JWH-073

Critical Review Report

Agenda item 4.11

Expert Committee on Drug Dependence

Thirty-eight Meeting

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World Health Organization

Contents

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Summary

JWH-073 is a synthetic cannabinoid receptor agonist (SCRA) with an aminoalkylindole structure used as an active ingredient of products sold as cannabis substitutes. JWH-073 has no known therapeutic or medical use. In different regions it is being used and abused for non-medical purposes. Furthermore some countries have put JWH-073 under national control. Since the 36th ECDD less seizures of JWH-073 have been recorded.

When smoked, JWH-073 produces cannabimimetic effects like Δ9-tetrahydrocannabinol (THC). Doses needed to produce these effects are in the same range as THC doses. 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. The abuse potential potential seems to be similar to cannabis. Compared to JWH-018, JWH-073 is less potent and tends to show lower efficacy. JWH-018 is an analogue of JWH-073 and has been included in Schedule II of the Psychotropic Substances Convention (1971) since 2015.

1. Substance identification

A. International Nonproprietary Name (INN)

Not applicable

B. Chemical Abstract Service (CAS) Registry Number

208987-48-8
1415744-43-2 (JWH-073-d_7)
1538556-32-9 (JWH-073-$^{13}C_4$)
1346601-94-2 (JWH-073-d_9)

C. Other Chemical 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JWH-073 was found as an additive in over 60 different brands of 'herbal mixtures' in Germany alone (Auwärter unpublished data).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. [1]

F. Physical Appearance

White crystalline solid (in pure form)

G. WHO Review History

During its 36th meeting, the WHO Expert Committee on Drug Dependence discussed the critical review report on JWH-073 and concluded that owing to the current insufficiency of data regarding dependence, abuse and risks to public health, JWH-073 should not be placed under international control at this time but be kept under surveillance.

New information on its pharmacology and abuse potential warranted an update of the critical review report on behalf of the 38th ECDD.

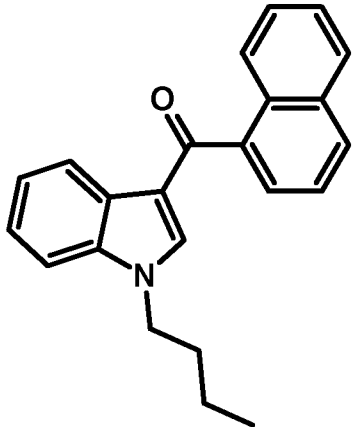
2. Chemistry

A. Chemical Name

IUPAC Name: (1-Butyl-1*H*-indol-3-yl)(naphthalen-1-yl)methanone
CA Index Name: 1-Naphthalenyl(1-butyl-1*H*-indol-3-yl)-methanone

B. Chemical Structure

Free base:



Molecular Formula: $C_{23}H_{21}NO$
Molecular Weight: 327.41 g/mol

C. Stereoisomers

None

D. Methods and Ease of Illicit Manufacturing

JWH-073 is a naphtoylindole alkylated at the indole nitrogen.
Synthesis of JWH-073 can be carried out in analogy to the synthesis strategies described for various aminoalkylindoles. [2,3] 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*-indole, 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.

E. Chemical Properties

Melting point: 99.8°C [4]
Boiling point: n/a
Solubility: JWH-073 is soluble in organic solvents such as ethanol, DMSO and dimethylformamide, which should be purged with an inert gas.
The solubility of JWH-073 in these solvents is approximately 10 mg/ml. [5]

F. Identification and Analysis

The analytical profile of JWH-073 has been described in various papers. Utilized methods include LC-MS/MS [6], GC-EI-MS [1, 7-18], HRMS [19-22], NMR [15, 16], IR-ATR [23], DART-MS [24] and UV-VIS detection [13, 14, 25]. Detection in biological matrices was described in serum [26-28], whole blood [29-35], hair [36-38], and oral fluid [39-43] targeting JWH-073. In urine samples, the main metabolites are the analytical targets. [44-50]

3. Ease of convertibility into controlled substances

JWH-073 is not readily converted into other internationally controlled substances. [51]

4. General pharmacology

A. 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.[51, 52] 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.[53] Furthermore, oral consumption of the compound was described by various users on the Internet.[53] Based on information posted at Internet forums, 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.

Reports suggest a duration of action for JWH-073 of 1-2 hours when smoked.[51] Users reported cannabimimetic effects after smoking the drug. Potency was reported to be about half of the potency of JWH-018.

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)[16], Japan (24.7 – 107 mg/g)[14], 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, 9-12, 54, 55] 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, 7, 9, 56, 57] 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 the authors was ten.

Analysis of JWH-073 powder ordered from one online retailer revealed a purity of 96.5 %. [25] Furthermore, the smell of naphthalene was noticeable in the sample.

B. Pharmacokinetics

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).[47, 49, 50] 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.[58]

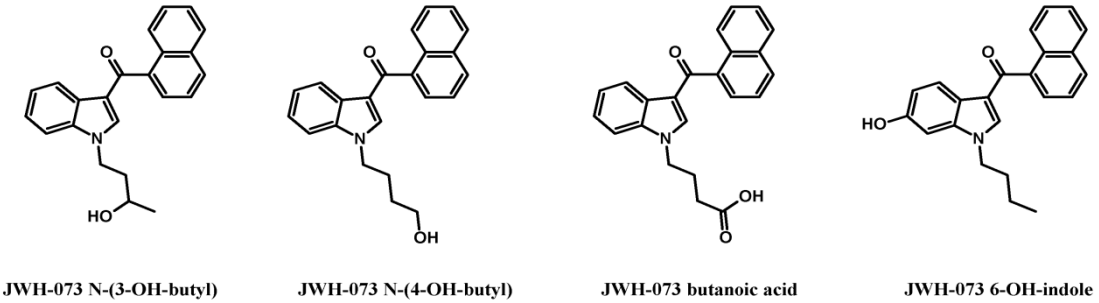


Figure 2: Major metabolites of JWH-073

Almost all of the JWH-073 metabolites are excreted in urine in the form of glucuronides. Conjugation to glucuronic acid via various UDP-glucuronosyltranseferase enzymes (predominately hepatic UGT1A1, UGT1A9 and UGT2B7) has been shown for the various JWH-073 metabolites.[59]

Hegstad et al. report data from consecutive urine specimens from five subjects after ingestion of SCRAs. Urinary concentrations of the carboxylic acid metabolites JWH-073-COOH were measured by ultra-performance liquid chromatography-tandem mass spectrometry with a limit of quantification of 0.1 ng/mL. In these subjects, specimens remained positive over a period of 11-25 (mean 19) days for JWH-073-COOH. Detection times were shorter for subjects that appeared to have ingested only one, or a few, doses prior to urine collection in the study. Mean elimination half-live in urine was 9.3 (range 3.6-16.8) days for JWH-073-COOH. These data show that urine samples could be positive for JWH-073-COOH for more than 3 weeks after ingestion.[60]

JWH-073 concentrations in biological samples:
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).[33]

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. [27]

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.[26]

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) (Auwärter unpublished data).

Salomone et al. developed a method for the detection of 23 SCRAs in hair samples. After validation, they applied the method to the analysis of 344 hair samples previously tested in their laboratory for the most common drugs. Overall, 15 samples were found positive for at least one SCRA. The drug most frequently detected was JWH-073 (11 samples) generally at low concentration (mean 7.69 ± 14.4 pg/mg, median 1.9 pg/mg, range 1.6-50.5 pg/mg).[61]

C. Pharmacodynamics

Biochemical effects:
JWH-018 possesses a relatively high binding affinity (expressed as IC_{50} (occupation of 50% of the receptors)) towards the cannabinoid receptor type 1 (CB1) of 8.9 ± 1.8 nM and a similar binding affinity towards the cannabinoid receptor type 2 (CB2) of 38.0 ± 24 nM 62-64 compared to the binding affinities of delta-9 tetrahydrocannabinol (THC) of 40.7 ± 1.7 nM at the CB1 and 36.4 ± 10 nM at the CB2 receptor.[85, 66]. Furthermore, Griffin et al. tested the biological effects by in vitro [35S] guanosine-5'-O-(3-thio)-triphosphate ([^{35}S]GTPγS) binding assay, measuring partial agonistic properties (maximum receptor stimulation: 19-40 %) 64, while Brents et al. describe JWH-073 as full agonist.[67]

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 cannabinoid 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.[68]

JWH-073 inhibited adenylyl cyclase activity in Neuro2AWT cells with an IC50 of 53.54 ± 6.74 nM).[69]

Wiley et al. examined the binding affinities of first-generation indole-derived SCRAs at both cannabinoid and non-cannabinoid receptors. Except JWH-391, all other compounds including JWH-073 had favorable affinity (≤159 nM) for both cannabinoid receptors. In contrast, binding at non-cannabinoid receptors was absent or weak.[70]

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: Ki at CB1 receptor: 38.4 ± 0.8 nM)[66], 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).[67]

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]GTPγS 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.[67]

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 [^{35}S]GTPγS 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.[71] As CB2 receptors are highly expressed in immune cell types, JWH-073 uptake might modulate immune function.

The 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 [^{3}H]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.[69] 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.[69]

Functional effects:
Ossato et al. investigated the pharmacological activity of JWH-250 and JWH-073 in male CD-1 mice. Both compounds induced a marked hypothermia, increased pain threshold to both noxious mechanical and thermal stimuli, caused catalepsy, reduced motor activity, impaired sensorimotor responses (visual, acoustic and tactile), caused seizures, myoclonia, hyperreflexia and promote aggressiveness. Furthermore both compounds stimulated dopamine release in the nucleus accumbens in a dose-dependent manner after systemic administration. This was demonstrated in a microdialysis study in freely moving mice. All effects were fully prevented by the selective CB1 receptor antagonist/inverse agonist AM251.

An interesting finding was that co-administration of ineffective doses of JWH-250 and JWH-073 impaired visual sensorimotor responses, improved mechanical pain threshold and stimulated mesolimbic DA transmission in mice. All other behavioural and physiological parameters remained unchanged. It suggests the potential for synergistic action when SCRAs are co-administered in low doses.[72]

Tai et al. looked at tolerance/cross-tolerance of THC and SCRAs after repeated administration in mice. First of all dose-effect relationships for hypothermic effects

were determined in order to confirm that JWH-018 and JWH-073 are agonists in mice. Thereafter separate groups of mice were treated with either saline, sub-maximal hypothermic doses of JWH-018 or JWH-073 (3.0 mg/kg or 10.0 mg/kg, respectively) or a maximally hypothermic dose of 30.0 mg/kg THC once per day for 5 consecutive days. Core temperature and locomotor activity were monitored via biotelemetry. Repeated administration of all drugs resulted in tolerance to hypothermic effects, but not to locomotor effects. This tolerance was still evident 14 days after the last drug administration. In another experiment mice were treated with 30.0 mg/kg THC once per day for 4 days, then tested with one of the SCRAs on day 5. Mice with a THC history were cross-tolerant to both SCRAs, and this cross-tolerance also persisted 14 days after testing. Taken together these data demonstrate that repeated administration of THC, JWH-018 or JWH-073 can induce long-lasting tolerance to some of the pharmacological effects.[73]

Marshell et al. demonstrated that the SCRAs JWH-073 and JWH-018 elicit dose-dependent, CB1 receptor-mediated THC-like effects in mice when delivered via inhalation or via intraperitoneal injection. Both SCRAs elicited THC-like effects across both routes of administration, and effects following inhalation were attenuated by pretreatment with the CB1 antagonist/inverse agonist rimonabant. No cataleptic effects were observed following inhalation, but all compounds induced catalepsy following injection. Injected JWH-018 and JWH-073 fully substituted for THC, but substitution was partial (JWH-073) or required relatively higher doses (JWH-018) when drugs were inhaled.[74]

Behavioural effects:
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.[75] 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.[62]

Wiley et al. studied the effects of first-generation indole-derived SCRAs in a functional observational battery (FOB) and on drug discrimination in mice. In the FOB, THC and six agonists, including JWH-073, disrupted behaviors in CNS activation and muscle tone/equilibrium domains. Unlike THC, however, SCRAs impaired behavior across a wider dose and domain range, producing autonomic effects and signs of CNS excitability and sensorimotor reactivity. Furthermore mice acquired JWH-018 discrimination, and THC and JWH-073 produced full substitution. Together, these results show that, while first-generation SCRAs shared some effects that were similar to those of THC, but they also possessed effects that differed from traditional cannabinoids.[70]

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.[76, 77] 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 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.

Apart from this study, no data regarding the toxicity of JWH-073 are published in the literature so far, and in particular there are 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.[78] 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 of synthetic cannabis receptor agonists
Adverse effects described in the literature after the consumption of SCRAs include tachycardia, hypertension, chest pain, agitation, hallucination, extreme anxiety leading to panic attacks and acute psychosis, minor elevation of blood glucose, hypokalemia, vomiting, seizures and myoclonia.[51, 79-81]

Non-fatal cases of JWH-073 intoxications
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.[82]

Further two cases of adverse effects after analytically confirmed JWH-073 consumption are described by Simmons et al.[83] 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. 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 cannabis receptor agonist 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.[84]

Schneir et al. describe two patients who were presented to the emergency department after consumption of a 'herbal mixture' (later confirmed to contain JWH-018 and JWH-073).[85] 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.

Fucci and Pascali describe a case of a 17-year old girl who is admitted to the emergency room with a drug resistant epilepsy. Routine analysis on urine and blood revealed the presence of cannabis-like substances. Therefore it was decided to perform hair testing. In the proximal segment (4 cm) JWH-073 was detected in a concentration of 0.2 ng/mg. Although this value is within the range earlier described for JWH-073, it seems to be higher than in other real samples analyzed in 2013.[86]

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

7. Dependence potential

A. Animal Studies

No information available.

B. Human Studies

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.

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.[51]
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.[51] The EMCDDA states that 'user consider its effects to be short acting and describe an extreme urge to re-dose'.[87]

8. Abuse potential

A. 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.[51, 88, 89, 90] 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). 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.[88]

Further studies conducted by Hruba 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.[91]

Cha et al. evaluated three SCRAs with different binding affinities for the CB1 receptor, JWH-073, 081, and 210, for their abuse potential. The conditioned place preference test (CPP) (unbiased method, using mice) and self-administration test (fixed ratio of 1, using rats) were conducted. All animals administered JWH-073, JWH-081, or JWH-210 showed significantly increased time spent at unpreferred space in a dose-dependence manner in the CPP. In contrast, all tested substances except THC showed aversion phenomenon at high doses in the CPP. However, in rats no change in self-administration was observed. They also calculated Ki values of the three compounds using a receptor binding assay to compare abuse potential with CB1 receptor binding affinity. The order of affinity to the CB1 receptor in this receptor binding assay was JWH-210 > JWH-081 >> JWH-073, which was in agreement with the results from the CPP.[92]

B. Human Studies

As SCRAs are not included in the practice of routine toxicological screening it makes these compounds 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.[93]

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

JWH-073 has no known therapeutic/medical use.

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 medicinal product)

JWH-073 has never been marketed as a medicinal product.

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 SCRAs 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 SCRAs in general, without identifying the particular substance (consumers usually do not know the composition of the products).

At present, SCRAs 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 the difficulty to detect them, easy availability and strong effects.

SCRAs 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. The first notifications of JWH-073 occurred in 2009.[94] In 2012, 30 new SCRAs were formally notified to the EWS.[95]

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 SCRAs among 12th graders was reported.[96] 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.[97]

Heltsley et al. analyzed urine samples from 5,956 US athletes (collected: 24.01.2011 – 28.10.2011) of which 4.5% were tested positive for metabolites of JWH-018 and/or JWH-073.[98]

Castaneto et al. screened 20,017 randomly collected US military urine specimens (collected between July 2011 and June 2012) with an immunoassay for SCRAs. A total of 1432 presumptive positive specimens were found. When analyzing these presumptive positive specimens with their qualitative SCRA LC-MS/MS method, 290 positive specimens were detected. These 290 specimens confirmed positive for 22 metabolites from 11 parent SCRAs. The five most predominant metabolites were JWH-018 pentanoic acid (93%), JWH-N-hydroxypentyl (84%), AM-2201 N-hydroxypentyl (69%), JWH-073 butanoic acid (69%), and JWH-122 N-hydroxypentyl (45%). So, less than 1.5% was tested positive for a SCRA.[99]

Davies et al. looked at the prevalence of metabolites of SCRAs in suspects of impaired driving in Washington, DC (between June 2012 and August 2013). A total of 526 urine samples were screened for metabolites of 12 SCRAs by LC-MS/MS. Nineteen cases (3.6%) confirmed positive for the following metabolites of SCRAs: UR-144 N-pentanoic acid (n = 17; 89%), JWH-073 butanoic acid (n = 3; 16%), JWH-018 pentanoic acid (n = 3; 16%), AM-2201 4-hydroxypentyl (n = 3; 16%) and 5-fluoro PB22 3-carboxyindole (n = 1; 5%).[100]

The Drug Abuse Warning Network (DAWN), a public health surveillance system monitoring drug-related emergency department (ED) visits in the USA, reports 11,406 SCRAs related ED visits and 28,531 in 2011.[101] In 2010, 2,906 calls to poison centers for exposure to SCRAs 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 SCRAs and three deaths from January 1, 2010 through June 30, 2013.[101]

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.[51]

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.[1, 9, 68, 69] 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.[102] Apart from that, various authors identified further pharmacologically active substances in 'herbal mixtures', such as the benzodiazepine phenazepam [103], the kratom alkaloid mitragynine [104] or potent hallucinogens like N-(2-methoxy)benzyl phenethylamines [105]. These additives bear potential health risks of their own and may potentiate the risks connected to the use of the SCRAs.

During 2010, 418 SCRAs 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 SCRAs exposures were classified as 'moderate effect', while more marijuana exposures were classified as 'no effect'.[106] 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 SCRAs.

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

Up to 2012 JWH-073 ranged second among the top five synthetic cannabinoids reported to UNODC (Global Smart), with 57 reports.[107] Based on data retrieved from the UNODC Early Warning Advisory on NPS, 29 countries reported the emergence of JWH-073 up to December 2013.

The primary source of origin for synthetic cannabinoids is identified to be Asia (China and India), followed by Europe, 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.[107]

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, Romania, Slovakia, Slovenia, Sweden, Turkey, United Kingdom.[90] Also controlled in Australia, Japan, New Zealand, 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 38th ECDD: Evaluation of JWH-073

Data was obtained from 47 Member States (6 AFR, 2 EMR, 26 EUR, 7 PAH, 1 SEAR and 5 WPR).

A total of 42 Member States (4 AFR, 2 EMR, 23 EUR, 7 PAH, 1 SEAR and 5 WPR) answered the questionnaire for JWH-073. Of these, 27 respondents (1 AFR, 1 EMR, 20 EUR, 3 PAH and 2 WPR) had information on this substance.

LEGITIMATE USE

There were 24 countries that reported no approved medical products containing JWH-073 for human or veterinarian indications. There was also no reported industrial use in 19 countries.

JWH-073 is not currently being used in any medical or scientific research (excluding use as an analytical reference standard) in 20 countries.

JWH-073 was not reported to be used for any cultural, religious or ceremonial purposes in 19 countries.

EPIDEMIOLOGY OF NON-MEDICAL/NON-SCIENTIFIC USE – USE FOR PSYCHOACTIVE PURPOSES OR RECREATIONAL DRUG USE

There were 18 countries that reported JWH-073 as being misused for its psychoactive properties (as a recreational drug). Common routes of administration for non-medical/non-scientific purposes are oral (3 countries), sniffing (1 country), inhalation (1 country) and smoking (15 countries). The main route of administration for JWH-073 was specified as smoking (11 countries) and oral (1 country).

Formulations reported for non-medical/non-scientific purposes were powder (6 countries) and tablets (1 country). The most commonly reported formulation was plant material impregnated with the JWH-073 (16 countries). One country commented that it is prepared this way to resemble cannabis.

There were 11 countries which reported that the source of JWH-073 for non-medical/non-scientific use was smuggling.

Party settings, people attending parties or dance festivals, are specified as a subpopulation known to misuse JWH-073 by two countries. Another country specified that youths and young adults were a subpopulation known to misuse JWH-073.

The level of negative health-impact originating from this substance's non-medical consumption was reported as either negligible (1 country), substantial (5 countries) or serious (4 countries). For the countries that indicated a substantial or serious level of negative health-impact, they specified that it was due to the association of JWH-073 with adverse events

including intoxications, seizures and substance induced psychosis. It was also commented that JWH-073 has a high risk of addiction.

Two countries reported that there had been emergency room/department visits related to the non-medical use of JWH-073. One country reported 1 case in 2011.

The adverse effects which presented for JWH-073 at the emergency room/department included somnolence, mydriasis, tachycardia, chest pain, nausea, vomiting and psychiatric complications.

One country reported that people presented to drug dependence treatment centres due to the use of JWH-073, however, they were unsure if was specifically for this psychoactive substance, rather it is for synthetic cannabinoids generally.

STATUS OF NATIONAL CONTROL AND POTENTIAL IMPACT OF INTERNATIONAL CONTROL

There were 25 countries reported that JWH-073 was under national control. The legislation the control is based upon included the Medicines Act (3 countries), Controlled Substances Act (19 countries), Criminal Law Act (1 country) and other specific legislation (3 countries stated it was specific legislation for new psychoactive substances). In one country the control is a temporary provision. One country stated that there had been challenges to implementing controls of JWH-073, however, no details were provided.

The scope of the controls includes production (21 countries), manufacturing (24 countries), exporting (22 countries), importing (24 countries), distribution (24 countries), use (19 countries) and possession (23 countries).

Reported illicit activities involving JWH-073 include manufacture of the substance by chemical synthesis (1 country), production of consumer products (2 countries), trafficking (9 countries), smuggling (1 country), diversion (1 country), domestic internet sales (2 countries), internet sales from abroad (7 countries), internet sales from unknown locations (4 countries) and finally sales to people who use this substance (5 countries).

There were 17 countries which completed the section on the number of seizures. The combined number of seizures was 38 (2014), 12 (2015) and 5 (2016 to date). One country commented that they had noticed a decline of cases as soon as the substance was placed under control by national legislation.

If JWH-073 was placed under international control, 26 countries responded that they would have the capacity to enforce the control at the national level. There were 26 countries which responded that they would have the forensic laboratory capacity to analyse the substance.