UNODC
United Nations Office on Drugs and Crime

Synthetic cannabinoids
in herbal products

Background

The recent appearance of synthetic cannabinoids in herbal products ('Spice'), easily available over the internet, has brought to the attention of the international community, the need for sharing of information and greater awareness of this phenomenon. This report was prepared pursuant to the Commission on Narcotic Drugs Resolution 53/11 *(Para 6: Requests the United Nations Office on Drugs and Crime to share information on the issue of cannabinoid receptor agonists with the Expert Committee on Drug Dependence of the World Health Organization to increase its understanding and awareness of the issue).*

The report aims to provide a comprehensive overview of the synthetic cannabinoids with the main focus on compounds which surfaced in herbal products as psychoactive adulterants. It reflects the situation as of January 2011 and gives information about the pharmacological activity, potential toxicity and recommendations regarding the legal handling of this new phenomenon.

Methodological Approach

Literature search was performed by using common databases such as 'PubMed and 'ScienceDirect'. Using the search term 'synthetic cannabinoid' on PubMed, about 100 publications were found per year with increasing frequency since the year 2000, reaching a peak in 2009 with 163 hits. With regard to the 'Spice' phenomenon, 8 articles were published in 2009 and 20 in 2010. Additional information was gathered through personal communication with scientists, law enforcement officials and medical practitioners in countries affected by problems arising from the use of herbal products containing synthetic cannabinoids.

Terminology and Abbreviations

CB_1 and CB_2 receptors:	Cell membrane receptors mediating typical effects occurring after cannabis use.
Aminoalkylindoles (AAIs):	A class of chemical compounds comprising hundreds of CB_1 agonists mimicking effects of the cannabis constituent Δ^9-Tetrahydrocannabinol.
THC:	Δ^9-Tetrahydrocannabinol, the main psychoactive substance found in cannabis.
EWS:	'Early Warning System' of the EMCDDA (European Monitoring Centre for Drugs and Drug Addiction)

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1 Introduction and chemistry of synthetic cannabinoids

1.1 Emergence of synthetic cannabinoids in herbal products

Since 2004, herbal mixtures called 'Spice' have been available in several European countries such as Germany, Switzerland and Great Britain. Initially, these products were not popular and were used by only a small group of experimental users. However, numerous reports on these products surfaced in German newspapers and television in 2008 proclaiming their use as 'legal' cannabis substitutes. This consequently increased their popularity and the number of users rose dramatically in the course of the year [1]. The same phenomenon has since been observed in France, Great Britain and many other European countries.

The first generation 'Spice' products were declared as incense or herbal blends and carried names such as 'Spice Silver', 'Spice Gold', 'Spice Diamond', 'Yucatan Fire' and 'Smoke' (Figure 1). Usually 0.5 to 3 g of finely cut green/brown plant material is presented in colourful and professionally designed packets. Various herbs such as *Pedicularis densiflora*, *Nymphacea caerulea*, *Leonotis leonurus*, *Leonurus sibiricus, Carnavalia maritima* and *Zornia latifolia* were declared as ingredients without mentioning any synthetic additives. On the packaging labels, these herbs were claimed to be able to produce cannabis-like effects when consumed [2] which obviously aimed to make users believe that these products are pharmacologically active due to the sophisticated blending of natural constituents only.

Figure 1: Herbal products containing synthetic cannabinoids.

Initially, these products could be purchased mainly via the Internet. However, with increasing popularity, the products are available through so-called 'headshops' (shops mainly selling accessories for smoking cannabis) and local tobacco shops. Many vendors sold 'Spice' without age restriction, while some claimed to have only sold to customers above 18. According to the instructions found on the packets or on some of the websites offering 'Spice', the products were not meant to be used for human consumption, nevertheless many users

reported in Internet forums to have smoked or taken the products orally in order to become intoxicated. Most users described the effects after consumption to be very 'cannabis-like'.

By end of 2008, several laboratories identified the synthetic additives present in 'Spice' and related herbal products. The compounds found in the first generation 'Spice' products were the C8 homologues of the non-classical cannabinoid CP-47,497 [3, 4] and the aminoalkylindole JWH-018 [3], which are potent cannabimimetics. Soon after these substances were put under legal control in several countries, many other similar compounds of the aminoalkylindole family appeared on the market [5-7]. Since then, the number of 'Spice' products and new synthetic cannabinoids has increased continuously.

At present, there is a large variety of 'Spice' brands available in the market carrying names such as *Dream*, *Monkees go Bananas!* and *Jamaican Spirit* in Germany; *K'*, *Tai High* and *Amped* in USA; and *Enigma*, *Kamikadze*, *Napalm* and *Chernobyl* in Russia. These products usually contain one or a mixture of synthetic cannabinoids. However, some 'Spice' products were also found to be free of any synthetic additives.

In many of these brands, the same product was found to vary not only in the amount but also in the type of synthetic cannabinoids added [5]. For example, Lindigkeit *et al*. [6] reported 5.4 and 11 mg/g of CP-47,497-C8 in two different samples of 'Spice Gold'. The overall range of concentrations in 9 different brands investigated in this study was between 3-11 mg/g of CP-47,497-C8 and 6-23 mg/g of JWH-073. Interestingly, one sample contained only 2.3 mg/g of JWH-018 while two other samples were found to be free of synthetic cannabinoids. In another study by Uchiyama *et al*. [7], 1-17 mg/g of CP-47,497-C8 and 2-36 mg/g of JWH-018 were found in 46 'Spice' products of different brands. Similarly, 2 samples were also found to be unadulterated with any synthetic cannabinoids.

While these products were initially found to be popular among users of different ages and socioeconomic status, a recent survey [8] suggest that the use of these products has dropped significantly. However, it is still increasingly popular among users who have to undergo regular urine drug screenings as current screening methods do not detect synthetic cannabinoids. This observation was confirmed by a recent study on forensic psychiatric inpatients, which showed very high prevalence rates of synthetic cannabinoid use [9].

1.2 Definition/Structural classification of synthetic cannabinoids

Synthetic cannabinoids are referred to as substances with structural features which allow binding to one of the known cannabinoid receptors, i.e. CB_1 or CB_2, present in human cells and compounds with similar chemical structures. The CB_1 receptor is located mainly in the brain and spinal cord and is responsible for the typical physiological and particularly the psychotropic effects of cannabis, whereas the CB_2 receptor is located mainly in the spleen and cells of the immune system and may mediate immune-modulatory effects [10-12]. Synthetic cannabinoids can be divided into cannabinomimetics which show cannabis-like pharmacological activity

(mainly agonists at CB_1); antagonists which bind to one of the CB receptors without producing cannabis-like effects but blocking the receptors for other compounds, and substances which do not bind to these receptors significantly and hence do not have pharmacological effects mediated by one of these two receptors.

The classification of the synthetic cannabinoids, based on the chemical structures of the molecules, has been suggested by Howlett *et al*. and Thakur *et al*. [13, 14]. This classification, shown below, has also been referred to in a report by the British Advisory Council on the Misuse of Drugs (ACMD) which deals with the generic definition of synthetic cannabinoids [15]:

1. **Classical cannabinoids** (THC, other constituents of cannabis; and their structurally related synthetic analogues e. g. HU-210, AM-906, AM-411, O-1184)
2. **Nonclassical cannabinoids** (cyclohexylphenols or 3-arylcyclohexanols such as CP-47,497-C8, CP-55,940, CP-55,244)
3. **Hybrid cannabinoids** (combinations of structural features of classical and non-classical cannabinoids, e. g. AM-4030)
4. **Aminoalkylindoles** (AAIs), which can be further divided into naphtoylindoles (e. g. JWH-018, JWH-073, JWH-398, JWH-015, JWH-122, JWH-210, JWH-081, JWH-200, WIN-55,212); phenylacetylindoles (e. g. JWH-250, JWH-251); naphthylmethylindoles and benzoylindoles (e. g. pravadoline, AM-694, RSC-4).
5. **Eicosanoids** (endocannabinoids such as anandamide, and their synthetic analogs e. g. methanandamide)
6. **Others**, diarylpyrazoles (selective CB_1 antagonist Rimonabant®), naphtoylpyrroles (JWH-307), naphthylmethylindenes or derivatives of naphthalene-1-yl-(4-pentyloxynaphthalen-1-yl)methanone (CRA-13).

In most cases with the classical, non-classical and hybrid cannabinoids, one specific stereoisomer is much more potent than the other(s), whereas most of the AAIs, eicosanoids and 'others' do not possess an asymmetric center.

The interest in synthesizing cannabinoids began with the complete synthesis of THC in 1965 by Mechoulam and Gaoni [16]. Subsequently, several research groups and commercial companies focused on synthesizing compounds with cannabimimetic activity. Initially, only classical cannabinoids (e. g. Levonantradol [17] and HU-210 [18]) were synthesized. Non -classical cannabinoids (e. g. CP-59,540 and CP-47,497 [19, 20]) and AAIs [21] were developed in the 80's and 90's after the so-called cannabinoid receptors CB_1 [22] and CB_2 [11] were identified and cloned. Since then, scientific interest in these compounds has increased leading to the synthesis of more than 100 substances with high or medium affinity to the CB_1 receptor.

Some of these substances were experimented on various cell and animal models to get an insight into their modes of action and pharmacological properties (e. g. by triggering the so-called 'tetrad' of effects in mice:

depression of locomotion, antinociception, hypothermia and catalepsy [10]). However, for many substances, only receptor affinities assessed in binding studies are available. In Table 1, the compounds identified in herbal products are given in chronological order together with receptor affinities. As a rule, the greater the affinity (K_i) to the CB_1 receptor, the higher the pharmacological potency of the compound [23]. The structures of these compounds are shown in Figure 2.

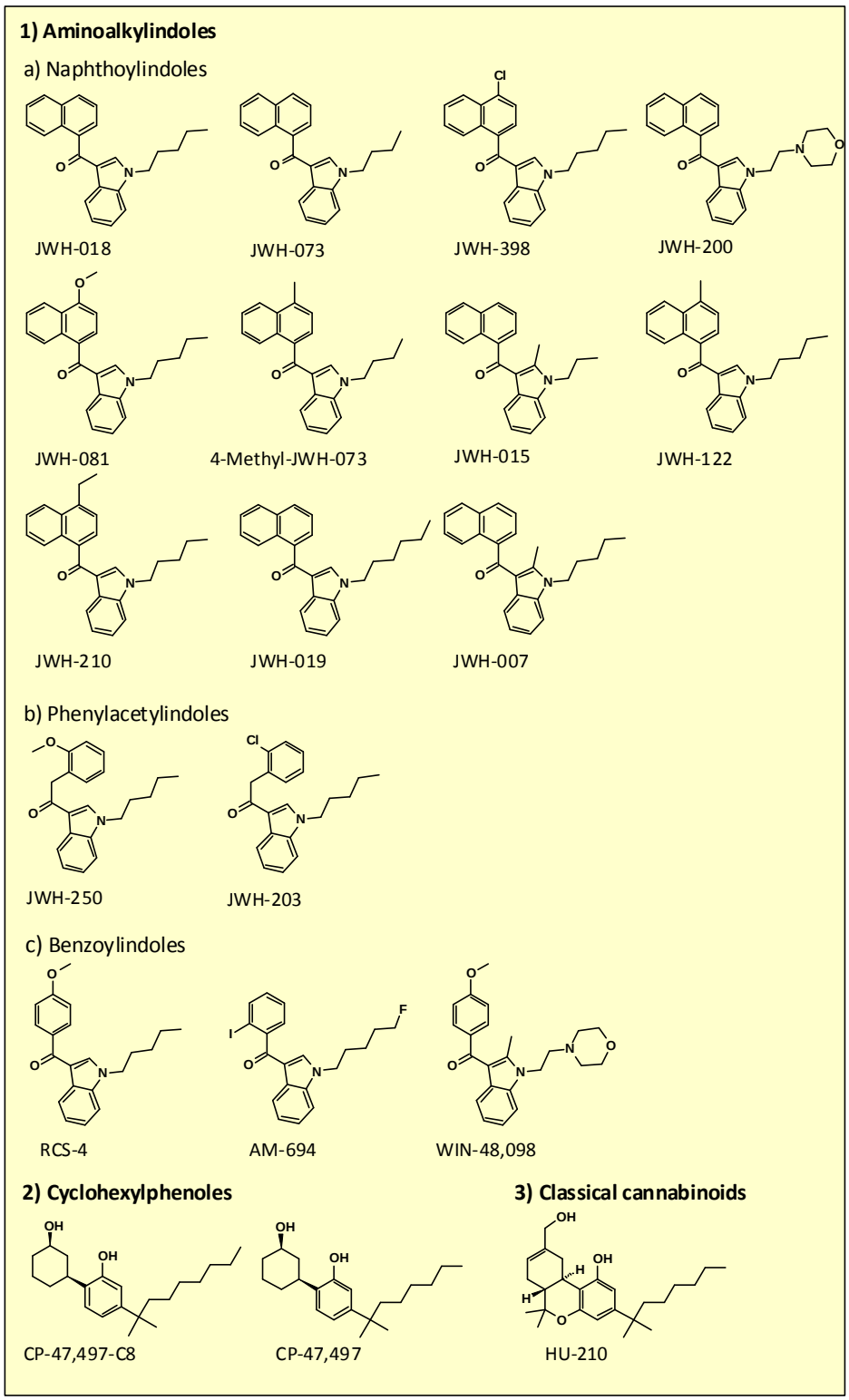

Figure 2: Chemical structures of synthetic cannabinoids found in herbal products.

Table 1: List of cannabimimetic compounds identified in herbal products so far in the order of their first appearance. Receptor affinities (K_i) are given as far as available.

Compound name	Date and place of first identification	Group type	K_i in nM (CB_1)	Cannabimimetic activity
JWH-018	December 2008 (Germany, Japan)	Naphtoylindole	9 [24], 9.5 [25]	High (animal model [24], autaptic hippocampal neurons [26])
CP-47,497-C8	December 2008 (Germany, Japan)	Cyclohexylphenol	0.83 [27], 4.73 [10]	High (animal model [19])
CP-47,497	December 2008 (Germany, Japan)	Cyclohexylphenol	2.20 [27]	High (animal model [19])
JWH-073	January 2009 (Germany)	Naphtoylindole	8.9 [28], 22 [21]	Not investigated
HU-210	January/June 2009 (USA, UK)	Classical cannabinoid	0.061 [13], 0.73 [25]	High (animal model [29])
JWH-250	October 2009 Germany)	Phenylacetylindole	11 [30]	Not investigated
JWH-398	October 2009 (UK)	Naphtoylindole	2.3 [23]	Not investigated
JWH-200	December 2009 (Russia)	Naphtoylindole	42 [31]	Not investigated
JWH-081	March 2010 (Germany)	Naphtoylindole	1.2 [28]	Not investigated
4-Methyl-JWH-073	April 2010 (Germany)	Naphtoylindole	Unknown	Not investigated
RCS-4	May 2010 (Germany)	Benzoylindole	Unknown	Not investigated
JWH-015	June 2010 (Austria)	Naphtoylindole	164 [21, 24], 336 [28], 292 [25]	Low (animal model [24])
AM-694	July 2010 (Ireland)	Benzoylindole	0.08 [32]	Not investigated
JWH-122	July 2010 (Latvia)	Naphtoylindole	0.69 [31]	Not investigated
JWH-210	September 2010 (Germany)	Naphtoylindole	0.46 [33]	Not investigated
JWH-019	September 2010 (Germany)	Naphtoylindole	9.8 [28]	Not investigated
JWH-203	October 2010 (Germany)	Phenylacetylindole	8.0 [30]	Not investigated
WIN-48,098 (Pravadolin)	November 2010 (Germany)	Benzoylindole	3155 [34]	Medium (animal models [35])
JWH-007	November 2010 (Germany)	Naphtoylindole	9.5 [28]	Not investigated

* Due to differences in experimental conditions the absolute values of the receptor affinities K_i (CB_1) from different laboratories vary significantly

1.3 Current medicinal/industrial use of synthetic cannabinoids and potential for abuse

Many of these synthetic cannabinoids are used in pharmacological studies involving structure-activity relationships (SAR), receptor binding studies and detailed mechanisms of action of these drugs. Among the most common cannabinoids in this respect are CP-55,940 (a non-classical cannabinoid), WIN-55,212-2 (an aminoalkylindole) and anandamide (an eicosanoid).

Some synthetic cannabinoids have been used for medicinal purposes:

- *Rimonabant* (Acomplia®): A selective CB_1 receptor antagonist which was used to treat obesity for some time, but was withdrawn from the market because it showed severe side effects.
- *Nabilone* (Cesamet®): A synthetic cannabinoid used for treatment of anorexia and for its antiemetic effects (e. g. in cancer patients under chemotherapy); its chemical structure is closely related to THC.
- *Dronabinol* (Marinol®): Synthetically produced pure THC which is applied in multiple sclerosis and pain patients.

Some medicinal products also contain natural cannabinoids:

- *THC and Cannabidiol* (Sativex®): Oramucosal spray developed for multiple sclerosis and pain patients, derived from cannabis plant material.
- *Hemp flowers* (Bediol®, Bedrobinol®, Bedrocan®): Cannabis flowers containing standardised amounts of THC.

In general, compounds with agonist effect and sufficient affinity to the CB_1 receptor (expressed as K_I, nM; the smaller the value, the higher the affinity to the receptor) have a potential for abuse as cannabis substitutes. The K_I values of most these compounds, obtained by performing relatively simple experiments, are available in the literature [36]. However as the potency is also influenced by factors such as the extent of agonist activity, bioavailability and other pharmacokinetic parameters, it is not possible to define a 'cut-off' value for the K_I with regard to cannabimimetic activity.

Recently, JWH-015, a compound with a relatively low affinity to CB_1 (K_I = 164 nM [24]), was found in some herbal products. Since a variety of high potency cannabinoids, well characterized by means of their CB_1 affinity, is available, it is unusual from the perspective of the illicit producer to market a product which requires relatively higher doses for the same desired effect.

1.4 Mode of administration

The synthetic cannabinoids are generally administered by smoking. Werse *et al.* reported smoking as a joint or in a water-pipe as the usual modes of administration in a user survey carried out in Frankfurt, Germany [8]. Most of these substances are highly lipophilic and vaporize without decomposition under smoking conditions.

It stands to reason that this mode of administration is preferred by the users because of the relatively quick onset of pharmacological effects [3] which allows for titration to the desired pharmacological action.
In contrast to cannabis where heating through smoking is required to convert the non-psychoactive THC acid A present to the desired psychoactive THC, the synthetic cannabinoids are already present in their stable psychoactive forms.

In Internet forums there are also some reports of oral consumption. The use as herbal tea is uncommon. Following oral consumption, the onset of action may be delayed due to variations in the extent of the first pass effect (metabolism of a drug during the first liver passage, i. e. before reaching systemic circulation). There is therefore the possibility of the user not attaining the desired effect due to the possibility of under- or over-dosing the drug.

The preparation of infusions and use of synthetic cannabinoids as herbal tea is unlikely because of the low solubility of these highly lipophilic compounds in water. The administration via parenteral routes has not been reported in humans so far.

1.5 Methods of synthesis

Methods for synthesizing synthetic cannabinoids have been described in detail in scientific literature (e. g. by Melvin *et al*. for CP-47,497 [20] and Bell *et al*. [37] or Huffman *et al*. [33] for a variety of AAIs). Furthermore, a creative chemist would be able to easily synthesize hundreds of similar compounds with a high probability of showing cannabimimetic action by the addition of a halogen, alkyl, alkoxy or other substituents to one of the aromatic ring systems. Other small changes such as variation of the length and configuration of the alkyl chain can also be made. In general, syntheses of classical, nonclassical or hybrid cannabinoids are much more elaborate and complicated than syntheses of molecules without asymmetric centers like most AAIs. This is because stereoisomers could show big differences in activity and in some cases the inversion of an asymmetric center could change a receptor agonist into an antagonist. As a result, stereo-selective synthesis or elaborate separation of stereoisomers are often necessary.

Common precursors for syntheses of AAIs, by Friedel-Crafts acylation at C_3 followed by N-alkylation of a (substituted) indole or vice versa, are:
1-alkylindoles and 1-alkyl-2-methylindoles (alkyl = butyl, pentyl, hexyl or others)
1-naphthoyl chlorides (where applicable substituted at C_4)

For cyclohexylphenols of the CP-47,497-type, commonly obtainable precursors such as (3-(benzyloxy)phenyl]acetonitrile and cyclohex-2-en-1-one are required. It should to be noted that alternative approaches for synthesis are possible.

2 Pharmacological and toxicological aspects

2.1 Pharmacokinetics

At present, not much is known about pharmacokinetic parameters of these compounds.

Bioavailability: As mentioned above, bioavailability depends strongly on the mode of administration. While preparations of 'herbal' teas will most probably contain only a small proportion of the substances present in the product due to their highly lipophilic nature, oral intake of the products will result in a certain loss of drug by first pass metabolism. As the AAIs investigated thus far show a rather complex and extensive metabolism, a pronounced first pass effect can be expected. So far, for CP-47,497-C8, neither the compound itself nor easily detectable amounts of metabolites were found in urine samples after the use of products containing this drug [65]. This may be a result of low metabolic rates but could also be attributed to an elimination occurring mainly via faeces. Therefore no conclusion can be made at present to the extent of first pass metabolism for this compound.

Absorption: After smoking, onset of action usually occurs within minutes, similar to cannabis use. This is due to instant absorption via the lungs and redistribution into other organs like the brain within minutes after use. There is a delay in absorption following oral consumption due to food intake and digestion activity.

Distribution: High volumes of distribution can be expected for these lipophilic compounds, but no experimental data is available at present. As a result after chronic consumption, accumulation of the substances and/or their metabolites in fat containing compartments of the body is very likely. This is in line with the detection of AAIs in blood samples of forensic psychiatric inpatients after believably claiming abstinence for a couple of days [9].

Metabolism: So far metabolism studies are available only for the AAIs, WIN-55,212-2 [38], JWH-015 [39], JWH-018 [40-43], JWH-073 [44] and the cyclohexylphenol CP-55,940 [45]. These studies are based on experiments with human liver microsomes or on analysis of urine specimens of drug users having smoked products containing the respective synthetic cannabinoids. In general, no unchanged drug is found in the urine specimens.

For the AAIs, the monohydroxylated compounds and their glucuronides seem to be the main metabolites, but N-dealkylation, multiple hydroxylation, a combination of hydroxylation and dealkylation or oxidation of the terminally hydroxylated N-alkyl moiety to the corresponding carboxylic acid were also observed. Additionally, arene oxidation leads to dihydrodiol formation. For phenylacetylindoles, there may be additional metabolites by reaction with the enolized form (e. g. glucuronidation or sulfation).

At the moment, no data is available in literature about human metabolism of CP-47,497 or its homologues. However, a preliminary study showed the presence of low concentrations of monohydroxylated CP-47,497-C8 in urine after recent uptake of this compound by inhalation [65].

Elimination: Excretion of AAIs seem, to a certain extent, to be via urine in the form of various metabolites carrying more polar groups. An unknown proportion is expected to be excreted via faeces. In the case of CP-47,497-C8, urine metabolite concentrations are very low, resulting in difficulty to detect consumption by analyzing urine with standard laboratory equipment.

2.2 Health-related effects associated with the abuse of synthetic cannabinoids

The health-related problems associated with the use of 'Spice' products have been reported to be similar to those after cannabis use [46-51]. Cardiovascular problems and psychological disorders such as panic attacks were among the frequently reported symptoms. These symptoms are also likely to occur after cannabis use in cannabis naive users or after using relatively high doses. For some particular products, e. g. 'Lava Red', increasing numbers of users were hospitalized with severe intoxications. Another potential problem observed is the unknown cumulative toxic effects these compounds or their metabolites may have.

2.3 Toxicity of synthetic cannabinoids

There is no valid data on the toxicity of these compounds so far. Nevertheless it can be speculated that some of the metabolites, particularly of the AAIs carrying a naphthyl moiety, may have carcinogenic potential [52]. Although cannabis itself has a comparatively low acute toxicity, it cannot be dismissed that at least some of these compounds could cause severe or even life-threatening intoxications when overdosed. This is particularly likely for compounds which act as full agonists at the CB_1 receptor, e. g. HU-210, CP-55,940 or WIN-55,212-2 considering that THC only acts as a partial agonist at this same receptor site [19, 34].

Recently, an increase in the number and severity of symptoms observed in hospitalized persons after consumption of herbal mixtures containing JWH-122, e. g. 'Lava Red' and 'OMG', was observed in Germany [65] and Italy (EWS report, 07.12.2010). Some of these patients suffered from generalised muscular spasms and/or loss of consciousness, requiring artificial ventilation. This emphasizes that even slight changes in the molecular structure might lead to a dramatic increase in toxicity, bearing in mind that with JWH-018 such symptoms were not reported.

2.4 Addictive potential of synthetic cannabinoids

Some reports suggest that a number of these substances may have a higher addictive potential compared to cannabis due to quicker development of tolerance [26, 53].

In a case report published by Zimmermann *et al*. in 2009 [53], withdrawal phenomena and a dependence syndrome occurred after repeated consumption of relatively high doses of 'Spice gold', i.e. 3 g per day. From experiments carried out with autaptic hippocampal neurons, it was shown that JWH-018 could potently induce rapid and robust CB_1 receptor internalization, highlighting the potential of developing tolerance and dependence on this substance [26].

3 Illicit manufacture and diversion

3.1 Possibility for illicit manufacture

Most of the AAIs can be easily synthesized with standard laboratory equipment and readily available reagents. The synthesis of cyclohexylphenols requires more elaborate equipment and technical know how, but it should not pose too much of a challenge for a chemist with a sound basic training in organic synthesis.

3.2 Diversion

Some of the synthetic cannabinoids present in these products can be bought from reputable chemical companies, but the prices for these high purity chemicals are much too high for use in 'Spice' preparations. Cheaper alternatives are provided by several companies located mainly in China who offer a growing variety of these compounds for prices in the range of USD 3,500 – 7,500 per kilogram. The quality of these compounds in general does not meet pharmaceutical standards and they are often contaminated with synthetic byproducts and derivatives originating from inefficient synthetic processes. In addition, these products are usually shipped using wrong declarations, e. g. 'polyphosphate', 'maleic acid', 'fluorescent whitening agent' or 'ethyl vanillin'.

3.3 Regional trends/differences

In Europe, there is a strong tendency for the producers to quickly adapt to changes in legislations by innovatively using similar compounds that are yet to be controlled. Moreover, since most European countries do not use a generic definition for controlling these synthetic cannabinoids, there is a continuous supply of 'legal' mixtures available at all times. Although this phenomenon was first discovered in Europe, the abuse of synthetic cannabinoids seems to be an issue now in almost all developed countries throughout the world.

In US, only some States have put cannabimimetics under control so far and hence, not so many changes in product composition were seen here. JWH-018, JWH-073 and CP-47,497-C8 are still among the most prominent synthetic cannabinoids encountered. Recently, in November 2010, the United States Drug Enforcement Administration (DEA) announced the emergency scheduling of five compounds, namely, JWH-018, JWH-073, CP-47,497, CP-47,497-C8 and JWH-200 as 'Schedule I' substances [54].

In some countries, e. g. Japan, it is a very difficult task to change the legal status of these substances. New compounds cannot be controlled unless the pharmacological activity is proven. This requires acquisition of reference materials which in turn may slow down the process. Furthermore, assessing pharmacological activity of every single compound is time-consuming and hence hampering initiatives to control these substances.

In Russia, a great variety of 'Spice'-like products are available with JWH-018, JWH-073 and CP-47,497-C8 among the compounds predominantly encountered. These compounds are however been increasingly substituted by compounds that are yet to be controlled, e. g. JWH-250, JWH-251, JWH-210, JWH-019, JWH-203 and AM-694 [55].

4 Current situation

4.1 Prevalence of abuse

There is a lack of reliable data on this topic at present. Before 2008, the use of products containing synthetic cannabinoids seems to have been restricted to a small number of experimental drug users. However, in 2008 these products achieved immense popularity in Germany and some other European countries through numerous media reports in various newspapers and television channels, where they were called a 'legal alternative' to cannabis, thereby promoting the abuse of these drugs. This led to an abrupt increase in sales and number of cannabis abusers experimenting on these new products.

The results of a pilot study conducted by Werse *et al*. [56], show that about 6 % of pupils in Frankfurt, Germany, aged between 15 and 18 had used 'Spice' products at least once by the end of 2008. However, an assessment by headshop personnel, the main customers purchasing these products were between the ages of 25 to 40 years, with over 80% of this group being male.

When these herbal products were exposed as products adulterated with pharmacologically active chemicals of unknown toxicological properties and coupled with legal prohibition of some of these cannabimimetic compounds, the popularity of these products decreased significantly. However, demand for these products is still very much alive as new products continuously emerge in the market.

Since January 2009, when the 'Spice' products were made illegal in Germany, the number of actual users was observed to have dropped significantly as shown in a small scale investigation in samples analyzed for drugs of abuse in Germany in the context of driving under the influence of drugs [58]. Moreover, the profile of users changed from 'curious' one-timers to users who take advantage of the limitation of drug screening tests or as a cannabis substitute in times of low availability as shown by Werse *et al*. 2010 [8]. Almost all of these users were found to have at least some experience using cannabis and a majority had also used other 'hard' drugs in the past.

Currently, these products are still popular among users having to undergo regular drug screenings (e. g. army personnel, inpatients of forensic psychiatric clinics, prisoners and persons convicted of driving offences under the influence of drugs). This has been reflected in a study with toxicological analysis of forensic psychiatric patients which showed more than 50 % of blood samples being tested positive for AAIs [9]. In addition, there is also a growing interest among laboratories to analyse synthetic cannabinoids in urine samples of military personnel in USA and Russia [57].

4.2 Control status and monitoring

None of the synthetic cannabinoids found so far in 'Spice' and 'Spice'-like products are internationally controlled under the 1961 or 1971 UN Drug control conventions. At present, the control status of these compounds differs significantly from country to country. Table 2 gives an overview on the legal status of synthetic cannabinoids in various countries.

Table 2: Overview on the legal status of synthetic cannabinoids in various countries

Country	**Enforcement Date**	**Controlled substances / Remarks**
Austria	January 2009 October 2010	'Spice' products classified as medicinal preparations CP-47,497-C6/C7/C8/C9, JWH-018, HU-210, JWH-015, JWH-019, JWH-073, JWH-081, JWH-200, JWH-250
Denmark	March 2010	CP-47,497-C6/C7/C8/C9, JWH-018, JWH-073, HU-210, JWH-250, JWH-398, JWH-200
Estonia	July 2009	CP-47,497-C6/C7/C8/C9, JWH-018, JWH-073, HU-210
Finland	Not controlled	JWH-018, JWH-073, JWH-200, HU-210, CP-47,497-C6/C7/C8/C9 classified as medicinal preparations
France	February 2009	JWH-018, CP-47,497-C6/C7/C8/C9, HU-210
Germany	January 2009 January 2010 Planned for 2011	emergency regulation, JWH-018, CP-47,497-C6/C7/C8/C9 permanent control and addition of JWH-019, JWH-073 JWH-015, JWH-081, JWH-200, JWH-250, JWH-122
Ireland	May 2010	generic approach
Italy	June 2010	JWH-018, JWH-073
Japan	November 2009 September 2010	controlled as 'designated substances' under the Pharmaceutical Affairs Law: CP-47,497-C7/C8, JWH-018, HU-210 JWH-073, JWH-250
Latvia	November 2009	JWH-018, JWH-073, CP-47,497-C6/C7/C8/C9, HU-210, Leonotis Leonurus and Nymphacea caerulea
Lithuania	May 2009	CP-47,497-C6/C7/C8/C9, JWH-018, JWH-073, HU-210, JWH-250, JWH-398, JWH-200

Country	Enforcement Date	Controlled substances / Remarks
Luxembourg	May 2009	generic approach
New Zealand	Not controlled	HU-210 may be regarded as an THC analog
Poland	May 2009	JWH-018, Leonotis Leonurus, Nymphacea caerulea
Romania	February 2010	CP-47,497-C6/C7/C8/C9, JWH-018, JWH-073, JWH-250
Russia	December 2009	CP-47,497-C6/C7/C8/C9, HU-210, JWH-007, JWH-018, JWH-073, JWH-081, JWH-098, JWH-122, JWH-149, JWH-166, JWH-175, JWH-176, JWH-184, JWH-185, JWH-192, JWH-193, JWH-194, JWH-195, JWH-196, JWH-197, JWH-198, JWH-199, JWH-200
South Korea	July 2009	JWH-018, HU-210, CP-47,497
Sweden	September 2009	CP-47,497-C6/ C7/C8/C9, JWH-018, JWH-073,HU-210
Switzerland	May 2009 December 2010	control of 'Spice herbal mixes' under food regulation (5 grams allowed for personal use) JWH-018, JWH-019, JWH-073, JWH-250, CP-47,497-C6/C7/C8/C9
United Kingdom	December 2009	generic approach
USA	Not controlled under federal law* November 2010	HU-210 is scheduled as an analog of THC DEA announcement to emergency schedule JWH-018, JWH-073, CP-47,497, CP-47,497-C8 and JWH-200

*Several states passed acts banning the sale of 'Spice' and related products, among them Kansas (March 2010: JWH-018, JWH-073, HU-210), Kentucky (April 2010: HU-210, JWH-073, JWH-018, CP-47,497), North Dakota (April 2010), Georgia (May 2010: JWH-018, HU-210, CP-47,497), Alabama (July 2010: HU-210, JWH-018, JWH-073), Arkansas (July 2010: temporary emergency ban covering JWH-018 and JWH-073), Iowa (July 2010: temporary emergency ban covering HU-211, JWH-018, CP-47,497), Tennessee (July 2010), Louisiana, Missouri and Hawaii (August 2010), Mississippi (September 2010), Michigan (October 2010: HU-210, CP-47,497 and homologues, JWH-018, JWH-073, JWH-015, JWH-200, JWH-250), Oklahoma (November 2010), Illinois (January 2011: JWH-018, JWH-073).

In UK, a generic definition was chosen to cover not only substances already present in herbal products, but also structurally similar compounds. Therefore, all compounds structurally derived from five template structures by substitution at various positions were classified as 'Class B' controlled drugs. In all other countries having taken control measures without a generic approach, new uncontrolled substances continuously appear and hence, require a constant need to schedule these substances and update the lists of controlled drugs regularly. This process in general is time consuming and it is very likely that these lists will be outdated as soon as they are revised. However, even the generic approach used by the UK is not full proof [59] as despite having chosen quite a comprehensive generic definition of synthetic cannabinoids, there are still new compounds appearing

in the market containing substances such as AM-694, RSC-4 or other compounds of the benzoylindole type which do not fall under this generic definition.

Currently, there is no systematic monitoring of this phenomenon and any information gathered so far has been based on initiatives of forensic scientists analysing samples seized in the course of criminal investigations and samples sporadically ordered from the Internet. In 2011, a project will be launched in the framework of the 'Drug Information and Prevention Programme', financially supported by the EU-Commission focusing on the monitoring of herbal products, which will not only provide valuable and timely information on the product compositions but also toxicological and epidemiological data on synthetic cannabinoids and their use.

4.3 Current methods of analysis used for seized material and biological specimens

Reliable identification and particularly quantification of synthetic cannabinoids in herbal products and their metabolites in biological specimens of users requires the use of reference material. However, due to the immense variety of synthetic cannabinoids in the market, reference material for most of these compounds is currently unavailable. Table 3 shows the limited number of reference material available through commercial sources which includes substances found in herbal products and their metabolites as well as isotope labeled compounds.

Table 3: Reference material for synthetic cannabinoids currently available thru commercial sources

Commercial Sources	Substances available
1. Cayman Chemical Company, 1180 East Ellsworth Road, Ann Arbor, Michigan 48108, USA (http://www.caymanchem.com)	JWH-018, JWH-081, JWH-073, HU-210, CP-47,497, CP-47,497-C8, JWH-200, JWH-250, JWH-015, JWH-019, JWH-018 2-hydroxyindole metabolite, JWH-018 N-pentanoic acid metabolite, JWH-018 4-hydroxyindole metabolite, JWH-018 5-hydroxyindole metabolite, JWH-018 N-(5-hydroxypentyl) metabolite, JWH-018 7-hydroxyindole metabolite, JWH-018 6-hydroxyindole metabolite, JWH-073 N-(5-hydroxybutyl) metabolite, JWH-073 5-hydroxyindole metabolite, JWH-073 N-butanoic acid metabolite, JWH-073 4-hydroxyindole metabolite, JWH-073 7-hydroxyindole metabolite, JWH-073 6-hydroxyindole metabolite

Commercial Sources	Substances available
	JWH-018 N-pentanoic acid metabolite-d4, JWH-073 N-butanoic acid metabolite-d5, JWH-007-d9, JWH-018-d9, JWH-073-d7
2. LGC Standards, Queens Road, Teddington, Middlesex, TW11 0LY, United Kingdom (http://lgcstandards.com):	JWH-018, CP-47,497, HU-210, JWH-073
3. Tocris Bioscience, Tocris House, IO Centre, Moorend Farm Avenue, Bristol, BS11 0QL, United Kingdom (http://www.tocris.com)	JWH-018, HU-210, JWH-015, CP-47,497
4. Chiron AS, Stiklestadveien 1, NO-7041 Trondheim, Norway (http://chiron.no)	JWH-018, JWH-073 JWH-018-d9, JWH-073-d11

4.3.1 Analysis of herbal products

A basic method used to analyse synthetic additives in herbal mixtures is to initially extract the lipophilic compounds located mainly on the surface of the plant material with an organic solvent at room temperature. Using higher temperatures, longer extraction times or techniques such as the soxhlet extraction may lead to higher extraction yields but would also produce more complex chromatograms making it difficult to differentiate between natural constituents and synthetic drugs.

The extract can then be analyzed by Gas Chromatography – Mass Spectrometry (GC-MS) in scan mode to identify the main active compounds by comparison to a spectra library containing spectra of known synthetic cannabinoids. Whenever new compounds appear, the best way to elucidate the chemical structure is to isolate the respective compound by means of preparative gel chromatography or High Performance Liquid Chromatography (HPLC). Subsequently, the pure compound can then be analyzed by ^{1}H- and ^{13}C-NMR (Nuclear Magnetic Resonance). High resolution mass spectrometry can also help in identification as it provides the sum molecular formula of the compound and in combination with MS^{n} allows for more gains in structural information [60]. This technique is also valuable for identifying minor components such as synthetic by-products or contaminants.

Another approach for identification of such compounds could be the utilization of two dimensional gas chromatography coupled with mass spectrometry (GC-GC-MS), providing the possibility of a simple ‘profiling’

strategy which may be helpful in identifying synthetic additives originating from the same clandestine laboratory [61].

4.3.2 Analysis of biological samples

The only published methods to date for the detection of synthetic cannabinoids in biological samples target the unchanged compounds in blood or serum. Teske *et al*. published a method for the detection of JWH-018 in 2010 [62] and Dresen *et al*. added a method recently covering 10 synthetic cannabinoids, e. g. JWH-018, JWH-073, JWH-081, JWH-122 and JWH-250 [9]. Both methods used a simple liquid-liquid extraction followed by a liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis.

For urine analysis, the main target compounds are metabolites as the unchanged compounds are usually not found in urine after the use of these substances. There are a few reports on the detection of major metabolites of JWH-018 and JWH-073 in urine [40-43]. However, the fast growing number of new compounds makes it difficult to adapt urine analysis methods to encompass all these compounds as their specific metabolisms are still unknown. Moreover, the fact that there are no pure reference materials for most of these compounds makes this a challenging task.

4.4 Challenges faced

As mentioned in 4.3, the lack of reference material for identification and development of bio-analytical methods is one of the major challenges encountered in this area of synthetic cannabinoids. This is further complicated by the continuous introduction of new substances in the market with no information in scientific literature. Although instruments such as the EWS of the EMCDDA is capable of swift collection and dissemination of information about these new substances, timely identification is not always an easy task as it may involve elaborate purification of the suspected new compound for structure elucidation by NMR spectroscopy after extraction from the product.

In many countries a generic definition of controlled drugs is not possible due to legal and constitutional incompatibilities. This leads to a cat and mouse game as experienced with amphetamine- and cathinone-derived designer drugs as well as with phenylpiperazines and other compounds.

Another problem is the lack of information on the prevalence of abuse and demographics of its users. In most countries very little or nothing is known about the kind of people attracted by these products.

Furthermore, metabolism of most of these compounds is yet unknown, leading to major challenges to confirm consumption of these compounds in urine specimens for abstinence control in the context of forensic investigations, workplace drug testing and driving liability testing.

5 Conclusions

The 'Spice' phenomenon did not seem to disappear in countries which prohibited either single compounds or a broader spectrum of compounds by a generic definition although the number of users may have significantly been reduced since then due to lower availability and lesser media presence. There is still a great variety of products available on the Internet and new substances constantly appear in the continuously changing market.

The majority of synthetic cannabinoid users seem to be experienced drug users with a history of abusing cannabis and/or 'hard' drugs of which some are undergoing obligatory regular drug screenings. As outlined by Griffiths *et al*., 'Spice' may be a transient product, but it provides an excellent case study of how globally connected the world in which we now live in is challenging existing models of drug control [63].

For the above mentioned challenges, the most effective way to reduce drug demand should be the swift development and validation of analytical methods to detect synthetic cannabinoid consumption via blood and urine analysis. Knowing that a recent use of these drugs is detectable by drug screening procedures will remove one of the main motivations for use. Therefore it is necessary for the international community to share information such as mass spectrometric and chromatographic data as well as increase efforts to make a wider spectrum of reference material readily available.

The use of a generic definition for controlling synthetic cannabinoids still bears the risk of not covering all possible derivatives. However, this approach seems to be the most appropriate for controlling these substances. Scheduling single substances will not be effective as there are hundreds of compounds which can quickly replace the ones being controlled. On the other hand, the use of a generic definition may lead to production of other compounds containing halogen substituents, e. g. AM-694, or other functional groups which may lead to enhanced toxicity. Moreover, the generic definition may also hamper research in the area of synthetic cannabinoids [64].

As some countries need to prove pharmacological activity of a substance before being able to schedule it, scientific research in this regard should be strongly encouraged. An alternative to controlling these substances as a 'narcotic drug' could be by the medicinal product legislation, although this approach may have its own disadvantages depending on the laws of each individual country. Another means of supply reduction could be to implement more effective control measures in the producing/exporting countries, e. g. China and India.

For prevention and information purposes, it could be very useful to strengthen research on the toxicological properties of these compounds as some of the AAIs may have carcinogenic potential and/or acute toxicity. As recently proposed by Griffiths *et al*. [63], a minimum public health response would be to warn consumers that the product contained undeclared compounds, although this could unnecessarily lead to a renewed interest in these products and hence indirectly promoting its abuse.

As there is currently insufficient information on the prevalence of ‘Spice’ use, further epidemiological research combined with forensic-toxicological investigations in blood and urine samples of potential users would be very helpful to assess the dimension of the problem.

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