

**JWH-073**  
**Critical Review Report**  
**Agenda item 4.6**

**Expert Committee on Drug Dependence**  
**Thirty-sixth Meeting**  
**Geneva, 16-20 June 2014**





## Acknowledgments

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## Summary

JWH-073 is an aminoalkylindole used as an active ingredient of products sold as cannabis substitutes. When smoked, JWH-073 produces cannabimimetic effects like  $\Delta^9$ -tetrahydrocannabinol (THC). Doses needed to produce these effects are in the same range as THC doses (JWH-073 seems to be equipotent to THC). Many of the risks linked to cannabis use are also present in the case of JWH-073, 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-073. Due to its nearly full agonistic action at the CB1 receptor, the side effects of higher doses may 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. Compared to JWH-018, JWH-073 is less potent and tends to show lower efficacy (depending on the used assay). Regarding chronic toxicity, risks are very difficult to estimate on the basis of the available data. However, there are concerns about potential carcinogenic effects, which may be aggravated by the relatively high doses required to produce the desired effects.

## 1. Substance identification

**A. International Nonproprietary Name (INN)**

Not applicable

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

208987-48-8

**C. Other Names**

JWH-073

**D. Trade Names**

None

**E. Street Names**

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

JWH-073 was found as an additive in over 60 different brands of ‘herbal mixtures’ in Germany alone (own unpublished data). These products were carrying fantasy names like e.g.: ‘Aura Blond’, ‘Diamond’, ‘Lunar Gold’, ‘Nightmare’, ‘Spike 99 Ultra’ and ‘Toxic Waste’.

Mixtures sold under specific brand names do not always contain the same substance or mixture of substances over time <sup>[1]</sup>.

**F. Physical properties**

White crystalline solid (in pure form)

**G. WHO Review History**

JWH-073 was not previously pre reviewed or critically reviewed. A direct critical review is proposed based on information brought to WHO’s attention that JWH-073 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.

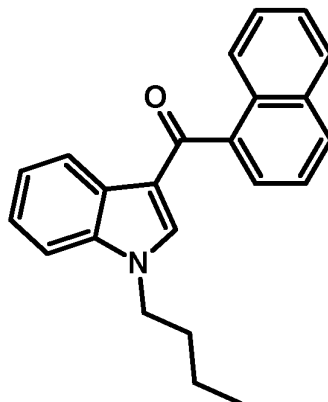
## 2. Chemistry

**A. Chemical Name**

**IUPAC Name:** (1-butyl-1H-indol-3-yl)(naphthalen-1-yl)methanone

**CA Index Name:** 1-naphthalenyl(1-butyl-1H-indol-3-yl)-methanone



**B. Chemical Structure****Free base:**

<b>Molecular Formula:</b>	C <sub>23</sub> H <sub>21</sub> NO
<b>Molecular Weight:</b>	327.41 g/mol
<b>Melting point:</b>	99.8°C <sup>[4]</sup>
<b>Boiling point:</b>	n/a
<b>Fusion point:</b>	n/a

**C. Stereoisomers**

None

**D. Synthesis**

Synthesis of JWH-073 can be carried out in analogy to the synthesis strategies described for various aminalkylindoles<sup>[2, 3]</sup>. 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-bromobutane. The synthesis can also be performed vice versa. Common precursors are the above mentioned 1-*H*-indol, naphthalene-1-carbonyl chloride and 1-bromobutane. Alternatively, 1-butyl-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-073 is a naphthoylindole alkylated at the indole nitrogen.

#### **F. Chemical properties**

Chemically, JWH-073 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-073 has been described in various papers. Utilized methods include LC-MS/MS<sup>[5]</sup>, GC-EI-MS<sup>[1, 6-17]</sup>, HRMS<sup>[18-21]</sup>, NMR<sup>[14, 15]</sup>, IR-ATR<sup>[22]</sup>, DART-MS<sup>[23]</sup> and UV-VIS detection<sup>[12, 13, 24]</sup>. Detection in biological matrices was described in serum<sup>[25-27]</sup>, whole blood<sup>[28-34]</sup>, hair<sup>[35-37]</sup>, and oral fluid<sup>[38-42]</sup> targeting JWH-073. In urine samples, the main metabolites are the analytical targets<sup>[43-49]</sup>.

### **3. Ease of convertibility into controlled substances**

JWH-073 is not considered an immediate precursor of any internationally controlled substance<sup>[50]</sup>

### **4. General pharmacology**

#### **4.1. Pharmacodynamics**

JWH-018 possesses a relatively high binding affinity (expressed as IC<sub>50</sub> (occupation of 50% of the receptors)) towards the cannabinoid receptor type 1 (CB1) of  $8.9 \pm 1.8$  nM and a similar binding affinity towards the cannabinoid receptor type 2 (CB2) of  $38.0 \pm 24$  nM<sup>[51-53]</sup> compared to the binding affinities of delta-9 tetrahydrocannabinol (THC) of  $40.7 \pm 1.7$  nM at the CB1 and  $36.4 \pm 10$  nM at the CB2 receptor [54, 55]. Furthermore, Griffin et al. et al. tested the biological effects by in vitro [35S] guanosine-5'-O-(3-thio)-triphosphate ([35S]GTP $\gamma$ S) binding assay, measuring partial agonistic properties (maximum receptor stimulation: 19-40 %) [53], while Brents et al. describe JWH-073 as full agonist<sup>[56]</sup>.

Studies conducted by Atwood et al. showed that JWH-073 decreased the magnitude of excitatory postsynaptic currents (EPSCs) in a concentration-dependent manner. Furthermore, it was demonstrated that these effects were a result of CB1 receptor activation. JWH-073 promotes receptor internalization at a slower rate than the synthetic cannabinoids JWH-018 with a half-life of 74.2 min (JWH-018: 22.9 min) However, it remains to be determined if and how it produces tolerance in vivo. The authors further observed that the effects differ from THC, which produces no inhibition of EPSCs<sup>[58]</sup>.

JWH-073 inhibited adenylyl cyclase activity in Neuro2AWT cells with an IC<sub>50</sub> of  $53.54 \pm 6.74$  nM<sup>[59]</sup>.

Based on this data and clinical observations, it can be assumed that JWH-073 shows typical effects of CB1 agonists including sedation, cognitive dysfunction, tachycardia, postural hypotension, dry mouth, ataxia, immunosuppression and psychotropic effects<sup>[57]</sup>.

A pronounced difference with regard to THC is the formation of potentially pharmacologically active JWH-073 metabolites. While in the case of THC, only one of

the various THC-metabolites is known to be psychoactive and retains binding affinity towards cannabinoid receptors (11-OH-THC:  $K_i$  at CB1 receptor:  $38.4 \pm 0.8$  nM)<sup>[55]</sup>, several JWH-073 metabolites retain high CB1 receptor binding affinity (relative rank of binding affinities: JWH-073 > JWH-073 (4-OH-indole) > THC > JWH-073 (7-OH-indole) > JWH-073 N-(4-OH-butyl) >> JWH-073 butanoic acid)<sup>[56]</sup>.

Furthermore, partial agonist properties have been shown for JWH-073 (4-OH-indole), JWH-073 (6-OH-indole) and JWH-073 N-(4-OH-butyl) applying [35S]GTP $\gamma$ S binding assays. JWH-073 (7-OH-indole) did not produce G-protein activation, despite of an affinity for the CB1 receptor in the intermediate nanomolar range. Furthermore, this metabolite acted as a neutral antagonist at the CB1 receptor, as it produced a concentration-dependent shift-to-the-right of the JWH-018, JWH-073 and CP-55,940 curve without affecting the maximum efficacy. In vivo studies showed that JWH-073 (7-OH-indole) administration (10 mg/kg) significantly antagonizes JWH-018 (3 mg/kg) induced hypothermia in mice<sup>[56]</sup>.

Similar to the retention of CB1 receptor affinity, metabolites of JWH-073 also bind to the CB2 receptor with high affinity (relative rank of binding affinities: JWH-073 > THC > JWH-073-N-(3-OH-butyl) > JWH-073 (4-OH indole) > JWH-073 N-(4-OH-butyl) > JWH-073 (5-OH indole) > JWH-073 (6-OH indole) >> JWH-073 butanoic acid). Utilizing [35S]GTP $\gamma$ S binding assays and adenylyl cyclase assays to measure the intrinsic activity, JWH-073 showed full agonistic properties and JWH-073 (4-OH indole) as well as JWH-073 (5-OH indole) partial agonist activity. The results from measuring the binding affinity as well as the intrinsic activity also suggest that JWH-073 N-(4-OH-butyl) may couple more efficiently to CB2 receptors thus requiring occupancy of fewer receptors to produce equivalent levels of adenylyl activity<sup>[60]</sup>. As CB2 receptors are highly expressed in immune cell types, JWH-073 uptake might modulate immune function which could lead to immune suppression.

### **Neuropharmacology and effects on the central nervous system**

A case report published by Rominger et al. describes short-term alterations of dopamine D<sub>2/3</sub> 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<sup>[61]</sup>. Unfortunately, the consumed herbal mixture was not analyzed in this case and as a consequence no conclusion can be drawn on which particular 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 CB<sub>1</sub> activity) by Poklis et al.<sup>[62]</sup>. After inhalation the body temperature of all tested mice dropped more than after inhalation of 200 mg marijuana (3.5 % THC), and the mice remained cataleptic for at least 20 min. JWH-073 was detected in the brain tissue of the animals.

Furthermore, Wiley et al. also observed hypomotility, antinociception, and hypothermia in mice after injection of JWH-073 <sup>[51]</sup>

Based on drug discrimination studies carried out in THC trained rhesus monkeys, JWH-073 appeared to be equipotent to THC. However, THC had a significantly longer duration of action compared with JWH-073 (4 h vs. 1 h). The same authors also carried out drug discrimination studies in rimonabant trained rhesus monkeys, and in this study JWH-073 dose-dependently decreased the response rate, indicating a mediation of the THC-like effects through CB1-receptors <sup>[63]</sup>.

As a consequence of the above drug discrimination study data, it can be concluded that JWH-073 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 <sup>[63]</sup>.

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-073 and THC, as cross-tolerance was observed after 3 days of THC treatment for THC but no cross-tolerance for JWH-073 <sup>[64]</sup>.

Furthermore, the National Institute on Drug Abuse (NIDA) conducted pharmacological studies on JWH-073, concluding that the discriminative stimulus effects of JWH-073 are similar to those of THC, as JWH-073 fully substituted these effects in rats <sup>[50]</sup>.

#### **Effects on cognition in humans**

No study data available.

#### **Effects in humans**

Apart from user reports on the Internet, there is no data available. Users reported cannabimimetic effects after smoking the drug. Potency was reported about half of the potency of JWH-018.

#### **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), 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 <sup>[59]</sup>. 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.

## **4.2. Routes of administration and dosage**

JWH-073 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 <sup>[50, 57]</sup>. 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 [65]. Furthermore, oral consumption of the compound was described by various users on the Internet [65]. Based on information posted at Internet fora, common dosages are in the range of 4 to 10 mg when smoked/vaporized (erowid.org, land-der-traeume.de). Doses for oral application can be assumed to be significantly higher due to lower bioavailability (first pass effect).

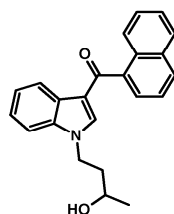
Reports suggest a duration of action for JWH-073 of 1-2 hours when smoked [50].

JWH-073 content was analyzed by several authors in various ‘herbal mixtures’ purchased in the USA (0.04 – 26 mg/g) [1], Germany (5.8 – 22.9 mg/g) [66], Japan (24.7 – 107 mg/g) [13], Italy (44 & 47 mg/g) [8], and Korea (0.4 – 41.8 mg/g) [9]. Doses can be adjusted by the amount of ‘herbal mixture’ used to prepare a joint.

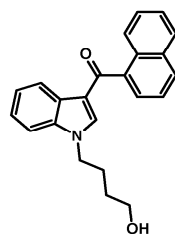
It has to be considered that many of the ‘herbal mixtures’ are inhomogeneous with respect to the content of active ingredients, as it has been shown by Choi et al., Langer et al., Logan et al. Ng et al., and Zuba et al. [1, 9-11, 67, 68]. In some cases the JWH-073 content ranged from 3.2 to 16.6 mg/g within one product [9]. Furthermore, quite often more than one synthetic cannabinoid is added to ‘herbal mixtures’ [1, 9, 69-71]. In Japan, Kikura-Hanajiri et al. detected an average number of 2.6 synthetic cannabinoids per product. [70] The maximum number of synthetic cannabinoids detected in one mixture by the authors was ten.

Analysis of JWH-073 powder ordered from one online retailers revealed a purity of 96.5 % [24]. Furthermore, the smell of naphthalene was noticeable in the sample.

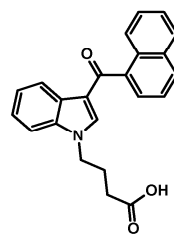
#### 4.3. Pharmacokinetics



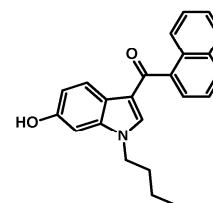
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JWH-073 N-(4-OH-butyl)



JWH-073 butanoic acid



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Reports suggest a duration of action for JWH-073 of 1-2 hours when smoked [50].

JWH-073 content was analyzed by several authors in various ‘herbal mixtures’ purchased in the USA (0.04 – 26 mg/g) [1], Germany (5.8 – 22.9 mg/g) [66], Japan (24.7 – 107 mg/g) [13], Italy (44 & 47 mg/g) [8], and Korea (0.4 – 41.8 mg/g) [9]. 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. [1, 9-11, 67, 68]. In some cases the JWH-073 content ranged from 3.2 to 16.6 mg/g within one product [9]. Furthermore, quite often more than one synthetic cannabinoid is added to ‘herbal mixtures’ [1, 9, 69-71]. In Japan, Kikura-Hanajiri et al. detected an average number of 2.6 synthetic cannabinoids per product. [70] The maximum number of synthetic cannabinoids detected in one mixture by the authors was ten.

Analysis of JWH-073 powder ordered from one online retailers revealed a purity of 96.5 % [24]. Furthermore, the smell of naphthalene was noticeable in the sample.

The primary metabolites detected in authentic urine samples are JWH-073 N-(3-OH-butyl), JWH-073 N-(4-OH-butyl), JWH-073 butanoic acid and JWH-073 (6-OH-indole) (Figure 2) [46, 48, 49]. 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 [72].

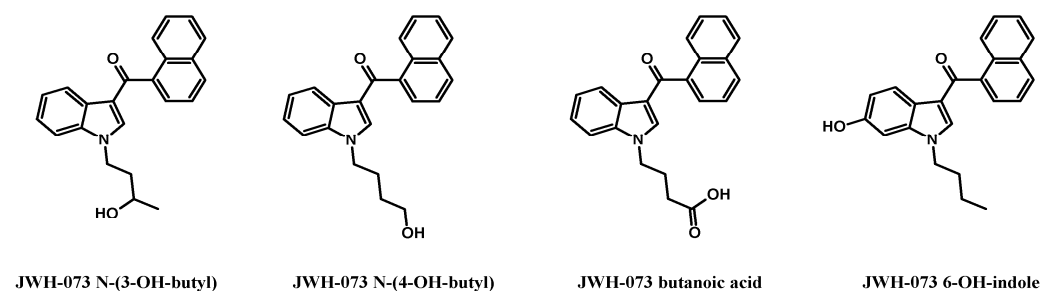


Figure 2: Major metabolites of JWH-073

Almost all of the JWH-073 metabolites are excreted in 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-073 metabolites <sup>[73]</sup>.

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 <sup>[50]</sup>.

## 5. Toxicology

Koller et al. studied the cytotoxic, genotoxic, immunomodulatory as well as the hormonal activity of JWH-073 in human cell lines (hepatoma line (HepG2); mammary line (MCF-7); buccal epithel cells (TR146)) and primary cell lines <sup>[74, 75]</sup>. No significant acute toxicity and no estrogenic activity were observed for JWH-073. However, approximately 7-fold higher anti-estrogenic properties were seen for JWH-073 than for THC. JWH-073 showed cytotoxicity at the highest concentration level tested (100 µM) in HepG2 and TR146 cells. Furthermore, JWH-073 induced DNA damage in buccal and liver cells as observed in Single Cell Gel Electrophoresis (SCGE) experiments, suggesting potential carcinogenic effects. This may be aggravated by the relatively high doses of JWH-073 required to produce the desired effects. THC showed cytotoxicity at 75 µM and additionally induced damage of the mitochondria and inhibited cell proliferation. JWH-073 showed no alteration of the immune function in the applied assay. In comparison to the serum levels typically reached in humans (highest concentration: 21 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.

Apart from this study, no data regarding the toxicity of JWH-073 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 <sup>[76]</sup>. It is not known whether JWH-073 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) <sup>[50, 77-79]</sup>.

### Cases of JWH-073 intoxications in humans published in the literature:

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 caffeine <sup>[80]</sup>.

Further two cases of adverse effects after analytically confirmed JWH-073 consumption are described by Simmons et al <sup>[81]</sup>. Case 1, a 21-year-old male 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 could be drawn whether JWH-018 or a combination of JWH-018 and JWH-073 was consumed. The second case describes a 19-year-old male who suffered from paranoia and delusions 1 hour after smoking a herbal mixture. Similar to case one, the urine sample was positive for JWH-018 and JWH-073 metabolites.

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<sup>[82]</sup>.

Schneir et al. describes two patients who were presented to the emergency department after consumption of a 'herbal mixture' (later confirmed to contain JWH-018 and JWH-073)<sup>[83]</sup>. 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.

#### **Fatal cases**

No fatal case in which JWH-073 could be detected in post-mortem samples was described in the literature so far.

#### **JWH-073 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 7-8 mg JWH-073 (next to JWH-018). The highest whole blood concentration of JWH-073 was detected in the sample obtained 19 min after consumption (4.2 ng/ml)<sup>[32]</sup>.

JWH-073 serum concentrations ranged from < 0.1 to 0.6 ng/ml in six JWH-073 positive cases out of 101 serum samples analyzed by Dresen et al. in 2010<sup>[26]</sup>.

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, 6 were positive for JWH-073 with a median concentration of 0.85 ng/ml and the highest concentration detected was 7.1 ng/ml<sup>[25]</sup>.

Based on the analysis of 32 JWH-073 positive serum samples in Germany (mainly from forensic psychiatric hospitals for abstinence control), the concentration ranged from < 0.1 to 7.1 ng/ml (mean: 1.2 ng/ml; median: 0.28 ng/ml) (own unpublished data).

**Adverse effects associated with use of synthetic cannabinoids without analytical confirmation:**

Two cases of acute ischemic stroke are reported by Bernson-Leung et al. after first-time consumption of synthetic cannabinoids [84].

## 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 [85]. 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). Extrapolation from this report to potential effects of JWH-073 may not be appropriate. However, it suggests that structurally related drugs acting in the same way may put users at similar risks.

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 [61]. 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 [50].

The US Department of Health and Human Services expect that the physical dependence liability of synthetic cannabinoids will be similar than the one of THC as they act through the same molecular target [50]. The EMCDDA states that ‘user consider its effects to be short acting and describe an extreme urge to redose’ [86].

## 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 [87, 88] [63] [50]. As a consequence, JWH-073 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 <sup>[89]</sup>.

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

JWH-073 has not been used in therapy.

## **10. Listing on the WHO Model List of Essential Medicines**

JWH-073 is not listed on the WHO Model List of Essential Medicines.

## **11. Marketing authorizations (as a medicine)**

Not applicable.

## **12. Industrial use**

JWH-073 has no industrial use.

## **13. Non-medical use, abuse and dependence**

JWH-073 was quite often sold 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-073 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-073 are reported from Austria, Belgium, Bulgaria, Croatia, Czech Republic, Cyprus, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Netherlands, Norway, Poland, Romania, Slovakia, Spain, UK and Turkey <sup>[90]</sup>. The first notifications of JWH-073 occurred in 2009 <sup>[91]</sup>. In 2012, 30 new synthetic cannabinoids were formally notified to the EWS <sup>[92]</sup>. In the 2012 UNODC survey on new psychoactive substances, JWH-018 was identified as the most widespread synthetic cannabinoids.

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 <sup>[93]</sup>. 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 <sup>[94]</sup>. 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 <sup>[95]</sup>.

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 <sup>[96]</sup>. 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 <sup>[96]</sup>.

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 <sup>[50]</sup>.

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 <sup>[1, 9, 67, 68]</sup>. 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 <sup>[97]</sup>. Apart from that, various authors identified further pharmacologically active substances in ‘herbal mixtures’, such as the benzodiazepine phenazepam <sup>[98]</sup>, the kratom alkaloid mitragynine <sup>[99]</sup> or potent hallucinogens like N-(2-methoxy)benzyl phenethylamines <sup>[100]</sup>. 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’ <sup>[101]</sup>. 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.

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

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## 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

Up to 2012 JWH-073 ranged second among the top five synthetic cannabinoids reported to UNODC (Global Smart), with 57 reports <sup>[102]</sup>. Based on data retrieved from the UNODC Early Warning Advisory on NPS, 29 countries reported the emergence of JWH-073 up to December 2013. In 2012 45 countries reported seizures of synthetic cannabinoids making them the most frequently seized NPS. Furthermore, the number of countries reporting seizures of larger quantities (more than 1 kg) increased from 3 in Europe in 2009 to 16 in 2011 covering regions worldwide. One large seizure was also reported from the United States counting 4.8 million packages in one operation 2012.

The primary source of origin for synthetic cannabinoids is identified to be Asia (China and India), followed by Europe (Czech Republic, Hungary, Netherlands, Portugal, Spain, Ukraine and United Kingdom), the Americas, Africa and Oceania. Availability over the Internet is high in general and online shops seem to play the most important role in marketing and distribution worldwide. This can also be seen in the number of online shops selling 'legal highs' which increased from 170 in 2010 to 690 in 2012 in Europe only. <sup>[102]</sup>

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, Czech Republic, Denmark, Estonia, Finland, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Norway, Poland, Portugal, Slovakia, Slovenia, Sweden, Turkey, United Kingdom (according to the EDND of the EMCDDA). Also controlled in Australia, 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-073**

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

A total of 67 Member States answered the questionnaire for JWH-073. Of these, only 34 respondents (AFR 1, AMR 5, EUR 23, SEAR 1, WPR 4 ) had information on this substance.

#### **LEGITIMATE USE**

None reported that JWH-073 was currently authorized or is in the process of being authorized/registered as a medical product in their country. Seven respondents stated that this substance was used in medical and scientific research including as analytical standards. There was no use stated for animal/veterinary care

#### **HARMFUL USE**

Twenty-two respondents confirmed that there was recreational/harmful use of JWH-073; the common routes of administration were stated as inhaling/sniffing by 14, oral/inhaling/sniffing by two and oral/ injection/ inhaling/sniffing by two and as oral by one. Thirteen respondents stated this was obtained only via trafficking, 4 via trafficking plus clandestine manufacturing and 1 each via clandestine manufacturing and diversion plus trafficking. Fourteen respondents reported on the common formulations of JWH-018 available with 11 reporting powder and one each tablet, powder/liquid and liquid forms. Four respondents also mention that JWH-073 is often smoked and six that JWH-073 is often found in herbal mixtures. When asked if JWH-073 was used by any special populations 6 respondents stated only general population while two each stated only clubs and general population and clubs. Two respondents reported emergency room visits; two and more than 10 respectively in 2012. Three respondents reported withdrawal, tolerance and other adverse effects or medical illnesses caused by JWH-073. These include nausea, vertigo, paranoia, panic attacks, mydriasis, unconsciousness etc. One respondent reported drug related crimes involving postal delivery of NPS.

Additional data provided, ‘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-073 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-073 cannot be made. These reports usually describe behavioral 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 related cannabinoid 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).’

## CONTROL

Of those with information on this substance, 31 reported that JWH-073 was controlled under legislation that was intended to regulate its availability; 25 under “controlled substance act”, 3 under “medicines law” and 2 under “other” legislations. Only 3 respondents stated that there were challenges with the implementation of this legislation. On illicit activities related to JWH-073, four respondents reported clandestine manufacture with two the synthesis of the product itself. Ten respondents reported processing into consumer product, 17 reported trafficking, 3 reported diversion and 14 an internet market.

Details on seizures are presented below.

	<b>2011 (number of respondents)</b>	<b>2012 (number of respondents)</b>
Total number of seizures	931 (14)	283 (14)
Total quantity seized (kg)	1,165.64 (9) some include other cannabinoids	39.53 (9) some include other cannabinoids
Others seized	Wraps, also plant and herbal products	Wraps, also report plant and herbal products

## IMPACT OF SCHEDULING

Twenty nine respondents reported that if JWH-073 was placed under international control, they would have the laboratory capacity to identify the substance. There is no reported medical use.