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WHO Expert Committee on Drug Dependence

Thirty-eighth report

World Health Organization

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Geneva, Switzerland, 14–18 November 2016

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Abbreviations

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
4,4´-DMAR	*para*-methyl-4-methylaminorex
DUID	driving under the influence of drugs
ECDD	Expert Committee on Drug Dependence
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
EML	WHO Model List of Essential Medicines
EMP	WHO Department of Essential Medicines and Health Products
ethylone	1-(2*H*-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
5F-APINACA	*N*-(adamantan-1-yl)-1-(5-fluoropentyl)-1*H*-indazole-3-carboxamide
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICD-11	International Classification of Diseases
INCB	International Narcotics Control Board
JWH-073	(1-butyl-1*H*-indol-3-yl)(1-naphthyl)methanone
MDMA	3,4-methylenedioxymethamphetamine
MDMB-CHMICA	methyl *N*-{[1-(cyclohexylmethyl)-1*H*-indol-3-yl] carbonyl}-3-methyl-L-valinate
4-MEC	2-(ethylamino)-1-(4-methylphenyl)propan-1-one
3-MMC	2-(methylamino)-1-(3-methylphenyl)propan-1-one
MPA	*N*-methyl-1-(thiophen-2-yl)propan-2-amine

MSB/MSD	WHO Management of Substance Abuse Unit at the Department of Mental Health and Substance Abuse
MT-45	1-cyclohexyl-4-(1,2-diphenylethyl)piperazine
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 Organization
XLR-11	[1-(5-fluoropentyl)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone

Introduction

The thirty-eighth meeting of the World Health Organization (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 the time and effort they had dedicated to the thorough review of the substances on the agenda of this ECDD meeting. She outlined the central role of scientific evidence in the decision-making process of Expert Committees and in WHO's normative and standard-setting role.

Dr Kieny reiterated the importance of the international drug control conventions and of the recommendations of the Special Session of United Nations General Assembly (UNGASS) on the world drug problem, that guide WHO's work towards positioning health at the centre of responses to the world drug problem and achieving the health-related objectives of the Sustainable Development Goals (SDGs). She emphasized the need for WHO to work closely with the United Nations Office on Drugs and Crime (UNODC), the International Narcotics Control Board (INCB) and other global and regional entities, as well as Member States, to achieve efficient and successful implementation of the UNGASS operational recommendations and tackle the world drug problem.

Dr Kieny discussed that at its thirty-eighth meeting, the ECDD would assess 12 new psychoactive substances (NPS). WHO's 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 end, a systematic and evidence-based prioritization of NPS had been carried out in advance of the thirty-eighth meeting of the ECDD and a number of Member States had contributed by sharing published and unpublished data.

Dr Kieny noted that the Expert Committee would also discuss an update on cannabis and cannabis resin in light of the growing interest of Member States in its medical use 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 ECDD at its thirty-seventh meeting, the WHO Secretariat had collected new data and commissioned systematic reviews on medical use and on dependence and harm of cannabis and cannabis resin. The available scientific evidence and public health considerations would 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 EMP, provided the Committee with 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 for expert advisory panels and committees (1)* as well as the *Guidance on the WHO review of psychoactive substances for international control (2)*.

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 were 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 D. 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 – methyl *N*-{[1-(cyclohexylmethyl)-1*H*-indol-3-yl]carbonyl}-3-methyl-L-valinate (MDMB-CHMICA) – under consideration by the ECDD at its thirty-eighth meeting.

Dr Edmundus J.M. Pennings declared that he has been a member of the Committee for the Risk Assessment of NPS in the Netherlands 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 had never carried out a risk assessment for any of the substances that would be critically reviewed at the thirty-eighth meeting of the ECDD.

The disclosed interests were considered by the Secretariat of the thirty-eighth ECDD as not in conflict with any issues to be discussed at the meeting or with the recommendations to be issued by the Expert Committee. No other interests declared by members of the Expert Committee 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 Single Convention on Narcotic Drugs, 1961 *(3)*, 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 10 members are elected from a list of candidates nominated by governments.

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

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 worldwide, the report highlights the main impediments to better availability. These include fear of addiction and lack of awareness on the proper use of internationally controlled drugs for medical purposes, as well as constraints on both human and financial resources.

The report makes recommendations to governments on how this situation can be improved. To bridge the knowledge gap, for example, it is necessary to develop and implement educational programmes and disseminate information to overcome cultural resistance, where necessary. Many countries continue to experience difficulties in properly estimating their needs for opioid analgesics and psychotropic substances and in monitoring their consumption. The report therefore calls on governments to make use of the INCB/WHO *Guide on estimating requirements for substances under international control (4)*. In addition, governments should review national legislation, regulatory and administrative mechanisms and procedures, including domestic distribution channels, with the aim of simplifying and streamlining the processes. This would involve removing 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 UNODC, informed the Committee that NPS continued to appear at a fast pace on drug markets worldwide and their use had been associated with 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 characterized by heterogeneity in the nature and scope of the problem, the transient nature of some of the substances reported and a paucity of information on public health harm. A recent trend in the marketing of blends or mixtures of NPS, makes the interpretation of data on their associated harm particularly challenging. UNODC research and trend analysis contributes to improving the understanding of, and shaping the response to, the NPS issue through knowledge products and early warnings. These efforts 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. Its EWA on NPS is actively used by Member States and international organizations, such as WHO, in the context of the selection of substances for consideration by the ECDD and to inform the scheduling decisions of the CND.

He emphasized 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 10 NPS under international control. Pursuant to these scheduling decisions, UNODC supported their implementation by Member States through the development and dissemination of a series of recommended laboratory methods of analyses. It provided more than 1400 units of chemical reference materials for these substances to forensic institutions in 55 countries. In addition, selected substances were introduced in UNODC's international collaborative exercises, a biannual proficiency test scheme for national drug laboratories. This scheme currently supports more than 250 laboratories from 70 countries, to enhance their preparedness to identify these threats. To further aid in implementation of the scheduling decisions, UNODC revised its *Multilingual dictionary of narcotic drugs and psychotropic substances under international control (5)*, the *Multilingual dictionary of precursors and chemicals frequently used in the illicit manufacture of narcotic drugs and psychotropic substances under international control (6)* and the *Terminology and information on drugs (7)*.

Dr Tettey described a comprehensive programme of training to enhance law enforcement capacity in identifying NPS and substances under international control that 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 infrared spectrometers for training in field testing for drugs and precursors, 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 humankind. In September 2016, UNODC, in collaboration with WHO, convened a meeting of experts on substance disorders from around the world to explore new frontiers of health protection with regard to NPS. The participants discussed key aspects of NPS, in particular diagnostic approaches and treatment options, with the goal of developing a practical tool to be used by clinicians worldwide.

Dr Tettey went on to describe the continuing efforts to operationalize the recommendations on NPS outlined in the outcome document of the UNGASS 2016. Specifically, the third UNODC-WHO Expert Consultation in Geneva in May 2016 focused 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 towards addressing the paucity of data on the harm of NPS. Global trends in emergence of NPS continue to evolve rapidly. The past 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 harm to public health has been immense. In this context, on 25 October 2016, the UN Secretary-General notified states parties of the communication sent by the United States of America, further to the provisions in the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988, 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, to 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 to share its findings with WHO.

The Committee was informed that, at its fifty-ninth 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 *(3, 8)*. On 17 May 2016, the Secretary-General notified states parties of these scheduling decisions. The revised schedules under the 1961 and the 1971 Conventions came into effect on 18 May 2016 and 13 November 2016, respectively.

Dr Tettey concluded that UNODC will continue to extend support to Member States through research and trend analysis to improve understanding of the NPS problem. It will also provide the relevant tools and services to support Member States' implementation of the new scheduling decisions.

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

Dr Gilles Forte, Coordinator, Policy, Governance and Knowledge Management, provided an update from the WHO EMP.

Dr Forte emphasized that WHO is committed to implementing the UNGASS recommendations related to health, and will work closely with UNODC, the 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 *(9)*, underscores that the availability of internationally controlled drugs for medical and scientific purposes remains low to non-existent in many countries and emphasizes the need for international cooperation to promote measures to improve access to 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 ensuring 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 to address barriers to access, while 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 on 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 undertakes regular reviews of the efficacy and safety of medicines, including controlled medicines. These reviews inform recommendations for the inclusion in or exclusion of medicines from the WHO Model List of Essential Medicines (EML). The WHO Secretariat had 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 at its meeting in March 2017. Also, the WHO Secretariat has developed guidelines for the management of persisting pain in children and is currently developing new guidelines for the management of cancer pain in adults.

In collaboration with UNODC and the Union for International Cancer Control, WHO is part of the Joint Global Programme on Access to Controlled Drugs for Medical Purposes while Preventing Diversion and Abuse, in particular for the management of pain. The programme is currently supported by Australia and Belgium and implemented in the Democratic Republic of the Congo, Ghana and Timor-Leste. 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 that will improve practices and enhance 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 to support the development of balanced national policies on controlled substances that ensure availability and accessibility, while preventing misuse and abuse.

1.4 Update from the WHO Department of Mental Health and Substance Abuse

Dr Vladimir Poznyak, Coordinator, Management of Substance Abuse unit of the Department of Mental Health and Substance Abuse (MSB/MSD), informed the Committee about the outcomes of the UNGASS on the world drug problem (April 2016). He also described WHO's work on three of the five public health pillars, and critical elements of the public health dimension of the world drug problem as described in the report by the Secretariat to the sixty-ninth World Health Assembly. These three pillars are: (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. WHO's new estimates of drug-attributable disease burden indicate that more than 450 000 deaths globally are attributed to illicit drug use, including cannabis use. The main conditions contributing to drug-

attributable deaths are drug use disorders, hepatitis C virus (HCV), human immunodeficiency virus (HIV), road traffic injuries and suicide. The impact of cannabis use on mental health and on the health of people other than regular cannabis users requires further research. The increasing availability of cannabis in many countries may have a negative impact on population health and needs to be monitored closely. It is still difficult to quantify the impact of NPS on health at a population level and specific strategies need to be developed to fill this gap. The draft version of the revised International Classification of Diseases (ICD-11) provides additional possibilities for coding and reporting health conditions resulting from the use of synthetic cannabinoids and cathinones, as well as the use of cocaine, 3,4-methylenedioxymethamphetamine (MDMA), phencyclidine; 1-(1-phenylcyclohexyl)piperidine (PCP) and related drugs.

1.5 Update from the WHO Department of HIV/AIDS

Dr Andrew Ball, Senior Adviser 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 drugs have chronic HCV infection. WHO's HIV department has synthesized the evidence for a public health approach to injecting drug use, based on harm reduction principles, and has developed normative guidance on HIV and hepatitis prevention, diagnosis, treatment and care. A comprehensive package of evidence-based interventions to reduce the harm 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 *(10)*.

Given the evidence of the utility of harm reduction approaches in addressing drug use and drug use disorders and in 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 harm 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 General Assembly High-Level Meeting

on Ending AIDS and the UNGASS on the world drug problem, as well as the International AIDS Conference and the Global Hepatitis Summit. Furthermore, the SDGs' 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, WHO is now focusing on providing technical support to countries implementing a public health sector response. Countries are also being supported to improve their strategic information systems and in the use of 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 of HIV/AIDS also manages a special web page on access to controlled medicines such as methadone, buprenorphine and oral morphine as part of the AIDS Medicines and Diagnostics Services database.

Finally, the Dr Ball described the work of the Department of HIV/AIDS on outlining the structural barriers that impede implementation and scale-up of services for people whose behaviour tends to be criminalized, including for people who use and inject drugs. Measures to address these barriers 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's work

Dr Eda Lopato, Technical Officer, Innovation, Access and Use, EMP, briefed the Committee and the observers on the process of prioritization of psychoactive substances to be reviewed by the ECDD.

Dr Lopato discussed the recent CND resolution 59/8 (2016) entitled "Promotion of measures to target new psychoactive substances and amphetamine-type stimulants" *(11)*, which recognized the added value of WHO in the international response to NPS and noted WHO's 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 the ECDD. These challenges include the transient nature of psychoactive substances and the changing patterns of supply as well as countries' lack of capacity and expertise for the identification of substances (e.g. fentanyls), which leads to underreporting of use, adverse events and drug seizures. The situation is further complicated by polydrug use that makes the evaluation of harm related to each substance difficult, and the marketing of mixtures of different substances hampers the interpretation of toxicological data. In addition, published data on harm to health, adverse effects, abuse and dependence potential for NPS are scarce.

When prioritizing substances for review by the Committee, the WHO ECDD Secretariat should proactively search for and analyse data on harm to health (e.g. non-fatal or fatal intoxications), on abuse and dependence potential, and on prevalence (e.g. Is it found in more than one country or region?). To facilitate access to information that would assist in prioritization of substances for discussion at the thirty-eighth meeting of the ECDD, the Secretariat had collaborated with UNODC, the INCB, the EMCDDA, Uppsala Monitoring Centre (UMC) and with Member States. A thorough analysis of the data obtained had led to the selection of a final list of 12 substances to be reviewed.

3. Update from the first Informal Working Group of the ECDD

Professor Bruna Brands (Chair of the ECDD) provided an overview of the activities of the first Informal Working Group of the ECDD, which met in Geneva, Switzerland, on 5 and 6 May 2016.

Professor Brands explained that the working group was composed of six members of the thirty-seventh ECDD and that its aim was to propose improved methods related to the review of substances as addressed in the *Guidance on the WHO review of psychoactive substances for international control (2)*.

Aspects such as the prioritization process for NPS and the development of training materials for new members of the ECDD and for temporary advisers were addressed. A session on terminologies and on proposed classes of psychoactive substances was organized in the context of the ongoing revisions of ICD-11.

The working group also discussed the revision of the template for the critical review reports that had been used for the first time for the thirty-eighth meeting of the ECDD. ECDD members who carried out critical reviews of substances generally agreed that the new template was an improvement compared to the ones from previous ECDDs in terms of the greater clarity of the content for each section and the harmonization of information provided in the reviews.

Professor Brands also informed the Committee that the working group's revised template for the WHO questionnaire for psychoactive substances, which is used for collection of data from Member States, was used for the first time for the thirty-eighth meeting. 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 put them to the working group. Professor Brands stated that comments and questions from members and temporary advisers would be welcomed and encouraged. The working group would then try to address them during its 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 on the recommendations made at the thirty-seventh meeting of the ECDD and informed the Committee about the decisions of the CND (2016).

The thirty-seventh meeting of the WHO ECDD had taken place in Geneva, Switzerland from 16 to 20 November 2015 and the Committee had recommended that seven of the eight substances it had critically reviewed be placed under international control and 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 CND in March 2016.

4.1 Acetylfentanyl

As recommended by the ECDD at its thirty-seventh meeting, 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).

4.2 MT-45

As recommended by the ECDD at its thirty-seventh meeting, 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).

4.3 *para*-Methoxymethylamphetamine (PMMA)

As recommended by the ECDD at its thirty-seventh meeting, 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).

4.4 α-Pyrrolidinovalerophenone (α-PVP)

As recommended by the ECDD at its thirty-seventh meeting, 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).

4.5 *para*-Methyl-4-methylaminorex (4,4´-DMAR)

As recommended by the ECDD at its thirty-seventh meeting, 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).

4.6 Methoxetamine (MXE)

As recommended by the ECDD at its thirty-seventh meeting, 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).

4.7 Phenazepam

As recommended by the ECDD at its thirty-seventh meeting, 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 (2)* "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 of which has two enantiomers (*cis*, 1*R*,2*R*, and 1*S*,2*S*; *trans*, 1*R*,2*S* and 1*S*,2*R*).

Previous review

U-47700 has not previously been pre-reviewed or critically reviewed by the Committee. A direct critical review was proposed based on information brought to the attention of WHO that U 47700 is clandestinely manufactured, poses a 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 that is structurally related to U-47700 is AH-7921, and they are structural isomers of one another. AH-7921 is controlled as a Schedule I drug under the Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol, in 2015. U-47700 binds and has functional activity at the mu opioid receptor and at the delta opioid receptor. It has antinociceptive activity in mice, with about 7.5 times the potency of morphine. Similar to morphine, case reports indicate that it produces pinpoint pupils, respiratory depression, cyanosis and depressed consciousness that is clinically reversible with naloxone. Confirmed fatalities (>15) associated with the use of U-47700 have occurred in Europe and in the United States.

Dependence potential

No controlled laboratory studies in animals or humans 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 use of U-47700, suggestive of physical dependence.

Actual abuse and/or evidence of likelihood of abuse

No controlled laboratory studies in animals or humans have been reported regarding the abuse potential 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 have also been many seizures in Europe and in North America, some single seizures involving hundreds of pills. Users report administering 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 (14 November 2016) the United States placed U-47700 under its Controlled Substances Act stating that this was necessary to avoid an imminent hazard to public safety.

Therapeutic usefulness

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

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 Single Convention on Narcotic Drugs of 1961. 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 to 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 was proposed based on information brought to the attention of WHO that butyrfentanyl is clandestinely manufactured, poses a 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 to other fentanyls. Fentanyl is a Schedule I drug under the UN Single Convention on Narcotic Drugs, 1961. 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 1.5 times that of morphine and 30 times less than that of fentanyl. Case studies report clinical features that include typical opioid symptoms such as respiratory depression, apnoea and loss of consciousness, and one report indicated responsiveness to naloxone.

Dependence potential

Butyrfentanyl demonstrates cross-dependency in the morphine-dependent rhesus monkey. There are no reports of controlled studies of physical dependence or cross-dependency in human subjects.

Actual abuse and/or evidence of likelihood of abuse

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

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 Single Convention on Narcotic Drugs, 1961. It can also be converted into fentanyl. 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 to 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 thirty-sixth meeting of the WHO ECDD. 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 that had emerged from *in vitro* and *in vivo* studies since the thirty-sixth ECDD meeting prompted the current critical review.

Similarity to known substances and effects on the central nervous system

4-MEC has a homologue, 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, norepinephrine (noradrenaline) and serotonin. Also, 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. User reports of negative effects associated with 4-MEC mention 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 limited. This profile is consistent with amphetamine-like effects and it is likely that 4-MEC would produce adverse effects consistent with those associated with amphetamine.

Dependence potential

No controlled laboratory studies of the dependence potential of 4-MEC in animal or human subjects have 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 studies on the abuse potential of 4-MEC have not been conducted in humans. 4-MEC has been detected worldwide and is marketed as a "research chemical"; it has also been detected as a constituent in branded products available for purchase via the Internet and from brick-and-mortar shops. Responses 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 various regions have placed 4-MEC under national control.

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 4-MEC has similar abuse and similar ill-effects to substances in Schedule II of the UN Convention on Psychotropic Substances of 1971. 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 (2)*, 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 of the UN Convention on Psychotropic Substances of 1971.

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 side chain, so two enantiomers exist: (*R*)-3-MMC and (*S*)-3-MMC.

Previous review

3-MMC has not previously been pre-reviewed or critically reviewed. A direct critical review was proposed based on information brought to the attention of WHO that 3-MMC is clandestinely manufactured, poses a 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 Convention on Psychotropic Substances

of 1971. 3-MMC, however, is not readily converted into 4-MMC. There has been one controlled animal pharmacological study of 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. Hospitalizations have been reported, with a few being due to 3-MMC use alone. Fatalities involving polydrug abuse in which 3-MMC was detected have been reported, but its toxicological significance was low or unclear.

Dependence potential

No controlled studies on dependence potential of 3-MMC have been conducted in humans or laboratory animals.

Actual abuse and/or evidence of likelihood of abuse

No controlled laboratory studies of abuse liability have been conducted in animals or humans. In response to the WHO questionnaire for review of psychoactive substances, several countries reported abuse of 3-MMC, as a recreational drug, for its psychoactive properties. Most reports noted that the negative impact on health originating from consumption was substantial. In one country that administered a self-reporting questionnaire, 67.9% of respondents indicated they had tried 3-MMC, and 26.8% indicated that they had been using it for more than one year. In a study in another country, 66 instances of driving under the influence of drugs (DUID) involved 3-MMC; in 19 of these cases, 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 (more than 40 lifetime occasions of use). 3-MMC is a controlled substance in several countries in various regions.

Therapeutic usefulness

3-MMC has no known medical applications.

Recommendation

The Committee deliberated at length regarding the information 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 available, and the ensuing discussions, were inadequate to enable a consensus and a 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 (2)*, and as supported by its procedural reference to the thirty-fourth report of the WHO Expert Committee on Drug Dependence *(11)*, "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." In accordance with these guidelines, the Committee requested that the Secretariat arrange another critical review of 3-MMC at a subsequent meeting of the Expert Committee.

5.5 Ethylone (3,4-methylenedioxy-N-ethylcathinone; bk-MDEA; MEDEC)

Substance identification

Chemically, ethylone is 1-(2*H*-1,3-benzodioxol-5-yl)-2-(ethylamino)propan-1-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 has not previously been pre-reviewed or critically reviewed. A direct critical review was proposed based on information brought to the attention of WHO that ethylone is clandestinely manufactured, poses a 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), which is included in Schedule II of the Convention on Psychotropic Substances of 1971. However, it would be likely to 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 that it would be likely to 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

No controlled studies in humans or laboratory animals regarding the potential physical dependence effects of ethylone have been reported.

Actual abuse and/or evidence of likelihood of abuse

Results of controlled laboratory studies in animals or humans characterizing the abuse potential of ethylone have not been reported. Seizures of ethylone, or its detection in biosamples, have been reported from 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 administering the drug via the oral, rectal, insufflation, sublingual and intravenous routes. Ethylone has been associated with deaths (more than eight reports). 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-(2*H*-1,3-benzodioxol-5-yl)-2-(ethylamino)propan-1-one) is substantial. Therapeutic usefulness has not been recorded. It recognized that ethylone has similar abuse and similar ill-effects to substances in Schedule II of the Convention on Psychotropic Substances of 1971. 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 (2)*, 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 of the Convention on Psychotropic Substances of 1971.

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 pre-reviewed or critically reviewed by the Committee. A direct critical review was proposed based on information brought to WHO's attention that pentedrone is clandestinely manufactured, poses a 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 and to the noradrenergic transporters and inhibits dopamine and noradrenergic uptake, but binds poorly to the serotonergic transporter 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 thirty-eighth meeting of the ECDD indicated that the adverse effects experienced by people who present with pentedrone intoxication at emergency departments 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 case.

Dependence potential

No controlled studies in humans or laboratory animals regarding the potential physical dependence effects of pentedrone have been reported.

Actual abuse and/or evidence of likelihood of abuse

Pentedrone has been detected in commercial products or in biosamples in Canada, several European countries and in the United States. Hundreds of kilograms of pentedrone have been seized in the European Union alone. User reports

indicate that pentedrone is administered via the oral, insufflation, inhalation and intravenous routes. Several countries in different regions have placed 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 pentedrone has similar abuse and similar ill-effects to substances in Schedule II of the UN Convention on Psychotropic Substances of 1971. 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 (2)*, 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 of the UN Convention on Psychotropic Substances of 1971.

5.7 Ethylphenidate (EPH)

Substance identification

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

Previous review

Ethylphenidate has not previously been pre-reviewed or critically reviewed. A direct critical review was proposed based on information brought to the attention of WHO that ethylphenidate is clandestinely manufactured, poses a 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 Convention on Psychotropic Substances of 1971. Ethylphenidate can be converted into methylphenidate and vice versa. 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 has clinical effects typical of amphetamine-like stimulants, including tachycardia, hypertension, dilated pupils, palpitations, 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

No controlled studies in humans or laboratory animals regarding the potential physical dependence effects of ethylphenidate have been reported. One brief case study has been published 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 use of a higher drug dose to achieve the same effect and also describe a strong urge to re-dose. Ethylphenidate has been placed under national 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 ethylphenidate has similar abuse and similar ill-effects to substances in Schedule II of the UN Convention on Psychotropic Substances of 1971. 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 (2), 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 Convention on Psychotropic Substances of 1971.

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 thirty-sixth 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 at that time but be kept under surveillance. Subsequent data collected from the literature and from different countries indicating that this substance may cause substantial harm and that it has no medical use warranted 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 reported following administration include 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

No controlled studies in humans or laboratory animals regarding the potential physical dependence effects of methiopropamine have 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 administering methiopropamine by insufflation, inhalation or the oral route. 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 has been placed under national control 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 methiopropamine has similar abuse and similar ill-effects to substances in Schedule II of the UN Convention on Psychotropic Substances of 1971. 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 (2)*, 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 Convention on Psychotropic Substances of 1971.

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 was proposed based on information brought to the attention of WHO that MDMB-CHMICA is clandestinely manufactured, poses a 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-tetrahydrocannabinol (THC). Few reports of pharmacodynamic studies in laboratory animals or humans 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 seizures. MDMB-CHMICA has been associated with 53 analytically confirmed cases of serious adverse events in Europe and at least 28 deaths. While in most instances other drugs (typically other SCRAs) were also present, MDMB-CHMICA was the sole substance detected in some cases.

Dependence potential

No controlled studies in humans or laboratory animals regarding the potential physical dependence or tolerance effects of MDMB-CHMICA have been reported. Withdrawal-like symptoms associated with abstinence from 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, information on duration of use, pattern and amount consumed over time was not available.

Actual abuse and/or evidence of likelihood of abuse

There are no available reports of controlled studies involving the dependence potential or abuse potential of MDMB-CHMICA in laboratory animals or human subjects. Epidemiological reports of the incidence and prevalence of MDMB-CHMICA use are also apparently unavailable. MDMB-CHMICA is easily purchased on the Internet. It is sold online as a commercially branded legal high or as a research chemical in various countries in different regions. More than 3600 seizures or reports of detection of MDMB-CHMICA in 21 European countries were reported in February 2016. In addition to the non-fatal and fatal intoxications, analytically confirmed MDMB-CHMICA use has been related to DUID and violent public behaviour. A number of countries in different regions have placed 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)-1*H*-indol-3-yl]carbonyl}-3-methyl-L-valinate) is substantial. Therapeutic usefulness has not been recorded. It recognized that MDMB-CHMICA has similar abuse and similar ill-effects to substances in Schedule II of the UN Convention on Psychotropic Substances of 1971. 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 (2)*, 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 Convention on Psychotropic Substances of 1971.

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 Committee. A direct critical review was proposed based on information brought to the attention of WHO that 5F-APINACA is clandestinely manufactured, poses a 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 CB_1 and CB_2 receptors with greater potency than THC and activates the 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 CB_1 cannabinoid receptor antagonist/inverse agonist, AM251, blocks several *in vivo* effects of 5F-APINACA in mice including its induced spontaneous and stimulated

aggressiveness, hypothermic effects and antinociceptive effects. The *in vitro* binding and functional activity effects of 5F-APINACA, together with its *in vivo* effects of hypothermia, and 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 and hyperthermia have been reported by users of 5F-APINACA on blogs and forums. Recently, there have been a number of reports 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

No controlled studies in humans or laboratory animals regarding the potential of 5F-APINACA to produce physical dependence or tolerance have 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 more than 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 about adverse effects. The development of thoughts about smoking and cravings first thing in the morning can occur 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 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*-(adamantan-1-yl)-1-(5-fluoropentyl)-1*H*-indazole-3-carboxamide) is substantial. Therapeutic usefulness has not been recorded. It recognized that 5F-APINACA has similar abuse and similar ill-effects to substances in Schedule II of the UN Convention on Psychotropic Substances of 1971. 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 control (2)*, 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 Convention on Psychotropic Substances of 1971.

5.11 JWH-073

Substance identification

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

Previous review

During its thirty-sixth meeting, the WHO ECDD had discussed the critical review report on JWH-073 and concluded that owing to the 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 thirty-eighth meeting of the ECDD.

Similarity to known substances and effects on the central nervous system

JWH-073 is a homologue of JWH-018, which has been included in Schedule II of the Convention on Psychotropic Substances of 1971 since 2015. JWH-073 binds to the CB_1 and CB_2 cannabinoid receptors and exhibits functional *in vitro* activity. Several metabolites of JWH-073 also bind to the CB_1 receptor. Similar to THC, JWH-073 induces marked hypothermia in mice, increases the 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 and hyperreflexia, and promotes aggression. All these effects are fully prevented by the selective CB_1 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 palpitations. One user reported that she felt like she was "becoming psychotic". Potency is reported to be about half that of JWH-018. There have been several reports of patients presenting with analytically confirmed JWH-073 consumption. These patients exhibited 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 postmortem samples have been reported so far.

Dependence potential

No controlled studies in humans or laboratory animals regarding the potential physical dependence or tolerance effects of JWH-073 have 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 onto plant material (e.g. damiana (*Turnera diffusa*)). 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 using 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 placed 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-1*H*-indol-3-yl)(1-naphthyl)methanone) demonstrate that this substance has the capacity to produce some effects similar to its homologue, JWH-018, which is included in Schedule II of the UN Convention on Psychotropic Substances of 1971. However, the data currently available do 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)-1*H*-indol-3-yl] (2,2,3,3-tetramethylcyclopropyl)methanone.

Previous review

XLR-11 has not previously been pre-reviewed or critically reviewed. A direct critical review was proposed based on information brought to WHO's attention that XLR-11 is clandestinely manufactured, poses a 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 CB_1 and CB_2 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 CB_1 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 users who had been hospitalized. Analytically determined use of XLR-11 has been confirmed in DUID cases. Confirmed presence of XLR-11 has been associated with two deaths.

Dependence potential

No controlled studies in humans or laboratory animals regarding the potential physical dependence or tolerance effects of XLR-11 have been reported.

Actual abuse and/or evidence of likelihood of abuse

XLR-11 produces THC-like discriminative stimulus effects in mice and rats indicating that it would be able to produce THC's subjective effects and that it is likely have a similar abuse potential. The discriminative stimulus effects of XLR-11 are antagonized by rimonabant. XLR-11 is often sold in the form of herbal mixtures 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 has been placed under national control in a number of countries and different regions.

Therapeutic usefulness

There are no approved therapeutic applications for the clinical 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)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone) is substantial. Therapeutic usefulness has not been recorded. It recognized that XLR-11 has similar abuse and similar ill-effects to substances in Schedule II of the UN Convention on Psychotropic Substances of 1971, 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 (2)*, 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 Convention on Psychotropic Substances of 1971.

6. Updates

6.1 Cannabis and cannabis resin

At its thirty-seventh meeting the ECDD requested the Secretariat to begin collecting data that would inform a pre-review of cannabis, cannabis resin, extracts and tinctures of cannabis, at a future meeting. In accordance 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 Single Convention on Narcotic Drugs of 1961 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 Convention on Psychotropic Substances of 1971.

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 (2)* 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 18 months of the thirty-eighth meeting.

7. Follow-up on recommendations from international meetings and consultations

7.1 Follow-up on implementation of recommendations of UNGASS and of the 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 how Resolution S-30/1 *(9)* 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 new psychoactive substance 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 WHO had held several meetings after the UNGASS 2016 during which the recommendations on NPS were discussed. These meetings included the third UNODC-WHO Expert Consultation

on NPS that took place on 3 and 4 May 2016 at WHO headquarters, where the prioritization of the most harmful, prevalent and persistent NPS for evaluation by the ECDD was discussed. In addition to collecting data for prioritization from the 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 and Interpol). This would facilitate collection of data on confiscations and seizures as indicators for market presence. It was also proposed to increase Member States' contributions. It was noted that the availability of reference standards and established standardized methodologies for identification were necessary to improve forensic laboratory capacity for detection and identification of NPS.

Dr Lopato emphasized that an efficient early warning system (EWS) relies on continuous and dynamic data collection at the 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 the quality of data was also considered critical for future evaluation of psychoactive substances.

Dr Justice Tettey, Observer from the UNODC, provided a summary of the above-mentioned third UNODC-WHO Expert Consultation on NPS held in Geneva in May 2016, following CND resolution 58/7. It 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 on strengthening national forensic and law enforcement capacity to aid in the identification and detection of NPS.

Dr Tettey informed the Committee 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, had 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 EWA on NPS will be expanded to include a system for collecting and disseminating information on the harm caused by NPS.

Dr Tettey further described ongoing activities to improve the capacity of national drug testing laboratories. These included UNODC's international collaborative exercises, the provision of reference standards, guidance on the

laboratory analysis of NPS, and 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 SMART programme, as well as through the provision of drug detection kits for use in the field.

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 CND resolution 59/8 (March 2016) *(11)* which invited WHO, with the support of UNODC, 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. Dr Lopato's briefing touched on several points.

There is a need to establish a new surveillance system at the international level 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) would allow information to be collated that could then be used to inform future ECDD deliberations as well as in the process of prioritizing substances for review.

Currently, 11 substances are being kept under WHO surveillance, 10 of which were critically reviewed by the ECDD at its thirty-sixth meeting in 2014 and one that was reviewed at its thirty-seventh meeting in 2015. As there was insufficient evidence on harm and risks to health arising from use of these substances at the time of the review, the Committee recommended that they should not be placed under international control, but be kept under surveillance. Substances in the current WHO surveillance list had been considered during the prioritization process for their possible evaluation by the ECDD at its thirty-eighth meeting.

A surveillance system was discussed during the third UNODC-WHO Expert Consultation on NPS and at the meeting of the first Informal Working Group of the ECDD in May 2016. After consideration, it was proposed that a list of substances under surveillance by WHO should be actively maintained through the proactive collection of data from international organizations (e.g. UNODC, the INCB and the World Customs Union), regional organizations (e.g. EMCDDA) and national observatories and Member States. WHO should accumulate data continuously. This will mainly rely on collaborative arrangements

with multiple organizations and bodies, including UNODC (e.g. through the SMART programme and the EWA on NPS), the EMCDDA (EU EWS), and other regional organizations 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 are predictive of adverse events; and reports coming 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 would be fatalities, in addition to other serious adverse events (e.g. non-fatal intoxications) and other public health risks (e.g. reports of DUID and harm to others). Other criteria and data for consideration would include available pharmacological information and context or mode of use. It was emphasized that there must also be criteria for excluding substances from the WHO surveillance list.

Dr Lopato explained that numerous important challenges need to be faced in the satisfactory maintenance of a surveillance list, including the development of a pipeline for health-related data from Member States, maintaining a database on 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 to be 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 would be published on the ECDD website.

Ms Beate Hammond, Observer from the INCB, presented an update on the INCB's international operations on 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 this way the project contributes to preventing harm to human health. Project ION has received political support from the international community in CND resolution 59/8 *(6)* and, most recently, in the UNGASS outcome document. In the six months preceding the ECDD meeting, the number of people using IONICS, the incident communication system for the exchange of information on NPS, as well as the number of incidents communicated had increased by more than 25%.

In cooperation with UNODC, the INCB was organizing a conference on NPS in Bangkok in early 2017 to take stock of achievements and discuss the challenges ahead. It was expected that the conference would result in the adoption

of an outcome document and operational recommendations that will translate UNGASS commitments into actions. Future plans included an intelligence-gathering survey on opioid-type NPS which have been causing serious harm to health in North America and a time-bound operation on NPS in other regions.
The 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 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 18 months following the thirty-eighth meeting.

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SELECTED WHO PUBLICATIONS OF RELATED INTEREST

WHO Expert Committee on Drug Dependence
Thirty-seventh report
WHO Technical Report Series, No. 998, 1999, ISBN 978 92 4 120998 4 (34 pages)

WHO Expert Committee on Drug Dependence
Thirty-sixth report
WHO Technical Report Series, No. 991, 2015, ISBN 978 92 4 120991 5 (62 pages)

Ensuring balance in national policies on controlled substances: guidance for availability and accessibility of controlled medicines
World Health Organization, Geneva, 2011, ISBN 978 92 4 156417 5 (78 pages)

Persisting pain in children package: WHO guidelines on pharmacological treatment of persisting pain in children with medical illnesses
World Health Organization, Geneva, 2011, ISBN 978 92 4 154812 0 (229 pages)

WHO Expert Committee on Drug Dependence
Thirty-fifth report
WHO Technical Report Series, No. 973, 2012, ISBN 978 92 4 120973 1 (27 pages)

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WHO Technical Report Series, No. 942, 2006, ISBN 978 92 4 120942 7 (27 pages)

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WHO Technical Report Series, No. 915, 2003, ISBN 978 92 4 120915 1 (25 pages)

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Thirty-second report
WHO Technical Report Series, No. 903, 2001, ISBN 978 92 4 120903 8 (26 pages)

The Selection and Use of Essential Medicines
Report of the WHO Expert Committee, 2015 (including the 19th WHO Model List of Essential Medicines and the 5th WHO Model List of Essential Medicines for Children)
WHO Technical Report Series, No. 994, 2015, ISBN 978 92 4 120994 6 (546 pages)

Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence
World Health Organization, Geneva, 2009, ISBN 978 92 4 154754 3 (129 pages)

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

The report summarizes the review of twelve substances and the ECDD recommendations for the scheduling of ten substances. Furthermore, the ECDD discussion and recommendation for pre-reviews of pre-reviews of cannabis and its component substances are included in this report. The report also contains updates from international bodies concerned with controlled substances, as well as summaries of the follow up on the recommendations made at the previous Committee meeting, and on the discussions of prioritization of substances, surveillance systems of new psychoactive substances and terminology. Issues identified for consideration at future Expert Committee meetings are also listed.

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