

Cannabis and cannabis resin

Information Document

Agenda item 8.2

Expert Committee on Drug Dependence

Thirty-sixth Meeting

Geneva, 16-20 June 2014



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Introduction

Cannabis is scheduled in Schedules I and IV of the Single Convention on Narcotic Drugs as amended by the 1972 Protocol (the “Single Convention”). A review of cannabis and cannabis resin by the World Health Organization is necessary for multiple reasons, the foremost being that the medical use of cannabis appears to have increased in recent years. Cannabis and cannabis resin has not been scientifically reviewed by the Expert Committee since the review by the Health Committee of the League of Nations in 1935. An increasing number of countries are adopting varying policies on cannabis and cannabis resin different from prohibition to mitigate the harm due to cannabis. In addition, the Commission on Narcotic Drugs in its Resolution 52/5 from 2009 stated that it looks forward to an updated report on cannabis by the Expert Committee on Drug Dependence . The International Narcotics Control Board, in its annual report for 2013, invited WHO, in view of its mandate under the 1961 Convention, to evaluate the potential medical utility of cannabis and the extent to which cannabis poses dangers to human health.

This document lists a number of aspects to be considered by WHO and the WHO Expert Committee on Drug Dependence (ECDD): they include procedural aspects of such a review; considerations regarding the current level of control ; ECDD assessment requirements (including aspects that need specific attention); and some other considerations such as quality assurance of medicinal cannabis. The purpose of this document is to guide discussions during the 36th meeting of ECDD.

History of the review and control of cannabis and cannabis resin

Cannabis and Cannabis Resin are both scheduled in Schedules I and IV of the Single Convention on Narcotic Drugs since this Convention came into force in December 1964. (1) These substances were discussed internationally for drug control because Italy and the United States raised the question of “Indian hemp” (cannabis) at the The Hague Conference of 1912, (2) but it was only the second Opium Convention of 1925 that regulated the international trade of “Indian hemp”, its resin and its galenic preparations. It allowed for the medical and scientific use of galenic preparations. (2, 3)

Cannabis was reviewed by the Health Committee of the League of Nations in 1935, which recommended that preparations obtained from cannabis extract or tincture were placed under control of the second Opium Convention. (2, 3)

After World War II, WHO became responsible for the health functions of the League of Nations. The Expert Committee on Drugs Liable to Produce Addiction, later called the Expert Committee on Addiction-Producing Drugs (and today called the ECDD) spoke out against the medical use of cannabis repeatedly (e.g. fifth (1955), 11th (1960), 14th (1965) and 16th Meetings (1968)). (4,5,6,7) However, in none of these cases was there a review of the dependence-producing properties of the substance. WHO published a literature review on the physical and mental effects of cannabis in 1955, which was prepared by a former WHO staff member for the Commission on Narcotic Drugs. (8) However, it is not clear if this report was discussed by the Expert Committee on Drugs Liable to Produce Addiction, because it is not mentioned or cited in the Expert Committee’s reports.

Because of their inclusion in the 1925 Opium Convention, cannabis and cannabis resin were included in Schedule I of the Single Convention on Narcotic Drugs. When the Schedules of the Single Convention were drawn up, the Expert Committee on Addiction-Producing Drugs stated that it “believed that the composition of the schedules [on the draft list for the Single Convention] should be most carefully reviewed before they become an established part of the new Convention”. (9) However, the Expert Committee’s tenth report only mentions that substances in Schedule III were reviewed individually. No reference can be found to a review of cannabis and/or its resin. (3, 5) The Expert Committee’s 13th Report also mentions a review of substances for the Single Convention, but again, no specific reference to a review of cannabis or cannabis resin is made. (10)

The Technical Committee of the Plenipotentiary Conference which negotiated the Single Convention included both substances also in Schedule IV. The Technical Committee used the following criteria for inclusion: Substances “(a) Having strong addiction-producing properties or a liability to abuse not offset by therapeutic advantages which cannot be afforded by some other drug; and/or (b) For which the deletion from general medical practice is desirable because of the risk to public health”. (11)

After 1968, cannabis does not appear on the agenda of the Expert Committee. Therefore, even if reviews were conducted in the past by WHO, the most recent reviews of cannabis and cannabis resin were conducted when review methods and the knowledge of dependence and substance abuse were less developed than they are today. WHO published a report on the health effects of cannabis in 1997, but this report was not prepared for the purpose of reviewing the scheduling of cannabis and therefore, was not discussed by the Expert Committee on Drug Dependence. (12)

In its 2009 Resolution 52/5 “Exploration of all aspects related to the use of cannabis seeds for illicit purposes”, the Commission on Narcotics Drugs (CND) requested “the United Nations Office on Drugs and Crime to share information regarding the health risks posed by cannabis with the Expert Committee on Drug Dependence of the World Health Organization, and, in that regard, looks forward to an updated report on cannabis by the Expert Committee, subject to the availability of extrabudgetary resources”. (13) The 35th Expert Committee on Drug Dependence agreed to review cannabis in a future meeting of the Committee. (14) Moreover, an author group consisting of WHO staff, experts and consultants related to WHO’s work on substance misuse recommended that substances that not reviewed for a long period of time, should be re-reviewed regularly using modern methods for the purpose of improving the credibility of scheduling. (3)

In recent years, many countries developed strategies that acknowledge differences in safety between psychoactive substances. Recently, the use of cannabis for recreational use was legalized in Uruguay and in Colorado and Washington State in the United States of America. (15, 16).

In the last fifteen years, many countries have allowed the medical use of cannabis. Its current scheduling in Schedule IV is based on the assumption that there is little or no therapeutic role for cannabis.

It is against this background that the Secretariat is planning a review of cannabis and cannabis resin. However, because of the complexity of such a review, it was decided not to include a review as such on the agenda of the 36th ECDD, but first to develop this discussion paper on the modalities of such a review.

In this document, considerations for preparing a review of cannabis are discussed. This document will discuss:

- Procedural aspects of the ECDD review of cannabis and cannabis resin
- Aspects of changing the scope of control
 - Scheduling options for the committee
 - Definition
 - Current control of legal production of cannabis for medical and scientific purposes
- Aspects to include in an ECDD assessment
 - Aspects listed in the guidance (19)
 - Among aspects listed in the guidance, aspects that need specific attention
- Aspects related to different properties of various types of cannabis and its resin
- Other Considerations
 - Quality assurance of medicinal cannabis

Procedural aspects of the ECDD review of cannabis and cannabis resin

The WHO review procedure, grounded in considerations of public health and with an evidence-based approach, utilizes the best available relevant information. Consistent with the requirements of the 1961 and 1971 Conventions, WHO develops scheduling recommendations guided by the provisions in the Conventions regarding the changes in the scope of control of substances and also taking into account the preambles of the Conventions, the need to reduce the risk to public health, including the risk of abuse and ensuring medical availability, and the relevant resolutions of its governing bodies. The Conventions are legal instruments; the WHO review procedure is applied in a manner consistent with the letter and the spirit of the Conventions.

The functions of the Expert Committee are to review information available to it on substances being considered for international control and for exemptions, and to advise the Director-General on such control. The advice of the Expert Committee concerns scientific, medical and public health findings and must comply with the criteria established in the Conventions. The Expert Committee is assisted by a secretariat, in particular by the Expert Committee's Secretary and furthermore by staff members from appropriate WHO programmes, consultants and temporary advisers, as required.

The Expert Committee deliberations are facilitated by documents provided by the Secretariat. Proposals for the change in control of a substance should be subjected to the same assessment that is given to substances proposed for initial scheduling. The relevant criteria in this regard are set out in paragraphs 43; 46 to 59 of the *Guidance on the WHO review of psychoactive substances for international control*, adopted by the WHO Executive Board in at its 126th session. The Expert Committee should follow the sequence for analysis established

by the guidelines for all substances that is, first consider applicability of the Single Convention and, if it is not found to apply, then the Convention on Psychotropic Substances of 1971. Further information regarding the assessment process can be found in the *Guidance on the WHO review of psychoactive substances for international control*, particularly in paragraphs 43; 46 to 59 (17)

Aspects related to potentially changing scheduling status

Scheduling options for the Committee

Currently, both Cannabis and Cannabis resin are scheduled on two schedules simultaneously: Schedule I and Schedule IV. Therefore, changes that the Committee can propose are:

- a. Removal from Schedule IV, while maintaining it on Schedule I
- b. Removal from Schedule IV, and moving it from Schedule I to Schedule II
- c. Removal from both Schedule I and IV
- d. Combine placing on Schedule I or II with an exemption for certain preparations by placing these preparations on Schedule III

A fifth option for the committee will be not to make change in status. For assessing whether to recommend scheduling and if yes, which schedule to recommend, the Committee should follow the criteria and procedures as provided in the Conventions and further elaborated in the *Guidance on the WHO review of psychoactive substances for international control*, (17) in particular the paragraphs 43; 46 – 59.

Paragraph 6 of Article 3 of the Single Convention clarifies that for drugs already scheduled, the CND may, in accordance with the recommendation of the World Health Organization, amend any of the Schedules by transferring a substance from Schedule I to Schedule II or from Schedule II to Schedule I or deleting a drug or a preparation as the case may be, from a Schedule.

While evaluating cannabis and its resin, the Committee should consider all scheduling options mentioned above

Definition

According to the Convention, cannabis is defined as “the flowering or fruiting tops of the cannabis plant (excluding the seeds and leaves when not accompanied by the tops) from which the resin has not been extracted, by whatever name they may be designated.” Cannabis resin means “separated resin, whether crude or purified, obtained from the cannabis plant.” These definitions are narrower than the botanical definition and as a consequence, certain parts of the plant are not under international control.

While evaluating cannabis and its resin, the Committee should decide whether the review will be limited only to those parts currently controlled

Current control of legal production of cannabis for medical and scientific purposes

It should be noted that medicinal cannabis is used in a number of countries. Some of these countries cultivate cannabis for domestic medical use: Canada, Israel, the Netherlands, the United Kingdom and a number of states in the United States (see under *Aspects to Assess, (9) Therapeutic applications, extent of therapeutic use and epidemiology of medical use*). Article 28 requires that the country applies the same controls as listed in Article 23, paragraph 2 for the production of opium. The agencies should supervise the cultivation and take possession of the produced cannabis no later than four months after the harvest.

All the countries mentioned here established one or more state agencies as required in Article 28 of the Convention. Entities carrying out the functions of such an agency were also identified by the Governments of Austria and the Czech Republic, but the cultivation has not yet started. In the USA, functions are carried out by NIDA and the DEA, but they are involved with the production for scientific purposes only and not with the production for medical purposes by the states.

Nutt et al. describe the mechanisms of current control that hamper research with cannabis (and other strictly controlled medicines in Schedules I of the Single Convention and the Psychotropic Substances Convention). (19)

A critical review report for the Committee should contain details of medical use and how this is regulated in different countries, so that the Committee understands the epidemiology of use and regulations to make appropriate decisions.

Aspects to include in an ECDD Assessment

Aspects listed in the Guidance

For Cannabis assessment, all aspects mentioned in the WHO Guidance (17) need to be followed. Furthermore, based on CNDR Resolution 52/5 any pertinent information from UNODC and also other relevant sources such as INCB should be considered for the review report, for example the UNODC discussion paper “Cannabis, A short review” (20)

Aspects that need specific attention

(5) Toxicology and (6) Adverse reactions in humans

There is no known LD₅₀ for cannabis and cannabis resin. For its main active principle dronabinol, the LD₅₀ has been shown to be higher than 9000 mg/kg in primates, corresponding to a dose of over 3 kg strong cannabis (~23% THC) in humans. (21) The Expert Committee need to examine the ill effects as compared to other substances under control.

(7) Dependence potential (8) Abuse potential

These important criteria for international control need to be evaluated with recent evidence. To understand harm due to cannabis better, it is also important to understand whether lack of availability of cannabis due to control is associated with the increasing use – dependence

and abuse - of potentially more dangerous synthetic cannabinoids and thus the relative harm.

(9) Therapeutic applications, extent of therapeutic use and epidemiology of medical use

Since the last decade of the twentieth century, evidence for medical uses increased considerably (22, 23,24). Indications being considered among others include spasticity, chronic pain and some neuropsychiatric symptoms. In different ways, various countries recognized a role for safe and effective medicinal use of cannabis.

Currently, medical use of cannabis is allowed in a number of countries. In the past 20 years, its (legal) medical consumption has gone up from almost non-existent to 23.7 tonnes in 2011 and 77 tonnes in 2014(25).

The United Kingdom produces cannabis for the production of a dronabinol-cannabidiol combination preparation for the treatment of spasticity due to multiple sclerosis (Sativex®) that is prepared using cannabinoids extracted from plant material¹. This preparation has been approved as a medicine in 24 countries (including Austria, Australia, Belgium, Canada, the Czech Republic, Finland, Germany, Hungary, Iceland, Italy, the Netherlands, New Zealand, Norway, Poland, Portugal, Slovakia, Spain, Sweden, Switzerland, and the United Kingdom).

(17) Current international controls and their impact; and (18) Current and past national controls

The current international controls are the strictest controls possible under the Conventions: stricter control than that effected through being placed in Schedules I and IV of the Single Convention is not possible. Since the 1970s, some countries have decriminalized, condoned or legalized the possession of cannabis and sometimes also the distribution and production.

When the Committee will evaluate cannabis and its resin, it is recommended that it reviews all aspects listed in the Guidance, with special attention to a) its absolute acute toxicity, b) its relative harmfulness compared to other substances under control, c) to the medical use of cannabis, and d) current controls and their impact.

The Secretariat, while preparing a critical review report, should ensure that this report entails sufficient documentation on all aspects listed in paragraph 23 of the guidance and in particular on:

- *toxicology and adverse reactions in humans,*
- *dependence and abuse potential*
- *therapeutic applications, extent of therapeutic use and epidemiology of medical use; and*
- *current international controls and their impact, and current and past national controls.*

¹ It should be noted that although the starting materials for Sativex are extracted from cannabis, dronabinol and its preparations are controlled under the United Nations Convention on Psychoactive Substances and cannabidiol is not subject to substance control.

Aspects related to different properties of various types of cannabis and its resin

Cannabis and cannabis resin are separately scheduled in the Single Convention. Over 60 cannabinoids were identified in *Cannabis sativa* L., but many of these are not or only marginally explored for their properties. (26) They may be agonists, partial antagonists, antagonists or pharmacologically inactive cannabinoids. Moreover, plant material contains also many substances from various other classes. The typical number of substances that can be identified in a plant is 700 – 1000, most of them not psychoactive substances. However, it should be considered that the non-psychoactive constituents may influence the uptake of the psychoactive and other constituents (e.g. terpenes) or may partially counteract the psychoactivity as a partial antagonist (e.g. (+)-cannabidiol or cannabinal; the latter being a decomposition product). Both genotype and phenotype can make a difference for the actual composition of a cannabis batch. These differences can have consequences for the psychopharmacological and other pharmacological activity of the plant. (27)

Therefore, there is not “one cannabis”, but the actual content of THC can vary from very low (under 0.9% for the approved industrial varieties in the EU to up to 28% (strength based on content of the flowering tops). Moreover, also the variety in cannabinoid profiles and the divergent presence of uptake enhancers causes a diversity of properties of the many cannabis varieties. The question is whether this makes a difference for the scheduling of cannabis and cannabis resin.

When the Committee will evaluate cannabis and its resin, it is recommended that it considers whether all cannabis and cannabis resin, mild intermediate and strong, should be scheduled in the same way; the review report should therefore, if possible, contain the information that warrants a Committee decision.

Other considerations

Quality assurance of medicinal cannabis

Where there is no government control over the cultivated medicinal cannabis, producers do not necessarily apply basic Good Production Practices like GAP, GMP, GLcP and GDP practices. This is even more prominent in case of seized cannabis for medical use. This has consequences for the safety and efficacy of the medicinal cannabis:

- there can be considerable batch-to-batch variation in strength and the qualitative composition of the medicine, resulting in varying effectiveness.
- cannabis is known for containing *Aspergillus fumigatus* L., a fungus that can infect the user and produces toxins that may provoke a psychosis. A Dutch study compared illegal cannabis batches with medicinal cannabis produced under state control. Some samples of the former contained up to 480,000 CFU/gram, while the latter was produced with very low levels of the fungus and then sterilized. (28)
- contamination can also derive from pesticides used during production or from heavy metals in the substrate (e.g. rockwool).

An example of production with good quality assurance is the Dutch medicinal cannabis. This is produced under responsibility of the Ministry of Health and meets a number of quality requirements: constant strength on dronabinol and constant composition of secondary cannabinoids, absence of microbiological contamination, pesticides and heavy metals, and humidity. Where there is a norm provided in the European Pharmacopoea, this norm is followed. (29)

When the Committee will evaluate the medical and scientific use of cannabis and its resin, it is recommended that it reports on the necessity of a safe and constant product assured by a system of quality assurance and standardized cultivation, and free of microbiological and chemical contamination and that it explains the health hazards related to varying composition and contamination.

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