WHO Technical Report Series

1013

WHO Expert Committee on Drug Dependence

Fortieth report

World Health Organization

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Geneva, Switzerland, 4–7 June 2018

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Abbreviations

AIDS	acquired immunodeficiency syndrome
BHO	butane hash oil
CBD	cannabidiol
CBDA	cannabidiolic acid
CND	Commission on Narcotic Drugs
DALY	disability-adjusted life year
ECDD	Expert Committee on Drug Dependence
EML	WHO Model List of Essential Medicines
EMP	Essential Medicines and Health Products
EWA	(UNODC) Early Warning System
FDA	Food and Drug Administration
INCB	International Narcotics Control Board
INN	International Nonproprietary Name
NIDA	National Institute of Drug Abuse
NPS	new psychoactive substances
RCT	randomized controlled trial
THC	tetrahydrocannabinol
UNGASS	United Nations General Assembly Special Session
UNODC	United Nations Office on Drugs and Crime
US	United States
WHO	World Health Organization

1. Introduction

The fortieth meeting of the World Health Organization (WHO) Expert Committee on Drug Dependence (ECDD) was held from 4–7 June 2018 at WHO headquarters in Geneva, Switzerland. The meeting was dedicated to the review of cannabis and its component substances.

Commission on Narcotic Drugs (CND) Resolution 52/5 noted that the health effects of cannabis had not been recently reviewed and requested that the WHO ECDD provide an updated report. The thirty-seventh ECDD (2015) requested that the ECDD Secretariat begin collecting data that would inform the review of cannabis, cannabis resin and extracts and tinctures of cannabis at a future meeting. Two reports on cannabis were presented in 2016 at the thirty-eighth meeting of the ECDD.

The thirty-eighth ECDD recognized:

1. the increase in the use of cannabis and its components for medical purposes;
2. the emergence of new cannabis-related pharmaceutical preparations for therapeutic use; and
3. that cannabis had never been subject to a formal pre-review or critical review by the ECDD.

Therefore, the Committee recommended that pre-reviews of cannabis and its component substances be evaluated at an ECDD meeting specifically dedicated to those substances.

In response to those recommendations, the fortieth meeting of the ECDD was designated a special session dedicated to the review of cannabis and cannabis-related components that are currently scheduled under the 1961 and 1971 Conventions. A separate pre-review of cannabidiol was carried out during the thirty-ninth meeting of the ECDD.

Dr Mariângela Simão, Assistant Director-General for Access to Medicines, Vaccines and Health Products opened the meeting by welcoming all participants on behalf of the WHO Director-General. She then thanked the ECDD members for the time and effort they had dedicated to the review of the substances on the agenda of the meeting. Dr Simão reiterated the mandate of WHO under the 1961 Single Convention on Narcotic Drugs *(1)* and the 1971 Convention on Psychotropic Substances *(2)* to undertake the assessment of psychoactive substances with potential for abuse and dependence and that cause harm to health. She explained that, where relevant, the importance of therapeutic use of

these substances is also assessed. She emphasized that evidence-based assessment of psychoactive substances as mandated by the International Drug Control Conventions is central to the work of the ECDD. Participants were reminded that they were acting in their personal capacities and not as representatives of their governments.

Mr Jakob Quirin of the WHO Office of the Legal Counsel then reminded the participants that the Expert Committee is convened in accordance with WHO's *Regulations for expert advisory panels (3)* and the *Guidance on the WHO review of psychoactive substances for international control (4)*. In accordance with this guidance, the functions of the ECDD 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 members of the Expert Committee elected a chair, co-chair and a rapporteur. The chair welcomed all participants and the agenda, as proposed by the Secretariat, was approved.

Declarations of interest

The competing interests that may occur in health care result in the potential for conflicts of interest and may lead to biased generation or assessment of evidence and to misinformed health care policies. WHO has stringent policies for avoiding, or at least limiting, conflicts of interest, particularly in the development of official guidance documents that affect health care. As declaration of conflict of interests is insufficient to neutralize potentially harmful effects, the Organization has accurate mechanisms for identifying relevant conflicts of interest and approaches for managing such conflicts (for example, exclusion of members, recusal from participation in meeting sessions, restricting participation), thus ensuring the validity and transparency of the decision-making process and the credibility of the Expert Committee's decisions.

Before the opening of the meeting and in accordance with WHO policy, all members of the Expert Committee and all temporary advisers attending the meeting submitted written disclosures of potential conflicts of interest that may affect, or may be reasonably perceived to affect, their objectivity and independence in relation to the subject matter of the meeting. The WHO ECDD Secretariat received the following disclosures and sought the advice of the Office of Compliance, Risk Management and Ethics:

Professor Bruna Brands, Expert Panel Member, declared having received research support from the Canadian Institutes of Health Research and Public Safety Canada. The funding was to investigate the effects of cannabis on driving performance.

Professor Raka Jain, Expert Panel Member, declared several interests not pertaining to the substances being reviewed at the fortieth meeting of the ECDD. This included research funding from the Indian government.

Professor Jason White, Expert Panel Member, declared that he acts as an expert witness for the courts on judicial matters relating to cannabis.

Dr Giuseppe Cannazza, Temporary Adviser, declared receiving research support from Linnea pharmaceuticals to investigate the chemical composition of extracts of industrial hemp.

Dr Jenny Wiley, Temporary Adviser, declared that she receives research support from the United States National Institute of Drug Abuse (NIDA), National Institutes of Health and the Food and Drug Administration (FDA) to carry out research on cannabinoids.

Dr Kevin Hill, Temporary Adviser, declared that he receives research support from US NIDA for the treatment of cannabis-related disorders.

Dr Jonathon Arnold, Temporary Adviser, declared that he holds provisional patents on minor cannabinoids. He has provided reports on medical cannabis to the state government in Australia. These contracts ceased in 2016. His employer, University of Sydney, contributed to his travel costs to attend the ECDD meeting.

The disclosed interests were considered by the Secretariat of the fortieth ECDD as not in conflict with any issues to be discussed at the meeting or with the recommendations to be issued by the Expert Committee. No other interests declared by members of the Expert Committee or temporary advisers were deemed relevant to the work of the group.

2. WHO Expert Committee on Drug Dependence (ECDD): review procedures and processes

2.1 Pre-reviews and critical reviews

As per WHO procurement guidelines, WHO issued a public Request for Proposals for authors of pre-review reports that would inform the deliberations of the fortieth ECDD. Proposals were solicited from individuals with demonstrated scientific expertise relating to cannabis and cannabis-related substances in the fields of chemistry, toxicology, pharmacology, epidemiology and therapeutic use.

2.2 Member State questionnaires

At its 126th session in January 2010, the Executive Board approved the publication *Guidance on the WHO review of psychoactive substances for international control (4)* (Annex 6), which requires the Secretariat to request relevant information from ministries of health in Member States and to prepare a report for submission to the ECDD.

For this purpose, a questionnaire was designed to gather information on the legitimate use, harmful use, status of national control and potential impact of international control for each substance under evaluation. As in the past, Member States were invited to collaborate in this process by providing accurate information, as requested in the questionnaires, concerning substances under review.

The questionnaire was available in three languages (English, Spanish and French) and was open for responses between March and May 2018. Member States were also invited to provide additional relevant information to supplement their responses.

3. Open session

The purpose of the open session was to afford the Expert Committee the opportunity, before its meeting, to receive presentations and to question representatives of interested parties concerning data that had been provided about substances under review.

The Expert Committee received presentations and written submissions from individuals and representatives of public institutions, private institutions and civil society organizations. The open session was opened by Dr Mariângela Simão, Assistant Director-General and chaired by Dr Gilles Forte, Coordinator. The session was attended by Committee members, the ECDD Secretariat and external observers.

Presentations and/or statements relevant to the agenda of the fortieth meeting of the ECDD were made by the following participants:

- Agence Nationale de Sécurité du Médicament et des Produits de Santé, France
- Americans for Safe Access, United States of America
- Amy King, United States of America
- Associazione Luca Coscioni, Forum Droghe, Società della Ragione and DRCNet Foundation, Italy
- Beckley Foundation, England
- Brazilian Federal Senate Commission on Human Rights and Participatory Legislation, Brazil
- Caryle Hearte, United States of America
- Crohn Consult, the Netherlands
- Drug and Chemical Advisory Group, United States of America
- Drug Policy Alliance, United States of America
- Entourage Clinical Services, United States of America
- Epistemonikos Foundation, Chile
- European Industrial Hemp Association, Germany
- Familias con Retos Especialies, Mexico
- Fields of Green for All, South Africa
- For Alternative Approaches to Addiction – Think & do tank, France
- Instituto RIA, Mexico
- International Association for Cannabinoid Medicines, Germany
- International Drug Policy Consortium, England

- Julie Fry, United States of America
- Mamá Cultiva, Argentina
- Medical Cannabis Awareness, New Zealand
- Mexico United Against Crime, Mexico
- Nephrology and Urology Institute, Uruguay
- PhytoSciences, United States of America
- Rossner & Sohn GmBH, Germany
- Scottish Youth Parliament, Scotland
- Sylvie Massart, France
- The Hemp Foundation, New Zealand
- Tilray Global, United States of America
- Veterans for Medical Cannabis Access, United States of America
- Willem Scholten Consultancy, the Netherlands

4. Briefings from international organizations on their work on the public health dimension of the world drug problem

4.1 Update from the international Narcotics Control Board

Mr Rossen Popov presented an update on behalf of the International Narcotics Control Board (INCB). The INCB is an independent and quasi-judicial control organ, established by treaty, for monitoring the implementation of the United Nations International Drug Control Conventions. The Board consists of 13 members who are elected by the Economic and Social Council and who serve in their personal capacity, not as government representatives. Three members with medical, pharmacological or pharmaceutical experience are elected from a list of persons nominated by WHO and 10 members are elected from a list of persons nominated by governments. The Board also supports governments in ensuring the availability of narcotic drugs and psychotropic substances for medical and scientific purposes while preventing their diversion and abuse.

Pursuant to the Conventions, the use of narcotic drugs and psychotropic substances is limited to medical and scientific purposes. All other uses are incompatible with the international legal framework on drug control.

The Board had carefully examined the terminology related to the therapeutic use of cannabis. Drawing on the Single Convention on Narcotic Drugs of 1961, the Board had pointed out that when considering the possibility of using cannabis derivatives for the treatment of certain health conditions, it is most appropriate to avoid the notion of "medical cannabis". This is intended to ensure that when reference is made to medicinal products, it is understood to refer to products that have been appropriately tested, have passed a full scientific evaluation including clinical trials and are licensed as medicines.

A growing number of governments around the world are authorizing the use of cannabis derivatives for medicinal purposes. The 1961 Convention assigns national authorities the responsibility for permitting the use of those substances for medical purposes, as the Board stated in its annual report for 2003. Such use is permissible under the 1961 Convention as amended by the 1972 Protocol, provided that a number of conditions are met. This refers to the requirements of Articles 23 and 28 of the 1961 Convention, particularly regarding preparation and submission of estimates, reporting the area and geographical location of cultivation, the establishment of a cannabis agency, and of a licensing and import/export authorization system. In its annual report for 2014, the Board devoted a special topic to the control measures applicable to programmes for the use of cannabinoids for medical purposes pursuant to the 1961 Convention.

The Board stressed in its annual report for 2017 that governments that are considering the medical use of cannabinoids should examine the results of scientific studies and medical trials. They should ensure that the prescription of such substances for medical use is performed with competent medical knowledge and supervision and that prescription practice is based on available scientific evidence and takes into consideration the potential side-effects.

Finally, governments should ensure that cannabinoids are made available to patients in line with relevant WHO guidelines and with the International Drug Control Conventions.

4.2 Update from the United Nations Office on Drugs and Crime

Mr Justice Tettey presented an update on the priorities of the United Nations Office on Drugs and Crime (UNODC). He explained that in the outcome document of the special session of the United Nations General Assembly on the world drug problem held in April 2016, Member States reaffirmed the role of UNODC as the leading United Nations entity for addressing and countering the world drug problem.

UNODC's three-pronged approach to implementing this mandate involves: research that ensures that policy is evidence-based; a strong legal framework that helps states address the issues of drugs, crime and terrorism according to the rule of law; and an operational response that is made possible by the political ownership of the states concerned. UNODC delivers results through its headquarters in Vienna and a global network of field offices, which operate in more than 150 countries.

At the 2016 United Nations General Assembly Special Session on Drugs (UNGASS), Member States committed to implementing more than 100 recommendations on prevention and treatment; availability of controlled substances for medical and scientific purposes; countering drug-related crime; addressing issues of human rights, gender and youth; emerging challenges; international cooperation and alternative development.

To effectively address and counter the world drug problem in all its complexity, UNODC works with a wide range of United Nations partners, including WHO, INCB and other international organizations, academia and civil society.

In the context of the work of the WHO ECDD, the 2016 UNGASS urged the sharing of information and strengthening of the capacities of the relevant international and regional organizations to prioritize the review of the most prevalent, persistent and harmful new psychoactive substances (NPS) and to facilitate informed scheduling decisions by the CND.

UNODC outlined the progress made to date on this priority. In 2017, UNODC completed the extension of its Early Warning System on New Psychoactive Substances to collect toxicology information on NPS. With over 16 000 data-points on more than 810 substances identified in over 100 countries since monitoring started in 2013, the evidence-based identification of the most harmful, prevalent and persistent substances is well within the reach of the international community.

The trends of emergence of NPS currently show an apparent decrease in innovation since the peak in 2013. The recommendations of WHO have resulted in decisions by the CND to place more than 30 NPS under control since 2015.

Mr Tettey described newly emerging realities on the drug markets that would define the priorities of UNODC for the coming years. These include the increasing emergence of fentanyl analogues, some of which have been implicated in opioid overdose deaths in North America; the tramadol crisis in West Africa, covered extensively in the 2018 World drug report *(5)*; and the concomitant use of benzodiazepines with opioids.

UNODC is developing an Opioid Strategy that seeks to engage international partners such as WHO and INCB, as well as regional partners, to help protect the health and welfare of humankind while ensuring access to this important class of medicines.

Mr Tettey concluded by expressing UNODC's confidence that the WHO ECDD review of cannabis and related substances would lead to outcomes that continue to reflect scientific rigour and that would result in recommendations based on the best available evidence.

4.3 Update from the World Health Organization

Dr Gilles Forte provided an update on behalf of WHO. He explained that WHO has six main functions in addressing the world drug problem:

- to provide technical support to countries that do not have sufficient capacity of their own;
- to develop norms and standards on health issues;
- to monitor and assess global health trends in coordination with other agencies;
- to strengthen health systems;
- to manage research agendas; and
- to promote health security by addressing common threats and vulnerability.

Several World Health Assembly resolutions and decisions have been made to address the public health aspects of the world drug problem. Most recently, in 2017, the World Health Assembly requested the WHO Director-General to continue efforts to improve coordination between WHO, UNODC and INCB, within their existing mandates, in addressing and countering the world drug problem. This decision also requested the WHO Director-General to keep the CND appropriately informed of relevant programmes and progress.

Dr Forte went on to describe the work of the WHO ECDD in the context of these decisions and resolutions. The Committee makes its recommendations based on a thorough evidence-based analysis of the abuse and dependence potential, harm to health and therapeutic uses of substances that are reviewed. Meetings are held annually, but, exceptionally, the Committee was to meet twice in 2018.

The WHO ECDD carries out its prioritization process by determining the most prevalent and harmful psychoactive substances with the support of UNODC, INCB, regional institutions and Member States. The ECDD reviews both published and unpublished data from sources including the UNODC Early Warning System (EWA), the European Monitoring Centre for Drugs and Drug Addiction, Member States and the Uppsala Monitoring Centre. By collecting information from these sources, the ECDD ensures that enough robust data are available to enable a review.

Dr Forte highlighted several priority areas for the ECDD. First, WHO seeks to increase its capacity to review psychoactive substances by holding annual meetings of the ECDD. The Committee is also seeking to expand its consideration of data beyond peer-reviewed publications by working more closely with countries and regional organizations to collect unpublished information from reliable sources. For substances that may present substantial or serious risk to public health, but for which limited data are available to meet the requirements for scheduling, WHO is developing a system of surveillance. The surveillance system is complementary to the scheduling process and aims to rapidly communicate the dangers of harmful substances to countries, particularly the dangers of NPS.

WHO works to ensure access to controlled medicines within the International Drug Control Conventions. It also regularly updates the WHO Model List of Essential Medicines (EML), and reviews controlled medicines to be added to the EML. In addition to its work to develop and promote new guidelines on the management of pain, WHO supports countries in assessing the availability of controlled medicines, in developing balanced policies and regulations, and improving quantification, prescribing and use.

5. Review of substances

At its 126th session in January 2010, the WHO Executive Board approved the publication *Guidance on the WHO review of psychoactive substances for international control (4)*. In accordance with this document, WHO carries out its reviews of psychoactive substances in two steps.

The first step is referred to as pre-review; this is a preliminary review carried out by the Committee to determine whether a fully documented review (critical review) of the substance is required. A pre-review is initiated when a proposal has been submitted to the Expert Committee with supporting information by (1) the Secretariat, (2) any member of the Expert Committee, or (3) representatives of other organizations invited to participate in the Expert Committee meeting.

If a preceding meeting of the Committee found that a critical review of a substance is warranted, the Secretariat will prepare such a review for the next meeting of the Committee. However, a pre-review is not always needed and in certain cases a critical review can be undertaken directly.

According to the *Guidance on the WHO review of psychoactive substances for international control (4)* a critical review is initiated by the Expert Committee in any of the following cases:

1. there has been notification from a Party to the 1961 Single Convention on Narcotic Drugs and the 1971 Convention on Psychotropic Substances concerning the scheduling of a substance;
2. there has been an explicit request from CND to review a substance;
3. a pre-review of a substance has resulted in an Expert Committee recommendation for critical review; or
4. information has been brought to WHO's attention that a substance is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any Party.

In respect of case *(4)*, if therapeutic use of the substance is confirmed subsequently by any Party, the substance shall be subjected to a pre-review.

6. Cannabidiol

6.1 Substance identification

Chemically, cannabidiol (CBD) is 2-[(6R)-3-methyl-6-prop-1-en-2-ylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol. CBD is one of the naturally occurring cannabinoids found in cannabis plants. It is a 21-carbon terpenophenolic compound that is formed following decarboxylation from a cannabidiolic acid (CBDA) precursor, although it can also be produced synthetically. CBD has two stereoisomers but is normally taken to refer to the naturally occurring (−)-enantiomer. (+)-CBD has been synthesized but has received little attention.

6.2 Chemistry

In plants, Δ^9-tetrahydrocannabinol (Δ^9-THC) and CBD are derived from their acidic precursors Δ^9- tetrahydrocannabinolic acid (THCA) and CBDA, respectively. Subsequent decarboxylation of THCA and CBDA via light exposure, heating or ageing, results in Δ^9-THC or CBD. Synthetic routes are available to produce CBD, but some of the published methods yield only small amounts. There are several published methods for the analytical detection of CBD in various biological samples.

6.3 Ease of convertibility into controlled substances

There is some evidence that CBD can be converted in the laboratory to Δ^9-THC, which is controlled under the 1971 United Nations Convention on Psychotropic Substances. The laboratory conversion of CBD to Δ^9-THC results in a preparation of uncertain purity. There is limited in vitro evidence that this conversion can occur spontaneously in the presence of acid. Overall, however, there is no evidence that this transformation occurs in humans after oral CBD administration

6.4 General pharmacology

In clinical trials and research studies, CBD is generally administered orally as either a capsule or dissolved in an oil solution (for example, olive or sesame oil). Probably due to its poor solubility in water, the absorption of CBD from the gastrointestinal tract is erratic, and the resulting pharmacokinetic profile is variable. CBD is extensively metabolized in the liver and, as a result, bioavailability from oral delivery is estimated to be only 6%. CBD may preferentially accumulate in adipose tissues due to its high lipophilicity. In in vitro models, CBD has been shown to modify concentrations of other drugs through the inhibition of cytochrome P450 (CYP) isozymes, but it is not clear whether the same effects occur with clinical doses.

There are two types of cannabinoid (CB) receptors: CB_1, which are primarily located in the central nervous system with some expression in peripheral tissues, and CB_2, which can be found in the periphery on cells with immune function, in the gastrointestinal tract, and at low densities in the central nervous system. CBD does not appear to act directly at CB_1 receptors, and most studies find no agonist effects at this receptor. CBD also shows low affinity at CB_2 receptors.

In human and animal studies, CBD has been shown to have very different effects from those of Δ^9-THC. In mice, CBD fails to produce the behavioural characteristics (for example, suppression of locomotor activity, hypothermia, antinociception) associated with CB_1 activation, whereas Δ^9-THC generates all the effects that occur when CB_1 is activated. Neuroimaging studies in humans and animals have shown that CBD has effects that are generally opposite to those of Δ^9-THC. In contrast to Δ^9-THC, CBD does not affect heart rate or blood pressure under normal conditions. CBD may interact with the endocannabinoid system through indirect mechanisms and several non-endocannabinoid signalling systems as well, but it is not clear which, if any, of these other mechanisms are responsible for any of CBD's potential clinical or other effects.

6.5 Toxicology

In general, CBD has been found to have low toxicity, although studies are limited and not all potential effects have been explored.

6.6 Adverse reactions in humans

CBD does not produce the effects that are typically seen with Δ^9-THC. CBD has been found to be generally well tolerated with a good safety profile across several controlled and open-label trials investigating its potential therapeutic effects. Adverse events reported in clinical studies investigating the therapeutic possibilities of CBD have included, but have not been limited to, somnolence, decreased appetite, diarrhoea and fatigue.

6.7 Dependence potential

It was not possible to identify any reports on controlled studies of the physical dependence potential of CBD in laboratory animals or humans. Tolerance to CBD has not been observed.

6.8 Abuse potential

Several laboratory animal studies indicate that CBD does not produce effects common to many drugs of abuse, nor, more specifically, effects comparable to those of Δ^9-THC. In particular, unlike other drugs of abuse, it does not activate the mesolimbic dopamine (reward) pathway in the brain or potentiate the effect

of rewarding electrical stimulation. CBD fails to show an effect in the conditioned place preference model of reinforcement, and its effects do not resemble those of Δ^9-THC in the drug discrimination model of subjective drug effects.

Clinical studies have shown that even high doses of oral CBD do not cause Δ^9-THC-like effects (for example, impairment of cognitive and psychomotor function, increased heart rate/tachycardia and dry mouth). When evaluated in healthy volunteers, administration of single oral doses of up to 600 mg of CBD had placebo-like effects on physiological measures and on the scales of the Addiction Research Centre Inventory. In a randomized, double-blind, within-subject laboratory study in recreational cannabis users, CBD produced no significant psychoactive, cardiovascular or other effects at doses up to 800 mg orally. Overall, there is no evidence that oral CBD administration in humans results in clinically relevant Δ^9-THC-like subjective or physiological effects. Co-administration of oral CBD does not affect the intensity of Δ^9-THC subjective effects. There are no case reports of abuse or dependence relating to the use of CBD.

6.9 Therapeutic applications, extent of therapeutic use and epidemiology of medical use

CBD is presently marketed in several countries in combination with Δ^9-THC in a 1:1 ratio (Sativex®). CBD is in development for a variety of therapeutic applications including schizophrenia, fragile X syndrome, encephalopathies, childhood absence seizures, neonatal hypoxic–ischaemic encephalopathy and perinatal asphyxia. The clinical use of CBD is most advanced in the treatment of epilepsy. In clinical trials, CBD has demonstrated effectiveness for treating at least some forms of epilepsy, with one pure CBD product (Epidiolex®) found effective in clinical studies of Lennox-Gastaut syndrome (a severe form of epileptic encephalopathy that produces various types of seizures) and Dravet syndrome (a complex childhood epilepsy disorder that has a high mortality rate), which are often resistant to other forms of medication.

In 2015, the US FDA granted fast-track designation for intravenous CBD to treat neonatal hypoxic–ischaemic encephalopathy. The European Commission also granted orphan designation for CBD to be used in the treatment of perinatal asphyxia. Currently there are no other treatments available for these conditions, but there is evidence of the effectiveness of CBD in animal models.

6.10 Listing in the WHO Model List of Essential Medicines

Cannabidiol is not listed in the WHO EML (20th list) or the WHO Model List of Essential Medicines for Children (6th list).

6.11 Marketing authorizations (as a medicinal product)

One pure CBD product (Epidiolex®) was under consideration for registration at the time of the ECDD meeting. There are several other CBD products in development.

6.12 Industrial use

Pure CBD has no legitimate industrial uses.

6.13 Non-medical use, abuse and dependence

There are no case reports of abuse or dependence relating to the non-medical use of pure CBD. CBD-based products are, however, used for a variety of medical indications in preparations that are not regulated by pharmaceutical authorities.

6.14 Nature and magnitude of public health problems related to misuse, abuse and dependence

No public health problems (for example, driving under the influence of drugs, harm to health or comorbidities) have been associated with the use of pure CBD.

6.15 Licit production, consumption and international trade

Licit production for medical research is described in section *6.11* (Marketing authorizations).

6.16 Illicit manufacture and traffic and related information

There are no published statistics (for example, country data on seizures of illicit CBD) available.

6.17 Current international controls and their impact

CBD is not explicitly specified for inclusion in the schedules of the 1961 and the 1971 United Nations International Drug Control Conventions, nor is it included in the *List of precursors and chemicals frequently used in the illicit manufacture of narcotic drugs and psychotropic substances (6)* under the United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988. However, if prepared as an extract or tincture of cannabis it is controlled in Schedule I of the Single Convention on Narcotic Drugs, 1961.

6.18 Current and past national controls

Several countries have CBD under some form of regulatory control. However, some have relaxed their control in recent years, in part to make CBD more accessible for medical use or research.

6.19 WHO review history

A pre-review of CBD was undertaken during the thirty-ninth meeting of the ECDD in November 2017 following a recommendation from the thirty-eighth ECDD that pre-review documentation on cannabis-related substances, including CBD, be prepared and evaluated at a subsequent Committee meeting. Following its pre-review at the thirty-ninth ECDD meeting, the Committee recommended that extracts and preparations containing almost exclusively CBD be subject to critical review at the fortieth meeting of the ECDD.

6.20 Recommendation

CBD is one of the naturally occurring cannabinoids found in cannabis plants. There are no case reports of abuse or dependence relating to the use of pure CBD. No public health problems have been associated with CBD use.

CBD has been found to be generally well tolerated and to have a good safety profile. Adverse effects of CBD use include loss of appetite, diarrhoea and fatigue.

Therapeutic applications of CBD are being researched for a variety of clinical uses. Research in this area is most advanced in the treatment of epilepsy. In clinical trials, one pure CBD product has demonstrated effectiveness for treating some forms of epilepsy, such as Lennox-Gastaut syndrome and Dravet syndrome, which are often resistant to other forms of medication.

CBD is not specifically listed in the schedules of the 1961, 1971 or 1988 United Nations International Drug Control Conventions. However, if prepared as an extract or tincture, it is controlled under Schedule I of the 1961 Single Convention on Narcotic Drugs.

There is no evidence that CBD as a substance is liable to similar abuse or leads to similar ill-effects to substances controlled under the 1961 or 1971 Conventions such as cannabis or Δ^9-THC, respectively.

The Committee recommended that preparations considered to be pure CBD should not be scheduled.

7. Cannabis and cannabis resin

7.1 Substance identification

7.1.1 Cannabis plant

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.

7.1.2 Cannabis resin

The separated resin, whether crude or purified, obtained from the cannabis plant.

7.2 Chemistry

Cannabis sativa (*C. sativa*) is one of the world's oldest cultivated plants. Cannabis is an annual flowering plant, generally dioecious (i.e. with the male and female flowers on separate plants), although monoecious plants, where the male and female flowers are on the same plant, can also be found. To date, more than 500 naturally occurring compounds have been identified in the cannabis plant, including cannabinoids (more than 100 chemicals unique to the plant), terpenoids and alkaloids. Cannabis contains a characteristic class of terpenophenolic secondary metabolites, named phytocannabinoids to distinguish them from synthetic and endogenous cannabinoids. To date, 120 phytocannabinoids have been recorded for *C. sativa*, and can be classified into 11 general types. Δ^9-tetrahydrocannabinol (Δ^9-THC) and CBD are the most important of the plant cannabinoids. Δ^9-THC is thought to be the principal intoxicant constituent of *C. sativa*. In plants, Δ^9-THC and CBD are derived from their acidic precursors Δ^9-tetrahydrocannabinolic acid (THCA) and CBDA, respectively. Subsequent decarboxylation of THCA and CBDA, via light exposure, heating or ageing, results in Δ^9-THC or CBD. Concentrations of Δ^9-THC or THCA contained in cannabis vary across strains and across the plant itself, with resin (i.e. hashish) and unfertilized female flowers (i.e. sinsemilla) having higher concentrations than other parts such as the leaf. Once dried, the foliage and floral material are stripped from the stalk and twigs, which are almost devoid of cannabinoids. The resinous secretions of the plant, which are produced in the glandular trichomes, can be collected to yield a product with a higher concentration of Δ^9-THC than occurs in the whole plant inflorescence. In addition to the secretions, cannabis resin consists of finer plant material and appears as a loose or pressed sticky powder, depending on the method of production.

7.3 Ease of convertibility into controlled substances

Not applicable.

7.4 General pharmacology

Cannabis tops and cannabis resin (i.e. hashish) are typically administered via inhalation after combustion (i.e. by smoking). Most of the existing research on the pharmacokinetics of cannabis has focused on Δ^9-THC. Records from the United Kingdom of Great Britain and Northern Ireland and the USA show that average concentrations of Δ^9-THC contained in cannabis plants bred for non-medical use have increased over time (from approximately 4% in 1995 to approximately 12% in 2014). Some cannabis plants bred for medicinal use may have decreased concentrations of Δ^9-THC and increased concentrations of CBD. Absorption of Δ^9-THC in smoked cannabis is rapid, and measurable levels are observed in plasma within seconds after the first puff. Bioavailability of Δ^9-THC after cannabis smoking ranges from 10 to 56%. This percentage is affected by dose, history of use and individual differences in physiology. It also depends on factors such as smoking topography and efficiency. Δ^9-THC has an active metabolite, 11-hydroxy-Δ^9-tetrahydrocannabinol (11-OH-Δ^9-THC). The principal metabolite, 11-nor-carboxy-Δ^9-THC, is inactive.

Body fat serves as a storage reservoir for Δ^9-THC, particularly in people who consume the drug daily or almost daily. Among such people Δ^9-THC is eliminated slowly from fat tissues.

The pharmacokinetics of CBD and other minor phytocannabinoids contained in the cannabis plant, including cannabinol, cannabigerol and tetrahydrocannabivarin, following smoking of cannabis, resemble the pattern observed with Δ^9-THC.

Psychoactive effects of cannabis associated with its abuse are mediated via Δ^9-THC interaction with the endocannabinoid system in the brain. Specifically, Δ^9-THC is a partial agonist at CB_1 receptors. Δ^9-THC is also an agonist at the CB_2 receptor, which mediates some of its peripheral effects. Cannabis/Δ^9-THC interaction with other major neurotransmitter systems (such as dopamine, opioid) is mainly indirect through the interplay of these systems with the endocannabinoid system. The pharmacological effects of minor cannabinoids (for example, tetrahydrocannabivarin, cannabigerol and cannabichromene) have not been studied in detail.

A hypothesis that other cannabis plant constituents may interact with Δ^9-THC and alter its effects is referred to as the "entourage effect". So far, no clear scientific support for this hypothesis with regard to Δ^9-THC psychoactive effects has been published.

7.5 Toxicology

Most of the evidence on the toxicology of cannabis comes from observational population studies from which causation cannot be inferred. Cardiovascular effects of cannabis appear minimal or transient. Initial ingestion promotes tachycardia and increases blood pressure, but this subsides with tolerance and may even result in the opposite effects. There is limited evidence for a modestly increased risk of myocardial infarction associated with cannabis use. Smoking cannabis is linked to the typical ill-effects of smoking any substance, including the risk of chronic bronchitis.

Maternal cannabis users give birth to babies with birthweights that are on average 109 g lower than those born to mothers who do not use cannabis. There is limited evidence for a modest increase in the risk of birth defects. Impaired brain development, as demonstrated by poor connectivity, may contribute to the association between early, regular cannabis use and a decline in IQ, although the extent of these cognitive difficulties appears equivocal. Cannabis smoking has been reported to lead to a 2.5-fold increase in the risk of testicular cancer.

7.6 Adverse reactions in humans

The acute consumption of cannabis can induce euphoria, laughter and talkativeness, change sensory and time perception, and compromise motor control and judgement. It can stimulate appetite and promote dry mouth and dizziness. Acute cannabis use impairs certain types of cognitive function and can interfere with attention, learning and memory. It can also precipitate a short-lasting psychotic state in healthy individuals, which reverses once the effects of the drug have abated. Cannabis can impair driving skills and people driving under the influence of cannabis are 20–30% more likely to be involved in a car accident. Children who consume cannabis are at risk of possible respiratory depression, tachycardia and coma.

Most of the adverse effects associated with cannabis result from chronic use, according to data accumulated among recreational (non-medical) users. Chronic regular (daily or near daily) cannabis use is particularly problematic for young people, whose brains continue to develop into their mid-twenties. A modest proportion of people who initiate cannabis use in adolescence show decreased IQ (by as much as 8 points when cannabis is used from the ages of 13 to 38 years). Regular cannabis use is associated with an increased risk of anxiety, depression and psychotic illness, and cannabis use may worsen the course of these disorders. Population studies report that cannabis use leads to a twofold increase in the risk of schizophrenia, although the majority of cannabis users will not develop a psychotic disorder and those who do are likely to have some

genetic vulnerability to cannabis-induced psychosis. Regular cannabis use may be associated with poor school performance, lower income, increased likelihood of requiring socioeconomic assistance, unemployment, criminal behaviour and decreased satisfaction with life.

7.7 Dependence potential

The number of studies investigating physical dependence potential in laboratory animals is limited. When exposed to cannabis smoke, mice and rats can be made physically dependent, and withdrawal effects can be reversed by intravenous administration of Δ^9-THC. However, rhesus monkeys exposed to cannabis smoke once daily or twice weekly for one year did not show behavioural signs of withdrawal upon abrupt termination.

Human users of cannabis can become physically dependent, and clinical diagnostic manuals such as the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) and the International Classification of Diseases, tenth revision (ICD-10) recognize the existence of a cannabis use disorder. It is estimated that the percentage of regular cannabis users who have experienced at least one episode of cannabis withdrawal during abstinence ranges from 16 to 33%. The onset of withdrawal typically occurs within 24 to 48 hours of abstinence following a period of regular use, with peak intensity usually occurring 2 to 6 days after last use. The withdrawal syndrome may include mood changes, irritability, increased anger, anxiety, craving, restlessness, sleep impairment, stomach pain and decreased appetite.

7.8 Abuse potential

Preclinical research on cannabis smoke has been limited. Mice exposed to cannabis smoke show typical effects of Δ^9-THC including catalepsy, antinociception, hypothermia and hypolocomotion, and these effects can be antagonized by the CB_1 receptor antagonist, rimonabant.

In humans, self-reported subjective effects associated with smoked cannabis in laboratory studies include dose-dependent increases in ratings of "drug effect", "high" or "stoned". The reinforcing effects of smoked cannabis have been demonstrated in several laboratory-based self-administration studies with smoked cannabis being readily self-administered by experienced users. Similar effects are produced by Δ^9-THC alone when administered orally or when smoked. Increases in the intensity of self-reported subjective effects of cannabis (for example, "high" or "stoned") are associated with increasing concentrations of Δ^9-THC.

7.9 Therapeutic applications, extent of therapeutic use and epidemiology of medical use

Several countries have laws on medicinal cannabis in effect. An international survey of 953 medicinal cannabis users from 31 countries found that most of them were current users under the care of a health professional and had been using cannabis-based medications for several years. The five medical conditions for which cannabis and cannabis-based medications were most often used as a treatment in this survey were back pain, sleep disorders, depression, post-injury pain and multiple sclerosis.

Research on the potential medical applications of cannabis is ongoing. The results of randomized controlled trials (RCTs) show that smoked cannabis can enhance weight gain in HIV patients (1 RCT) and treat neuropathic pain (3 RCTs). Inhaled aerosolized cannabis leads to dose-dependent reductions in spontaneous pain ratings among patients with treatment-refractory pain due to diabetic peripheral neuropathy. Two open-label, uncontrolled, observational studies of smoked cannabis or vaporized cannabis reported significantly decreased motor disability and pain scores in patients with Parkinson's disease.

7.10 Listing on the WHO Model List of Essential Medicines

Cannabis plant and cannabis resin are not included in the WHO EML (20th list) or the WHO Model List of Essential Medicines for Children (6th list).

7.11 Marketing authorizations (as a medicinal product)

Bedrocan Cannabis has been granted marketing authorization in the Netherlands to produce five standardized plant varieties (whole dried flower) that are available to patients under direct physician care. Cannabis for both medicinal and research use is available in several countries.

7.12 Industrial use

Low potency (0.2–0.3% Δ^9-THC) cannabis plants (hemp) are cultivated to produce paper, textiles, rope or twine, and construction materials based on fibre from stalks. Grain from industrial hemp is used in food products, cosmetics, plastics and fuel. Cannabis plants grown for these purposes are excluded from control under the 1961 Convention.

7.13 Non-medical use, abuse and dependence

Non-medical cannabis use is global, with an estimated prevalence of 3.8% in 2015, which means more than 183 million adults used cannabis in that year. Prevalence

can vary widely across countries, from less than 1% to over 38%. The estimates of the risk of developing cannabis use disorder among users vary among studies and countries, but it appears that 1 in 10 or 1 in 11 is a representative figure.

7.14 Nature and magnitude of public health problems related to misuse, abuse and dependence

The global burden of disease attributable to cannabis use disorder, expressed in disability-adjusted life years (DALYs) (one DALY represents one year of life lost either due to premature mortality or due to living with disability) was 646 480 DALYs in 2016. Driving under the influence of cannabis increases the risk of accidents and is therefore a public health threat.

7.15 Licit production, consumption and international trade

This is addressed under Section 7.11 (Marketing authorizations (as a medicinal product)).

7.16 Illicit manufacture and traffic and related information

Cannabis is the most widely illicitly produced drug worldwide, cultivated in at least 135 countries covering 92% of the global population. Cannabis seizures made up 53% of all drug seizures worldwide in 2015.

7.17 Current international controls and their impact

Cannabis, cannabis resin, extracts and tinctures of cannabis are grouped together in Schedule I of the 1961 United Nations Single Convention on Narcotic Drugs. Cannabis plants and resin are also under Schedule IV of this Convention, which contains substances that are particularly liable to abuse and to produce ill-effects and do not have therapeutic advantages that offset these effects.

7.18 Current and past national controls

Cannabis, including plants and resin, is controlled in most WHO Member States. A growing number of countries, however, have endorsed regulations enabling the medical use of cannabis plants to relieve the symptoms of specific medical conditions. The European Medicines Agency has stated that the use of cannabis as medicine must follow the laws of each member.

7.19 WHO review history

Cannabis and cannabis resin have not previously been formally reviewed by the ECDD.

7.20 Recommendation

Cannabis is defined as the flowering tops or separated resin of the *C. sativa* plant. Cannabis contains 121 reported phytocannabinoids, the most prominent being Δ^9-THC and CBD. Δ^9-THC is thought to be the principal intoxicant constituent of cannabis.

When used acutely, cannabis causes adverse effects such as dizziness and impairment of motor control and cognitive function. Cannabis use can impair driving. There are particular risks reported for children, such as respiratory depression, tachycardia and coma. The adverse effects of cannabis consumption are similar to those produced by Δ^9-THC alone.

Most of the adverse effects associated with cannabis result from chronic use. Regular cannabis use is associated with increased risk of mental health disorders such as anxiety, depression and psychotic illness. Chronic regular cannabis use is particularly problematic for young people as a result of its effects on the developing brain.

Cannabis can cause physical dependence in humans as evidenced by the onset of cannabis withdrawal symptoms upon abstinence. Withdrawal symptoms include mood changes, irritability and sleep impairment. Clinical diagnostic guidelines such as DSM-5 and ICD-10 recognize cannabis use disorder.

The Committee considered information regarding the therapeutic indications of cannabis and ongoing research into its possible medical applications. Several countries permit the use of cannabis for the treatment of medical conditions such as back pain, sleep disorders, depression, post-injury pain and multiple sclerosis.

Cannabis plant and cannabis resin are included in Schedule I and Schedule IV of the 1961 Single Convention on Narcotic Drugs. Substances that are included in both these schedules are particularly liable to abuse and to produce ill-effects. Other substances that are included in both Schedules I and IV are fentanyl analogues and other opioids that are considered especially dangerous.

The evidence presented to the Committee did not indicate that cannabis plant and cannabis resin were liable to produce ill-effects similar to the other substances in Schedule IV of the 1961 Convention on Narcotic Drugs. The inclusion of cannabis and cannabis resin in Schedule IV may not be consistent with the criteria for inclusion in Schedule IV.

The Committee concluded that there is sufficient evidence to recommend a critical review of cannabis plant and cannabis resin at a future ECDD meeting and to explore further the appropriateness of their current scheduling within the 1961 Convention.

8. Extracts and tinctures of cannabis

8.1 Substance identification

Extracts and tinctures of cannabis are preparations that have been extracted from the leaves and flowers of *C. sativa*. They include oils, rosin, distillates and pharmaceutical products containing a mixture of Δ^9-THC and CBD.

8.2 Chemistry

8.2.1 Cannabis extracts

There are several methods for preparing the different cannabis extracts (i.e. extract mixtures from the leaves and flowers of *C. sativa*). These include:

- *Supercritical carbon dioxide (CO_2) extraction*

  Cannabis inflorescence is treated with supercritical CO_2, which is highly pressurized liquid CO_2. The extract is separated from the CO2 that is recovered and passed back through the cannabis inflorescence several times until the extraction process is complete. The most significant advantage of CO_2 extraction is that it leaves no harmful residues in the resulting product.

- *Butane hash oil (BHO)*

  BHO is a resinous, nonpolar extract of cannabis inflorescence made using butane as a solvent, which is eventually purged under vacuum at room temperature. The final extract can contain from 50 to 90% of the active ingredient, either (–)-*trans*-delta-9-tetrahydrocannabinol (Δ^9- THC) or CBD. The terpene content ranges from 0.1 to 34%, but this can be increased by dipping BHO in a vial of terpenes prior to use ("terpene dipping").

- *Propane hash oil (PHO)*

  PHO is similar to BHO, but it uses propane as the solvent.

- *Rosin*

  The rosin method exploits heat and pressure to squeeze a resinous product from the plant material. Industrial-sized presses capable of processing large amounts of hashish oil within seconds are available. As no solvent is used in the process, it is not an extract or

tincture according to the usual definitions, but is included here for completeness.

- *Distillates*

  Distillates are concentrated extracts of cannabis inflorescence through which a specific solvent passes and collects cannabinoids and terpenes.

- *Other organic extracts*

  Other hydrocarbon solvents that can be employed for cannabis extraction include chloroform and hexane. Oils such as olive oil or sesame oil may also be used.

8.2.2 Tinctures of cannabis

The *tinctures of cannabis* are extracts of the flowering tops or other parts of *C. sativa* where alcohol (ethanol) is used as the solvent. Ethanol is a very effective solvent for the extraction of most of the substances contained in cannabis inflorescences. It has a high extraction efficiency and is more effective than water and hydrocarbon solvents (for example, hexane).

- *Cannabis oils*

  Cannabis oils may contain Δ^9-THC and other cannabinoids obtained using a method of extraction as described above. However, some oils, such as essential oil and hemp seed oil, do not contain significant concentrations of Δ^9-THC. *Medicinal cannabis oil* is an extraction of *C. sativa* typically made with olive oil or sesame oil, which is used in pharmacy for the preparation of medicinal extracts.

- *Aqueous extracts*

  An aqueous extract of *C. sativa* is often referred to as a tea. The use of boiling water is a simple and probably one of the oldest methods for preparing a cannabis extract for oral administration. The amount of Δ^9-THC extracted using this method is only a fraction of that obtainable using other extraction methods. To compensate for the low solubility of Δ^9-THC in water, users of tea often add a small amount of vegetable oil or butter and increase boiling time.

- *CBD in preparations with other cannabis-related ingredients.*

  Sativex® is a pharmaceutical formulation manufactured in the United Kingdom of Great Britain and Northern Ireland by incorporating purified botanically derived drug substances containing an accurately

measured 1:1 ratio of Δ^9-THC and CBD into a final product containing ethanol, propylene glycol and peppermint oil as excipients. Sativex® is in the form of an oromucosal spray approved for treating spasticity in patients with multiple sclerosis. Each 0.1 mL spray contains 2.7 mg of Δ^9-THC and 2.5 mg of CBD. Two cannabis plant strains are grown under regulated glasshouse conditions, principally producing Δ^9-THC and CBD. The dried plant material, including the foliage and inflorescence, is uniformly heated to decarboxylate the precursors, THCA and CBDA, to Δ^9-THC and CBD, respectively. The plant material is then extracted by supercritical liquid CO_2 extraction to obtain the two soft extracts with trade names Tetranabinex (>90% Δ^9-THC) and Nabidiolex (>85% CBD).

One or more of a variety of methods can be used for detection of the presence of cannabinoids in these substances. These methods include colour tests, thin-layer chromatography, gas chromatography, liquid chromatography, nuclear magnetic resonance and immunoassay.

8.3 Ease of convertibility into controlled substances

Not applicable.

8.4 General pharmacology

In humans, cannabis extracts may be delivered through various routes of administration, including sublingual, oral, inhalation (smoking or vaping), rectal and transdermal. "Dosage" of cannabis extracts most often refers to the amount of Δ^9-THC contained in the preparation. Tinctures are usually administered sublingually or used to infuse edibles or beverages (i.e. oral administration). Oils may be incorporated into food or beverages for oral administration or may be vaped or "dabbed". Sativex® is formulated into an oromucosal spray.

In the few studies that have been done, pharmacokinetic profiles of vaped versus smoked cannabis/cannabis extracts appear to be similar. Absorption of Δ^9-THC from inhalation is rapid and measurable levels are observed in plasma within seconds after the first puff. While peak plasma levels typically occur within 3–10 minutes after smoking, peak "highs" do not occur until 20–30 minutes after smoking. Absorption of Δ^9-THC following oral ingestion is slower and maximal plasma levels are lower, typically resulting in flatter concentration–time curves. The pharmacokinetics of CBD and Δ^9-THC in Sativex® are similar. The metabolism of Δ^9-THC and CBD is described elsewhere in this report.

To date, more than 500 naturally occurring compounds have been identified in cannabis, including cannabinoids (more than 100 chemicals unique

to the plant), terpenoids and alkaloids. However, except for Δ^9-THC and CBD (in some plants), most of these compounds are present in the plant in relatively small quantities. In addition, the extraction process is designed to concentrate the desired constituents (usually Δ^9-THC and/or CBD). Hence, the degree to which other compounds may contribute to the array of pharmacological and behavioural effects produced by cannabis extracts is largely unknown. However, because many extracts that may be used for smoking or vapour inhalation contain high concentrations of THC, there is the potential for relatively strong and immediate effects of Δ^9-THC.

8.5 Toxicology

Little information is available on the toxicology of cannabis extracts, tinctures, oils and tea. The toxicity produced by Δ^9-THC-rich cannabis extracts, tinctures, oils and tea are similar to those observed with Δ^9-THC, but, as noted above, the effects may be more pronounced with greater risk of adverse effects when extracts with high Δ^9-THC concentrations are inhaled.

Depending on the method used, cannabis extract may contain residual solvents (naphtha, isopropanol, acetone, hexane, ethyl alcohol or butane) that 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 smooth 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).

Sativex® appears not to be mutagenic, carcinogenic or teratogenic.

8.6 Adverse reactions in humans

Adverse reactions to Δ^9-THC-rich cannabis extracts, tinctures, oils and tea are similar to those observed with Δ^9-THC, but, as noted above, the effects may be more pronounced with greater risk of adverse effects when extracts with high Δ^9-THC concentrations are inhaled.

Common adverse effects of Sativex® 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, diarrhoea, anxiety and headache. Transient adverse effects such as increased heart rate and blood pressure, disorientation, depression, euphoria, transient psychotic reactions and dissociation have also been reported. In rare instances, oromucosal sprays may cause pain, discomfort, distorted taste, mouth ulceration and glossodynia (burning sensation in the mouth and tongue). There are no reported cases of driving under the influence of Sativex®.

8.7 Dependence potential

There are no published scientific studies that have evaluated the dependence potential of pure cannabis extracts or Sativex® in laboratory animals. However, the psychoactive constituent, Δ^9-THC, present in most extracts, has been separately examined and shown to have dependence potential. Frequent BHO use among cannabis users has been associated with physical dependence and perceived impaired control over cannabis use.

The dependence potential of Sativex® has not been evaluated in humans. However, there is limited evidence of a withdrawal syndrome associated with Sativex® treatment. When a mistake in a trial led to a 2-week period of abstinence, 44% of participants experienced one or more signs associated with withdrawal (for example, sleep disruption, appetite changes, mood changes or vivid dreams).

8.8 Abuse potential

There are few published reports of studies that have evaluated the abuse potential of cannabis extracts in animals. When injected and when inhaled via modified e-cigarette apparatus, cannabis extract produced Δ^9-THC-like behavioural effects in rodents. In one study, when cannabis extract was inhaled via a vaporizer, it produced place preference in a conditioned place preference procedure. There is evidence from animal studies indicating the abuse potential of Δ^9-THC as a pure substance whereas CBD does not have abuse potential.

Vaping and smoking routes are known to produce rapid psychoactive effects. However, the abuse potential of high-potency cannabis extracts administered via vaporizing has not been studied in humans. In drug-naive healthy volunteers, an orally administered cannabis extract containing a 2:1 ratio of Δ^9-THC to CBD induced fatigue, drowsiness, dizziness and feeling "high".

A clinical trial to evaluate the abuse potential of Sativex® in recreational cannabis users showed that high doses (21.6 or 43.2 mg) of Δ^9-THC induced cannabis-like effects, but this did not occur at a lower dose. Abuse has not been reported in post-market surveillance of Sativex®. However, euphoria has been reported as an adverse effect of Sativex®.

8.9 Therapeutic applications, extent of therapeutic use and epidemiology of medical use

Sativex® is being investigated for a variety of indications including, but not limited to, treatment of spasticity due to multiple sclerosis, chronic pain, anxiety disorder, cannabis use disorder, attention-deficit/hyperactivity disorder, and depression and sleep disorders.

8.10 Listing on the WHO Model List of Essential Medicines

Cannabis extracts and tinctures are not listed on the WHO EML (20th list) or the WHO Model List of Essential Medicines for Children (6th list).

8.11 Marketing authorizations (as a medicinal product)

Sativex® has been granted marketing authorization for treatment of spasticity due to multiple sclerosis in at least 20 countries.

8.12 Industrial use

Cannabis extracts and tinctures have no known industrial uses.

8.13 Non-medical use, abuse and dependence

Worldwide, cannabis is mainly used in the forms of herbs and resins for recreational (non-medical) purposes or self-medication; extracts and tinctures are thought to play a smaller role.

A global online survey in several countries reported that 7% of the past-year cannabis users had used BHO. Two surveys conducted in the USA found rates of vaporization of cannabis oil and wax of 15.5% and 10.2% among lifetime cannabis users and 22.9% and 14.8% among those with lifetime e-cigarette use, respectively. An additional study in the USA found that among past-year cannabis users, 44% (n = 121) had used BHO in the previous 12 months and that frequent BHO use was associated with higher levels of physical dependence. There are no reports of misuse of pharmaceutical products containing a mixture of Δ^9-THC and CBD.

8.14 Nature and magnitude of public health problems related to misuse, abuse and dependence

The public health problems related to the use of cannabis extracts and tinctures are difficult to assess, in part because existing reports rarely specify the form of cannabis used. There is some evidence linking the use of butane cannabis oil to dependence. The risk of burns has been reported during the preparation of extracts where solvents are used.

8.15 Licit production, consumption and international trade

Licit production is important for medical research into the therapeutic potential of cannabis preparations.

8.16 Illicit manufacture and traffic and related information

There is evidence of the illicit marketing of cannabis extracts and tinctures for recreational (non-medical) uses through online pharmacies. Cannabis extracts are extensively described on Internet forums and are offered for sale via the Internet.

8.17 Current international controls and their impact

Cannabis extracts and tinctures of cannabis are listed in Schedule I of the Single Convention on Narcotic Drugs, 1961.

8.18 Current and past national controls

Cannabis, including its extracts and tinctures, is controlled in most Member States. A growing number of countries, however, have adopted regulations that enable the medical use of cannabis extracts and tinctures to relieve the symptoms of specific medical conditions.

8.19 WHO review history

Cannabis extracts and tinctures have never been formally reviewed by the ECDD.

8.20 Recommendation

Extracts and tinctures of cannabis are substances that have been extracted from the *C. sativa* plant. They include cannabis oils, teas and an extract with approximately equal quantities of Δ^9-THC and CBD. These substances can be administered through various routes including orally and by smoke inhalation.

Evidence on the dependence potential of extracts and tinctures of cannabis varies by substance. There are no published studies that have evaluated the dependence potential of mixtures of Δ^9-THC and CBD, but there is limited evidence of a withdrawal syndrome upon abrupt cessation (for example, sleep disruption and mood changes). Frequent use of the BHO extract has been associated with physical dependence. The psychoactive constituent, Δ^9-THC, present in most extracts has been separately studied and has been shown to have dependence potential.

Few published studies have evaluated the abuse potential of cannabis extracts in animals or humans. There are, however, studies that have investigated the abuse potential of various components of extracts and tinctures of cannabis. While particular components, such as Δ^9-THC, have demonstrated abuse potential, other components in these preparations, such as CBD, have not.

The Committee recognized that the term "extracts and tinctures" as cited in the 1961 Single Convention on Narcotic Drugs encompasses preparations that have psychoactive properties as well as those that do not. The Committee also recognized that the psychoactive properties of these preparations are due principally to Δ^9-THC, which is currently scheduled in the 1971 Convention on Psychotropic Substances. Among the substances that are not psychoactive in the preparations that are derived as extracts or tinctures of cannabis are some that have promising therapeutic indications, such as CBD.

Cannabis extracts and tinctures are placed in Schedule I of the 1961 Single Convention on Narcotic Drugs. The Committee noted that the category "extract and tinctures of cannabis" encompasses very diverse formulations with varying ratios of cannabis components, in particular Δ^9-THC, and with or without psychoactive properties.

The Committee therefore concluded that there is sufficient information to recommend a critical review of extracts and tinctures of cannabis at a future ECDD meeting to address the necessity of continuing to include the term "extracts and tinctures of cannabis" in the 1961 Convention.

9. Delta-9-tetrahydrocannabinol (Δ^9-THC; dronabinol)

9.1 Substance identification

Delta-9-tetrahydrocannabinol (Δ^9-THC; dronabinol) refers to the following four stereoisomers:

a. (−)-*trans*-Δ^9-tetrahydrocannabinol (also known as dronabinol)
b. (+)-*trans*-Δ^9-tetrahydrocannabinol
c. (−)-*cis*-Δ^9-tetrahydrocannabinol
d. (+)-*cis*- Δ^9-tetrahydrocannabinol

The stereoisomer (−)-*trans*-Δ^9-THC is the only one that occurs naturally in the cannabis plant and is generally the only stereoisomer that has been studied. Dronabinol is the International Nonproprietary Name (INN) for this isomer. Where the term "Δ^9-THC" is used in this report without further specification, it refers to (−)-*trans*-Δ^9-THC or dronabinol. If reference is made to a different isomer, this is explicitly specified.

9.2 Chemistry

(−)-*Trans*-Δ^9-THC does not occur at a significant concentration in cannabis plants. The plant synthesizes primarily the carboxylic acid form of (−)-*trans*-Δ^9-THC, namely, Δ^9-tetrahydrocannabinolic acid (THCA) from cannabigerolic acid and this substance accumulates in the glandular trichomes of flowers and leaves. THCA is thermally unstable and can be quickly decarboxylated to (−)-*trans*-Δ^9-THC when exposed to heat via smoking or baking; this conversion can also occur spontaneously during storage. (−)-*Trans*-Δ^9-THC can be extracted from the plant after it has been heated; THCA can be extracted from the plant and then converted to (−)-*trans*-Δ^9-THC; or it can be synthesized from terpene and olivetol.

Synthetic methods for the other isomers have been reported.

Several analytical methods are available for the measurement of (−)-*trans*-Δ^9-THC in different matrices such as cannabis plant, cannabis extracts and biological fluids. These are mostly chromatographic methods coupled to detection techniques such as ultraviolet and mass spectrometry.

9.3 Ease of convertibility into controlled substances

The only controlled substance that (−)-*trans*-Δ^9-THC can be converted into is its isomer (−)-*trans*- Δ^8-THC, which is in Schedule I of the 1971 Convention.

9.4 General pharmacology

Δ^9-THC is highly lipophilic and animal studies have found that it is readily absorbed and distributed to the brain and other organs following various routes of administration. These include the intraperitoneal, oral, intramuscular, intravenous and inhalation routes. In humans, the predominant route of administration of pure Δ^9-THC is oral. The stereochemical variants of Δ^9-THC are not routinely administered.

Compared to absorption of Δ^9-THC in smoked cannabis, maximal plasma levels after oral administration are lower, typically resulting in flatter concentration–time curves. Peak plasma levels usually occur 60–120 minutes after ingestion although delays of up to 4–6 hours have also been reported. Estimated bioavailability averages 6%, with considerable variability among individuals. Ingestion is accompanied by significant first-pass metabolism in the liver, further decreasing the amount of Δ^9-THC that reaches sites of action. Δ^9-THC is strongly bound to plasma proteins and is readily distributed to highly vascularized tissues (for example, the liver, heart and lungs) after absorption.

Metabolism of orally administered Δ^9-THC occurs primarily in the liver and is extensive, with almost 100 metabolites having been identified. 11-hydroxy-Δ^9-tetrahydrocannabinol (11-OH-Δ^9-THC) is an active metabolite. Owing to its extensive metabolism, relatively little Δ^9-THC is eliminated from the body unchanged. Δ^9-THC is excreted primarily in the faeces (65–80%) and in the urine (20–35%).

When administered to animals, Δ^9-THC produces a characteristic profile of pharmacological effects. These include:

- a tetrad of effects – locomotor suppression, antinociception, hypothermia and catalepsy – in mice and rats;
- discriminative stimulus effects in rats, mice, pigeons and rhesus monkeys;
- reinforcing effects in squirrel monkeys; and
- static ataxia in dogs.

These cannabimimetic effects are produced through interaction with an endogenous cannabinoid system that includes two cannabinoid receptors, CB_1 and CB_2. CB_1 receptors are widespread and abundant in the brain and periphery, CB_2 receptors are confined primarily to the periphery. The psychoactive effects of Δ^9-THC are mediated via activation of CB_1 receptors in the brain.

The limited information on the pharmacology of the stereochemical variants of (–)-*trans*-Δ^9-THC suggests that they have little activity. (–)-*Trans*-Δ^9-THC was at least tenfold more potent in the dog static ataxia model than (+)-cis-Δ^9-THC or (+)-*trans*-Δ^9-THC, neither of which produced the full syndrome of

cannabinoid effects at the highest dose administered. In addition, (–)-*trans*-Δ^9-THC exhibited a tenfold greater hypothermic effect in mice and was 100-fold more potent at decreasing schedule-controlled responding in rhesus monkeys than (+)-Δ^9-THC.

9.5 Toxicology

Δ^9-THC has very low potential to produce lethal effects. Following oral administration, the median lethal dose (LD50) is 800 mg/kg in rats, up to 3000 mg/kg in dogs and up to 9000 mg/kg in monkeys. It has been calculated that a lethal dose for a 70-kg human would be approximately 4 g and that such a dose would not typically be achieved in a human following oral consumption, smoking or vaporizing the substance.

Acute Δ^9-THC exposure in humans produces tachycardia with an average increase in heart rate of eight beats per minute. Tolerance may occur to these effects, and decreases in blood pressure and heart rate may occur with subsequent exposures. Δ^9-THC is a bronchodilator. In vitro and in vivo animal studies demonstrate that high doses of Δ^9-THC can modulate the immune system in complex ways. In two human studies using low-dose Δ^9-THC no significant effects on the immune system were observed.

According to a comprehensive assessment by the US National Toxicology Program, Δ^9-THC does not have mutagenic or carcinogenic effects. Oral administration of Δ^9-THC to rats for 77 days reduced the size of the seminal vesicles, seminal fluid volume, spermatogenesis and the number of Leydig cells in the testis. However, sperm count, mating success and testosterone levels were not affected. No data are available on teratogenicity in humans. In animal studies, administration of Δ^9-THC during gestation promotes a slight decrease in fetal weight. It crosses the placental barrier and is secreted in the mother's milk.

In a randomized controlled trial with 329 multiple sclerosis patients, following daily administration of Δ^9-THC at doses of up to 28 mg/day for three years, low to moderate toxicity and a low incidence of other adverse effects were reported. There were no differences in the median number of adverse events between the placebo and Δ^9-THC-treated groups. Δ^9-THC-treated patients experienced more dizziness and light-headedness as well as dissociative thinking and perception disorders.

9.6 Adverse reactions in humans

In humans, Δ^9-THC has very similar pharmacological and subjective effects to those of cannabis. Users may exhibit euphoria, laughter and increased loquacity. Δ^9-THC increases appetite, promotes dry mouth and occasional dizziness, and produces apparent enhancement of visual, olfactory and auditory perceptions.

Exposure to Δ^9-THC may also cause nausea and vomiting in some users. Following repeated exposure, users generally develop tolerance to the effects of Δ^9 THC. Δ^9-THC exposure can cause subtle cognitive deficits such as impairment of attention and short-term memory. Higher doses of Δ^9-THC are associated with anxiety, panic, confusion and disorientation in some users. Δ^9-THC can also provoke transient psychosis-like psychological phenomena in some healthy participants.

Oral Δ^9-THC is reported to cause impairment of driving skills in both driving simulators and on roads. Doses of 10 and 20 mg of Δ^9-THC increased standard deviation of lateral position – indicative of loss of road tracking control – and time taken to adapt speed – indicative of increased reaction times.

9.7 Dependence potential

Rapid and profound tolerance develops to numerous acute effects of Δ^9-THC following chronic administration to animals. Chronic administration of Δ^9-THC can induce physical dependence in laboratory animals as evidenced by withdrawal effects that can emerge spontaneously or be precipitated by the cannabinoid receptor antagonist, rimonabant.

Two studies in humans have demonstrated the development of tolerance to the self-reported effects of Δ^9-THC. These studies also reported withdrawal effects indicative of physical dependence. The symptoms of withdrawal that were observed included hyperactivity, increased salivation, irritability, marked changes in sleep patterns and restlessness. In one study, sleep disruption was found to persist for up to seven nights. Most withdrawal symptoms were alleviated within 96 hours or immediately if participants re-administered Δ^9-THC.

9.8 Abuse potential

One laboratory reported the successful intravenous self-administration of Δ^9-THC in squirrel monkeys, the rates of which were attenuated by the administration of rimonabant. Several other laboratories have failed to establish the self-administration of Δ^9-THC in animals.

Δ^9-THC has clear discriminative effects in several species, including rats, rhesus monkeys, mice and pigeons. Δ^9-THC-like discriminative effects are produced by other cannabinoids or cannabis preparations that have been reported to be cannabis-like in humans, including Δ^8-THC, cannabinol, hashish, CP55,940, WIN55,212-2, and an array of abused synthetic cannabinoids (for example, JWH-018, XLR-11, UR-144, AB-CHMINACA). CBD, however, does not produce such effects.

Oral administration of Δ^9-THC produces subjective effects that resemble those of cannabis. Humans readily distinguish the effects of oral Δ^9-THC as being cannabis-like and as different from alcohol or *d*-amphetamine. Furthermore, when orally administered or smoked Δ^9-THC is compared directly to cannabis administered via the same route, both Δ^9-THC and cannabis produce a similar profile of subjective effects including increased feelings of "drug effect", experience of a "drug high" and increased ratings of cannabis-like effects.

In controlled laboratory settings, oral self-administration of Δ^9-THC has been demonstrated; however, results suggest that it is a weak reinforcer at best. A multi-method review revealed little evidence that oral Δ^9-THC is used for non-medical purposes.

9.9 Therapeutic applications and extent of therapeutic use and epidemiology of medical use

Δ^9-THC or dronabinol has approval in a number of countries for indications including anorexia associated with weight loss in patients with acquired immunodeficiency syndrome (AIDS) and for nausea and vomiting associated with cancer chemotherapy in patients who do not gain adequate relief from conventional antiemetic treatment.

Δ^9-THC has been explored for other indications. For example, it has demonstrated at least partial effectiveness in decreasing neuropathic pain, reducing anxiety in patients with chronic pain, increasing weight gain in patients with anorexia nervosa, decreasing pain intensity and increasing patient satisfaction when given as an adjunct to opioids for chronic pain, reducing spasticity in patients with multiple sclerosis, and for improving tics (or a trend towards such improvement) in patients with Tourette syndrome.

9.10 Listing on the WHO Model List of Essential Medicines

Δ^9-THC (dronabinol) is not listed on the WHO EML (20th list) or the WHO Model List of Essential Medicines for Children (6th list).

9.11 Marketing authorizations (as a medicinal product)

Dronabinol (Marinol®) is supplied as round, soft gelatine capsules for oral use (AbbVie, Inc.), and Syndros is supplied as an oral solution (INSYS Therapeutics, Inc.).

9.12 Industrial use

Δ^9-THC has no legitimate industrial uses.

9.13 Non-medical use, abuse and dependence

Δ^9-THC does not appear to be abused. A multi-method review revealed little evidence that its oral formulation was used for non-medical purposes. Phenomena such as "doctor-shopping" or "script-chasing" (i.e. obtaining multiple prescriptions from multiple doctors for the same substance) are not common.

9.14 Nature and magnitude of public health problems related to misuse, abuse and dependence

Δ^9-THC does not appear to have caused a public health problem related to misuse, abuse or dependence. See section 9.13.

9.15 Licit production, consumption and international trade

Licit production and trade occur with the medicinal products mentioned in 9.11 (Marketing authorizations).

9.16 Illicit manufacture and traffic and related information

There are no data on the illicit manufacture of pure Δ^9-THC.

9.17 Current international controls and their impact

Dronabinol, the INN of (–)-*trans*-Δ^9-THC, and its stereochemical variants are included in Schedule II of the Convention on Psychotropic Substances of 1971.

9.18 Current and past national controls

Dronabinol is presumed to be controlled in all WHO Member States, except Uruguay where the production, sale and use of cannabis for medical or non-medical purposes was legalized in 2016.

9.19 WHO review history

Δ^9-Tetrahydrocannabinol (Δ^9-THC) and its stereochemical variants, with one variant being dronabinol ((–)-*trans*-Δ^9-THC), are currently listed in Schedule II of the 1971 Convention on Psychotropic Substances. Δ^9-THC was originally included in Schedule I of the 1971 Convention at the time of its adoption, together with its stereochemical variants.

- In 1989, the WHO ECDD recommended, based on the critical review of dronabinol ((–)-*trans*-Δ^9-THC) undertaken at its twenty-sixth meeting in 1988, that dronabinol be moved to Schedule II while keeping the other isomers and stereochemical variants in Schedule I.

WHO's proposal to transfer dronabinol to Schedule II was rejected by the CND at its eleventh special session in 1990.

- At its twenty-seventh meeting in 1990, the ECDD carried out a critical review of updated information on Δ^9-THC. It recommended that Δ^9-THC and stereochemical variants be rescheduled from Schedule I to Schedule II of the 1971 Convention. This was done to avoid a distinction between Δ^9-THC and its stereochemical variants leading to their placement under different schedules and to prevent potential legal and forensic analytical problems. This recommendation was adopted by the CND at its thirty-fourth session in 1991.
- At the thirty-third ECDD meeting in 2002, Δ^9-THC was again critically reviewed. The Committee recommended that dronabinol and its stereochemical variants be rescheduled from Schedule II to Schedule IV of the 1971 Convention. However, no further procedural steps were taken, i.e. there was no formal communication of this recommendation from WHO to the CND.
- At its thirty-fourth meeting in 2006, the ECDD carried out an assessment of an updated critical review report on dronabinol. The Committee concluded that although dronabinol constitutes a substantial risk to public health, this risk is different from those related to cannabis – controlled under the 1961 Convention. The substance was found to have moderate therapeutic usefulness, with a likelihood of an increase in its medical use in light of continuing clinical research. Therefore, the Committee recommended that dronabinol and its stereochemical variants be rescheduled from Schedule II to Schedule III of the 1971 Convention.
- In March 2007, at its fiftieth session, the CND decided by consensus not to vote on the recommendation of the WHO ECDD to transfer dronabinol and its stereochemical variants from Schedule II to Schedule III of the 1971 Convention. Furthermore, the CND requested WHO, in consultation with the INCB, as appropriate, to undertake, for consideration by the Commission, a review of dronabinol and its stereochemical variants when additional information became available (CND Decision 50/2).
- At its thirty-fifth meeting in 2012, the ECDD discussed the CND's recommendations of 2007. The Committee did not carry out a review of dronabinol, but reinstated the recommendation made at the thirty-fourth meeting of the ECDD to move dronabinol and its stereochemical variants from Schedule II to Schedule III of the 1971 Convention. The Committee decided that the previous ECDD

decision on dronabinol and its stereochemical variants should stand, since it was unaware of any new evidence that was likely to materially alter the scheduling recommendation made at its thirty-fourth meeting. This recommendation was communicated by the Director-General of WHO to the Secretary-General in October 2012.

- The CND reconsidered this issue in March 2013 at its fifty-sixth session. Concern was expressed by several delegations that, despite the recommendation received from WHO, no decision had yet been taken by the Commission to reschedule dronabinol and its stereochemical variants. A number of delegations noted that they were not able to support the recommendation made by WHO regarding dronabinol, as that recommendation could hinder efforts to prevent international cannabis abuse and could send a confusing message regarding the harm associated with the use of cannabis. It was suggested that WHO should continue to review dronabinol.
- In March 2014, based on the recommendation made by the ECDD at its thirty-fifth meeting in 2012, the CND voted against moving dronabinol and its stereochemical variants from Schedule II to Schedule III of the 1971 Convention.
- At its thirty-eighth meeting in 2016 the ECDD requested that Δ^9-tetrahydrocannabinol (Δ9-THC) be pre-reviewed along with cannabis and cannabis resin, extracts and tinctures of cannabis, cannabidiol (CBD) and isomers of THC.
- At its fortieth meeting in June 2018, the ECDD evaluated the above-mentioned pre-reviews and recommended to proceed to the critical reviews of cannabis and cannabis resin, extracts and tinctures of cannabis, Δ^9-THC and isomers of THC at the forty-first meeting in November 2018.

9.20 Recommendation

Δ^9-tetrahydrocannabinol (Δ^9-THC) refers to four stereoisomers of Δ^9-THC. One of these stereoisomers is found in the cannabis plant and is also known by the INN dronabinol; it has recognized therapeutic uses.

Chronic administration of Δ^9-THC can induce physical dependence in laboratory animals and in humans. This has been demonstrated by the presence of withdrawal effects in animals and human subjects. The subjective effects of Δ^9-THC when administered orally resemble those of cannabis. However, there is little evidence that oral Δ^9-THC is used for non-medical purposes so as to cause a public health problem.

Δ^9-THC (dronabinol) has approval in a number of countries for therapeutic indications including anorexia associated with weight loss in patients with AIDS and for nausea and vomiting associated with cancer chemotherapy. Δ^9-THC (dronabinol) is routinely administered orally.

Δ^9-THC and its stereoisomers are listed in Schedule II of the Convention on Psychotropic Substances of 1971. In previous ECDD reviews, Δ^9-THC, and especially dronabinol, had been considered in a synthetic form as a pharmaceutical preparation.

However, the Committee recognized that Δ^9-THC, in particular, its active and naturally occurring stereoisomer, dronabinol, today also refers to the main psychoactive component of cannabis and cannabis-derived psychoactive products. In this form, dronabinol produces similar ill-effects, dependence and abuse potential to cannabis, which is placed under the 1961 Single Convention. A substance liable to similar abuse and productive of similar ill-effects to those of a substance already scheduled within the 1961 Convention would normally be scheduled in the same way as that substance.

The Committee concluded that there is sufficient information to recommend a critical review of Δ^9-THC at a future ECDD meeting in order to address the appropriateness of its placement within the Conventions.

10. Tetrahydrocannabinol (Isomers of THC)

10.1 Substance identification

The isomers of THC include six molecules that are identified in Schedule I of the Convention on Psychotropic Substances of 1971 including their stereochemical variants. These molecules with their chemical designations are listed in Table 1. This entry in the schedules does not include delta-9-tetrahydrocannabinol (dronabinol).

Table 1.
Molecules of THC with their chemical designations

Molecule	Substance identification
delta-6a(10a)-THC	7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
delta-6a(7)-THC	(9R,10aR)-8,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
delta-7-THC	(6aR,9R,10aR)-6a,9,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
delta-8-THC	(6aR,10aR)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
delta-10-THC	6a,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol
delta-9(11)-THC	(6aR,10aR)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6H-dibenzo[b,d]pyran-1-ol

10.2 Chemistry

Methods have been developed for synthesis of these isomers.

10.3 Ease of convertibility into controlled substances

It is possible to convert (–)-*trans*-Δ^8-THC into (–)-*trans*-Δ^9-THC in laboratory facilities.

10.4 General pharmacology

Δ^8-THC and $\Delta^{9(11)}$-THC each produce Δ^9-THC-like pharmacological effects in some animal models, whereas Δ^{10}-THC does not. In humans, Δ^8-THC is active when administered via several different routes, for example, oral, intravenous and inhalation. One stereoisomer of $\Delta^{6a,10a}$-THC ((S)-(–)- $\Delta^{6a,10a}$-THC) has psychoactive effects in humans similar to those of Δ^9-THC but is quantitatively less potent (1:3 to 1:6), while the (R)-(+)-$\Delta^{6a,10a}$-THC, a second stereoisomer was inactive. $\Delta^{6a(10a)}$-THC also produces Δ^9-THC-like effects when smoked, but the effects are less marked and have a shorter duration than those of Δ^9 THC. None of the other isomers have been tested in humans.

10.5 Toxicology

Very little information exists on the toxicology of these isomers. There are limited preclinical toxicity data, and the isomers have not been administered to humans for extended periods. Limited toxicology data are available only for Δ^{8}-THC, $\Delta^{6a,10a}$-THC and $\Delta^{9\,(11)}$-THC.

The oral median lethal dose (LD50) of Δ^{8}-THC in rats is 2000 mg/kg. Subcutaneous administration of Δ8-THC (up to 40 mg/kg) in rats prior to conception or during gestation did not have teratogenic effects. From the limited data available, Δ^{8}-THC does not appear to be mutagenic.

In mice, intravenous administration of 200 mg/kg $\Delta^{6a,10a}$-THC did not promote mortality. $\Delta^{6a,10a}$-THC does not reduce locomotor activity in mice.

When administered to humans via smoking, $\Delta^{6a,10a}$-THC has much lower psychoactivity than Δ^{9}-THC. The effects of smoking 15 mg $\Delta^{6a,10a}$-THC are less marked and have a shorter duration than a 12-mg dose of Δ^{9}-THC. $\Delta^{6a,10a}$ THC produced symptoms of light-headedness, numbness and tingling in the extremities and face, fatigue, cold perspiration, drowsiness and a feeling of relaxation. Impairment of thinking and the perception of time were less pronounced than with Δ^{9}-THC.

$\Delta^{9\,(11)}$-THC has an intravenous LD50 of 93 mg/kg in mice, which is double that found for Δ^{9}-THC.

10.6 Adverse reactions in humans

Only Δ^{8}-THC and $\Delta^{6a,10a}$-THC have been tested in humans. The acute intoxicating effects of these molecules are similar in quality but less potent than acute doses of Δ^{9}-THC. These molecules are not available for medical or non-medical purposes, so little is known about their adverse effects in humans.

10.7 Dependence potential

No reports are available of studies that have assessed the potential of THC isomers for inducing physical dependence in laboratory animals or humans

10.8 Abuse potential

Data on the specific abuse potential of the six isomers are sparse. Of the six THC isomers reviewed here, preclinical assessment of abuse liability of three isomers has been evaluated for their pharmacological similarity to Δ^{9}-THC, particularly in discrimination tests for substitution of the Δ^{9}-THC discriminative stimulus. $\Delta^{9(11)}$-THC demonstrated the cannabimimetic tetrad of characteristic Δ^{9}-THC-like effects, including suppression of locomotor activity, hypothermia, antinociception and ring immobility in animal studies, and was found to be several-fold less potent than Δ^{9}-THC for each dependent measure. It has also been shown to produce Δ^{9}-THC-like discriminative effects but at lower potency than Δ^{9}-THC.

Δ^8-THC also produces Δ^9-THC-like discriminative effects but at lower potency, and induces the characteristic tetrad of Δ^9-THC-like effects as described in the paragraph above.

Δ^{10}-THC, the third isomer that has been tested, did not produce Δ^9-THC-like discriminative effects.

Few studies addressing the abuse potential of THC isomers have been undertaken in humans. The information on abuse potential of THC isomers is based primarily on early observational studies in which their subjective or physiological effects in human volunteers were compared to those reported following Δ^9-THC administration. Of the six THC isomers reviewed here, only Δ^8-THC and $\Delta^{6a,10a}$-THC have been tested in humans. The acute intoxicating effects of these substances are similar to those of Δ^9-THC, but they are less potent.

10.9 Therapeutic applications, extent of therapeutic use and epidemiology of medical use

No medical or veterinarian use of these isomers has been reported.

10.10 Listing in the WHO Model List of Essential Medicines

None of the isomers is listed in the WHO EML (20th list) or the WHO Model List of Essential Medicines for Children (6th list).

10.11 Marketing authorizations (as a medicinal product)

There are no known marketing authorizations for these isomers.

10.12 Industrial use

These isomers have no known legitimate industrial use.

10.13 Non-medical use, abuse and dependence

No case reports of abuse or dependence relating to the use of these isomers were available. Between 1995 and 2014, one study reported a change in the potency of seized cannabis products in the USA. The data showed that before 2009, Δ^8-THC had not been detected in cannabis seizures in the USA. A gradual increase in Δ^8-THC content was observed from 0.01% to 0.07% in 2014. However, compared to Δ^9-THC, Δ^8-THC content was lower by a factor of 10, and increasing potency of Δ^8-THC did not appear to impact Δ^9-THC concentrations.

10.14 Nature and magnitude of public health problems related to misuse, abuse and dependence

These isomers appear not to have been available for use. At present no public health problems (for example, driving under the influence of drugs or comorbidities) have been associated with their use.

10.15 Licit production, consumption and international trade

There is no known licit production of these isomers.

10.16 Illicit manufacture and traffic and related information

There appears to be no illicit manufacture or traffic of these isomers.

10.17 Current international controls and their impact

These isomers are included in Schedule I of the Convention on Psychotropic Substances of 1971.

10.18 Current and past national controls

The extent to which the isomers of THC, other than Δ^9-THC, are controlled depends on the exact wording of the legislation in each jurisdiction.

10.19 WHO review history

The isomers of Δ^9-THC have never been subject to a critical review or pre-review by the ECDD.

10.20 Recommendation

There are currently six isomers of THC listed in Schedule I of the 1971 Convention. Of the six THC isomers reviewed here, the abuse potential of only two, Δ^8-THC and $\Delta^{6a,10a}$-THC, have been evaluated in a few human studies. These studies found that the acute intoxicating effects of these substances are similar to those of Δ^9-THC, but they are less potent.

There are no reports that THC isomers induce physical dependence. There are no reported medical or veterinary uses of these isomers.

There is no evidence that any of these listed isomers are being abused or are likely to be abused so as to constitute a public health or social problem. However,

the Committee noted the potential difficulty of differentiating these six isomers (listed in Schedule 1 of the 1971 Convention) from Δ^9-THC (listed in Schedule II of the 1971 Convention) using standard methods of chemical analysis owing to their chemical similarities. The Committee further noted that this is an important factor to consider in the scheduling of these isomers.

The Committee concluded that there is sufficient information to recommend a critical review of the isomers of THC at a future ECDD meeting and to explore further the relevance of their current scheduling within the 1971 Convention.

11. Summary

The fortieth ECDD undertook a critical review of cannabidiol (CBD) and pre-reviews of cannabis plant and resin; extracts and tinctures of cannabis; Δ^9-tetrahydrocannabinol (Δ^9-THC); and isomers of THC. The following recommendations were made:

Cannabidiol

The Committee recommended that preparations considered to be pure CBD should not be scheduled within the International Drug Control Conventions.

Cannabis plant and resin

The Committee concluded that there is sufficient evidence to proceed to a critical review.

Extracts and tinctures of cannabis

The Committee concluded that there is sufficient evidence to proceed to a critical review.

Δ^9-THC

The Committee concluded that there is sufficient evidence to proceed to a critical review.

Tetrahydrocanabinol (Isomers of THC)

The Committee concluded that there is sufficient evidence to proceed to a critical review.

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References

1. Guidance on the WHO review of psychoactive substances for international control. Geneva: World Health Organization; 2010. (http://www.who.int/medicines/areas/quality_safety/GLS_WHORev_PsychoactSubst_IntC_2010.pdf).
2. 1961 Single Convention on Narcotic Drugs (https://www.unodc.org/pdf/convention_1961_en.pdf).
3. 1971 Convention on Psychotropic Substances (https://www.unodc.org/pdf/convention_1971_en.pdf).
4. Regulations for expert advisory panels and committees: Report by the Secretariat. Geneva: World Health Organization; 1998. (http://apps.who.int/iris/bitstream/handle/10665/79146/ee21.pdf?sequence=1&isAllowed=y).
5. 2018 World drug report. Vienna: United Nations Office on Drugs and Crime; 2018 (https://www.unodc.org/wdr2018/).
6. List of precursors and chemicals frequently used in the illicit manufacture of narcotic drugs and psychotropic substances. Vienna: International Narcotics Control Board; 2017.

SELECTED WHO PUBLICATIONS OF RELATED INTEREST

The Selection and Use of Essential Medicines
Report of the WHO Expert Committee, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children)
WHO Technical Report Series, No. 1006, 2017, ISBN 978 92 4 121015 7 (604 pages)

WHO Expert Committee on Drug Dependence
Thirty-eighth report
WHO Technical Report Series, No. 1005, 2017, ISBN 978 92 4 1210140 (44 pages)

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This report presents the recommendations of the fortieth WHO Expert Committee on Drug Dependence (ECDD). The ECDD is responsible for the assessment of psychoactive substances for possible scheduling under the International Drug Control Conventions. The ECDD reviews the therapeutic usefulness, the liability for abuse and dependence, and the public health and social harm of each substance. The ECDD will advise the Director-General of WHO, to schedule or to amend the scheduling status of a substance. The Director-General will, as appropriate, communicate the recommendations to the Secretary-General of the United Nations, who will in turn communicate the advice to the Commission on Narcotic Drugs (CND).

The report summarizes the findings of the fortieth meeting, which was dedicated to the review of cannabis and its component substances. This included a critical review of cannabidiol and pre-reviews of cannabis plant and resin; extracts and tinctures of cannabis; Δ^9-tetrahydrocannabinol ((Δ^9-THC)); and isomers of THC. The Committee recommended that preparations considered to be pure cannabidiol should not be scheduled within the International Drug Control Conventions. The Committee concluded that there is sufficient evidence to proceed to a critical review of cannabis plant and resin; extracts and tinctures of cannabis; Δ^9-THC and isomers of Δ^9-THC.

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