



## WHO Expert Committee on Drug Dependence Pre-Review:

### Delta-9-tetrahydrocannabinol (THC)

#### Expert Peer Review 1

##### 1. Comments based on the review report

###### a. Evidence on dependence and abuse potential

*Dependence potential:* Animal studies have shown rapid and profound tolerance develops to numerous acute preclinical effects of  $\Delta^9$ -THC following chronic administration, including anti-nociception and locomotion. It appears this is due to downregulation and desensitization of brain CB<sub>1</sub> receptors to which  $\Delta^9$ -THC binds. In terms of physical dependence, despite some variability in findings, animal studies have shown a lack of somatic signs of withdrawal (i.e. anxiety and pain) following abrupt termination of chronic dosing with  $\Delta^9$ -THC even after administration of extremely high doses. In humans, limited research has examined the dependence potential of  $\Delta^9$ -THC specifically (compared to cannabis plant) and all studies have reportedly involved doses higher than recommended for some therapeutic indications of dronabinol (the stereochemical variant (-)-*trans*- $\Delta^9$ -THC). Some work has found that high doses orally administered produced a “high” and increase in heart rate that dissipated with time and repeated administration, suggesting the development of rapid tolerance. A lower dose study dose demonstrated similar development of tolerance to the subjective effects of  $\Delta^9$ -THC, but not to its appetite enhancing effects. Abrupt cessation of administration after a 4-day repeated dosing regimen resulted in symptoms of withdrawal, including irritability, restlessness, and sleep disruption but this was not observed when repeated dosing was shorted to 3 days.

Overall, available data indicate  $\Delta^9$ -THC has dependence potential but research on the dependence potential of all the various stereochemical variants of  $\Delta^9$ -THC in animals and humans has not been reported.

*Abuse potential:* In animals, the abuse potential of  $\Delta^9$ -THC has been evaluated in intravenous self-administration and drug discrimination procedures with self-administration demonstrated in defined species only. In this species, the  $\Delta^9$ -THC self-administration behavior was comparable in intensity to that maintained by cocaine under identical conditions, and was obtained using a range of doses similar to those self-administered by humans smoking a single marijuana cigarette. The results of intracranial self-stimulation and conditioned place preference experiments in animals have been inconsistent in assessing abuse potential but drug discrimination studies are deemed to be more effective and have shown a pharmacological specific response to  $\Delta^9$ -THC (i.e.  $\Delta^9$ -THC produces its own subjective effects that do not substitute for any other psychoactive substance aside from synthetic cannabinoid receptor agonists). The Pre-Review report demonstrates that with few exceptions, human studies relevant to the abuse potential of pure or synthetic  $\Delta^9$ -THC (i.e. excluding cannabis and plant-derived extracts) have used dronabinol and an oral route of administration. Whilst oral  $\Delta^9$ -THC has been found to have subjective effects that resemble those of cannabis plant, it has been shown to be a weak reinforcer in self-administration studies and 80% of participants chose to take a 'marijuana cigarette' instead if given the opportunity. Similarly with animals,  $\Delta^9$ -THC discrimination in humans has been shown to be pharmacologically selective. Of note is that dronabinol has not been reported to be abused.

Overall, available data indicate  $\Delta^9$ -THC has abuse potential and whilst research on the abuse potential of all the various stereochemical variants of  $\Delta^9$ -THC has not been reported in humans, limited animal studies suggest the (-) stereoisomers are more potent (in ataxia and hypothermic models) than the (+) stereoisomers. Whether this is reflected in abuse potential is unclear.

**b. Risks to individual and society because of misuse**

- c. There do not appear to be any instances of misuse of  $\Delta^9$ -THC by individuals, including the medicinal stereochemical variant, dronabinol. No instances of non-fatal or fatal toxicity have been reported. Nevertheless, some adverse effects have been reported, especially in studies or therapeutic instances with dronabinol, including confusion, anxiety, euphoria, nausea, vomiting, diarrhea, mood changes, fatigue and dry mouth. Furthermore, a dose dependent effect of  $\Delta^9$ -THC on the heart has been studied, with an initial increase in heart rate that diminishes with time and with persistent use. The Pre-Review report outlines studies (although there are many more) showing  $\Delta^9$ -THC (as dronabinol) can cause driving impairment as

well as cognitive deficits such as impaired attention and short-term memory impairment with higher doses being associated with anxiety, panic, confusion, and disorientation. It is also reported that  $\Delta^9$ -THC exposure can provoke transient psychosis-like psychological phenomena in some healthy study participants. However, these effects were modest in magnitude and reversible. In one study of 22 participants, any psychosis-related effects completely resolved and did not prompt hospitalization.

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

There do not appear to be any instances of misuse, illicit production or smuggling, etc of  $\Delta^9$ -THC itself (as opposed to cannabis plant, etc).

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

Therapeutic use of  $\Delta^9$ -THC appears to be restricted to the stereochemical variant (-)-*trans*- $\Delta^9$ -THC (dronabinol). Dronabinol marketed as Marinol® has approval in the United States of America for the treatment of anorexia associated with weight loss in patients with Acquired Immune Deficiency Syndrome (AIDS) and for nausea and vomiting associated with cancer chemotherapy (CINV) in patients who have failed to respond adequately to conventional antiemetic treatment. Dronabinol is either approved or available under 'special access rules' in the United Kingdom, Scandinavian countries, and most Western European countries. For example, it is approved in Austria, Denmark and Ireland for CINV unresponsive to conventional treatment in oncology and palliative care and for cancer pain in Denmark. In Ireland, dronabinol is approved for appetite stimulation in HIV. Dronabinol can be prescribed for any type of chronic pain and for any condition in palliative care in Germany.  $\Delta^9$ -THC has also been studied for other indications, including; abdominal pain, dementia, multiple sclerosis, neuropathic pain and for nausea and vomiting.

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

$\Delta^9$ -THC has no industrial or other use.

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

No information provided in the Pre-Review report.

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

No specific information but it may affect current or future therapeutic applications.  $\Delta^9$ -THC is not listed on the WHO Model List of Essential Medicines.

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

The four stereochemical variants of  $\Delta^9$ -THC are currently listed as Schedule II substances in the 1971 Convention on Psychotropic Substances. However, the stereochemical variant (-)-*trans*- $\Delta^9$ -THC (dronabinol) has the most available data, whereas data for the other stereochemical variants of  $\Delta^9$ -THC are predominantly lacking in all report sections for review. Whilst it does not likely affect any scheduling recommendation, the Pre-Review report does omit some detail and various studies, in particular those in relation to drug driving.

**3. Other comments or opinions**

It should be noted that (-)-*trans*- $\Delta^9$ -THC (dronabinol) is cited as being the primary psychoactive substance in botanical cannabis. Therefore, due to the nature of the substance with  $\Delta^9$ -THC being an active component of the cannabis plants and associated products, it is important to separate out the data involving  $\Delta^9$ -THC itself (including stereochemical variants) only and the Pre-Review report has achieved this.