European Monitoring Centre
for Drugs and Drug Addiction

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PERSPECTIVES ON DRUGS

Synthetic cannabinoids in Europe

Synthetic cannabinoids represent the largest group of substances currently monitored in Europe by the EMCCDA through the EU Early Warning System. Current knowledge on these substances and trends in production, availability, use and harms are presented in this analysis.

Synthetic cannabinoids are a group of substances that mimic the effects of (–)-*trans*-Δ9-tetrahydrocannabinol (THC), which is the substance that is primarily responsible for the major psychoactive effects of cannabis. Like THC, the synthetic cannabinoids bind to the cannabinoid receptors in the body. This is why these substances have been used to create a large range of 'legal high' products sold as legal replacements for cannabis. They are the largest group of new psychoactive substances monitored by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA).

'Legal high' products containing synthetic cannabinoids have been sold as 'herbal smoking mixtures' since the mid-2000s. These products do not contain cannabis, but when smoked produce similar effects. They have been subject to innovative marketing approaches and are widely and openly available on the web, and in some countries in bricks-and-mortar ('head' and 'smart') shops.

The number of synthetic cannabinoids, their chemical diversity and the speed of their emergence make this group of compounds particularly challenging in terms of detection, monitoring, and responding. Suppliers simply aim to mimic the effects of THC. In essence, this makes each synthetic cannabinoid disposable. When one synthetic cannabinoid is, or is about to be, legally controlled manufacturers can have one or more replacement substance ready for sale.

Little is known about how these substances work and their toxic effects in humans. However, their use has caused many serious poisonings and even deaths — sometimes these have manifested as outbreaks of mass poisonings. It is possible that, along with being highly potent, some may also have long half-lives, potentially leading to a prolonged psychoactive effect. In addition, it appears that at least some of these

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emcdda.europa.eu/topics/pods/synthetic-cannabinoids

substances have an effect on other physiological functions in the body beyond effects on the cannabinoid receptors.

This analysis aims to provide an update on the current knowledge of these substances and their effects, and trends in production, availability and use.

The emergence of synthetic cannabinoids

Despite internet rumours since the mid-2000s of 'herbal smoking mixtures' sold as 'legal highs' that could produce 'strong' cannabis-like effects, it wasn't until 2008 that forensic investigators in Germany and Austria first detected the synthetic cannabinoid JWH-018, in a product sold under the brand name 'Spice'. Subsequently several cannabinoids were detected in smoking mixtures or so-called incense/room odorisers. Typical of these were Spice Gold, Spice Silver and Yucatan Fire, but many other products later appeared. Many of the cannabinoids that have been detected in these products were first developed by scientists investigating how cannabinoids affect the body and to see if they could work as medicines to treat a number of diseases and their symptoms — such as neurodegenerative diseases, drug dependence, pain disorders and cancer. However, so far it has proved difficult to separate the desired medicinal properties from unwanted psychoactive effects.

The number of synthetic cannabinoids detected through the EU Early Warning System continues to grow. One was reported in 2008; 9 in 2009; 11 in 2010; 23 in 2011; 30 in 2012; 29 in 2013; 30 in 2014; and 25 in 2015 — with a total of 160 synthetic cannabinoids having been notified to the EMCDDA as of December 2015 ([1]).

Synthetic cannabinoids play an important role in the rapidly evolving 'legal highs' market. 'Legal highs' is an umbrella term used to describe non-regulated (new) psychoactive substances that are usually intended to mimic the effects of controlled drugs and are sold on the open market. This is an area characterised by limited data on use, with the risks and harms largely unknown, and where highly potent drugs are of serious concern. In the case of smoking mixtures containing synthetic cannabinoids, for example, there can be considerable variability both within and between different batches of the products, in terms of both the substances and the amount present.

The manufacture of synthetic cannabinoid products

Most of the synthetic cannabinoids that are used in 'legal high' products are manufactured by chemical companies based in China. They are shipped as bulk powders to Europe using express mail and courier companies; larger amounts may by shipped by air or sea cargo. Multi-kilogram shipments are frequently intercepted by authorities in Europe. While the purity of these bulk powders are rarely determined, one study from South Korea reported purities of between 75 % and 90 % for bulk powder samples. In 2014 almost 30 000 seizures (29 395) were reported to the EMCDDA weighing more than 1.3 tonnes (1 355 kg), of which almost 350 kg (343.973 kg) was bulk powder. Once in Europe, the retail products are put together. Damiana (*Turnera diffusa*) and Lamiaceae herbs such as *Melissa*, *Mentha* and *Thymus* are commonly used as the plant base for the smoking mixtures. The synthetic cannabinoids are mixed with or sprayed onto the plant material, typically on an industrial scale using solvents such as acetone or methanol to dissolve the powders; equipment like cement mixers are then used to mix the ingredients together. From there, the mixture is then dried and packaged. They are then sold on the internet by 'legal high' retailers and in bricks-and-mortar head shops.

Due to the high potency of some synthetic cannabinoids, the amount of powder needed for each packet can be in the order of a few tens of milligrams. This means that each kilogram of bulk powder may produce thousands of packets of 'legal highs'. The discovery of processing and packaging facilities and large quantities of synthetic cannabinoids in the Netherlands and Belgium suggests the involvement of organised crime in the distribution process. There is also evidence of a significant internet retail trade within Europe,

([1]) For the purposes of monitoring within the framework of the EU Early Warning System, the term 'synthetic cannabinoids' is used here to include: the large number of synthetic cannabinoid receptor agonists (such as JWH-018 which is a CB1 and CB2 receptor agonist) that have been detected on the European drug market; a much smaller number of allosteric modulators (such as Org 27569) that change the structure of the cannabinoid receptors leading to altered activity when a ligand binds to the receptors; and substances that act as inhibitors of fatty-acid amide hydrolase (FAAH), which is the enzyme responsible for breaking down the endocannabinoid anandamide (such as URB597). This Perspective on Drugs only discusses the synthetic cannabinoid receptor agonists.

Facts and figures

98 new psychoactive substances were reported to EMCDDA in 2015, **24** were synthetic cannabinoids

160 synthetic cannabinoids in total are currently monitored by the EMCDDA through the EU Early Warning System

14 recognisable chemical families of synthetic cannabinoids are known

2008 — a synthetic cannabinoid, **JWH-018**, first detected in Spice products

with customs and police making regular seizures of small quantities of these products.

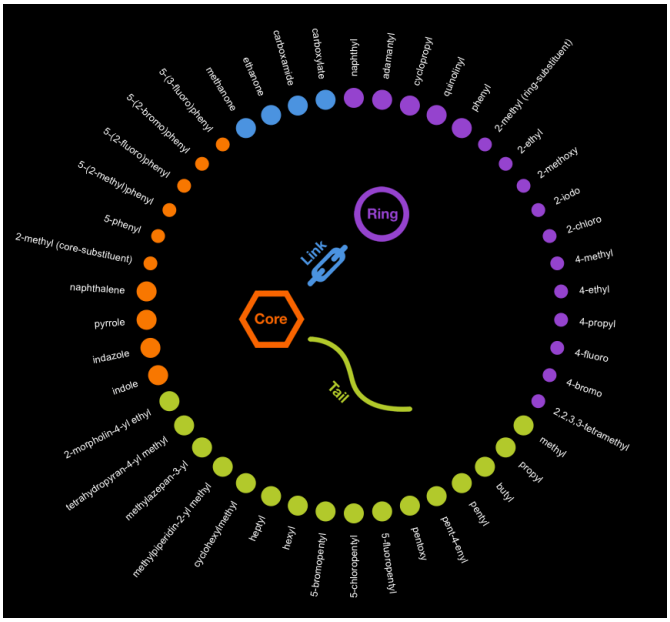
Monitoring of online shops selling 'legal high' products provides some insight into the range of smoking mixtures available for purchase, many of which are likely to contain synthetic cannabinoids. Such monitoring, when combined with test purchasing of products for sale, is also a way of both keeping track of how the substances contained in a product change over time, and helping in the early detection of new cannabinoids that appear on the market.

Prevalence

Information on the extent to which synthetic cannabinoid products are used is limited; however, knowledge of the situation is improving as more countries incorporate questions about their use in general population surveys. From the information that is available, it would appear that the prevalence of their use in the general population is low in Europe. A number of surveys aimed at examining the prevalence of use of 'Spice'-like products have been launched but their coverage and representativeness remains limited.

There are notable differences between the prevalence of use of synthetic cannabinoid products between the European and US drug markets. The most recent US prevalence data comes from the 2014 US Monitoring the Future survey of students, which suggests use is declining, with last year prevalence for 17- to 18-year-olds of 5.8 % in 2014, down from 7.9 % in 2013 and 11.3 % in 2012. A number of surveys in European countries also report on the use of synthetic cannabinoids, although they are not comparable as they use different methods, sampling frames and terminology. Overall, these studies indicate very low prevalence levels. The United Kingdom (England and Wales) asked about the use of 'Spice' in two consecutive household surveys and reported lifetime prevalence levels for adults (16–64) at 0.2 % in 2010/2011 and 0.1 % in 2011/2012. In the latest British Crime Survey for

Interactive element



Interactive: demystifying the chemistry available on the EMCDDA website: emcdda.europa.eu/topics/pods/synthetic-cannabinoids

England and Wales covering 2014/2015 a total of 0.9 % of adults (16–59) had used new psychoactive substances in the last year, of which 61 % had used a herbal smoking mixture. The question was not repeated in subsequent years due to the low prevalence rate. In Spain a 2012 national survey on drug use among students aged 14–18 with a sample of 27 503 also identified low levels of use of 'Spice' products, with prevalence rates of 1.4 % for lifetime use, 1.0 % for last year use and 0.6 % for last month use, which indicated a small increase from the previous survey results from 2010 (1.1 %; 0.8 %; and 0.5 % respectively). This compares with 0.5 %, 0.1 % and 0 % in a more general Spanish survey of 15- to 64-year-olds conducted in 2013. In France in 2014 a survey of adults (18–64) with a question about the use of 'synthetic cannabinoids' reported lifetime use of 1.7 %. First-time users of these new synthetic products are mostly males (2.3 % vs. 1.2 % of females) and from the youngest generation (under 35 years): 4.0 % of 18- to 34-year-olds had tried synthetic cannabinoid compared to 0.6 % of 35- to 64-year-olds. Another survey in France, among young people aged 17, reported that 1.7 % of them have previously used a synthetic cannabinoid. The German city of Frankfurt has studied the use of smoking mixtures and 'Spice' among students aged 15–18. They reported lifetime levels of use of 7 % in 2009; 9 % in 2010; and 7 % in 2011 and 2012. In 2013 lifetime use of smoking mixtures fell to 5 %, and although it increased to 6 % in 2014 it was still below the values from 2009–12. Students reporting the consumption of 'Spice' were, for the most part, experienced cannabis consumers. Finally, a number of studies among particular groups (clubbers, internet users, etc.) with non-probabilistic samples have

generally identified higher levels of synthetic cannabinoid use than among the general population. The 2012 Global Drug Survey, for example, reported last year prevalence levels of 3.3 % among all UK respondents (not representative of the general population) and 5.0 % among UK regular clubbers.

Synthetic cannabinoid related harms

The adverse health effects associated with synthetic cannabinoids are linked to both the intrinsic properties of the substances, what the body does to the substances, and to the way the products are produced. There has been a large number of non-fatal poisonings, and a smaller number of deaths are associated with their use. As some of these compounds are very potent, the potential for toxic effects appears to be high. These risks may be added to by the manufacturing process, which can lead to an uneven distribution of the substances within the plant material. This may result in some products containing 'hot pockets' where the cannabinoid is highly concentrated, leading to doses that are higher than intended and increasing the risk of serious adverse events. It is also possible that some of the adverse effects are due to mechanisms other than interaction with the cannabinoid receptors, for example by interfering with other physiological functions in the body.

A recent systematic review of adverse events associated with synthetic cannabinoid products found that agitation, nausea and an abnormally fast, racing heartbeat were frequently reported poisoning symptoms; while serious adverse events — such as stroke, seizure, heart attack, breakdown of muscle tissue, kidney damage, psychosis and severe or prolonged vomiting — and associated deaths were less common. Symptoms suggestive of dependence and withdrawal have also been reported. Overall, estimating how common these adverse events are is difficult because, among other things, the total number of people exposed to the drugs is unknown.

One of the most striking features of synthetic cannabinoid products is their ability to cause outbreaks of mass poisonings. Sometimes this involves hundreds of people over a short period of time — which has been a major problem in the past few years in the United States and Russia. In 2014 in Russia the cannabinoid MDMB-FUBINACA was linked to more than 600 poisonings, including 15 deaths, over a two-week period. Early in 2016 this substance was identified on the European market, triggering a public health alert from the EMCDDA to its early warning network. In 2015 there was another large outbreak in the United States, which appears to have been linked partly to a substance called ADB-FUBINACA. While these types of outbreaks appear to be rare in Europe, in 2015 more than 200 hospital emergencies were reported in less than a week after people were reported to have smoked a product called 'Mocarz' in Poland.

EMCDDA monitoring of such serious adverse events and current knowledge of the pharmacological and toxicological effects of some synthetic cannabinoids, show that these compounds can cause serious harm to human health. However, at present the mechanisms of how this happens are poorly understood.

Recent developments

From the start of the synthetic cannabinoid phenomenon these substances have largely been detected in products sold as 'herbal smoking mixtures'. More recently, however, several countries have also reported finding the substances in products that look like cannabis resin, either in branded 'legal high' products such as 'Afghan Incense' or simply passed off as cannabis resin on the illicit market. This development is likely to be a response to the popularity of cannabis resin in many countries. Synthetic cannabinoids have also been detected in mixtures containing other new psychoactive substances, such as stimulants, hallucinogens and sedative/hypnotics; this may be deliberate or accidental. In a small number of cases, the presence of synthetic cannabinoids has been detected in what appear to be ecstasy tablets or capsules. In Hungary and the United States this has led to clusters of acute poisonings. Another recent development has been the discovery of synthetic cannabinoids in the liquid-filled cartridges for use in electronic cigarettes; this most likely reflects the recent popularity of 'vaping' among young people.

The EMCDDA has been closely monitoring developments relating to synthetic cannabinoids since their identification on the European market in 2008. A striking feature has been the way in which this chemical family has evolved and adapted during this time. It is clear that the innovative chemical substitution patterns that have characterised this phenomenon mean that continued close monitoring of new developments in the field — including synthetic cannabinoid-related harms — will be essential.

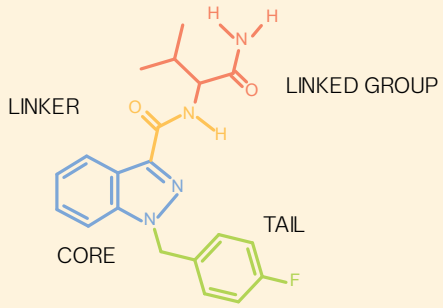
Chemistry and naming of the synthetic cannabinoids

Many of the synthetic cannabinoids monitored by the EMCDDA through the EU Early Warning System have code names that relate to their discovery. In some cases they are derived from the initials of the name of the scientists that first synthesised them: e.g. 'JWH' compounds after John W. Huffman and 'AM' compounds after Alexandros Makriyannis. In other cases code names may originate from the institution or company where they were first synthesised, the 'HU' series of synthetic cannabinoids being from the Hebrew University in Jerusalem, or 'CP' from Carl Pfizer. In some cases names have probably been chosen by those making 'legal high' products to help market the products. Striking examples of this are 'AKB-48' and '2NE1', alternative names used for APINACA and APICA. 'AKB-48' is the name of a popular Japanese girl band and '2NE1' is the name of a girl band from South Korea. Finally, the synthetic cannabinoid XLR-11, appears to have been named after the first liquid fuel rocket developed in the USA for use in aircraft, perhaps alluding to the vendor's intention for those who consume the substance.

Many synthetic cannabinoids are now given code names that are derived from their long chemical names, such as APICA from N-(1-adamantyl)-1-pentyl-1H-indole-3-carboxamide, and APINACA from N-(1-adamantyl)-1-pentyl-1H-indazole-3-carboxamide. The EMCDDA has systematised this method in order to apply it to newly emerging substances and show how the various constituent parts can be put together. The structures of many synthetic cannabinoids can be categorised into four components: tail, core, linker and linked group. Assigning each component a code name allows the chemical structure of the cannabinoid to be identified without the long chemical name. The proposed naming syntax for the synthetic cannabinoids that follow this pattern is as follows:
LinkedGroup – TailCoreLinker

Ordering the components in this manor follows the ordering as seen in their longer chemical names, as with **APICA**: N-(1-adamantyl)-1-pentyl-1H-indole-3-carboxamide. When a tail substituent is present (i.e. 5F), this will be displayed at the front of the name and linked group substituents will be placed before the linked group; core substituents will be placed at the end of the code.

Applying the new system to a recently notified synthetic cannabinoid:



N-(1-carbamoyl-2-methyl-propyl)-1-[(4-fluorophenyl)methyl] indazole-3-carboxamide

Current name: AB-FUBINACA
New name: MABO-FUBINACA

The letter codes used are based not only on the letters used but the ordering of letters. For example, A identifies the amine in the linked group. CA identifies the carboxamide. By following the syntax and codes described, synthetic cannabinoids that follow this structure will have a unique short name.

Visit the POD website for more information: www.emcdda.europa.eu/topics/pods/synthetic-cannabinoids

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