# 4TH REVIEW OF PSYCHOACTIVE SUBSTANCES FOR INTERNATIONAL CONTROL

Geneva, 14-18 September 1981

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1. Introduction and Scope of Meeting

On behalf of the Director-General of WHO, Dr N. Sartorius, Director, Division of Mental Health welcomed the participants and emphasized the role and cooperation of representatives of other organizations including the United Nations Division of Narcotic Drugs (UNDND), International Narcotics Control Board (INCB), International Criminal Police Organization, International Council on Alcohol and Addiction and the WHO Collaborating Centres on Research and Training in Drug Dependence. The unique aspects of the current meeting were emphasized. Firstly, the active involvement of the concerned pharmaceutical companies who submitted their data to WHO to assist deliberations was initiated with the acknowledgement of the Director-General. Secondly, the consideration of a new class of analgesic drugs would involve the group in discussions of a primary problem in medicine - the development of new drugs for the relief of pain and suffering. Thirdly, the results of the deliberations of the group would relate and affect parallel activities of the Division of Mental Health. These include (1) the development of guidelines in the context of the international treaties for the control of psychotropic and narcotic substances at the national level; (2) revision of the list of essential drugs for psychiatry and (3) the programme planning for the next decade. The objectives of the meeting were listed to include (1) review of opiate agonist/antagonists analgesics, (2) review of various notifications, (3) advice on future activities for this group and related groups during the next 3 to 5 years, and (4) consideration of the process itself whereby WHO conducts its responsibilities under the 1961 Single Convention on Narcotics and 1971 Convention on Psychotropic Substances.

Dr Sankaran, Director, Division of Diagnostic, Therapeutic and Rehabilitative Technology, informed the Group of the importance of their deliberations in regard to the forthcoming revision of the list of essential drugs which includes analgesics and psychotropics and the production of technical information sheets on drugs designed to be used at the first level hospital.

The Group was then informed of the actions taken at the twenty-ninth session of the United Nations Commission on Narcotic Drugs with regards to recommendations formulated by the Review Group 22-24 September 1980 (MNH/80.28). The recommendations of WHO concerning preparations exempted by the People's Republic of Bulgaria and the Government of Mexico in accord with article 3, paragraph 4 of the 1971 Convention were accepted by the Commission. The Commission also accepted the recommendation of WHO with regard to the request of the Federal Republic of Germany that preparations containing 150 mg or less of dextropropoxyphene be included in Schedule III of the Single Convention on Narcotic Drugs, 1961. With regard to the notification of the Government of Austria made pursuant to article 3, paragraph 1 of the Single Convention on Narcotic Drugs, 1961, that pentazocine be placed in Schedule I, the Commission initially voted for temporary control. That decision on temporary control was later rescinded, with a provision that WHO act expeditiously in providing a recommendation. The Government of Spain had requested review of Commission decision I (S-VI), in accord with article 3, paragraph 8 of the 1961 Convention. The Commission voted to maintain that decision and, at a later date, the Economic and Social Council confirmed the decision of the UN Commission on Narcotic Drugs to control dextropropoxyphene under Schedule II of the Single Convention.

The Group was then informed of the project initiated in response to WHA resolution 33.27, paragraph 7 (3) on the development of guidelines in the context of the international treaties for the control of narcotic and psychotropic substances. WHO missions have visited Malaysia and Panama for a detailed review of national drug abuse policies. Further missions are planned to take place in Kuwait, Thailand, Morocco and Nigeria. These Guidelines are scheduled for presentation to the WHO Executive Board in January 1984.
2. Review of agonist/antagonist drugs

The discussion of agonist/antagonist drugs centered upon the pharmacology, toxicology, dependence liability and particularly the possible public health and social consequences that might attend the use of these agents.

2.1 Chemistry, Pharmacology, Toxicology

The chemical structures of the compounds under consideration are shown below:

![Chemical structures](image)

Figure 1: a, Pentazocine; b, cyclazocine; c, nalbuphine; d, butorphanol; e, buprenorphine.

These compounds are not readily convertible into drugs in Schedule I and II of the Single Convention on Narcotic Drugs, 1961.
The pharmacology and toxicology of the agonist/antagonist analgesics were discussed. As a class they have both analgesic and narcotic antagonist activity in both animals and humans. While there are some quantitative differences in this regard they are qualitatively similar. At equianalgesic doses they all depress respiration to the same degree as morphine. Unlike morphine, however, larger doses of the agonist/antagonist analgesics do not cause greater respiratory depression and therefore apnea never or rarely occurs. With the exception of buprenorphine their respiratory depressant effects can be reversed by the pure antagonist naloxone, although it requires a higher dose than that needed with the narcotics. The respiratory depressant effect of buprenorphine is only partially reversed by naloxone.

The cardiovascular effects of these drugs are mild and there are qualitative differences. Butorphanol, nalbuphine and buprenorphine lower blood pressure and produces bradycardia. Pentazocine and cyclazocine elevate blood pressure and produce tachycardia. In general, the acute and chronic toxicity of these compounds are unremarkable with the exception of hyperexcitability in the rat with butorphanol and hair loss in rats and dogs with buprenorphine. Effects on reproduction are minor and teratologic effects were not seen.

The drugs are rapidly absorbed after intramuscular and subcutaneous administration with a half life varying from about 2 hours with pentazocine to about 4 hours with buprenorphine. Pentazocine is the only drug of the group presently marketed as an oral formulation while buprenorphine is available as a sublingual medication. Pentazocine, cyclazocine and butorphanol are excreted mainly in the urine while nalbuphine and buprenorphine are excreted mainly in the faeces. Drug metabolism does occur and they are all excreted mainly as conjugates.

The side effects of this class of drugs are not, in the main, serious. The most frequently observed signs are sedation, dizziness, nausea and vomiting. Disturbing subjective effects at therapeutic doses are infrequent but occur most often with cyclazocine and pentazocine and least with nalbuphine.

2.2 Dependence Potential in Animals

Animal data relevant to predicting the dependence potential of pentazocine, cyclazocine, nalbuphine, butorphanol and buprenorphine were reviewed by the Group. Specifically, the drugs were considered in terms of their:

(1) Morphine antagonist effects as revealed by the drugs ability to precipitate withdrawal signs in morphine dependent monkeys.

(2) Physical dependence potential of the morphine type as revealed by the drugs ability to both suppress withdrawal signs in morphine dependent animals and produce physical dependence when repeatedly administered.

(3) Reinforcing effects.

(4) Ability to substitute for morphine as a discriminative stimulus.

The reinforcing and discriminative stimulus effects were considered to be important predictors of the drugs ability to produce psychological dependence.

The evidence revealed that:

1. All five drugs, except butorphanol in rhesus monkeys, precipitated withdrawal signs in morphine dependent rats, dogs and/or rhesus monkeys. The antagonistic effect was most prominent for cyclazocine and buprenorphine in morphine dependent rhesus monkeys.
2. None of the five drugs suppressed withdrawal signs in morphine dependent rhesus monkeys. All of these drugs except buprenorphine did produce physical dependence when repeatedly administered. However, the spectrum of the withdrawal signs differed from those of morphine withdrawal. Further, the intensity of the withdrawal syndrome associated with these drugs was significantly less than that associated with codeine or morphine. Withdrawal signs were most severe with butorphanol dependent monkeys, but were less severe than those observed in codeine dependent monkeys.

3. The reinforcing effects of all the drugs, except cyclazocine, has been clearly established in rhesus monkeys, rats and baboons. Cyclazocine has been found to be aversive. Data from progressive ratio studies demonstrated that decreased rank ordering in terms of relative reinforcing efficacy was codeine, pentazocine, buprenorphine which were the only drugs studied.

4. The discriminative stimulus effects of nalbutphine, butorphanol, and buprenorphine were morphine-like in rhesus monkeys. Cyclazocine did not substitute for morphine as a discriminative stimulus but did substitute for nalorphine. Pentazocine discriminative stimulus effects were variable depending on dose.

In summary, these studies would predict that all of these drugs would have a dependence potential less than that of codeine.

2.3 Human Pharmacology

Cyclazocine, pentazocine, nalbuphine, butorphanol and buprenorphine have shown efficacy in relieving pain and have been proposed or used as analgesics of lesser abuse potential than morphine. Of the many studies reviewed, those relating to cardiovascular effects, depression of respiratory function and dependence potential were considered most germane to the issue of public health problems resulting from abuse. In human volunteers, analgesic therapeutic doses of these agonist/antagonist drugs and morphine depress the respiratory response to carbon dioxide to equal degrees. Increasing the doses of morphine increase respiratory depression up to the point of apnea. Increasing the doses of these five agonist/antagonist drugs produce no further respiratory depression above that produced with therapeutic doses. Pentazocine and cyclazocine increase blood pressure while butorphanol, nalbuphine and buprenorphine, like morphine, decrease blood pressure.

When given to narcotic addict volunteers, cyclazocine does not produce euphoria but produces dysphoria and does not suppress the morphine withdrawal syndrome. Abrupt termination of repeatedly given cyclazocine produces a withdrawal syndrome that does not lead to drug seeking.

Pentazocine given to non-dependent former narcotic addicts produces a euphoria in therapeutic doses but with larger doses produces dysphoria. The drug does not suppress morphine withdrawal in addicts. Pentazocine itself will precipitate abstinence in morphine dependent subjects. Naloxone will precipitate abstinence following repeated administration of pentazocine. Abrupt termination after repeated administration of pentazocine produces a withdrawal syndrome with mild drug seeking.

The effects of butorphanol in addicts are similar to pentazocine differing possibly in a lesser ability to produce dysphoria and inability to precipitate a withdrawal syndrome in morphine dependent subjects.

The effect of nalbuphine in addicts is again similar to pentazocine but with a definite lesser ability to produce dysphoria.
When given to non-dependent former addicts, buprenorphine produces a degree of morphine-like euphoria. The drugs will precipitate abstinence to some degree in morphine dependent subjects. Abrupt withdrawal of repeatedly given buprenorphine produces no clinically significant withdrawal signs or symptoms.

In conclusion, human pharmacology studies indicate that cyclazocine, pentazocine, butorphanol, nalbuphine and buprenorphine do not produce (1) a dependence profile of the morphine or codeine type; and (2) the severe respiratory depression or apnea that is the primary cause of death in accidental or intentional poisoning with morphine, codeine and other opioids. These drugs can all produce morphine-like subjective effects in therapeutic doses; however, in contrast to morphine, increasing doses generally lead to dysphoria which limits dependence potential.

2.4 Public Health and Social Problems

Drug dependence in humans cannot be viewed purely in medical or scientific terms because of its essentially social context; it is also true that drug abuse does not always follow neat pharmacological and experimental pathways. Therefore, to find out if a particular drug has a potential for abuse and/or is currently being abused, it is not sufficient to examine its reinforcing properties or even to search for physical symptoms of withdrawal. It is among other factors, necessary to determine its black market value and to see how it changes hands at street level.

As far as deciding whether a particular drug should be internationally controlled, the WHO Expert Committee on Drug Dependence in 1969 (TRS 407 page 11) emphasized that "risk to public health is the prime determining factor in deciding for or against control". The importance of the public health problems associated with the misuse of drugs was also emphasized by the 1971 Convention on Psychotropic Substances when it was stipulated that one of the criteria calling for control is the finding by WHO that "there is sufficient evidence that the substance is being, or is likely to be abused, so as to constitute a public health and social problem warranting the placing of the substance under international control". In 1978, in its 21st report (TRS 618), the WHO Expert Committee on Drug Dependence recognized that "non-medical drug use does not of itself, or necessarily, constitute a public health problem. What is important is the degree of harm that may ensue from such drug use".

In 1978, WHO formalized arrangements with Interpol and the United Nations Division of Narcotic Drugs to seek information from countries on drugs to be reviewed each year by WHO for possible international control. Data on the appearance of drugs in the illicit traffic and the existence of clandestine laboratories, as well as additional information on the public health and social problems is sought through these two channels.

WHO Technical Report Series, No. 656, 1981, is concerned with the methodology needed for assessment of the public health and social problems associated with the use of psychotropic drugs. This report also covers the technology for assessment of the extent of use of psychotropic substances as an essential prerequisite for the problems associated with their use. WHO also convened a meeting in Finland, in June 1981, when further details of establishing these public health problems were discussed within the light of the situation in Finland and 14 other participating countries. Their major recommendation is to initiate studies in developing countries in general hospitals with psychiatric beds, on drug utilization, incidence of acute intoxication and other health problems, road traffic accidents and forensic deaths and to establish the cause/effect relationship between the use of psychotropic drugs and morbidity and mortality.

Report in print.
Through the regional offices of WHO, efforts have also been made to collect information from countries on the availability of drugs under review, status of their control, their utilization pattern and the associated public health and social problems.

INCB has data only on those drugs which are already under international control. Interpol and the UNDND received information from only 30% of the countries written to. This year many replies were negative and out of the positive responses only pentazocine, among the agonist/antagonists under review was listed as having appeared in the illicit traffic, but no clandestine laboratories were observed. Only 20 replies were received through WHO regional offices and this channel of data collection needs further improvement.

The Group felt that despite the efforts of WHO, UNDND and Interpol, the response to specific requests for data on agonist/antagonists has been less than adequate.

As noted in the introduction the active involvement of the pharmaceutical companies was sought with the agreement of the Director-General of the World Health Organization. This contact with companies manufacturing products containing the drugs under review took place at two levels:

1. The submission of written scientific material to members of the Group some time prior to the meeting of the Group; and

2. Oral evidence from scientists to the Chairman, a Rapporteur, and the secretary of the Group a week before the meeting of the Group. At this pre-review meeting further scientific data was available and the scientists for the companies were able to respond to specific questions put to them and to discuss relevant issues. Specific questions included those concerning data on the distribution of products to countries and regions. It was learnt, for example, that pentazocine was available in 127 countries in 15 of which varying degrees of control had been applied and in 5 of which it was rigidly controlled as a narcotic.

When evaluating the public health and social problems associated with the use of a particular drug, it has to be remembered that there is a time interval between the introduction of a drug into medical practice and the widespread experience of its effects by the public and its eventual abuse (if any). In the past, this chain of events has taken two to three decades for strong dependence-producing drugs and the narcotic antagonist-analgesics may at present be in a similar process.

Although all narcotic antagonist-analgesics, due to their mood-elevating effects, are possible potential candidates for misuse, those which do not produce drug agonistic effects (e.g. naloxone and naltrexone) have not apparently been abused. Drugs such as buprenorphine, butorphanol and nalbuphine, are relatively new drugs and there are only a few case reports of their abuse, although their reinforcing effects in laboratory studies indicates that they do have dependence potential. As yet it is probably too early in their "career" for any definitive evidence about their abuse potential. The available data on the public health and social problems associated with the most widely used narcotic antagonist-analgesic, pentazocine, is as yet limited. There has also been a few reports on morbidity, mortality and abuse of pentazocine from one or two localities in the world but which the Group considered insufficient to fulfill the WHO criteria for control measures.

3. Notification from the Government of Austria

The Group discussed pentazocine in response to the notification from the Government of Austria (transmitted by the Secretary-General in circular letter NAR/CL.19/1980 of 20 August 1980) and in the light of the previous conclusions of WHO Expert Committee on Drug Dependence
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The Group reviewed the data submitted by the Austrian Government as well as other information submitted to WHO to determine whether experience over the last ten years (especially in regard to clinical experience, pharmacology, toxicology, dependence potential, morbidity and mortality, abuse, illicit manufacture and seizures) would indicate a change in opinions of previous Expert Committees regarding pentazocine.

The Group concluded that pentazocine was clearly different from cocaine and cannabis. The Group further concluded that the effects of pentazocine were qualitatively and quantitatively different from morphine and other opioids listed in the 1961 Convention. In addition, the Group found that the prevalence and incidence of abuse had not increased to the extent that there was a public health problem sufficient to regard it as liable to similar abuse and productive of similar ill effects as drugs in Schedule I or II of the Single Convention. They further found no evidence that pentazocine is convertible into a drug controlled in those schedules.

The Group noted that the evidence collected in relation to public health and social problems resulting from use of pentazocine does not justify, at the present time, the recommendation for control under the 1961 Convention.

The Group considered that this drug should continue to be kept under close review by WHO in collaboration with the member states.

4. Abuse of Mixtures of Pentazocine and Tripelenamine

The reports on the abuse of mixtures of pentazocine and tripelenamine in the USA gave cause for concern. The Group recommended that research should be initiated to gain more data on the interaction of agonist/antagonists with antihistamines so that advice can be given regarding the possible need for international control of the constituents.

5. Control of Agonist/Antagonists drugs under the 1961 Convention

The Group reviewed data submitted on the other members of this class of drugs with regard to possible scheduling under the Single Convention on Narcotic Drugs, 1961. It was concluded that cyclazocine has little or no abuse potential. The data on buprenorphine, butorphanol and nalbuphine indicated that these drugs produce some degree of dependence but this is less than that of codeine. A review of the epidemiological data revealed little actual abuse. This may be due to the recent introduction of these drugs into clinical practice. For this reason, it is recommended that epidemiological data continue to be collected and the drugs kept under review. The Group recommended that at the present time buprenorphine, butorphanol, cyclazocine and nalbuphine not be controlled under the Single Convention on Narcotic Drugs, 1961.

6. Scheduling of Agonist/Antagonists Drugs under the 1971 Convention

The Group discussed possible scheduling of the agonist antagonist drugs under the 1971 Convention on Psychotropic Drugs. When considered in light of the criteria and procedures reported by the WHO Expert Committee on Drug Dependence 21st Report, No. 618, the Group concluded that, at the present time, there was insufficient evidence to indicate that
buprenorphine, butorphanol, cyclazocine, nalbuphine or pentazocine are being or are likely to be abused so as to constitute a public health and social problem warranting the placing of the substances under international control.

7. Notification from the Government of Belgium

With regard to the notification received from the Government of Belgium concerning the combination product Valoron N (Tilidine and Naloxone) circulated by the Secretary-General of the United Nations under reference NAR/CL.26/1980 dated 26 November 1980, the Group took note of the present intention of the Government of Belgium to carry out further investigations into the question of the advisability of placing such a combination product in Schedule III of the 1961 Convention. Pending receipt of the additional findings of the Government of Belgium, it was felt that no further action should be taken, thus leaving the combination product in question subject to the stricter provisions applicable to substances in Schedule I. The group felt that additional data could usefully be collected on the following points:

(a) Data on subjective, and reinforcing effects of Tilidine and the mixture on humans and animals.

(b) Epidemiological studies to correlate patterns and amounts of use of Tilidine N with the frequency of its abuse and severity of various types of health disorders.

8. Review of Exempt Preparations under article 3 of 1971 Convention

8.1 WHO Review Procedures

The Group indicated its desire to review the basic criteria to be used in examining the exemption of preparations in order to assist WHO in responding to the request of the Commission on Narcotic Drugs that these criteria be presented to it at its thirtieth session in 1983. The present criteria figures in paragraph 10 of the 1977 report of WHO. The Group felt that until the Commission had taken a definitive stand on the issue, the present criteria should be considered as an appropriate general guidelines. In this context, the work of the Group would be greatly facilitated if governments exempting preparations would submit the detailed exemption at the national level as well as justification of their decisions, indicating why they believe the provisions of article 3, paragraph 2 have been met and provide the data in support of that statement. The length of time the preparation has been released for use in appropriate medical practice, the quantity manufactured during the last 3 years and the export trade during this period in the preparation (if any) would also be useful additional data for reaching a decision. In the case of preparations concerning two or more substances belonging to the same pharmacotherapeutic group it would be helpful to provide data relative to potentiation of effects resulting from such mixtures. When ever possible summaries should be included of pharmacology, toxicology, clinical indications, adverse effects and abuse of active ingredients that are not scheduled under International Conventions.

In examining the preparations which had been exempted by Chile, Hungary and Sweden, the Group noted with satisfaction that certain supplementary data which it had requested had been included in the notifications. On the other hand, (a) specification of the total package dispensed, (b) description of the formulation and (c) therapeutic indication(s) were still not provided to the Group and such data would be most useful in future notifications under article 3.

1 Reference MNH/78.13 paragraph 10.
2 See MNH/80.28, page 3 under "Recommendations for future review of preparations".
The representative of the UN Division of Narcotic Drugs took note of the Group's position concerning both the use of the guidelines in preparing notifications and the supplementary data which would aid the deliberations of the Group.

The Group welcomed the comments made by the USA on the preparations exempted by Chile, Hungary and Sweden.

8.2 Review of Notification of Exemptions under article 3 of the 1971 Convention

8.2.1 The Group reviewed, in accordance with article 3, paragraph 4 of Convention on Psychotropic Substances, the list of preparations which the Government of Chile has decided to exempt in accordance with article 3, paragraph 3 of that Convention. The Government of Chile has decided to exempt the preparations listed below from the measures of control provided under article 11, paragraphs 2, 3 and 4.

The Group examined each of these preparations in regard to the evidence that they were compounded in such a way that they present no, or a negligible risk of abuse and that the substance cannot be recovered by readily applicable means in a quantity liable to abuse so that the preparation does not give rise to public health and social problems.

(a) Pectoserum liquid: The Group recommends that the exemption not be terminated.

(b) Ritalin tablets: The Group recommends that the exemption be terminated since the information received indicates that the preparation contains only methylphenidate and does not represent a preparation with a lesser risk of abuse or lesser liability to be recovered.

(c) Filinasma tablets: The Group recommended that the exemption not be terminated.

8.2.2 The Group reviewed, in accordance with article 3, paragraph 4 of 1971 Convention on Psychotropic Substances, the list of preparations which the Government of the People's Republic of Hungary has decided to exempt from all measures of control provided by the Convention except those in article 3 (a) to (f) of that Convention in accordance with article 3, paragraph 3 of that Convention.

The Group examined each of these preparations in regard to the evidence that they were compounded in such a way that they present no, or a negligible risk of abuse and that the substance cannot be recovered by readily applicable means in a quantity liable to abuse so that the preparation does not give rise to public health and social problems.

(a) Barbamid tablets: The Group recommended that the exemption not be terminated.

(b) Salvador tablets: The Group recommended that the exemption not be terminated.

(c) Asthmamid tablets: The Group recommended that the exemption not be terminated.

(d) Legatins pills: The Group recommended that the exemption not be terminated.

(e) Meristin suppositories: The Group recommended that the exemption not be terminated.

(f) Meristin tablets: The Group recommended that the exemption not be terminated.

Although the substance contains codeine and phenobarbital the Group concluded that the drug units were low and that the preparation was composed in such a way that it presents a negligible risk of abuse and is unlikely that the drugs can be recovered by readily applicable means in a quantity liable to abuse.
(g) Radipon tablets: The Group recommended that the exemption not be terminated.

(h) Sevenaletta tablets: The Group recommended that the exemption be terminated since the information received indicated that the preparation contained only phenobarbital and did not represent a preparation with a risk of lesser abuse than phenobarbital itself nor lesser liability to be recovered.

(i) Triospan tablets: The Group recommended that the exemption not be terminated.

(j) Troparin comp. tablets: The Group recommended that the exemption not be terminated.

(k) Valeriana comp. tablets: The Group recommended deferment of the review of this preparation until supporting information was submitted to indicate if the addition of dry extract of valerian resulted in a preparation with a lesser risk of abuse nor lesser liability to be recovered.

(l) Pilula Coffobarbitali: The Group recommended that the exemption be terminated since the information provided indicated that the preparation contained phenobarbital and caffeine with no information to indicate that the formulation represented a preparation with a lesser risk of abuse than phenobarbital itself or less liable to be recovered.

(m) Pilula Valerosedative: The Group recommended deferment of the review of this preparation until supporting information was submitted to indicate if the addition of valerian powder produced a preparation of phenobarbital less liable to abuse or less liable to be recovered.

(n) Pulvis analgeticus: The Group recommended that the exemption not be terminated.

(o) Pulvis antispasmodoloricus: The Group recommended that the exemption not be terminated.

(p) Pulvis antispasticus: The Group recommended that the exemption not be terminated.

(q) Pulvis asthmalyticus: The Group recommended that the exemption not be terminated.

(r) Pulvis asthmalyticus fortis: The Group recommended that the exemption not be terminated.

(s) Pulvis sedans: The Group recommended that the exemption be terminated since the preparation contained potassium bromide along with phenobarbital. The known abuse potential of potassium bromide led the Group to conclude that this preparation did not represent one with a less risk of abuse than phenobarbital itself.

(t) Solutio kalii jodati comp.: The Group recommended that the exemption be terminated since the preparation contained potassium bromide along with phenobarbital. The known abuse potential of potassium bromide led the Group to conclude that this preparation did not represent one with a less risk of abuse than phenobarbital itself.

(u) Suppositorium analgeticum: The Group recommended that the exemption not be terminated.

8.2.3 The Group reviewed, in accordance with article 3, paragraph 4 of 1971 Convention on Psychotropic Substances, the list of preparations which the Government of Sweden has decided to exempt in accordance with article 3, paragraph 3 of that Convention.
Preparations containing substances in Schedule III are exempted from the requirements of article 9 (Prescriptions) paragraph 2, article 11 (Records), except paragraphs 6 and 7, and article 12 (Provisions relating to international trade) paragraph 2.

Preparations containing substances in Schedule IV are exempted from the requirements of article 9 (Prescriptions) paragraph 2, and article 11 (Records), except paragraphs 6 and 7.

The Group examined each of these preparations in regard to the evidence that they were compounded in such a way that they present no, or a negligible risk of abuse and that the substance cannot be recovered by readily applicable means in a quantity liable to abuse so that the preparation does not give rise to public health and social problems.

(a) **Anervan suppositories**: The Group recommended that the exemption not be terminated.

(b) **Anervan tablets**: The Group recommended that the exemption not be terminated.

(c) **Daribamat tablets**: The Group recommended deferement of the review of this preparation until information was submitted to indicate if the addition of oxyphencyclimine HCl to meprobamate produced a preparation of lesser abuse liability or makes meprobamate less liable to recover.

(d) **Ecrotina comp. pills**: The Group recommended that the exemption not be terminated.

(e) **Mepro-Alvedon tablets**: The Group recommended deferement of the review of this preparation until information was submitted to indicate if the addition of paracetamol to meprobamate produced a preparation of lesser abuse liability or makes meprobamate less liable to be recovered.

(f) **Stembanit pills**: The Group recommended that the exemption not be terminated.

(g) **Kinytal**: The Group recommended that the exemption not be terminated.

(h) **Klimerco**: The Group recommended termination of this exemption since the addition of methallenestril to amobarbital did not represent a preparation with a less abuse liability or less liable to be recovered.

(i) **Lobac Natt**: The Group recommended deferement of the review to determine if the addition of paracetamol to amobarbital and chlormezanon produced a preparation with a less risk of abuse or less liable to be recovered.

(j) **Oxyphyllin comp. suppositories**: The Group recommended termination of this exemption since the addition of theophylline to amobarbital did not produce a preparation less liable to be abused or less liable to be recovered.

(k) **Oxyphyllin comp. tablets**: The Group recommended the termination of this exemption since the addition of theophylline to amobarbital did not produce a preparation of less risk of abuse or less liable to be recovered.

(l) **Sorbangil comp.**: The Group recommended deferement of the review until information was submitted to determine if the addition of isosorbide dinitrate to amobarbital resulted in a preparation with less risk of abuse or less liable to be recovered.

(m) **Spasmolysin suppositories**: The Group recommended that the exemption not be terminated.
(a) **Spasmodysin tablets**: The Group recommended that the exemption not be terminated.

(o) **Gamadorm tablets**: The Group recommended that the exemption be terminated since the addition of acetylsalicylic acid to codeine, pentobarbital and phenpropamate did not produce a preparation with lesser risk of abuse nor with lesser liability to be recovered.

(p) **Theon-Mebumal suppositories**: The Group recommended that the exemption be terminated since the addition of proxphylline to pentobarbital sodium does not produce a preparation of lesser risk of abuse nor with lesser liability to be recovered.

(q) **Terginox tablets**: The Group recommended that the exemption be terminated since the addition of acetylsalicylic acid to pentobarbital, phenpropamate and dextropropoxyphene did not produce a preparation with lesser risk of abuse nor with lesser liability to be recovered.

(r) **Tikanox tablets**: The Group recommended deferement of the review until information is submitted to determine if the addition of paracetamol to codeine, pentobarbital and hydroxyzine HCl produces a preparation of lesser risk of abuse or less liable to be recovered.

(s) **Umenox tablets**: The Group recommended deferement of the review until information is submitted to determine if the addition of paracetamol to pentobarbital and hydroxyeine HCI produces a preparation of lesser risk of abuse or with lesser liability to be recovered.

(t) **Belladenal tablets**: The Group recommended that the exemption not be terminated.

(u) **Bellergal pills**: The Group recommended that the exemption not be terminated.

(v) **Bellergal retard tablets**: The Group recommended that the exemption not be terminated.

(w) **Dolviran suppositories**: The Group recommended that the exemption not be terminated.

(x) **Dolviran N tablets**: The Group recommended that the exemption not be terminated.

(y) **Franyl tablets**: The Group recommends termination of this exemption since the addition of ephedrine and theophylline to phenobarbital did not produce a preparation of much lesser risk of abuse or with lesser liability to be recovered.

(z) **Franyl-Expect syrup**: The Group recommended deferement of the review until information was submitted to indicate if the addition of guaifenesin to phenobarbital, ephedrine and theophylline produced a preparation with a lesser risk of abuse or lesser liability to be recovered.

(a) **Hypertonal**: The Group recommended that the exemption not be terminated.

(a,a) **Myocardon tablets**: The Group recommended that the exemption not be terminated.

(a,b) **Neurol comp. pills**: The Group recommends deferement of the review until supporting information was submitted to indicate if the addition of valerian extract to phenobarbital resulted in a preparation with lesser risk of abuse or lesser liability to be recovered.

(a,c) **Sedapersantin pills**: The Group recommended that the exemption not be terminated.
8.2.4 The Group reviewed, in accordance with article 3, paragraph 4 of the Convention on Psychotropic Substances, a notification dated 23 July 1981 concerning preparations exempted for certain control measures by the USA. In view of the large number of exempted preparations and the manner of presentation of data with respect to these preparations, the Group concluded that it could not examine the issue in detail at the present meeting. In the light of the Group's deliberation as reflected in paragraph 8.1 of the present report, the Division of Narcotic Drugs was asked to facilitate the work of the future WHO review as related to this notification.

9. The Group discussed a communication from the Republic of Ireland concerning dextropropoxyphene. As noted by the representative of UNDND's response to the Government of Ireland, the scheduling of dextropropoxyphene in Schedule II of the Single Convention automatically covered isomers and salts. As to the matter of exemption of oral preparations containing 150 mg or less of dextropropoxyphene salts, it was noted that the 1980 WHO group intended this to represent 150 mg of dextropropoxyphene hydrochloride or 135 mg dextropropoxyphene base. In the matter of levopropoxyphene, the Group noted that there was little available information as to the dependence liability of this compound. If exemption is desired, an interested party should submit an appropriate notification to the Secretary-General accompanied by relevant data.

10. Selection of Topics for Future Considerations

The Group reviewed and selected, on the basis of a paper "Selection of Psychoactive Substances for Assessment of need for International Control in the years 1981-1984" prepared by Professor T. L. Chrusciel. The following are the topics for future consideration of need for international control, if any, by the forthcoming meetings of the WHO review Groups:

1. a) Analgesic drugs not subjected to international control
   c) Sedative, hypnotic and anxiolytic drugs (with the exception of benzodiazepines) not subjected to international control.
   d) Derivatives and congeners of analgesic, sedative, hypnotic and anxiolytic substances already scheduled under 1971 Convention.

2. a) Precursors and intermediates of drugs listed in schedules of international drug conventions
   b) Synthetic and natural stimulants not in schedules of international drug conventions.
   c) Derivatives and congeners of stimulants already scheduled under 1971 Convention.

3. a) Antipsychotic and antidepressant drugs with dependence potential and abuse liability.
   b) Derivatives and congeners of tetrahydrocannabinols with regard to their dependence potential, abuse liability and therapeutic usefulness.

11. Recommendations Relating to the WHO Process whereby Drugs are Considered for International Control

11.1 If the major pharmacological and therapeutic effects and modes of action of the drugs to be reviewed are similar to those scheduled under the Single Convention, these drugs are to be reviewed first under the context of that Convention. If the major pharmacological and therapeutic effects and modes of action of the drugs to be reviewed are different from those scheduled under the Single Convention, these drugs are to be reviewed under the context of the Psychotropic Convention.
In the future, WHO should collect the following information on drugs to be reviewed. The major sources to be contacted for obtaining this information are the governments and pharmaceutical manufacturers of drugs to be reviewed including the manufacturers who initially developed such drugs, and such concerned bodies as UNDND, INCB, WHO Collaborating Centres, NGOs and Interpol. This information should reach WHO three months prior to the meeting and to the participants preferably six weeks prior to the meeting.

11.2.1 Type of data to be collected:

11.2.1.1 Chemistry and information on the various preparations
11.2.1.2 Pharmacology
11.2.1.3 Toxicology
11.2.1.4 Dependence potential and abuse liability
11.2.1.5 Therapeutic usefulness
11.2.1.6 Post-market monitoring reports (abuse case reports)
11.2.1.7 Summary of the above data (up to 10 pages)
11.2.1.8 Companies' comments on abuse liability, abuse cases, illicit traffic, etc., if available.
11.2.1.9 Abuse case reports/statistics
11.2.1.10 Epidemiological records on morbidity and mortality
11.2.1.11 International illicit traffic data.

11.3 The Group recommended that a participant from the Committee on Problems of Drug Dependence (CPDD) be invited to participate as an observer in future meetings. The CPDD has international membership and is the repository of extensive data concerning the dependence liability of a wide variety of drugs.

11.4 The Group recommended the computerization of data on exempted preparations. Steps should be taken by the INCB/WHO to computerize data concerning the listing of exempted preparations. A close collaboration between INCB and WHO is highly desirable in developing this important system.

11.5 The Group recommended that knowledge of the demonstrated efficacy of agonist/antagonist drugs in relieving pain and their greater safety and lesser dependence liability than morphine or codeine should be communicated to the group in WHO developing lists of essential drugs in medicine and psychiatry.

11.6 The Group recommends continued and additional research into the dependence liability and ill effects of mixtures of psychotropic substances and/or narcotic drugs covered under the 1961 and 1971 Conventions.

11.6.1 The Group recommends continued and additional research into the dependence liability and ill effects of mixtures of opioid agonists and antagonist analgesics with pure antagonists.

11.6.2 The Group recommends research into the dependence liability and ill effects of mixtures of antihistamines and opioid agonist/antagonists.

11.7 The Group recommends that a system be developed whereby the suppliers of a drug or substances controlled under the 1961 and 1971 Conventions make available, especially to developing nations, data allowing the assessment of benefit/risk ratio at the time of registration and re-registration in the importing country.
12. List of Participants

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Dr C. R. Schuster, Department of Psychiatry, University of Chicago, Chicago, USA (Chairman)

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International Criminal Police Organization

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International Council on Alcohol and Addiction

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World Federation of Associations of Clinical Toxicology Centres and Poison Control Centres (Lyon)*

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Dr P. Kalix, Centre médical Universitaire, Département de Pharmacologie, Geneva.

List of Background Documents


2. MNH/R4/81.1 - Behavioural Pharmacology of Mixed Agonist/Antagonist Analgesics by Dr C. R. Schuster

3. MNH/R4/81.4 - The Pharmacology and Toxicology of the Narcotic-Antagonist Analgesics by Louis S. Harris, Ph.D.

4. Management of Drug Abuse in Saudi Kingdom, An Islamic Trial by Dr Osama M. Al-Radi

5. MNH/R4/81.6 - Public Health and Social Consequences by A. Hamid Chodae, M.D.

6. MNH/R4/81.2 - Information on Pharmaceutical Preparations Exempted by Chile, Hungary and Sweden from Measures of Control under the Convention on Psychotropic Substances by Dr Peter Kalix

7. MNH/R4/81.3 - Considerations on the Abuse Potential of Pharmaceutical Preparations Combining Tilidine and Naloxone (II) by Dr Peter Kalix

8. Public Health and Social Problems by Dr Inayat Khan

9. MNH/R4/81.7 - Chemistry Preparation and Availability in Different Countries by Mr S. Tembo


12. Selection of Psychoactive, including Narcotic Substances for Assessment of Need for International Control in the years 1981-1984 by Dr T. L. Chrusciel

13. DND 421/12(1) WHO - Report compiled by the Division of Narcotic Drugs (September 1981)

14. Agonist/Antagonists: BUPRENORPHINE, BUTORPHANOL, CYCLAZOCINE, NALBUPHINE and PENTAZOCINE, Department of Health and Human Services, US Government

15. Interpol Report for the 4th Review of Psychotropic Substances for International Control


17. Statement by Bristol Laboratories on the Control of Butorphanol Tartrate

18. Statement by Endo Laboratories on the Control of Nalbuphine

19. Statement by Sterling Drug Co. on the Control of Pentazocine and Cyclazocine

20. Statement by Reckitt and Coleman on the Control of Buprenorphine

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