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WHO EXPERT COMMITTEE ON DRUG DEPENDENCE

Sixteenth Report

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WHO EXPERT COMMITTEE ON DRUG DEPENDENCE

Geneva, 1-7 October 1968

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WHO EXPERT COMMITTEE ON DRUG DEPENDENCE *

Sixteenth Report

The WHO Expert Committee on Drug Dependence met in Geneva from 1 to 7 October 1968.

Dr P. Dorolle, Deputy Director-General, on behalf of the Director-General opened the meeting and welcomed the members of the Committee, the representatives of the Secretary-General of the United Nations, and the representatives of the International Narcotics Control Board and of the International Council on Alcohol and Addictions. He referred to the functions of this Expert Committee as the advisory body in respect of measures to be taken, nationally as well as internationally, against drug abuse and recalled its responsibilities within the framework of the international narcotics control instruments. While the Committee had formerly been concerned largely with the determination of the control status of drugs falling under the terms of these instruments, developments in the field of drug abuse made it necessary to extend its interest and concern to include other aspects of drug dependence and abuse. As examples, he commented on the increasing attention being given to (1) the role of the host and his environment in drug dependence and related abuse and (2) the wide variety of psychotropic substances now being abused. This breadth of concern was clearly reflected in the agenda of the present meeting.

Dr N. B. Eddy was elected Chairman. Dr M. Granier-Doyeux Vice-Chairman and Dr L. Goldberg Rapporteur.

1. DRUG DEPENDENCE AND ABUSE: EVALUATION AND CRITERIA FOR CONTROL

The Committee recognized that authoritative data and criteria were required in order to determine the degree of hazard and the need for control of drugs of abuse, whether or not new international control regimes were to be established. Moreover the Committee emphasized that the criteria

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* Earlier WHO Expert Committees that produced reports concerned with drug dependence were known, until 1956, as " Expert Committee on Drugs Liable to Produce Addiction ", from 1956 until 1964 as " Expert Committee on Addiction-Producing Drugs " and from 1964 until 1966 as " WHO Expert Committee on Dependence-Producing Drugs ".

would have to be kept under continuing review in the light of rapidly developing scientific knowledge and accelerating social change.

1.1 Definitions

The Committee adopted the following definitions for use in the present context :

Drug. Any substance that, when taken into the living organism, may modify one or more of its functions.[1]

Drug abuse. Persistent or sporadic excessive drug use inconsistent with or unrelated to acceptable medical practice.

Drug dependence. A state, psychic and sometimes also physical, resulting from the interaction between a living organism and a drug, characterized by behavioural and other responses that always include a compulsion to take the drug on a continuous or periodic basis in order to experience its psychic effects, and sometimes to avoid the discomfort of its absence. Tolerance may or may not be present. A person may be dependent on more than one drug.

Physical dependence capacity (PDC). The ability of a drug to act as a substitute for another upon which an organism has been made physically dependent, i.e., to suppress abstinence phenomena that would otherwise develop after abrupt withdrawal of the original dependence-producing drug.

Drug control. National law or international agreement governing and restricting production, movement and use of a drug to medical and scientific needs in the interest of public health and for the prevention of drug abuse.

1.2 The problem

There are many drugs that, when taken into the body, will produce in some persons a reaction that is satisfying or attractive to them and will persuade them to continue the use of the drug even to the point of abuse or dependence. If such a drug abuse or dependence is likely to be, or is known to be, only sporadic or infrequent in the population, if there is little danger of its spread to others, and if its adverse effects are likely to be, or are known to be, limited to the individual user, there is no public health problem. Such forms of abuse may be prevented or managed by adequate information and appropriate medical care. On the other hand, if the drug dependence is associated with behavioural or other responses that adversely affect the user's interpersonal relations or cause adverse physical, social, or economic

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[1] This definition is intentionally broader than that used in connexion with substances intended always to be of benefit to a patient. See *Wld Hlth Org. techn. Rep. Ser.*, 1966, No. 341, p. 7 (section 2).

consequences to others as well as to himself, and if the problem is actually widespread in the population or has a significant potential for becoming widespread, then a public health problem does exist. Society must then, among other things, take the responsibility for determining whether or not the drug in question should be controlled. The purpose of the following exposition is to characterize the principles involved and the kinds of data needed in making such judgements.

1.3 Evaluation of dependence liability of drugs

Persons may become dependent upon a wide variety of substances that produce central nervous system (CNS) effects, such as stimulation, depression and/or disturbances of perception and cognition. All such agents have one common attribute : the creation of a behavioural response or a particular state of mind termed psychic dependence. There is a feeling of gratification, a mood change, and a psychic drive for periodic or continuous administration of the drug to experience its effect. This mental state is the most powerful of all the factors involved in chronic or repeated intoxication with psychotropic drugs and with some may be the only one, even in the case of most intense craving and perpetuation of compulsive abuse.

1.3.1 *Psychic dependence*

At the present time, evidence concerning the presence and degree of psychic dependence is drawn mainly from case histories, subjective statements and general observation. More reliable evidence may be obtained from a controlled, double-blind, quantitative procedure for the measurement of subjective effects and behavioural responses. Some quantitative measures are available and others are being developed experimentally, but in regard to the administration of drugs to man for this purpose major difficulties may be encountered in the selection of patients and in providing ethical justification.[1] Nevertheless, three types of patients have voluntarily participated in studies : (1) those with illness requiring continuing medication, with or without persistent pain ; (2) those with terminal illness, especially of a painful character ; and (3) persons who are already drug dependent, have been incarcerated for law violation, and have relapsed to drug abuse many times after periods of enforced abstinence and treatment. In cases (1) and (2), experimental drugs should be used only if there is reason to believe they may be of benefit to the patient involved. Advantage can then be taken of the existing clinical situation to compare the effects of an experimental drug with those of a known agent having the same

[1] See *Wld Hlth Org. techn. Rep. Ser.*, 1968, No. 403 (section 4).

therapeutic indication. Careful attention must be given to administration under controlled, double-blind conditions and to accurate observation and reporting. Similarly in case (3), if drug dependence develops, it is a part of a clinical history already established. Techniques that may be employed with all three types of patients are well documented.[1]

Many investigators have employed adjective check lists or some form of questionnaire to assess subjective reactions. At the Addiction Research Center (USA) this method of assessment has been carried further by assembling the Addiction Research Center Inventory (ARCI) which consists of 550 questions or items answerable by " yes " or " no ".[2] This has been tested against crossover administration of placebo and each of seven drugs: morphine, amphetamine, pentobarbital, alcohol, lysergic acid diethylamide (LSD)[3], pyrahexyl[4] and chlorpromazine.[5] The subjects were persons admitted for drug dependence of morphine type, but the work has extended over a number of years and consequently not all comparisons have been made on the same subjects. They had had experience with all or nearly all of the drugs tested, but had been drug free for some time when these comparisons were made. Lists, or drug scales, were established of ARCI items that discriminated the particular drug effect from the placebo condition. Two scales were developed for each drug tested: (1) a " significant scale ", a list of items that discriminated between the placebo and the drug both in a test group of 50 and in a second confirmatory group of 50 subjects at better than the 5% level of significance; (2) a " marginally significant scale ", consisting of items that differentiated between the placebo and the drug condition (at the 5% level or better) only on the basis of the results in the entire group of 100.

Use of the ARCI in connexion with drug administrations and comparison of the result with the above-mentioned drug scales may serve at least to categorize a drug's subjective effects in terms of known agents with drug dependence-producing capability. It may also imply ability to produce drug dependence of the same type. It should be borne in mind that the ARCI and other inventories require validation and calibration on a wider variety of populations and in other types of situation than has hitherto been possible.

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[1] Cass, L. J., Laing, J. T. & Frederik, W. S. (1961) *Curr. ther. Res.*, **3**, 289; Eddy, N. B., Lee, L. E. jr & Harris, C. A. (1959) *Bull. Narcot.*, **11**, No. 1, 3; Eddy, N. B., Piller, M., Pirck, L. A., Schrappe, O. & Wende, S. (1960) *Bull. Narcot.*, **12**, No. 4, 1; Halbach, H. & Eddy, N. B. (1963) *Bull. Wld Hlth Org.*, **28**, 139; Hollister, L. E. & Glazener, F. S. (1960) *Psychopharmacologia*, **1**, 336.

[2] Haertzen, C. A., Hill, H. E. & Belleville, R. E. (1963) *Psychopharmacologia*, **4**, 155.

[3] Proposed International Non-Proprietary Name: lysergide.

[4] pyrahexyl = 7,8,9,10-tetrahydrocannabinol.

[5] Hill, H. E., Haertzen, C. A., Wolbach, A. B. jr & Miner, E. J. (1963) *Psychopharmacologia*, **4**, 184,

Work being carried out in several centres employing electroencephalographic techniques to study problems associated with drug effects, including those occasioned by withdrawal, opens up an area for study that might well be developed further using neurophysiological methods in man as well as in animals.[1] Another fruitful area for study concerns the effects of dependence-producing drugs on central nervous system (CNS) transmitter systems. These several methods may well aid also in the classification of drugs and their dependence-producing liability.

Experimental procedures in animals are being developed that may assist in the estimation of psychic dependence. These depend on technical arrangements that give the animal the opportunity to self-administer a drug through drinking or via permanently implanted intragastric or intravenous catheters. Information can be obtained on the animal's response to the drug in respect of (1) " liking " or " aversion ", (2) choice, when the drug and other alternatives are made available and (3) the degree of drive to continue administration. Various conditions that may affect drug-seeking behaviour, including drug interaction, are being investigated. In addition, a broad range of substances must be tried. These should include those known to be abused and to produce psychic dependence in man, substances of related chemical structure or pharmacological properties, as well as new chemical types screened as CNS stimulants, depressants or hallucinogens. These methods are yielding interesting and suggestive data but none has yet reached a level of refinement and reproducibility that would make it acceptable as yielding conclusive evidence of the possibility of man developing psychic dependence on a new agent. The techniques have been described.[2]

1.3.2 *Physical dependence*

Techniques for detecting the development of physical dependence are much more advanced than those for detecting psychic dependence and taken together may be considered reliable both in " yes " and " no " terms and for assessing the degree of dependence liability in comparison with known agents. Methods are available for the study of drug dependence of morphine-type in monkeys and other species (mice, rats and dogs), of drug dependence of barbiturate-type in monkeys and dogs, and of drug dependence of both types in man.[3] The tests for drug dependence of

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[1] *Wld Hlth Org. techn. Rep. Ser.*, 1968, No. 381.

[2] Deneau, G. A., Yanagita, T. & Seevers, M. H. (1964) *Pharmacologist*, **6**, 182; Harris, R. T., Claghorn, J. L. & Schoolar, J. C. (1968) *Psychopharmacologia (Berl.)*, **13**, 81; Nichols, J. R. (1963) *Psychol. Rep.*, **13**, 895; Pickens, R. & Harris, W. C. (1968) *Psychopharmacologia (Berl.)*, **12**, 158; Pickens, R. & Thompson, T. (1968) *J. Pharmacol. exp. Ther.*, **161**, 122; Weeks, R. J. (1962) *Science*, **138**, 143.

[3] Halbach, H. & Eddy, N. B. (1963) *Bull. Wld Hlth Org.*, **28**, 139; *Wld Hlth Org. techn. Rep. Ser.*, 1964, No. 287.

morphine-type in mice and rats are mainly exploratory, but they are a fruitful source of information on tolerance and may even have some predictive value if comparisons are made between the test substance and a known agent. The results with morphine-like agents in monkeys and with barbiturate-like agents in dogs have been found to be qualitatively very similar to those in man and often show a good quantitative correlation as well. The general principles of these methods are: (1) to develop a physical dependence with a known agent of the type to which the test agent is believed to belong and then to determine the ability of the test agent to suppress, permanently or temporarily, associated abstinence phenomena by single or repeated administrations, i.e., to determine the physical dependence capacity (PDC) of the test agent; (2) to determine whether or not physical dependence develops following repeated administration of the test agent and whether an abstinence syndrome can be produced. In this second method, an effective concentration of the test agent is maintained continuously in the organism for variable periods of time, and the demonstration of an abstinence syndrome is achieved through the administration of a specific antagonist and/or final abrupt withdrawal.

When the results of these methods are unequivocally positive they may be used as a sound basis for evaluating the liability of a specific agent to produce physical dependence in man and sometimes for assessing the degree of risk to public health involved. In support of this statement it may be noted that positive evidence of physical dependence capacity in monkeys has been confirmed in man. Results and comparisons are at present less extensive in respect of barbiturate-like physical dependence capacity in dogs, but some positive results have been confirmed in clinical experience.

If tests of an agent in animals give doubtful or perhaps even negative results, whereas other studies indicate a resemblance to a known dependence-producing agent, exploration for dependence-producing properties in man may be required.

The procedure used for testing morphine-like analgesic agents and barbiturate-like sedatives in patients receiving indicated medication differs from that used in drug-dependent recidivists, but the principles are the same: (1) continuous administration at dose levels needed to provide symptomatic relief and permitted by the absence of toxic signs; (2) careful observation of behavioural responses and assessment of patients' " liking " of the agent; if possible, there should be periodic substitution of a placebo; and (3) except in terminal cases, subsequent withdrawal, at least temporarily, for detection of abstinence phenomena.

In studies on drug-dependent recidivists, substitution of the test substance for the drug on which dependence has been established, may be useful. In addition, in the case of potential morphine-like agents, intermittent challenge by administration of a specific opiate antagonist will precipitate withdrawal signs if physical dependence is developing.

The self-administration techniques in animals referred to under psychic dependence are also relevant for the study of physical dependence produced by a wide range of drugs.

1.4 Criteria for determining the need for drug control

There are two main conditions, at least one of which must exist for a drug to be considered in need of control:

(1) The drug is known to be abused other than sporadically or in a local area and the effects of its abuse extend beyond the drug taker; in addition, its mode of spread involves communication between existing and potential drug takers, and an illicit traffic in it is developing.

(2) It is planned to use the drug in medicine and experimental data show that there is a significant psychic or physical dependence liability; the drug is commercially available or may become so.

If neither of these conditions is fulfilled, there is no need for an agent to come under consideration for control.

The characteristics of drug dependence of various types have been described.[1] Society has already decided that when certain types of dependence (morphine, cocaine, cannabis) are demonstrated, specific national and international control measures should be applied. National controls of varying comprehensiveness have been established in some countries over additional types of substances (stimulants, sedatives and hallucinogens). It is not pertinent to discuss here the kind or extent of control needed, or whether it can be handled nationally or needs to be applied internationally, though a WHO Expert Committee has described some minimum requirements [2] and the World Health Assembly has recommended certain controls.[3] It must be noted, however, that current social trends and medical research developments have given rise and will continue to give rise to situations where early consideration must be given to the need for control of certain drugs. It must be emphasized further that risk to public health is the prime determining factor in deciding for or against control of a particular type of drug.

1.4.1 *Drugs already in use*

In the " after-the-fact situation ", where a drug is already in use, the decision on the need for control must be based upon evaluation of the

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[1] *Wld Hlth Org. techn. Rep. Ser.*, 1964, No. 273, p. 13 (Annex 1); Eddy, N. B., Halbach, H., Isbell, H. & Seevers, M. H. (1965) *Bull. Wld Hlth Org.*, **32**, 721.

[2] *Wld Hlth Org. techn. Rep. Ser.*, 1965, No. 312, p. 9 (section 7).

[3] *Off. Rec. Wld Hlth Org.*, 1965, **143**, 31 (Resolution WHA 18.47); 1967, **160**, 26 (Resolutions WHA 20.42, WHA 20.43); 1968, **168**, 20 (Resolution WHA 21.42).

risk; this may lead to a recommendation for control at the national or international level, depending upon the interpretation of "local area", seriousness of adverse effects, degree of communicability, and the extent of illicit traffic. This situation will apply particularly to abuse of drugs for which there is no essential medical need, such as LSD and substances introduced to produce similar effects. If available information on the specific "abused" drug is not sufficiently explicit, comparison with a reference substance by the techniques for the evaluation of subjective effects and behavioural responses mentioned earlier will be indicated.

The kind and extent of control of a given drug are related to the degree of its acceptance, the nature of use and abuse, and the type and degree of hazard to public health. Pronouncements by authoritative bodies on the risks pertaining to particular substances should be taken into account.

Sound decisions on control measures can be taken only if reliable and comprehensive data are available. Very often the quality and quantity of information are inadequate. Reliable, comprehensive data can be provided by a single discipline, but often a multidisciplinary approach is required. Sociological, psychological and epidemiological approaches, with their specialized techniques and experience, will be particularly important. Research, for instance, into the attitudes towards drugs, their patterns of use and abuse, and the changes in such attitudes and patterns with time would provide important data concerning possible dangers of increasing incidence of drug dependence and related abuse and the potential for epidemic spread. In addition, material essential for the development of legislative, educational and therapeutic strategies would be obtained. At a practical level, highly mobile emergency teams trained in such disciplines will have an important part to play in assessing the relevant facts, such as the real extent of the problem, the epidemic risk, and possible methods of spread, and will provide information useful in developing corrective strategies along public health lines. The value of data obtained from cross-sectional and longitudinal studies of drug-dependent persons needs stressing, as does the fact that there are very few adequately conducted studies of this kind. Also of great importance would be the scientific evaluation of possible consequences of changes in control measures, whether these consequences relate to drug use and abuse or to other forms of behaviour.

Another recent development that can provide reliable data is the testing of biological fluids, especially urine, for the presence of drugs. These methods are objective and do not depend upon reports by the user or the suspected user. These techniques are therefore useful not only in diagnosis and in the therapeutic supervision of users, but also to supplement other methods in epidemiological studies of the prevalence and incidence of drug abuse.

Support for the expansion of a wide range of facilities and activities will clearly be required if data of the quality and quantity needed are to be forthcoming.

1.4.2 *Drugs being developed for medical use*

The concern in this " before-the-fact situation " is to protect the public from potential risks of drug dependence and related abuse as new drugs are developed for and introduced into medical use. In seeking to ensure such protection, there should be no interference with the availability of drugs for necessary research. The public is protected in most countries by national arrangements for screening and for limiting the availability of drugs in preliminary investigational stages. Once the decision is taken to make a drug available for medical practice, both national and international controls may be required, depending on how the drug will be marketed and the extent of the risk of illicit diversion or traffic. In developing recommendations about drug control, consideration must also be given to the type of formulation and the intended medical use. The minimum additional information for a decision must comprise :

(1) pharmacological data that include comparisons with a known drug having similar properties ;

(2) the results of evaluation of physical dependence capacity (PDC) in the appropriate species against the appropriate standard ; if the PDC evaluation is equivocal, comparison in man with appropriate agent(s) by techniques for determining psychic and physical dependence are necessary, with due attention to the ethical questions involved ; [1]

(3) evaluation of ability to produce tolerance in more than one species.

In the case of mixtures containing substances already subject to control, the availability of the controlled agent must be the decisive factor and the effectiveness of other agents in the mixture as deterrents to abuse must generally be doubted. When the possibility of declaring such a mixture an " exempt " preparation is considered it can be decided affirmatively only if :

(1) consumption of multiple doses to a level of abuse sufficient to create or support a dependence is precluded ;

(2) the primary controlled ingredient cannot be separated or recovered from the mixture by means simpler or less expensive than its original preparation ; and

(3) there is unequivocal evidence that the added ingredient(s) deter(s) abuse and/or abolish(es) the development of dependence.

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[1] *Wld Hlth Org. techn. Rep. Ser.*, 1968, No. 403 (section 4).

2. WORK OF INTERNATIONAL BODIES CONCERNED WITH DRUG DEPENDENCE

2.1 WHO activities

The Committee expressed its approval of the approach to problems of dependence on alcohol and on other drugs outlined in the fourteenth report of the WHO Expert Committee on Mental Health. The following passage was considered particularly important and is quoted *in extenso*: [1]

> The Committee agreed that, despite existing differences between dependence on alcohol and dependence on other drugs, there are many significant similarities in the causation and treatment of these conditions. While the extent and nature of the problem, i.e., type of drug dependence and patterns of use and abuse, vary widely from country to country, the relatively frequent transfer from one drug of dependence to another, the not infrequent abuse of drugs in combination, the complex and changing patterns of abuse, and the rapid development of new drugs with potentialities for abuse, make it important that dependence on alcohol and other drugs be considered as facets of one problem, psychic dependence of various kinds being the common factor. To the degree that dependence-producing drugs interfere substantially with the normal functioning of the abuser and/or become a problem for other persons or society, they give rise to health problems that are susceptible of medical identification, classification and treatment. This does not imply that the problems under discussion come exclusively within the field of health. Social, cultural, legal, economic and other factors also play a role in causation, treatment, prevention and control. *It is imperative that dependence on alcohol and other drugs be recognized as creating major health problems, which have to be considered not only in terms of the agents involved but also from the point of view of the host and the environment.*
>
> A combined approach to the problems of alcoholism and drug dependence does not apply equally to all aspects of the problems. Differences in local conditions, such as social structure, personal and cultural attitudes, and the incidence and prevalence of dependence on various agents have to be taken into account. In general, a combined approach will apply most usefully to research and will be less applicable to control measures, with treatment and education falling in between.

The Committee considered that one of the major contributions of this concept of a combined approach would be the beneficial influence it would have on the attitudes of those working in this field.

Also noted were the valuable contributions made by the WHO Scientific Group on Research in Psychopharmacology [2] and by the WHO Scientific Group on Neurophysiological and Behavioural Research in Psychiatry.[3]

2.1.1 *Monitoring of adverse drug reactions*

The Committee noted that WHO is giving increasing attention to the development of techniques for monitoring adverse drug reactions as one means of obtaining, at an early stage, knowledge of possible risks to public

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[1] *Wld Hlth Org. techn. Rep. Ser.*, 1967, No. 363, p. 8 (section 1.1.1).

[2] *Wld Hlth Org. techn. Rep. Ser.*, 1967, No. 371.

[3] *Wld Hlth Org. techn. Rep. Ser.*, 1968, No. 381.

health arising from the use of medicaments. The Committee was pleased to note that, following the suggestion made in its fourteenth report,[1] drug dependence had been included among the adverse reactions to be monitored. A number of preferred terms pertaining to drug dependence and abuse, including withdrawal states, have been proposed for use in a WHO Pilot Research Project for International Drug Monitoring. This project involves close co-operation between international and national agencies. A monitoring system allowing rapid access to data collected from many areas may give early warning of possible abuse of a drug, especially of a new agent, and may also help in the identification of the characteristics of dependence and abuse of the drug. In addition, such a system may be of value in the study of the epidemiology of drug dependence and related abuse.

Attention is also drawn to the inclusion of drug dependence of different types in the recent revision of the International Classification of Diseases,[2] which will further facilitate the early recognition and understanding of dependence and abuse and the accumulation of information on these and related problems.

2.2 United Nations Commission on Narcotic Drugs

The Committee noted that in the reports of its twenty-first and twenty-second sessions, the Commission on Narcotic Drugs of the United Nations Economic and Social Council,[3] had accepted the majority of the recommendations of earlier WHO Expert Committees concerned with drug dependence. The Commission had concluded, however, at its twenty-second session,[4] that one of the recommendations first put forward in 1963 by the WHO Expert Committee on Addiction-Producing Drugs [5] could

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[1] *Wld Hlth Org. techn. Rep. Ser.*, 1965, No. 312, p. 11 (section 10).

[2] World Health Organization (1967) *Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death*, 1965 revision, Geneva.

[3] United Nations, Commission on Narcotic Drugs (1966) Document E/4294; (1968) Document E/4455 (*Economic and Social Council: Official Records*).

[4] United Nations, Commission on Narcotic Drugs (1968) Document E/4455, p. 5 (para 41-42) (*Economic and Social Council: Official Records*).

[5] Considering the need to ensure that the Schedules in the Single Convention would be up-to-date at the time of its coming into force, the United Nations Commission on Narcotic Drugs, at its 1962 session, invited WHO " to make recommendations regarding the necessary amendments " (Document E/3648; E/CN.7/432, p. 36, para. 251).

A WHO Expert Committee on Addiction-Producing Drugs, meeting in November 1963, recommended in respect to Schedule I, *inter alia*, " the following text should be added (after the entry ' Trimeperidine '):

> ' Any other product obtained from any of the phenanthrene alkaloids of opium or ecgonine alkaloids of the coca leaf, not listed in Schedule I or II, and neither made nor utilized exclusively for authorized domestic research, unless the government concerned finds that the product in question does not have morphine-like or cocaine-like [dependence-producing] effects.' "

See: *Wld Hlth Org. techn. Rep. Ser.*, 1964, No. 273, p. 8 (section 3). The bracketed words were added in *Wld Hlth Org. techn. Rep. Ser.*, 1966, No. 343, p. 8 (section 4).

not be accepted in the form then proposed. This recommended that a "product obtained from any of the phenanthrene alkaloids of opium or ecgonine alkaloids of the coca leaf" should, in specified circumstances, be included in Schedule I of the Single Convention on Narcotic Drugs, 1961. Since this recommendation was made, there has been a rapid development of specific narcotic antagonists,[1] many of which qualify as products obtained from phenanthrene alkaloids of opium. Desirable as the "preventive value"[2] might have been at the time of the original recommendation, it now appears that chemical structure can no longer be considered a reliable guide to probable dependence liability for purposes of control. In view of the foregoing, the Committee recommended that no further action on this question be taken.

2.3 United Nations Division of Narcotic Drugs

The Committee noted the activities of the United Nations Division of Narcotic Drugs in furthering the improvement of services available to narcotic-dependent persons. These included a South-East Asia Study Tour of Treatment and Rehabilitation Facilities for Narcotic Addicts in February 1968, the inclusion of treatment and rehabilitation information in seminars organized for enforcement officers, and the submission to governments of a questionnaire concerning their interest in fellowships in the field of drug dependence during the coming five years.

The Committee was informed of the third revision of the *Multilingual List of Narcotic Drugs Under International Control*.[3] The Committee commended the work carried out by the Secretariat of the United Nations and its consultants in revising the list, which has been greatly expanded. The Committee was also informed that in future the *List of Drugs Under International Control*, published annually by the Division, and the *List of Narcotic Drugs Under International Control* issued by the International Narcotic Control Board, will be combined.

2.4 International Narcotics Control Board

The Committee noted that, on 2 March 1968, the Permanent Central Narcotics Control Board (PCNB) and the Drug Supervisory Body (DSB) were succeeded by the International Narcotics Control Board (INCB), in accordance with the provisions of the Single Convention on Narcotic

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[1] See also section 7.

[2] *Wld Hlth Org. techn. Rep. Ser.*, 1966, No. 343, p. 8 (section 4).

[3] United Nations (1968) *Narcotic drugs under international control. Multilingual list*, 3rd ed. (Document E/CN.7/513).

Drugs, 1961. In their Final Report,[1] the PCNB and the DSB provided an excellent description of the evolution of international narcotics control, as well as the present situation in that field.

2.5 Problems outside the scope of the Single Convention

The Committee also noted the extensive interest in and the increasing attention given by various international bodies to the problems of abuse and control of drugs outside the scope of the Single Convention. The activities are noted in greater detail under section 3 of this report.

3. ABUSE AND CONTROL OF DRUGS NOT UNDER INTERNATIONAL CONTROL

The Committee noted the previous recommendations of WHO Expert Committees,[2] of the World Health Assembly [3] and of other international organizations [4] concerning the abuse and control of drugs not now under international control and reaffirmed the opinions expressed by these bodies that international control of some such substances is urgently necessary.

The Committee discussed the characteristics of the substances not under international control that are now known to produce drug dependence of different types with a risk to public health.[5] Such substances can be classi-

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[1] United Nations, Permanent Central Narcotics Board and Drug Supervisory Body (1967) *Final Report*, Document E/OB/23-E/DSB/25 (*Economic and Social Council: Official Records*).

[2] *Wld Hlth Org. techn. Rep. Ser.*, 1952, No. 57, p. 11 (section 8); 1954, No. 76, p. 11 (section 8); 1957, No. 116, p. 10 (section 10); 1964, No. 273, p. 11 (section 7); 1965, No. 312, p. 9 (section 7); 1966, No. 343, p. 11 (section 8).

[3] *Off. Rec. Wld Hlth Org.*, 1965, **143**, 31 (Resolution WHA 18.47); 1967, **160**, 26 (Resolutions WHA 20.42 and WHA 20.43); 1968, **168**, 20 (Resolution WHA 21.42).

[4] United Nations, Commission on Narcotic Drugs (1956) Document E/2891, p. 38 (para. 328); (1957) Document E/3010/Rev.1, p. 40 (para. 388); (1962) Document E/3648, p. 31 (para. 205); (1966) Document E/4294, p. 38 (para. 305); (1968) Document E/4455, p. 34 (para. 325); p. 36 (para. 335) (*Economic and Social Council: Official Records*).

United Nations, Economic and Social Council (1967) *Official Records, Forty-Second Session, Resolutions, Supplement No. 1*, Document E/4393, p. 5 (Resolution 1197); (1968) *Official Records, Forty-Fourth Session, Resolutions, Supplement No. 1*, Document E/4548, p. 6 (Resolution 1293), p. 7 (Resolution 1294).

United Nations, Permanent Central Narcotics Board (1965) Document E/OB/21, p. XXXI (para. 164); (1966) Document E/OB/22, p. XXIX (para. 128) (*Report to the Economic and Social Council on the Work of the Board*).

United Nations, Permanent Central Narcotics Board and Drug Supervisory Body (1967) *Final Report*, Document E/OB/23-E/DSB/25, p. 24 (para. 112-164) (*Economic and Social Council: Official Records*).

[5] *Wld Hlth Org. techn. Rep. Ser.*, 1964, No. 273, p. 13 (Annex 1); 1964, No. 287, p. 4 (section 2); Eddy, N. B., Halbach, H. Isbell, H. & Seevers, M. H. (1965) *Bull. Wld Hlth Org.*, **32**, 721.

fied on the basis of chemical structure or of pharmacological effect. Classifications of this kind are useful for theoretical purposes and for identifying, at an early stage in development, new drugs that might have a potential for abuse. The pharmacological classification is also useful in determining the kind of scientific testing required to evaluate the dependence liability of a new substance. Chemical or pharmacological classifications cannot, however, be used as the basis for determining the need for control nor the type of control required because

(1) small changes in chemical structure may cause great changes in dependence liability;

(2) drugs with different chemical structures may fall within the same pharmacological groups, and cause similar types of drug dependence; and

(3) within any group there is wide variation in activity and degree of abuse liability.

Furthermore, kinds of drug dependence differing from those now known may appear in the future.

For these reasons the Committee concluded that the need, type and degree of international control must be based on two considerations: (*a*) the degree of risk to public health and (*b*) the usefulness of the drug in medical therapy.

The Committee also suggested that recommendations in regard to control should embody certain principles:

(1) the degree of control should be based on the considerations in the preceding paragraph;

(2) the provisions should be flexible, so that a drug can readily be placed under appropriate control if new knowledge indicates that this is desirable;

(3) there should be provision for making even the most dangerous substances available for scientific research, when justified, but only under appropriate safeguards.

In emphasizing the need for varying levels of control, the Committee suggested that the following groups of drugs could be defined on the basis of the principles mentioned above:

(*a*) Substances that at present have no accepted use in medical practice but carry a high degree of hazard to public health. This group might include such drugs as lysergic acid diethylamide (LSD) and the tetrahydrocannabinols. The strictest type of control would be applied to substances in this group, which would be available only for scientific research.

(*b*) Drugs extensively used in medical practice, or with the potential for such use, but also presenting a substantial risk to public health. This

group might include certain drugs that produce barbiturate or amphetamine type dependence. Such drugs would be available under strict control for medical practice.

(*c*) This group would include drugs similar in type to those in group (*b*) but presenting a much lower degree of hazard. Drugs in this group would be available for medical practice under less strict control than those in group (*b*). They might include such substances as the benzodiazepines and some long-acting barbiturates.

(*d*) Drugs contained in groups (*b*) or (*c*) but compounded with non-dependence producing ingredients in such low concentrations or in such other manner as to render their abuse unlikely and to make recovery of the active ingredient very difficult. Examples of such preparations are some mixtures of long-acting barbiturates with such substances as belladonna alkaloids. Control of such preparations would be less strict than for those in group (*c*).

(*e*) Drugs that may present some, but very low, risk of creating drug dependence or related abuse. Examples might include certain antihistamines and antidepressants. The purpose of this group would be primarily to alert governments to a potential but low degree of hazard and to encourage them to monitor the use of such drugs and report instances of abuse.

The Committee considered the possibility of an additional group to include chemical precursors capable of relatively simple transformation into dependence-producing drugs. It recognized, however, that there were great difficulties in defining the criteria for inclusion of substances in such a group and doubted the practicability of developing one at this time. In some instances, the Committee suggested, the precursor might be placed in the same group as the drug of which it was a precursor.

The Committee concluded that in general each substance would require individual evaluation before recommendations concerning level of control could be made.

4. CANNABIS *

As pointed out by previous WHO Expert Committees concerned with drug dependence,[1] medical need for cannabis as such no longer exists. However, the non-medical use of this substance persists and has been increasing in a number of countries. In some countries, there are consider-

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* Ganga, hashish, kif, maconha, marihuana and " pot " are but a few of the names commonly used in referring to cannabis. (See : United Nations (1968) *Narcotic drugs under international control. Multilingual list*, 3rd ed. (Document E/CN.7/513)).

[1] *Wld Hlth Org. techn. Rep. Ser.*, 1952, No. 57, p. 11 (section 7) ; 1961, No. 211, p. 11 (section 3) ; 1965, No. 312, p. 11 (section 9).

able differences of opinion about questions of dependence liability, the acute and chronic effects on the individual user and the community, and the type and nature of the controls to be applied.

This Committee strongly reaffirms the opinions expressed in previous reports [1] that cannabis is a drug of dependence, producing public health and social problems, and that its control must be continued.

It was generally recognized that more basic data on the acute and chronic effects of cannabis on the individual and society are needed to permit accurate assessment of the degree of hazard to public health. It was also noted that tetrahydrocannabinols, which are important constituents of cannabis, have been isolated in pure form and completely synthesized. The availability of these compounds will make it possible to intensify basic research into such matters as tolerance, dependence potential, abuse liability, and specific acute and chronic toxic effects.

5. COCA LEAVES AND COCAINE

It was noted that, at the Second Meeting of the International Narcotics Control Board, a question was raised concerning the value of coca leaf and its preparations in medical practice. The Committee expressed the opinion that such materials had no place in modern medicine. Indeed, in the fourteenth report of the WHO Expert Committee on Dependence-Producing Drugs,[2] the opinion was expressed that cocaine itself, though still used in some areas, was " virtually obsolete " in medical practice. A number of effective local anaesthetics without established dependence and abuse liability are available.

The Committee noted with concern the continuing widespread use of coca leaves in certain areas and confirmed the opinions expressed in previous reports.[2, 3]

6. METHADONE MAINTENANCE

Recent experience with methadone maintenance for heroin-dependent persons, a method mentioned in an earlier report,[4] was reviewed. The Committee noted that several variants of the method are now being used. The most extensive experience so far described has been with a high-dose technique, but a low-dose method is also being employed.

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[1] *Wld Hlth Org. techn. Rep. Ser.*, 1955, No. 95, p. 12 (section 12); 1964, No. 273, p. 15 (Annex 1).

[2] *Wld Hlth Org. techn. Rep. Ser.*, 1965, No. 312, p. 10 (section 8).

[3] *Wld Hlth Org. techn. Rep. Ser.*, 1964, No. 273, p. 6 (section 2).

[4] *Wld Hlth Org. techn. Rep. Ser.*, 1966, No. 343, p. 9 (section 6).

On the basis of data now available, the Committee was of the opinion that methadone maintenance for drug dependence of morphine type remains experimental, and that it is not suitable for utilization by individual physicians. It requires for its operation the full support of a multidisciplinary medical service to effect the therapeutic, social and rehabilitation measures that may be necessary and to check for possible relapse or multiple drug use, and also to provide data for scientific evaluation and other research.

The Committee believes that despite verified reports of dramatic improvement in patients with a history of repeated treatment failures, methadone maintenance has not yet been adequately evaluated. The techniques of well-designed clinical drug trials, including scientifically controlled series and/or comparison groups, are required. In these trials it is important that the influence of factors other than methadone itself be evaluated. The various methadone maintenance programmes all include therapeutic measures in addition to the use of methadone. To date, the patients have, in the main, been highly motivated and carefully selected, and an after-care programme has been organized so as to develop a supportive group process. Furthermore, these patients have not been shown to be a representative sample of the drug-dependent population in other respects, e.g., age, ethnic grouping and educational level.

Finally, it must not be forgotten that methadone itself is a drug of dependence and that persons taking it regularly in the methadone programme continue to have a dependence of the morphine type. It will therefore be necessary to keep in view the question of final withdrawal of methadone from these patients.

7. SPECIFIC OPIATE ANTAGONISTS IN THERAPY

The use of cyclazocine as a deterrent in persons with dependence of the morphine type was reviewed in the fifteenth report of the WHO Expert Committee on Dependence-Producing Drugs.[1] The drug continues to be used with some therapeutic success when its administration is one element of a comprehensive programme. Although cyclazocine is a narcotic antagonist, it does have some morphine-like properties, but there were no data available to the Committee to suggest the need for present consideration of its control under international instruments.

Another antagonist, naloxone, which appears to have no morphine-like properties, has also been used as a deterrent in treating persons with dependence of the morphine type. Further testing will be required, however, to determine whether it is of practical use.

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[1] *Wld Hlth Org. techn. Rep. Ser.*, 1966, No. 343, p. 9 (section 6).

8. EVALUATION OF TREATMENT PROGRAMMES

The Committee noted with satisfaction the development in several countries of systems for recording data designed not only to gain information concerning the population referred for treatment but also to permit assessment of the outcome at follow-up.

In the opinion of the Committee, standardization of clinical records, both nationally and internationally, is vital not only to allow objective evaluation of the effects of treatment programmes and valid comparisons between the results obtained in various places, but also to ensure proper treatment based upon consideration of all possible factors involved.

9. CO-ORDINATION OF EDUCATIONAL EFFORTS

The Committee commended the efforts being made in various countries to improve, co-ordinate, and evaluate educational materials and activities, and to provide retrieval systems for data on all aspects of drug abuse and related dependence. It was noted that, too often, the information being disseminated by various sources to different groups was incorrect or misleading. A number of countries have attempted to co-ordinate and evaluate efforts in the educational field by such means as the establishment of governmental and non-governmental agencies to advise on or prepare materials designed for the information of specific groups in the population. The Committee recognized the importance of well-designed educational programmes as a fundamental means of prevention. It stressed the need for international co-operation in order to improve the quality of the information provided, to protect against undesirable duplication, and to develop specialized educational material.

10. NOTIFICATIONS

Bezitramide [1]

The Committee considered the notification by the Government of Belgium under Paragraph 1 of Article 1 of the 1948 Protocol and the notification by the World Health Organization under Article 3, Paragraph 1 of the Single Convention on Narcotic Drugs, 1961, concerning bezitramide. The Committee considered that bezitramide (1) produces morphine-like effects, and (2) suppresses abstinence phenomena of a known dependence

[1] International non-proprietary name proposed for 1-(3-cyano-3,3-diphenylpropyl)-4-(2-oxo-3-propionyl-1-benzimidazolyl)-piperidine.

of morphine type. Evidence on these points was derived in part from experiments in monkeys. Experience has shown that results obtained in the monkey correlate highly with those in man, so that, when the former are unequivocal, they may be accepted as evidence of what is to be expected in man.

Consequently, the Committee was of the opinion that bezitramide must be considered to be a dependence-producing drug of the morphine type and that

(1) bezitramide and its salts should fall under the regime laid down in the 1931 Convention for the drugs specified in Article 1, Paragraph 2, Group I, and

(2) in accordance with Article 3, Paragraph 3(iii) bezitramide and its salts should be recommended for inclusion in Schedule I of the Single Convention on Narcotic Drugs, 1961.

11. DRUGS PREVIOUSLY REVIEWED

Because of claims that there was abuse of dextromethorphan, dextropropoxyphene and pentazocine, the Committee reviewed the data now available on these drugs. All three drugs are effective and useful remedies in clinical medicine. The prevalence and incidence of their abuse appear to be so low as not now to constitute a public health problem. The Committee therefore concluded that the evidence still did not warrant a recommendation for control. However, it is important that a careful scrutiny of the use of drugs of this type be maintained. Additional research as a part of such continued scrutiny is being undertaken. Efforts to improve the completeness and quality of information available on such abuse as occurs must be increased.

Annex

LIST OF DRUGS UNDER INTERNATIONAL NARCOTICS CONTROL[1]

Common name or INN *	*Chemical designation*	*WHO Expert Committee on Drug Dependence* [2]		*Control regime*	
		Report number	*Reference*	*1931 Convention Group*	*1961 Convention Schedule* [3]
acetorphine *	6,7,8,14-tetrahydro-7α-(1-hydroxy-1-methylbutyl)-6,14-*endo*-ethenooripavine 3-acetate	15	1966, **343**, 3	I	I/IV
acetyldihydrocodeine	acetyldihydrocodeine	1	1949, **19**, 30	II	II
acetylmethadol *	3-acetoxy-6-dimethylamino-4,4-diphenylheptane	1	1949, **19**, 31	I	I
allylprodine *	3-allyl-1-methyl-4-phenyl-4-propionoxypiperidine	10	1960, **188**, 3	I	I
alphacetylmethadol *	α-3-acetoxy-6-dimethylamino-4,4-diphenylheptane	4	1954, **76**, 7	I	I
alphameprodine *	α-3-ethyl-1-methyl-4-phenyl-4-propionoxypiperidine	7	1957, **116**, 8	I	I
alphamethadol *	α-6-dimethylamino-4,4-diphenyl-3-heptanol	4	1954, **76**, 7	I	I
alphaprodine *	α-1,3-dimethyl-4-phenyl-4-propionoxypiperidine	1	1949, **19**, 30	I	I
anileridine *	1-(*p*-aminophenethyl)-4-phenylpiperidine-4-carboxylic acid ethyl ester	7	1957, **116**, 7	I	I
benzethidine *	1-(2-benzyloxyethyl)-4-phenylpiperidine-4-carboxylic acid ethyl ester	10	1960, **188**, 4	I	I

* Proposed international non-proprietary name (INN).

[1] As of January 1969. For details such as synonyms and the date of coming into force of international control, see *Multilingual List of Narcotic Drugs under International Control* (UN document E/CN.7/513) and *List of Narcotic Drugs under International Control* (published annually by UN, Division of Narcotic Drugs); also *Annex to the statistical forms "Yellow List"* published annually by the International Narcotics Control Board.

[2] The references given in this column are to *World Health Organization Technical Report Series*, with the exception of the report published in 1949 which appeared in *Official Records of the World Health Organization, No. 19*. For the names of earlier Committees, see footnote on page 5.

[3] In Schedule I of the 1961 Convention are included:

The isomers, unless specifically excepted, of the drugs in this Schedule whenever the existence of such isomers is possible within the specific chemical designation;

The esters and ethers, unless appearing in another Schedule, of the drugs in this Schedule whenever the existence of such esters and ethers is possible;

The salts of the drugs listed in this Schedule, including the salts of esters, ethers, and isomers as provided above whenever the existence of such salts is possible.

In Schedule II of the 1961 Convention are included:

The isomers, unless specifically excepted, of the drugs in this Schedule whenever the existence of such isomers is possible within the specific chemical designation;

The salts of the drugs listed in this Schedule, including the salts of the isomers as provided above whenever the existence of such salts is possible.

In Schedule IV of the 1961 Convention are included the salts of the drugs listed in this Schedule whenever the formation of such salts is possible.

Common name or INN *	*Chemical designation*	*WHO Expert Committee on Drug Dependence* [2]		*Control regime*	
		Report number	*Reference*	*1931 Convention Group*	*1961 Convention Schedule* [3]
benzylmorphine	3-benzylmorphine			I	I
betacetylmethadol *	β-3-acetoxy-6-dimethylamino-4,4-diphenylheptane	4	1954, **76**, 7	I	I
betameprodine *	β-3-ethyl-1-methyl-4-phenyl-4-propionoxypiperidine	3	1952, **57**, 7	I	I
betamethadol *	β-6-dimethylamino-4,4-diphenyl-3-heptanol	5	1955, **95**, 8	I	I
betaprodine *	β-1,3-dimethyl-4-phenyl-4-propionoxypiperidine	1	1949, **19**, 30	I	I
bezitramide *	1-(3-cyano-3,3-diphenylpropyl)-4-(2-oxo-3-propionyl-1-benzimidazolyl)-piperidine	16	1969, **407**, 22	I	I
cannabis and cannabis resin	*Cannabis sativa* L.			I	I/IV
clonitazene *	2-*p*-chlorbenzyl-1-diethylaminoethyl-5-nitrobenzimidazole	11	1961, **211**, 4	I	I
coca leaf	*Erythroxylon coca* L.			I	I
cocaine	methyl ester of benzoylecgonine			I	II
codeine	3-methylmorphine			II	II
codoxime *	dihydrocodeinone-*O*-(carboxymethyl)oxime			I	I
concentrate of poppy straw					I I
desomorphine *	dihydrodeoxymorphine			I	I/IV
dextromoramide *	(+)-4-[2-methyl-4-oxo-3,3-diphenyl-4-(1-pyrrolidinyl)butyl] morpholine	8	1958, **142**, 8	I	I
diampromide *	*N*-[2-(methylphenethylamino)-propyl]-propionanilide	11	1961, **211**, 5	I	I
diethylthiambutene *	3-diethylamino-1,1-di-(2′-thienyl)-1-butene	6	1956, **102**, 10	I	I
dihydrocodeine	7,8-dihydrocodeine	1	1949, **19**, 30	II	II
dihydromorphine	7,8-dihydromorphine			I	I
dimenoxadol *	2-dimethylaminoethyl-1-ethoxy-1,1-diphenylacetate	9	1959, **160**, 9	I	I
dimepheptanol *	6-dimethylamino-4,4-diphenyl-3-heptanol	1	1949, **19**, 31	I	I
dimethylthiambutene *	3-dimethylamino-1,1-di-(2′-thienyl)-1-butene	4	1954, **76**, 9	I	I
dioxaphetyl butyrate *	ethyl 4-morpholino-2,2-diphenylbutyrate	6	1956, **102**, 9	I	I
diphenoxylate *	1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylic acid ethyl ester	11	1961, **211**, 5	I	I
dipipanone *	4,4-diphenyl-6-piperidino-3-heptanone	5	1955, **95**, 8	I	I
ecgonine	(−)-3-hydroxytropane-2-carboxylate			I	I
ethylmethylthiambutene *	3-ethylmethylamino-1,1-di-(2′-thienyl)-1-butene	4	1954, **76**, 9	I	I

Common name or INN *	*Chemical designation*	*WHO Expert Committee on Drug Dependence* [2]		*Control regime*	
		Report number	*Reference*	*1931 Convention Group*	*1961 Convention Schedule* [3]
ethylmorphine	3-ethylmorphine			II	II
etonitazene *	1-diethylaminoethyl-2-*p*-ethoxybenzyl-5-nitrobenzimidazole	11	1961, **211**, 7	I	I
etorphine *	6,7,8,14-tetrahydro-7α-(1-hydroxy-1-methylbutyl)-6,14-*endo*-ethenooripavine	15	1966, **343**, 5	I	I/IV
etoxeridine *	1-[2-(2-hydroxyethoxy)ethyl]-4-phenylpiperidine-4-carboxylic acid ethyl ester	8	1958, **142**, 9	I	I
fentanyl *	1-phenethyl-4-*N*-propionylanilinopiperidine	13	1964, **273**, 4	I	I
furethidine *	1-(2-tetrahydrofurfuryloxyethyl)-4-phenylpiperidine-4-carboxylic acid ethyl ester	10	1960, **188**, 5	I	I
heroin	diacetylmorphine			I	I/IV
hydrocodone *	dihydrocodeinone			I	I
hydromorphinol *	14-hydroxydihydromorphine	11	1961, **211**, 7	I	I
hydromorphone *	dihydromorphinone			I	I
hydroxypethidine *	4-(*m*-hydroxyphenyl)-1-methylpiperidine-4-carboxylic acid ethyl ester	1	1949, **19**, 30	I	I
isomethadone *	6-dimethylamino-5-methyl-4,4-diphenyl-3-hexanone	1	1949, **19**, 31	I	I
ketobemidone *	4-(*m*-hydroxyphenyl)-1-methyl-4-propionylpiperidine	1	1949, **19**, 30	I	I/IV
levomethorphan *	(−)-3-methoxy-*N*-methylmorphinan	3	1952, **57**, 6	I	I
levomoramide *	(−)-4-[2-methyl-4-oxo-3,3-diphenyl-4-(1-pyrrolidinyl)-butyl]morpholine	8	1958, **142**, 8	I	I
levophenacylmorphan *	(−)-3-hydroxy-*N*-phenacylmorphinan	10	1960, **188**, 5	I	I
levorphanol *	(−)-3-hydroxy-*N*-methylmorphinan	3	1952, **57**, 6	I	I
metazocine *	2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan	10	1960, **188**, 6	I	I
methadone *	6-dimethylamino-4,4-diphenyl-3-heptanone	1	1949, **19**, 30	I	I
methadone-intermediate	4-cyano-2-dimethylamino-4,4-diphenylbutane	12	1962, **229**, 7	I	I
methyldesorphine *	6-methyl-Δ^6-deoxymorphine	4	1954, **76**, 6	I	I
methyldihydromorphine *	6-methyldihydromorphine	5	1955, **95**, 5	I	I
metopon *	5-methyldihydromorphinone	1	1949, **19**, 30	I	I
moramide-intermediate	2-methyl-3-morpholino-1,1-diphenylpropane carboxylic acid	12	1962, **229**, 7	I	I
morpheridine *	1-(2-morpholinoethyl)-4-phenylpiperidine-4-carboxylic acid ethyl ester	8	1958, **142**, 8	I	I

Common name or INN *	*Chemical designation*	*WHO Expert Committee on Drug Dependence* [2]		*Control regime*	
		Report number	*Reference*	*1931 Convention Group*	*1961 Convention Schedule* [3]
morphine				I	II
morphine-*N*-oxide				I	I
morphine pentavalent nitrogen derivatives				I	I
myrophine *	myristylbenzylmorphine	5	1955, **95**, 6	I	I
nicocodine *	6-nicotinoylcodeine	12	1962, **229**, 6	II	II
nicodicodine *	6-nicotinoyldihydrocodeine	15	1966, **343**, 5	I	I
nicomorphine *	3,6-dinicotinoylmorphine	9	1959, **160**, 4	I	I
noracymethadol *	(+)-α-3-acetoxy-6-methylamino-4,4-diphenylheptane	12	1962, **229**, 5	I	I
norcodeine *	*N*-demethylcodeine	9	1959, **160**, 5	II	II
norlevorphanol *	(−)-3-hydroxymorphinan	10	1960, **188**, 6	I	I
normethadone *	6-dimethylamino-4,4-diphenyl-3-hexanone	5	1955, **95**, 7	I	I
normorphine *	demethylmorphine	9	1959, **160**, 5	I	I
norpipanone *	4,4-diphenyl-6-piperidino-3-hexanone	13	1964, **273**, 4	I	I
opium				I	II
oxycodone	14-hydroxydihydrocodeinone			I	I
oxymorphone *	14-hydroxydihydromorphinone	5	1955, **95**, 6	I	I
pethidine *	1-methyl-4-phenylpiperidine-4-carboxylic acid ethyl ester	1	1949, **19**, 30	I	I
pethidine-intermediate A	4-cyano-1-methyl-4-phenylpiperidine	12	1962, **229**, 7	I	I
pethidine-intermediate B	4-phenylpiperidine-4-carboxylic acid ethyl ester	12	1962, **229**, 7	I	I
pethidine-intermediate C	1-methyl-4-phenylpiperidine-4-carboxylic acid			I	I
pethidine-intermediate C, esters of		5	1955, **95**, 9	I	I
phenadoxone *	6-morpholino-4,4-diphenyl-3-heptanone	1	1949, **19**, 31	I	I
phenampromide *	*N*-(1-methyl-2-piperidinoethyl)propionanilide	11	1961, **211**, 7	I	I
phenazocine *	2′-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan	10	1960, **188**, 6	I	I
phenomorphan *	3-hydroxy-*N*-phenethylmorphinan	6	1956, **102**, 8	I	I
phenoperidine *	1-(3-hydroxy-3-phenylpropyl)-4-phenylpiperidine-4-carboxylic acid ethyl ester	11	1961, **211**, 8	I	I
pholcodine *	morpholinylethylmorphine	3	1952, **57**, 5	II	II
piminodine *	4-phenyl-1-(3-phenylaminopropyl)piperidine-4-carboxylic acid ethyl ester	10	1960, **188**, 7	I	I

Common name or INN *	*Chemical designation*	*WHO Expert Committee on Drug Dependence* [2]		*Control regime*	
		Report number	*Reference*	*1931 Convention Group*	*1961 Convention Schedule* [3]
piritramide *	1-(3-cyano-3,3-diphenylpropyl)-4-(1-piperidino)-piperidine-4-carboxylic acid amide	14	1965, **312**, 3	I	I
proheptazine *	1,3-dimethyl-4-phenyl-4-propionoxyazacycloheptane	6	1956, **102**, 11	I	I
properidine *	1-methyl-4-phenylpiperidine-4-carboxylic acid isopropyl ester	5	1955, **95**, 9	I	I
racemethorphan *	(±)-3-methoxy-*N*-methylmorphinan	3	1952, **57**, 7	I	I
racemoramide *	(±)-4-[2-methyl-4-oxo-3,3-diphenyl-4-(1-pyrrolidinyl)butyl]morpholine	8	1958, **142**, 8	I	I
racemorphan *	(±)-3-hydroxy-*N*-methylmorphinan	3	1952, **57**, 6	I	I
thebacon *	acetyldihydrocodeinone			I	I
thebaine	3,6-dimethyl-8-dehydromorphine			I	I
trimeperidine *	1,2,5-trimethyl-4-phenyl-4-propionoxypiperidine	8	1958, **142**, 9	I	I