European Monitoring Centre
for Drugs and Drug Addiction

New psychoactive substances: global markets, glocal threats and the COVID-19 pandemic

An update from the EU Early Warning System

December 2020

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Purpose

A three-step legal framework of early warning, risk assessment and control measures allows the European Union to rapidly detect, assess and respond to the public health and social threats caused by new psychoactive substances in Europe. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is responsible for the first two steps of this system, namely operating the EU Early Warning System on new psychoactive substances in close cooperation with Europol and conducting risk assessments. The European Commission is responsible for proposing control measures.

The purpose of this report is to provide a high-level overview of the situation in Europe regarding new psychoactive substances to support stakeholders with their ongoing preparedness planning and response activities in relation to the public health and social threats caused by these substances, within the context of the coronavirus disease (COVID-19) pandemic. The report is based on the EMCDDA's early warning and risk assessment activities from 1 January 2019 until 31 October 2020 and includes an assessment of information reported through the EU Early Warning System and supplemented with other information available to the Agency. This includes case reports of event-based data, including data on law enforcement seizures and serious adverse events (typically reports of acute poisonings and deaths), aggregated law enforcement seizure data and information from partners in Europe, third countries and international organisations, as well as the grey and scientific literature. It also includes the key findings of the initial report on and risk assessment of isotonitazene — a potent opioid of the benzimidazole family, of which five members have now appeared on the drug market in Europe and which may replace fentanyl derivatives — and the initial reports on MDMB-4en-PINACA and 4F-MDMB-BICA, both potent synthetic cannabinoids, which together are linked to at least 25 deaths in Europe in 2020. In addition, the report takes into consideration some of the possible impacts of the COVID-19 pandemic on the availability, supply, and use of, and harms resulting from new psychoactive substances.

Statement on the United Kingdom

The United Kingdom had left the European Union as of 1 February 2020. However, during the transitional period, the United Kingdom continues to participate in the European Union Early Warning System on new psychoactive substances. Unless stated otherwise, for the purpose of this report, the term 'Member States' includes the United Kingdom.

Introduction

Background

New psychoactive substances make up a broad range of drugs that are not controlled by the United Nations international drug laws. They include synthetic cannabinoids, stimulants, benzodiazepines (and other sedative-hypnotics), opioids, hallucinogens and dissociatives. Many of these substances are intended to mimic the effects of internationally controlled drugs and are traded as 'legal' replacements for them. While new substances have always appeared on the drug market, since around 2008 there has been a large increase in the number, type and availability of and, subsequently, harms caused by these substances in Europe and, increasingly, elsewhere, including the United States, Russia, Australia and New Zealand.

Much of the growth in this market has been due to a shift from the production of a handful of substances in relatively small-scale illicit laboratories to production in chemical and pharmaceutical companies operating predominantly in China which are capable of mass-producing a large range of new psychoactive substances. This has been driven by globalisation and new technologies, such as the internet, allowing new psychoactive substances to be produced, sold and supplied on an industrial scale. These factors create a resilient and highly dynamic new psychoactive substances market, making it more difficult to disrupt.

Despite this resilience, there have been some encouraging developments in Europe, which have been particularly visible from around 2015 onwards. These include a decrease in the number of new substances identified for the first time each year and an overall decrease in seizures of new substances, largely driven by a drop in seizures of synthetic cannabinoids and cathinones — the two largest groups of new substances monitored by the EMCDDA. 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. However, since 2015 a greater proportion of substances associated with problematic use — particularly opioids (see Section 'Opioids') and benzodiazepines (see Section 'Benzodiazepines') — have appeared on the market, bringing a new set of problems, while the market in synthetic cannabinoids, once the epitome of the 'legal highs' phenomenon, has also evolved to pose a threat to health security (see Section 'Synthetic cannabinoids') (EMCDDA, 2018). During this time, the new psychoactive substances market has also developed stronger links with markets in established controlled drugs.

Global markets, glocal threats and the COVID-19 pandemic

Over the past decade, the globalisation of drug markets and new technologies have led to an increase in the number and types of risks for people who use both new psychoactive substances and controlled drugs. These risks relate both to the increase in the availability of a large range of new substances on the drug market, including new products and new ways of buying and using them, and to the emergence of new user groups.

The appearance of a substance in a new geographical area or new groups of users should always be a cause of concern for public health, as, at least initially, the population will have little or no experience of its effects and how to use it. Similar concerns apply to new ways of using a substance, new products and new patterns of use. While some risks might be known, others are unknown and some will not become known until larger numbers of people have been exposed to the substance. In addition, the very nature of unregulated markets means that these risks may be amplified by uncertainty regarding the doses that are used, and the potential for the substance to be substituted for or adulterated with another substance, all without the knowledge of the user.

A growing number of highly potent substances that pose a high risk of acute poisoning are also being reported. These include synthetic cannabinoids, opioids, benzodiazepines and a range of other substances. Strong links also exist between the trade in new psychoactive substances and markets in established controlled drugs, with the increasing use of new benzodiazepines to make fake versions of common anti-anxiety medications, such as fake alprazolam (Xanax) and diazepam, indicating this. The use of new psychoactive substances by high-risk drug users and other marginalised and vulnerable populations also appears to have increased in some places, including in prisons. In addition, unregulated, globalised supply chains and markets, where new psychoactive substances and related ingredients can be manufactured in one country, brokered and used to make products in another country and, finally, used in other countries still, increase the opportunity for miscommunication, substitution, mislabelling, adulteration, contamination and dilution of new psychoactive substances and controlled drugs with a range of potentially dangerous and sometimes highly

toxic substances. The recent detection of the rat poison brodifacoum in synthetic cannabinoid smoking mixtures in the United States is an example of this (Moritz et al., 2018; US CDC, 2018). Overall, these types of substances pose a high risk of life-threatening poisoning to users and are capable of causing outbreaks of mass poisonings (Adamowicz, 2016; Adams et al., 2017; Andonian et al., 2017; Arens et al., 2016; Edison et al., 2017; Horth et al., 2018; Kasper et al., 2015, 2019; Klar et al., 2016; Los Angeles County Department of Public Health, 2016; Monte et al., 2014; Moritz et al., 2018; Pap, 2016, 2018; Papadopoulos et al., 2017; Schwartz et al., 2015; Shevyrin et al., 2015; Springer et al., 2016; Sutter et al., 2017; Tomassoni et al., 2017; Trecki et al., 2015; Tyndall et al., 2015; US CDC, 2013, 2018; Vallersnes et al., 2009). Such mass casualty incidents are generally characterised by sudden and unexpected cases of acute poisoning that can range from several to hundreds of victims, and can rapidly overwhelm first responders, first receivers and, more generally, local healthcare systems. While formal estimates are lacking, responding to such outbreaks is also invariably financially costly. Such substances can also pose serious cross-border threats to health (European Parliament and Council of the European Union, 2013, 2017a,b; WHO, 2015), especially as a result of the growth of online markets (EMCDDA, 2017).

Despite the globalised nature of the market, the threats posed in a particular area are shaped by the interaction of a range of global and local — 'glocal' — factors. These include the availability and supply of new psychoactive substances, as well as the local drug situation (including drug supply and use, public health and social problems, drug policy and responses) and the physical, social, cultural, economic and political environment, country size, population, structure, geography, healthcare, public health systems and resources.

COVID-19 pandemic

The COVID-19 pandemic has brought into sharp focus the importance of 'complex, transboundary, multifactorial' approaches to tackling health challenges, the need to strengthen health security and the interconnected nature of health in our globalised world (Mackenzie and Jeggo, 2019; Wolicki et al., 2016). Adding to the complexity of the new psychoactive substances market, the pandemic and related response measures — such as the closure of public spaces and 'stay-at-home' measures — bring new challenges arising from the resulting effects on existing drug markets, drug use, drug services and other response measures in many, and perhaps unpredictable, ways at different times. As part of preparedness planning, scenario planning allows planners and practitioners to plan for uncertainty and prepare for the worst — to think the unthinkable. Such a proactive approach may be better informed if we consider how the COVID-19 pandemic may adversely interact with the existing drugs and NPS problem (and vice versa) exacerbating the health and social harms caused by both. Such a syndemic-like state, or synergistic epidemic, has the potential to increase vulnerability and negative outcomes for people who use drugs and society in general.

The effect of the pandemic on the drug situation, including the new psychoactive substances market, is likely to become increasingly important as countries in Europe face the second wave of the outbreak during autumn and winter 2020 and into 2021. Reflecting the complexity of the current situation, the title, and theme, of this report is *New Psychoactive Substances: Global Markets, Glocal Threats and the COVID-19 Pandemic*. It aims to encourage the reader to think about how the issues highlighted, and more generally how the availability and use of new psychoactive substances, may apply to their country, region or neighbourhood, as well as how the pandemic may have an impact. This requires consideration of what the current and future threats and vulnerabilities may be, as well as what practical, actionable measures are needed to deal with them — whether this be prevention, health protection, treatment and supply reduction measures, or policy development and implementation. It will also require consideration of what resources are available to respond to health threats, including relevant capacity and capability. For example, it is important to consider that the same personnel (public health personnel, health professionals and law enforcement personnel) and resources used to respond to outbreaks caused by new psychoactive substances will be the same as those used to respond to COVID-19 outbreaks.

In April 2020, the EMCDDA issued an alert to the EU Early Warning System Network across Europe, highlighting the potential impact of the pandemic on drug markets and risks to people who use drugs, and the need for a high level of vigilance to ensure early detection, reporting, assessment and responses to changes to the drug markets that may have a high impact on public health (EMCDDA, 2020a).

Although evidence is currently limited, based on previous experiences of disruptions to drug markets, the impact of the pandemic could lead to localised or broader changes in drug use and patterns of use, as well as an increased risk of substitution, misselling, adulteration, contamination and dilution with a range of potentially dangerous and

sometimes highly toxic substances; in some cases, this could cause outbreaks of mass poisonings, which could overload healthcare systems already struggling with the pandemic.

These may be single 'one off' events or short-lived or longer lasting changes. Laboratory (analytically) confirmed reports from forensic and toxicology laboratories will continue to play a central role in the early detection of and response to such events and changes. It is also important to note that, in some settings, there may be a risk of delays in detecting, reporting, assessing and responding to changes in drug markets, and resulting harms due to the potentially reduced capacity of early warning systems, including forensic and toxicology laboratories, as a result of the pandemic. It is important for public health protection that, where possible, and according to relevant policies and procedures, changes to drug markets and related events that may have a high impact on public health continue to be reported in a timely manner to the relevant agencies.

Early detection, reporting, assessment and response

There is much speculation about, but currently only limited data to analyse and assess, the impact of the pandemic on the availability, supply and use of new psychoactive substances. Providing reliable information is critical to facilitate an effective public health response, including prevention, health protection, treatment, supply reduction, and policy development and implementation. The EU Early Warning System and national early warning systems play a central role by providing such information in a timely manner and in sufficient detail to the right people, in the right place, at the right time, to allow them to assess the information and, where necessary, respond through timely and effective actions to prevent or reduce the risk of harm (EMCDDA, 2020b).

The different types of response actions taken depend on the substance of interest, the type and level of threat, the individuals who are at risk and the roles of the organisations and people who are responding. Actions may be taken at the levels of practice, research and policy.

For example, at national level, the formal notification of a new psychoactive substance (see Section 'Overview of notifications') ensures that the Early Warning System Network across Europe is alerted as soon as possible when a new psychoactive substance is identified for the first time on the European drug market (EMCDDA, 2018). This allows the network to detect and assess any potential threats, as well as to identify and implement any response measures that might be required. Importantly, the information provided in the formal notification allows forensic and toxicology laboratories to include the substance in their analytical screening, allowing it to be identified and therefore monitored for in law enforcement seizures and serious adverse events (such as acute poisonings and deaths).

Actions may also include communicating risk to relevant agencies, as well as to people who use drugs, such as when a toxic or otherwise dangerous substance or situation is detected, and ensuring that sufficient preparations have been made to deal with a situation that has the potential to cause an outbreak, including mass poisoning events. Related to this, actions may also extend to ensuring that there is a sufficient supply and sufficient availability of medical countermeasures, such as the opioid antidote naloxone, should there be a sudden increase in the availability of highly potent opioids.

As the amount of information is usually limited when a substance is first identified on the drug market, actions may also include research to better understand the risks of a particular substance. This may include research to understand its pharmacological and toxicological effects and its epidemiology (who is using the substance, how many people are using it and how it is being used, etc.).

In other cases, actions may include formal risk assessment at national level or by the EMCDDA at European level, which may lead to control or other types of restrictive measures that are intended to reduce the supply and availability of a substance.

Within this context, the report discusses recent developments in the market and use of new psychoactive substances, and highlights some of the major emerging issues and threats. These include developments in the markets for synthetic cannabinoids, opioids and benzodiazepines. Finally, the report highlights the need to continue to invest in developing and maintaining strong early warning and response systems for new psychoactive substances and illicit drugs to protect public health.

Key methodological points

Data regarding first identifications in Europe (formal notification data) relate to the period from 1 January 2005 to 31 October 2020.

The seizure data used in this report are from 1 January 2005 to 31 December 2019.

Law enforcement seizures of new psychoactive substances reported to the EMCDDA should be understood as minimum values. This is because data are drawn from case reports rather than routine monitoring systems. Reports are influenced by a range of factors such as increasing awareness of new substances, their changing legal status, law enforcement capacities and priorities, the reporting practices of agencies and the structure of national early warning systems (which differ widely across Europe). The seizure data are not directly comparable with the data on established controlled drugs. Quantitative data on the amount of new psychoactive substances present in a seizure (purity) are typically not available, as this type of analysis is not routinely performed by laboratories. As a result, seizures are not adjusted for purity. Seizures are also not adjusted for the potency of the substance. In addition, a new psychoactive substance may be found in a mixture with one or more new psychoactive substances and, in such cases, the first new psychoactive substance reported by the laboratory is taken as the substance in the seizure.

The data also include an increasing number of formerly identified new psychoactive substances that are now controlled under the United Nations international drug laws. These include 2C-B, GHB, some synthetic cathinones (such as mephedrone), synthetic cannabinoids (such as 4F-MDMB-BINACA) and opioids (such as carfentanil).

The figures depicting trends in the quantity of material seized aggregate quantities for all forms reported in mass (kg) and exclude all material reported as tablets (units), volume (litres) and/or other forms. Trends are presented for the EU Member States (EU) and the EU Member States plus Norway and Turkey (EU+2).

Situation in Europe

Overview of notifications

By 31 October 2020, the EMCDDA was monitoring more than 820 new psychoactive substances that have appeared on Europe's drug market since monitoring began in 1997 (Figure 1). This includes 53 substances that were notified for the first time in 2019 (Annex 1) and 38 substances that had been notified in 2020 (up to the end of October) (Annex 2). This represents a decrease from the close to 100 new psychoactive substances introduced to the European market each year between 2014 and 2015. At least in part, this drop in notifications is likely to reflect the results of sustained efforts to control and otherwise restrict the sale of new substances in Europe, particularly their open sale as 'legal highs', which in many countries included open sale on the high street (Evans-Brown and Sedefov, 2018). It may also reflect control measures in source countries, such as China, aimed at restricting the production and trade of these substances.

Despite the general decrease in the number of substances newly introduced to the European market each year, since 2015 approximately 400 previously reported new psychoactive substances have been identified each year (Figure 2). This suggests that many substances remain in circulation, albeit in varying amounts. Among other problems, this can increase the risk of them being sold either deliberately or accidentally as other drugs. In some cases, such as when synthetic cannabinoids are sold as ecstasy, this has caused outbreaks of mass poisonings.

FIGURE 1

Numbers and categories of new psychoactive substances reported to the EU Early Warning System for the first time, 2005-2020 (up to 31 October)

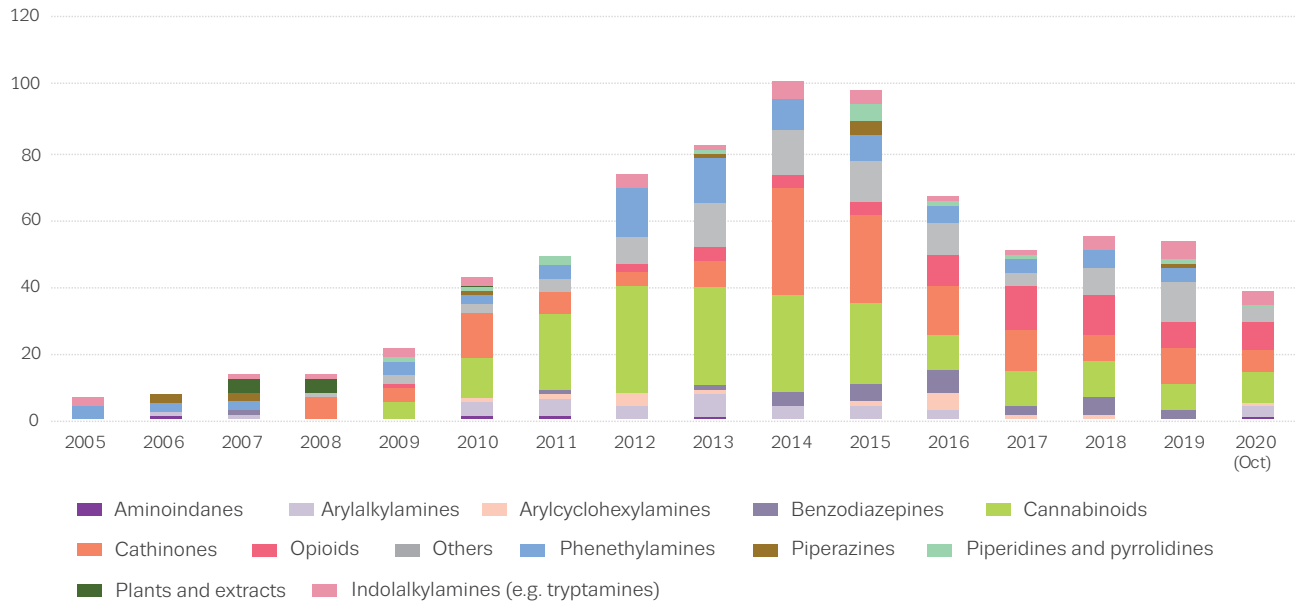


FIGURE 2

Numbers and categories of new psychoactive substances detected each year, following their first identification, 2005-2019

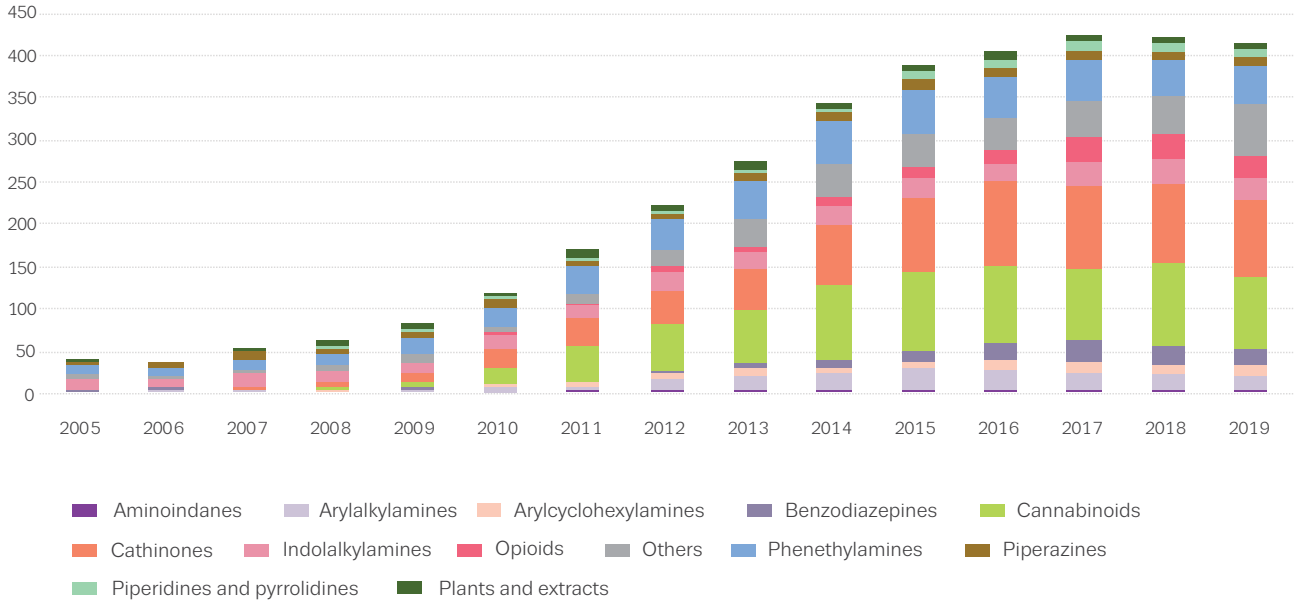
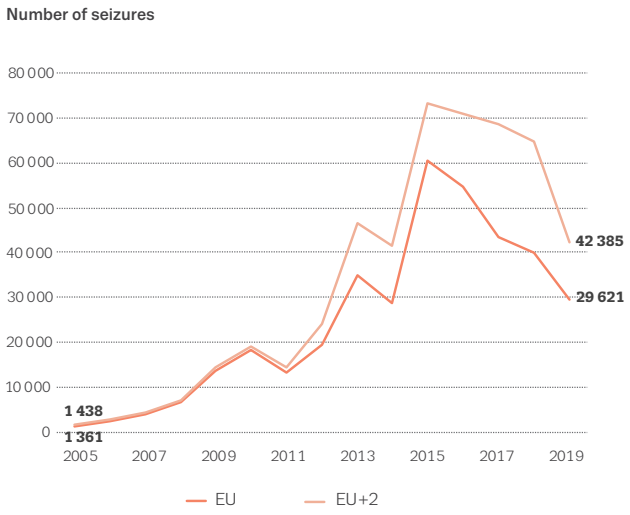
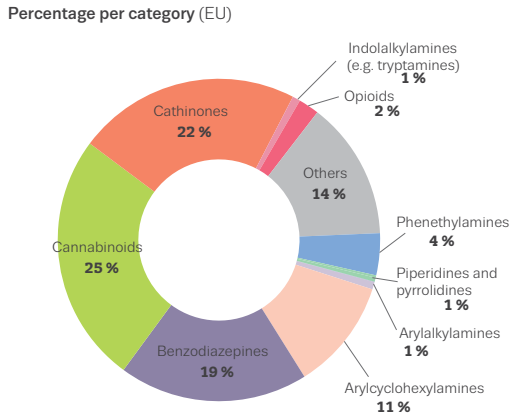
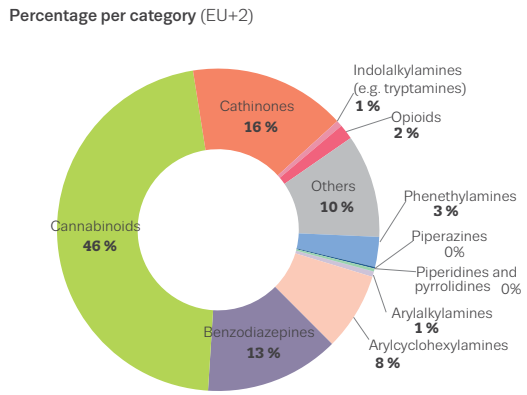


FIGURE 3

Seizures of new psychoactive substances reported to the EU Early Warning System: trends in total numbers of seizures, 2005-2019, and percentages of seizures by category in 2019 (EU and EU+2)







Note: The 'plants and extracts' category is excluded from the seizure data presented.

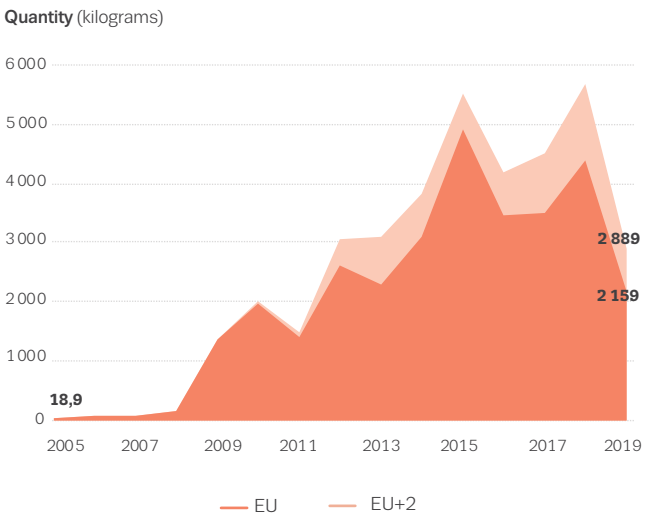
Overview of seizures, 2019

The number and amount of new psychoactive substances seized by law enforcement agencies in Europe rose sharply until 2015. Since then, this trend seems to have stabilised or reversed towards a decline, depending on the region. During 2019, 42 385 seizures of new psychoactive substances were reported to the EU Early Warning System; of these, 29 621 seizures were reported by EU Member States (Figure 3). Together, this represents a decrease of 42 % and 51 %, respectively, in the number of seizures compared with those reported in 2015.

In 2019, seizures of more than 2.8 tonnes of new psychoactive substances, mostly in the form of powders, were reported to the EU Early Warning System; of this total, approximately 2.2 tonnes were reported by the EU Member States. Together, this represents a decrease of 47 % and 56 %, respectively, in seizure quantities compared with those reported in 2015. In addition, 976 litres of liquids and 3.3 million tablets and capsules were also found to contain new psychoactive substances. Seizures of new psychoactive substances continue to be dominated by synthetic cannabinoids and cathinones, which together accounted for 62 % of all seizures reported in 2018 (47 % for the EU Member States) (Figure 4).

FIGURE 4

Seizures of new psychoactive substances reported to the EU Early Warning System: trends in quantity of material seized, for all forms reported in mass (2005-2019) (EU and EU+2)



Note: The 'plants and extracts' category is excluded from the seizure data presented.

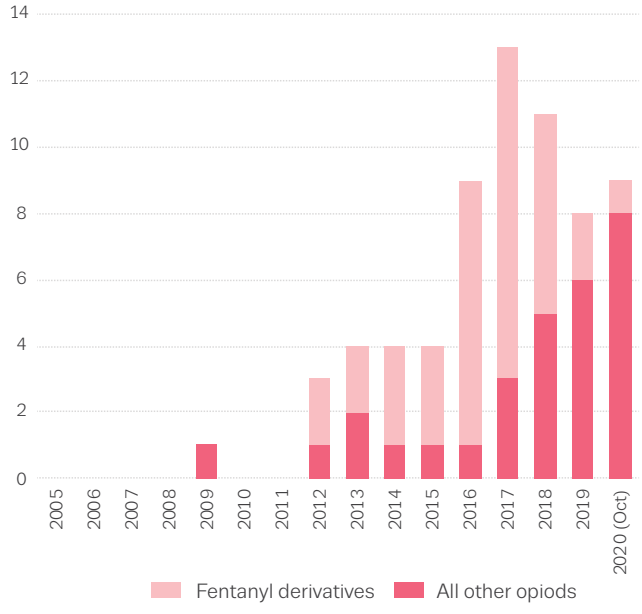
Despite the decrease in seizures of new psychoactive substances in Europe, their overall availability and accessibility appears to be relatively high. It remains easy to buy substances on demand from online suppliers in both wholesale and retail amounts (Evans-Brown and Sedefov, 2018), while in some regions some new substances are also commonly sold at street level, often as part of the existing drug market. In the latter case, this includes new benzodiazepines, such as etizolam, which are increasingly used to make fake benzodiazepine medicines.

Opioids

While currently playing a small role in the overall market, new opioids are of particular concern for public health because they pose a high risk of life-threatening poisoning, as an overdose can cause respiratory depression. Since 2009, a total of 66 new opioids, many of which are highly potent, have been identified on the drug market in Europe — including nine that have been reported during 2020 so far. Similar to 2019, only one of these opioids reported in 2020 was a fentanyl derivative, isobutyrfentanyl, which is a much smaller proportion than in previous years (Figure 5). The remaining eight opioids (etazene, brorphine, metodesnitazene, nortilidine, metonitazene, carbonyl-bromadol, AP-238 and O-AMKD) are all chemically different from fentanyl, despite giving rise to similar concerns in respect to toxicity.

FIGURE 5

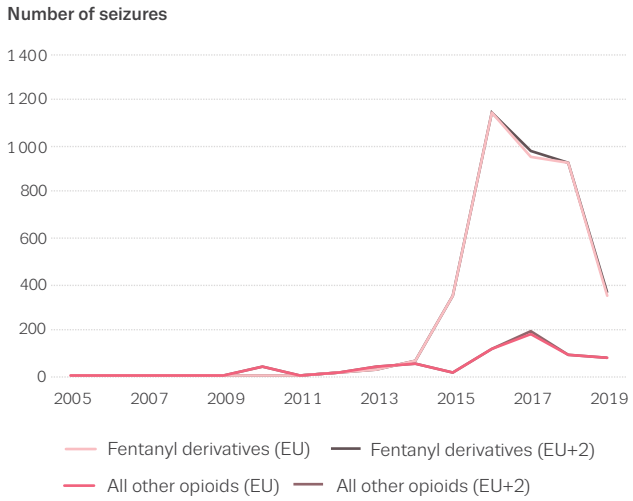
Numbers and types of new synthetic opioids notified to the EU Early Warning System for the first time, 2005-2020

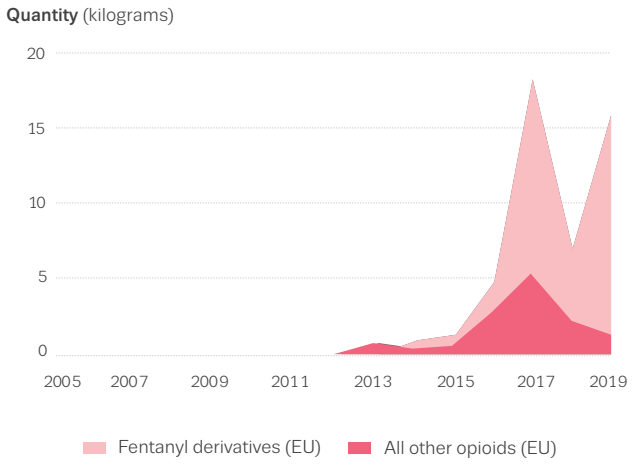


In 2019, approximately 439 seizures of new opioids were reported to the EU Early Warning System (435 (99 %) of which were reported by the Member States), representing around 2 % of the total number of seizures of new psychoactive substances. This amounted to approximately 17 kg of material (almost 95 % were fentanyl derivatives), of which 12 kg was in the form of powders (almost 91 % were fentanyl derivatives, of which almost 84 % was carfentanil) (Figure 6) (Table 1). This is an increase from the total quantity of 1.9 kg reported in 2018, which was almost exclusively due to a single large seizure of approximately 10 kg of carfentanil reported by Latvia.

FIGURE 6

Seizures of opioids reported to the EU Early Warning System: trends in numbers of seizures and quantities seized, reported in mass, 2005-2019 (EU and EU+2)





Note: Seizures of tramadol were excluded. EU and EU+2 data practically overlap due to the low number of seizures reported by Turkey and Norway.

TABLE 1

The most commonly seized opioids reported to the EU Early Warning System: numbers of seizures (a) and quantities seized reported in mass (b) and units (c), 2019

(a) Opioids	Number of seizures
Carfentanil	234
Furanylfentanyl	43
Isotonitazene	25
2-methyl-AP-237	23
Ocfentanil	16

(b) Opioids	Powder (grams)
Carfentanil	10 044.2
Tianeptine	783.5
Methoxyacetylfentanyl	485.1
Isotonitazene	110.0
Piperidylthiambutene	100.2

(c) Opioids	Tablets (units)
2F-viminol	497
2-methyl-AP-237	213
U-47700	126

Moreover, seizures amounting to 41 millilitres of liquids and 853 tablets and capsules (excluding tramadol) were also reported. The high potency of some new opioids means that even small quantities could yield many thousands of street doses.

Less commonly, new opioids have also been found in blotters, herbal smoking mixtures and fake benzodiazepine medicine tablets (such as fake Xanax tablets). In these cases, there may be no indication to users that they contain potent opioids, posing a poisoning risk, particularly for people with no existing tolerance to opioids.

Initially, much of the growth of the market in new opioids in Europe was driven by an increase in the availability of derivatives of fentanyl, such as carfentanil and cyclopropylfentanyl, between 2016 and 2018. Fentanyl is a highly potent opioid widely used in human medicine in anaesthesia and for pain management. Fentanyl derivatives are highly potent and difficult to dose, and thus pose a very high risk of fatal poisoning. Reflecting this, more than 250 deaths involving fentanyl derivatives were reported to the EU Early Warning System during 2016 and 2018, while thousands of deaths have been reported in the United States and Canada.

However, since 2019, the market in Europe has changed. Fewer new fentanyl derivatives have been identified for the first time, while more 'obscure' groups of opioids have been identified. These include piperidylthiambutene, AP-237, 2-methyl-AP-237, AP-238, 2F-viminol, brorphine and substances from the highly potent benzimidazole group of opioids — isotonitazene, etazene, metodesnitazene and metonitazene. While the causes of this shift away from fentanyl derivatives are unclear, the shift coincides with the introduction of generic control measures for fentanyl derivatives in China, where many of these substances are manufactured (UNODC, 2019).

A similar policy response in the United States as well as responses in Europe to restrict availability may also have played a role (US DEA, 2018).

During 2020, signals related to isotonitazene led the EMCDDA to launch an initial report (EMCDDA, 2020c) on the substance because of concerns of potential EU-level threats, resulting in a risk assessment of this substance being carried out in May 2020.

Focus on isotonitazene

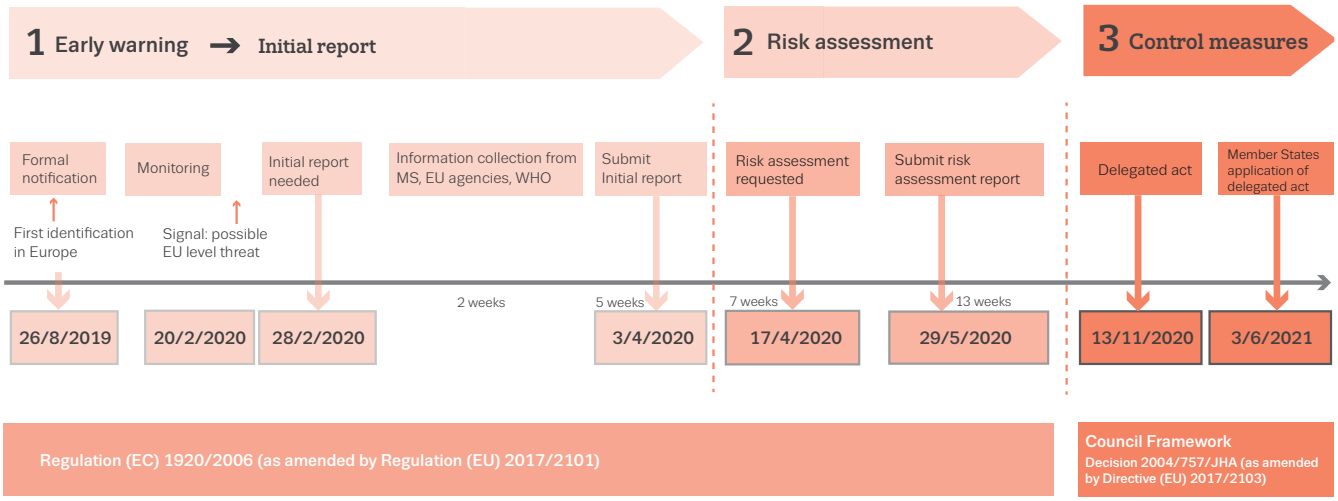
During the mid-1950s, attempts to develop better and safer opioid analgesics led to the discovery of a series of 2-benzylbenzimidazole compounds with levels of analgesic potency several orders of magnitude higher than that of morphine. This group of structurally distinct opioid analgesics includes isotonitazene, which first appeared on the European drug market in March 2019, as well as etonitazene and metonitazene, which are closely related homologues, and clonitazene. Both etonitazene and clonitazene are controlled under the United Nations Single Convention on Narcotic Drugs of 1961 (ECAPD, 1961; UNODC, 2019).

Although isotonitazene was first synthesised in the mid-1950s (Hoffmann et al., 1959, 1960; Hunger et al., 1960a), no additional reports related to the substance could be found prior to its identification on the illicit drug market in 2019 (Blanckaert et al., 2020; EMCDDA, 2020c; Ujváry, 2020).

Isotonitazene has been available on the drug market in Europe since at least April 2019 and has been identified in six countries (Belgium, Estonia, Germany, Latvia, Sweden and the United Kingdom). Law enforcement seizures have been reported by four Member States (Estonia, Germany,

FIGURE 7

Timeline of EU early warning and response actions to the potent opioid isotonitazene



Latvia and Sweden). The most recent identification of isotonitazene reported to the EMCDDA was from a seizure made in May 2020.

As isotonitazene has only recently emerged on the drug market in Europe (Figure 7), it is important to note that its presence on the drug market and it being the cause of serious adverse events may be undetected, since the substance is not routinely screened for in some laboratories. In addition, the ongoing COVID-19 pandemic may have reduced the capacity of early warning systems to detect and report events involving isotonitazene.

It appears that at least some of the isotonitazene on the market in Europe has been supplied from China. Isotonitazene is sold online as a powder in wholesale and small amounts; it is also sold as ready-to-use nasal sprays. Isotonitazene is also sold on the illicit drug market, including, it appears, on street-level opioid markets. Based on the limited information, it is presumed, but not confirmed, that isotonitazene is being injected intravenously by high-risk opioid users in some parts of Europe.

Isotonitazene can be administered in a range of ways. These include orally, intranasally, by smoking or vaporising, and by injection.

A total of two deaths involving isotonitazene have been reported to the EMCDDA by Germany and the United Kingdom, although few additional details are currently available on these cases. Deaths have also been reported in Canada (three cases) and the United States (18 cases). In the latter case, at least some of the individuals were high-risk drug users and included people who had a history of injecting illicit opioids such as heroin. Polydrug use, especially the use of two or more central nervous system depressants (which increases the risk of life-threatening respiratory depression), was also common in these individuals.

As isotonitazene has only recently emerged on the drug market, there is limited information on the substance. In particular, formal epidemiological studies have not been conducted, which limits understanding of the frequency and patterns of use.

Although the size of the market is unknown, isotonitazene is sold online as a legal replacement for controlled opioids; it also appears to have been sold on the illicit opioid market at street level in a few countries. Similar to other opioid analgesics, the most serious acute health risk from using isotonitazene is likely to be respiratory depression, which in the event of an overdose could lead to apnoea, respiratory arrest and death.

Since the risk assessment on isotonitazene was carried out, a further three benzimidazole opioids have been identified on the European drug market — etazene (Figure 8), metodesnitazene and metonitazene — suggesting that this group of substances may replace fentanyl derivatives. In an animal model of analgesia, etazene was assessed to be 70 times as potent as morphine (Hunger et al., 1960a,b).

FIGURE 8

Nasal sprays and powder containing the potent opioid etazene seized by Finnish customs in March 2020 and June 2020, respectively

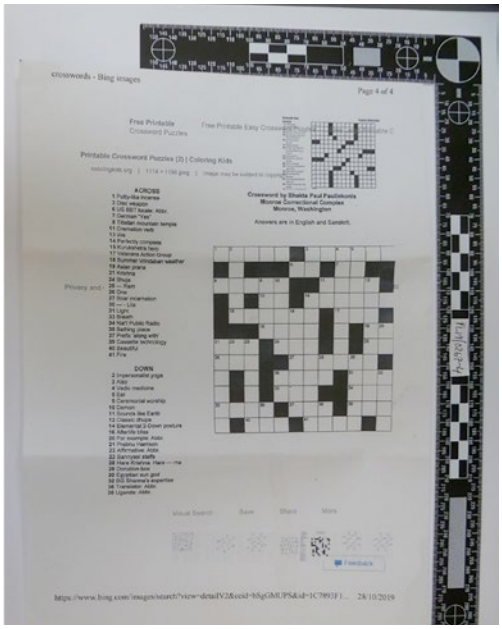
Photos © Finnish Customs, 2020.

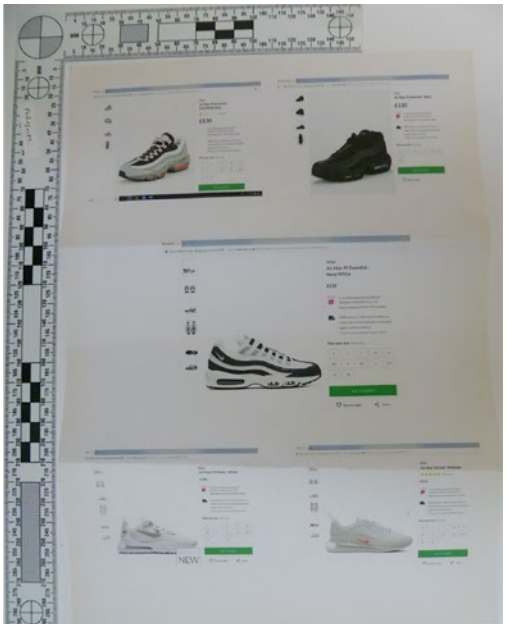
Synthetic cannabinoids

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 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. 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

FIGURE 9

Typical A4-sized papers impregnated with synthetic cannabinoids





Note: The papers, seized in a prison in Scotland, United Kingdom, during 2019, were impregnated with MDMB-4en-PINACA and 5F-MDMB-PICA.
Photos © Dr Craig McKenzie, Leverhulme Research Centre for Forensic Science, University of Dundee

cases, the users believed that they were using cannabidiol (CBD) or tetrahydrocannabinol (THC).

Three main types of products containing synthetic cannabinoids are sold on the drug market. Typically, these cannabinoids are sprayed on to or mixed with herbal plant material or tobacco and smoked as a joint or inhaled from a vaporiser or bong. In recent years, there has also been an increase in e-liquid products, where a solution of the cannabinoid is prepared by mixing it with a solvent, which is then vaped using an electronic cigarette. In addition, it appears that an increasingly commonly approach to smuggling synthetic cannabinoids into prison in some countries is by impregnating paper with the cannabinoids — including letters, greeting cards, photographs and children's drawings; images of crossword puzzles, Sudoku puzzles and print outs from online catalogues are also common (Figure 9). The cannabinoids are 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 cannabinoids can pose a high risk of poisoning because the amount of cannabinoid can vary greatly in different parts of the paper (Norman et al., 2020).

Because of their high potency and the unintentionally high doses that users may be exposed to, synthetic cannabinoids can pose a high risk of severe poisoning, which in some cases can be fatal. These factors could also have been responsible for the outbreaks of mass poisonings seen with synthetic cannabinoids, which have ranged from a handful of people to over 800, some of whom have died (Figure 10). While many of the outbreaks reported so far have been in the United States, they have also occurred in Russia, Canada and Europe. Increasingly, some of these outbreaks are due to misselling or adulteration. For example, in Europe, outbreaks have been caused by synthetic cannabinoids sold as ecstasy, while, in Canada and the United States, outbreaks have been caused by adulterating opioids such as heroin with synthetic cannabinoids (Cruz et al., 2019; EMCDDA, 2018; NPS Discovery, 2018). Such outbreaks have the potential to overwhelm local healthcare systems, which is of particular concern given the ongoing COVID-19 pandemic and the additional burden already on healthcare systems as a result. With the increased popularity of CBD products, synthetic cannabinoids have also been identified in e-liquids sold as CBD in Europe. Another concerning development is the increase in the identification of synthetic cannabinoids in low-THC cannabis products in Zurich, Switzerland (Saferparty, 2020). Overall, such

FIGURE 10

Timeline of major events involving synthetic cannabinoids since they first appeared on the drug market in 2006

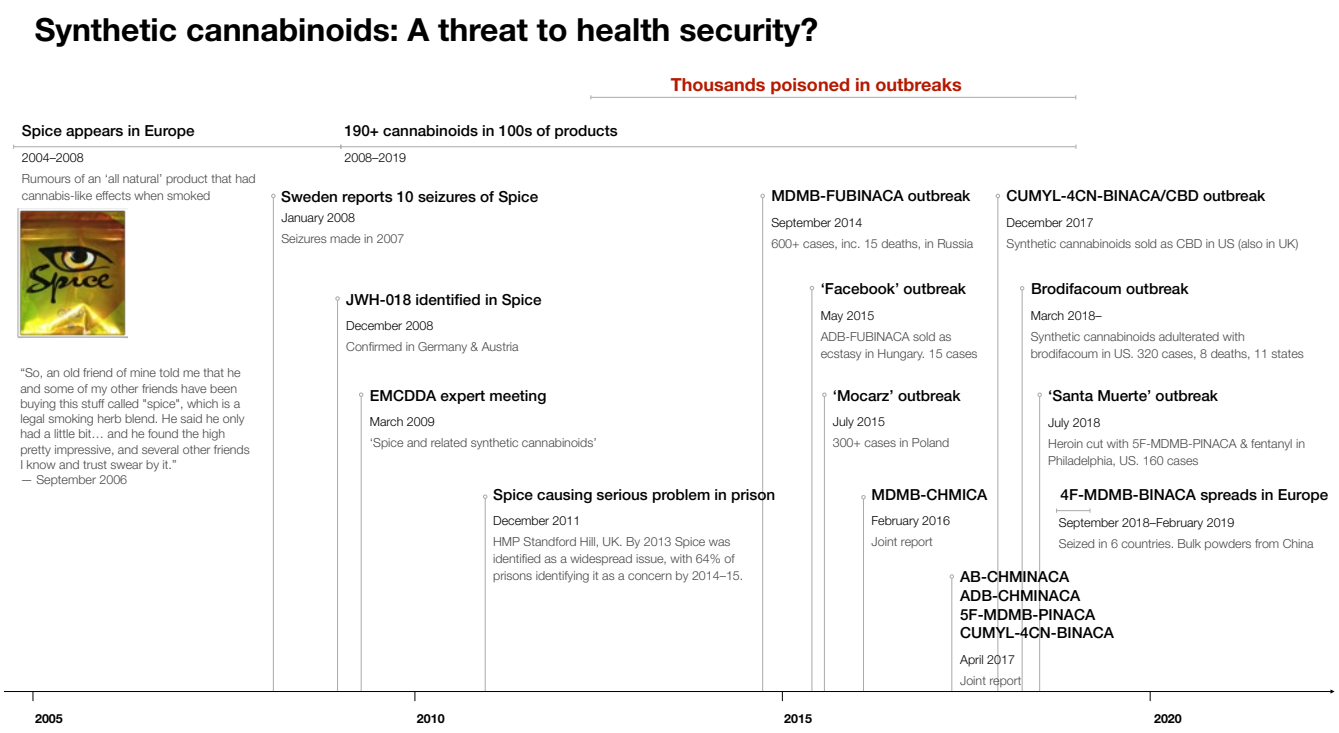


FIGURE 11

Number of synthetic cannabinoids formally notified to the EU Early Warning System for the first time, 2005-2020 (EU and EU+2)

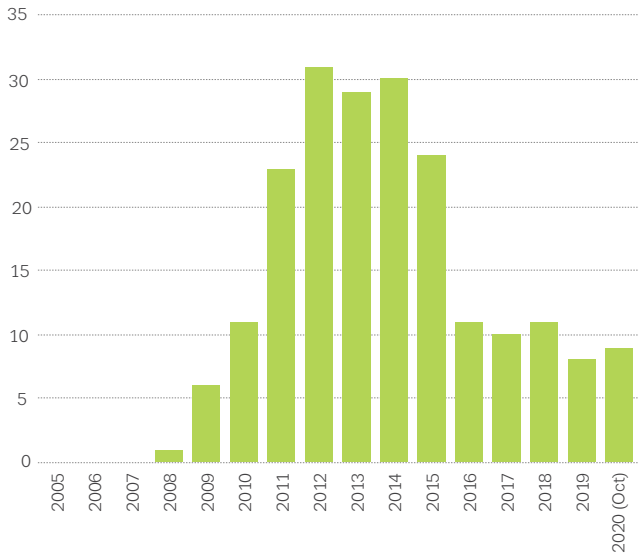
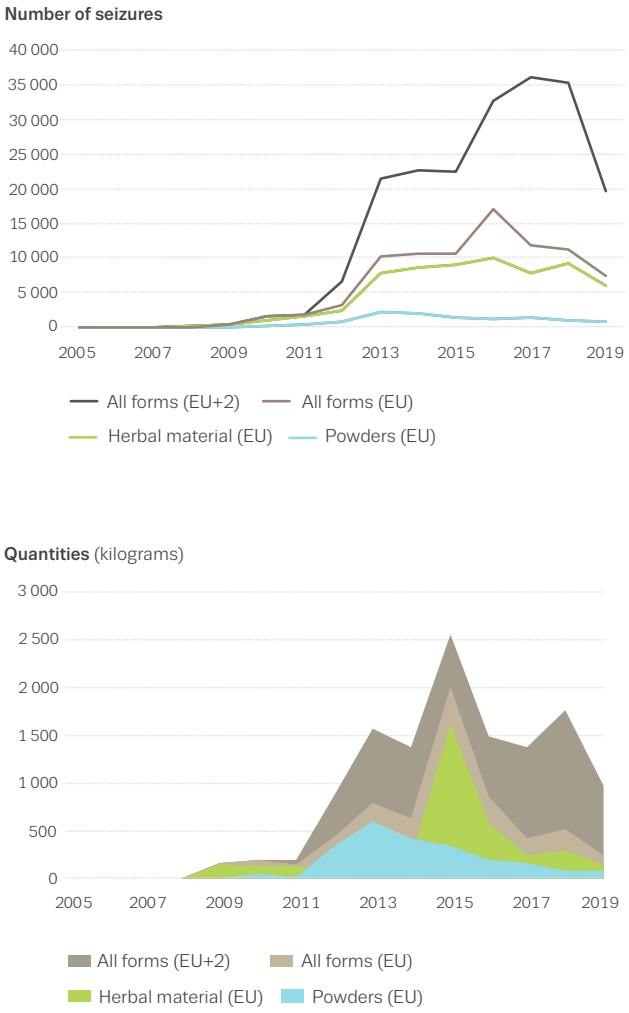


FIGURE 12

Seizures of synthetic cannabinoids reported to the EU Early Warning System: trends in number of seizures and quantity of powders and herbal smoking mixtures, reported in mass, 2005-2019 (EU and EU+2)



Note: Seizures reported by Turkey do not specify the physical form. As such, the differences between EU and EU+2 dataset cannot be distinguished when the data is broken down by physical form.

adulterated products pose a high risk of poisoning to users. Although the information is limited, similar adulteration has also been reported in at least three Member States since July 2020.

By the end of October 2020, the EMCDDA was monitoring 207 synthetic cannabinoids that have appeared on the drug market since 2008. These include nine reported for the first time in 2020 (up to the end of October). Whereas an average of 27 cannabinoids appeared each year in Europe between 2011 and 2015, since 2016 the number has dropped to around 10 (Figure 11).

In 2019, 19 705 seizures of synthetic cannabinoids were reported to the EU Early Warning System, which represents around 46 % of the total number of seizures reported during that year (25 % in the Member States). In the European Union, most of these detections were in the form of herbal plant material (5 977 cases, 138 kg) and in powders (728 cases, 84 kg) (Figure 12) (Table 2). In recent years, there has been a marked decrease in both the number of new cannabinoids appearing on the market and the quantity of powders and herbal material containing synthetic cannabinoids seized in the European Union. 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 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.

During 2020, signals related to two synthetic cannabinoids, MDMB-4en-PINACA (EMCDDA, 2020d) and 4F-MDMB-BICA (EMCDDA, 2020e), led the EMCDDA to launch initial reports on the substances because of concerns of potential EU-level threats.

TABLE 2

The most commonly seized synthetic cannabinoids reported to the EU Early Warning System, numbers of seizures (a) and quantities seized reported in mass (b, c), 2019

(a) Cannabinoids	Number of seizures
5F-MDMB-PICA	2 710
5F-MDMB-PINACA	864
4F-MDMB-BINACA	837
5F-Cumyl-PeGaClone	666
Cumyl-CH-MeGaClone	356

(b) Cannabinoids	Powder (grams)
4F-MDMB-BINACA	38 052.5
5F-MDMB-PICA	24 435.4
AM-2201	7 051.8
5F-MDMB-PINACA	5 320.6
Cumyl-CH-MeGaClone	3 101.4

(c) Cannabinoids	Herbal material (grams)
AMB-CHMICA	24 703.7
5F-MDMB-PICA	23 158.7
MDMB-CHMICA	17 056.4
5F-MDMB-PINACA	12 508.5
5F-Cumyl-PeGaClone	10 253.7

Focus on MDMB-4en-PINACA

MDMB-4en-PINACA has been available on the drug market in Europe since at least 2017. The substance is sold as a 'legal' replacement for cannabis and other controlled synthetic cannabinoids. Limited information suggests that MDMB-4en-PINACA is a potent CB_1 receptor agonist and, as such, shares some pharmacological similarities with THC, which is responsible for the major psychoactive effects of cannabis and other synthetic cannabinoids, such as JWH-018, which are under international control.

As at October 2020, MDMB-4en-PINACA had been identified in 20 Member States, as well as in Norway and Turkey, and 768 seizures had been reported, including seizures of approximately 47 kg of powder and 4.7 kg of smoking mixtures. Although MDMB-4en-PINACA was first identified on the drug market in 2017, it has been only since 2019 that there has been a large increase in the number of Member States identifying the substance for the first time. In addition, during 2020 there was a large increase in the quantity of MDMB-4en-PINACA seized by customs, with approximately 99 % of the total amount of powder (44 kg) being seized by customs between April and June 2020.

A total of 11 acute non-fatal poisonings associated with confirmed exposure to MDMB-4en-PINACA have been reported by the United Kingdom. The cases occurred between January and August 2020. While exposure to other substances was also reported in most cases, including other synthetic cannabinoids, at least some of the clinical features of the poisonings were consistent with exposure to synthetic cannabinoids. In 10 of the cases, the poisoning was reported to be life threatening and required the individual to be hospitalised.

A total of four deaths associated with confirmed exposure to MDMB-4en-PINACA have been reported by Sweden and the United Kingdom. The deaths occurred between January 2019 and June 2020. In three of the cases, MDMB-4en-PINACA was reported to have been the cause of death or to have contributed to the death.

In prisons, alongside the adverse health effects, the market in synthetic cannabinoids has been linked to an increase in aggression, violence, bullying and debt. In some cases, this has caused a serious threat to the overall safety and security of the prison environment. This is a concern given that six Member States have reported seizures of MDMB-4en-PINACA in prisons and other custodial settings and that, overall, approximately 15 % of all seizures of MDMB-4en-PINACA made by police occurred in these settings.

MDMB-4en-PINACA is subject to restrictive measures in 14 Member States, Norway and Turkey. It is unknown if MDMB-4en-PINACA is controlled in China, from where at least some of the substance on the European market has been sourced.

Based on the information reported to the EMCDDA, there are indications that MDMB-4en-PINACA has the potential to continue to spread rapidly in Europe. Of note is that, similar to 4F-MDMB-BICA, which is also the subject of an initial report (EMCDDA, 2020e), the recent increase in seizures of consignments of bulk powder MDMB-4en-PINACA made by European customs agencies appears to have coincided with the decision to internationally control two closely related synthetic cannabinoids commonly found on the drug market in Europe: 4F-MDMB-BINACA and 5F-MDMB-PICA. Therefore, it is possible that MDMB-4en-PINACA will be a replacement for these substances.

Focus on 4F-MDMB-BICA

4F-MDMB-BICA has been available on the drug market in Europe since at least March 2020. The substance is sold as a 'legal' replacement for cannabis and other controlled synthetic cannabinoids. Limited information suggests that 4F-MDMB-BICA is a potent CB_1 receptor agonist and, as such, shares some pharmacological similarities with THC, which is responsible for the major psychoactive effects of cannabis and other synthetic cannabinoids, such as JWH-018, which are under international control.

The available information suggests that 4F-MDMB-BICA is manufactured by chemical companies based in China. It is imported into Europe as bulk powders and then sold and distributed in wholesale and retail amounts within Europe either as a powder for processing into products or as finished consumer products.

As at October 2020, 4F-MDMB-BICA had been identified in 10 Member States and 108 seizures had been reported, including seizures of 5.6 kg of powder and 0.6 kg of smoking mixtures.

A total of 21 deaths associated with confirmed exposure to 4F-MDMB-BICA have been reported by Hungary. The deaths occurred over a relatively short period of time, between May and August 2020. Further information on the role of 4F-MDMB-BICA in the deaths is currently unavailable.

In prisons, alongside the adverse health effects, the market in synthetic cannabinoids has been linked to an increase in aggression, violence, bullying and debt. In some cases, this has caused a serious threat to the overall safety and security of the prison environment. This is concerning given the reports of seizures of 4F-MDMB-BICA in prisons and other custodial settings in at least five Member States.

There is no information on whether or not criminal groups are involved in the manufacture, trafficking and distribution of 4F-MDMB-BICA within Europe. The effect of the ongoing COVID-19 pandemic on the manufacture, trafficking, distribution and use of 4F-MDMB- BICA is currently unknown. However, seizures of bulk powders by national European customs agencies during the pandemic suggest that 4F-MDMB-BICA continues to be imported into and distributed within Europe. It is possible that, in the case of a reduction in the availability of cannabis and other synthetic cannabinoids in Europe, criminal groups, as well as drug users, may use a range of replacement substances, including 4F-MDMB-BICA.

4F-MDMB-BICA is subject to restrictive measures in 12 Member States, Norway and Turkey. It is unknown if 4F-MDMB-BICA is controlled in China, from where at least some of the substance on the European market has been sourced. 4F-MDMB-BICA has not been subject to assessment nor is it currently under assessment by the United Nations system.

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

Benzodiazepines

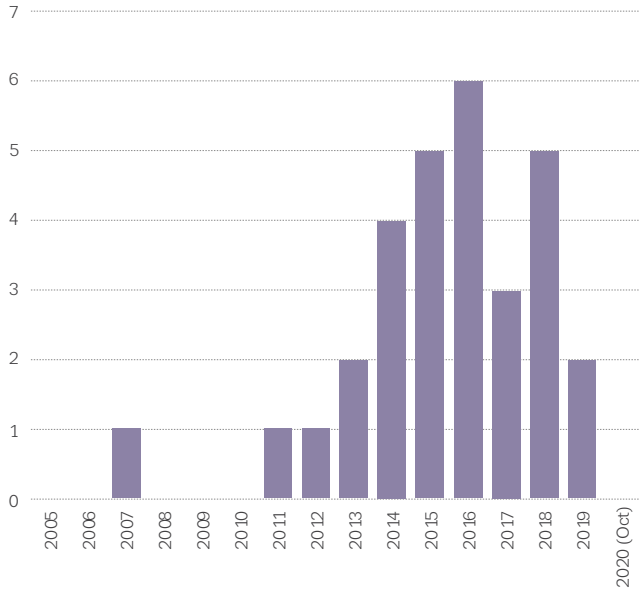
Benzodiazepines are one of the most important groups of medicines that are specifically produced for sedation and to aid sleep. They are the most widely prescribed group of medicines in the world and are used to treat anxiety, insomnia, epilepsy and alcohol withdrawal. Given the large demand from consumers, they are a target for criminal groups that divert legitimate products from the market, sell unlicensed products or make fake versions of legitimate medicines. In the case of fake versions of medicines, new benzodiazepines are increasingly being used, particularly to produce fake diazepam tablets (Valium) and fake alprazolam tablets (Xanax).

As at 31 October 2020, the EMCDDA was monitoring 30 new benzodiazepines — 21 (70 %) of which have been identified in Europe since 2015 (Figure 13). Despite this relatively large number, the market in Europe is dominated by only a handful of substances (Table 3), currently most notably etizolam and flualprazolam, although this may change in the next few months, as both these substances are now under international control.

In 2019, 5 716 seizures of new benzodiazepines were reported to the EU Early Warning System (5 622 (98 %) of which were reported by the Member States), reflecting around 13 % of the total number of seizures of new psychoactive substances (19 % in the Member States). This amounted to approximately 6.1 kg of material and 2.4 million tablets (Figure 14).

FIGURE 13

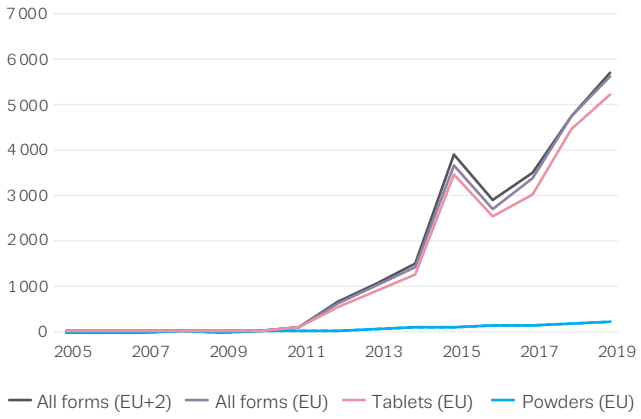
Number of benzodiazepines formally notified to the EU Early Warning System for the first time, 2005-2020 (EU and EU+2)



Note: No benzodiazepines were formally notified to the EU Early Warning System for the first time between January and 31 October 2020.

FIGURE 14

Seizures of benzodiazepines reported to the EU Early Warning System: trends in number of seizures of powders and tablets, 2005-19 (EU and EU+2)



Note: EU and EU+2 data practically overlap due to the low number of seizures in powder and tablet form reported by Turkey and Norway.

Potential changes to the market in new benzodiazepines

In the past few years, etizolam and flualprazolam, in particular, have played an increasingly important role in the new benzodiazepine market in some parts of Europe, especially in making fake diazepam and alprazolam tablets (Moritz et al., 2018; Schier et al., 2009; US CDC, 2018; Vallersnes et al., 2009). In 2020, based on a recommendation from the World Health Organization, the United Nations Commission on Narcotic Drugs decided to control etizolam and flualprazolam owing to the harms that they pose (Klar et al., 2016; Pap, 2016). These control measures came into effect on 3 November 2020 (Klar et al., 2016). As a result, it is possible that other benzodiazepines will replace etizolam and flualprazolam.

TABLE 3

The most commonly seized benzodiazepines reported to the EU Early Warning System, numbers of seizures (a) and quantities seized reported in mass (b) and units (c), 2019

(a) Benzodiazepines	Number of seizures
Etizolam	4 747
Flualprazolam	434
Clonazolam	201
Diclazepam	82
Fonazepam	20

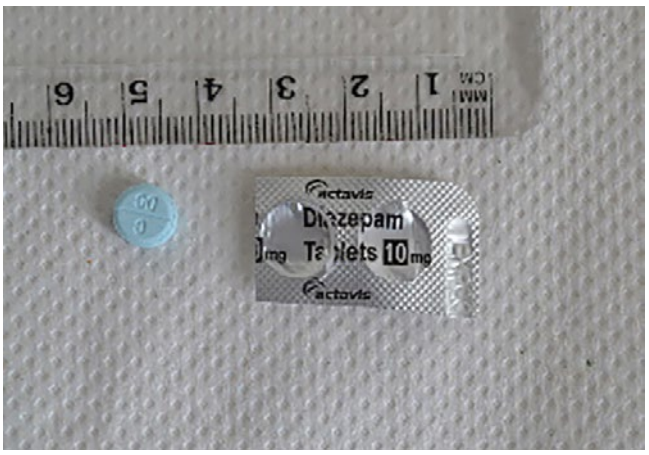
(b) Benzodiazepines	Powder (grams)
Etizolam	2 821.6
Flualprazolam	95.8
Diclazepam	40.8
Fluclotizolam	11.1
Flunitrazolam	10.3

(c) Benzodiazepines	Tablets (units)
Etizolam	2 285 568
Flualprazolam	33 112
Clonazolam	19 492
Diclazepam	19 373
Fonazepam	11 371

One such possibility is the re-emergence of flubromazolam, which was first notified in Europe in 2014 (Tomassoni et al., 2017). Data from the Welsh Emerging Drugs & Identification of Novel Substances Project (Wedinos), the drug testing service operated by Public Health Wales, United Kingdom, appear to suggest that flubromazolam has recently re-emerged on the drug market in the United Kingdom and is being used to make fake diazepam, fake alprazolam, fake temazepam and fake zopiclone (Sutter et al., 2017). In some cases, the fake tablets were packaged into blister packs resembling legitimate products, which makes it more difficult for consumers to spot the fakes (Figure 15). Recent poisonings in the United Kingdom have been linked to flubromazolam sold as fake benzodiazepine medicines (Horth et al., 2018). In the United States, there has also been a recent increase in detections of this substance in toxicology analyses (NPS Discovery, 2020). While the amount of flubromazolam in the tablets is unknown, the substance appears to be a highly potent hypnotic (Adams et al., 2016; Arens et al., 2016; Edison et al., 2017).

FIGURE 15

Fake tablets packaged in blister packs resembling legitimate products



Note: Sample of tablet purchased as 'Diazepam Activis' but found to contain flubromazolam and diazepam on analysis by Wedinos in May 2020.

Photo © Wedinos, 2020.

Global markets, glocal threats: the case for strengthened early warning, preparedness and response measures

Over the past decade, the globalisation of drug markets and new technologies such as the internet have led to an increase in the number and types of risks facing people who use both new psychoactive substances and controlled drugs. These factors also create a resilient and highly dynamic new psychoactive substances market, making it more difficult to disrupt. Adding to this, the COVID-19 pandemic and related response measures have brought into sharp focus the importance of understanding how our health is intricately linked to our environment and globalisation, and how this can shape drug use.

Although evidence is currently limited, based on previous experiences of disruptions to drug markets, the impact of the pandemic could lead to localised or broader changes in drug use and patterns of use, as well as an increased risk of substitution, misselling, adulteration, contamination and dilution with a range of potentially dangerous and sometimes highly toxic substances; in some cases, this could cause outbreaks of mass poisonings, which could overload healthcare systems already struggling with the pandemic.

Providing reliable information is critical for an effective public health response, including prevention, health protection, treatment, supply reduction, and policy development and implementation. The EU Early Warning System and national early warning systems play a central role by providing such information in a timely manner and in sufficient detail to the right people, in the right place, at the right time, to allow them to assess the information and, where necessary, respond through timely and effective actions to prevent or reduce the risk of harm (EMCDDA, 2020b).

Given the growing complexity of the new psychoactive substances 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 new psychoactive substances, whether this be by detecting and responding to a specific, immediate threat or through longer-term input into drug policy.

References

Adamowicz, P. (2016), 'Fatal intoxication with synthetic cannabinoid MDMB-CHMICA', *Forensic Science International* 261, pp. e5-10, doi.org/10.1016/j.forsciint.2016.02.024.

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

Andonian, D. O., Seaman, S. R. and Josephson, E. B. (2017), 'Profound hypotension and bradycardia in the setting of synthetic cannabinoid intoxication-a case series', *American Journal of Emergency Medicine* 35, P940.e5-P940.e6, doi.org/10.1016/j.ajem.2017.01.011.

Arens, A. M., van Wijk, X. M., Vo, K. T., Lynch, K. L., Wu, A. H. and Smollin, C. G. (2016), 'Adverse effects from counterfeit alprazolam tablets', *JAMA Internal Medicine* 176, pp. 1554-1555, doi.org/10.1001/jamainternmed.2016.4306.

Blanckaert, P., Cannaert, A., Van Uytfanghe, K., Hulpia, F., Deconinck, E., Van Calenbergh, S. and Stove, C. (2020), 'Report on a novel emerging class of highly potent benzimidazole NPS opioids: chemical and in vitro functional characterization of isotonitazene', *Drug Testing and Analysis* 12, pp. 422-430, doi.org/10.1002/dta.2738.

Cruz, M. D., Ershad, M., Mostafa, A., Khalid, M. M., Arnold, R. and Hamilton, R. (2019), 'A case series of heroin adulterated with the novel synthetic cannabinoid, 5F-MDMB-PINACA, in Philadelphia, Pennsylvania, USA', ACMT 2019 Annual Scientific Meeting Abstracts—San Francisco, CA, *Journal of Medical Toxicology* 15, pp. 53-107, doi.org/10.1007/s13181-019-00699-x.

ECAPD (Expert Committee on Addiction-Producing Drugs) (1961), *Expert Committee on Addiction-Producing Drugs — Eleventh Report*, World Health Organization Technical Report Series No 211, WHO, Geneva (https://apps.who.int/iris/handle/10665/40481).

Edison, L., Erickson, A., Smith, S., Lopez, G., Hon, S., King, A., Nydam, N., O'Neal, J. P. and Drenzek, C. (2017), 'Notes from the field: counterfeit percocet-related overdose cluster — Georgia, June 2017', *Morbidity and Mortality Weekly Report* 66, p. 1119, doi.org/10.15585/mmwr.mm6641a6.

EMCDDA (European Monitoring Centre for Drugs and Drug Addiction) (2018), *Fentanils and synthetic cannabinoids: driving greater complexity into the drug situation — An update from the EU Early Warning System*, Rapid Communications, Publications Office of the European Union, Luxembourg (https://www.emcdda.europa.eu/publications/rapid-communications/fentanils-and-synthetic-cannabinoids-ews-update_en).

EMCDDA (2020a), *EU Early Warning System Alert. Potential impact of the coronavirus disease (COVID-19) pandemic on the drug markets and risks to people who use drugs — Europe, January 2020-ongoing*, EU-EWS-RCS-AL-2020-0001, date issued: 22 April 2020.

EMCDDA (2020b), *Early Warning System on NPS*, https://www.emcdda.europa.eu/publications/topic-overviews/eu-early-warning-system_en, accessed on 26 November 2020.

EMCDDA (2020c), *EMCDDA initial report on the new psychoactive substance N,N-diethyl-2-[[4-(1-methylethoxy) phenyl]methyl]-5-nitro-1H-benzimidazole-1-ethanamine (isotonitazene)*, Publications Office of the European Union, Luxembourg (https://www.emcdda.europa.eu/publications/initial-reports/isotonitazene_en).

EMCDDA (2020d), *EMCDDA initial report on the new psychoactive substance methyl 3,3-dimethyl-2-(1-(pent-4-en-1-yl)-1*H*-indazole-3-carboxamido)butanoate (MDMB-4en-PINACA)*, Publications Office of the European Union, Luxembourg (https://www.emcdda.europa.eu/publications/initial-reports/mdmb-4en-pinaca_en).

EMCDDA (2020e), *EMCDDA initial report on the new psychoactive substance methyl 2-({[1-(4-fluorobutyl)-1*H*-indol-3-yl]carbonyl}amino)-3,3-dimethylbutanoate (4F-MDMB-BICA)*, Publications Office of the European Union, Luxembourg (https://www.emcdda.europa.eu/publications/initial-reports/4f-mdmb-bica_en).

EMCDDA and Europol (2017), *Drugs and the darknet: perspectives for enforcement, research and policy*, Publications Office of the European Union, Luxembourg (https://www.emcdda.europa.eu/publications/joint-publications/drugs-and-the-darknet_en).

European Parliament and Council of the European Union (2013), 'Decision No 1082/2013/EU of the European Parliament and of the Council of 22 October 2013 on serious cross-border threats to health and repealing Decision No 2119/98/EC', *Official Journal of the European Union* L 293, 5.11.2013, pp. 1-15 (https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32013D1082).

European Parliament and Council of the European Union (2017a), Directive (EU) 2017/2103 of the European Parliament and of the Council of 15 November 2017 amending Council Framework Decision 2004/757/JHA in order to include new psychoactive substances in the definition of 'drug' and repealing Council Decision 2005/387/JHA (https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2017.305.01.0012.01.ENG).

European Parliament and Council of the European Union (2017b), Regulation (EU) 2017/2101 of the European Parliament and of the Council of 15 November 2017 amending Regulation (EC) No 1920/2006 as regards information exchange on, and an early warning system and risk assessment procedure for, new psychoactive substances (https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32017R2101).

Evans-Brown, M. and Sedefov, R. (2018), 'Responding to new psychoactive substances in the European Union: early warning, risk assessment, and control measures', in Maurer, H. and Brandt, S. (eds), *New psychoactive substances: handbook of experimental pharmacology*, vol. 252, Springer, Cham, pp. 3-49, doi.org/10.1007/164_2018_160.

Hoffmann, K., Hunger, A., Kebrle, J. and Rossi, A. (1959), 'Verfahren für Herstellung analgetisch wirksamer Benzimidazole', Bundesrepublik Deutschland Patent No DBP 1057123.

Hoffmann, K., Hunger, A., Kebrle, J. and Rossi, A. (1960), 'Benzimidazoles', US Patent No 2935514.

Horth, R. Z., Crouch, B., Horowitz, B. Z., Prebish, A., Slawson M., McNair, J. Elsholz, C., et al. (2018), 'Notes from the field: acute poisonings from a synthetic cannabinoid sold as cannabidiol — Utah, 2017-2018', *Morbidity and Mortality Weekly Report* 67, pp. 587-588, doi.org/10.15585/mmwr.mm6720a5.

Hunger, A., Kebrle, J., Rossi, A. and Hoffmann, K. (1960a), 'Benzimidazole-Derivate und verwandte Heterocyclen III. Synthese von 1-Aminoalkyl-2-benzyl-nitro-benzimidazolen', *Helvetica Chimica Acta* 43, pp. 1032-1046, doi.org/10.1002/hlca.19600430412.

Hunger, A., Kebrle, J., Rossi, A. and Hoffmann, K. (1960b), 'Benzimidazol-Derivate und verwandte Heterocyclen. II. Synthese von 1-Aminoalkyl-2-benzyl-benzimidazolen', *Helvetica Chimica Acta* 43, pp. 800-809, doi.org/10.1002/hlca.19600430323.

Kasper A. M., Ridpath, A. D., Gerona, R. R., Cox, R., Galli, R., Kyle, P. B., Parker, C., et al. (2015), 'Severe illness associated with reported use of synthetic cannabinoids — Mississippi, United States, April 2015', *Morbidity and Mortality Weekly Report* 64, pp. 1121-1122, doi.org/10.15585/mmwr.mm6439a7.

Kasper, A. M., Ridpath, A. D., Gerona, R. R., Cox, R., Galli, R., Kyle, P. B., Parker, C., et al. (2019), 'Severe illness associated with reported use of synthetic cannabinoids: a public health investigation (Mississippi, 2015)', *Clinical Toxicology* 57, pp. 10-18, doi.org/10.1080/15563650.2018.1485927.

Klar, S. A., Brodkin, E., Gibson, E., Padhi, S., Predy, C., Green, C. and Lee, V. (2016), 'Furanyl-fentanyl overdose events caused by smoking contaminated crack cocaine—British Columbia, Canada, July 15-18, 2016', *Morbidity and Mortality Weekly Report* 65, pp. 1015-1016, doi.org/10.15585/mmwr.mm6537a6.

Los Angeles County Department of Public Health (2016), *Outbreak of synthetic cannabinoid ('Spice') overdoses*, Los Angeles County Department of Public Health, LA (http://publichealth.lacounty.gov/eprp/LAHAN/lahanarchive.html).

Mackenzie, J. S. and Jeggo, M. (2019), 'The One Health approach — why is it so important?', *Tropical Medicine and Infectious Diseases* 4, p. 88, doi.org/10.3390/tropicalmed4020088.

Monte, A. A., Bronstein, A. C., Cao, D. J., Heard, K. J., Hoppe, J. A., Hoyte, C. O., Iwanicki, J. L. and Lavonas, E. J. (2014), 'An outbreak of exposure to a novel synthetic cannabinoid', *New England Journal of Medicine* 370, pp. 389, doi.org/10.1056/NEJMc1313655.

Moritz, E., Austin, C., Wahl, M., DesLauriers, C., Navon, L., Walblay, K., Hendrickson, M., et al. (2018), 'Notes from the field: outbreak of severe illness linked to the vitamin K antagonist brodifacoum and use of synthetic cannabinoids — Illinois, March-April 2018', *Morbidity and Mortality Weekly Report* 67, pp. 607-608, doi.org/10.15585/mmwr.mm6721a4.

Norman, C., Walker, G., McKirdy, B., McDonald, C., Fletcher, D., Antonides, L. H., Sutcliffe, O. B., Nic Daéid, N. and McKenzie, C. (2020), 'Detection and quantitation of synthetic cannabinoid receptor agonists in infused papers from prisons in a constantly evolving illicit market', *Drug Testing and Analysis* 12, pp. 538-554, doi.org/10.1002/dta.2767.

NPS Discovery (2018), *Information regarding 'Santa Muerte' stamped drug seizures causing hospitalizations in the Greater Philadelphia Area*, Center for Forensic Science Research and Education (CFSRE), Willow Grove, PA (https://www.npsdiscovery.org/wp-content/uploads/2019/07/Santa-Muerte-Philadelphia.pdf).

NPS Discovery (2020), *Trend Report: Q1 2020 — NPS benzodiazipenes in the United States*, Center for Forensic Science Research and Education (CFSRE), Willow Grove, PA (https://www.npsdiscovery.org/wp-content/uploads/2020/04/2020-Q1_NPS-Benzodiazepines_Trend-Report.pdf)

Pap, C. (2016), 'ADB-FUBINACA in the real world: a case series of 15 poisonings', *Clinical Toxicology* 54, p. 384, doi.org/10.3109/15563650.2016.1165952.

Pap, C. (2018), '5F-MDMB-PINACA on the streets: case series of 17 poisonings', *Clinical Toxicology* 56, p. 503, doi.org/10.1080/15563650.2018.1457818.

Papadopoulos, E. A., Cummings, K. R., Marraffa, J. M., Aldous, K. M., Li, L. and Ahmad, N. (2017), 'Reports of adverse health effects related to synthetic cannabinoid use in New York State', *American Journal on Addictions* 26, pp. 772-775, doi.org/10.1111/ajad.12636.

Saferparty (2020), *Synthetische cannabinoide: Ergebnisse aus dem Drug-Checking der Stadt Zürich, Januar bis August 2020* (https://www.saferparty.ch/tl_files/images/download/file/aktuelles%202020/Synthetische%20Cannabinoide%20Auswertung%20August%202020.pdf).

Schier, J. G., Rubin, C. S., Miller, D., Barr, D. and McGeehin, M. A. (2009), 'Medication-associated diethylene glycol mass poisoning: a review and discussion on the origin of contamination', *Journal of Public Health Policy* 30, pp. 127-143, doi.org/10.1057/jphp.2009.2.

Schwartz, M. D., Trecki, J., Edison, L. A., Steck, A. R., Arnold, J. K. and Gerona, R. R. (2015), 'A common source outbreak of severe delirium associated with exposure to the novel synthetic

cannabinoid ADB-PINACA', *Journal of Emergency Medicine* 48, pp. 573-580, doi.org/10.1016/j.jemermed.2014.12.038.

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

Springer, Y. P., Gerona, R., Scheunemann, E., Shafer, S. L., Lin, T., Banister, S. D., Cooper, M. P., et al. (2016), 'Increase in adverse reactions associated with use of synthetic cannabinoids — Anchorage, Alaska, 2015-2016', *Morbidity and Mortality Weekly Report* 65, pp. 1108-1111, doi.org/10.15585/mmwr.mm6540a4.

Sutter, M. E., Gerona, R. R., Davis, M. T., Roche, B. M., Colby, D. K., Chenoweth, J. A., Adams, A. J., et al. (2017), 'Fatal fentanyl: one pill can kill', *Academic Emergency Medicine* 24, pp. 106-113, doi.org/10.1111/acem.13034.

Tomassoni, A. J., Hawk, K. F., Jubanyik, K., Nogee, D. P., Durant, T., Lynch, K. L., Patel, R., Dinh, D., Ulrich, A. and D'Onofrio, G. (2017), 'Multiple fentanyl overdoses—New Haven, Connecticut, 23 June 2016', *Morbidity and Mortality Weekly Report* 66, p. 107, doi.org/10.15585/mm6604a4.

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

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

Ujváry, I. (2020), *Technical review of new synthetic opioids identified on the European drug market. Part 1. Benzimidazole opioids*, EMCDDA Contract Code CT.20.SAS.00017.1.0.

UNODC (United Nations Office on Drugs and Crime) (2019), *Schedules of the Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol, as at 24 May 2019*, United Nations, New York, NY (https://www.unodc.org/unodc/en/commissions/CND/conventions.html).

US CDC (United States Centers for Disease Control and Prevention) (2013), 'Severe illness associated with reported use of synthetic marijuana — Colorado, United States, August-September 2013', *Morbidity and Mortality Weekly Report* 62, pp. 1016-1017 (https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6249a7.htm).

US CDC (2018), *Outbreak of life-threatening coagulopathy associated with synthetic cannabinoids use*, CDCHAN-00410, Center for Preparedness and Response (https://emergency.cdc.gov/han/han00410.asp).

US DEA (United States Drug Enforcement Administration) (2018), *Schedules of Controlled Substances: temporary placement of fentanyl-related substances in Schedule I*, DEA, Department of Justice (https://www.deadiversion.usdoj.gov/fed_regs/rules/2018/fr0206_4.htm).

Vallersnes, O. M., Lund, C., Duns, A. K., Netland, H. and Rasmussen, I. A. (2009), 'Epidemic of poisoning caused by scopolamine disguised as Rohypnol™ tablets', *Clinical Toxicology* 47, pp. 889-893, doi.org/10.3109/15563650903333804.

Wedinos (Welsh Emerging Drugs & Identification of Novel Substances Project) (2020), *Welcome*, https://www.wedinos.org, accessed on 10 August 2020.

WHO (World Health Organization) (2015), *International Health Regulations (2005) and chemical events*, WHO, Geneva (http://www.who.int/iris/handle/10665/249532).

Wolicki, S. B., Nuzzo, J. B., Blazes, D. L., Pitts, D. L., Iskander, J. K. and Tappero, J. W. (2016), 'Public health surveillance: at the core of the Global Health Security Agenda', *Health Security* 14, pp.185-188, doi.org/10.1089/hs.2016.0002.

Annex 1

Notifications of new psychoactive substances under the terms of Regulation (EC) No 1920/2006 (as amended) and Council Framework Decision 2004/757/JHA (as amended) — 2019

1. APP-BINACA (*N*-(1-amino-1-oxo-3-phenylpropan-2-yl)-1-butyl-1*H*-indazole-3-carboxamide), United Kingdom, 9 January 2019
2. 2F-QMPSB (quinolin-8-yl 3-((4,4-difluoropiperidin-1-yl) sulfonyl)-4-methylbenzoate), Italy, 10 January 2019
3. Baclofen (4-amino-3-(4-chlorophenyl)butanoic acid), Germany, 15 January 2019
4. EPT (*N*-(2-(1*H*-indol-3-yl)ethyl)-*N*-ethylpropan-1-amine), Slovenia, 21 January 2019
5. Piperidylthiambutene (1-(4,4-di(thiophen-2-yl) but-3-en-2-yl)piperidine), Slovenia, 22 January 2019
6. *N*-Ethylheptedrone (2-(ethylamino)-1-phenylheptan-1-one), Hungary, 5 February 2019
7. Amantadine (adamantan-1-amine), Finland, 15 February 2019
8. Cyproheptadine (4-(5*H*-dibenzo[a,d][7]annulen-5-ylidene)-1-methylpiperidine), Finland, 18 February 2019
9. Promethazine (*N,N*-dimethyl-1-(10*H*-phenothiazin-10-yl)propan-2-amine), Finland, 25 February 2019
10. 1B-LSD (4-butyryl-*N,N*-diethyl-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-fg]quinoline-9-carboxamide), Austria, 7 March 2019
11. 4′-Ethyl-α-PVP (1-(4-ethylphenyl)-2-(pyrrolidin-1-yl) pentan-1-one), Hungary, 7 March 2019
12. 5F-A-P7AICA (*N*-(adamantan-1-yl)-1-(5-fluoropentyl)-1*H*-pyrrolo[2,3-b]pyridine-3-carboxamide), Germany, 2 April 2019
13. 2-Methyl-AP-237 (1-[2-methyl-4-(3-phenylprop-2-en-1-yl)piperazin-1-yl]butan-1-one), Sweden, 3 April 2019
14. Bentazepam (5-phenyl-1,3,6,7,8,9-hexahydro-2*H*-[1] benzothieno[2,3-*e*][1,4]diazepin-2-one), Sweden, 4 April 2019
15. 4F-furanylfentanyl (*N*-(4-fluorophenyl)-*N*-(1-phenethylpiperidin-4-yl)furan-2-carboxamide), Italy, 15 April 2019
16. Isohexedrone (4-methyl-2-(methylamino)-1-phenylpentan-1-one), Sweden, 29 April 2019
17. AP-237 (1-[4-(3-phenylprop-2-en-1-yl)piperazin-1-yl] butan-1-one), Germany, 3 May 2019
18. Cinazepam (4-[[7-bromo-5-(2-chlorophenyl)-2-oxo-1,3-dihydro-1,4-benzodiazepin-3-yl] oxy]-4-oxo-butanoic acid), Sweden, 7 May 2019
19. 5F-JWH-398 (1-(5-fluoropentyl)-3-(4-chloro-1-naphthoyl)indole), Germany, 7 May 2019
20. Hexylone (1-(1,3-benzodioxol-5-yl)-2-(methylamino) hexan-1-one), Germany, 7 May 2019
21. Pagoclone (2-(7-chloro-1,8-naphthyridin-2-yl)-2,3-dihydro-3-(5-methyl-2-oxohexyl)-1*H*-isoindol-1-one), Sweden, 29 May 2019
22. Furanyl UF-17 (*N*-[2-(dimethylamino)cyclohexyl]-*N*-phenyl-furan-2-carboxamide), United Kingdom, 5 June 2019
23. Isohexylone (1-(1,3-benzodioxol-5-yl)-4-methyl-2-(methylamino)pentan-1-one), United Kingdom, 6 June 2019
24. 2C-B aminorex (5-(4-bromo-2,5-dimethoxy-phenyl)-4,5-dihydrooxazol-2-amine), Sweden, 7 June 2019
25. 4-AcO-MPT (3-(2-[methyl(propyl)amino]ethyl)-1*H*-indol-4-yl acetate), Sweden, 11 June 2019
26. BOD (2-(2,5-dimethoxy-4-methylphenyl)-2-methoxyethan-1-amine), Slovenia, 17 June 2019
27. 6-BR-DMPEA (2-bromo-4,5-dimethoxyphenethylamine), Denmark, 21 June 2019
28. 4-PrO-DMT (3-[2-(dimethylamino)ethyl]-1*H*-indol-4-yl propanoate), Sweden, 2 July 2019
29. Pregabalin methyl ester (methyl 3-(aminomethyl)-5-methylhexanoate), Sweden, 2 July 2019

30. 2F-viminol (2-[di(butan-2-yl)amino]-1-[1-(2-fluorobenzyl)-1*H*-pyrrol-2-yl]ethan-1-ol), Sweden, 4 July 2019

31. 4-Fluorophenibut (4-amino-3-(4-fluorophenyl) butanoic acid), Sweden, 4 July 2019

32. 4-AcO-MALT ([3-[2-[allyl(methyl)amino]ethyl]-1*H*-indol-4-yl] acetate), Netherlands, 5 July 2019

33. 3,4-CFP (1-(3-chloro-4-fluorophenyl)piperazine), Poland, 10 July 2019

34. *p*BPP (1-(4-bromophenyl)piperazine), Poland, 11 July 2019

35. 4C-D (1-(2,5-dimethoxy-4-methylphenyl)butan-2-amine), Netherlands, 12 July 2019

36. MDMB-CHMINACA (methyl 2-[1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamido]-3,3-dimethylbutanoate, Poland, 12 July 2019

37. 4′-Methylhexedrone (2-(methylamino)-1-(4-methylphenyl)-1-hexanone), Poland, 13 August 2019

38. *N*-ethylhexylone (1-(1,3-benzodioxol-5-yl)-2-(ethylamino)hexan-1-one), Poland, 14 August 2019

39. Isotonitazene (*N,N*-diethyl-2-[[4-(1-methylethoxy) phenyl]methyl]-5-nitro-1*H*-benzimidazole-1-ethanamine, Belgium, 26 August 2019

40. 3F-α-PHiP (1-(3-fluorophenyl)-4-methyl-2-(pyrrolidin-1-yl)pentan-1-one), Sweden, 27 August 2019

41. MDPEP (1-(1,3-benzodioxol-5-yl)-2-(pyrrolidin-1-yl) heptan-1-one), Sweden, 6 September 2019

42. ADB-BUTINACA (*N*-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-butyl-1*H*-indazole-3-carboxamide), Sweden, 23 September 2019

43. SL-164 (5-chloro-3-(4-chloro-2-methylphenyl)-2-methyl-4(3*H*)-quinazolinone), Sweden, 24 September 2019

44. Crotonylfentanyl (*N*-phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]-2-butenamide), the Netherlands, 15 October 2019

45. *N*-ethylheptylone (1-(1,3-benzodioxol-5-yl)-2-(ethylamino)heptan-1-one), Sweden, 18 October 2019

46. 1-Cp-LSD (4-(cyclopropanecarbonyl)-*N,N*-diethyl-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*] quinoline-9-carboxamide), Sweden, 21 October 2019

47. 4-MeO-MiPT (*N*-[2-(4-methoxy-1*H*-indol-3-yl)ethyl]-*N*-methylpropan-2-amine), Sweden, 21 November 2019

48. Methyl 2-phenyl-2-(pyrrolidin-1-yl)acetate, Sweden, 22 November 2019

49. CUMYL-CBMICA (1-(cyclobutylmethyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indol-3-carboxamide), Germany, 29 November 2019

50. Nitromethaqualone (3-(2-methoxy-4-nitrophenyl)-2-methylquinazolin-4-one), Germany, 3 December 2019

51. 1-(4-Bromo-2,5-dimethoxyphenyl)ethanamine, Germany, 6 December 2019

52. Xylazine (*N*-(2,6-dimethylphenyl)-5,6-dihydro-4*H*-1,3-thiazin-2-amine), France, 13 December 2019

53. UR-144 degradant (3,3,4-trimethyl-1-(1-pentyl-1*H*-indol-3-yl)pent-4-en-1-one), France, 18 December 2019

Annex 2

Notifications of new psychoactive substances under the terms of Regulation (EC) No 1920/2006 (as amended) and Council Framework Decision 2004/757/JHA (as amended) — 2020

1. α-Pyrrolidinocyclohexylphenone/α-PCYP (2-cyclohexyl-1-phenyl-2-(pyrrolidin-1-yl)ethan-1-one), Sweden, 9 January 2020
2. Methoxpropamine (2-(3-methoxyphenyl)-2-(propylamino)cyclohexan-1-one), Denmark, 24 January 2020
3. 3F-α-PHP (1-(3-fluorophenyl)-2-(pyrrolidin-1-yl) hexan-1-one), Sweden, 28 January 2020
4. BOH-PHP (1-phenyl-2-(pyrrolidin-1-yl)hexan-1-ol), Slovenia, 2 March 2020
5. BENZYL-4CN-BINACA (*N*-benzyl-1-(4-cyanobutyl)-1*H*-indazole-3-carboxamide), Sweden, 3 March 2020
6. Nefiracetam (*N*-(2,6-dimethylphenyl)-2-(2-oxopyrrolidin-1-yl)acetamide), Sweden, 26 March 2020
7. *N*-Methyltryptamine (2-(1*H*-indol-3-yl)-*N*-methyl-ethanamine), the Netherlands, 31 March 2020
8. Clozapine (3-chloro-6-(4-methylpiperazin-1-yl)-11*H*-benzo[*b*][1,4]benzodiazepine), the United Kingdom, 15 April 2020
9. Citicoline (5-(4-amino-2-oxopyrimidin-1-yl)-3,4-dihydroxyoxolan-2-yl]methoxy-hydroxyphosphoryl] 2-(trimethylammonium)ethyl phosphate), Germany, 22 April 2020
10. 4F-3-methyl-α-PVP (1-(4-fluoro-3-methylphenyl)-2-(pyrrolidin-1-yl)pentan-1-one), Sweden, 30 April 2020
11. CUMYL-CBMINACA (1-(cyclobutylmethyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide), Germany, 6 May 2020
12. Etazene (2-[(4-ethoxyphenyl)methyl]-*N,N*-diethyl-1*H*-benzimidazole-1-ethanamine), Poland, 1 June 2020
13. Brorphine (1-[1-[1-(4-bromophenyl)ethyl]-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one), Sweden, 4 June 2020
14. BOH-2C-B (2-amino-1-(4-bromo-2,5-dimethoxyphenyl)ethanol), Sweden, 9 June 2020
15. 5-MeO-AI (5-methoxy-2,3-dihydro-1*H*-inden-2-amine), Poland, 18 June 2020
16. PTI-3 (*N*-({2-[1-(5-fluoropentyl)-1*H*-indol-3-yl]-1,3-thiazol-4-yl}methyl)-2-methoxy-*N*-methylethanamine), Hungary, 22 June 2020
17. Metodesnitazene (*N,N*-diethyl-2-[2-[(4-methoxyphenyl)methyl]benzimidazol-1-yl] ethanamine), Belgium, 26 June 2020
18. Cumyl-CB-MeGaClone (5-(cyclobutylmethyl)-2-(1-methyl-1-phenyl-ethyl)pyrido[4,3-*b*]indol-1-one), Hungary, 30 June 2020
19. 4F-MDMB-BICA (methyl 2-({[1-(4-fluorobutyl)-1*H*-indol-3-yl]carbonyl}amino)-3,3-dimethylbutanoate), Belgium, 2 July 2020
20. 5F-EMB-PICA (ethyl 2-[[1-(5-fluoropentyl)indole-3-carbonyl]amino]-3-methyl-butanoate), Belgium, 3 July 2020
21. *N,N*-Diethylpentylone (1-(1,3-benzodioxol-5-yl)-2-(diethylamino)pentan-1-one), Spain, 13 July 2020
22. 5-Br-DMT (2-(5-Bromo-1*H*-indol-3-yl)-*N,N*-dimethylethan-1-amine), Slovenia, 17 July 2020
23. 5-Cl-DMT (2-(5-Chloro-1*H*-indol-3-yl)-*N,N*-dimethylethan-1-amine), Slovenia, 17 July 2020
24. Isobutyrfentanyl (2-Methyl-*N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide), Italy, 24 July 2020
25. 4,4-Dimethyl-1-phenyl-1-pyrrolidin-1-yl-pentan-3-one, the United Kingdom, 24 July 2020
26. Nortilidine (ethyl 2-methylamino-1-phenylcyclohex-3-ene-1-carboxylate), Poland, 30 July 2020
27. Mephedrene (*N*-methyl-1-(5-methyl-2-thienyl) propan-2-amine), Germany, 31 July 2020
28. MDPHiP (1-(1,3-benzodioxol-5-yl)-4-methyl-2-pyrrolidin-1-yl-pentan-1-one), Sweden, 19 August 2020

29. 5F-EDMB-PICA (ethyl 2-(1-(5-fluoropentyl)-1*H*-indole-3-carboxamido)-3,3-dimethylbutanoate), Hungary, 8 September 2020

30. Metonitazene (*N*,*N*-diethyl-2-[2-[(4-methoxyphenyl) methyl]-5-nitro-benzimidazol-1-yl]ethanamine), Germany, 14 September 2020

31. 3-Methoxyphenmetrazine (2-(3-methoxyphenyl)-3-methylmorpholine), Finland, 16 September 2020

32. 5-MeO-DBT (*N*-butyl-*N*-[2-(5-methoxy-1*H*-indol-3-yl) ethyl]butan-1-amine), Finland, 18 September 2020

33. 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), Germany, 30 September 2020

34. 4F-ABINACA (*N*-(adamantan-1-yl)-1-(4-fluorobutyl)-1*H*-indazole-3-carboxamide), Sweden, 9 October 2020

35. Carbonyl-bromadol ((4-bromophenyl)-(1-(dimethylamino)-4-hydroxy-4-phenethylcyclohexyl) methanone), Germany, 15 October 2020

36. 3F-*N*-ethylhexedrone (2-(ethylamino)-1-(3-fluorophenyl)hexan-1-one), Sweden, 20 October 2020

37. AP-238 (1-[2,6-dimethyl-4-(3-phenylprop-2-enyl) piperazin-1-yl]propan-1-one), Germany, 22 October 2020

38. O-AMKD (3-(4-acetyl-1-methylpiperidin-4-yl)phenyl acetate), Germany, 27 October 2020

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emcdda

About this report

In this update from the EU Early Warning System, the EMCDDA aims to provide insights into what is happening with new psychoactive substances in Europe, based on data from the agency's early warning and risk-assessment activities. This report covers the period until October 2020.

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 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.

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