European Monitoring Centre
for Drugs and Drug Addiction

New psychoactive substances: 25 years of early warning and response in Europe

An update from the EU Early Warning System

June 2022




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Introduction

New psychoactive substances (NPS) are a broad range of drugs that are not controlled by the United Nations Drug Control Conventions. They include stimulants, synthetic cannabinoids, opioids, benzodiazepines (and other sedative-hypnotics), hallucinogens and dissociatives. Many of these substances are intended to mimic the effects of internationally controlled drugs and are sold as 'legal' replacements for them.

A three-step legal framework of early warning, risk assessment and control measures allows the EU to rapidly detect, assess and respond to threats caused by NPS. The EMCDDA is responsible for the first two steps of this system, namely operating the EU Early Warning System (EU EWS) on NPS in close cooperation with Europol and conducting risk assessments. The European Commission is responsible for proposing control measures.

Operational since 1997, the EU EWS was the first regional early warning system to be established to monitor NPS. As these substances have spread around the world, the European system has been recognised as a model for national, regional and international early warning systems.

Learn more about this work

Early Warning System on NPS:
https://www.emcdda.europa.eu/publications/topic-overviews/eu-early-warning-system_en

Reflecting this work and its world-leading expertise, the EMCDDA plays a key role in supporting organisations across the globe to build and strengthen their early warning and risk assessment capabilities in response to the public health threats posed by NPS. This includes supporting and contributing to the work of the World Health Organization (WHO) and the United Nations Office on Drugs and Crime (UNODC).

The purpose of this report is to overview the NPS situation in Europe today and to highlight emerging threats to support early warning, preparedness planning and response measures. In addition, 16 June 2022 marks 25 years since legislation was adopted in the EU allowing it to rapidly react to threats caused by NPS (Council of the European Union, 1997). Since then, the market has undergone periods of significant growth and change. The anniversary provides an opportunity to reflect on these changes and the lessons learned. This will help inform the direction of work and policy so that the EU remains prepared and at the forefront of the response to NPS, helping protect public health.

The report is divided into three parts. The first looks back at the major developments, challenges, accomplishments and lessons learned from the NPS phenomenon over the last 25 years. The second provides an update on the NPS situation up to the end of December 2021, including a more in-depth look at synthetic cathinones, synthetic cannabinoids, opioids and benzodiazepines. The third part looks forward and builds on the lessons from the last 25 years and reflects on the benefits that could accrue from working together at the international level to respond to the future challenges posed by NPS.

PART 1

The EU Early Warning System: 25 years of monitoring the appearance of NPS in Europe

Europe has been at the forefront of the response to NPS since before they were widely recognised as a global policy issue and public health threat (CND, 2005, 2010, 2012).

The NPS market has been fuelled by globalisation, the internet and attempts to circumvent new control measures, and by exploiting differences in drug laws and regulatory approaches (EMCDDA, 1998, 2015a, 2015b, 2018, 2020a) (Figure 1 and box 'Early warning and risk assessment activities from 1997 to 2021').

During the last 25 years, the health risks associated with the use of NPS have also grown. During this period, we have seen the introduction of more novel and sometimes highly potent substances from a wider set of chemical classes. As regulatory measures have increased, we have also seen greater interaction between the established illicit drug market and the market for NPS, including growth in illicit production of some substances within the EU. We have also seen the adulteration and mis-selling of both established controlled drugs and NPS products. This can mean that consumers may be unknowingly exposed to highly potent and toxic substances.

In response to these developments, EU legislation has been strengthened twice over the last 25 years with the intention of providing a stronger and faster response to this complex public health issue. The EU response has also provided added value to national and international actions. The system is based on the foundation that 'good decisions begin with good data'. Critical information on NPS from across Europe is shared in a timely manner through the EWS. This is intended as 'information for action' to raise awareness and support preparedness and response activities. A focus on cross-border threats has helped reduce the impact of NPS on public health across Europe and beyond. The development of standards and best practice in the early warning and risk assessment fields, such as operating guidelines, standardised data collection tools and a pan-European information system, has also provided a stronger basis for evidence-based decision-making.

The work of the EU in this area has also promoted networking and supported research programmes. It has developed expertise within Europe, and informed the training of the next generation of scientists, public health practitioners, law enforcement and early warning specialists.

Early warning and risk assessment activities from 1997 to 2021

- 884 NPS were formally notified for the first time; 52 were formally notified in 2021;
- 283 500 seizures of NPS have been reported in the EU since 2005; 21 200 seizures were reported in the EU in 2020;
- 31.6 tonnes of NPS have been seized in the EU since 2005; 5.1 tonnes were reported in the EU in 2020;
- 168 public health risk communications were issued by the EMCDDA to the EWS Network; 7 were issued in 2021;
- 37 substances were risk assessed by the EMCDDA; 2 were risk assessed in 2021:
  - 27 substances were brought under EU control; 2 were controlled in 2021;
  - 26 of these substances were subsequently controlled internationally.

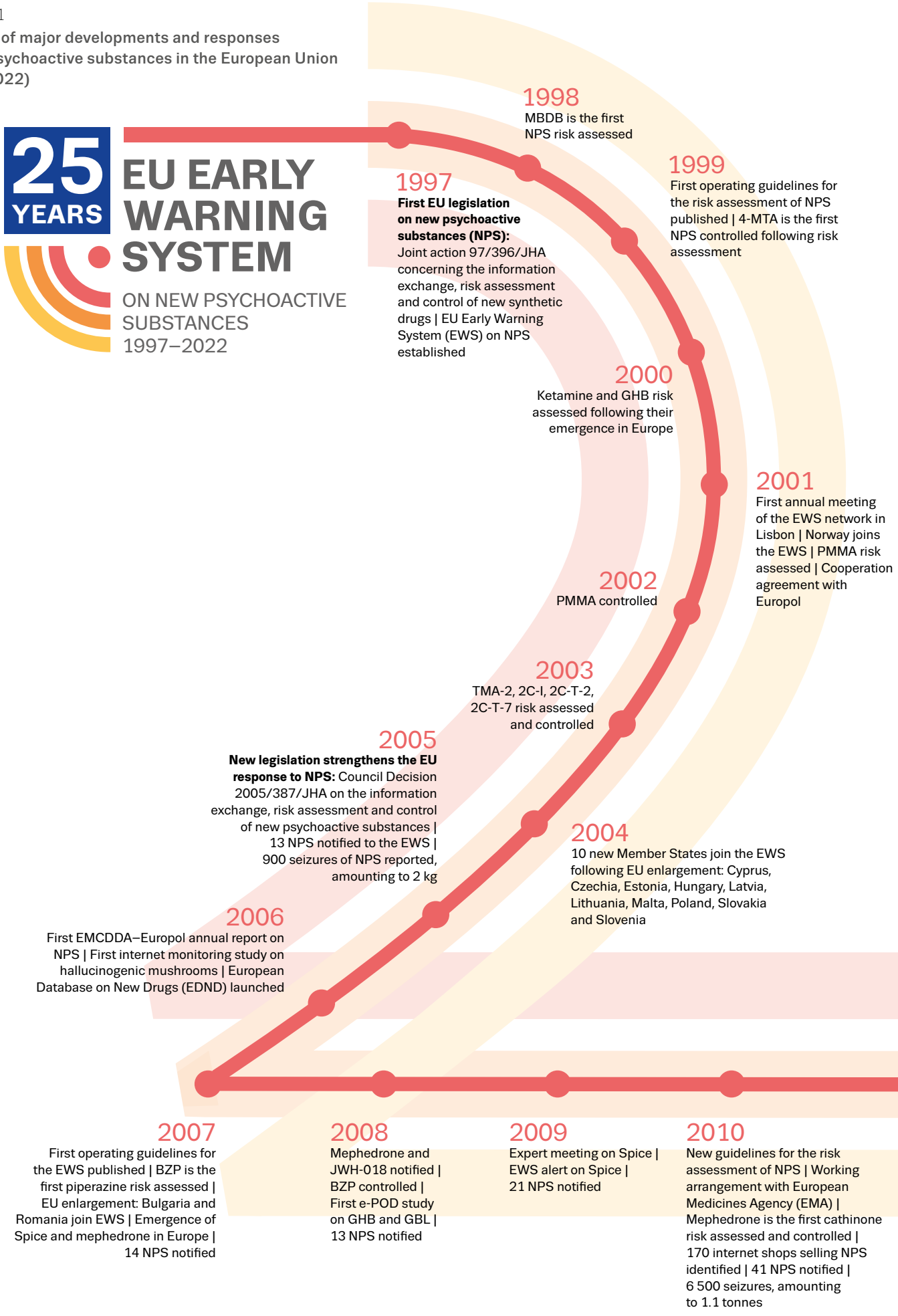
The first 10 years, 1997-2007

The EU EWS was established in 1997 after concerns that the emergence of ecstasy (MDMA) had revealed a lack of capacity in Europe to identify and respond to the appearance of uncontrolled substances that could be used for their psychoactive properties and cause harm.

However, the period between 1997 and 2007 was characterised by the appearance of only a relatively small number of NPS. Overall, this was a small group of esoteric synthetic substances, often known at the time as 'new synthetic drugs' but also some plant-based substances, so-called 'herbal highs', such as *Salvia divinorum* and magic mushrooms. The new synthetic drugs appearing at this time were typically stimulants and hallucinogens/psychedelics often made in small illicit laboratories in Europe. Some were mis-sold as amphetamine or ecstasy. PMMA, for example, was often sold as ecstasy (MDMA) and was linked with a number of deaths. The internet also began to emerge as a platform for selling NPS during this period. BZP, often sold as 'party pills', was perhaps the first synthetic substance more widely known from being sold online (EMCDDA, 2009a). Signals also began to be detected during this period suggesting that companies in China were playing a role in the supply of bulk quantities of NPS, marking a transition away from production in small-scale illicit laboratories in Europe. However, it was with the emergence and detection of Spice — a herbal

FIGURE 1

Timeline of major developments and responses to new psychoactive substances in the European Union (1997-2022)



2020

New risk assessment operating guidelines | Isotonitazene is the first benzimidazole opioid risk assessed and controlled | MDMB-4en-PINACA and 4F-MDMB-BICA risk assessed | Alerts: impact of COVID-19 pandemic on drug markets; low-THC cannabis adulterated with synthetic cannabinoids | 46 NPS notified | 21 200 seizures, amounting to 5.1 tonnes

2021

3-MMC and 3-CMC risk assessed | Alerts: benzimidazole opioids in fake medicines; risks posed by cannabis edibles | Outbreak of bleeding linked to brodifacoum in Israel | 52 NPS notified | EMCDDA monitoring 884 NPS

2022

EMCDDA celebrates 25 years of early warning and response to NPS in Europe | EU control measures on 3-MMC and 3-CMC adopted

2019

New EWS operating guidelines | New EDND launched | Alerts: flualprazolam, etizolam | Isotonitazene is the first benzimidazole opioid notified | Working arrangements with EU agencies: ECHA, EFSA | 53 NPS notified

2017

MDMB-CHMICA is the first synthetic cannabinoid controlled | Alert: increase in carfentanil seizures and deaths | Acryloylfentanyl, furanylfentanyl, AB-CHMINACA, ADB-CHMINACA, 5F-MDMB-PINACA, CUMYL-4CN-BINACA, 4F-iBF, THF-F and carfentanil risk-assessed | 51 NPS notified

2018

New legislation strengthens the EWS and brings faster response to NPS: Regulation (EU) 2017/2101 and Directive (EU) 2017/2103 enter into force | Working arrangements with EU agencies: ECDC, EMA, Europol | Methoxyacetylfentanyl and cyclopropylfentanyl risk assessed | Alerts: fentanils in fake medicines; risk of occupational exposure to fentanils; CBD e-liquids adulterated with synthetic cannabinoids | 55 NPS notified | 33 600 seizures, amounting to 4.1 tonnes

2016

MDMB-CHMICA is the first synthetic cannabinoid risk assessed | Alerts: ocfentanil sold as heroin; acryloylfentanyl deaths | MDA 19 (BZO-HEXOXIZID) notified | 66 NPS notified | 46 000 seizures, amounting to 3.2 tonnes

2015

Toxicovigilance, signal management, open source information monitoring and risk communication systems established | Acetylfentanyl is the first fentanil causing EU concern | α-PVP risk assessed | Alert: 'Mocarz' mass poisoning by synthetic cannabinoids | BZP, mephedrone, 25I-NBOMe, AH-7921, MDPV controlled internationally | 98 NPS notified | 34 200 seizures, amounting to 4.6 tonnes

2014

Cooperation on NPS strengthened with World Health Organization and United Nations Office on Drugs and Crime | Turkey joins EWS | AH-7921 is the first opioid risk assessed and controlled | MDPV, 25I-NBOMe, methoxetamine, MT-45, 4,4'-DMAR risk assessed | Alert: MDMB-CHMICA poisonings | 101 NPS notified

2013

5-IT risk assessed | EU enlargement: Croatia joins EWS | Alerts: AH-7921 deaths; 25I-NBOMe poisonings | Online interactive resource on synthetic cannabinoids | 81 NPS notified | 25 200 seizures, amounting to 1.9 tonnes

2012

First international conference on NPS in Budapest | 4-Methylamphetamine risk assessed | Alert on 5-IT deaths | National EWS profiles published | 693 internet shops identified | 74 NPS notified

2011

First international forum on NPS in Lisbon | First meeting on wastewater analysis of NPS | Alert on 4-methylamphetamine deaths | 314 internet shops identified | 48 NPS notified

mixture containing synthetic cannabinoids — and mephedrone that led to growing public and professional interest in what was known at the time as the 'legal highs' and 'research chemical' phenomenon. At this stage, however, few people were aware of the significance that these substances would play in the future (Griffiths et al., 2010; Hillebrand et al., 2010).

This period also saw the EWS beginning to develop its approach to detecting new substances appearing in Europe. The system was established as a multidisciplinary network composed of the EMCDDA, Europol, 15 national early warning systems, and the European Medicines Agency. The EWS used common reporting tools and benefitted from shared EU and national investment. Around this period, the term 'new psychoactive substances' started to replace 'new synthetic drugs', and this term was used in new EU legislation introduced during 2005 (Council of the European Union, 2005) to broaden the scope of substances that could be monitored and to strengthen the system overall. In 2006, the European Database on New Drugs (EDND) was established. The EDND was the first multidisciplinary information system on NPS in the world. It provided experts from across Europe with detailed information on NPS, including law enforcement seizures, collected samples, poisoning cases, chemistry and identification methods, pharmacology, toxicology, epidemiology, harms, and response measures.

Of the 60 or so substances notified between 1997 and 2007, risk assessments were carried out on 10 of them, most of which were stimulants: MDMB, 4-MTA, GHB, ketamine, PMMA, TMA-2, 2C-T-2, 2C-T-7, 2C-I and BZP. Of these, 4-MTA, PMMA, TMA-2, 2C-T-2, 2C-T-7, 2C-I and BZP were brought under control throughout the EU. Subsequently, 4-MTA, GHB, PMMA and BZP were controlled under the UN system.

Legal highs and research chemicals, 2008-2015

This period was characterised by a rapid increase in the number, type and availability of NPS in Europe. Most were produced by chemical and pharmaceutical companies in China and imported into Europe. They were attractively packaged and sold openly on the high street and the internet in hundreds of branded products marketed as 'legal highs' and 'research chemicals' in attempts to circumvent legal controls.

This period was also marked by the development and use of a range of novel methodologies by the EMCDDA to strengthen the monitoring of NPS, specifically to detect, track and understand emerging trends. They included:

- the E-POD studies that triangulated information from a wide range of formal and informal sources (EMCDDA, 2006, 2008);
- monitoring of online sales of NPS (EMCDDA, 2011a);
- analysis of wastewater and injecting equipment to detect and track NPS use.

Monitoring by the EMCDDA identified a rapid increase in online shops selling NPS (EMCDDA, 2011a; EMCDDA, 2012a), from 170 in January 2010 to 314 in January 2011 and 693 in January 2012 — a 300 % increase in just two years.

Much of the growth in the market was driven by sales of Spice, sold as a 'legal' replacement to cannabis (EMCDDA, 2009b), as well as mephedrone and other synthetic cathinones, sold as a 'legal' replacement to MDMA, amphetamine and cocaine (EMCDDA, 2011b; EMCDDA and Europol, 2010). Both 2014 and 2015 saw the appearance of 100 new substances in Europe. Most were synthetic cannabinoids and cathinones, but a broad range of other substances were also reported, including ketamine-like substances, and over time benzodiazepines and opioids. Seizures by law enforcement also grew rapidly, as did poisonings reported by the network. During 2015, over 34 000 seizures of NPS amounting to 4.6 tonnes were reported in the EU.

In response, the EMCDDA developed new methods to strengthen the ability of the EWS to detect, assess, prioritise and respond to threats in a timelier manner. They included:

- a toxicovigilance system that harmonised the way that information on serious adverse events, particularly acute poisonings and deaths, was reported and analysed;
- a methodology for monitoring open source information that used the internet to detect serious and urgent threats, such as outbreaks, and other key information;
- a signal management approach that provided a more robust method for identifying and assessing emerging threats based on their type, seriousness and urgency in order to prioritise them and identify response options;
- a risk communication system that strengthened the way alerts were shared within the EWS Network.

The period also saw increased national and EU investment in this area, including creating new national and EU-funded projects, such as test-purchase programmes targeting NPS of concern; strengthening forensic and toxicology capacity; and helping to increase awareness of the public health threats of NPS. In 2013, the UNODC also set up the

Early Warning Advisory to provide early warning information at the global level.

Increasingly, countries responded to these developments by restricting the availability of NPS, including their open sale (EMCDDA, 2015b). National early warning systems were also strengthened (EMCDDA, 2012b).

Almost 480 substances were notified during this period. Risk assessments were carried out on 10 of them: mephedrone, 4-MA, 5-IT, AH-7921, methoxetamine, 25I-NBOMe, MDPV, MT-45, 4,4'-DMAR and α-PVP. All of them were brought under control throughout the EU. This work also informed international assessments by the WHO, leading to many of these substances being controlled at the international level. Most of the substances that were assessed were stimulants; however, two were opioids (AH-7921 and MT-45), a class of drug that would become increasingly important in the future.

Greater complexity and integration with the illicit market, 2016-2022

This period was characterised by a shift away from 'legal highs' and 'research chemicals', and a drop in the number of substances appearing each year to around 50. We also began to see growing complexity as more highly potent substances emerged that were often linked to more problematic patterns of use or targeting more marginalised or chronic and long-term drug-using populations. They included new opioids, with large numbers of fentanyl derivatives appearing. These were often linked to outbreaks of poisonings or deaths but tended to disappear quickly only to be replaced by other opioids, including highly potent benzimidazole opioids. The number of new benzodiazepines appearing also increased during this period (EMCDDA, 2019).

Just over 320 substances were notified in this period, with risk assessments carried out on 17 substances. These were mostly synthetic cannabinoids and opioids (typically fentanyl derivatives): MDMB-CHMICA, acryloylfentanyl, furanylfentanyl, AB-CHMINACA, ADB-CHMINACA, 5F-MDMB-CHMINACA, CUMYL-4CN-BINACA, 4F-iBF, THF-F, carfentanil, cyclopropylfentanyl, methoxyacetylfentanyl, isotonitazene, MDMB-4en-PINACA, 4F-MDMB-BICA, 3-methylmethcathinone and 3-chloromethcathinone. Twelve were brought under control throughout the EU, with five being simultaneously assessed and controlled internationally.

It was also a period of growing integration with the established illicit drug market. This was partially reflected in the increased use of new benzodiazepines to make falsified (fake) versions of commonly prescribed benzodiazepine medicines, such as Valium and Xanax. Greater diversification of the supply chain also appears to have taken place, making the market more resilient to control measures — with India becoming a prominent source of synthetic cathinones from around 2019-2020. There were also more reports of illicit production of synthetic cathinones in Europe.

Towards the end of 2018, new legislation came into force intended to further strengthen the EU system and make it respond faster (European Parliament and Council of the European Union, 2017a, 2017b). New EU EWS and risk assessment operating guidelines were published (EMCDDA, 2019; 2021c), along with common reporting tools. This also included the launch of a redesigned EDND in 2019, providing the EU with a next-generation information system capable of electronic data management. Together, these updates provide a more efficient response to NPS, allowing the EU to react to substances posing EU-level threats in just over 10 weeks.

PART 2
Update on the work of the EU EWS in 2020-2021

Number of NPS on the market

By 31 December 2021, the EMCDDA was monitoring 884 NPS that had appeared on Europe's drug market since monitoring began in 1997; this includes 52 substances that were notified for the first time in 2021 (Figure 2 and Annex 1).

The number of NPS notified in 2021 continues the trend seen since 2016 of around 50 new substances appearing for the first time each year; this is down from the high of 100 substances observed in both 2014 and 2015. This drop likely reflects sustained efforts to control and otherwise restrict the sale of NPS in Europe as well as measures introduced to restrict the production and trade in source countries, such as China.

Since 2015, around 400 previously reported NPS are also identified each year as still being present on the market in Europe. This suggests that many substances remain in circulation, albeit in varying amounts and with some in very small quantities.

Overview of law enforcement seizures

In 2020, just over 21 000 seizures amounting to more than 5 tonnes of NPS were reported to the EU EWS by the Member States (Figure 2). In addition, approximately 230 litres of liquids and 840 000 tablets and capsules containing NPS were reported. Over 41 000 seizures amounting to 6.9 tonnes of NPS were reported in total by EU Member States plus Norway and Turkey (EU+2).

The seizure data collected on NPS in this report should be regarded as minimum estimates due to the lack of standardised reporting in this area. The data are not directly comparable with the data on established illicit drugs.

Synthetic cathinones dominated the seizures made in 2020. Mostly these were trafficked to Europe from India and seized at the external EU border by customs agencies. Overall, 65 % of the materials seized (3.3 tonnes) were cathinone powders. In addition, almost 1.2 tonnes of the materials seized (23 % of the total) were arylcyclohexylamines, of which ketamine accounted for almost all the quantity seized (1.1 tonnes (93 %).

Risk communications

Risk communications are regularly produced by the EWS and intended to provide timely evidence-based messages that raise awareness and knowledge, and increase the understanding of the public health and social threats associated with NPS. This includes highlighting important gaps in information as well as stimulating the reporting of data that can facilitate further assessment and understanding. Risk communications also provide material to inform preparedness planning and response activities, including information on possible response options.

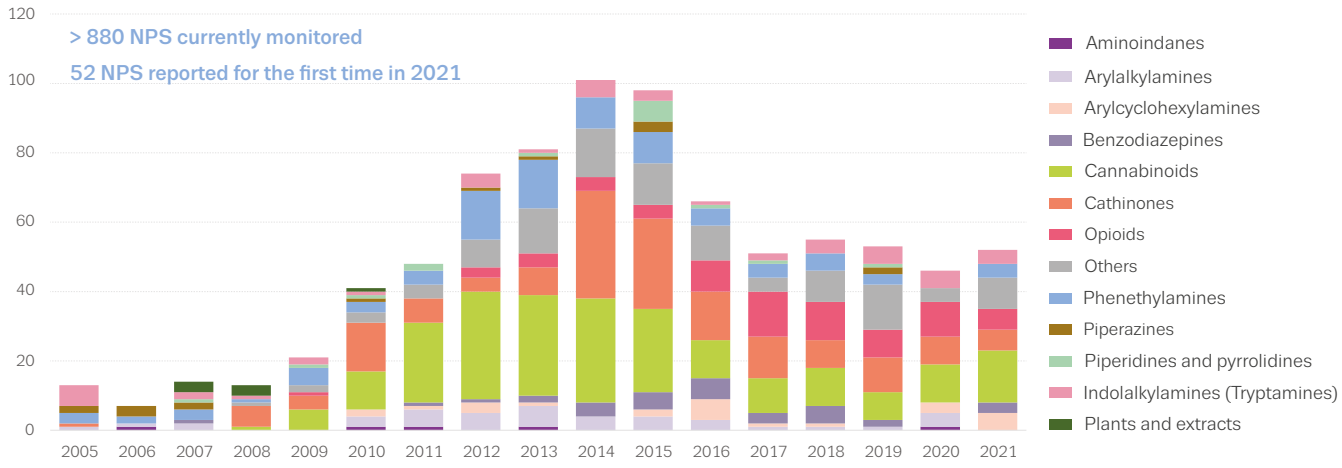
During 2021, the EMCDDA issued seven public health risk communications to the EWS Network based on EU-relevant threats (Annex 2). These included advisories on the spread of low-THC cannabis adulterated with synthetic cannabinoids in Europe, and the detection of fake opioid analgesic medicines containing highly potent opioids. An alert on the detection of tablets containing DOC, a potent hallucinogen, that were mis-sold as 2C-B was also issued. An alert was also issued describing an outbreak of poisonings outside of Europe caused by a highly toxic rat poison in synthetic cannabinoid smoking mixtures. Some of these threats are discussed below.

FIGURE 2

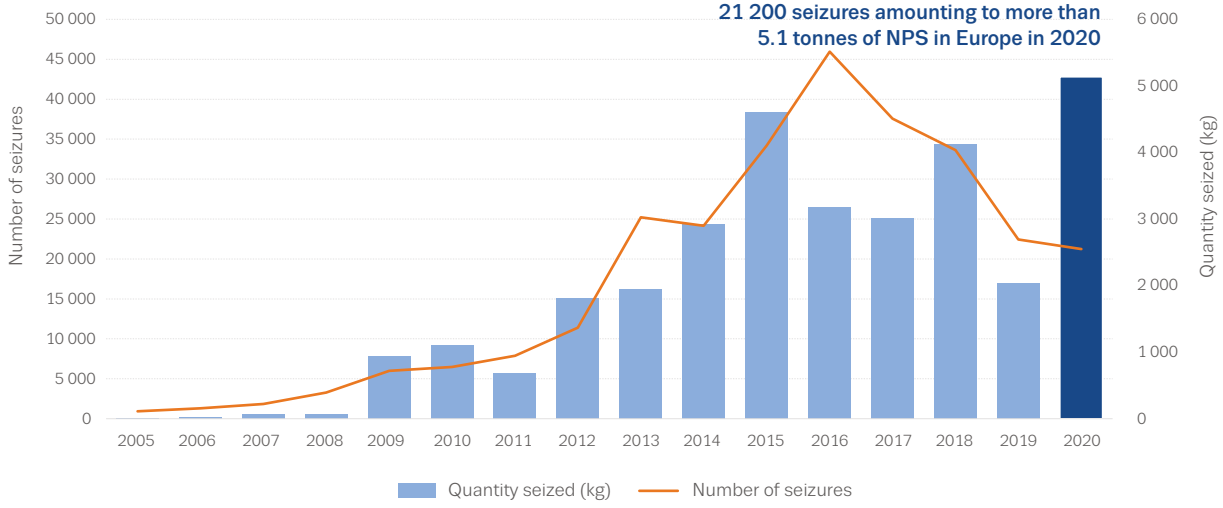
Infographic on new psychoactive substances

New psychoactive substances

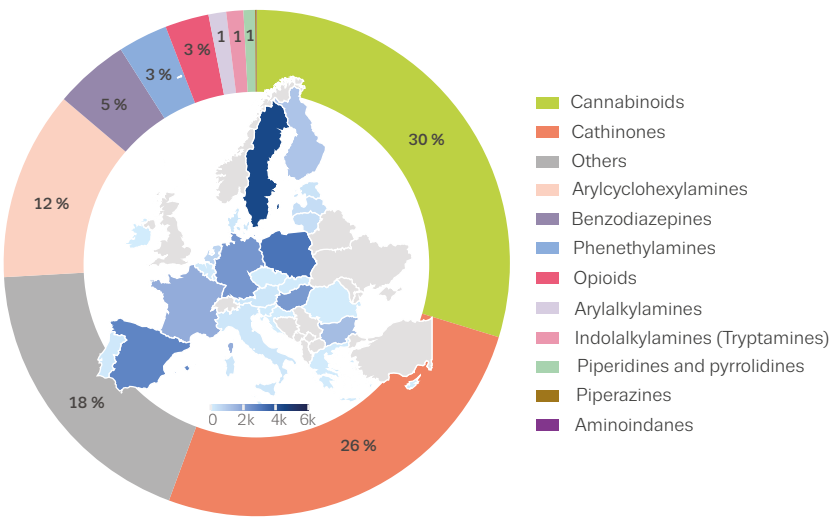
a) Number of NPS notified for the first time, 2005-2021 (EU+2)



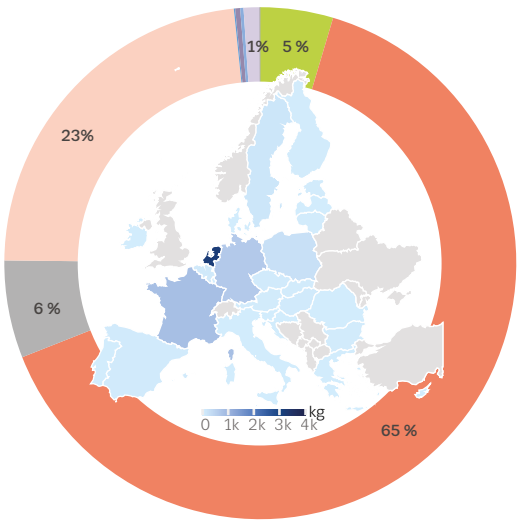
b) Trends in the number of seizures and quantities seized for all physical forms reported in weight, 2005-2020 (EU)



c) Number of NPS seizures by country and substance, 2020 (EU)



Quantity of NPS seized by country and substance, 2020 (EU)



Synthetic cathinones

Synthetic cathinones are sold as 'legal' alternatives to controlled stimulants such as amphetamine, MDMA and cocaine. In a small number of cases, such as mephedrone, they have become sought-after substances in their own right. By 31 December 2021, the EMCDDA was monitoring 162 synthetic cathinones, making them the second-largest category of NPS monitored after synthetic cannabinoids. Seizures of synthetic cathinones in Europe sharply increased to 3.3 tonnes in 2020, after falling from a peak of 1.9 tonnes in 2016. This was driven by a small number of large seizures of *N*-ethylhexedrone (NEH) (1180 kg; 36 %), 3-methylmethcathinone (3-MMC) (750 kg; 23 %) and 3-chloromethcathinone (3-CMC) (860 kg; 26 %) by customs agencies (Figure 3).

Most bulk quantities of synthetic cathinones seized at the external EU borders in 2020 originated in India, where they are apparently produced on a large scale (Case study 1). Before 2020, the origin of comparable consignments, where known, was China. However, since 2015 onwards, China has introduced legal controls for a range of substances, including 3-MMC and 3-CMC. Supply disruption due to the COVID-19 pandemic may have also contributed to increased production and trafficking moving from China to India.

In November 2021, the EMCDDA risk assessed 3-MMC (EMCDDA, 2022a) and 3-CMC (EMCDDA, 2022b) — substances that were first reported in Europe in 2012 and 2014, respectively, but re-emerged in around 2020 (Case study 2). Based on the risk assessments, on 18 March 2022 the European Commission adopted a proposal to control the substances across Europe (EMCDDA, 2022c).

Case study 1: Large-scale seizure of synthetic cathinones originating from India — Leipzig Airport, Germany, 2020

On 26 May 2020, NPS were detected in cargo shipments by customs officials at Leipzig Airport, Germany. A total of 31 plastic drums that originated from India were inspected and found to contain six different types of NPS weighing 450 kilograms. Almost all of the NPS (98 %) were synthetic cathinones: 100 kilograms of 4-CMC, 105 kilograms of 3-MMC, 60 kilograms of 3-CMC, 75 kilograms of alpha-PHP, and 100 kilograms of NEH. The shipments were destined for a company in the Netherlands. The market value of the substances was estimated to be more than EUR 8.3 million (BKA, 2021).

Initial indications are that large-scale seizures of synthetic cathinones originating from India continued during 2021, dominated by 3-MMC and 3-CMC.

In addition, there has been an increase in the number of illicit laboratories producing synthetic cathinones seized in Europe (Case study 3).

From 2015 to 2020, approximately 3.3 tonnes of cathinone precursors were seized in Europe. Most were α-bromoketone derivatives (also called bromo propiophenones) (EMCDDA, 2022a) needed to make mephedrone (1.7 tonnes; 52 % of all precursors seized) and clephedrone (1.2 tonnes; 36 %). Roughly 40 % of the precursor shipments originated from outside the EU, in China but also India. The final destination of the cathinone precursors included the Netherlands, Poland, Spain, and the United Kingdom. Seizures of cathinone precursors (1.9 tonnes; 57 %) typically occurred in illicit cathinone laboratories, mainly in Hungary, the Netherlands and Poland.

In addition, chemically masked derivatives of synthetic cathinones have been produced, presumably to circumvent legal controls and/or avoid detection by law enforcement agencies. In this procedure, the cathinone is chemically masked to produce a non-controlled substance which is converted back into the parent drug through relatively simple steps. For example, during 2019, Dutch police seized 350 kilograms of chemically masked 3-MMC at a site linked to a producer/distributor that had apparently imported the substance from India. The 3-MMC was masked as *N*-acetyl-3-MMC ([1]). It is thought that this derivative was intended to be converted to 3-MMC, for example by acid hydrolysis using hydrochloric acid. Approximately 150 kilograms of 3-MMC was also seized at the site. These masked drugs are not controlled and can therefore be ordered and transported using the same channels as used for NPS but then easily converted into the parent drug when within Europe. More than 90 % of the dismantled laboratories were in the Netherlands and Poland. A significant amount of precursor material destined for these countries was also intercepted. Possibly to reduce the risk of detection, precursors and material for the synthesis may sometimes be obtained via neighbouring countries, including Germany, France and Luxembourg.

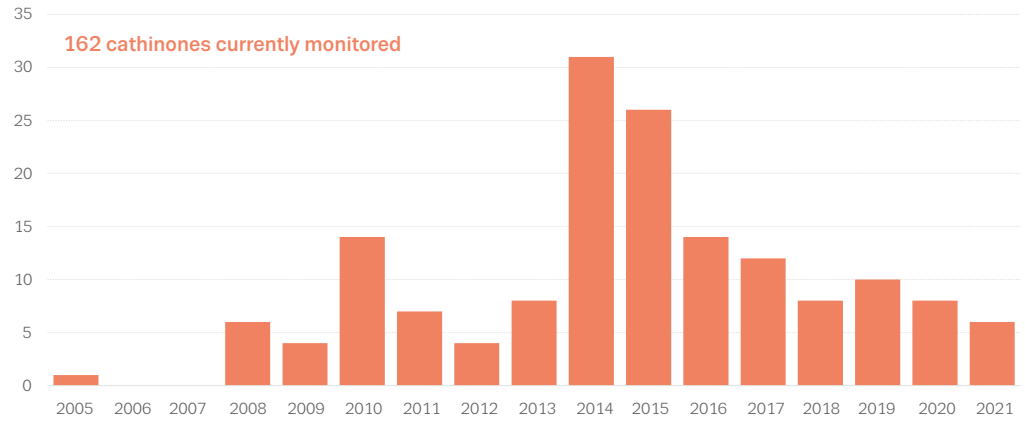
([1]) It is unknown whether *N*-acetyl-3-MMC is hydrolysed to 3-MMC in human stomach acid. No information is available on the pharmacology or toxicology of this masked derivative.

FIGURE 3

Infographic on synthetic cathinones

Synthetic cathinones

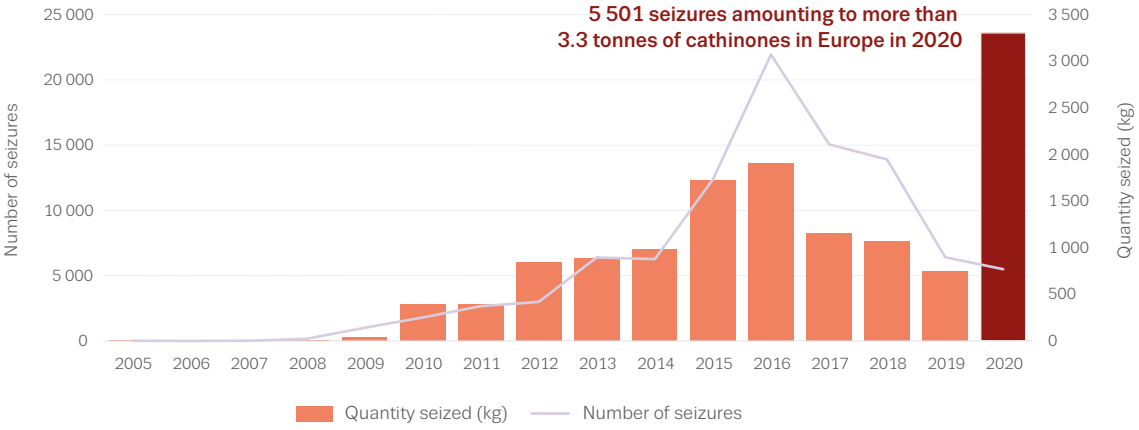
a) Number of synthetic cathinones notified for the first time, 2005-2021 (EU+2)



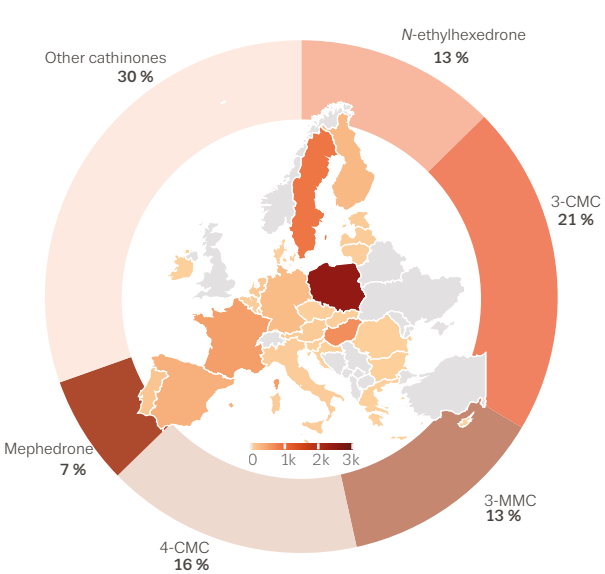
Related case studies:

- Large-scale seizure of synthetic cathinones originating from India — Leipzig Airport, Germany, 2020
- Re-emergence of 3-MMC and 3-CMC in Europe: role of producers in India
- Illicit production of synthetic cathinones in Europe

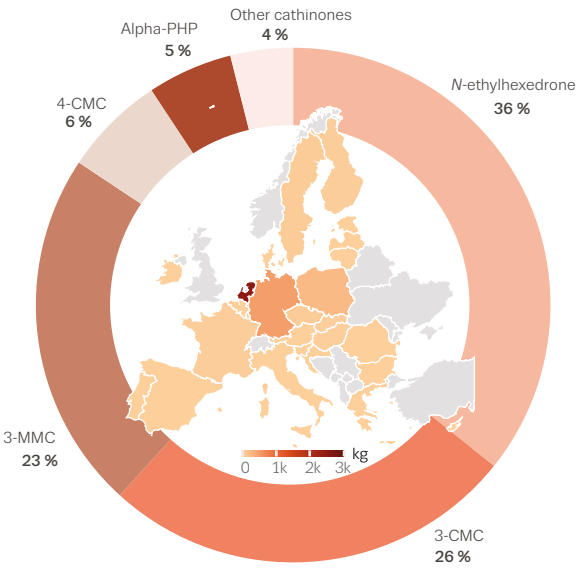
b) Trends in the number of seizures and quantity of powder seized, 2005-2020 (EU)



c) Number of cathinone seizures by country and substance, 2020 (EU)



Quantity of cathinone powders seized by country and substance, 2020 (EU)



Case study 2: Re-emergence of 3-MMC and 3-CMC in Europe — role of producers in India

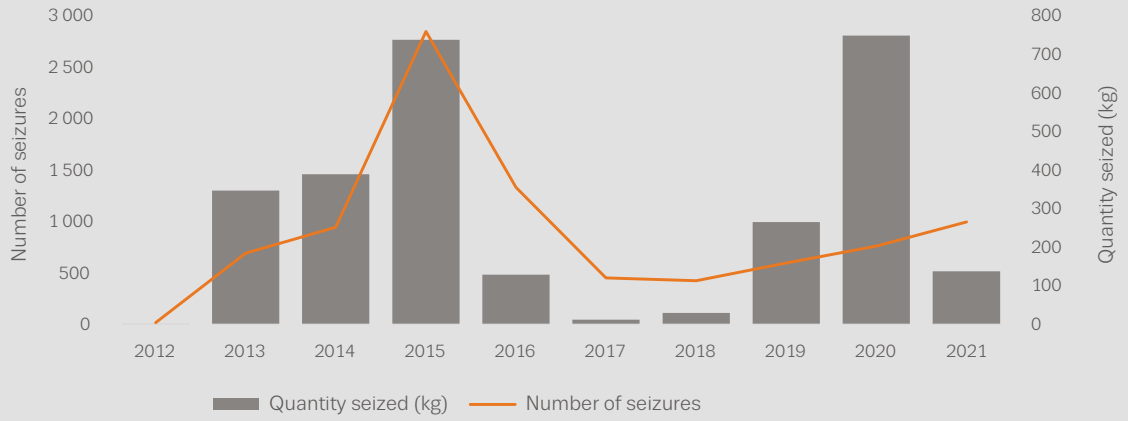
3-MMC and 3-CMC were first identified on the drug market in Europe in June 2012 and September 2014, respectively. Following their control in China in 2015, the quantities of 3-MMC seized in Europe significantly declined. While 3-CMC appeared to play a small role in the European market at this time. During 2020, signals suggested their re-emergence in Europe (Figure 4 and Figure 5). This was based on seizures at the EU border of large-scale quantities of the substances from India and reports of increased availability and associated harms in some European countries such as the Netherlands.

3-MMC and 3-CMC are sold as legal replacements to the closely related substances mephedrone (4-methylmethcathinone, 4-MMC) and clephedrone (4-chloromethcathinone, 4-CMC) that were controlled internationally in 2015 and 2020, respectively. Most use appears to be in recreational settings and involves snorting or ingesting, but injecting has also been reported in high-risk settings or contexts, such as 'chemsex' parties.

During 2020, 3-MMC accounted for 750 kilograms and 3-CMC for 880 kilograms of the total quantity of the cathinones seized. In 2021, a combined amount of 1 500 kilograms of 3-MMC and 3-CMC originating in India was reported to the EMCDDA. This change in the source country for supplies of 3-MMC and 3-CMC is thought to have facilitated its re-appearance in Europe following control measures introduced in China.

FIGURE 4

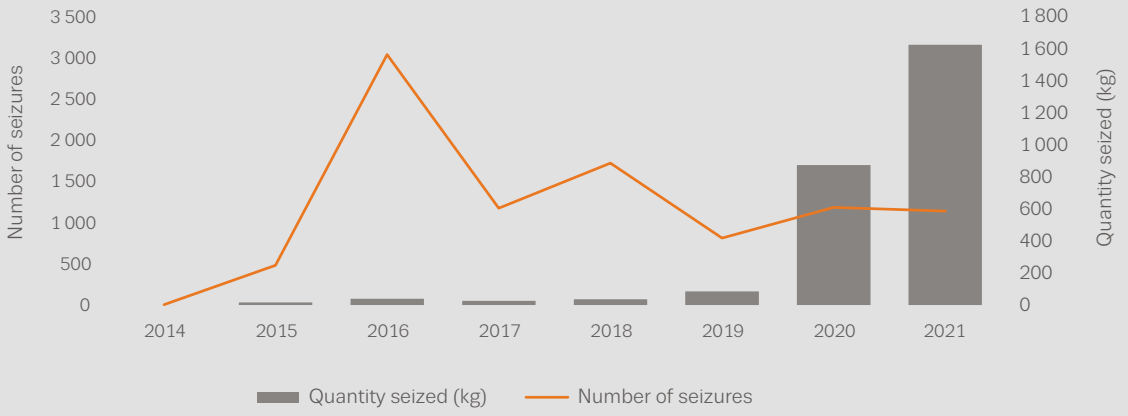
Seizures of 3-MMC: trends in number of seizures and quantities of powder seized, 2012-2021 (EU+2)



Note: Data for 2021 is partial.

FIGURE 5

Seizures of 3-CMC: trends in number of seizures and quantities of powder seized, 2014-2021 (EU+2)



Note: Data for 2021 is partial.

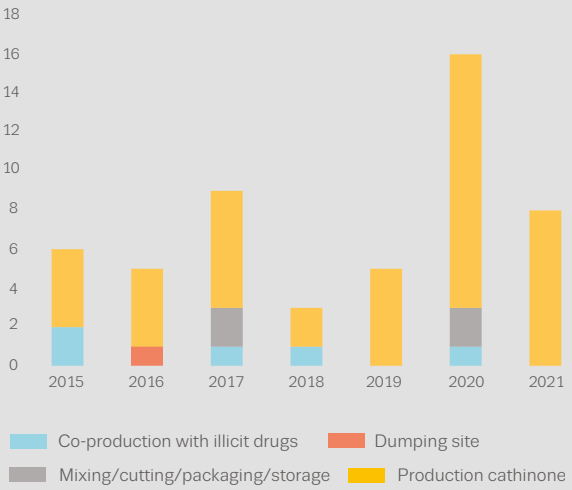
Case study 3: Illicit production of synthetic cathinones in Europe

In addition to the supply of synthetic cathinones from China and India, production appears to be growing within the EU.

From 2015 to 2021, at least 52 sites involved in the production of cathinones have been seized in Europe, with half dismantled during 2020-2021 (Figure 6). Typically, the laboratories produced mephedrone and clephedrone. The size of the laboratories varied from 'kitchen-type' in homes, to higher throughput facilities operated by multiple 'cooks' producing several dozens of kilograms of synthetic cathinones per batch in special reactors (Figure 7). Importantly, in at least five sites, the production of cathinones occurred with the storage and/or production of other controlled stimulants such as MDMA, amphetamine and/or the controlled precursors needed to produce these drugs (PMK, BMK and APAAN). This suggests the involvement of European-based criminal networks that are established producers of other synthetic drugs but who may now diversify product lines to meet a market demand for cathinones. Given Europe's position as a key global producer of synthetic drugs (EMCDDA and Europol, 2019), and that the synthesis of cathinones is not entirely dissimilar to the synthesis of MDMA or amphetamine (EMCDDA, 2022a), the infrastructure, specialist knowledge, equipment and the precursor chemicals needed to make more cathinones are likely to be available to those already involved in synthetic drug production in Europe.

FIGURE 6

Number and type of dismantled sites associated with cathinone production in Europe, 2015-2021



Source: EMCDDA-Europol, European Reporting Instrument on Sites related to Synthetic Production (ERISSP).

FIGURE 7

Reactors for the production of cathinones with cooling, heating, mixing and temperature control. Seized by Polish police in a mephedrone lab in 2021

Source: Central Bureau of Investigation, Polish Police.

Together, these data support the recent European Union Serious and Organised Crime Threat Assessment that the production of synthetic drugs in the EU is expanding and becoming increasingly sophisticated and diverse (Europol, 2021). The illicit production of cathinones also poses a health risk to those operating and dismantling the laboratories, including a risk of explosion (EMCDDA, 2022a). The dumping of hazardous chemical waste from production sites may pose safety risks to the public and result in environmental damage.

Synthetic cannabinoids

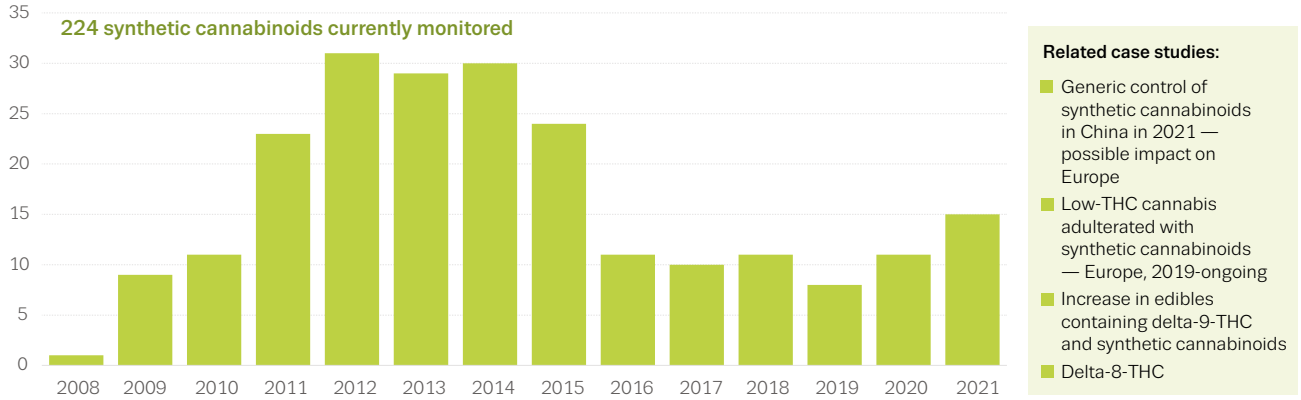
Synthetic cannabinoids are sold as 'legal' replacements to cannabis but may sometimes also be sought after in their own right as strong intoxicants. They are increasingly associated with use by marginalised groups, such as homeless people, prisoners and other vulnerable populations, because they cause profound intoxication, may be easy to conceal, and are cheaper than other drugs. They are also used by people subject to drug testing, such as prisoners or those in drug treatment, as some routine tests cannot detect synthetic cannabinoids that are new to the drug market. In some parts of Europe, there has also been an increase in reports of the vaping of synthetic cannabinoids using electronic cigarettes; in some cases, individuals are unaware they are using synthetic cannabinoids as the products are mis-sold as containing THC or cannabidiol (CBD).

Synthetic cannabinoids may be available in a number of different forms in Europe (EMCDDA, 2021a). Commonly, synthetic cannabinoids are sprayed on herbal material or tobacco and smoked. They are also sold as e-liquids for vaping. Infusing paper (such as letters and photos) and clothing (such as underwear) is a common way to smuggle them into prison. The items are then smoked, vaped or boiled to extract the substances. Synthetic cannabinoids may also be sold in the form of powders or occasionally tablets.

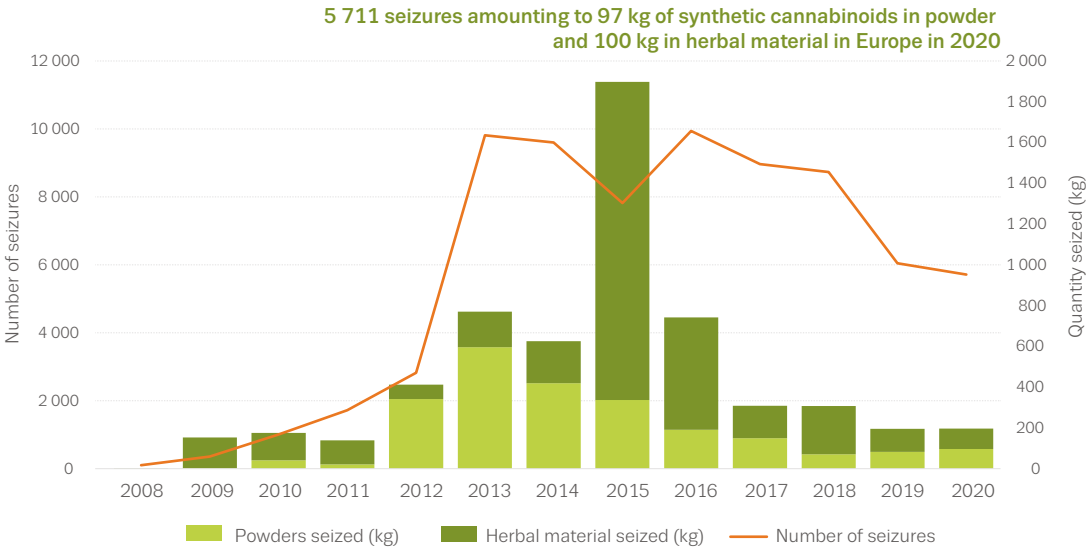
FIGURE 8
Infographic on synthetic cannabinoids

Synthetic cannabinoids

a) Number of synthetic cannabinoids notified for the first time, 2008-2021 (EU+2)



b) Trends in the number of seizures and quantity of powders and herbal material seized, 2008-2020 (EU)

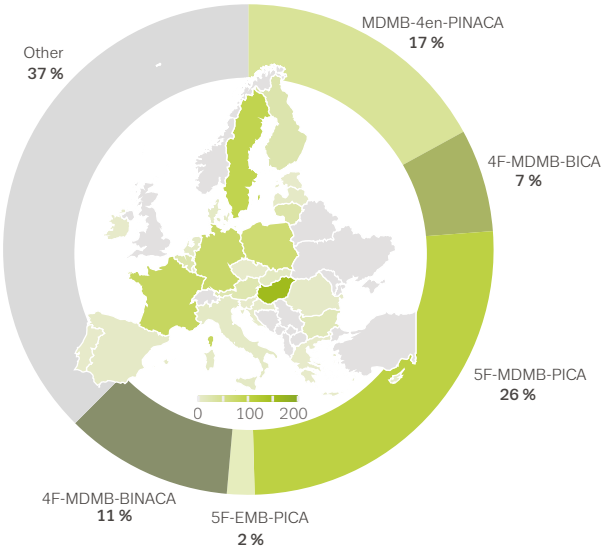


Synthetic cannabinoids can pose a high risk of poisoning both because of their high potency and because the amount of cannabinoid can vary greatly in the product/item, leading to 'hot pockets' where the substance is highly concentrated. Drinking these substances when extracted from clothing poses similar risks, as users may have no control or knowledge of the dose they are taking.

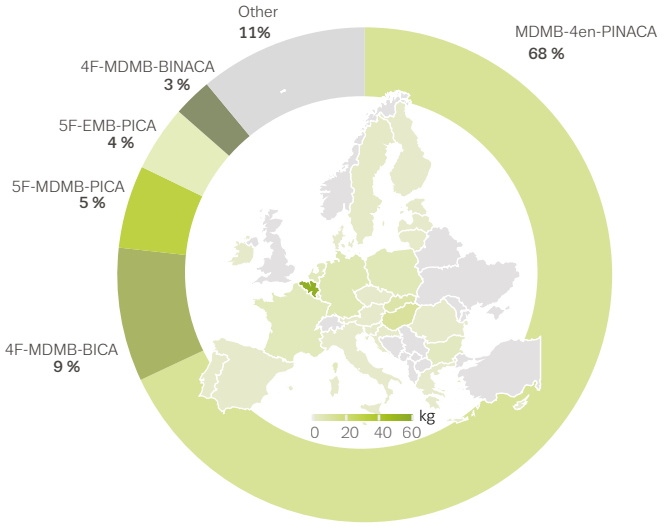
By 31 December 2021, the EMCDDA was monitoring 224 synthetic cannabinoids that have appeared on the drug market since 2008, including 15 that were notified in 2021. This makes them the largest group of substances being monitored (Figure 8).

Between 2016 and 2020, the number of new synthetic cannabinoids appearing on the market was stable at around 10 per year, down from an average of 27 per year during the peak of the 'legal highs' phenomenon between 2011 and 2015. Interestingly, there was an increase in 2021 in the number notified, with 15 substances reported. Similar increases have also been reported in the US (Krotulski et al., 2021). These developments are likely to reflect attempts to supply new cannabinoids that circumvent generic legislation in China that came into force in July 2021 to control a large number of the existing synthetic cannabinoids on the market (Case study 4).

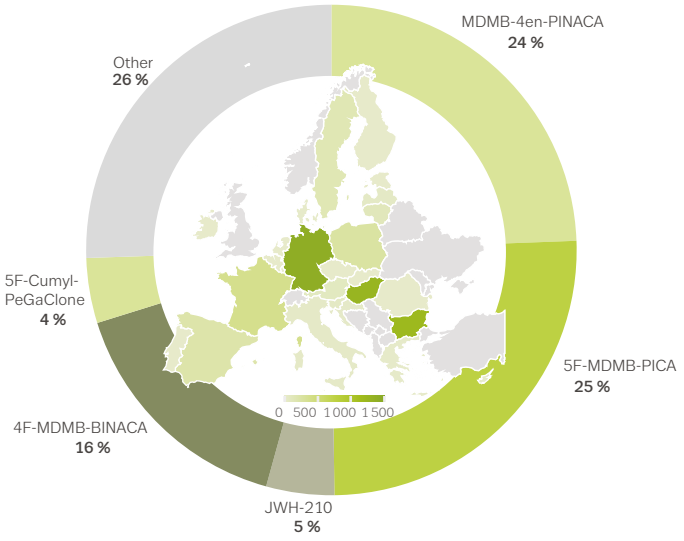
c) Number of powder seizures by country and substance, 2020 (EU)



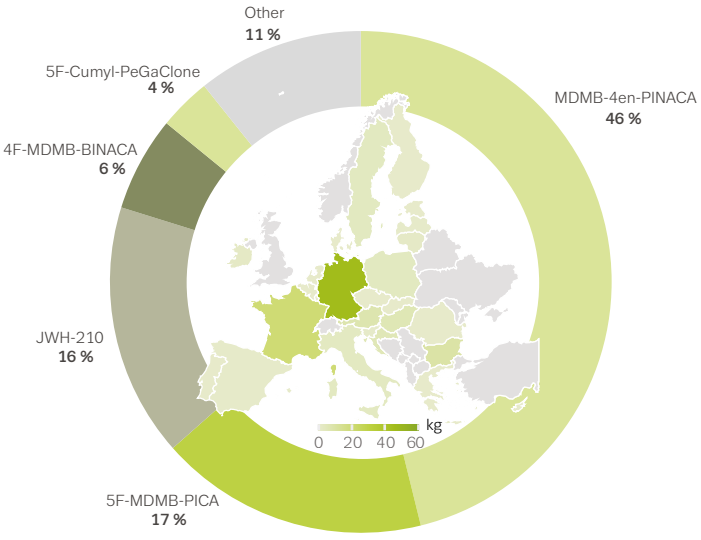
Quantity of powders seized by country and substance, 2020 (EU)



Number of seizures of herbal material by country and substance, 2020 (EU)



Quantity of herbal material seized by country and substance, 2020 (EU)



Case study 4: Generic control of synthetic cannabinoids in China in 2021 — possible impact on Europe

Historically, many European countries listed controlled substances individually by name in their national drug laws. However, as the number of NPS increased, more countries sought to control entire groups of substances by defining the groups based on commonly occurring parts of their chemical structure (known as 'generic' controls). Recently, China has used this approach to control fentanyl derivatives in 2019 and synthetic cannabinoids in 2021.

The chemical structure of many synthetic cannabinoids can be categorised into four components: tail, core, linker and linked group (Figure 9). Structural modification is possible across these components, with the core undergoing considerable modification recently. The indole and indazole cores first emerged on the market in Spice, followed by benzimidazole, carbazole, azaindole, pyrazole and oxo-indole.

Prior to 2021, China controlled more than 50 synthetic cannabinoids by listing them individually in drug legislation (UNODC, 2014, 2015, 2018). In some cases, this led to closely related substances appearing, such as 4F-MDMB-BINACA that replaced 5F-MDMB-PINACA when it was controlled in 2018 (Halter et al., 2020) (Figure 10).

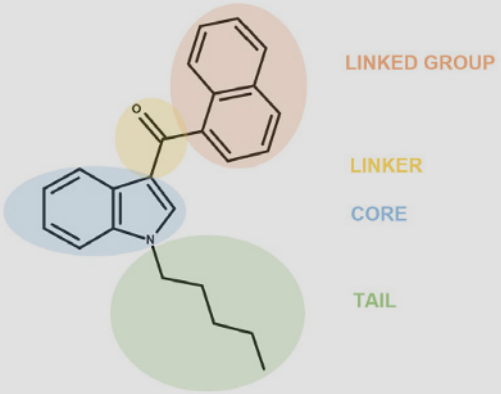
In July 2021, China used generic legislation to control a broad range of synthetic cannabinoids, essentially resulting in a class-wide ban which included many traditional indole and indazole structural cores (Liu et al., 2022). Soon after this, however, synthetic cannabinoids containing an oxo-indole core (*) and structurally related to MDA 19 appeared on the NPS market. This group of synthetic cannabinoids, also known as 'OXIZIDs', did not meet the conditions included in the generic definition (Krotulski et al., 2021) and therefore emerged as replacements to the indole and indazole based synthetic cannabinoids.

(*) These cannabinoids, like MDA 19, contain an isatin-like core, where the oxo group of the 3-position of the ring is replaced by a nitrogen.

FIGURE 9

The four components of synthetic cannabinoids and types of cores: (a) JWH-018 is composed of a pentyl tail, an indole core, a methanone linker and a naphthyl linked group; (b) Emergence of different cores

a)



b)

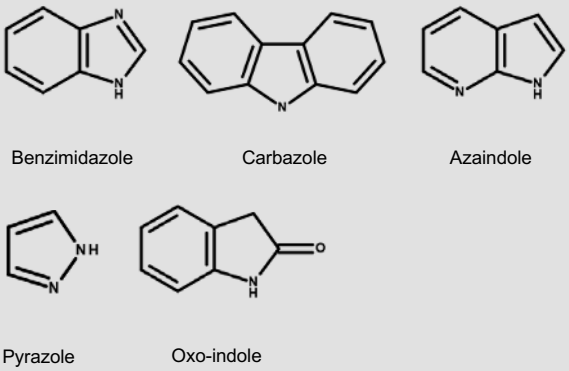
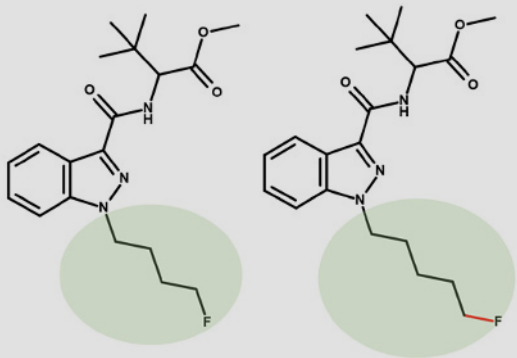


FIGURE 10

Molecular structure of 4F-MDMB-BINACA and 5F-MDMB-PINACA



In 2020, just over 6 300 seizures of synthetic cannabinoids were reported to the EU EWS, which represents around 27 % of the total number of seizures reported during that year by the Member States. Most of these detections were in the form of herbal material (5 100 cases, 97 kg) and powders (600 cases, 100 kg) (Figure 8).

During 2020, the quantity of powders and herbal material containing synthetic cannabinoids seized in the EU continued to remain much lower than the peaks of 2013 and 2015 (Figure 8). This probably reflects 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 NPS market in Europe between 2008 and 2015.

Nonetheless, large quantities of bulk powders sufficient to make many hundreds of thousands of user doses continue to be seized at the external EU border each year. During 2020, almost 66 kilograms of MDMB-4en-PINACA powder was seized, with almost 70 % (44 kg) seized in 13 seizures made by Belgian customs (EMCDDA, 2020b).

New threats have also emerged more recently, such as the adulteration of low-THC cannabis (hemp) with synthetic cannabinoids, probably as a result of the easy availability of low-THC cannabis (Case study 5) (EMCDDA, 2020c). Cannabis edibles also appear to have become more commonly available in Europe and sometimes these have been adulterated with synthetic cannabinoids (Case study 6).

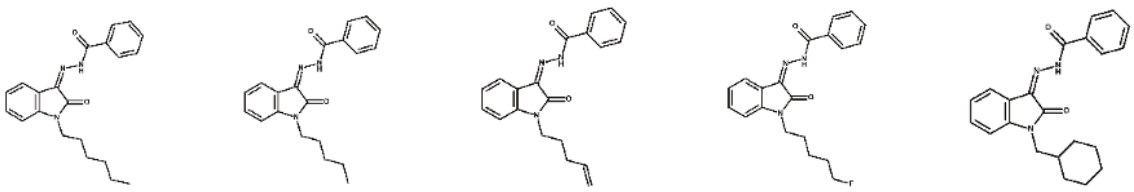
A new cannabinoid, delta-8-THC, has also recently emerged on the market (Case study 7).

The threat of synthetic cannabinoid smoking mixtures contaminated with brodifacoum, a highly toxic rat poison, re-appeared recently with new outbreaks reported in Israel in September and the US in December 2021. Poisoning with brodifacoum causes life-threatening bleeding and requires urgent medical treatment. So far, three outbreaks have been reported since 2018, severely poisoning more than 500 and killing at least 17 (Feinstein et al., 2022). Although no cases have been reported in Europe, a possible threat cannot be excluded because it is unknown where in the supply chain this poison is added. Due to this, as a precautionary measure the EMCDDA issued an alert to the EWS Network in October 2021.

In the last six months of 2021, four cannabinoids closely related to MDA 19 appeared in Europe: MDA 19 pentyl analogue (BZO-POXIZID), MDA 19 4en pentyl analogue (BZO-4en-POXIZID), MDA 19 5 fluoropentyl analogue (5F-BZO-POXIZID) and CHM-MDA-19 (BZO-CHMOXIZID) (Figure 11). These substances may be responsible for the apparent increase in new synthetic cannabinoids appearing in 2021. As the supply of synthetic cannabinoids to Europe is largely from China, other substances not covered by the generic controls are likely to emerge in Europe in the coming months. Little is known about the effects and risks of these new substances.

FIGURE 11

Molecular structure of MDA 19 and four closely related cannabinoids



MDA 19

MDA 19 pentyl analogue (BZO-POXIZID)

MDA 19 4en pentyl analogue (BZO-4en-POXIZID)

MDA 19 5 fluoropentyl analogue (5F-BZO-POXIZID)

CHM-MDA-19 (BZO-CHMOXIZID)

Case study 5: Low-THC cannabis adulterated with synthetic cannabinoids — Europe, 2019-ongoing

In January 2019, the first case of low-THC cannabis (hemp) adulterated with synthetic cannabinoids was identified in Switzerland (Von Schläpfer et al., 2020). By late 2019, more cases were being reported in the country (Monti et al., 2022; Oomen et al., 2022; Von Schläpfer et al., 2020). During 2020, the EMCDDA started to receive reports of similarly adulterated cannabis in the EU. Although the extent of the adulteration is unclear, alongside Switzerland, tainted products have been identified in at least 10 countries: Germany, France, Croatia, Italy, Cyprus, Luxembourg, the Netherlands, Austria, Slovenia and Sweden. In the United Kingdom, vapes containing synthetic cannabinoids mis-sold as THC and CBD have been reported (Oomen et al., 2022).

Since 2020, there have been reports in Europe from clients of drug-checking services who submitted samples after experiencing unusual effects from cannabis. These data played a useful role in the early detection and monitoring of this development (Monti et al., 2022; Oomen et al., 2022). Customs and police also seized products at borders and at street-level. Some are relatively large seizures, in some cases up to 30 kilograms. Worryingly, in western Piedmont, Italy, testing found that 5 % of herbal cannabis samples (11/213 samples) seized between November 2020 and February 2021 were adulterated with synthetic cannabinoids (Gerace et al., 2022).

Initially, many samples contained MDMB-4en-PINACA, a synthetic cannabinoid that was risk assessed by the EMCDDA and is now under international control. During 2021, cannabis containing ADB-BUTINACA became more common, which coincided with increased availability of the substance in Europe. A range of other synthetic cannabinoids have also been identified in products.

The reason for the adulteration is not entirely clear, but increased cultivation of low-THC industrial hemp in Switzerland led to an oversupply and a sharp drop in its price (Von Schläpfer et al., 2020). Low-THC herbal cannabis products have also become more commonly available in some EU countries. These products can have a similar appearance, smell and flavour to 'genuine' cannabis. Simply spraying a small amount of synthetic cannabinoids on it is a cheap and easy way to give the product a powerful cannabis-like effect, making it easy to deceive dealers and users (Figure 12). Production facilities and equipment used to spray synthetic cannabinoids on low-THC cannabis have been seized by Swiss police, including one in autumn 2021 (Figure 13).

FIGURE 12

Samples of low-THC cannabis adulterated with synthetic cannabinoids compared with 'genuine' illicit cannabis seized

(a) Low-THC cannabis adulterated with MDMB-4en-PINACA seized by police, Cyprus, February 2021

Source: Forensic Science and Toxicology Laboratory, State General Laboratory, Cyprus.

(b) Low-THC cannabis with EDMB-PINACA and ADB-BUTINACA collected by drug checking service Checkit!, Austria, June 2021

Source: Checkit!, Suchthilfe Wien gGmbH.

(c) Low-THC cannabis with ADB-BUTINACA collected by drug checking service Checkit!, Austria, November 2021

Source: Checkit!, Suchthilfe Wien gGmbH.

(d) Low-THC cannabis with ADB-BUTINACA collected by drug checking service DrogArt, Slovenia, November 2021

Source: Slovenian National Laboratory of Health, Environment and Food.

(e) 'Genuine' illicit cannabis

Source: Checkit!, Suchthilfe Wien gGmbH.

FIGURE 13

Equipment including a compressor/sprayer from a production site used for spraying low-THC cannabis with synthetic cannabinoids seized by Swiss police, autumn 2021

Note: In total, 200 grams of a powder containing a mixture of pure MDMB-4en-PINACA, 4F-MDMB-BICA and ADB-4en-PINACA was seized, along with 2 litres of solvent containing MDMB-4en-PINACA, 4F-MDMB-BICA and ADB-4en-PINACA; 16 kilograms of low-THC hemp containing ADB-4en-PINACA; and 4 kilograms of low-THC hashish containing ADB-4en-PINACA.

Source: Dr Christian Bissig, Narcotics Analysis, Zurich Forensic Science Institute, Switzerland.

Typically, consumers think they have bought 'genuine' illicit cannabis. Unless tested in a laboratory, adulterated low-THC cannabis may be indistinguishable from illicit cannabis, so consumers may be unknowingly exposed to synthetic cannabinoids. Adulteration poses a risk of poisoning because of the high potency of synthetic cannabinoids compared to natural cannabis products. Poisonings have been reported in France (Goncalves et al., 2021). Cannabis is the most commonly used drug in Europe, so a relatively large number of people could potentially be at risk of inadvertently using adulterated cannabis if it remains on the market. At the time of writing in April 2022, adulterated cannabis continues to be reported, although the number of reports seem to have decreased in recent months.

During 2020-2021, the EMCDDA issued three risk communications to the EWS Network highlighting the spread of adulterated cannabis, the risks it posed, and possible response options.

Case study 6: Increase in edibles containing delta-9-THC and synthetic cannabinoids

Cannabis edibles are foods that are infused with cannabis extract, typically delta-9-tetrahydrocannabinol (delta-9-THC), the main psychoactive substance in cannabis (Barrus et al., 2016). A range of products are available, including sweets, chocolate and baked goods. Following legalisation of cannabis in Canada and parts of the US, commercial edibles have become increasingly popular. In part this is reported to be because of a perceived different 'high' compared to smoking or vaping the drugs, the dislike of smoking by some individuals, and because it is an easy and discreet way of using cannabis, especially in public settings.

During 2020-21, seizures of edibles appear to have increased in parts of Europe (Figure 14). Some poisonings have also been reported, including in children in Europe (Mattimoe et al., 2021). Edibles are sold on darknet markets, via social media channels (such as TikTok, Instagram and Snapchat), and at street-level. Although it is unclear where the products are made, it is suspected that at least some might be imported from outside the EU.

Because absorption of THC into the body is slower with edibles compared to smoking, there is a delay in the onset of the 'high'. This can be 30 to 60 minutes or longer for edibles compared to almost immediate effects when smoked. The duration of effects with edibles is also longer. People are often unaware of the delayed onset of effects of edibles and may eat multiple servings in close succession before experiencing the 'high' from the initial serving — leading to overconsumption and a greater risk of poisoning (Hancock-Allen et al., 2015).

As edibles closely resemble regular food, such as sweets and chocolate, they can be accidentally eaten. This is a particular concern in children because poisoning with THC can be more severe and prolonged than for adults (Blohm et al., 2019).

FIGURE 14

Examples of cannabis edibles seized in Europe

(a) Cannabis edibles analysed by Forensic Science Ireland

Source: Forensic Science Ireland.

(b) Cannabis edibles seized in Germany

Source: Anna Duffert, SO 22 (Synthetic Drugs/NPS), Federal Criminal Police Office (BKA), Germany; Dr Rainer Dahlenburg, KT 45 (Toxicology), Federal Criminal Police Office (BKA), Germany.

FIGURE 15

A total of 37 kilograms of sweets containing the synthetic cannabinoid 5F-EDMB-PICA seized by Swedish customs, Sweden, August-September 2021

Source: Swedish Customs.

During 2021, sweets containing synthetic cannabinoids were seized in at least five countries: Belgium, Estonia, Ireland, Slovakia and Sweden. Usually they contained 5F-EDMB-PICA. In mid-2021, Swedish customs seized 37 kilograms of sweets containing the substance (Figure 15). The source of these products is not known.

People who use edibles adulterated with synthetic cannabinoids will be unaware of their content and could be at risk of poisoning. The EMCDDA issued a risk communication in 2021 to the EWS Network to highlight these issues, including the high risk of poisoning from using these products.

Case study 7: Delta-8-THC

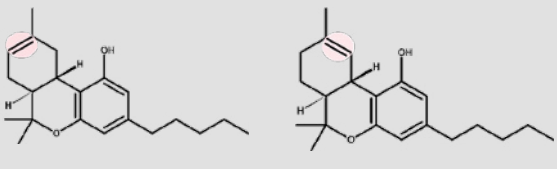
During 2020, products containing delta-8-tetrahydrocannabinol (delta-8-THC), an isomer of delta-9-tetrahydrocannabinol (THC) (Figure 16), began to appear in the US (Erickson, 2021). While the substance is under international control, manufacturers claim that delta-8-THC derived from hemp is legal (Erickson, 2021). Delta-8-THC is synthetically produced from hemp-derived CBD through a relatively straightforward and inexpensive process. The substance seems to produce similar psychoactive effects to THC, but only limited research has been done on this substance (Hollister and Gillespie, 1973). It has been suggested that the effects of delta-8-THC are milder than delta-9-THC, and sometimes it is advertised as a 'light' form of cannabis (Erickson, 2021).

An increase in poisonings associated with delta-8-THC was reported in the US during 2020-2021 (CDC, 2021). Concerns have also been raised over the safety of delta-8-THC products because they may contain potentially harmful by-products and impurities (Meehan-Atrash and Rahman, 2022).

Although their appearance to date is rare, products containing delta-8-THC have also been reported to the EMCDDA by two countries since November 2020: Spain and Italy. Separately, a report from Sweden highlights that delta-8-THC appeared earlier, in April 2020, indicating that the substance has been known to be sold in Europe (Helander et al., 2022).

FIGURE 16

Molecular structures of delta-8-THC and delta-9-THC



delta-8-THC delta-9-THC

Note: The substances only differ on the position of the double bond (marked).

Opioids

New opioids play a relatively small role in the drug market in Europe, but are of particular concern for public health because of the high risk of life-threatening poisoning from respiratory depression. Timely use of the antidote naloxone and supportive care are essential to treating poisoning.

Since 2009, a total of 73 new opioids have been identified on the drug market in Europe, including six that were notified during 2021, making them the fourth-largest group of substances monitored (Figure 17).

During 2020 and 2021, the shift away from fentanyl derivatives and towards benzimidazole opioids continued. Of concern is that many of the benzimidazole opioids are at least as potent as fentanyl (Ujváry et al., 2021).

In 2020, almost 600 seizures of new opioids were reported to the EU EWS by the Member States, representing around 3 % of the total number of seizures of NPS. This amounted to approximately 5.6 kilograms of powders (Figure 17). Reflecting changes in the market and the shift from fentanyl derivatives, just over 60 % of the powders seized were benzimidazole opioids (of which 95 % was isotonitazene seized mostly in Latvia (2.96 kg)) compared to 27 % that were fentanyl derivatives (of which 88 % was carfentanil seized mostly in Latvia) (Figure 17). Most of the seizures occurred in northern Europe.

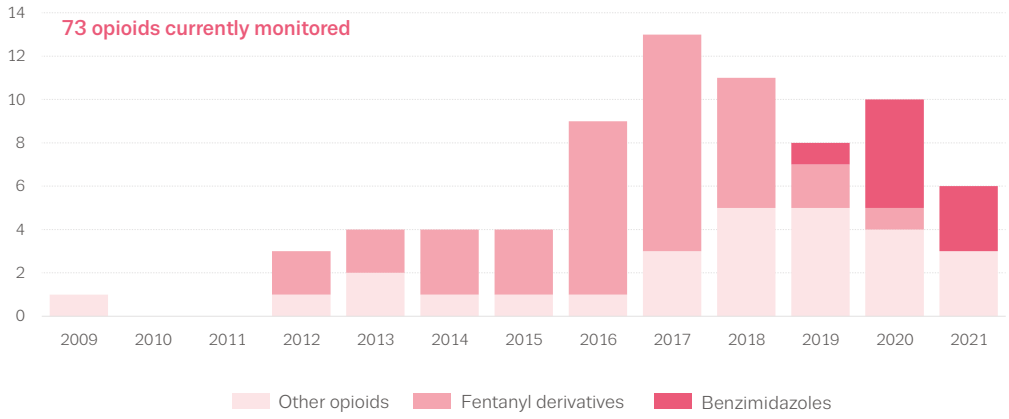
Despite the relatively small quantities seized, the high potency of many of the opioids means that even small quantities could yield many thousands of street doses. In addition, new opioids may also be mis-sold as or used to adulterate heroin and other established opioids. Most recently, an outbreak of poisonings, including deaths, was reported in southern England in 2021 linked to the adulteration of heroin with isotonitazene (De Baerdemaeker et al., 2022). Isotonitazene was risk assessed (EMCDDA, 2020d) and controlled across Europe in 2020 (Council of the European Union, 2020) and is now also under international control (UNODC, 2022).

New opioids are also used to make fake benzodiazepine medicines, such as fake Xanax and Valium (Swedish Police, 2018). Consumers are unaware that these fakes contain potent opioids, so they pose a risk of life-threatening poisoning, especially to people with no existing tolerance to opioids. New opioids are also known to be used to make fake opioid analgesic medicines, such as fake oxycodone tablets (Case study 8).

FIGURE 17
Infographic on opioids

Opioids

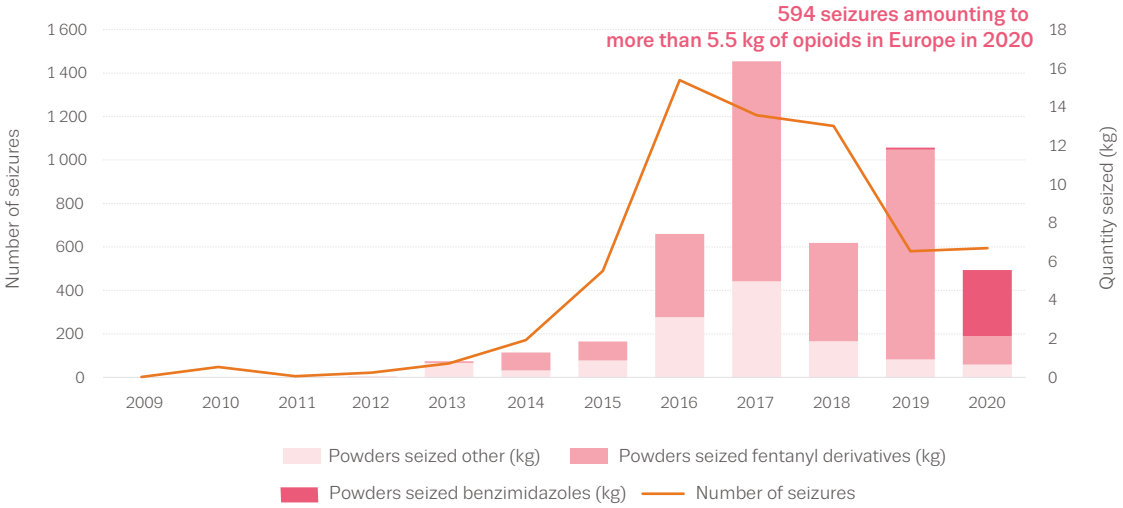
a) Number and types of new synthetic opioids notified for the first time, 2009-2021 (EU+2)



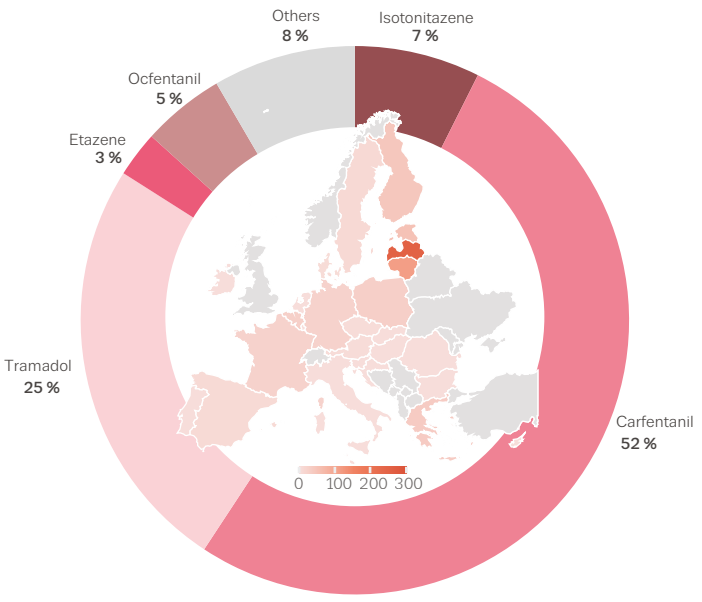
Related case study:

Fake oxycodone tablets containing benzimidazole opioids — Europe, 2021-2022

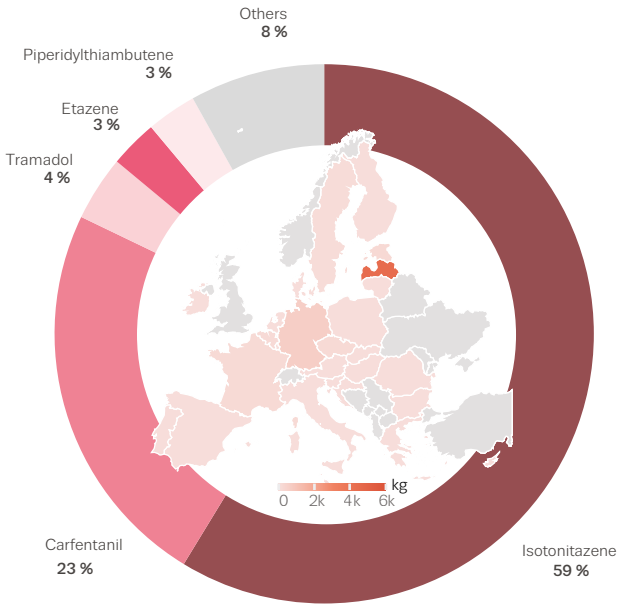
b) Trends in the number of seizures and quantity of powder seized, 2009-2020 (EU)



c) Number of opioid seizures by country and substance, 2020 (EU)



Quantity of opioid powders seized by country and substance, 2020 (EU)



Case study 8: Fake oxycodone tablets containing benzimidazole opioids — Europe, 2021-2022

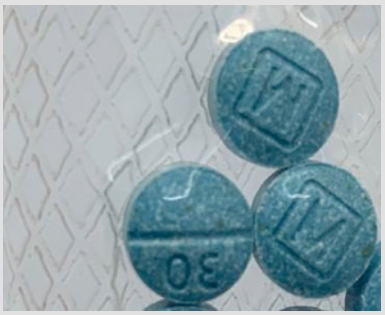
During 2021-2022, the EMCDDA received reports from Ireland, Slovenia, and, Norway of fake oxycodone tablets containing the benzimidazole opioids metonitazene and etonitazepyne, as well as the related opioid, brorphine. The tablets looked similar to commercially produced oxycodone tablets (Figure 18). Users are therefore unlikely to be unaware they are using a highly potent opioid that poses a risk of life-threatening poisoning. In some cases, these tablets were known to be sold on the darknet and were advertised as oxycodone (Pucci et al., 2021; Razinger et al., 2021). It is unclear how common these tablets are, and only a small number of reports have been made to date in Europe. Similar tablets have caused large numbers of poisonings, including mass poisoning events, in the US and Canada in recent years. As the supply chain for these products is globalised through darknet markets, the availability of these products elsewhere in Europe is a possibility.

Although fake tablets appear to be relatively uncommon in Europe, due to the high risk of life-threatening poisoning, the EMCDDA issued a risk communication to the EWS Network to highlight their possible availability and health risks.

FIGURE 18

Fake oxycodone tablets seized in Europe in 2021-2022

(a) Fake oxycodone tablets containing metonitazene seized by Norwegian customs, Norway, July 2021

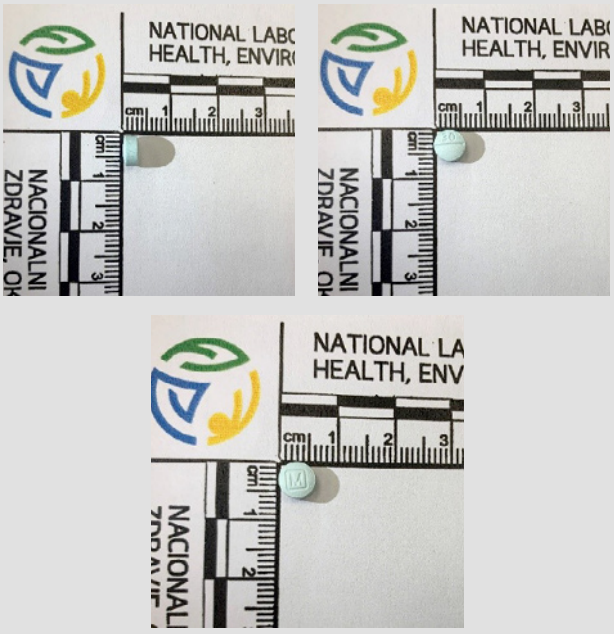


Source: Norwegian Customs Laboratory.

(b) Fake oxycodone tablets containing metonitazene seized by Irish customs, Ireland, January 2022

Source: Enforcement Section, Irish Health Products Regulatory Authority.

(c) Fake oxycodone tablets containing etonitazepyne collected by drug checking service DrogArt, Slovenia, November 2021



Source: Slovenian National Laboratory for Health, Environment and Food.

(d) Fake oxycodone tablets containing brorphine collected by the Centre for Clinical Toxicology and Pharmacology, University Clinical Centre Ljubljana, Slovenia, January 2021

Source: Slovenian National Laboratory for Health, Environment and Food.

Benzodiazepines

First developed during the 1950s, benzodiazepines, such as diazepam (Valium) and alprazolam (Xanax), are an important group of medicines that produce sedation and sleep (EMCDDA, 2021b). They are the most widely prescribed group of medicines in the world and used to treat conditions such as anxiety, insomnia, epilepsy and alcohol withdrawal. However, there is a high risk of misuse, and they can rapidly cause tolerance and dependence. This can lead to severe and sometimes life-threatening withdrawal symptoms. Due to this, strict restrictions are often placed on prescribing them. When used for non-therapeutic purposes, benzodiazepines are often used in combination with other psychoactive substances and this can increase the risks of individuals experiencing adverse consequences. For example, the consumption of benzodiazepines with opioids or alcohol increases the risk of fatal and non-fatal poisonings (Gudin et al., 2013; McAuley, 2022).

Given the potentially large demand for benzodiazepines, they are a major target for criminals that divert legitimate products from the market, sell unlicensed products, or make falsified versions of legitimate medicines. Falsified versions of legitimate medicines have been found to contain both controlled benzodiazepines and new benzodiazepines. Fake diazepam and alprazolam tablets in particular have been observed on the drug market (Case study 9).

New benzodiazepines are also sold as substances in their own right for recreational use, to enhance or prolong the effects of other drugs such as opioids, and to self-medicate (EMCDDA, 2021b).

As of 31 December 2021, the EMCDDA was monitoring 33 new benzodiazepines, including three that were notified in 2021 (Figure 19).

In 2020, just over 1 000 seizures of new benzodiazepines were reported to the EU EWS by the Member States, reflecting around 5 % of the total number of seizures of NPS. This amounted to approximately 4.4 kilograms of material, with liquids accounting for 3.3 kilograms, and just over 65 000 tablets and capsules (Figure 19). Most of the seizures were in northern Europe.

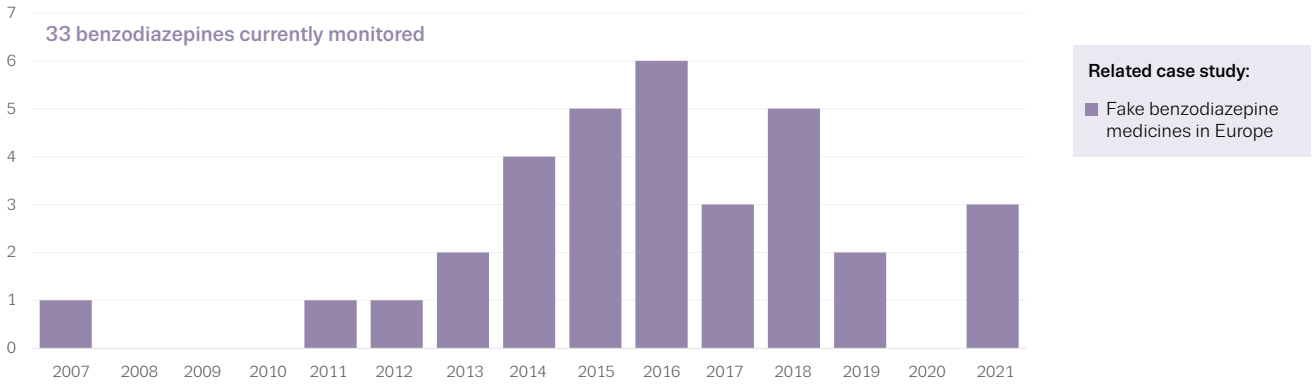
Despite the relatively large number of new benzodiazepines that have appeared in Europe, during 2020 the market continued to be dominated by just a handful of substances, most notably etizolam and flualprazolam (Figure 19). Together these two substances were responsible for 65 % of the seizures, almost 70 % of the quantity of powder seized, and almost 80 % of the tablets and capsules seized.

FIGURE 19

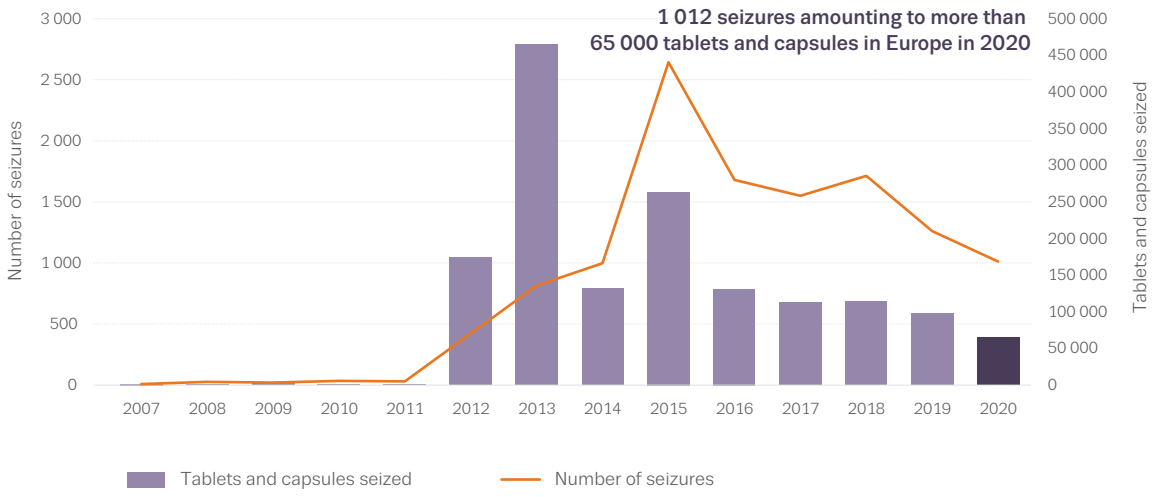
Infographic on benzodiazepines

Benzodiazepines

a) Number of benzodiazepines notified for the first time, 2007-2021 (EU+2)



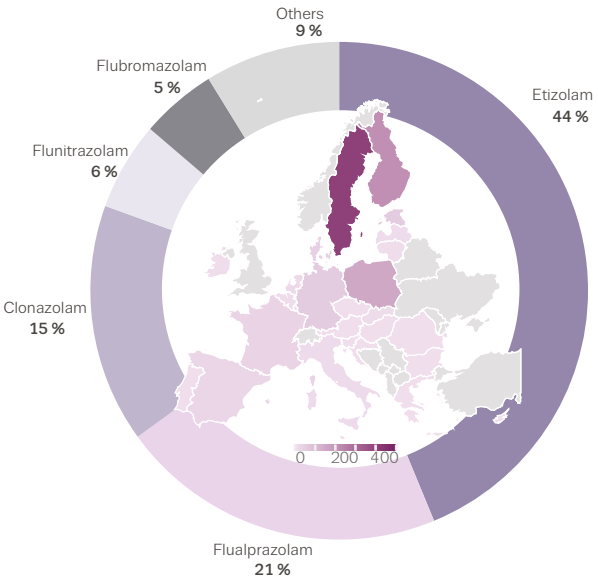
b) Trends in the number of seizures and quantity of tablets and capsules seized, 2007-2020 (EU)



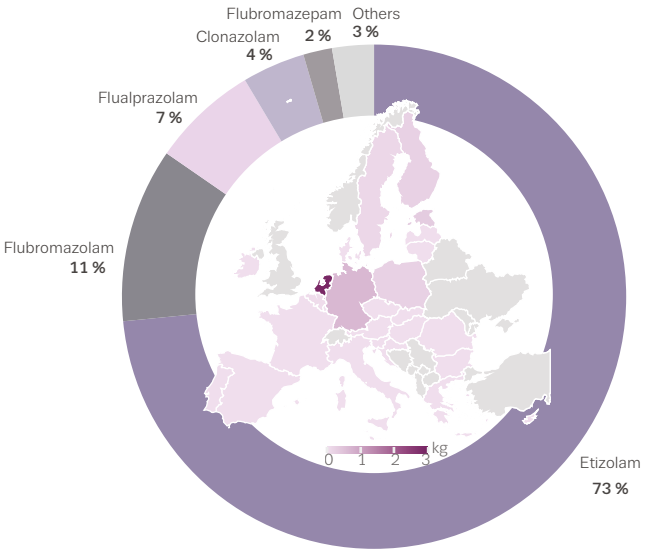
Etizolam and flualprazolam were controlled internationally in 2020, with controls coming into force in November the same year (CND, 2020a, 2020b). As there is significant variation between countries in the time it takes to implement these controls in national legislation, it is still unclear how and when they may affect the market, particularly in respect to production and supply. One possibility is that producers and distributors will switch to other new benzodiazepines, underlining the importance of the work of the EU EWS to detect and report on the appearance of new drugs within the EU.

Many new benzodiazepines are potent substances. The dose used in fake medicines can also be significantly higher than those used in legitimate medicines. New benzodiazepines have been involved in acute poisonings and deaths, particularly in parts of northern Europe (Essink et al., 2022; Kriikku et al., 2020; Rice et al., 2021). In the latter case, many of the deaths involve vulnerable people who also use other depressants, especially opioids (Kriikku et al., 2020; McAuley et al., 2022; Rice et al., 2021).

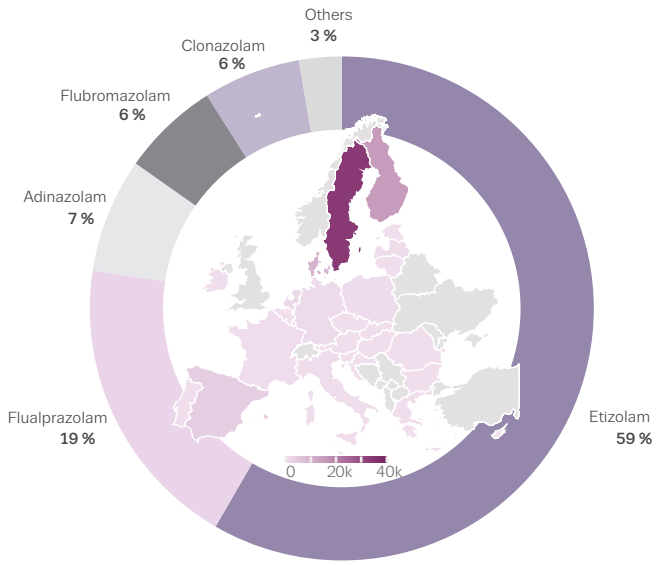
c) Number of seizures by country and substance, 2020 (EU)



Quantity seized for all physical forms reported in weight by country and substance, 2020 (EU)



Quantity of tablets and capsules seized by country and substance, 2020 (EU)



Case study 9: Fake benzodiazepine medicines in Europe

In Europe, new benzodiazepines are used to make fake tablets of commonly prescribed benzodiazepine medicines, such as Valium and Xanax. Often, those tablets look exactly like genuine medicines, making them difficult to spot. In some cases, this is all the more difficult because they are packaged to look like legitimate medicines. Of concern is the involvement of criminal networks in producing such fake tablets (EMCDDA, 2021b).

Following the international control of etizolam and flualprazolam in November 2020 (UNODC, 2022), other benzodiazepines re-emerged in Europe, including meclonazepam which was first notified in 2014. In September 2021, Spanish customs seized more than 70 000 fake alprazolam tablets containing meclonazepam (Figure 20). They were packaged to look like genuine Trankimazin 2 mg alprazolam tablets made by Pfizer.

One of the most recent benzodiazepines identified in Europe is flubrotizolam. First identified in June 2021, it has already been detected in five countries, mostly in Xanax-type bars marked as 'FANAX' (Figure 21) that are sold as a replacement to etizolam. Little is known about the effects of flubrotizolam.

FIGURE 20

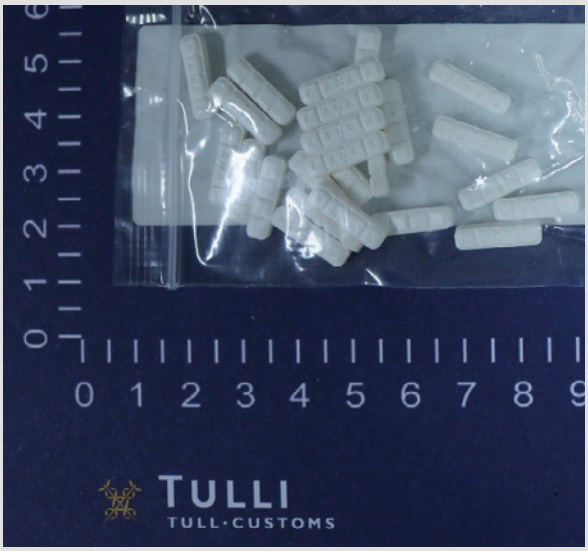
Fake Trankimazin 2 mg alprazolam tablets containing meclonazepam seized by Spanish customs — Spain, September 2021

Source: Spanish Customs/AEAT, Ministry of Economy and Finance.

FIGURE 21

'Fanax' tablets containing flubrotizolam seized by customs, June to August 2021

(a) Fanax tablets containing flubrotizolam seized by Finnish customs, Finland, August 2021



Source: Finnish Customs Laboratory.

(b) Fanax tablets containing flubrotizolam seized by Danish customs, Denmark, June 2021

Source: Section of Forensic Chemistry, University of Copenhagen.

(c) Fanax tablets containing flubrotizolam seized by Norwegian customs, Norway, August 2021

Source: Norwegian Customs Laboratory.

PART 3
Lessons learned from 25 years of monitoring NPS in Europe

Global markets create glocal threats

The globalisation of drug markets and greater prevalence of technologies such as the internet have led to an increase in the number, type, availability and harms caused by NPS. These factors have also helped to create a more resilient and highly dynamic market that is more challenging to disrupt.

The threats in a particular area are shaped by both global and local factors (glocal). They include the availability and supply of NPS, the local drug situation, including drug supply and use, public health and social problems, drug policy and responses.

The appearance of an NPS in a new geographical area or in a new group of users is always a cause of concern for public health. While some risks might be known, others are unknown and will not become apparent until larger numbers of people have been exposed to the substance. In addition, the 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 mis-sold for or adulterated with another substance, all without the knowledge of the user.

As part of preparedness planning, public health officials need to think about how the availability and use of NPS apply to their country, region or neighbourhood. This requires consideration of both current and possible future threats and vulnerabilities, and what actions are likely to be needed to constitute an effective response.

Highly potent substances that pose a high risk of severe acute poisoning continue to be reported. The NPS and controlled drug markets are also becoming increasingly integrated. The use of NPS by high-risk drug users and other marginalised and vulnerable populations has also increased in some places. In addition, unregulated, globalised supply chains and markets — where NPS and related ingredients can be manufactured in one country, brokered and used to make products in another country and, finally, used in other countries — increase the opportunity for miscommunication, mis-selling, mislabelling, adulteration, contamination and dilution of NPS and controlled drugs with a range of potentially dangerous and sometimes highly toxic substances. Many of the case studies in this report, such as the adulteration of low-THC cannabis and edibles with synthetic cannabinoids, are examples of these concerns.

Overall, these types of substances pose a high risk of life-threatening poisoning and can even on occasion cause outbreaks of mass poisonings. Such incidents are characterised by sudden and unexpected cases of acute poisoning that can rapidly overwhelm healthcare systems. They are also financially costly (Rowley et al., 2017).

These substances also pose serious cross-border threats to health, especially as a result of the growth of online and transnational markets. These issues are important globally as well as for Europe.

In North America, NPS have contributed to the public health crisis linked to the opioid epidemic (Bowles et al., 2021; Friedman et al., 2022; Laing et al., 2021; Pardo, 2022; Reyes et al., 2012; Wong et al., 2008). In China, recent reports suggest an increase in the use of synthetic cannabinoids commonly found in Europe and the US (Fan et al., 2022; Liu et al., 2021); use of ketamine-like NPS, such as 2-fluorodeschloroketamine, has also been reported (Shao et al., 2021). New benzodiazepines have also been identified in fake medicines in Australia (Blakey et al., 2022), and in New Zealand fake oxycodone tablets containing the highly potent opioid etonitazepyne have recently been identified (Highalert, 2022). In Brazil, similar to what has been noted in Europe, reports now exist of paper being infused with synthetic cannabinoids for the purpose of smuggling them into prisons (Rodrigues et al., 2022). Smoking mixtures made of synthetic cannabinoids, controlled drugs and herbal material have also been reported in Egypt (Hussien et al., 2022). In West Africa, there are signals of an increase in non-medical use of non-controlled medicines (UNODC, 2021). In Argentina, the adulteration of cocaine with carfentanil, a highly potent opioid, has also been reported and linked to deaths and non-fatal poisonings (Di Nicola, 2022; Ministerio de Salud, 2022).

These examples all demonstrate both the increasing global impact of NPS and the role of glocal factors in shaping the different types of threats encountered. They also serve to highlight the need for international collaboration.

Build, maintain and strengthen early warning systems

Good decisions begin with good data

Monitoring of NPS in Europe over the past 25 years has demonstrated that reliable and timely information is critical for an effective public health response in this area. Local, national, regional and international early warning systems have all played a valuable role in providing information for action and helping shape regulatory and public health responses.

Information from early warning systems can be used to strengthen situational awareness, increase preparedness and inform the need for response measures. Importantly, early warning systems have the potential to provide value by:

- identifying the appearance of a new psychoactive substance on the drug market for the first time;
- identifying other substances of interest, related to mis-selling, adulteration, contamination or dilution, that may pose a high risk to public health;
- describing, analysing and assessing the distribution, use and spread of a new psychoactive substance;
- identifying, describing and estimating the magnitude of a public health or social threat caused by a new psychoactive substance;
- detecting outbreaks and epidemics;
- monitoring changes in the NPS market;
- identifying research needs and facilitating epidemiologic and laboratory research;
- facilitating planning and informing policy;
- detecting and monitoring changes in use and patterns of use;
- identifying and evaluating response measures, including restrictive measures.

However, experience with the evolving NPS phenomenon in Europe over the last 25 years has demonstrated that early warning systems need to continuously adapt to the ever-changing drug markets to ensure they are fit for purpose and systems benefit by being closely integrated with other drug monitoring and epidemiologic surveillance activities. Co-production as well as engagement between partners at local, national and international level has also proved critically important. Attention also needs to be paid to creating mechanisms to facilitate information exchange and risk communication.

Conclusion

Over the last 25 years, the NPS phenomenon has changed beyond recognition in Europe. Thanks to the foresight and timely actions of policy- and decision-makers as well as a multidisciplinary group of practitioners, Europe has been well prepared and able to rapidly respond to protect public health. Despite this, NPS remain an intractable policy issue and threat to public health in their own right.

Currently, the NPS market is characterised by complexity and increased integration with the market for established controlled drugs. The market continues to grow, is resilient and highly dynamic, and rapidly adapts to attempts to disrupt it.

The issues highlighted in this report span 25 years of experience in early warning and response to NPS in Europe. Together, they serve to highlight the increasing complexity of the NPS phenomenon, and the importance of how global markets create glocal threats that drive the availability, use and types of public health threats caused by NPS. Reflecting on this, the EMCDDA's experience is that the following lessons have been learned:

- Investment in early warning, preparedness and response planning has demonstrated its value in this area.
- Effective actions are informed by the existence of good data.
- Success depends on engagement with partners and collaboration.
- Forensic and toxicological information sources are critically important but there remains a need for investment in forensic, analytical and toxicological capacity.
- To make information available to inform action, there is a need to develop effective mechanisms to report, collect, analyse, share and communicate information in a timely and accessible way.
- The NPS and drug markets are highly dynamic. There is therefore a need for rapid and proactive capacity to collect information and target new or unexpected areas.
- Learn from the past: previous experience is critical to informing future threats and how to respond to them.
- Rapid action may be needed: in the real world, timely responses often need to be based on partial and incomplete data, meaning evaluation and regular review of the impact of responses is also required.

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Annex 1

List of new psychoactive substances notified by the EMCDDA on behalf of the Member States under the terms of Regulation (EC) no 1920/2006 and Council Framework Decision 2004/757/JHA — European Union, 2021

1. 3-Me-PCP (1-[1-(3-methylphenyl)cyclohexyl] piperidine), Hungary, 11 January 2021
2. 4F-Deprenyl (*N*-[1-(4-fluorophenyl)propan-2-yl]-*N*-methylprop-2-yn-1-amine), Germany, 18 January 2021
3. α-D2PV (1,2-diphenyl-2-(pyrrolidin-1-yl)ethan-1-one), Slovenia, 22 January 2021
4. 3-Cl-PCP (1-[1-(3-chlorophenyl)cyclohexyl]piperidine), Slovenia, 26 January 2021
5. ABO-4en-PINACA (*N*-(1-amino-1-oxobutan-2-yl)-1-(pent-4-en-1-yl)-1*H*-indazole-3-carboxamide), France, 3 February 2021
6. BDMT (2,2′-(1*H*,1′*H*-[2,2′-biindole]-3,3′-diyl)*bis*(*N,N*-dimethylethan-1-amine)), Germany, 10 February 2021
7. 3-Methylmethamphetamine (3-MMA; *N*-methyl-1-(3-methylphenyl)propan-2-amine), Sweden, 12 February 2021
8. Etonitazepyne (2-(4-ethoxybenzyl)-5-nitro-1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-benzo[*d*]imidazole), Belgium, 17 February 2021
9. Butonitazene (2-[(4-butoxyphenyl)methyl]-*N,N*-diethyl-5-nitro-1*H*-benzimidazole-1-ethanamine), Belgium, 18 February 2021
10. CUMYL-NBMINACA ((1-(bicyclo[2.2.1]heptan-2-yl) methyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide), Germany, 23 February 2021
11. Deoxymethoxetamine (2-(ethylamino)-2-(3-methylphenyl)-cyclohexanone), Denmark, 11 March 2021
12. Phenylpiracetam (2-(2-oxo-4-phenylpyrrolidin-1-yl) acetamide), Germany, 17 March 2021
13. ADB-4en-PINACA (*N*-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(pent-4-en-1-yl)-1*H*-indazole-3-carboxamide), Hungary, 23 March 2021
14. 4-HO-MALT (3-2-[methyl(prop-2-en-1-yl)amino] ethyl-1*H*-indol-4-ol), Slovenia, 9 April 2021
15. CHM-MDMB-CHMINACA (cyclohexylmethyl 2-(1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamido)-3,3-dimethylbutanoate), Germany, 23 April 2021
16. 4F-3-Methyl-α-PHP (1-(4-fluoro-3-methyl-phenyl)-2-pyrrolidin-1-yl-hexan-1-one), Sweden, 29 April 2021
17. 5-Chloro-alpha-methyltryptamine (1-(5-chloro-1*H*-indol-3-yl)propan-2-amine), Slovenia, 4 May 2021
18. 2C-T-21 (2-[4-(2-fluoroethylsulfanyl)-2,5-dimethoxy-phenyl]ethanamine), the Netherlands, 5 May 2021
19. 4Cl-MAR (5-(4-chlorophenyl)-4-methyl-4,5-dihydro-1,3-oxazol-2-amine), Slovenia, 11 May 2021
20. 4Br-MAR (5-(4-bromophenyl)-4-methyl-4,5-dihydro-1,3-oxazol-2-amine), Slovenia, 11 May 2021
21. Protonitazene (*N,N*-diethyl-5-nitro-2-[(4-propoxyphenyl) methyl]-1*H*-benzimidazole-1-ethanamine), Germany, 20 May 2021
22. EDMB-PINACA (ethyl 3,3-dimethyl-2-[(1-pentylindazole-3-carbonyl)amino]butanoate), France, 26 May 2021
23. 4-(Trifluoromethyl) U-47700 (*N*-(2-(dimethylamino) cyclohexyl)-*N*-methyl-4-(trifluoromethyl)benzamide), Germany, 2 June 2021
24. 1cP-AL-LAD (4-(cyclopropanecarbonyl)-*N,N*-diethyl-7-(prop-2-en-1-yl)-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*] quinoline-9-carboxamide), France, 28 June 2021
25. PEAP (*N*-ethyl-1-phenylpentan-2-amine), Sweden, 30 June 2021
26. 2′-Me-PVP (1-(2-methylphenyl)-2-(pyrrolidin-1-yl) pentan-1-one), Sweden, 6 July 2021
27. Ephinazone (2-ethyl-3-phenylquinazolin-4(3*H*)-one), Germany, 12 July 2021
28. ADB-HEXINACA (*N*-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-hexyl-1*H*-indazole-3-carboxamide), Germany, 16 July 2021

29. Hydroxetamine (2-(ethylamino)-2-(3-hydroxyphenyl)-cyclohexanone), Slovenia, 5 August 2021

30. 3F-NEB (2-(ethylamino)-1-(3-fluorophenyl)butan-1-one), Sweden, 10 August 2021

31. 3-Methyl-*N*-propyl-cathinone (2-(propylamino)-1-(3-methylphenyl)-1-propanone), Hungary, 11 August 2021

32. 3-Chlorophenmetrazine (2-(3-chlorophenyl)-3-methylmorpholine), Sweden, 13 August 2021

33. Deschloroclotizolam (2-chloro-9-methyl-4-phenyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine), Sweden, 15 September 2021

34. Bretazenil (1,1-dimethylethyl 8-bromo-11,12,13,13a-tetrahydro-9-oxo-9*H*-imidazo[1,5-*a*]pyrrolo[2,1-*c*][1,4] benzodiazepine-1-carboxylate), Sweden, 17 September 2021

35. Dipyanone (4,4-diphenyl-6-(pyrrolidin-1-yl)heptan-3-one), Germany, 29 September 2021

36. MDA-19 pentyl analogue (BZO-POXIZID; *N*-[(*Z*)-(2-oxo-1-pentyl-indolin-3-ylidene)amino]benzamide), Bulgaria, 21 October 2021

37. Iso-3-CMC (1-(3-chlorophenyl)-1-(methylamino) propan-2-one), Sweden, 25 October 2021

38. Desmethylmoramide (4-(4-morpholinyl)-2,2-diphenyl-1-(1-pyrrolidinyl)-1-butanone), Germany, 9 November 2021

39. MDA-19 4en-pentyl analogue (BZO-4en-POXIZID; *N*-[(*Z*)-(2-oxo-1-pent-4-enyl-indolin-3-ylidene)amino] benzamide), Hungary, 11 November 2021

40. MDA-19 5-fluoropentyl analogue (*N*-[(*Z*)-[1-(5-fluoropentyl)-2-oxo-indolin-3-ylidene]amino] benzamide), Bulgaria, 25 November 2021

41. 4-Cl-3-MMC (1-(4-chloro-3-methylphenyl)-2-(methylamino)propan-1-one), Sweden, 29 November 2021

42. 1V-LSD (*N,N*-diethyl-7-methyl-4-pentanoyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*] quinoline-9-carboxamide), Germany, 2 December 2021

43. 4-AcO-EPT ([3-[2-[ethyl(propyl)amino]ethyl]-1*H*-indol-4-yl] acetate), Sweden, 6 December 2021

44. CUMYL-TsINACA (*N*-(2-phenylpropan-2-yl)-1-tosyl-1*H*-indazole-3-carboxamide), Germany, 9 December 2021

45. Fenozolone (2-(ethylamino)-5-phenyl-4(5*H*)-oxazolone), Denmark, 13 December 2021

46. 5,3-AB-CHMFUPPYCA (*N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-5-(4-fluorophenyl)-1*H*-pyrazole-3-carboxamide), Germany, 14 December 2021

47. 3,5-ADB-4en-PFUPPYCA (*N*-(1-carbamoyl-2,2-dimethyl-propyl)-5-(4-fluorophenyl)-2-pent-4-enyl-pyrazole-3-carboxamide), Hungary, 14 December 2021

48. 5,3-ADB-4en-PFUPPYCA (*N*-(1-carbamoyl-2,2-dimethyl-propyl)-5-(4-fluorophenyl)-1-pent-4-enyl-pyrazole-3-carboxamide), France, 15 December 2021

49. CHM-MDA-19 (*N*-[(*Z*)-[1-(cyclohexylmethyl)-2-oxo-indolin-3-ylidene]amino]benzamide), Hungary, 17 December 2021

50. ADB-FUBIACA (*N*-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1*H*-indole-3-acetamide), Germany, 21 December 2021

51. Flubrotizolam (2-bromo-4-(2-fluorophenyl)-9-methyl-6*H*-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine), Denmark, 22 December 2021

52. 3-Me-PCPy (1-[1-(3-methylphenyl)cyclohexyl] pyrrolidine), France, 22 December 2021

Annex 2

List of public health risk communications issued by the EMCDDA to the EWS Network — European Union, 2021

1. Fake oxycodone tablets containing brorphine — Slovenia, 2021, Advisory, 22 January 2021
2. Cannabis adulterated with synthetic cannabinoids — Europe, 2020-ongoing, Advisory update, 9 March 2021
3. 'Tesla' tablets containing a high dose of DOC (2,5-dimethoxy-4-chloroamphetamine) missold as 2C-B — Netherlands, April 2021, Alert, 14 April 2021
4. Cannabis adulterated with synthetic cannabinoids — Europe, 2020-ongoing, Advisory update, 12 August 2021
5. Outbreak of bleeding linked to use of synthetic cannabinoid smoking mixtures containing brodifacoum (rat poison) — Israel, September 2021-ongoing, Alert, 8 October 2021
6. Fake Percocet tablet containing highly potent opioid *N*-pyrrolidino etonitazene (etonitazepyne) sold on darknet — Europe, 2021, Alert, 22 November 2021
7. Increase in identifications and potential risks posed by cannabis edibles — Europe, 2020-21, Advisory, 17 December 2021

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25 YEARS EU EARLY WARNING SYSTEM ON NEW PSYCHOACTIVE SUBSTANCES 1997–2022

About this report

This update from the EU Early Warning System overviews the NPS situation in Europe in 2020-2021 and highlights emerging threats to support early warning, preparedness planning and response measures. In addition, it reflects on the changes and the lessons learned from 25 years of monitoring NPS in Europe.

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.

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