WHO Expert Committee on Drug Dependence Pre-Review:

Delta-9-tetrahydrocannabinol (THC)

Expert Peer Review 2

1. Comments based on the review report

a. Evidence on dependence and abuse potential

Dependence potential:

The pre-review summarizes animal studies showing that rapid and profound tolerance develops to numerous acute preclinical effects of $\Delta^9$-THC following chronic administration. It is suggested that the involvement of the pharmacokinetics of $\Delta^9$-THC on the development of tolerance seems minor. In contrast, the pharmacodynamic mechanisms play a central role through substantial down-regulation and desensitization of cannabinoid CB$_1$ receptors in several brain regions. The physical dependence associated with $\Delta^9$-THC is less robust. No somatic signs of spontaneous withdrawal have been observed following abrupt termination of chronic dosing with $\Delta^9$-THC. However, termination of $\Delta^9$-THC administration results in decreased responding for food reinforcement.

There is limited research in humans on the dependence potential of $\Delta^9$-THC specifically. Oral administration of $\Delta^9$-THC up to a total daily dose of 210 mg produced ratings of “high” and increased heart rate that decreased with repeated administration, indicative of tolerance. Tolerance also occurred with lower doses of $\Delta^9$-THC (80-120 mg daily, p.o.). Abrupt termination of $\Delta^9$-THC administration after a 4-day repeated dosing regimen resulted in withdrawal symptoms. In contrast, when a 3-day repeated dosing regimen was employed, the development of tolerance and physical dependence had not occurred.

Research on the dependence potential of the stereochemical variants of $\Delta^9$-THC has not been reported in either animals or humans.
Abuse potential:

$\Delta^9$-THC self-administration has been described in squirrel monkeys in one laboratory. These effects were reversed by the cannabinoid CB$_1$-receptor antagonist, rimonabant. Other attempts to establish $\Delta^9$-THC self-administration have not been successful. However, $\Delta^9$-THC has been shown to produce robust discriminative stimulus effects in several species. Full substitution for $\Delta^9$-THC has been demonstrated for cannabinoids including $\Delta^8$-THC, cannabidiol, hashish, synthetic cannabinoid agonists (CP55,940, WIN55,212-2), and abused synthetic cannabinoids (e.g. JWH-018, XLR-11, UR-144, AB-CHMINACA). The discriminative stimulus effects of $\Delta^9$-THC were reported to be attenuated by administration of a selective CB$_1$ receptor antagonist, but not by a CB$_2$ receptor antagonist. These effects were not reversed by antagonists of other neurotransmitter systems, including dopamine, acetylcholine, norepinephrine, and opioid antagonists, suggesting the pharmacological selectivity of $\Delta^9$-THC’s discriminative stimulus effects.

In human studies, the results of $\Delta^9$-THC self-administration demonstrated that it is a weak reinforcer. However, oral $\Delta^9$-THC has robust subjective effects that are similar to those of cannabis. Both $\Delta^9$-THC and cannabis (each containing 8.4 or 16.9 mg $\Delta^9$-THC) produced a similar profile of subjective effects on the Addiction Research Center Inventory. As was the case in animal studies, $\Delta^9$-THC discrimination was pharmacologically selective.

b. Risks to individual and society because of misuse

There is no reported misuse of pure $\Delta^9$-THC. The pre-review describes that acute exposure to $\Delta^9$-THC can cause transient cognitive deficits such as impairment of attention and short-term memory. Moreover, there are reports of $\Delta^9$-THC provoking modest and transient psychosis-like psychological phenomena in some healthy participants.

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

There are no reported problems in any countries.

d. Need of the substance for medical (including veterinary) practice
The therapeutic applications of Δ⁹-THC and the use of Δ⁹-THC in combination with other substances (e.g. cannabidiol) are reported. The dronabinol (Marinol®) is a synthetic form of Δ⁹-THC (dronabinol) that has been approved by the FDA in the United States for anorexia associated with weight loss in patients with Acquired Immune Deficiency Syndrome (AIDS) and for nausea and vomiting associated with cancer chemotherapy (CINV). Moreover, dronabinol has also been approved or is available under special access rules in several countries such as for CINV unresponsive to conventional treatment in Australia, Denmark and Ireland, for appetite stimulation in HIV in Ireland, for any type of chronic pain and for any condition in palliative care in Germany.

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

Δ⁹-THC has no industrial or other use.

f. **Measures taken by countries to curb misuse**

There is no information in the pre-review report.

g. **Impact if this substance is scheduled**

Not applicable

2. **Are there absent data that would be determinative for scheduling?**

None

3. **Other comments or opinions**

None