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 compounds currently monitored in Europe by the EU Early Warning System on new psychoactive substances. Current knowledge on these substances, as well as trends in production, availability and use, are presented in this analysis.

Synthetic cannabinoids, or more correctly, synthetic cannabinoid receptor agonists, mimic the effects of cannabis and are the largest group of compounds monitored at European level by the EU Early Warning System on new psychoactive substances (EWS). 'Legal high' products containing synthetic cannabinoids have probably been sold as herbal smoking mixtures since at least 2006. These products do not necessarily contain tobacco or cannabis but when smoked, produce effects similar to those of cannabis. Recently, new liquid products containing synthetic cannabinoids have emerged for use with electronic cigarettes. They have been subject to innovative marketing approaches and are widely available on the Internet and in some shops in urban areas (often called 'head' or 'smart' shops).

The number of substances, their chemical diversity and the rate of their emergence makes this group of compounds particularly challenging in terms of detection and monitoring.

The common property of all synthetic cannabinoids is that they act upon the cannabinoid receptors in the body, mimicking to variable degrees the effects of Δ9-THC, the main active chemical found in cannabis. However, little is known about the pharmacology and toxicology of this group of substances in humans. It is possible that apart from high potency, some of these substances could have particularly long half-lives, potentially leading to a prolonged psychoactive effect. This analysis aims to provide an update on the current knowledge of these substances and their effects, as well as trends in production, availability and use.

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

## The emergence of synthetic cannabinoids

It was not until 2008 that forensic investigators in Germany and Austria first detected the substance JWH-018, a synthetic cannabinoid, in Spice products. Subsequently several cannabinoids were detected in herbal 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 subsequently been detected on the open market were first developed by scientists investigating the mode of action of cannabinoids on signalling pathways in the body, as well as their potential as therapeutic agents, such as analgesics. However, so far it has proved difficult to separate the desired therapeutic properties from unwanted psychoactive effects.

The number of synthetic cannabinoids detected through the EWS continues to grow year on year. There were 9 reported in 2009, 11 in 2010, 23 in 2011, 30 in 2012, 29 in 2013 and 30 in 2014 with a total of 134 synthetic cannabinoids having been notified to the EMCDDA as of December 2014.

Synthetic cannabinoids play an important role in the rapidly evolving 'legal highs' market. 'Legal highs' is an umbrella term used to describe unregulated (new) psychoactive substances that are usually intended to mimic the effects of controlled drugs and sold on the open market. This is an area characterised by limited data on use, with the risks and harms largely unknown, and where high potency levels are of serious concern. There can be, for example, considerable inter-and intra-batch variability in 'legal high' products containing synthetic cannabinoids, both in terms of the substances present and their concentrations.

## Manufacture of synthetic cannabinoid products

Most of the synthetic cannabinoid powders that are used in 'legal high' products are manufactured in China and then are shipped in bulk using established legitimate transport and distribution networks. Multi-kilo shipments are frequently intercepted by authorities in Europe but the purity is rarely determined. One study from South Korea reported purities of between 75% and 90% for bulk powder samples. In 2013, over 21 000 seizures of synthetic cannabinoids were reported to the EWS amounting to more than 1.5 tonnes of material, of which almost 600 kilograms was bulk powder material, with China being a notable source country. Once in Europe, the retail products are put together. Damiana (Turnera diffusa) and lamiaceae herbs such as Mellissa, Mentha and Thymus are commonly used as the herbal base for the active synthetic chemical ingredients. The bulk chemicals are mixed with or sprayed onto the herbs, typically on an industrial scale often using equipment like cement mixers and liquid solvents

such as acetone or methanol to dissolve the powders. Once mixed, the herbs are then dried and packaged for sale, either on the Internet by 'legal high' retailers or from certain shops in urban areas.

Due to the high potency of some synthetic cannabinoids, the amount of powder needed for each product unit can be in the order of a few tens of milligrams. Therefore, each kilogram of powder may be used to produce thousands of 'legal high' products. Discovery of processing and packaging facilities and large quantities of synthetic cannabinoids in the Netherlands and Belgium suggest the involvement of organised crime in the distribution process. There is also evidence of a significant Internet retail trade within the European Union, with customs and police making regular seizures of small quantities of these products.

Systematic monitoring of online shops selling 'legal high' products provides some insight into the range of smoking and herbal 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, as well as helping in the early detection of new cannabinoids that appear on the market.

## Prevalence

The extent to which synthetic cannabinoid products are used is largely unknown, however the situation is improving as more countries incorporate questions about use of new drugs into their general surveys. From the information that is currently available, it would appear that the prevalence of synthetic cannabinoids in the general population is very low. 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.

## Facts and figures

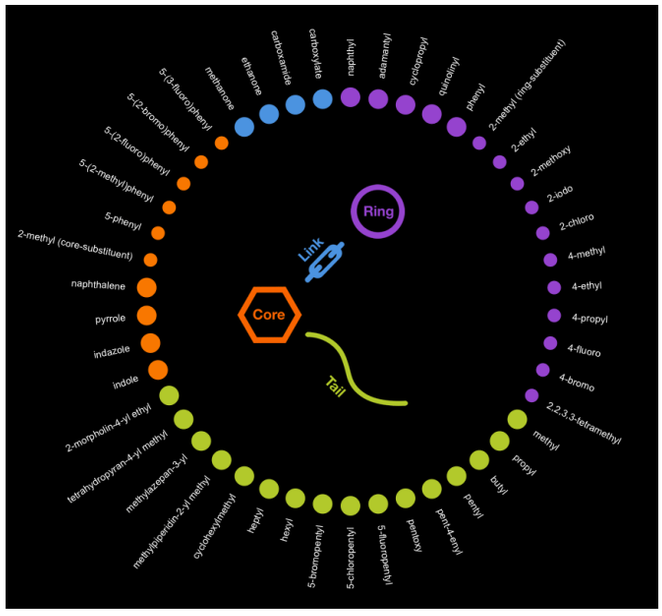
**101** new psychoactive substances were reported to EMCDDA in 2014, **30** were synthetic cannabinoids

**137** synthetic cannabinoids in total being monitored by EU Early Warning System (February 2015)

**14** recognisable chemical families of synthetic cannabinoids are known

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

## Interactive element




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

There are notable differences between the prevalence of synthetic cannabinoids in the European and American 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 use of synthetic cannabinoids for 17/18 year olds of 5.8% in 2014, down from 7.9% in 2013 and 11.3% in 2012. A number of surveys in EU countries also report on the use of synthetic cannabinoids, although they are not comparable because of different methods, sampling frames and terminology. Overall, however, these individual studies indicate very low prevalence levels. The United Kingdom (England and Wales) asked about use of 'Spice' in two consecutive household surveys and reported lifetime prevalence levels for adults (16 to 64) at 0.2% in 2010/2011 and 0.1% in 2011/2012. The question was not repeated in subsequent years due to the low prevalence rate. In Spain, a 2012 national survey on drug use in students aged 14 to 18 years with a sample of 27 503, also identified low levels of use of 'Spice' products with 1.4%, 1.0% and 0.6% reported for lifetime, last year and last month prevalence, respectively, 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 15-64 year olds conducted in 2013. In France, in 2014, a global survey for adults (18 to 64) with a question about use of "synthetic cannabinoids" reported an experimentation of 1.7 %. First time users of these new synthetic products are mostly men (2.3% vs. 1.2% of women) and from the youngest generation (under 35 years): 4.0% of 18-34 years old have tried synthetic cannabinoid against only 0.6% of 35-64 (Baromètre Santé). Another survey in France, for young people aged 17, reported that 1.7 % of them have already used a synthetic cannabinoid (ESCAPAD). In Germany, the city of Frankfurt has studied the use of herbal mixtures and 'Spice' among students aged 15 to 18 years. They reported lifetime levels of use at 7% in 2009, 9% in 2010, 7% in 2011 and 7% in 2012. In 2013, lifetime use of herbal mixtures dropped to 5%. 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.

### Adverse health consequences associated with synthetic cannabinoids

The adverse health effects associated with synthetic cannabinoids are linked to both the intrinsic properties of the substances and to the way the products are produced. There have been numerous reports of non-fatal intoxications and a smaller number of deaths associated with their use. As some of these compounds are very potent, the potential for toxic effects is high. This may be compounded by the manufacturing process which can lead to the uneven distribution of the substances within the herbal material, which may result in some products containing doses that are higher than intended.

There have been several notable outbreaks of serious acute intoxications linked to legal high products containing synthetic cannabinoids in countries outside the EU. It is of concern that the cannabinoids in question have also often been seized in the EU, leading the EU Early Warning System to issue public health alerts to its network across

Europe. During 2013, five deaths associated with the use of 5F-PB-22 were reported in the United States. In 2014, an outbreak of non-fatal intoxications occurred in Colorado, United States associated with ADB-PINACA. While towards the end of 2014, media outlets in Russia reported two large outbreaks of adverse events associated with the smoking of a 'legal designer drug' or 'Spice', most probably a synthetic cannabinoid.

The reported adverse effects of synthetic cannabinoid products include agitation, vomiting, drowsiness and confusion. Although some of these are similar to symptoms observed after a high dose of cannabis, researchers have suggested that products containing synthetic cannabinoids are potentially more harmful than cannabis. Some of the more serious effects include kidney damage, pulmonary and cardiovascular effects and convulsions. A case report published in 2013 associated the use of JWH-018 with acute ischemic strokes in two otherwise healthy males. In addition, there is some evidence to suggest that synthetic cannabinoids can be associated with psychiatric symptoms, including psychosis. It is probable that some of the adverse effects are due to mechanisms other than interaction with the cannabinoid receptors, for example, the inhibition of monoamine oxidase.

From the monitoring of such adverse events by the EU Early Warning System and from our current knowledge of the physiological and toxicological effects of selected synthetic cannabinoids, it is clear that these compounds carry the potential to cause harm to human health, although the mechanisms of how this happens are poorly understood at present.

## Recent developments

Since the beginning of the synthetic cannabinoid phenomenon, these substances were largely 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 Insense' or simply masquerading 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. 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 EWS has been closely monitoring developments among synthetic cannabinoids since their arrival 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 which have characterised this phenomenon, mean that close surveillance of new developments in the field, as well as of synthetic cannabinoid-related harms, will remain paramount in the future.

## Chemistry and naming of the synthetic cannabinoids

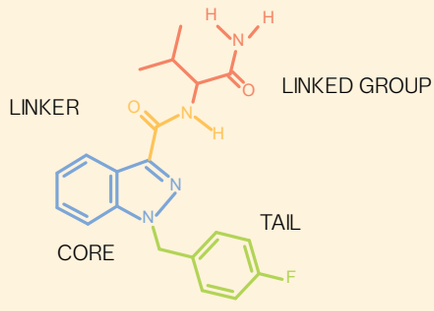
Many of the compounds monitored by the EWS have code names that relate to their discovery. In some cases they are derived from the initials of the name of the scientists that first synthesised them: e.g. 'JWH' compounds after John W. Huffman and 'AM' compounds after Alexandros Makriyannis. In other cases they 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' for Carl Pfizer. In some cases, names have probably been chosen 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 substances are now given code names that are derived from their long chemical names such as: **APICA** from N-(1-**a**damantyl)-1-**p**entyl-1H-**i**ndole- 3-**c**arbox**a**mide and **APINACA** from N-(1-**a**damantyl)-1-**p**entyl-1H-**in**d**a**zole-3-**c**arbox**a**mide. 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 4 components: tail, core, linker and linked group. Assigning each component a codename 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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