

**WHO Responses to CND questions asked during the 4th Intersessional meeting
of the 62nd session of the Commission on Narcotic Drugs on 24 June 2019**

Questions received in WHO on 27 June 2019

5.0 General Questions

Question from Canada

- In addition to our written questions which had been submitted in advance, we also asked what complementary or supplementary considerations the WHO's guidance on the WHO review of psychoactive substances under international control had added to the ECDD's consideration of the criteria stipulated in the Conventions, in developing its recommendations regarding cannabis?

WHO response

The *Guidance on the WHO review for psychoactive substances for international control* was approved by WHO's Executive Board in January 2010. The *Guidance* sets out guidelines establishing the underlying principles of the review procedure, working arrangements within the Secretariat and with external bodies, and the nature of the documentation to be prepared in relation to the ECDD process. The guidelines cover WHO's responsibilities under Article 3 of the 1961 Convention and Article 2 of the 1971 Convention concerning whether or not to recommend international control of substances, as well as the assessment of exempted preparations under Article 3 of the 1971 Convention.

As per the *Guidance*, WHO performed its review of cannabis and related substances by carrying out a two-stage process to first determine, through a so-called pre-review, whether there was adequate information about cannabis and cannabis-related substances to justify a so-called critical review, before arriving at its recommendations through this critical review process. The *Guidance* explains that the Expert Committee shall recommend a critical review if it finds that information may justify the scheduling or a change in the scheduling of the substance.

The set template for the review of psychoactive substances included in the *Guidance*, ensures that the same assessment criteria are applied to all substances that are under review, to comply with the Conventions.

The review process ensures that the recommendations are based on scientific and public health principles, and that assessments made by the Expert Committee are based on robust evidence primarily about the harms, dependence potential, and abuse potential of substances whilst also ensuring that therapeutic and scientific uses are considered so as not to restrict access to substances in this regard.

The *Guidance* ensures that WHO systematically collects data and additional information from Member States and other interested parties, and that ECDD documentation is available on the WHO website for the sake of transparency and commentary.

The *Guidance* is available on the WHO website.

Questions from Mexico

- Do the medical and scientific communities have the same tools now that they had when the Single Convention and the other two Conventions were crafted?
- Does the knowledge about the different components of Cannabis is the same in 2019 than 50, 60 or more years ago?
- Is there now a better understanding by the scientific and medical communities both of the different components of Cannabis, well beyond the differentiation captured in the Single Convention, as well as the differences of their characteristics and properties?

WHO response

There has been a vast change in our understanding of cannabis since the establishment of the 1961 Single Convention. At that time, there was little understanding of the hundreds of compounds present in cannabis, and it was not known which compounds had psychoactive properties and which did not. There was also little research that investigated the medical uses of cannabis. Furthermore, when the Conventions were established, cannabis resin was the only known preparation that was derived from cannabis.

Since the establishment of the Conventions, there have been a number of developments that have increased our scientific understanding of cannabis and its components and enabled us to better understand their respective harms and therapeutic applications. For example, whilst cannabis resin was the only known preparation of cannabis at the time it entered into the Conventions, we now recognise that there are a range of preparations that could be derived from cannabis, and that these could have varying strengths and levels of psychoactivity. In addition, delta-9-THC has been recognised as the main active constituent of cannabis while compounds such as cannabidiol have been shown not to have psychoactive effects. There has been increasing research on the medical use of cannabis, and there is also more research into non-medical preparations.

Questions from Mexico

- Could you confirm if the "single species concept" was still widely accepted by the time of the drafting of the Single Convention?
- Could you confirm if the original concept of Cannabis as a "single species" has finally been fully overcome? Should it be not the case, could you elaborate in which circles is this outdated notion still en vogue?
- Is there a different perception regarding the Poppy plant and seeds versus opium and heroin, or the Coca plant and leaves versus cocaine than there is between Cannabis as a plant and as a narcotic drug? Did this difference prevail in the Single Convention? If so, what were the reasons?

WHO response

The history of the taxonomy of cannabis dates back several hundred years and is complex. At the time of drafting the Single Convention, cannabis was widely regarded as a single species with two or more sub-species. It is currently considered as monospecific (*Cannabis sativa* L.) with two subspecies (*Cannabis sativa* L. subsp. *sativa*, and *cannabis sativa* L. subsp. *indica*) and four varieties.

Cannabis sativa subsp. *Sativa* is a plant of limited intoxicant ability, Δ^9 -THC usually comprising less than 0.3% (dry weight) of upper third of flowering plants (sometimes up to 1%) and usually less than half of cannabinoids of resin. This plant is cultivated for fibre or oil or growing wild in regions where such cultivation has occurred.

Cannabis sativa subsp. *indica* (Lam.) is a plant of considerable intoxicant ability, Δ^9 -THC usually comprising more than 1% (dry weight) of upper third of flowering plants and frequently more than half of cannabinoids of resin. This plant is cultivated for intoxicant properties or growing wild in regions where such cultivation has occurred.

Morphine and cocaine as active principles of opium poppy and coca leaf are in the same convention and the same schedule (1961, Schedule I) as opium poppy and coca leaf respectively. Meanwhile, cannabis plant is in the 1961 Convention and delta-9-THC, the active principle of cannabis, is in the 1971 Convention. This can be explained by the fact that delta-9-THC was unknown when the 1961 Convention was established.

5.1 Cannabis and cannabis resin

Question from Canada

- Under recommendation 5.1, we asked whether ECDD was able to take into consideration comparisons between cannabis and other substances which are not controlled under the Conventions, including alcohol and tobacco. This was particularly relevant in light of ECDD's consideration of the harms associated with use, such as rates of substance use disorders and driving under the influence of cannabis.

Questions from Mexico

- If Δ^9 -THC is the only psychoactive constituent of Cannabis then, why continue to refer to Cannabis as whole, when addressing the narcotic effects of just one of its constituents?
- If the Committee "did not consider that Cannabis is associated with the same level of risk to health of most of the other drugs that have been placed in Schedule I", then why it still "recommended that Cannabis and Cannabis resin continue to be included in Schedule I of the 1961 Single Convention on Narcotic Drugs"?
- If toxicity and mortality are out of the question as Cannabis doesn't relate at all to the other two substances on these fields, what are then the other "public health problems arising from Cannabis use and the global extent of such problems", referred in the report?
- What is the metric for determining that there are "high rates" of those public health problems?
- What would be the difference between those "health problems" and problems arising from the consumption of other substances such as sugar, not to mention alcohol or tobacco, or modern practices such as "work burn out"?

Questions from Nigeria

- Nigeria Drug Use Survey indicate that 14million used drug in 2017 and cannabis was the most abused and given the INCB Report on the medical use of cannabis as not the first line of treatment, what is the justification for the rescheduling when the abuse is high and the harm and impact not abating?
- Secondly, in view of Article 3 of the Single Convention particularly in paragraphs 3 and 5, can we justify the recommendations in view of the fact that information on the therapeutic value is not available or substantial enough to offset the impact of the abuse?

Questions from the Russian Federation

- Which criteria did the ECDD apply to recommend the exclusion of cannabis from Schedule IV of the 1961 Single Convention on Narcotic Drugs?
- Why was the argument about alleged barriers to scientific research and medical use of cannabis, which was initially used by the WHO, replaced by the principle of similarity?
- How does the similarity criterion correlate with the provisions of Article 3 Paragraph 5, where it is clearly stated that a drug could be placed in Schedule IV if it "is particularly liable to abuse and to produce ill effects and that such liability is not offset by substantial therapeutic advantages not possessed by substances other than drugs in Schedule IV".
- Are cannabis or its derivatives used as the first line or only treatment option for any medical condition?

WHO response

Schedule I

The 1961 Single Convention makes specific reference to the control of cannabis in several articles, along with two other plants, namely opium poppy and coca leaf, and provides definitions of cannabis, cannabis plant, and cannabis resin. These provisions would continue to apply if the CND followed WHO's recommendations concerning cannabis and related substances.

The ECDD recommended that cannabis continue to be included in Schedule I of the 1961 Convention because it was considered that cannabis is liable to similar abuse and productive of similar ill effects as drugs in Schedule I of the 1961 Convention (Article 3.3.iii).

That evidence is outlined in the Committee's report and more detail can be found in the critical review. However, some of the main points were as follows:

- In controlled laboratory studies, cannabis produces effects on mental state and behaviour typical of abused drugs.
- Dependence on cannabis is recognised and it includes the development of withdrawal symptoms on cessation of regular use. Approximately 1 in 10 cannabis users develop a cannabis use disorder.

- Cannabis has adverse effects that include impairment of cognitive function, impairment of driving, increased risk of psychosis, but it is not lethal and does not increase the lethality of other drugs.
- For some cannabis preparations with high THC content, the risks will be elevated above those due to cannabis in plant form.

When making a recommendation regarding Schedule I or Schedule II, the Conventions require the Expert Committee to assess a substance's similarity in terms of liability to abuse and producing ill effects with other substances already within these schedules. It is not within ECDD's mandated role to carry out comparisons with substances not controlled under the Conventions such as alcohol or tobacco.

Regarding the Expert Committee's recommendation that cannabis remain in Schedule I of the 1961 Convention, the Committee recognised that preparations, as defined in Article 1, of cannabis are, in principle, subject to the same measures of control as cannabis itself.

The Committee was aware that there are preparations of cannabis being produced illicitly that have high levels of THC and produce harms to public health. Public health problems arising from cannabis use include high rates of abuse and dependence that are considered as a cannabis use disorder. There are also high rates of driving under the influence of cannabis, which the Committee considered to pose a threat to public health.

Schedule IV

The Committee considered that cannabis and cannabis resin did not meet the threshold of being "particularly" liable to abuse and to produce ill-effects, which would warrant inclusion in Schedule IV.

It arrived at this conclusion on the basis that cannabis is not more liable to produce abuse and ill-effects than other Schedule I substances. Substances in Schedule I, but not in Schedule IV, include the two other plants included in the 1961 Convention, coca leaf and opium poppy, as well as the drugs cocaine, morphine, methadone and many other opioids. The Committee carefully considered the information on the level of ill-effects produced by cannabis as well as the abuse associated with the use of cannabis. The evidence clearly indicates that cannabis, including preparations from cannabis, do not produce a level of ill effects that is greater than these other substances currently in Schedule I but not in Schedule IV. While there are significant ill-effects associated with cannabis use, these effects cannot be considered to be greater than those of substances such as cocaine and morphine. The Committee also concluded that while cannabis abuse is a significant problem, the level of abuse of cannabis and cannabis preparations does not exceed the level of abuse of substances such as morphine and cocaine.

As an additional consideration, cannabis is equally not liable to produce ill-effects or abuse in a manner comparable to drugs in Schedule IV. The Committee carefully considered the evidence regarding abuse and ill-effects of these substances and compared them to cannabis. It is clear from this evidence that the substances currently in Schedule IV, with the exception of cannabis, are especially dangerous with a high risk of death associated with their use and such as opioids. Cannabis is not associated with such risk. With regard to liability to abuse, the evidence does not indicate that cannabis is associated with a liability comparable to that of other substances in

Schedule IV. For example, the level of physical dependence is much lower for cannabis than for the other drugs in Schedule IV which all produce opioid physical dependence.

Demonstrated therapeutic advantages

The Expert Committee acknowledged that in 1961, when the Convention was established and cannabis was included in Schedule IV, cannabis and cannabis preparations were not recognised to have any therapeutic use or therapeutic potential. There is now evidence that cannabis preparations have therapeutic advantages not possessed by other substances.

Effective therapeutic use of cannabis preparations has been demonstrated in a number of clinical trials for a range of therapeutic indications, such as the control of muscle spasticity associated with multiple sclerosis. The granting of marketing authorisation by medicines regulatory authorities in a large number of countries of the cannabis preparation known as Sativex, for the control of muscle spasticity, is further recognition of such clinical effectiveness and added value.

Some patients with chronic pain have also been shown to obtain relief from cannabis preparations when other available medications have not been effective. Many clinical trials on therapeutic use of cannabis preparations are ongoing and have shown cannabis to be an effective analgesic with demonstrated reduction in diabetic peripheral neuropathy and central neuropathic pain related to spinal cord injury and disease among patients with treatment-refractory pain.

From current evidence, cannabis preparations are not likely to be first line medications for most indications for which they are used, but it is considered to be common and good medical practice to have multiple levels of interventions available. This is because first line interventions do not work for all, or sometimes multiple levels of interventions must be used concurrently for the treatment of medical conditions. What is important is that cannabis preparations, even as a second or third line therapeutic option, have the potential to produce beneficial effects in patients who do not obtain such benefits from other medications. This means that the cannabis preparations have therapeutic advantages not possessed by the other substances used therapeutically.

5.2 Delta-9-tetrahydrocannabinol (dronabinol)

Question from Canada

- Under recommendation 5.2, we asked for clarification about what had changed to lead the ECDD to develop a different recommendation regarding dronabinol than it had on previous occasions.

Questions from Mexico

- Could you elaborate on why Δ^9 -THC was and continue to be paragoned to fentanyl, heroin and other opioids, given that in terms of toxicity and mortality are completely different? Is there any medical or scientific reason, other than the prevailing lack of knowledge and understanding, that would continue to justify the inclusion of THC within the same List as

those substances?

- If $\Delta 9$ -THC was already identified by 1971 as being the only narcotic agent present in Cannabis, why did the international regime on Cannabis control was never updated?
- What would be the rationale for ECDD to compare the "active and naturally occurring stereoisomer of $\Delta 9$ -THC known as dronabinol" to synthetic versions? Is it even scientifically sound to address together and to paragon any natural product with synthetic ones?
- Does $\Delta 9$ -THC at concentrations as high as 90% of exists naturally or is the result of human manipulation or bioengineering? If it is not naturally produced then, is it scientifically sound to address the natural concentrations of $\Delta 9$ -THC together with manipulated versions?
- Are you familiar with the work on sugar and yeast of companies such as San Francisco based CB Therapeutics?
- Could you elaborate on the last paragraph in relation to the requests received by Member States and information by UN agencies? Who, what and why? Could you elaborate on why listing dronabinol and $\Delta 9$ -THC "would greatly facilitate the implementation of the control measures of the Conventions in Member States"?
- Bearing in mind that ECDD undoubtedly affirms that Cannabis cannot be associated to the same level of risk to health than other substances scheduled in Lista 1 of the Single Conventions, at the same time it recommends to place individually dronabinol and TCH on that List. Is it not a contradiction?

WHO Response

Delta-9-THC was identified as a major active compound in cannabis in 1971 but at that time, the evidence wasn't convincing that it was the only psychoactive compound. Now it is known that it is the main psychoactive compound and the ECDD recognised that while dronabinol can be chemically synthesised, there is no difference in the effects of natural and synthetic dronabinol.

This is outlined in the report of the 41st ECDD meeting as follows:

"In previous ECDD reviews, the active and naturally occurring stereoisomer of $\Delta 9$ -THC known as dronabinol had been considered in a synthetic form as a pharmaceutical preparation. Following a recommendation from the ECDD at its twenty-seventh meeting, dronabinol was placed in Schedule II of the 1971 Convention on Psychotropic Substances. However, the CND did not adopt a subsequent recommendation to place dronabinol in Schedule III of the 1971 Convention on Psychotropic Substances.

The Committee noted that whereas in these previous ECDD reviews $\Delta 9$ -THC, and especially its active stereoisomer dronabinol, had been considered in a synthetic form as a pharmaceutical preparation, $\Delta 9$ -THC today also refers to the main psychoactive component of cannabis and the principal compound in illicit cannabis-derived psychoactive products. Some of these products contain $\Delta 9$ -THC at concentrations as high as 90%. Butane hash oil is an example of a cannabis-derived product containing high-purity delta-9 THC which have recently emerged."

The criterion for recommending that dronabinol be included in Schedule I of the 1961 Convention was the criterion of similarity in liability to abuse and to produce ill effects to cannabis and preparations of cannabis. Cannabis preparations with high purity delta-9 THC produce ill-effects and abuse potential that are at least as great as those produced by cannabis, which is placed in schedule I of the 1961 Single Convention.

It is also the case for opium and coca leaf that the plant and the drug that is included in the plant (morphine and cocaine, respectively) are controlled within the same schedule and the same 1961 Convention. Placing delta 9-THC, the principal active compound in cannabis, in the same Schedule as cannabis would be consistent with this approach.

The Committee considered new information that had arisen about delta-9-THC since its last recommendation in 2012, and recognised the emergence of high potency THC preparations such as butane hash oil since that time. These substances require significant human interventions to produce them, and there are no naturally occurring forms of cannabis that contain this content. Cannabis and cannabis preparations have to be considered together because the Conventions mandate that if a drug is included in a schedule then preparations of that drug are also included in the same schedule. There is no specification about the type of preparation or the strength of preparations. What this means is that cannabis in plant form which has an average THC content of 10-15% would also be grouped with preparations that have 90% - but this is the nature of the Conventions.

In the case of an illicit preparation with high levels of THC, currently this could be controlled as a preparation of cannabis under the 1961 Convention, but it could also be controlled under the 1971 Convention as a preparation of dronabinol. There are now preparations that range from low THC concentration to nearly pure THC, and therefore there is some ambiguity about whether they would be controlled as preparations of cannabis, or preparations of dronabinol. The implementation of the WHO recommendation to schedule dronabinol under the 1961 Convention would address this ambiguity.

There are a large number of companies producing and carrying out research on cannabis products. The Committee does not generally look at the work of private industry other than that which is reported in scientific peer reviewed papers, recognizing that commercial developers have proprietary interests which may influence or may be perceived to have influenced research outcomes.

5.3 Tetrahydrocannabinol (isomers of THC)

No questions

5.4 Extracts and tinctures of cannabis

No questions

5.5 Cannabidiol preparations

Question from Canada

- Finally, under 5.5, we asked for clarification on the origin of the proposed 0.2% threshold and of ECDD's statement that it had considered leaving the matter of defining a threshold for THC content in CBD preparations to the member states themselves.

Questions from Mexico

- How did the ECDD come to the range of 0.2% of THC for making this recommendation?
- Could it not be somewhat arbitrarily to set a specific percentage?

Question from the Russian Federation

- CBD might be easily converted into delta-9 THC (dronabinol) with acid and heat (or light). Has the WHO considered that removal of CBD preparations from the international control might lead to its misuse for the illicit production of dronabinol?

WHO response

When produced from the plant, cannabidiol preparations will contain trace amounts of THC as well as other cannabinoids and non-cannabinoid plant substances.

Evidence from clinical trials conducted with a product containing no more than 0.15% delta-9-THC as a proportion of the total mass from the cannabis plant showed that this did not produce characteristics or effects similar to cannabis.

For Member States to control preparations that contain up to 0.15% delta-9-THC as a proportion of the total mass from the cannabis plant, the Expert Committee recognised the difficulty in measurement to this high degree of accuracy (0.15%) and therefore adopted 0.2% as a more reliable measure that would allow Member States to control.

The value of 0.2% for delta-9 THC was specified as WHO had requests from Member States to indicate what maximum percentage was considered appropriate and to ensure that the currently registered CBD medication was exempted from control.

Epidiolex is the brand name for the cannabidiol preparation that has been approved in the US and contains 0.15% of delta-9-THC, as indicated in the patent, as a total proportion of delta-9-THC relative to the entire plant content and expressed by weight. Therefore, the ECDD's report expressed its threshold of 0.2% delta-9-THC as a proportion of the entire plant content.

It is important to note that the amount of delta-9-THC as a proportion of the total weight of the finished product (w/w of the finished product), will be much lower as a result of the addition of excipients to the cannabis plant extract. However, and in order to prevent confusion, and as other manufacturers may in the future use different amounts or types of excipients, it is important to specify the delta-9-THC content relative to the entire plant content by weight which includes CBD and other cannabis compounds.

With regard to the conversion of CBD to THC mentioned, this method was described in a scientific paper over 50 years ago (Gaoni, Y. and R. Mechoulam, Hashish-VII. The isomerization of cannabidiol to tetrahydrocannabinols. Tetrahedron Vol. 22. 1966. 1481–1488) and has been the subject of a patent application. The method is not simple, the yield is uncertain, as are the by-products and their side-effects. There have been no published reports that this method has been used illicitly for the production of THC.

5.6 Pharmaceutical Preparations of Cannabis and delta-9-tetrahydrocannabinol (Dronabinol)

Questions from Mexico

- Could you reconfirm that the statement “There is no difference in the therapeutic effects or adverse effects of synthetic Δ 9-THC compared to Δ 9-THC from the Cannabis plant”, refers exclusively to the current/known versions of synthetic Δ 9-THC approved for medical use? Hence, would it be safe to affirm that new versions of synthetic Δ 9-THC should be addressed on their own?
- Could you elaborate further on what would be covered by the term “pharmaceutical preparations of Cannabis” in relation to this recommendation?

Questions from Pakistan

- What is the scientific evidence to prove that benefits of research and utilization of preparations of cannabis are greater than its risks.
- what are the areas and aspects which need further research and investigation for enabling the Member States to reach consensus and understanding on the way forward on this issue.

WHO response

“pharmaceutical preparations” refers to substances that are intended for medical use and that are, therefore, in dosage forms appropriate for such medical use.

These pharmaceutical preparations encompass the ones requiring pre-market approval and the ones produced extemporaneously according to a prescription and to agreed good manufacturing practices.

It was considered that individual Member States will have their own criteria for assessing whether a product is for medical use. The evidence from medical use of these preparations showed that they were not associated with abuse or dependence.

With respect to the statement referred to above, “There is no difference in the therapeutic effects or adverse effects of synthetic Δ 9-THC compared to Δ 9-THC from the Cannabis plant”, it should be noted that dronabinol is the international non-proprietary name for (-)-trans- Δ 9-THC, whether it is found naturally in the cannabis plant or produced synthetically.

Delta-9 THC pharmaceutical preparations are typically consumed through oral administration. Placement of pharmaceutical preparations of cannabis and dronabinol in Schedule III would require that delta-9-THC is not readily recoverable, which means that it cannot be used as a vapor inhalation method or smoking method as other non-medical delta-9 THC preparations described.

With respect to the question on comparing the benefits of research and utilization of preparations of cannabis versus their risks, it is beyond the mandate of the ECDD to make this comparison. However, under section 5.1 in this document, it is said that the ECDD recommended to maintain cannabis and cannabis preparations under Schedule I because of similar abuse potential to cannabis and similar ill effects as other substances under schedule I.

ECDD also acknowledges the recognised scientific evidence for therapeutic use of cannabis preparations in important conditions such as the management of pain and of muscle spasticity in multiple sclerosis.

In all areas of public health, research that is based on robust scientific evidence is needed to ensure better health and wellbeing for people, in particular the most vulnerable. Scientific research on the use of cannabis is no exception and there are currently several hundreds of clinical trials that are being performed to explore efficacy and safety profiles of cannabis for therapeutic use.