European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), Thematic Paper 2009

UNDERSTANDING THE 'SPICE' PHENOMENON

Overview

Smokable herbal mixtures under the brand name 'Spice' are known to have been sold on the Internet and in various specialised shops since at least 2006 and metadata reports (Google Insights web searches) suggest that those products may have been available as early as 2004. Although advertised as an 'exotic incense blend which releases a rich aroma' and 'not for human consumption', when smoked, 'Spice' products have been reported by some users to have effects similar to those of cannabis.

There are a number of products marketed under the 'Spice' brand — these include, but are not limited to: Spice Silver, Spice Gold, Spice Diamond, Spice Arctic Synergy, Spice Tropical Synergy, Spice Egypt, etc. In addition, there are many other herbal preparations for which the claim is made that they have a similar make-up to 'Spice' — e.g. Yucatan Fire, Smoke, Sence, ChillX, Highdi's Almdröhner, Earth Impact, Gorillaz, Skunk, Genie, Galaxy Gold, Space Truckin, Solar Flare, Moon Rocks, Blue Lotus, Aroma, Scope, etc. It should be noted that the speed of innovation in this area means that any list of products is likely to become quickly outdated.

Following a report from the Swedish Reitox national focal point (NFP), of a small number (around 10) of seizures of 'Spice' products in 2007, the Reitox early-warning system (EWS) on new psychoactive substances began, from the start of 2008, formally monitoring these products. However, despite various media reports and users' accounts on the Internet, little verifiable information on the psychoactive and other effects of 'Spice' was officially reported to the EMCDDA prior to December 2008.

Towards the end of 2008, forensic investigations were undertaken by German and Austrian authorities in order to identify the psychoactive ingredients of 'Spice'. On 19 December 2008, the Austrian NFP formally notified to the EMCDDA the new psychoactive substance **JWH-018** (Naphthalen-1-yl-(1-pentylindol-3-yl)methanone) ([1]) — a synthetic cannabinoid receptor (CB) agonist ([2]) that had been identified in 'Spice' products in Austria by AGES PharmMed ([3]). The compound was detected in at least three products (Spice Gold, Silver and Diamond). Information received from the German NFP reported that JWH-018 had also been identified a few days earlier (on 15 December) in 'Spice' products in Germany by THC-Pharm (Steup, 2008) ([4]). JWH-018 is a synthetic substance first synthesized in 1995 for experimental purposes. It is a naphthoylindole, which belongs to the aminoalkylindole family (Wiley et al., 1998; Huffman, 2009; Chin et al., 1999), i.e. the chemical structure differs substantially from Δ^9-tetrahydrocannabinol (THC), but it produces similar effects in animal experiments and has been reported to be more potent than THC; see Uchiyama, 2009 and Auwärter et al., 2009 for analytical details. JWH-018 has also been reported by Poland, the United Kingdom, Slovakia, Finland and Ireland.

Subsequently, on 20 January 2009, the German NFP informed the EMCDDA that a team of German forensic experts from the University of Freiburg and the German Federal Criminal Police Office (BKA) had also identified in 'Spice' products the C8 homologue of the synthetic cannabinoid **CP 47,497** (2-[(1R,3S)-3-Hydroxycyclohexyl]-5-(2-methyloctan-2-yl)phenol) (Weissman et al., 1982; Compton et al., 1992; Compton et al., 1993; Huffman et al., 2008) — a synthetic cannabinoid receptor (CB) agonist with potency greater than THC as measured by the affinity constant Ki ([5]). According to the original publication (Auwärter et al., 2009), not only the C8 homologue, but CP 47,497 and the non-active trans diastereomers of both compounds, as well as oleamide ([6]) (Lambert and Di Marzo, 1999; Leggett et al., 2004) were also identified in the seven 'Spice' products tested. CP 47,497 compounds have also been reported by the United Kingdom, Slovakia and Finland.
Outside of Europe, in March 2009, the United States Drug Enforcement Administration (DEA, 2009) reported that another potent synthetic cannabinoid, **HU-210** — (6aR,10aR)-9-(Hydroxymethyl)-6,6-dimethyl-3-(2-methyloctan-2-yl)-6a,7,10,10a-tetrahydrobenzo[c]chromen-1-ol ([7]) (Mechoulam et al., 1988; Glass and Northup, 1999; Ottani and Giuliani, 2001; Jiang et al., 2005; Pertwee, 2005) — had been found in 'small but verifiable

---

([1]) The common chemical name for JWH-018 is 1-Pentyl-3-(1-naphthoyl)indole.

([2]) An agonist is a chemical substance that binds to a specific receptor of a cell and triggers an activity by the cell. An agonist often mimics the action of endogenous or naturally occurring substances.

([3]) The work on Spice was commissioned by the Ministry of Health, Family and Youth. AGES PharmMed is the branch of the Austrian Agency for Health and Food Safety responsible for pharmaceuticals.

([4]) The work on Spice was commissioned by the city of Frankfurt am Main. THC-Pharm is a pharmaceutical company that specialises in production of medicinal products based on natural cannabinoids.

([5]) The affinity constant ([K_i]=nM) is the equilibrium dissociation constant used in drug-receptor binding to describe how tightly a ligand (drug) binds to a particular receptor; small variations in K_i values occur between different publications.

([6]) Oleamide is a fatty acid amide which occurs naturally in animals, but which is also synthetically produced for industrial use.

([7]) HU-210 is a full agonist at CB_1.

amounts' in 'Spice' products seized by the US Customs and Border Protection Service. In June 2009, HU-210 was identified for the first time in three 'Spice' products in the United Kingdom.

In the first trimester of 2009, two Member States — Denmark and the Netherlands —informed the EMCDDA about seizures of another synthetic cannabinoid from the JWH family — **JWH-073** ([8]), a lower alkyl homologue of JWH-018. Similarly to JWH-018, this compound acts as a (partial) agonist at CB_1 and CB_2 receptors and, therefore, can be expected to produce cannabis-like effects. In both cases, JWH-073 was not detected in 'Spice' samples, but as powders seized by law enforcement authorities. On 20 April 2009, the German NFP informed the EMCDDA that the substance had also been identified in 'Spice'-like products (Scope and others) in Germany, and it has also been identified in Finland.

In October 2009, two new JWH synthetic cannabinoids were reported for the first time by the United Kingdom and Germany. The napthoylindole **JWH-398** (1-Pentyl-3-(4-chloro-1-naphthoyl)indole) was found in three separate 'herbal incense' products purchased by TICTAC Communications Ltd from online shops from February to June 2009. JWH-398 acts as an agonist both at the CB_1 and the CB_2 receptors, having a slight selectivity for the former. The phenylacetylindole **JWH-250** (2-(2-Methoxyphenyl)-1-(1-pentylindol-3-yl)ethanone) was seized in May 2009 by the German Federal Criminal Police; it acts as an agonist mainly at the CB_1 receptor.

These relatively obscure substances added to the herbal mixtures sold as 'Spice' were all originally developed through research aimed at deciphering the molecular and biochemical intricacies of the endocannabinoid system. None of the above synthetic cannabinoids is internationally controlled as a drug and there is no information on any of them having been authorised as a medicinal product in the European Union. Importantly, there is no officially published safety data and almost nothing is known about their effects in humans. Some of the characteristics of these compounds, e.g. volatility (and hence 'smokability') and activity in small doses, are likely to present further analytical and toxicological challenges.

It can be assumed that different amounts or combinations of synthetic cannabinoids may have been added to some 'Spice' products to produce cannabis-like subjective effects. Media information suggests that some 'Spice' products may have been produced in Asia (e.g. China), but it remains unclear where and how the actual production of the herbal mixtures, the synthetic cannabinoids and their addition to the herbal mixtures takes place.

Although available in some specialised shops, 'Spice' products appear to be largely an Internet phenomenon. An EMCDDA survey established that 'Spice' products are available on national websites in two-thirds of the European Union Member States, but the actual accessibility and levels of use are difficult to assess. Anecdotal reports of the subjective effects of 'Spice' consumption can be found in Internet forums and elsewhere and range from reports of a strong cannabis-like effect, to the mixture having insignificant or non-detectable psychoactive action.

Responding to potential health concerns, Austria, Germany, France, Luxembourg, Poland, Lithuania, Sweden and Estonia (in chronological order) have taken legal actions to ban or otherwise control 'Spice' products and related compounds. Other Member States are also now considering if measures in this area are merited.

1. Introduction and background

The EMCDDA has been monitoring 'Spice' products since 2008. The information exchange mechanism of the Council Decision (the EWS) (Council Decision, 2005) has facilitated the sharing and disseminating of information between the Member States, initially assisting the efforts to identify the potential psychoactive components of the herbal ingredients of 'Spice'. This resulted in the dissemination of analytical information ([9]) useful for identification purposes to the EWS partners (Reitox NFPs, Europol, the European Medicines Agency and the Commission). This information was obtained from Austria (Austrian Ministry of Health, Family and Youth and the NFP), as well as the German NFP and the United Kingdom NFP ([10]) and the EMCDDA would like to acknowledge the important work conducted in this area by these partners.

At the beginning of 2009, a meeting took place between the EMCDDA and Europol to examine the information available on 'Spice' and related compounds and to decide upon the necessity of further actions. The two agencies concluded that, at that time, JWH-018, CP 47,497 and its homologues did not fulfil the criteria set up by the 'EWS Operating guidelines' (EMCDDA, 2007) to trigger the launch of a Europol–EMCDDA Joint report. However, this situation remains under review with ongoing monitoring to ensure that, should the criteria be met, appropriate actions could be quickly instigated.

It is important to note that the information exchange mechanism of the Council Decision is designed and geared towards notification and monitoring of individual substances, which is technically a sound practice. Therefore,

([8]) The IUPAC systematic name of JWH-073 is Naphthalene-1-yl-(1-butylindol-3-yl)methanone.
([9]) MS spectra and chemical information for JWH-018, CP 47,497-C8, HU-210 and JWH-398.
([10]) Information from the United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA).

groups of substances ('analogues') cannot be notified, monitored and risk assessed as a single category. This would imply that information collection and monitoring, potentially leading to risk assessment(s), should be done separately for each individual substance if the risk assessment process linked to the Council Decision were to be triggered.

Upon a request from the EMCDDA Management Board (December 2008), and in response to the substantial interest of policymakers, experts and the media, in January 2009 the EMCDDA launched a survey among the Reitox NFPs to collect some preliminary data on the availability of 'Spice' products in Europe. The first results of the study were presented to an expert meeting convened by the EMCDDA in March 2009. The meeting was attended by experts from the Member States with particular experience in this area, as well as representatives from the European Medicines Agency, EMCDDA staff and the chairperson of the Scientific Committee ([11]). The resulting report includes data and information presented at the meeting; however, interpretations and conclusions are those of the EMCDDA. This Thematic paper reflects the situation as of the first trimester of 2009 and is intended to provide insight and, as far as it is possible, evidence-based answers to the following questions:

1. What do we know about the nature, availability and use of 'Spice' products?
2. What do we know about synthetic cannabinoids found in 'Spice' products?
3. Why did it take such a long time to establish the psychoactive principles in the 'Spice' products?
4. Are those products dangerous for the consumer?
5. Is there a specific demand and will the market of non-scheduled synthetic (designer) cannabinoids with a THC-like mode of action (e.g. acting at CB_1 receptors) continue to develop?
6. Where are the synthetic cannabinoids produced, and how are they added to the herbal products?

2. Herbal components of 'Spice' products

The labels on the colourful 'Spice' packages indicate that the product contains between 0.4–3.0 g of a mixture said to consist of several potentially psychoactive plants (see Table 1).

Table 1: Herbal components of 'Spice' (a non-exhaustive list)

Common name	Species	Family
Beach bean	*Canavalia maritima*; syn. *C. rosea*	Fabaceae
White and blue water lily	*Nymphaea alba* and *N. caerulea*	Nymphaeaceae
Dwarf skullcap	*Scutellaria nana*	Lamiacae
Indian warrior	*Pedicularis densiflora*	Orobanchaceae
Lion's ear/tail, Wild dagga	*Leonotis leonuru*	Lamiacae
'Maconha brava'	*Zornia latifolia* or *Z. diphylla*	Fabaceae
Blue/Sacred lotus	*Nelumbo nucifera*	Nelumbonaceae
Honeyweed/Siberian motherwort	*Leonurus sibiricus*	Lamiaceae
Marshmallow	*Althaea officinalis*	Malvaceae
Dog rose/Rosehip	*Rosa canina*	Roseceae

These plants seem to have been chosen because some of them have been traditionally known as 'marijuana substitutes' so users can expect effects similar to that of smoked cannabis. An assumption, based on the known chemical content of the plants, is that at least two of the mentioned ingredients, 'Indian warrior' (*Pedicularis densiflora*) and 'Lion's tail' (*Leonotis leonurus*), may have some psychoactive effect. However, there is a lack of information about their complete chemical make-up and, overall, little is known about the pharmacology and toxicology of the plant materials purportedly contained in the 'Spice' products. Thus, no strong conclusions can be drawn about the public health implications of the consumption of these mixtures. However, concerns have been raised that some of these mixtures may contain heavy metal residues that may be harmful to health. Without further analysis, the veracity of this concern is difficult to assess, but in general, the smoking of any mixture is likely to be a concern from a public health perspective.

Specific worries about the pharmacology and toxicology of these herbs have to be evaluated in the context in which it appears that most of the ingredients listed on the packaging are actually not present in the 'Spice' products. It is now generally assumed that the biological and psychological effects described by users are due to the added synthetic cannabinoids, which are not reported on the label. This raises the possibility that there may be a deliberate marketing strategy to represent this product as natural. It also raises questions of consumer protection and product misrepresentation.

([11]) See the 'Acknowledgements' section for the list of participants of the EMCDDA expert meeting 'Spice and related synthetic cannabinoids', 6 March 2009, EMCDDA, Lisbon.

3. Synthetic cannabinoid receptor agonists: a brief chemical overview

Synthetic cannabinoid receptor agonists, often referred to as 'synthetic cannabinoids', are a large family of chemically unrelated structures functionally similar to Δ^9-tetrahydrocannabinol (THC), the active principle of cannabis. Like THC, they bind to the same cannabinoid receptors in the brain and other organs as the endogenous ligand anandamide ([12]). They were developed over the past 40 years as potential pharmaceutical agents, often intended for pain management. However, it proved difficult to separate the desired properties from unwanted psychoactive effects — see the EMCDDA drug profile on synthetic cannabinoids (EMCDDA, n.d.) for a comprehensive review.

The two main cannabinoid receptors (CB) were discovered in the 1980s. Type CB_1, found mostly in the central nervous system (CNS), is associated with psychoactive effects, while type CB_2 is associated with the immune system. Other receptors are believed to exist in the CNS and other tissues. Anandamide, discovered in 1992, was the first identified substance of several closely related endogenous agonists for these cannabinoid receptors.

Δ^9-tetrahydrocannabinol (THC) is the principal naturally-occurring exogenous agonist for CB_1 and CB_2. Following the isolation of THC in the 1960s, a large series of synthetic exogenous cannabinoid receptor agonists were synthesised. They fall into four major groups:

- Analogues of THC, so-called classical cannabinoids, are based on a dibenzopyran ring. They were developed from the 1960s and include HU-210 ('HU' stands for Hebrew University) (Mechoulam et al., 1988; Glass and Northup, 1999; Ottani and Giuliani, 2001; Jiang, 2005; Pertwee, 2005), Nabilone and Dronabinol and many others. Some, like Nabilone and Dronabinol, have limited therapeutic use, e.g. in treating nausea following chemotherapy. HU-210 is reported to have 100 times the potency of THC, as measured by K_i.
- In the 1970s, Pfizer developed the cyclohexylphenol (CP) series. Examples include CP 59,540, CP 47,497 and their n-alkyl homologues (Weissman et al., 1982; Compton et al., 1992; Compton et al., 1993; Huffman et al., 2008). In the scientific literature they are referred to as 'non-classical' cannabinoids.
- In the 1990s, J.W. Huffman et al. at Clemson University, USA created a large series of naphthoylindoles, naphthylmethylindoles, naphthoylpyrroles, naphthylmethylindenes and phenylacetylindoles (i.e. benzoylindoles) (known as aminoalkylindoles or JWH compounds — after the name of their inventor). Examples of naphthoylindoles include JWH-015, its n-pentyl homologue JWH-018 (Chin et al., 1999; Uchiyama et al., 2009), JWH-073 (an alkyl homologue of JWH-018) (Aung et al., 2000), and JWH-398. An example of phenylacetylindole is JWH-250, identified in 'Spice' products in Germany (LKA Bayern and Schleswig-Holstein).
- Miscellaneous compounds, possibly including fatty acid amides (e.g. oleamide). Although similar in structure to anandamide, the status of oleamide as a cannabinoid receptor agonist is uncertain; it is used as an anti-slip agent and is a common contaminant from plastics.

Examples from all four groups have been reported in 'Spice' and 'Spice'-like samples in Europe — HU-210; CP 47,497 and its homologues; JWH-018, JWH-073, JWH-398, JWH-250; and oleamide. (See Annex 1 for the basic chemical features and structure of exogenous synthetic cannabinoid receptor agonists found in 'Spice' products.)

The above CB_1/CB_2 agonists are lipid-soluble, non-polar, small molecules (typically 20–26 carbon atoms). They are fairly volatile (and hence, 'smokable'). Many are much more potent than THC, thus the 'typical' doses may be less than 1 mg. Their detailed pharmacology has not been investigated.

4. Forensic identification, pharmacology and toxicology of synthetic cannabinoids

Towards the end of 2008, extensive forensic science investigations were undertaken in Germany and Austria. In December 2008, chemical analysis revealed that the psychoactive effects of the herbal mixture were due to added synthetic cannabinoids. Since then, several analytical laboratories in Europe (Germany, Austria, Finland, France, Hungary, Poland, Slovakia, Slovenia and the United Kingdom) have confirmed the presence of at least one such substance in 'Spice' products.

On 16 December 2008, through a self-report study and chemical analysis of plant extracts and plasma samples after consumption, a team of German scientists (Auwärter et al., 2009) clearly identified the presence of added synthetic compounds. Using an extract of Spice Diamond, by combining the mass spectral information and the results of nuclear magnetic resonance spectroscopy (NMR), the authors found the C8 homologue of the synthetic cannabinoid CP 47,497 to be the main active component of the 'Spice' variants analysed.

One day earlier, THC-Pharm, a pharmaceutical company mandated by the city of Frankfurt, had found a 'cannabimimetic' aminoalkylindole called JWH-018 to be present in some samples of 'Spice' products by

([12]) Also known as N-arachidonoylethanolamine, anandamide is one of the endogenous ligands for cannabinoid receptors in the CNS and other organs.

comparing one of the unknown mass spectra generated from the extract with the mass spectrum of a JWH-018 standard, which they had in stock (Steup, 2008).

Both JWH-018 and CP 47,497-C8 act as agonists at CB_1 receptor and, therefore, produce cannabis-like effects. Due to their high pharmacological potency *in vitro*, it is likely that relatively low doses are sufficient for activity. The duration of effects in humans compared to THC seems to be shorter for JWH-018 (1–2 hours) and considerably longer for CP 47,497-C8 (5–6 hours), as reported in a self-experiment (Auwärter et al., 2009). Furthermore, JWH-073 (an alkyl homologue of JWH-018) was identified in Scope and other products in Germany, as well as in seizures of the substance in Denmark, the Netherlands and Finland.

On June 2009, HU-210 was identified for the first time in Europe, in the United Kingdom. Recently, two new synthetic cannabinoids, the napthoylindole JWH-398 and the phenylacetylindole JWH-250, have been identified in 'Spice' products in the United Kingdom and Germany, respectively.

Why did it take such a long time to establish the psychoactive principles in 'Spice'?

A number of factors may have contributed to this problem, among them the content (design) of the 'Spice' products:

- listing various herbs on the label that in theory may have cannabis-like effects by themselves;
- the extracts of the mixtures rendered very complex matrices;
- the addition of high amounts of non-psychoactive compounds such as vitamin E (tocopherol) to 'mask' the active components;
- selection of cannabinoids that are not present in common mass or UV spectra libraries and do not show cross-reactivity to commonly used drug test assays based on antibodies.

For these reasons, the synthetic additives are difficult to detect and identify.

More general factors may also have contributed. For example, the legal sale of 'Spice' products as a commodity via the Internet or in specialised shops, rather than clandestine production and illegal circulation as a drug, did not generate seizures or indicate criminality that might have prompted the interest and involvement of specialised law enforcement agencies. To some extent, this is a conceptual problem reflecting the lack of consensus on how this type of product should be viewed. Thus, the distribution and sale of these products took place in a 'grey zone' where the potentially responsible institutions (public health authorities, consumer protection agencies or the competent authorities for medicinal products) did not assume direct responsibility.

Are those products dangerous for the consumer?

The pharmacology of cannabis and THC, the main psychoactive ingredient of the plant, as well as the human body's endocannabinoid system has been known for 15–20 years. Several *in vitro* and animal studies (Aung et al., 2000), including structure-activity relationship studies (Wiley et al., 1998; Huffman, 2009; Compton et al., 1993; Huffman et al., 2005; Vann et al., 2009) aiming mostly at separating the undesired psychoactive effects from the therapeutically useful ones, have been published in the medical literature in the last two decades. However, no pharmaceutical product has emerged and no human studies with these cannabinoids have been carried out.

So far, little is known about metabolism and toxicology of the synthetic cannabinoid compounds. It cannot be assumed that the risks associated with the use of synthetic cannabinoids will be necessarily comparable to those seen with THC, and indeed there are some reasons for concerns that these drugs may have a greater potential to cause harm. Because the synthetic cannabinoids in the 'Spice' products have only been tested in the laboratory (*in vitro* or in animals), the health risk of the inhaled smoke is unknown. In the case of JWH-018, it can be speculated that, due to structural features, there may be a certain carcinogenic potential. Furthermore, accidental overdosing with a risk of severe psychiatric complications may be more likely to occur because the type and amount of cannabinoid may vary considerably from batch to batch even within the same product. In general, there may be a risk of the appearance of a full CB receptor agonist leading to life-threatening conditions if overdosed (unlike THC, which acts only as a partial agonist). Furthermore, it seems that tolerance to these synthetic cannabinoids may develop fairly fast, and arguably this might be associated with relatively high potential to cause dependence (Zimmermann et al., 2009). What is clear is that further studies are needed to assess these risks reliably.

Methods for the forensic analysis of blood samples for synthetic cannabinoids known to be used in 'herbal smokes' are already available in some laboratories (detection of recent intake). However, the detection of metabolites in urine samples, which would potentially provide a longer observational window, still requires further development.

5. EMCDDA survey

Rationale

The considerable professional and public interest in 'Spice' products resulted in a number of information requests to the EMCDDA: prompted by the lack of information, the Centre launched a short survey in January 2009 to collect some basic information on the availability of these products in the European Union Member States. The survey was carried out as part of the ongoing work to monitor the European drug problem and was a limited exercise that should not be confused with the more formal and legally binding data collection procedures possible under the auspices of the information exchange mechanism established by Council Decision 2005/387/JHA (Council Decision, 2005).

Methodology

A short questionnaire (eight questions, see below) was sent by e-mail to the Heads of Reitox NFPs on 20 January 2009. The questions covered 'Spice' products and JWH-018, but not CP 47,497 and its homologues, JWH-073 or HU-210, as at that time these compounds were not yet reported to the EMCDDA. However, later the EMCDDA contacted the NFPs and requested them to also include information on CP compounds. Responses from all surveyed NFPs (30 out of 30 — 27 EU Member States plus Croatia, Turkey and Norway) were received between 23 January and 3 March 2009. Where necessary, reminders were sent in order to ensure a full coverage of the survey, and brief telephone interviews were carried out with clarification questions. The questionnaires were completed by a national EWS system correspondent, a national forensic expert or the head of the respective focal point, based on their knowledge of the current situation. As such, the results should be regarded as an expert opinion.

Results

Availability of 'Spice' products

'Spice' products were identified in 21 out of the 30 participating countries. For the purpose of the survey, 'identification' means that these types of products were available in some way in the country (confirmation by forensic analysis was not a prerequisite, see the next question below). At the time of the survey, 'Spice' products were not identified in Belgium, Bulgaria, Denmark, Estonia, Greece, Malta, the Netherlands, Norway and Turkey.

'Spice' products and/or JWH-018 identified by means of toxicological or forensic analysis

JWH or CP compounds were identified by forensic/toxicological analysis in eight out of 21 countries where the products were available — Austria, Germany, Finland, France, Hungary, Poland, Slovenia and the United Kingdom. In four countries — Cyprus, Luxembourg, Lithuania and Sweden — analysis was under way. The following substances were identified:

- Austria: JWH-018 and CP 47,497-C8 homologue were identified in different 'Spice' samples (December 2008).
- Germany: JWH-018, CP 47,497-C8 homologue, but also the leading substance of the CP 47,497 series were identified in different 'Spice' samples (December 2008). Furthermore, JWH-073 was found by different laboratories (BKA, Bavarian Police, University of Freiburg, University of Braunschweig) in several samples of Scope Vanilla, Scope Wildberry, Scope Sex on the beach, Suncoast Herbal Teas SH, Sencation and Forest Humus (information as of 20 April 2009).
- France: four different 'Spice' products (Gold, Diamond, Arctic Synergy and Tropical Energy) were ordered directly from the Internet. All contained CP 47,497. Spice Arctic Synergy and Spice Tropical Energy were found also to contain JWH-018, vitamin E, caffeine and menthol (February 2009).
- Hungary: Spice Diamond and Spice Gold were analysed. The latter was found to contain JWH-018; the samples had a high content of chromium (February 2009).
- Poland: JWH-018 was found in the investigated products Spice Arctic Synergy, Smoke and Genie (end of January 2009).
- Slovenia: in a seizure of a cigarette with the original inscription Spice Gold, CP 47,497-C8 homologue and vitamin E were found (February 2009).
- United Kingdom: the MHRA obtained samples of Spice Gold, Spice Silver and Spice Diamond in November 2008 from a shop in Bournemouth. Later, they were found to contain JWH-018 ([13]).
- Finland: identification (not specified) in products ordered on the web or seized from incoming mail.

These data should be interpreted with caution and in the context of the analytical difficulties posed by the task of identifying synthetic cannabinoids. Forensic data are limited, in part because these substances are not controlled

([13]) In Jersey, the British Crown Dependency, JWH-018 and CP 47,497 were identified in Spice (data reported to the EMCDDA by the United Kingdom NFP on March 2009).

in most Member States and, therefore, unlikely to be submitted to forensic science services for analysis. Moreover, when analysis is conducted as a number of JWH and CP compounds exist, it is possible that laboratories will not always look for the full spectrum of substances and this may result in inconsistencies between reports.

Websites in national languages and other sources of supply

Countries were asked to provide information on national websites offering 'Spice' products but also to indicate any other sources of supply. In most cases it was reported that 'Spice' products were sold on the Internet (see Annex 2) and less frequently in head shops and in smart shops (Austria, Germany, Hungary, Ireland, Luxembourg, Lithuania, Latvia, Portugal and the United Kingdom), sex shops (Lithuania), and fuel stations (Luxembourg).

Patterns of use (user groups, settings)

Information on patterns of use was collected mostly through Internet forums, where users are sharing experiences. 'Spice' products can be smoked, sometimes together with cannabis, or consumed orally as an infusion. Spain reported that 'users recommend using pipes' while Slovakia reports that 'the fumes of the burning mixture could be inhaled'.

It was reported that 'Spice' products were generally used by teenagers and young people. Other notable issues reported by the countries are:

- cannabis users have used 'Spice' products as a substitute, to enable them to pass drug-screening tests (Germany);
- people interested in using legal biogenic ([14]) drugs are using 'Spice' (Germany);
- sensation-seekers and experimental drug users are attracted to 'Spice' by media coverage (Germany);
- 'Spice' has been reported as a problem in prisons and the probation service (Sweden).

Information on dosage, effects and reported health problems

Information reported in this area is very limited, which can be explained by the fact that 'Spice' products have arrived relatively recently on the drug market.

An article published by a German researcher (Auwärter et al., 2009) reports that the effects of 'Spice' are similar to the effects of cannabis consumption.

> To prove pharmacological activity and to gain drug positive blood and urine samples, a self-experiment was conducted by two of the authors. One cigarette containing 0.3 g of Spice Diamond was smoked and several blood and urine samples were collected. Approximately 10 minutes post application, the first noticeable effects occurred in the form of considerably reddened conjunctivae, significant increase of pulse rates, xerostomia (dry mouth) and an alteration of mood and perception. In objective psychomotor tests, no abnormalities were detected, although the subjects had the impression of being moderately impaired. The effects continued for about six hours under slow attenuation. The whole next day, some minor after-effects were still noticeable. These findings were consistent with the majority of reports available on the Internet and confirmed the presence of pharmacologically active compounds ([15]).
>
> (Auwärter et al., 2009, p. 832)

Some emergency cases were reported in Germany ('effects on the cardiovascular and nervous system like tachycardia and, in some cases, short-term loss of consciousness'). These had been reported in the mass media and via personal communication (Poison Control Centre, Mainz). Italy reported a single case of a 53-year old woman with diabetes, who smoked 'Spice' and was treated in an emergency room, one hour after consumption. She was in an excited state and in psychomotor agitation that was successfully treated with benzodiazepines. For a few hours, the patient was monitored and no alteration of vital parameters was registered. After 12 hours in an emergency room, the patient was discharged in a stable condition. In all cases, the presence of the synthetic cannabinoids was not confirmed by toxicological analysis.

During 2008, the Swedish Poison Information Centre had 51 inquiries (45 cases in total) — 40 of these cases originated from the health care system, i.e. physicians treating patients who reported use of 'Spice'. None of these cases was toxicologically confirmed.

Based on a few accounts from counselling centres in Austria, the subjective effects of 'Spice' were reported as highly variable, ranging from mild to strong, and it was reported that they could be similar to cannabis or,

([14]) Produced by living organisms or biological processes; naturally occurring.

([15]) C8 homologue of CP 47,497 was found to be the main active component of the investigated 'Spice' variants (see section 4 above).

alternatively, completely different. Similar reports from users in Romania suggested that 'Spice' tasted like herbal cannabis and the effects could be similar or even 'better'.

Specific measures to address availability and/or use of 'Spice' products

In Austria, Cyprus, Finland, Germany, France, Hungary, Italy, Lithuania, Luxembourg, Poland ('legal highs' in general), Sweden, Slovenia and the United Kingdom, the availability and use of 'Spice' products were reported to be of concern. Measures have been taken in some Member States in order to limit the availability, constrain use and avoid any potential health risks for those using the product. Eight countries (Austria, Germany, France, Luxembourg, Poland, Lithuania, Sweden and Estonia) have enacted specific legal measures (see section 7 below). In Hungary, Portugal, Slovakia and the United Kingdom, regulations are under consideration or in process or in preparation.

Additional information on 'Spice' products and/or JWH-018 reported by national informants

Experts completing the questionnaire were also asked to report any additional elements or observations that they consider useful. These are noted below.

- Austria noted that CP 47,497 and HU-210 seemed more important than JWH-018.
- Germany noted that it remained unclear how synthetic cannabinoids were added, and which was the source of the synthetic cannabinoids.
- Italy noted that JWH-018 was being researched as an analgesic to be used in transdermal patches, and that the Japan Shohin-Bonsai Association and the International Bonsai Society had certified JWH-018 as a safe fertiliser for use at bonsai plant international competitions.
- France reported that information from the French EWS suggested that the presumed target population for these drugs (mainly partygoers) showed little interest in these types of products.
- Hungary noted that an Internet site marketed 'Spice' products as coming from an eco-farm, without any chemical substances present.
- The Netherlands noted that websites selling 'Spice' products, even though they had a .nl domain, excluded the Netherlands from delivery, and consequently no consumption of 'Spice' products was reported in the country.
- The United Kingdom noted that a Google search produced over 11 million hits for Spice Gold (higher than most of the commonly used illicit drugs).

Similar products being marketed in Member States

Similar herbal products with different brand names were mentioned by Germany, Lithuania, Poland and the United Kingdom (see Annex 2). In most cases, advertising strategies for these products suggested they would create effects similar to 'Spice' products.

6. Internet information

EMCDDA Internet annual snapshot

To identify current developments in the online drug market, the EMCDDA initiated in 2008 an annual snapshot study. The snapshot was repeated in 2009 and surveyed 115 online shops based in 17 European countries. EU country code domains (e.g. United Kingdom, France, Germany) or other indications of being EU-based (e.g. contact address) were used to identify the country of origin. In 2009, the majority of online retailers identified were based in the United Kingdom (37 %), Germany (15 %), the Netherlands (14 %) and in Romania (7 %).

Among 115 investigated online shops, 48 % of the retailers based in 14 different European countries offered 'Spice' products for sale. For the majority of these, retailers were based in the United Kingdom (53 %), followed by Romania, Ireland and Latvia. 'Spice' products were no longer offered for sale in online shops based in Germany, Austria and France following legal actions to ban or otherwise control 'Spice' products.

The average Internet price of 'Spice' products varied, but was generally between EUR 20 and EUR 30 per 3 g package, depending on the country and the 'strength' of the product. Provided that one 3 g package is sufficient for seven 'joints' (0.4 g per joint), the price is roughly comparable to that of cannabis in Europe, i.e. approximately EUR 3–4 per joint.

Compared to 2008, a greater range of alternative smoking blends to 'Spice' was being advertised by retailers. A total of 27 different herbal smoking blends were identified across all investigated retailers (e.g. Yucatan Fire, Sence, Genie). They were advertised as containing plant-based ingredients, however, according to retailer-supplied information; some also contain the hallucinogenic mushroom Amanita muscaria (e.g. Pep Spice Twisted).

Among the alternatives offered for sale in Austria and Germany were herbal smoking blends such as Space, Scope, Relax and Bull Titan, sold as room odourisers (incense).

The EU Psychonaut web-mapping project

Since 2007, the EU Psychonaut web-mapping project ([16]) has recorded a rapid diffusion of 'Spice' products over the Internet. More specifically, Google Insights shows that a substantial amount of searches were conducted on 'Spice' products from the end of 2004. However, these increased exponentially in the second part of 2008, presumably as media reports of the drug raised awareness. The majority of the searches for Spice Gold, for instance, came from the Russian Federation, followed by Austria, Sweden, Hungary, Poland, Germany and the United Kingdom. Interestingly, these searches were also linked with key words such as: 'spice gold shop', 'spice gold buy' and 'spice gold smoke'.

7. Control measures

Neither the purported herbal ingredients of 'Spice' and 'Spice'-like products, nor any of the synthetic cannabinoids found in them are internationally controlled under the 1961 or 1971 UN drug control conventions (Single Convention on Narcotic Drugs, 1961; Convention on Psychotropic Substances, 1971). The individual herbal ingredients of 'Spice' products do not seem to be controlled under drugs control legislation (i.e. national legislation implementing the 1961 and 1971 UN conventions) in any of the European Union Member States, except in Poland (see below). Responding to potential health concerns, Austria, Germany, France, Luxembourg, Poland, Lithuania, Sweden and Estonia have recently taken legal actions to ban or otherwise control 'Spice' products and related compounds.

In Austria, a decree under the Pharmaceutical Law (Federal Gazette II No 6/2009 of 7 January 2009) declares that 'smoking mixes containing JWH-018' are prohibited from being imported or marketed in the country. The identification of CP 47,497, its homologues CP 47,497-C6-homologue, CP 47,497-C8-homologue, CP 47,497-C9-homologue and HU-210 led to further amendment of the Pharmaceutical Law, and the Decree published in the Federal Gazette II No 6/2009 of 3 March 2009 prohibits the sale and import of products containing these substances. The Austrian authorities continue to monitor and review the situation in order to decide whether control is required under its Narcotic Drugs Law.

In Germany, following a rapid control under the Pharmaceutical Law, an emergency regulation in effect from 22 January 2009 brought three cannabinoids found in 'Spice' products and two pharmacologically active homologues under Annex II of the Narcotic Drugs Law. These include JWH-018, CP 47,497 and its three homologues (for comparison, also listed in this table are THC and 1-benzylpiperazine — BZP). Unauthorised sale and marketing, production, acquisition and possession of these active agents in any form are therefore illegal. This fast-track regulation is valid for one year; during this time, the German government may pass a standard regulation to bring the substance permanently under control.

Following a scheduling proposal by the Narcotics and Psychotropics National Commission (CNSP) of 19 February 2009, on 24 February the French Minister of Health and Sports classified six synthetic cannabinoids as narcotics in Annexe IV of the Arrêté of 22 February 1990. These are JWH-018, CP 47,497 and its three homologues that were found in 'Spice' products in France as well as HU-210.

By a decree on Amendment of Regulation on Psychotropics signed on 20 April 2009, Luxembourg added as of 4 May 2009, CP 47,497, JWH-018 and HU-210 and other 'synthetic agonists of cannabinoid receptors or synthetic cannabinomimetics' to the list of psychotropic substances subject to the national drug control legislation.

The Polish Parliament adopted the Act of law amending the Act on Counteracting Drug Addiction on 20 March 2009 (Dz.UNr 63 z 23 kwietnia 2009/pozycja Nr 520), which entered into force on 8 May 2009. According to this act, JWH-018 and some of the claimed herbal ingredients of 'Spice', such as *Leonotis leonurus* and *Nymphaea caerulea*, were put on the list of controlled substances.

In Lithuania, JWH-018, JWH-073, HU-210, CP-47,497 and homologues were added to the first schedule of plants, narcotic and psychotropic substances, by a decree of the Health Ministry that entered into force as of 27 May 2009.

The Swedish government classified seven synthetic cannabinoids (CP 47,497, and its C6, C8, and C9 homologues, JWH-018, JWH-073 and HU-210) as narcotics in the law 1992:1554. The Government decision was made on 30 July 2009 and this entered into force on 15 September 2009.

In Estonia, from 24 July 2009, the following synthetic cannabinoids are controlled by the Narcotic Drugs and Psychotropic Substances Act: CP 47,497, and its C6, C8, and C9 homologues, HU-210 and JWH-018.

([16]) The Commission-funded Psychonaut web-mapping project continuously monitors the web for novel compounds, using nine languages, with the support of different tools/software (e.g. Google Insights, Blue Crab, Boolean Search, InSite, Advanced Web Ranking and SerpSpy). The project monitors regularly more than 200 websites, forums and blogs that provide information on many compounds.

On 12 August 2009 the Advisory Council on the Misuse of Drugs (ACMD) advised the United Kingdom government to classify and control a broad range of synthetic cannabinoids by the Misuse of Drugs Act (1971) (Advisory Council on the Misuse of Drugs, 2009). The recommendation proposed the cannabinoids to be brought under control by means of generic definitions, in order to cover the products that are, or could in the future, be used in preparations. Five substances were named for specific control: HU-210, WIN-55, 212-2, HU-243 and CP 50,5561. These five and the generically defined substances should be placed under Schedule 1, while Nabilone (a component of the existing medicinal product Cesamet®) should be placed under Schedule 2 of the Misuse of Drugs Regulations (2001).

In Hungary, a formal decision of 9 March 2009 (OTH 233-10/2009 and KNRI 3991-3/2009) of the Regional Chief Medical Officer on behalf of the Central Hungarian Regional Institute of National Public Health and Medical Officer's Service, prohibits the distribution of herbal mixtures named as Spice Gold, Spice Diamond and Sence and any other products containing the same herbal mixture. The decision is not an overall prohibition of the distribution of 'Spice' products, but solely applies to a specific distributor. Furthermore, Hungary reported that it is working on the suppression of distribution of 'Spice' ingredients that are listed as plants not allowed for food supplements. Two ingredients of 'Spice' (*Nelumbo nucifera* and *Nymphaea alba*) are already listed in an annex of a regulation controlling plants and parts of plants not recommended for use as food supplements.

8. Conclusions

The appearance of various 'herbal highs' — herbal mixtures whose contents may vary from innocuous, non-psychoactive vegetable matter to synthetic chemicals with marked psychoactive properties poses a range of difficult questions for drug policy. These range from the conceptual — how to define which products are of interest, given that the wide variety of 'Spice' and 'Spice'-like products and herbal mixtures are sold for many reasons, including alternative health remedies, and as foodstuffs — to the practical and methodological — how to monitor the products sold, identify the synthetic compounds that they may contain and assess their health risks.

'Spice' and other 'herbal' products are often referred to as 'legal highs' or 'herbal highs', in reference to their legal status and purported natural herbal make-up (McLachlan, 2009; Lindigkeit et al., 2009; Zimmermann et al., 2009). However, albeit not controlled, it appears that most of the ingredients listed on the packaging are actually not present in the 'Spice' products and it is seems likely that the psychoactive effects reported are most probably due to added synthetic cannabinoids, which are not shown on the label. There is no evidence that JWH, CP and/or HU compounds are present in all 'Spice' products or even batches of the same product. Different amounts or combinations of these substances seem to have been used in different 'Spice' products to produce cannabis-like effects. It is possible that substances from these or other chemical groups with a cannabinoid agonist or other pharmacological activity could be added to any herbal mixture ([17]) (Griffiths et al., 2009).

The emergence of new, smokable herbal products laced with synthetic cannabinoids can also be seen as a significant new development in the field of so-called 'designer drugs'. With the appearance, for the first time, of new synthetic cannabinoids, it can be anticipated that the concept of 'designer drugs' being almost exclusively linked to the large series of compounds with phenethylamine and tryptamine nucleus will change significantly ([18]). There are more than 100 known compounds with cannabinoid receptor activity and it can be assumed that further such substances from different chemical groups will appear (with direct or indirect stimulation of CB_1 receptors). So far, the 'Spice' and 'Spice'-like preparations in Europe have been found to contain at least nine new substances from three chemically distinct groups of synthetic cannabinoids (JWH, CP and HU), plus a fatty acid amide with cannabinoid-like activity (oleamide). This presents an ongoing challenge, not only for their forensic and toxicological identification, but also for risk assessment and the development of possible control strategies.

At present, almost nothing is known about the pharmacology, toxicology and safety profile of such compounds in humans. However, since the type and amount of added synthetic cannabinoids may vary considerably and some of the compounds may be active in very small doses, the possibility of accidental overdosing with a risk of severe psychiatric complications cannot be excluded. Furthermore, the appearance of full CB receptor agonists could potentially lead to life-threatening conditions in the case of overdose.

([17]) For example, in February 2009, the Austrian Federal Ministry of Health analysed a sample of Highdi´s Almdröhner leading to identification of mitragynin (the main psychoactive alkaloid of the plant Kratom). Similarly, in June 2009, a metabolite of the synthetic opioid analgesic Tramadol was found by German researchers in an incense preparation called 'Krypton', advertised as a Kratom-based product.
Kratom is controlled in several south-east Asian states, but in the EU only Lithuania, Denmark and Latvia control both the plant and its main psychoactive principle.

([18]) Phenethylamines are also referred to as amphetamine type stimulants — a group that includes amphetamines and ecstasy drugs (MDMA and its congeners); the tryptamine group includes drugs like psilocin, DMT and DET.

Media information suggests that some 'Spice' products may have been produced in Asia (e.g. China), whereas the synthetic cannabinoids may have been produced in various countries that offer cheap organic syntheses. However, it remains unclear where and how the actual production of the herbal mixtures, the synthetic cannabinoids and their addition to the herbal mixtures takes place. In terms of detecting the availability of new synthetic drugs, the 'Spice' phenomenon serves as a useful example of how these developments can be difficult to detect. First, because 'Spice' was sold as a commodity only available through the Internet, or in specialised shops, rather than through clandestine production and illegal circulation, this did not generate seizures or indicate criminality that might have prompted the interest and involvement of specialised law enforcement agencies. Second, the limited knowledge about the chemistry and effects of the new compounds contributed to the creation of a 'grey zone' where the potentially responsible institutions (public health authorities or the competent authorities for medicinal products) did not assume immediate responsibility. A question for the future is what sort of mechanisms are appropriate to monitoring the appearance of products such as 'Spice' and accessing their possible impact? It appears likely that if such developments are to be detected at an early stage, a more proactive strategy may be necessary.

In many countries where 'Spice' and related substances are available, they have now become a concern. Various national control measures have been implemented in Austria, Germany, France, Luxembourg, Poland, Lithuania, Sweden and Estonia and are under consideration in other Member States. Nevertheless, the sheer number of potentially psychoactive synthetic cannabinoids means that control measures targeting individual chemicals can easily be circumnavigated. Therefore, it may be useful to consider experiences from Member States where a more generic approach to controlling drugs exists. Furthermore, even if control legislation is adopted, the unavailability of analytical data and reference samples, as well as methodologies for toxicological identification of metabolites in urine, are likely to pose challenges to the effective implementation of control measures.

The extent to which 'Spice' products are used in Europe is unknown, and the users seem to be a heterogeneous group. They may include those wanting a legal alternative to illegal drugs, or drug users wishing to pass successfully an employment/other drug testing procedure aimed at detecting illicit drug use. This may be an important issue for any setting where drug abstinence control is obligatory (e.g. specific psychiatry or prison settings, driving liability testing, etc.). In general, it can be argued that legally available substances that can be legitimately promoted may have a greater potential for diffusion than controlled substances, especially if the price is comparable and they deliver similar effects. However, to date as far as we can tell, the substances JWH-018, JWH-073, JWH-398, JWH-250, CP 47,497 and its C6, C8 and C9 homologues, and HU-210 have not been widely used as psychoactive drugs in their own rights, but have been surreptitiously added to 'Spice' products, which have been misrepresented as herbal products. Therefore, it remains an open question if there is, or will be, a wider, specific demand for any of these particular substances. With this in mind, the need for further action as stipulated by Council Decision 2005/387/JHA (Council Decision, 2005) remains an option for future review. The EWS will remain vigilant in this respect, as various new ('Spice' or 'Spice'-like) herbal products with different packaging and names appear to be continuously appearing. This, together with the variety and number of synthetic cannabinoids (or other substances) that could be potentially added to the herbal products, continues to pose challenges for identification, monitoring and risk appraisal of the phenomenon.

Acknowledgements

Authors: Roumen Sedefov (EMCDDA), Ana Gallegos (EMCDDA), Les King (United Kingdom Reitox national focal point, Department of Health, United Kingdom), Dominique Lopez (EMCDDA), Volker Auwärter (University Medical Centre Freiburg, Institute of Forensic Medicine, Germany), Brendan Hughes (EMCDDA) and Paul Griffiths (EMCDDA).

The EMCDDA would like to thank the following for their help and for participating in the EMCDDA expert meeting '"Spice" and related synthetic cannabinoids', organised on 6 March 2009, in Lisbon:

- Reitox national focal points, and specifically their early-warning systems;
- Johanna Schopper (Bundesministerium für Gesundheit — Leiterin der Abteilung III/B/6 (Drogen und Suchtmittel), Austria);
- Michel Mallaret (Centre d'Evaluation et d'Information sur les Pharmacodépendances — CHU de Grenoble, France);
- Ingo Michels (Office of the Federal Drug Commissioner — Federal Ministry of Health (Bundesministerium für Gesundheit), Germany);
- Wim Best (Health Care Inspectorate, the Netherlands);
- István Ujváry (iKem BT, Hungary);
- Paolo Deluca (Web Mapping Project, National Addiction Centre, Institute of Psychiatry — King's College London);

- Andrew Jack (*Financial Times*);
- Florence Butlen and Sahid Hocine (European Medicines Agency);
- Michael Farrell (Chairman of the EMCDDA Scientific Committee, National Addiction Centre — Kings College London);
- EMCDDA colleagues Jennifer Hillebrand, Roland Simon and Anabela Almeida.

References

Advisory Council on the Misuse of Drugs (2009), 'Consideration of the major cannabinoid agonists. Available at: http://drugs.homeoffice.gov.uk/drugs-laws/acmd/.

Aung.,M. M., Griffin, G., Huffman, J. W., et al. (2000), 'Influence of the N-1 alkyl chain length of cannabimimetic indoles upon CB_1 and CB_2 receptor binding', *Drug and Alcohol Dependence* 60, pp. 133–140.

Auwärter, V., Dresen, S., Weinmann, W., et al. (2009), 'Spice and other herbal blends: harmless incense or cannabinoid designer drugs?' *Journal of Mass Spectrometry* 44 (5), pp. 832–837.

Chin, C., Murphy, J. W., Huffman, J. W. and Kendall, D. A. (1999), 'The third transmembrane helix of the cannabinoid receptor plays a role in the selectivity of aminoalkylindoles for CB_2, peripheral cannabinoid receptor', *The Journal of Pharmacology and Experimental Therapeutics* 291 (2), pp. 837–844.

Compton, D. R., Johnson, M. R., Melvin, L. S. and Martin, B. R. (1992) 'Pharmacological profile of a series of bicyclic cannabinoid analogs: classification as cannabimimetic agents', *Journal of Pharmacology and Experimental Therapeutics* 260 (1), pp. 201–209.

Compton, D. R., Rice, K. C., de Costa, B. R., et al. (1993), 'Cannabinoid structure-activity relationships: correlation of receptor binding and in vivo activities', *Journal of Pharmacology and Experimental Therapeutics* 265 (1), pp. 218–226.

Convention on Psychotropic Substances (1971), United Nations.

Council Decision (2005), 'Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk-assessment and control of new psychoactive substances', *Official Journal of the European Union* 127, pp. 32–37, 20.5.2005.

DEA (US Drugs Enforcement Administration) (2009), *Microgram Bulletin*, 42 (3).

European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (2007), *Early-warning system on new psychoactive substances — Operating guidelines*, European Monitoring Centre for Drugs and Drug Addiction, Lisbon.

EMCDDA Drug profile on synthetic cannabinoids. Available at: http://www.emcdda.europa.eu/publications/drug-profiles

Glass, M. and Northup, J. K. (1999), 'Agonist selective regulation of G proteins by cannabinoid CB_1 and CB_2 receptors', *Molecular Pharmacology* 56, pp. 1362–1369.

Griffiths, P., Sedefov, R., Gallegos, A. and Lopez, D. (2009), 'How globalisation and market innovation challenge how we think about and respond to drug use: "Spice" — a case study', *Addiction*, submitted.

Howlett, A. C., Barth, F., Bonner, T. I., et al. (2002), 'International union of pharmacology. XXVII. Classification of cannabinoid receptors', *Pharmacological Reviews* 54 (2), pp. 161–202.

Huffman, J. W. (2009), 'Cannabimimetic indoles, pyrroles, and indenes: structure-activity relationships and receptor interactions', in Reggio, P. H. (ed.), *The cannabinoid receptors*, Humana Press, Totowa, NJ.

Huffman, J. W., Mabon, R., Wu, M.-J., et al. (2003), '3-Indolyl-1-naphthylmethanes: new cannabimimetic indoles provide evidence for aromatic stacking interactions with the CB_1 cannabinoid receptor', *Bioorganic and Medicinal Chemistry* 11, pp. 539–549.

Huffman, J. W., Thompson, A. L. S., Wiley, J. L. and Martin, B. R. (2008), 'Synthesis and pharmacology of 1-Deoxy Analogs of CP-47,497 and CP-55,940', *Bioorganic and Medicinal Chemistry* 16 (1), pp. 322–335.

Huffman, J. W., Zengin, G., Wu, M. J., et al. (2005), 'Structure-activity relationships for 1-alkyl-3-(1-naphthoyl)indoles at the cannabinoid CB_1 and CB_2 receptors: steric and electronic effects of naphthoyl substituents. New highly selective CB_2 receptor agonists', *Bioorganic and Medicinal Chemistry* 13, pp. 89–112.

Jiang, W., Zhang, Y., Xiao ,L., et al. (2005), 'Cannabinoids promote embryonic and adult hippocampus neurogenesis and produce anxiolytic- and antidepressant-like effects', *The Journal of Clinical Investigation* 115 (11), pp. 3104–3116.

Lambert, D. and Di Marzo, V. (1999), 'The Palmitoylethanolamide and oleamide enigmas: are these two fatty acid amides cannabimimetic?', *Current Medicinal Chemistry* 6, pp. 757–773.

Leggett, J. D., Aspley, S., Beckett, S. R. G., et al. (2004), 'Oleamide is a selective endogenous agonist of rat and human CB_1 canabinoid receptors', *British Journal of Pharmacology* 141, pp. 253–262.

Lindigkeit, R., Boehme, A., Eiserloh, I., et al. (2009), 'Spice: a never ending story?', *Forensic Science International* 191 (1–3), pp. 58–63.

McLachlan, G. (2009), 'Taking the spice out of legal smoking mixtures', *The Lancet* 374, p. 600.

Mechoulam, R., Feigenbaum, J. J., Lander, N., et al. (1988), 'Enantiomeric cannabinoids: stereospecificity of psychotropic activity', *Experientia* 44, pp. 762–764.
Ottani, A. and Giuliani, D. (2001), 'HU 210: a potent tool for investigations of the cannabinoid system', *CNS Drug Reviews* 7 (2), pp. 131–145.
Pertwee, R. G. (2005), 'The therapeutic potential of drugs that target cannabinoid receptors or modulate the tissue levels or actions of endocannabinoids', *The AAPS Journal* 7 (3), Article 64, E625–E654.
Single Convention on Narcotic Drugs (1961), 'Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol amending the Single Convention on Narcotic Drugs, 1961', United Nations.
Steup, C. (2008), 'Untersuchung des Handelsproduktes "Spice"', THC Pharm GmbH, 30 December 2008.
Uchiyama, N., Kikura-Hanajiri, R., Kawahara, N. and Goda, Y. (2009), 'Identification of a cannabimimetic indole as a designer drug in a herbal product', *Forensic Toxicology* 27, 61–66.
Vann, R. E., Warner, J. A., Bushell, K., et al. (2009), 'Discriminative stimulus properties of Δ^9-tetrahydrocannabinol (THC) in C57BL/6J mice', *European Journal of Pharmacology* 615 (1–3), pp. 102–107.
Weissman, A., Milne, G. M. and Melvin, L. S., Jr. (1982), 'Cannabimimetic activity from CP-47,497, a derivative of 3-phenylcyclohexanol', *Journal of Pharmacology and Experimental Therapeutics* 223 (2), pp. 516–523.
Wiley, J.L., Compton, D.R., Dai, D., et al. (1998), 'Structure-activity relationships of indole- and pyrrole-derived cannabinoids', *The Journal of Pharmacology and Experimental Therapeutics* 285 (3), pp. 995–1004.
Zimmermann, U. S., Winkelmann, P.R., Pilhatsch, M., et al. (2009), 'Withdrawal phenomena and dependence syndrome after the consumption of "Spice Gold"', *Deutsches Aerzteblatt International* 106 (27), pp. 464–467.

Legal notice

This report is based on the contribution of the Reitox early-warning system and the results of the EMCDDA expert meeting 'Spice and related synthetic cannabinoids', which took place on 6 March 2009 in Lisbon. The original version of the report has been updated on a regular basis, following the identification of new substances and implemented control measures.

This paper has no legal meaning under the terms of Council Decision 2005/387/JHA.

Cais do Sodré, 1249-289 Lisbon, Portugal
Tel. (351) 211 21 02 00 • Fax (351) 218 13 17 11
info@emcdda.europa.eu
http://www.emcdda.europa.eu

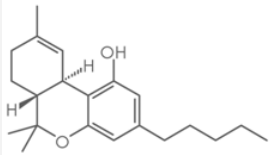
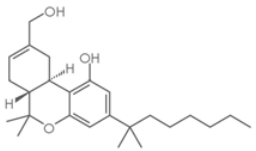
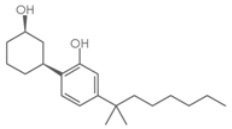
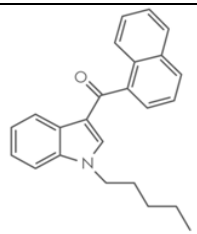
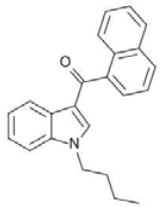
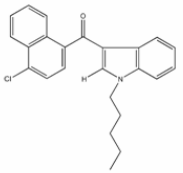
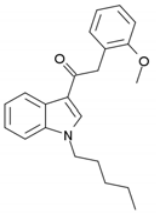
This publication is available in English. Cataloguing data can be found below. Reproduction is authorised provided the source is acknowledged.

Cataloguing data

European Monitoring Centre for Drugs and Drug Addiction
EMCDDA 2009 Thematic paper — Understanding the 'Spice' phenomenon
Luxembourg: Office for Official Publications of the European Communities
2009 — 37 pp. — 21 x 29.7 cm
ISBN 978-92-9168-411-3
doi: 10.2810/27063

Toxichem Krimtech 2010;77(1):42

Annex 1
Δ^9-THC and six synthetic cannabinoids with high affinity for cannabinoid (CB_1) receptors found in 'Spice' products

	Δ^9-THC	HU-210	CP 47,497	JWH-018	JWH-073	JWH-398	JWH-250
Family/group	Naturally occurring dibenzopyran	'Classical' cannabinoid (dibenzopyran)	Cyclohexylphenol	Naphthoylindole	Naphthoylindole	Naphthoylindole	Phenylacetylindole/ benzoylindole
Subgroup	Tricyclic terpenoid derivative with a dibenzopyran ring	Δ^9-THC analog	AC-bicyclic cyclohexylphenol	1-alkyl-3-(1-naphthoyl)indole	- 1-alkyl-3-(1-naphthoyl)indole	3-(4-halo-1-naphthoyl)indole	1-pentyl-3-phenylacetylindole
Structure							
Potency and selectivity	Reference. Partial agonist at CB_1	Full non-selective agonist at CB_1/CB_2	Potent selective CB_1 agonist	Very potent selective CB_2 agonist (also potent CB_1 agonist)	Potent selective CB_1 agonist (also weaker CB_2 agonist)	Very potent non-selective CB_1/CB_2 agonist	Potent selective CB_1 agonist (also weaker CB_2 agonist)
Binding affinity for CB_1 _ Ki [nM] (Advisory Council on the Misuse of Drugs, 2009)	**10.2** (Advisory Council on the Misuse of Drugs, 2009)	**0.06** (Howlett et al., 2002)	**9.54** (Auwärter et al., 2009)	**9** (Huffman, 2009; Huffman et al., 2003)	**8.9** (Huffman, 2009; Huffman et al., 2003)	**2.3** (Huffman, 2009)	**11** (Huffman, 2009)
Synthesised by	Naturally occurring phytochemical	R. Mechoulam	Pfizer	J. W. Huffman	J. W. Huffman	J. W. Huffman	J. W. Huffman
First notified by	N/A	United Kingdom	Germany	Austria	Netherlands	United Kingdom	Germany
Control measures (as of 9/10/2009)	Internationally controlled	Austria, Estonia, France, Lithuania, Luxembourg, Sweden	Austria, Estonia, France, Germany, Lithuania, Luxembourg, Sweden	Austria, Estonia, France, Germany, Lithuania, Luxembourg, Poland, Sweden	Lithuania, Luxembourg, Sweden	—	—

Annex 2
List of additional names and national websites collected through the questionnaire on 'Spice' products

Country	Additional names	List website
Belgium		http://www.cannaclopedia.be/ (not for supply)
Czech Republic		http://www.spiceceska.com/
Germany		http://www.spice-store.de/ (Spice is no longer available) http://smoketown-headshop.de/ (Spice is no longer available) http://www.spice-nice.de/ (Spice is no longer available) http://www.udopea.de/ (Spice is no longer available) http://www.jsy-store.de (Spice is no longer available) http://www.smoketime.de (Spice is no longer available) http://www.spiceladen.de/ (all products are JWH-018 free) http://www.hanf-hanf.at (Spice is no longer available)
Ireland	Smoke, Sence and Chill X	http://www.nirvanaheadshop.com/ http://www.irishheadstores.com/
Spain	2Spicy, Algerian Blend	www.spice-gold.eu/ES/spice_introduction_ES.html www.sjamaan.com/es/index.html www.cahuinadencul.com.ar www.psicoactivo.cl/index.php www.azarius.es www.laplantamagica.com www.grasscity.com/is-bin/INTERSHOP.enfinity/WFS/SJV-Grasscity-Site
France	Yucatan Fire, Mojo,Sence, Genie	http://www.biosmoke.com/ http://buythemg.com/
Italy		http://www.sjamaan.com/it/0155_Spice_Gold_-_3_gr_-_10_unita.html http://www.narghile.it/spice_gold.htm http://www.grasscity.com/is-bin/INTERSHOP.enfinity/WFS/SJV-Grasscity-Site/it_IT/-/USD/ViewStandardCatalog-Browse?CatalogCategoryID=3.fAqAHAi6YAAAETFqcdTLpm http://www.spice-gold.eu/IT/spice_background_IT.html http://italian.alibaba.com/search/indole-1.html http://moksha.splinder.com/post/19371311/JWH-018:+ingrediente+attivo+de
Latvia	Sence, Smoke, Yucatan Fire, Genie Incense, Majo, Morning Glory (Ipomea). Also possible to buy Kratom, Salvia and Poppers	www.bongs.lv www.spais.lv www.happyfaces.lv
Lithuania	Yukatan Fire, Genie, Spice Gold Joint, Algerian Blend, Blue Lotus, Chacruna, Jurema, Ourinhos, Marshmallow, Anadenathera Colubrina, Damiana, Calea, Wild Dagga, Sincuichi, Aphrodisia, Ice Bud, Smoke, Ex-ses Gold, Ex-ses Platinum, Cahoots, Chill, Ignite, Red Ball, Vortex, Dream, Zohai RX, Spike 99 Ultra, Spike 99 — herbal mixes for smoking; Snow Blow, Charge, Blow Out, Snow Berry — herbal mixes for snuff	www.buzas.lt www.headshop.lt www.laimeskrautuve.lt www.rastashop.lt www.amsterdamas.eu spicegold.biz herbalking.tk.
Hungary	Yucatan Fire, Sence	www.zolderdo.hu http://www.greenshop.hu/
Netherlands		www.consiousdreams.nl www.desjamaan.nl
Poland	Smoke: Scullcap extract, Kanna extract, Blue Lotus extract, Kratom leaves, Wild Dagga extract, Mexican Tarragon extract, Red Raspberry Leaf, Dream Herb extract, *Verbascum Thapsis, Leonurus Sibiricus* extract, Jasmine Flower… Sence: Scullcap extract, Kanna extract, Blue Lotus extract, Kratom leaves, Wild Dagga extract, Mexican Tarragon extract, Red Raspberry Leaf, Dream Herb extract,	www.dopalacze.com http://www.smartszop.pl/ www.legalfun.pl www.seed.pl

	Verbascum Thapsis, *Leonurus Sibiricus* extract, Jasmine Flower… Ex-ses: Baybean (Canavalia martima), Blue Lotus (*Nymphaea caeulea and Nymphaea alba*), Indian Warrior (*Pedicularis densiflora*), Maconha Brava (*Zornia latifolia*), Damiana (*Turnera aphrodisiaca*), Marshmallow (Althaea officinalis)… Dream: Baybean — *Canavalia maritima*, Blue Lotus — *Nymphaea caerulea* and *Nymphaea alba*, Dwarf scullcap — Scuttelaria *nana*, Indian Warrior — *Pedicularis densiflora*, Lion\'s Tail — *Leonotis leonurus*, Maconha Brava — *Zornia latifolia*, Pink Lotus — Nelumbo nucifera, Siberian Motherwort — *Leonurus sibiricus*	
Romania	products labelled as being of 'herbal origin' — Skunk, Genie, Ice, Spike, etc.	www.spiceblend.ro www.etnoplant.ro www.spiceshoponline.ro www.spicegold.ro www.spice-gold.ro espice.ro www.magic-ro.com www.ihigh.ro www.etnotrip.ro
Slovenia		www.marlek.si www.cannajoy.com www.headshop.si www.kanabis.org (in croatia)
Slovakia		http://www.spice-shop.sk/ http://www.spice-shop.k/spice-incense-online-shop http://www.spice-shop.sk/spice-zlozenie http://www.champlegals.co.uk/showthread.php?t=8075&page=2 http://www.cannabisculture.com/v2/node/16909 http://www.tradekey.com/product_view/id/811392.htm http://www.erowid.org/chemicals/spice_product/
Finland	Yukatan Fire. Dream, Sence and Smoke	
Sweden	Mojo, Genie and Zohaii	http://www.spicenordic.com/index.php http://www.prylshoppen.se/index.php
Croatia		http://www.kanabis.org http://vutra.org/

Annex 3
Selected scientific articles

Bertol, E., Fineschi, V., Karch, S. B., Mari, F. and Riezzo, I. (2004), 'Nymphaea cults in ancient Egypt and the New World: a lesson in empirical pharmacology', *Journal of the Royal Society of Medicine* 97, pp. 84–85.
Choo, T. P., Lee, C. K., Low, K. S. and Hishamuddin, O. (2006), 'Accumulation of chromium (VI) from aqueous solutions using water lilies (*Nymphaea spontanea*)', *Chemosphere* 62, pp. 961–967.
Cravatt, B., Prospero-Garcia, O., Siuzdak, G., et al. (1995), 'Chemical characterisation of a family of brain lipids that induce sleep', *Science* 268, pp. 1506–1509.
Dai, S. J., Liang, D. D., Ren, Y., Liu, K. and Shen, L. (2008), 'New neo-Clerodane Diterpenoid alkaloids from *Scutellaria barbata* with Cytotoxic activities', *Chemical and Pharmaceutical Bulletin* 56(2), pp. 207–209.
Damodaran, M. and Narayanan, K. G. A. (1939), 'CCXVI. The preparation of canavanine from *canavalia obtusifolia*', *Biochemistry* 33, pp. 1740–1742.
De Vry, J., Denzer, D., Reissmueller, E., et al. (2004), '3-[2-Cyano-3-(trifluoromethyl)phenoxy]phenyl-4,4,4-trifluoro-1-butanesulfonate (BAY 59-3074): a novel cannabinoid CB_1/CB_2 receptor partial agonist with antihyperalgesic and antiallodynic effects', *The Journal of Pharmacology and Experimental Therapeutics* 310, pp. 620–632.
De Vry, J., Jentzsch, K. R. (2004), 'Discriminative stimulus effects of the structurally novel cannabinoid CB_1/CB_2 receptor partial agonist BAY 59-3074 in the rat', *European Journal of Pharmacology* 505, pp. 127–133.
Di Marzo, V., Sepe, N., De Petrocellis, L., et al. (1998), 'Trick or treat from food endocannabinoids?' *Nature* 396, pp. 636–637.

Dziadulewicz, E. K., Bevan, S. J., Brain, C. T., et al. (2007), 'Naphthalen-1-yl-(4-pentyloxynaphthalen-1-yl)methanone: a potent, orally bioavailable human CB_1/CB_2 dual agonist with antihyperalgesic properties and restricted central nervous system penetration', *Journal of Medicinal Chemistry* 50, pp. 3851–3856.
Gertsch, J., Leonti, M., Raduner, S., et al. (2008), 'Beta-caryophyllene is a dietary cannabinoid', *Proceedings of the National Academy of Sciences* 105 (26), pp. 9099–9104.
Hosking, R. D. and Zajicek, J. P. (2008), 'Therapeutic potential of cannabis in pain medicine', *British Journal of Anaesthesia* 101 (1), 59–68.
Huffman, J. W. and Duncan, S. G. (1997), 'Synthesis and pharmacology of the 1',2'-dimethylheptyl- Δ^8-THC isomers: exceptionally potent cannabinoids', *Bioorganic and Medicinal Chemistry Letters* 7 (21), pp. 2799–2804.
Huffman, J. W., Szklennik, P. V., Almond, A., et al. (2005), '1-Pentyl-3-phenylacetylindoles: a new class of cannabimimetic indoles', *Bioorganic and Medicinal Chemistry Letters* 15, pp. 4110–4113.
Khanolkar, A. D., Palmer, S. L. and Makriyanniset, A. (2000), 'Molecular probes for the cannabinoid receptors', *Chemistry and Physics of Lipids* 108, pp. 37–52.
Kubota, S. and Nakashima, S. (1930), 'The study of *leonurus sibiricus*, L. I.Chemical study of the alkaloid "leonurin" isolated from *leonurus sibiricus* L.', *Yakugaku Zasshi* 11 (2), pp. 153–158.
Kubota, S. and Nakashima, S. (1930), 'The study of *leonurus sibericus* L. II. Pharmacological study of the alkaloid "leonurin" isolated from *leonurus sibericus* L.', *Yakugaku Zasshi* 11 (2), pp. 159–167.
Lavid, N., Barkay, Z. and Tel-Or, E. (2001), 'Accumulation of heavy metals in epidermal glands of the waterlily (*Nymphaeaceae*)', *Planta* 212, pp. 313–322.
Mackie, K. (2007), 'Understanding cannabinoid psychoactivity with mouse genetic models', *PLoS Biology* 5(10), p. e280.
Marquina, S., Bonilla-Barbosa, J. and Alvarez, L. (2005), 'Comparative phytochemical analysis of four Mexican *Nymphaea* species', *Phytochemistry* 66, pp. 921–927.
Mauler, F., Mittendorf, J., Horváth, E., De Vry, J. (2002) 'Characterization of the diarylether sulfonylester (-)-(R)-3-(2-Hydroxymethylindanyl-4-oxy)phenyl-4,4,4-trifluoro-1-sulfonate (BAY 38-7271) as a potent cannabinoid receptor agonist with neuroprotective properties', *Journal of Pharmacology and Experimental Therapeutics* 302, pp. 359–368.
Mc Donald, G. R., Hudson, A. L., Dunn, S. M. J. et al. (2008), 'Bioactive contaminants leach from disposable laboratory plasticware', *Science* 322, p. 7.
Padgett, L. W. (2005), 'Recent developments in cannabinoid ligands', *Life Sciences* 77, pp. 1767–1798.
Palmer, S. L., Thakur, G. A., Makriyannis, A. (2002) 'Cannabinergic ligands', *Chemistry and Physics of Lipids* 121, pp. 3-19.
Park, H. G., Yoon, S. Y., Choi, J. Y., et al. (2007), 'Anticonvulsant effect of wogonin isolated from *Scutellaria baicalensis*', *European Journal of Pharmacology* 574, pp. 112–119.
Pertwee, R. G. (2006), 'Cannabinoid pharmacology: the first 66 years', *British Journal of Pharmacology* 147, S163–S171.
Pertwee, R. G. (2005), 'Pharmacological actions of cannabinoids', in Pertwee, R. (ed.), *Cannabinoids*, Springer, Berlin.
Piggee, C. (2009), 'Investigating a not-so-natural high', *Analytical Chemistry* 81 (9), pp. 3205–3207.
Samecka-Cymerman, A. and Kempers, A.J. (2001), 'Concentrations of heavy metals and plant nutrients in water, sediments and aquatic macrophytes of anthropogenic lakes (former open cut brown coal mines) differing in stage of acidification', *The Science of the Total Environment* 281, pp. 87–98.
Satoh, M., Satoh, Y., Isobe, K. and Fujimoto, Y. (2003), 'Studies on the constituents of Leonurus sibiricus L.', *Chemical and Pharmaceutical Bulletin* 51 (3), pp. 341–342.
Stafford, G. I., Pedersen, M. E., van Staden, J. and Jäger, A. K. (2008), 'Review on plants with CNS-effects used in traditional South African medicine against mental diseases', *Journal of Ethnopharmacology* 119, pp. 513–537.
Sugimoto, Y., Furutani, S., Itoh, A., et al. (2008), 'Effects of extracts and neferine from the embryo of *Nelumbo nucifera* seeds on the central nervous system', *Phytomedicine* 15, pp. 1117–1124.
Thakur, G. A., Duclos, R. I. and Makriyannis, A. (2005), 'Natural cannabinoids: templates for drug discovery', *Life Sciences* 78, pp. 454–466.
Tytgat, J., Van Boven, M. and Daenens, P. (2000), 'Cannabinoid mimics in chocolate utilised as an argument in court', *International Journal of Legal Medicine* 113, pp. 137–139.
Uchiyama, N., Kikura-Hanajiri, R., Kawahara, N., Haishima, Y. and Goda, Y. (2009), 'Identification of a cannabinoid analog as a new type of designer drug in a herbal product', *Chemical and Pharmaceutical Bulletin* 57(4), pp. 439–441.

Die Wiedergabe des Beitrages erfolgt mit freundlicher Genehmigung der Autoren. Der Beitrag wurde erstmals durch das European Monitoring Centre for Drugs and Drug Addiction in Lissabon am 5. November 2009 präsentiert. Der Originalbeitrag ist zugängig unter www.emcdda.europa.eu.