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1018

# WHO Expert Committee on Drug Dependence

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Forty-first report



World Health  
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Forty-first report

This report contains the views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization



**World Health  
Organization**

WHO Expert Committee on Drug Dependence: forty-first report

(WHO Technical Report Series, No. 1018)

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# WHO Expert Committee on Drug Dependence

Geneva, Switzerland, 12–16 November 2018

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## Abbreviations

AIDS	acquired immunodeficiency syndrome
CND	Commission on Narcotic Drugs
DALY	disability-adjusted life years
ECDD	Expert Committee on Drug Dependence
EMP	Essential Medicines and Health Products
INCB	International Narcotics Control Board
INN	International Nonproprietary Name
NPS	new psychoactive substances
THC	tetrahydrocannabinol
UNODC	United Nations Office on Drugs and Crime
US	United States
WHO	World Health Organization
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

## Introduction

The forty-first meeting of the World Health Organization (WHO) Expert Committee on Drug Dependence (ECDD) was held from 12–16 November 2018 at WHO headquarters in Geneva, Switzerland.

### Open session

Prior to the start of the ECDD meeting, an open session was held to afford the Expert Committee the opportunity 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, both of the Access to Medicines, Vaccines and Pharmaceuticals Cluster, WHO.

Dr Simão noted that the open session was an opportunity for attendees to share with the Expert Committee members their views and experiences relating to the benefits and risks of the substances under review. She described how the Commission on Narcotic Drugs (CND) in March 2019 was an important milestone to assess the implementation of the 2009 Political Declaration and Plan of Action and the 2016 United Nations General Assembly Special Session on the World Drug Problem (UNGASS) commitments.

She asserted that there were two major challenges in tackling the world drug problem: first in preventing and managing the harm related to drug use. Half a million people die each year as a result of drug use. Most of these deaths are due to communicable diseases or overdoses, and are therefore preventable. The second challenge is ensuring access to controlled medicines for those who need them. Many people in some of the poorest countries in the world suffer from treatable pain because they do not have access to the medicines they need. Both of these challenges should be addressed by positioning public health and human rights at the centre of the international drug policy dialogue. In May 2018 the World Health Assembly approved WHO's new strategy: the thirteenth Global Programme of Work, which is a suitable framework to address the world drug problem from the health sector's perspective.

Dr Simão went on to describe WHO's main areas of work related to the world drug problem. Through the work of the ECDD, WHO continues to monitor psychoactive substances that are prevalent and harmful. In November 2017, the WHO ECDD recommended that a number of opioids be placed under international control. These opioids have no medical value but cause severe harm to public health. This included a recommendation that carfentanil, a tranquillizer

for large animals, which has been used in the production of street drugs, be placed under the strictest level of international control. The CND unanimously accepted these recommendations and these dangerous substances are now under international control.

In June 2018, the ECDD critically reviewed cannabidiol. The ECDD recommended that preparations considered to be pure cannabidiol should not be placed under international control because it was not found to have psychoactive properties or the potential for abuse or dependence.

Dr Simão described the substances being reviewed at the forty-first meeting of the ECDD, including tramadol and pregabalin. She mentioned that the forty-first meeting was the first time that WHO would carry out a formal critical review of cannabis and cannabis components together.

The objective of the Committee was to review the current evidence of harm and medical use of cannabis and its components. The Committee needed to ensure that recommended international control measures are relevant to protect health and that they do not act as barriers to access to cannabis-based medicines. Dr Simão emphasized that it is not the Committee's mandate to issue recommendations on matters other than the level of control of cannabis, such as legalization of cannabis.

Dr Simão described WHO's work in improving access to opioids for the treatment of pain, particularly in low-income countries that do not have adequate access to opioid analgesics for pain relief and palliative care. Very little of the world's morphine supply is distributed to low- and middle-income countries, meaning that millions of patients and their families in some of the poorest countries of the world are left to suffer due to treatable pain. As part of its commitment to achieving universal health coverage, WHO works to ensure that opioid analgesics and other controlled medicines are available to all people who need them to reduce their pain and suffering.

Dr Simão welcomed Member States, civil society groups, the private sector and other non-state actors' active contribution to support the evidence-based decision-making processes of the ECDD. She also acknowledged the close collaboration and dialogue with the United Nations Office on Drugs and Crime (UNODC) and the International Narcotics Control Board (INCB).

Dr Gilles Forte, Coordinator, Access to Medicines, Vaccines and Pharmaceuticals Cluster, went on to describe the role and mandate of the ECDD with respect to the international drug control conventions.

Presentations relevant to the agenda of the forty-first meeting of the ECDD were then accepted from the following participants:

- Richard Dart, Rocky Mountain Poison & Drug Center, USA
- Bien Matawaran, University of Santo Tomas, the Philippines
- Christa Cepuch, Médecins San Frontières, Switzerland

- Ebtesam Ahmed, International Association for Hospice and Palliative Care, USA
- Mahmoud Elhabiby, Ministry of Health, Egypt
- Silvia Allende Perez, Instituto Nacional de Cancerologia, Mexico
- Ernest Yorke, Korle-Bu Teaching Hospital, Ghana
- Ramani Vijayan Sannasi, University of Malaya, Malaysia
- Kelly Dunn, Johns Hopkins School of Medicine, USA
- Axel Klein, ACK Consultants, England
- Christopher Hallam, International Drug Policy Consortium, England
- Francis D'Ambrosio, D'Ambrosio Medical Group, USA
- Zaffalon Luciana, Brazilian Drug Policy Platform, Brazil
- Kenzi Riboulet Zemouli, FAAAT, Spain
- Koichi Maeda, Japan Medical Marijuana Association, Japan

## Closed session

### Welcoming remarks

The meeting resumed with the closed session. Dr Mariângela Simão welcomed 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. She reminded participants that they were acting in their personal capacities and not as representatives of their governments.

### Statement of confidentiality

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 document, 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. Mr Quirin also reminded participants of the confidentiality of the ECDD's deliberations.

## 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 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 several disclosures and sought the advice of the Office of Compliance, Risk Management and Ethics on addressing them.

The disclosed interests were considered by the Secretariat of the forty-first 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.

## Election of chairperson, co-chairperson and rapporteur

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.

# 1. Update on priorities from international agencies

## 1.1 United Nations Office on Drugs and Crime (UNODC)

Mr Justice Tetley made a statement on behalf of the UNODC. Scheduling of substances under the three international drug control conventions continues to be a cornerstone of the rule-based system of ensuring access to substances for medical and scientific use, while preventing their abuse.

UNODC's role in scheduling has been to facilitate Member States' understanding of the procedures, and the scientific and technical reasons behind the recommendations of the treaty bodies. This is vital to ensuring effective implementation of scheduling decisions. UNODC continues to find value in engaging in the risk assessments carried out by WHO with regard to the 1961 and 1971 Conventions, and the International Narcotics Control Board (INCB) with regard to the 1988 Conventions, with support from their respective scientific advisory groups or expert panels, as appropriate and where possible.

Since 2015, the CND has taken decisions to schedule 39 substances under the 1961 and 1971 Conventions, and to schedule two precursors of fentanyl and its analogues under the 1988 Convention.

Mr Tetley then explained how support is provided to Member States in the implementation of these decisions. A supplement of the *Multilingual dictionary of narcotic drugs and psychotropic substances under international control* (5) and an addendum to the manual on *Clandestine manufacture of substances under international control* (6), were published to cover the 10 substances scheduled by the Commission in 2017. In 2018, 282 national drug testing laboratories from 86 countries worldwide participated in the biannual UNODC International Collaborative Exercises, which assist laboratories to continuously monitor their performance on a global scale and take corrective actions, where required. The exercises included analysis of some recently scheduled substances. As part of the additional support offered to laboratories under the programme, chemical reference standards and manuals on recommended laboratory methods of analysis of substances under international control were provided. These included *Recommended methods for the identification and analysis of fentanyl and its analogues in biological specimens* (7) and *Guidelines on use of handheld Raman field identification devices for drugs* (8).

The UNODC Early Warning Advisory is actively monitoring more than 850 new psychoactive substances (NPS), reported in 116 countries and territories. It gathers valuable evidence for the identification of the most harmful, persistent and prevalent NPS. Since September 2018, this has been made possible through collaboration with the International Association of Forensic Toxicologists and some national agencies to collect toxicology data.

With more than 20 000 reports on NPS, the Early Warning Advisory will continue to inform prioritization of substances for action by the treaty bodies. In addition, the biannual Threat Assessment Reports should ensure early identification and anticipation of threats, the timely reduction of associated risks, and support to enable Member States and the international community to implement appropriate supply reduction and prevention strategies. The biannual “Global SMART update” series continued to raise awareness of the way that NPS transform synthetic drug markets, the role of non-scheduled fentanyl analogues and benzodiazepines in the opioid crisis, and the risks associated with the continuing expansion of the methamphetamine markets globally.

On 25 June 2017, UNODC launched an integrated strategy for a timely and comprehensive organization-wide response to the global opioid crisis. The strategy includes: coordinating the international response; promoting early warning mechanisms; reducing the supply of opioids for nonmedical use; ensuring access to opioids for medical and scientific use; and promoting prevention and treatment programmes.

Significant events under the strategy to leverage interagency cooperation included the sixth UNODC-WHO expert consultation on NPS (24–25 September 2018, in Switzerland), which focused on the challenges posed by the nonmedical use of synthetic opioids. UNODC, in partnership with INCB and WHO, planned an intergovernmental expert meeting in December 2018 in Vienna, Austria. The aim was to provide an opportunity to learn more about synthetic opioids and propose core elements for responding to the challenges posed by their nonmedical use.

UNODC will be working closely with national, regional and international partners to develop a comprehensive toolkit for assisting Member States in addressing the synthetic drugs issue. The wide-ranging scope of the toolkit will cover, for example, precursor control, national legislation for class-wide scheduling, forensic capacity, disposal of chemicals used in the illicit manufacture of drugs, and access to controlled substances for medical and scientific purposes. UNODC expected to launch this toolkit in March 2019.

As WHO continues its treaty function of evaluating substances and presenting recommendations for the consideration of the Commission on Narcotic Drugs, UNODC is confident that the rule-based international system of control will continue to benefit from the best available science and ensure a robust and relevant international order.

## **1.2 International Narcotics Control Board (INCB)**

Professor Jallal Toufiq informed the Expert Committee about the role and functions of INCB. Established by the 1961 Single Convention on Narcotic Drugs, INCB consists of 13 members who are elected by the Economic and Social Council and

serve in their personal capacity. Three members with medical, pharmacological or pharmaceutical experience are elected from a list of candidates nominated by WHO and 10 members are elected from a list of candidates nominated by governments.

In the update, Professor Toufiq highlighted the main messages from the annual report of INCB and its thematic chapter on treatment, rehabilitation and social reintegration of people affected by drug use disorders. Treatment of drug dependence is highly cost-effective as well as being much less expensive than criminal justice interventions, and the report emphasized that treatment of drug dependence should be seen as an element of the right to health.

Professor Toufiq also stressed the importance of collaboration between INCB and WHO and acknowledged the valuable support of WHO for the activities of the INCB Learning Project. This project provides specialized training to competent national authorities on the regulatory control and monitoring of licit trade in narcotic drugs, psychotropic substances and precursor chemicals.

Referring to the risks of long-term opioid use and the consumption of opioid analgesics, Professor Toufiq noted the steady increase in the consumption of these drugs in some high-income countries. In this regard, INCB encouraged the adoption of measures to promote the rational prescribing of medicines containing narcotics and psychotropic substances, to train authorities and health care professionals, and educate the public about their appropriate use.

While opioids were overused in a few countries, most countries in the world did not have adequate access to opioid analgesics. More had to be done to close this global pain divide and ensure adequate access to opioid analgesics in countries with low levels of consumption. Addressing this gap would include ensuring access to internationally controlled drugs in emergency situations and improving availability of these drugs for the treatment of opioid dependence.

### 1.3 WHO

Ms Wil de Zwart, Technical Officer, Access to Medicines, Vaccines and Pharmaceuticals Cluster, provided the Expert Committee with an update on the activities of the Cluster.

In 2017 the World Health Assembly (WHA70), having considered the report of the Secretariat, endorsed a Decision requesting the Director-General to continue efforts to improve coordination and collaboration of WHO with UNODC and INCB, within their existing mandates, in addressing and countering the world drug problem. Moreover, the World Health Assembly requested the Director-General to report on the implementation of this Decision to the seventy-first, seventy-third and seventy-fifth World Health Assemblies, and to continue to keep the CND appropriately informed of relevant programmes and progress in accordance with its treaty-based mandates.

The ECDD plays a crucial role in executing WHO's mandate within the international drug control conventions by reviewing psychoactive substances to determine whether they should be placed under international control. The Expert Committee reviews the most prevalent and harmful psychoactive substances. To decide on the prioritization of psychoactive substances to be reviewed by the ECDD, data are collected from UNODC, INCB and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), in particular from their early warning systems. Other information sources include Member States, institutions such as the Uppsala Monitoring Centre for International Drug Monitoring and user forums. Scientific data on toxicology, pharmacology and dependence relating to the potential substances for review are collected, including data on substances under surveillance from previous ECDD meetings.

Until 2014, the ECDD convened once every two years. Since 2014, however, the Committee has met annually, and in 2018 it met twice. The more intensive pace of work of the ECDD is a response to the increasing number and variety of NPS that have entered the drug markets in the past decade. Although there are indications that the growth in the number of NPS has slowed down, the new substances seem to be more potent and thus more dangerous to health and they have spread among a broad range of user groups.

To facilitate the review of a large volume of substances by the ECDD, WHO has formally established an Advisory Group. The Advisory Group will support and prepare the work of the ECDD, particularly in the process of prioritizing substances for pre-review or critical review. It will meet at least twice a year.

WHO is currently developing a system of surveillance and health alerts for substances that pose substantial or serious risks to public health. It focuses on substances for which scarce evidence or evidence that is of weak scientific quality means that the requirements for a formal review by ECDD and/or for scheduling cannot be met.

The surveillance system is complementary to the ECDD review process. It aims at disseminating information on health risks posed by harmful substances, particularly NPS, and at communicating rapidly to countries on the dangers associated with specific NPS. In addition to health risks, the surveillance system will provide information on prevention and treatment interventions. WHO collaborates in this initiative with other international and regional organizations such as UNODC, INCB and EMCDDA, and health authorities of Member States.

WHO works closely with UNODC and INCB in addressing the world drug problem. On 24 and 25 September 2018 WHO hosted the fifth WHO-UNODC Expert Consultation on New Psychoactive Substances, which focused specifically on the nonmedical use of opioids. A trend towards increasing nonmedical use of opioids, both medicines and NPS with opioid effects, such as fentanyl analogues, has recently been observed. Several of these substances

are extremely potent and harmful and this is a great concern for public health and law enforcement authorities in many countries. More than 50 experts from countries and organizations in Africa, Asia, Europe, the Middle East, and North and South America, discussed current challenges and solutions from the supply and demand sides to be implemented at country, regional and global level.

In line with the international drug control conventions, the WHO approach is to strive for policies and programmes that ensure access to essential controlled medicines for all people in need while minimizing misuse or diversion of these medicines. As part of its standard-setting mandate, WHO carries out biannual reviews of the efficacy and safety of medicines, and updates the WHO Model List of Essential Medicines (EML) accordingly. A number of controlled medicines are included in the WHO EML and are considered essential to alleviate pain and suffering, enable surgery, treat mental health conditions, support dignified and comfortable end-of-life care, help people to overcome addiction and to save lives.

The importance of access to controlled medicines for public health has also been emphasized in several World Health Assembly resolutions. These resolutions reflect Member States' commitment to access to controlled medicines and also provide WHO with a strong mandate for supporting Member States' efforts to remove barriers to access to these medicines. WHO has recently produced guidelines for the management of persisting pain in children and for the management of cancer pain in adolescents and adults. WHO is supporting countries in the assessment of availability and prices of medicines, the development of balanced policies and regulations, as well as improved quantification, and prescribing and use of medicines.

Dr Vladimir Poznyak, Coordinator, Management of Substance Abuse of the Department of Mental Health and Substance Abuse provided an update on the work on the eleventh revision of the International Classification of Diseases (ICD) with regard to disorders and health conditions due to psychoactive substance use, and plans for an update of WHO terminology for alcohol and drugs.

## 2. 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 Expert 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 either 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, following consideration of a pre-review, the Committee may decide to progress to a critical review during the same meeting.

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.

## 3. Fentanyl analogues

### 3.1 Para-fluoro-butyrylfentanyl

#### Substance identification

*Para*-fluoro-butyrylfentanyl (*N*-(4-fluorophenyl)-*N*-[1-(2-phenylethyl)piperidin-4-yl]butanamide) is a synthetic analogue of the opioid analgesic fentanyl. Samples obtained from seizures and from other sources suggest that *para*-fluoro-butyrylfentanyl is available in the form of a powder, tablet, nasal spray and a preparation for vaping.

#### WHO review history

*Para*-fluoro-butyrylfentanyl has not been previously pre-reviewed or critically reviewed by the WHO ECDD. A direct critical review was proposed based on information brought to WHO's attention that *para*-fluoro-butyrylfentanyl poses a serious risk to public health and has no recognized therapeutic use.

#### Similarity to known substances and effects on the central nervous system

*Para*-fluoro-butyrylfentanyl has a higher affinity to  $\mu$ -opioid receptors than to  $\kappa$ - and  $\delta$ -opioid receptors and has been shown to act as a partial agonist at the  $\mu$ -opioid receptor. In animals, it produces typical opioid effects, including analgesia, with a potency between that of morphine and fentanyl. In cases of non-fatal intoxication in humans, *para*-fluoro-butyrylfentanyl has produced signs and symptoms such as disorientation, slurred speech, unsteady gait, hypotension and pupil constriction that are consistent with an opioid mechanism of action.

*Para*-fluoro-butyrylfentanyl can be readily converted to its isomer *para*-fluoro-isobutyrylfentanyl (*N*-(4-fluorophenyl)-2-methyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide), which is an opioid listed in Schedule I of the 1961 Single Convention on Narcotic Drugs.

#### Dependence potential

There are no studies of the dependence potential of this substance in humans or laboratory animals. However, based on its mechanism of action, *para*-fluoro-butyrylfentanyl would be expected to produce dependence similar to other opioid drugs.

#### Actual abuse and/or evidence of likelihood of abuse

No controlled studies of the abuse potential of *para*-fluoro-butyrylfentanyl have been reported and there is very little information on the extent of its abuse. The substance has been detected in biological samples obtained in cases of fatal and

non-fatal intoxication. Fatalities have been reported in some countries where the compound has been identified in biological fluids in combination with other drugs. There have also been cases where death has been attributed to the effects of *para*-fluoro-butyrylfentanyl.

### Therapeutic usefulness

*Para*-fluoro-butyrylfentanyl is not known to have any therapeutic uses.

### Recommendation

*Para*-fluoro-butyrylfentanyl is an opioid receptor agonist that has significant potential for dependence and likelihood of abuse. The limited evidence available indicates that it has adverse effects typical of opioids, which include the potential to cause death due to respiratory depression. *Para*-fluoro-butyrylfentanyl has caused substantial harm and has no therapeutic use. It is liable to similar abuse and produces similar ill-effects to those of many other opioids placed in Schedule I of the 1961 Single Convention on Narcotic Drugs:

- **Recommendation:** The Committee recommended that *para*-fluoro-butyrylfentanyl (*N*-(4-fluorophenyl)-*N*-[1-(2-phenylethyl)piperidin-4-yl]butanamide) be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

## 3.2 Para-methoxy-butyrylfentanyl

### Substance identification

*Para*-methoxy-butyrylfentanyl (*N*-(4-methoxyphenyl)-*N*-[1-(2-phenylethyl)piperidin-4-yl]butanamide) is a synthetic analogue of the opioid analgesic fentanyl. Samples obtained from seizures and from other sources suggest that *para*-methoxy-butyrylfentanyl is available in the form of a powder, tablet and a nasal spray.

### WHO review history

*Para*-methoxy-butyrylfentanyl has not been previously pre-reviewed or critically reviewed by the WHO ECDD. A critical review was proposed based on information brought to WHO's attention that *para*-methoxy-butyrylfentanyl poses serious risk to public health and has no recognized therapeutic use.

### Similarity to known substances and effects on the central nervous system

*Para*-methoxy-butyrylfentanyl has a higher affinity to  $\mu$ -opioid receptors than to  $\kappa$ - and  $\delta$ -opioid receptors and has been shown to act as a partial agonist at

the  $\mu$ -opioid receptor. In animals, it produces typical opioid effects including analgesia and, in some animal studies, it had a potency higher than that of morphine and close to that of fentanyl.

Reported clinical features of intoxication involving *para*-methoxy-butyrylfentanyl included the typical opioid effects of reduced level of consciousness, respiratory depression and pupil constriction. In some cases, treatment with the opioid antagonist naloxone was shown to reverse the drug-induced respiratory depression. While this is consistent with an opioid mechanism of action, it should be noted that in all such cases at least one other opioid was present.

### Dependence potential

No studies of the dependence potential of this substance in humans or laboratory animals have been reported. However, based on its mechanism of action, *para*-methoxy-butyrylfentanyl would be expected to produce dependence similar to other opioid drugs.

### Abuse potential and/or evidence of likelihood of abuse

No controlled studies of the abuse potential of *para*-methoxy-butyrylfentanyl have been reported and very little information is available on the extent of its abuse. *Para*-methoxy-butyrylfentanyl has been detected in biological samples obtained from a limited number of cases of acute intoxication. Reported clinical features are consistent with opioid effects, including respiratory depression. However, in all of the documented cases of severe adverse events associated with use of *para*-methoxy-butyrylfentanyl, other fentanyl analogues were also detected and the role of *para*-methoxy-butyrylfentanyl is therefore not clear.

### Therapeutic usefulness

*Para*-methoxy-butyrylfentanyl is not known to have any therapeutic uses.

### Recommendation

The limited information available indicates that *para*-methoxy-butyrylfentanyl is an analogue of the opioid analgesic fentanyl. There is evidence of its use in a limited number of countries, with few reports of intoxication and no reports of death. In the cases of intoxication, the role of *para*-methoxy-butyrylfentanyl was not clear owing to the presence of other opioids. It has no therapeutic use. Currently, there is little evidence that *para*-methoxy-butyrylfentanyl is causing substantial harm that would warrant its placement under international control.

- **Recommendation:** The Committee recommended that *para*-methoxy-butyrylfentanyl (*N*-(4-methoxyphenyl)-*N*-[1-(2-phenylethyl)]

piperidin-4-yl]butanamide) be kept under surveillance by the WHO Secretariat.

### 3.3 Ortho-fluorofentanyl

#### Substance identification

*Ortho*-fluorofentanyl (*N*-(2-fluorophenyl)-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide) is a synthetic analogue of the opioid analgesic fentanyl. It has two positional isomers (*para*-fluorofentanyl and *meta*-fluorofentanyl).

#### WHO review history

*Ortho*-fluorofentanyl has not been previously pre-reviewed or critically reviewed by the WHO ECDD. A direct critical review was proposed based on information brought to WHO's attention that *ortho*-fluorofentanyl poses a serious risk to public health and has no recognized therapeutic use.

#### Similarity to known substances and effects on the central nervous system

Receptor binding data show that *ortho*-fluorofentanyl has a higher affinity to  $\mu$ -opioid receptors than to  $\kappa$ - and  $\delta$ -opioid receptors. No animal or human studies have been published in the scientific literature. However, the clinical features present in non-fatal cases of intoxication include characteristic opioid effects such as loss of consciousness, pupil constriction and respiratory depression. The effects of *ortho*-fluorofentanyl can be reversed by the administration of the opioid antagonist naloxone, further confirming its opioid agonist mechanism of action.

#### Dependence potential

No studies of the dependence potential of *ortho*-fluorofentanyl in humans or laboratory animals have been reported. However, based on its mechanism of action, it would be expected to produce dependence similar to other opioid drugs.

#### Actual abuse and/or evidence of likelihood of abuse

No animal or human studies are available to assess the abuse liability of *ortho*-fluorofentanyl. There is evidence of its use from several countries, including seizures in Europe and the United States. A number of confirmed fatalities have been reported associated with this substance (one in Europe and 16 in the United States since 2016). As a consequence of *ortho*-fluorofentanyl cross-reacting with standard fentanyl immunoassays, it is possible that deaths due to *ortho*-fluorofentanyl have been attributed to fentanyl and hence the number of recorded deaths due to *ortho*-fluorofentanyl may be an underestimate. Several

countries in different parts of the world have placed *ortho*-fluorofentanyl under national control.

### Therapeutic usefulness

*Ortho*-fluorofentanyl is not known to have any therapeutic use.

### Recommendation

*Ortho*-fluorofentanyl is an opioid receptor agonist that has the potential for dependence and is subject to abuse. The limited evidence available indicates that it produces typical opioid adverse effects that include the potential to cause death due to respiratory depression. *Ortho*-fluorofentanyl has caused substantial harm and has no therapeutic use. It is liable to similar abuse and produces similar ill-effects to those of many other opioids placed in Schedule I of the 1961 Single Convention on Narcotic Drugs:

- **Recommendation:** The Committee recommended that *ortho*-fluorofentanyl (*N*-(2-fluorophenyl)-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide) be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

## 3.4 Methoxyacetylfentanyl

### Substance identification

Methoxyacetylfentanyl (2-methoxy-*N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]acetamide) is a synthetic analogue of the opioid fentanyl. Samples obtained from seizures and from other sources suggest that methoxyacetylfentanyl is available in the form of powders, liquids and tablets.

### WHO review history

Methoxyacetylfentanyl has not been previously pre-reviewed or critically reviewed by the WHO ECDD. A critical review was proposed based on information brought to WHO's attention that methoxyacetylfentanyl poses a serious risk to public health and has no recognized therapeutic use.

### Similarity to known substances and effects on the central nervous system

Methoxyacetylfentanyl has a higher affinity to  $\mu$ -opioid receptors than to  $\kappa$ - and  $\delta$ -opioid receptors and has been shown to act as an agonist at the  $\mu$ -opioid receptor. In animals, it produces analgesia with a potency higher than that of morphine and close to that of fentanyl. The analgesia was blocked by the opioid antagonist naltrexone, confirming its opioid mechanism of action.

The most serious acute health risk is respiratory depression, which in the case of an overdose can lead to respiratory arrest and death. This is consistent with its opioid mechanism of action.

## Dependence potential

There are no studies of the dependence potential of this substance in humans or laboratory animals. However, based on its mechanism of action, methoxyacetylfentanyl would be expected to produce dependence similar to other opioid drugs.

## Actual abuse and/or evidence of likelihood of abuse

In the animal drug discrimination model of subjective drug effects, methoxyacetylfentanyl produced effects similar to those of morphine. It also decreased activity levels and both the discriminative and rate-decreasing effects were blocked by the opioid antagonist naltrexone. Based on its receptor action and these effects in animal models, it would be expected that methoxyacetylfentanyl would be subject to abuse in a manner comparable to that of other opioids.

There is evidence that methoxyacetylfentanyl has been administered by injection and by nasal insufflation of powder. A large number of seizures of this substance have been reported in Europe and the United States. A number of deaths have been reported in Europe and the United States following which methoxyacetylfentanyl was detected in postmortem samples. While other drugs were also present in most of these cases, methoxyacetylfentanyl was deemed the cause of death or a major contributor to death in a significant proportion of them. Several countries have placed methoxyacetylfentanyl under national control.

## Therapeutic usefulness

Methoxyacetylfentanyl is not known to have any therapeutic use.

## Recommendation

The Committee considered that methoxyacetylfentanyl is a substance with high abuse liability and dependence potential. It is an opioid agonist that is more potent than morphine and its use has contributed to a large number of deaths in different regions. It has no therapeutic use and it poses a significant risk to public health. The Committee considered that the evidence of its abuse warrants placement under international control.

- **Recommendation:** The Committee recommended that methoxyacetylfentanyl (2-methoxy-*N*-phenyl-*N*-[1-(2-phenylethyl)

piperidin-4-yl] acetamide) be added to Schedule I of the Single Convention on Narcotic Drugs of 1961.

### 3.5 Cyclopropylfentanyl

#### Substance identification

Cyclopropylfentanyl ((*N*-phenyl-*N*-1-(2-phenylethyl)-4-piperidyl) cyclopropanecarboxamide) is a synthetic analogue of the opioid fentanyl. Samples obtained from seizures and from other sources suggest that cyclopropylfentanyl is available in the form of powders, liquids and tablets.

#### WHO review history

Cyclopropylfentanyl has not been previously pre-reviewed or critically reviewed by the WHO ECDD. A critical review was proposed based on information brought to WHO's attention that cyclopropylfentanyl poses a serious risk to public health and has no recognized therapeutic use.

#### Similarity to known substances and effects on the central nervous system

Cyclopropylfentanyl has a higher affinity to the  $\mu$ -opioid receptor than to the  $\delta$ - and  $\kappa$ -opioid receptors. There is no further information on the actions and effects of cyclopropylfentanyl from controlled studies. Based on its role in numerous deaths (see below), it is reasonable to assume that cyclopropylfentanyl acts as a  $\mu$ -opioid receptor agonist similar to morphine and fentanyl.

#### Dependence potential

No preclinical or clinical studies have been published in the scientific literature concerning dependence on cyclopropylfentanyl. However, based on its mechanism of action, cyclopropylfentanyl would be expected to produce dependence similar to other opioid drugs.

#### Actual abuse and/or evidence of likelihood of abuse

Numerous seizures of cyclopropylfentanyl have been reported from different regions. In some countries, this substance has been among the most common fentanyl analogues detected in postmortem samples. In almost all of these cases, cyclopropylfentanyl was determined to have either caused or contributed to death, even in the presence of other substances.

#### Therapeutic usefulness

Cyclopropylfentanyl is not known to have any therapeutic use.

## Recommendation

The available evidence indicates that cyclopropylfentanyl has opioid actions and effects. It has been extensively trafficked and has been administered by several different routes. Its use has been associated with a large number of documented deaths, in most of which it was found to be the principal cause of death. Cyclopropylfentanyl has no known therapeutic use and has been associated with substantial harm.

- **Recommendation:** The Committee recommended that cyclopropylfentanyl (*N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]cyclopropanecarboxamide) be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

## 4. Synthetic cannabinoids

### 4.1 ADB-FUBINACA

#### Substance identification

ADB-FUBINACA (*N*-[(2*S*)-1-amino-3,3-dimethyl-1-oxobutan-2-yl]-1-[(4-fluorophenyl)methyl]-1*H*-indazole-3-carboxamide) is available as a powder, in solution or is sprayed on plant material that mimics the appearance of cannabis. It is sold as herbal incense or branded products under a variety of different names.

#### WHO review history

ADB-FUBINACA has not been previously pre-reviewed or critically reviewed by the WHO ECDD. A critical review was proposed based on information brought to WHO's attention that ADB-FUBINACA poses a serious risk to public health and has no recognized therapeutic use.

#### Similarity to known substances and effects on the central nervous system

ADB-FUBINACA is similar to other synthetic cannabinoid receptor agonists that are currently scheduled under the Convention on Psychotropic Substances of 1971. It binds to both the CB<sub>1</sub> and CB<sub>2</sub> cannabinoid receptors with full agonist activity as demonstrated by *in vitro* studies. The efficacy and potency of ADB-FUBINACA is substantially greater than that of  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC). Reported clinical features of intoxication include confusion, agitation, somnolence, hypertension and tachycardia, similar to intoxication with other synthetic cannabinoid receptor agonists.

#### Dependence potential

No controlled experimental studies examining the dependence potential of ADB-FUBINACA in humans or animals were available. However, based on its central nervous system action as a full CB<sub>1</sub> agonist, ADB-FUBINACA would be expected to produce dependence in a manner similar to or more pronounced than cannabis.

#### Actual abuse and/or evidence of likelihood of abuse

ADB-FUBINACA is sold and used as a substitute for cannabis. It is smoked (as preparations of drug components introduced onto plant material) or vaped (i.e. using an e-cigarette). Owing to the nature of synthetic cannabinoid products, users cannot tell which synthetic cannabinoid is contained in such products. Evidence from case reports in which ADB-FUBINACA has been detected in biological samples has demonstrated that use of this substance has contributed

to severe adverse reactions in humans, including death. However, in most cases it was noted that other substances, including other synthetic cannabinoids, were also present in the urine or blood samples taken following non-fatal and fatal intoxication and/or in the product used. Evidence of use has been reported from Asia, Europe and the United States. In recognition of its potential for abuse and associated harm, ADB-FUBINACA has been placed under national control in a number of countries in several different regions.

### Therapeutic usefulness

ADB-FUBINACA is not known to have any therapeutic use.

### Recommendation

ADB-FUBINACA is a synthetic cannabinoid receptor agonist that is administered by smoking plant material sprayed with the substance or inhaling vapour after heating. Its mode of action suggests the potential for dependence and the likelihood of abuse. Its use has been associated with a range of severe adverse effects, including death. These effects are similar to those produced by other synthetic cannabinoids that have the same mechanism of action as ADB-FUBINACA and which are placed in Schedule II of the Convention on Psychotropic Substances of 1971. ADB-FUBINACA has no therapeutic use.

- Recommendation: The Committee recommended that ADB-FUBINACA (N-[(2S)-1-amino-3,3-dimethyl-1-oxobutan-2-yl]-1-[(4-fluorophenyl)methyl]-1H-indazole-3-carboxamide) be added to Schedule II of the Convention on Psychotropic Substances of 1971.

## 4.2 FUB-AMB

### Substance identification

FUB-AMB (methyl (2S)-2-({1-[(4-fluorophenyl)methyl]-1H-indazole-3-carbonyl}amino)-3-methylbutanoate) is a synthetic cannabinoid that is also referred to as MMB-FUBINACA and AMB-FUBINACA. FUB-AMB is available as a powder, in solution or sprayed on plant material that mimics the appearance of cannabis. It is sold as herbal incense or branded products under a variety of different names.

### WHO review history

FUB-AMB has not been previously pre-reviewed or critically reviewed by the WHO ECDD. A critical review was proposed based on information brought to WHO's attention that FUB-AMB poses a serious risk to public health and has no recognized therapeutic use.

## Similarity to known substances and effects on the central nervous system

FUB-AMB is similar to other synthetic cannabinoid receptor agonists that are currently scheduled under the Convention on Psychotropic Substances of 1971. It binds to both the CB<sub>1</sub> and CB<sub>2</sub> cannabinoid receptors with full agonist activity as demonstrated by in vitro studies. The efficacy and potency of FUB-AMB is substantially greater than that of  $\Delta^9$ -THC and it has effects similar to those of other synthetic cannabinoids, including severe central nervous system depression.

## Dependence potential

No reports of controlled experimental studies examining the dependence potential of FUB-AMB in humans or animals were available. However, based on its central nervous system action as a full CB<sub>1</sub> agonist, FUB-AMB would be expected to produce dependence in a manner similar to or more pronounced than cannabis.

## Actual abuse and/or evidence of likelihood of abuse

Consistent with its CB<sub>1</sub> cannabinoid receptor agonist activity, FUB-AMB produces complete dose-dependent substitution for the discriminative stimulus effects of  $\Delta^9$ -THC when administered to mice by various routes. This suggests that it has abuse potential similar to that of  $\Delta^9$ -THC.

Use of FUB-AMB has been reported from Europe, New Zealand and the United States. It is smoked (as preparations of drug components introduced onto plant material) or vaped (i.e. using an e-cigarette). Owing to the nature of synthetic cannabinoid products, users cannot tell which synthetic cannabinoid is contained in such products.

FUB-AMB use was confirmed in case reports of a mass intoxication in the United States. The predominant symptom was severe central nervous system depression, resulting in markedly slowed behaviour and speech. It was reported that in New Zealand, there were at least 20 deaths related to the use of FUB-AMB. The amounts of FUB-AMB in confiscated products in New Zealand were found to be 2 to 25 times greater than those reported in the incident in the United States.

## Therapeutic usefulness

FUB-AMB is not known to have any therapeutic uses.

## Recommendation

FUB-AMB is a synthetic cannabinoid receptor agonist that is administered by smoking plant material sprayed with the substance or inhaling vapour after heating. Its mode of action suggests the potential for dependence and the likelihood of

abuse. Its use has been associated with a range of severe adverse effects including a number of deaths. Its mechanism of action and manner of use are similar to those of other synthetic cannabinoids placed in Schedule II of the Convention on Psychotropic Substances of 1971. FUB-AMB has no therapeutic use.

- **Recommendation:** The Committee recommended that FUB-AMB (methyl (2S)-2-({1-[(4-fluorophenyl)methyl]-1H-indazole-3-carbonyl}amino)-3-methylbutanoate) be added to Schedule II of the Convention on Psychotropic Substances of 1971.

### 4.3 ADB-CHMINACA

#### Substance identification

ADB-CHMINACA (*N*-[(2S)-1-amino-3,3-dimethyl-1-oxobutan-2-yl]-1-(cyclohexylmethyl)indazole-3-carboxamide) is a synthetic cannabinoid that is also referred to as MAB-CHMINACA. ADB-CHMINACA is available as a powder, in solution or sprayed on plant material that mimics the appearance of cannabis. It is sold as herbal incense or branded products with a variety of different names.

#### WHO review history

ADB-CHMINACA has not been previously pre-reviewed or critically reviewed by the WHO ECDD. A critical review was proposed based on information brought to WHO's attention that ADB-CHMINACA poses a serious risk to public health and has no recognized therapeutic use

#### Similarity to known substances and effects on the central nervous system

ADB-CHMINACA is similar to other synthetic cannabinoid receptor agonists that are currently scheduled under the Convention on Psychotropic Substances of 1971. It binds to both the CB<sub>1</sub> and CB<sub>2</sub> cannabinoid receptors with full agonist activity as demonstrated by in vitro studies. The efficacy and potency of ADB-CHMINACA is substantially greater than that of Δ<sup>9</sup>-THC and it is among the most potent synthetic cannabinoids studied to date. It has a profile of central nervous system-mediated effects similar to those of other synthetic cannabinoids. In mice, ADB-CHMINACA causes decreased locomotor activity in a dose-dependent fashion, with a rapid onset of action and long-lasting effects.

Signs and symptoms of intoxication associated with the use of ADB-CHMINACA have included tachycardia, unresponsiveness, agitation, combativeness, seizures, hyperemesis, slurred speech, delirium and sudden death. These are consistent with the effects of other synthetic cannabinoids.

## Dependence potential

No controlled experimental studies examining the dependence potential of ADB-CHMINACA in humans or animals were available. However, based on its central nervous system action as a full CB<sub>1</sub> agonist, ADB-CHMINACA would be expected to produce dependence in a manner similar to or more pronounced than cannabis.

## Actual abuse and/or evidence of likelihood of abuse

Consistent with its activity as a CB<sub>1</sub> cannabinoid receptor agonist, ADB-CHMINACA fully substituted for Δ<sup>9</sup>-THC in drug discrimination tests. This suggests that it has abuse potential similar to that of Δ<sup>9</sup>-THC.

Evidence of the use of ADB-CHMINACA has been reported from Europe, Japan and the United States, including cases of driving under the influence. It is smoked (as preparations of drug components introduced onto plant material) or vaped (i.e. using an e-cigarette). Owing to the nature of synthetic cannabinoid products, users cannot tell which synthetic cannabinoid may be contained within such products.

ADB-CHMINACA use was analytically confirmed in case reports of several drug-induced clusters of severe illness and death in the United States. In Europe, 13 deaths associated with analytically confirmed use of ADB-CHMINACA were reported between 2014 and 2016, and another death occurred in Japan.

## Therapeutic usefulness

ADB-CHMINACA is not known to have any therapeutic use.

## Recommendation

ADB-CHMINACA is a synthetic cannabinoid receptor agonist that is used by smoking plant material sprayed with the substance or inhaling vapour after heating. It has effects that are similar to those of other synthetic cannabinoid receptor agonists placed in Schedule II of the Convention on Psychotropic Substances of 1971. Its mode of action suggests the potential for dependence and the likelihood of abuse. There is evidence that ADB-CHMINACA has been associated with numerous cases of fatal and non-fatal intoxications in a number of countries. The substance causes substantial harm and has no therapeutic use.

- **Recommendation:** The Committee recommended that ADB-CHMINACA (*N*-[(2*S*)-1-amino-3,3-dimethyl-1-oxobutan-2-yl]-1-(cyclohexylmethyl)-1*H*-indazole-3-carboxamide) be added to Schedule II of the Convention on Psychotropic Substances of 1971.

## 4.4 CUMYL-4CN-BINACA

### Substance identification

CUMYL-4CN-BINACA (1-(4-cyanobutyl)-*N*-(2-phenylpropan-2-yl)-1H-indazole-3-carboxamide) is a synthetic cannabinoid. It is available as a powder, in solution or sprayed on plant material that mimics the appearance of cannabis. It is sold as herbal incense or branded products under a variety of different names.

### WHO review history

CUMYL-4CN-BINACA has not been previously pre-reviewed or critically reviewed by the WHO ECDD. A critical review was proposed based on information brought to WHO's attention that CUMYL-4CN-BINACA poses serious risk to public health and has no recognized therapeutic use.

### Similarity to known substances and effects on the central nervous system

CUMYL-4CN-BINACA is similar to other synthetic cannabinoid receptor agonists that are currently scheduled under the Convention on Psychotropic Substances of 1971. It binds to both the CB<sub>1</sub> and CB<sub>2</sub> cannabinoid receptors with full agonist activity as demonstrated by *in vitro* studies. The efficacy and potency of CUMYL-4CN-BINACA is substantially greater than that of  $\Delta^9$ -THC and it shares a profile of central nervous system-mediated effects with other synthetic cannabinoids. Data have shown that it produced hypothermia in mice in common with other CB<sub>1</sub> cannabinoid receptor agonists.

### Dependence potential

No controlled experimental studies examining the dependence potential of CUMYL-4CN-BINACA in humans or animals were available. However, based on its central nervous system action as a full CB<sub>1</sub> agonist, CUMYL-4CN-BINACA would be expected to produce dependence in a manner similar to or more pronounced than cannabis.

### Actual abuse and/or evidence of likelihood of abuse

Consistent with its CB<sub>1</sub> cannabinoid receptor agonist activity, CUMYL-4CN-BINACA fully substituted for  $\Delta^9$ -THC in drug discrimination tests. This suggests that it has abuse potential similar to that of  $\Delta^9$ -THC.

Currently, use of CUMYL-4CN-BINACA has been reported only from Europe, but this may be due to underreporting including through lack of detection in other countries. In Europe, CUMYL-4CN-BINACA has been among the most frequently seized synthetic cannabinoids. It is smoked (as preparations of drug components introduced onto plant material) or vaped (i.e. using an e-cigarette)

but owing to the nature of synthetic cannabinoid products, users cannot tell which synthetic cannabinoid is contained within such products.

A number of cases of non-fatal intoxication involving CUMYL-4CN-BINACA have been reported. CUMYL-4CN-BINACA has been analytically confirmed as being present in samples from 11 fatalities and five non-fatal intoxications in Europe. In two cases of fatal intoxication, CUMYL-4CN-BINACA was the only drug present.

### Therapeutic usefulness

CUMYL-4CN-BINACA is not known to have any therapeutic use.

### Recommendation

CUMYL-4CN-BINACA is a synthetic cannabinoid receptor agonist that is used by smoking plant material sprayed with the substance or inhaling vapour after heating. It has effects that are similar to those of other synthetic cannabinoid receptor agonists placed in Schedule II of the Convention on Psychotropic Substances of 1971. Its mode of action suggests the potential for dependence and the likelihood of abuse. There is evidence that CUMYL-4CN-BINACA has been associated with fatal and non-fatal intoxications in a number of countries. The substance causes substantial harm and has no therapeutic use.

- **Recommendation:** The Committee recommended that CUMYL-4CN-BINACA (1-(4-cyanobutyl)-*N*-(2-phenylpropan-2-yl)-1H-imidazole-3-carboxamide) be added to Schedule II of the Convention on Psychotropic Substances of 1971.

## 5. Cathinone

### 5.1 N-ethylnorpentylone

#### Substance identification

*N*-ethylnorpentylone (1-(2H-1,3-benzodioxol-5-yl)-2-(ethylamino)pentan-1-one) is a ring-substituted synthetic cathinone analogue that originally emerged in the 1960s during pharmaceutical drug development efforts. It is also known as ephylone and *N*-ethylpentylone. In its pure form, *N*-ethylnorpentylone exists as a racemic mixture in the form of a powder or crystalline solid. However, the substance is usually available as a capsule, powered tablet, pill or powder often sold as “Ecstasy” or MDMA. *N*-ethylnorpentylone is also available in its own right and is advertised for sale by Internet retailers.

#### WHO review history

*N*-ethylnorpentylone has not been previously pre-reviewed or critically reviewed by the WHO ECDD. A critical review was proposed based on information brought to WHO’s attention that *N*-ethylnorpentylone poses a serious risk to public health and has no recognized therapeutic use.

#### Similarity to known substances and effects on the central nervous system

The information currently available suggests that *N*-ethylnorpentylone is a psychomotor stimulant, as users exhibit effects including sweating, agitation, paranoia, tachycardia and cardiac arrest, which are consistent with other cathinones and psychomotor stimulant drugs. Not all reported adverse effects could be causally linked to *N*-ethylnorpentylone alone.

Its molecular mechanism of action is similar to the synthetic cathinones MDPV and  $\alpha$ -PVP which are both listed in Schedule II of the Convention on Psychotropic Substances of 1971. In vitro investigations showed that *N*-ethylnorpentylone inhibited the reuptake of dopamine, noradrenaline and, to a lesser extent, serotonin, which is consistent with other closely related cathinones with known abuse liability.

There is no specific information available to indicate that *N*-ethylnorpentylone may be converted into a substance currently controlled under the UN conventions.

#### Dependence potential

No controlled experimental studies examining the dependence potential of *N*-ethylnorpentylone in humans or animals were available. However, based on its action in the central nervous system, it would be expected that *N*-ethylnorpentylone would have the capacity to produce a state of dependence

similar to that of other stimulants such as the ones listed in Schedule II of the Convention on Psychotropic Drugs of 1971.

### **Actual abuse and/or evidence of likelihood of abuse**

In rodent drug discrimination studies, *N*-ethylnorpentylone fully substituted for methamphetamine and cocaine, and it was also shown to increase activity levels, suggesting it has potential for abuse similar to other psychomotor stimulants.

*N*-Ethylnorpentylone has been detected in biological fluids collected from a number of cases of fatal and non-fatal intoxication. It is frequently used in combination with other drugs.

A number of countries in various regions have reported use or detection of this compound in seized materials or biological samples, including cases of driving under the influence of drugs. Increased seizures of *N*-ethylnorpentylone have been reported by the United States over the past 2 years. Between 2016 and 2018, a total of 125 toxicological reports associated with *N*-ethylnorpentylone were documented.

### **Therapeutic usefulness**

*N*-Ethylnorpentylone is not known to have any therapeutic use.

### **Recommendation**

*N*-Ethylnorpentylone is a synthetic cathinone with effects that are similar to other synthetic cathinones listed as Schedule II substances in the Convention on Psychotropic Substances of 1971. Its mode of action and effects are consistent with those of other cathinones, indicating that it has the potential for dependence and the likelihood of abuse. There is evidence of use of *N*-ethylnorpentylone in a number of countries in various regions, which has resulted in fatal and non-fatal intoxication. The substance causes substantial harm and has no therapeutic use.

- **Recommendation:** The Committee recommended that *N*-ethylnorpentylone (1-(2H-1,3-benzodioxol-5-yl)-2-(ethylamino)pentan-1-one) be added to Schedule II of the 1971 Convention on Psychotropic Substances.

## 6. Medicines

### 6.1 Pregabalin

#### Substance identification

Chemically, pregabalin is (3S)-3-(aminomethyl)-5-methylhexanoic acid, a white to off-white crystalline solid. It is the (S)-(+)-isomer of 3-isobutyl-gamma-aminobutyric acid. Pregabalin is produced in various formulations including capsules, solution and extended-release tablets available as pharmaceutical products to be taken orally.

#### WHO review history

Pregabalin was pre-reviewed by the ECDD at its thirty-ninth meeting in November 2017 and it was recommended that a critical review be undertaken.

#### Similarity to known substances and effects on the central nervous system

Pregabalin is an inhibitor of alpha-2-delta subunit-containing voltage-gated calcium channels. Through this mechanism it decreases the release of neurotransmitters such as glutamate, noradrenaline and substance P. It has been suggested that pregabalin exerts its therapeutic effects by reducing the neuronal activation of hyper-excited neurons while leaving normal activation unaffected. The mechanism(s) by which pregabalin produces euphoric effects or induces physical dependence is unknown.

Despite being a chemical analogue of the neurotransmitter gamma-aminobutyric acid (GABA), pregabalin does not influence GABA activity via either GABA receptors or benzodiazepine receptors. However, pregabalin has been found to produce effects that are similar to those produced by controlled substances, such as benzodiazepines, that increase GABA activity.

#### Dependence potential

Tolerance has been shown to develop to the effects of pregabalin, particularly the euphoric effects. A number of published reports have described physical dependence associated with pregabalin use in humans. The withdrawal symptoms that occur following abrupt discontinuation of pregabalin include insomnia, nausea, headache, anxiety, sweating and diarrhoea. Current evidence suggests that the incidence and severity of withdrawal symptoms may be dose-related and hence those taking doses above the normal therapeutic range are most at risk of developing withdrawal symptoms. At therapeutic doses, withdrawal symptoms may be minimized by gradual dose-tapering.

## Actual abuse and/or evidence of likelihood of abuse

While some preclinical research using self-administration and conditioned place preference models has shown reinforcing effects of pregabalin, overall, the results from such research are contradictory and inconclusive.

In clinical trials, patients have reported euphoria, although tolerance to this effect develops rapidly. Laboratory research on humans is very limited and only a relatively low dose of pregabalin has been tested in a general population sample; the results indicated low abuse liability. However, when a higher dose of pregabalin was administered to users of alcohol or sedative/hypnotic drugs, it was rated similar to diazepam, which is indicative of abuse liability.

Pregabalin is more likely to be abused by individuals who are using other psychoactive drugs (especially opioids) and there is a significant potential for adverse effects among these subpopulations. The adverse effects of pregabalin include dizziness, blurred vision, impaired coordination, impaired attention, somnolence, confusion and impaired thinking. Other reported types of harm associated with nonmedical use of pregabalin include suicidal ideation and impaired driving. Users of pregabalin in a number of countries have sought treatment for dependence on the drug.

While pregabalin has been cited as the main cause of death in more than 30 documented cases of fatality following overdose, very few cases of fatal intoxication have resulted from pregabalin use alone and the vast majority of instances involve other central nervous system depressants such as opioids and benzodiazepines.

Only limited information is available regarding the illicit trade in pregabalin, but there is evidence of illicit marketing through online pharmacies.

Pregabalin has been placed under national control in many countries in different regions of the world.

## Therapeutic usefulness

Pregabalin is used for the treatment of neuropathic pain, including painful diabetic peripheral neuropathy and postherpetic neuralgia, fibromyalgia, anxiety and the adjunctive treatment of partial seizures. The exact indications for which pregabalin has received approval vary across countries. Pregabalin has also been used to treat conditions such as substance use disorders, alcohol withdrawal syndrome, restless legs syndrome and migraine.

## Recommendation

The Committee noted that there has been increasing concern in many countries regarding the abuse of pregabalin. Cases of dependence have been reported and

there are increasing numbers of reports of adverse effects. While these problems are concentrated in certain drug-using populations, there are limited data on the extent of the problems related to pregabalin abuse in the general population. The Committee also noted that pregabalin has approved therapeutic uses for a range of medical conditions, including some for which there are few therapeutic options. Given the limitations of the available information regarding the abuse of pregabalin:

- **Recommendation:** The Committee recommended that pregabalin ((3S)-3-(aminomethyl)-5-methylhexanoic acid) should not be scheduled but should be kept under surveillance by the WHO Secretariat.

## 6.2 Tramadol

### Substance identification

Tramadol ((1R\*,2R\*)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexan-1-ol) is marketed as the hydrochloride salt and is available in a variety of pharmaceutical formulations for oral (tablets, capsules), sublingual (drops), intranasal, rectal (suppositories), intravenous, subcutaneous and intramuscular administration. It is also available in combination with acetaminophen (paracetamol). Preparations of tramadol are available as immediate- and extended-release formulations.

### WHO review history

Tramadol has been considered for critical review by the ECDD five times: in 1992, 2000, 2002, 2006 and 2014. Tramadol was pre-reviewed at the thirty-ninth meeting of the ECDD in November 2017 and it was recommended that tramadol be subject to a critical review at a subsequent ECDD meeting. The Committee requested the ECDD Secretariat to collect additional data for the critical review, including information on the extent of problems associated with tramadol misuse in countries. Also, the Committee asked for information on the medical use of tramadol, including the extent to which low-income countries, and aid and relief agencies, use and possibly rely on tramadol for provision of analgesia. In response to these requests, the ECDD Secretariat collected data from Member States and relief agencies on the extent of medical use of tramadol, its misuse and on the level of control implemented in countries.

### Similarity to known substances and effects on the central nervous system

Tramadol is a weak opioid analgesic that produces opioid-like effects primarily due to its metabolite, *O*-desmethyltramadol. The analgesic effect of tramadol is

also believed to involve its actions on noradrenergic and serotonergic receptor systems. The adverse effects of tramadol are consistent with its dual opioid and non-opioid mechanisms of action and they include dizziness, nausea, constipation and headache. Overdose leads to symptoms such as lethargy, nausea, agitation, hostility, aggression, tachycardia, hypertension and other cardiac complications, renal complications, seizures, respiratory depression and coma. Serotonin syndrome (a group of symptoms associated with high concentrations of the neurotransmitter serotonin that include elevated body temperature, agitation, confusion, enhanced reflexes and tremor and, in some instances, seizures and respiratory arrest) is a potential complication of the use of tramadol in combination with other serotonergic drugs. Tramadol has been detected in a number of postmortem samples. It is often present along with other drugs, including opioids, benzodiazepines and antidepressants, but fatalities have also been reported due to tramadol alone.

### **Dependence potential**

Evidence suggests that the development of physical dependence to tramadol is dose-related, and administration of supra-therapeutic doses leads to a similar dependence profile to that of morphine and other opioids such as oxycodone and methadone. There are reports of considerable numbers of people seeking help for tramadol dependence. Withdrawal symptoms include those typical of opioids such as pain, sweating, diarrhoea and insomnia. There are also symptoms not normally associated with opioid use, which are related to noradrenergic and serotonergic activity, such as hallucinations, paranoia, confusion and sensory abnormalities. Low-dose tramadol used over extended periods is associated with a lower risk of dependence.

### **Actual abuse and/or evidence of likelihood of abuse**

Consistent with its opioid mechanism of action, human brain imaging has shown that tramadol activates brain reward pathways associated with abuse. While tramadol has been reported to produce opioid-like reinforcing effects in controlled settings and in experienced opioid users, these effects may be weaker than those produced by opioids such as morphine. They may also be partially offset by unpleasant effects of tramadol such as sweating, tremor, agitation, anxiety and insomnia.

Abuse, dependence and tramadol overdose have emerged as serious public health concerns in countries across several regions. Epidemiological studies in the past have reported a lower tendency for tramadol misuse when compared to other opioids, but more recent information indicates a growing number of people abusing tramadol, particularly in a number of African and Middle

Eastern countries. The sources of tramadol include diverted medicines as well as falsified medicines containing high doses of tramadol. Seizures of illicitly trafficked tramadol, particularly in African countries, have risen dramatically in recent years.

The oral route of administration has been the predominant mode of tramadol abuse as it results in a greater opioid effect than other routes. It is unlikely that when used nonmedically, tramadol is injected to any significant extent. Abuse of tramadol is likely to be influenced by genetic factors such that some people will experience a much stronger opioid effect following tramadol administration than others. The genetic factors are present at different rates in different populations across different parts of the world.

Many countries have placed tramadol under national control.

### Therapeutic usefulness

Tramadol is used to treat both acute and chronic pain of moderate to severe intensity. The conditions for which tramadol has been used include osteoarthritis, neuropathic pain, chronic low back pain, cancer pain and postoperative pain. It has also been used for treatment of restless legs syndrome and in opioid withdrawal management. As is the case with abuse potential, the analgesic efficacy and the nature of adverse effects experienced are strongly influenced by genetic factors. Systematic reviews have suggested that the ability of tramadol to control chronic pain such as cancer pain is less than that of strong opioids such as morphine, and its use is associated with a relatively high prevalence of adverse effects.

Tramadol is listed on the national essential medicines lists of many countries across diverse regions, but it is not listed on the WHO EML.

As an opioid analgesic available in generic forms, which is not under international control, tramadol is widely used in many countries where access to other opioids for the management of pain is limited. It is also used extensively by international aid organizations in emergency and crisis situations for the same reasons.

### Recommendations

The Committee was concerned by the increasing evidence of tramadol abuse in a number of countries in diverse regions, in particular the widespread abuse of tramadol in many low-to-middle-income countries. Equally concerning was the clear lack of availability of alternative analgesics in a number of countries and in emergency and crisis situations where tramadol is used for treatment of moderate to severe pain. The Committee was strongly of the view that the extent of abuse and evidence of public health risks associated with tramadol warranted consideration of scheduling. However, it recommended that tramadol not be

scheduled at this time in order to avoid an adverse impact on access to this medication, especially in countries where tramadol may be the only available opioid analgesic, or in crisis situations where there is little or no access at all to other opioids.

The Committee also strongly urged WHO and its partners to address, as a high priority, the grossly inadequate access to and availability of opioid pain medication in low-income countries. WHO and its partners are also strongly encouraged to update and disseminate WHO pain management guidelines and to support both country-specific capacity-building needs and prevention and treatment initiatives in order to address the tramadol crisis in low-income countries. The Committee also recommended that WHO and its partners support countries in strengthening their regulatory capacity and mechanisms for preventing the supply and use of falsified and substandard tramadol.

- **Recommendation:** The Committee recommended that the WHO Secretariat should continue to keep tramadol under surveillance, collect information on the extent of problems associated with tramadol misuse and on its medical use, and that tramadol be considered for review at a future meeting.

## 7 Cannabis and cannabis-related substances

In response to CND Resolution 52/5 (2009), which requested an updated report on cannabis from WHO (subject to the availability of extrabudgetary resources) and to CND Resolution 50/2 requesting WHO, in consultation with INCB, as appropriate, to undertake a review of dronabinol and its stereoisomers when additional information became available, and recognizing that a formal review of the scheduling of cannabis had not previously been carried out by the ECDD, WHO undertook to review the scheduling of cannabis and cannabis-related substances.

During the review, the Committee noted that cannabis and cannabis-related substances are scheduled under both the Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol, and the Convention on Psychotropic Substances, 1971 as follows:

### 1961 Convention

- *Cannabis and cannabis resin are included in Schedules I and IV.*
- *Extracts and tinctures of cannabis are included in Schedule I.*

### 1971 Convention

- *$\Delta^9$ -tetrahydrocannabinol is included in Schedule II as dronabinol and its stereoisomers.*
- *The tetrahydrocannabinol isomers  $\Delta^{6a(10a)}$ -tetrahydrocannabinol,  $\Delta^{6a(7)}$ -tetrahydrocannabinol,  $\Delta^7$ -tetrahydrocannabinol,  $\Delta^8$ -tetrahydrocannabinol,  $\Delta^{10}$ -tetrahydrocannabinol and  $\Delta^{9(11)}$  tetrahydrocannabinol are included in Schedule I.*

The Committee noted that a number of important developments had occurred since the scheduling of these substances. These developments need to be considered in any deliberation on the scheduling of cannabis and cannabis-related substances. In particular:

1. At the time of the adoption of the Single Convention on Narcotic Drugs, the main active compound in cannabis had not been established. Subsequent scientific research has clearly identified  $\Delta^9$ -THC as the main psychoactive compound.
2. In view of this, it can now be understood that whereas the main active compounds in opium and coca leaf (morphine and cocaine,

respectively) were known at the time of the establishment of the 1961 Convention and were included in Schedule I along with the respective plants, “extracts and tinctures of cannabis”, which were understood to contain the active substance in cannabis, were included in Schedule I in lieu of a known active substance.

3. Dronabinol ((-)-trans- $\Delta^9$ -THC), the active stereoisomer of  $\Delta^9$  THC, was originally understood to refer only to this substance in its medicinal form. It is currently included under Schedule II of the 1971 Convention, but there have been several recommendations to change its status. Earlier recommendations to the CND were based on the understanding that  $\Delta^9$ -THC as a pure substance existed only in this medicinal form. However, particularly in the past 10 years, there has been increasing use of illicit substances prepared from the cannabis plant. These substances contain  $\Delta^9$ -THC with a range of purities, and particularly its active stereoisomer (-) trans- $\Delta^9$ -THC or dronabinol, up to 90% purity. Such substances pose several difficulties within the current scheduling:
  - It is unclear whether these substances should be considered as examples of extracts and tinctures (and therefore considered under the 1961 Convention) or, particularly when the purity of  $\Delta^9$ -THC is relatively high, whether they should be considered as forms of  $\Delta^9$ -THC (in particular, its active stereoisomer dronabinol) under the 1971 Convention.
  - This situation is further complicated as some preparations with high  $\Delta^9$  THC concentrations are produced in such a way that they are not captured within the definition of an extract or tincture, while others clearly do meet the usual criteria for this definition. Appropriate regulation of these substances would therefore require knowledge of the method of production, which could only be determined by complex and burdensome chemical analysis.
  - While smoked forms of high-purity  $\Delta^9$ -THC are associated with significant risks to public health, the medicinal forms of  $\Delta^9$ -THC, which are administered orally, have not been associated with the same risks.
4. One of the substances in the cannabis plant that does not have psychoactive properties, cannabidiol, has recently been shown to be effective as a medication for treatment-resistant childhood epilepsy

and has been registered as a medicine for this purpose. At its fortieth meeting in June 2018, the Committee recommended that cannabidiol in its pure form not be controlled under the conventions. However, if it is obtained as an extract or tincture of cannabis (which is the method of production of the currently registered pharmaceutical product) then cannabidiol could be considered a controlled substance under the 1961 Convention. The Committee noted that for many years medicinal products that do not have psychoactive effects and are not subject to abuse and dependence have been derived from the opium poppy. These medicinal products, containing substances such as noscapine and papaverine, are not regulated under the conventions as the preparations do not contain significant amounts of the opium-derived substances (such as morphine and codeine) that are controlled under the 1961 Convention. The difficulty arises with non-psychoactive products from the cannabis plant that have potential medical uses because of the inclusion in the Schedules of all extracts and tinctures of cannabis, irrespective of whether or not they have psychoactive properties.

5. The Committee noted that the 1961 Convention specifically excludes from control, plants of the genus *Cannabis* that are used for industrial or horticultural purposes. These plants are commonly known as hemp and contain very low concentrations of  $\Delta^9$ -THC. The Committee noted that in recent years cannabis plants have been bred that have very low concentrations of  $\Delta^9$ -THC but are not used for industrial or horticultural purposes and would not normally be considered as hemp plants. These plants are bred mainly to contain high concentrations of cannabidiol. The breeding of these plants has been carried out by pharmaceutical companies but also by individuals with no pharmaceutical qualifications or involvement. The status of these plants in the Conventions is uncertain, particularly when they have not been bred and produced within international and national regulatory frameworks.

The Committee noted that these developments had the potential to complicate the interpretation of the current scheduling of cannabis and cannabis-related substances. It undertook to consider these developments and how they can be best addressed in a manner that provides greatest clarity, while recognizing the intent of the Conventions to enable use of drugs for medical purposes while also enabling their control so as to minimize problems of abuse and dependence.

## 7.1 Cannabis and cannabis resin

### Substance identification

Cannabis is a flowering plant, generally dioecious (i.e. with the male and female flowers on separate plants). It has a characteristic odour, which is mainly attributable to a mixture of volatile compounds, including monoterpenes, sesquiterpenes and other terpenoid-like compounds.

Cannabis tops and cannabis resin (sometimes referred to as “hashish”) are typically administered via inhalation after combustion (i.e. by smoking).

Cannabis is defined in the 1961 United Nations Single Convention on Narcotic Drugs as 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.

Cannabis resin is defined as the separated resin, whether crude or purified, obtained from the cannabis plant. The resinous secretions of the plant can be collected to yield a product with a higher concentration of  $\Delta^9$ -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.

### WHO review history

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 plant and resin are also included in 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.

A pre-review of cannabis and cannabis resin was carried out at the fortieth meeting of the ECDD, at which time the Committee recommended a critical review. Prior to this, cannabis had never been subject to a formal review by WHO.

### Similarity to known substances and effects on the central nervous system

The consumption of cannabis can induce euphoria, laughter and talkativeness, change sensory and time perception, and compromise motor control and judgement.

Cannabis can stimulate appetite and produce dry mouth and dizziness. Acute cannabis use impairs certain types of cognitive function such as attention, learning and memory.

## Dependence potential

In controlled laboratory studies, experienced cannabis users readily smoke cannabis and choose higher over lower doses. Human subjects can be trained to readily discriminate cannabis smoke from placebo smoke. Self-reported subjective effects associated with smoked cannabis in laboratory studies include dose-dependent increases in ratings of “drug effect”, “high” or “stoned”. Similar effects are produced by  $\Delta^9$ -THC alone when administered orally or when smoked, indicating that the cannabis constituent responsible for the plant’s reinforcing effects is  $\Delta^9$ -THC. The CB<sub>1</sub> receptor antagonist, rimonabant, was shown, at least in some instances, to reverse the intoxication induced by cannabis.

International clinical diagnostic guidelines recognize the existence of cannabis dependence: this includes the development of withdrawal symptoms upon cessation of regular use. Symptoms of withdrawal include mood changes, irritability, increased anger, anxiety, craving, restlessness, sleep impairment, gastrointestinal disturbance and decreased appetite, with most individuals reporting four or more symptoms. These symptoms typically occur within 1 to 2 days of stopping regular use, usually peak 2 to 6 days after last use, and may last for 2 to 3 weeks. While dependence may develop as a result of regular use of cannabis with a low percentage of  $\Delta^9$ -THC, regular use of cannabis with a high percentage of  $\Delta^9$ -THC is associated with a greater severity of withdrawal symptoms. Approximately 1 in 10 cannabis users develop a cannabis use disorder, but this figure varies between studies and countries. The rates of cannabis use and of cannabis use disorder differ considerably between countries and in different regions of each country. Cannabis use disorder is most common in people under 30 years of age.

## Actual abuse and/or evidence of abuse

Preclinical studies suggest that a lethal dose of cannabis and cannabis resin is not likely to be obtainable by humans and there is insufficient evidence to suggest that cannabis use increases overdose lethality from other drugs like opioids. Cardiovascular effects following acute administration, such as tachycardia and increased blood pressure, appear minimal or transient, and subside with tolerance. Some studies have suggested a link between cannabis use and heart attack, but the association is uncertain.

Young children may be particularly vulnerable to the effects of cannabis. Case reports indicate that young children who accidentally ingest cannabis can experience respiratory depression, tachycardia and temporary coma.

Cannabis consumption causes euphoria and can alter time perception. Some users may experience anxiety and panic reactions. Acute cannabis intoxication can precipitate a short-lasting psychotic state which reverses once the effects of the drug have abated.

Cannabis intoxication can impair cognitive function with effects including decreased attention and short-term memory. Cannabis use can impair driving, leading to a low-to-moderate (20–30%) increase in the risk of accidents. Cannabis use impairs reaction time, lane control, speedometer monitoring, hand and body steadiness and braking time as well as promoting inappropriate responses in an emergency scenario.

In addition to the acute effects of cannabis, there are effects of long-term use. Cannabis use in young people has been associated with an increased risk of developing psychotic disorders, although the relationship is complex and likely to be moderated by genetic factors. Women who smoke cannabis during pregnancy give birth to babies with birth weights that are, on average, lower than those of women who do not smoke cannabis during pregnancy. Cannabis smoking has been reported to lead to a 2.5-fold increase in the risk of testicular cancer.

### **Therapeutic usefulness**

Cannabis has shown both positive outcomes and a lack of significant effect in the treatment of loss of appetite associated with HIV/AIDS, chronic pain, Crohn's disease, diabetic neuropathy, neuropathic pain, migraine and cluster headaches, and Parkinson's disease. Further data are required to enable full assessment of the efficacy of cannabis; however, studies have shown its possible value in a variety of therapeutic indications.

Cannabis preparations are currently subject to the same level of control as cannabis under the 1961 Single Convention on Narcotic Drugs, Article 2, Paragraph 3. Preparations of cannabis are used in the control of muscle spasticity associated with multiple sclerosis, which are not always controlled by other medications. Some patients with chronic pain have also been shown to obtain relief from cannabis preparations when other available medications have not been effective.

Preclinical reports indicate that cannabinoids reduce cancer cell proliferation, inducing apoptosis in these cells, as well as inhibiting cancer cell migration and angiogenesis in numerous cancer cell types. Cannabinoids and cannabis use have also been shown to have immunosuppressant and anti-inflammatory effects in laboratory animals and humans, respectively. These findings suggest other possible therapeutic applications for cannabis and cannabinoids.

Cannabis and cannabis resin are not included in the WHO EML or the WHO Model List of Essential Medicines for Children.

### **Recommendation**

In the 1961 Single Convention on Narcotic Drugs, cannabis and cannabis resin are described, respectively, as 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 and as the separated resin, whether crude or purified, obtained from the cannabis plant. Reference to cannabis will be taken to also include cannabis resin. Of the many compounds in cannabis, *delta*-9-tetrahydrocannabinol ( $\Delta^9$ -THC) is the principal psychoactive constituent, while cannabidiol is also present but is not psychoactive.

Following the consumption of cannabis, the adverse effects experienced include dizziness and impairment of motor control and cognitive function. As a result of its effects on movement and cognition, cannabis use can impair driving ability. These acute adverse effects of cannabis consumption are similar to those produced by  $\Delta^9$ -THC alone. There are particular risks associated with cannabis exposure in young children, such as respiratory depression, tachycardia and coma.

Various adverse effects are associated with long-term cannabis use, particularly an increased risk of mental health disorders such as anxiety, depression and psychotic illness. Chronic regular cannabis use is particularly problematic for young people because of its effects on the developing brain.

Cannabis can cause physical dependence in people who use the drug daily or near daily. This is evidenced by the onset of cannabis withdrawal symptoms that occur upon abstinence; these symptoms include gastrointestinal disturbance, appetite changes, irritability, restlessness and sleep impairment. Clinical diagnostic guidelines such as the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) and the International Statistical Classification of Diseases and Related Health Problems, tenth revision (ICD-10) recognize cannabis dependence and other disorders related to cannabis use.

The Committee considered information regarding the therapeutic indications for cannabis and ongoing research into its possible medical applications. Several countries permit the use of cannabis for the treatment of medical conditions such as chemotherapy-induced nausea and vomiting, pain, sleep disorders and spasticity associated with multiple sclerosis. The Committee recognized the limited robust scientific evidence on the therapeutic use of cannabis. However, some oral pharmaceutical preparations of cannabis have therapeutic advantages for treatment of conditions such as certain forms of pain and epilepsy. Preparations of cannabis are defined as a mixture, solid, or liquid containing cannabis and are generally subject to the same control measures as cannabis and cannabis resin as per Article 2.3 of the 1961 Single Convention on Narcotic Drugs.

Cannabis 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 and have little or no therapeutic use. Other substances that are included in both

Schedules I and IV are fentanyl analogues, heroin and other opioids that are considered especially dangerous. Use of all these substances is associated with a significant risk of death, whereas cannabis use is not associated with such risk.

The evidence presented to the Committee did not indicate that cannabis and cannabis resin were particularly liable to produce ill-effects similar to the effects of the other substances in Schedule IV of the 1961 Single Convention on Narcotic Drugs. In addition, preparations of cannabis have shown therapeutic potential for treatment of pain and other medical conditions such as epilepsy and spasticity associated with multiple sclerosis, which are not always controlled by other medications. Cannabis and cannabis resin should therefore be scheduled at a level of control that will prevent harm caused by their use but, at the same time, will not act as a barrier to access and to research and development of cannabis-related preparations for medical use.

The Committee concluded that cannabis and cannabis resin do not meet the criteria for placement in Schedule IV.

The Committee then considered whether cannabis and cannabis resin were better placed in Schedule I or Schedule II of the 1961 Single Convention on Narcotic Drugs. While the Committee did not consider that cannabis is associated with the same level of risk to health as that posed by most of the other drugs placed in Schedule I, it noted the high rates of public health problems arising from cannabis use and the global extent of such problems. For these reasons, it recommended that cannabis and cannabis resin continue to be included in Schedule I of the 1961 Single Convention on Narcotic Drugs.

- **Recommendation:** The Committee recommended that cannabis and cannabis resin be deleted from Schedule IV of the 1961 Single Convention on Narcotic Drugs.

## 7.2 delta-9-tetrahydrocannabinol ( $\Delta^9$ -THC; dronabinol)

### Substance identification

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.  $\Delta^9$ -THC is thought to be the principal intoxicant constituent of *Cannabis sativa*.

*Delta-9-tetrahydrocannabinol* refers to the following four stereoisomers:

- (-)-*trans*-delta-9-tetrahydrocannabinol (also known as dronabinol)
- (+)-*trans*-delta-9-tetrahydrocannabinol
- (-)-*cis*-delta-9-tetrahydrocannabinol
- (+)-*cis*-delta-9-tetrahydrocannabinol

The stereoisomer (–)-trans- $\Delta^9$ -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 INN for this isomer. Where the term “ $\Delta^9$ -THC” is used in this report without further specification, it refers to (–)-trans- $\Delta^9$ -THC or dronabinol. If reference is made to a different isomer, this will be explicitly specified.

For therapeutic use, dronabinol is supplied as gelatine capsules (Marinol®) for oral use, and as an oral solution (Syndros®).

#### WHO review history

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

- In 1989, the WHO ECDD recommended, based on the critical review of dronabinol 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  $\Delta^9$ -THC. It recommended that  $\Delta^9$ -THC and its stereochemical variants be rescheduled from Schedule I to Schedule II of the 1971 Convention. This was proposed in order to avoid a distinction between  $\Delta^9$ -THC and its stereochemical variants, 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 its thirty-third meeting in 2002,  $\Delta^9$ -THC was again critically reviewed by the ECDD. 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 of dronabinol. The Committee concluded that although dronabinol constitutes a substantial risk to public health, this risk is different from those related to cannabis, which is controlled under the 1961 Convention. The substance was found to have moderate therapeutic usefulness, and an increase in its medical use was likely as a result 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 WHO 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 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 its thirty-fourth meeting to move dronabinol and its stereochemical variants from Schedule II to Schedule III of the 1971 Convention. The ECDD decided that its earlier 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 UN 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 reviewing 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  $\Delta^9$ -THC be pre-reviewed together with cannabis and cannabis resin, extracts and tinctures of cannabis, cannabidiol 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,  $\Delta^9$ -THC and isomers of THC at the forty-first meeting in November 2018.

## Similarity to other known substances and effects on the central nervous system

In humans,  $\Delta^9$ -THC has very similar pharmacological and subjective effects to those of cannabis. Users may exhibit euphoria, laughter and increased talkativeness.  $\Delta^9$ -THC increases appetite, causes dry mouth and occasional dizziness and alters visual, olfactory and auditory perceptions.  $\Delta^9$ -THC can cause subtle cognitive deficits such as impairment of attention and short-term memory. Higher doses of  $\Delta^9$ -THC are associated with anxiety, panic, confusion and disorientation in some users.  $\Delta^9$ -THC can also provoke transient psychosis-like phenomena in some healthy participants.

$\Delta^9$ -THC has very low potential to produce lethal effects. 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 exposure of humans to  $\Delta^9$ -THC produces tachycardia; however, tolerance may occur to these effects, and decreases in blood pressure and heart rate may occur with subsequent exposures.  $\Delta^9$ -THC is a bronchodilator. While in vitro and in vivo studies in animals demonstrate that high doses of  $\Delta^9$ -THC can modulate the immune system in complex ways, two studies in humans in which low doses of  $\Delta^9$ -THC were administered, found no significant effects on the immune system.

Oral  $\Delta^9$ -THC is reported to cause impairment of driving skills in both driving simulators and on roads. Doses of 10 and 20 mg of  $\Delta^9$ -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).

## Dependence potential

In animal models, marked tolerance develops to the effects of  $\Delta^9$ -THC. The effects of spontaneous withdrawal following cessation of chronic administration appear relatively mild, but antagonist-precipitated withdrawal is characterized by clear somatic signs such as tremor and ataxia.

Tolerance has also been demonstrated in humans and there is evidence of a withdrawal syndrome on cessation following administration for a period as short as 4 days. The doses of  $\Delta^9$ -THC administered in the studies demonstrating withdrawal exceeded the doses used in clinical trials for therapeutic applications.

Sleep disruption appears to be the most prominent symptom of withdrawal from  $\Delta^9$ -THC.

### **Actual abuse and/or evidence of abuse**

Pharmaceutical products containing  $\Delta^9$ -THC do not appear to be abused. Orally administered pharmaceutical preparations containing  $\Delta^9$ -THC appear to have only weak reinforcing properties in humans, with low and variable rates of self-administration. Smoked cannabis is much preferred. Evidence concerning the medical use of  $\Delta^9$ -THC shows no diversion of the pharmaceutical product for nonmedical purposes and no evidence of abuse.

There is no significant evidence concerning the reinforcing effects of smoked or vaporized pure  $\Delta^9$ -THC in humans. However, newer (nonmedical) preparations of the cannabis plant, principally as extracts, contain very high concentrations of  $\Delta^9$ -THC, sometimes exceeding 80%. Such preparations, including butane hash oil, are administered by inhalation of vapour after heating. Previously, the only relatively pure  $\Delta^9$ -THC preparations were medicinal. The development of high-purity  $\Delta^9$ -THC products is associated with significant health risks, including increased risk of dependence.

### **Therapeutic usefulness**

$\Delta^9$ -THC (dronabinol) is approved 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.

$\Delta^9$ -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's syndrome.

$\Delta^9$ -THC (dronabinol) is not listed on the WHO EML (twentieth list) or the WHO Model List of Essential Medicines for Children (sixth list).

### **Recommendation**

The main psychoactive substance in the cannabis plant is one of the four stereoisomers of  $\Delta^9$ -THC. This substance has therapeutic uses and is sometimes known by its International Nonproprietary Name dronabinol. It is currently placed in Schedule II of the 1971 Convention on Psychotropic Substances.

At the time of the adoption of the 1961 Single Convention on Narcotic Drugs, scientific research had not identified  $\Delta^9$ -THC as the main psychoactive compound in cannabis. Subsequently,  $\Delta^9$ -THC was included in the 1971 Convention on Psychotropic Substances at its inception. In previous ECDD reviews, the active and naturally occurring stereoisomer of  $\Delta^9$ -THC known as dronabinol had been considered in a synthetic form as a pharmaceutical preparation. Following a recommendation from the ECDD at its twenty-seventh meeting, dronabinol was placed in Schedule II of the 1971 Convention on Psychotropic Substances. However, the CND did not adopt a subsequent recommendation to place dronabinol in Schedule III of the 1971 Convention on Psychotropic Substances.

The Committee noted that whereas in these previous ECDD reviews  $\Delta^9$ -THC, and especially its active stereoisomer dronabinol, had been considered in a synthetic form as a pharmaceutical preparation,  $\Delta^9$ -THC today also refers to the main psychoactive component of cannabis and the principal compound in illicit cannabis-derived psychoactive products. Some of these products contain  $\Delta^9$ -THC at concentrations as high as 90%. Butane hash oil is an example of a cannabis-derived product containing high-purity  $\Delta^9$ -THC, which has recently emerged and is used by heating and inhalation of the vapour. In derived forms of such high purity,  $\Delta^9$ -THC produces ill-effects, dependence and abuse potential that is at least as great as that produced by cannabis, which is placed in Schedule I of the 1961 Single Convention on Narcotic Drugs.

A substance liable to similar abuse and productive of similar ill-effects to those of a substance already scheduled within the 1961 Single Convention on Narcotic Drugs would normally be scheduled in the same way as that substance. As  $\Delta^9$ -THC is liable to similar abuse to cannabis and has similar ill-effects, it meets the criteria for inclusion in Schedule I of the 1961 Single Convention on Narcotic Drugs. It was further recognized that cocaine, the principal active compound in coca is placed together with coca leaf in Schedule I of the 1961 Single Convention on Narcotic Drugs. Furthermore, morphine, the principal active compound in opium, is placed with opium in the same Schedule. Placing  $\Delta^9$ -THC, the principal active compound in cannabis, in the same Schedule as cannabis would be consistent with this approach.

- **Recommendation:** The Committee recommended that dronabinol and its stereoisomers (*delta*-9- tetrahydrocannabinol) be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

As indicated in the *Guidance on the WHO review of psychoactive substances for international control* (4), to facilitate efficient administration of the international control system, it is not advisable to place a substance under more than one Convention. Accordingly:

- **Recommendation:** The Committee recommended the deletion of dronabinol and its stereoisomers (*delta*-9-tetrahydrocannabinol) from the 1971 Convention on Psychotropic Substances, Schedule II, subject to the Commission's adoption of the recommendation to add dronabinol and its stereoisomers (*delta*-9- tetrahydrocannabinol) to Schedule I of the 1961 Single Convention on Narcotic Drugs.

Based on requests received from Member States and information received from other United Nations agencies, the Committee understood that placing  $\Delta^9$ -THC under the same Convention and in the same Schedule as cannabis – Schedule I of the 1961 Single Convention on Narcotic Drugs – would greatly facilitate the implementation of the control measures of the conventions in Member States.

### 7.3 Tetrahydrocannabinol (isomers of THC)

#### 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. Most exist only for the purpose of scientific research; however, there appears to be no ongoing scientific research about their use. This entry in the Schedules does not include *delta*-9-tetrahydrocannabinol (dronabinol).

**Table 1.**  
Molecules of THC with their chemical designations

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

## WHO review history

Isomers of THC were pre-reviewed at the fortieth ECDD meeting and recommended for a critical review.

## Similarity to known substances and effects on the central nervous system

Both  $\Delta^8$ -THC and  $\Delta^{9,11}$ -THC produce  $\Delta^9$ -THC-like pharmacological effects in some animal models, whereas  $\Delta^{10}$ -THC does not. In humans,  $\Delta^8$ -THC is active when administered via several different routes, for example, oral, intravenous and inhalation.  $\Delta^{6a,10a}$ -THC has psychoactive effects in humans similar to those of  $\Delta^9$ -THC but is less potent.  $\Delta^{6a,10a}$ -THC also produces  $\Delta^9$ -THC-like effects when smoked, but the effects are less marked and have a shorter duration than those of  $\Delta^9$ -THC. None of the other isomers have been tested in humans.

## Dependence potential

There is no available evidence from either animal or human studies to determine the potential for dependence of any of the six isomers of THC. Moreover, there has been no definitive study of the mechanism(s) of action of the isomers and hence it is not possible to extrapolate from an understanding of the mechanism to the likely dependence potential.

## Actual abuse and/or extent of abuse

Data from both human and animal studies relevant to abuse potential are at best very limited and, for some isomers, non-existent. It is not possible to assess the abuse potential of any of the isomers based on a clearly established mechanism of action. There is no evidence of actual abuse (in contrast to abuse potential) for any of the isomers studied.

In animal drug discrimination tests,  $\Delta^{9,11}$ -THC has been shown to substitute for  $\Delta^9$ -THC in most studies and induces characteristic  $CB_1$  agonist effects, including suppression of locomotor activity, hypothermia, antinociception and ring immobility.  $\Delta^8$ -THC induces characteristic  $CB_1$  agonist effects and  $\Delta^9$ -THC-like discriminative effects. These two compounds were less potent than  $\Delta^9$ -THC. In contrast,  $\Delta^{10}$ -THC failed to show  $\Delta^9$ -THC-like discriminative effects in an animal model.

Only very limited data on the abuse potential of these isomers in humans are available. The two isomers that were assessed,  $\Delta^8$ -THC and  $\Delta^{6a,10a}$ -THC, each produced similar subjective effects to those of  $\Delta^9$ -THC when administered by various routes.

In summary, there is evidence from animal and human studies that  $\Delta^8$ -THC has abuse potential of a type similar to  $\Delta^9$ -THC. There is much more limited evidence of abuse potential for  $\Delta^{9,11}$ -THC and  $\Delta^{6a,10a}$ -THC based on animal and

human research, respectively. For  $\Delta^{10}$ -THC, the only evidence is negative and for the two remaining isomers there is no evidence.

### Therapeutic usefulness

The six isomers listed under Schedule I of the 1971 Convention on Psychotropic Substances are not known to have any therapeutic uses.

### Recommendations

There are currently six isomers of THC listed in Schedule I of the 1971 Convention on Psychotropic Substances. These six isomers are chemically similar to  $\Delta^9$ -THC, which is currently listed in Schedule II of the 1971 Convention on Psychotropic Substances. The Committee has recommended deleting  $\Delta^9$ -THC from this Schedule and including it in Schedule I of the 1961 Single Convention on Narcotic Drugs.

While the six isomers are chemically similar to  $\Delta^9$ -THC, there is little or no evidence concerning their abuse potential and acute intoxicating effects. There are no reports that the THC isomers listed in Schedule I of the 1971 Convention induce physical dependence, or that they are being abused or are likely to be abused so as to constitute a public health or social problem. There are no reported medical or veterinary uses of these isomers.

While the Committee recognized that available evidence has not demonstrated abuse and ill-effects of these isomers similar to those associated with  $\Delta^9$ -THC, it noted that, due to the chemical similarity of each of the six isomers to  $\Delta^9$ -THC, it is very difficult to differentiate any of these six isomers from  $\Delta^9$ -THC using standard methods of chemical analysis.

**Recommendation:** The Committee recommended that tetrahydrocannabinol (understood to refer to the six isomers currently listed in Schedule I of the 1971 Convention on Psychotropic Substances) be added to Schedule I of the 1961 Single Convention on Narcotic Drugs, subject to the Commission's adoption of the recommendation to add dronabinol (*delta*-9-tetrahydrocannabinol) to Schedule I of the 1961 Single Convention on Narcotic Drugs.

As indicated in the *Guidance on the WHO review of psychoactive substances for international control* (4), to facilitate efficient administration of the international control system, it is not advisable to place a substance under more than one Convention.

- **Recommendation:** The Committee recommended that tetrahydrocannabinol (understood to refer to the six isomers currently listed in Schedule I of the 1971 Convention on Psychotropic Substances) be deleted from the 1971 Convention on Psychotropic Substances, subject to the Commission's adoption of the

recommendation to add tetrahydrocannabinol to Schedule I of the 1961 Single Convention on Narcotic Drugs.

The Committee acknowledged that placing these six isomers under the same Convention and in the same Schedule as  $\Delta^9$ -THC would facilitate the implementation of international control of  $\Delta^9$ -THC, as well as assist Member States in the implementation of control measures at country level.

## 7.4 Extracts and tinctures of cannabis

### Substance identification

Extracts and tinctures of cannabis are preparations that have been extracted from the leaves and flowers of *Cannabis sativa*. They include cannabis oils, teas and Sativex® (an extract with approximately equal quantities of  $\Delta^9$ -THC and cannabidiol). Cannabis undergoes an extraction process in order to separate the desired compounds such as cannabinoids from the undesired products. Extracts can exhibit variations of shade of colour, taste, smell and consistency, ranging from a runny oil to a solid depending on the manufacturing process. They can also take the form of alcohol or aqueous preparations.

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  $\Delta^9$ -THC contained in the preparation. Tinctures are usually administered sublingually or added to edibles or beverages for oral consumption. Oils may be incorporated into food or beverages for oral administration or may be vaped or “dabbed” (inhalation of vapour from a heated preparation). Sativex® is formulated into an oromucosal spray.

### Oils

Oils can be produced with a range of  $\Delta^9$ -THC concentrations. Those with the highest concentration are butane hash oil and propane hash oil, which may contain from 50 to 90% of the active ingredient,  $\Delta^9$ -THC. Oils with high concentrations of cannabidiol can also be produced by extraction using a variety of methods. Some oils, such as essential oil and hemp seed oil, do not contain significant concentrations of  $\Delta^9$ -THC or cannabidiol.

Cannabis oil extracts can also be incorporated into a wide range of food products.

### Aqueous extracts

An aqueous extract of *C. sativa* is often referred to as a tea. The addition of boiling water is a simple and probably one of the oldest methods for preparing a cannabis extract for oral administration. The amount of  $\Delta^9$ -THC extracted using

this method is significantly lower than what would be obtainable using other methods.

### Sativex®

Sativex® is a unique cannabis extract with an approximate 1:1 ratio of  $\Delta^9$ -THC to cannabidiol, as the principal cannabinoids, together with other minor cannabinoids delivered as an oromucosal spray approved for medical purposes.

### WHO review history

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

Cannabis extracts and tinctures were pre-reviewed at the fortieth meeting of the ECDD and were recommended for critical review.

### Similarity to known substances and effects on the central nervous system

Effects produced by  $\Delta^9$ -THC-rich cannabis extracts, tinctures, oils and tea are similar to those observed with  $\Delta^9$ -THC, but, as noted above, the effects may be more pronounced and associated with a greater risk of adverse effects, such as cardiovascular effects, when extracts with high  $\Delta^9$ -THC concentrations are inhaled.

The most common adverse effects of Sativex® are mild to moderate dizziness and fatigue. Transient adverse effects such as increased heart rate and blood pressure, disorientation, depression, euphoria, transient psychotic reactions and dissociation have also been reported.

### Dependence potential

The psychoactive constituent,  $\Delta^9$ -THC, present in most of the extracts, has been shown to have dependence potential, as supported by numerous animal and human studies. There is evidence that regular use of certain cannabis extracts with high concentrations of  $\Delta^9$ -THC, such as butane hash oil, increases the probability and severity of dependence.

### Actual abuse and/or extent of abuse

There is little epidemiological information on the extent of use of cannabis extracts. The information that is available suggests that extracts in the form of oil or wax containing high levels of  $\Delta^9$ -THC are used by a minority of cannabis users. However, this rate may be increasing and the use of such extracts appears to be associated with higher levels of physical dependence on cannabis.

Information on the toxicology of cannabis extracts, tinctures, oils and tea is also very limited. The toxicity produced by  $\Delta^9$ -THC-rich cannabis extracts,

tinctures, oils and tea is similar to the toxicity of  $\Delta^9$ -THC. However, as noted above, the effects may be more pronounced, with a greater risk of adverse effects, when extracts with high  $\Delta^9$ -THC concentrations are inhaled.

Depending on the method used to produce it, cannabis extract may contain residual solvents (naphtha, isopropanol, acetone, hexane, ethyl alcohol or butane), which are harmful if ingested by the user and may cause serious burns when ignited. Some extracts contain contaminants such as pesticides. Thinning agents such as propylene glycol and polyethylene glycol 400 (used to smooth the flow of viscous cannabis oils from vaping 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).

Vaping and smoking 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.

A clinical trial to evaluate the abuse potential of Sativex<sup>®</sup> in recreational cannabis users showed that high doses of  $\Delta^9$ -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<sup>®</sup>. However, euphoria has been reported as an adverse effect of Sativex<sup>®</sup>.

## Therapeutic usefulness

Sativex<sup>®</sup> has been granted marketing authorizations for treatment of spasticity due to multiple sclerosis in several countries, and for treatment of neuropathic pain in multiple sclerosis and chronic cancer pain. Sativex<sup>®</sup> is being investigated for a variety of other indications including, but not limited to, anxiety disorder, cannabis use disorder, attention-deficit/hyperactivity disorder, and depression and sleep disorders.

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

## Recommendations

Extracts and tinctures of cannabis include preparations that are produced by application of solvents to cannabis, and they are currently in Schedule I of the 1961 Single Convention on Narcotic Drugs. Extracts and tinctures include both medical preparations, such as that containing an approximately equal mixture of  $\Delta^9$ -tetrahydrocannabinol (dronabinol;  $\Delta^9$ -THC) and cannabidiol and nonmedical preparations with high concentrations of  $\Delta^9$ -THC such as butane hash oil. While the medical extracts and tinctures are administered orally, nonmedical preparations such as butane hash oil are normally inhaled through vaporization. There are also extracts with no psychoactive effects that contain cannabidiol.

The Committee recognized that the term “extracts and tinctures of cannabis” as cited in the 1961 Single Convention on Narcotic Drugs encompasses these diverse preparations some of which have psychoactive properties and some which do not. The Committee also recognized that the variability in psychoactive properties of these preparations is due principally to varying concentrations of  $\Delta^9$ -THC, which is currently scheduled in the 1971 Convention on Psychotropic Substances, and that some extracts and tinctures of cannabis without psychoactive properties, and including predominantly cannabidiol, have promising therapeutic applications.

As per the 1961 Single Convention on Narcotic Drugs, preparations are defined as mixtures, solid, or liquid containing a substance in Schedule I or II and are generally subject to the same measures of control as that substance. The Committee noted that, by this definition, the 1961 Single Convention on Narcotic Drugs may cover all products that are “extracts and tinctures” of cannabis as “preparations” of cannabis and also, if the Committee’s recommendation to move dronabinol to Schedule I of the 1961 Single Convention on Narcotic Drugs was adopted, as “preparations” of dronabinol and its stereoisomers.

**Recommendation:** The Committee recommended deleting “extracts and tinctures of cannabis” from Schedule I of the 1961 Single Convention on Narcotic Drugs.

The Committee acknowledged that the fact that diverse preparations with a variable concentration of  $\Delta^9$ -THC are controlled within the same entry “extract and tinctures” under the same Schedule, is a challenge for the authorities responsible for implementing control measures in their respective countries.

## 7.5 Cannabidiol preparations

At its fortieth meeting the ECDD considered a critical review of cannabidiol and recommended that preparations considered to be pure cannabidiol should not be scheduled within the international drug control conventions. Cannabidiol is found in cannabis and cannabis resin, but does not have psychoactive properties and has no potential for abuse and no potential to produce dependence. It does not have significant ill-effects. Cannabidiol has been shown to be effective in the management of certain treatment-resistant, childhood-onset epilepsy disorders. It was approved for this use in the United States in 2018 and is currently under consideration for approval by the European Union.

- Cannabidiol can be chemically synthesized or it can be prepared from the cannabis plant. The approved medication (Epidiolex®) is a preparation of the cannabis plant. The Committee noted that medicines without psychoactive effects that are produced as preparations of the cannabis plant will contain trace amounts of  $\Delta^9$ -

THC (dronabinol). The cannabidiol preparation approved for the treatment of childhood-onset epilepsy, Epidiolex<sup>®</sup>, contains not more than 0.15%  $\Delta^9$ -THC by weight and has no effects indicative of potential for abuse or dependence. In keeping with the recommendation of the fortieth ECDD that preparations considered pure cannabidiol not be controlled, the Committee recognized that trace levels of  $\Delta^9$ -THC may be found in such preparations, such as the concentration of 0.15% in Epidiolex<sup>®</sup>. The Committee acknowledged that chemical analysis of  $\Delta^9$ -THC to an accuracy of 0.15% may be difficult for some Member States, and considered existing national capacities to accurately detect trace amounts of  $\Delta^9$ -THC up to 0.2%.

- **Recommendation:** The Committee recommended that a footnote be added to Schedule I of the 1961 Single Convention on Narcotic Drugs to read: “Preparations containing predominantly cannabidiol and not more than 0.2 per cent of delta-9-tetrahydrocannabinol are not under international control.”

The Committee noted precedence in the use of footnotes in the Schedules relating to levomethorphan and levorphanol, whose stereoisomers, dextromethorphan and dextrorphan, would normally be subject to the same level of control under Schedule I of the 1961 Convention. Because these substances are not liable to abuse or to produce dependence and are used medically, a footnote was used to indicate that dextromethorphan and dextrorphan are not under international control.

## 7.6 Pharmaceutical preparations of cannabis and delta-9-tetrahydrocannabinol (dronabinol)

There are currently two main types of registered medicines that contain  $\Delta^9$ -THC (dronabinol). One is a preparation of cannabis that contains both the psychoactive  $\Delta^9$ -THC and the non-psychoactive cannabidiol in approximately equal concentrations (Sativex<sup>®</sup>). This is used for the treatment of spasticity and neuropathic pain due to multiple sclerosis, and to treat chronic cancer pain.

The second type contains only  $\Delta^9$ -THC as the active compound and is used for the treatment of anorexia associated with weight loss in patients with AIDS and for nausea and vomiting associated with cancer chemotherapy in patients who have not responded adequately to conventional antiemetic treatments. Currently approved medicines with  $\Delta^9$ -THC as the only active compound (for example, Marinol<sup>®</sup>, Syndros<sup>®</sup>) use synthetically produced  $\Delta^9$ -THC, although it is possible in the future that medicines with equivalent amounts of  $\Delta^9$ -THC could be prepared from cannabis. There is no difference between the therapeutic effects or adverse effects of synthetic  $\Delta^9$ -THC and  $\Delta^9$ -THC produced from cannabis

plants. These medicines are all taken orally and are approved for use in a number of countries.

These  $\Delta^9$ -THC-containing medicines have not been found to be associated with problems of abuse and dependence and they are not diverted for the purpose of nonmedical use.

The Committee recognized that such pharmaceutical preparations are formulated in a way that means they are not likely to be abused. Furthermore, there is no evidence of actual abuse or ill-effects to an extent that would justify the current level of control associated with Schedule I of the 1961 Single Convention on Narcotic Drugs for cannabis-based preparations such as Sativex<sup>®</sup>, or the level of control associated with Schedule II of the 1971 Convention on Psychotropic Substances, for preparations using synthetic  $\Delta^9$ -THC such as Marinol<sup>®</sup> and Syndros<sup>®</sup>.

In order not to impede access to these medicines and in reference to Article 3.4 of the 1961 Single Convention on Narcotic Drugs:

- **Recommendation:** The Committee recommended that preparations containing *delta*-9-tetrahydrocannabinol (dronabinol), produced either by chemical synthesis or as a preparation of cannabis, that are compounded as pharmaceutical preparations with one or more other ingredients and in such a way that *delta*-9-tetrahydrocannabinol (dronabinol) cannot be recovered by readily available means or in a yield which would constitute a risk to public health, be added to Schedule III of the 1961 Convention on Narcotic Drugs.

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The report summarizes the findings of the forty-first meeting at which the Committee reviewed 16 substances and made recommendations. The report also contains updates from international bodies concerned with controlled substances.

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