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WHO Expert Committee on Drug Dependence

Twenty-fifth Report

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WHO EXPERT COMMITTEE ON DRUG DEPENDENCE

Geneva, 18–23 April 1988

*Members**

Dr T.L. Chrusciel, Professor and Chairman, Department of Clinical and Social Pharmacology, Centre for Postgraduate Medical Education, Warsaw, Poland

Professor J.C. Ebie, Office of the Chief Medical Director, University of Benin Teaching Hospital, Benin City, Nigeria

Dr J.C. Garcia-Fernandez, Professor of Toxicology, Faculty of Pharmacy and Biochemistry, University of Buenos Aires, Buenos Aires, Argentina

Professor A.H. Ghodse, Professor and Director, Department of Addiction Behaviour, St George's Hospital Medical School, University of London, London, England (*Vice-Chairman*)

Dr J.H. Jaffe, Director, Addiction Research Center, National Institute on Drug Abuse, Rockville, MD, USA (*Rapporteur*)

Professor G. Lagier, Department of Clinical Pharmacology, Fernand-Widal Hospital, Paris, France

Professor H. Maghazaji, Head, Neuropsychiatric Department, Medical City Teaching Hospital, Baghdad, Iraq

Dr A. Showanasai, Adviser in Neuropsychiatry, Pramongkut Khao Army General Hospital, Bangkok, Thailand

Professor T. Yanagita, Director, Preclinical Research Laboratories, Central Institute for Experimental Animals, Kawasaki, Japan (*Chairman*)

Representatives of other organizations

International Criminal Police Organization (ICPO)

Mr I.H. Bain, ICPO-INTERPOL Drugs Sub-Division, St Cloud, Paris, France

Mr T.W. Woodworth, ICPO-INTERPOL Drugs Sub-Division, St Cloud, Paris, France

International Narcotics Control Board (INCB)

Professor S.O. Kayaalp, Member, INCB, Ankara, Turkey

United Nations Division of Narcotic Drugs

Dr K. Szendrei, Senior Scientific Officer, Applied Scientific and Technical Information Section, United Nations Division of Narcotic Drugs, Vienna International Centre, Vienna, Austria

Secretariat

Dr I. Khan, Senior Medical Officer, Division of Mental Health, WHO, Geneva, Switzerland (*Secretary*)

Dr N. Sartorius, Director, Division of Mental Health, WHO, Geneva, Switzerland

Dr Yng-Shiuh Sheu, Staff Pharmacologist for Medical and International Affairs, Office of the Director, National Institute on Drug Abuse, Rockville, MD, USA (*Temporary Adviser*)

---

* Unable to attend: Dr Hye Humayun, Director, Institute of Public Health, Dhaka, Bangladesh.

WHO EXPERT COMMITTEE ON DRUG DEPENDENCE

Twenty-fifth Report

1. INTRODUCTION

The WHO Expert Committee on Drug Dependence met in Geneva from 18 to 23 April 1988. The meeting was opened on behalf of the Director-General by Dr Hu Ching-Li, Assistant Director-General, who restated the general objectives of the Expert Committee and noted the important role of WHO in the control of drug abuse. He recalled that, under the two existing international treaties for drug control, namely the Single Convention on Narcotic Drugs, 1961 (as amended by the 1972 protocol), and the Convention on Psychotropic Substances, 1971, WHO had been assigned the important function of recommending to the Secretary-General of the United Nations, on the basis of evidence available to WHO, which narcotic drugs and psychotropic substances should be considered for international control at an appropriate level under one or other of the treaties. In January 1986 the WHO Executive Board had approved the *Guidelines for the WHO Review of Dependence-producing Psychoactive Substances for International Control* (*1*), and these had been used in preparing for the present meeting. Dr Hu noted that another of WHO's tasks was to prepare guidelines for the selection of narcotic drugs and psychotropic substances by the Programme Planning Working Group for pre-review evaluation. A consultant was currently preparing a document containing draft guidelines, which would be submitted to the Programme Planning Working Group at its sixth meeting planned for March 1989.

Dr Hu then drew attention to the agenda of the present meeting of the Expert Committee on Drug Dependence, which included 14 substances selected for review by the fourth Programme Planning Working Group. The Working Group had included a number of opioid agonist–antagonist drugs and sedative–hypnotics, since their review had been specifically requested by the United Nations Commission on Narcotic Drugs. The Eighth Special Session of the

Commission had also adopted a resolution [2(S-VIII)] in February 1984 requesting WHO to examine further the possibility of scheduling opioid agonist–antagonist drugs under the Single Convention on Narcotic Drugs, 1961.

The agenda included two notifications regarding exempted preparations under the Convention on Psychotropic Substances, 1971, of which the first concerned two preparations exempted by the Government of the United States of America, one containing propylhexedrine and the other containing levometamfetamine. The second notification had been received from the Government of Thailand and concerned a number of preparations containing phenobarbital. It was the opinion of the fifth Programme Planning Working Group which met in March 1988 that, if the WHO-recommended procedures concerning exempt preparations were used (*2*), no further action needed to be taken by WHO. These cases were therefore brought to the notice of the Committee for information only.

Dr Hu then outlined the objectives of the Committee at its present meeting:

(1) to recommend whether any or all of the 14 substances required international control, and if so, under which convention and at what level;
(2) to recommend to WHO any improvement that might be made to the guidelines for the review of substances for rescheduling or descheduling;
(3) to recommend to WHO any other technical activity that would promote the rational use of psychoactive substances.

The Committee was informed about some of WHO's activities during 1987 related to the control of drug abuse. A meeting on the role of schools of pharmacy in the rational use of psychoactive substances had been convened in London, and its report (*3*) had been discussed at the Tenth Special Session of the United Nations Commission on Narcotic Drugs, which noted its recommendations and adopted a resolution [1(S–X)] on the subject. The Committee also learned about WHO's efforts to alert countries to the possibility of the illicit production of substances and, in particular, of analogues of controlled substances (designer drugs). A meeting in Rabat had been held which brought together law enforcement and health officials in a discussion of the priorities to be established at national and international level to protect the population from

designer drugs in terms of both availability and adverse effects. WHO was also embarking on a project, in collaboration with a number of national authorities, international agencies and representatives of the International Federation of Pharmaceutical Manufacturers Associations, on the impact of scheduling benzodiazepines.

Dr N. Sartorius, Director, Division of Mental Health, also welcomed the members of the Expert Committee and, in view of recent reductions in the WHO budget, asked for suggestions on ways of increasing the efficiency of the process of reviewing drugs under the terms of the international treaties.

2. PREPARATION FOR THE MEETING AND FORMAT OF THIS REPORT

The WHO procedures for the review of dependence-producing psychoactive substances were followed in preparing for the meeting of the Expert Committee. In particular, the fifth Programme Planning Working Group met in March 1988 (*4*) and considered the critical review document produced by the WHO Secretariat (*5*).[1] An addendum to this document was then prepared, based on the discussions of the Working Group.

In response to suggestions from the United Nations Commission on Narcotic Drugs and the WHO Executive Board, the Programme Planning Working Group at its third meeting proposed a format for the Expert Committee on Drug Dependence to use in reporting the outcome of its review of each substance (*6*). The Expert Committee used this format in its twenty-third and twenty-fourth reports (*2, 7*) and it has been followed again in the present one.

[1] Prior to the meeting of the Expert Committee, the WHO Secretariat carries out a detailed assessment of all the drugs to be reviewed by the Committee and compiles all the relevant information in a critical review document; this document is then submitted to the Committee for discussion.

3. SEDATIVE–HYPNOTICS

3.1 Bromisoval

3.1.1 *Substance identification*

Bromisoval (INN, CAS 496-67-3),[1] chemically (2-bromo-3-methylbutyryl)urea, is also known as bromisovalum, bromisoval-erylurea and bromvalerocarbamide. There is one chiral carbon atom in the molecule, so that two stereoisomers and one racemate are possible.

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

Bromisoval has been classified as a non-barbiturate sedative–hypnotic of the bromoureide class, which includes acecarbromal and carbromal. It produces barbiturate-like sedative and hypnotic effects, such as dose-related drowsiness, confusion and motor incoordination. The drug is debrominated during metabolism, and after prolonged use chronic bromism may occur, with such signs and symptoms as loss of memory, confusion, inability to concentrate, hallucinations, delusions and delirium. Bromisoval, like the barbiturates, is metabolized mainly in the liver and is excreted in the bile as glutathione conjugates and in the urine as mercapturates.

3.1.3 *Dependence potential*

There is no information on the ability of bromisoval to produce physical or psychic dependence in either animals or human subjects in controlled laboratory studies. However, case reports of prolonged use of bromisoval indicate a possible barbiturate-like dependence potential, although this is probably less than that found with the barbiturates.

3.1.4 *Actual abuse and/or abuse liability (likelihood of abuse)*

Cases of excessive, suicidal or prolonged use of bromisoval leading to poisoning and death have been reported in Belgium, the

[1] The following abbreviations are used for substance identification: CAS (Chemical Abstracts Service), INN (International Nonproprietary Name).

Federal Republic of Germany and Switzerland in the 1970s and 1980s. These cases may include abuse of bromisoval, but no illicit manufacture or traffic over the period 1985–1987 was mentioned in the reports that were obtained by INTERPOL, the United Nations Secretary-General and WHO from 54 countries and included in the critical review document submitted to the Expert Committee on Drug Dependence at its present meeting. This may indicate that serious public health or social problems of international scope resulting from abuse of the drug do not exist.

3.1.5 *Therapeutic usefulness*

Bromisoval has been used as a sedative and hypnotic, and in a variety of combination preparations, but the bromoureides have been replaced by newer agents in recent medical practice. It appears to be marketed in only a few countries.

3.1.6 *Recommendation*

On the basis of the available data concerning its pharmacological profile, dependence potential, and actual abuse, the Committee rated the likelihood of abuse of bromisoval as moderate and the therapeutic usefulness as low. Very few public health and social problems have been found to be associated with the substance, and the Committee considered that they were not serious enough to warrant the placing of the substance under international control. The Committee did not recommend scheduling of bromisoval.

3.2 Carbromide

3.2.1 *Substance identification*

Carbromide (INN, CAS 511-70-6), chemically 2-bromo-2-ethylbutyramide, is also known as diethylbromoacetamide. No stereoisomeric forms are possible.

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

Carbromide is the primary active metabolite of carbromal. It is therefore assumed to have the pharmacological properties of a non-

barbiturate sedative–hypnotic of the bromoureide class. The parent compound, carbromal, was reviewed by the Expert Committee on Drug Dependence at its twenty-fourth meeting in April 1987 and was not recommended for placing under international control (*2*). Like carbromal, carbromide produces dose-related barbiturate-like sedative and hypnotic effects such as drowsiness, confusion and motor incoordination, and must be assumed to exhibit all the known pharmacological and toxic properties of carbromal. In the process of metabolism, the compound is debrominated. The bromide ion is excreted at a much slower rate than the organic component of the molecule. Consequently, with repeated use, bromide ion can accumulate and cause the signs and symptoms of bromism, including memory loss, confusion, inability to concentrate, hallucinations, delusions and delirium.

3.2.3 *Dependence potential*

Although there are very few clinical case reports of carbromide abuse, there is extensive literature on the dependence potential of the parent compound, carbromal, and of the related bromoureide acecarbromal, both of which are associated with a pattern of drug dependence similar to that seen with the barbiturates.

3.2.4 *Actual abuse and/or abuse liability (likelihood of abuse)*

Very few cases of carbromide abuse have been documented and, at present, no major abuse problems appear to exist. In the past, its precursor, carbromal, was associated with public health problems in certain countries, e.g., the Federal Republic of Germany. Carbromide is no longer marketed. With the ready availability of newer anxiolytics and hypnotics, the reappearance of carbromide as a therapeutic agent is unlikely.

3.2.5 *Therapeutic usefulness*

Carbromide now has extremely limited use as a therapeutic agent.

3.2.6 *Recommendation*

On the basis of the available data concerning its pharmacological profile, dependence potential and actual abuse, the Committee rated

the likelihood of abuse of carbromide as moderate and the therapeutic usefulness as very low. Very few public health and social problems have been found to be associated with the substance, and the Committee considered that they were not serious enough to warrant placing it under international control. The Committee did not recommend scheduling of carbromide.

3.3 Methaqualone

Methaqualone was included in Schedule IV of the original draft of the Convention on Psychotropic Substances, 1971, and came under international control when the Convention was enforced. However, because of diversion of methaqualone into illicit channels and increased evidence of its abuse, it was placed in 1979 in Schedule II of the Convention following a recommendation by WHO (*8*).

In 1987, at its twenty-fourth meeting, the Expert Committee on Drug Dependence reviewed non-barbiturate sedatives and hypnotics and considered the need to recommend rescheduling methaqualone to Schedule I of the 1971 Convention (*2*). It became clear that many countries had withdrawn methaqualone from the market because of widespread abuse and serious illicit trafficking. The Committee recommended a thorough re-examination of the situation and the inclusion of methaqualone in the critical review document for formal consideration at its twenty-fifth meeting. The Committee agreed that methaqualone should be considered in accordance with established WHO procedures for the review of psychoactive substances and was of the opinion that the Secretary-General of the United Nations should notify the governments of Member countries that the drug was being considered for rescheduling to Schedule I.

During 1987, when data were being collected for the critical review document for consideration by the Expert Committee, explicit information on methaqualone was requested in communications from the Secretary-General of the United Nations and from the Director-General of WHO to Member countries. In addition, the records of the International Narcotics Control Board and of INTERPOL on the use and abuse of methaqualone were available to WHO.

3.3.1 *Substance identification*

Methaqualone (INN, CAS 72-44-6) is 2-methyl-3-*o*-tolyl-4(3*H*)-quinazolinone. No stereoisomeric forms are possible.

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

Methaqualone is a depressant of the central nervous system similar in its actions and effects to the barbiturates. In addition to sedative–hypnotic properties, methaqualone possesses anticonvulsant, antispasmodic, local anaesthetic and weak antihistaminic properties. It also has antitussive activity comparable with that of codeine. Cases of acute intoxication, methaqualone-related suicides, and deaths in drug abusers due to methaqualone overdoses have been reported in several countries.

3.3.3 *Dependence potential*

Methaqualone is known to produce tolerance and physical dependence of the barbiturate type in animals and humans. It is self-administered by rhesus monkeys and produces euphoria as well as pentobarbital-like subjective effects in humans.

3.3.4 *Actual abuse and/or abuse liability (likelihood of abuse)*

Methaqualone has been widely abused, mainly by young people, particularly in such countries as the Federal Republic of Germany, Japan and the USA. It has been reported to produce a dissociative "high", without the drowsiness caused by barbiturates. Some abusers state that the effects resemble those of opiate drugs. Methaqualone is often taken with diphenhydramine by drug abusers; methaqualone preparations containing diphenhydramine (e.g., Mandrax) have been frequently abused in south-east Asia, and a preparation of this type has been reported to be very popular among heroin-dependent users in the United Kingdom. Part of the attraction of the substance as a drug of abuse may be linked to a belief among users that the drug reduces sexual inhibitions.

Because of substantial abuse problems, methaqualone has been removed from the market by government action in many countries, and production has been reduced or stopped by a number of pharmaceutical manufacturers.

Severe depression of the central nervous system may occur when methaqualone is taken in combination with ethanol or other depressants of the central nervous system. The symptoms of acute poisoning are quite similar to those produced by the barbiturates and most other hypnotics. Severe overdose of methaqualone in

combination with diphenhydramine results in tachycardia, restlessness, delirium, hypertonia and hyper-reflexia, convulsion, coma and sometimes death.

Data available to the International Narcotics Control Board show that annual legal consumption of methaqualone amounts to approximately 20 tonnes and is distributed among 33 countries and regions. In the large majority of states and regions, namely 153 of the 186 defined in the Convention on Psychotropic Substances, 1971, methaqualone is not used for medical purposes. Three countries account for 60%, i.e., approximately 12 tonnes, of the total consumed.

Data from 22 countries, including ten developing countries in Africa but not including the United States, show that more than 7 million tablets were seized in 1987. It is not clear how much of this methaqualone was diverted from legitimate production and how much was produced in clandestine laboratories. Over the past few years a number of illicit laboratories have been discovered and closed. Recently, successful efforts to prevent the establishment of at least one large-scale clandestine laboratory in Africa probably helped to keep the illicit supply from increasing still further.

3.3.5 *Therapeutic usefulness*

Methaqualone has been used as a hypnotic and sedative, its hypnotic effect being reported to be enhanced by diphenhydramine. The therapeutic usefulness of methaqualone has been reviewed by WHO several times in the past (e.g., *8*), and it was concluded that it has no particular advantages over other available hypnotics. Because of the high abuse liability of methaqualone and the serious social problems caused by such abuse, the drug has been replaced by others in medical practice in many countries. Its use as a therapeutic agent is becoming progressively more limited as more countries remove it from the market.

3.3.6 *Recommendation*

On the basis of the available data concerning its pharmacological profile, dependence potential, and particularly its actual abuse over the past decade, the Committee rated the dependence potential and

abuse liability of methaqualone as high, in agreement with a previous WHO review group (*8*). The drug continues to be shipped illegally across international boundaries.

Information made available to the Expert Committee showed that, even when specifically advised that the drug was being considered for rescheduling from Schedule II to Schedule I of the Convention on Psychotropic Substances, 1971, no country indicated that methaqualone had any special therapeutic advantages that would strongly argue for its continued availability in the face of the public health and social problems associated with its abuse. Such problems persist because methaqualone remains available and illicit traffic in it continues despite its rescheduling to Schedule II of the Convention in 1979.

Although methaqualone is still available for legitimate clinical use in 33 countries and regions, the Committee judged that the extent of the abuse and of the public health and social problems associated with this substance on an international scale might warrant its placing under even stricter controls under the terms of the Convention on Psychotropic Substances, 1971, i.e., rescheduling it to Schedule I if such a shift was consistent with the terms of the Convention. In making this judgement, the Committee weighed the therapeutic usefulness of the drug, the extent and persistence of public health and social problems associated with its use, and the availability of other satisfactory therapeutic alternatives. The Committee was aware that the placing of a drug having some medical usefulness, however modest, in Schedule I, together with agents that have no medical usefulness whatsoever, might be establishing a precedent not intended by the Convention. The Committee was also aware that not all countries where methaqualone is produced are signatories to the Convention, that it is relatively easy to synthesize and that clandestine production might well replace the diversion from legitimate production, if any, that now supplies the illicit traffic.

The Committee was unanimous in recommending to the Director-General of WHO that every effort should be made to urge all countries, whether or not they are signatories to the Convention on Psychotropic Substances, 1971, to stop producing methaqualone and to ban its import or export. Furthermore, countries now using methaqualone for medical purposes should be strongly encouraged to end such use so as to reduce the need for its legitimate production anywhere in the world.

The Committee further recommended that the Director-General of WHO should continue to collect data on the use of the drug and to submit it for consideration by the WHO Expert Committee at some future date.

3.4 Paraldehyde

3.4.1 *Substance identification*

Paraldehyde (INN, CAS 123-63-7), chemically 2,4,6-trimethyl-*s*-trioxane, is also known as paracetaldehyde, paraldehydum or paral. It has two stereoisomeric forms (*cis* and *trans*).

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

Paraldehyde has been classified as a non-barbiturate sedative–hypnotic. In addition to its sedative and hypnotic effects, it also has some analgesic and anticonvulsant properties. Overdose of the drug produces headache, tachycardia, hypotonia, nausea and vomiting as well as symptoms similar to those of alcohol intoxication. Chronic paraldehyde use may result in chronic poisoning characterized by hallucinations, delusions, impairment of memory and intellect, anxiety, impaired speech, unsteady gait, paraesthesias and tremors. It is metabolized in the liver to acetaldehyde, which is then metabolized to carbon dioxide and water. Some of the ingested paraldehyde is exhaled.

3.4.3 *Dependence potential*

In dogs, acute tolerance to paraldehyde and cross-tolerance between paraldehyde and barbiturates can occur. In humans, in the case of chronic intoxication, an alcohol-like physical dependence is observed, with withdrawal signs on cessation of use.

An unpleasant taste and associated burning sensation probably tend to prevent paraldehyde abuse. Notwithstanding these unpleasant effects, psychological and physical dependence on the drug has been observed after prolonged and excessive use.

3.4.4 *Actual abuse and/or abuse liability (likelihood af abuse)*

In the past, paraldehyde was abused by many former alcohol abusers, particularly when they were abstaining completely from

alcohol. No significant public health problems resulting from such abuse have ever been reported.

3.4.5 *Therapeutic usefulness*

Although paraldehyde has been used for the treatment of alcoholic delirium tremens, status epilepticus, excitement states in psychiatry, eclampsia and tetanus, it is currently a drug of limited therapeutic usefulness and has been replaced by other drugs in clinical practice in many countries.

3.4.6 *Recommendation*

On the basis of the available data concerning its pharmacological profile, dependence potential and actual abuse, the Committee rated the likelihood of abuse of paraldehyde as moderate and the therapeutic usefulness as low. Very few public health and social problems have been found to be associated with the substance, and the Committee considered that they were not serious enough to warrant placing it under international control. The Committee did not recommend scheduling of paraldehyde.

4. OPIOID AGONIST–ANTAGONIST ANALGESICS

4.1 General

In accordance with the wishes of the United Nations Commission on Narcotic Drugs (resolution 2(S-VIII) of February 1984), the Committee was asked to examine the case for the scheduling of opioid agonist–antagonist analgesics under the Single Convention on Narcotic Drugs, 1961, in accordance with the new WHO procedures for the review of psychoactive substances for international control (*1*).

The Committee carefully examined the texts of the two existing international conventions for drug control and analysed the pharmacological characteristics of six agonist–antagonist substances. It concluded that, to describe fully the criteria used for including any of the substances under one or other of the two conventions, it was first necessary to summarize some of the scientific developments that have occurred since the treaties covering opiate narcotic drugs were first drafted and ratified.

4.1.1 *Receptors for drug action*

It is now recognized that the classic opiate drugs such as morphine, heroin and the related semi-synthetic drugs of this type act on specific receptors located on or within certain cells in the body, and especially on cells in the nervous system. To act, a drug must bind to these opioid receptors, several types of which have been described, namely the mu, kappa, delta, sigma and epsilon receptors. The mu receptor was named after the drug morphine, since it is predominantly the activation of mu receptors which produces the typical pattern of effects seen after the administration of morphine and of drugs closely related to it. Such drugs are now also referred to as mu-receptor agonists or mu agonists. When an opioid receptor on a cell is activated, the function of that cell is altered so that it becomes more or less likely to respond to a neurotransmitter or to release its own neurotransmitter substance(s).

The various types of opioid receptors are distributed in distinct patterns through the central and peripheral nervous systems, so that activation of each receptor type produces a different pattern of pharmacological actions, depending on which and how many cells and systems are affected. For example, the mu and delta receptors are heavily concentrated in areas where neurons are involved in the transmission and perception of pain and the control of respiration. Kappa and sigma receptors have different patterns of distribution. Activation of kappa receptors produces some analgesia and respiratory depression (frequently with the ceiling effect described below), endocrine effects, sedation and perhaps some degree of dysphoria. Activation of sigma receptors (which are often not considered to be opioid receptors in the strict pharmacological sense because the effects of their activation are not antagonized by naloxone) is associated with dysphoria, perceptual changes and hallucinations. Delta receptors activated mainly by natural opioid peptides also play a role in modifying transmission in pain pathways.

The number of opioid receptors of each type and their patterns of distribution in the nervous system differ considerably from one species to another. Consequently, the pattern of effects produced by a given drug may also differ among species. Although in some species, particularly in certain primates, the effects may frequently resemble those seen in humans, no single animal species has been found to be a perfectly reliable model for predicting all the effects in humans of drugs acting at various opioid receptors.

4.1.2 *Receptor binding and receptor activation*

Different drugs fit into (bind to) the various opioid receptor types to different degrees. Drugs that fit a receptor type so well that only a very small number of molecules are needed to occupy a high proportion of the receptors available are said to have a high affinity for that receptor type. A drug may have a high affinity for one receptor type and a low affinity for another. For example, the morphine-like mu agonists covered under the Single Convention on Narcotic Drugs, 1961, tend to have a high affinity for mu receptors, a lower affinity for kappa and delta receptors and a much lower affinity for sigma receptors. Thus, morphine and closely related semi-synthetic drugs do not produce hallucinations and dysphoria to any significant degree.

Fitting into or binding to a receptor is a necessary but not sufficient step in the action of the drugs considered by the Committee. To affect cell function, the drug must also either activate the receptor or displace an active substance that is already present on it. Drugs (and endogenous substances such as opioid peptides) differ not only in how well they bind to different receptor types but also to what degree they activate the receptors. Drugs exemplified by the classic mu agonists such as morphine produce the maximum degree of activation at a receptor and are now referred to as full agonists (i.e., full mu agonists); the effects that they produce increase with increases in dose up to a certain maximum. Some drugs produce less than the maximum degree of activation at a receptor, i.e., there is a "ceiling" to their effects, and are referred to as partial agonists (or more often as agonist–antagonists, since a partial agonist can lessen or antagonize the effects of a full agonist when it displaces the latter from its receptor). At the other extreme are drugs which bind to a receptor but produce no action at it. These drugs are pure antagonists. Thus naloxone is considered to be a relatively pure mu-receptor antagonist. It also binds to a lesser degree to kappa and delta receptors, where it also acts as an antagonist. A drug can vary in its activity, being a full agonist at one receptor and an antagonist or partial agonist at another; it may also vary in its affinity, having a high affinity for some receptors and little or no affinity for others.

The profile of pharmacological actions produced by a drug is the result of the net balance of its agonist, partial agonist and antagonist actions at the various receptor types to which it binds. The classic opiate drugs covered by the Single Convention on Narcotic Drugs,

1961, and exemplified by morphine and semi-synthetic drugs closely related to it are full mu agonists with little or no sigma activity. To avoid the use of a long descriptive term, the Committee in this report refers to the classic mu-agonist opiates as "prototypic mu agonists". To what degree activation of kappa and delta receptors contributes to the pharmacological profile of prototypic mu agonists under clinical circumstances is not yet clear. The tools needed to obtain information on the effects of very selective kappa- and delta-receptor agonists and pure antagonists in humans are still under development.

Chronic agonist action at mu or kappa receptors induces tolerance and physical dependence in the systems that are influenced by these receptor types. Withdrawal of the agonists (or their displacement by an antagonist or partial agonist) produces a withdrawal syndrome which is characteristic for the receptor type. Mu-receptor physical dependence appears to produce more severe withdrawal manifestations and to be associated with considerably more drug-seeking behaviour than kappa-receptor physical dependence. There is little cross-tolerance or cross-dependence between the substances acting at the various receptor types: a kappa agonist will not suppress a mu-agonist withdrawal syndrome. Delta-receptor tolerance and withdrawal are, at present, less well understood.

Binding and activity at any of the opioid receptor types are sufficient to define a drug as an opioid for teaching purposes. However, such a drug cannot necessarily be reliably predicted to resemble closely the prototypic mu agonists in patterns of abuse, dependence, production of drug-seeking behaviour and serious public health and social problems. For example, a drug that has substantial mu-agonist activity may also have such prominent pharmacological effects mediated by kappa and sigma receptors that its dysphoric and hallucinatory actions, and the resultant profile of behaviours, preclude any clinical utility and minimize the likelihood of its abuse.

4.1.3 *Other factors and limits on knowledge*

Factors other than those related to the mechanism of action of an opioid drug can also profoundly affect the likelihood that it will give rise to similar abuse or produce similar ill effects to the drugs covered by Schedule I or Schedule II of the Single Convention on Narcotic Drugs, 1961. For example, if a drug does not readily enter the central

nervous system when taken by the usual therapeutic routes of administration, the likelihood of its abuse is minimal even if it has classic mu-opioid actions when given directly into the brain of a laboratory animal; and a drug which binds so firmly to its receptor that withdrawal symptoms develop only gradually when drug use is stopped is less likely to generate desperate drug-seeking behaviour. Patterns of abuse and ill effects are also affected by the solubility of drugs; totally insoluble substances are unlikely to be abused by injection.

The Committee recognized that, given the many variables that determine abuse patterns and probable ill effects, especially with newer drugs acting on multiple receptor systems, prediction based on the results of studies on animal models is more difficult and less certain than it is for morphine. In some cases, some of the necessary information on how best to characterize a drug for the purposes of international control may not emerge until a drug has been used by humans outside a laboratory setting.

4.1.4 *Conclusions*

Taking note of the progress achieved in both laboratory and clinical research, as briefly described above, and of the substantial differences in action that can result from minor changes in drug structure, the Committee concluded that, in categorizing a substance for inclusion in the schedules of the Single Convention on Narcotic Drugs, 1961, particular weight should be given, not to chemical class or even to the structural similarities between the drug considered and other substances, but to:

(1) the drug's pharmacological profile, which is a function of the net balance of its agonist and/or antagonist actions at various opioid receptors;
(2) specific physiological and behavioural responses in animal models and human volunteers under laboratory conditions;
(3) other actions and toxic effects produced by the drug at non-opioid receptor sites, as well as the physical and pharmacokinetic properties that can affect the likelihood of its misuse; and
(4) actual patterns of abuse, clinical effects, and public health and social problems resulting from abuse of the drug outside controlled laboratory settings.

Undoubtedly, many new substances will be considered and found appropriate for inclusion under the Single Convention on Narcotic Drugs, 1961. However, it should be recognized that that Convention categorizes substances having certain specific characteristics, and substances that act dissimilarly cannot be scheduled under it.

The Committee concluded, on the basis of the information currently available, that none of the six agonist–antagonist opioids considered at the meeting was appropriate for control under the terms of the Single Convention on Narcotic Drugs, 1961. This does not mean, however, that in the future a drug that has some of the characteristics of this group will not be found to fit the criteria for control under the Convention.

In section 4.7.2, pentazocine has been compared with prototypic mu agonists to illustrate how the general criteria outlined in section 4.1.4 may be applied to the problem of making a recommendation on the scheduling of an agonist–antagonist for purposes of international control. Although the reports on the other five agonist–antagonists are considerably briefer than that for pentazocine, the Committee followed the same general framework in analysing the data and in making a recommendation.

4.2 Buprenorphine

4.2.1 *Substance identification*

Buprenorphine (INN, CAS 52485-79-7), chemically 21-cyclopropyl-7α-((*S*)-1-hydroxy-1,2,2-trimethylpropyl)-6,14-*endo*-ethano-6,7,8,14-tetrahydrooripavine, is also known as Temgesic and Buprenex. It is closely related in structure to acetorphine and etorphine (both controlled under Schedules I and IV of the Single Convention on Narcotic Drugs, 1961), but it cannot be easily converted into them. The number of theoretically possible stereoisomers is 128, but only two have been reported.

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

Buprenorphine can be classified pharmacologically as a partial agonist at mu opioid receptors; it is claimed that it also has antagonist activity at the kappa opioid receptor. Its analgesic potency is estimated to be 25–40 times that of morphine. The

duration of action is longer, probably because of tighter receptor binding. With respect to both analgesic and subjective effects and respiratory depression, there appears to be a ceiling effect so that as the dose is further increased agonist effects do not increase in proportion (see sections 4.1.1 and 4.7.2). Respiratory depression cannot be reversed by the usual clinical doses of naloxone but clinical reports indicate that it can probably be antagonized by very high doses of naloxone. Its subjective effects and side-effects resemble those of low doses of full mu agonists. However, differences between buprenorphine and prototypic mu agonists such as morphine, methadone and pethidine are also worthy of note, for example differences in the time course and intensity of physical dependence (see section 4.1.2).

The drug has a low degree of bioavailability after oral administration because of extensive first-pass metabolism in the liver. It is promptly and well absorbed after sublingual administration, an important consideration in its clinical use as an analgesic.

4.2.3 *Dependence potential*

Buprenorphine precipitates a withdrawal syndrome in morphine-dependent monkeys and produces partial suppression of morphine withdrawal signs in such monkeys only after 15 hours of withdrawal. It is self-administered by the monkeys. However, neither abrupt withdrawal nor challenges with the pure opiate antagonist naloxone produce an abstinence syndrome in monkeys chronically treated with buprenorphine.

In humans, little or no effect is observed over the first 48 hours after drug withdrawal, and only mild signs of abstinence are noted from the third to the tenth day. In one study, among a few subjects, relatively marked withdrawal effects including nausea, vomiting, restlessness, insomnia and diarrhoea were noted on the fourteenth day. Naloxone in doses of up to 4 mg does not precipitate buprenorphine withdrawal in subjects given buprenorphine chronically, but clinical reports suggest that higher doses of naloxone can reverse the effects of buprenorphine and, theoretically, should precipitate a withdrawal syndrome. When buprenorphine is administered to heroin addicts who are then challenged with large parenteral doses of prototypic mu agonists, the subjective effects of

the latter are markedly attenuated, probably because buprenorphine acts on the mu receptors as an agonist–antagonist.

4.2.4 *Actual abuse and/or abuse liability (likelihood of abuse)*

Abuse of buprenorphine has been reported in the medical and scientific literature in Australia, the Federal Republic of Germany, New Zealand and the United Kingdom, and in newspapers in Finland, Ireland, Italy and Spain. While most of these reports are of misuse by injection of buprenorphine by heroin addicts, members of the Committee were aware of some instances when the drug was misused by individuals who were not already using heroin or other opiates. Because the number of such cases is relatively small, the patterns of abuse have not been clearly delineated.

4.2.5 *Therapeutic usefulness*

Buprenorphine is currently marketed as an analgesic in injectable and sublingual preparations. It has been used in the management of acute pain and for intractable pain due to malignant disease. It is considered to be particularly useful because of its prompt onset of effect after sublingual administration and its duration of action, which is longer than that of many other orally administered opioid analgesics, and because severe respiratory depression is very unlikely. Since abrupt withdrawal of buprenorphine produces only a mild abstinence syndrome with a delayed onset, and since it suppresses heroin use in heroin addicts and has reinforcing effects so that it is acceptable to opioid abusers, it is currently being developed by the National Institute on Drug Abuse in the USA for possible use in the treatment and detoxification of heroin addicts.

4.2.6 *Recommendation*

On the basis of the available data concerning its pharmacological profile, dependence potential and actual abuse, the Committee rated the likelihood of abuse of buprenorphine as moderate and the therapeutic usefulness as moderate to high. The degree of seriousness of the public health and social problems associated with the abuse of this drug was not found to be great in terms of the numbers of individuals involved and the impact of the abuse on their well-being. It is possible, however, that problems of considerably greater

magnitude may develop as its reinforcing effects and ability to suppress opioid withdrawal symptoms become better known to those who are already abusing opiates such as heroin. The Committee judged that the potential for more widespread misuse by the parenteral route was serious enough to constitute a public health and social problem warranting the placing of the substance under international control. The Committee was also of the opinion that, on the basis of current understanding of opioid pharmacology as outlined in section 4.1.2, the differences between the partial mu agonist buprenorphine and such prototypic mu agonists as heroin, morphine and methadone warrant the use of the Convention on Psychotropic Substances, 1971, for the control of buprenorphine. The Committee recommended the placing of the drug in Schedule III of that Convention.

4.3 Butorphanol

4.3.1 *Substance identification*

Butorphanol (INN, CAS 42408-82-2), chemically (−)-17-(cyclobutylmethyl)morphinan-3,14-diol, is also known as (−)-butorphanol and Stadol. It is closely related in structure to levorphanol, norlevorphanol, levomethorphan, racemethorphan and racemorphan (Schedule I of the Single Convention on Narcotic Drugs, 1961), but cannot easily be converted into them. There are three chiral carbon atoms in the molecule, so that eight stereoisomeric forms plus racemates are possible.

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

Butorphanol is an opioid agonist–antagonist with analgesic and antitussive effects. A parenteral dose of 2 mg is stated to have an equianalgesic effect with 10 mg of morphine. It produces dose-related depression of respiration with a ceiling effect (see sections 4.1.1 and 4.7.2) that is reversible by naloxone. It has a pharmacological profile similar to that of pentazocine, and can be categorized with respect to its receptor affinities in different ways depending on the species in which it is tested. It is claimed to have affinity for the mu, kappa and sigma receptors. Its affinity for the sigma receptor is believed to be responsible for its psychotomimetic effects in human subjects.

Its opioid antagonist potency is approximately equivalent to that of nalorphine, 30 times that of pentazocine, and 1/40 of that of naloxone when antagonism is measured by the reversal of morphine analgesia in animals. Among side-effects, sedation is observed most frequently, but there may also be drowsiness, weakness, sweating, feelings of floating and nausea.

4.3.3 *Dependence potential*

In single-dose suppression studies, butorphanol failed to suppress the withdrawal signs produced in morphine-dependent and withdrawn rhesus monkeys and instead caused a mild exacerbation of the signs. However, in non-withdrawn monkeys smaller doses of butorphanol did not precipitate withdrawal signs; higher doses caused seizures, preventing further increase of the dose. Abrupt discontinuation of chronic butorphanol administration produced a less severe withdrawal syndrome than did morphine withdrawal in both animals and human subjects.

Butorphanol was found to be a positive reinforcer in self-administration studies in animals; however, in human volunteers single doses of butorphanol were reported to cause subjective effects that resembled those produced by cyclazocine, pentazocine and nalorphine, rather than those caused by morphine. Methadone-dependent subjects experienced withdrawal syndromes following administration of butorphanol.

4.3.4 *Actual abuse and/or abuse liability (likelihood of abuse)*

Butorphanol has been available for more than six years in the United States as a prescription drug without special controls. According to the manufacturer, utilization of butorphanol in the USA exceeds that of injectable pentazocine. There have been some reports of abuse and a number of individual case reports of butorphanol dependence have been published. Some reports of butorphanol misuse from hospital emergency rooms have been recorded by the Drug Abuse Warning Network in the United States[1] over the past few years; however, in only one year did they exceed ten, the number which represents the threshold for routine

[1] This system, which records episodes of drug misuse receiving attention at hospital emergency rooms or causing death, has been in place for almost 15 years and generally reflects any significant problems caused by drug abuse or misuse.

reporting by this network. There has also been one STRIDE (System to Retrieve Information from Drug Evidence) report on butorphanol in the United States.[1] No illicit production has been reported.

4.3.5 *Therapeutic usefulness*

Butorphanol is reported to be an analgesic that is more suitable for acute than for chronic pain. It is used in the postoperative care of patients and can also be used for preoperative or preanaesthetic medication. It is available for medical use in about 15 countries, in many of which it is available on prescription; in some, however, it is under national control.

4.3.6 *Recommendation*

On the basis of the available data concerning its pharmacological profile, dependence potential and actual abuse, the Committee rated the likelihood of abuse of butorphanol as low to moderate and the therapeutic usefulness as moderate to high. Few public health and social problems are currently associated with the abuse of butorphanol and the Committee considered that they were not serious enough to warrant placing it under international control. The Committee did not recommend scheduling of butorphanol.

4.4 Dezocine

4.4.1 *Substance identification*

Dezocine (INN, CAS 53648-55-8), chemically (–)-13-amino-5,6,7,8,9,10,11,12-octahydro-5-methyl-5,11-methanobenzocyclodec-en-3-ol, is also known as (–)-dezocine and Dalgan. There are three chiral carbon atoms in the molecule, so that eight stereoisomeric forms plus racemates are possible. Only two stereoisomers and a racemate have been reported.

[1] STRIDE is a computerized system that collects, stores, processes and retrieves laboratory-analysis information from drug evidence samples submitted to Drug Enforcement Agency laoratories in the United States. The appearance of a drug in STRIDE is indicative of its involvement in illicit drug traffic.

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

Dezocine has been classified pharmacologically as a partial agonist at mu opioid receptors with little affinity for kappa receptors. In rats it is approximately one-quarter as potent as nalorphine as an opioid antagonist. In humans, it is a potent analgesic with a profile somewhat similar to that of buprenorphine. Its pharmacological actions are more easily reversed by naloxone than are those of buprenorphine. Its analgesic potency is estimated to be equal to that of morphine. Like morphine, it depresses respiration, but its action in depressing blood pressure may be less than that of morphine. Its effects on the central nervous system can be reversed by mu-receptor antagonists such as naloxone.

Dezocine is rapidly distributed after intramuscular injection, with a mean half-life of 2.5 hours. It is metabolized mainly by glucuronidation.

4.4.3 *Dependence potential*

In non-dependent drug abusers single doses of dezocine produce miosis, other opioid effects, "liking" (i.e., subjects like the effects of the drug) and euphoria. There is no evidence of dysphoric sedative and hallucinogenic effects such as those seen with pentazocine. The potential for physical dependence on dezocine has not been studied in humans, and the character, intensity and time course of withdrawal phenomena, if any, are unknown. The drug produces physical dependence in rodents but only minimal physical dependence in monkeys; it does not suppress morphine abstinence. It substitutes for codeine in animal self-administration experiments and the pattern of response is similar to that seen after buprenorphine, butorphanol and nalbuphine. In animals trained to discriminate between a mu agonist (etorphine) and a kappa agonist (ethylketazocine), dezocine was generalized to etorphine, which indicates that it acts predominantly as a mu agonist.

4.4.4 *Actual abuse and/or abuse liability (likelihood of abuse)*

Dezocine is neither registered nor marketed in any country, but is subject to national control in five of 37 reporting countries. No cases of abuse or of illicit manufacture or traffic have been reported. Its low potential for physical dependence in animals, failure to

suppress morphine withdrawal signs in monkeys, limited respiratory depressant activity and antagonist activity suggest that the abuse liability of dezocine is less than that of morphine.

4.4.5 *Therapeutic usefulness*

Dezocine is not yet available commercially. It has many of the same therapeutic indications as morphine. The Committee provisionally rated the therapeutic usefulness of dezocine as potentially moderate to high but decided to reserve giving a more definite opinion until more data become available following registration of the drug and more widespread experience with it.

4.4.6 *Recommendation*

On the basis of the available data concerning its pharmacological profile and its dependence potential in animals, and the absence of reports of actual abuse, the Committee rated the likelihood of abuse of dezocine as moderate and the therapeutic usefulness as potentially moderate to high. The degree of seriousness of the public health and social problems that might be associated with abuse of the drug was predicted to be not great enough to warrant international control at this time. However, the Committee recognized that, because of the limited experience with the drug in vulnerable populations, it will need to be carefully monitored when it enters clinical use. The Committee did not recommend scheduling of dezocine.

4.5 Meptazinol

4.5.1 *Substance identification*

Meptazinol (INN, CAS 54340-58-8), chemically *m*-(3-ethylhexahydro-1-methyl-1*H*-azepin-3-yl)phenol, is also known as Meptid. There is one chiral carbon atom in the molecule, so that two stereoisomers and one racemate are possible.

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

Meptazinol is a centrally acting agonist–antagonist opioid. Its pharmacological profile in both animals and humans is consistent

with a drug whose action is predominantly mediated through the mu receptors. It is claimed that the analgesic effect of meptazinol is primarily supraspinal, and that such analgesia is associated with low levels of respiratory depression and sedation. The drug also has anticholinesterase activity. The most frequently reported adverse effects have been nausea, vomiting, dizziness, diarrhoea, sweating and hypotension. Some of these may be related to meptazinol's anticholinesterase activity which, at higher doses, could produce the kind of toxic effects that are associated with cholinesterase inhibitors. Oral administration of meptazinol to healthy subjects results in rapid absorption and peak plasma concentrations are reached within 0.5–2 hours; intramuscular injections produce peak plasma levels within 30 minutes.

4.5.3 *Dependence potential*

Following chronic administration, abrupt withdrawal of meptazinol produced minimal withdrawal signs in rhesus monkeys; naloxone also precipitated only slight withdrawal signs in these animals. Meptazinol failed to substitute for morphine in morphine-dependent and withdrawn animals. In self-administration studies of meptazinol in rhesus monkeys, response rates for all doses of meptazinol were significantly lower than for codeine. In a drug-discrimination study, meptazinol was generalized to the prototypic kappa agonist ethylketazocine in rhesus monkeys. It was also generalized to the prototypic mu agonist etorphine at some doses.

Meptazinol does not suppress opioid withdrawal signs and symptoms in human subjects dependent on morphine; administered to methadone-maintained patients, it provokes a mild to moderate opioid withdrawal syndrome in about half of them. In non-dependent heroin abusers, doses in the therapeutic range are identified as having mild morphine-like effects, and produce limited "liking" and some dysphoria; higher doses do not increase scores on a euphoria or sedation scale but do increase scores on a dysphoria scale.

4.5.4 *Actual abuse and/or abuse liability (likelihood of abuse)*

Meptazinol is registered in 23 countries but is reported to be available for medical use in only a few. No cases of abuse have been reported. There is no evidence of illicit trafficking or manufacture.

4.5.5 *Therapeutic usefulness*

Meptazinol is reported to be a useful analgesic for the treatment of postoperative, obstetric and chronic pain. It has been reported to produce less respiratory depression and sedation than prototypic mu agonists and other opioid agonist–antagonists, but to have certain side-effects that may be associated with its cholinomimetic actions.

4.5.6 *Recommendation*

On the basis of the available data concerning its pharmacological profile, dependence potential and actual abuse, the Committee rated the likelihood of abuse of meptazinol as moderate and the therapeutic usefulness as moderate to high. The degree of seriousness of the public health and social problems that might be associated with the abuse of the drug was predicted to be not great enough to warrant international control at this time. The Committee did not recommend scheduling of meptazinol.

4.6 Nalbuphine

4.6.1 *Substance identification*

Nalbuphine (INN, CAS 20594-83-6), chemically 17-(cyclobutylmethyl)-4,5α-epoxymorphinan-3,6α-14-triol, is also known as Nubain. Nalbuphine is closely related in structure to hydromorphinol (controlled in Schedule I of the Single Convention on Narcotic Drugs, 1961), but cannot easily be converted into it. There are five chiral carbon atoms in the molecule, so that 32 stereoisomeric forms plus racemic mixtures are possible, but only three stereoisomers have been reported.

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

Nalbuphine is believed to be either a mu antagonist or a partial mu agonist in humans; it also has high affinity for and agonist actions at kappa receptors. It produces analgesia and sedation, as well as respiratory depression with ceiling effects, as described in section 4.1.1. In contrast to pentazocine it rarely produces, even in high doses, psychotomimetic effects such as dysphoria and distortion of body image.

In both laboratory animals and humans nalbuphine has high systemic clearance and low oral bioavailability as a result of extensive first-pass metabolism, mainly by glucuronidation; the glucuronide conjugate is pharmacologically inactive. The plasma half-life of nalbuphine is about 5 hours.

4.6.3 *Dependence potential*

Rats, baboons and rhesus monkeys will self-administer nalbuphine. In non-withdrawn morphine-dependent mice, nalbuphine precipitates withdrawal signs similar to those observed after naloxone administration. Experienced morphine users usually identify nalbuphine as morphine-like, but occasionally as barbiturate- or amfetamine-like. After continuous administration of nalbuphine, administration of naloxone produces a withdrawal syndrome which is less severe than that produced by naloxone in morphine-dependent human subjects. As a mu-opioid antagonist, nalbuphine is approximately one-quarter as potent as nalorphine.

4.6.4 *Actual abuse and/or abuse liability (likelihood of abuse)*

Infrequent abuse of nalbuphine has been reported, and the potential for abuse is rated as less than that of morphine. The producer of the drug has reported 77 individual abuse cases with an estimated incidence of one case per million therapeutic doses supplied. The majority of cases of abuse have occurred among health care personnel.

4.6.5 *Therapeutic usefulness*

Nalbuphine is indicated for the relief of moderate to severe pain. Unlike several other opioid agonist–antagonists, it produces minimal behavioural or autonomic effects in animals even in large doses. In humans, large doses of nalbuphine cause few psychotomimetic effects. The drug produces sedation, but rarely significant euphoria. The respiratory depression, gastrointestinal inhibition and cardiovascular effects are less marked than those produced by morphine.

Nalbuphine antagonizes morphine strongly enough to reverse mu-agonist-induced respiratory depression and to produce withdrawal manifestations in mu-agonist-dependent subjects. Its

limited effects on respiration mean that it can be used in burns patients with respiratory impairment and in patients with septic shock in whom morphine would be contraindicated.

4.6.6 *Recommendation*

On the basis of the available data concerning its pharmacological profile, dependence potential and actual abuse, the Committee rated the likelihood of abuse of nalbuphine as low to moderate, and the therapeutic usefulness as moderate to high. It considered that the degree of seriousness of the public health and social problems associated with the abuse of this substance was not great enough to warrant international control. The Committee did not recommend scheduling of nalbuphine.

4.7 Pentazocine

Pentazocine has been previously reviewed by WHO (*9–11*). In 1984, pentazocine was placed in Schedule III of the Convention on Psychotropic Substances, 1971. However, at the Eighth Special Session of the United Nations Commission on Narcotic Drugs, an extensive debate took place, resulting in a resolution requesting re-examination of the possibility of scheduling pentazocine under the Single Convention on Narcotic Drugs, 1961.

4.7.1 *Substance identification*

Pentazocine (INN, CAS 359-83-1), chemically 1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol, is also known as Talwin and Sosegon. Pentazocine is closely related in structure to metazocine and phenazocine (controlled in Schedule I of the Single Convention on Narcotic Drugs, 1961), but cannot easily be converted into them.

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

Pentazocine, a benzomorphan derivative, has been classified pharmacologically in two different ways over the past 20 years: as a partial agonist at mu opioid receptors and an agonist at kappa and sigma opioid receptors or as a weak antagonist at mu receptors with

agonist actions at kappa and sigma receptors. It produces analgesia, sedation and respiratory depression, and inhibits intestinal motility. As an opioid antagonist at the mu receptor, its potency is approximately 1/50 of that of nalorphine. In opiate-dependent patients it may precipitate withdrawal symptoms. In high, and sometimes at therapeutic doses, it may produce psychotomimetic effects (e.g., anxiety, nightmares and hallucinations). High doses also produce respiratory depression (which can be antagonized by naloxone) associated with increased blood pressure, tachycardia and the above-mentioned psychotomimetic effects. Tripelennamine enhances the reinforcing and analgesic effects of pentazocine.

Pentazocine is metabolized extensively in the liver and its metabolites are excreted by the kidney.

While pentazocine has some pharmacological properties similar to those of the prototypic mu agonists, such as morphine, which are scheduled under the Single Convention on Narcotic Drugs, 1961, it differs from them in a number of important respects outlined here and in sections 4.1.2, 4.1.3, and 4.7.4 below (see also section 4.1.4).

Thus pentazocine can antagonize some of effects of the prototypic mu agonists on the central nervous system and may precipitate a typical mu-agonist withdrawal syndrome in humans physically dependent on such drugs.

In addition, the respiratory depressant effect of pentazocine is less severe than that of the prototypic mu agonists. As the dose is increased, the respiratory depression does not increase proportionately. The drug is thus far less likely to produce death due to respiratory failure. The ceiling effect found with pentazocine, while not as clearly demonstrable as it is with other agonist–antagonists such as nalbuphine and buprenorphine, nevertheless differentiates pentazocine from prototypic mu agonists.

Finally, the actions of pentazocine at kappa and sigma receptors, which are not offset by significant mu-agonist actions, produce progressive increases in dysphoria and other adverse subjective effects as the dose is increased. These non-mu-agonist actions tend to limit its abuse potential.

4.7.3 *Dependence potential*

Controlled studies have shown that pentazocine produces physical dependence in both animals and humans. However, it does not substitute for morphine in morphine-dependent subjects; high

doses of pentazocine can precipitate withdrawal symptoms in humans dependent on morphine or other prototypic mu agonists. Furthermore, the physical dependence produced by pentazocine results in a withdrawal syndrome which is substantially less severe than that of prototypic mu agonists. While the syndrome bears some resemblance to the withdrawal syndromes produced by mu agonists, it also resembles those produced by mu antagonists with kappa and sigma agonist actions, such as cyclazocine and ethylketocyclazocine, which have little or no abuse potential. Physical dependence on pentazocine does not typically produce, on withdrawal, drug-seeking behaviour of the same degree or intensity as that found with prototypic mu agonists.

4.7.4 *Actual abuse and/or abuse liability (likelihood of abuse)*

Soon after initial marketing in 1967 a few scattered cases of pentazocine abuse were reported, primarily among patients under medical treatment and previously dependent on pethidine. However, no significant abuse of pentazocine among heroin addicts occurred until the late 1970s. After that time, hundreds of cases of pentazocine abuse were recorded in two countries (the Federal Republic of Germany and the USA) and some abuse also occurred in other countries.

Although actual abuse of pentazocine exists, the pharmacological and toxicological differences described above as well as the differences in dependence potential between pentazocine and the prototypic mu agonists result in dissimilarities between the drugs in patterns of abuse. Two patterns of pentazocine abuse have been identified, of which the first involves parenteral abuse of medically prescribed injectable pentazocine, while the second, which is restricted almost entirely to the USA, involves intravenous abuse of pentazocine tablets (intended for oral use) in combination with tripelennamine ("Ts and Blues"). Numerous cases of illicit trafficking and thefts from legitimate supplies have been reported from the majority of countries where the drug is marketed.

The Committee noted that the social consequences of pentazocine abuse are also typically dissimilar to those of abuse of the prototypic mu agonists in at least two important respects: (1) illicit synthesis of pentazocine has not been reported and the illicit manufacture of preparations from licitly produced, diverted substance has been very rarely reported; and (2) illicit diversion of pentazocine into

international trafficking is almost non-existent and hence significantly less common than that of the prototypic mu agonists such as heroin and morphine.

The introduction, in the USA, of a new oral preparation in which pentazocine is combined with naloxone has been associated with a reduction in the prevalence of abuse in that country. Since the scheduling of pentazocine under the terms of the Convention on Psychotropic Substances, 1971, there has been no other significant or important change in the prevalence of pentazocine abuse or in the character or seriousness of the public health and social problems associated with its use.

4.7.5 *Therapeutic usefulness*

Pentazocine, which is available in some 100 countries, is used for the relief of moderate to severe pain in various medical conditions, oral administration being preferable for the treatment of chronic pain. It is indicated as a supplement to surgical anaesthesia.

4.7.6 *Recommendation*

The Committee carefully examined the scheduling criteria of the Single Convention on Narcotic Drugs, 1961, and the Convention on Psychotropic Substances, 1971, and discussed pentazocine in detail in the light of these criteria and of current understanding of the biology of psychoactive drugs. It unanimously concluded that the patterns of abuse produced by pentazocine are sufficiently dissimilar to those of the prototypic mu agonists scheduled under the Single Convention on Narcotic Drugs, 1961, for it not to be controlled under that Convention. In addition, the chemical conversion of pentazocine into such opioid narcotic drugs would not seem to be possible in the foreseeable future. In view of the foregoing, the Committee concluded that the transfer of pentazocine from the schedules of the Convention on Psychotropic Substances, 1971, to those of the Single Convention on Narcotic Drugs, 1961, was not warranted.

On the basis of the available data concerning its pharmacological profile, dependence potential and actual abuse, the Committee rated the likelihood of abuse of pentazocine as moderate and the therapeutic usefulness as moderate to high. The Committee concluded that, except for the problems which developed in one or

two countries, the degree of seriousness of the public health and social problems associated with the abuse of this drug was not great in terms of the numbers of individuals involved.

The Committee recognized that there had been an appreciable decrease in the incidence of pentazocine abuse in the USA that seemed to coincide with the introduction of an oral preparation of the drug which incorporates naloxone. However, the Committee concluded that from a worldwide perspective there had been no change in the potential for abuse of pentazocine itself, especially when combined with tripelennamine.

The Committee recommended that pentazocine should remain in Schedule III of the Convention on Psychotropic Substances, 1971.

5. STIMULANTS AND MISCELLANEOUS DRUGS

5.1 Clonidine

5.1.1 *Substance identification*

Clonidine (INN, CAS 4205-90-7) exists in two tautomeric forms, 2-[(2,6-dichlorophenyl)imino]imidazolidine and 2-(2,6-dichloroanilino)-2-imidazoline, and is also known as clonidin, clonidinum and Catapres. No stereoisomeric forms exist.

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

Clonidine is a centrally active drug which appears to exert its actions at alpha$_2$ adrenoceptors. Acting at these sites, it reduces blood pressure; decreases release of norepinephrine and typically produces sedation. In laboratory animals clonidine exhibits analgesic actions. It has some anxiolytic effects in humans, but is not a reliable anti-anxiety agent. While it does not act at morphine receptors, clonidine suppresses some of the signs and symptoms of the morphine withdrawal syndrome in physically dependent laboratory animals, in human subjects in controlled experiments and in clinical situations. In most respects clonidine does not resemble any known psychoactive substance scheduled under either international treaty.

In humans, about 40–50% of the dose absorbed is excreted as unchanged clonidine. None of the drug's several metabolites appear

to be pharmacologically active. The duration of action of clonidine is 6–8 hours and it must be given several times daily to maintain its effects.

5.1.3 *Dependence potential*

Clonidine is self-administered at some doses by rats and monkeys. Its reinforcing effects do not appear to be strong and are not reliably found by all investigators. Self-administration is blocked by dopaminergic antagonists, but is not attenuated by naloxone. These findings suggest that catecholaminergic rather than opioid mechanisms are involved. In drug-discrimination studies where animals were trained to discriminate between morphine and saline, clonidine was generalized to saline. When clonidine was given repeatedly, tolerance developed to its sedative effects, and in some cases also to its analgesic effects. Primary physical dependence has not been demonstrated in animals. Clonidine does not produce classical opioid effects nor does it substitute completely for morphine in morphine-withdrawn animals, but it does suppress in a dose-related manner some of the signs (e.g., hyperactive adrenergic effects) of morphine withdrawal induced by opioid antagonists or drug deprivation. Experiments on cross-tolerance between opioids and clonidine have given inconclusive results.

Most human subjects given clonidine find that it produces a form of sedation that is not associated with euphoria. Subjects treated with clonidine usually stop taking it because they dislike the side-effects. Even subjects undergoing methadone detoxification sometimes prefer placebo to clonidine.

Nevertheless, tolerance and a form of physical dependence develop in humans when clonidine is given chronically. The withdrawal syndrome includes agitation, restlessness, insomnia, headache, palpitations, tachycardia, sweating, nausea, vomiting and abdominal pain. However, no drug-seeking behaviour is associated with these symptoms. Blood pressure begins to rise about 18 hours after administration of the drug is discontinued. A number of other antihypertensive agents also sometimes cause withdrawal symptoms.

5.1.4 *Actual abuse and/or abuse liability (likelihood of abuse)*

There are no well documented reports of clonidine abuse, nor is there any evidence of recreational use, despite widespread

availability in many countries where it is not subject to special controls. No known social or public health problems are associated with its use.

5.1.5 *Therapeutic usefulness*

Clonidine is used widely in the treatment of hypertension, and has been marketed in Europe since 1966 and in the USA since 1974. The drug is also available elsewhere and has been tried in the treatment or prevention of a number of other clinical conditions, for example in migraine prophylaxis. Clonidine is also used for symptomatic relief of opioid withdrawal symptoms. More recently it has been tried in the treatment of alcohol and nicotine withdrawal syndromes.

5.1.6 *Recommendation*

On the basis of the available data concerning its pharmacological profile, dependence potential and actual abuse, the Committee rated the likelihood of abuse of clonidine as very low and the therapeutic usefulness as moderate to high. The public health and social problems associated with the substance are very few, if any, and the Committee considered that they did not warrant placing it under international control. The Committee did not recommend scheduling of clonidine.

5.2 Pemoline

Pemoline was first reviewed at the twenty-second meeting of the Expert Committee on Drug Dependence (*12*). The view of the Committee at that time was that it was not likely to be associated with significant public health problems; it was therefore not recommended for control. Because of recent reports of significant illicit trafficking in Africa, Europe and South America, pemoline was recommended for re-evaluation and for possible scheduling.

5.2.1 *Substance identification*

Pemoline (INN, CAS 2152-34-3) exists in two tautomeric forms, 2-amino-5-phenyl-2-oxazolin-4-one and 2-imino-5-phenyl-4-oxazolidinone. It is also known as phenoxazole, phenylisohydantoin and phenylpseudohydantoin. There is one chiral carbon atom in the molecule, so that two stereoisomers and one racemate are possible.

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

Pemoline has been classified pharmacologically as an amfetamine-like, indirect dopaminergic agonist. It increases locomotor activity in a variety of animal species. In humans, it decreases appetite and produces central stimulant effects. While not similar to amfetamine with respect to some neurochemical mechanisms, its psychotoxic effects can resemble those of that substance. In large doses it can produce motor stimulation, hyperactivity, dyskinesia, seizures, insomnia and hallucinations, and may also aggravate or produce psychosis.

Pemoline is metabolized partially to less active metabolites which are excreted as conjugates in the urine. It is not readily soluble in water and is usually administered orally as magnesium pemoline. Pemoline has a less rapid onset of action than amfetamine, and its actions on the central nervous system do not peak until 2–3 hours after oral ingestion.

5.2.3 *Dependence potential*

Pemoline is not self-administered by rhesus monkeys and does not act as a reinforcer in these animals. Recent studies in non-dependent substance abusers demonstrate that its reinforcing properties in humans are quite limited. It is typically not reinforcing or euphoriant at doses of up to 37.5 mg and is toxic and dysphoric at doses of 150 mg. At doses of 75 mg it has mild effects on the central nervous system, roughly equivalent to those of 15 mg of amfetamine. Its euphoric effects at this dose are significantly less than those observed with 30 mg of amfetamine. In contrast to the value placed on 15 mg of amfetamine, subjects did not view any dose of pemoline as having any monetary value. Since the drug is not readily soluble, parenteral abuse of it is not likely. The dependence potential of pemoline in humans has not been established and the evidence for or against it is not convincing.

5.2.4 *Actual abuse and/or abuse liability (likelihood of abuse)*

A few isolated case reports of dependence on pemoline have been published. There have also been reports of its abuse from the governments of Belgium, the Federal Republic of Germany, Thailand and the United Kingdom, and a few mentions from

hospital emergency rooms have appeared in the reports of the Drug Abuse Warning Network each year. A few cases of pemoline abuse and dependence have been seen each year over the last few years in several psychiatric hospitals in Argentina. Pemoline is marketed illicitly "on the street" in the United Kingdom as "speed", and its use has been suspected in some cases of drugging of athletes and doping of racehorses. During the few years preceding the Committee's 1985 review of pemoline there had been reports of illicit trafficking in pemoline and two seizures of the drug.

In 1985, at its twenty-second meeting, the Expert Committee on Drug Dependence reviewed pemoline in order to determine whether international control was appropriate (*12*). At that time, the Committee concluded that "while pemoline has been in use in many countries, the available data do not indicate that the drug has been or is likely to be associated with significant public health problems". It therefore concluded that international control was not necessary. However, since then, there has been a significant increase in the amount of pemoline shipped across national borders and in international illicit trafficking, as judged by seizures of the drug by law enforcement authorities.

For example, the number of seizures of pemoline in the United Kingdom increased from 12 (8064 dosage units) in 1985 to 17 (1 818 240 dosage units) in 1987. Seizures have been reported in ten other countries, including the Netherlands, where 6750 kg were seized during April 1988; this large quantity, which originated in Eastern Europe, was destined for Africa via Western Europe. Exports of pemoline from one European country to Nigeria increased from 75 million dosage units in 1985 to 146 million in 1986, but fell to 78 million in 1987. There is no apparent legitimate medical use of pemoline in Nigeria and the Nigerian Ministry of Health has not authorized any importation of it. Pemoline exports from another European country increased from 7768 kg in 1985 to 9323 kg in 1986. This pemoline was shipped indirectly to Africa, Asia and South America, and the method of payment and shipment was such as to indicate clearly that the intention was to distribute the drug for non-medical purposes. At present there is very little information on what happens to all this pemoline, and estimates of the resulting public health and social problems must remain inferences drawn from the quantities of the drug moving in international non-medical channels. Nevertheless, international traffic is now of such magnitude as to be difficult to ignore.

5.2.5 *Therapeutic usefulness*

Pemoline is available for medical use in a number of countries, where it may be indicated in child and adult psychiatry for attention deficit disorders. It has also been tried in geriatrics to treat lethargy and depressive syndromes induced both by medicines and by physical and mental fatigue. In some countries, concerns about abuse and/or severe restrictions on the availability of other amfetamine-like agents have sometimes resulted in a relative increase in the therapeutic use of pemoline.

5.2.6 *Recommendation*

On the basis of the available data concerning its pharmacological profile, dependence potential and documented cases of abuse, the Committee rated the dependence potential of pemoline as low. The apparent demand for the drug for non-medical purposes suggests that more data are required to resolve the discrepancy between laboratory-based estimates of a low abuse liability and the higher abuse liability suggested by the illicit traffic and case reports. Reliable evidence of extensive abuse or of serious public health problems related to the non-medical use of pemoline was not presented to or uncovered by the Committee. However, given the amount of pemoline reported to be moving in international channels, which exceeds what is required to meet any reasonable medical need, serious public health and social problems are assumed to be developing, and are likely to become increasingly obvious if current levels of non-medical use persist. The Committee rated the therapeutic usefulness of pemoline as low to moderate. In the light of this assessment, the Committee recommended scheduling of the drug in Schedule IV of the Convention on Psychotropic Substances, 1971.

5.3 Propylhexedrine

A notification (DND 411/1(2) WHO, 421/12(1-35/36))[1] and note verbale (NAR/CL.10/1986) from the Government of the United States of America concerning the descheduling of propylhexedrine have been transmitted to the Director-General of

[1] A copy of this notification can be obtained by writing to: United Nations Division of Narcotic Drugs, Vienna International Centre, P.O. Box 500, A-1400 Vienna, Austria.

WHO pursuant to Article 2, Paragraph 7 of the Convention on Psychotropic Substances, 1971. Propylhexedrine is at present controlled under Schedule IV of this Convention. It was last reviewed at the twenty-second meeting of the Expert Committee on Drug Dependence (*12*).

5.3.1 *Substance identification*

Propylhexedrine (INN, CAS 101-40-6) is chemically *N*,α-dimethylcyclohexaneethylamine. It has one chiral carbon atom in the molecule, so that two stereoisomeric forms and one racemate are possible.

5.3.2 *Similarity to already known compounds and effects on the central nervous system*

Animal pharmacological studies indicate that propylhexedrine has some stimulant actions, for example on locomotor activity, and pressor effects in common with amfetamine.

In humans, propylhexedrine produces pressor and stimulant effects similar to those of *d*-amfetamine but is less potent. Administered by inhalation, it has local vasoconstrictor activity similar to that of amfetamine, but the duration of the activity is longer. Mucosal rebound congestion and chronic rhinitis may occur following excessive use of propylhexedrine in nasal inhalers. Amfetamine-like intoxication symptoms have been observed after oral or intravenous abuse.

5.3.3 *Dependence potential*

Studies in rats infused with propylhexedrine indicate that it acts as a typical stimulant of the central nervous system to which some tolerance develops; there is initial loss of body weight. In drug-discrimination studies, propylhexedrine has amfetamine-like effects in the monkey. It is self-administered by monkeys trained to self-administer cocaine, but much less intensively.

There have been no formal laboratory studies of the dependence potential of propylhexedrine in human subjects.

5.3.4 *Actual abuse and/or abuse liability (likelihood of abuse)*

Oral and intravenous abuse of propylhexedrine has been documented over a period of about 30 years, usually in the form of single case reports. Some of these reports mention severe adverse reactions, including myocardial infarction, "shock lung" syndrome and death. Since 1985, when the Committee last reviewed propylhexedrine, more information has become available on the incidence of abuse. Although there was a report in 1986 of seven cases of abuse of propylhexedrine extracted from nasal inhalers, a more typical response to the drug is that of people who abuse a variety of drugs on a chronic basis but do not find propylhexedrine very reinforcing and rarely bother to use it despite its easy availability.

Illicit traffic has been observed in five countries, but mainly in the USA and Canada, where it appears that propylhexedrine is extracted from inhalers. No illicit manufacturing has been reported. Data from the Drug Abuse Warning Network in the USA were also considered by the Committee. This network has not detected a significant amount of propylhexedrine abuse over the past five years. The threshold for inclusion in the list of "most frequently mentioned drugs" (which recently contained 256 drugs) is ten reported episodes of abuse in any one year. Propylhexedrine did not exceed this threshold in 1983, 1984 or 1986. Since 1982, there have been only 47 mentions of propylhexedrine abuse out of a total of almost a million reported episodes of drug abuse.

5.3.5 *Therapeutic usefulness*

Propylhexedrine is used in an inhalant form for nasal decongestion. The hydrochloride has been used as an anorectic agent in the treatment of obesity and is also available in a form for oral use. A number of alternative agents are available for both these indications. The Committee rated the therapeutic usefulness of propylhexedrine as low to moderate.

5.3.6 *Recommendation*

The Committee carefully reviewed its previous findings on the pharmacological profile and therapeutic usefulness of propylhexedrine. The Committee also considered more recent laboratory data showing that, in animals, it shares some stimulant and

reinforcing properties with prototypic stimulants of the central nervous system that are already controlled under the Convention on Psychotropic Substances, 1971. In assessing the public health and social problems associated with the use of this substance, the Committee attempted to weigh the published case reports of intravenous abuse against the very low levels of abuse indicated by organized drug-abuse reporting systems, such as the Drug Abuse Warning Network in the USA, where the substance has been available without prescription. In 1985, the Committee was of the opinion that the recommendation for scheduling in Schedule IV of the above-mentioned Convention was reasonable in the light of the data available from the various sources and the other factors that are taken into account in its recommendations (*12*). The additional data from the Drug Abuse Warning Network presented at the present meeting showed little evidence of significant public health or social problems associated with the use of this substance and therefore confirmed and supplemented similar data presented previously. The Committee's concern about the possibility that abuse of propylhexedrine might cause serious public health problems was therefore reduced by the accumulated data showing that such abuse is not taking place.

While recognizing the difficulty of conclusively proving the absence of a problem, the Committee was nevertheless impressed by the very low incidence of cases of abuse since its 1985 review of propylhexedrine, especially in the USA, where not only is the drug available without prescription but an organized drug-abuse reporting system also exists.

The Committee concluded that additional epidemiological data confirming current trends would, in the absence of new reports of intravenous use or of public health problems associated with propylhexedrine, argue strongly for a conclusion that the substance no longer required international control and for a Committee recommendation for descheduling. Such epidemiological data would be even more persuasive if some data could also be presented on comparisons of the drug, in humans, with prototypic reinforcing agents.

The Committee recommended that no change be made in the current scheduling of propylhexedrine but that the substance should be reviewed again in two years' time.

5.4 Pyrovalerone

A notification (DND 411/1(2) WHO, DND 421/12(1-35/36))[1] and note verbale (NAR/CL.11/1986) from the Government of the United States of America concerning descheduling of pyrovalerone have been transmitted to the Director-General of WHO pursuant to Article 2, Paragraph 7 of the Convention on Psychotropic Substances, 1971. Pyrovalerone is at present controlled under Schedule IV of this Convention. It was last reviewed at the twenty-second meeting of the Expert Committee on Drug Dependence (*12*).

5.4.1 *Substance identification*

Pyrovalerone (INN, CAS 3563-49-3) is chemically 4′-methyl-2-(1-pyrrolidinyl)valerophenone. There is one chiral carbon in the molecule, so that two stereoisomeric forms and one racemate are possible.

5.4.2 *Similarity to already known compounds and effects on the central nervous system*

Pyrovalerone is believed to be a potent inhibitor of norepinephrine uptake, but no data more recent than those reported in 1978 are available concerning its actions at various receptors or its pharmacological profile in humans.

5.4.3 *Dependence potential*

The Expert Committee was unable to find any results of experimental animal or human studies on the dependence potential of pyrovalerone. Clinical observation of abusers of the drug (see below) indicates that intravenously used pyrovalerone produces amfetamine-like stimulation, tolerance and psychological dependence.

5.4.4 *Actual abuse and/or abuse liability (likelihood of abuse)*

In 1975, about 200 cases of intravenous abuse of pyrovalerone tablets were reported in France in individuals who had previously

[1] A copy of this notification can be obtained by writing to: United Nations Division of Narcotic Drugs, Vienna International Centre, P.O. Box 500, A-1400 Vienna, Austria.

been heroin and/or amfetamine abusers. Thrombophlebitis was observed in nearly all of these cases. Pyrovalerone was withdrawn from the market in France and Switzerland, but is still available in Luxembourg. Despite efforts to obtain relevant information from the manufacturer, none was received. No illicit traffic or illicit manufacture of pyrovalerone has been reported recently.

5.4.5 *Therapeutic usefulness*

Pyrovalerone has been used medically to treat asthma and reactive depressive states. It is available in very few countries.

5.4.6 *Recommendation*

On the basis of the previously available data concerning its pharmacological profile, dependence potential and actual abuse, the Committee again rated the likelihood of abuse of pyrovalerone as moderate and the therapeutic usefulness as low. Consistent with the extremely limited availability of the drug, the public health and social problems currently associated with it have been found to be few and not serious. However, no new data were presented to suggest that the public health problems previously associated with pyrovalerone are not likely to re-emerge. The Committee recommended retaining pyrovalerone under international control in Schedule IV of the Convention on Psychotropic Substances, 1971.

6. GENERAL RECOMMENDATIONS

6.1 Procedural guidelines for review of substances for rescheduling or descheduling

WHO is requested to review periodically the status of substances already under international control. Occasionally a request is made to remove a drug from control entirely or to subject it to stricter control so that it is no longer available for medical use. It would be extremely useful for the review process itself, for countries, and for the pharmaceutical industry if such reviews were to be carried out in accordance with a set of procedural guidelines. Since no such guidelines currently exist, it is recommended that they should be developed.

6.2 Data on the utilization of psychoactive drugs

In evaluating psychoactive drugs for purposes of international control, the WHO Expert Committee on Drug Dependence is obliged to develop benefit–risk ratios for the particular substances it is asked to consider. Data on drug utilization are essential for this purpose.

WHO has developed a methodology for investigating utilization data for pharmaceuticals in general. For psychoactive substances in particular, greater efforts to collect such data are needed. Data on the utilization of psychoactive drugs can be useful to groups other than the WHO Expert Committee on Drug Dependence; for example, physicians who prescribe these substances can be guided by such data and those who finance health services may be better able to make funding decisions. It is therefore recommended that special efforts should be made to develop further the necessary methodologies, especially community studies, and to obtain these essential data.

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