

## WHO Expert Committee on Drug Dependence Pre-Review:

### Extracts and tinctures of cannabis

#### Expert Peer Review 1

##### 1. Comments based on the review report

The pre-review report defined Cannabis extracts as plant extract mixtures from the leaves and flowers of *Cannabis sativa*. These extracts include those for recreational use (e.g. Butane Hash Oil (BHO), Propane Hash Oil (PHO), other solvent extracts, rosin and distillates), cannabis oils (e.g., hemp seed oil, essential oil, and medicinal cannabis oil), aqueous extracts (e.g. marijuana tea) and nabiximols /CBD (cannabidiol) in preparation with other cannabis-related ingredients. The primary targets for cannabis extractions are mainly delta-9-tetrahydrocannabinol ( $\Delta^9$ -THC) and/or CBD; terpenes are secondary targets. The ratio of  $\Delta^9$ -THC: CBD contained in an extract is determined by the ratio of the cannabinoids in the plant strain and also by the part(s) of the plant used to make the extract. Nabiximols is a cannabis extract with equal proportions of plant-derived tetrahydrocannabinol (THC) and CBD.

##### a. Evidence on dependence and abuse potential

###### *Dependence potential:*

The dependence potential of cannabis extracts has not been studied explicitly in animals. However  $\Delta^9$ -THC, the primary psychoactive constituent in many extracts, has been investigated in numerous studies. Weak physical signs of withdrawal were observed in rodents with spontaneous termination of repeated  $\Delta^9$ -THC administration. Conversely, antagonist-precipitated withdrawal was associated with more pronounced signs. Rimonabant administration induced somatic signs such as wet dog shakes, paw tremors, facial rubbing and ataxia as well as behavioral signs such as suppression of operant responding for food. Rimonabant-precipitated withdrawal from  $\Delta^9$ -THC was also reported in rhesus monkeys and in dogs. The report stated that the dependence potential of nabiximols has not been evaluated in animals. A major metabolite of  $\Delta^9$ -THC, 11-OH- $\Delta^9$ -THC, is psychoactive, as indicated by its cannabimimetic effects in mice. It substitutes for  $\Delta^9$ -THC in rat drug discrimination and has similar psychological effects in men.

### Human Studies:

The dependence potential of cannabis extracts has also not been specifically evaluated in humans. However, studies have shown that regular exposure to cannabis containing high concentrations of  $\Delta^9$ -THC increased the probability and severity of dependence. Apart from nabiximols the dosage of cannabis extracts are often self-determined by the user and has been associated with the development of tolerance. Withdrawal symptoms occur within 24 to 48 hours of abstinence following regular use of cannabis. Physical and psychological symptoms comprising the Cannabis withdrawal syndrome include mood changes, irritability, increased anger, anxiety, craving, restlessness, sleep impairment, stomach pain, and decreased appetite. It has been suggested that regular use of some types of extracts would be more likely to be associated with dependence than others. Tinctures have varied concentrations of  $\Delta^9$ -THC while cannabis oil extracts have the highest concentrations of  $\Delta^9$ -THC and the highest potential for dependence. In surveys of college students and regular cannabis users, frequent use of butane hash oil, was associated with greater dependence and perceived lack of control over cannabis use.

The dependence potential of nabiximols has not been evaluated in humans. The pre-review report described an unpublished study in an earlier review of its abuse and dependence potential in which 44% of patients who experienced a 2-week interruption of nabiximols treatment exhibited an increase in some signs of cannabis withdrawal (e.g., disrupted sleep). Other studies have examined the efficacy of nabiximols for the treatment of cannabis withdrawal syndrome and reported that it was effective in ameliorating withdrawal symptoms in treatment and non-treatment seeking cannabis users.

### *Abuse potential:*

Specific evaluation of cannabis extracts (vs. pure  $\Delta^9$ -THC) is not available. However there has been preclinical animal research on the abuse potential of  $\Delta^9$ -THC. Out of the two main cannabis extract constituents, only  $\Delta^9$ -THC produces classic  $\Delta^9$ -THC-like pharmacological effects in animals; available evidence suggests that CBD does not have abuse potential. Most research that examined the abuse potential of cannabis in animal models used systemic injection or combusted or aerosolized  $\Delta^9$ -THC as a proxy. Self-administration of  $\Delta^9$ -THC was shown in squirrel monkeys but was not significant in rats. However, self-administration of the synthetic aminoalkylindole cannabinoid, WIN55, 212-2, had been reported. Vigorous and pharmacologically selective discriminative stimulus effects were produced by  $\Delta^9$ -THC in rats, rhesus monkeys, mice and pigeons. In rodents and/or rhesus monkeys, full substitution for  $\Delta^9$ -THC has been demonstrated for other psychoactive phytocannabinoids, CP55, 940, WIN55, 212-2, and a range of abused synthetic cannabinoids. Studies have shown that exposure to cannabis smoke containing  $\Delta^9$ -THC (following aerosolized  $\Delta^9$ -THC, cannabis extracts, or synthetic cannabinoids) produced a concentration-dependent profile of cannabinoid effects in rodents and rats such as locomotor suppression, antinociception, hypothermia and

catalepsy; also reported were discriminative stimulus effects (in rats, mice, pigeons, rhesus monkeys) and reinforcing effects in squirrel monkeys (which were reversed by rimonabant). Conditioned place aversion was reported following intraperitoneal (but not aerosolized)  $\Delta^9$ -THC in rats. Aerosolized  $\Delta^9$ -THC did not also produce conditioned place preference.

The report stated that the abuse potential of nabiximols has not been explicitly evaluated in animals. However its two constituents ( $\Delta^9$ -THC and CBD) have been tested in drug discrimination and place conditioning studies. CBD failed to substitute for  $\Delta^9$ -THC in male Long-Evans rats trained to discriminate 3 mg/kg  $\Delta^9$ -THC from vehicle, when tested alone at doses up to 10 times the  $\Delta^9$ -THC training dose. It also did not alter  $\Delta^9$ -THC's discriminative stimulus or response rates when tested at CBD: $\Delta^9$ -THC ratios of 1:1 to 10:1. In contrast, CBD at 1:1 and 10:1 CBD: $\Delta^9$ -THC ratios attenuated the conditioned aversive effects produced by 10 mg/kg  $\Delta^9$ -THC in ICR mice. In rats trained to self-administer i.v.  $\Delta^9$ -THC, CBD also did not affect  $\Delta^9$ -THC's reinforcing effects. These results suggest that CBD contained in nabiximols may attenuate the aversive effects of  $\Delta^9$ -THC, but is unlikely to affect its subjective or reinforcing effects.

#### Human Studies:

The abuse potential of cannabis extracts has not been specifically evaluated in humans. On the other hand,  $\Delta^9$ -THC is responsible for the reinforcing and subjective effects seen with cannabis extracts. As a result of the different concentrations of  $\Delta^9$ -THC in the different types of extracts, they are associated with variations in abuse potential. However, empirical data to support this hypothesis are lacking. In a study, oral administration of cannabis extract containing a 2:1 ratio of  $\Delta^9$ -THC and CBD were associated with tiredness, dizziness, and drowsiness. The abuse potential of high potency cannabis extracts, especially via vaporizer, has also not been evaluated.

A clinical trial to evaluate the abuse potential of nabiximols in recreational cannabis users showed that nabiximols containing high concentrations (21.6, or 43.2 mg) of  $\Delta^9$ -THC induced cannabis-like effects (e.g., drug-liked, stoned, and increased marijuana ratings on the Addiction Research Center Inventory). Subjective effects associated with cannabis use were not induced at a lower dose of 10.8 mg. Another study reported similar findings with lower doses of nabiximols. Abuse has not been reported in post-market surveillance of nabiximols. However, euphoria has been reported as an adverse effect of nabiximols.

#### **b. Risks to individual and society because of misuse**

Common adverse effects with nabiximols are mild to moderate dizziness and fatigue. Other common side effects are nausea and vomiting, hypotension, somnolence, disturbance of attention, confusion, asthenia (weakness), dry mouth, diarrhea, anxiety,

and headache. These adverse effects are transient. In rare instances oromucosal sprays could cause pain, discomfort, distorted taste, mouth ulceration and glossodynia (burning sensation in the mouth and tongue). Serious psychiatric adverse events have been reported with nabiximols such as disorientation, depression, euphoria and dissociation. Transient psychotic reactions have also been observed.

There is very little information on the toxicology of cannabis extracts, tinctures, oils and tea. Adverse reactions and toxicity produced by  $\Delta^9$ -THC-rich cannabis extracts, tinctures, oils and tea are similar to those observed with  $\Delta^9$ -THC and  $\Delta^9$ -THC-rich cannabis that also contain low concentrations of cannabinoids, terpenoids, and flavonoids. Cannabinoid toxicity is dose-dependent.

There is an increasing concern for the abuse of cannabis extracts for recreational purposes. Acute exposure to very high  $\Delta^9$ -THC doses increases the likelihood of tachycardia, orthostatic hypotension, fainting and drug-induced psychotic reactions. Restlessness, anxiety, memory impairment has been reported with butane hash oil in a cross-sectional survey. The pre-review report did not describe drug related deaths following misuse, abuse or overdose of cannabis extracts or tinctures. A suspected case of non-fatal cannabinoid poisoning in a child who consumed hemp seed oil was reported. However the amount of  $\Delta^9$ -THC in the product was very low.

Cannabis extract may contain residual solvents (naphtha, isopropanol, acetone, hexane, ethyl alcohol or butane) which are harmful if ingested by the user. Some are found to contain contaminants such as pesticides. Thinning agents such as propylene glycol and polyethylene glycol 400 (used to allow easy flow of viscous cannabis oils from cartridges) can produce high concentrations of toxic acetaldehyde and formaldehyde when heated in certain devices. In addition, terpenes can be converted to the toxic degradants methacrolein (an irritant) and benzene (a carcinogen).

Nabiximols (Sativex) was shown to have no effect on driving-related ability in some multiple sclerosis patients using the Vienna test system. The effect of on driving performance in a driving simulator or in an on-road test has not been assessed.

### **c. Magnitude of the problem in countries (misuse, illicit production, smuggling etc)**

The nature and magnitude of the public health problem related to the use of cannabis extracts and tinctures is extensive but difficult to assess. This is because a number of reports did not differentiate between the forms of cannabis use, i.e. whether it is used in the form of herbs, resin, extracts or tinctures. Worldwide, cannabis is mainly used in the forms of herbs and resins for recreational purposes or self-medication; extracts and tinctures were said to play a smaller role. For non-medical use, cannabis extracts and tinctures are usually consumed in the form of oil or as wax e.g. butane cannabis oil (BCO). Cannabis has been the most prevalent illicit drug for decades with a global

prevalence of 3.8% among the 15-64-year-old population in 2015, corresponding to an estimated 183 million users in that year.

With the rise of legal recreational and medicinal cannabis, the production of cannabis concentrates especially with solvent based methods of extraction, have proliferated in the United States of America and other regions in the world. Illicit/unregulated manufacture is carried out in various forms. Disastrous fires and explosions have occurred with solvent based methods causing serious injury to some workers. These methods are banned in California. Burn injuries related to BCO production are a public health concern in the United States. In four states with legalization of cannabis, an increase in burn injuries related to BCO production was recorded within a seven year period. Patients required a mean of 12+/-48.4 ventilator days, and 27.1+/-59.4 days in the hospital. In addition, three patients died as a result of their injuries. A steep rise in the number of patients presenting with burn-associated BCO production has been reported. Since the legalization of cannabis in Colorado, hydrocarbon burns associated with cannabis oil production has increased. A study showed that 29 cases of BCO burns were admitted to the local burn center from January 1st, 2008, through August 31st, 2014. There were no cases prior to the liberalization of medical use; 19 (61.3%) cases following medical liberalization (October 2009-December 2013) and 12 (38.7%) in 2014 since legalization. Nineteen patients required skin grafting, eight received wound care only, one required surgical fracture repair, and one required surgical debridement.

Data regarding the exact scope and magnitude of Illicit/unregulated production and illicit trade of cannabis extracts and tinctures in various countries were not stated in the pre-review report. However there is evidence regarding illicit marketing of cannabis extracts and tinctures for recreational uses through online pharmacies. According to the last World Drug Report, seizures of tinctures played comparatively a negligible role in 2015. Reports on illicit production and trade are made by UNODC annually.

#### **d. Need of the substance for medical (including veterinary) practice**

Nabiximols has received marketing authorization for the treatment of spasticity due to multiple sclerosis (MS) in Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Iceland, Ireland, Italy, Lichtenstein, Luxembourg, Netherlands, Norway, Poland, Portugal, Slovakia, Spain, Sweden, Switzerland and the United Kingdom. It has regulatory approval for MS spasticity in Canada, Australia, New Zealand, Brazil, Colombia, Chile, United Arab Emirates, Kuwait and Israel. Nabiximols has also been approved in Canada and Israel for neuropathic pain in MS and for chronic cancer pain. Nabiximols is not listed on the WHO Model List of Essential Medicines.

Therapeutic use of cannabis extracts for different purposes have been evaluated in some studies. Nabiximols was observed to reduce anxiety in patients with multiple sclerosis; in those with ADHD, it showed significant improvement in

hyperactivity/impulsivity and cognitive measure of inhibition. Treatment with nabiximols significantly reduced cannabis withdrawal symptoms but not craving in persons with cannabis use disorder. It also improved overall quality of life but not pain in those with advanced cancer pain refractory to opioids and improved sleep quality and sleep disturbance in those with Sleep Disorder.

Hemp seed and evening primrose oils have been reported to reduce extended disability status scores and lower liver transaminase levels in patients with multiple sclerosis. Also, cannabis oil containing THC has been used as an add-on pharmacotherapy for dementia. Cannabis extracts have been observed to improve neurogenic symptoms in patients with chronic medical illnesses including multiple sclerosis and improve modified Ashworth Scale and pain scores in those with motor neuron disease. They have also been found to improve symptoms in patients with sleep disorders and those with chemotherapy-associated nausea and vomiting. Hemp seed oils are rich in various nutrients and a broad range of vitamins and minerals and are used as food. Cold pressed seed oils also contain antioxidants.

Hemp seed oils and a mushy residue, the “husk”, are used as fertilizer or compressed into tablets and used for cattle feed. It is used as animal feed in many countries.

**e. Need of the substance for other purposes (e.g. industrial)**

Cannabis extracts and tinctures have no known industrial uses.

**f. Measures taken by countries to curb misuse**

Cannabis extracts and tinctures (along with cannabis and cannabis resin) are currently listed in Schedule I of the Single Convention on Narcotic Drugs of 1961. In the United States of America, Cannabis is classified as a Schedule I drug (those with a high potential for abuse and no acceptable medical use) under the Controlled Substances Act of 1970. Despite this federal prohibition, some States and Local Governments have enacted legislation permitting exemptions for various uses, mainly for medical and industrial use. As of January 2018, Alaska, California, Colorado, Maine, Massachusetts, Nevada, Oregon, Vermont and Washington have made the sale and possession of cannabis legal for both medicinal and recreational use. Cannabis for recreational and medical use or cultivation of cannabis is considered illegal in a number of countries including the United Kingdom. Other countries however have different regulations for recreational use, medical uses and the cultivation of cannabis.

Data is not available on the specific control of the extracts and tinctures of cannabis in various countries (especially as they may be grouped together with cannabis and cannabis resins). Though, they may be covered by legislations regulating medical and

recreational cannabis. There is an ongoing review of nabiximols data at the United States Food and Drug Administration

**g. Impact if this substance is scheduled**

There should be no impact for legitimate use.

**2. Are there absent data that would be determinative for scheduling?**

None

**3. Other comments or opinions**

Cannabis extracts exist in various forms and include solvent oil extracts, rosin and distillates, cannabis oils, aqueous extracts and nabiximols. They have varying concentrations and proportions of their principle constituents ( $\Delta^9$ -THC and/or CBD). Specifically, cannabis oil extracts have the highest concentrations of  $\Delta^9$ -THC, tinctures have varied concentrations, aqueous extracts relatively low concentrations of  $\Delta^9$ -THC while nabiximols has an almost equal concentration of  $\Delta^9$ -THC and CBD. Theoretically, Hemp seed oils should not contain significant cannabinoid content (but suboptimal manufacturing processes can lead to contamination with  $\Delta^9$ -THC). The concentrations and proportions of the main constituents are responsible for most individual pharmacodynamics and side effect/adverse effect profile. While CBD in its pure state does not appear to have abuse potential or cause harm and has even been suggested to attenuate the aversive effects of  $\Delta^9$ -THC,  $\Delta^9$ -THC on the other hand has significant psychoactive effects and is the main constituent in some of the cannabis extracts. Its major metabolite, 11-OH- $\Delta^9$ -THC, is also psychoactive. This explains why nabiximols preparations containing lower concentrations of THC are preferred over those with higher concentrations.

In the 1961 Convention, cannabis and cannabis resin, extracts and tinctures of cannabis are grouped together in Schedule I; Cannabis plant and cannabis resin are also in Schedule IV of the 1961 Convention. At present, there are published reports describing therapeutic uses of some cannabis extracts and tinctures. This has resulted in the logical separation of cannabis extracts and tinctures from cannabis with reference to discussions, reviews, pre-reviews and possible subsequent critical reviews.

The pre-review report evaluated cannabis extracts and tinctures making creditable efforts to separately describe their chemistry, pharmacology, abuse and dependence liabilities and toxicity profile. Unfortunately, there was insufficient data regarding abuse and dependence liability specific to cannabis extracts and tinctures. Most of the information were extrapolations from different studies using  $\Delta^9$ -THC, its derivatives or other compounds. The scope and magnitude of public health concerns regarding the various extracts and tinctures were more difficult to individualize. Data, specific to cannabis extracts especially extracts employed for therapeutic purposes will therefore be useful.

Due to the varying concentrations of their main constituents, issues regarding cannabis extracts and tinctures may also be difficult to harmonize and should be individualized as much as possible. However since CBD has been found to have therapeutic benefits and does not appear to have abuse potential, the concentration of  $\Delta^9$ -THC that should be considered maximal (or safe) in cannabis extract preparations for therapeutic use needs to be established. This will contribute to determinative deliberations regarding cannabis extracts and tinctures.