WHO Expert Committee on Drug Dependence

Thirty-eighth 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
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WHO Expert Committee on Drug Dependence
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Abbreviations

3-MMC  2-(methylamino)-1-(3-methylphenyl)propan-1-one
4,4-DMAR  para-methyl-4-methylaminorex
4-MEC  2-(ethylamino)-1-(4-methylphenyl)propan-1-one
5F-APINACA  N-(adamantan-1-yl)-1-(5-fluoropentyl)-1H-indazole-3-carboxamide
AIDS  Acquired Immunodeficiency Syndrome
ANPP  4-anilino-N-phenethylpiperidine
ATS  amphetamine-type stimulants
Butyrfentanyl  N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]butanamide
CB  cannabinoid
CND  Commission on Narcotic Drugs
DG  Director-General
DUID  driving under the influence of drugs
EB  Executive Board
ECDD  Expert Committee on Drug Dependence
EMCDDA  European Monitoring Centre for Drugs and Drug Addiction
EML  WHO Model List of Essential Medicines
EMP  Department of Essential Medicines and Health Products, WHO
Ethylone  1-(2H-1,3-benzodioxol-5-yl)-2-(ethylamino)propan-1-one
Ethylphenidate  ethyl phenyl(piperidin-2-yl)acetate
EWA  Early Warning Advisory
EWS  Early Warning System
HCV  Hepatitis C virus
HIV  Human Immunodeficiency Virus
ICD-11  International Classification of Diseases
INCB  International Narcotics Control Board
INN  International Nonproprietary Name
JWH-073  (1-butyl-1H-indol-3-yl)(1-naphthyl)methanone
MDMA  3,4-methylenedioxymethamphetamine
MDMB-CHMICA  methyl N-{[1-(cyclohexylmethyl)-1H-indol-3-yl]carbonyl}-3-methyl-L-valinate
MPA  N-methyl-1-(thiophen-2-yl)propan-2-amine
MS Multiple Sclerosis
MSB/MSD Management of Substance Abuse Unit at the Department of Mental Health and Substance Abuse, WHO
MT-45 1-cyclohexyl-4-(1,2-diphenylethyl)piperazine
NGO Nongovernmental Organization
NPP N-phenethyl-4-piperidinone
NPS New Psychoactive Substances
PCP phencyclidine; 1-(1-phenylcyclohexyl)piperidine
Pentedrone 2-(methylamino)-1-phenylpentan-1-one
PMMA para-methoxymethylamphetamine
SCRA Synthetic Cannabinoid Receptor Agonist
SDG Sustainable Development Goals
SMART Synthetics Monitoring: Analysis, Reporting and Trends
THC Tetrahydrocannabinol
U-47700 3,4-dichloro-N-(2-dimethylamino-cyclohexyl)-N-methyl-benzamide
UMC Uppsala Monitoring Centre
UNAIDS Joint United Nations Programme on HIV/AIDS
UNGASS United Nations General Assembly Special Session
UNODC United Nations Office on Drugs and Crime
WHA World Health Assembly
WHO World Health Organisation
XLR-11 [1-(5-fluoropentyl)-1H-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone
Introduction

The thirty-eighth meeting of the WHO Expert Committee on Drug Dependence (ECDD) took place in Geneva, Switzerland from 14 to 18 November 2016.

Dr Suzanne Hill, Director, WHO Department of Essential Medicines and Health Products (EMP), opened the meeting. She welcomed all participants on behalf of the WHO Director-General.

Dr Marie-Paule Kieny, Assistant Director-General, Health Systems and Innovation, of WHO, thanked the ECDD members for their time and efforts dedicated to the thorough review of the substances on the agenda of the ECDD meeting. She outlined the central role of scientific evidence in the decision making process of Expert Committees and in WHO normative and standard setting role.

Dr Kieny reiterated the importance of the International Drug Control Conventions and of the United Nations General Assembly Special Session (UNGASS) recommendations, that are a guide to WHO’s work for positioning health at the centre of the world drug problem and for achieving the health related Sustainable Development Goals (SDG) objectives.

She indicated that it was important for WHO to work closely with UNODC, INCB and other global and regional entities as well as Member States, for achieving efficient and successful implementation of the UNGASS operational recommendations and for tackling the world drug problem. Dr Kieny discussed how the 38th ECDD will assess 12 New Psychoactive Substances (NPS). WHO objective is not to review the hundreds of (NPS) reported globally to date, but to focus on the ones that are the most prevalent, persistent and harmful. To this effect, a systematic and evidence-based prioritization of NPS has been carried out in advance to the 38th ECDD and a number of Member States have contributed by sharing published and unpublished data.

Dr Kieny noted that the 38th ECDD will also discuss an update on cannabis and cannabis resin because of the growing interest of Member States on the medical use of cannabis and also in response to the 2009 Commission on Narcotic Drugs (CND) Resolution that requested WHO to provide regular updates on the cannabis plant and resin.

As recommended by the 37th ECDD, the WHO Secretariat collected new data and commissioned systematic reviews on medical use and on dependence and harms of cannabis and cannabis resin. The available scientific evidence and public health considerations will be
the main criteria guiding the Committee’s recommendations, in particular because of the sensitive nature of the issue.

In that regard, Dr Kieny reminded the Committee members that in the exercise of their function, they shall act as international experts serving the Organization exclusively; in that capacity they shall not request or receive instructions from any government or authority external to the Organization. Furthermore, they shall disclose all circumstances that could give rise to a potential conflict of interest and in accordance with the mechanisms established by the Director-General for that purpose.

Dr Gilles Forte, Coordinator, Policy, Governance and Knowledge Management, Department of Essential Medicines and Health Products (EMP), then addressed the Committee and provided an overview of procedural matters. The international drug control conventions describe the mandate and roles of WHO. A key WHO role within this framework is to assess the therapeutic usefulness, the liability for abuse and dependence and the harm to health of any substance, pure chemical or plant material, and to advise the CND on whether or not substances should be placed under international control.

WHO also follows the relevant guidance of its governing bodies, in particular WHO’s Regulations on expert advisory panels and committees as well as the Guidance on the WHO review of psychoactive substances for international control.

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 have been asked to disclose any circumstances that could represent a potential conflict of interest (i.e. any interest that may affect, or may reasonably be perceived to affect, an expert’s objectivity and independence) in relation to the subject matter of the meeting.

Dr Simon Brandt declared that he was involved in the preparation of technical reports and presentations to the Scientific Committee of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) on NPS and attended the EMCDDA risk assessment meeting on one of the substances (MDMB-CHMICA) under consideration by the 38th ECDD.

Dr Edmundus J.M. Pennings declared that he is a member of the Committee for the Risk Assessment of NPS in the Netherlands and has been since 1998. This committee carries out science-based risk assessments of NPS and advises the Dutch government on issues related to their misuse. Dr Pennings stated that the committee has never carried out a risk assessment for any of the substances that will be critically reviewed by the 38th ECDD.
The disclosed interests were considered by the WHO 38th ECDD Secretariat 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 were deemed relevant to the work of the group.

The Expert Committee elected a Chair, Co-Chair and Rapporteur. The Chair welcomed all participants and the agenda as proposed by the Secretariat was approved.
1. Briefings from International Organizations on their work on the public health element of the world drug problem

1.1 Update from the International Narcotics Control Board

Dr Viroj Sumyai, Observer for the International Narcotics Control Board (INCB) and Chair of the INCB Standing Committee on Estimates, informed the Committee about the role and functions of the INCB. Established by the 1961 Single Convention on Narcotic Drugs, the INCB consists of 13 members who are elected by the Economic and Social Council and who serve in their personal capacity. Three members with medical, pharmacological or pharmaceutical experience are elected from a list of candidates nominated by WHO and ten members are elected from a list of candidates nominated by Governments.

In the update, Dr Viroj Sumyai referred to the recently published annual report of the INCB and its thematic chapter on the challenges and opportunities of international drug control which stresses that concern for health and welfare should be at the core of drug policy and action at national and international levels. In addition, INCB calls for balance in implementing drug control policy and for the observance of human rights standards for treatment and rehabilitation of drug use.

Ms Beate Hammond briefed the ECDD on the INCB special report on ensuring adequate access to internationally controlled drugs. Noting that there were still large disparities in the consumption of drugs in the world, the report highlights the main impediments to better availability, which include fear of addiction, lack of awareness on the proper use of internationally controlled drugs for medical purposes as well as both human and financial resource constraints.

The report makes recommendations to Governments on how this situation can be improved. To overcome the knowledge gap, for example, it is necessary to develop and implement educational programs and disseminate information to overcome cultural resistance, where necessary. As many countries continue to experience difficulties in properly estimating their needs for opioid analgesics and psychotropic substances and to monitor their consumption, the report calls on Governments to make use of the INCB/WHO Guide on Estimating Requirements for Substances under International Control. In addition, Governments should review national legislation, regulatory and administrative mechanisms and procedures including domestic distribution channels with the aim to simplify and
streamline the processes, remove unduly restrictive regulations and impediments to ensure accessibility while maintaining adequate control systems.

1.2 Update from the United Nations Office on Drugs and Crime

Dr Justice Tettey, Observer for the United Nations Office on Drugs and Crime (UNODC), informed the Committee that NPS continue to appear at a fast pace on drug markets worldwide and their use have been associated with several adverse events, including fatalities. To date, 730 NPS have been reported in 102 Member States and territories to the UNODC Early Warning Advisory (EWA). The market continues to be characterised by heterogeneity in the nature and scope of the problem, the transient nature of some of the substances reported and paucity of information on public health harms. A recent trend in the marketing of blends/mixtures of NPS, presents a particular challenge with regard to the interpretation of data of their associated harms. UNODC research and trend analysis contributes to improve the understanding of, and shape the response to, the NPS issue through knowledge products and early warnings. This will continue with the publication of an extended chapter on the latest trends and developments in NPS and amphetamine-type stimulants (ATS) markets in the 2017 World Drug Report.

Dr Tettey reported that under its global Synthetics Monitoring: Analysis, Reporting and Trends (SMART) programme, UNODC continues to monitor, analyse and share information on NPS at the global level, with its Early Warning Advisory on NPS being actively used by Member States and international organizations, such as the World Health Organization, in the context of the selection of substances for consideration by the ECDD and to inform the scheduling decisions of the Commission on Narcotic Drugs (CND).

He underscored that reducing the supply of NPS through scheduling under the international conventions continues to be a viable measure. In 2015, the CND decided to place ten (10) NPS under international control. Pursuant to these scheduling decisions, UNODC supported implementation by Member States through the development and dissemination of a series of recommended laboratory methods of analyses and provided over 1400 units of chemical reference materials of these substances to forensic institutions in 55 countries. In addition, selected substances were introduced in the UNODC international collaborative exercises, a biannual proficiency test scheme for national drug laboratories which currently supports over 250 laboratories from 70 countries, to enhance their preparedness to identify these threats. To further aid in implementation of the scheduling
decisions, UNODC has revised its *Multilingual Dictionaries of Narcotic Drugs and Psychotropic Substances Under International Control*, the *Multilingual Dictionary of Precursors and Chemicals Frequently Used in the Illicit Manufacture of Narcotic Drugs and Psychotropic Substances under International Control* and the *Terminology and Information on Drugs*.

Dr Tettey described that a comprehensive programme of training to enhance law enforcement capacity in identifying NPS and substances under international control was implemented across the Pacific Island States, South East Asia, South Asia and West Africa in 2015, and in Central Asia and South Asia in 2016. These included the deployment of modern hand-held technologies, e.g. Raman and Fourier Transform Infra-Red spectrometers in field drug and precursor testing training, to cope with the unprecedented numbers of reported NPS.

He emphasized that a health-based approach to the NPS problem is essential to support the tenet of the International Drug Control Conventions – protecting the health and welfare of mankind. In September 2016, UNODC in collaboration with the WHO convened a meeting of experts on substance disorders from across the world, to explore new frontiers of health protection with regard to NPS. The meeting discussed key aspects of the NPS issue, in particular diagnostic approaches and treatment options, with the goal of developing a practical tool to be used by clinicians around the world.

He went on to explain that efforts continue to be made to operationalize the recommendations on NPS outlined in the outcome document of the 2016 UN General Assembly Special Session on Drugs. Specifically, the 3rd UNODC-WHO Expert Consultation in Geneva in May 2016 focussed on practical approaches to identifying the most harmful, prevalent and persistent NPS for international action. Further to this, UNODC has enhanced its engagement with the global forensic toxicology community, as a first step to addressing the paucity of data on the harms of NPS. Global trends in NPS emergence continue to evolve rapidly. The last few years have seen the emergence of a number of synthetic opioids, including fentanyl analogues. While these only account for approximately 1% of all NPS reported to UNODC, the associated harms to public health have been immense. In this context, on 25 October 2016, the Secretary General notified States parties of the communication sent by the USA, further to the provisions in the 1988 Convention, to initiate steps to add N-phenethyl-4-piperidinone (NPP) and 4-anilino-N-phenethylpiperidine (ANPP), common precursors in the synthesis of fentanyl and a number of its analogues, in the Tables of the 1988 Convention.
He noted that further to the CND Decision 58/2 (2015), UNODC continues to monitor the illicit trafficking and use of ketamine, and share with WHO such information as it becomes available.

He reported that at its 59th regular session in March 2016, the CND decided to place seven NPS under international control under the relevant schedules of the Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol and the Convention on Psychotropic Substances of 1971. On 17 May 2016, the Secretary General notified States parties of these scheduling decisions. The revised schedules under the 1961 Convention and the 1971 Conventions became effective on 18 May 2016 and 13 November 2016.

Dr Tettey concluded that the UNODC will continue to extend support to Member States through research and trend analysis to better understand the NPS problem. It will also provide the relevant tools and services previously outlined to support Member States’ implementation of these new scheduling decisions.

1.3 Update from the Department of Essential Medicines and Health Products, WHO

Dr Gilles Forte, Coordinator, Policy, Governance and Knowledge Management, provided an update from the WHO Department of Essential Medicines and Health Products.

Dr Forte emphasized that the World Health Organization, is committed to implementing the UNGASS recommendations related to health, and will work closely with UNODC, INCB, civil society and other international and regional partners to fulfil this commitment.

The United Nations General Assembly Resolution S-30/1, adopted on 19 April 2016, underscores that the availability of internationally controlled drugs for medical and scientific purposes remains low to non-existent in many countries and emphasises the need for international cooperation to promote measures to improve access for these medicines.

Controlled medicines are needed to alleviate pain and suffering, enable surgery, treat physical and mental health issues, support dignified and comfortable end-of-life care, help people to overcome addiction, and to save lives. Health systems cannot work effectively without essential controlled medicines. However, despite their vital importance, access to controlled medicines remains inadequate around the world.

Dr Forte reiterated that the importance of access to controlled medicines for public health has been emphasized in several World Health Assembly (WHA) resolutions. These WHA Resolutions reflect Member States’ commitment to ensure access to controlled
medicines for palliative care (WHA67.19), for emergency and essential surgical care and anaesthesia (WHA68.15) and for epilepsy (WHA68.20). These resolutions also provide WHO with a strong mandate to support Member States efforts for addressing barriers to access, whilst preventing risks for diversion and abuse.

Barriers to access have been well addressed in the UNGASS outcome document. They relate to lack of knowledge on efficacy, safety and appropriate use of medicines; unduly restrictive regulations for supply and dispensing; and inefficiency of supply chains which leads to poor availability and affordability of medicines.

As part of its standard setting mandate, and based on rigorous scientific evidence, the WHO Secretariat carries out regular reviews of the efficacy and safety of medicines, including controlled medicines. These reviews inform recommendations for the inclusion or exclusion of these medicines in WHO Model List of Essential Medicines (EML). The WHO Secretariat has carried out a review of medicines for pain that could be considered for addition to the WHO EML by the WHO Expert Committee on the Selection and Use of Essential Medicines in March 2017.

The WHO Secretariat has recently developed guidelines for the management of persisting pain in children and is currently developing new guidelines for the management of cancer pain in adults.

WHO is part of the Joint Global Programme (in collaboration with UNODC and the Union for International Cancer Control (UICC)) on access to controlled drugs for medical purposes, in particular for the management of pain. The programme is currently supported by Australia and Belgium and implemented in Ghana, Timor-Leste and in the Democratic Republic of Congo. It aims to support countries to identify potential barriers to access, through the assessment of policies, legislation and the supply chain, and to identify strategies and interventions for improved practices and for enhanced capacity building.

Dr Forte indicated that work with countries will also focus on the use of tools and guidance to ensure more accurate quantification of requirements for controlled medicines; to explore measures to improve the efficiency and integrity of supply chains; and support the development of balanced national policies on controlled substances that ensure availability and accessibility, whilst preventing misuse and abuse.
1.4 Update from the Department of Mental Health and Substance Abuse, WHO

Dr Vladimir Poznyak, Coordinator, Management of Substance Abuse unit at the Department of Mental Health and Substance Abuse (MSB/MSD), informed the Committee about the outcomes of the UN General Assembly Special Session on the world drug problem (April 2016) and on WHO work on three of the five public health pillars and critical public health elements of the world drug problem as described in the report by the Secretariat to the 69th World Health Assembly: (1) prevention of drug use and reduction of vulnerability and risks; (2) treatment and care for people with drug use disorders and (3) monitoring and evaluation.

Dr Poznyak informed the Committee about recent MSB/MSD activities including the publication and dissemination of the report on the health and social consequences of non-medical use of cannabis, of a policy brief on drug use and road safety and of new estimates of drug-attributable disease burden. The epidemics of opioid overdose deaths in several countries and the misuse and abuse of psychoactive prescription medicines continue to present significant public health challenges. The new WHO estimates of drug-attributable disease burden indicate that more than 450,000 deaths globally are attributed to illicit drug use, including cannabis use, and the main conditions contributing to drug-attributable deaths are drug use disorders, Hepatitis C virus (HCV), Human Immunodeficiency Virus (HIV), road traffic injuries, and suicides. The impact of cannabis use on mental health and health of people other than regular cannabis users require further research. The increasing availability of cannabis in populations of many countries may have a negative impact on population health and needs to be monitored closely. The impact of NPS on health is still difficult to quantify at a population level and specific strategies need to be developed to fill this gap. The draft version of ICD-11 provides additional possibilities for coding and reporting health conditions due to the use of synthetic cannabinoids and cathinones, as well as the use of cocaine, 3,4-methylenedioxymethamphetamine (MDMA), phencyclidine (PCP) and related drugs.

1.5 Update from the Department of HIV/AIDS, WHO

Dr Andrew Ball, Senior Advisor on Strategy, Policy and Equity in the WHO Department of HIV and the Global Hepatitis Programme provided a brief overview of HIV and viral hepatitis as global public health issues for people who use drugs, particularly for those who inject drugs. People who inject drugs are up to 24 times more likely to acquire HIV than the
general population and an estimated 10 million people who inject have chronic HCV infection.

The WHO HIV Department has synthesised the evidence for a public health approach to injecting drug use, based on harm reduction principles, and developed normative guidance on HIV and hepatitis prevention, diagnosis, treatment and care. A comprehensive package of evidence-based interventions to reduce the harms associated with (injecting) drug use has been outlined in a technical guide issued jointly by WHO, UNAIDS and UNODC in 2009 and revised in 2012.

Given the evidence of the utility of harm reduction approaches in addressing drug use and drug use disorders and improving broader health outcomes, such interventions need to be a key component of a comprehensive response to substance use. There is also strong evidence that programmes that reduce the short- and long-term harms to substance users benefit the entire community through addressing HIV and hepatitis epidemics, and reducing crime and public disorder, in addition to the benefits that accrue from the inclusion into mainstream life of previously marginalized members of society.

In 2016, the Global Health Sector Strategies on HIV and Viral Hepatitis were adopted by the World Health Assembly. Both strategies include harm reduction as an essential set of interventions that should be delivered through national health programmes and supported by national health budgets. WHO therefore continues to advocate for a public health approach to the drug problem at major global events such as the UN High Level Meeting on Ending AIDS, the UNGASS on the World Drug Problem as well as the International AIDS conference and the Global Hepatitis Summit. Furthermore, the Sustainable Development Goals targets will not be met if harm reduction is not brought to scale and if people who use drugs are not accessing HIV prevention, testing, treatment and care services.

After having developed comprehensive normative guidance, the focus of WHO is now on providing technical support to countries on implementing a public health sector response. In addition, countries are being supported to improve their strategic information systems and use standardized indicators to monitor progress and measure services access and coverage of people who inject drugs along the HIV and hepatitis prevention, testing and treatment cascades.

The Department also manages a special webpage on controlled medicines for access to methadone, buprenorphine and oral morphine as part of the AIDS Medicines and Diagnostics Services database.
Finally, the Department has outlined structural barriers that impede implementation and scale up of services for people whose behaviour tends to be criminalised, including for people who use and inject drugs. Issues to address include the revision of laws and legislation to promote a public health approach as an alternative to criminalization of drug using behaviours, stigma and discrimination in the health sector, as well as appropriate funding for harm reduction.

2. **Principles for prioritizing and assessing substances as part of ECDD work**

Dr Eda Lopato, Technical Officer, Innovation, Access and Use, Department of Essential Medicines and Health Products (EMP), briefed the Committee and the Observers on the process of prioritization of psychoactive substances to be reviewed by the Expert Committee on Drug Dependence.

Dr Lopato discussed the recent Commission on Narcotic Drugs (CND) resolution 59/8 (2016) entitled “Promotion of measures to target new psychoactive substances and amphetamine-type stimulants”(5), which recognized the added value of WHO in the international response to tackle NPS and noted WHO efforts to monitor and carry out regular annual reviews of NPS. The resolution invited, “WHO, with the support of the UNODC, relevant regional organizations and Member States, to continue conducting regular, efficient, transparent and timely reviews of the most harmful, prevalent and persistent new psychoactive substances and to use the potential impact of toxicity at both the population and individual levels as the primary factor in prioritizing substances for review”.

Dr Lopato described the challenges faced when prioritizing substances to be reviewed by ECDD. These challenges include the transient nature of psychoactive substances and the changing patterns of supply; the lack of countries capacity and expertise for the identification of substances (e.g. fentanyl) that leads to underreporting of use, adverse events and drug seizures; the poly-drug use that makes the evaluation of harm related to each substance difficult and the marketing of mixtures of different substances a challenge for the interpretation of toxicological data. In addition, published data on harm to health, adverse effects, abuse and dependence potential for NPS is lacking.

When prioritizing substances for review by the Committee, the WHO ECDD Secretariat shall proactively search for and analyse data on harm to health (e.g. non-fatal or
fatal intoxications), on abuse and dependant potential, on prevalence (e.g. is it found in more than one country or region). In order to facilitate access to information for prioritization of substances for the 38th ECDD, the Secretariat collaborated with UNODC, INCB, EMCDDA, Uppsala Monitoring Centre (UMC) and with Member States. A thorough analysis of the data obtained, led to select a final list of 12 substances to be reviewed by the 38th ECDD.

3. **Update from the 1st Informal Working Group of the ECDD**

Professor Bruna Brands (Chair of ECDD) provided an overview of the activities of the 1st Informal Working Group of the Expert Committee on Drug Dependence that took place in Geneva, Switzerland, on 5 and 6 May 2016.

Professor Brands explained that the working group was composed of six members of the 37th ECDD and that its aim was to propose improved methods related to the review of substances and as addressed in the *Guidance on the WHO review of psychoactive substances for international control*[^4].

Issues such as the prioritization process of NPS, the development of training materials for new members of the ECDD and temporary advisers were addressed.

A session on terminologies and on proposed classes of psychoactive substances was organised at the working group and in the context of the ongoing ICD 11 revisions.

The discussion revolved also around the working group’s revision of the template for the critical review reports that was used for the first time for the 38th ECDD. ECDD members who carried out critical reviews of substances generally agreed that the new template represented an improvement compared to the ones from previous ECDDs in terms of the greater clarity of the content for each section and for the harmonization of information provided in the reviews.

Professor Brands also informed the Committee that the working group's revision of the template for the WHO Questionnaire for psychoactive substances, which is used for data collection from Member States, was used for the first time for the 38th ECDD. The wording of this questionnaire had been simplified and clarified.

At the close of Professor Brands’ presentation, a suggestion was put forward that the Secretariat collect subsequent questions by Committee members regarding terminology or the review template in general and then put them to the working group. Professor Brands stated
that comments and questions from members and temporary advisers would be welcomed and encouraged. She indicated that the working group would then try and address these during their next meeting.

4. **Follow-up on recommendations made by the ECDD at its thirty-seventh meeting**

Dr Eda Lopato gave an overview of the follow up of 37th ECDD recommendations and informed the Committee about the decisions of the Commission on Narcotic Drugs (2016). The thirty-seventh meeting of the WHO ECDD took place in Geneva, Switzerland from 16 to 20 November 2015 and the Committee recommended that seven substances, of the eight substances critically reviewed, be placed under international control and recommended that one substance be kept under surveillance. The recommendations on the following substances to be placed under international control were conveyed to the Secretary-General of the United Nations and discussed at the fifty-ninth session of the Commission on Narcotic Drugs (CND) in March 2016.

1. **Acetylfentanyl**

As recommended by the 37th ECDD, on 18 March 2016, the CND decided to include acetylfentanyl in Schedules I and IV of the Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol (Decision 59/1).

2. **MT-45**

As recommended by the 37th ECDD, on 18 March 2016, the CND decided to include MT-45 in Schedule I of the Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol (Decision 59/2).

3. **para-Methoxymethylamphetamine (PMMA)**

As recommended by the 37th ECDD, on 18 March 2016, the CND decided to include para-methoxymethylamphetamine (PMMA) in Schedule I of the Convention on Psychotropic Substances of 1971 (Decision 59/3).
4. α-Pyrrolidinovalerophenone (α-PVP)

As recommended by the 37th ECDD, on 18 March 2016, the CND decided to include α-pyrrolidinovalerophenone (α-PVP) in Schedule II of the Convention on Psychotropic Substances of 1971 (Decision 59/4).

5. para-Methyl-4-methylaminorex (4,4-DMAR)

As recommended by the 37th ECDD, on 18 March 2016, the CND decided to include para-methyl-4- methylaminorex (4,4’-DMAR) in Schedule II of the Convention on Psychotropic Substances of 1971 (Decision 59/5).

6. Methoxetamine (MXE)

As recommended by the 37th ECDD, on 18 March 2016, the CND decided to include methoxetamine (MXE) in Schedule II of the Convention on Psychotropic Substances of 1971 (Decision 59/6).

7. Phenazepam

As recommended by the 37th ECDD, on 18 March 2016, the CND decided to include phenazepam in Schedule IV of the Convention on Psychotropic Substances of 1971 (Decision 59/7).

5. Critical review of psychoactive substances

The review of psychoactive substances by WHO is carried out in two steps. The first step is referred to as pre-review; this is a preliminary review carried out by the Committee to determine whether or not a fully documented review (critical review) of the substance is required. If a preceding meeting of the Committee found that a critical review of a substance is warranted, the Secretariat will prepare such a review for the next meeting of the Committee. However, a pre-review is not always needed and in certain cases a critical review can be undertaken directly.
According to the *Guidance on the WHO review of psychoactive substances for international control* (4) “a critical review is initiated by the Expert Committee in any of the following cases:

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

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

### 5.1 U-47700

**Substance identification**

Chemically, U-47700 is 3,4-dichloro-N-(2-dimethylamino-cyclohexyl)-N-methyl-benzamide. U-47700 has two chiral centres resulting in four isomers; cis and trans conformations each have two enantiomers [cis: are (1R,2R), and (1S,2S); trans are (1R,2S) and (1S,2R)].

**Previous review**

U-47700 was not previously pre-reviewed or critically reviewed by the Committee. A direct critical review proposed based on information brought to the attention of the WHO that U-47700 is clandestinely manufactured, poses risk to public health and society, and has no recognized therapeutic use by any Party.

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

The closest controlled substance structurally related to U-47700 is AH-7921, and they are structural isomers of one another. AH-7921 was placed into Schedule I of the 1961 Single Convention, as amended by the 1972 Protocol, in 2015. U-47700 binds and has functional
activity at the mu opioid receptor and to the delta opioid receptor. It has antinociceptive activity in mice with about 7.5x the potency of morphine. Similar to morphine, case reports indicate that it produces pinpoint pupils, respiratory depression, cyanosis and depressed consciousness that is reversible with naloxone clinically. There have been confirmed fatalities (>15) associated with the use of U-47700 in Europe and in the United States.

**Dependence potential**

Neither controlled laboratory animal nor human studies have been reported regarding the dependence effects of U-47700. Users, however, report the induction of tolerance and the emergence of withdrawal signs and symptoms upon discontinuing U-47700's use suggestive of physical dependence.

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

Neither controlled laboratory animal nor human studies have been reported regarding the abuse potential effects of U-47700. U-47700, however, is aggressively marketed on the internet, often as a heroin or an oxycodone substitute, as itself, or in combination with other drugs. There also have been many seizures in North America and in Europe, some single seizures involving hundreds of pills. Users report using U-47700 via the oral, insufflation, intravenous, and rectal routes, and via an inhaler using a liquid solution. Some countries have placed U-47700 under national control, and recently (November 14, 2016) the United States of America placed U-47700 under its Controlled Substances Act stating that it was necessary to avoid an imminent hazard to the public safety.

**Therapeutic usefulness**

Although investigated preclinically as an analgesic, U-47700 has no history as a marketed medical product, nor are there known current marketing authorizations as a medicinal product for it.

**Recommendation**

U-47700 (3,4-dichloro-N-(2-dimethylamino-cyclohexyl)-N-methyl-benzamide) is a compound liable to similar abuse and with similar ill-effects to controlled opioids such as morphine and AH-7921 that are included in Schedule I of the 1961 Single Convention on Narcotic Drugs. It has no recorded therapeutic use, and its use has resulted in fatalities. There
is sufficient evidence that it is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control. Thus, because it meets the required condition of similarity, it is recommended that U-47700 be placed in Schedule I of the Single Convention on Narcotic Drugs, 1961, as consistent with Article 3, paragraph 3 (iii) of that convention in that the substance is liable to similar abuse and productive of similar ill effects as drugs in Schedule I.

5.2 Butyrfentanyl (Butyrylfentanyl)

**Substance identification**
Chemically, butyrfentanyl is \(N\)-phenyl-\(N\)-[1-(2-phenylethyl)-4-piperidinyl]butanamide.

**Previous review**
Butyrfentanyl has not been previously pre-reviewed or critically reviewed by the Committee. A direct critical review is proposed based on information brought to the attention of the WHO that butyrfentanyl is clandestinely manufactured, poses risk to public health and society, and has no recognized therapeutic use by any Party.

**Similarity to known substances and effects on the central nervous system**
Butyrfentanyl contains a carboxamide group that can be easily hydrolysed in strong acid or strong base when heated and subsequently converted by condensation into another carboxamide such as fentanyl and other fentanyls. Fentanyl is a Schedule I drug under the UN 1961 Single Convention on Narcotic Drugs. Similar to morphine, butyrfentanyl binds and has functional activity at the mu opioid receptor and produces antinociceptive activity in chemical and thermal assays in mice with a potency about 1.5x that of morphine and 30x less than fentanyl. Case studies report clinical features that include typical opioid symptoms such as respiratory depression, apnoea and loss of consciousness, and with one report indicating responsiveness to naloxone.

**Dependence potential**
Butyrfentanyl demonstrates cross-dependency in the morphine-dependent rhesus monkey. There are no controlled-studies of physical dependence or cross-dependency using human subjects.
Actual abuse and/or evidence of likelihood of abuse

There are no known reports of controlled abuse potential studies using human or laboratory animal subjects. Butyrfentanyl, however, is actively sold through internet websites. It has been associated with several cases of drug seizures, and of fatal and non-fatal intoxications in both the United States of America and in Europe. Current estimates of use are likely underestimates because butyrfentanyl is not included in most drug screens. Routes of administration include insufflation, rectal, intravenous, and sublingual use. Re-dosing is apparently a common phenomenon.

Therapeutic usefulness

There are no known approved therapeutic applications for butyrfentanyl.

Recommendation

Butyrfentanyl (N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]butanamide) is a compound liable to similar abuse and with similar ill effects to controlled opioids such as morphine and fentanyl that are included in Schedule I of the 1961 Single Convention on Narcotic Drugs. It can be converted into fentanyl as well. It has no recorded therapeutic use and its use has resulted in fatalities. There is sufficient evidence that it is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control. Thus, because it meets either of the required conditions of similarity or convertibility, it is recommended that butyrfentanyl be placed in Schedule I of the Single Convention on Narcotic Drugs, 1961, as consistent with Article 3, paragraph 3 (iii) of that convention, in that the substance is liable to similar abuse and productive of similar ill effects as drugs in Schedule I.

5.3 4-Methylethcathinone (4-MEC)

Substance identification

Chemically, 4-methylethcathinone (4-MEC) is 2-(ethylamino)-1-(4-methylphenyl)propan-1-one. 4-MEC has a chiral centre giving rise to an enantiomeric pair of (S)-4-MEC and (R)-4-MEC isomers.
Previous review
A critical review report on 4-MEC was discussed in June 2014 at the 36th meeting of the WHO Expert Committee on Drug Dependence. The Committee recommended that 4-MEC not be placed under international control at that time due to insufficiency of data regarding dependence, abuse and risks to public health, but be kept under surveillance. 4-MEC continues to appear as a psychostimulant with monoamine transporter activity with indications of abuse liability. New data have emerged from in vitro and in vivo studies since the 36th ECCD meeting that has prompted the current critical review.

Similarity to known substances and effects on the central nervous system
4-MEC has a homolog, mephedrone (4-methylmethcathinone), which is listed as a Schedule II substance under the 1971 United Nations Convention on Psychotropic Substances. Similar to controlled psychostimulants, 4-MEC elevates extracellular neurotransmitter levels, most notably, dopamine (DA), norepinephrine (noradrenaline, NE) and serotonin (5-HT). Also similar, in rodents 4-MEC increases locomotor activity and produces sensitization, fully substitutes for the discriminative stimulus effects of cocaine and (in one of two reports) also of methamphetamine, establishes conditioned place preference, and reduces thresholds of intracranial self-stimulation. Negative effects from user reports associated with 4-MEC use include excessive sweating, nausea, vomiting, jaw clenching, heart palpitations, loss of sight and migraine. The number of case reports that demonstrate a causal relationship between 4-MEC consumption and fatal intoxication is relatively limited. This profile is consistent with amphetamine like effects and it would be likely that 4-MEC would produce adverse effects consistent with amphetamine.

Dependence potential
Controlled, laboratory studies of the dependence potential of 4-MEC in animal or human subjects have not been reported. Urge to re-dose when using 4-MEC was considered weak and short-lived with low incidence of negative after-effects (compared to mephedrone), although users with a history of synthetic cathinone use and less potent experiences with 4-MEC reported higher and more frequent dosing.
Actual abuse and/or evidence of likelihood of abuse

The ability of 4-MEC to occasion the discriminative stimulus effects of cocaine, and at least in one study, methamphetamine, suggests the ability to produce their subjective effects and associated abuse potential. 4-MEC’s ability to induce conditioned place preference and reduce intracranial self-stimulation thresholds, and to increase locomotor activity and produce sensitization to it, is consistent with this prediction. Controlled human studies regarding the abuse potential of 4-MEC have not been conducted. 4-MEC has been detected across the globe and marketed as a "research chemical", although it has also been detected as a constituent in branded products available for purchase via the internet and brick-and-mortar shops. Responses obtained to the UNODC questionnaire on NPS (up to 2012) revealed that 4-MEC was ranked fourth with regard to numbers of reports received. User reports suggest that 4-MEC produces euphoria, a sense of well being, and psychostimulant effects. A survey of a group of injecting drug users of NPS reported that 4-MEC was injected more often per day compared to what might be expected from heroin use. A number of countries in different regions have controlled 4-MEC.

Therapeutic usefulness

There are no known approved therapeutic applications for 4-MEC.

Recommendation

The Committee considered that the degree of risk to public health and society associated with the abuse of 4-MEC (2-(ethylamino)-1-(4-methylphenyl)propan-1-one) is substantial. Therapeutic usefulness has not been recorded. It recognized that it has similar abuse and similar ill-effects as substances in Schedule II of the UN 1971 Convention on Psychotropic Substances. The Committee considered that there is sufficient evidence that 4-MEC is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control. As per the Guidance on the WHO review of psychoactive substances for international control, higher regard was accorded to the substantial public health risk than to the lack of therapeutic usefulness. The Committee recommended that 4-MEC be placed in Schedule II under the UN 1971 Convention on Psychotropic Substances.
5.4  3-Methylmethcathinone (3-methyl-N-methylcathinone; 3-MMC)

*Substance identification*
Chemically, 3-MMC is 2-(methylamino)-1-(3-methylphenyl)propan-1-one. 3-MMC contains a chiral centre at the C-2 carbon of the propane sidechain, so two enantiomers exist: (R)-3-MMC and (S)-3-MMC.

*Previous review*
3-MMC was not previously pre-reviewed or critically reviewed. A direct critical review is proposed based on information brought to the attention of the WHO that 3-MMC is clandestinely manufactured, poses serious risk to public health and society, and has no recognized therapeutic use by any Party.

*Similarity to known substances and effects on the central nervous system*
3-MMC is a positional isomer of 4-methylmethcathinone (4-MMC, mephedrone), which is a Schedule II substance under the 1971 Convention. 3-MMC, however, is not readily converted into 4-MMC. There is one controlled animal pharmacological study with 3-MMC. Data from case reports (including clinically described intoxications) and user reports indicate that 3-MMC displays similar properties to mephedrone and amphetamines. Adverse effects following its use have included tachycardia, agitation, reduced level of consciousness, dilated pupils, hallucinations, diaphoresis, seizures and hyperthermia. Users have also reported insomnia, difficulties in concentrating and tingling in the arms and legs. There have been hospitalisations, with a few due to 3-MMC use alone. There have been fatalities involving polydrug abuse in which 3-MMC was detected but its toxicological significance was low or unclear.

*Dependence potential*
No controlled human or laboratory animal dependence potential studies have been conducted with 3-MMC.

*Actual abuse and/or evidence of likelihood of abuse*
No controlled laboratory animal or human abuse liability studies have been conducted. In response to the WHO Questionnaire for Review of Psychoactive Substances, several
countries reported 3-MMC as being abused for its psychoactive properties as a recreational drug, with most reporting the level of negative health-impact originating from consumption as substantial. In one country employing a self-reporting questionnaire, 67.9% of respondents indicated they had tried 3-MMC, with 26.8% indicating they had been using it for more than a year. In a study in another country, 66 instances of driving under the influence of drugs (DUID) occurred where 3-MMC was encountered; in 19 of these 3-MMC was determined to be the only substance present. 3-MMC is generally administrated by insufflation, inhalation, orally or by injection. User reported effects include production of euphoria, excitement, feelings of empathy, stimulation and enhanced awareness. Some users have reported repeated use over long periods of time (greater than 40 lifetime occasions of use). 3-MMC is a controlled substance in several countries and different regions.

Therapeutic usefulness
3-MMC is not used for any known medical applications.

Recommendation
The Committee deliberated at length regarding the information available pertinent to the degree of risk to public health and society associated with the abuse of 3-MMC (2-(methylamino)-1-(3-methylphenyl)propan-1-one). The Committee decided that the information as currently provided, and the ensuing discussions that had occurred, were inadequate to form a consensus and confident recommendation regarding the scheduling of 3-MMC. As per paragraph 59 of the Guidance on the WHO review of psychoactive substances for international control\(^4\), and as supported by its procedural reference to the Thirty-fourth report of the WHO Expert Committee on Drug Dependence\(^6\), "... in cases where additional information concerning the substance under review is required, the Committee may decide that it will reach a final opinion at a subsequent meeting." "... then it should request another critical review in order to refer the matter to a subsequent Expert Committee." As directed by these guidelines, the Committee requested that the Secretariat arrange another critical review of 3-MMC at a subsequent Expert Committee.
5.5 Ethylone (3,4-methylenedioxy-N-ethylcathinone; bk-MDEA; MEDEC)

Substance identification
Chemically, ethylone is \(1-(2H-1,3\text{-benzodioxol-5-yl})-2\text{-}(ethylamino)propan-1\text{-one}\). It is a chiral compound with isomers, and its hydrochloride salt can exist in two conformations (polymorphs) at the C-C bond linking the side chain to the aromatic ring.

Previous review
Ethylone was not previously pre-reviewed or critically reviewed. A direct critical review is proposed based on information brought to the attention of the WHO that ethylone is clandestinely manufactured, poses serious risk to public health and society, and has no recognized therapeutic use by any Party.

Similarity to known substances and effects on the central nervous system
Ethylone can be considered a slight chemical modification of methylone (3,4-methylenedioxymethcathinone) that is in Schedule II of the Convention on Psychotropic Substances of 1971. However, it would likely be inefficient to intentionally synthesize ethylone to convert it to methylone. Similar to cocaine-like drugs, ethylone has relatively nonselective monoamine uptake inhibition at dopamine, serotonin, and norepinephrine transporters. It substitutes completely for the methamphetamine and cocaine discriminative stimuli in rats suggesting it would likely produce their subjective effects. Reported clinical effects (often observed when accompanied by other drugs) include impaired driving, slurred speech, bloodshot watery eyes, dilated pupils, involuntary muscle movements and elevated pulse and blood pressure.

Dependence potential
Controlled, human and laboratory animal studies regarding the potential physical dependence effects of ethylone have not been reported.

Actual abuse and/or evidence of likelihood of abuse
Results of controlled laboratory animal or human studies characterizing the abuse potential of ethylone have not been reported. Seizures of ethylone, or its detection in biosamples, have
occurred in several countries and regions. Within the first six months of 2015, ethylone had become the 12th most confiscated drug in the United States. Ethylone is aggressively marketed on the internet and has been sold as a bath salt, plant food and cleaning product. Users report using oral, rectal, insufflation, sublingual, and intravenous routes of administration. Ethylone has been associated with deaths (>8). Several countries in different regions have imposed regulatory controls over ethylone.

*Therapeutic usefulness*

Ethylone was originally patented for its potential antidepressant and antiparkinsonian properties in 1995, but no currently approved medical applications exist for it.

*Recommendation*

The Committee considered that the degree of risk to public health and society associated with the abuse of ethylone (1-(2H-1,3-benzodioxol-5-yl)-2-(ethylamino)propan-1-one) is substantial. Therapeutic usefulness has not been recorded. It recognized that it has similar abuse and similar ill-effects as substances in Schedule II of the UN 1971 Convention on Psychotropic Substances. The Committee considered that there is sufficient evidence that ethylone is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control. As per the *Guidance on the WHO review of psychoactive substances for international control*, higher regard was accorded to the substantial public health risk than to the lack of therapeutic usefulness. The Committee recommended that ethylone be placed in Schedule II under the UN 1971 Convention on Psychotropic Substances.

5.6 **Pentedrone (α-Methylaminovalerophenone)**

*Substance identification*

Chemically, pentedrone is 2-(methylamino)-1-phenylpentan-1-one. It has a chiral centre giving rise to two stereoisomers, (S)- and (R)- pentedrone.

*Previous review*

Pentedrone has not been previously reviewed or critically reviewed by the Expert Committee on Drug Dependence of the WHO. A direct critical review is proposed based on information
brought to WHO’s attention that pentedrone is clandestinely manufactured, poses serious risk to public health and society, and has no recognized therapeutic use by any Party.

**Similarity to known substances and effects on the central nervous system**
Pentedrone is a substituted phenethylamine derivative that belongs to the class of cathinones, many of which are controlled under the Convention on Psychotropic Substances of 1971. It is unlikely that pentedrone could easily be converted into an existing controlled substance. Pentedrone binds to the dopamine (DAT) and to the noradrenergic transporters (NAT) and inhibits dopamine and noradrenergic uptake, but poorly binds to the serotonergic transporter (SERT) and does not meaningfully inhibit serotonergic uptake. It induces climbing behaviour, increases locomotor activity and produces conditioned place preference in mice, and maintains intravenous self-administration in rats. These *in vitro* and *in vivo* effects are consistent with a profile similar to an abused stimulant such as methamphetamine. Importantly, it generalizes to cocaine and to methamphetamine in rat discrimination tests, suggesting that it can produce their subjective effects and has an abuse liability similar to these drugs. Non-fatal intoxications have been reported, and pentedrone has been associated with several DUID cases, although typically accompanied by other drugs. Responses to the WHO Questionnaire for Review of Psychoactive Substances for the 38th ECDD reported that the adverse effects experienced by people who present for pentedrone intoxication at the emergency room/department include impaired consciousness, tachycardia, hypotension, nausea, vertigo, hallucinations, high body temperature and sweating. Users of pentedrone report MDMA-like stimulating effects, such as euphoria, openness and increased sociability and sexual drive. Pentedrone has been associated with at least six fatalities, although other drugs were present in each.

**Dependence potential**
Controlled, human and laboratory animal studies regarding the potential physical dependence effects of pentedrone have not been reported.

**Actual abuse and/or evidence of likelihood of abuse**
Pentedrone has been detected in commercial products or in biosamples in several European countries, in Canada and in the United States of America. Hundreds of kilograms of pentedrone have been seized in the EU alone. User reports indicate that the oral, insufflation,
inhalation and intravenous routes of administration are used with pentedrone. Several countries across different regions have brought pentedrone under national control.

Therapeutic usefulness
No therapeutic or medical use has been described for pentedrone.

Recommendation
The Committee considered that the degree of risk to public health and society associated with the abuse of pentedrone (2-(methylamino)-1-phenylpentan-1-one) is substantial. Therapeutic usefulness has not been recorded. It recognized that it has similar abuse and similar ill-effects as substances in Schedule II of the UN 1971 Convention on Psychotropic Substances. The Committee considered that there is sufficient evidence that pentedrone is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control. As per the Guidance on the WHO review of psychoactive substances for international control, higher regard was accorded to the substantial public health risk than to the lack of therapeutic usefulness. The Committee recommended that pentedrone be placed in Schedule II under the UN 1971 Convention on Psychotropic Substances.

5.7 Ethylphenidate (EPH)

Substance identification
Chemically, ethylphenidate is ethyl phenyl(piperidin-2-yl)acetate.

Previous review
Ethylphenidate was not previously pre-reviewed or critically reviewed. A direct critical review is proposed based on information brought to the attention of the WHO that ethylphenidate is clandestinely manufactured, poses serious risk to public health and society, and has no recognized therapeutic use by any Party.

Similarity to known substances and effects on the central nervous system
Ethylphenidate is a structural analogue of methylphenidate, which is controlled as a Schedule II substance under the UN 1971 Convention on Psychotropic Substances. Ethylphenidate can
be converted into methylphenidate and vice versa. In addition, ethylphenidate is also produced as a metabolite from the co-ingestion of methylphenidate and alcohol (ethanol), and it has been suggested as one determinant of co-abuse of these substances. Ethylphenidate is a selective and potent dopamine uptake inhibitor. It is more potent than cocaine in inhibiting dopamine uptake, and also more selective than cocaine for the dopamine relative to the noradrenergic or serotonergic transporters. Similar to psychostimulants, it increases locomotor activity in rodents and can induce stereotypies. Ethylphenidate demonstrates clinical effects typical of amphetamine-like stimulants, including tachycardia, hypertension, dilated pupils, palpatations, fever, anxiety, agitation, paranoia and tremor. Ethylphenidate use has been associated with deaths due to mixed drug toxicity, and in one documented instance, ethylphenidate alone was detected.

**Dependence potential**
Controlled, human and laboratory animal studies regarding the potential physical dependence effects of ethylphenidate have not been reported. There is one brief published case study describing an individual who developed dependence on ethylphenidate purchased from the internet. The subject had previously been dependent on cannabis, heroin/morphine and had occasionally used stimulants.

**Actual abuse and/or evidence of likelihood of abuse**
Ethylphenidate is sold over the internet and discussed on drug-user websites, and has been identified in confiscated material. Routes of administration reported by users include nasal insufflation, oral, anal, vapour inhalation and intravenous injection. Users report an immediate and intense rush of pleasurable stimulation, which is characterized by alertness and a general mood lift. Other effects reported include increased self-confidence, improved ability to focus and concentrate, and enhanced social interaction and social skills. The pro-social effects appear similar to those reported by users of MDMA. Users on internet forums report tolerance to some of its effects, leading to a higher drug dose to achieve the same effect and also describe a strong urge to re-dose. Ethylphenidate is under control in several countries in different regions.

**Therapeutic usefulness**
There are currently no known therapeutic applications for ethylphenidate.


**Recommendation**

The Committee considered that the degree of risk to public health and society associated with the abuse of ethylphenidate (ethyl phenyl(piperidin-2-yl)acetate) is substantial. Therapeutic usefulness has not been recorded. It recognized that it has similar abuse and similar ill-effects as substances in Schedule II of the UN 1971 Convention on Psychotropic Substances. The Committee considered that there is sufficient evidence that ethylphenidate is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control. As per the *Guidance on the WHO review of psychoactive substances for international control*, higher regard was accorded to the substantial public health risk than to the lack of therapeutic usefulness. The Committee recommended that ethylphenidate be placed in Schedule II under the UN 1971 Convention on Psychotropic Substances.

**5.8 Methiopropamine (MPA)**

*Substance identification*

Chemically, methiopropamine is \( N \)-methyl-1-(thiophen-2-yl)propan-2-amine. It has a chiral centre with two enantiomers.

*Previous review*

Methiopropamine was previously critically reviewed by the Committee at its 36th meeting. Owing to the insufficiency of data regarding dependence, abuse and risks to public health, the Committee recommended that methiopropamine not be placed under international control but be kept under surveillance. Subsequent data collected from the literature and from different countries indicated that this substance may cause substantial harm and that it has no medical use warranting an updated critical review.

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

Methiopropamine is a thiophene analogue of methamphetamine, but is not readily converted into other controlled substances. It increases the synaptic levels of dopamine and noradrenaline, an effect similar to that of methamphetamine. Also similar to methamphetamine, it increases locomotor activity and induces its sensitization in mice.
Adverse effects following administration that have been reported are tachycardia, anxiety, panic attacks, perspiration, headache, nausea, difficulty in breathing, vomiting, difficulty urinating and sexual dysfunction. Case reports indicate that methiopropamine induces palpitations, chest tightness, anxiety, nausea, vomiting, and visual hallucinations. Methiopropamine has been associated with 62 deaths; in at least 14 of these it was thought to have contributed to death even though other drugs were present. One death was thought to be solely related to methiopropamine use.

**Dependence potential**
Controlled, human and laboratory animal studies regarding the potential physical dependence effects of methiopropamine have not been reported.

**Actual abuse and/or evidence of likelihood of abuse**
Methiopropamine is sold on internet websites as a “research chemical” or in branded products, predominantly in powder form. Methiopropamine abuse has been reported in many countries in different regions. Users report using methiopropamine by insufflation, inhalation or orally. Case reports and user reports indicate that methiopropamine displays similar properties to methamphetamine, including stimulation, alertness and increase of focus and energy as well as talkativeness. Methiopropamine is a controlled substance in a number of countries in different regions.

**Therapeutic usefulness**
There are currently no known therapeutic applications for methiopropamine.

**Recommendation**
The Committee considered that the degree of risk to public health and society associated with the abuse of methiopropamine (N-methyl-1-(thiophen-2-yl)propan-2-amine) is substantial. Therapeutic usefulness has not been recorded. It recognized that it has similar abuse and similar ill-effects as substances in Schedule II of the UN 1971 Convention on Psychotropic Substances. The Committee considered that there is sufficient evidence that methiopropamine is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control. As per the **Guidance on the WHO review of psychoactive substances for international control**, higher regard was
accorded to the substantial public health risk than to the lack of therapeutic usefulness. The Committee recommended that methiopropamine be placed in Schedule II under the UN 1971 Convention on Psychotropic Substances.

5.9 MDMB-CHMICA

Substance identification
Chemically, MDMB-CHMICA is methyl \(N\)-\{[1-(cyclohexylmethyl)-1\(H\)-indol-3-yl]carbonyl\}-3-methyl-L-valinate. MDMB-CHMICA has a chiral carbon in the butanoic chain. Therefore, two stereoisomers exist: \((S)\)-MDMB-CHMICA and \((R)\)-MDMB-CHMICA.

Previous review
MDMB-CHMICA has not been previously pre-reviewed or critically reviewed. A direct critical review is proposed based on information brought to the attention of the WHO that MDMB-CHMICA is clandestinely manufactured, poses serious risk to public health and society, and has no recognized therapeutic use by any Party.

Similarity to known substances and effects on the central nervous system
MDMB-CHMICA belongs to the group of Synthetic Cannabinoid Receptor Agonists (SCRAs). MDMB-CHMICA has been shown to activate \(CB_1\) and \(CB_2\) cannabinoid receptors with preference for \(CB_1\) receptors over \(CB_2\) receptors. MDMB-CHMICA is a highly efficacious compound with full agonist properties at the \(CB_1\) receptor of the endocannabinoid system and with a greater potency than \(\Delta^9\)-THC. Few other laboratory animal or human pharmacodynamic reports are available that describe the pharmacology of MDMB-CHMICA. Case reports and user reports indicate that MDMB-CHMICA can induce acute toxicity and serious adverse events including nausea, confusion, agitation, hallucinations, loss of consciousness, emesis, bradycardia or tachycardia, spontaneous urination and defecation, respiratory insufficiency and acidosis, hypothermia, mydriasis, hypoglycaemia, and seizures including tonic-clonic. MDMB-CHMICA has been associated with 53 analytically confirmed cases of serious adverse events in Europe and at least 28 deaths. Whilst in most instances other drugs (typically other SCRA) were also present, MDMB-CHMICA was the sole substance detected in some cases.
Dependence potential

Controlled, human and laboratory animal studies regarding the potential physical dependence or tolerance effects of MDMB-CHMICA have not been reported. Withdrawal-like symptoms from abstinence of MDMB-CHMICA such as numbing of skin, cravings, mental fog, depressed mood, nausea and abdominal pain have been reported by poison information centres and on user websites. However, in such circumstances information on duration of use, pattern and amount consumed over time has not been described.

Actual abuse and/or evidence of likelihood of abuse

There are no reports of controlled studies involving the dependence potential or abuse potential of MDMB-CHMICA in laboratory animal or human subjects available. Epidemiological reports of the incidence and prevalence of MDMB-CHMICA also appear unavailable. MDMB-CHMICA is easily purchased on the internet (sold online) as a commercially branded legal high or as a research chemical in various countries in different regions. Over 3600 seizures or detections of MDMB-CHMICA involving 21 European countries were reported in February 2016. In addition to the non-fatal and fatal intoxications, MDMB-CHMICA use (analytically confirmed) has been related to DUIDs and violent public behaviour. A number of countries in different regions have MDMB-CHMICA under some level of national control.

Therapeutic usefulness

There are no known approved therapeutic applications for MDMB-CHMICA.

Recommendation

The Committee considered that the degree of risk to public health and society associated with the abuse of MDMB-CHMICA (methyl N-((1-(cyclohexylmethyl)-1H-indol-3-yl)carbonyl)-3-methyl-L-valinate) is substantial. Therapeutic usefulness has not been recorded. It recognized that it has similar abuse and similar ill-effects as substances in Schedule II of the UN 1971 Convention on Psychotropic Substances. The Committee considered that there is sufficient evidence that MDMB-CHMICA is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control. As per the Guidance on the WHO review of psychoactive substances for international control, higher regard was accorded to the substantial public health risk than to
the lack of therapeutic usefulness. The Committee recommended that MDMB-CHMICA be placed in Schedule II under the UN 1971 Convention on Psychotropic Substances.

5.10 5F-APINACA (5F-AKB-48)

Substance identification
Chemically, 5F-APINACA is \( N\)-(adamantan-1-yl)-1-(5-fluoropentyl)-1\(H\)-indazole-3-carboxamide.

Previous review
5F-APINACA has not been previously pre-reviewed or critically reviewed by the Expert Committee on Drug Dependence of the WHO. A direct critical review is proposed based on information brought to the attention of the WHO that 5F-APINACA is clandestinely manufactured, poses serious risk to public health and society, and has no recognized therapeutic use by any Party.

Similarity to known substances and effects on the central nervous system
5F-APINACA (5F-AKB-48) is an analogue of APINACA (AKB-48) fluorinated on the terminal carbon of the pentyl chain. 5F-APINACA binds to cannabinoid \( \text{CB}_1 \) and \( \text{CB}_2 \) receptors with greater potency than THC and activates the \( \text{CB}_1 \) receptor as a full agonist. 5F-APINACA induces a prolonged release of dopamine in the shell of the nucleus accumbens in awake mice. The \( \text{CB}_1 \) cannabinoid receptor antagonist/inverse agonist, AM251, blocks several \textit{in vivo} effects of 5F-APINACA in mice including its induced spontaneous and stimulated aggressiveness, hypothermic effects, and antinociceptive effects. The \textit{in vitro} binding and functional activity effects of 5F-APINACA, along with its \textit{in vivo} effects of hypothermia, cataleptic and antinociceptive effects that are blocked by AM251, are consistent with a THC-like cannabinoid compound. In contrast to THC, high doses of 5F-APINACA induce spontaneous and handling-induced convulsions, hyperreflexia and myoclonus in mice. Anxiety, paranoia, dry mouth, headache, hyperthermia have been reported by users of 5F-APINACA on blogs and forums. Recently, there have been a number of non-fatal intoxications involving 5F-APINACA in several countries. Adverse events described in one analytically confirmed case report were agitation, tachycardia, hypertension, twitching, and chest pain.
Dependence potential

Controlled, human and laboratory animal studies regarding the potential of 5F-APINACA to produce physical dependence or tolerance have not been reported. Users report acute physical withdrawal symptoms when attempting to reduce use including chest pains, chest pressure, tachycardia and palpitations, lower extremity pain and spasms, nausea, sweating, diarrhoea, and vomiting, which were easily resolved by resuming smoking of 5F-APINACA. Psychological withdrawal symptoms included insomnia (for over 3 weeks), internal restlessness, urge to re-dose, anxiety, agitation and paranoia.

Following initial use of between one and four grams per day of herbal mixtures containing 5F-APINACA, users report that the amount used increases quickly. Compulsive re-dosing occurs despite recognition of loss of control, awareness of tolerance and fears around adverse effects. The development of thoughts and cravings about smoking first thing in the morning can develop rapidly following initial patterns of use of 5F-APINACA.

Actual abuse and/or evidence of likelihood of abuse

5F-APINACA is sold over the internet. It has been detected in commercial or seized products in several countries in different regions. One country has reported four DUID cases in which 5F-APINACA was detected. A number of countries are directly controlling 5F-APINACA under national legislation.

Therapeutic usefulness

There are no known approved therapeutic applications for 5F-APINACA.

Recommendation

The Committee considered that the degree of risk to public health and society associated with the abuse of 5F-APINACA \((N\text{-}(adamantan-1-yl)-1\text{-}(5\text{-}fluoropentyl)-1H\text{-}indazole\text{-}3\text{-}carboxamide)\) is substantial. Therapeutic usefulness has not been recorded. It recognized that it has similar abuse and similar ill-effects as substances in Schedule II of the UN 1971 Convention on Psychotropic Substances. The Committee considered that there is sufficient evidence that 5F-APINACA is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control. As per the Guidance on the WHO review of psychoactive substances for international
higher regard was accorded to the substantial public health risk than to the lack of therapeutic usefulness. The Committee recommended that 5F-APINACA be placed in Schedule II under the UN 1971 Convention on Psychotropic Substances.

5.11 JWH-073

Substance identification
Chemically, JWH-073 is (1-butyl-1H-indol-3-yl)(1-naphthyl)methanone.

Previous review
During its 36th meeting, the WHO Expert Committee on Drug Dependence discussed the critical review report on JWH-073 and concluded that owing to the current insufficiency of data regarding dependence, abuse and risks to public health, JWH-073 should not be placed under international control at that time but be kept under surveillance. New information on its pharmacology and abuse potential warranted an update of the critical review report for discussion at the 38th ECDD.

Similarity to known substances and effects on the central nervous system
JWH-073 is a homologue of JWH-018 that has been included in Schedule II of the Psychotropic Substances Convention (1971) since 2015. JWH-073 binds to the CB₁ and CB₂ cannabinoid receptors and exhibits functional *in vitro* activity. Several metabolites of JWH-073 also bind to the CB₁ receptor. Similar to THC, JWH-073 induces in mice a marked hypothermia, increases pain threshold to both noxious mechanical and thermal stimuli, causes catalepsy, reduces motor activity, and stimulates dopamine release in the nucleus accumbens in a dose-dependent manner after systemic administration. In addition, it impairs sensorimotor responses (visual, acoustic and tactile), causes seizures, myoclonia, hyperreflexia and promotes aggression. All these effects are fully prevented by the selective CB₁ receptor antagonist/inverse agonist, AM251. Repeated administration of JWH-073 can induce tolerance to some of its effects, and repeated administration of THC can produce cross-tolerance to some of the effects of JWH-073. Users have reported anxiety, tremulousness, and experiencing palpitations. One user reported that she felt like "becoming psychotic". Potency is reported to be about half of the potency of JWH-018. There have been several patients presenting with analytically confirmed JWH-073 consumption. These
patients presented with some of the following signs: chest pain, tachycardia followed by bradycardia, hypertension, agitation, paranoia and delusions, abdominal cramps with nausea and vomiting, anxiety, and tremulousness. However, these reports typically involved the presence of other drugs and it is difficult to draw a direct linkage between these adverse effects and JWH-073. No fatal cases in which JWH-073 was detected in post-mortem samples have been reported so far.

Dependence potential
Controlled, human and laboratory animal studies regarding the potential physical dependence or tolerance effects of JWH-073 have not been reported.

Actual abuse and/or evidence of likelihood of abuse
In rats and rhesus monkeys, JWH-073 produces the discriminative stimulus effects of THC. Additionally, both THC and JWH-073 substitute for the discriminative stimulus effects of JWH-018 in mice. Repeated administration of THC, however, produces tolerance to its discriminative effects in rhesus monkeys, but not cross-tolerance to JWH-073. In common with THC, JWH-073 is not self-administered by rats.

JWH-073 is sold over the internet and has been sold as an additive in commercially available "herbal mixtures". It is sold as a powder or, when sold in herbal mixtures, the chemical has been sprayed on plant material (e.g. damiana). Based on user reports and on the dosage forms offered, the primary route of administration is inhalation either by smoking the ‘herbal mixture’ as a ’joint’ or utilizing a vaporizer, bong or pipe. Abuse has been reported in a number of countries in different regions. A number of countries in different regions have brought JWH-073 under national control.

Therapeutic usefulness
There are no known approved therapeutic applications for JWH-073.

Recommendation
The available pharmacodynamic data related to JWH-073 (1-butyl-1H-indol-3-yl)(1-naphthyl)methanone) demonstrates that this substance has the capacity to produce some effects similar to its homologue, JWH-018, that is included in Schedule II of the UN 1971 Convention on Psychotropic Substances. However, the data currently available does not
make it possible to establish a direct link between JWH-073 abuse and appearance of public health and social problems that would be a requirement for placing this substance under international control. It is therefore recommended not to place JWH-073 under international control but to continue to keep it under surveillance.

5.12 XLR-11

Substance identification
Chemically, XLR-11 is [1-((5-fluoropentyl)-1H-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone.

Previous review
XLR-11 has not been previously pre-reviewed or critically reviewed. A direct critical review is proposed based on information brought to WHO’s attention that XLR-11 is clandestinely manufactured, poses serious risk to public health and society, and has no recognized therapeutic use by any Party.

Similarity to known substances and effects on the central nervous system
Metabolites of XLR-11 include UR-144, a compound recognized for its own abuse potential. XLR-11 binds to cannabinoid CB₁ and CB₂ receptors with greater affinity than THC. XLR-11 acts as a full agonist at both these receptors. XLR-11 produces all four effects in the THC tetrad test in the mouse, all components of which, except catalepsy, are antagonized by the CB₁ receptor antagonist, rimonabant. Adverse effects associated with XLR-11 use include nausea, vomiting, low body temperature, rigid muscle tone, back and abdominal pain, hypertension, slurred speech, lack of convergence, and body and eyelid tremors. Of particular concern was the reported association of XLR-11 use and acute kidney injury in hospitalisations. Analytically determined use of XLR-11 has been confirmed in driving-under-the-influence cases. Confirmed presence of XLR-11 has been associated with two deaths.

Dependence potential
Controlled, human and laboratory animal studies regarding the potential physical dependence or tolerance effects of XLR-11 have not been reported.
Actual abuse and/or evidence of likelihood of abuse

XLR-11 produces THC-like discriminative stimulus effects in mice and rats that predict it would be able to produce THC’s subjective effects and likely have an abuse potential similar to it. The discriminative stimulus effects of XLR-11 are antagonized by rimonabant. XLR-11 is often sold in the form of herbal mixtures, and designed for smoking purposes. XLR-11 has been encountered in seizures or as an abused substance in a number of countries in different regions. XLR-11 is under national controls in a number of countries and different regions.

Therapeutic usefulness

There are no approved therapeutic applications for the clinical or veterinary use of XLR-11.

Recommendation

The Committee considered that the degree of risk to public health and society associated with the abuse of XLR-11 ([(1-(5-fluoropentyl)-1H-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone) is substantial. Therapeutic usefulness has not been recorded. It recognized that it has similar abuse and similar ill-effects as substances in Schedule II of the UN 1971 Convention on Psychotropic Substances such as JWH-018 and AM-2201. The Committee considered that there is sufficient evidence that XLR-11 is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control. As per the Guidance on the WHO review of psychoactive substances for international control, higher regard was accorded to the substantial public health risk than to the lack of therapeutic usefulness. The Committee recommended that XLR-11 be placed in Schedule II under the UN 1971 Convention on Psychotropic Substances.

6. Updates

6.1 Cannabis and cannabis resin

At the 37th ECDD meeting the Committee requested that Secretariat begin collecting data towards a pre-review of cannabis, cannabis resin, extracts and tinctures of cannabis at a future
meeting. Consistent with this request, two updates on the scientific literature on cannabis were prepared and subsequently presented to the Expert Committee: 1) 'Abuse and dependence potential of Cannabis sativa and nabiximols'; and 2) 'Systematic reviews on the therapeutic efficacy and safety of Cannabis (including extracts and tinctures) for patients with multiple sclerosis, chronic neuropathic pain, tics associated with Tourette syndrome, HIV/AIDS, and cancer patients receiving chemotherapy'. The Committee then discussed the content of the material presented.

In addition to the WHO commissioned reports, the Committee was made aware of other reports submitted to the Secretariat.

**Recommendation**

The Committee noted that the current Schedule I of the 1961 Single Convention on Narcotic Drugs groups together cannabis and cannabis resin, extracts and tinctures of cannabis. Cannabis plant and cannabis resin are also in Schedule IV of the 1961 Convention. The Committee further noted that there are natural and synthetic cannabinoids in Schedule I and Schedule II of the 1971 Convention.

The committee recognized:
- An increase in the use of cannabis and its components for medical purposes;
- The emergence of new cannabis-related pharmaceutical preparations for therapeutic use;
- That cannabis has never been subject to a formal pre-review or critical review by the ECDD.

The Committee requested that the Secretariat prepare relevant documentation in accordance with the *Guidance on the WHO review of psychoactive substances for international control* in order to conduct pre-reviews for the following substances:

- Cannabis plant and cannabis resin
- Extracts and tinctures of cannabis
- Delta-9-tetrahydrocannabinol (THC)
- Cannabidiol (CBD)
- Stereoisomers of THC

The Committee recommended that these pre-reviews be evaluated at a specific ECDD meeting dedicated to cannabis and its component substances to be held within the next eighteen months from the 38th ECDD meeting.

7. Follow up on recommendations from international meetings and consultations

7.1 Follow up on implementation of recommendations of UNGASS and of UNODC-WHO Expert Consultation on NPS

Dr Lopato provided an introduction to the implementation of recommendations of the UNGASS on the world drug problem by describing that the resolution S-30/1(7) adopted by the UNGASS on 19 April 2016 entitled, “Our joint commitment to effectively addressing and countering the world drug problem”, included operational recommendations responding to NPS abuse. One of the recommendations specified: “Share relevant information with ... and strengthen the capacity of the World Health Organization, the United Nations Office on Drugs and Crime, the International Narcotics Control Board and other relevant international and regional organizations to prioritize the review of the most prevalent, persistent and harmful new psychoactive substances and to facilitate informed scheduling decisions by the Commission on Narcotic Drugs”. Another operational recommendation on NPS pertained to surveillance and specified: “Actively participate in early warning networks and promote the use of relevant surveillance lists and voluntary controls and the sharing of information through the International Narcotics Control Board, the United Nations Office on Drugs and Crime and the World Health Organization... and enhance bilateral, subregional, regional and international cooperation in the identification and reporting of new psychoactive substances and incidents involving such substances...”.

Dr Lopato informed the Committee that the WHO had several meetings after the UNGASS 2016 during which the recommendations on NPS were discussed. One of these meetings included the 3rd UNODC-WHO Expert Consultation on NPS that took place on 3 to 4 May 2016 at WHO headquarters where the prioritization of the most harmful, prevalent
and persistent NPS for evaluation by ECDD was discussed. In addition to collecting data for prioritization from INCB, UNODC, EMCDDA, the UMC and Member States, it was proposed to include other international organizations in the prioritization process (e.g. the World Customs Organization 'WCO' and Interpol) to facilitate data collection regarding confiscations and seizures as indicators for market presence. It was also proposed to increase Member States’ contributions. It was remarked that the availability of reference standards and established standardized methodologies for identification were necessary in order to improve forensic laboratory capacity for detection and identification of NPS.

Dr Lopato emphasized that an efficient early warning systems (EWS) relies on ongoing and dynamic data collection at national and regional levels, which then feed into an international EWS. It was mentioned that the network for data exchange needs two-way communication. Effective and timely notification of health-related risks involving the use of NPS was also considered important. The publication of surveys, reports, and results of scientific studies was encouraged, as evidence-based information should be disseminated. Improving quality of data was also considered critical for future evaluation of psychoactive substances.

Dr Justice Tettey, UNODC, provided a summary of the third UNODC-WHO Expert Consultation on NPS held in Geneva in May 2016, following CND resolution 58/7, that had brought together experts from international and regional organizations and subject-matter experts to explore practical ways for collecting robust data for the prioritization of the most harmful NPS, as well as for establishing efficient surveillance systems. In the context of UNODC’s mandates, the Expert Consultation made further recommendations with regard to strengthening national forensic and law enforcement capacity to aid in the identification and detection of NPS.

Dr Tettey provided information on progress made since the Expert Consultation in promoting effective international exchange of information for identifying the most harmful, prevalent and persistent NPS. An international expert consultation on forensic toxicology and drug control held in Vienna, Austria in June 2016, resulted in a successful pilot exercise to develop a tool to collect and disseminate toxicological data on adverse health consequences and fatalities associated with NPS use. The UNODC Early Warning Advisory on NPS will be expanded to include a feature for collecting and disseminating information on the harms due to NPS.
Dr Tettey further described on-going activities to improve the capacity of national drug testing laboratories that included its International Collaborative Exercises, the provision of reference standards, the guidance provided on the laboratory analysis of NPS, and through workshops and training. The enhancement of law enforcement capacity to detect NPS is being pursued through a number of national and regional training workshops conducted through the Global Synthetic Monitoring Analysis and Trends (SMART) programme, as well as through the provision of field drug detection kits.

7.2 WHO and other agencies surveillance mechanisms and lists

Dr Lopato briefed the Committee on the WHO surveillance mechanisms and list. She described the Commission on Narcotic Drugs (CND) Resolution 59/8 (March 2016) which invited the WHO, with the support of the United Nations Office on Drugs and Crime, relevant regional organizations and Member States, to disseminate its surveillance list of substances of concern, in order to proactively collect evidence on these substances to support future evidence-based reviews and for issuing public health alerts when there is sufficient evidence that a new psychoactive substance poses a risk to public safety. The content of Dr Lopato's briefing touched on several points.

There is a need for establishing a new surveillance system at the international level in order to facilitate the scheduling process and to respond effectively to prevent harm to public health arising from the use of NPS. The maintenance of a WHO surveillance list (with special attention to NPS) will allow information to be collated that can be used in future ECDD deliberations as well as in the prioritisation process of substance review.

Currently, there are eleven substances kept under the WHO surveillance that were already critically reviewed by 36th ECDD in 2014 (10 substances) and 37th ECDD in 2015 (1 substance). As there was insufficient evidence on harms and risks to health arising from use of these substances at that time, the Committee recommended that they should not be placed under international control, but be kept under surveillance. Substances in the current WHO surveillance list were considered during the prioritization process for their possible evaluation by 38th ECDD meeting.

A surveillance system was discussed during the 3rd UNODC-WHO Expert Consultation on New Psychoactive Substances (NPS) and the 1st Informal Working Group of the ECDD in May 2016. It was considered, and then proposed, that a list of substances under
surveillance by WHO shall be actively maintained through the proactive collection of data from international organisations (e.g. UNODC, INCB, and WCO), regional organisations (e.g. EMCDDA) and national observatories and Member States. WHO should accumulate data continuously. This will mainly rely on collaborative arrangements with multiple organisations and bodies, including the UNODC (e.g. through Global Synthetics Monitoring, Analyses, Reporting and Trends 'SMART' programme and the Early Warning Advisory (EWA) on NPS), the EMCDDA (EU EWS), other regional organisations, and Member States.

Information potentially useful in placing a substance under surveillance includes: the known or likely mechanism of action relevant to predicting that significant adverse events can be expected; direct evidence of adverse effects such as forensic data regarding overdose events; fatal and non-fatal intoxications; laboratory data that is predictive of adverse events; and reports directly from users or health authorities in contact with users (with some evidence that the substance in question is correctly identified).

The primary criteria for harm shall be fatalities, in addition to other serious adverse events (e.g. non-fatal intoxications) and other public health risks (e.g. DUIDs and harms to others). Other criteria and data for consideration would include available pharmacological information and context or mode of use. It was also emphasized that there must also be criteria for excluding substances from the WHO surveillance list.

Dr Lopato stated that there are numerous important challenges confronting the satisfactory employment of a surveillance list, including the development of a pipeline of health-related data from Member States, maintaining a database of a large number of frequently changing substances, developing criteria to be used for inclusion of a substance in the surveillance list, determining conditions for issuing a health alert on a substance, deciding how much information is included about each substance on the list, and disseminating the surveillance list and health alerts.

Dr Lopato concluded by noting that the updated surveillance list will be published on the ECDD website.

Ms Beate Hammond, Observer from INCB, presented an update on INCB international operations on new psychoactive substances (NPS), known as Project ION. The objective of Project ION is to reduce the supply of NPS and therefore prevent them from reaching consumer markets. In doing so, the project contributes to preventing harms to
human health. Project ION has received political support from the international community in Commission on Narcotic Drugs resolution 59/8(5) and, most recently, in the UNGASS outcome document. Over the last six months, the number of persons using IONICS, the incident communication system for the exchange of information on NPS, as well as the number of communicated incidents has increased by more than 25 per cent.

In cooperation with UNODC, INCB will organize a conference on NPS in Bangkok early 2017 to take stock of achievements and discuss the challenges ahead. It is expected that the conference will result in the adoption of an outcome document and operational recommendations that will translate UNGASS commitments into actions. Future plans include an intelligence-gathering survey on opioid-type NPS which have been causing serious health harms in North America and a time-bound operation on NPS in other regions.

INCB also has an NPS surveillance list that is regularly updated, as the prevalence of substances can change quickly and some substances will be placed under international control. Although the list is not compiled for scheduling purposes, several of the substances have in fact now been scheduled or are being reviewed by the ECDD.
8. Future agenda items

The Committee agreed that it would request that the Secretariat arrange a critical review of 3-MMC for a subsequent Expert Committee meeting.

In addition, the Committee requested that the Secretariat prepare pre-review documentation on cannabis-related substances. The following specific pre-reviews were requested:

- Cannabis plant and cannabis resin
- Extracts and tinctures of cannabis
- Delta-9-tetrahydrocannabinol (THC)
- Cannabidiol (CBD)
- Stereoisomers of THC

The Committee recommended that these pre-reviews be evaluated at a specific ECDD meeting dedicated to cannabis and its component substances to be held within the next eighteen months following the 38th ECDD meeting.
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