EIHA statement on recommendations of the 40th ECDD on Cannabidiol and contribution to the 41st ECDD Critical reviews of Cannabis-related substances

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Introduction

The European Industrial Hemp Association (EIHA) welcomes an independent scientific evaluation of all substances related to the *Cannabis sativa* L. plant.

However, besides the weak points of the data collection process prior to the 40th ECDD[1], we would like to point out inconsistencies in the Critical review papers.

However, we would like to point out several inconsistencies and weak points of the data collection process, and of the Review papers.

As in June, we formally object to the late publication of reports and non-timely deadlines. The *Guidance on the WHO review of psychoactive substances for international control* states that documentation should be provided and uploaded on the WHO website at least 30 days prior to the meeting. In June, the documentation was provided only 5 days before the meeting, this time, the documentation has been made public 18 days before.

Critical Review Report on Cannabidiol (CBD) and Recommendations of the 40th ECDD

Pure Cannabidiol (whether produced synthetically or by isolation from *Cannabis* plants) has been given a clear "carte blanche" by the outcome of the 39th ECDD Pre-review. This has been acknowledged by all United Nations Member States at the 61st session of the Commission on Narcotic Drugs (E/CN.7/2018/CRP.3) where it was announced that data was being collected for a Critical Review of "[Extracts or] Preparations containing almost exclusively cannabidiol (CBD)."

Pure CBD has never been agreed by the ECDD experts to be critically reviewed, to the contrary, the outcome of the Pre-review clearly places it out of the scope of the work of the Committee. However, a critical review of "Extracts or preparations containing almost exclusively cannabidiol" was convened by decision of the ECDD experts, in November 2017.

The ECDD Secretariat, however, sent distinct requests for information to countries, varying importantly between languages:

- "*Extracts and tinctures containing cannabidiol (CBD)*" (English version),
- "Cannabidiol (CBD)" (French version: "L*es questions ont trait au cannabidiol (CBD)*"),
- "Extracts and preparations that contain cannabidiol (CBD)" (Spanish version: "*Extractos y preparaciones que contienen cannabidiol (CBD)*").

[1] M. Krawitz, K. Riboulet Zemouli et al., ECDD40 Procedural, methodological and terminological bias. Joint Civil Society Contribution to the 40th Meeting of the WHO Expert Committee on Drug Dependence. FAAAT editions, June 2018. http://faaat.net/cannabis#ecdd40

And yet, we have witnessed that the 40th ECDD meeting has undertaken a Critical Review of Cannabidiol (CBD).

Besides this shaky preparation process, EIHA generally welcomes the final outcome, recommending not to include products considered to be pure Cannabidiol (CBD) in the Schedules of the International Drug Control Conventions, published in a Note Verbale to the United Nations Secretary-General dated July 23rd, 2018.

However, EIHA formally objects to the reasoning of the Experts according to which "… ***if prepared as an extract or tincture of cannabis [Cannabidiol] is controlled in Schedule I of the 1961 Single Convention on Narcotic Drugs.*****"**

While, in the case of Nabiximols (Sativex®), its inclusion in schedules of the Single Convention (1961) is given (1) by its nature being a 1:1-mixture of extracts high in CBD and high in THC and (2) by its pharmaceutical purpose, the assignment to Schedule I of Cannabidiol isolated from plants of genus *Cannabis* and its preparations does not hold up at all.

An outcome adding complexity and ignoring international standards

A highly purified substance derived from a plant extract **is equivalent** to the synthetically produced substance insofar as both comply with the same specification and their impurity profile is similar.

Notwithstanding the fact that Schedule I should only include pharmaceutical drugs and compounds, and therefore ignore CBD which is widely used industrially, in food supplements, pet-food or cosmetics, a misguided reading of this outcome could lead to differentiation between cannabidiol produced synthetically and by isolation from the *Cannabis* plants. For example, German DAC/NRF monograph C-052 on Cannabidiol[2] mentions a chromatographic purity between 98.0–102.0% and defines Δ9-THC, Δ8-THC and Cannabinol (CBN) as "specified impurities". Moreover, it states that the CBD may be of natural as well as of synthetic origin. Without prejudice to other legal requirements concerning the manufacture of the extracts of cannabis and subsequent isolation of CBD there from, considering "Cannabidiol" of natural origin as an "extract of cannabis" does not hold up to principles of any of the relevant international standards: the nomenclature of organic chemistry (IUPAC) system, Chemical Abstracts Service (CAS), as well as WTO Harmonized System Codes:

- *Extract of cannabis.: CAS# 6465-30-1, HS Code 1302.19 – Vegetable saps and extracts*
- *Cannabidiol: CAS# 13956-29-1, HS Code 2907.29 – Phenols; phenol-alcohols.*

The toxicological and pharmacological properties of a substance or extract as well as its potential for abuse mainly depend on its constituents and composition. **What matters, is the content of a drug component and the substance's effect, not the origin of the substance or its manufacturing procedure.**

Moreover, the impurity profile of an isolated chemical compound (in this case with Δ9-THC as an impurity) may not be unique or characteristic in order to distinguish it from a synthetic version. The impurity profile (by-products) of a synthetic product may even be very similar to the "impurity profile" of the natural isolated product, in particular if the synthetic pathway is a biomimetic one.

Thus, in the future there could be offered in the market a generic "CBD-based medicinal product", where both naturally isolated or synthetically manufactured Cannabidiol would be used as an active substance. (As is already a common practice in several countries where CBD is used in pharmacy-compounded preparations.)

A similar story on pure substances isolated from plant extracts and the same substances produced synthetically is that of flavouring substances. Eventually the distinction between flavouring substances of natural origin and their chemically equivalent synthetic counterparts in the EU Union list[3] had been given up in European regulations, except for the labelling requirements (e.g. Vanillin). Similar evidence-based regulatory practices should be followed by the WHO.

The same lapse of logic could be demonstrated on Dronabinol: (-)-trans-delta-9-THC has been placed under Schedule II of the 1971 Convention on psychotropic substances, and was until recently almost entirely produced synthetically (e.g. Marinol®). Following the logic currently used by the WHO, should a naturally derived Dronabinol (e.g. produced by a generic producer, and thus complying with the Pharmacopoeia specification) also fall under the Schedule I of the 1961 Convention on Narcotic drugs for being considered a Cannabis extract? Certainly not!

We can further substantiate our opinion based on a citation from a Guidance for Industry on Drug Substance Manufacturing published by the USA Food and Drug Administration: "A chemical substance (e.g. plant extract) used to produce a semisynthetic drug substance or a crude drug substance derived from a plant [...]

[2] DAC/NRF 2016/2, C-052, Cannabidiol, 12 pages.

[3] Regulation (EC) 1334/2008 on Flavourings, Annex I, Part A.

starting material is considered an intermediate".[4] This statement makes clear that a plant extract used for isolating a pure chemical substance as an Active Pharmaceutical Ingredient (API) is **not** the API itself, neither it is the medicinal product made from it. The plant extract is only an intermediate in the processing to yield the pure API.

On these same grounds, purified Cannabidiol (CBD) obtained from the herbal source IS NOT an Extract of "cannabis" and therefore IS NOT scheduled under the Single Convention (1961).

Obviously the distinction between CBD produced from the Cannabis plant and the synthetically manufactured CBD is made because the former could still contain traces of psychoactive cannabinoids as impurities. Apart from the fact that synthetic CBD can also contain them, it is scientifically not proven that a CBD produced from the Cannabis plant will have narcotic/psychotropic effects due to the traces of, for example Δ9-THC it may contain. A Human Abuse Potential Study[5] with a pure CBD produced from the natural source shows that this CBD does not produce any of the known THC-effects in the "Drug Liking test", moreover THC plasma levels were much lower than those to be expected after administration of the equivalent trace amounts of Dronabinol, a fact which points to a non-linear pharmacokinetics.

Also on these grounds it is not justified to regard as scheduled under the Single Convention a (pure) CBD produced from the Cannabis sativa plant.

A stronger approach to cannabis than to opium

The case of opium, that is a natural material controlled as a narcotic drug similarly to cannabis, is interesting to explore. Individual substances obtained from opium do not fall under international control, unless they have been specifically scheduled as a narcotic drug. While morphine, codeine or thebaine are narcotic drugs, other substances extractable from opium, such as noscapine and papaverine, are not under international control. If noscapine and papaverine extracted from opium are not narcotic drugs, then CBD, even when prepared as an extract of cannabis, should not be considered as a narcotic drug unless if it was recommended for scheduling – which was ruled out by ECDD's 40th meeting.

[4] FDA (2010): Guidance for Industry, Drug Substance Chemistry, Manufacturing and Controls Information. Page 52.
[5] US Department of Health and Human Services, Letter to the DEA, May 2018, Document prepared by FDA's Controlled Substance Staff, "Basis for the Recommendation to place Cannabidiol in Schedule V of the Controlled Substances Act", p. 9 ff.

Comments on the Critical review documents

Critical Review of Cannabis and cannabis resin

EIHA welcomes the fact that the WHO has corrected a major terminology error, using now "cannabis" in the 41st ECDD documents, instead of "cannabis plant" in its 40th ECDD Pre-Review documents (see below).

Critical Review of Extracts and tinctures of cannabis

While EIHA applauds to the clear endorsement of a unique nutritional profile for hemp seeds, the very inclusion of "hemp seed oil" / "hemp oil" (*Cannabis sativa* Semen Oleum) in the process is confusing. Seeds are specifically excluded from the definition of cannabis in the 1961 Convention and, therefore, any reference to them in this context appears to be inappropriate clearly not in line with article 28 (2) of the 1961 Convention.

Similarly, the "Essential oil", a steam distillate of the freshly-cut *Cannabis* plants containing the terpenes only, does in no way match any criterion of relevance for international scrutiny. Even the United Nations Office on Drugs and Crime (UNODC) mentions in its 2009 "***Recommended methods for the identification*** *and analysis of* ***cannabis*** *and* ***cannabis*** *products*", that "the essential oil does not contain THC".

For better distinction of the various products from the *Cannabis* plant, inspiration should have been taken from the international harmonized tariff system of the World Trade Organization (WTO), which already clearly differentiates the following substances:

- *Hemp Seed Oil (1515.90) as "Other Fixed vegetable fats and oils";*
- *Hemp Essential Oil (3301.90) as "Other Essential oils" (non-fixed);* and
- *Cannabis [flower] extract (1302.19) as "Other Vegetable saps and extracts"*

Cannabis sativa **Essential oils and** ***Cannabis sativa*** **Semen Oleum (seed oil) should be completely excluded from this discussion.**

The definition of Extracts and tinctures of cannabis used by the WHO for the review process is not the same as that used in the reference text of the Single Convention on Narcotic drugs.

According to the Convention:

- "*Cannabis* plant" is the whole *Cannabis sativa* L. plant,
- while "cannabis" definition is restricted to "the flowering or fruiting tops of the *Cannabis* plant (excluding the seeds and leaves if not accompanied by the tops) from which the resin has not been extracted, by whatever name they may be designated".

The Single Convention differentiates between "cannabis" and *Cannabis* plant, and thus an Extract and tincture of cannabis is an extract/tincture from the flowering or fruiting tops. only, and not from *Cannabis* plant as a whole or from other parts of the Cannabis plant.

But the WHO uses a much too broad definition, that comprises the whole plant *Cannabis sativa*. For instance, it is to be noted that CAS-No. 89958-21-4 is not the CAS-No. of "Extract and tinctures of cannabis" but it is the CAS-No. of "*Cannabis sativa, ext.*", as listed in the European Inventory of Chemicals[6].

Therefore, this CAS-No. is that of an extract from the whole plant *Cannabis sativa*, and not from "cannabis" as such.

Extract of cannabis itself has CAS-No 6465-30-1. The International Narcotics Control Board (INCB) acknowledges this in its last version of the "yellow" List of Narcotic Drugs under International Control (see July 2017 edition): under the entry IDS Code NC008 "Cannabis resin, extracts and tinctures" is listed together with the CAS-No. 6465-30-1. This is what the WHO should have used!

See explanatory schedule below:

This distinction is important because there are also extracts from the *Cannabis sativa* plant which do not contain "cannabis" (they do not contain any flowering or fruiting tops), however the WHO Pre-review also comprises these extracts which we regard as inappropriate.

The Toxicology part (Section 3) lacks preciseness and sound research which is demonstrated by the following citation from Para 2.2.: "The adverse reactions produced by Δ9-THC-rich cannabis extracts, tinctures, oils and tea in humans are likely to be similar to those observed with Δ9-THC-rich cannabis and Δ9-THC." Likelihood is neither evidence nor proof.

Section 4 on therapeutic use is nearly exclusively on Nabiximols and it does not consider at all recent authorizations for medical prescription of cannabis in many countries, for example Germany, Australia and Canada.

Section 5 – Epidemiology – completely disregards the licit production of "cannabis" extracts for therapeutic purposes, which is considerable, as the INCB report for 2017 has noted.

There is very little on *Cannabis* plant extracts, which are (very) low in THC and high in other cannabinoids, i.e. high in CBD and/or Cannabigerol (CBG), and there is no distinguished assessment on those. A differentiated assessment of the effects and toxicity of the low-THC extracts and tinctures is also missing (see cit. lit. 4).

Finally, it is NOT mentioned that there are physically processed extracts which may contain zero THC and/or Cannabinol (CBN) (or nearly nothing) and therefore should not fall under any measure related to international control.

In undertaking its Critical Reviews the ECDD should consider reassessing their approach, to make definitely clear that the extracts of *Cannabis sativa* L. plant that contain almost exclusively unscheduled cannabinoids, have no justification to fall under any sort of international drug-related control measure.

Extracts and tinctures of *cannabis*	***Cannabis sativa, ext.* (Hemp Extract)**	**Hempseed/ Hemp oil**	**Hemp Essential oil**
CAS-No.: 6465-30-1	CAS-No.: 89958-21-4	CAS-No.: 8016-24-8	CAS-No.: none particular
HS Code: 1302.19	HS Code: 1302.19	HS Code: 1515.90	HS Code: 3301.90
IDS Code: NC008	IDS Code: **N/A**	IDS Code: **N/A**	IDS Code: **N/A**

[6] https://echa.europa.eu/de/information-on-chemicals/ec-inventory

The reason for international control of "cannabis" and "extracts of cannabis" is the fact that they both contain THC in quantities liable to substance use disorders[7]. By contrast, in "[industrial] hemp plant extracts", the starting material is already low in THC and the content of THC may be further reduced through purification under the limits set by the regulatory authorities. Thus, due to their low THC content, these products cannot be, in practice, liable to produce use disorders or the THC recovered from them. Extracts from the *Cannabis sativa* L. plant, or "Hemp plant extracts" so become *products not covered by the 1961 Convention*: they are neither a narcotic drug nor psychotropic substance, even if narcotic drugs were the starting material in the process of their manufacture.

Further to this approach, the ECDD, the mandate of which is to recommend international regulation on drugs liable to provoke use disorders, should focus on controlling THC, and rather set up a category that could be named "Extracts or preparations of cannabis that contain almost no THC" and expressly propose to Governments to exempt them from the scope of the 1961 and 1971 Conventions.

Proposal for the Scheduling of extracts and tinctures of Cannabis plant low in THC

EIHA would like to make proposals for exemptions of certain hemp extracts from scheduling as follows.

Current status of Scheduling under the Narcotic drugs control Convention (1961) is:

- Cannabis, cannabis resin, Extracts and tinctures of cannabis in Schedule I, and
- Cannabis and cannabis resin in Schedule IV

Schedule I includes drugs whose control provisions constitute the standard regime under the Single Convention, and Schedule IV includes drugs, such as heroin, that are considered to have "particularly dangerous properties" in comparison to other drugs.

The current status and definition of extracts of *Cannabis sativa* L. implies severe drawbacks for the industrial hemp sectors around the globe.

Proposal to the Experts regarding the wording for the 1961 Convention

1. *All extracts of "the* Cannabis sativa *L. plant" that are not extracts of "cannabis", regardless of their purpose, should continue being exempted from any scheduling and thus from international and national control over narcotic substances,*

and

2. *Extracts (or tinctures) of "cannabis" for medicinal products, but also for foods and food supplements, pet-foods and cosmetics, provided they have a maximum content of 0.2 weight-% of total Δ^9THC should be exempted from any scheduling and thus from international and national control over narcotic substances.*

Proposal to the Experts regarding the wording for the 1971 Convention

3. *Preparations for medicinal products, foods and food supplements, pet-foods and cosmetic, provided they do not exceed a maximum content of 0.2 weight-% of total Δ^9THC should be exempted from any scheduling and thus from international and national control over psychotropic substances.*

Beyond the Critical-review: Proposal to the WHO for providing public health and safety guidance

- *Complementarily to the evaluation process, an additional criterion that the WHO could consider recommending to national authorities to establish evidence-based regulations over extracts of the* Cannabis sativa *L. for foods and food supplements could be a maximum uptake of human consumption of 7 µg of Δ^9THC per kilogram of body weight per day*[8].

[7] Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), American Psychiatric Association, USA, 18th May 2013, ISBN 978-0-89042-554-1.

[8] EIHA (2017): Reasonable guidance values for THC (Tetrahydrocannabinol) in food products. http://eiha.org/media/2017/09/17-09-18-THC-Position-paper_EIHA.pdf