

JWH-018
Critical Review Report
Agenda item 4.5

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Summary

JWH-018 is an aminoalkylindole used as an active ingredient of products sold as cannabis substitutes. When smoked, JWH-018 produces cannabimimetic effects in doses lower than the doses of Δ^9 -tetrahydrocannabinol (THC) needed to produce effects of similar strength (higher potency). Many of the risks linked to cannabis use are also present in the case of JWH-018, among them complications in patients suffering from cardiovascular diseases and triggering of acute psychosis. Abuse potential and dependence potential seem to be similar to cannabis. One of the major differences between cannabis and this synthetic cannabinoid is the greater acute toxicity of JWH-018. Due to its full agonistic action at the CB1 receptor, the side effects of higher doses can be life-threatening. This is aggravated by the fact that dosing is very difficult due to changing contents of active ingredients in different products, different batches of the same product and even within one packet. Regarding chronic toxicity, risks are very difficult to estimate on the basis of the available data. However, there are concerns about potential carcinogenic effects.

1. Substance identification

A. *International Nonproprietary Name (INN)*

Not applicable

B. *Chemical Abstract Service (CAS) Registry Number*

209414-07-3

C. *Other Names*

JWH-018, AM-678

D. *Trade Names*

None

E. *Street Names*

‘Spice’, ‘K2’, ‘legal weed’, ‘synthetic cannabis’, ‘herbal incense’

JWH-018 was found as an additive in more than 60 different brands of ‘herbal mixtures’ in Germany alone (own unpublished data). These products were carrying fantasy names like e.g.: ‘Atomic Bomb’, ‘Dragon’, ‘Monkees Go Bananas’, ‘Rockstar’, ‘Spike 99’, ‘Ultra’ and ‘Wasted’.

Mixtures sold under specific brand names do not always contain the same substance or mixture of substances over time [67].

F. *Physical properties*

White crystalline solid (in pure form)

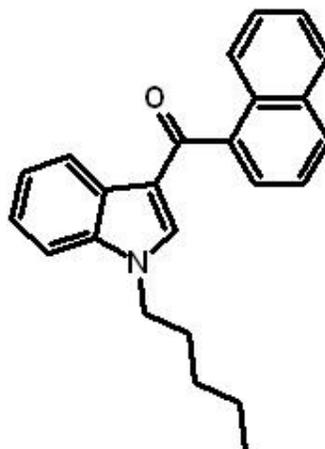
G. *WHO Review History*

JWH-018 was not previously pre-reviewed or critically reviewed. A direct critical review is proposed based on information brought to WHO’s attention that JWH-018 is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any party. Preliminary data collected from literature and different countries indicated that this substance may cause substantial harm and that it has no medical use.

2. Chemistry

A. *Chemical Name*

IUPAC Name: Naphthalene-1-yl(1-pentyl-1*H*-indol-3-yl)methanone
CA Index Name: 1-Naphthalenyl(1-pentyl-1*H*-indol-3-yl)-methanone

B. Chemical Structure

Molecular Formula:	C ₂₄ H ₂₃ NO
Molecular Weight:	341.45 g/mol
Melting point:	65-67°C [27] or 51,9°C [97]
Boiling point:	N/A
Fusion point:	N/A

C. Stereoisomers

None

D. Synthesis

Synthesis of JWH-018 can be carried out in analogy to the synthesis strategies described for various aminalkylindoles [12, 27, 49]. 1*H*-indol-3-yl(naphthalen-1-yl)methanone is prepared by Friedel-Crafts acylation using 1-*H*-indole and naphthalene-1-carbonyl chloride (prepared from naphthalene-1-carboxylic acid and thionyl chloride). Afterwards, *N*-alkylation is performed by addition of 1-bromopentane. The synthesis can also be performed vice versa. Common precursors are the above mentioned 1-*H*-indol, naphthalene-1-carbonyl chloride and 1-bromopentane. Alternatively, 1-pentyl-indole can be used as a precursor in order to skip the *N*-alkylation step.

Commercially available domestic or industrial products, which could be used for synthesis may contain other potentially toxic substances, including heavy metals and organic solvents. Use of such products as reagents may result in serious toxic effects if the resultant impure product is consumed. The herbal material which is used as a basis for the smoking mixtures may contain toxicologically relevant substances like e.g. pesticides, too.

E. Chemical description

JWH-018 is a naphthoylindole alkylated at the indole nitrogen.

F. Chemical properties

Chemically, JWH-018 can be regarded as relatively inert as it is substituted at the reactive C-3 position with the naphthoyl moiety. Due to the aromaticity of the indole system the nitrogen does not lead to considerable basicity.

G. Chemical identification

The analytical profile of JWH-018 has been described in various papers. Utilized methods include LC-MS/MS[90], GC-EI-MS [23, 28, 33, 67, 101, 103, 105, 118, 119], HRMS [39, 48, 89], NMR [66, 101], IR-ATR [97], and UV-VIS detection [37, 101, 103]. Detection in biological matrices was described in serum [30, 58, 75, 98] [31], whole blood [6, 45, 55, 63, 91, 100, 115], hair [51, 57, 84], and oral fluid [25, 59, 60, 82, 96] targeting JWH-018. In urine samples, the main metabolites are the analytical targets [7, 20, 26, 40, 50, 71, 113].

3. Ease of convertibility into controlled substances

JWH-018 is not considered an immediate precursor of any internationally controlled substance [5].

4. General pharmacology

4.1. Pharmacodynamics

JWH-018 possesses a relatively high binding affinity (expressed as IC₅₀ (occupation of 50% of the receptors)) towards the cannabinoid receptor type 1 (CB1) of 9.0 nM ± 5 and towards the cannabinoid receptor type 2 (CB2) of 2.94 nM ± 2.65 [9, 111, 112] compared to the binding affinities of delta-9 tetrahydrocannabinol (THC) of 40.7 nM ± 1.7 at the CB1 and 36.4 nM ± 10 at the CB2 receptor [24, 92]. Chimalakonda et al. tested the biological effects by applying an in vitro [³⁵S] guanosine-5'-O-(3-thio)-triphosphate ([³⁵S]GTPγS) binding assay and the compound showed full agonistic properties [21]. JWH-018 induces inhibition of forskolin-stimulated cAMP accumulation in CHO cell lines expressing CB1 receptors with an EC₅₀ 14.7 ± 3.9, maximum inhibition 79% [22] and in Neuro2AWT cells with an EC₅₀ of 5.31 ± 0.4 nM [17]. Based on this data and clinical observations, it can be assumed that JWH-018 shows typical effects of CB1 agonists including sedation, cognitive dysfunction, tachycardia, postural hypotension, dry mouth, ataxia, immunosuppression and psychotropic effects [10].

A pronounced difference with regard to THC is the formation of potential pharmacologically active JWH-018 metabolites. While in the case of THC, only one of the major THC-metabolites is known to be psychoactive and retains binding affinity towards cannabinoid receptors (11-OH-THC: K_i at the CB1 receptor: 38.4 nM ± 0.8 [24]), several JWH-018 metabolites retain high CB1 receptor binding affinity (relative rank of binding affinities: JWH-018 > JWH-018 N-(4-OH-pentyl) > JWH-018 N-(5-OH-pentyl) > JWH-018 (5-OH-indole) = THC = JWH-018 (6-OH-indole) = JWH-018 N-(5-OH-pentyl) > JWH-073 N-(4-OH-butyl)) >> JWH-018 pentanoic acid [15, 16, 21]). Furthermore, full agonistic binding has been shown for JWH-018, JWH-018 (5-OH-indole), JWH-018 (6-OH-indole) as well as for JWH-018 N-(5-OH-pentyl)

applying [³⁵S]GTP γ S binding assays, and partial agonist activity for JWH-073 (6-OH-indole) and JWH-073 N-(4-OH-butyl) [15, 16, 21]. The glucuronidated JWH-018 N-(5-OH-pentyl) metabolite retains binding affinity towards the CB1 receptor and activity as a neutral antagonist (K_i: 922 nM) [88]. No data is available concerning the question whether this metabolite of JWH-018 is capable of antagonizing pharmacological effects of JWH-018 in vivo, and if sufficient concentrations are formed at the site of action.

Similar to the retention of CB1 receptor affinity, metabolites of JWH-018 also bind with high affinity at the CB2 receptor (relative rank of binding affinity: JWH-018 > JWH-073 > THC > JWH-073-N-(3-OH-butyl) > JWH-018 N-(5-OH-pentyl) > JWH-018 (6-OH-indole) > JWH-018 N-(4-OH-pentyl) > JWH-073 N-(4-OH-butyl) > JWH-073 (6-OH indole) >> JWH-018 pentanoic acid and JWH-073 butanoic acid). Utilizing a [³⁵S]GTP γ S binding assay and an adenylyl cyclase assay to measure intrinsic activity, JWH-018 showed full agonist activity at CB2 receptors. The results from measuring the binding affinity as well as the intrinsic activity suggest that JWH-018 binds more efficiently to CB2 receptors thus requiring occupancy of fewer receptors to produce equivalent levels of adenylyl activity [81]. As CB2 receptors are predominantly expressed in various immune cell types, JWH-018 uptake might modulate immune function which could lead to immune suppression.

Investigations on effects of JWH-018 on 12-O-tetradecanoylphorbol-13-acetate (TPA) induced inflammation and carcinogenesis in mice were carried out by Nakajima et al., showing a higher anti-inflammatory activity of JWH-018 when compared to indomethacin [74]. Furthermore, JWH-018 (0.02 μ M JWH-018/mouse and 0.2 μ M JWH-018/mouse) inhibited tumor promotion by TPA in mouse skin carcinogenesis model.

Neuropharmacology and effects on the central nervous system

Atwood et al. investigated the effects of JWH-018 on glutamatergic neurotransmission in cultured autaptic hippocampal neurons and activation of ERK1/2 mitogen activated protein kinase (MAPK) as well as the internalization of CB₁ receptors [8]. JWH-018 inhibited excitatory postsynaptic currents in a concentration and CB₁ receptor dependent manner (IC₅₀: 14.9 nM), increased MAPK phosphorylation and induced rapid and robust receptor internalization, therefore indicating that the typical effects after JWH-018 consumption are very likely due to CB₁ receptor activation.

A case report published by Rominger et al. describes short-term alterations of dopamine D2/3 receptors availability in a patient before and after acute detoxification from a 'herbal mixture' product, concluding that consumption of synthetic cannabinoids can lead to serious health problems, where substantial alterations of the dopaminergic system have to be taken into account [83]. Unfortunately, the consumed herbal mixture was not analyzed in this case and as a consequence no conclusion can be drawn on which synthetic cannabinoid was consumed.

Effects on cardiovascular, respiratory, gastrointestinal, liver, kidneys and genitourinary systems

No study data available. However, a marked elevation of the heart rate is one of the clinical signs very often seen after intoxication with synthetic cannabinoids.

Behavioural studies in animals

Behavioural effects in mice after the inhalation of smoke from 200 mg of a herbal mixture containing 3.6% JWH-018, 5.7% JWH-073 and less than 0.1 % JWH-398 were studied utilizing the tetrad test (response in all four categories suggest CB₁ activity) by Poklis et al. [79]. After inhalation the body temperature of all tested mice dropped more than after smoking of 200 mg marijuana (3.5 % THC), and the mice remained cataleptic for at least 20 min. Wiebelhaus et al. also performed tetrad testing in mice, by exposing the animals to the smoke of 10, 20 or 50 mg of a 5.4% JWH-018 containing herbal mixture [109]. The study animals showed hypomotility, antinociception, catalepsy, and hypothermia in a dose related manner. The behavioural effects were blocked by rimonabant (CB₁ receptor antagonist), strengthening the observation that the effects are mediated by CB₁ receptor activation. Further observations in the study animals included ptosis, hyperreflexive responses and straub tail. 50 mg of the herbal mixture was found to produce similar effects as 200 mg marijuana (14.8 mg THC). In both studies JWH-018 was detected in the brain tissue of the animals. Wiley et al. also observed hypomotility, antinociception, catalepsy, and hypothermia in mice after injection of JWH-018 [111, 112]

Based on drug discrimination studies carried out in THC trained rats, JWH-018 appeared to be 8 times more potent than THC. Presence of rimonabant resulted in a 4.4-fold parallel shift to the right of the JWH-018 dose-response curve, suggesting antagonism and mediation through CB₁ receptors [53, 54]. Additionally, drug discrimination studies were also carried out in THC trained rhesus monkeys by Ginsburg et al. [38]. In the tested monkeys JWH-018 also increased the response on the THC-lever in a dose dependent manner and was 3.4-fold more potent than THC. However, THC had a significantly longer duration of action compared with JWH-018 (4 h vs. 2 h). The same authors also carried out drug discrimination studies in rimonabant trained rhesus monkeys, whereas JWH-018 dose-dependently decreased the response rate, indicating a mediation of the THC-like effects through CB₁ receptors. This is in accordance to the results obtained from the drug discrimination studies in rats.

As a consequence from the above drug discrimination study data, it can be concluded that JWH-018 is pharmacologically active and users are likely to experience marijuana-like effects. Furthermore, Ginsburg et al. come to the conclusion that the shorter duration of action could evoke a more frequent use, and might therefore increase abuse and dependence liability [38].

Investigations of the effects of JWH-018 on electroencephalogram (EEG) power spectra and locomotor activity in rats by Uchiyama et al. indicated that the effect on the EEG is different from that of THC as JWH-018 increased the EEG power up to 3.9 fold and reduced the EEG activity, whereas THC reduced the EEG power [102]. Furthermore, locomotor activity was reduced more strongly and for a longer time by JWH-018 than by THC. The experiments showed that JWH-018 changed the EEG power spectra and suppressed the locomotor activity of rats more significantly and for a longer duration than THC, indicating potent pharmacological action in the central nervous system.

Vardakou et al. reported the observation of a severe lethargic, unresponsive catatonic state at all doses tested in a rat repeat dose study (0.1 to 10 mg/kg). Furthermore, at 10 mg/kg breathing frequency decreased and one rat died. However, the exact methodology of the study is not stated [107].

Further studies conducted by Hrubá et al. in rhesus monkeys came to the conclusion that there may be differences in the dependence liability between JWH-018 and THC, as tolerance was observed after 3 days of THC treatment for THC but no cross-tolerance for JWH-018 [47].

Behavioral responses to acute and sub-chronic administration of JWH-018 in adult mice were investigated by Macri et al. [69]. Intraperitoneal injection of JWH-018 reduced general locomotion and body temperature, resembling the effects exerted by classical cannabinoids. Furthermore, JWH-018 administration reduced pain sensitivity. The authors observed that some of the effects were not present when the mice were exposed to prenatal corticosterone administration (mimicking precocious stress), indicating differences in the individual reactivity to psychotropic drugs.

Furthermore, the National Institute on Drug Abuse (NIDA) conducted pharmacological studies on JWH-018, concluding that the discriminative stimulus effects of JWH-018 are similar to those of THC, as JWH-018 fully substituted these effects in rats [5].

Effects on cognition in humans

No study data available.

Effects in humans

Apart from user reports on the Internet, two self experiments with a description of experienced effects are available in the literature. Auwärter et al. described reddened conjunctivae, significant increase in pulse rates, xerostomia and alteration of mood and perception after smoking 300 mg of a ‘herbal mixture’ containing the C8 homolog of CP47,497 and JWH-018 [11].

Teske et al. published a self-experiment including two volunteers who reported sickness, sedation and xerostomia immediately after smoking an approximate 50 µg/kg dose of JWH-018. Additionally hot flushes, burning eyes and a subjectively felt thought disruption were experienced. Maximum JWH-018 serum concentrations in these two volunteers were approximately 10 ng/ml [98].

Interactions with other substances and medicines

Drug-drug interaction of JWH-018 and JWH-073 was investigated by Brents et al., showing synergistic effects of these two compounds in THC-like discriminative stimulus effects, analgesia (ratio JWH-018 : JWH-073 of 2:3), and displacement of [3H]CP55,940 from CB1 receptors, whereas only additive interaction could be observed for analgesia when testing a JWH-018 : JWH-073 ratio of 1:1 and for the inhibition of the adenylyl cyclase activity [17]. Furthermore, a combination of JWH-018 and JWH-073 showed antagonistic interaction for hypothermia and subadditive suppression of food-maintained responding in mice (surrogate for task-disruptive adverse effects such as dizziness, drowsiness and mental confusion). The above results suggest that JWH-018 and JWH-073 may bind at separate sites of the CB1 receptors and the synergistic effects might be mediated via intracellular effectors other than adenylyl cyclase.

Furthermore, Chimalakonda et al. investigated inhibition of oxidation of JWH-018 in human liver microsomes by sulfaphenazole (selective CYP2C9 inhibitor) and α -naphthoflavone (selective CYP1A2 inhibitor) [18]). The results of the study support the finding that CYP1A2 and CYP2C9 mediate JWH-018 oxidation as both compounds inhibited formation of the JWH-018 N-(5-OH-pentyl) metabolite in a dose-dependent manner. Combination of both inhibitors showed a clear additive effect. Based on this

data it seems likely that drug-drug interactions can occur when JWH-018 is co-administered with drugs inhibiting CYP1A2 (e.g. ciprofloxacin, fluvoxamine) or CYP2C9 (e.g. sulfaphenazole, valproic acid). Additionally, higher JWH-018 concentrations may be reached in populations with polymorphic alleles of these enzymes leading to reduced enzyme activity.

4.2. Routes of administration and dosage

JWH-018 is mainly offered on the Internet either in the form of ‘herbal mixtures’, where the chemical has been sprayed on plant material (e.g. damiana), or as a powder [5, 10]. Based on user reports and on the dosage forms offered, the primary route of administration is inhalation either by smoking the ‘herbal mixture’ as a joint or utilizing a vaporizer, bong or pipe [114]. Furthermore, oral consumption of the compound was described by various users on the Internet [114]. Based on information posted at Internet for a, common dosages are in the range of 2 to 5 mg when smoked/vaporized (erowid.org). Doses for oral application can be assumed to be significantly higher due to lower bioavailability (first pass effect).

Reports suggest a duration of action for JWH-018 of approximately 1-2 hours when smoked [5].

JWH-018 content was analyzed by several authors in various ‘herbal mixtures’ purchased in the USA (0.21 – 49 mg/g) [67], Germany (2.3 ng/g) [66], Japan (< 1 – 35.9 mg/g) [103], Italy (14 mg/g) [105], and Korea (6.8 – 46.9 mg/g) [23]. Doses can be adjusted by the amount of ‘herbal mixture’ used to prepare a joint.

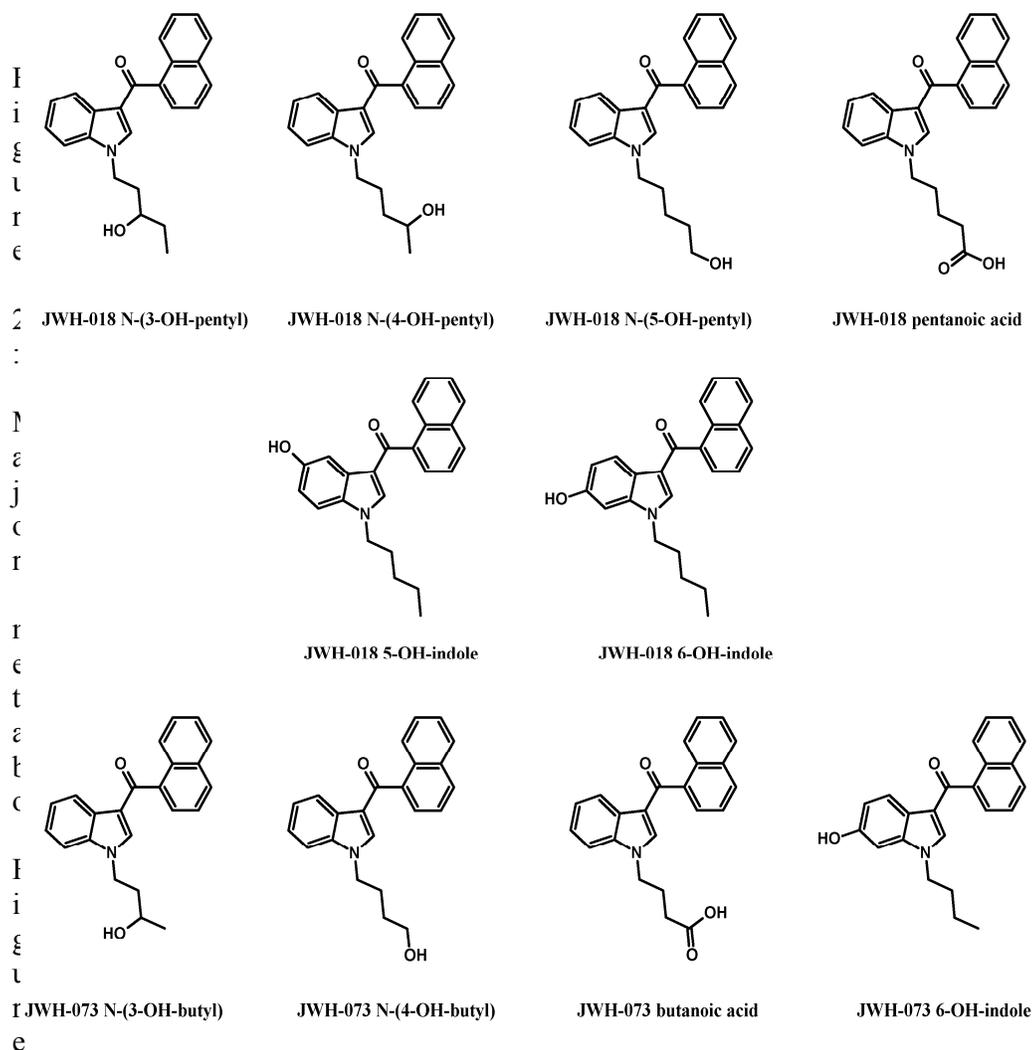
It has to be considered that many of the ‘herbal mixtures’ are inhomogeneous with respect to the content of active ingredients, as it has been shown by Choi et al., Langer et al., Logan et al. Ng et al., and Zuba et al. [23, 64, 67, 76, 118, 119]. In some cases the JWH-018 content ranged from 6.8 to 44.4 mg/g within one product [23]. Furthermore, quite often more than one synthetic cannabinoid is added to ‘herbal mixtures’ [23, 29, 41, 56, 67]. In Japan, Kikura-Hanajiri et al. detected an average number of 2.6 synthetic cannabinoids per product [56]. The maximum number of synthetic cannabinoids detected in one mixture by these authors was ten.

Analysis of JWH-018 powder ordered from three different online retailers revealed a purity ranging from 75 to 91% [37]. Furthermore, the smell of naphthalene was noticeable in two of the three samples.

4.3. Pharmacokinetics

JWH-018 is metabolized by various enzymes of the CYP450 family. Using human liver microsomes (HLM) and recombinant human protein, Chimalakonda et al. [21] identified CYP2C9 and CYP1A2 as the major enzymes involved in the metabolic oxidation of JWH-018, whereas the contribution of CYP2C19, 2D6, 2E1 and 3A4 was relatively small for this metabolic step. The primary metabolites detected in authentic urine samples were JWH-018 N-(3-OH-pentyl), JWH-018 N-(4-OH-pentyl), JWH-018 N-(5-OH-pentyl), JWH-018 pentanoic acid, JWH-018 (5-OH-indole), JWH-018 (6-OH-indole), JWH-073 N-(3-OH-butyl), JWH-073 N-(4-OH-butyl), JWH-073 butanoic acid and JWH-073 (6-OH-indole) (Figure 2) [14, 50, 52, 94]. The main metabolites

following HLM incubation were JWH-018 N-(4-OH-pentyl) (21%), JWH-018 N-(5-OH-pentyl) (18%), JWH-018 (6-OH-indole) (36%) and JWH-018 (5-OH-indole) (19%).



2: Major metabolites of JWH-018 lites of JWH-018

The reactions followed classic Michaelis Menten kinetics in case of the JWH-018 N-(4-OH-pentyl) and JWH-018 N-(5-OH-pentyl) metabolite [21]. Furthermore, Lovett et al. detected (3-(3-(1-naphthoyl)-1H-indol-1-yl) propanoic acid (= JWH-072 propanoic acid) in samples of JWH-018, JWH-073 and AM-2201 consumers, thus proposing it as a common biomarker [68].

Almost all of the JWH-018 metabolites are excreted in the urine in the form of glucuronides. Conjugation to glucuronic acid via various UDP-glucuronosyltransferase enzymes (predominately hepatic UGT1A1, UGT1A9 and UGT2B7) has been shown for the various JWH-018 metabolites [19].

5. Toxicology

Koller et al. studied the cytotoxic, genotoxic, immunomodulatory as well as the hormonal activity of JWH-018 in human cell lines (hepatoma line (HepG2); mammary line (MCF-7); buccal epithel cells (TR146)) and primary cell lines [61, 62]. No significant acute toxicity and no estrogenic activity were observed for JWH-018. However, approximately 10-fold higher anti-estrogenic properties were seen for JWH-018 than for THC. JWH-018 showed cytotoxicity at the highest concentration level tested (100 µM) in MCF-7 and TR146 cells. THC showed cytotoxicity at 75 µM and additionally induced damage of the mitochondria and inhibited cell proliferation. JWH-018 showed no alteration of the immune function in the applied assay. In comparison to the serum levels typically reached in humans (highest concentration: 32.2 nM) the concentrations resulting in toxicity were two to three orders of magnitude higher. However, epithelial cells in the upper aerodigestive tract are likely to be exposed to higher concentrations, which could result in cell damage.

Toxicity of JWH-018 has also been investigated on primary neuronal cells of the forebrain, showing an induction of cytotoxicity in a concentration-dependent manner [99]. Using preincubation with a CB₁ selective antagonists (AM-251) JWH-018 (30 µM) cytotoxicity was suppressed, indicating an important role of CB₁ receptors in the induction of cytotoxicity in this cell line. Furthermore, the JWH-018 cytotoxicity proceeded via apoptosis and was mediated by caspases, revealing a strong neurotoxic effect according to the authors. However, considering the concentrations tested in the above study of 10 µM and 30 µM JWH-018, conclusions on the cytotoxicity in vivo have to be drawn with utmost care as serum concentration levels published in the literature or from analysis of clinical or forensic samples were not higher than 32.2 nM (11 ng/ml) and are therefore 300-fold lower than the concentrations applied by Tomiyama et al. Nevertheless, due to the lipophilic character of JWH-018, it can not be excluded that higher concentrations may occur in deeper (fat-rich) compartments after continued abuse and accumulation or in epithelial cells of the aerodigestive tract.

Apart from these studies, no data regarding the toxicity of JWH-018 is published in the literature so far, and in particular there is no data on potential teratogenic effects. However, it has to be noted that the endocannabinoid system is present from conception onwards in the developing central nervous system and that THC, as well as the cannabimimetic WIN-55,212-2, interfere with the endocannabinoid system to cause anencephaly and neurobehavioural deficiencies in the offspring [80]. It is not known whether JWH-018 crosses the placental barrier. However, based on its physico-chemical properties, it can be assumed to effectively reach the fetal tissue via the placenta.

6. Adverse reactions in humans

Non-fatal Cases

Adverse effects described in the literature after the consumption of synthetic cannabinoids include tachycardia, agitation, hallucination, hypertension, minor elevation of blood glucose, hypokalemia, vomiting, chest pain, seizures, myoclonia, extreme anxiety leading to panic attacks and acute psychosis (risk of suicide) [5, 43, 77, 78].

Cases of JWH-018 intoxications in humans published in the literature:

A healthy 48-year-old man developed a generalized seizure and supraventricular tachycardia 30 minutes after ingestion of an ethanolic JWH-018 mixture. JWH-018 metabolites were analytically confirmed in the patient's urine, with an approximate JWH-018 pentanoic acid concentration of 74 ng/ml [65].

Young et al. report of a 17-year-old male with chest pain, tachycardia and then bradycardia within 10 min after smoking a herbal mixture containing JWH-018 and JWH-073 and one hour after uptake of 100 mg of caffeine [116].

Further three cases of adverse effects after analytically confirmed JWH-018 consumption are described by Simmons et al.[93]. Case 1, a 25-year-old male developed seizures, tachycardia, acidosis and unresponsiveness after smoking a 'herbal mixture', and his urine was tested positive for JWH-018 metabolites. The second case was a 21-year-old male who was found unresponsive (Glasgow Coma Score of 7) with hypertension, warm dry skin, and agitated. JWH-018 and JWH-073 metabolites were detected in the obtained urine sample, however based on the metabolites no conclusion can be drawn whether JWH-018 or a combination of JWH-018 and JWH-073 was consumed. The third case describes a 19-year-old male who suffered from paranoia and delusions 1 hour after smoking a herbal mixture, similar to case two, the urine sample was tested positive for JWH-018 and JWH-073 metabolites.

Hermanns-Clausen et al., describe seven cases of acute intoxications with analytically confirmed uptake of JWH-018 [44]. Symptoms observed included restlessness (n=3), changes of perception (n=2), vertigo (n=1), somnolence (n=1), anaesthesia (n=1), shivering (n=2), tachycardia (n=4), hypertension (n=2), thoracic pain (n=1), nausea/vomiting (n=1), dry mouth (n=2), mydriasis (n=3), conjunctival hyperemia (n=3), and hypokalemia (n=1). However, evaluation of the contribution of JWH-018 to the symptoms is hampered by the fact that in four cases further synthetic cannabinoids were present in the biological samples.

A 19-year-old male, became unresponsive, vomited repeatedly and was found in a comatose state without sufficient respiration, requiring mechanical ventilation for three hours. 0.39 ng/ml JWH-018 along with JWH-122 (230 ng/ml) and JWH-210 (7.8 ng/ml) were detected in the serum sample obtained from the patient two hours after the last consumption [43].

A 19-year-old man had two generalized convulsions (duration 1-2 min) and vomited soon after smoking a 'herbal mixture' containing JWH-018, JWH-081, JWH-250 and AM-2201 [86]. Hopkins et al. report a case of cannabinoid hyperemesis syndrome in a consumer with a self-reported highly frequent synthetic cannabinoid consumption who had developed recurring and severe crampy abdominal pain associated with intractable nausea and vomiting. Urine samples of the patient tested positive for JWH-018, JWH-073 and AM-2201, and negative for THC. Furthermore, the patient reported that after two weeks of sobriety his symptoms completely resolved [46].

Two, previously healthy siblings suffered from acute embolic-appearing ischemic strokes. Patient 1 (26 years, male) had a sudden onset of dysarthria, expressive aphasia, and right face and arm weakness. The patient stated smoking a 'herbal mixture' a few hours prior to experiencing these symptoms and use of marijuana a couple of days

earlier. A urine sample of the patient was tested positive for cannabinoids and no test was conducted for synthetic cannabinoids. Patient 2 (19 years, female), lost consciousness and vomited a few minutes after smoking a 'herbal mixture'. This was followed by several hours of persistent altered mental status and 'shaking movements' of the arms and legs. A serum sample obtained from this patient was positive for JWH-018 and it is stated that she smoked the same mixture as patient 1 [36].

Every-Palmer interviewed 15 patients with serious mental illness regarding the use and effects of JWH-018, and 9 of the patients reported that they experienced or exhibited symptoms consistent with psychotic relapse after smoking a JWH-018 containing herbal mixture [34]. The author comes to the conclusion that it seems likely that JWH-018 can precipitate psychosis in vulnerable individuals. However, as the study is based on self-reports only, it can not be assumed that JWH-018 was consumed exclusively.

Schneir et al. describe two patients who were presented to an emergency department after consumption of a 'herbal mixture' (later confirmed to contain JWH-018 and JWH-073) [87]. Patient one (22 years, female), felt anxious, tremulous and experienced palpitations. Physical examination revealed normal vital signs, occasional inappropriate laughter, normal-sized pupils, bilaterally injected conjunctivae and a few beats of lateral gaze nystagmus. Patient two (20 years, female) also felt anxious and felt like 'becoming psychotic'. Physical examination revealed normal sized pupils, bilaterally injected conjunctivae, and tachycardia.

A case report published by Vearrier and Osterhandt describes a 17-year-old female who was presented to the emergency department with tachycardia, agitation, muscle fasciculations, and hypokalemia after smoking JWH-018. Furthermore, her urine drug screen was tested positive for Δ^9 -tetrahydrocannabinol [108].

Fatal cases

Three fatal cases in which JWH-018 could be detected in post-mortem blood samples are published. One occurred in Germany, where a 36-year-old man collapsed after smoking 'herbal mixtures'. He suffered from seizures and died after admission to the hospital despite continued resuscitation attempts. The residue of the joint consumed contained the synthetic cannabinoids JWH-122, AM-2201, MAM-2201 and UR-144. JWH-018 could be detected in the femoral blood sample of the deceased at a concentration of 0.1 ng/ml as well as in gastric content (~9.0 μ g absolute), hair (~0.05 ng/mg) and adipose tissue (~30 ng/g). Furthermore, the synthetic cannabinoids AM-2201 (1.4 ng/ml), JWH-122 (0.3 ng/ml), MAM-2201 (1.5 ng/ml) and UR-144 (6 ng/ml) as well as a high concentration of amphetamine (250 ng/ml) were also detected in the femoral blood indicating an acute influence of several synthetic cannabinoids and amphetamine [85]. In this case, the presence of various substances in the femoral blood hampers an evaluation of the contribution of JWH-018 to the lethal outcome.

The second case describes a fatal methoxetamine intoxication of a 26-year-old male in Sweden, where it cannot be ruled out that the presence of three synthetic cannabinoids (femoral blood: AM-2201 (0.3 ng/g), AM-694 (0.09 ng/g) and JWH-018 0.05 ng/g) may have contributed to the lethal outcome. [110].

Furthermore, a 19-year-old student died four days after collapsing on a basketball court, and the coroner appointed drug toxicity and organ failure as the cause of death because toxicological analysis revealed ingestion of JWH-018 [5] and other causes were absent.

Cases of persons driving a motor vehicle under the suspected influence of synthetic cannabinoids:

Whole blood concentrations of JWH-018 in samples collected from Norwegian drivers ranged from 0.08 to 0.46 ng/ml (n = 5) [100]. Serum concentrations of persons driving a vehicle after uptake of JWH-018 in Germany ranged from 0.17 to 1.9 ng/ml (n = 3) [72]. The symptoms as well as other drugs detected in these individuals are listed in Table 1.

Case No.	Patient details	Reference	Clinical presentation	Comments
1	19 y, m	Musshoff et al. 2013 (Germany)	Arrived with car in a very intoxicated state, police noted: 'not able to follow instructions, retarded sequence of movements, lazy, cumbersome, confused and disorientated, slurred and babbled speech, inappropriate freezing, reduced breathing and enlarged pupils'. At the hospital very dizzy and nearly unconscious.	Uptake of AM-2201 and JWH-018
2	21 y, m	Musshoff et al. 2013 (Germany)	General road traffic control. Police noted: 'delayed reactions, retarded sequence of movements, nervous, lazy, known drug user'; 81 min later physician noted: 'constricted pupils, no reaction of the pupils to light, dizzy mind, and depressive mood'.	Uptake of JWH-018, JWH-122 and JWH-210
3	22 y, m	Musshoff et al. 2013 (Germany)	On a motorbike, about to be checked at a general road traffic control. Firstly, escaped by overrunning red traffic lights, later he skedaddled by foot. Police noted after arrest: 'retarded sequence of movements, apathetic, nervous, inert, delayed reactions of pupils. One hour 35 min later, physician noticed no abnormalities.	Uptake of AM-2201, JWH-018, JWH-122, JWH-210, JWH-307, MAM-2201 and UR-144

Similar to most other cases, several synthetic cannabinoids were detected in the serum of the respective person, suggesting synergistic effects.

JWH-018 metabolites were detected in the urine of a driver in the US who drove through a residence and claimed to have no memory of the event [5].

JWH-018 serum / blood concentrations found in the literature

Kacinko *et al.*, conducted a self-experiment in which one volunteer smoked parts of a joint containing approximately 6 mg of JWH-018. The highest whole blood JWH-018 concentration was detected in the samples obtained 19 min after consumption (4.8 ng/ml) [55].

JWH-018 serum concentrations ranged from 0.3 to 8.17 ng/ml (median 0.64 ng/ml) in nine JWH-018 positive cases out of 101 serum samples analyzed by Dresen et al. in 2010 [30].

Kneisel and Auwärter analyzed 833 authentic serum samples obtained between August 2011 and January 2012 (mainly from forensic psychiatric clinics and rehabilitation clinics). Of the 227 samples tested positive for synthetic cannabinoids, 23 were positive for JWH-018 with a median concentration of 0.28 ng/ml, and the highest concentration detected was 11 ng/ml [58].

JWH-018 concentrations in whole blood samples obtained from persons accused of petty drug offences or driving under the influence of drugs in Sweden ranged from 0.05 to 11 ng/g (median: 0.1 ng/g; n=115) [63].

Based on the analysis of 185 JWH-018 positive serum samples in Germany (mainly from forensic psychiatric hospitals, analyzed for abstinence control), the concentrations ranged from < 0.1 to 15 ng/ml (mean: 1.6 ng/ml; median: 0.4 ng/ml) (own unpublished data).

Adverse effects associated with use of synthetic cannabinoids without analytically confirmation:

Two cases of acute ischemic stroke were reported by Bernson-Leung *et al.*, after first-time consumption of synthetic cannabinoids [13].

7. Dependence potential

There is evidence that synthetic cannabinoids can produce tolerance and withdrawal symptoms when substance use is abruptly discontinued following a regular use of high doses.

A cases report from Germany, describes the withdrawal symptoms of a 20-year-old male who had consumed the herbal mixture ‘Spice Gold’ on a daily basis. He developed tolerance and increased the dose to 3 g per day. The patient felt a continuous desire for the drug and kept on using it despite the development of persistent cognitive impairment. During withdrawal he developed inner unrest, drug craving, nocturnal nightmares, profuse sweating, nausea, tremor, and headache. The authors interpreted the symptoms as a dependence syndrome corresponding to ICD-10 and DSM-IV criteria, resembling the withdrawal syndrome in cannabis dependence [117]. Although the composition of the ‘herbal mixture’ was not determined by the authors, it can be assumed that it contained either CP47,497-C8 or JWH-018 or both (based on analytical data from a product monitoring program, own unpublished data).

Rominger et al. describe the withdrawal symptoms of a 23-year-old male who smoked 10 g of a herbal mixture (containing synthetic cannabinoids not stated in the article) on a daily basis [83]. Symptoms included anxiety, unstable mood, crying fits, feeling of inner emptiness, spatial disorientation, hyperacusis, somatic pain, shortness of breath, hyperventilation, intense sweating and sensations of motor and inner restlessness.

The most commonly reported withdrawal effects from synthetic cannabinoids in an internet based survey study were headaches, anxiety, coughing, insomnia, anger, impatience, difficulties in concentrating, restlessness, nausea, and depression [5].

The US Department of Health and Human Services expect that the physical dependence liability of synthetic cannabinoids will be similar like the one of THC as they act through the same molecular target [5]. The EMCDDA states that ‘user consider its effects to be short acting and describe an extreme urge to redose’ [32]

8. Abuse potential

Animal studies:

Drug discrimination studies conducted with JWH-018 and JWH-073 in rats and monkeys suggest that synthetic cannabinoid administration produces similar effects like THC [53, 54] [38] [5]. As a consequence, JWH-018 is very likely to have a high potential to be abused e.g. as a substitute for cannabis.

Human data:

One of the main reasons for abuse of synthetic cannabinoids is the difficulty of detecting consumption by analysis of biological samples. The non-detectability of these compounds makes them very attractive for persons undergoing regular drug tests (e.g. patients of forensic clinics/withdrawal clinics, workplace drug testing or driving licence re-granting candidates). In a survey conducted by Vandrey et al. including adults from 13 different countries who reported at least one lifetime use of synthetic cannabinoids, 38% of the study completers were subject to drug testing procedures [106].

The US Department of Health and Human Services review states that the synthetic cannabinoids JWH-018, JWH-073, JWH-200, CP-47,497 and cannabicyclohexanol exhibit a high potential for abuse similar to that of marijuana [5].

9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use

JWH-018 has not been used in therapy.

Studies in mice conducted by Nakajima et al. showed anti-inflammatory and chemopreventive properties of JWH-018 [74].

10. Listing on the WHO Model List of Essential Medicines

JWH-018 is not listed on the WHO Model List of Essential Medicines.

11. Marketing authorizations (as a medicine)

Not applicable

12. Industrial use

JWH-018 has no industrial use.

13. Non-medical use, abuse and dependence

JWH-018 was quite often found as an additive in commercially available ‘herbal-mixtures’. However, in ‘new generation’ products mostly other synthetic cannabinoids are found due to the fact that many countries put JWH-018 under the control of narcotics laws. Most reports and surveys are based on products containing synthetic cannabinoids in general, without identifying the particular substance (consumers usually do not know the composition of the products).

At present, synthetic cannabinoids appear to be mainly consumed in Europe, Japan, Russia and the USA. They have a wide-ranging abuse potential as substitutes for cannabis due to their non-detectability, easy availability and strong effects.

Synthetic cannabinoids are monitored through the European early-warning system (EWS). The main aim of the EWS is the rapid collection, analysis and exchange of information on new synthetic substances as soon as they appear in Europe. Seizures of JWH-018 were reported from Austria, Belgium, Bulgaria, Cyprus, Czech Republic, France, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Malta, Netherlands, Poland, Slovakia, Spain, and UK [4, 32] The first notification of JWH-018 occurred in Germany in 2008 [2]. In 2012, 30 new synthetic cannabinoids were formally notified to the EWS [1] and in the 2012 UNODC survey on new psychoactive substances, JWH-018 was identified as the most widespread synthetic cannabinoid.

In a nation-wide survey regarding ‘herbal mixture’ consumption among 14- to 18-year-old pupils in Spain in 2010, 1.1% for lifetime prevalence and 0.8% for last year prevalence were reported. In the USA 12% last year prevalence for synthetic cannabinoids among 12th graders was reported [3]. A representative survey conducted among students aged between 15 and 18 years at schools in the area of Frankfurt/Main, Germany, found that about 6% of respondents reported having used ‘Spice’ at least once, and 3% had used it during the last 30 days [2]. Heltsley *et al.* analyzed urine samples from 5,956 U.S. athletes (collected: 24.01.2011 – 28.10.2011) of which 4.5% were tested positive for metabolites of JWH-018 and/or JWH-073 [42].

The Drug Abuse Warning Network (DAWN), a public health surveillance system monitoring drug-related emergency department (ED) visits in the USA, reports 11,406 synthetic cannabinoids related ED visits and 28,531 in 2011 [70]. In 2010, 2,906 calls to poison centers for exposure to synthetic cannabinoids were reported across the USA by the American Association of Poison Control Centers. This number increased to 6,968 in 2011 and slightly declined to 5,228 calls in 2012. The Texas Poison Center Network further reported 1,869 calls regarding exposure to synthetic cannabinoids and three deaths from January 1, 2010 through June 30, 2013 [70].

The US Department of Health and Human Services reports of 5,450 reports from state and local forensics laboratories in 39 States of JWH-018, JWH-073, JWH-200, CP-47,497 and cannabicyclohexanol for a period from January 2009 to December 2011 [5].

Please refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

14. Nature and magnitude of public health problems related to misuse, abuse and dependence

A major health problem arises from inhomogeneities of the mixtures with regard to the content of active ingredients [23, 64, 67, 76]. As a consequence, it is not possible for the consumer to individually dose the compound. Two joints prepared from the same mixture could contain significantly different amounts of the drug. Furthermore, the composition of the 'herbal mixtures' change rapidly over time and therefore a certain product name does not guarantee the same composition of compounds between batches [90]. Apart from that, various authors identified further pharmacologically active substances in 'herbal mixtures', such as the benzodiazepine phenazepam [95], the kratom alkaloid mitragynine [73] or potent hallucinogens like N-(2-methoxy)benzyl phenethylamines [104]. These additives bear potential health risks of their own and may potentiate the risks connected to the use of the synthetic cannabinoids.

During 2010, 418 synthetic cannabinoids exposures without involvement of other substances were reported to the Texas poison center network, in comparison to 99 sole marijuana exposures. Forrester et al. further state that significantly more synthetic cannabinoid exposures were classified as 'moderate effect', while more marijuana exposures were classified as 'no effect' [35]. Out of the ten most frequently reported adverse clinical effects, nine were similar to the ones reported for marijuana. Tachycardia, agitation, hallucinations, and hypertension were significantly more frequently associated with the use of synthetic cannabinoids.

In 2013, 39 countries reported the emergence of AM-2201 (UNODC questionnaire on NPS 2013), one of the substances which replaced JWH-018 in cannabimimetics products.

Please refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

15. Licit production, consumption and international trade

Not applicable. Please refer Annex 1: Report on WHO questionnaire for review of psychoactive substances

16. Illicit manufacture and traffic and related information

In 2012, 45 countries reported seizures of synthetic cannabinoids [UNODC questionnaire on NPS 2012]. Please refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

17. Current international controls and their impact

Not applicable.

18. Current and past national controls

Controlled in Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Norway, Portugal, Romania, Slovakia, Slovenia, Sweden, Turkey, United Kingdom (according to the EDND of the EMCDDA) [32]. Also controlled in Japan, Russian Federation, Switzerland and the USA.

Please refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

19. Other medical and scientific matters relevant for a recommendation on the scheduling of the substance

No data.

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Annex 1:

Report on WHO Questionnaire for Review of Psychoactive Substances for the 36th ECDD: Evaluation of JWH-018

Data were obtained from 72 WHO Member States (18 AFR, 13 AMR, 5 EMR, 29 EUR, 3 SEAR, 4 WPR).

A total of 66 Member States answered the questionnaire for JWH-018. Of these, only 36 respondents (AFR 1, AMR 5, EMR 1, EUR 24, SEAR 1, WPR 4) had information on this substance.

LEGITIMATE USE

None reported that JWH-018 was currently authorized or in the process of being authorized/registered as a medical product in their country. Nine respondents stated that this substance was used in medical and scientific research including as reference analytical standards. There was no use stated for animal/veterinary care

HARMFUL USE

Twenty-five respondents confirmed that there was recreational/harmful use of JWH-018; the common route of administration was stated as inhaling/sniffing by 15, oral, inhaling/sniffing by 3, oral, injection, inhaling/sniffing by 2 and oral by one. Fifteen respondents stated this was obtained only via trafficking, 4 via trafficking and clandestine manufacturing and one each via clandestine manufacturing, diversion and diversion plus trafficking. Nineteen respondents reported on the common formulations of JWH-018 available with 14 reporting powder, 3 liquid forms, 1 tablet and 1 tablet/liquid. Four respondents also mention that JWH-018 is often smoked and six that JWH-018 is often found in herbal mixtures. When asked if JWH-018 was used by any special populations 7 stated general population, 2 stated clubs and one both general population and clubs. One death was reported in 2012 by one respondent in 2012. This same respondent reported 8 emergency room visits. Two other respondents reported two and more than 10 visits respectively in 2012. Four respondents reported withdrawal, tolerance and other adverse effects or medical illnesses caused by JWH-018. The features described included anacatharsis, tachycardia, nausea, dyspnea, somnolence, visual disturbances, agitation, hypocalcemia, raised blood sugar level (in one case even 300 mg/dL), mydriasis, hypertension, intoxication, spasms, hallucination, trepidation, paranoia, panic attacks, psychosis, delusions, disorientation, confusion, coordination and concentration difficulties and loss of consciousness. One respondent reported drug related crimes involving postal delivery of NPS.

Additional information provided 'JWH-018 and other synthetic cannabinoids are inhaled by smoking. The powder form is dissolved in acetone and applied to plant material and smoked. The use of JWH-018 containing products in adolescents and young adults in the United States is documented. Since the mid-2000s, herbal mixtures containing synthetic "designer cannabinoids" (including JWH-018) have appeared in "head shops" and online internet vendor sites (Schneir et al. 2010). The psychoactivity of herbal blends is due to the presence of several synthetic cannabinoid analogs, including JWH-018 (Auwarter et al. 2009; Sobolevsky et al. 2010). In 2012, the American Association of Poison Control Centers (AAPCC) reported receiving an excess of 5,200 exposure calls corresponding to products purportedly laced with synthetic cannabinoids, although the data provided does not generally

include biological sample testing that would confirm to which cannabinoid the user was exposed. Beyond the poison control center reports, the majority of reports documenting the behavioral effects and overdose with JWH-018 or its analogues are case reports and media reports (Auwarter et al. 2009; Lapoint et al. 2011; Muller et al. 2010a; Muller et al. 2010b; Zimmermann et al. 2009). These case reports are often based upon “Spice” or “K2” consumption, so a direct link to JWH-018 cannot be made. These reports usually describe behavioural effects similar to those seen with marijuana (Schedule I), including alterations of mood and perception, panic attack, acute psychosis, and agitation (Every-Palmer 2010; Vearrier and Osterhoudt 2010). Users on internet discussion forums have reported tachyphylaxis following the use of JWH-018 for three days (Wells and Ott 2011), and interviews from patients with mental illness suggest that JWH-018 precipitates psychosis (Every-Palmer 2011). The DEA reports that in addition to anecdotal reports of vehicular accidents and acute overdose by individuals and military personnel, one murder-suicide and two suicides have been linked to the abuse of synthetic cannabinoids such as JWH-018. In a murder-suicide that occurred in Omaha Nebraska, JWH-018 and JWH-250 metabolites were verified in the individual’s system. In another case report, an individual drove a vehicle through a private residence. A laboratory analysis of the smoked product and pipe verified the presence of JWH-018 and no other drugs of abuse (DEA scheduling request submitted to FDA, 2011).’

CONTROL

Of those with information on the substance, 32 reported that JWH-018 was controlled under legislation that was intended to regulate its availability - 27 under “controlled substance act”, 3 under “medicines law” and 2 as “other” legislations. Only three stated that there were challenges with the implementation of this legislation. On illicit activities involving JWH-018, six respondents reported clandestine manufacture and two the synthesis of the product itself. Ten respondents reported processing into the consumer product, 16 reported trafficking, three reported diversion and 14 an internet market.

Details on seizures are presented below.

	2011 (number of respondents)	2012 (number of respondents)
Total number of seizures	3,912 (16)	1,432 (18)
Total quantity seized (kg)	144.30 (13) in some cases it is total cannabinoids	140.03 (15) in some cases it is total cannabinoids
Total quantity seized (tablets/pills)		980 (1)
Others seized	Wraps Plant material and herbal substance also reported	Wraps Plant material and herbal substance also reported

IMPACT OF SCHEDULING

Twenty-eight respondents reported that if JWH-018 was placed under international control, they would have the laboratory capacity to identify the substance. There is no reported medical use.