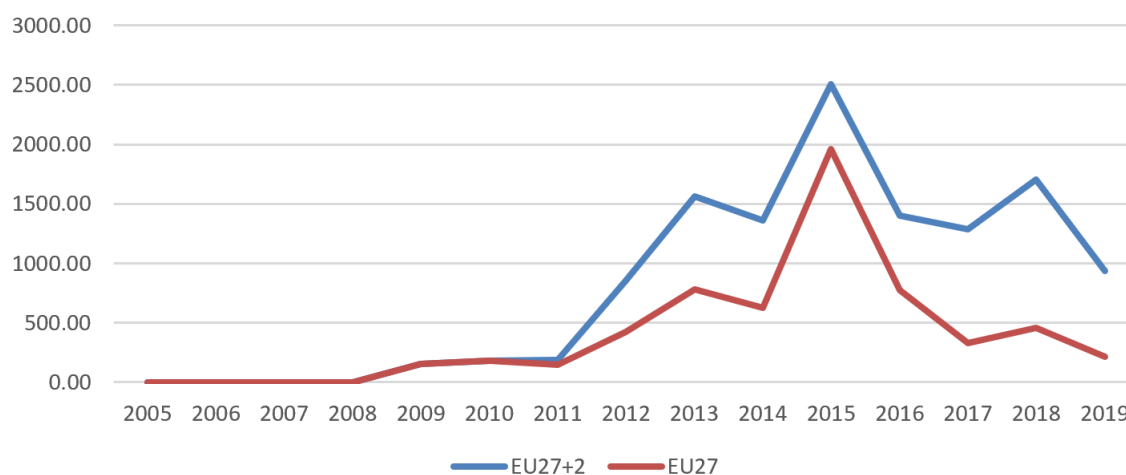


In recent years, there has been a marked decrease in both the number of new synthetic cannabinoids appearing on the market for the first time and the quantity of powders and herbal material containing synthetic cannabinoids seized in the European Union (Figure 2). Overall, these developments may in part reflect a decrease in large-scale processing of synthetic cannabinoids into herbal smoking mixtures, particularly the 'legal high' products that typified a large part of the new psychoactive substances market in Europe between 2008 and 2015. Nonetheless, relatively large amounts of bulk powders sufficient to make many

hundreds of thousands of street doses continue to be seized at Europe's borders each year, including throughout the COVID-19 pandemic.

## 3.3. Response to synthetic cannabinoids

Since 2016, a total of seven synthetic cannabinoids have been formally risk assessed by the EMCDDA. These were MDMB-CHMICA, in 2016; AB-CHMINACA, ADB-CHMINACA, 5F-MDMB-PINACA and CUMYL-4CN-BINACA, during 2017; and MDMB-4en-PINACA and 4F-MDMB-BICA, in 2020.

Across the world, many countries have implemented legal responses to control synthetic cannabinoids, with many countries having used or amended existing legislation and others having introduced innovative legal instruments including generic definitions (by chemical structure or pharmacological effects). An example is given in Box 1.

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**Box 1. Responses in Germany**

Legislation

The first identification of synthetic cannabinoids in herbal blends in Germany was reported by Auwärter and colleagues in 2008 (Auwärter et al., 2009). The synthetic cannabinoids detected were JWH-018, CP-47,497 and CP-47,497-C8. In January 2009, JWH-018, CP-47,497 and three of its homologues were scheduled under the German Narcotics Law because of their potential for abuse and their widespread use. In the following years, further synthetic cannabinoids emerged and were subsequently scheduled. Owing to the time lag between the emergence of new substances and their scheduling, distributors of new, unscheduled synthetic cannabinoids were prosecuted using the German Medicines Law. However, an appeal to the German Federal Supreme Court led to the European Court of Justice reviewing the classification of herbal products containing synthetic cannabinoids as medicines according to the Medicines Law. The European Court of Justice announced its decision on 10 July 2014 and concluded that, owing to the absence of therapeutic potential and the associated harms, the products could not be regarded as medicinal products as defined in Article 1 No 2 of Directive 2001/83/EC. The resulting regulatory gap led to the German 'Act to combat the distribution of new psychoactive substances' (NpSG) which became effective on 26 November 2016. In contrast to the Narcotics Law, which controls single substances as enumerated in the annexes of the law, the NpSG uses a generic approach by defining groups of substances based on their chemical structure. Particularly dangerous substances continue to be placed under the Narcotics Act and, if a substance falls under both laws, the stricter Narcotics Act is applied. The definition of a synthetic cannabinoid according to the NpSG comprises four structural elements: core structure, side chain, linker and a linked group. In the original version of the NpSG from November 2016, five core structural elements were defined. On 13 July 2019, an amendment came into force in which further core structures that had emerged on the market since 2016 were added. In response to the identification, shortly after, of cyclobutylmethyl side chains, which were not covered by the act, another amendment was prepared, which came into force on 9 July 2020. Meanwhile, synthetic cannabinoids carrying bicyclic side chains have emerged, and a third amendment is currently in preparation.

Impact on the market

Shortly after the inclusion of recently emerged synthetic cannabinoids in the annexes of the German Narcotics Act, new substances with structural modifications appeared on the market, presumably as a response by producers to the control measures. Common strategies were the substitution of a hydrogen atom by a fluorine atom at the terminal position of the side chain or modifications at the linked group.

In December 2016, Angerer et al. (2018a) test-purchased herbal smoking mixtures containing the synthetic cannabinoid CUMYL-PeGACLONE, which was not covered by the NpSG at that time. Furthermore, other synthetic cannabinoids with core structures not covered by the NpSG emerged on the German drug market, such as those containing 7-azaindole cores. CUMYL-PeGACLONE was added to the annex of the Narcotics Law in July 2018 by an amendment. With the emergence of its fluorinated analogue (5F-Cumyl-PeGaClone), the control measures in place were again circumvented. However, with the amendment to the NpSG of July 2019, azaindoles and the γ-carbolinones are now included, the latter by modifying the definition of the linker.

Following the introduction of the NpSG, some new synthetic cannabinoids that are not covered by the generic definitions have appeared on the drug market. These gaps in the definitions can be closed by amendments to the NpSG.

In the future, as producers continue their attempts to circumvent control measures in Europe and elsewhere, it is unclear what new synthetic cannabinoids may be developed and what risks they may pose to health, especially with regard to the potential introduction of remote structural candidates. It is important that early warning systems can detect such substances in a timely manner so that public health agencies can respond through timely and effective actions to prevent or reduce the risk of harm.

Figure 3 shows a heat map in which the relative positivity rate of 20 selected synthetic cannabinoids in urine samples analysed in the Institute of Forensic Medicine Freiburg (Germany) is presented for 2015 to 2019, including the five compounds described in detail in Annex 1 of this report (i.e. CUMYL-PeGACLONE, CUMYL-5F-P7AICA/5F-CUMYL-P7AICA, AB-FUBINACA, AMB-FUBINACA, and 5F-MDMB-PICA).

FIGURE 3

**Heat map presenting the relative positivity rate of 20 selected synthetic cannabinoids in urine samples analysed in the Institute of Forensic Medicine Freiburg (Germany), 2015 to 2019**
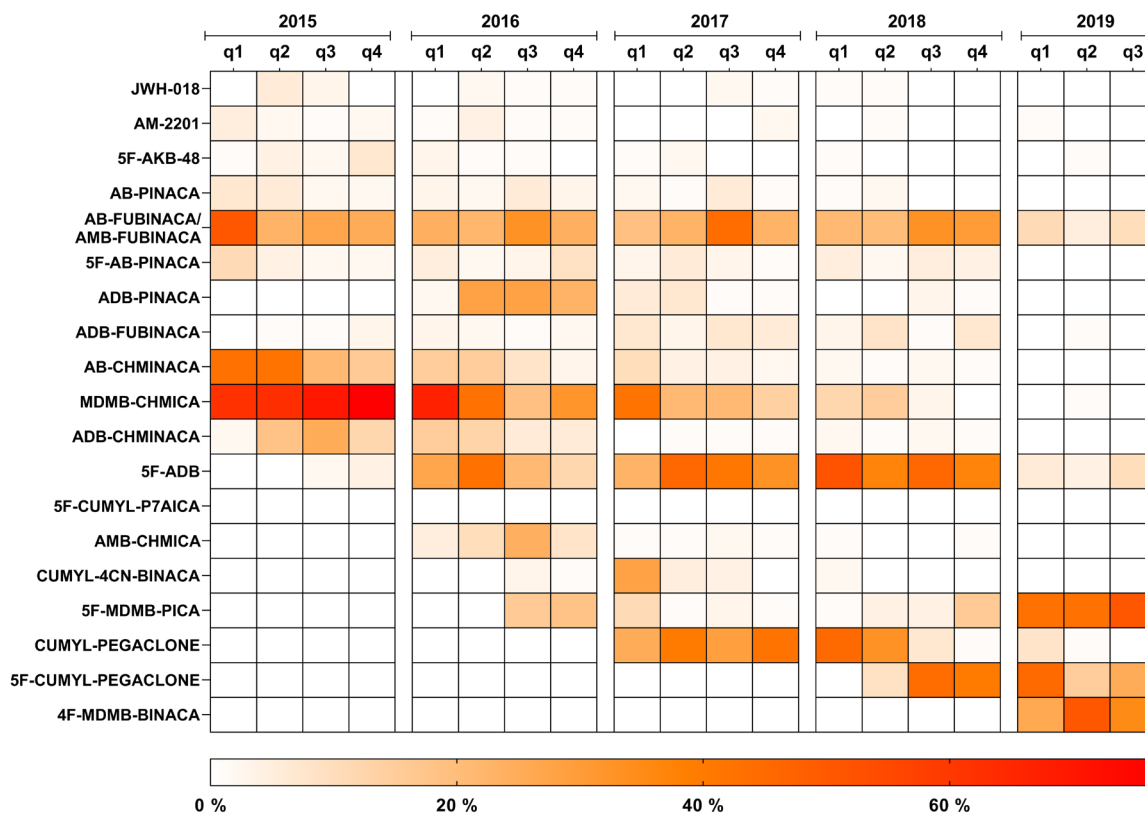


## 3.4. Replacement

Synthetic cannabinoids that may emerge as new psychoactive substances

In the past, legal restrictions on synthetic cannabinoids – regardless of whether a substance-by-substance approach or a generic approach was used – led to the continual appearance of structurally modified compounds, as shown by many examples, such as the γ-carbolinones (e.g. CUMYL-PeGACLONE) or the more recent norbornyl derivatives (e.g. Cumyl-NB-MeGaClone, also known as Cumyl-BC-HpMeGaClone-221). A different strategy for the drug market could be the use of previously described 'classical' or 'non-classical' synthetic cannabinoids that show higher structural similarity to $\Delta^9$-THC (Howlett et al., 2002). As a possible reaction to the ongoing amendments to the German NpSG, *O*-774 (7-[(6aR,10aR)-1-hydroxy-6,6,9-trimethyl-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromen-3-yl]-7-methyloctanenitrile) (Figure 4) has been discussed as a compound of interest in relevant online discussion boards. However, such structures might not be very attractive for producers owing to comparatively complicated and expensive syntheses.

Another alternative might be the synthesis of synthetic cannabinoids with new, non-regulated core structures as described in the patent literature. For example, Diaz et al. (2017) and Leftheris et al. (2003) described tricyclic or bicyclic heteroaromatic compounds as depicted in Figure 5a and b.

FIGURE 4

**Chemical structure of O-774**
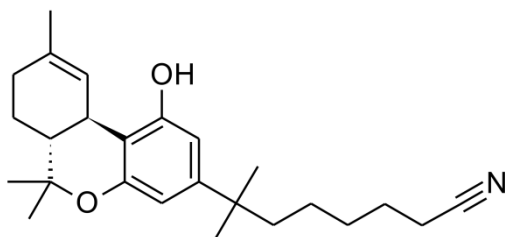


FIGURE 5

**Potential core structures of synthetic cannabinoids that might be used for the production of new psychoactive substances, as proposed by (a) Diaz et al. (2017) and (b) Leftheris et al. (2003)**



a)

9*H*-β-carboline

2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole

2,3,4,9-tetrahydro-1*H*-β-carboline

b)

2,3-dihydro[1,4]oxazino [2,3,4-*h*]indazole

2,3-dihydro[1,4]oxazino [2,3,4-*h*]indole

1,5,6,7-tetrahydro-4*H*-pyrrolo[3,2-*c*]pyridin-4-one
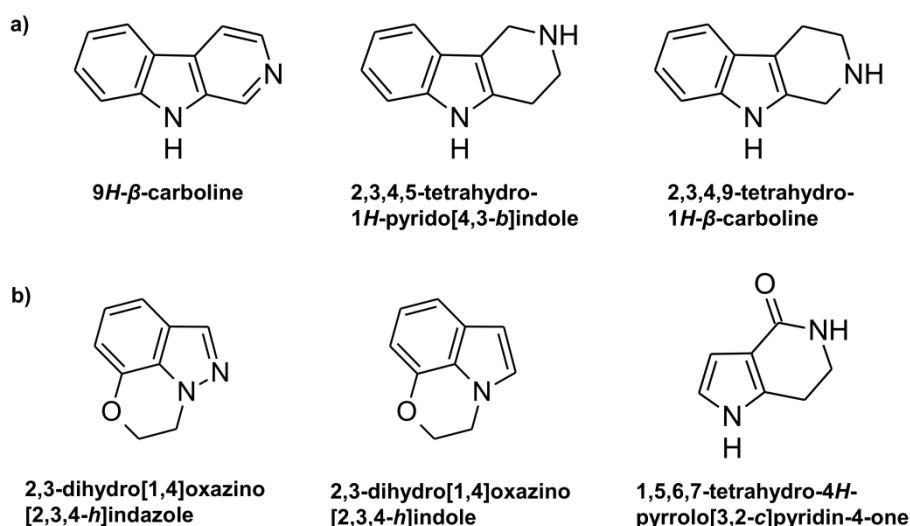
Although not likely, other strategies could include targeting the degradation of endocannabinoids by inhibiting fatty acid amide hydrolase (FAAH) enzymes or the reuptake of endocannabinoids by uptake inhibitors such as LY-2183240 (*N*,*N*-dimethyl-5-[(4-phenylphenyl)methyl]-1-tetrazolecarboxamide), which has already been detected in 'legal high' products in Japan (Uchiyama et al., 2014).

Finally, the market could shift towards compounds already controlled by national law, depending on regulations in the producing countries. This was seen, for example, in Germany in the shift from 5F-ADB to 5F-MDMB-PICA and 4F-MDMB-BINACA in 2019 after a ban on 5F-ADB was introduced in China (Halter et al., 2020).

# 4. Physical, chemical and pharmacological description

## 4.1. Physical and chemical description

Structural/chemical classification

Synthetic cannabinoids derive from chemically quite different classes of substances, because binding and activation of the cannabinoid receptors can be achieved with a wide range of molecules. Historically, the first synthetic cannabinoids that occurred on the drug market were cyclohexylphenols (e.g. CP-47,497-C8) and naphthoylindoles (e.g. JWH-018). Substances from the broader group of aminoalkylindoles, including halogenated derivatives and linker groups other than carbonyl (e.g. carboxyl), were then introduced (e.g. AM-2201, 5F-UR-144 (XLR-11), UR-144 and AM-2201 carboxylate analogue quinolinyl derivative (5F-PB-22)). Later, indole derivatives with amino acid-like groups linked via a carboxamide linker (e.g. MDMB-CHMICA and 5F-MDMB-PICA) and their indazole analogues (e.g. 5F-AKB48, AB-CHMINACA, AB-PINACA, 5F-MDMB-PINACA (5F-ADB) and AB-FUBINACA) emerged and began to dominate the market. Recent developments include the introduction of cumyl derivatives, often linked to indoles or indazoles by a carboxamide linker (e.g. CUMYL-5F-PINACA/5F-CUMYL-PINACA), 7-azaindoles (e.g. 5F-AB-P7AICA and CUMYL-5F-P7AICA/5F-CUMYL-P7AICA), carbazoles (e.g. EG-018 and MDMB-CHMCZCA), *γ*-carbolinones (e.g. CUMYL-PeGACLONE, 5F-Cumyl-PeGaClone, Cumyl-CH-MeGaClone) and compounds with modified side chains (e.g. CUMYL-CBMINACA or Cumyl-NB-MeGaClone).

Identification and analytical profile

Comprehensive guidance on the recommended methods for use in forensic laboratories for the identification and analysis of synthetic cannabinoids in seized materials is provided in the United Nations Office on Drugs and Crime manual (Tettey et al., 2021).

*Physical description*

Synthetic cannabinoids in their pure form are usually described as white or yellowish, odourless, crystalline powders. Less pure substances may show brownish discoloration and have an unpleasant 'chemical' smell due to impurities from synthesis and solvent residues. Most synthetic cannabinoids are highly lipophilic and generally insoluble in water, but are soluble in aliphatic alcohols and non-polar organic solvents such as methanol, ethanol, acetonitrile, ethyl acetate, acetone or isooctane (Tettey et al., 2021). Typical octanol−water partition coefficients (expressed as log $K_{OW}$ or log $P$) as predicted *in silico* (ACD/Labs Percepta Platform – PhysChem Module) range between 4.5 (MDMB-CHMINACA) and 7 (JWH-018). Melting points typically range from 55 °C (5F-AKB48) to 145 °C (AM-2233).

*Chemical stability*

In general, pure and dried synthetic cannabinoids can be regarded as chemically stable. However, in solutions or when heated they can be unstable, in particular when containing

structural elements prone to hydrolysis, such as esters or primary amides, or when constrained ring moieties are present (e.g. UR-144).

Hutter et al. (2013) analysed smoke condensates of cigarettes laced with the synthetic cannabinoid AM-2201 and found small amounts of JWH-018 and JWH-022 as thermal degradation products. In another study, smoking of 3,5-AB-CHMFUPPYCA (AB-CHMFUPPYCA) was shown to result in thermal cleavage of the terminal amide (Franz et al., 2017a). A further study, by Franz et al. (2016), showed that 5F-PB-22 (AM-2201 carboxylate analogue quinolinyl derivative) and AB-CHMINACA undergo ester and amide cleavage, respectively, when smoked, and it was highlighted that the cleavage products were also formed during metabolism, leading to the potential for misinterpretation of results, particularly of hair analysis. Nash et al. (2019) recently showed that CUMYL-PeGACLONE is thermally degraded by loss of the cumyl moiety.

Kneisel et al. (2013) tested the stability of 11 synthetic cannabinoids in oral fluid stored in glass or polypropylene tubes. They pointed out that adsorption at the plastic surface might lead to considerable loss of analytes. Hess et al. (2017) investigated the freeze–thaw stability of 82 synthetic cannabinoids and found that most were stable in spiked serum samples for at least 1 month at – 20 °C when undergoing three freeze–thaw cycles. However, substances of the 'AMB' and the 'SDB' type showed instability at higher temperatures, probably due to hydrolysis (Hess et al., 2017). Fort et al. (2017) investigated the stability of 5F-UR-144 (XLR-11), UR-144, AB-PINACA and AB-FUBINACA in spiked human whole-blood specimens. They found all analytes to be stable for at least 12 weeks when stored frozen (– 20 °C). However, stored at ambient temperature (22 °C) or refrigerated (4 °C), 5F-UR-144 (XLR-11), but not the other three analytes, showed significant degradation. Kevin et al. (2019a) investigated the thermal degradation of various carboxamide synthetic cannabinoids (CUMYL-PICA, 5F-CUMYL-PICA (CUMYL-5F-PICA), AMB-FUBINACA, MDMB-FUBINACA, NNEI (AM-6527) and MN-18) and found a range of potentially toxic degradants (naphthalene, 1-naphthylamine, toluene and cyanide) at the temperatures typically reached when smoking herbal material. Stability varied among the compounds investigated, with some showing 'extensive degradation' at temperatures between 400 and 600 °C.

*Analytical profile*

Owing to the presence of conjugated π-electron systems, synthetic cannabinoids can generally be detected by ultraviolet (UV) spectroscopy; however, UV spectra can be very similar for compounds with the same chromophore, which then requires a chromatographic separation for unambiguous identification. Mass spectrometric techniques, nuclear magnetic resonance (NMR) and infrared or Raman spectroscopy are also suitable for identification.

It is reported that heating synthetic cannabinoids containing a tetramethylcyclopropyl ring, such as UR-144, as occurs during smoking or on exposure to high temperatures inside a gas chromatography–mass spectrometry (GC-MS) injection port, results in opening of the cyclopropyl ring, which is thermally unstable, creating the thermodynamic product 2,3,3-trimethyl-1-butene side chain (Adamowicz et al., 2013; Eckre et al., undated; Grigoryev et al., 2013a; Kaizaki-Mitsumoto et al., 2017; Thomas et al., 2017). Thermal rearrangement

produces two peaks with similar mass spectra when using GC-MS, and it has been suggested that it should be treated as a GC-MS artefact (Adamowicz et al., 2013; Kaizaki-Mitsumoto et al., 2017). During analysis, it was confirmed that UR-144 is almost completely changed to its degradant by heating at 300 °C for 10 minutes (Kaizaki-Mitsumoto et al., 2017). However, ring-opening reactions in substances containing tetramethylcyclopropyl rings have also been reported to occur during prolonged storage and not only during heating (Creary et al., 1977; Thomas et al., 2017).

It is also reported that the use of solvents such as methanol or ethanol for extraction of cannabimimetic quinolinyl carboxylates, such as PB-22 (JWH-018 quinolinecarboxylate analogue), 5F-PB-22 (AM-2201 carboxylate analogue quinolinyl derivative) and FUB-PB-22, may cause transesterification to occur (Tettey et al., 2021). 8-Quinolinol has been observed as a degradation product during GC-MS analysis (Uchiyama et al., 2013a).

For the analysis of biological samples, liquid chromatography–tandem mass spectrometry (LC-MS/MS) or liquid chromatography–high-resolution mass spectrometry (LC-HRMS) is usually applied after liquid–liquid or solid-phase extraction. Given the immense structural variability of synthetic cannabinoids, the dynamic market and the expected concentrations in the low or sub-nanograms per millilitre range, immunoassays cannot be recommended to screen biological materials such as serum or urine (Franz et al., 2017b). Another group claimed 'good diagnostic efficiency' for an enzyme-linked immunosorbent assay (ELISA) kit (Spinelli et al., 2015), but it has to be acknowledged that the study was carried out retrospectively, and by the time of the study the substances available on the market had already changed. In contrast to blood or serum samples, in urine samples the parent compound is often not detectable after exposure to synthetic cannabinoids. Therefore, in abstinence screening, the main metabolites have to be targeted. Most laboratories perform an enzymatic cleavage before the analysis and target the main phase I metabolites.

Methods and chemical precursors used for the manufacture

Aminoalkylindoles, aminoalkylindazoles and aminoalkyl-7-azaindoles are currently the most prevalent synthetic cannabinoids on the drug market, and routes of synthesis are well described in the patent literature. Typical precursors are 1-alkylindoles, 1-alkylindazoles and 1-alkyl-7-azaindoles (alkyl is often a pentyl, 5-fluoropentyl or cyclohexylmethyl, but can also be replaced by 4-fluorobenzyl or other substituents), which can be easily obtained by N-alkylation of indole, indazole or 7-azaindole using, for example, an alkyl bromide. These can be acylated at C3 by a Friedel–Crafts reaction using activated carboxylic acids (e.g. 1-naphthoyl chloride, which reacts to JWH-018 with 1-pentylindole). For the synthesis of carboxamide-type synthetic cannabinoids, Banister et al. (2016) described an effective pathway using trifluoroacetic acid anhydride for the formation of the 3-carboxy-alkylindole (can also be applied to indazoles and 7-azaindoles) followed by establishing the amide bond (e.g. the reaction of cyclohexylmethylindazole with methyl *tert*-leucinate leads to MDMB-CHMINACA).

There is no information on the actual manufacturing methods used to make the synthetic cannabinoids that have been identified on the drug market in Europe. However, the synthesis

of 5F-MDMB-PICA and 5F-MDMB-PINACA, for example, has been described by Banister et al. (2016). The synthesis of 5F-MDMB-PICA starts with indole, which is reacted with methyl L-*tert*-leucinate, yielding (*S*)-5F-MDMB-PICA. The synthesis of 5F-MDMB-PINACA starts with methyl 1*H*-indazole-3-carboxylate, which is reacted with methyl L-*tert*-leucinate, yielding (*S*)-5F-MDMB-PINACA. The (*R*)-enantiomers of both substances may be synthesised under identical conditions using methyl D-*tert*-leucinate instead of methyl L-*tert*-leucinate. Using methyl *tert*-leucinate as a racemate would lead to the production of the racemic substance.

The synthesis of 4F-MDMB-BICA may be carried out in the same way as the synthesis of its higher homologue, 5F-MDMB-PICA (EMCDDA, 2020a), and synthesis of MDMB-4en-PINACA may be carried out in the same way as the synthesis of 5F-MDMB-PINACA (EMCDDA, 2020b).

Potential precursors of 4F-MDMB-BICA are indole-3-carboxylic acid, indole-3-carboxylic acid methyl ester, indole, L-*tert*-leucine methyl ester (for the synthesis of the (*S*)-enantiomer) and 1-bromo-4-fluorobutane (EMCDDA, 2020a). Potential precursors of MDMB-4en-PINACA are methyl 1*H*-indazole-3-carboxylate, 5-bromo-1-pentene and L-*tert*-leucine methyl ester (for the synthesis of the (*S*)-enantiomer; EMCDDA, 2020b).

## 4.2. Physical and pharmaceutical form

Currently, three main types of products containing synthetic cannabinoids are sold on the drug market in Europe: smoking mixtures, e-liquids and papers. Most commonly, synthetic cannabinoids are sprayed onto or mixed with herbal plant material or tobacco to produce a mixture that is then smoked as a joint or inhaled from a vaporiser or bong. In recent years, there has also been an increase in e-liquid products, in which a solution of the synthetic cannabinoid is mixed with a solvent, which is then vaped using an electronic cigarette (Figure 6).

FIGURE 6

**E-liquid containing 5F-MDMB-PICA intended for vaping in an electronic cigarette, seized by Italian Carabinieri in June 2020**



Photo © Italian National Institute of Health.

In addition, it appears that in some countries an increasingly common method of smuggling synthetic cannabinoids into prison is by means of impregnating paper with the cannabinoids – including letters, greeting cards, photographs, children's drawings and printouts (Figure 7) (EMCDDA, 2020c). The impregnated paper is then smoked with tobacco or vaped using an electronic cigarette. To a lesser extent, users may prepare their own similar products using cannabinoids in powder form purchased from a vendor or dealer. Paper impregnated with synthetic cannabinoids can pose a high risk of poisoning because the amount of cannabinoid can vary greatly in different parts of the paper (Figure 8) (Angerer et al., 2018b; Norman et al., 2020).

FIGURE 7

**A4-sized printouts, seized in a prison in Scotland, United Kingdom, during 2019, that were impregnated with MDMB-4en-PINACA and 5F-MDMB-PICA**
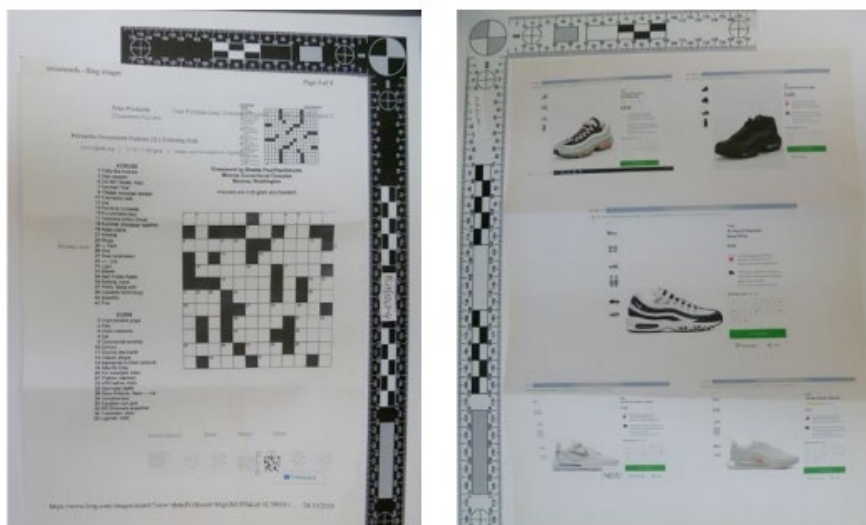


Photos © Dr Craig McKenzie, Leverhulme Research Centre for Forensic Science, University of Dundee, United Kingdom.

FIGURE 8

**MDMB-CHMICA concentration mapping across impregnated paper showing a significant variation in concentration across the paper sheet**
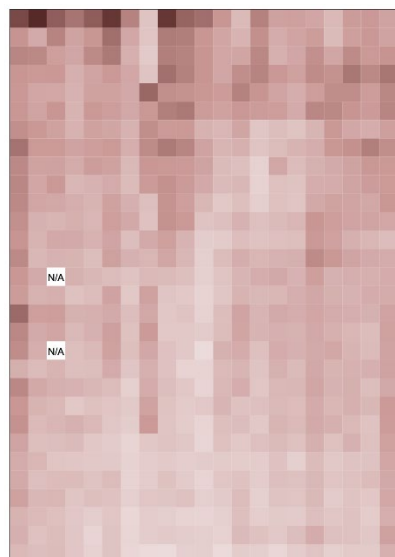


*Source:* Originally presented by Angerer et al. (2018b)
Photo © Forensic Toxicology Department, Institute of Forensic Medicine, Medical Center, University of Freiburg, Germany.

To a much smaller extent, clothing and other textiles impregnated with synthetic cannabinoids have been also reported (Figure 9).

FIGURE 9

**Socks impregnated with 4F-MDMB-BINACA seized by Lithuanian police in January 2019**



Photo © Forensic Science Centre of Lithuania.

Production of smoking mixtures

The most common type of products containing synthetic cannabinoids are herbal smoking mixtures. For the production of smoking mixtures, the synthetic cannabinoids are usually dissolved in an organic solvent (e.g. acetone or ethanol) and sprayed onto or mixed with the plant material. Plants such as damiana (*Turnera diffusa*) and marsh-mallow (*Althaea officinalis*) are often used as the herbal basis owing to their low cost. Cement mixers have sometimes been used to mix the plant material with the dissolved synthetic cannabinoids (EMCDDA, 2016a). The soaked plant material is subsequently dried and packaged in units of typically 1–5 g before being sold to consumers. The process of adding the synthetic cannabinoids to the plant material can lead to products containing dangerous amounts of substances. 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 in both products that contain toxic amounts of the substances in general (Ernst et al., 2017; Frinculescu et al., 2017; Langer et al., 2014: Langer et al., 2016) and products in which the cannabinoids are clumped together, forming highly concentrated pockets of the synthetic cannabinoid within the plant material (Frinculescu et al., 2017; Moosmann et al., 2015; Schäper, 2016).

Production of e-liquids

e-Liquids (liquids used in electronic vaping devices) containing synthetic cannabinoids have become increasingly popular over the past few years, coinciding with the wider availability and use of e-cigarettes and vaporisers. e-Liquids generally consist of a polar mixture of propylene glycol, vegetable glycerin and ethanol; aroma compounds; and an active substance (e.g. synthetic cannabinoids; Münster-Müller et al., 2020). A prerequisite for the production of e-liquids is the solubility of the synthetic cannabinoids in the liquid base (usually propylene glycol and/or glycerol). Therefore, often relatively polar compounds such as CUMYL-5F-PINACA (5F-CUMYL-PINACA) (Angerer et al., 2019; Münster-Müller et al., 2020) are used to prepare such formulations.

Production of impregnated papers

An increasingly common method of smuggling synthetic cannabinoids into prisons in some countries is by impregnating paper with the cannabinoids. The variation in synthetic cannabinoid concentration in these papers has been attributed to the method employed for the preparation of synthetic cannabinoid-impregnated papers, with the synthetic cannabinoid solution likely to have been added to the centre of the paper and diffusing outwards (Norman et al., 2020). In a simulated test, the authors demonstrated that the distribution of a synthetic cannabinoid across an impregnated paper was less variable when the paper was laid flat than when hung up to dry, which method resulted in concentrations considerably higher at the bottom of the papers hung up to dry (Norman et al., 2020).

Another study investigated preparation techniques of soaking paper with synthetic cannabinoid solutions with a focus on visibility of this manipulation. The authors demonstrated that soaking paper with a 25 mg/ml MDMB-CHMICA solution did not lead to visible changes. In contrast, soaking with a 100 mg/ml solution produced visible anomalies on the paper (Angerer et al., 2018b).

## 4.3. Pharmacology

Endocannabinoid system and cannabinoid receptors

The expression of two types of cannabinoid receptors ($CB_1$ and $CB_2$) plays a fundamental part in the human endocannabinoid system, with endogenous compounds being referred to as endocannabinoids (e.g. anandamide and 2-arachidonoylglycerol), which bind to these receptors and activate them. While $CB_1$ receptors are most abundant in central neuronal tissue (with low abundance in peripheral tissue, e.g. endocrine cells), $CB_2$ receptors are mainly expressed in immune cells. The psychological and physiological functions influenced by the modulation of $CB_1$ receptor activity include pain perception, appetite, cognition, motivation, mood, memory and neuromotor functioning. The influence on these functions can be explained by the main localisations of $CB_1$ receptors in the brain (the cortex, amygdala, hippocampus, basal ganglia and cerebellum). The psychotropic effects of cannabinoid receptor agonists are mainly mediated through stimulation of $CB_1$ receptors. In contrast, stimulation of $CB_2$ receptors is suggested to result in anti-inflammatory and analgesic effects, and $CB_2$ receptors are regarded as a potential target for the development of medicines for the treatment of pain and inflammation (Greco et al., 2014). Selective agonists at $CB_2$ receptors are believed to have promising therapeutic potential while avoiding the adverse psychotropic effects of $CB_1$ agonists.

The cannabinoid receptors are members of the family of $G_{i/o}$ protein-coupled receptors (GPCRs). In most tissues and cells, activation of $CB_1$ receptors inhibits adenylyl cyclase, resulting in a decrease in the intracellular second messenger cyclic adenosine monophosphate (cAMP). Following this, depending on the type of neuron, different ion channels are regulated, leading to the inhibition of glutamatergic, GABAergic, glycinergic, cholinergic, noradrenergic or serotoninergic neurotransmission (Szabo and Schlicker, 2005). The inhibition of neurotransmitter release may lead to excitatory (GABAergic neurons) or inhibitory (glutamatergic) effects. However, evidence exists showing that some isoforms of

the cannabinoid receptors are $G_s$PCRs, thus leading to stimulation of adenylyl cyclase (Mukhopadhyay et al., 2000). Additional pathways (e.g. leading to the activation of mitogen-activated protein kinases) have been described (Powles et al., 2005). Some studies also suggest that $CB_1$ receptor activation might lead to tissue-dependent formation of intra- and transcellular dimers, oligomers and heterodimers as a potential explanation for different pharmacological outcomes in various tissues (Wager-Miller et al., 2002). Although it has become clear in recent decades that the endocannabinoid system regulates numerous somatic and mental functions, the complexity of the underlying biomolecular mechanisms remains to be investigated.

Cannabinoid receptors are activated by the endogenous eicosanoids anandamide and 2-arachidonylglycerol. While anandamide acts as a selective agonist at $CB_1$ receptors, 2-arachidonylglycerol shows affinity to both $CB_1$ and $CB_2$ receptors. The promiscuity and pleiotropic effects of these endocannabinoids in the central nervous system have been shown through experiments with $CB_1$ receptor knockout mice by Di Marzo et al. (2000).

Stimulation of $CB_1$ receptors also leads to the association with intracellular β-arrestin. These complex molecules play a crucial role in the desensitisation of GPCRs. Binding of β-arrestin to a receptor initiates internalisation of the GPCR (Jin et al., 1999; Kouznetsova et al., 2002), a compensatory process that is believed to play a role in the development of tolerance. This biomolecular mechanism is often observed after the activation of $CB_1$ receptors through efficacious cannabinoid receptor agonists (Hsieh et al., 1999). Case reports suggest that tolerance and withdrawal symptoms may develop quickly after repeated consumption of synthetic cannabinoids (Zimmermann et al., 2009).

Inactivation of endocannabinoids, especially in the synaptic gap, is catalysed by FAAH (Deutsch and Chin, 1993). FAAH has turned out to be a possible target for the indirect activation of the endocannabinoid system. Inhibitors of this enzyme can potentially lead to an increase in endocannabinoid concentrations in the central nervous system and produce cannabis-like effects. In 2016, a clinical trial (phase I) investigating the clinical safety of an inhibitor of FAAH (BIA-102474) was halted after 4 out of 90 test subjects developed severe neurological injuries and one death case (Chin, 2016). The mechanism responsible for these adverse events remains unknown. Of note is that two FAAH inhibitors, URB597 and LY2183240, have been detected on the European drug market, including in 'legal high' products (EMCDDA, 2016b).

Pharmacodynamics

Synthetic cannabinoids are functionally similar to the main active substance of $Δ^9$-THC found in *Cannabis sativa*. While THC acts as a partial agonist at the cannabinoid receptors, synthetic cannabinoids are often full agonists at $CB_1$ and sometimes $CB_2$ receptors (see the subsection '*In vitro* studies'). In the 1990s, the identification of cannabinoid receptors and their endogenous ligands triggered an exponential growth of studies exploring the endocannabinoid system. The $CB_1$ receptor turned out to be a promising target for a wide range of pathological conditions. Activation of the neuronal endocannabinoid system showed potential for the treatment of a variety of diseases, ranging from neuropathic pain and

neuromotor disorders, such as amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease and Huntington's disease, to conditions such as anorexia and emesis (e.g. induced by chemotherapy). However, the therapeutic application of cannabinoid receptor modulators is still limited to pure $\Delta^9$-THC (dronabinol – active ingredient of Marinol®); nabilone (e.g. Cesamet®), which is chemically similar to $\Delta^9$-THC; cannabidiol (e.g. Epidiolex®); and *Cannabis sativa* (the pure herbal drug, usually the flowers of the female plant) and its extracts (e.g. Sativex®) (EMCDDA, 2018a).

Although synthetic cannabinoids were first developed with the intention of treating the previously stated diseases and their symptoms, most of them are not used as therapeutics owing to their high potency at the $CB_1$ receptor (high affinity and efficacy), which has been associated with psychoactive side effects with the potential for abuse, thus resulting in an unfavourable risk–benefit profile for medical applications.

Since the endocannabinoid system turned out to be a promising target for the treatment of eating disorders such as anorexia, it seems plausible that antagonism of cannabinoid receptors is a reasonable approach for the treatment of obesity. Rimonabant (Acomplia®), a selective inverse $CB_1$ receptor agonist, was developed for the treatment of patients with a body mass index of over 27 kg/m$^2$. The approval for rimonabant as a medicine was withdrawn in 2008 by the European Medicines Agency owing to its psychiatric side effects (depression and anxiety). While rimonabant increases the likelihood of depressive and anxiogenic conditions, this effect is more pronounced in patients with a predisposition to depression, suggesting that blocking $CB_1$ receptors through an inverse agonism is more likely to intensify existing conditions rather than to cause them in healthy individuals (Moreira and Crippa, 2009). In contrast to a neutral antagonist, rimonabant acts as an inverse agonist at the $CB_1$ receptor. This means that not only does it prevent the activation of the receptor, but it also decreases the constitutive activity of the neuronal endocannabinoid system (Erdozain et al., 2012; Fong, 2014), and this may explain the serious psychiatric side effects of rimonabant. A decrease in $CB_1$ receptor activity implies the presence of constitutive or basal activity, which was shown in both expression systems and native tissues in the absence of endocannabinoids (Pertwee, 2004). Although cannabinoid receptor antagonists did not pass the risk–benefit assessment for the treatment of obesity, they might be of interest for the use as antidotes in cases of synthetic cannabinoid poisoning with highly potent compounds (described in Section 5.1, 'Acute toxicity').

*In vitro studies*

The pharmacological characteristics of many synthetic cannabinoids have been investigated in *in vitro* receptor binding studies. While receptor affinity describes the ability of a ligand to bind to the receptor, the intrinsic activity describes the effects produced after binding and their strength. To illustrate this principle, rimonabant, an inverse antagonist at the $CB_1$ receptor, shows a high binding affinity towards $CB_1$ receptors, but leads to no activation of the $G_{i/o}$PCR. Since the affinity of rimonabant to the receptor in its inactive state is much higher than in the active state (and vice versa for synthetic cannabinoids), the activity of $CB_1$ receptors is decreased in its presence.

For the determination of receptor binding affinity, the most commonly used method is the competitive ligand-binding assay using radioactively labelled cannabinoid receptor agonists (e.g. [$^3$H]CP-55,940, [$^3$H-HU]243 or [$^3$H]WIN-55,212-2). Firstly, the affinity of the competitive radioligand towards the respective receptor needs to be determined ($K_D$ through saturation binding assay). Secondly, the competitive binding assay is conducted with varying concentrations of the test compound in the presence of the radioligand (bound to the receptor), which is then replaced by the test compound in a concentration-dependent manner. The turning point of the resulting binding curve represents the half-maximal inhibitory concentration (IC$_{50}$). The calculation of the $K_i$ value is performed with the Cheng–Prusoff equation (parameters: $K_D$, IC$_{50}$ and the concentration of radioligand). The resulting $K_i$ value is a measure of the affinity of a test compound towards the receptor investigated (Cheng and Prusoff, 1973).

The determination of the intrinsic activity of a test compound can be achieved through various assay systems. The most common methods are the [$^{35}$S]GTP$\gamma$S-mediated receptor activation assay (Nakajima et al., 2011), the fluorometric imaging plate reader (FLIPR) membrane potential assay (Banister et al., 2015) and the cAMP accumulation assay (Drabczyńska et al., 2011). These assays reveal concentration-dependent activation/inactivation of a GPCR caused by a ligand (half-maximal effective concentration (EC$_{50}$) values).

The properties of $\Delta^9$-THC in these assays are shown in Table 1. The activation of human CB$_1$ receptors is observed with EC$_{50}$ values between 154 nM and 171 nM. $\Delta^9$-THC acts as a partial agonist at the CB$_1$ receptors (61 % maximal effect when compared to the maximal effect of CP-55,940). While the data regarding intrinsic activity appear to be reproducible, investigations on receptor-binding affinity have produced widely varying K$_i$ values for $\Delta^9$-THC (3.87–80.3 nM). This finding should be kept in mind when comparing affinity data received under different assay conditions (human versus rat or mouse CB$_1$ receptors; assay principle; and used concentrations).

TABLE 1

**Pharmacological properties of $\Delta^9$-THC towards $CB_1$ receptors**

| Receptor affinity ($K_i$ in nM) | Receptor activation ($EC_{50}$ in nM) | Receptor types | Assay principle | Source | $K_D$ (in nM) of the radioligand |
|---|---|---|---|---|---|
| | 171 | Human (murine neuroblastoma cells) | FLIPR membrane potential | Banister et al. (2016) | |
| | 154 (maximal effect compared to CP-55,940 = 61 %) | Human (fragments of human embryonic kidney cell membrane) | [$^{35}$S]GTPγS | Own data | |
| 3.87 | | Human (Chinese hamster ovary cells) | [$^3$H]CP-55,940 | Hess et al. (2016) | 2.40 |
| 5.05 | | Human (Chinese hamster ovary cells) | [$^3$H]CP-55,940 | Iwamura et al. (2001) | 0.57 |
| 8.33 | | Mouse | [$^3$H-CP-55,940 | Iwamura et al. (2001) | 0.70 |
| 13.5 | | Rat | [$^3$H]CP-55,940 | Iwamura et al. (2001) | 0.16 |
| 6.6 | | Human (fragments of human embryonic kidney cell membrane) | [$^3$H]CP-55,940 | Own data | — |
| 80.3 | | Rat | [$^3$H]HU243 | Rhee et al. (1997) | — |
| 40.7 | | Rat | [$^3$H]CP-55,940 | Compton et al. (1992) | 0.68 |
| 10.2 | | Rat | [$^3$H]WIN-55212-2 | Kuster et al. (1993) | 2.00 |

*Animal studies*

One of the most common animal models for investigating the pharmacological potency of cannabinoids is the observation of behavioural and physiological changes in mice. Inhibition of locomotor activity, antinociception, hypothermia and catalepsy are typical effects of cannabinoids and are known as the 'tetrad' of cannabimimetic effects in the mouse model. Another technique commonly employed in animal studies is known as the drug discrimination model, in which animals are trained to discriminate between two substances, placebo and $\Delta^9$-THC, injected intraperitoneally, using food reinforcement. The animals are first conditioned, using food rewards, to produce a particular response to a stimulus while under the influence of $\Delta^9$-THC and a different response to the same stimulus when given the placebo. Thus, the pharmacological effect of the cannabinoid controls the animal's behaviour, making them produce the appropriate response in order to gain a food reward. The choice the animal takes after application of a test compound has shown to be conclusive

for the similarity of the effects between the substance the mice were trained with and the test compound (e.g. synthetic cannabinoids compared to $\Delta^9$-THC; Martin et al., 1991).

Poklis et al. (2012) studied the effects caused by inhalation of the smoke of a herbal blend (0.2 g), containing JWH-018 (7.2 mg) as the active ingredient, in mice. The effects observed in the animals tested (hypothermia, catalepsy, Straub tail and ptosis) were consistent with $CB_1$ receptor activation. Similar observations after inhalation of JWH-018 (hypomotility, antinociception, catalepsy and hypothermia) were made by Wiley et al. (2017) and Wiebelhaus et al. (2012). Interestingly, in the latter study, 2.7 mg of JWH-018 produced antinociceptive and hypothermic effects that were similar to the effects caused by 14.8 mg of $\Delta^9$-THC (in marijuana). MDMB-FUBINACA and 5F-AMB (5F-AMB-PINACA) induced dose-dependent hypothermia and bradycardia in mice (0.1–1 mg/kg body weight). The effects were reversed by pretreatment with the inverse $CB_1$ receptor agonist rimonabant (Banister et al., 2016).

In drug discrimination studies, Järbe et al. (2011) examined synthetic cannabinoids for their cannabimimetic ($\Delta^9$-THC-like) effects. JWH-018 and AM-5983 appeared to be eight times more potent than $\Delta^9$-THC, followed by AM-2233 (twice as potent as THC), and equipotent to WIN-55-212-2. While the effects of JWH-018, AM-5983 and AM-2233 were completely blocked by pre-administration of rimonabant, WIN-55-212-2 seemed to interact differently with rimonabant, probably because these two compounds bind to different sites on the $CB_1$ receptor. Ginsburg et al. (2012) used $\Delta^9$-THC-trained monkeys for the evaluation of JWH-018 (which is about three to four times as potent as $\Delta^9$-THC) and JWH-073 (which is approximately equipotent to $\Delta^9$-THC). The duration of action was shown to be 4 hours for $\Delta^9$-THC, 2 hours for JWH-018 and 1 hour for JWH-073. The authors concluded that these findings suggested a greater dependence liability for the synthetic cannabinoids investigated.

Cannabinoids are also known to be effective antiemetic drugs. Nabilone (e.g. Cesamet®) and dronabinol (e.g. Marinol®) are approved for the treatment of chemotherapy-induced nausea and vomiting (EMCDDA, 2018a). As rats are unable to vomit, a selective measure for nausea in this species is the state of conditioned gaping. Studies show that gaping under the influence of emetic agents can be effectively erased by the application of natural and synthetic cannabinoids. Parker and Mechoulam (2003) studied the antiemetic effects of $\Delta^9$-THC and the synthetic cannabinoid HU-210 in rats. They showed that these substances interfered with the establishment and expression of lithium-induced conditioned gaping in rats. Furthermore, the antiemetic effects were reversed by the application of the $CB_1$ receptor antagonist rimonabant.

## *Human studies*

Systematic research on the pharmacology of synthetic cannabinoids in humans has not been published so far.

However, there are some reports on self-experiments conducted with synthetic cannabinoids. Auwärter et al. (2009) smoked a herbal blend containing JWH-018 and CP-47,497-C8 and reported cannabis-like effects that began 10 minutes after smoking and

lasted for about 6 hours. Teske et al. (2010) reported on a self-experiment that involved the smoking of about 4 mg of JWH-018 by cannabis-naive individuals, resulting in cannabis-like effects including thought disruptions. Further self-experiments involving the oral application of various synthetic cannabinoids have also been reported (e.g. Angerer et al., 2019; Hutter et al., 2013). In these studies, the individuals did not experience noticeable effects, probably because of the relatively low doses, in combination with a pronounced first-pass effect, which can be expected after oral administration.

In a recent pilot study (placebo-controlled, cross-over), six volunteers (occasional cannabis users) vaped 2 mg or 3 mg of JWH-018 (Theunissen et al., 2018), resulting in maximum serum concentrations of 2.9–9.9 ng/ml (Toennes et al., 2017). The effects occurred within the first 2 hours after application, and no serious side effects were reported. Effects were mild compared with a typical recreational dose of cannabis (probably because of delivery by the vaping device was suboptimal) and included behavioural impairment. In a similar study, the same group investigated the effects of doses equivalent to 75 µg/kg body weight (up to 6.2 mg) in 17 volunteers (Theunissen et al., 2019), resulting in a mean maximal JWH-018 concentration of 7.5 ng/ml (1.7–22.3 ng/ml). Again, no serious side effects were experienced although some participants reported dissociation, amnesia and confusion. Effect size and cognitive impairment were more pronounced than in the pilot study, which had lower doses.

Pharmacokinetics

*Absorption*

The most common form of consumption of synthetic cannabinoids is the inhalation of burned or heated plant material laced with synthetic cannabinoids ('herbal smoking mixtures'). Such mixtures are usually smoked like cannabis, often combined with tobacco in a joint or a water pipe. Another method of administration is inhalation after vaporisation of the substance using a 'vaporiser' or by using e-liquids vaporised in electronic cigarettes. The rapid absorption through pulmonary alveoli usually leads to maximum concentrations ($C_{max}$) after a few minutes. In an administration study with 4 mg of JWH-018, the $C_{max}$ was reached after 5 minutes (accompanied by the occurrence of psychotropic effects; Teske et al., 2010), and this finding has been confirmed in other studies (Theunissen et al., 2018, 2019).

As oral consumption can lead to unpredictable poisonings due to erratic absorption, this route of administration is not common among users of synthetic cannabinoids. The absorption of the drug is influenced by a wide range of factors (e.g. fasted versus fed state of the stomach, the activity of multidrug resistance proteins, passive or active transport through intestinal barriers and the dissolution rate of the formulation). Compared with inhalation, $C_{max}$ is delayed and is usually achieved between 30 minutes and several hours after administration (Castaneto et al., 2015). Hutter et al. (2013) observed that $C_{max}$ was reached approximately 1.5 hours after a single oral administration of AM-2201. A wide range of xenobiotics are partly eliminated after intestinal absorption by a first-pass effect in the liver, thereby reducing the bioavailability. Therefore, the dose needed for the desired effects after oral uptake exceeds the amount needed when inhaling. In the study of Hutter et al. (2013),

5 mg of AM-2201 orally taken did not result in psychotropic effects, although – considering the potency of AM-2201 – this dose, if smoked, would lead to perceptible effects.

So far, there appear to have been no reports of users of synthetic cannabinoids using intravenous injection or rectal application as the route of administration. However, anecdotal data suggest that marginalised, high-risk drug users do, on rare occasions, intravenously inject synthetic cannabinoids.

*Metabolism and excretion*

Synthetic cannabinoids are metabolised differently depending on their structure. The main metabolic reactions include the oxidation of aromatic and alkyl structures. Aromatic core structures such as indole, indazole, 7-azaindole and γ-carbolinone are known to be oxidised to mono-/dihydroxylated or dihydrodiol metabolites (Franz et al., 2019; Mogler et al., 2018a). Terminal hydroxyalkyl groups are often further oxidised to the corresponding carboxylic acids, probably catalysed by alcohol / aldehyde dehydrogenases or CYP450 enzymes (Chimalakonda et al., 2012; Holm et al., 2016). In some cases, further degradation of the carboxylic acid metabolite by decarboxylation has been observed. The γ-carbolinone-derived synthetic cannabinoids CUMYL-PeGACLONE and 5F-Cumyl-PeGaClone have been shown to be metabolised to their propionic acid metabolites by gradual alkyl chain degradation, as detected in human urine specimens (Mogler et al., 2018a, 2019).

The replacement of hydrogen by a fluorine atom is a strategy commonly applied by manufacturers to circumvent legal restrictions and increase pharmacological potency at the same time (Banister et al., 2015). Defluorination of terminally fluorinated alkyl groups leads to ω-hydroxyalkyl metabolites. This biotransformation has been described for AM-2201 (Hutter et al., 2013), 5F-AKB48 (Holm et al., 2015), 5F-MDMB-PICA (Mogler et al., 2018b) and 4F-MDMB-BINACA (Haschimi et al., 2019). Although some studies show that defluorination is catalysed by CYP1A2, CYP2C9 and CYP2C19 (Chimalakonda et al., 2012), the formal reaction of fluoroalkyl to hydroxyalkyl is chemically not an oxidation but a hydrolytic substitution, and the exact mechanism of defluorination remains to be investigated. In contrast to synthetic cannabinoids with a terminally fluorinated alkyl group, oxidation of substances with a non-fluorinated alkyl chain occurs only rarely at the terminal carbon atom, and, instead, occurs mainly at C2. Differentiation between the uptake of a fluorinated and a non-fluorinated analogue can therefore be achieved through analysis of these different hydroxylated metabolites in urine.

The structure–metabolism relationships of the subclass of synthetic cannabinoids with valine- and *tert*-leucine-derived structures (emergence in 2012; Uchiyama et al., 2013b) have been described comprehensively by Franz et al. (2019). Their study included data about the *in vitro* metabolism of methyl valinates, methyl *tert*-leucinates, valinamides and *tert*-leucinamides using a pooled human liver microsome assay. Compounds with a valine moiety generally underwent more pronounced hydrolysis than their *tert*-leucine analogues, probably caused by the additional methyl group leading to higher metabolic stability. Furthermore, hydrolytic dehalogenation of the alkyl chain was more predominant in *tert*-leucine analogues. Compounds containing a terminal methyl ester at the amino acid tail showed higher

hydrolysis rates than their amide analogues. Methyl *tert*-leucinate-derived synthetic cannabinoids showed the highest mean relative abundance for oxidative *N*-dealkylation. In addition, dehydrogenation was predominantly observed in the valinamide derivatives, probably leading to energetically favoured structures (Franz et al., 2019).

Thomsen et al. (2015) showed enzymatic activity of the carboxyl esterase 1b (CES1b) towards BB-22 (JWH-methylcyclohexane-8quinolinol), PB-22 (JWH-018 quinolinecarboxylate analogue), 5F-PB-22 (AM-2201 carboxylate analogue quinolinyl derivative) and the valinamide synthetic cannabinoids AB-PINACA and AB-FUBINACA.

Glucuronidation is the most common phase II biotransformation of synthetic cannabinoids. 5F-MDMB-P7AICA and PB-22 (JWH-018 quinolinecarboxylate analogue) / 5F-PB-22 (AM-2201 carboxylate analogue quinolinyl derivative) are conjugated with glucuronic acid after phase I functionalisation (linked to the hydroxyl or carbon acid function; Richter et al., 2019; Wohlfarth et al., 2014). Therefore, when analysing human urine specimens, cleavage of glucuronic acid conjugates with β-glucuronidase is essential.

Most synthetic cannabinoids undergo renal excretion only after metabolic transformation. Therefore, the detection of metabolites is essential for the unambiguous proof of exposure in forensic urine analysis. Nonetheless, in some cases, the parent compound is eliminated in urine, with the highest abundance relatively to the metabolites detected. Giorgetti et al. (2020) observed that 5F-AB-P7AICA, the 7-azaindole derivative of 5F-AB-PINACA, shows lower metabolic degradation than its indazole analogue.

*Interindividual genetic variability in metabolising enzymes and pharmacokinetic interactions*

Chimalakonda et al. (2013) described the pharmacokinetic interactions between JHW-018 and medicines, especially regarding their metabolism. Co-administration of JWH-018 and inhibitors of the metabolising enzymes CYP1A2 (e.g. ciprofloxacin and fluvoxamine) or CYP2C9 (e.g. fluconazole and valproic acid) may lead to slower elimination of JWH-018 and thus to higher serum concentrations and longer lasting effects of the synthetic cannabinoids (Chimalakonda et al., 2013). CYP1A2 and CYP2C9 are involved in the metabolism of several xenobiotics and endogenous substances. Genetic polymorphisms (a poor metaboliser versus an extensive and ultrarapid metaboliser) may also influence serum levels of synthetic cannabinoids (Gunes and Dahl, 2008). Higher serum levels of synthetic cannabinoids might increase the risk of poisoning.

Interactions

Interactions regarding pharmacodynamics were described by Brents et al. (2013) for JWH-018 and JWH-073. Combining both synthetic cannabinoids showed synergistic and additive effects in mice regarding analgesia and hypothermia (a leftwards shift of dose–response curves). Luszczki and Florek-Łuszczki (2012) described a synergistic interaction between pregabalin and the synthetic cannabinoid WIN-55,212-2 in a fixed dose ratio of 1:1 in the mouse model of acute thermal pain. The review article of Manzanares et al. (1999) summarises studies demonstrating the phenomena of cross-tolerance and mutual

potentiation of hypothermia, sedation, hypotension, inhibition of motor activity and antinociception between cannabinoids and opioids.

Structure–activity relationships and drug design

Since the identification of the cannabinoid receptors $CB_1$ and $CB_2$ and their corresponding endogenous ligands (see Section 4.3, 'Pharmacology'), numerous structurally diverse synthetic cannabinoids have been discovered. In addition, systematic investigations of structure–activity relationships have been undertaken to identify high-potency cannabinoids with high specificity for one or both cannabinoid receptors.

The influence on $CB_1$ and $CB_2$ binding affinities of alkyl chain length at N1 of cannabimimetic indoles was studied by Aung et al. (2000). For this purpose, the morpholinoethyl moiety of WIN-55,212-2 was substituted by alkyl chains of varying length (homologous series from methyl to heptyl). These structural changes revealed that the pentyl chain showed the highest cannabinoid receptor affinity, and that the core structure of WIN-55,212-2 afforded a chain length of three to six carbon atoms, resulting in high binding affinity.

The structure–activity relationship of compounds with 1-pentyl- and 1-propyl-3-(1-naphthoyl)indole-core structures towards the cannabinoid receptors were studied by Huffman et al. (2005). They mainly investigated the position of the methoxy group at the naphthoyl residue. While methoxy substitution at C4 enhanced affinity towards the CB receptor, substitution at C6 and C7 seemed to have little effect, and the introduction of a 2-methoxy substituent completely revoked affinity towards the $CB_1$ receptor.

The side chain of indazole-based *tert*-leucine synthetic cannabinoids has a large influence on $CB_1$ receptor affinity. 5F-MDMB-PINACA (5F-ADB), MDMB-FUBINACA and MDMB-CHMINACA differ only in the presence of a 5-fluoropentyl, fluorobenzyl and cyclohexylmethyl group as substitution at N1 of the indazole core structure. All show high receptor binding, but the 5-fluoropentyl moiety (5F-MDMB-PINACA) leads to the highest potency at the $CB_1$ receptor ($EC_{50}$ 0.59 nM), followed by MDMB-FUBINACA ($EC_{50}$ 3.9 nM) and then MDMB-CHMINACA ($EC_{50}$ 10 nM) (Banister et al., 2016).

The work of Longworth et al. (2017) demonstrated that valine- and *tert*-leucine-derived synthetic cannabinoids, with a substituted indole or indazole core structure, exhibit high cannabimimetic potency *in vivo* and *in vitro*. The activity of the most abundant metabolites of the synthetic cannabinoids APICA (JWH-018 adamantyl carboxamide) and ADB-PINACA were measured in a FLIPR assay of membrane potential. The formation of a free carboxylic group (through oxidation of the alkyl chain or hydrolysis of amide or ester functionality) generally reduces pharmacological activity (Longworth et al., 2017).

The bioisosteric substitution of hydrogen by a fluorine atom is a common strategy used by manufacturers to circumvent legal restrictions and increase pharmacological potency. The synthetic cannabinoids JWH-018, UR-144, JWH-018 quinolinecarboxylate analogue (PB-22) and APICA (JWH-018 adamantyl carboxamide) and their respective fluorinated analogues (AM-2201, 5F-UR-144 (XLR-11), AM-2201 carboxylate analogue quinolinyl derivative (5F-

PB-22) and STS-135) do all bind as agonists to the $CB_1$ receptor. The substitution of hydrogen with fluorine commonly results in increased potency (Banister et al., 2015).

Recently, the crystal structure of the human $CB_1$ receptor ($hCB_1R$) was revealed by Hua et al. (2017). The $hCB_1R$ was crystallised in a complex with the agonists AM-11542 and AM-841, and the resulting structure provided insight into the binding mode of endogenous ligands, synthetic cannabinoids and naturally occurring cannabinoids. The utility of the crystal structure may provide a fundamental base for structure-based drug design of novel $hCB_1R$-targeting pharmaceuticals.

# 5. Health and social risks

The scientific data related to the acute toxic effects of synthetic cannabinoids are still limited, despite the relatively widespread use of these compounds, as reflected by multiple reports on poisonings, including deaths, involving the substances. The toxicity profile of these substances seems to have some similarities to that of cannabis, although more serious adverse health effects are often seen with the former. Some of the reasons for synthetic cannabinoids' greater potential for harm compared with cannabis include their typically full agonism at the $CB_1$ and $CB_2$ receptors and the extremely high potency of many synthetic cannabinoids. The type and amount of synthetic cannabinoids in products can differ within smoking mixtures sold under the same name, and several examples of false labelling have been reported. In an online survey, 11 % of synthetic cannabinoid users reported having experienced unpredicted effects, despite consumption of the same brand of 'Spice' (Vandrey et al., 2012), which might in part be caused by inhomogeneity of the distribution of synthetic cannabinoids in herbal blends, producing a higher risk of overdoses even in highly experienced users (Moosmann et al., 2015). Unknown to users, synthetic cannabinoids have also been mis-sold as ecstasy/3,4-methylenedioxymethamphetamine (MDMA), other illicit drugs, and CBD and THC e-liquids. In some cases, this has led to severe poisoning (Allibe et al., 2016; Brenneman et al., 2016; Horth et al., 2018; Pap, 2016). Another concerning development is the increase in the identification of synthetic cannabinoids in low-THC cannabis products, which was first reported in Switzerland (Saferparty, 2020). Since July 2020, the EMCDDA has received an increasing number of reports of the adulteration of cannabis products with highly potent synthetic cannabinoids, such as MDMB-4en-PINACA (EMCDDA, 2021a). Typically, the adulterated cannabis products are low-THC herbal material or resins. While the prevalence of these adulterated products is unknown, at least six countries that are part of the EU Early Warning System have reported this type of adulteration. In terms of look, smell and flavour, these adulterated products would be very difficult to distinguish from 'genuine' illicit cannabis products and, as a result, users may be unaware that they are using synthetic cannabinoids. For this reason, and as synthetic cannabinoids are highly potent substances, users of these products could be at high risk of poisoning – an issue reflected by reports of poisonings in some countries. The reason for adulteration is unclear, but one possibility is that low-THC industrial hemp is cheap, is widely available and has a similar look, smell and flavour to 'genuine' cannabis (making it easy to dupe unsuspecting users), while only a small amount of synthetic cannabinoids would be required to give a potent cannabis-like high.

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

For most of the synthetic cannabinoids that have emerged on the drug market, prospective or controlled animal or human studies are scarce or missing, although some *in vitro* cellular studies have been performed. Studies conducted in human-derived cell lines with an assessment of the cytotoxic/genotoxic effects of synthetic cannabinoids (JWH-018, JWH-073, JWH-122, JWH-210, JWH-250 and AM-694) and the influences on hormone levels and the immune system have demonstrated only weak cytotoxicity, as such effects generally were observed at concentrations much higher than those expected in synthetic cannabinoid users (Koller et al., 2013, 2014). The compounds investigated did not cause oxidative damage to the DNA, but affected processes such as the synthesis of proteins and the homeostasis of membranes, ultimately leading to chromosomal damage. Neither modifications of the oestrogen levels nor abnormalities of immunomodulation were seen in the same study (Koller et al., 2013). Chromosomal aberrations, but no oxidation-induced damage, were found in a study conducted by Ferk et al. (2016) involving 5F-UR-144 (XLR-11). Oxidative stress due to the production of reactive oxygen species in human endometrial stromal cells was recently demonstrated for JWH-122, UR-144 and WIN-55,212-2 (Fonseca et al., 2019). While this effect was compensated for by the consumption of glutathione for JWH-122 and UR-144, WIN-55,212-2 induced apoptotic cell death.

## 5.1. Acute toxicity

The acute toxicity of a limited number of synthetic cannabinoids has been partially studied in the non-clinical setting, and animal models are extremely useful both to compare adverse effects of synthetic cannabinoids with those produced by cannabis and to tentatively assess the dose at which adverse or lethal effects may occur. Furthermore, animal models can help to establish a tentative dose–dependence relationship. However, data mainly refer to relatively 'old' compounds, such as WIN-55,212-2, while novel substances that have appeared on the drug market, for example those bearing a cumyl substituent, have not been tested. The interpretation of animal data is complicated by differences in pharmacokinetic behaviour and differences in the CB receptors between various species. In addition, models of synthetic cannabinoid intake used in animal experiments, such as intraperitoneal application, do not have a direct correlate in humans.

Clinical studies and studies involving human participants are extremely rare because of the unpredictability of effects, which pose a serious risk to the health of the subjects involved, leading to ethical issues. Therefore, evidence on acute toxicity is mainly derived from case reports and case series or from clinical reviews reporting on acute poisonings and/or deaths. One major limitation of case reports is that the exposure to synthetic cannabinoids is often self-reported, or only circumstantial evidence exists, rather than analytical confirmation from a biological sample or epidemiologically linked physical sample.

<u>Animal data</u>

Based on *in vitro* and animal studies, the potency of synthetic cannabinoids has been estimated to be 2–100 times that of $\Delta^9$-THC (Castaneto et al., 2014).

Some preclinical studies have focused on the evaluation of the effects of synthetic cannabinoids on cognitive processes such as attention. Sixty rats were trained for a period of

5 months to detect visual stimuli (a lateralised reaction time task). They were then administered WIN-55,212-2 intraperitoneally (1.0 or 2.5 mg/kg) and compared with a negative control. Accuracy, errors and response times were monitored. WIN-55,212-2 was shown to decrease the number of correct choices, increase omissions and increase response times in a dose-dependent manner; thus, it was suggested that WIN-55,212-2 induced impairments in attention performances (Arguello and Jentsch, 2004). Deleterious effects on sustained attention were also seen in the trial performed by Miller et al. (2013), who tested rats with a two-choice reaction time task 30 minutes after intraperitoneal administration of 0.02, 0.04, 0.08 or 0.16 mg/kg AM 4054. Several investigations have also shown a significant effect of synthetic cannabinoids on working memory in rodents after the administration of JWH-081 and HU-210, with worsening of performances in maze-based tasks and of cognitive flexibility (i.e. the ability to think more than one thing simultaneously or to switch between concepts) after a single administration of 0.2 mg/kg HU-210 (Cohen and Weinstein, 2018).

A decrease in the respiratory rate (oligopnoea) and behaviour effects (including seizure-like behaviour) were observed after intraperitoneal injection of 5 and 15 mg/kg MAM-2201 in 6-week-old rats. A decrease in glutamic acid (one of the main excitatory brain neurotransmitters) and changes in energy metabolism were demonstrated by a mass spectrometry-based metabolomics study and were suggested as a possible underlying cause of such acute symptoms (Zaitsu et al., 2015). Within 20 minutes of acute administration of AM-2201 (2 mg/kg) and AB-CHMINACA (1 mg/kg), abnormal spike waves were seen in mice monitored by electroencephalography (EEG). Epileptic behaviour with rigidity and tonic–clonic movements were also noted. Thirty minutes after administration, catalepsy also developed. These effects, which were antagonised by selective $CB_1$, but not $CB_2$, receptor antagonists, were also accompanied by a change in glutamate concentration, further confirming the possible role of this neurotransmitter (Funada and Takebayashi-Ohsawa, 2018). JWH-018, administered at doses of 1.5, 2.5 and 5 mg/kg, also triggered seizures in mice, as recorded by EEG and videography, in a dose-dependent manner (Malyshevskaya et al., 2017). More recently, myoclonic jerks, 'gasping' reaction and other seizure-like activities were demonstrated in mice 2–3 minutes after the injection of a novel synthetic cannabinoid (CUMYL-4CN-BINACA) at doses of 0.3 and 1 mg/kg (Kevin et al., 2019b).

In an experiment designed to test the acute toxicity of a single dose of the THJ-2201 (AM-2201 indazole analogue), mice were administered THJ-2201 orally at a dose of 5, 50, 300 or 2 000 mg/kg (Bakdash et al., 2018). Several symptoms, including tachycardia, seizures, locomotor agitation and dyspnoea developed, and their occurrence was seen in a dose-dependent manner. By contrast, only slight modifications of the haematological parameters, with an increase of lymphocyte counts, were noted. Even at low doses, histological examination of the liver and, to a minor extent, of the kidneys of the treated mice showed congestion, lymphocytic infiltration and necrosis. Finally, a median lethal dose ($LD_{50}$) of 822.20 mg/kg was calculated for THJ-2201 (Bakdash et al., 2018), which points towards a relatively low acute toxicity.

Taken together, these data support the hypothesis that cognitive and behaviour effects, with the development of seizures and agitation, respiratory depression and cardiovascular

abnormalities, are toxic effects dose-dependently occurring after an acute intake of synthetic cannabinoids.

To assess the cardiovascular effects of synthetic cannabinoids, several groups have experimented on isolated heart muscle preparations. For example, Bonz et al. (2003) found that anandamide and the synthetic cannabinoid HU-210 decreased the contractility of human atrial muscles when stimulated by an electrical field. More recently, incubation with $CB_{1/2}$ receptor agonists (WIN-55,212-2 and the selective $CB_2$ agonist JWH-133) was shown by Maggo and Ashton (2018) to have a moderate positive chronotropic effect on isolated rat atria. The authors suggest that tachycardia, a well-known effect of synthetic cannabinoids that is believed to be mediated by central $CB_1$ stimulation, could in part be provoked by myocardial $CB_1$ receptor activation.

*In vivo* studies include that by Schmid et al. (2003), who evaluated cardiovascular and respiratory effects in urethane-anaesthetised rats that received 0.03, 0.1, 0.3 or 1 mg/kg WIN-55,212-2, WIN-55,212-3 or CP-55,940 intravenously. Arterial pressure reduction, a decrease in heart rate and a decrease in the plasma noradrenaline levels were seen in animals challenged with synthetic cannabinoids, and the effects appeared to be dose related. Changes were accompanied by a reduction in respiratory rate, a decrease in the partial pressure of oxygen and a decrease in blood pH. Two out of nine animals immediately stopped breathing after administration of the highest dose of CP-55,940. In another study, a dose of 0.01 mg/kg HU-210 produced a reduction in mean blood pressure, while not significantly affecting heart rate, and decreased the cardiac index in anaesthetised rats (Wagner et al., 2001). Finally, bradycardia lasting up to 10 minutes was seen in conscious and freely moving rats administered WIN-55,212-2 (0.15 mg/kg), while different cardiovascular effects were described in spontaneously hypertensive rats (Wheal et al., 2007).

Some data on animals are also available owing to accidental poisonings of domestic pet animals with 'Spice' products, which may occur following the ingestion of synthetic cannabinoid-containing food or plant material or after the inhalation of side-stream smoke (Brutlag and Hommerding, 2018). Clinical signs might be reported to pet poison helplines, although the limitations of such data are that co-ingestants cannot be ruled out and synthetic cannabinoid intake is not analytically confirmed by laboratory tests in all cases reported. However, such data may allow for a comparison of effects in animals and humans. In a study involving almost 60 cases of pet (mostly canine) poisonings with synthetic cannabinoids, lethargy (41 %) and ataxia (52 %) were the symptoms most commonly reported, followed by vomiting (21 %). The sedative effect sometimes also led to a reduction in the level of consciousness (stupor) and to respiratory depression in 5–7 % of the cases. Depressant neuromotor effects were also seen, with lateral recumbency (i.e. animals were unable to rise, once lying down) reported in 19 % of cases. This effect was much more common after reported synthetic cannabinoid intake than with accidental cannabis or CBD intake. Agitation/irritability, mydriasis, tremors and twitching movements were described in 12–16 % of cases. Surprisingly, bradycardia was more frequently reported than tachycardia, occurring in about 16 % of cases (Brutlag and Hommerding, 2018). Effects on neuromotor and cardiovascular function were confirmed in one case, namely the poisoning of a dog after

alleged exposure to a herbal smoking mixture ('Potpourri'), with the dog developing progressive ataxia, marked hypothermia and bradycardia (Williams et al., 2015).

Human data

Data on humans are mostly available from retrospective studies of patients who seek medical attention after the consumption of synthetic cannabinoids, from calls to poison information centres or from case reports and case series of poisonings. However, these cases may not be fully representative, as serious poisonings are typically overrepresented. Although many cases of poisonings are described in the literature, it is also important to highlight that in only some of these cases was exposure to synthetic cannabinoids analytically confirmed from analysis of biological samples taken from the patients. This represents a further limitation in the evaluation of human data, as the reliability of circumstantial data is low and the co-consumption of other synthetic cannabinoids or other drugs (possibly without involvement of synthetic cannabinoids) cannot be excluded. In some cases, the intake of synthetic cannabinoids is self-reported by the patients, and test results of general toxicological screenings are negative (often performed only in a clinical, not a forensic, setting) or synthetic cannabinoids are identified in exhibits such as smoked products (Zawilska and Wojcieszak, 2014). Moreover, no data on the precise dose ingested can be obtained from such cases.

Controlled administration studies are much rarer. In a self-experiment, 0.3 g of a 'Spice' product containing CP-47,497 was smoked, and the two participants showed increased pulse rates and alterations of mood and perception within 10 minutes after intake. They also reported cognitive impairment, which subjectively continued, with minor effects, until the next day (Auwärter et al., 2009).

One male and one female volunteer smoked a cigarette containing 100 (female volunteer) and 150 mg (male volunteer) of a smoking mixture containing 2.9 % JWH-018 (2.9 and 4.3 mg, equivalent to a dose of 40 and 50 µg/kg, respectively) and reported sickness, sedation and xerostomia immediately after the self-administration, followed by a state of light tiredness and exhaustion attenuating 6–12 hours after intake. Increased pulse rate, in accordance with previous data, mydriasis and altered pupil reaction were also noted. Maximum concentrations were approximately 10 ng/ml 5 minutes after smoking (Teske et al., 2010).

Mood and perception alterations, subjective impairment, anxiety and loss of concentration were also experienced by more than half of six volunteers after inhalation of 0.3 g of herbal blends containing JWH-018 and JWH-073. Sedation and paranoia were seen in a minority of cases. Tachycardia was confirmed in all subjects, who also showed a reddening of the conjunctivae and manifested xerostomia. A hangover effect lasted for 6–12 hours in three volunteers (Logan et al., 2011).

In further experiments involving oral ingestion of 10 mg of AM-694, 26 mg of JWH-018 adamantoyl derivative (AB-001), 5 mg of AM-2201 and 2.5 mg of 5F-AB-P7AICA, despite the known potency of these synthetic cannabinoids, no effects were noted (Giorgetti et al., 2020;

Grigoryev et al., 2012; Grigoryev et al., 2013b; Hutter et al., 2013), probably because of a pronounced first-pass effect.

Recently, Theunissen et al. (2021) published the results of a placebo-controlled, double-blind, within-subjects trial in which 24 healthy participants with no history of mental illness inhaled vapour of placebo or JWH-018 at a dose of 75 µg/kg body weight. On average, participants received a total dose of 5.52 mg of JWH-018 (regarded by the authors as a 'moderate' dose). The findings demonstrated that healthy volunteers who are intoxicated by a moderate dose of the synthetic cannabinoid JWH-018 experience pronounced psychedelic and dissociative symptoms and feelings of confusion.

Some data on the toxicity of synthetic cannabinoids can also be derived from patients receiving chronic pain treatment. Adverse effects reported in the short-term treatment of chronic pain with cannabis (Vučković et al., 2018) or nabilone (McGolrick and Frey, 2018) were mostly mild or moderate in severity. Dizziness, drowsiness, faintness, cognitive impairment and fatigue were among the most commonly reported adverse effects. Nausea, xerostomia and cardiovascular effects such as tachycardia and hypertension also occurred. The reasons for withdrawal mostly consisted in the occurrence of psychiatric effects. It has to be stressed that $\Delta^9$-THC and nabilone are partial agonists at the $CB_1$ receptor and that no such data are available for the structurally different synthetic cannabinoids that have been sold on the drug market and that are typically full agonists. Therefore, an extrapolation to synthetic cannabinoids used as 'legal highs' might not be justified.

*Acute poisonings*

In a retrospective study involving 29 emergency department patients, whose exposure to synthetic cannabinoids (mainly JWH series) was analytically confirmed, central nervous system and cardiovascular effects, and particularly tachycardia, were the most commonly reported symptoms (Hermanns-Clausen et al., 2013a). Among nervous system effects, restlessness/agitation was seen in 41 % of the patients. In terms of frequency, these effects were closely followed by changes in perception (38 %), including hyperreactivity to light and external stimuli, vertigo and anxiety attacks (24 % and 21 %, respectively). However, depression of the nervous system with somnolence, often lasting for several hours, confusion/disorientation and unconsciousness were also frequent (17 %, 14 % and 17 %, respectively). Apart from tachycardia (heart rates between 90 and 170 beats/minute), other common effects on cardiovascular function included hypertension (median values: 160 mmHg systolic and 85 mmHg diastolic pressure), dyspnoea and electrocardiographic changes. Among gastrointestinal symptoms, nausea and vomiting were encountered in 28 % of patients. While the majority of these effects are consistent with those of intake of a high dosage of $\Delta^9$-THC, this is not the case for agitation and epileptic seizures, which seem, for some reason, to be more common with synthetic cannabinoids (Hermanns-Clausen et al., 2013a). In a large survey with 15 200 responses, users reported more and stronger negative effects after smoking synthetic cannabinoids than after taking cannabis, with worse hangover effects and paranoia (Winstock and Barratt, 2013). However, prospective studies in synthetic cannabinoid users, especially in comparison with cannabis, have not been conducted so far; thus, the relative risk cannot be precisely characterised.

According to the available studies, tachycardia (37–40 %), agitation (18–23 %), drowsiness (13–18.5 %), nausea/vomiting (9.9–15.7 %) and hallucinations (9.4–10.8 %) are the symptoms most frequently reported by poison information centres (Forrester et al., 2011; Hoyte et al., 2012). Despite the usefulness of such data, it has to be remembered that, in studies based on data from poison information centres, the exposure of patients to synthetic cannabinoids is often not analytically confirmed (Forrester et al., 2011; Hoyte et al., 2012).

*Neurological and respiratory effects*

Neurological symptoms can vary widely in synthetic cannabinoid-poisoned patients and range from agitation to various grades of central nervous system depressant effects including ataxia, confusion, drowsiness, dizziness, muscle weakness, numbness, slurred speech, paralysis, respiratory depression, lethargy and coma.

Respiratory depression requiring intubation was reported in a series of calls to poison information centres, and occurred only in association with alcohol and/or benzodiazepines co-consumption (Forrester et al., 2011). In a survey, synthetic cannabinoid users reported non-serious symptoms such as a sensation of light-headedness, impairment of memory functions and troubles with 'thinking clearly' (Gunderson et al., 2014; Vandrey et al., 2012). Somnolence, confusion and retrograde amnesia were reported in three adolescents whose blood serum samples tested positive for MAM-2201 and UR-144; JWH-081 and JWH-073; and JWH-122 (Hermanns-Clausen et al., 2013b). Lethargy was observed in several patients during an outbreak in New York, United States, where analysis of serum samples confirmed the presence of the AMB-FUBINACA acid metabolite in 8 out of 18 patients in concentrations ranging from 77 to 636 ng/ml (Adams et al., 2017). Confusion, psychomotor agitation and psychosis were seen in five patients after smoking herbal blends containing 5F-MDMB-PINACA (5F-ADB) and 5F-AMB-PICA (MMB-2201) (Barceló et al., 2017).
Alon and Saint-Fleur (2017) reported on a series of four patients who presented to an intensive care unit with acute respiratory distress after alleged consumption of synthetic cannabinoids (which was not analytically confirmed). All patients required endotracheal intubation in the absence of a concomitant pulmonary disease and two had seizure activity. The respiratory distress resolved in less than 24 hours and the patients presented agitated/aggressive behaviour. Subsequently, aspiration pneumonia occurred in three of the four cases.

In a case series of six patients who reported the use of synthetic cannabinoids, two patients presented to the emergency department with seizures, two with tachycardia and two with hallucinations (Harris and Brown, 2013). Perceptual changes and anxiety were also described as 'the main psychoactive findings' in a series of 16 adolescents seeking medical attention after synthetic cannabinoid use (Besli et al., 2015). Psychotic episodes may occur particularly in patients with known psychiatric disorders, as shown by Every-Palmer (2011) through semi-structured interviews with patients with a history of serious mental illness in a forensic facility. The data presented suggested that 9 of the 13 patients who repeatedly smoked a product most likely containing JWH-018 experienced symptoms consistent with psychotic relapse caused by JWH-018. Convulsions were witnessed in an adolescent after smoking a herbal blend that was analytically confirmed to contain JWH-018, JWH-081, JWH-

250 and AM-2201 (Schneir and Baumbacher, 2012). The analysis of a plasma sample showed JWH-methylcyclohexane-8quinolinol (BB-22), AM-2233, JWH-018 quinolinecarboxylate analogue (PB-22), AM-2201 carboxylate analogue quinolinyl derivative (5F-PB-22) and JWH-122 in a patient admitted twice to hospital because of seizures after smoking 'K2' (Schep et al., 2015). Tonic–clonic seizures were also reported immediately after the consumption of a 'Bonzai' herbal blend, with serum and urine confirmation of JWH-122, JWH-210 and JWH-018 (Hermanns-Clausen et al., 2013b). Seizures and refractory supraventricular tachycardia were seen in a patient hospitalised after ingestion of JWH-018, analytically confirmed in urine by detection of its metabolites (Lapoint et al., 2011).

Some of the features of poisoning associated with synthetic cannabinoid consumption – 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 (Tait et al., 2016).

*Cardiovascular effects*

Adverse cardiovascular effects associated with exposure to synthetic cannabinoids include tachycardia as well as a range of dysrhythmias and electrocardiographic (ECG) changes including bradycardia, although the latter seems to be relatively rare (1.3 % of 464 cases (Forrester et al., 2001) and 1.5 % of 1 898 cases (Hoyte et al., 2021)). Hypertension, chest pain and, to a lesser extent, hypotension are also reported by users, as determined from calls to poisoning centres (Forrester et al., 2011; Hoyte et al, 2012). Hypertension and tachycardia were demonstrated in two cases of exposure to 'Spice' and JWH-018 and JWH-073 were detected in the urine (Simmons et al., 2011). Myocardial infarction was diagnosed based on electrocardiogram changes and elevated troponin levels in four adolescents seeking medical attention owing to chest pain, within 2 hours and 1 week after exposure to 'Spice' products. However, exposure to cannabinoids was not confirmed analytically (Mir et al., 2011; McKeever et al., 2015). In addition, Young et al. (2012) reported the case of an individual who experienced chest pain 10 minutes after smoking a herbal blend containing JWH-018 and JWH-073 and in whom tachycardia and bradycardia were later confirmed in hospital. Analytical confirmation of the presence in urine of an adamantyl-type synthetic cannabinoid (not specified) was achieved in one individual with chest pain and ST-elevation on ECG (McIlroy et al., 2016). Cardiac arrest in a 56-year-old man with multiple cardiovascular risk factors (past myocardial infarction, treated with four-vessel bypass) and a history of increasing 'K2' consumption has also been reported (Ibrahim et al., 2014). Finally, cases of ischaemic stroke connected to synthetic cannabinoid use deemed to be cardioembolic in nature and triggered by cardiac arrhythmia have also been reported in the literature (Tait et al., 2016).

*Gastrointestinal effects*

Gastrointestinal effects of synthetic cannabinoids include nausea and vomiting, which according to a literature review, are symptoms seen in 13–94 % of presentations. Furthermore, two cases of hyperemesis following alleged synthetic cannabinoid use have

been reported (Tait et al., 2016). While food craving and increased appetite are commonly experienced in association with cannabis, these were reported far less after smoking synthetic cannabinoids (Winstock and Barratt, 2013). Very few patients complained about abdominal pain, anorexia/weight loss or haematemesis (Forrester et al., 2011).

*Other effects*

Rhabdomyolysis, accompanied by psychomotor agitation and hyperthermia, has also been clinically assessed in cases of alleged exposure to synthetic cannabinoids (Adedinsewo et al., 2016; Durand et al., 2015). Rhabdomyolysis and an increase in creatinine kinase serum levels can be associated with kidney damage.

The Centers for Disease Control and Prevention reported 5F-UR-144 (XLR-11) involvement in 7 of 16 patients diagnosed with acute kidney injury (AKI) after presenting to the emergency department with nausea, vomiting and flank pain within days/hours after allegedly smoking synthetic cannabinoids. Renal biopsy confirmed acute tubular injury and acute interstitial nephritis in eight of these patients, five of whom required haemodialysis. None of these patients died (CDC, 2013). Similarly, in another study, AKI was diagnosed in nine patients presenting to the emergency department with nausea and flank/abdominal pain. One clinical and two product samples were positive for 5F-UR-144 (XLR-11) (Buser et al., 2014). AKI without signs of rhabdomyolysis was seen in an agitated patient who was brought to the emergency department. He had allegedly consumed 'synthetic weed' in the previous 2 days (Gudsoorkar and Perez, 2015).

Other adverse effects include anticholinergic symptoms, such as xerostomia, warm/dry skin, mydriasis, hyperglycaemia, hypokalaemia, hypothermia, pallor or minor dermal manifestations, and reddening of the conjunctivae, both in self-administration studies and in cases with analytically confirmed exposure to synthetic cannabinoids (Auwärter et al., 2009; Hermanns-Clausen et al., 2013b; Kersten and McLaughlin, 2015; Teske et al., 2010).

*Death cases*

Since their appearance on the NPS market, a number of case reports and case series of deaths involving synthetic cannabinoids have been published (Labay et al., 2016; Kraemer et al., 2019). Clearly, the number of publications cannot reflect the full dimension of the issue, as not all cases involving synthetic cannabinoids are detected, let alone published. Furthermore, since the detection of synthetic cannabinoids requires a continuous update of analytical methods, it is also possible that new compounds are not detected in post-mortem cases, depending on the type of analysis performed. Additionally, the results from investigations into death cases are difficult to compare, owing to differences related to a number of factors, such as the timing of post-mortem sampling, type of toxicological analyses, cause of death, co-consumption of other substances, and so on. Recently, a case series involving 5F-Cumyl-PeGaClone also showed that even the results of analysis of post-mortem blood using LC-MS/MS methods fully validated for serum samples should not be used uncritically, owing to the possibility of strong matrix effects. Whenever possible, the standard addition method should be preferred for quantitation in post-mortem investigations

(Giorgetti et al., 2020). The interpretation of blood concentrations is, per se, difficult, and this finding further confirms that valid interpretation affords a comprehensive analysis of all of the data available on the case (Angerer et al., 2016; Kraemer et al., 2019). So far, it has not been possible to clearly correlate synthetic cannabinoid levels in the blood with toxic effects. Thus, it is not possible to delineate toxic or fatal concentration ranges, as have been reported for many drugs and medicines, despite several intrinsic limitations (Kraemer et al., 2019).

Labay et al. (2016) reported 25 death cases involving synthetic cannabinoids and asked different evaluators to assess the contributory role of the compounds involved regarding the cause of death. This kind of evaluation demonstrates how challenging it can be to attribute an interpretative weight to a substance, especially when, as for synthetic cannabinoids, pharmacological knowledge is limited. Indeed, in all but three cases, synthetic cannabinoids were deemed to have contributed to the cause of death through two or more of the following categories: 'behavioural and physical', 'behavioural', 'contributed', 'sole poisoning' and 'contribution unknown'; in only a minority of cases was there unanimous consent. Behavioural toxicity was the category that was most likely to lead to a fatal outcome, while cardiopulmonary diseases represented the most important contributing factors (Labay et al., 2016). Finally, the authors also stated that, as the knowledge of the effects is poor and the blood levels do not seem to correlate well with toxic effects, caution should be exercised whenever synthetic cannabinoids are involved in a death case (Labay et al., 2016).

Synthetic cannabinoids have been involved in a number of mono- and mixed-drug poisonings. Polydrug use cases can involve alcohol and antidepressant/neuroleptic drugs, such as quetiapine, amitriptyline, pregabalin, gabapentin, cathinones, amphetamines, opioids and dissociative anaesthetics such as diphenidine (Kraemer et al., 2019). In such cases, the interpretation of the contributory role of synthetic cannabinoids is further complicated, especially when other NPS are co-consumed.

As clinically cardiovascular effects are among the most commonly reported harms, cardiac toxicity with a fatal outcome can be expected. Indeed, cardiac arrhythmia and/or cardiac death are frequently reported as the cause/mechanism of death in cases involving synthetic cannabinoids. For example, Paul et al. (2018) reported on two death cases of adolescents, involving AB-CHMINACA in one case and UR-144, 5F-UR-144 (XLR-11) and JWH-022 in the other. The drug concentrations were relatively high (8.2 ng/ml for AB-CHMINACA and 12.3 ng/ml for UR-144). In both cases, the cause of death was deemed sudden death, probably due to cardiovascular toxicity, and in the first case a pre-existing cardiomyopathy was considered to be a contributory factor (Paul et al., 2018). An acute circulatory failure due to poisoning with synthetic cannabinoids was reported in a 23-year-old male who died 3.5 hours after multiple drug intakes, having experienced a cardiopulmonary arrest. In this case, the presence of mepirapim (950 ng/ml), in combination with α-ethylaminopentiophenone (EAPP) (3 100 ng/ml), was detected in serum samples collected at the hospital (Fujita et al., 2016). A sudden cardiac death following the intake of MDMB-CHMICA (1.4 ng/ml, as confirmed in a serum sample collected before death) occurred in a 22-year-old man, who was found asystolic 15 minutes after smoking a herbal blend. He eventually died of hypoxic brain damage (Westin et al., 2016). Shanks et al. (2016) reported a case of a 41-year-old female who smoked a product known as 'Mojo', developed agitation

and started to behave aggressively, and then suddenly became unresponsive and died. At the autopsy, the cause of death was ruled to be a coronary artery thrombosis after synthetic cannabinoid intake (ADB-FUBINACA, 7.3 ng/ml). A potential causality was assumed because of the short interval between smoking and the onset of behavioural symptoms.

In a case reported by Rojek et al. (2017), the development of behavioural symptoms is considered to have led to death, as a fall from height was attributed to drug-induced psychosis. The deceased had smoked a cigarette, manifested hallucinations and jumped out of a second-floor window. Post-mortem blood analysis revealed UR-144 (2.1 ng/ml) but no other drugs (Rojek et al., 2017). In a similar case, in which an individual who had consumed MDMB-CHMICA (the post-mortem blood level was 1.7 ng/ml) died after falling from a height, blood analysis revealed the presence of amphetamine (1 050 ng/ml), MDMA (275 ng/ml) and 3,4-methylenedioxyamphetamine (MDA) (22 ng/ml) (Gaunitz et al., 2018).

Poisonings involving synthetic cannabinoids may also lead to death by inducing a state of reduced consciousness, with subsequent aspiration of gastric content and asphyxia. This was the case for a 34-year-old man who was found unresponsive at his home, where three packages of herbal blends were retrieved. ADB-CHMINACA (MAB-CHMINACA) (6.05 ng/ml) was detected in post-mortem blood of the deceased, whose airway was found at autopsy to be occluded by a mass of material consistent with gastric content, suggesting that aspiration of gastric content was the cause of death (Hasegawa et al., 2015).

In many of the reported death cases, the precise mechanism of death and/or the likely contribution of synthetic cannabinoids was not specified owing to a lack of circumstantial information or lack of knowledge of the specific drug potency/toxicity.

*Occupational exposure*

Occupational exposure to synthetic cannabinoids mainly involves seizures of synthetic cannabinoids by law enforcement personnel from illicit laboratories or shops, customs or postal seizures, and staff involved in processing the evidence. Given the large number of seizures, it is surprising that very little is known so far regarding occupational exposures to synthetic cannabinoids.

Recently, a study was undertaken focusing on nine law enforcement agents following a raid on a laboratory manufacturing illicit substances in the United States, which aimed to evaluate the occupational health hazards from synthetic cannabinoid exposure. Disposable protective clothing was not used systematically and the agents ate and drank during the handling of the evidence. Urine samples from four agents tested positive for AB-PINACA and from six agents tested positive for mitragynine, whereas pre-raid collected urine samples were negative for both compounds (Tapp et al., 2017). Under such working conditions, seven of the nine agents reported symptoms such as a cough or eye/nasal/skin/throat irritation, four reported having felt 'light-headed' and 'high', and three reported having experienced memory and concentration impairment at least once during previous drug raids.

Symptoms including dizziness, blurred vision, weakness, confusion and lethargy lasting for up to 2 days were reported by three customs inspectors working at an airport whose hands

accidentally came into contact with a liquid (Dobaja et al., 2017). NMR analysis of the liquid revealed that it contained CUMYL-PINACA. The men presented with mydriasis and tachycardia and blood samples tested positive for CUMYL-PINACA. The patients recovered 2 days after the transdermal poisoning and reported amnesia and slowed perception of time after exposure (Dobaja et al., 2017).

<u>Managing poisoning</u>

Currently, there is no authorised antidote that can reverse the effects of synthetic cannabinoids. It seems plausible that, for example, rimonabant would be effective, but a formal protocol for the treatment of synthetic cannabinoids poisoning has not yet been established. The inhomogeneity of herbal blends, which sometimes also contain other illicit or licit drugs, and the continual emergence of novel compounds in the market could further limit the possibility of identifying a suitable antidote for synthetic cannabinoids (Müller et al., 2016). Future studies should investigate if the application of $CB_1$ receptor antagonists might be an option for the treatment of synthetic cannabinoid toxicity. Studies have been conducted with selective $CB_1$ antagonists, such as AM-11503. This substance was shown to reverse hypothermia induced by acutely administered JWH-018 (6 mg/kg) in mice, as well as to block tremors and convulsions caused by a 'suprapharmacological' dose of 18 mg/kg (Vemuri et al., 2019).

Guidance on the management of acute and chronic harms of new psychoactive substances is provided in the Novel Psychoactive Treatment UK Network (NEPTUNE) guidelines (Abdulrahim and Bowden-Jones, 2015). Part V of the guidelines is dedicated to synthetic cannabinoids and suggests some measures for the clinical management of acute synthetic cannabinoid toxicity. Case reports suggest that hydration and monitoring may be sufficient for patients with mild to moderate poisoning. In patients with anxiety, panic attacks or agitation, treatment with benzodiazepines can be of benefit. Aggressive and agitated patients with a history of psychotic disorders might be medicated with neuroleptic agents. Owing to the lack of an antidote, symptomatic and supportive treatment is recommended. In the case of seizures, intravenous benzodiazepines have been reported to be effective. In the majority of cases, the effects of consumption of NPS seem to be self-limiting and can be treated symptomatically with intravenous fluids, benzodiazepines, supplemental oxygen and antiemetics.

The management of synthetic cannabinoid poisonings might be complicated by the fact that typical symptoms are unspecific and might be confused with symptoms arising from other types of medical conditions or poisonings (Tait et al., 2016). This overlap in clinical features, however, has also led to the realisation that patients presenting with somnolence and hypoventilation, with confirmation of acute synthetic cannabinoid poisoning, might show a positive response to naloxone infusion, similar to patients presenting with acute opioid poisoning (Richards et al., 2017). In some cases, symptom improvement was reported after naloxone administration to patients who had reported 'Spice' consumption and tested negative for opioids. However, these results are preliminary and should viewed with caution, especially as it is not known if the improvement in symptoms would have occurred spontaneously, even without any form of pharmacotherapy (Jones et al., 2017).

In clinical settings, diagnosis of synthetic cannabinoid poisonings should be approached with caution, and an in-depth study of the case is needed. Therapy remains supportive and symptom related (Castellanos and Gralnik, 2016). The clinical presentation alone may not be sufficient to demonstrate synthetic cannabinoid intake, and multiple illnesses such as hypoglycaemia, infections, thyroid hyperactivity, head trauma, other types of poisoning and mental diseases can cause similar symptoms (Tait et al., 2016). Owing to similarities in the clinical presentation, the treatment of acute poisoning partly overlaps with that of withdrawal symptoms.

The majority of poisoned patients present with relatively mild symptoms and do not require hospitalisation (Tait et al., 2016; Castellanos and Gralnik, 2016). According to a study of synthetic cannabinoid exposures reported to the poison center, symptoms resolved within 8 hours in 78.4 % of the cases and within 24 hours in 16.6 % of the cases (Hoyte et al., 2012). In another survey, among users of cannabis and synthetic cannabinoids who had sought medical attention (n = 21), there was no difference between groups in the number of users who reported having been admitted to hospital or in time to recovery. The majority recovered within 24 hours; however, 28.6 % of synthetic cannabinoid-poisoned patients took 2 weeks to recover (Winstock et al., 2015). Indeed, the setting in which poisoning is managed (i.e. in an outpatient clinic or in hospital) strongly depends on the severity of the symptoms (Castellanos and Gralnik, 2016). In a study performed by Hermanns-Clausen et al. (2013a), severe symptoms, assessed by the Poisoning Severity Score, were seen in only 1 case out of 29.

Monitoring is a fundamental part of the clinical management of synthetic cannabinoid poisonings, and should be carried out in a quiet environment, focusing on cardiovascular function, as poisoning commonly results in cardiovascular symptoms (often tachyarrhythmia). Accurate monitoring of neurological functions is also useful, given that poisoning is likely to result in central nervous system depression to some degree and the risk of respiratory depression, which may eventually require protection of the airways (Müller et al., 2016). ECG monitoring, pulse oximetry and a wide range of clinical and laboratory tests, depending on the particular case, are also suggested, including screening for other drugs of abuse and medications that might have been co-ingested (Müller et al., 2016).

As shown in some retrospective case series, supportive care, with intravenous fluid administration and eventually potassium supplementation, is the preferred method of treatment (Forrester et al., 2011; Hermanns-Clausen et al., 2013a; Hoyte et al., 2012) and is generally sufficient in patients presenting with mild to moderate symptoms (Castellanos and Gralnik, 2016). Supportive care could be particularly helpful in the case of vomiting and dehydration or for the recovery of renal function (Müller et al., 2016). Furthermore, fluids were sufficient to treat hypotension and bradycardia in the cases presented by Forrester et al. (2011). Intravenous fluids, airways protection, cardiac monitoring and the prevention of rhabdomyolysis were described as the primary goals in cases of synthetic cannabinoids poisoning by Tait et al. (2016).

Further therapies are influenced by the specific symptoms manifested by patients. In particular, benzodiazepines represent a first-line treatment for patients who present with

agitation, anxiety, acute psychosis and seizures (Cooper, 2016), coupled with neuropsychiatric supportive assessment (Müller et al., 2016). Antipsychotics such as haloperidol and quetiapine can also be applied in cases of acute panic, hallucinations (Hermanns-Clausen et al., 2013a), delusion and psychosis (Müller et al., 2016). In one detoxification centre that administered diazepam (5–25 mg orally for, on average, 4 days) and quetiapine (25–475 g for, on average, 8 days) to counteract withdrawal symptoms, patients described antipsychotics as more effective than benzodiazepines (Macfarlane and Christie, 2015). Similar results were reported by Nacca et al. (2013): relief of withdrawal symptoms in a patient who was unresponsive to benzodiazepines, hydroxyzine and diphenhydramine was achieved by quetiapine administration.

Phenobarbital, for the treatment of anxiety and prophylaxis of seizures, was used in a detoxification case in combination with naltrexone to control drug cravings (Rodgman et al., 2014).

Antiemetics can be administered in the presence of nausea or hyperemesis syndrome, although such compounds have not always proven beneficial (Hermanns-Clausen et al., 2013a), as in the case reported by Ukaigwe et al. (2014), in which the use of ondansetron was not an effective approach. The role of gastrointestinal decontamination, in the context of synthetic cannabinoids poisoning, is limited by two factors: the preferential parenteral intake through smoking and the limited toxicity, which is self-resolving in most cases. In the series reported by Forrester et al. (2011), less than 5 % of patients were treated with some kind of decontamination (e.g. activated charcoal, lavage or irrigation/dilution).

Finally, intravenous lipid emulsion was administered in four users rushed to the emergency department after reported use of synthetic cannabinoids (Aksel et al. 2015). Cardiovascular recovery, with normal blood pressure and pulse rate, as well as neurological recovery (testified by an improvement in Glasgow Coma Scale score), was seen in three out of the four patients, but treatment was ineffective in the one individual in whom co-consumption of heroin was considered likely. Intravenous administration of lipid emulsion is useful in the setting of highly lipophilic drugs, and intoxicated unstable patients may benefit from it, according to a case series published by Aksel et al. (2015). However, it has to be kept in mind that there is no high-level evidence to support the use of this therapy in the context of synthetic cannabinoids poisoning.

## 5.2. Chronic toxicity

The effects of chronic exposure to synthetic cannabinoids are largely unknown. No study has clearly documented the effects in humans of long-term consumption of synthetic cannabinoids, which – unlike cannabis – are not used as prescription medicines (with the exception of nabilone) (EMCDDA, 2018a). However, as already mentioned, some studies on animals or cell models and case reports on humans suggest that synthetic cannabinoids can cause certain forms of chronic toxicity.

Koller et al. (2013) demonstrated that JWH-018, JWH-073, JWH-122, JWH-210 and AM-694 did not show cytotoxic or genotoxic effects in various human cell lines at concentrations reached in the body of consumers. CP-47,497-C8 was shown to have weak cytotoxic

properties, but is known to cause chromosomal damage (Koller et al., 2014). Bileck et al. (2016) found that CP-47,497-C8 has pro-inflammatory effects and can induce DNA damage. In another study, Koller el al. (2015) investigated the genotoxic properties of AM-2201, UR-144, 5F-AKB48 and AM-2201-IC at elevated concentrations and demonstrated chromosomal damage, but no gene mutations. Tomiyama and Funada (2014) showed potential neurotoxic effects of eight synthetic cannabinoids (CP-55,940, CP-47,497, CP-47,497-C8, HU-210, JWH-018, JWH-210, AM-2201 and MAM-2201) in a mouse brain cell line. Ferk et al. (2016) found that 5F-UR-144 (XLR-11) and RCS-4 induced micronuclei, which are formed as a consequence of chromosomal aberrations. Chronic use of synthetic cannabinoids has been associated with a greater risk of developing a mental health disorder than use of cannabis (Cohen and Weinstein, 2018; Skryabin and Vinnikova, 2018), which may include dependence. Acute and chronic use of synthetic cannabinoids has also been associated with detrimental effects on cardiovascular health (Ozturk et al., 2019; Pacher et al., 2018).

Animal data

The cognitive effects of the long-term administration of CP-55,940 were studied in adolescent and adult mice, which were challenged with increasing doses of 0.15, 0.20 and 0.30 mg/kg, each administered for 7 consecutive days. Animals were tested in tasks of object recognition (i.e. discrimination of a novel object from a familiar one) and object location (i.e. the ability to identify an object moved to a new place). While no significant effects were seen in adult mice, the chronic exposure to CP-55,940 in adolescence led to impairments in the cognitive processes investigated, involving spatial and short-term memory (Renard et al., 2013). A lasting impairment of memory, together with the development of anxiety (as assessed through social interaction tests) resulting in a decrease in social interaction, was seen in adolescent, but not adult, rats exposed to incremental doses of CP-55,940 (0.15, 0.20 and 0.30 mg/kg for 3, 8 and 10 days) (O'Shea et al., 2004). The effects of repeated administration of WIN-55,212-2 have also been studied in a number of animal models. Pubertal treatment with the synthetic cannabinoid at a dose of 1.2 mg/kg in a chronic administration setting led to deficiency in object recognition memory and in sensorimotor gating, which is a model to study sensory overstimulation. Cognitive fragmentation, attention impairments and anhedonia were also assessed in the same animal study. These functions are all involved in the development of schizophrenia; thus, their disruption in cases of adolescent chronic cannabinoid exposure indicates that synthetic cannabinoids could be implicated in the development of signs of mental disease (Schneider and Koch, 2003). Chronic administration of WIN-55,212-2 (1.2 mg/kg for 25 days) induced cellular long-term modifications in areas of the brain involved in the development of substance abuse and behavioural effects, which included the disruption of sensorimotor gating, increased motor activity and reduced anxious behaviour (Wegener and Koch, 2009). As many of these effects were proven in adolescent animals and not in adults, the chronic effects of synthetic cannabinoids seem to be dependent on the age at exposure and on the dose administered (Castaneto et al., 2014).

Human data

While there are no data on the long-term safety of synthetic cannabinoids, long-term effects may partially be inferred from what happens following the prolonged consumption of cannabis, which is associated with an increased risk of psychosis and hallucinations (McGrath et al., 2010). Signs of psychosis with perceptual alterations and hallucinations were experienced by 10 otherwise healthy young men who reported having consumed synthetic cannabinoids on several occasions (from four times over 3 weeks up to daily use over 1.5 years), and symptoms persisted for up to more than 5 months (Hurst et al., 2011).

Heavy and prolonged cannabis consumption can also be associated with changes in brain volume, especially the hippocampus, which plays a major role in memory, and the amygdala, a region known to be crucial for emotional processing. Similar effects might be expected from synthetic cannabinoids, although no data on humans are available so far (Seely et al., 2012).

Recently, Cohen et al. (2017) compared executive function in non-users, recreational cannabis users and synthetic cannabinoid users (38 individuals who had consumed synthetic cannabinoids at least 10 times in the last year without binge consumption). Computerised cognitive function tests, the classical Stroop word–colour task, the n-back task and a free-recall memory task were used. In the synthetic cannabinoids group, impairment of cognitive function, and particularly of working memory, long-term memory and inhibitory control, abilities was demonstrated to be greater among synthetic cannabinoid users than among cannabis users (Cohen et al., 2017).

## 5.3. Psychological and behavioural effects

The typical effects of synthetic cannabinoids are similar to the known effects of cannabis and include relaxation, mild euphoria, lethargy, sedation, confusion, anxiety, fear, amnesia, derealisation, depersonalisation, psychotropic effects (changed perception), cognitive dysfunction, impaired motor performance and ataxia (Theunissen et al., 2021). However, users of synthetic cannabinoids often exhibit agitation, rather than sedation, particularly after consumption of higher doses. Severely intoxicated patients may also present with hallucinations, panic attacks and psychosis. These dose-dependent effects appear to be much more pronounced and severe than those of cannabis (Ford et al., 2017; Zaurova et al., 2016). Specifically, psychotic episodes, confusion, paranoia, and aggressive and violent behaviour have been reported for a number of synthetic cannabinoids, including 5F-MDMB-PINACA (EMCDDA, 2018b; WHO, 2017).

## 5.4. Dependence and abuse potential

Animal *in vivo* and *in vitro* data

The limited data available on synthetic cannabinoids suggest a high potential for abuse and the potential for tolerance, dependence and withdrawal symptoms after chronic or long-term consumption. In general, drug discrimination studies, preference test studies and particularly the assessment of tolerance and reinforcement would be suitable tools to evaluate the dependence and abuse potential of synthetic cannabinoids.

Chronic administration of WIN-55,212-2 (1.2 mg/kg for 25 days) induced cellular long-term modifications in areas of the brain involved in the development of substance abuse and behavioural effects, which included the disruption of sensorimotor gating, increased motor activity and reduced anxious behaviour (Wegener and Koch, 2009).

Sim-Selley and Martin (2002) found that administration of escalating doses of WIN-55,212-2 for 15 days in mice led to tolerance to acute injection of cannabinoids, as demonstrated by behavioural effects such as hypoactivity, nociception and hypothermia. Moreover, autoradiographic studies showed that $[^{35}S]$GTPγS binding in all brain regions was decreased after chronic treatment.

Chronic treatment with CP-55,940 (0.4 mg/kg intraperitoneally twice a day for 6.5 days) produced tolerance to synthetic cannabinoid-mediated analgesic effects in rats and downregulation of CB receptors in several parts of the brain; in addition, in the case of $CB_1$ receptor antagonist administration, an abstinence syndrome was precipitated (Rubino et al., 2000).

As for physical dependence induced by synthetic cannabinoids, a withdrawal syndrome could be precipitated after 4 days' treatment with WIN-55,212-2 at any dose (1–16 mg/kg/day) by the administration of a $CB_1$ receptor antagonist (with symptoms occurring within 1 hour). Furthermore, spontaneous withdrawal symptoms were seen 24 hours after stopping the administration of medium doses (2–16 mg/kg/day) without the administration of an antagonist. In contrast, following 4 days' treatment with $Δ^9$-THC, only precipitated (but no spontaneous) withdrawal effects were demonstrated (Aceto et al., 2001), suggesting that full agonist synthetic cannabinoids having greater potential to produce dependence than cannabis.

Human data

The limited data available on synthetic cannabinoids suggest that the consumption of synthetic cannabinoids can produce tolerance and withdrawal-like symptoms when regular use is discontinued. These include anxiety, unstable mood, crying fits, feelings of inner emptiness, spatial disorientation, hyperacusis (i.e. an increased sensitivity to ordinary environmental sounds), somatic pain, shortness of breath, hyperventilation, intense sweating and sensations of motor and inner restlessness. Regular use of synthetic cannabinoids can lead to dependence, as seen in a case report of a patient who reported continued and escalating consumption of 'Spice Gold' for 8 months. Owing to the tolerance developed, the patient progressively increased the dose, finally reaching 3 g/day. Despite cognitive impairment and negative effects on his professional life, he continued to use the substance (Zimmermann et al., 2009).

In a survey of synthetic cannabinoid users, some participants reported the use of 'Spice' in hazardous situations, inability to stop consumption despite interference with daily life and use for a longer period than intended (Vandrey et al., 2012). Difficulty in stopping use, together with the development of withdrawal symptoms, was reported by 41 of 47 patients with problematic daily synthetic cannabinoids use who presented to a detoxification centre

(Macfarlane and Christie, 2015). The most commonly reported symptoms included agitation/irritability (83–89 %), anxiety (55%), and mood swings (55 %). Nausea and vomiting (44 %) and loss of appetite (17 %) were also frequently reported (Macfarlane and Christie, 2015). Neurological examination and ECG in two patients who reported smoking 3 g of herbal smoking mixture daily for more than 1 year revealed severe anxiety and sinus tachycardia as withdrawal symptoms (Nacca et al., 2013). Nervousness, irritability, insomnia and impatience were also reported by 11–15 % of synthetic cannabinoid users experiencing withdrawal syndrome (Vandrey et al., 2012).

## 5.5. Effects on ability to drive and operate machines

Owing to the psychological and behavioural impairment they induce, synthetic cannabinoids can negatively affect ability to drive and safely operate machines (Capron, 2016; Griffiths and Griffin, 2016; Kaneko, 2017; Karinen et al., 2015; Musshoff et al., 2014; Peterson and Couper, 2015). Driving while under the influence of synthetic cannabinoids places users and others at risk of injury.

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

Peterson and Couper (2015) reported 33 cases of suspected driving under the influence of drugs in which AB-CHMINACA was detected in blood samples. In 23 of these samples, no further drugs were detected. Drug recognition expert exams were performed in 10 of the 33 cases. The most common finding was extreme lane travel with near collisions and, in nine cases, the driver was found unconscious or slumped over the wheel. Horizontal gaze nystagmus was detected in 50 % and a lack of convergence was observed in 30 % of the drug recognition expert cases (Peterson and Couper, 2015).

Similarly, the operation of machinery while under the influence of synthetic cannabinoids may place the people who use these substances, and others, at risk of injury.

## 5.6. Social risks

While studies on the social risks of synthetic cannabinoids are rare, the available data from acute poisonings and self-reported user experiences suggest that the acute behavioural effects of synthetic cannabinoids and the associated social risks might be similar to those of cannabis. Such risks include negative impacts on social functioning and criminal activities, such as the involvement of organised crime in the manufacture, trafficking and distribution of the substance. Social risks connected to the long-term use of cannabis include, but are not restricted to, (reversibly) impaired cognitive functioning, amotivational syndrome and dependence.

Of particular note is that synthetic cannabinoids are increasingly used by vulnerable groups, such as people in prison and people experiencing homelessness. Reports suggest that this has caused new health and social problems and has exacerbated existing problems among these groups. For example, in prisons, alongside the adverse health effects of these

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

In addition, the detection of synthetic cannabinoids in cases of suspected driving under the influence of drugs indicates a potential for a wider risk to public safety.

# 6. Extent and patterns of use, availability and potential for diffusion

## 6.1. Prevalence of use

Data on the prevalence of use of synthetic cannabinoids are based on population and subpopulation surveys. In population-based studies, the prevalence of current synthetic cannabinoid use is generally found to be less than 1 %. The most recent national surveys found that last year use of synthetic cannabinoids among 15- to 34-year-olds ranged from 0.3 % in Spain and Lithuania to 0.6 % in Italy (EMCDDA, 2020d). In the case lifetime prevalence, the numbers can be higher and, in a population of German pupils aged 15–18 years in the area of Frankfurt/Main, reached 5–7 % when considering use over previous years, although the prevalence of use in the last month was much lower (about 1 %) (Werse et al., 2014). In the most recent European School Survey Project on Alcohol and Other Drugs (ESPAD) ,in 2019, 3.1 % of students (average calculated across 20 out of 35 countries) reported having used synthetic cannabinoids at least once in their lifetime, ranging from 1.1 % in Slovakia to 5.2 % in France (ESPAD Group, 2020).

In the United States, prevalence was found to be particularly high in high school students during 2011, when these substances first emerged in the country, although the available data suggest a steady decline since then. Palamar et al. (2017) found the prevalence of use among a group of high school seniors in the United States to be 2.9 % (past 30-day use) for the period 2014–2015 (*n* = 7 805). In that study, synthetic cannabinoid users were more likely to report the use of other (non-cannabis) drugs (Palamar et al., 2017). In a sample of 54 865 high school students (aged 13–19 years), the prevalence of past-year synthetic cannabinoid use was found to decrease across the study period. For example, past-year use among 12th grade students decreased from 11.86 % in 2011 to 4.75 % in 2015 (Keyes et al., 2016). In another study, the prevalence of synthetic cannabinoid use among attendees of electronic dance music parties in New York City in 2015 (*n* = 682) was reported to be 16.3 % (Palamar et al., 2016).

Characteristics of user groups

Synthetic cannabinoids may be sold and used as a 'legal' replacement for cannabis (EMCDDA, 2009, 2017). Because products containing synthetic cannabinoids rarely state the ingredients, some users will not know that they are using synthetic cannabinoids, and most who do know will be unaware of what substances they are consuming. Some users specifically seek out synthetic cannabinoids because these have a reputation for causing profound intoxication and they can be comparatively cheaper than other drugs.

It is known that synthetic cannabinoid users tend to also use cannabis (Gunderson et al., 2014), and that polydrug use is also common among this group (Joseph et al., 2019).

Several subpopulations of cannabis users show a relatively high prevalence of synthetic cannabinoids use, among them marginalised people (e.g. people experiencing homelessness, prisoners and injecting drug users) (Campbell and Poole, 2020; Gray et al., 2021). People who undergo regular drug testing (such as people in drug treatment, prisoners and drivers) may seek out synthetic cannabinoids because some drug tests/screens will be

unable to detect some cannabinoids (especially those that are relatively new to the drug market). People who use synthetic cannabinoids may also include recreational users (including cannabis users) and groups who experiment with substances (sometimes referred to as 'psychonauts').

There is some evidence that, in some countries, the prevalence of synthetic cannabinoids use is higher among psychiatric patients, and in particular psychotic patients, than in other populations. Welter et al. (2017) found that 7.2 % of psychiatric patients in Germany enrolled in a prospective pilot study (*n* = 332) reported synthetic cannabinoids consumption, with psychotic patients showing a higher prevalence than non-psychotic patients (10 % versus 4.5 %, respectively).

Although limited, there is some information to suggest a recent increase in the vaping of synthetic cannabinoids using electronic cigarettes by young people, including teenagers, in some parts of Europe; in some cases, the users believed that they were using CBD or THC (EMCDDA, 2020c).

## 6.2. Patterns of use

Route of administration

The most common way of using synthetic cannabinoids is by smoking either ready-to-use or homemade 'smoking mixtures' as a cigarette ('joint') or by using a vaporiser, 'bong' or pipe. Some synthetic cannabinoids have also been offered in the form of e-liquids for vaping in e-cigarettes. In addition, users might also prepare e-liquids containing synthetic cannabinoids at home. In prison settings, papers impregnated with synthetic cannabinoids are then smoked with tobacco or vaped using an electronic cigarette. Other routes of administration, such as oral administration or by injection, appear to be rare.

Dosage

Doses of synthetic cannabinoids that produce psychoactive effects vary with the potency of the substance. Many highly potent substances, such as MDMB-CHMICA, can cause psychoactive effects at doses less than 1 mg. Typical doses of less potent compounds, such as JWH-018, have been reported to be 2–5 mg (WHO, 2014). The dosage regimens used for synthetic cannabinoids can differ within and between individuals depending on the tolerance of the user, the concomitant use of other drugs and the desired effects. The purity, amount and/or composition of the substance ingested are not typically known by the user. In addition, the actual composition of the substance may differ over time and place.

Products containing synthetic cannabinoids rarely state the correct ingredients and/or their concentrations. Consequently, people who use such products will be unaware that they are using this substance and will be unable to obtain accurate dosage information.

In addition, in the case of herbal smoking mixtures, the process for mixing the synthetic cannabinoids with the plant material can lead to heterogeneity of composition and dangerous amounts of the substances in the products. This is because producers have to determine

what quantity of substances should be added, while the mixing process makes it difficult to dilute them sufficiently and distribute them consistently throughout the plant material. This can result both in products that contain toxic amounts of the substances in general (Ernst et al., 2017; Frinculescu et al., 2017; Langer et al., 2014: Langer et al., 2016) and in products in which the solid particles of synthetic cannabinoids are clumped together, forming highly concentrated areas ('hot' pockets) within the plant material (Frinculescu et al., 2017; Moosmann et al., 2015; Schäper, 2016). In fact, in the latter case, simply tapping a packet containing a smoking mixture can dislodge the substances from the plant material. Paper (e.g. blotters and cards) impregnated with synthetic cannabinoids can pose a similar high risk of poisoning because the method of soaking and drying the paper, for example, can result in the synthetic cannabinoid being unevenly distributed in different parts of the paper, sometimes forming highly concentrated sections on the paper (Norman et al., 2020). These issues are made worse because the products are smoked or vaped, allowing the substances to be rapidly absorbed into the bloodstream and to reach the central nervous system and other parts of the body to cause their effects. Accounts from patients and people who witness poisonings suggest that, in some cases, a small number of puffs from a cigarette ('joint') have been sufficient to cause severe or even fatal poisoning.

Together, these factors, coupled with the typically high potency of synthetic cannabinoids, make it difficult for users to control the dose that they are exposed to. This can lead to the unintentional administration of a toxic dose.

## 6.3. Availability, supply and involvement of organised crime

The overall availability of synthetic cannabinoids on the market remains high, despite legal steps taken in many European countries and elsewhere. During the first years of the phenomenon, open sale in bricks-and-mortar head shops was permitted in some countries, but as result of the implementation of legal restrictions this practice has been stopped, or severely restricted, in many countries. Herbal smoking mixtures can be obtained from online retailers but may be also be acquired through dealer networks or from friends. The supply of bulk quantities of synthetic cannabinoids (pure substances) that are used to make products such as smoking mixtures and e-liquids largely appears to be from companies based in China.

Production

The production of the pure substances and the manufacture of (ready-to-use) products containing synthetic cannabinoids such as herbal mixtures and e-liquids have to be differentiated.

In general, most of the synthetic cannabinoids that emerge on the European drug market are patented substances originally synthesised for medical research. The majority of bulk powders of synthetic cannabinoids appear to be produced in laboratories based in China. From here, the synthetic cannabinoids are shipped to distributors, who process the powders into products, as well as to online retailers and, to a lesser extent, consumers in Europe and elsewhere (EMCDDA and Europol, 2019).

Trafficking

The available information suggests that synthetic cannabinoids are typically ordered from chemical companies based in China, which ship the substances, typically as powders, by mail and courier services to distributors and retailers in Europe. Similar to other NPS, in some cases consignments containing synthetic cannabinoids are misdeclared or concealed (EMCDDA and Europol, 2019).

Distribution among users, so called 'social supply', also seems to play an important role, in particular for polydrug users (Gunderson et al., 2014; Higgins et al., 2019; Werse et al., 2019).

Internet markets

The drug market has changed significantly over the last decade. While illicit drug markets have in the past been located on physical locations, the internet as a drug market has become increasingly popular. At least initially, the majority of synthetic cannabinoids were offered as herbal blends, e-liquids or research chemicals via internet shops on the surface web. However, synthetic cannabinoids and products containing synthetic cannabinoids have also become available on the darknet. The shops on the surface web offer a range of delivery and payment options. Payment options include debit and credit cards, bank transfer and e-commerce payment systems. More recently, payment by cryptocurrency, such as bitcoin, has also been accepted. Delivery is usually by express mail and courier services, as well as postal services.

Darknet markets have many similarities to marketplaces such as eBay and Amazon. As on the surface web, customers are able to compare and rate the various vendors and their products. However, in contrast to the surface web, buyers can act anonymously in the darknet. Both information about payment and the location of the servers that are involved in a transaction are concealed. Therefore, sellers' and buyers' privacy is better protected on the darknet. It is estimated that about two thirds of the offers on darknet markets are drug related, with the remainder related to a range of other illicit goods and services (EMCDDA and Europol, 2017). Darknet markets are most often global and operate in English, although some cater for a particular country or language group.

While attention is often focused on the use of the darknet for drug trafficking, the use of mainstream applications may be equally important, and such applications are more readily accessible. Following the development of social platforms such as Facebook, YouTube and Twitter, and their widespread use among young people, these platforms are being increasingly used by drug suppliers and dealers (EMCDDA and Europol, 2019).

At present, online markets are believed to account for a small proportion of the trade in illicit drugs, and many of the transactions are at the consumer level. However, the potential exists for further expansion of online drug trading.

Quality of the products on the market

*Typical impurities*

Impurities are defined as compounds that were intentionally added as reactants to a synthesis but were not completely turned into products of the reaction. Intermediate products of the synthesis could also be impurities.

Münster-Müller et al. (2020) investigated synthesis-related impurities in the synthetic cannabinoids CUMYL-5F-PINACA and MDMB-CHMICA. In CUMYL-5F-PINACA, 12 synthesis-related impurities were detected during the study. Several of these impurities could lead back to an incomplete reaction and therefore to intermediate reaction products (e.g. the molecules without the fluorpentyl side chain or without the linked group). Cumylamine dimers and fluoropentyl indole carboxamide dimers were also detected as common impurities. Additionally, compounds with the fluoropentyl chain in an undesired position could be identified during the study. In another study by the same authors (Münster-Müller et al., 2019), impurities from the synthesis of MDMB-CHMICA were investigated. In this case, 15 synthesis-related impurities could be identified. Similar to the previous case, most impurities were undesired intermediate products or compounds with some moieties found in another part of the target molecule. Interestingly, 5F-MDMB-PICA could be detected as an impurity during this study, although it technically constitutes a contaminant. Oberenko et al. (2019) detected three types of synthesis-related impurities in a study that was conducted in the Siberian region of Russia: unreacted main reagents for synthesis, purification reagents (used at the final stage of individual synthetic cannabinoid synthesis) and supplementary reagents (e.g. pH regulators).

*Contaminants and adulterants*

In March 2018, the United States Centers for Disease Control and Prevention reported an outbreak of life-threatening coagulopathy associated with the consumption of synthetic cannabinoids. Toxicological testing indicated that the affected individuals had been exposed to brodifacoum, a long-acting anticoagulant rodenticide. Overall, there were at least 324 cases of severe poisoning including eight deaths in 10 states (CDC, 2018). It was speculated that synthetic cannabinoid products were laced with brodifacoum to extend the 'high' after smoking, although there are no data supporting this assumption.

On occasion, opioids (e.g. U-47,700 and furanylfentanyl) 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 and Cordonnier, 2017).

# 7. Conclusions

Synthetic cannabinoids are the largest group of new psychoactive substances monitored by the EMCDDA through the EU Early Warning System, with 209 reported between 2008 and 2020. When synthetic cannabinoids first appeared on the market in Europe, around 2006, they were sold as legal replacements for cannabis. While this continues to be the case, they have also gained a reputation for having powerful intoxicating effects and, as a result, some users use them specifically for this reason. Although synthetic cannabinoids are used recreationally, in some places they are also used by people experiencing homelessness, prisoners and other vulnerable groups because of the profound intoxication they can cause while being comparatively cheaper than other drugs. They also continue to be used by those who are subjected to drug-testing procedures, including those in prison or undergoing drug treatment, as some tests cannot detect synthetic cannabinoids that have recently appeared on the drug market.

In Europe, since 2015, there has been a decrease in the number of synthetic cannabinoids identified for the first time each year and an overall decrease in seizures of the substances by law enforcement agencies. In part, these changes appear to be related to a disruption in the 'legal high' trade, which for a period saw synthetic cannabinoids being sold openly as 'legal' replacements to cannabis on the high street and on the internet in many countries in Europe. More generally, broader policy responses designed to restrict the availability of new psychoactive substances are also likely to have had an effect. This positive development, however, has taken place in the context of increasing concerns associated with the use of these substances. As noted, in some areas there has been an increase in use by vulnerable groups, such as prisoners and people experiencing homelessness. In addition, not only are some of the synthetic cannabinoids recently introduced to the market highly potent, but there are increasing reports of these substances being mis-sold or used to adulterate illicit drugs. For example, with the increased popularity of CBD and THC products, synthetic cannabinoids have been identified in e-liquids sold as CBD and THC in Europe. Another concerning development is the adulteration of low-THC cannabis products with synthetic cannabinoids. Overall, such adulterated products pose a high risk of poisoning to users.

In the future, it can be expected that compounds with a high potency and that are easy to synthesise will continue to be introduced into the market. In addition, there might be a continuation of current efforts by manufacturers to circumvent the (chemical) definition of generic approaches, as has been seen for other NPS.

The ongoing COVID-19 pandemic and the related response measures may affect, in unpredictable ways, existing markets in synthetic cannabinoids, their use and their patterns of use. It is possible that, in the event of reduced availability of cannabis in Europe, criminal groups, as well as people who use drugs, may use a range of replacement substances, including synthetic cannabinoids.

Given the growing complexity of the NPS market and its strong links with the broader illicit drug market, there is a need to ensure that Europe continues to strengthen its ability to detect, assess and respond to existing and new threats in a timely and effective way to

prevent or reduce the public health and social harms caused by synthetic cannabinoids, whether this is through detecting and responding to a specific, immediate threat or via longer term inputs into drug policy. The EU Early Warning System, operated by the EMCDDA and Europol, plays a central role in supporting national- and EU-level preparedness and responses to new psychoactive substances, including synthetic cannabinoids.

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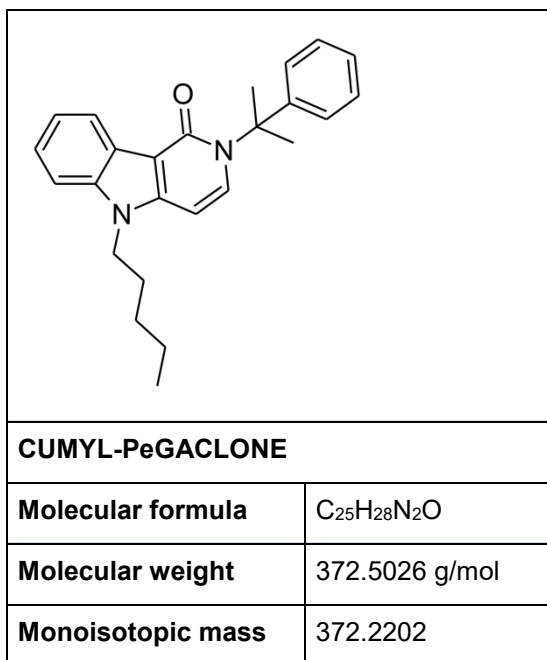
# Annexes

## Annex 1. Profiles of selected synthetic cannabinoids

### CUMYL-PeGACLONE

### Background information

CUMYL-PeGACLONE was the first representative of synthetic cannabinoids based on a *γ*-carbolinone scaffold. Structurally related compounds were originally developed by Bristol-Myers in 2001 (Leftheris et al., 2003). CUMYL-PeGACLONE emerged on the European drug market in December 2016, first detected in herbal blends test-purchased by the Institute of Forensic Medicine, Freiburg (Germany). It has been suggested that the substance may have been synthesised for the German drug market in order to circumvent a new national generic drug law that came into force in November 2016 (called NpSG) (Angerer et al., 2018a).



| CUMYL-PeGACLONE | |
|---|---|
| **Molecular formula** | $C_{25}H_{28}N_2O$ |
| **Molecular weight** | 372.5026 g/mol |
| **Monoisotopic mass** | 372.2202 |

### Chemical and physical description

Chemical description and names

International Union of Pure and Applied Chemistry (IUPAC) name(s): 5-pentyl-2-(2-phenylpropan-2-yl)-2,5-dihydro-1*H*-pyrido-[4,3-*b*]indol-1-one; 2-(1-methyl-1-phenyl-ethyl)-5-pentyl-pyrido[4,3-b]indol-1-one

CUMYL-PeGACLONE is characterised by a cumyl linking group (CUMYL) and a pentyl side chain (Pe) attached to a *γ*-carbolinone core system (GACLONE). The chemical structure lacks an open bridge scaffold. In this compound, the frequently used carboxamide linker is

directly attached to the indole nitrogen by an ethylene bridge, resulting in a tricyclic core system.

| IUPAC International Chemical Identifier (InChI) | InChI=1S/C25H28N2O/c1-4-5-11-17-26-21-15-10-9-14-20(21)23-22(26)16-18-27(24(23)28)25(2,3)19-12-7-6-8-13-19/h6-10,12-16,18H,4-5,11,17H2,1-3H3 |
|---|---|
| Standard InChI Key | AWHWTKXMUJLSRM-UHFFFAOYSA-N |
| Simplified Molecular-Input Line-Entry System (SMILES) | CCCCCN1C2=C(C3=CC=CC=C31)C(=O)N(C=C2)C(C)(C)C4=CC=CC=C4 |
| Chemical Abstract Service Registry Number (CAS RN) | 2160555-55-3 |
| Other names | SGT-151 |

Stereochemistry

CUMYL-PeGACLONE does not contain a chiral centre.

Physical description

Pure CUMYL-PeGACLONE is a crystalline solid. Melting point, boiling point or solubility data are not available in the literature. The substance is poorly soluble in water.

Analytical profile

The analytical profile of CUMYL-PeGACLONE has been described in publications using GC-MS, LC-HRMS, NMR, and infrared and ultraviolet–visible spectroscopy (Angerer et al., 2018a; Ernst et al., 2017). A thermal degradation product (*N*-pentyl-*γ*-carbolinone) was detected by Nash et al. (2019), with the product being produced in significant amounts at temperatures above 250 °C, which are commonly reached during smoking, the preferred route of administration.

**Pharmacology**

CUMYL-PeGACLONE has been shown to be a full agonist at both CB receptors, with binding affinities in the low nanomolar range ($K_i$ ($CB_1$) = 1.37 ± 0.24 nM; $K_i$ ($CB_2$) = 2.09 ± 0.33 nM) (Angerer et al., 2018a). The substance is extensively metabolised after consumption (no parent compound is detected in urine samples). Two main metabolites were described as suitable for urine screenings (hydroxylation of the core structure and hydroxylation with further oxidation at the pentyl side chain as the main phase I biotransformation steps) (Mogler et al., 2018a). No data are available in the literature describing the pharmacokinetic properties of CUMYL-PeGACLONE.

In a panel of 21 synthetic cannabinoids chosen to cover a broad diversity in chemical structures, CUMYL-PeGACLONE was among the most potent and efficacious compounds in

two NanoBiT® bioassays assessing $CB_1$ receptor activation (mini-$G\alpha_i$ assay: $EC_{50}$ = 0.07 nM (CP-55,940: 0.12 nM), $E_{max}$ = 261 % (CP55,940 set to 100 %); β-arrestin2 assay: $EC_{50}$ = 0.09 nM (CP-55,940: 0.48 nM), $E_{max}$ = 655 % (CP-55,940 set to 100 %)) (Wouters et al., 2020).

## Toxicology

Twenty-seven non-fatal and fatal poisonings involving CUMYL-PeGACLONE were reported by Halter et al. (2019), with serum or femoral blood concentrations ranging from 0.12 to 13 ng/ml. In all six death cases presented, the compound was assigned a low toxicological significance, suggesting an alternative cause of death (Halter et al., 2019).

Five CUMYL-PeGACLONE-related fatalities in the Northern Territory of Australia were recently reported by Tiemensma et al. (2021), with a concentration range in post-mortem blood of 0.73–3.0 ng/ml. In most cases, concurrent alcohol use and underlying cardiovascular disease were considered relevant factors. However, in four of the cases, the presence of CUMYL-PeGACLONE was considered highly significant with respect to the cause of death (Tiemensma et al., 2021).
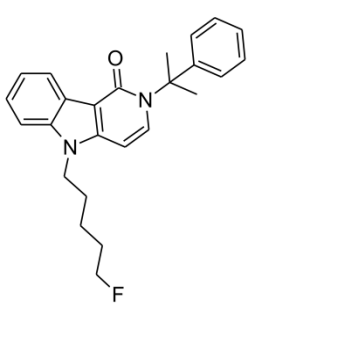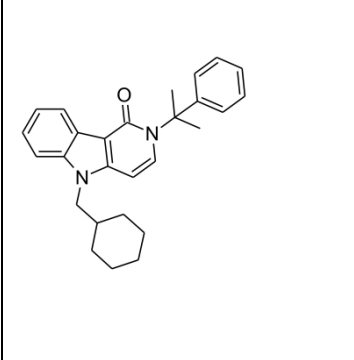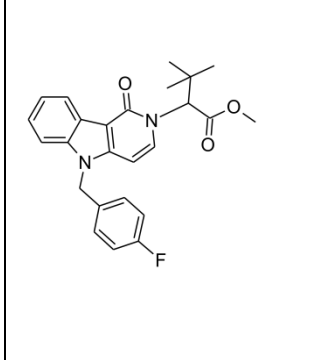
## Dependence and abuse potential

There are no data available in the literature on the potential of CUMYL-PeGACLONE to produce dependence or on its abuse liability.

## Epidemiology in Germany

During the market monitoring of products test-purchased and analysed in the Institute of Forensic Medicine, Freiburg (Germany), CUMYL-PeGACLONE was detected in 25 % of all products between January and December 2017 (*n* = 288). Detections continued to occur during the first half of 2018, until it was almost completely replaced by 5F-Cumyl-PeGaClone after CUMYL-PeEGACLONE was scheduled under the German Narcotics Act in July 2018. In the following years, the compound was no longer detected. At the Institute of Forensic Medicine in Freiburg, CUMYL-PeGACLONE was the synthetic cannabinoid detected most often in serum and urine screenings in 2017 and in the first half of 2018 (own unpublished data). After July 2018, the prevalence dropped sharply, with only sporadic detection of the compound (serum) or its metabolites (urine).

## Structurally related synthetic cannabinoids

So far, five structurally related *γ*-carbolinone derivatives have emerged on the synthetic cannabinoids market. 5F-Cumyl-PeGaCLone(5F-SGT-151) was first detected in December 2017 in Germany after CUMYL-PeGACLONE was scheduled under the German Narcotics Act. Cumyl-CH-MeGaClone was reported to the EMCDDA in November 2018 by Hungary. Cumyl-CB-MeGaClone was formally notified by the EMCDDA on behalf of Hungary in June 2020 and Cumyl-BC-HpMeGaClone-221 (also known as CUMYL-NB-MeGaClone) was formally notified on behalf of Germany in September 2020. 'MDMB-FUBGACLONE' is a *γ*-carbolinone derivative that is sold online, although it has not been formally notified up to now.

| | 5F-Cumyl-PeGaClone | Cumyl-CH-MeGaClone | 'MDMB-FUBGACLONE' |
|---|---|---|---|
| |  |  |  |
| **Molecular formula** | $C_{25}H_{27}FN_2O$ | $C_{27}H_{30}N_2O$ | $C_{23}H_{30}N_2O_3$ |
| **Molecular weight** | 390.4931 g/mol | 398.5399 g/mol | 382.4959 g/mol |
| **Monoisotopic mass** | 390.2107 | 398.2358 | 382.2256 |

## CUMYL-5F-P7AICA

### Background information

CUMYL-5F-P7AICA is the first synthetic cannabinoid showing a 7-azaindole core structure and was first reported to the EMCDDA in February 2015 by Slovenia. Synthetic cannabinoids comprising cumyl substituents were first mentioned in a patent application of Bowden and Williamson (2014). However, in this patent, no synthetic cannabinoid with a 7-azaindole core was mentioned. The emergence of 7-azaindole synthetic cannabinoids appears to have coincided with the introduction of generic NPS laws in Europe, which typically included variations of compounds based on indole or indazole core structures, and is an indicator of producers' ability to adapt the control measures in place.
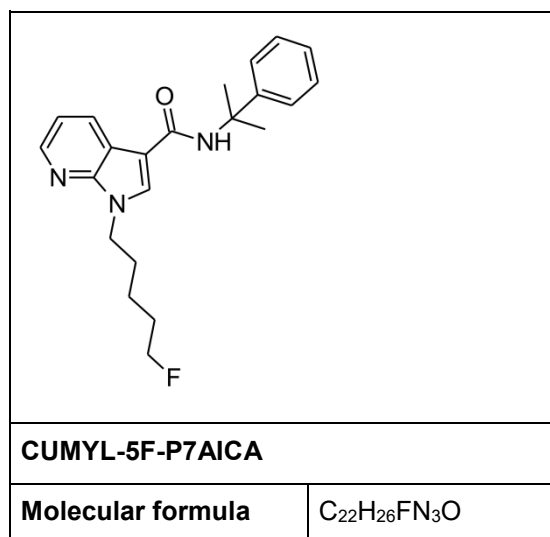


| CUMYL-5F-P7AICA | |
|---|---|
| **Molecular formula** | $C_{22}H_{26}FN_3O$ |

| Molecular weight | 367.4597 g/mol |
| --- | --- |
| Monoisotopic mass | 367.2060 |

## Chemical and physical description

Chemical description and names

IUPAC name: 1-(5-fluoropentyl)-*N*-(2-phenylpropan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxamide

CUMYL-5F-P7AICA can be regarded as the 7-azaindole (7AI) analogue of the indazole carboxamide synthetic cannabinoid CUMYL-5F-PINACA (CUMYL-5F-PINACA/SGT-25). The position of the nitrogen in the pyridine ring was confirmed by NMR analysis (EMCDDA, 2021b). To differentiate from possible azaindole isomers, Martek et al. (2019) proposed [1]H–[15]N heteronuclear multiple-bond correlation NMR as a tool for rapid and unambiguous identification. The first azaindole monitored by the EMCDDA (5F-PCN) was a 5-azaindole.

| IUPAC International Chemical Identifier (InChI) | InChI=1S/C22H26FN3O/c1-22(2,17-10-5-3-6-11-17)25-21(27)19-16-26(15-8-4-7-13-23)20-18(19)12-9-14-24-20 |
| --- | --- |
| Standard InChI Key | MXJYOUMYJGNQEY-UHFFFAOYSA-N |
| Simplified Molecular-Input Line-Entry System (SMILES) | O=C(NC(C)(C)C1=CC=CC=C1)C2=CN(CCCCCF)C3=C2C=CC=N3 |
| Chemical Abstract Service Registry Number (CAS RN) | — |
| Other names | SGT-263 |

Stereochemistry

CUMYL-5F-P7AICA does not contain a chiral centre.

Physical description

Pure CUMYL-5F-P7AICA is described as a neat solid. Its melting point is 174–176 °C (Banister et al., 2019). Boiling point or solubility data are not available in the literature. The substance is poorly soluble in water.

Analytical profile

The analytical profile of CUMYL-5F-P7AICA has been comprehensively described in the literature, including routes of synthesis and GC-MS, LC-HRMS and NMR data (Asada et al., 2018; Banister et al., 2019).

## Pharmacology

The binding affinities and functional activities of CUMYL-5F-P7AICA were evaluated by Banister et al. (2019) and compared with corresponding indole and indazole analogues. CUMYL-5F-P7AICA showed high binding affinities and activities at both CB receptors ($K_i$ (CB$_1$) = 174 nM, EC$_{50}$ (CB$_1$) = 4.7 nM, $K_i$ (CB$_2$) = 75.9 nM, EC$_{50}$ (CB$_2$) = 11.3 nM), but both affinity and activity were lower than those of the indole and indazole analogues (Banister et al., 2019). Metabolism of the substance in humans was studied by Staeheli et al. (2019). Major *in vivo* biotransformation steps in human metabolism were oxidative defluorination followed by carboxylation, and monohydroxylation followed by sulfatation and glucuronidation. No data are available in the literature describing the pharmacokinetic properties of the substance.

## Toxicology

One report of poisoning involving CUMYL-5F-P7AICA with unknown causality described has been published, by Piontek and Hannemann (2018).

## Dependence and abuse potential

There are no data available in the literature on the potential of CUMYL-5F-P7AICA to produce dependence or its abuse potential.

## Epidemiology in Germany

During the market monitoring of products test-purchased and analysed in the Institute of Forensic Medicine, Freiburg (Germany), CUMYL-5F-P7AICA has been detected relatively seldomly (in approximately 2 % of all products between 2016 and 2018 and no further detections since December 2020; the compound was scheduled under the German Narcotics Act in July 2018). In serum and urine samples screened at the Institute of Forensic Medicine, Freiburg, there were very few positives for the compound or its metabolites in 2017 and no positives thereafter (own unpublished data). There were no epidemiological data on CUMYL-5F-P7AICA found in the literature.

## Structurally related synthetic cannabinoids

To date, five 7-azaindole-derived synthetic cannabinoids, in addition to CUMYL-5F-P7AICA, have emerged on the drug market. All of them are 7-azaindole analogues of well-known indole- or indazole-based synthetic cannabinoids.
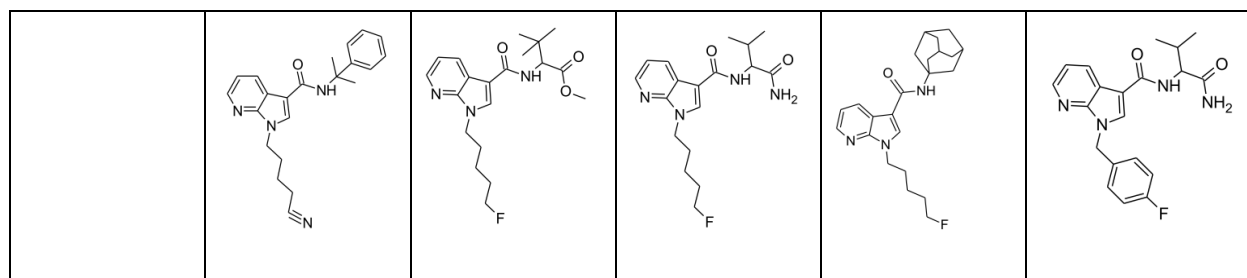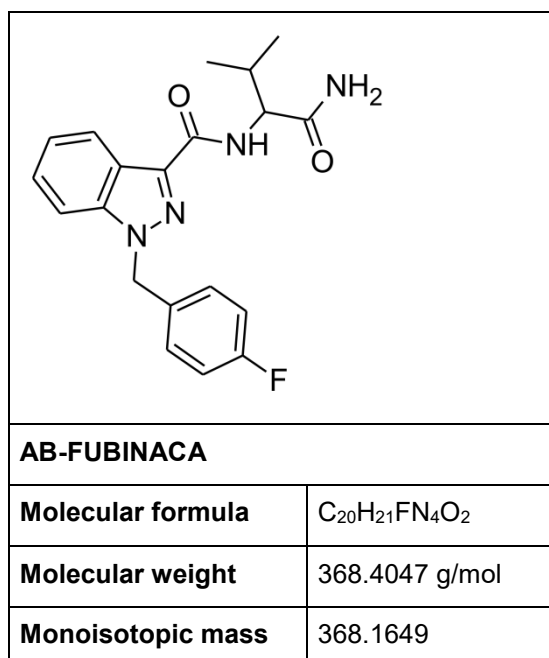
| | CUMYL-4CN-B7AICA | 5F-MDMB-P7AICA | 5F-AB-P7AICA | 5F-A-P7AICA | AB-FUB7AICA |
|---|---|---|---|---|---|
| **Molecular formula** | $C_{22}H_{24}N_4O$ | $C_{20}H_{28}FN_3O_3$ | $C_{18}H_{25}FN_4O_2$ | $C_{23}H_{30}FN_3O$ | $C_{20}H_{21}FN_4O_2$ |
| **Molecular weight** | 360.4522 g/mol | 377.4530 g/mol | 348.4151 g/mol | 383.5022 g/mol | 368.4047 g/mol |
| **Monoisotopic mass** | 360.1950 | 377.2115 | 348.1962 | 383.2373 | 368.1649 |

## AB-FUBINACA

## Background information

AB-FUBINACA was one of the first synthetic cannabinoids to emerge, in 2012, on the Japanese drug market and features a valinamide linker group (Uchiyama et al., 2013c). It is structurally closely related to AB-PINACA and other valinamide derivatives that were originally synthesised by Pfizer in 2009 (Buchler et al., 2009).



| **AB-FUBINACA** | |
|---|---|
| **Molecular formula** | $C_{20}H_{21}FN_4O_2$ |
| **Molecular weight** | 368.4047 g/mol |
| **Monoisotopic mass** | 368.1649 |

## Chemical and physical description

Chemical description and names

IUPAC name: *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamide

AB-FUBINACA is an indazole carboxamide synthetic cannabinoid (INACA) with a *(L)*-valinamide linker group (AB). It is the first synthetic cannabinoid with a 4-fluorobenzyl side chain (FUB) that was notified to the EMCDDA.

| | |
|---|---|
| IUPAC International Chemical Identifier (InChI | InChI=1S/C20H21FN4O2/c1-12(2)17(19(22)26)23-20(27)18-15-5-3-4-6-16(15)25(24-18)11-13-7-9-14(21)10-8-13/h3-10,12,17H,11H2,1-2H3,(H2,22,26)(H,23,27)/t17-/m0/s1 |
| Standard InChI Key | AKOOIMKXADOPDA-KRWDZBQOSA-N |
| Simplified Molecular-Input Line-Entry System (SMILES | CCCCCN1C2=C(C3=CC=CC=C31)C(=O)N(C=C2)C(C)(C)C4=CC=CC=C4 |
| Chemical Abstract Service Registry Number (CAS RN | 1629062-56-1 (racemate); 1185282-01-2 ((*S*)-AB-FUBINACA) |
| Other names | — |

Stereochemistry

AB-FUBINACA contains a chiral centre. It is assumed that, because of the route of synthesis and the availability of synthesis precursors, AB-FUBINACA occurs mainly as the (*S*)-enantiomer, which can be expected to be much more potent than the (*R*)-enantiomer (Antonides et al., 2019).

Physical description

Pure AB-FUBINACA is a crystalline solid. Its melting point is 163.0–165.5 °C (Longworth et al., 2016). Boiling point and solubility data are not available in the literature. It is described as soluble in organic solvents (~0.5 mg/ml in a 1:1 ratio of dimethyl sulfoxide to phosphate buffered saline at pH 7.2; ~3, 10 and 5 mg/ml in ethanol, dimethyl sulfoxide and N,N-dimethyl formamide) (Cayman Chemical Company, 2019).

Analytical profile

In the literature, AB-FUBINACA was identified for the first time in drug products by Uchiyama and colleagues in 2012 using NMR, GC-MS and LC-HRMS (Uchiyama et al., 2013c). A route for the synthesis of AB-FUBINACA and of structurally related indole and indazole carboxamide-type synthetic cannabinoids has been published in the literature (Banister et al., 2015; Longworth et al., 2016). Electrospray ionisation fragmentation pathways of 'FUBINACA'-type synthetic cannabinoids were recently described by Sekuła et al. (2018).

**Pharmacology**

In the studies of Banister et al. (2015), AB-FUBINACA showed high functional activity at both types of CB receptors ($hCB_1$ $EC_{50}$ = 1.8 nM; $hCB_2$ $EC_{50}$ = 3.2 nM). The administration of AB-FUBINACA and structurally related synthetic cannabinoids to mice was performed by Canazza et al. (2017). In comparison with $\Delta^9$-THC, AB-FUBINACA was shown to be much more potent in the tetrad model. In higher doses, severe neurological effects, such as seizures, myoclonia and hyperreflexia, including the promotion of aggressiveness, were observed. In this study, the binding affinities of AB-FUBINACA were determined using Chinese hamster ovary membranes ($hCB_1$ $K_i$ = 0.734 ± 0.071 nM; $hCB_2$
$K_i$ = 0.933 ± 0.082 nM) (Canazza et al., 2017).

The main metabolic reaction of AB-FUBINACA was shown to be hydrolysis of the terminal amide function, which is mainly catalysed by carboxylesterases (Thomsen et al., 2015). This metabolite was also reported as the predominant biotransformation product found in human urine samples (Castaneto et al., 2015).

**Toxicology**

Supraventricular tachycardia and acute confusion were reported in a healthy 24-year-old man who ingested e-cigarette fluid purchased on the internet, which was later analysed and found to contain AB-FUBINACA and ADB-FUBINACA. Somnolence, confusion and agitation, coupled with gastrointestinal symptoms, such as vomiting, developed 30 minutes after consumption and required attendance at the emergency department, where the intake was confirmed by serum analysis (AB-FUBINACA 5.6 ng/ml and ADB-FUBINACA 15.6 ng/ml). The patient presented with high blood pressure, low body temperature (36.3 °C) and tachycardia (Lam et al., 2017). He recovered and was discharged 22 hours after admission.

A case of fatal poisoning was reported in which a combination of EAM-2201, AB-PINACA, AB-FUBINACA and a synthetic cathinone (α-PVP) was identified in post-mortem samples (Yamagishi et al., 2018). However, AB-FUBINACA was not quantified in the blood and information on the case is limited. A fatality was also reported involving 2.0 ng/ml AB-FUBINACA (Fernandez et al., 2016). A propensity for sedation, tachycardia and hypothermia was also seen in a case series of four patients who reported ingestion of 'molly' and in whom urine samples tested positive for AB-FUBINACA (Brenneman et al., 2016). A blood concentration of 0.97 ng/ml AB-FUBINACA was reported in a death case described by Hess et al. (2015), in combination with AB-CHMINACA (2.8 ng/ml), 5F-AMB (0.19 ng/ml), 5F-AKB48 (0.51 ng/ml), STS-135 (0.16 ng/ml) and THJ-2201 (0.16 ng/ml). The 25-year-old male had a history of synthetic cannabinoid use and died from diabetic ketoacidosis. Synthetic cannabinoids were considered the main reason for him skipping the administration of his daily insulin dose (Hess et al., 2015).
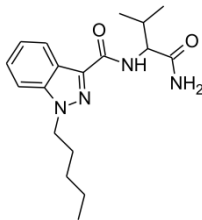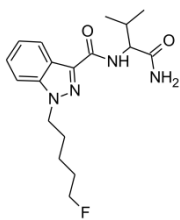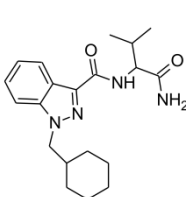
**Dependence and abuse potential**

In a recent study, repeated administration of AB-FUBINACA was found to induce physical dependence in mice. Although mice did not develop tolerance to AB-FUBINACA or cross-tolerance to THC, somatic precipitated withdrawal signs were observed (Trexler et al., 2020).

## Epidemiology in Germany

During the market monitoring of products test-purchased and analysed at the Institute of Forensic Medicine, Freiburg, Germany (EU-funded projects SPICE, SPICE II plus and SPICE Profiling), AB-FUBINACA was detected mainly in 2014 (in more than 20 % of all test-purchased products; it was scheduled under the German Narcotics Act in December 2014). AB-FUBINACA continued to be detected in about 4 % of all products analysed between December 2015 and September 2018 ($n = 2\,474$). In 2019 and 2020, it was not detected at all. In urine analysis, it is usually not possible to distinguish between the consumption of AB-FUBINACA and AMB-FUBINACA because the main metabolite of both compounds is the same. The common metabolite was detected in more than 60 % of all positive urine samples in 2014, about 35 % in 2015, more than 20 % in 2016 and about 15 % in 2013, 2017 and 2018. In 2019, the metabolite was detected in less than 10 % of positive samples, and this dropped further, to about 5 %, in 2020. In serum samples, AB-FUBINACA was last detected in 2017 (about 3 % of the positive samples; no positives in 2019 and 2020) (own unpublished data).

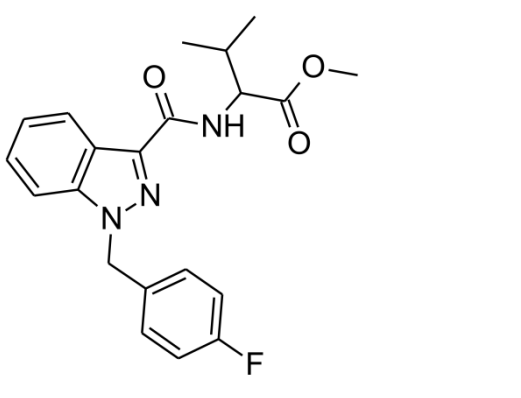## Structurally related synthetic cannabinoids

Several structurally related valinamide derivatives were reported to the EMCDDA. Structural modifications are the exchange of the 4-fluorobenzyl group by pentyl, 5-fluoropentyl or cyclohexylmethyl scaffolds.

| |  |  |  |
|---|---|---|---|
| | **AB-PINACA** | **5F-AB-PINACA** | **AB-CHMINACA** |
| **Molecular formula** | $C_{18}H_{26}N_4O_2$ | $C_{18}H_{25}FN_4O_2$ | $C_{20}H_{28}N_4O_2$ |
| **Molecular weight** | 330.4246 g/mol | 348.4151 g/mol | 356.4619 g/mol |
| **Monoisotopic mass** | 330.2056 | 348.1962 | 356.2212 |

## AMB-FUBINACA

### Background information

AMB-FUBINACA is structurally closely related to AB-FUBINACA, with the terminal amide group being replaced by a methoxy group. AMB-FUBINACA was the first synthetic cannabinoid with valinate linking groups to emerge on the European drug market, in 2014.



| AMB-FUBINACA | |
|---|---|
| **Molecular formula** | $C_{21}H_{22}FN_3O_3$ |
| **Molecular weight** | 383.4161 g/mol |
| **Monoisotopic mass** | 383.1645 |

### Chemical and physical description

Chemical description and names

IUPAC name(s): methyl-2-(1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamide)-3-methylbutanoate; methyl 2-[[1-[(4-fluorophenyl)methyl]indazole-3-carbonyl]amino]-3-methyl-butanoate

AMB-FUBINACA differs from AB-FUBINACA in having a methylbutanoate (AMB) scaffold.

| IUPAC International Chemical Identifier (InChI) | InChI=1S/C21H22FN3O3/c1-13(2)18(21(27)28-3)23-20(26)19-16-6-4-5-7-17(16)25(24-19)12-14-8-10-15(22)11-9-14/h4-11,13,18H,12H2,1-3H3,(H,23,26) |
|---|---|
| Standard InChI Key | FRFFLYJQPCIIQB-UHFFFAOYSA-N |
| Simplified Molecular-Input Line-Entry System (SMILES) | CC(C)C(C(=O)OC)NC(=O)C1=NN(C2=CC=CC=C21)CC3=CC=C(C=C3)F |
| Chemical Abstract Service Registry Number (CAS RN) | 1715016-76-4 |
| Other names | FUB-AMB, MMB-FUBINACA |

Stereochemistry

Like its valinamide analogue AB-FUBINACA, AMB-FUBINACA contains a chiral centre. Given the route of synthesis and availability of synthesis precursors, it is presumed that AMB-FUBINACA mainly occurs in the form of the (*S*)-enantiomer (Antonides et al., 2019).

Physical description

Pure AMB-FUBINACA is a crystalline solid. In the literature, it has also been described as a colourless oil (Banister et al., 2016). Melting point, boiling point or solubility data are not available in the literature.

Analytical profile

The analytical profile of AMB-FUBINACA has been described in the literature, including the synthetic pathway and NMR data (Banister et al., 2016). GC-MS, high-performance liquid chromatography time-of-flight (HPLC-TOF) and Fourier-transform infrared spectroscopy attenuated total reflection (FTIR-ATR) data were reported to the EMCDDA by the Slovenian National Focal Point (RESPONSE, 2015).

**Pharmacology**

In a study by Banister et al. (2016), AMB-FUBINACA showed functional activity at both types of CB receptors ($hCB_1$ $EC_{50}$ = 2.0 nM; $hCB_2$ $EC_{50}$ = 18 nM). The receptor-binding affinities were determined in a study by Schoeder et al. (2018) ($hCB_1$ $K_i$ = 0.387 ± 0.135 nM; $hCB_2$ $K_i$ = 0.536 ± 0.115 nM). AMB-FUBINACA is mainly metabolised to the carboxylic acid metabolite by terminal methylester hydrolysis (Apirakkan et al., 2020). In a recent study, Finlay et al. (2019) compared the activity profile of AMB-FUBINACA with 'traditional research cannabinoids' such as CP-55,940 and $\Delta^9$-THC and found significant discrepancies in the activity of AMB-FUBINACA in different cellular pathways, which might be related to divergent physiological $CB_1$-mediated effects of AMB-FUBINACA and other synthetic cannabinoids.

**Toxicology**

In July 2016, an outbreak of mass poisoning caused by AMB-FUBINACA occurred in New York, United States. Thirty-three patients presented with 'altered mental status', including lethargy and a reduction in the Glasgow Coma Scale score. AMB-FUBINACA was identified in a sample of product recovered from one of the patients. Metabolite of AMB-FUBINACA was also detected in biological samples from eight patients (Adams et al., 2017).

Adamowicz et al. (2019) reported the fatal poisoning of a 27-year-old male involving AMB-FUBINACA. The autopsy revealed pleural adhesions and pulmonary oedema, while samples collected during post-mortem examinations showed both AMB-FUBINACA and EMB-FUBINACA in tissues but not in blood. Concentrations in solid tissues ranged from 0.2 to 0.9 ng/ml and from 0.2 to 3.5 ng/ml, respectively (Adamowicz et al., 2019).
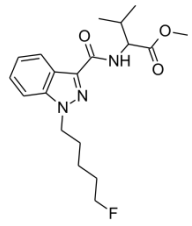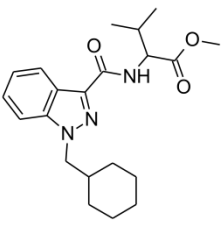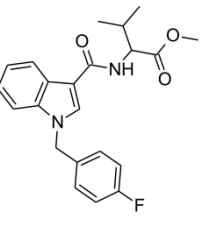
### Dependence and abuse potential

There are no data available in the literature on the potential of AMB-FUBINACA to produce dependence or on its abuse potential.

### Epidemiology in Germany

AMB-FUBINACA was regularly detected during the market monitoring of products test-purchased and analysed in the Institute of Forensic Medicine, Freiburg (Germany), between 2015 and 2018 (not detected in 2019 and 2020), with a maximum between 2015 and 2016 (AMB-FUBINACA was scheduled under the German Narcotics Act in June 2016). In urine analysis, it is not usually possible to distinguish between consumption of AB-FUBINACA and AMB-FUBINACA because the main metabolite of both compounds is the same. The common metabolite was detected in more than 60 % of all positive urine samples in 2014, about 35 % in 2015, more than 20 % in 2016 and about 15 % in 2013, 2017 and 2018. In 2019, the metabolite was detected in less than 10 % of the positive samples, and this dropped further to about 5 % in 2020. In serum samples, AMB-FUBINACA was detected in about 5 to 10 % of the positive samples until the second half of 2019, with only sporadic detection thereafter (own unpublished data).

### Structurally related synthetic cannabinoids

Several structurally related synthetic cannabinoids showing valinate moieties have been reported to the EMCDDA. Structural modifications include the exchange of the 4-fluorobenzyl group by 5-fluoropentyl or cyclohexylmethyl scaffolds and/or the replacement by the indazole ring with an indole core.

| | 5F-AMB-PINACA | AMB-CHMINACA | AMB-FUBICA |
|---|---|---|---|
| |  |  |  |
| **Molecular formula** | $C_{19}H_{26}FN_3O_3$ | $C_{21}H_{29}N_3O_3$ | $C_{22}H_{23}FN_2O_3$ |
| **Molecular weight** | 363.4264 g/mol | 371.4733 g/mol | 382.4280 g/mol |
| **Monoisotopic mass** | 363.1958 | 371.2210 | 382.1693 |

## 5F-MDMB-PICA

## Background information

5F-MDMB-PICA emerged on the European drug market in 2016 (Mogler et al., 2018b). It was synthesised by Banister et al. (2016) to study the structure–activity relationship of synthetic cannabinoids carrying *tert*-leucinate scaffolds.



| 5F-MDMB-PICA | |
|---|---|
| **Molecular formula** | $C_{21}H_{29}FN_2O_3$ |
| **Molecular weight** | 376.4650 g/mol |
| **Monoisotopic mass** | 376.2162 |
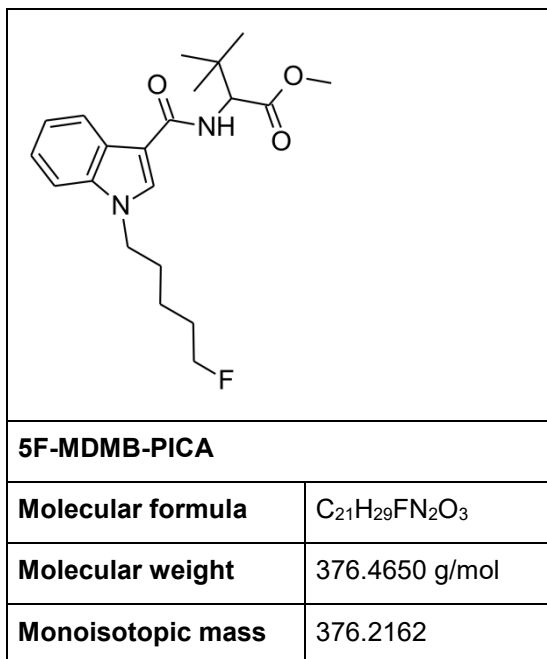
## Chemical and physical description

Chemical description and names

IUPAC name(s): methyl 2-[[1-(5-fluoropentyl)indole-3-carbonyl]amino]-3,3-dimethyl-butanoate; methyl *N*-{[1-(5-fluoropentyl)-1*H*-indol-3-yl]carbonyl}-3-methylvalinate

5F-MDMB-PICA is the indole analogue of the highly prevalent indazole carboxamide SC 5F-ADB (5F-MDMB-PINACA).

| IUPAC International Chemical Identifier (InChI) | InChI=1S/C21H29FN2O3/c1-21(2,3)18(20(26)27-4)23-19(25)16-14-24(13-9-5-8-12-22)17-11-7-6-10-15(16)17/h6-7,10-11,14,18H,5,8-9,12-13H2,1-4H3,(H,23,25)/t18-/m1/s1 |
|---|---|
| Standard InChI Key | CHSUEEBESACQDV-GOSISDBHSA-N |
| Simplified Molecular-Input Line-Entry System (SMILES) | CC(C)(C)C(C(=O)OC)NC(=O)C1=CN(C2=CC=CC=C21)CCCCCF |
| Chemical Abstract Service Registry Number (CAS RN) | 1971007-88-1 |

| Other names | 5F-MDMB-2201, MDMB-2201 |
|---|---|

Stereochemistry

5F-MDMB-PICA shows a chiral centre. It is assumed (based on the route of synthesis and the availability of synthesis precursors) that 5F-MDMB-PICA occurs mainly in the form of the (*S*)-enantiomer (Antonides et al., 2019).

Physical description

Pure 5F-MDMB-PICA is a crystalline solid. Its melting point is 82–84 °C (Banister et al., 2016). Boiling point and solubility data are not available in the literature.

Analytical profile

The analytical profile of 5F-MDMB-PICA has been described in the literature, including the synthetic pathway and NMR, GC-MS, high-performance liquid chromatography with diode array detection (HPLC-DAD) and liquid chromatography quadrupole time of flight mass spectrometry (LC-QTOF-MS) data (Banister et al., 2016; Mogler et al., 2018b; Risseeuw et al., 2017).

**Pharmacology**

A study by Banister et al. (2016) assessed the functional activity of 5F-MDMB-PICA and 16 other valinate and *tert*-leucinate synthetic cannabinoids at human $CB_1$ and $CB_2$ receptors. 5F-MDMB-PICA ($EC_{50}$ = 0.45 nM) was found to be about 380 times more potent than $\Delta^9$-THC ($EC_{50}$ = 171 nM) at the $CB_1$ receptor in the assay. Of all the cannabinoids investigated in this study, 5F-MDMB-PICA was reported to be the most potent. Regarding human metabolism, the product of ester hydrolysis has been shown to be the main phase I metabolite (Mogler et al., 2018b).

**Toxicology**

Cases of severe and fatal poisonings involving 5F-MDMB-PICA have been reported in the literature (Kleis et al., 2020; Nogee et al., 2019).

**Dependence and abuse potential**

There are no data available in the literature on the potential of 5F-MDMB-PICA to produce dependence or on its abuse potential.
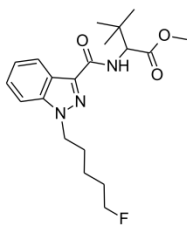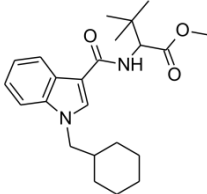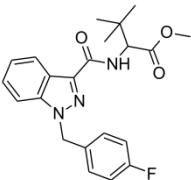
**Epidemiology in Germany**

Shortly after 5F-MDMB-PICA was reported to the EMCDDA, 25 herbal blends containing 5F-MDMB-PICA were seized by police during a raid on a head shop in Germany. During the market monitoring of products test-purchased and analysed at the Institute of Forensic Medicine, Freiburg (Germany), 5F-MDMB-PICA was one of the most frequently detected

synthetic cannabinoids from the second half of 2016 onwards. Despite its regulation under the German NpSG, which entered into force in November 2016, it was still detected in approximately 20 % of all test-purchased products in 2019, but with declining prevalence in 2020 (it was scheduled under the German Narcotics Act in July 2020). In urine samples analysed at the Institute of Forensic Medicine, Freiburg, the first positive samples occurred in 2016 (making up about 8 % of all positive samples). In 2017 and 2018, the prevalence dropped to less than 5 %. In 2019, the prevalence in urine samples sharply increased, with more than 45 % of all positive samples testing positive for its metabolites. In 2020, the prevalence rose to more than 50 % from January to June and dropped in the second half of the year (although it was still more than 20 % in the final quarter of 2020). A similar trend was seen for serum samples positive for AMB-FUBINACA (own unpublished data). This might be a consequence of the control, for example of 5F-ADB and AMB-FUBINACA, but not 5F-MDMB-PICA, put in place in August 2018 in China (UNODC, 2018).

**Structurally related synthetic cannabinoids**

Most of the structurally related indole or indazole carboxamide-type synthetic cannabinoids showing *tert*-leucinate linker groups emerged on the European drug market between 2015 and 2016. The most prominent representatives are 5F-ADB (5F-MDMB-PINACA), MDMB-CHMICA and MDMB-FUBINACA.

| |  |  |  |
|---|---|---|---|
| | **5F-MDMB-PINACA** | **MDMB-CHMICA** | **MDMB-FUBINACA** |
| **Molecular formula** | $C_{20}H_{28}FN_3O_3$ | $C_{23}H_{32}N_2O_3$ | $C_{22}H_{24}FN_3O_3$ |
| **Molecular weight** | 377.4530 g/mol | 384.5118 g/mol | 397.4427 g/mol |
| **Monoisotopic mass** | 377.2115 | 384.2413 | 397.1802 |

**Annex 2. Synthetic cannabinoids monitored by the EMCDDA through the EU Early Warning System on new psychoactive substances (as of 16 April 2021)**

| Common name | IUPAC name | Date of formal notification |
|---|---|---|
| ADB-4en-PINACA | *N*-(1-Amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(pent-4-en-1-yl)-1*H*-indazole-3-carboxamide | 23 March 2021 |
| CUMYL-NBMINACA | (1-(Bicyclo[2.2.1]heptan-2-yl)methyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide | 23 February 2021 |
| ABO-4en-PINACA | *N*-(1-Amino-1-oxobutan-2-yl)-1-(pent-4-en-1-yl)-1*H*-indazole-3-carboxamide | 3 February 2021 |
| CUMYL-NBMICA | *N*-[(1-Fenyl-1-methyl)ethyl]-1-(2-norbornyl)methyl-1*H*-indool-3-carboxamide | 23 December 2020 |
| 5B-AKB48 | *N*-(1-Adamantyl)-1-(5-bromopentyl)indazole-3-carboxamide | 14 December 2020 |
| 4F-ABINACA | *N*-(Adamantan-1-yl)-1-(4-fluorobutyl)-1*H*-indazole-3-carboxamide | 9 October 2020 |
| Cumyl-BC-HpMeGaClone-221 | (5-(Bicyclo[2.2.1]hept-2-yl)methyl)-2-(2-phenylpropan-2-yl)-2,5-dihydro-1*H*-pyrido[4,3-b]indol-1-one | 30 September 2020 |
| 5F-EDMB-PICA | Ethyl 2-(1-(5-fluoropentyl)-1*H*-indole-3-carboxamido)-3,3-dimethylbutanoate | 8 September 2020 |
| 5F-EMB-PICA | Ethyl 2-[[1-(5-fluoropentyl)indole-3-carbonyl]amino]-3-methyl-butanoate | 3 July 2020 |
| 4F-MDMB-BICA | Methyl 2-({[1-(4-fluorobutyl)-1*H*-indol-3-yl]carbonyl}amino)-3,3-dimethylbutanoate/methyl *N*-[1-(4-fluorobutyl)-1*H*-indole-3-carbonyl]-3-methylvalinate | 2 July 2020 |

| Common name | IUPAC name | Date of formal notification |
|---|---|---|
| Cumyl-CB-MeGaClone | 5-(Cyclobutylmethyl)-2-(1-methyl-1-phenyl-ethyl)pyrido[4,3-b]indol-1-one | 30 June 2020 |
| PTI-3 | *N*-({2-[1-(5-Fluoropentyl)-1*H*-indol-3-yl]-1,3-thiazol-4-yl}methyl)-2-methoxy-*N*-methylethanamine | 22 June 2020 |
| CUMYL-CBMINACA | 1-(Cyclobutylmethyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide | 6 May 2020 |
| BENZYL-4CN-BINACA | *N*-Benzyl-1-(4-cyanobutyl)-1*H*-indazole-3-carboxamide | 3 March 2020 |
| UR-144 degradant | 3,3,4-Trimethyl-1-(1-pentyl-1*H*-indol-3-yl)pent-4-en-1-one | 18 December 2019 |
| CUMYL-CBMICA | 1-(Cyclobutylmethyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indol-3-carboxamide | 29 November 2019 |
| ADB-BUTINACA | *N*-(1-Amino-3,3-dimethyl-1-oxobutan-2-yl)-1-butyl-1*H*-indazole-3-carboxamide | 23 September 2019 |
| MDMB-CHMINACA | Methyl 2-[1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamido]-3,3-dimethylbutanoate | 12 July 2019 |
| 5F-JWH-398 (CL-2201) | 1-(5-Fluoropentyl)-3-(4-chloro-1-naphthoyl)indole | 7 May 2019 |
| 5F-A-P7AICA | *N*-(Adamantan-1-yl)-1-(5-fluoropentyl)-1*H*-pyrrolo[2,3-b]pyridine-3-carboxamide | 2 April 2019 |
| 2F-QMPSB | Quinolin-8-yl 3-((4,4-difluoropiperidin-1-yl)sulfonyl)-4-methylbenzoate | 10 January 2019 |
| APP-BINACA | *N*-(1-Amino-1-oxo-3-phenylpropan-2-yl)-1-butyl-1*H*-indazole-3-carboxamide | 9 January 2019 |

| Common name | IUPAC name | Date of formal notification |
|---|---|---|
| 5F-AKB57 | Adamantan-1-yl 1-(5-fluoropentyl)-1*H*-indazole-3-carboxylate | 6 December 2018 |
| 4F-MDMB-BINACA | Methyl 2-(1-(4-fluorobutyl)-1*H*-indazole-3-carboxamido)-3,3-dimethylbutanoate | 20 November 2018 |
| Cumyl-CH-MeGaClone | 5-(Cyclohexylmethyl)-2-(1-methyl-1-phenyl-ethyl)pyrido[4,3-b]indol-1-one | 14 November 2018 |
| 5F-AB-P7AICA | *N*-(1-Amino-3-methyl-1-oxobutan-2-yl)-1-(5-fluoropentyl)-1*H*-pyrrolo[2,3-b]pyridine-3-carboxamide | 9 October 2018 |
| AMB-4en-PICA | Methyl 3-methyl-2-[1-(pent-4-en-1-yl)-1*H*-indole-3-carboxamido]butanoate | 24 August 2018 |
| MDMB-4en-PINACA | Methyl 3,3-dimethyl-2-(1-(pent-4-en-1-yl)-1*H*-indazole-3-carboxamido)butanoate | 23 August 2018 |
| MPhP-2201 | Methyl 2-{[1-(5-fluoropentyl)-1*H*-indol-3-yl]formamido}-3-phenylpropanoate | 22 August 2018 |
| A-CHMINACA | *N*-(1-Adamantyl)-1-(cyclohexylmethyl)indazole-3-carboxamide | 3 July 2018 |
| MBA-CHMINACA | 2-[[1-(Cyclohexylmethyl)indazole-3-carbonyl]amino]-3-methyl-butanoic acid | 22 June 2018 |
| DMBA-CHMINACA | 2-[[1-(Cyclohexylmethyl)indazole-3-carbonyl]amino]-3,3-dimethyl-butanoic acid | 22 June 2018 |
| 5F-MDMB-P7AICA | Methyl 2-{[1-(5-fluoropentyl)-1*H*-pyrrolo[2,3-b]pyridin-3-yl]formamido}-3,3-dimethylbutanoate | 16 February 2018 |
| 5F-Cumyl-PeGaClone | 5-(5-Fluoropentyl)-2-(1-methyl-1-phenyl-ethyl)pyrido[4,3-b]indol-1-one | 21 December 2017 |

| Common name | IUPAC name | Date of formal notification |
|---|---|---|
| CUMYL-4CN-B7AICA | 1-(4-Cyanobutyl)-*N*-(1-methyl-1-phenyl-ethyl)pyrrolo[2,3-b]pyridine-3-carboxamide | 4 July 2017 |
| 5Cl-MDMB-PINACA | Methyl 2-[[1-(5-chloropentyl)indazole-3-carbonyl]amino]-3,3-dimethyl-butanoate | 29 June 2017 |
| 5F-3,5-AB-PFUPPYCA | *N*-(1-Carbamoyl-2-methyl-propyl)-2-(5-fluoropentyl-5-(4-fluorophenyl)pyrazole-3-carboxamide | 8 June 2017 |
| SDB-006 *N*-phenyl analogue | 1-Pentyl-*N*-phenyl-indole-3-carboxamide | 22 May 2017 |
| 5F NNEI 2′-naphthylisomer | 1-(5-Fluoropentyl)-*N*-(2-naphthyl)indole-3-carboxamide | 19 May 2017 |
| MDMB-PCZCA | Methyl 3,3-dimethyl-2-[(9-pentylcarbazole-3-carbonyl)amino]butanoate | 11 May 2017 |
| 5Cl-AB-PINACA | *N*-(1-Carbamoyl-2-methyl-propyl)-1-(5-chloropentyl)indazole-3-carboxamide | 4 May 2017 |
| 5-Chloropentyl JWH-018 indazole analogue (5Cl-THJ-018) | [1-(5-Chloropentyl)indazol-3-yl]-(1-naphthyl)methanone | 6 April 2017 |
| CUMYL-PeGACLONE | 2-(1-Methyl-1-phenyl-ethyl)-5-pentyl-pyrido[4,3-b]indol-1-one | 6 February 2017 |
| MO-CHMINACA | 1-Methoxy-3,3-dimethyl-1-oxobutan-2-yl 1-(cyclohexylmethyl)-1*H*-indazole-3-carboxylate | 20 December 2016 |
| MDA 19 | *N*-[(Z)-(1-Hexyl-2-oxo-indolin-3-ylidene)amino]benzamide | 19 October 2016 |

| Common name | IUPAC name | Date of formal notification |
|---|---|---|
| AMB-FUBICA | Methyl 2-[[1-[(4-fluorophenyl)methyl]indole-3-carbonyl]amino]-3-methyl-butanoate | 3 October 2016 |
| 5F-MDMB-PICA | Methyl 2-[[1-(5-fluoropentyl)indole-3-carbonyl]amino]-3,3-dimethyl-butanoate | 30 September 2016 |
| 5F-EDMB-PINACA | Ethyl-2-[1-(5-fluoropentyl)-1*H*-indazole-3-carboxamido]-3,3-dimethylbutanoate | 21 September 2016 |
| FUB-NPB-22 | 8-Quinolyl 1-[(4-fluorophenyl)methyl]indazole-3-carboxylate | 9 September 2016 |
| CUMYL-4CN-BINACA | 1-(4-Cyanobutyl)-*N*-(1-methyl-1-phenyl-ethyl)indazole-3-carboxamide | 4 March 2016 |
| AKB-57 | 1-Adamantyl 1-pentylindazole-3-carboxylate | 23 February 2016 |
| LTI-701 | 1-(5-Fluoropentyl)-*N*-phenyl-1*H*-indole-3-carboxamide | 23 February 2016 |
| EG-2201 | (9-(5-Fluoropentyl)-9*H*-carbazol-3-yl)(naphthalen-1-yl)methanone | 22 February 2016 |
| MDMB-FUBINACA | Methyl 2-[[1-[(4-fluorophenyl)methyl]indazole-3-carbonyl]amino]-3,3-dimethyl-butanoate | 11 January 2016 |
| JWH-018 cyclohexymethyl derivative | [1-(Cyclohexylmethyl)-1*H*-indol-3-yl](naphthalen-1-yl)methanone | 16 December 2015 |
| AMB-CHMICA | Methyl 2-[[1-(cyclohexylmethyl)indole-3-carbonyl]amino]-3-methyl-butanoate | 26 October 2015 |
| MDMB-CHMCZCA | 9-(Cyclohexylmethyl)-*N*-(1-methoxycarbonyl-2,2-dimethyl-propyl)carbazole-3-carboximidic acid | 26 October 2015 |

| Common name | IUPAC name | Date of formal notification |
|---|---|---|
| FUB-JWH-018 | [1-(4-Fluorobenzyl)-1*H*-indol-3-yl](naphthalen-1-yl)methanone | 11 September 2015 |
| AB-CHMFUPPYCA (3,5-AB-CHMFUPPYCA) | *N*-(1-Amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-3-(4-fluorophenyl)-1*H*-pyrazole-5-carboxamide | 7 August 2015 |
| 5-Fluoropentyl-3-pyridinoylindole | [1-(5-Fluoropentyl)-1*H*-indol-3-yl](pyridin-3-yl)methanone | 6 July 2015 |
| CBL-018 | Naphthalen-1-yl 1-pentyl-1*H*-indole-3-carboxylate | 2 July 2015 |
| 5F-EMB-PINACA | Ethyl 2-[[1-(5-fluoropentyl)indazole-3-carbonyl]amino]-3-methyl-butanoate | 17 June 2015 |
| EMB-FUBINACA | Ethyl 2-[[1-[(4-fluorophenyl)methyl]indazole-3-carbonyl]amino]-3-methyl-butanoate | 17 June 2015 |
| 5C-AKB48 | *N*-(1-Adamantyl)-1-(5-chloropentyl)indazole-3-carboxamide | 17 June 2015 |
| 5F-PY-PINACA | [1-(5-Fluoropentyl)-1*H*-indazol-3-yl](pyrrolidin-1-yl)methanone | 17 June 2015 |
| 5F-PY-PICA | [1-(5-Fluoropentyl)-1*H*-indol-3-yl](pyrrolidin-1-yl)methanone | 12 June 2015 |
| 5F-AB-FUPPYCA (5F-5,3-AB-PFUPPYCA) | 2-[[1-(5-Fluoropentyl)-5-(4-fluorophenyl)-1*H*-pyrazol-3-yl]formamido]-3-methylbutanamide | 12 June 2015 |
| AMB-CHMINACA | Methyl 2-[[1-(cyclohexylmethyl)indazole-3-carbonyl]amino]-3-methyl-butanoate | 28 May 2015 |
| MDMB-FUBICA | Methyl 2-[[1-[(4-fluorophenyl)methyl]indole-3-carbonyl]amino]-3,3-dimethyl-butanoate | 4 May 2015 |

| Common name | IUPAC name | Date of formal notification |
|---|---|---|
| APP-CHMINACA | *N*-(2-Amino-1-benzyl-2-oxo-ethyl)-1-(cyclohexylmethyl)indazole-3-carboxamide | 14 April 2015 |
| AB-PINACA N-(2-fluoropentyl) isomer | *N*-(1-Amino-3-methyl-1-oxobutan-2-yl)-1-(2-fluoropentyl)-1*H*-indazole-3-carboxamide | 7 April 2015 |
| 5F-ADB-PINACA | *N*-(1-Amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(5-fluoropentyl)-1*H*-indazole-3-carboxamide | 31 March 2015 |
| SDB-005 | Naphthalen-1-yl 1-pentyl-1*H*-indazole-3-carboxylate | 31 March 2015 |
| M-CHMIC | Methyl 1-(cyclohexylmethyl)indole-3-carboxylate | 10 March 2015 |
| CUMYL-5F-P7AICA | 1-(5-Fluoropentyl)-*N*-(2-phenylpropan-2-yl)-7-azaindole-3-carboxamide | 25 February 2015 |
| FUB-144 | [1-(4-Fluorobenzyl)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone | 9 February 2015 |
| ADAMANTYL-THPINACA | *N*-(1-Adamantyl)-1-(tetrahydropyran-4-ylmethyl)indazole-3-carboxamide | 14 January 2015 |
| 5F-MDMB-PINACA (5F-ADB) | Methyl 2-[[1-(5-fluoropentyl)indazole-3-carbonyl]amino]-3,3-dimethyl-butanoate | 8 January 2015 |
| AMB-FUBINACA | Methyl 2-[[1-[(4-fluorophenyl)methyl]indazole-3-carbonyl]amino]-3-methyl-butanoate | 10 December 2014 |
| 5F-AMB-PICA | Methyl 2-[[1-(5-fluoropentyl)indole-3-carbonyl]amino]-3-methyl-butanoate | 5 December 2014 |
| 5F-APP-PICA | *N*-(1-Amino-1-oxo-3-phenylpropan-2-yl)-1-(5-fluoropentyl)-1*H*-indole-3-carboxamide | 25 November 2014 |
| APP-FUBINACA | *N*-(2-Amino-1-benzyl-2-oxo-ethyl)-1-[(4-fluorophenyl)methyl]indazole-3-carboxamide | 6 November 2014 |

| Common name | IUPAC name | Date of formal notification |
|---|---|---|
| 5F-APP-PINACA | *N*-(2-Amino-1-benzyl-2-oxo-ethyl)-1-(5-fluoropentyl)indazole-3-carboxamide | 6 November 2014 |
| CUMYL-5FPINACA | 1-(5-Fluoropentyl)-*N*-(1-methyl-1-phenylethyl)-1*H*-indazole-3-carboxamide | 13 October 2014 |
| CUMYL-THPINACA | *N*-(1-Methyl-1-phenylethyl)-1-[(tetrahydro-2*H*-pyran-4-yl)methyl]-1*H*-Indazole-3-carboxamide | 23 September 2014 |
| ADB-CHMICA | *N*-(1-Amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indole-3-carboxamide | 23 September 2014 |
| CUMYL-PICA | 1-Pentyl-*N*-(2-phenylpropan-2-yl)-1*H*-indole-3-carboxamide | 23 September 2014 |
| CUMYL-5FPICA | 1-(5-Fluoropentyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indole-3-carboxamide | 23 September 2014 |
| CUMYL-BICA | 1-Butyl-*N*-(2-phenylpropan-2-yl)-1*H*-indole-3-carboxamide | 23 September 2014 |
| CUMYL-PINACA | 1-Pentyl-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide | 23 September 2014 |
| ADB-CHMINACA | *N*-[1-(Aminocarbonyl)-2,2-dimethylpropyl]-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide | 12 September 2014 |
| MDMB-CHMICA | Methyl 2-[[1-(cyclohexylmethyl)indole-3-carbonyl]amino]-3,3-dimethyl-butanoate | 12 September 2014 |
| 5F-SDB-005 | Naphthalen-1-yl 1-(5-fluoropentyl)-1*H*-indazole-3-carboxylate | 8 September 2014 |
| NM-2201 | Naphthalen-1-yl 1-(5-fluoropentyl)-1*H*-indole-3-carboxylate | 4 September 2014 |

| Common name | IUPAC name | Date of formal notification |
|---|---|---|
| AB-FUBINACA 2-fluorobenzyl isomer | *N*-(1-Carbamoyl-2-methyl-propyl)-1-[(2-fluorophenyl)methyl]indazole-3-carboxamide | 4 August 2014 |
| FUB-AKB48 | *N*-(1-Adamantyl)-1-[(4-fluorophenyl)methyl]indazole-3-carboxamide | 18 July 2014 |
| MN-18 | *N*-(Naphthalen-1-yl)-1-pentyl-1*H*-indazole-3-carboxamide | 9 July 2014 |
| EG-018 | Naphthalen-1-yl(9-pentyl-9*H*-carbazol-3-yl)methanone | 20 June 2014 |
| JWH-071 | (1-Ethyl-1*H*-indol-3-yl)(naphthalen-1-yl)methanone | 19 June 2014 |
| 5F-AMB (5F-AMB-PINACA) | Methyl 2-({[1-(5-fluoropentyl)-1*H*-indazol-3-yl]carbonyl}amino)-3-methylbutanoate | 18 June 2014 |
| 5F-AMBICA | *N*-(1-Carbamoyl-2-methyl-propyl)-1-(5-fluoropentyl)indole-3-carboxamide | 29 April 2014 |
| AB-CHMINACA | *N*-(1-Amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide | 10 April 2014 |
| AM-2201 benzimidazole analogue (FUBIMINA) | [1-(5-Fluoropentyl)-1*H*-benzimidazol-2-yl](naphthalen-1-yl)methanone | 4 April 2014 |
| Mepirapim | (4-Methylpiperazin-1-yl)(1-pentyl-1*H*-indol-3-yl)methanone | 25 February 2014 |
| JWH-018 indazole analogue | Naphthalen-1-yl(1-pentyl-1*H*-indazol-3-yl)methanone | 21 February 2014 |
| FDU-PB-22 | Naphthalen-1-yl 1-(4-fluorobenzyl)-1*H*-indole-3-carboxylate | 12 February 2014 |

| Common name | IUPAC name | Date of formal notification |
|---|---|---|
| PB-22 indazole analogue | Quinolin-8-yl 1-pentyl-1*H*-indazole-3-carboxylate | 21 January 2014 |
| 5F-PB-22 indazole analogue | Quinolin-8-yl 1-(5-fluoropentyl)-1*H*-indazole-3-carboxylate | 21 January 2014 |
| FUB-PB-22 | 1-[(4-Fluorophenyl)methyl]-1*H*-indole-3-carboxylic acid 8-quinolinyl ester | 19 December 2013 |
| SDB-006 | *N*-Benzyl-1-pentyl-1*H*-indole-3-carboxamide | 19 December 2013 |
| 5F-SDB-006 | *N*-Benzyl-1-(5-fluoropentyl)-1*H*-indole-3-carboxamide | 19 December 2013 |
| PTI-1 | *N*-Ethyl-*N*-[[2-(1-pentylindol-3-yl)thiazol-4-yl]methyl]ethanamine | 18 December 2013 |
| A-796,260 isomer | (E)-3,4,4-Trimethyl-1-[1-(2-morpholinoethyl)indol-3-yl]pent-2-en-1-one | 18 December 2013 |
| 1-(Cyclohexylmethyl)-2-[(4-ethoxyphenyl)methyl]-*N,N*-diethyl-1*H*-benzimidazol-5-carboxamide | 1-(Cyclohexylmethyl)-2-[(4-ethoxyphenyl)methyl]-*N,N*-diethyl-benzimidazole-5-carboxamide | 18 December 2013 |
| PTI-2 | *N*-(2-Methoxyethyl)-*N*-[[2-(1-pentylindol-3-yl)thiazol-4-yl]methyl]propan-2-amine | 18 December 2013 |
| ADB-PINACA | *N*-(1-Amino-3,3-dimethyl-1-oxobutan-2-yl)-1-pentyl-1*H*-indazole-3-carboxamide | 3 December 2013 |
| ADB-FUBINACA | *N*-(1-Carbamoyl-2,2-dimethyl-propyl)-1-[(4-fluorophenyl)methyl]indazole-3-carboxamide | 28 November 2013 |

| Common name | IUPAC name | Date of formal notification |
|---|---|---|
| AM-2201 indazole analogue | [1-(5-Fluoropentyl)-1*H*-indazol-3-yl](naphthalen-1-yl)methanone | 15 November 2013 |
| AM-6527 5-fluoropentyl derivative | 1-(5-Fluoropentyl)-*N*-1-naphthalenyl-1*H*-Indole-3-carboxamide | 7 November 2013 |
| ADBICA | *N*-(1-Amino-3,3-dimethyl-1-oxobutan-2-yl)-1-pentyl-1*H*-indole-3-carboxamide | 11 October 2013 |
| AM-1248 Azepane isomer | (Adamant-1-yl)[1-(1-methylazepan-3-yl)-1*H*-indol-3-yl]methanone | 26 September 2013 |
| LY2183240 | 5-([1,1′-Biphenyl]-4-ylmethyl)-*N,N*-dimethyl-1*H*-tetrazole-1-carboxamide | 10 September 2013 |
| 5F-AB-PINACA | *N*-(1-Carbamoyl-2-methyl-propyl)-1-(5-fluoropentyl)indazole-3-carboxamide | 5 July 2013 |
| JTE-907 | *N*-(1,3-Benzodioxol-5-ylmethyl)-2-hydroxy-7-methoxy-8-pentoxy-quinoline-3-carboxamide | 4 July 2013 |
| AB-FUBINACA | *N*-(1-Amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamide | 4 July 2013 |
| A-836,339 | *N*-[(2Z)-3-(2-Methoxyethyl)-4,5-dimethyl-1,3-thiazol-2(3*H*)-ylidene]-2,2,3,3-tetramethylcyclopropanecarboxamide | 3 June 2013 |
| AB-PINACA | *N*-(1-Amino-3-methyl-1-oxobutan-2-yl)-1-pentyl-1*H*-indazole-3-carboxamide | 21 May 2013 |
| URB-597 | 3′-Carbamoylbiphenyl-3-yl cyclohexylcarbamate | 24 April 2013 |
| UR-144 heptyl derivative | (1-Heptylindol-3-yl)-(2,2,3,3-tetramethylcyclopropyl)methanone | 17 April 2013 |

| Common name | IUPAC name | Date of formal notification |
|---|---|---|
| JWH-307 brominated analogue | [5-(2-Bromophenyl)-1-pentyl-pyrrol-3-yl]-(1-naphthyl)methanone | 4 April 2013 |
| JWH-145 | 1-Naphthyl-(1-pentyl-5-phenyl-pyrrol-3-yl)methanone | 4 April 2013 |
| JWH-030 | Naphthalen-1-yl(1-pentyl-1*H*-pyrrol-3-yl)methanone | 4 April 2013 |
| AM-2201 carboxylate analogue quinolinyl derivative (5F-PB-22) | 1-(5-Fluoropentyl)-1*H*-indole-3-carboxylic acid 8-quinolinyl ester | 15 March 2013 |
| EAM-2201 | [1-(5-Fluoropentyl)-1*H*-indol-3-yl]-(4-ethyl-naphthalen-1-yl)methanone | 15 February 2013 |
| JWH-368 | [5-(3-Fluorophenyl)-1-pentyl-pyrrol-3-yl]-(1-naphthyl)methanone | 7 February 2013 |
| JWH-methylcyclohexane-8quinolinol (BB-22) | 8-Quinolinyl 1-(cyclohexylmethyl)-1*H*-indole-3-carboxylate | 29 January 2013 |
| A-834,735 | [1-[(Tetrahydro-2H-pyran-4-yl)methyl]-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)-methanone | 29 January 2013 |
| UR-144 N-(5-chloropentyl) derivative | [1-(5-Chloropentyl)indol-3-yl]-(2,2,3,3-tetramethylcyclopropyl)methanone | 7 December 2012 |
| 4-HTMPIPO | 4-Hydroxy-3,3,4-trimethyl-1-(1-pentyl-1*H*-indol-3-yl)pentan-1-one | 30 November 2012 |
| JWH-018 quinolinecarboxylate analogue (PB-22) | Quinolin-8-yl 1-pentyl-1*H*-indole-3-carboxylate | 20 November 2012 |

| Common name | IUPAC name | Date of formal notification |
|---|---|---|
| AB-005 azepane isomer | [1-(1-Methylazepan-2-yl)indol-3-yl]-(2,2,3,3-tetramethylcyclopropyl)methanone | 20 November 2012 |
| AB-005 | [1-[(1-Methyl-2-piperidyl)methyl]indol-3-yl]-(2,2,3,3-tetramethylcyclopropyl)methanone | 20 November 2012 |
| AM-2201 indazolecarboxamide analogue | 1-(5-Fluoropentyl)-*N*-1-naphthalenyl-1*H*-indazole-3-carboxamide | 30 October 2012 |
| 5F-AKB48 | *N*-(1-Adamantyl)-1-(5-fluoropentyl)indazole-3-carboxamide | 27 September 2012 |
| AM-1248 | 1-Adamantyl-[1-[(1-methyl-2-piperidyl)methyl]indol-3-yl]methanone | 24 September 2012 |
| JWH-018 N-(5-bromopentyl) derivative | [1-(5-Bromopentyl)-1*H*-indol-3-yl](naphthalen-1-yl)methanone | 31 July 2012 |
| JWH-018 N-(5-chloropentyl) derivative | [1-(5-Chloropentyl)-1*H*-indol-3-yl](naphthalen-1-yl)methanone | 31 July 2012 |
| JWH-122 pentenyl 2-methylindole derivative | (4-Methyl-1-naphthyl)-(2-methyl-1-pent-4-enyl-indol-3-yl)methanone | 18 July 2012 |
| AM-694 methyl substituted for iodine | [1-(5-Fluoropentyl)-1*H*-indol-3-yl](2-methylphenyl)methanone | 18 July 2012 |
| JWH-122 pentenyl derivative | (4-Methylnaphthalen-1-yl)[1-(pent-4-en-1-yl)-1*H*-indol-3-yl]methanone | 18 July 2012 |
| AM-694 ethyl substituted for iodine | (2-Ethylphenyl)[1-(5-fluoropentyl)-1*H*-indol-3-yl]methanone | 18 July 2012 |

| Common name | IUPAC name | Date of formal notification |
|---|---|---|
| MAM-2201 chloropentyl derivative | [1-(5-Chloropentyl)indol-3-yl]-(4-methyl-1-naphthyl)methanone | 18 July 2012 |
| AM-6527 | 1-Pentyl-*N*-(naphthalen-1-yl)-1*H*-indole-3-carboxamide | 16 July 2012 |
| JWH-018 adamantyl carboxamide (Apica) | *N*-(1-Adamantyl)-1-pentyl-indole-3-carboximidic acid | 13 July 2012 |
| STS-135 | *N*-(1-Adamantyl)-1-(5-fluoropentyl)indole-3-carboximidic acid | 26 June 2012 |
| UR-144 (-2H) | [1-(Pent-4-en-1-yl)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone | 14 June 2012 |
| Apinaca | *N*-(1-Adamantyl)-1-pentyl-1*H*-indazole-3-carboxamide | 21 May 2012 |
| A-796,260 | [1-[2-(4-Morpholinyl)ethyl]-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)-methanone | 18 April 2012 |
| 5F-UR-144 (XLR-11) | [1-(5-Fluoropentyl)indol-3-yl]-(2,2,3,3-tetramethylcyclopropyl)methanone | 30 March 2012 |
| URB-754 | 6-Methyl-2-[(4-methylphenyl)amino]-4*H*-3,1-benzoxazin-4-one | 27 February 2012 |
| 3-(p-Methoxybenzoyl)-N-methylindole | (4-Methoxyphenyl)(1-methyl-1*H*-indol-3-yl)methanone | 3 February 2012 |
| Trans-CP-47,497-C8 | 5-(1,1-Dimethyloctyl)-2-[(1*S*,3*S*)-3-hydroxycyclohexyl]phenol | 3 February 2012 |
| UR-144 | (1-Pentylindol-3-yl)-(2,2,3,3-tetramethylcyclopropyl)methanone | 1 February 2012 |

| Common name | IUPAC name | Date of formal notification |
|---|---|---|
| JWH-370 | 1-Naphthyl-[5-(*o*-tolyl)-1-pentyl-pyrrol-3-yl]methanone | 1 February 2012 |
| AM-679 | (2-Iodophenyl)(1-pentyl-1*H*-indol-3-yl)methanone | 27 January 2012 |
| WIN-55,212-2 | [(3*R*)-2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenyl-methanone | 27 January 2012 |
| HU-331 | 3-Hydroxy-2-(6-isopropenyl-3-methyl-cyclohex-2-en-1-yl)-5-pentyl-1,4-benzoquinone | 12 January 2012 |
| AM-694 chloro derivative | [1-(5-Chloropentyl)-1*H*-indol-3-yl](2-iodophenyl)-methanone | 21 December 2011 |
| AM-2232 | 5-[3-(Naphthalen-1-ylcarbonyl)-1*H*-indol-1-yl]pentanenitrile | 6 December 2011 |
| JWH-022 | 1-Naphthyl-(1-pent-4-enylindol-3-yl)methanone | 30 November 2011 |
| Org 29647 | *N*-(1-Benzylpyrrolidin-3-yl)-5-chloro-3-ethyl-1*H*-indole-2-carboxamide | 5 August 2011 |
| Org 27759 | *N*-[2-[4-(Dimethylamino)phenyl]ethyl]-3-ethyl-5-fluoro-1*H*-indole-2-carboxamide | 5 August 2011 |
| AM-2233 | (2-Iodophenyl){1-[(1-methylpiperidin-2-yl)methyl]-1*H*-indol-3-yl}methanone | 5 August 2011 |
| Org 27569 | 5-Chloro-3-ethyl-*N*-[2-[4-(1-piperidinyl)phenyl]ethyl]-1*H*-indole-2-carboxamide | 5 August 2011 |
| JWH-307 | [5-(2-Fluorophenyl)-1-pentyl-pyrrol-3-yl]-(1-naphthyl)methanone | 5 August 2011 |

| Common name | IUPAC name | Date of formal notification |
|---|---|---|
| JWH-412 | (4-Fluoronaphthalen-1-yl)(1-pentyl-1*H*-indol-3-yl)methanone | 20 July 2011 |
| JWH-387 | (4-Bromonaphthalen-1-yl)(1-pentyl-1*H*-indol-3-yl)methanone | 20 July 2011 |
| RCS-4(C4) | (1-Butyl-1*H*-indol-3-yl)(4-methoxyphenyl)methanone | 30 June 2011 |
| MAM-2201 | [1-(5-Fluoropentyl)indol-3-yl]-(4-methyl-1-naphthyl)methanone | 20 June 2011 |
| WIN-48,098 (pravadoline) | (4-Methoxyphenyl)-[2-methyl-1-(2-morpholin-4-ylethyl)indol-3-yl]methanone | 26 May 2011 |
| AM-1220 | [1-[(1-Methyl-2-piperidinyl)methyl]-1*H*-indol-3-yl]-1-naphthalenyl-methanone | 25 May 2011 |
| JWH-007 | (2-Methyl-1-pentyl-indol-3-yl)-(1-naphthyl)methanone | 25 May 2011 |
| AM-1220 azepane isomer | [1-(Hexahydro-1-methyl-1*H*-azepin-3-yl)-1*H*-indol-3-yl]-1-naphthalenyl-methanone | 25 May 2011 |
| RCS-4 ortho isomer | (2-Methoxyphenyl)(1-pentyl-1*H*-indol-3-yl)methanone | 20 April 2011 |
| JWH-250 1-(2-methylene-N-methyl-piperidyl) derivative | 2-(2-Methoxyphenyl)-1-[1-[(1-methyl-2-piperidyl)methyl]indol-3-yl]ethanone | 17 March 2011 |
| JWH-182 | (1-Pentylindol-3-yl)-(4-propyl-1-naphthyl)methanone | 1 March 2011 |
| JWH-018 adamantoyl derivative (AB-001) | 1-Adamantyl-(1-pentylindol-3-yl)methanone | 22 February 2011 |

| Common name | IUPAC name | Date of formal notification |
|---|---|---|
| JWH-251 | 2-(*o*-Tolyl)-1-(1-pentylindol-3-yl)ethanone | 22 February 2011 |
| AM-2201 | [1-(5-Fluoropentyl)-1*H*-indol-3-yl](naphthalen-1-yl)methanone | 18 January 2011 |
| CRA-13 | Naphthalen-1-yl-(4-pentyloxynaphthalen-1-yl)methanone | 11 January 2011 |
| 3-(4-Hydroxymethylbenzoyl)-1-pentylindole | [4-(Hydroxymethyl)phenyl](1-pentyl-1*H*-indol-3-yl)methanone | 9 November 2010 |
| JWH-019 | (1-Hexylindol-3-yl)-(1-naphthyl)methanone | 26 October 2010 |
| JWH-203 | 2-(2-Chlorophenyl)-1-(1-pentyl-1*H*-indol-3-yl)ethanone | 14 October 2010 |
| JWH-210 | (4-Ethyl-1-naphthyl)-(1-pentylindol-3-yl)methanone | 22 September 2010 |
| CP-47,497 (C8 C2) | N/A | 17 August 2010 |
| JWH-015 | (2-Methyl-1-propyl-1*H*-indol-3-yl)(naphthalen-1-yl)methanone | 27 July 2010 |
| JWH-122 | (4-Methyl-1-naphthyl)-(1-pentylindol-3-yl)methanone | 23 July 2010 |
| AM-694 | [1-(5-Fluoropentyl)-1*H*-indol-3-yl](2-iodophenyl)methanone | 19 July 2010 |
| JWH-073 methyl derivative | (1-Butyl-1*H*-indol-3-yl)(4-methyl-1-naphthalenyl)-methanone | 30 June 2010 |

| Common name | IUPAC name | Date of formal notification |
|---|---|---|
| JWH-081 | (4-Methoxy-1-naphthyl)-(1-pentylindol-3-yl)methanone | 2 June 2010 |
| RCS-4 | (4-Methoxyphenyl)(1-pentyl-1*H*-indol-3-yl)methanone | 25 May 2010 |
| JWH-200 | [1-[2-(4-Morpholinyl)ethyl]-1*H*-indol-3-yl]-1-naphthalenyl-methanone | 3 December 2009 |
| JWH-250 | 2-(2-Methoxyphenyl)-1-(1-pentyl-1*H*-indol-3-yl)ethanone | 6 October 2009 |
| JWH-398 | (4-Chloronaphthalen-1-yl)(1-pentyl-1*H*-indol-3-yl)methanone | 6 October 2009 |
| HU-210 | (6a*R*,10a*R*)-3-(1,1-Dimethylheptyl)-9-(hydroxymethyl)-6,6-dimethyl-6a,7,10,10a-tetrahydrobenzo[c]chromen-1-ol | 22 June 2009 |
| JWH-073 | (1-Butyl-1*H*-indol-3-yl)(naphthalen-1-yl)methanone | 6 March 2009 |
| CP-47,497 | 5-(1,1-Dimethylheptyl)-2-[(1*R*,3*S*)-3-hydroxycyclohexyl]-phenol | 23 February 2009 |
| JWH-018 | Naphthalen-1-yl(1-pentyl-1*H*-indol-3-yl)methanone | 19 December 2008 |
| JWH-302 | 2-(3-Methoxyphenyl)-1-(1-pentyl-1*H*-indol-3-yl)ethanone | N/A |
| Methanandamide | (5Z,8Z,11Z,14Z)-*N*-(2-Hydroxy-1-methyl-ethyl)icosa-5,8,11,14-tetraenamide | N/A |
| JWH-412 5-fluoropentyl derivative | (4-Fluoronaphthalen-1-yl)[1-(5-fluoropentyl)-1*H*-indol-3-yl]methanone | N/A |

| Common name | IUPAC name | Date of formal notification |
|---|---|---|
| 5F-ADBICA | *N*-(1-Amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(5-fluoropentyl)-1*H*-indole-3-carboxamide | N/A |