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# **WHO Expert Committee on Drug Dependence**

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## **Twenty-second Report**

World Health Organization  
Technical Report Series  
729

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World Health Organization, Geneva 1985

ISBN 92 4 120729 9

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ISSN 0512-3054

PRINTED IN SWITZERLAND

85/6470 - Schüler S.A. - 6800

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Geneva, 22-27 April 1985

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# WHO EXPERT COMMITTEE ON DRUG DEPENDENCE

## Twenty-second Report

### INTRODUCTION

The WHO Expert Committee on Drug Dependence met in Geneva from 22 to 27 April 1985. The meeting was opened on behalf of the Director-General by Dr Lu Rushan, Assistant Director-General, who drew attention to the important work of the Expert Committee in making recommendations for the international control of narcotic drugs and psychotropic substances. Under the terms of the Single Convention on Narcotic Drugs adopted in 1961 and the Convention on Psychotropic Substances adopted in 1971, WHO must pass on these recommendations to the Secretary-General of the United Nations. The present meeting of the Expert Committee was convened to reach a final decision on draft proposals to be recommended, in accordance with the new procedures for the review of psychoactive substances for international control which were approved by the WHO Executive Board at its seventy-third session.<sup>1</sup> Dr Lu Rushan outlined the tasks of the Expert Committee as follows:

- (a) to make recommendations regarding the need for and level of control of the substances under review;
- (b) to make recommendations on the notifications from Finland, France, Hungary, and the USA concerning exempt preparations;
- (c) to advise on the effectiveness of the WHO procedures for the review of psychoactive substances.

### 1. GENERAL CONSIDERATIONS

The WHO Executive Board, at its seventy-third session, approved the new procedures for the review of substances to be recommended

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<sup>1</sup> WHO handbook of resolutions and decisions of the World Health Assembly and the Executive Board. Geneva, World Health Organization, Volume II, 1985, p. 109 (resolution EB73.R11).

for international drug control under the responsibilities assigned to WHO under the Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol, and under the Convention on Psychotropic Substances, 1971.<sup>1</sup> The Expert Committee at its present meeting used these revised procedures for the first time to review 28 phenethylamines. The new procedures include a set of guidelines, a procedural sequence, and a time-schedule for the review process.<sup>2,3</sup> In addition, the procedures specify that a review process should accumulate detailed information on each substance from a wide variety of sources, including individual experts, research groups (e.g., WHO Collaborating Centres), the pharmaceutical industry, and relevant publications.

In March 1984, the first meeting of the Programme Planning Working Group, a new organizational element in the review process, was held and its report specified a time-schedule for the current review, a tentative agenda for the current, twenty-second meeting of the Expert Committee on Drug Dependence, and a framework for the review process.<sup>4</sup>

In March 1984, WHO made a request for information on the 28 substances under review. Contact was established with, and considerable help obtained from, the International Federation of Pharmaceutical Manufacturers' Associations (IFPMA), which, in turn, requested information from its member associations in April 1984. In addition, WHO contacted the United Nations Division of Narcotic Drugs, the International Criminal Police Organization (Interpol), the Committee on Problems of Drug Dependence, Inc. (USA), and WHO Collaborating Centres to obtain relevant information. The Committee on Problems of Drug Dependence held a scientific symposium on the substances, and the proceedings of this symposium were made available to the World Health Organization.

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<sup>1</sup> *WHO handbook of resolutions and decisions of the World Health Assembly and the Executive Board*. Geneva, World Health Organization, Volume II, 1985, p. 109 (resolution EB73.R11).

<sup>2</sup> *Guidelines for the WHO review of dependence producing psychoactive substances for international control* (unpublished WHO document MNH/PAD/84.1).

<sup>3</sup> KHAN, I. & JAYASURIYA, D.C. Guidelines relating to international drug control treaties. *WHO Chronicle*, **38**: 17-20 (1984).

<sup>4</sup> *WHO's new procedures for the review of dependence producing psychoactive substances for international control. Report of the first meeting of the Programme Planning Working Group, Geneva, 12-16 March 1984* (unpublished WHO document MNH/PAD/84.2).

All the information was assembled and collated by WHO, and a first draft of the critical review, the second new element in the review process, was prepared in September 1984. This draft review was examined by a number of experts; in November 1984, their comments and criticisms were incorporated, together with new information. In early December 1984, a draft of the relevant sections of the document was sent to the pharmaceutical companies who had provided information on their products; they were requested to examine and comment on the statements concerning their substances. Most of these comments were incorporated into the final draft of the critical review,<sup>1</sup> copies of which were returned to the pharmaceutical companies. This version of the review was examined at the meeting of the second Programme Planning Working Group in March 1985.<sup>2</sup> The Group was asked to assess the adequacy of the information obtained on each of the 28 substances. In addition, it chose to hear the comments of individual companies as well as those of two nongovernmental organizations, namely, the International Federation of Pharmaceutical Manufacturers' Associations and the International Organization of Consumer Unions.

Following the meeting of the second Programme Planning Working Group, an addendum to the critical review was prepared that summarized the views of the meeting and also included additional comments and new information from pharmaceutical companies. Thus, the Expert Committee had available the complete file on the review, all information from the original sources described above, as well as the critical review, the addendum to the critical review, and additional comments made by the nongovernmental organizations.

The Expert Committee considered that, in general, the Programme Planning Working Group should be the channel of approach by nongovernmental organizations and pharmaceutical manufacturing companies, but that, if additional information were to be required, then experts should be invited to provide it. However, it was decided that no such consultation was needed for the present meeting.

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<sup>1</sup> *Critical review of information on 28 uncontrolled phenethylamines for the 22nd Expert Committee on Drug Dependence* (unpublished WHO document MNH/PAD/84.13).

<sup>2</sup> *Report of the meeting of the second Programme Planning Working Group, Geneva, 4-9 March 1985* (unpublished WHO document MNH/PAD/85.2).

## 2. ASSESSMENT OF TWENTY-EIGHT PHENETHYLAMINES

### 2.1 Cathine

Cathine, chemically  $(+)$ -*threo*-2-amino-1-hydroxy-1-phenylpropane, is one of the active principles of the abused plant material *Catha edulis* (khat). It is the single optical isomer of a structure that contains two asymmetric centres. This means that the compound can exist as two racemates (*threo* and *erythro*), each of which has two isomers,  $(+)$  and  $(-)$ . The *erythro* racemate is commonly known as phenylpropanolamine and is widely used medically as a nasal decongestant. Phenylpropanolamine has only a low level of activity as a central stimulant, is not self-administered by experimental animals, and is not widely abused by man despite its widespread medical use.

Cathine has similar central stimulatory activity to amphetamine, but is about 7–10 times less potent. Its toxicity in animals and man resembles that of amphetamine with a reduced incidence of stereotypy. Animal data indicate that cathine is discriminated as being amphetamine-like.

Cathine is marketed widely as an anorectic in a variety of pharmaceutical forms and preparations. From a number of countries there are reports of the abuse of anorectics containing cathine by man. There have been numerous reports of small seizures of the drug.

On the basis of the data outlined above it was the consensus of the Expert Committee that cathine met the criteria in article 2, paragraph 4, for control under the Convention on Psychotropic Substances and should be placed in Schedule II of the Convention.

The Expert Committee also noted that there are few or no data available on the racemate and the  $(-)$ -isomer of cathine. These forms may be expected to have similar properties to cathine in the same way as amphetamine and cathinone resemble each other. Further study of the abuse potential of the racemate and the  $(-)$ -isomer was suggested by the Expert Committee.

### 2.2 Cathinone

Cathinone, chemically  $(S)$ -2-amino-1-phenyl-1-propanone, is the major psychoactive component of the khat plant (*Catha edulis*). The



racemate and the (+)-isomer have also been prepared and submitted to limited pharmacological study.

Cathinone stimulates the central nervous system and shares most of the pharmacological properties of amphetamine; however, it is about half as potent as amphetamine. In addition, there is cross tolerance to amphetamine as an anorectic. The toxicology of cathinone is also similar to that of amphetamine. Cathinone is well absorbed after oral administration and is rapidly metabolized. The main excretion product is (–)-norephedrine.

The dependence potential of cathinone has been studied extensively in animals. The drug is discriminated as amphetamine-like and is readily self-administered by rhesus monkeys under experimental conditions. The racemate shares these properties. Knowledge of the human pharmacology of cathinone is based on experience with khat, the abuse of which has been reported to cause a major public health problem in certain areas of the world where it is available.

There is no known medical use of cathinone and there is no evidence of illicit trafficking in the substance.

On the basis of the data outlined above, it was the consensus of the Expert Committee that cathinone met the criteria in article 2, paragraph 4, for control under the Convention on Psychotropic Substances. Since cathinone has no medical use it was recommended that it be placed in Schedule I of the Convention.

### 2.3 Clobenzorex

Clobenzorex, chemically (+)-N-[(2-chlorophenyl)methyl]- $\alpha$ -methylbenzeneethanamine, is a centrally acting anorectic. The drug is rapidly absorbed and excreted in the urine, mainly in the glucuronide form. It is partially metabolized to amphetamine. No data are available concerning its dependence potential in either animals or man and only a few cases of abuse have been reported. No information is available on the therapeutic efficacy of clobenzorex, but it is marketed in a number of countries. There are very few reports of illicit trafficking in the substance.

In summary, there is no evidence, except for its structural resemblance to amphetamine and the possibility that it could be metabolized to amphetamine, that clobenzorex has a pharmacological profile or dependence potential similar to substances already controlled under the Convention on Psychotropic

Substances. Thus, the Expert Committee considered that it was not in a position to make any recommendation until more information is available about the substance. In addition, since no significant public health problems associated with the use or abuse of clobenzorex have been reported, no recommendation for urgent control seemed necessary.

#### **2.4 2,5-Dimethoxyamphetamine**

This substance, commonly known as DMA, is a racemic mixture that has a pharmacological profile similar to that of mescaline at low doses and of amphetamine at high doses. It apparently produces hallucinations in man. Drug discrimination studies indicate that its effects are similar to those observed with hallucinogens. 2,5-Dimethoxyamphetamine has no known medical use, but it is used in the photographic industry. There are a number of reports of illicit trafficking in the substance.

On the basis of the data outlined above, it was the consensus of the Expert Committee that 2,5-dimethoxyamphetamine met the criteria in article 2, paragraph 4, for control under the Convention on Psychotropic Substances. Since this substance has no known clinical use, the Expert Committee recommended that it be placed in Schedule I of the Convention.

#### **2.5 2,5-Dimethoxy-4-bromoamphetamine**

This substance, commonly known as DOB, is a racemic mixture having the pharmacological profile of a mescaline-like hallucinogen in both animals and man, with an affinity for serotonergic receptors. In the "spinal dog" the effects of the substance resemble those observed with LSD (lysergic acid diethylamide), with which it is cross-tolerant. In rodents it is discriminated as LSD-like. There is considerable evidence of abuse of this substance from several areas of the world. It has no known therapeutic use, and there are numerous reports of illicit trafficking in the substance.

On the recommendation of the Director-General of WHO, the United Nations Commission on Narcotic Drugs has already placed this substance under control in Schedule I of the Convention on Psychotropic Substances. The Expert Committee found no new evidence to recommend a change in this situation.

## **2.6 *N*-ethylamphetamine**

This substance is a racemic mixture with an amphetamine-like pharmacological profile. It is a central nervous system stimulant and is self-administered by the rhesus monkey under experimental conditions. No data are available on the clinical abuse liability of this substance, on the nature and magnitude of public health or social problems associated with its use or abuse, or on the epidemiology of its use and abuse. The substance is legislatively controlled in several countries and there are few reports on its therapeutic usefulness. Products containing the substance are marketed in several countries and there have been only a small number of reports of illicit trafficking in the drug.

On the basis of the data outlined above, it was the consensus of the Expert Committee that *N*-ethylamphetamine met the criteria in article 2, paragraph 4, for control under the Convention on Psychotropic Substances, and should therefore be placed in Schedule IV of the Convention.

## **2.7 Fenbutrazate**

Fenbutrazate has a number of asymmetric sites and does not have a clear-cut amphetamine-like structure. It is unlikely that it is metabolized to amphetamine. There is very little information available on its general pharmacology, toxicology, pharmacokinetics, dependence potential, or the nature and magnitude of public health or social problems associated with its use or abuse. Some cases of abuse have been reported in France. Although fenbutrazate is available in France, Hong Kong, the Federal Republic of Germany, and Spain, few data on its therapeutic usefulness are available. There have been few reports of illicit trafficking in the substance.

In summary, there is no evidence, except for its structural resemblance to phenmetrazine and the possibility that it could be metabolized to phenmetrazine, that fenbutrazate has a pharmacological profile or dependence potential similar to that of compounds already controlled under the Convention on Psychotropic Substances. Thus, the Expert Committee considered itself unable to make any recommendation until more information about the substance becomes available. In addition, since there have been no reports of significant public health problems associated with the

use or abuse of fenbutrazate, no recommendation for urgent control seemed to be necessary.

## **2.8 Fencamfamin**

Fencamfamin, chemically *N*-ethyl-3-phenylbicyclo[2,2,1]heptan-2-amine, is a central nervous system stimulant with a pharmacological profile that resembles that of amphetamine in most aspects. The toxicology of fencamfamin also resembles that of amphetamine, but it does not produce aggregate toxicity. Fencamfamin is not metabolized to amphetamine and has a half-life of about 16 hours.

Experimentally, fencamfamin is self-administered by both beagle dogs and monkeys and it shows the typical pattern of a central stimulant reinforcer. There is no evidence of clinical abuse liability or serious public health or social problems associated with its use or abuse, but there have been a few reports of social abuse by students in some countries.

Fencamfamin has been used clinically as an "energizing" drug since 1962 and is marketed in 32 countries, being prescription-controlled in many of them. There are a few examples of illicit trafficking in fencamfamin.

On the basis of the data outlined above, it was the consensus of the Expert Committee that fencamfamin met the criteria of article 2, paragraph 4, for control under the Convention on Psychotropic Substances and should be placed in Schedule IV of the Convention.

## **2.9 Fenetylline**

Chemically, fenetylline is a racemic ethyltheophylline derivative of amphetamine. Pharmacologically, it resembles amphetamine in some aspects, but there are a number of qualitative differences between the two substances. The pattern of toxicity in animals is similar to that observed with amphetamine. There is a low incidence of clinical side-effects. The drug is well absorbed, with an elimination half-life of about 1.3 hours. It is converted to a number of metabolites, including some amphetamine, that are slowly excreted.

In experiments, fenetylline is self-administered by rhesus monkeys but not to the same degree as amphetamine. In the most recent studies only 2 out of 5 animals self-administered the drug more frequently than they self-administered saline. In drug discrimination

studies in a number of species, fenetylline was discriminated as amphetamine-like in some cases. There are limited data on clinical dependence potential; but widespread and increasing abuse has been reported in the Federal Republic of Germany, with additional reports of abuse from Mexico, Sweden, and South-West Asia. The drug is used therapeutically mainly in paediatric and geriatric practice. It is marketed in a large number of countries.

In recent years there has been an increasing number of reports of illicit trafficking in fenetylline and it is under legislative control in many countries. Interpol has reported data on the seizure of the drug from 13 countries from 1981 to 1983, totalling approximately 20 million dosage units. Particular concern has been expressed by a number of countries from the eastern Mediterranean area and South-West Asia.

On the basis of the data outlined above, it was the consensus of the Expert Committee that fenetylline met the criteria of article 2, paragraph 4, for control under the Convention on Psychotropic Substances and should be placed in Schedule II of the Convention.

## **2.10 Fenproporex**

Fenproporex is the racemic *N*-cyanoethyl analogue of amphetamine. Pharmacologically, the compound appears to be amphetamine-like, but few published data are available. No animal toxicology studies are available; but, when given at therapeutic doses, the drug has been reported to alter colour vision in man. Fenproporex has been reported to be metabolized to amphetamine in man. No data are available concerning the preclinical or clinical dependence potential of the drug. There are a few reports of abuse from Chile and Mexico and the drug is controlled in several countries.

Fenproporex is used therapeutically as an appetite suppressant and is marketed widely. There are a number of reports of illicit trafficking in the drug.

On the basis of the data outlined above, it was the consensus of the Expert Committee that fenproporex met the criteria of article 2, paragraph 4, for control under the Convention on Psychotropic Substances and should be placed in Schedule IV of the Convention.

## 2.11 Furfenorex

Furfenorex is the racemic *N*-furfuryl analogue of methamphetamine. The drug is a sympathomimetic amine with anorectic activity. No toxicological data and few pharmacological data are available on the substance. It is possible that furfenorex is metabolized to methamphetamine in man.

No data are available concerning the dependence potential in animals or man, and the nature and magnitude of the public health or social problems associated with its use or abuse are unknown. Since 1970, there have been reports from France of varying degrees of abuse. Brazil is the only country in which the substance is controlled. It has been used therapeutically as an anorectic, but no data are available on its efficacy. There is little evidence of illicit trafficking in furfenorex.

In summary, there is no evidence, except for its structure and the possibility that it could be metabolized to methamphetamine, that furfenorex has a pharmacological profile or dependence potential similar to compounds already controlled under the Convention on Psychotropic Substances. Thus, the Expert Committee did not consider itself to be in a position to make any recommendation until more information about the compound becomes available. In addition, since no significant public health problems have been reported to be associated with the use or abuse of furfenorex, no recommendation for urgent control seemed to be necessary.

## 2.12 (–)-Isomer of amphetamine

The pharmacological profile of the (–)-isomer of amphetamine, for which the International Nonproprietary Name is levamfetamine, is very similar to that of the (+)-isomer, but it is about one-quarter to one-third as potent. No toxicological or pharmacokinetic data are available for this isomer.

(–)-Amphetamine is readily self-administered under experimental conditions by rhesus monkeys, rats, and dogs and differs only from (+)-amphetamine by being less potent. No information is available concerning its clinical abuse liability, on the nature of the public health or social problems associated with its use or abuse, or on the epidemiology of its use and abuse. The drug is controlled in a number of countries. It is available for medical use in the United Kingdom. No data are available concerning its

production. There have been some reports of illicit trafficking in the drug.

On the basis of the data outlined above, it was the consensus of the Expert Committee that (–)-amphetamine met the criteria in article 2, paragraph 4, for control under the Convention on Psychotropic Substances. Owing to its pharmacological similarity to (+)-amphetamine the Expert Committee recommended that it be placed in Schedule II of the Convention.

### **2.13 Levomethamphetamine**

Levomethamphetamine is the (–)-isomer of methamphetamine. It is a central nervous system stimulant with a pharmacological profile similar to that of the (+)-isomer, but it is less potent. No toxicological or pharmacokinetic data on the substance are available.

Levomethamphetamine is self-administered by rats under experimental conditions. There are no data available on clinical abuse liability, on the nature and magnitude of public health or social problems associated with this substance, or on the epidemiology of its use and abuse. The drug is controlled in several countries. In the USA, it is marketed as a nasal decongestant in an inhaler and this is an exempt preparation. There are some reports of illicit manufacture and trafficking in the drug.

On the basis of the data outlined above, it was the consensus of the Expert Committee that levomethamphetamine met the criteria in article 2, paragraph 4, for control under the Convention on Psychotropic Substances. On the basis of its marked chemical and pharmacological resemblance to (+)-methamphetamine the Expert Committee recommended that the drug be placed in Schedule II of the Convention.

### **2.14 Mefenorex**

Mefenorex is the racemic *N*-chloropropyl analogue of amphetamine. Mefenorex is an amphetamine-like stimulant with anorectic activity. It appears to have less effect on the cardiovascular system than amphetamine and does not produce stereotypic movements in the rat. The immediate cause of death in rats is respiratory paralysis. There is no enhancement of lethality in grouped animals such as occurs with (+)-amphetamine. Typical

sympathomimetic side-effects are observed in man. In man the drug is excreted partly unchanged and partly in the form of various hydroxylated metabolites.

Under experimental conditions, mefenorex is self-administered to some degree (2 out of 5) by the rhesus monkey and shows similar discriminative stimulus effects to amphetamine in both monkeys and pigeons; the drug is less potent than amphetamine in both procedures. There are no data available for this drug on clinical abuse liability, no reported public health or social problems associated with its use, and no information related to abuse epidemiology. The drug is under some form of control in many countries.

Mefenorex is used as an anorectic agent in the treatment of obesity and is marketed throughout the world. Some illicit trafficking in the drug has been reported.

On the basis of the data outlined above, it was the consensus of the Expert Committee that mefenorex met the criteria of article 2, paragraph 4, for control under the Convention on Psychotropic Substances and should be placed in Schedule IV of the Convention.

### **2.15 3,4-Methylenedioxyamphetamine**

In March 1984, the Director-General of WHO recommended 3,4-methylenedioxyamphetamine (MDA) for international control. The justification of the recommendation stated that MDA was capable of producing a state of dependence and central nervous system stimulation resulting in disturbances in behaviour and mood. MDA had the capacity to produce similar abuse and similar ill effects as STP and was being abused so as to constitute a public health and social problem warranting international control. There was no evidence of therapeutic use for MDA. Therefore, the World Health Organization recommended that MDA be added to Schedule I of the Convention on Psychotropic Substances, 1971. On the basis of this recommendation, the United Nations Commission on Narcotic Drugs placed MDA in Schedule I of the Convention on Psychotropic Substances.

A review of the general pharmacology of this compound shows certain similarities to currently controlled drugs. The pharmacological and neurochemical profiles of MDA are substantially similar to those of both LSD and amphetamine. In



animal experiments to assess its dependence potential, 3,4-methylenedioxyamphetamine has been shown to be a reinforcer and, in drug discrimination assays the *S*-(+)-isomer was found to be amphetamine-like. No data are available regarding its clinical abuse potential.

There is evidence from several countries of abuse of the drug and of its toxicity. Governmental seizures of the substance, including those that have occurred since March 1984, indicate that there has been illicit trafficking in the drug. The Expert Committee felt that there is enough evidence available to demonstrate that significant public health problems are associated with the use of this substance.

It was the consensus of the Expert Committee that the recommendation of the United Nations Commission on Narcotic Drugs to place 3,4-methylenedioxyamphetamine in Schedule I of the Convention on Psychotropic Substances should not be changed.

## **2.16 Morazone**

Morazone is an *N*-methylantipyrine-substituted phenmetrazine. The chemical structure of morazone raises theoretical concern that it could have a possible role as a pro-drug for phenmetrazine, a substance that is currently controlled as a central stimulant under the Convention on Psychotropic Substances. However, there were no data available to the Expert Committee indicating that morazone does act as a pro-drug for phenmetrazine. In addition, no data were available on its pharmacological profile.

It was not possible for the Expert Committee to obtain any dependence potential data for this drug from studies in animals or man.

Morazone is registered and available in several countries as an analgesic and as an anti-inflammatory and antipyretic agent. Medical use of morazone as an antipyretic and anti-inflammatory drug suggests that its pharmacological profile does not significantly resemble those of stimulants or hallucinogens.

In summary, there is no evidence, except for its structure and the possibility that it could be metabolized to phenmetrazine, that morazone has a pharmacological profile or dependence potential similar to that of compounds already controlled under the Convention on Psychotropic Substances. Thus, the Expert Committee considered itself unable to make any recommendation until more information becomes available about the substance. In

addition, since no significant public health problems have been associated with the use of morazone, no recommendation for urgent control seemed necessary.

#### **2.17 4-Methoxyamphetamine**

4-Methoxyamphetamine (*p*-methoxyamphetamine, PMA) is a racemic mixture with a pharmacological profile that is predominantly amphetamine-like. It also shows some pharmacological activity resembling LSD (e.g., visual tracking in monkeys and dogs). From studies in man, this substance has been estimated to be five times more potent as a psychotomimetic than mescaline.

In different studies of its dependence potential in rodents, the discriminative effect of 4-methoxyamphetamine was amphetamine-like or resembled LSD. It was not self-administered by baboons. No data are available from studies in man on the clinical abuse liability relevant to the dependence potential of this substance.

In isolated geographical areas, serious adverse reactions have been reported and fatal toxicity has appeared. The signs of intoxication include those observed with amphetamine and also with mescaline.

Data on governmental seizures of the drug indicate only isolated cases of illicit trafficking in the substance.

On the basis of the data outlined above, it was the consensus of the Expert Committee that 4-methoxyamphetamine met the criteria of article 2, paragraph 4, for control under the Convention on Psychotropic Substances. Since this substance has no therapeutic use, the Expert Committee recommended that it be placed in Schedule I of the Convention.

#### **2.18 Hydroxyamphetamine**

Hydroxyamphetamine is a racemic mixture. There is no substantial evidence that it affects the central nervous system or that it has dependence potential. Furthermore, there are no data available indicating abuse of this substance or that there are any existing public health problems associated with its use; the Expert Committee did not envisage any significant hydroxyamphetamine abuse in the future.

In summary, there is no evidence, except for its structure, that hydroxyamphetamine has a pharmacological profile or dependence liability similar to compounds already controlled under the Convention on Psychotropic Substances. The substance is used therapeutically as an ophthalmic solution to dilate the pupils. The Expert Committee considered international control of this drug unnecessary.

## **2.19 Pemoline**

Chemically, pemoline is 2-amino-5-phenyl-4(5*H*)-oxazolone. The predominant pharmacological property of pemoline is central nervous system stimulation. It increases locomotor activity in a variety of animal species and it will enhance motor performance in man at doses that have no significant effects on heart rate.

Pemoline is not similar to amphetamine in terms of neurochemical mechanisms. The central stimulant effect of pemoline may result from the inhibition of catecholamine uptake; this effect may also account for the decrease of brain catecholamine turnover.

From toxicological data it is clear that the adverse effects of pemoline are those characteristic of over-stimulation, namely, insomnia, anorexia, nausea, dizziness, motor stimulation, and hyperactivity. More serious adverse reactions such as hallucinations have only been reported following large doses. Pemoline is less likely than amphetamine to produce such stimulant effects.

In animal models of dependence potential, pemoline clearly differs from amphetamine. It does not act as a reinforcer and is not self-administered in animal studies. The dependence potential of the compound in man has been very thoroughly reviewed retrospectively and little substantial evidence of abuse has been established. There is evidence of some illicit trafficking in, and seizures of, pemoline. There have been no reports of pemoline being abused by the intravenous route and, since pemoline is not readily soluble in water, its intravenous abuse is unlikely.

Pemoline appears to have some therapeutic uses and products containing it are available on the market in a number of countries. Depending on the country, pemoline is indicated for medical use in child and adult psychiatry and in geriatrics. The main indications for use include attention-deficit disorders and somnolence and depressive syndrome induced by major tranquilizers, as well as physical and mental fatigue and somnolence in the elderly.

In summary, there are only limited similarities between pemoline and amphetamine and other substances controlled by the Convention on Psychotropic Substances. 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. On the basis of these findings, it was the consensus of the Expert Committee that international control of pemoline is not necessary.

## **2.20 Propylhexedrine**

Chemically, propylhexedrine is *N*, $\alpha$ -dimethylcyclohexaneethanamine. Animal pharmacology studies indicate that propylhexedrine has some stimulant actions in common with amphetamine, such as increased locomotor activity and pressor effects. No data on dependence potential are available from animal studies, but investigative reports in man indicate that propylhexedrine is capable of imitating at least some of the subjective effects of amphetamine, such as restlessness.

Toxicological data show that adverse reactions have occurred in man following oral abuse of propylhexedrine inhalers and also in certain cases of intravenous abuse reported from 1974 to 1982. Published reports describe severe acute toxic effects following abuse of the substance. In addition, a low level of propylhexedrine abuse has been reported in epidemiological observations based upon several abuse-reporting systems; these observations have been spread over a period of 30 years. It is important that propylhexedrine does not seem to be accepted by abusers when provided as a substitute for amphetamine in inhalant form.

Propylhexedrine is a sympathomimetic agent that is available without a prescription in an inhalant form for nasal decongestion. The hydrochloride acts as an anorectic agent in the treatment of obesity and is available in an oral form to be taken daily in divided doses.

On the basis of the data outlined above, it was the consensus of the Expert Committee that propylhexedrine met the criteria of article 2, paragraph 4, for control under the Convention on Psychotropic Substances and should be placed in Schedule IV of the Convention.

## **2.21 Pyrovalerone**

Pyrovalerone, chemically 1-(4-methylphenyl)-2-(1-pyrrolidinyl)-1-pentanone, is a potent inhibitor of norepinephrine uptake. The Expert Committee was unable to find either useful data on the pharmacological profile of this substance or the results of animal studies on its dependence potential. It has been used medically to treat asthma and reactive depression and as a stimulant for the relief of drug-induced lethargy. Following the intravenous abuse of a pyrovalerone preparation in France, the substance was withdrawn from the market in both France and Switzerland. Reports are available that appear to indicate that, when administered intravenously, it produces amphetamine-like central stimulation and psychological dependence. The drug is still available in Luxembourg, but, despite efforts to obtain relevant information for the Expert Committee, the manufacturer did not supply any.

On the basis of the data outlined above, it was the consensus of the Expert Committee that pyrovalerone met the criteria of article 2, paragraph 4, of the Convention and should be placed in Schedule IV of the Convention.

## **2.22 3,4,5-Trimethoxyamphetamine**

3,4,5-Trimethoxyamphetamine (3,4,5-TMA) is a racemic mixture with a similar pharmacological profile to that of LSD, with some amphetamine-like activity in the "spinal dog". It is cross-tolerant with LSD. No toxicological data are available.

In rodents 3,4,5-trimethoxyamphetamine produces discriminative effects similar to those of 2,5-dimethoxy- $\alpha$ ,4-dimethylbenzeneethanamine (DOM) another known hallucinogen of this series. No clinical abuse data are available, and the nature and magnitude of associated public health or social problems are unknown. No information is available on the epidemiology of its use and abuse. The substance is under national control in several countries. There is no known therapeutic use for the substance and thus no lawful production. Seizures of the drug and the discovery of a number of clandestine laboratories indicate that there is illicit trafficking in the substance in Canada and the United States of America.

On the basis of the data outlined above, it was the consensus of the Expert Committee that 3,4,5-trimethoxyamphetamine met the criteria in article 2, paragraph 4, for control under the Convention on Psychotropic Substances. Since it has no known clinical use, the

Expert Committee recommended that it be placed in Schedule I of the Convention.

#### **2.23 4-Bromo-2,5-dimethoxyphenethylamine**

No information is available for this substance concerning its general pharmacology, toxicology, pharmacokinetics, dependence potential, nature and magnitude of associated public health or social problems, or epidemiology of its use and abuse. The substance is under national control in three countries. It has no known therapeutic activity and there is no lawful production. There are only a few reports of illicit trafficking in the substance.

In summary, there is no evidence, except for its structure, that 4-bromo-2,5-dimethoxyphenethylamine has a pharmacological profile or dependence potential similar to compounds already controlled under the Convention on Psychotropic Substances. Thus, the Expert Committee did not consider itself in a position to make any recommendation until more information becomes available about the compound. Since it is structurally very similar to 2,5-dimethoxy-4-bromoamphetamine (DOB), which is already controlled, the Expert Committee recommended that pharmacological studies be promptly carried out on 4-bromo-2,5-dimethoxyphenethylamine.

#### **2.24 2,5-Dimethoxy-4-ethylamphetamine**

2,5-Dimethoxy-4-ethylamphetamine has been reported to have a hallucinogenic effect in man. In studies in the rat, this compound has been discriminated as hallucinogen-like, but there is some evidence that it may have a profile of pharmacological action different from that typical of hallucinogens in this series. No toxicological or pharmacokinetic data are available.

It is not self-administered by baboons. No data are available on its clinical abuse liability, on the nature or magnitude of associated public health or social problems, or on the epidemiology of its use or abuse. The drug is under national control in four countries. There is no known therapeutic use and no data on production. There is only one minor report of illicit trafficking.

On the basis of the data outlined above, it was the consensus of the Expert Committee that 2,5-dimethoxy-4-ethylamphetamine met the criteria in article 2, paragraph 4, for control under the Convention on Psychotropic Substances. Since the substance has no

therapeutic use, the Expert Committee recommended that it be placed in Schedule I of the Convention.

### **2.25 Dimethylamphetamine**

Chemically, dimethylamphetamine is *N,N*-dimethyl- $\alpha$ -methylbenzeneethanamine; its International Nonproprietary Name is dimetamfetamine. There is no information available on its pharmacological profile, toxicology, dependence potential, nature and magnitude of associated public health or social problems, or epidemiology of its use and abuse. There is some evidence in rats that the substance is metabolized to methamphetamine and amphetamine. The substance is not under national control in any country, it has no therapeutic use, and there is no information available concerning its production. Trade names exist for the substance, and it is present in a preparation available in the Federal Republic of Germany. There is some evidence of illicit trafficking in this substance in the United States of America.

In summary, there is no evidence, except for its structure and the possibility that it could be converted to methamphetamine, that dimethylamphetamine has a pharmacological profile or dependence potential similar to compounds already controlled under the Convention on Psychotropic Substances. Thus, the Expert Committee was unable to make any recommendation until more information becomes available about the compound. In addition, since no significant public health problems have been reported to be associated with dimetamfetamine, no recommendation for urgent control seemed necessary.

### **2.26 *N*-ethyl-3,4-methylenedioxyamphetamine**

This substance is closely related to 3,4-methylenedioxyamphetamine (MDA), which is already a controlled substance (see section 2.15). No data are available concerning its pharmacological profile, toxicology, pharmacokinetics, dependence potential, nature and magnitude of associated public health or social problems, or epidemiology of its use and abuse. The substance is under national control in Canada and the United Kingdom. It has no known therapeutic use and there are no data concerning its production. There have been reports of small seizures of the drug in the United States of America.

In summary, there is no evidence, except for its structure, that *N*-ethyl-3,4-methylenedioxyamphetamine has a pharmacological profile or dependence potential similar to compounds already controlled under the Convention on Psychotropic Substances. Thus, the Expert Committee was unable to make any recommendation until more information becomes available about the compound. Because of the close structural relationship of this substance to MDA, which is already controlled, the Expert Committee urged that efforts be made promptly to gather further pharmacological data on it.

#### **2.27 5-Methoxy-3,4-methylenedioxyamphetamine**

In the "spinal dog" 5-methoxy-3,4-methylenedioxyamphetamine (MMDA) has a pharmacological profile that resembles that of both LSD and amphetamine, but it also has other properties not exhibited by either drug. There are no data available on its toxicology, pharmacokinetics, dependence potential, nature and magnitude of associated public health or social problems, or epidemiology of its use and abuse. The substance is under national control in five countries. It has no known therapeutic use and no information is available concerning its production. There are some reports from the USA of minor incidences of illicit trafficking in this substance.

On the basis of the data outlined above, it was the consensus of the Expert Committee that 5-methoxy-3,4-methylenedioxyamphetamine met the criteria of article 2, paragraph 4, for control under the Convention on Psychotropic Substances. Since it has no known therapeutic use, the Expert Committee recommended that it be placed in Schedule I of the Convention.

#### **2.28 3,4-Methylenedioxymethamphetamine**

In mice, 3,4-methylenedioxymethamphetamine (MDMA) increases locomotor activity and produces analgesia. In dogs and monkeys the substance has a pharmacological profile similar to that of other substances already controlled under the Convention on Psychotropic Substances. There are contradictory reports of the hallucinogenic activity of this substance in man. The substance is a potent serotonin-releaser in rat whole-brain synaptosomes. Its toxicological properties have been studied extensively in animals.



The acute toxicity of this substance is about twice that of mescaline. No pharmacokinetic data are available.

3,4-Methylenedioxymethamphetamine has discriminative stimulus effects in common with amphetamine but not with 2,5-dimethoxy- $\alpha$ 4-dimethylbenzeneethanamine (DOM). No data are available concerning its clinical abuse liability, nature and magnitude of associated public health or social problems, or epidemiology of its use and abuse. The substance is under national control in Canada and the United Kingdom and its control has been proposed in the USA.

The substance has no well defined therapeutic use, but a number of clinicians in the USA have claimed that it is potentially valuable as a psychotherapeutic agent. No data are available concerning its lawful production. Evidence of some illicit trafficking in the substance has been reported from Canada and there have been extensive seizures of the drug in the USA.

On the basis of the data outlined above, it was the consensus of the Expert Committee that 3,4-methylenedioxymethamphetamine met the criteria of article 2, paragraph 4, for control under the Convention on Psychotropic Substances. Since there is insufficient evidence to indicate that the substance has therapeutic usefulness, the Expert Committee recommended that it be placed in Schedule I of the Convention.<sup>1</sup>

It should be noted that the Expert Committee held extensive discussions concerning the reported therapeutic usefulness of 3,4-methylenedioxymethamphetamine. While the Expert Committee found the reports intriguing, it felt that the studies lacked the appropriate methodological design necessary to ascertain the reliability of the observations. There was, however, sufficient interest expressed to recommend that investigations be encouraged to follow up these preliminary findings. To that end, the Expert Committee urged countries to use the provisions of article 7 of the Convention on Psychotropic Substances to facilitate research on this interesting substance.

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<sup>1</sup> One member, Professor Paul Grof (*Chairman*), felt that the decision on the recommendation should be deferred awaiting, in particular, the data on the substance's potential therapeutic usefulness and that at this time international control is not warranted.

### 3. RECOMMENDATIONS FOR EXEMPT PREPARATIONS

These recommendations concern preparations exempted under the provisions of article 3, paragraph 2, of the Convention on Psychotropic Substances, which stipulate that, under certain conditions, a Party may decide to exempt a preparation containing a psychotropic substance listed in Schedule II, III, or IV from certain measures of control provided for in the Convention. If this is the case, the Party shall notify the Secretary-General of the United Nations of any such decision, and the Secretary-General shall, in turn, transmit the notification to the other Parties, the International Narcotics Control Board, and WHO. WHO shall communicate to the Secretary-General an assessment of the preparation together with a recommendation, if necessary, of the control measures from which the preparation should not be exempted.

In this context, the Expert Committee examined the recommendations that had been made concerning a series of exempt preparations by a review group that met at WHO in Geneva in October 1984.<sup>1</sup> Using the guidelines adopted by the United Nations Commission on Narcotic Drugs in resolution 1(S-VIII),<sup>2</sup> this group had studied the preparations exempted by the Governments of Hungary, Finland, France, and the United States of America.<sup>3</sup> The preparations exempted by Chile had been examined at an earlier meeting.

#### 3.1 Chile

Of the nine preparations earlier recommended for termination of exemption, the Government of Chile informed WHO that none of the exemptions were still applied; no recommendation was therefore required.

<sup>1</sup> *Review of exempted preparations under Article 3 of the 1971 Convention on Psychotropic Substances, Geneva, 15–17 October 1984* (unpublished WHO document MNH/PAD/84.17).

<sup>2</sup> UNITED NATIONS, Commission on Narcotic Drugs. Report on the Eighth Special Session, 6–10 February 1984. *Economic and Social Council, Official Records, 1984, Supplement No. 3*. New York, 1984, pp. 43–44 (document E/1984/13, E/CN.7/1984/13).

<sup>3</sup> The second Programme Planning Working Group also gave an opinion on this subject (unpublished WHO document MNH/PAD/85.2).

### 3.2 Finland

The Expert Committee agreed with the recommendation of the review group that of the 59 preparations notified by the Government of Finland the exemption of 57 should be accepted and the exemptions of the preparations Neo-Ortoxin liquid and Veralgin tablets should be terminated. The Expert Committee was informed that the Government of Finland had agreed to these recommendations.

### 3.3 France

The Government of France notified 112 preparations. The Expert Committee agreed with the recommendation of the review group to terminate in full the exemption of the following preparations:

- Alepsal (1.5 cg) tablets
- Atrium 100 tablets
- Cantéine tablets
- Diacromone sédative tablets
- Frénantol Amobarbital tablets
- Nardyl tablets
- Neurinase tablets
- Sédaortine tablets
- Sédo-Intensain capsules
- Soméнал tablets
- Sympanal tablets
- Sympaneurol Papavérine tablets
- Sympathyl tablets
- Sympavagol tablets
- Tensophoril capsules
- Trinitrine Retard Phénobarbital Roger Bellon tablets
- Vagal

The Expert Committee recommended that the exemption of the preparation Clémodril be accepted provided that it remain prescription-controlled.

The Expert Committee also agreed with the recommendation of the review group that the exemption of the following preparations be terminated in part, i.e., from the requirements of article 8, paragraph 1, and of article 11, paragraph 5, of the Convention, inasmuch as they apply to importers and exporters:

Aéine  
 Aéine Vitaminée B1  
 Algisédal (with noramidopyrine)  
 Atherophylline Sedative  
 Chilral  
 Colchimax  
 Corverum  
 Déchophylline Phénobarbital  
 Décontractyl-Phénobarbital  
 Enurétine Vit. E  
 Ephédronal Lancelot  
 Ethaphylline Phénobarbital  
 Inophylline Sédatif  
 Kiadone  
 Neutraphylline-Papavérine-Phénobarbital  
 Pneumogéine-Barbital  
 Sédo-Caréna  
 Somalgine  
 Tédralan  
 Thyroidine Berthier (with phenobarbital)  
 Trinuride  
 Viaggio (with dimenhydrinate)

The Expert Committee recommended the same partial termination for the preparations Neurocalcium tablets and Neurocalcium granules.

Concerning the remaining preparations notified by the Government of France, the Expert Committee agreed with the recommendation of the review group that the exemptions be accepted.

### 3.4 Hungary

Concerning the preparation Sevenaletta, which had earlier been recommended for termination of exemption, WHO was informed by the Government of Hungary that this preparation was now under prescription control; the Expert Committee therefore agreed that the recommendation for termination of this exemption was not necessary.

### 3.5 United States of America

With regard to the 581 preparations notified by the Government of the United States of America, the Expert Committee agreed with the recommendation of the review group that the exemption of the preparations Orgaphen tablets and Orgaphen elixir should be terminated. These preparations have not been exported but, in accordance with the guidelines adopted by the United Nations Commission on Narcotic Drugs in resolution 1(S-VIII),<sup>1</sup> the Expert Committee recommended that since they might nevertheless constitute a danger to the public health of the country involved, WHO should draw this to the attention of the competent national authority and advise the Commission of its action.

The Expert Committee also agreed with the recommendation of the Review Group that the exemption of the following preparations be terminated in part—i.e., from the requirements of article 8, paragraph 1 and of article 11, paragraph 5 of the Convention, inasmuch as they apply to importers and exporters.

- Anaspaz PB tablets
- Barbidonna tablets and elixir
- Dilantin sodium with Phenobarbital, Kapseal capsules
- Donnatal tablets, capsules, extantabs, and elixir
- Equanitate 10/20 tablets
- Kinesed tablets
- Levsinex Timecaps capsules (with phenobarbital)
- Levsin drops (with phenobarbital)
- Levsin elixir (with phenobarbital)
- Milpath 200/400 tablets
- Milprem 200/400 tablets
- Miltrate 10/20 tablets
- PMB-200 tablets
- PMB-400 tablets
- Primatene P tablets
- Quadrinal tablets
- Quadrinal suspension
- Tedral tablets, elixir, and paediatric suspension
- Tedral SA tablets

<sup>1</sup> UNITED NATIONS, Commission on Narcotic Drugs. Report on the Eighth Special Session, 6–10 February 1984. *Economic and Social Council, Official Records, 1984, Supplement No. 3*. New York, 1984, pp. 43–44 (document E/1984/13, E/CN.7/1984/13).

Valpin 50-PB tablets  
Verguad suspension and tablets

With regard to all other preparations notified by the Government of the United States of America, the Expert Committee recommended that the exemptions be accepted.

#### 4. RECOMMENDATIONS

The Expert Committee recommended that a number of steps be taken to improve the review process. These steps can be divided into two categories. The first involves procedures that WHO can initiate to help the overall review process. The second involves recommendations to the Programme Planning Working Group to help improve the organization of data for presentation to the Expert Committee. The specific recommendations are detailed below:

1. WHO should encourage every government to designate one or more institutions or agencies that are involved in medical or public health matters to assist WHO in the collection of data on the medical and non-medical use and abuse of psychoactive substances. These institutions or agencies may include: departments of health, food and drug administrations, national medical societies, national pharmacological societies, and national pharmacy societies or other appropriate groups. As part of the data-gathering procedure, governments should be urged to provide a clear indication of the type of national control for both the licit and the illicit substances under review.

2. (a) Data concerning the dependence potential and abuse liability of a substance being considered for control under the Single Convention on Narcotic Drugs, 1961, and the Convention on Psychotropic Substances, 1971, are essential to the decision-making process. The Expert Committee recognized the importance of animal data and information from controlled clinical studies. However, data derived from the population actually abusing the substance can be especially important; the Expert Committee urged that efforts be made to encourage the systematic collection of such data.

(b) Further efforts should be made to facilitate the collection of data concerning the therapeutic usefulness of the substances under consideration for control. This information is essential in the decision-making process concerning substances with a medical use.

It would be helpful if there were greater cooperation from the various governmental agencies and from the pharmaceutical industry directly and through the International Federation of Pharmaceutical Manufacturers' Associations.

(c) WHO should consider special procedures for the review of emergency situations associated with the rapid development of an abuse problem with a particular substance; this is particularly important where serious public health and/or social problems are involved.

3. In assembling subsequent critical reviews, the Programme Planning Working Group should organize the substances in such a way as to reflect the relationships between the chemical structures, the similarity of pharmacological profiles, and the relative role of metabolic conversion to other controlled substances. In the review document, the Programme Planning Working Group should give some indication of the parity between the level of national control and the control level provided by the Conventions.

4. The Expert Committee encourages WHO, as well as the United Nations Division of Narcotic Drugs, to proceed with its plans to assemble a group of experts to discuss the role of structure-activity relationships, isomeric state, and drug metabolism, as factors in the decision-making process for control of substances under the Conventions. It is the Expert Committee's hope that a report from such a meeting will help to clarify the handling and listing of compounds affected by such factors by both the Programme Planning Working Group and the WHO Expert Committee on Drug Dependence.

#### ACKNOWLEDGEMENTS

The Expert Committee wishes to acknowledge the valuable contributions made by the following WHO staff members: Dr A. Arif, Senior Medical Officer, Drug Dependence, Division of Mental Health; Dr B. Sankaran, Director, Division of Diagnostic, Therapeutic, and Rehabilitative Technology; Dr M. ten Ham, Senior Scientist, Pharmaceuticals, Division of Diagnostic, Therapeutic, and Rehabilitative Technology; and Mr T. Topping, Legal Officer, Office of the Legal Counsel.

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