

# WHO Expert Committee on Drug Dependence Pre-Review

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## Isomers of THC

### Section 3: Toxicology



**World Health  
Organization**

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## Acknowledgments

This report was prepared by the Secretariat of the Expert Committee on Drug Dependence (ECDD) within the Department of Essential Medicines and Health Products (EMP) of the World Health Organization (WHO), Geneva, Switzerland. The WHO staff involved in the production of this document, developed under the overall guidance of Mariângela Simão (Assistant Director General, Access to Medicines, Vaccines, and Pharmaceuticals), Suzanne Hill (Director, Essential Medicines and Health Products), Gilles Forte, (Secretary of the Expert Committee on Drug Dependence) were Dilkushi Poovendran (Technical Officer, WHO Essential Medicines and Health Products) and Wil De Zwart (Technical Officer, WHO Essential Medicines and Health Products).

This report was commissioned as a background document for a preliminary review for the 40<sup>th</sup> Expert Committee on Drug Dependence (ECDD). WHO would like to acknowledge the contributions of the following individuals who authored this report:

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# 1. Toxicology

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Very little information exists on the isomers of THC listed in Schedule 1 of the 1971 Convention on Psychotropic Substances, other than  $\Delta^8$ -THC which is found in the plant [1]. The other THC isomers do not have a botanical origin and were synthesised by medicinal chemists. As a general statement, toxicity of these isomers is very low. However, there is limited preclinical toxicity data on these isomers and they have not been administered to humans for extended periods of time.

## 1.1 $\Delta^8$ -THC

(6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol is commonly known as  $\Delta^8$ -THC (dibenzopyran numbering,  $\Delta^6$ -THC in monoterpenoid numbering).  $\Delta^8$ -THC binds the cannabinoid CB1 receptor and CB2 receptor with lower and higher affinity than  $\Delta^9$ -THC respectively [2]. It has considerably lower potency than  $\Delta^9$ -THC in the mouse tetrad test and unlike  $\Delta^9$ -THC,  $\Delta^8$ -THC did not induce catalepsy or analgesic effects up to 20 mg/kg i.p. [2].

Lethality studies in animals show the doses of  $\Delta^8$ -THC needed to induce death are well beyond that which could possibly be consumed by humans. To put this in perspective, the oral LD<sub>50</sub> for  $\Delta^8$ -THC in rats is 2000 mg/kg [3, 4], which is higher than that found for  $\Delta^9$ -THC (800 mg/kg) [5]. In dogs the LD<sub>50</sub> of  $\Delta^8$ -THC is greater than 3000 mg/kg [6].

Following oral administration or smoking,  $\Delta^8$ -THC has approximately 50-75% the psychotropic potency of  $\Delta^9$ -THC [7-9].  $\Delta^8$ -THC slightly and transiently increases heart rate. Substantial subjective highs were noted at 20 - 40 mg oral doses, smoking doses of 5 - 20 mg and at i.v. doses of 1- 9 mg.

Repeated  $\Delta^8$ -THC dosing prior to conception or during gestation did not have teratogenic effects in rats (up to 40 mg/kg s.c.) [4]. There were no abnormalities in the F2 and F3 generations, although fertility may have been negatively impacted.

While limited data are available,  $\Delta^8$ -THC does not appear to be mutagenic. Blood incubated with  $\Delta^8$ -THC displayed decreased mitosis, although there were no histological abnormalities in the cells examined.  $\Delta^8$ -THC did not cause any abnormalities in chromosome morphology or number - there were no breaks, gaps, lesions or aneuploidy observed [4, 10].  $\Delta^8$ -THC reduces the growth and proliferation of cancer cells in

culture (Lewis lung carcinoma and leukaemia cells) [4].  $\Delta^8$ -THC has also been shown to reduce the proliferation of T and B lymphocytes and induce apoptosis, however this may bear little relevance to human plasma  $\Delta^8$ -THC concentrations attained following cannabis consumption [11].

## 1.2 $\Delta^{6a,10a}$ -THC

- *7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol* is also commonly referred to as  $\Delta^{6a,10a}$ -THC (dibenzopyran numbering,  $\Delta^3$ -THC in monoterpene numbering).  $\Delta^{6a,10a}$ -THC has low toxicity as it did not promote mortality following a dose of 200 mg/kg i.v. in mice [12].

$\Delta^{6a,10a}$ -THC has much less pharmacological activity than  $\Delta^9$ -THC. An early pharmacological screen of cannabinoid activity was based on the ability of  $\Delta^9$ -THC to induce seizures in a subset of rabbits due to autosomal recessive mutation (THC-SS rabbits). Based on this screen it was shown that  $\Delta^{6a,10a}$ -THC was 15 times less potent than  $\Delta^9$ -THC [13]. In another study, the minimum effective dose of  $\Delta^{6a,10a}$ -THC required to reduce muricidal behaviour, an early model of CNS activity, was double that required with  $\Delta^9$ -THC [14].  $\Delta^{6a,10a}$ -THC was inactive in reducing locomotor activity in mice, unlike  $\Delta^9$ -THC which promoted locomotor suppression.

$\Delta^{6a,10a}$ -THC has been safely administered to humans via smoking, where it had much lower psychoactivity than  $\Delta^9$ -THC [15, 16]. The effects of smoking 15 mg  $\Delta^{6a,10a}$ -THC were less marked and shorter in duration than a 12 mg  $\Delta^9$ -THC dose. The participants experienced light-headedness, numbness and tingling in their extremities and face, fatigue, cold perspiration, drowsiness and a feeling of relaxation. Impairment in thinking and the perception of time were less pronounced than with  $\Delta^9$ -THC. Only 3 of the 6 participants displayed reddened conjunctivae. Although, other studies reported no effects of higher smoked doses of  $\Delta^{6a,10a}$ -THC [15, 16].

## 1.3 $\Delta^{9,11}$ -THC

(*6aR,10aR*)-*6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6H-dibenzo[b,d]pyran-1-ol* is also more commonly known as  $\Delta^{9,11}$ -THC (dibenzopyran numbering,  $\Delta^{1,7}$ -THC in monoterpene numbering).  $\Delta^{9,11}$ -THC has low toxicity with an i.v. LD<sub>50</sub> of 93 mg/kg in mice which is double that found for  $\Delta^9$ -THC [17]. It has considerably less pharmacological activity than  $\Delta^9$ -THC. Cannabinoid-like effects were observed with  $\Delta^{9,11}$ -THC in the tetrad test in mice, however much higher ED<sub>50</sub> doses were required to

reduce locomotor activity and tail-flick latency, and to induce hypothermia and catalepsy -  $\Delta^{9,11}$ -THC was between 4 and 40 times less potent than  $\Delta^9$ -THC [18].  $\Delta^{9,11}$ -THC displaced CP 55,940 (a synthetic cannabinoid receptor agonist) from rat brain homogenates, indicating it binds cannabinoid receptors, albeit at a higher  $IC_{50}$  than  $\Delta^9$ -THC (ie 334 versus 218 nM).  $\Delta^{9,11}$ -THC however did not display  $\Delta^9$ -THC-like discriminative stimulus effects.  $\Delta^{9,11}$ -THC has been administered i.v. to rhesus monkeys where unlike  $\Delta^9$ -THC it did not promote ptosis, ataxia or sedation [17]. It hasn't been tested in humans, and high doses would be required to produce  $\Delta^9$ -THC-like intoxication [18].

#### 1.4 The remaining isomers

(9*R*,10*aR*)-8,9,10,10*a*-tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol ( $\Delta^{6a,7}$ -THC or  $\Delta^4$ -THC), (6*aR*,9*R*,10*aR*)-6*a*,9,10,10*a*-tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol ( $\Delta^7$ -THC or  $\Delta^5$ -THC) or 6*a*,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol ( $\Delta^{10}$ -THC or  $\Delta^2$ -THC) have not been assessed in any detail for their toxicity.  $\Delta^7$ -THC doesn't appear to have activity in animal models [19]. The others may not have been tested for pharmacological activity.

## 2. Adverse reactions in humans

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Only  $\Delta^8$ -THC and  $\Delta^{6a,10a}$ -THC have been tested in humans in pure form. As described above the acute intoxicating effects of these molecules was similar in quality but less potent than acute doses of  $\Delta^9$ -THC. These molecules are not available as recreational or therapeutic drugs, so we do not have a good understanding of their adverse effects in humans.



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