REVIEW OF PSYCHOTROPIC SUBSTANCES
Geneva, 27-29 September 1978

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1. Introduction

The meeting was opened by Dr N. Sartorius, Director, Division of Mental Health, World Health Organization. Dr Sartorius welcomed the participants on behalf of Dr H. Mahler, Director-General of WHO and expressed the concern of WHO regarding its role in the implementation of the international conventions concerning narcotic and psychotropic substances. He expressed WHO's cognizance of the problems resulting from the widespread use and abuse of psychotropic substances, particularly in regard to the developing nations. He noted that concern regarding the widespread misuse of psychotropic substances has led some countries to bring these agents under the strictest control, which has compromised the availability of valuable therapeutic agents for legitimate patients. Dr Sartorius asked the advisers to not only review and make recommendations regarding specific substances being considered on the agenda, but also to assist WHO in developing a detailed plan of action in which WHO can collaborate with countries in obtaining the necessary data for substance control decisions.

During the 5th Special Session of the United Nations Commission on Narcotic Drugs held in Geneva in February 1978, it was noted (Resolution 6 S-V. Notifications concerning the scope of control of substances under the 1971 Convention on Psychotropic Substances) that it had been seven years since the adoption of the Convention on Psychotropic Substances, 1971, and that during that period further evidence and experience have become available about the public health and social problems associated with the use of psychotropic substances already scheduled, which suggest that some of the contents of the schedules to the Convention need to be reviewed, and that additions to them may need to be made. The Commission invited the Director-General of the World Health Organization to submit to the United Nations Commission on Narcotic Drugs recommendations for rescheduling of any substances where the scheduling in which it is at present included no longer appears to be appropriate and, to consider the scheduling of any additional substances upon notification made by Parties or by WHO. In response to this request, WHO has convened this meeting so that a group of advisers can review the pharmacological, medical and epidemiological data and to make recommendations regarding the possible rescheduling of:

1. Methaqualone
2. Phenobarbital
3. Lefetamine (SPA)

To assist in this endeavour a variety of background documents were prepared by WHO (listed under item no. 9) and introduced as a basis for the discussion of the group.

Representatives of the International Narcotics Control Board and the United Nations Division of Narcotic Drugs reviewed the control regulations of psychotropic substances as provided for under each of the four schedules in the Convention on Psychotropic Substances, 1971. The current schedule status of methaqualone, phenobarbital, and lefetamine in the Convention on Psychotropic Substances and the preparations of nicocodine in the Single Convention were reviewed.

A report was given by a representative of the United Nations Division of Narcotic Drugs on replies received from governments to the note verbale, NAR/CL.11/78 of the Secretary General of the United Nations dated 4 August 1978. In this note verbale, governments were requested to provide data on methaqualone, phenobarbital and SPA concerning whether any of these substances have been seized from the illicit drug traffic during the last three years and if so, the amounts seized and, where this could be determined, the provenance of the drugs, as well as the importance and the frequency of the abuse of these drugs. The group reviewed this data and concluded that it demonstrated that methaqualone abuse did exist in a number of countries. The replies on SPA (lefetamine) indicated that there was no abuse of this drug. Replies to questions regarding phenobarbital indicated
only limited abuse. It was noted that replies were only received from a limited number of
governments queried and hence the data derived may not be representative of the total
problem of abuse of any of the substances. Similarly, the International Criminal Police
Organization (INTERPOL) requested its Member States to provide information on the number of
times the three psychotropic substances under review were identified in seized samples.

2. Methaqualone

The Group reviewed the data on methaqualone relevant to the items in Article 2,
paragraph 4 of the Convention on Psychotropic Substances, 1971, to consider in accordance
with paragraphs 1 and 6 of Article 2 of that Convention, its past and present control status.
Evidence exists that methaqualone produces (1) psychological and physical dependence and
(2) central nervous system depression resulting in (a) alterations in behaviour, mood,
thinking and perceptions that lead to abuse and (b) alterations in motor function that
result in ataxia. The abuse and ill effects of methaqualone are most similar to those of
the short acting barbiturates (e.g. pentobarbital, secobarbital). The actions by many
governments to place the strictest controls on methaqualone or to abolish its therapeutic
use, indicates a serious public health and social problem that warrants international control
There is no evidence of a therapeutic use for methaqualone that cannot be met by other
widely available drugs, some of which have less abuse potential.

The Group found evidence of world-wide abuse and a marked increase in illicit drug
traffic. Reports of recent actions by many governments to place strict controls on
methaqualone, also constituted new evidence of an increasingly serious international public
health and social problem sufficient to recommend stricter control measures.

2.1 Recommendation re control status

The Group concluded that the seriousness of the international problem required
inter-alia import and export controls and for this reason recommended that methaqualone be
transferred from Schedule IV to Schedule II.

3. Phenobarbital

In accordance with Article 2, paragraph 4 and 6 of the Convention on Psychotropic
Substances, 1971, the Group considered the past and present control status of phenobarbital:

It was noted that:

(a) Phenobarbital is a central nervous system depressant which has the capacity to
produce a state of both psychological and physical dependence. However, it has a
significantly lower abuse potential than the short acting barbiturates (e.g. secobarbital,
pentobarbital).

(b) There is evidence that phenobarbital has been and is being abused. However, there
is little evidence that this abuse represents a serious international public health or
social problem. On the other hand, phenobarbital has important therapeutic usefulness.
Indeed, phenobarbital is one of the most widely used drugs in the treatment of seizure
disorders and has been included in the WHO List of Essential Drugs.

Consideration was given to the fact that the cost of phenobarbital is low compared to
other drugs utilized for the same therapeutic indications. The Group regarded this to be
of particular importance to developing countries with limited resources. For this reason,
complete removal from the schedules of the 1971 Convention was also considered by the Group.

This was rejected on the basis that its occasional abuse, and its dependence potential suggest that unlicensed and thus uncontrolled production, trade and distribution might lead to increased international abuse of phenobarbital. It was noted that under Article 9, paragraph 3, Parties may allow distribution of psychotropic substances in Schedule IV for medical purposes without prescription if local conditions so require.

3.1 Recommendation re control status

For the above reasons, the Group recommended that phenobarbital remain in Schedule IV and that no recommendation for changing its present status should be made by WHO at this time.

4. Lefetamine (SPA)

The Group reviewed the data on lefetamine relevant to the items in Article 2, paragraph 4 of the Convention on Psychotropic Substances, 1971, to consider in accordance with paragraphs 1 and 6 of Article 2 of that Convention, its past and present control status.

Lefetamine has the capacity to produce psychological dependence and central nervous system stimulation when used parenterally. Animal experiments and clinical observations on abusers experienced with both lefetamine and methamphetamine indicate a reinforcing effect comparable to or even stronger than that of the amphetamines. The Group, however, noted that, unlike the case of the amphetamines, the epidemic of lefetamine abuse was limited to Japan. Further, in Japan the abuse was regional rather than nationwide. No indication of oral or parenteral abuse of a tablet preparation has been observed since the withdrawal of injectable preparations from the market, and no evidence of illicit production is known to date. Indeed, there is no evidence of current abuse.

4.1 Recommendation re control status

For the above reasons, the Group recommended that lefetamine remain in Schedule IV, and that no recommendations for changing its present status should be made by WHO at this time. However, the Group also recommended that research on the pharmacology of lefetamine be promoted in order to have a better basis for possible future scheduling decisions. At the present time, lefetamine is manufactured and distributed only in Japan. The Group advised that the distribution of lefetamine to countries other than Japan be watched by WHO in order to determine whether any abuse of this substance occurs.

5. Nicocodine

A notification was received from the Austrian Government (NAR/CL.12/1978 dated 7 August 1978) requesting that preparations of nicocodine (syrup, tablets, and drops) be placed in Schedule III, paragraph 1 of the Single Convention on Narcotic Drugs, 1961 and of that Convention as amended by the 1972 Protocol. The Group noted that nicocodine itself is currently listed in Schedule II of the Single Convention. Certain preparations of all other substances listed in Schedule II are controlled under Schedule III of that Convention.

The Group reviewed the relevant data on the dependence producing properties of nicocodine as revealed by animal experiments and concluded that it was comparable to codeine.

In letters provided by the Austrian Government from medical experts who have used nicocodine preparations in patients with respiratory diseases for its cough suppressant actions, it was stated that no cases of abuse were observed.
The issue of convertibility of nicocodine preparations into other narcotics was discussed. It was concluded that nicocodine could be hydrolyzed to codeine but that it could not readily be converted into morphine. Number 1 of Schedule III of the Single Convention provides that preparations should not contain more than 100 mg of the drug per dosage unit and with a concentration of not more than 2.5 per cent in undivided preparations. The Group concluded that since the relative therapeutic potency of nicocodine was equal to or less than codeine that no new wording regarding the amount of the drug contained in dosage units was necessary.

The Group was informed by the UN Division of Narcotic Drugs that the failure to place preparations of nicocodine in Schedule III in the past was because Austria was not a signatory to the Single Convention on Narcotic Drugs, 1961 and, therefore, could not make a formal request for this to be done.

5.1 Recommendation re control status

After consideration of all the factors listed above, the Group recommended that nicocodine as a substance remain in Schedule II but recommended that appropriate preparations of nicocodine be placed in Schedule III.

6. Suggestions for handling further cases regarding control of psychotropic substances

A discussion of the background document (MNH/78.22) provided by Dr T. L. Chrusciel was held by the Group. This document suggested certain specific factors to be considered in gathering data necessary for reaching scheduling decisions. The Group felt that the concepts in this document could be useful in providing a format for the staff at WHO to organize the data to be used in future scheduling considerations. Concern was expressed, however, that a too rigid format could interfere with decision-making and hence it should remain an informal guideline to WHO staff for the collection and organization of data.

A list of drugs for possible scheduling considerations was submitted by Dr Chrusciel. This list was derived from responses to a letter of enquiry sent to various drug experts in the international community. The Group considered this list and other suggestions and arrived at the following recommendations for drugs to be considered in the next year.

**Drugs to be considered for scheduling**

- d-propoxyphene
- tilidine
- benzodiazepines
- mecloqualone

It was further recommended that the drugs pentazocine, cyclazocine, butorphanol, nalbuphine and buprenorphine be considered as a group since they share certain pharmacological properties of being mixed agonist-antagonist of the opiate type. The question was raised as to whether these drugs should be considered for control under the Single Convention on Narcotic Drugs, 1961 or the 1971 Convention on Psychotropic Substances. It was, however, agreed that any formal recommendations by WHO in this respect should be held in abeyance until these substances are considered.

**Drug to be considered for re-scheduling**

- phencyclidine
6.1 Procedures for WHO to prepare data for scheduling recommendations

Dr T. Yanagita presented a format in which data might be collected and organized by WHO for drugs in which scheduling decisions are being considered. The Group reviewed and modified the format and concluded that it would be useful for guiding the staff at WHO in the organization of data.

The format was as follows:

1. Chemistry
2. General Pharmacology
3. Toxicology - including adverse reactions in man
4. Pharmacokinetics
5. Dependence potential
6. Epidemiology of abuse and the public health and social problems
7. National control
8. Therapeutic usefulness
9. Production, consumption, price and international trade
10. Illicit manufacture and traffic
11. Control and other legal and administrative consequences

7. Rhesus monkeys

The Group recognized the increasing difficulty of obtaining rhesus monkeys for laboratory assessment of dependence potential and central nervous system stimulatory or depressant effects of psychotropic substances. This assessment provides essential knowledge for consideration of scheduling or re-scheduling of substances in connexion with both the Convention on Psychotropic Substances, 1971 and the Single Convention, 1961.

The importance of such assessment and the necessity of the use of rhesus monkeys in such studies were strongly felt by the Group, particularly in light of the increasing difficulty of conducting such assessment in human subjects because of ethical limitations.

The Group recommended that WHO take appropriate measures to facilitate the international and national availability of rhesus monkeys for such assessment.
8. **List of participants**

Dr H. Halbach, Honorary Professor of Pharmacology, University of Munich, Federal Republic of Germany.

Dr L. Harris, Professor and Chairman, Department of Pharmacology, Virginia Commonwealth University, Richmond, Va. USA. (Chairman)

Dr J. Knoll, Professor and Head, Department of Pharmacology, University of Semmelweis, Medical School, Budapest, Hungary.

Dr D. R. Jasinski, Director, Addiction Research Center, National Institute on Drug Abuse, Lexington, Ky, USA.

Dr B. O. Osuntokun, Professor, Department of Medicine, University of Ibadan, Ibadan, Nigeria.

Dr T. Abdel Rahim, Consultant Psychiatrist, Port Sudan Hospital, Sudan.

Dr C. R. Schuster, Professor, Department of Psychiatry, University of Chicago, Ill, USA. (Rapporteur)

Dr T. Yanagita, Director, Preclinical Research Laboratories, Central Institute for Experimental Animals, Kawasaki, Japan.

**Representatives of Other Organizations**

**United Nations**

Miss E. Lumsden, Deputy Chief, Narcotics Laboratory, Division of Narcotic Drugs, United Nations, Geneva.

Mr A. Noll, Chief, Treaty Implementation and Commission Secretariat, Division of Narcotic Drugs, United Nations, Geneva.

**International Narcotics Control Board**

Dr T. L. Chrusciel, Professor Pharmacology, Institute for Drugs Research and Control, Warsaw, Poland.

Dr S. Kaymakçalan, Vice-President of the INCB, Professor and Chairman of the Department of Pharmacology, University of Ankara, Turkey.

Mr T. Falkowski, Chief, Psychotropic Substances Trade Control Section, International Narcotics Control Board, Geneva.

**Secretariat**

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

Dr A. Arif, Senior Medical Officer in Charge of Drug Dependence Programme, Division of Mental Health, WHO, Geneva, Switzerland.

Dr P. H. Hughes, Senior Medical Officer, Division of Mental Health, WHO, Geneva, Switzerland.

Dr C. L. Bolis, Senior Medical Officer, Division of Mental Health, WHO, Geneva, Switzerland.

Dr P. Kalix, Department of Pharmacology, Ecole de Médecine, University of Geneva, Switzerland.
9. List of background documents

(a) Replies received by 25 September 1978 from Governments to the Note Verbale NAR/CL.11/78 of the Secretary General dated 4 August 1978.


(c) Single Convention on Narcotic Drugs, 1961.


(g) Epidemiological Case Reporting of Drug Use - Meeting of Collaborating Investigators, Geneva, 10-12 October 1977.

(h) Literature Survey on Abuse and Use of Methaqualone. MNH/78.19. Peter Kalix and Inayat Khan.

(i) Barbiturates: Survey on Dependence Liability and Abuse. MNH/78.20. Peter Kalix and Inayat Khan.

(j) The Therapeutic Usefulness of Phenobarbital in Convulsive Disorders. B.O. Osuntokun and C.L. Bolis.

(k) Lefetamine: A working paper for the review meeting on Psychotropic Substances. Tomoji Yanagita.

(l) Nicocodine -
   (i) Notification from the Government of Austria NAR/CL.12/1978
   (ii) Study on Self-Administration of Nicocodine by Rhesus Monkeys. F. Hoffmeister.

(m) Priorities for Evaluation of Drugs for International Control. MNH/78.22. T.L. Chrusciel.
ANNEX I

SUMMARY OF DISCUSSIONS WITH REGARD TO WHO PROJECT ON KHAT

Geneva, 28 September 1978

(-)Cathinone, the main phenylalkylamine component of freeze-dried khat samples was found in all studies to be a highly potent central stimulant in behavioural tests. The results of the behavioural studies revealed that (-)cathinone exerts an amphetamine-like effect with a potency similar to that of (+)amphetamine, in some experimental situations even more potent than amphetamine. Cross tolerance between (+)amphetamine and (-)cathinone was demonstrated in both behavioural and cardiovascular studies, suggesting that the site of effect of the two compounds might be identical.

A comparison of the actions of amphetamine and cathinone on organs with pure noradrenergic transmission (vascular smooth muscle, nictitating membrane) showed (-)cathinone to be more potent than amphetamine in enhancing neuromuscular transmission.

The high potency of (-)cathinone in behavioural tests and the nature of its effects speak in favour of the assumption that this compound might be responsible for the abuse potential of khat.

The following studies were considered to be important for the more exact determination of the pharmacological profile of (-)cathinone (using (+)amphetamine as the reference substance):

(a) Self administration studies with (-)cathinone in monkeys (Schuster and Yanagita)

(b) Discrimination studies

(c) Some oral experiments in different species (Schuster)

(d) The analysis of the role of the noradrenergic and dopaminergic systems in the behavioural effects of (-)cathinone (Schuster, Knoll, Yanagita)

(e) Analysis of the effects of (-)cathinone on levels and turnover of both noradreneline and dopamine in different brain areas (Schuster, Harris)

(f) Analysis of the effect of (-)cathinone on the uptake and release of noradrenaline and dopamine in brain tissues (Schuster)

(g) Analysis of the effect of freeze-dried khat samples in teratogenic-tests (Harris)

100 g. of (-)cathinone has to be synthetized to carry out these studies.

A satellite session reviewing the data on khat and its active material is tentatively planned for the CPDD meeting, June 1979 in Philadelphia with the participation of WHO.
Participants

Dr L. Harris, Professor and Chairman, Department of Pharmacology, Virginia Commonwealth University, Richmond, Va. USA.

Dr H. Halbach, Honorary Professor of Pharmacology, University of Munich, Federal Republic of Germany.

Dr J. Knoll, Professor and Head, Department of Pharmacology, University of Semmelweis, Medical School, Budapest, Hungary.

Dr T. Abdel Rahim, Consultant Psychiatrist, Port Sudan Hospital, Sudan.

Dr C. R. Schuster, Professor, Department of Psychiatry, University of Chicago, Ill. USA.

Dr T. Yanagita, Director, Preclinical Research Laboratories, Central Institute for Experimental Animals, Kawasaki, Japan.

Miss E. Lumsden, Deputy Chief, Narcotics Laboratory, Division of Narcotic Drugs, United Nations Geneva.

Dr S. Kaymakçalan, Vice-President of the INCB, Professor and Chairman of the Department of Pharmacology, University of Ankara, Turkey.

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

List of papers presented to the group

1. Studies with (-)Cathinone, by J. Knoll
2. Studies on Cathinones at CIEA by T. Yanagita
3. Cross tolerance to dl-cathinone in amphetamine tolerant rats by C.R. Schuster
4. Verbal statement by L. Harris