Summary review of certain phenylethylamine related substances recommended for control by WHO

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The Twenty-second Expert Committee on Drug Dependence, which met at the World Health Organization, Geneva from 22 to 27 April 1985, recommended to the Director-General of the World Health Organization, the international control of 19 out of the 28 substances reviewed under Article 2, paragraph 4 of the Convention on Psychotropic Substances, 1971.

This review by the Expert Committee on Drug Dependence follows the new WHO procedures as adopted by the WHO Executive Board in its Resolution EB73.R11 of January 1984 and the consequent "Guidelines for the WHO Review of Dependence Producing Psychoactive Substances for International Control adopted by the Programme Planning Working Group.

The notifications from the Director-General of the World Health Organization to the Secretary-General of the United Nations based on the recommendations of the Twenty-second Expert Committee on Drug Dependence are accompanied by this summary review. This review follows exactly the information contained in the report of the Expert Committee which is to be published by WHO in the Technical Report Series and which should be available towards the end of 1985. The French and Spanish translations of the summary reviews will be available shortly.

Two of these substances, 3,4-Methylenedioxyamphetamine (MDA) and 2,5-Dimethoxy-4-bromo-amphetamine (DOB) had already been placed in Schedule I of the Convention on Psychotropic Substances, 1971 and no further action is needed.

1. Cathine

It was noted that cathine is one of the active principals of the abused plant material Catha edulis (khat). Chemically, it is d-threo-2-amino-1-hydroxy-1-phenylpropane, and, it is the single optical isomer of a structure which contains two asymmetric centres. Because of this, the compound can exist as two racemates (threo and erythro) and each as two pairs of 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 central stimulant activity, is not self-administered in animals and is not widely abused by man despite its widespread medical use.

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

Cathine is marketed as an anorectic in a wide variety of pharmaceutical forms and preparations and is widely distributed in the world. There are some reports of human abuse of anorectics containing cathine from a number of countries. Numerous reports of small seizures of the the drug have been made.

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

The Committee also noted that there was little or no data available on the racemate and (-)-isomer of cathine. If these forms follow the example of amphetamine and cathinone they will have similar properties to cathine. Further study of the abuse potential of the racemate and (-)-isomer was suggested.

2. Cathinone

Cathinone is the major psychoactive component of the khat plant (Catha edulis). Chemically it is (-)-alpha-aminopropriophenone. The racemate and (+)-isomer have also been prepared and studied pharmacologically to a small extent.

Cathinone is a central nervous system stimulant which shares most of the pharmacological properties of amphetamine with about half its potency. In addition, there is cross tolerance to amphetamine as an anorexiant. The toxicology of cathinone is also similar to that of amphetamine. Cathinone is well absorbed orally and rapidly metabolized. A main excretion product is (-)nor-ephedrine.

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. The racemate shares these properties. Knowledge of the human pharmacology of cathinone comes only from the experience with khat, which has widely been reported to be a public health problem of great magnitude 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 traffic with the substance.

On the basis of the data outlined above, it was the consensus of the Committee that cathinone met the criteria for control in Article 2 para. 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.

3. 2,5-Dimethoxyamphetamine

This substance, commonly known as DMA, is a racemic mixture which has a pharmacological profile similar to mescaline at low doses and amphetamine at high doses. It apparently produces hallucinations in man. Drug discriminiation studies indicate that it has common effects with hallucinogens. The substance has no known medical use, but it is used in the photographic industry. There are a number of reports of illicit traffic of the substance.

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

4. N-Ethylamphetamine

This substance is a racemic mixture whose pharmacological profile resembles that of amphetamine. It is a central nervous system stimulant which is self-administered by the rhesus monkey. No data were available on the clinical abuse liability, the nature and magnitude of public health and social

problems, or epidemiology of its use and abuse. The substance is legislatively controlled nationally by 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 the drug appearing in illicit traffic.

On the basis of the data outlined above, it was the consensus of the Committee that N-Ethylamphetamine met the criteria in Article 2, para. 4 for control under the Convention on Psychotropic Substances and should be placed in Schedule IV.

5. Fencamfamine

Chemically, fencamfamine is N-ethyl-3-phenylbicyclo(2,2,1)-heptan-2-amine. Pharmacologically, fencamfamine is a central nervous system stimulant which resembles amphetamine in most aspects. The toxicology of fencamfamine also resembles an amphetamine but it does not produce aggregate toxicity. Fencamfamine is not metabolized to amphetamine and has a half-life of about 16 hours.

Fencamfamine is self-administered in both beagle dogs and monkeys and shows the typical pattern of a central stimulant reinforcer. There was no evidence of clinical abuse liability or serious public health and social problems but there is some social abuse by students in some countries.

Fencamfamine has been used clinically as an "energizing" drug since 1962 and is marketed in 32 countries and prescription controlled in many of them. There were a few examples of fencamfamine appearing in illicit traffic.

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

6. Fenetylline

Chemically, fenetylline is a racemic ethyltheophylline derivative of amphetamine. Pharmacologically, it partly resembles amphetamine; however, there are a number of qualitative differences. The pattern of toxicity in animals is similar to 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 amphetamine to some extent and to a number of other metabolites which are slowly excreted.

Fenetylline is self-administered by rhesus monkeys but not to the same degree as amphetamine. In the most recent studies only two out five animals self-administered the drug at rates above saline levels. In drug discrimination studies in a number of species, fenetylline was discriminated as amphetamine in a portion of the subjects. There is limited data on clinical dependence potential but widespread and increasing abuse has been documented in the Federal Republic of Germany with additional reports from Mexico, Sweden and Middle East. Substantial illicit traffic has occurred in several countries and it is under legislative control in many countries.

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 fenetylline entering illicit traffic. Interpol has reported seizure data 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 Near and Middle East.

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

7. Fenproporex

Fenproporex is the racemic N-cyanoethyl analogue of amphetamine. Pharmacologically, the compound appears to be amphetamine-like but little published data are available. No animal toxicology was available but it has been reported to alter colour vision in man at therapeutic doses. Fenproporex has been reported to be metabolized to amphetamine in man. No data was 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 under control in several countries.

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

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

8. Levamphetamine

Levamphetamine is the l-isomer of amphetamine. Its pharmacological profile is very similar to that of d-amphetamine but it is a quarter to a third as potent. No toxicological or pharmacokinetic data was available.

Levamphetamine is readily self-administered by rhesus monkeys, rats and dogs and differs only from d-amphetamine by being less potent. No information was available concerning clinical abuse liability, the nature of the public health and social problems, or the epidemiology of drug use and abuse. The drug is under control in a number of countries. Levamphetamine is available for medical use at least in the United Kingdom. No data was available concerning production. There have been some reports of illicit traffic with the drug.

On the basis of the data outlined above, it was the consensus of the Committee that levamphetamine met the criteria in Article 2, para. 4 for control under the Convention on Psychotropic Substances. Because of its great chemical and pharmacological similarity to d-amphetamine the Committee recommended that it be placed in Schedule II.

9. Levomethamphetamine

Levomethamphetamine is opposite optical isomer of d-methamphetamine. It is a central nervous system stimulant whose pharmacological profile is very similar to the d-isomer but less potent. No toxicological or pharmacokinetic data was available.

Levomethamphetamine is self-administered by rats. There is no data on clinical abuse liability, the nature and magnitude of public health and social problems or the epidemiology of use and abuse. The drug is under control in several countries. It is marketed as an exempt preparation in the USA as a nasal decongestant in an inhaler. There are reports of illicit manufacture and traffic in the drug.

On the basis of the data outlined above, it was the consensus of the Committee that levomethamphetamine met the criteria in Article 2, para. 4 for control under the Convention on Psychotropic Substances. On the basis of its strong chemical and pharmacological resemblance to d-methamphetamine the Committee recommended that the drug be placed in Schedule II.

10. Mefenorex

Chemically, 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 and does not produce stereotypic movements in the rat. The acute cause of death in rats is respiratory paralysis. There is no enhancement of lethality in grouped animals such as occurs with d-amphetamine. Typical sympathomimetic side effects are seen in man. In man the drug is excreted unchanged and as various hydroxylated metabolites.

Mefenorex is self-administered to some degree (two out of five) by the rhesus monkey and has discriminative stimulus effects in common with amphetamine in both monkeys and pigeons. The drug was less potent than amphetamine in both procedures. There is no data on clinical abuse liability, no reported public health and social problems 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 widely sold worldwide. Some illicit traffic has been reported.

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

11. Paramethoxyamphetamine (PMA)

PMA is a racemic mixture whose pharmacological profile is predominantly amphetamine-like. It also shows some pharmacological activity resembling LSD (e.g., visual tracking in monkeys and dogs). In human subjective reports PMA was estimated as five times more potent as a psychotomimetic than mescaline.

Regarding its dependence potential, in different studies in rodents, its discriminative effect was amphetamine-like or somewhat resembling LSD. PMA was not self-administered in baboons. Data on clinical abuse liabilities from human studies relevant to the dependence potential of this substances are not available.

Serious adverse reactions and fatal toxicity appeared geographically isolated but disconcerting. Signs of intoxication include those observed with amphetamine and also with mescaline.

Data on governmental seizures indicated only isolated cases of illicit traffic in PMA.

On the basis of the data outlined above, it was the consensus of the Committee that paramethoxyamphetamine met the criteria of Article 2, para. 4 for control under the Convention on Psychotropic Substances. Since it has no therapeutic use, the Committee recommended that paramethoxyamphetamine be placed in Schedule I of the Convention.

12. Propylhexedrine

Chemically, propylhexedrine is racemic 1-cyclohexyl-2-methyl-aminopropane. Animal pharmacology studies indicate that propylhexedrine has some stimulant actions in common with amphetamine, such as increased locomotor activity and pressor effects. Regarding dependence potential, no data are available from animal studies but human investigative reports indicate that propylhexedrine is capable of imitating at least some of the subjective effects of amphetamine, such as restlessness.

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

Propylhexedrine is a sympathomimetic agent which has been used without a prescription in an inhalant form for nasal decongestion. Its hydrochloride is available in an oral form and given daily in divided doses as an anorectic agent in the treatment of obesity.

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

13. Pyrovalerone

Chemically, pyrovalerone is 1-(4-methylphenyl)-2-(1-pyrrolidinyl)-1-pentanone Pharmacologically, it is a potent inhibitor of norepinephrine uptake. The Committee was unable to find useful data on the pharmacological profile of this substances or animal studies relevant to its dependence potential. It has been in medical use for asthma, reactive depression, and as a stimulant for the relief of drug induced lethargy. A pyrovalerone preparation was abused in France by intravenous injection and was withdrawn from the market in both France and Switzerland. Reports are available which appear to indicate that, by the intravenous route, the drug produces amphetamine-like central stimulation and psychological dependence. It remains available in Luxembourg but the manufacturer supplied no information. Thus, despite systematic effort, virtually no relevant information from the manufacturer was available to the Committee.

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

14. 3,4,5-Trimethoxyamphetamine

3,4,5-Trimethoxyamphetamine (3,4,5-TMA) is a racemate which has a pharmacological profile similar to 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-TMA produces discriminative effects similar to DOM, another known hallucinogen of this series. No clinical abuse data are available and the nature and magnitude of public health and social problems is unknown. No information is available on the epidemilogy of its use and abuse. The substance is under national control in several countries. There is no known therapeutic use and thus no licit production. Seizures of the drug and the finding of a number of clandestine laboratories indicate the substance is in illicit traffic in and Canada and the United States.

On the basis of the data outlined above, it was the consensus of the Committee that 3,4,5-trimethoxyamphetamine met the criteria in Article 2, para. 4 for control under the Convention on Psychotropic Substances. Since it has no known clinical use, the Committee recommended that it be placed in Schedule I.

15. 2,5-Dimethoxy-4-ethylamphetamine

This substance, commonly known as DOET, has been reported to be hallucinogenic in man. DOET was discriminated as hallucinogen-like in the rat but there is some evidence that the substance may have a different profile of pharmacological action from that of the typical hallucinogens of this series. No toxicological or pharmacokinetic data is available. DOET is not self-administered by baboons. No data are available on clinical abuse liability on the nature or magnitude of 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 traffic.

On the basis of the data outlined above, it was the consensus of the Committee that 2,5-dimethoxy-4-ethylamphetamine met the criteria in Article 2, para. 4 for control under the Convention on Psychotropic Substances. Since the substance has no therapeutic use, the Committee recommends it to be placed in Schedule I.

16. 5-Methoxy-3,4-methylenedioxyamphetamine

This substance is commonly known as MMDA. In the spinal dog MMDA has a pharmacological profile which resembles both LSD and amphetamine but has other properties which are not shared by either drug. There are no data on the toxicology, pharmacokinetics, dependence potential, nature and magnitude of public health and 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. Minor encounters with this compound in illicit traffic have been reported by the United States.

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

17. 3,4-Methylnedioxymethamphetamine

This substance is commonly known as MDMA. In mice MDMA increased locomotor activity and produced analgesia. In dogs and monkeys the substance has a pharmacological profile similar to other substances already controlled

under the Convention on Psychotropic Substances. Reports in man are contradictory as to whether MDMA has hallucinogenic activity. The substance is a potent serotonin releaser in rat whole brain synaptosomes. The toxicological properties in animals have been studied extensively. The acute toxicity of MDMA is about twice that of mescaline. No pharmacokinetic data is available.

MDMA has discriminative stimulus effects in common with amphetamine but not DOM. No data are available concerning its clinical abuse liability, the nature and magnitude of public health and social problems or the epidemilogy of the use and abuse of this substance. The substance is under national control in Canada and the United Kingdom and it has been proposed for control in the USA.

There is no well defined therapeutic use but claims of its value as a psychotherapeutic agent have been put forward by a number of clinicians in the USA. No data is available concerning its licit production. Evidence for some illicit traffic with MDMA has been reported from Canada and there have been extensive seizures in the United States.

On the basis of the data outlined above, it was the consensus of the Committee hat 3,4-Methylnedioxymethamphetamine met the criteria of Article 2, para. 4 for control under the Convention on Psychotropic Substances. Since there is insufficient evidence to indicate that the substance has therapeutic usefulness, the Committee recommended that it be placed in Schedule I*.

It should be noted that the Committee held extensive discussions concerning the reported therapeutic usefulness of MDMA. While the Committee found the reports intriguing, it was 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 this end, the Committee urges nations to use the provisions of Article 7 of the Convention on Psychotropic Substances to facilitate research on this interesting substance.

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*Professor Grof 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.