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1. Comments based on the review report

a. Evidence on dependence and abuse potential

JWH-018, an aminoalkylindole with cannabimimetic effects in doses lower than the doses of Δ9-tetrahydrocannabinol (THC) is used as an active ingredient of products sold as cannabis substitutes. JWH-018 possesses a relatively high binding affinity towards both the cannabinoid receptor type 1 (CB1) and type 2 (CB2) compared to the binding affinities of delta-9 tetrahydrocannabinol. Compared to THC that only one of the major THC-metabolites is known to be psychoactive and retains binding affinity towards cannabinoid receptors (11-OH-THC), several JWH-018 metabolites retain high CB1 receptor binding affinity. A series of opposite or different clinical effects has been observed in animal studies between THC and JWH-018, though. For example, JWH-018 increased the EEG power up to 3.9 fold and reduced the EEG activity, whereas THC reduced the EEG power. 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. Further observations included ptosis, and hyperreflexive responses. Compared to THC, JWH-018 was shown to be more potent and with shorter duration of action. Based on this observation there are speculations that JWH-018 could evoke a more frequent use, and therefore increase abuse and dependence liability.

Reports of extreme urge to redoes following consumption of JWH-018 have been taken as evidence as a high potential for abuse of the compound. There are also case reports of withdrawal signs and symptoms following regular use of JWH-018 such as headaches, anxiety, coughing, insomnia, anger, impatience, difficulties in concentrating, restlessness, nausea, and depression.

b. Risks to individual and society because of misuse

As highlighted in the critical review, commercially available domestic or industrial products, which could be used for synthesis of JWH-018 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 such as pesticides, too. Therefore, the current evidence is limited in differentiating the toxic symptoms of JWH-018 and other harmful

substances present in the preparations. The WHO questionnaire report too lacks clear cut responses that could differentiate JWH-018 features from other substances commonly detected in herbal blends.

The CB1 agonists effect of JWH-018 include sedation, cognitive dysfunction, tachycardia, postural hypotension, dry mouth, ataxia, and psychotropic effects. A hyperemic conjunctivae, xerostomia, alteration of mood and perception have also been ascribed as JWH-018 effects. Additionally, JWH-018 binds more efficiently to CB2 receptors with a potential to modulate immune function and resultant immune suppression and presumed anti-inflammatory and chemopreventive properties.

c. Magnitude of the problem in countries (misuse, illicit production, smuggling etc)

At present, synthetic cannabinoids appear to be mainly consumed in Europe, Japan, Russia and the USA. Seizures of JWH-018 have been reported from Austria, Belgium, Bulgaria, Cyprus, Czech Republic, France, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Malta, Netherlands, Poland, Slovakia, Spain, and UK.

d. Need of the substance for medical (including veterinary) practice

Not known.

e. Need of the substance for other purposes (e.g. industrial)

Not known.

f. Measures taken by countries to curb misuse

JWH-018 is 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, Japan, Russian Federation, Switzerland and the USA.

g. Impact if this substance if scheduled

None.

2. Additional information to the review report

3. Other comments or opinions

As JWH-018 and JWH-073 may bind at separate sites of the CB1 receptors and the synergistic effects might be mediated via intracellular mechanisms other than THC-related effectors, speculation that JWH-018 should be regarded as a compound similar to THC might be hasty.

Currently cannabinoid research is a trendy area of substance-related studies. As far as we know a complicated and delicate interaction between cannabinoid activities and the neuroendocrine system is being exhumed. From a clinical point of view this balance would shed more light on interactions between consumption of cannabinoids and abuse of steroids and sex hormones, not to mention the interaction of those compounds with dopaminergic and GABAergic substances too. Therefore one may expect the current evidence on cannabinoids to flourish in recent future.

4. Expert reviewer's view on scheduling with rationale

I would prefer to look at JWH-018 as a synthetic cannabinoid from two different angles before making any suggestions:

a. In recent years a smooth trend towards easing of cannabis controls is seen in some countries. In case the general approach to cannabis is changing, would there be enough logic to schedule a synthetic cannabinoid at this time?

b. If consumption of natural cannabis is going to be more and more tolerated in coming years, would there be any need to leave the window open for synthetic compounds with higher potency and therefore theoretically higher potential for harmful use of the substances?

With the two different views expressed above, and the lack of sufficient evidence for actual effects of JWH-018 on human subjects, I would suggest that the compound just be kept under surveillance until ample data is available to lean towards either of the above conditions.