WHO Expert Committee on Drug Dependence Pre-Review

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Isomers of THC

Section 5: Epidemiology



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1. Epidemiology

Of the 95 studies relevant to THC, one study analyzed changes in potency of cannabis in the United States between 1995 and 2014 by both Δ^9 -THC and Δ^8 -THC content (8). Prior to 2009, Δ^8 -THC was not detected in cannabis seizures in the United States; a gradual increase in Δ^8 -THC was observed from 0.01% to 0.07% in 2014 (8). Compared to Δ^9 -THC, Δ^8 -THC content was lower by a factor of 10 and increasing potency of Δ^8 -THC did not appear to impact Δ^9 -THC concentrations (8)

2. Industrial use

No data available

3. Therapeutic use

No data available

4. Non-medicinal use, abuse, dependence

No data available

5. Nature and magnitude of the public health problems related to misuse, abuse, and dependence

No data available

6. Licit production, consumption, and international trade

No data available

7. Illicit manufacture and traffic

No data available

8. References

- 1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5th edition). Philadelphia, USA: American Psychiatric Association; 2013.
- 2. World Health Organization. The ICD-10 classification of mental and behavioural disorders: Diagnostic criteria for research. Geneva: 1993.
- 3. ElSohly MA, Slade D. Chemical constituents of marijuana: The complex mixture of natural cannabinoids. Life Sciences. 2005;78(5):539-48.
- 4. PRISMA. Prism Flow Diagram 2015 [Accessed: 04/04/2018]. Available from: <u>http://prisma-statement.org/prismastatement/flowdiagram.aspx</u>.
- International Narcotics Control Board. List of Psychotropic Substances under International Control. Green List. 2016 [04/04/2018]. Available from: <u>https://www.swissmedic.ch/dam/swissmedic/en/dokumente/bewilligungen/btm/conversion_factorspsychotropics.pdf.</u>
- 6. Hollister LE. Tetrahydrocannabinol isomers and homologues: contrasted effects of smoking. Nature. 1970;227(5261):968-9.
- 7. Huffman JW, Duncan Jr SG, Wiley JL, Martin BR. Synthesis and pharmacology of the 1',2'-dimethylheptyl-DELTA⁸-THC isomers: Exceptionally potent cannabinoids. Bioorganic and Medicinal Chemistry Letters. 1997;7(21):2799-804.
- 8. ElSohly MA, Mehmedic Z, Foster S, Gon C, Chandra S, Church JC. Changes in Cannabis Potency Over the Last 2 Decades (1995-2014): Analysis of Current Data in the United States. Biol Psychiatry. 2016;79(7):613-9.

Appendix 1: Search Strategy for isomers of THC

Following databases were searched using OVID on March 8, 2018:

- 1. Embase
- 2. Medline
- 3. PsycINFO

The search strategy (Table 1) was the same as for report 3, but for report 4, we further selected all articles which contained specific information on isomers (for a list of isomers see Table 2).

8.1.1 Table 1: Search strategy for Reports 3 and 4

No.	Searches	Results
1	Human/ or humans/	36244807
2	limit 1 to yr="2000 -Current"	21066974
3	(bibliography or case reports or clinical conference or conference abstract or conference paper or conference proceeding or "conference review" or comment or editorial or in vitro or letter).pt.	8530671
4	2 not 3	16300231
5	epidemiology or exp epidemiology/	3693795
6	prevalence or exp prevalence/	1580556
7	incidence or exp incidence/	1888341
8	population or exp population/	3537733
9	5 or 6 or 7 or 8	8094152
10	delta-9-tetrahydrocannabinol	6047
11	tetrahydrocannabinol or THC	25380
12	dronabinol or exp dronabinol/	13589
13	10 or 11 or 12	29610
14	4 and 9 and 13	1331
15	remove duplicates from 14	1055

8.1.2 Figure 1: PRISMA Diagram for Reports 3 and 4 (4)



8.1.3 Table 2: IUPAC and trivial names of THC isomers

IUPAC name	Trivial name
7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]	Δ-6a, 10a-tetrahydrocannabinol
pyran-1-ol	
(9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-	Δ-6a(7)-tetrahydrocannabinol
dibenzo[b,d]pyran-1-ol	
(6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl- 6H-	Δ-7-tetrahydrocannabinol
dibenzo[b,d]pyran-1-ol	
(6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-	Δ-8-tetrahydrocannabinol
dibenzo[b,d]pyran-1-ol	
6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]	Δ10-Tetrahydrocannabinol
pyran-1-ol	
(6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-	Δ-9(11)-tetrahydrocannabinol
3-pentyl-6Hdibenzo[b,d]pyran1-ol	

Trivial names from: (5)

Of 1055 studies retrieved from the search, 179 were included after screening of title and abstract (see Appendix 1 for Reports 3 and 4 for details). After full-text screening, 95 studies were ultimately included as relevant to THC.

Few articles focused on isomers of THC. The majority of articles retrieved in this search relevant to THC isomers were pharmacological and animal studies.

One study explored the different effects of smoking THC isomers and homologues, but only reported on Δ^9 -THC and Δ^3 -THC; the latter is not relevant to this report (6). Another study found the different structures of THC isomers to affect potency; Δ^8 -THC is reportedly extremely potent as defined by its affinity for the cannabinoid receptor measured by a competitive binding assay (7). Strictly relevant for epidemiology was only one study on increasing and Δ^8 -THC concentrations (8).