

Annex A

Terms of Reference: Chemistry

- The purpose of the Pre-Review is to synthesize existing scientific evidence about the therapeutic use and potential for dependence and abuse of cannabis-related compounds
- Any recommendations on the scheduling of the substances are to be made by the Expert Committee, and should not be included in the Pre-Review
- The WHO Pre-Review¹ template for substances under review by the Expert Committee on Drug Dependence comprises five scientific topics:
 - Chemistry
 - Pharmacology
 - Toxicology/ Adverse Effects
 - Epidemiology
 - Therapeutic Use
- The author will complete the Pre-Review report for the scientific topic of **chemistry** based on the template found on Annex Page 7
- The author will prepare **four separate** reports on the **chemistry** of the following cannabis related compounds:
 - Report 1: Cannabis plant and cannabis resin
 - Report 2: Extracts and tinctures of cannabis
 - Report 3: Delta-9-tetrahydrocannabinol (THC)
 - Report 4: Isomers of THC
- Where authors refer to a specific compound (e.g. type of cannabis plant, extract, or isomer), they are asked to clearly indicate this in the report
- The reports will be prepared in accordance with the specific inclusion and exclusion criteria to minimise overlap and repetition of information (Annex Pages 3-6).
- The reports should include information, where feasible, in all the required sections of the template in accordance with the *Guidance on the WHO review of psychoactive substances for international control* document. The guidance document is available online at the WHO Expert Committee on Drug Dependence website: <http://www.who.int/medicines/access/controlled-substances/ecdd/en/>
- The reports should be presented in a manner that will facilitate an evidence-based assessment by the Expert Committee.
- The reports should be written in an objective manner without bias or opinions.

¹ Pre-Review: An initial review to determine whether a critical review is warranted. If the Expert Committee finds the information may justify scheduling or a change in the scheduling of the substance they can recommend a Critical Review. A critical review is to consider whether the Expert Committee should advise the Director-General to recommend the scheduling of, or amending of the scheduling status of, a substance.

- The reports should summarise the literature in a manner that presents the relevant information, without necessarily producing an exhaustive report. The use of existing reviews is encouraged, provided adequate referencing is utilised.
- Preliminary drafts should be submitted to the WHO ECDD Secretariat for assessment of quality and suitability for the Expert Committee. The Secretariat may request editorial changes and follow up drafts, if deemed necessary.
- The final draft of the reports will be peer-reviewed by experts from WHO's Expert Advisory Panels. This will include an evaluation of the strength of evidence presented. If there are data limitations or omissions, they will be discussed with, and adapted as needed, by the author.
- Examples of previous Pre-Reviews are available on the WHO Expert Committee on Drug Dependence website. For example, two Pre-Reviews (phenazepam and etizolam) were prepared for the 37th ECDD in 2015.
- Authors should include a comprehensive list of references, and specify the methodology used in the report

Inclusion and Exclusion Criteria for Reports

Report 1: Cannabis plant and Cannabis Resin Pre-Review

Inclusion Criteria

Studies to be included in the report are those involving:

- Cannabis as defined by the International Drug Control Conventions as “the flowering tops of the cannabis plant from which the resin has not been extracted”². The term “cannabis” generally refers to a dried preparation of the flowering tops or other parts of the cannabis plant.
- Cannabis resin which is defined as “the separated resin, whether crude or purified, obtained from the cannabis plant”. It is normally in solid form and is sometimes known as hashish.

Exclusion Criteria

Studies to be excluded from the report:

- Tinctures and extracts of cannabis including preparations or mixtures of cannabis substances (e.g. nabiximols)
- Pure delta-9-tetrahydrocannabinol (THC) and its four stereochemical variants
 - (-)-trans-delta-9-tetrahydrocannabinol
 - (+)-trans-delta-9-tetrahydrocannabinol
 - (-)-cis-delta-9-tetrahydrocannabinol
 - (+)-cis-delta-9-tetrahydrocannabinol
- Pure cannabidiol (CBD)
- Isomers of tetrahydrocannabinol (THC)
 - 7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
 - (9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
 - (6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl- 6H-dibenzo[b,d]pyran-1-ol
 - (6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
 - 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
 - (6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6Hdibenzo[b,d]pyran-1-ol

²https://www.unodc.org/documents/commissions/CND/Int_Drug_Control_Conventions/Ebook/The_International_Drug_Control_Conventions_E.pdf

Report 2: Extracts and Tinctures of Cannabis

Inclusion criteria

Studies to be included in the report are those involving:

- Cannabis extracts: this term refers to a plant extract mixture from the leaves and flowers of Cannabis sativa
- Cannabis tinctures: this term refers to specific alcohol extractions of the flowering tops or other parts of Cannabis sativa.
- Cannabis oils e.g. Butane Hash Oil, Hemp Seed Oil
- Aqueous extracts e.g. marijuana tea
- Nabiximols (e.g. Sativex®)

Exclusion criteria

Studies to be excluded from the report:

- Cannabis plant (dried preparations of the flowering tops or other parts of the cannabis plant) and cannabis resin (separated resin obtained from the plant)
- Pure delta-9-tetrahydrocannabinol (THC) and its four stereochemical variants except when delta-9-THC is extracted from the cannabis plant.
 - (-)-trans-delta-9-tetrahydrocannabinol
 - (+)-trans-delta-9-tetrahydrocannabinol
 - (-)-cis-delta-9-tetrahydrocannabinol
 - (+)-cis-delta-9-tetrahydrocannabinol
- Pure cannabidiol (CBD) when not in a preparation with other cannabis related ingredients
- Isomers of tetrahydrocannabinol (THC)
 - 7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
 - (9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
 - (6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl- 6H-dibenzo[b,d]pyran-1-ol
 - (6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
 - 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
 - (6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6Hdibenzo[b,d]pyran-1-ol

Report 3: Delta-9-tetrahydrocannabinol

Inclusion criteria

Studies to be included in the report are those involving:

- Pure delta-9-tetrahydrocannabinol that is obtained either directly from the cannabis plant or synthesised.
- The stereochemical variants of delta-9-tetrahydrocannabinol:
 - (-)-trans-delta-9-tetrahydrocannabinol (also known as dronabinol)
 - (+)-trans-delta-9-tetrahydrocannabinol
 - (-)-cis-delta-9-tetrahydrocannabinol
 - (+)-cis-delta-9-tetrahydrocannabinol

Exclusion criteria

Studies to be excluded from the report:

- Cannabis plant (dried preparations of the flowering tops or other parts of the cannabis plant) and cannabis resin (separated resin obtained from the plant)
- Tinctures and extracts of cannabis including preparations or mixtures of cannabis substances (e.g. nabiximols), except those that are pure delta-9-THC
- Pure cannabidiol
- Isomers and stereochemical variants of tetrahydrocannabinol as listed in Schedule 1 of the 1971 Convention on Psychotropic Substances
 - 7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
 - (9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
 - (6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl- 6H-dibenzo[b,d]pyran-1-ol
 - (6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H- dibenzo[b,d]pyran -1- ol
 - 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
 - (6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene- 3-pentyl-6Hdibenzo[b,d]pyran-1-ol

Report 4: Isomers of THC

Inclusion criteria

Studies to be included in the report are those involving:

- Isomers and stereochemical variants of tetrahydrocannabinol as listed in Schedule 1 of the 1971 Convention on Psychotropic Substances:
 - 7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
 - (9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
 - (6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl- 6H-dibenzo[b,d]pyran-1-ol
 - (6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
 - 6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d] pyran-1-ol
 - (6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6Hdibenzo[b,d]pyran-1-ol

Exclusion criteria

Studies to be excluded from the report:

- Cannabis plant (dried preparations of the flowering tops or other parts of the cannabis plant) and cannabis resin (separated resin obtained from the plant)
- Tinctures and extracts of cannabis including preparations or mixtures of cannabis substances (e.g. nabiximols)
- Delta-9-tetrahydrocannabinol (THC) and its four stereochemical variants
 - (-)-trans-delta-9-tetrahydrocannabinol (also known as Dronabinol)
 - (+)-trans-delta-9-tetrahydrocannabinol
 - (-)-cis-delta-9-tetrahydrocannabinol
 - (+)-cis-delta-9-tetrahydrocannabinol
- Cannabidiol

Template for the review report

Chemistry

Pre-Review Report: Chemistry of (insert substance name/s)

I. Substance identification (1)³

International Nonproprietary Name (INN)

Chemical Abstract Service (CAS) Registry Number

Other Chemical Names

Trade Names

(Including brand names)

Street Names

Physical Appearance

(For example: color, taste and smell)

WHO Review History

(For example: previous reviews by the ECDD or WHO committees)

II. Chemistry (2)

Chemical Name

IUPAC Name:

CA Index Name:

Chemical Structure

Free base:

Molecular Formula:

Molecular Weight:

Stereoisomers

Methods and Ease of Illicit Manufacturing

(Diagrams of pathways during synthesis can be included. Effect of environment and climate on plant growth can be included)

³ () indicates corresponding report section in Paragraph 23: Guidance on the WHO Review of psychoactive substances for international control

http://www.who.int/medicines/areas/quality_safety/GLS_WHORev_PsychoactSubst_IntC_2010.pdf?ua=1

Chemical Properties

Melting point

Boiling point

Solubility

Identification and Analysis

(For example: chemical spot tests, immunoassays, mass spectrometry, chromatography)

III. Ease of Convertibility Into Controlled Substances (3)