

Response to *Pre-review:delta-9-tetrahydrocannabinol (THC)*

Authored by Americans for Safe Access and International Medical Cannabis Patients Coalition

4 June 2018

40th Meeting of ECDD

Thank you for allowing us to address World Health Organization's Expert Committee on Drug Dependence (ECDD). We are encouraged to see the agenda of the 40th meeting of ECDD dedicated to carrying out pre-reviews of cannabis and cannabis-related substances. Americans for Safe Access (ASA), the leading medical cannabis patient advocacy organization in the United States, represents over 100,000 individuals that are using medical cannabis and the International Medical Cannabis Patient Coalition (IMCPC) represents patients from thirty four countries.

We were engaged in United Nations General Assembly Special Session on Drugs in 2016 (UNGASS) meetings where the member states reiterated their "strong commitment to improving access to controlled substances for medical and scientific purpose by appropriately addressing existing barriers." We are grateful to have the opportunity to share our experiences and offer the assistance of our international coalition to ECDD. Below you will find our review, suggestions and response to the critical review document entitled *Pre-review:delta-9-tetrahydrocannabinol (THC)*.

Section 1 Chemistry

Overall, we agree with the authors section on Chemistry. $\Delta 9$ -THC is the key active compound justifying the international scrutiny and control over the whole cannabis plant. Crude cannabis, resin, extracts, tinctures and other preparations, systematically refer to $\Delta 9$ -THC – hence the importance of thoroughness and comprehensiveness of its assessment. The substance has previously been reviewed by the Expert Committee at its 17th, 21st, 26th, 27th, 31st, 32nd, 33rd and 34th meetings. Consensus has never been found on the name and the scope of the molecules, isomers and stereochemical variants to be included or not in the present category.

International control was first applied to $\Delta 9$ -THC and its 6 isomers under the name "tetrahydrocannabinols", later addressed as "dronabinol", a sole-stereochemical variant of the molecule, and finally until today, open to the 4 stereochemical variants of $\Delta 9$ -THC.

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As many as 8 meetings of the ECDD have reviewed the substance (among which three were critical reviews), the use or inclusion of previous critical review meeting documents and outcomes would have been expected to be central in this new review working document.

Section 2 Pharmacology

The Section 2 on Pharmacology would benefit from including numerous scientific discoveries about cannabinoids and the endocannabinoid system (ECS). The absolute lack of information concerning the endocannabinoid system is particularly surprising.

No mention is made of the mechanism of action of anandamide and 2-AG as well as of FAAH and monoacylglycerol lipase. No mention is made in the references of key researchers such as the Czech research team that isolated Δ^9 -THC before Mechoulam in 1964. Beyond these details the document also cites very few references, especially recent articles, while the Pharmacology section of the 2006 Critical review document edited for the 34th ECDD meeting provided far more evidence as well as a 2016 preparatory critical review document:

WHO ECDD34, Assessment of dronabinol and its stereo-isomers. Available on: www.who.int/medicines/areas/quality_safety/4.2DronabinolCritReview.pdf

Cannabis and Cannabis Resin- Critical Review Preparation Document 2016 (prepared by Americans for Safe Access). https://www.safeaccessnow.org/critical_review

This subsection of the report also lacks much emerging evidence indicating that the two-cannabinoid receptor theory might be incorrect. Beyond CB1 and CB2, the activation of some other receptors (e.g. GPR55, TRP channels et al.) by cannabinoids suggests that they may have a role in the wide-ranging neuro-modulatory effects of the endocannabinoid system.

Cannabinoids, and Δ^9 -THC in particular, not only have important brain-related activity, they also have notable gastrointestinal activity; not mentioned in the Pharmacology section.

This section could be greatly improved by utilizing more data regarding Marinol's® monograph:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/018651s025s026lbl.pdf

Section 3 Toxicology

We are in agreement with the author's analysis of pure THC's toxicology.

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Section 4 Therapeutic applications and extent of therapeutic use and epidemiology of medical use

We are in agreement with the authors' analysis of Marinol's therapeutic applications.

Section 5 Epidemiology

We agree with the author's statements in this section, such as, "*While pure THC has potential for non-medical use and abuse, such non-medical use seems to be rare*" and that there are no significant "*public health problems of pure THC*" that have been documented. However, the section is sparse and inadequate as is. This section can be improved by including the following documents in the subsections:

Wang, T., Collet, J.-P., Shapiro, S., & Ware, M. A. (2008). *Adverse effects of medical cannabinoids: a systematic review*. *CMAJ : Canadian Medical Association Journal = Journal De l'Association Medicale Canadienne*, 178(13), 1669–1678. <http://doi.org/10.1503/cmaj.071178>

Robson, P. (2011). *Abuse potential and psychoactive effects of δ -9-tetrahydrocannabinol and cannabidiol oromucosal spray (Sativex), a new cannabinoid medicine*. *Expert Opinion on Drug Safety*, 10(5), 675–685. <http://doi.org/10.1517/14740338.2011.575778>

Karschner, E. L., Darwin, W. D., McMahon, R. P., Liu, F., Wright, S., Goodwin, R. S., & Huestis, M. A. (2011). *Subjective and Physiological Effects After Controlled Sativex and Oral THC Administration*. *Clinical Pharmacology & Therapeutics*, 89(3), 400–407. <http://doi.org/10.1038/clpt.2010.318>

Cannabis and Cannabis Resin- Critical Review Preparation Document 2016 prepared by the Americans for Safe Access at their National Unity Conference
https://www.safeaccessnow.org/critical_review

Makela, P., Wakeley, J., Gijsman, H., Robson, P. J., Bhagwagar, Z., & Rogers, R. D. (2006). *Low doses of delta-9 tetrahydrocannabinol (THC) have divergent effects on short-term spatial memory in young, healthy adults*. *Neuropsychopharmacology*, 31(2), 462–470.

Lastly, we suggest including this article with your review, the article states that no abuse or diversion has been observed with pure THC and warranted removal of Marinol from Controlled Substances Act Schedule II to Schedule III.

Calhoun, S. R., Galloway, G. P., & Smith, D. E. (1998). *Abuse potential of dronabinol (Marinol)*. *J Psychoactive Drugs*, 30(2), 187-196.

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Additional Resources

ECDD40 Procedural, methodological and terminological bias. For Alternative Approaches to Addiction, Think & do tank. www.faaat.net/cannabis

International Medical Cannabis Patient Coalition (IMCPC)'s UNGASS 2016 Declaration delivered to the UN Commission on Narcotic Drugs in Vienna March 2015: <http://bit.ly/1TV0gNi>

Cannabis and Cannabis Resin- Critical Review Preparation Document 2016 prepared by the Americans for Safe Access at their National Unity Conference
https://www.safeaccessnow.org/critical_review

Testimony from WHO ECDD November 2015 Meetings:

Global Patient Populations Need International Medical Cannabis Policies to Evolve:
<http://bit.ly/1TV0G6l>
[pdf, 272kb Steph Sherer, Executive Director, Americans for Safe Access]

Cannabis, an irreplaceable botanical medicine of long standing human use <http://bit.ly/1TV0vbf>
[pdf, 50kb Michael Krawitz, Executive Director, Veterans For Medical Cannabis Access:
<http://bit.ly/1TV0vbf>]

The WHO cannabis background document: <http://bit.ly/1TV0nID>

Acknowledgments

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