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DEPENDENCE LIABILITY OF "NON-NARCOTIC" DRUGS

H. Isbell & T. L. Chruściel

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DEPENDENCE LIABILITY OF "NON-NARCOTIC" DRUGS

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INTRODUCTION

This publication was prepared because of the increasing concern that is felt in many responsible quarters about the self-administration of a number of psychoactive substances in order to experience their psychic effects. It presents technical data on 253 psychoactive drugs and herbs considered to have an actual or potential capacity to produce central nervous system stimulation, depression, or hallucinations or to produce distortions in perception, thinking or judgement and that may induce drug dependence. Substances of the types already under international "narcotics" control (opioids, coca leaves, cocaine and cannabis plants) are not included in this review.

In choosing the substances for review, the authors have compiled lists of (1) drugs already subjected to some national controls because of their dependence-producing properties, (2) compounds that are close chemical or pharmacological congeners of controlled drugs, and (3) other substances that have been abused, or might have such a potential because of their close chemical or pharmacological similarity. A few precursors of some hallucinogens are also considered.

TERMINOLOGY

The following four definitions, formulated by the WHO Expert Committee on Drug Dependence,[70] have been adopted in this publication.

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

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: "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."

For purposes of greater clarity the following additional descriptions are offered.

Psychic dependence: A compulsion that requires periodic or continuous administration of a drug to produce pleasure or avoid discomfort. This compulsion is the most powerful factor in chronic intoxication with psychotropic drugs, and with certain types of drugs may be the only factor involved in the perpetuation of abuse even in the case of most intense craving. Psychic dependence, therefore, is the universal characteristic of drug dependence. Operationally, it is recognized by the fact that the dependent continues to take the drug in spite of conscious admission that it is causing harm to his health and to his social and familial adjustment, and that he takes great risks to obtain and maintain his supply of the drug.

Physical dependence: A pathological state brought about by repeated administration of a drug and that leads to the appearance of a characteristic and specific group of symptoms, termed an abstinence syndrome, when the administration of the drug is discontinued or—in the case of certain drugs—significantly reduced. In order to prevent the appearance of an abstinence syndrome the continuous taking of the drug is required. Physical dependence is a powerful factor in reinforcing psychic dependence upon continuing drug use or in relapse to drug use after withdrawal.

Tolerance: The state in which repetition of the same dose of a drug has progressively less effect, or in which the dose needs to be increased to obtain the same degree of pharmacological effect as was caused by the original dose.

Cross-tolerance: The state in which tolerance to one drug has the effect of causing tolerance to another drug of the same or a different chemical type.

It should be borne in mind that the fact that a substance is termed a drug of dependence does not necessarily mean that it should be controlled, nationally or internationally, and, in addition, listing a substance as a drug of dependence does not indicate the type or degree of control which should be applied to a particular substance. The need for and the degree of control must be determined individually for each substance and must be based on the degree of risk to public health and the usefulness of the drug in medical practice.[70]

CLASSIFICATION

In order to facilitate the search for individual drugs a classification was developed which is partly pharmacological and partly chemical. This classification is followed in the tables. The compounds have been divided into five main categories:

1. Central nervous system depressants	Tables I-XI
2. Central nervous system stimulants	Tables XII-XV
3. Hallucinogens	Tables XVI-XIX
4. Crude plant drugs	Table XX
5. Precursors	Table XXI

The categories of central nervous system depressants, central stimulants and hallucinogens have been further subdivided into chemical classes: for example, the general category of central nervous system depressants was split into 13 chemical types: the diureides (barbiturates), the monoureides, etc. In the various chemical subgroups, each individual compound has been listed and assigned a number within that subgroup.

Where only one chemical was found in a particular group (bromide, paraldehyde, phencyclidine) no table has been prepared but the substance and its dependence potential are described in the text.

It is important to note that the central nervous system depressants do not include the reserpine, phenothiazine and butyrophenone groups of antipsychotic drugs. These groups do not appear to cause dependence or abuse (except, possibly, in so far as they may contribute in combinations). The antihistamines have also not been included, since there has been little abuse of these drugs. Alcohol has also been omitted because, although it is the most important central nervous system depressant causing dependence of the barbiturate-alcohol type, the problem of alcohol is so huge and so different in sociological, cultural and legal respects from dependence on other depressant drugs.

The central nervous system stimulants do not include the antidepressant dibenzazepines, such as imipramine or amitryptiline and the monoamine oxidase inhibitors, such as iproniazid or tranylcypromine, since neither of these two kinds of drugs has been widely abused.

MATERIAL INCLUDED

After the classification was settled, the literature was searched and the lists of individual substances compiled. The source material included compilations of drugs already subjected to special national controls; [6, 17, 22-37, 57] the manuals for physicians and pharmacists listing drugs available in particular countries; [9, 15, 40, 42, 45, 48, 51, 59, 66] the International Pharmacopoeia [58] and national formularies; [16, 50, 69] textbooks of pharmacology from various countries; [1, 5, 7, 11-13, 19-21, 38, 39, 41, 49, 56, 62, 64, 71] and some general articles dealing with problems of drug dependence in various countries.[2-4, 8, 10, 14, 18, 43, 44, 46, 47, 52-55, 61, 63, 65, 67, 68] No attempt has been made to list all compounds that have been synthesized in a particular chemical class. In categories 1 and 2, central nervous system depressants and stimulants that are, have been, or are likely to be available for therapeutic use have been selected. In many instances the drugs are obsolete, have been used very little. or are not yet on the market so that information is incomplete, but these substances have been included because of close chemical and pharmacological similarity to other drugs listed. There is also a large number of compounds for which it was difficult or impossible to find definite documentation regarding abuse or dependence. Such drugs have been categorized on the basis of analogies of chemical structure, pharmacodynamic properties and stated therapeutic indications. In the case of the hallucinogens it was manifestly impossible to include all the congeners of LSD that have been synthesized, all the hallucinogenic amphetamines and all the tetrahydrocannabinols. Those hallucinogens that have been included comprise substances that (1) have been shown to be hallucinogenic in man, and (2) have appeared in the illicit market somewhere in the world.

USE OF THE TABLES

The titles of Tables I to XIX indicate the chemical and pharmacological classification of the pure compounds. The subcodings of the tables are largely self-explanatory and further clarified by the footnotes. Column 1 shows the chemical formula and/or the commonly accepted short chemical name. Each compound or crude plant drug is assigned a numeral with the prefix S. The numbers are carried forward consecutively through the tables; that is, the last compound in Table I is No. S 66, the first compound in Table II is No. S 67, etc. In some cases the longer and more exact names according to the system of *Chemical Abstracts* are used. Column 2 lists the name of the substance as a drug. Whenever an International Nonproprietary Name (INN) is available, it is the name used. When no INN is available the fact is indicated by the entry " None ",

and the name used is, if possible, another nonproprietary name with the source of the name being identified by initials explained in a footnote. If no nonproprietary name is available, the leading name listed in the *Subsidia Pharmaceutica Index Nominum* [59] or the *Merck Index* [60] has been chosen. Column 3 tabulates some important symptoms of intoxication. Column 4 indicates whether or not tolerance develops (or lack of information). Column 5 states whether psychic dependence develops and sometimes gives a rough, non-quantitative descriptive rating of the degree of psychic dependence that can develop. Column 6 states whether physical dependence occurs and, where appropriate, lists the major manifestations of abstinence. Column 7 shows the therapeutic indications for the drug and, in some instances, the duration and onset of action after oral ingestion. Column 8 gives the major dangers of abuse. Column 9 shows an abuse-potential rating. A rating of " high " in column 9 indicates that the substance can create strong psychic dependence and that extensive abuse has occurred or is judged likely to occur if the drug was readily available. A rating of " moderate " indicates that the drug creates a less intense degree of psychic dependence and that some degree of abuse has occurred or is judged likely to occur if the drug was readily available. A rating of " low " indicates that the drug creates only mild psychic dependence and that only little or no abuse has occurred or is deemed likely to occur. If " None " appears in column 9, the compound is judged not to be a drug of dependence. Column 10 gives the bibliographical references on which the ratings were based. The references pertinent to a particular table appear at the end of the text relevant to that table. References have been numbered consecutively through the various reference lists, that is, the last number in " General References " below is No. 71, making the first number in the next reference list—under " Central nervous system depressants, Diureides (barbiturates) "—No. 72.

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CENTRAL NERVOUS SYSTEM DEPRESSANTS

GENERAL

The central nervous system depressants are drugs that relieve anxiety (sedatives) or induce sleep (hypnotics). Chemical groups of the monoureides (Table II), sulfonmethanes (Table X), and the miscellaneous agents (Table XI) comprise drugs which have low or no dependence liability but which have high central nervous system and other organ toxicity. These drugs are largely obsolete and production is generally low. The bromides have similar dangers.

The chemical groups of the barbiturates (Table I), chloral and derivatives (Table III), the tertiary acetylenic alcohols (Table IV), the carbamic acid esters of monohydroxy alcohols (Table V), the carbamic acid esters of glycols (Table VI), the piperidinediones (Table VII), the quinazolinones (Table VIII), the benzodiazepines (Table IX) and the sulfonmethanes (Table X) comprise drugs that cause, in high dose, sedation, stupor, coma, impaired cognition, loss of behavioural controls and ataxia. In addition, there is experimental or experiential evidence that at least one member of each of these subgroups causes dependence of the barbiturate-alcohol type, manifested by nervousness, agitation, insomnia, confusion, convulsions and delirium following abrupt discontinuation after long-continued high dosage. A small number of individual drugs have also been shown to substitute for barbital in dogs or monkeys dependent on those substances, that is, have been shown to have physical dependence capacity of the barbiturate type, and in such instances cross-tolerance was clearly demonstrated. The cyclic ether, paraldehyde, has similar characteristics.

DIUREIDES (BARBITURATES)

The fact that the barbiturates (Table I) are drugs of dependence is now so well accepted that it is difficult to remember how long this fact was denied and how long it took to gain general acceptance of barbiturate-type dependence. The first cases of dependence were described as long ago as 1914 [116] and 1915.[125] The general clinical aspects of the intoxication and of the withdrawal manifestations were reported in 1928 [119] and further detailed in a monograph [120] in 1934. Dependence with withdrawal convulsions in dogs was demonstrated in 1939 [128] and confirmed later.[84, 92] Numerous cases of withdrawal convulsions and delirium were reported around the world from 1914 to 1950, but the concept that the barbiturates caused physical dependence continued to be denied until the experimental demonstration of the condition in controlled experiments in man [78, 93, 95, 96, 103, 104, 106, 129] in 1950 and subsequent years.

Kalinowsky [111] was the first to recognize that convulsions on withdrawal of barbiturates, alcohol and other drugs represented a general type of reaction common to several different chemical types of central nervous system depressants. Kalinowsky's idea was expanded to include the group of drugs listed under substances that cause dependence of the barbiturate-alcohol type. [87]

The characteristics of dependence of the barbiturate-alcohol type include:

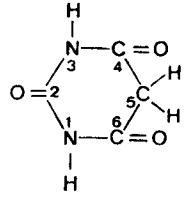
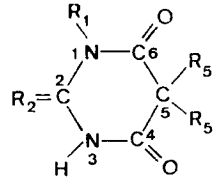
(1) strong psychic dependence;

(2) intoxication manifested by sedation, sleep, coma, stupor, impaired cognition and judgement, and ataxia;

(3) development of tolerance which is partly biochemical due to induction of increased amounts of drug-metabolizing enzymes in the liver and to "cellular" tolerance within the central nervous system (tolerance to this type of drug, in contrast to opiates, has a definite limit);

(4) partial crossed tolerance between members of the group;

(5) a dangerous type of physical dependence manifested by anxiety, insomnia, weakness, tremors, EEG abnormalities, convulsions and delirium on withdrawal.

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 1   Structural formula and numbering system for barbiturates	None; Barbituric acid	Drowsiness; Stupor; Coma	—	—	—	Not an active drug but a chemical; listed in order to facilitate chemical naming	—	None	
S 2 R_5-Allyl R_5-Allyl R_1-H R_2-O 5,5-diallylbarbituric acid	Allobarbital	Drowsiness; Stupor; Coma	Yes	Yes	Yes	Sedative; Hypnotic; 2-8 (0.25-0.5)	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Moderate to high	73, 74, 77, 78, 83, 84, 86-94, 98, 100-108, 110-112, 113, 117, 119, 121, 123, 128, 129
S 3 R_5-Allyl R_5-*n*-Butyl R_1-H R_2-O 5-allyl-5-*n*-butylbarbituric acid	None	Drowsiness; Stupor; Coma; Ataxia	Probable	Probable	Probable	Hypnotic; Probably obsolete	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Moderate to high	77, 86, 92, 93, 105, 106, 111, 112, 113, 119

[a] International Nonproprietary Name (INN) proposed by the World Health Organization, if any, or other nonproprietary name, if any; if there is no nonproprietary name, the main entry in the *Subsidia Pharmaceutica Index Nominum* or in the *Merck Index* or other generally accepted name. "None" indicates that an International Nonproprietary Name has not been proposed so far. The following abbreviations show the source of the name used; BAN = British Approved Name; DCF = Dénomination commune française; IN= *Subsida Pharmaceutica Index Nominum*; MI = *Merck Index*, 8th ed.; NFN = Nordisk Farmakopénaevn.

[b] Current therapeutic use, indications, and in some cases duration of action, in hours (and, in parentheses, onset of action, in hours).

TABLE I. CENTRAL NERVOUS SYSTEM DEPRESSANTS — DIUREIDES (BARBITURATES) *(continued)*

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 4 R_5-Ethyl R_5-Isoamyl R_1-H R_2-O 5-ethyl-5-isopentylbarbituric acid	Amobarbital; Sodium amobarbital 0.1-0.3 [c]	Drowsiness; Stupor; Coma; Ataxia	Yes	Yes	Yes	Sedative; Hypnotic; 2-8 (0.25-0.5)	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	High	72, 73, 74, 78, 79, 83, 84, 86-94, 100-108, 110-113, 119, 121, 123, 128-130
S 5 R_5-Allyl R_5-Isopropyl R_1-H R_2-O 5-allyl-5-isopropylbarbituric acid	Aprobarbital, 0.04-0.08; [c] Aprobarbital sodium	Drowsiness; Stupor; Coma; Ataxia	Yes	Yes	Yes	Sedative; Hypnotic; 2-8 (0.25-0.5)	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Moderate to high	77, 78, 84, 86, 87-94, 98, 100-108, 110-112, 117, 119, 121, 123, 126, 128, 129
S 6 R_5-Ethyl R_5-Phenyl R_1-H R_2-O (−)-*N*α-dimethylcyclohexaneethylamine compound with 5-ethyl-5-phenylbarbituric acid	Barbexaclone	No information	No information	Probable	No information	Antiepileptic	?	Low	99, 118
S 7 R_5-Ethyl R_5-Ethyl R_1-H R_2-O 5,5-diethylbarbituric acid	Barbital 0.3-0.5; [c] Sodium barbital 0.3-0.5 [c]	Drowsiness; Stupor; Coma; Ataxia; Uninhibited behaviour; Impaired cognition	Yes	Yes	Yes. Dog, monkey, man: convulsions, delirium	Sedative; Hypnotic; 4-12 (0.5-1)	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Moderate	73, 74, 87, 91, 92,93,100,104, 106, 112, 115, 116, 119, 120, 121, 123, 125, 128, 129
S 8 R_5-Allyl R_5-2-Bromoallyl R_1-H R_2-O 5-allyl-5-(2-bromoallyl)barbituric acid	None; Brallobarbital (DCF)	Drowsiness; Stupor; Coma; Ataxia; Uninhibited behaviour; Impaired cognition	Probable	Probable	Probable	Hypnotic	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Moderate	86, 87, 92, 93, 100, 103, 104, 107, 109, 112, 117, 119, 123, 126

[c] Average adult hypnotic dose (in g).

TABLE I. CENTRAL NERVOUS SYSTEM DEPRESSANTS

DIUREIDES (BARBITURATES) *(continued)*

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 9 R_5-2-Bromoallyl R_5-1-Methylbutyl R_1-H R_2-O 5-(2-bromoallyl)-5-(1-methylbutyl) barbituric acid	None; 0.1-0.2 [c]	Drowsiness; Stupor; Coma; Ataxia; Uninhibited behaviour; Impaired cognition	Probable	Probable	Probable	Hypnotic; 2-4 (0.5)	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Moderate to high	105, 107, 120
S 10 R_5-Ethyl R_5-3'-Bromophenyl R_1-H R_2-O 5-ethyl-5-(3'-bromophenyl)barbituric acid	None; Brophébarbital (DCF)	Drowsiness; Stupor; Coma; Ataxia; Uninhibited behaviour; Impaired cognition	No information	No information	Not proved	Sedative; Hypnotic	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Low to moderate	59, 66, 87
S 11 R_5-Butyl R_5-H R_1-Cyclohexyl R_2-O 5-butyl-1-cyclohexylbarbituric acid	Bucolome	No information	No information	No information	No information	Anti-inflammatory; Uricosuric; Not hypnotic; Sedative; Anaesthetic	Unknown	None	75, 76, 97
S 12 R_5-Allyl R_5-Isobutyl R_1-H R_2-O 5-allyl-5-isobutylbarbituric acid	Butalbital	No information	Probable	Probable	Probable	Hypnotic	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Moderate to high	73, 74, 77, 78, 86-94, 98, 100-108, 110-112, 113, 117, 119-121, 123, 126, 128
S 13 R_5-2'-Bromoallyl R_5-*sec*-Butyl R_1-H R_2-O 5-(2'-bromoallyl)-5-*sec*-butylbarbituric acid	None; Butallylonal (IN); 0.2 [c]	Drowsiness; Stupor; Coma; Ataxia	Probable	Probable	Probable	Hypnotic; 2-4 (0.5)	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Moderate to high	59, 78, 79, 83, 86-94, 98, 100-108, 110-112, 117, 119, 121, 123, 128-130
S 14 R_5-Ethyl R_5-2-butenyl R_1-H R_2-O 5-(2-butenyl)-5-ethylbarbituric acid	None; Crotarbital (IN)	Drowsiness; Stupor; Coma; Ataxia	Probable	Probable	Probable	Hypnotic	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Moderate	59, 87, 101, 105, 111, 117, 120, 128

[c] Average adult hypnotic dose (in g).

TABLE I. CENTRAL NERVOUS SYSTEM DEPRESSANTS

DIUREIDES (BARBITURATES) *(continued)*

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 15 R_5-Allyl R_5-Isobutyl R_1-H R_2-S 5-allyl-5-isobutyl-2-thiobarbituric acid	Buthalital sodium	Drowsiness; Coma; Ataxia; Stupor	Probable	Probable	Not proved	Anaesthetic	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Low	73, 74, 77, 78, 79, 86-94, 98, 100-108, 110-112, 114
S 16 R_5-Ethyl R_5-Butyl R_1-H R_2-O 5-butyl-5-ethylbarbituric acid	None; Butobarbital (DCF); 0.05-0.1 [c]	Drowsiness; Coma; Ataxia; Stupor	Probable	Probable	Probable	Hypnotic	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Moderate to high	78, 86, 87, 100-108
S 17 R_5-Ethyl R_5-1-Methylpropyl R_1-H R_2-S 5-ethyl-5-(1-methylpropyl)-2-thiobarbituric acid	None; Butylethylthiobarbituric acid (MI)	Drowsiness; Coma; Ataxia; Stupor	Probable	Probable	Not proved	Anaesthetic; Thioanalogue of secbutabarbital	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Low	78, 86-94, 98, 100-108
S 18 R_5-Butyl R_5-2-Carbamoyloxyethyl R_1-H R_2-O 5-butyl-5-(2-carbamoyloxyethyl)-barbituric acid	Carbubarb	No information	No information	No information	No information	Not hypnotic; Sedative	No information	Low	59
S 19 R_5-Ethyl R_5-Cyclohexenyl R_1-H R_2-O 5-ethyl-5(1-cyclohexen-1-yl)-barbituric acid	Cyclobarbital; Calcium cyclobarbital; 0.1-0.2 [c]	Drowsiness; Coma; Ataxia; Stupor	Yes	Yes	Yes	Hypnotic; 2-8 (0.25-0.5)	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	High	73, 74, 77, 78, 79, 83, 86-94, 98, 100-108, 110-112, 115, 117, 119, 120, 121, 123, 128, 129
S 20 R_5-Cyclohexen-1-yl R_5-Methyl R_1-H R_2-O 5-cyclohexen-1-yl-5-methylbarbituric acid	None	Drowsiness; Coma; Ataxia; Stupor	Probable	Probable	Not proved	Anaesthetic	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Low	73, 74, 87, 104, 107, 114

[c] Average adult hypnotic dose (in g).

TABLE I. CENTRAL NERVOUS SYSTEM DEPRESSANTS

DIUREIDES (BARBITURATES) *(continued)*

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 21 R_5-Allyl R_5-2-Cyclopenten-1-yl R_1-H R_2-O 5-allyl-5-(2-cyclopenten-1-yl) barbituric acid	None; Cyclopento-barbital (IN); 0.05-0.1 [c]	Drowsiness; Coma; Ataxia; Stupor	Probable	Probable	Probable	Hypnotic; Analgesic; Anti-spasmodic	Drunken-ness; Potentiation of CNS depressants; Coma; Death; Dependence	Moderate	73, 74, 77, 78, 80, 83, 86-95, 98, 100-108, 110-112, 114, 117, 119, 120, 121, 123, 128-130
S 22 R_5-Ethyl R_5-1,3-Dimethylbutyl R_1-H R_2-O 5-(1,3-dimethylbutyl)-5-ethylbarbituric acid	None	Drowsiness; Coma; Ataxia; Stupor	Probable	Probable	Probable	Hypnotic	Drunken-ness; Potentiation of CNS depressants; Coma; Death; Dependence	Moderate to high	87, 101, 105, 111, 113, 117, 119
S 23 R_5-Allyl R_5-Isopropyl R_1-Methyl R_2-O 5-allyl-5-isopropyl-1-methylbarbituric acid	None; Enally-propymal (IN)	Drowsiness; Coma; Ataxia; Stupor	Probable	Probable	Probable	Hypnotic; Intravenous anaesthetic	Drunken-ness; Potentiation of CNS depressants; Coma; Death; Dependence	Moderate	59, 74, 87
S 24 R_5-Ethyl R_5-Allyl R_1-H R_2-O 5-allyl-5-ethylbarbituric acid	None; Ethallo-barbital (DCF); Aethally-malum (NFN)	No information	Probable	Probable	Probable	Hypnotic	Drunken-ness; Potentiation of CNS depressants; Coma; Death; Dependence	Moderate to high	74, 77, 87-94, 98, 100-108, 110-112, 113-115, 118, 119, 121, 128-130
S 25 R_5-Ethyl R_5-2-Cyclohexylidenethyl R_1-H R_2-O 5-ethyl-5-(2-cyclohexylidenylethyl) barbituric acid	None	Convulsions	No information	Unlikely	No information (unlikely)	CNS stimulant; Not on the market; Brit. Patent 701.660 (1958)	Unknown	None	—

[c] Average adult hypnotic dose (in g).

TABLE I. CENTRAL NERVOUS SYSTEM DEPRESSANTS

DIUREIDES (BARBITURATES) *(continued)*

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 26 R_5-Ethyl R_5-Cyclopentenyl R_1-H R_2-O 5-ethyl-5-cyclopentenylbarbituric acid	None	Drunkenness; Coma; Stupor; Ataxia	Probable	Probable	Probable	Hypnotic 4-12 (0.5-1)	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Moderate	74, 78, 80, 83, 86-95, 98, 100-108, 110-112, 113, 117, 120, 121, 123, 126, 128
S 27 R_5-Ethyl R_5-2-Methylallyl R_1-H R_2-S 5-ethyl-5-(2-methylallyl)-2-thiobarbituric acid	None	Drunkenness; Ataxia; Coma; Stupor	No information	No information	No information	Hypnotic; Probably obsolete	Drunkenness; Potentiation of CNS depressants; Coma; Death	Low	—
S 28 R_5-Ethyl R_5-3-Methylbutyl R_1-H R_2-S 5-ethyl-5-(3-methylbutyl)-2-thiobarbituric acid	None	Drunkenness; Coma; Ataxia; Stupor	Probable	Probable	Probable	Anaesthetic; Probably not produced; Thioanalogue of amobarbital	Drunkenness; Potentiation of CNS depressants; Coma; Death	Low	—
S 29 R_5-Ethyl R_5-Phenyl R_1-2-diethylaminoethyl R_1-O 5-ethyl-5-phenyl-1(2-diethylaminoethyl) barbituric acid	None	No information	No information	No information	No information	Anti-arrhythmic tranquillizer	Unknown	None	59
S 30 R_5-Ethyl R_5-1-Piperidyl R_1-H R_2-O 5-ethyl-5-(1-piperidyl)barbituric acid	None	Drowsiness; Stupor; Coma; Ataxia	Probable	Probable	Probable	Hypnotic	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Moderate to high	78, 79, 83, 86-94, 96, 100-108, 110-112, 113, 115, 117, 119, 121
S 31 R_5-Furfuryl R_5-Isopropyl R_1-H R_2-O 5-furfuryl-5-isopropylbarbituric acid	None	Drowsiness; Stupor; Coma; Ataxia	Probable	Probable	Probable	Hypnotic; Probably obsolete	Drunkenness; Potentiation of CNS depressants; Coma; Death	Moderate to high	—

TABLE I. CENTRAL NERVOUS SYSTEM DEPRESSANTS

DIUREIDES (BARBITURATES) *(continued)*

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 32 R_5-Ethyl R_5-1-Cyclohepten-1-yl R_1-H R_2-O 5(1-cyclohepten-1-yl)-5-ethylbarbituric acid	Heptabarb; 0.1-0.4 [c]	Drowsiness; Stupor; Coma; Ataxia	Yes	Yes	Yes	Sedative; Hypnotic; 2-4 (0.5)	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	High	73, 74, 77, 78, 79, 83, 86-94, 98, 100-108, 110-112, 113, 117, 119, 120, 121, 126, 128-130
S 33 R_5-Ethyl R_5-*n*-Hexyl R_1-H R_2-O -ethyl-5-*n*-hexylbarbituric acid	None; Hexethal (IN); Sodium hexethal; Calcium hexethal; 0.2-0.4 [c]	Drowsiness; Ataxia; Coma; Stupor	Yes	Yes	Yes	Sedative; Hypnotic; Appears to be out of production; 2-4 (0.5)	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Moderate to high	73, 74, 77, 78, 84, 87, 92-94, 98, 100-108, 110-112, 113, 114, 117, 119, 121, 123, 126, 128-130
S 34 R_5-Methyl R_5-Cyclohexenyl R_1-CH_3 R_2-O 5-(1-cyclohexen-1-yl)-1,5-dimethyl-barbituric acid	Hexobarbital; Sodium hexobarbital; 0.25-0.4 [c]	Drowsiness; Ataxia; Coma; Stupor	No information	No information	Not proved	Intravenous anaesthetic; Hypnotic; 1-4 (0.25)	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Low	73, 74, 77, 78, 79, 86, 87, 91, 98, 100-108, 110-112, 113, 114, 117, 119, 121, 126, 127
S 35 R_5-Methyl R_5-Phenyl R_1-H R_2-O 5-methyl-5-phenylbarbituric acid	None; Méphébarbital (DCF); Heptobarbital (IN)	Drowsiness; Ataxia; Coma; Stupor	Probable	Probable	Probable	Anti-epileptic; Sedative	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Moderate	87, 107, 112, 113
S 36 R_5-Ethyl R_5-Ethyl R_1-Methyl R_2-O 5,5-diethyl-1-methylbarbituric acid	Metharbital	Drowsiness; Coma	Yes	Yes	Yes	Anti-convulsant; Sedative; Hypnotic	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Moderate	77, 78, 79, 86, 92-94, 98, 100-108, 109, 112, 113, 114, 117, 119, 121, 123, 124

[c] Average adult hypnotic dose (in g).

TABLE I. CENTRAL NERVOUS SYSTEM DEPRESSANTS

DIUREIDES (BARBITURATES) (*continued*)

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 37 R_5-2-(Methylthio)-ethyl R_5-1-Methylbutyl R_1-H R_2-S 5-(1-methylbutyl)-5-[(2-methylthio) ethyl]-2-thiobarbituric acid	Methitural; Sodium methitural	Drowsiness; Stupor; Coma; Ataxia; Uninhibited behaviour; Impaired cognition	No information	No information	Not proved	Intravenous anaesthetic; Ultra-short-acting	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Low	73, 74, 77, 78, 79, 86, 92-94, 98, 100-108, 112-114, 117, 120, 121
S 38 R_5-Allyl R_5-1-Methyl-2-pentynyl R_1-Methyl R_2-O (±)-5-allyl-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid (α-form)	Methohexital; Sodium methohexital	Drowsiness; Stupor; Coma; Ataxia; Uninhibited behaviour; Impaired cognition	No information	No information	Not proved	Intravenous anaesthetic; Ultra-short-acting	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Low	77, 78, 79, 86, 92-94, 98, 100-108, 109-115, 117, 119, 121, 124
S 39 R_5-Ethyl R_5-Phenyl R_1-Methyl R_2-O 1-methyl-5-ethyl-5-phenylbarbituric acid	Methylphenobarbital	Drowsiness; Stupor; Coma; Ataxia; Uninhibited behaviour; Impaired cognition	Yes; both "metabolic" (induction of oxidative liver enzymes) and cellular	Yes	Yes	Sedative; Antispasmodic; mild hypnotic; 1-4 (0.25)	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Moderate	73, 74, 77, 78, 79, 86, 92-94, 98, 100-108, 110-112, 113, 115, 117, 119, 121
S 40 R_5-2-Bromoallyl R_5-Isopropyl R_1-Methyl R_2-O 5-(2-bromoallyl)-5-isopropyl-1-methylbarbituric acid	None; Narcobarbital (IN)	Drowsiness; Stupor; Coma; Ataxia; Uninhibited behaviour; Impaired cognition	Probable	Probable	Probable	Hypnotic	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Low to moderate	78, 79, 86, 92-94, 98, 100-108, 109-112, 113, 114, 117, 119, 121
S 41 R_5-Allyl R_5-Neopentyl R_1-H R_2-O 5-allyl-5-neopentylbarbituric acid	Nealbarbital	Drowsiness; Stupor; Coma; Ataxia; Uninhibited behaviour; Impaired cognition	Probable	Probable	Probable	Sedative	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Moderate	—

TABLE I. CENTRAL NERVOUS SYSTEM DEPRESSANTS

DIUREIDES (BARBITURATES) *(continued)*

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 42 R_5-Ethyl R_5-1-Methylbutyl R_1-H R_2-O 5-ethyl-5-(1-methylbutyl)barbituric acid	Pentobarbital; Sodium pentobarbital; Calcium pentobarbital; 0.1-0.2 [c]	Drowsiness; Stupor; Coma; Ataxia; Uninhibited behaviour; Impaired cognition	Yes	Yes	Yes; dog, monkey, man	Hypnotic; 2-4 (0.5)	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	High	73, 74, 77, 78, 79, 80, 86-95, 98, 100-108, 110-112, 113-115, 119, 120
S 43 R_5-Phenyl R_5-Allyl R_1-O R_2-O 5-allyl-5-phenylbarbituric acid	None; Phenallymalum (NFN)	Drowsiness; Stupor; Coma; Ataxia; Uninhibited behaviour; Impaired cognition	Probable	Probable	Probable	Hypnotic	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Moderate to high	73, 74, 77, 86, 87, 103, 113, 123
S 44 R_5-Ethyl R_5-Phenyl R_1-H R_2-O 5-ethyl-5-phenylbarbituric acid	Phenobarbital; 0.1-0.2; [c] Sodium phenobarbital, 0.015-0.1 [c]	Drowsiness; Stupor; Coma; Ataxia; Uninhibited behaviour; Impaired cognition	Yes; both "metabolic" (induction of oxidative liver enzymes) and cellular	Yes	Yes	Sedative; Anticonvulsant; 4-12 (0.5-1)	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Moderate	73, 74, 77, 78, 79, 80, 81-94, 98, 100-108, 110-112, 113-115, 117, 119, 120-124
S 45 R_5-Ethyl R_5-Ethyl R_1-Phenyl R_1-O 5,5-diethyl-1-phenylbarbituric acid	Phetharbital	No information	No information	No information	No information	Anti-epileptic	No information	Low	59
S 46 R_5-Phenyl R_5-2-Piperidylmethyl R_1-H R_2-O 5-phenyl-5-(2-piperydylmethyl) barbituric acid	Prazitone	No information	No information	No information (unlikely)	No information (unlikely)	Anti-depressant; Not in the market	Unknown	None	—
S 47 R_5-Ethyl R_5-Isopropyl R_1-H R_2-O 5-ethyl-5-isopropylbarbituric acid	Probarbital sodium, 0.1-0.2; [c] Calcium probarbital, 0.12-0.25 [c]	Drowsiness; Stupor; Coma; Ataxia; Uninhibited behaviour; Impaired cognition	Yes; both "metabolic" (induction of oxidative liver enzymes) and cellular	Yes	Yes; dog, monkey, man	Hypnotic; 4-12 (0.5-1)	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	High	73, 74, 77, 78, 79, 86, 87, 98, 100-108, 110-114, 117, 119, 121, 123

[c] Average adult hypnotic dose (in g).

TABLE I. CENTRAL NERVOUS SYSTEM DEPRESSANTS

DIUREIDES (BARBITURATES) *(continued)*

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 48 R_5-2-Bromoallyl R_5-Isopropyl R_1-H R_2-O 5-(2-bromoallyl)-5-isopropylbarbituric acid	None; Propallylonal (IN); Ibomalum (NFN)	Drowsiness; Stupor; Coma; Ataxia; Uninhibited behaviour; Impaired cognition	Probable	Probable	Probable	Hypnotic; 2-4 (0.5)	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Moderate to high	77, 79, 86, 87, 92, 103, 105, 107, 113
S 49 R_5-Propyl R_5-Propyl R_1-H R_2-O 5,5-dipropylbarbituric acid	None; Propylbarbital	Drowsiness; Stupor; Coma; Ataxia; Uninhibited behaviour; Impaired cognition	Probable	Probable	Probable	Hypnotic	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Moderate to high	77-79, 86-94, 98, 100-108, 110-113, 117, 119, 121
S 50 R_5-3′,2′,1′-bicyclo-2′-octyn-2′-yl) R_5-Ethyl R_1-H R_2-O 5-[bicyclo(3.2.1)octen-2-yl]-5-ethylbarbituric acid	None; Reposal (MI)	Drowsiness; Stupor; Coma; Ataxia; Uninhibited behaviour; Impaired cognition	Probable	Probable	Probable	Hypnotic	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Moderate to high	87, 101, 105, 111, 113, 117, 119
S 51 R_5-Ethyl R_5-*sec*-Butyl R_1-H R_2-O 5-ethyl-5-*sec*-butylbarbituric acid	Secbutabarbital; Sodium butabarbital; 0.1-0.2 [c]	Drowsiness; Stupor; Coma; Ataxia; Inhibited behaviour; Impaired cognition	Yes; both "metabolic" (induction of oxidative liver enzymes) and cellular	Yes	Yes	Sedative; Hypnotic; 2-4 (0.5)	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	High	73, 74, 77, 78, 79, 80, 86-94, 96, 100-108, 110-115, 117, 119, 121
S 52 R_5-Allyl R_5-1-Methylbutyl R_1-H R_2-O 5-allyl-5-(1-methylbutyl)barbituric acid	Secobarbital; Sodium secobarbital; 0.1-0.2 [c]	Drowsiness; Stupor; Coma; Ataxia; Inhibited behaviour; Impaired cognition	Yes	Yes	Yes; dog, man	Hypnotic; 2-4 (0.5)	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	High	73, 74, 77, 78, 79, 80, 86-95, 96, 106, 110-115, 117, 119, 121

[c] Average adult hypnotic dose (in g).

TABLE I. CENTRAL NERVOUS SYSTEM DEPRESSANTS

DIUREIDES (BARBITURATES) *(continued)*

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 53 R_5 > Spiro-(2′-ethyl-3′ : 5′-dimethylcyclopentane R_5 > R_1-H R_2-O 5-spiro-(2′-ethyl-3′-5′-dimethylcyclopentyl)barbituric acid	None; Spirobarbital	Drowsiness; Stupor; Coma; Ataxia; Inhibited behaviour; Impaired cognition	Probable	Probable	Probable	Hypnotic	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Moderate to high	—
S 54 R_5 > Spiro-(2′-ethyl-3′ : 5′-dimethylcyclopentane) R_5 > R_1-H R_2-S Spiro-(2-ethyl-3,5-dimethylcyclopent-1-yl)-2-thiobarbituric acid	Spirothiobarbital (MI)	Drowsiness; Stupor; Coma; Ataxia; Inhibited behaviour; Impaired cognition	Probable	Probable	Probable	Hypnotic	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Moderate	60
S 55 R_5-Ethyl R_5-*sec*-Butyl R_1-H R_2-O 5-allyl-5-*sec*-butylbarbituric acid	Talbutal; 0.03-0.12 [c]	Drowsiness; Stupor; Coma; Ataxia; Inhibited behaviour; Impaired cognition	Yes	Yes	Yes	Hypnotic	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	High	77-80, 86-94, 96, 100-108, 110-115, 117
S 56 R_5-Ethyl R_5 1-Ethylbutyl R_1-H R_2-O 5-ethyl-5-(1-ethylbutyl)barbituric acid	Tetrabarbital	Drowsiness; Stupor; Coma; Ataxia; Inhibited behaviour; Impaired cognition	Probable	Probable	Probable	Hypnotic	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Moderate to high	77-80, 86-94, 96, 100-108, 110-115, 117, 119,121
S 57 R_5-Allyl R_5-2-Cyclohexen-1-yl R_1-H R_2-S 5-allyl-5-(2-cyclohexen-1-yl)-2-thiobarbituric acid	Thialbarbital	Drowsiness; Stupor; Coma; Ataxia; Inhibited behaviour; Impaired cognition	No information	Probable	Not proved	Intravenous anaesthetic	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Low	77, 79, 82, 83, 84-94, 96, 100-108, 110-115, 117, 119, 121

[c] Average adult hypnotic dose (in g).

TABLE I. CENTRAL NERVOUS SYSTEM DEPRESSANTS

DIUREIDES (BARBITURATES) *(continued)*

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 58 R_5-Allyl R_5-1-Methylbutyl R_1-H R_2-S 5-allyl-5-(1-methylbutyl)-2-thiobarbituric acid, monosodium derivative of	None; Thiamylal sodium (IN)	Drowsiness; Stupor; Coma; Ataxia; Inhibited behaviour; Impaired cognition	No information	No information	Not proved	Intravenous anaesthetic (0.25)	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Low	80, 86-94, 97, 100-108, 110-115, 117, 119, 121
S 59 R_5-Ethyl R_5-Ethyl R_1-H R_2-S 5-5,diethyl-2-thiobarbituric acid	None; Thiobarbital (MI)	Drowsiness; Stupor; Coma; Ataxia; Inhibited behaviour; Impaired cognition	Probable	Probable	Probable	Hypnotic; Probably no longer produced	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Low to moderate	60
S 60 R_5-Ethyl R_5-Hexyl R_1-H R_2-S 5-ethyl-5-hexyl-2-thiobarbituric acid	None; Thiohexethal	Drowsiness; Stupor; Coma; Ataxia; Inhibited behaviour; Impaired cognition	No information	Probable	Not proved	Intravenous anaesthetic	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Low	77-80, 86-94, 98, 100-108, 110-115, 119, 120
S 61 R_5-Allyl R_5-1-Methylpentyn-2-yl R_1-H R_2-S 5-allyl-5-(1-methylpentyn-2-yl)-2-thiobarbituric acid	None; Thiohexital (IN)	Drowsiness; Stupor; Coma; Ataxia; Inhibited behaviour; Impaired cognition	Probable	No information	No information	Hypnotic	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Low	59
S 62 R_5-Ethyl R_5-Butylthiomethyl R_1-H R_2-S 5-ethyl-5-butylthiomethyl-2-thiobarbituric acid	None; Thionarcon (MI)	Drowsiness; Stupor; Coma; Ataxia; Inhibited behaviour; Impaired cognition	Probable	Probable	Not proved	Anaesthetic	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Low	60

TABLE I. CENTRAL NERVOUS SYSTEM DEPRESSANTS

DIUREIDES (BARBITURATES) *(concluded)*

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 63 R_5-Ethyl R_5-1-methylbutyl R_1-H R_2-S 5-ethyl-5-(1-methylbutyl)-2-thiobarbituric acid, monosodium derivative of	Thiopental sodium	Drowsiness; Stupor; Coma; Ataxia; Inhibited behaviour; Impaired cognition	No information	No information	Not proved	Intravenous anaesthetic; Hypnotic; 1-4 (0.25)	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Low	73, 74, 76, 78-80, 86-94, 98, 100-108, 110-114, 119, 120
S 64 R_5-Ethyl R_5-1-Ethylbutyl R_1-H R_2-S 5-ethyl-5-(1-ethylbutyl)-2-thiobarbituric acid	Thiotetrabarbital	Drowsiness; Stupor; Coma; Ataxia; Inhibited behaviour; Impaired cognition	Probable	Probable	Not proved	Intravenous anaesthetic	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Low	74, 87
S 65 R_5-Ethyl R_5-1-Methyl-1-butenyl R_1-H R_2-O 5-ethyl-5-(1-methyl-1-butenyl) barbituric acid	Vinbarbital; 0.1-0.2 [c]	Drowsiness; Stupor; Coma; Ataxia; Inhibited behaviour; Impaired cognition	Yes	Yes	Yes	Hypnotic; 2-4 (0.5)	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	High	77-80, 86-94, 98, 100-108, 110-115, 117, 119, 121
S 66 R_5-1-Methylbutyl R_5-Vinyl R_1-H R_2-O 5-(1-methylbutyl)-5-vinylbarbituric acid	Vinylbital	Drowsiness; Stupor; Coma; Ataxia; Inhibited behaviour; Impaired cognition	Probable	Probable	Probable	Hypnotic; Long-acting	Drunkenness; Potentiation of CNS depressants; Coma; Death; Dependence	Moderate to high	77-80, 86-94, 98, 100-108, 110-115, 117, 119, 121, 123

[c] Average adult hypnotic dose (in g).

Dependence on barbiturates shows all the characteristics listed above. The condition is obviously dangerous to the individual and to public welfare. The individual may be harmed because of falls, etc., while intoxicated; he may set fires and burn while intoxicated; he may die from overdoses; and he may die from abstinence.[94] Public health and welfare may be harmed in many ways. The barbiturate dependent may assault other individuals or he may be responsible for automobile and other accidents. He cannot work efficiently and may become a parasite on his family or a public charge. He may be a source of " infection " and spread his dependence to other persons.

It is, of course, recognized that, like all forms of drug dependence, barbiturate dependence has a spectrum ranging from mild (use of barbiturates at night only) to severe (use of amounts sufficient to maintain a continuous high degree of intoxication). The severity of the dependence may also vary with the drug, although this is difficult to document.

Types of abuse range from occasional sprees to continued heavy drug-taking for months or years. Barbiturates are usually taken orally, but some dependents inject them.

Types of persons who become barbiturate abusers include neurotics who usually get their drugs from legal sources, alcoholics who substitute or supplement their alcohol with barbiturates, stimulant abusers who take barbiturates as antidotes to the stimulants, persons dependent on opiates and young thrill-seeking adolescents.

In the United States of America, the illicit market in barbiturates is probably quite large. The Food and Drug Administration has estimated that there are 500 000 barbiturate abusers in that country.[283] The illicit market is supplied chiefly by diversion from legal sources. There is no evidence of illicit manufacture. Some of the illicit market in the USA has been supplied by export of drugs manufactured in the USA to other countries with subsequent smuggling of the drugs back into the USA, largely by US citizens. Less is known about illicit traffic in other countries.

Sixty-five barbiturates are listed in Table I (barbituric acid is not counted since it is not a hypnotic drug but a chemical placed in the table in order to facilitate chemical naming). Of the 65 drugs, 12 are anaesthetic thiobarbiturates: buthalital (S 15); butylethylthiobarbituric acid (S 17); 5-cyclohexen-1-yl-5-methylbarbituric acid (S 20); 5-ethyl-5-(3-methylbutyl)-2-thiobarbituric acid (S 28); methitural (S 37); methohexital (S 38); thialbarbital (S 57); thiamylal (S 58); thiohexethal (S 60); thionarcon (S 62); thiopental (S 63); and thiotetrabarbital (S 64).

No documentation of abuse of or dependence on these anaesthetics could be found and they have not been studied for dependence potential in animals.

It is believed that their dependence potential is low or non-existent. In addition most of these compounds are sold only to hospitals, physicians, dentists and veterinarians in vials for anaesthetic use only, with resultant limited availability. Other short-acting anaesthetics compounds, hexobarbital (S 34) and thiopental (S 63), are marketed as hypnotics as well as anaesthetics, but no documentation of abuse was found.

Efforts to find compounds closely related to barbiturates which might antagonize their effects have led to several 5-alkyl-5-allylbarbituric acids with branchings at the unsaturated 3-position of the allyl group, for example, 5-ethyl-5-(2-cyclohexyl-idenylethyl)barbituric acid (S 25), which is a typical central nervous system stimulant (British Patent 701.660, 1958). In addition, bucolome (S 11), 5 - ethyl - 5-phenyl - 1(2-diethylaminoethyl)barbituric acid (S 29), and prazitone (S 46), are said to be devoid of sedative and hypnotic effects and are suggested for use for other purposes. There is probably no need to control barbituric acid derivatives which are devoid of sedative or hypnotic properties unless abuse should be documented or other means are devised to detect any possible abuse liability they may have. Moreover, the convulsant barbiturates are not likely to be manufactured and sold.

All the remaining compounds must be regarded as having some dependence potential. Barbital (S 7) and phenobarbital (S 44) warrant special mention. These were the first barbiturates to be used and were the first recognized to cause dependence.

Physical dependence can be induced more readily in dogs [88, 89, 92] and monkeys on barbital and phenobarbital than on the shorter and more rapidly acting hypnotic barbiturates such as pentobarbital (S 42). Physical dependence on barbital [116, 119, 120, 125] and phenobarbital [119, 120, 122, 124] can be severe in man. At one time abuse of barbital and phenobarbital was not uncommon, but, since the development of the rapidly acting hypnotics, cases of dependence on barbital and phenobarbital have become quite rare. Accordingly barbital and phenobarbital must be judged to have much lower dependence potential than the potent, quickly acting barbiturates despite

high physical dependence capacity. This is a good example of psychic dependence being a more potent factor in total dependence potential than physical dependence. Other long-acting barbiturates that are used primarily as sedatives and antiepileptics (compounds: barbexaclone (S 6); heptobarbital (S 35); metharbital (S 36); methylphenobarbital (S 39); narcobarbital (S 40); and phetharbital (S 45)) undoubtedly have, by pharmacological analogy, low to moderate abuse-potential similar to barbital and phenobarbital.

In contrast, the rapidly acting hypnotic barbiturates must be judged to have moderate to high dependence liability. Ample clinical, experimental or both clinical and experimental documentation is available for compounds S 4, amobarbital; [72, 79, 86, 106] S 19, cyclobarbital; [115, 119, 120] S 42, pentobarbital; [79, 86, 93, 95, 106] and S 52, secobarbital.[93, 95, 106] The fact that good documentation is available for these four compounds should not be construed as indicating that their dependence potential is greater than that of the other hypnotic barbiturates. It probably means only that they have been popular drugs, have had very large sales and, therefore, have been available to more people than the other hypnotics. By analogy, all other barbiturates marketed principally for hypnotic use must be regarded as having moderate to high dependence potential despite relative lack of documentation: allobarbital (S 2); 5-allyl-5-*n*-butyl-barbituric acid (S 3); brallobarbital (S 8); 5-(2-bromoallyl)-5-(1-methylbutyl)barbituric acid (S 9); brophébarbital (S 10); butalbital (S 12); butallylonal (S 13); crotarbital (S 14); butobarbital (S 16); cyclopentobarbital (S 21); 5-(1,3-dimethylbutyl)-5-ethylbarbituric acid (S 22); enallypropymal (S 23); ethallobarbital (S 24); 5-ethyl-5-cyclopentenylbarbituric acid (S 26); 5-ethyl-5-(1-piperidyl)barbituric acid (S 30); 5-furfuryl-5-isopropylbarbituric acid (S 31); heptabarb (S 32); hexethal (S 33); nealbarbital (S 41); propallylonal (S 48); propylbarbital (S 49); secbutabarbital (S 51); spirobarbital (S 53); talbutal (S 55); tetrabarbital (S 56); thiobarbital (S 59); vinbarbital (S 65); and vinylbital (S 66).

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MONOUREIDES

This is a group of very weak, slowly acting sedatives (Table II), some of which act by releasing bromine. In many countries, they are nearly obsolete and not readily available. A small number of cases of abuse can be documented for carbromal (S 70), bromisoval (S 69) and acecarbromal (S 67) and a few cases still seem to be occurring in some countries. They are not known to cause physical dependence. All three can cause bromide poisoning. No reference to abuse of the compound ectylurea (S 71), which does not contain bromine, was found. None of these compounds has had a thorough evaluation for dependence liability in animals.

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HALOGENS

Bromine is the only relevant representative of this class. At one time bromide poisoning was quite common; today it is rare but still occurs occasionally [140-144]. Bromides appear to cause only mild psychic dependence, no physical dependence and no tolerance. Bromides cause direct psychotoxicity manifested by drowsiness, impaired cognition, confusion, agitation, ideas of persecution and hallucinations. The dependence potential of bromides appears to be quite low.

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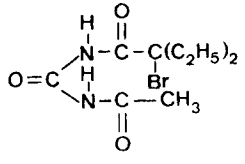
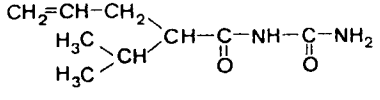
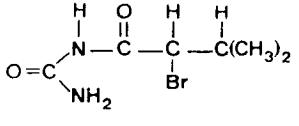
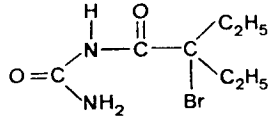
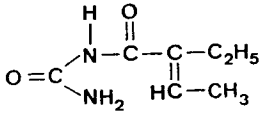
1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 67  1-acetyl-3-(α-bromo-α-ethylbutyryl)urea	Acecarbromal	Drowsiness; Ataxia; Psychosis; Bromide poisoning	No information	Yes	No information	Sedative; Releases bromide	Chronic toxicity, bromide type	Low	—
S 68  2-allyl-2-isopropylacetylurea	None; Apronalum (NFN); Apronalide (DCF)	Drowsiness; Ataxia	No information	No information	No information	Hypnotic	Drowsiness; Chronic toxicity; Thrombocytopenia	Unknown	131, 135
S 69  2-bromo-3-methylbutyrylurea	Bromisoval	Drowsiness; Ataxia; Psychosis	No information	Yes	No information	Sedative; Acts by releasing bromide	Chronic toxicity bromide type	Low	133

[a] International Nonproprietary Name proposed by the World Health Organization, if any, or other nonproprietary name, if any; if there is no nonproprietary name, the main entry in the *Subsidia Pharmaceutica Index Nominum* or in the *Merck Index* or other generally accepted name. "None" indicates that an International Nonproprietary Name has not been proposed so far. The following abbreviations show the source of the name used: BAN = British Approved Name; DCF = Dénomination commune française; IN = *Subsidia Pharmaceutica Index Nominum*; MI = *Merck Index*, 8th ed.; NFN = Nordisk Farmakopénaevn.

[b] Current therapeutic use and indications.

TABLE II. CENTRAL NERVOUS SYSTEM DEPRESSANTS

MONOUREIDES *(continued)*

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 70  2-bromo-3-ethylbutyrylurea	Carbromal	Drowsiness; Ataxia; Bromide poisoning; Psychosis	No information	Yes	No information	Sedative of very little use; Acts by releasing bromide	Chronic toxicity, bromide type	Low	132, 134, 136, 138, 139
S 71  *cis*-(2-ethylcrotonyl)urea	Ectylurea	Drowsiness; Ataxia	No information	Yes	No information	Sedative	Chronic toxicity	Low	135

CHLORAL AND DERIVATIVES

Apart from opium and alcohol, chloral hydrate (compound S 77; Table III) is the oldest of the central nervous system depressants. As might be expected, chloral was considerably abused in the latter part of the nineteenth century. Algernon Swinburne and Dante Gabriel Rossetti were said to be distinguished habitués of chloral. After the barbiturates were introduced, chloral lost popularity and the degree of abuse of it is now low.

The case for chloral causing dependence of the barbiturate-alcohol type is quite conclusive. A number of reports [145, 147] of delirium following withdrawal after long-maintained abuse exist. Chloral has been shown to suppress abstinence from barbital in dogs. Accordingly, chloral must be regarded as having moderate to high dependence potential.

As indicated in Table III, chloral is transformed into trichlorethanol in the body [147] and since trichlorethanol is the active metabolite of chloral, it must be judged to have the same liability for abuse as chloral. The other compounds (No. S 72–S 76 and S 78–S 93) are either hydrolysed to chloral in the gastrointestinal tract or are pharmacologically similar. Accordingly, they must be regarded, by analogy, as having dependence liability equal to that of chloral, except S 72, S 73 and S 81 which are rated "low" because of other pharmacological properties.

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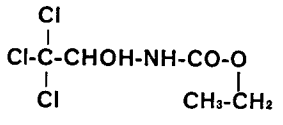
150. Sharpless, S. K. (1965) In: Goodman, L. S. & Gilman, A., ed., *The pharmacological basis of therapeutics*, 3rd ed., pp. 129-142, Macmillan Co., New York (Chapter 10: Hypnotics and sedatives. II. Miscellaneous agents)

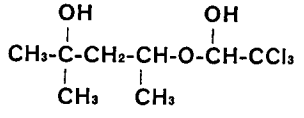
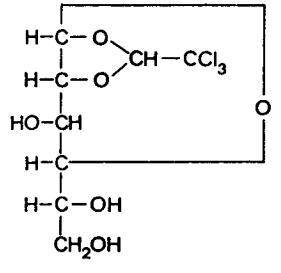
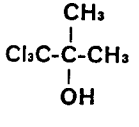
1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 72 $C \cdot Br_3CHO$ Tribromoacetaldehyde	None; Bromal (MI)	Drowsiness; Ataxia; Drunken behaviour	No information	Yes (presumed)	No information	Hypnotic	Chronic toxicity; Drunkenness; Coma	Low	145-150
S 73 $C \cdot Br_3CH(OH)_2$ Tribromoacetaldehyde hydrate	None; Bromal hydrate (MI)	Drowsiness; Ataxia; Drunken behaviour	No information	Yes (presumed)	No information	Hypnotic; Sedative	Chronic toxicity; Drunkenness; Coma	Low	60, 145-150
S 74 $CH_3CH\ Cl \cdot C\ Cl_2 \cdot CH(OH)_2$ 2,2,3-trichlorobutane-1,1-diol	None; Butylchloral hydrate (MI)	Drowsiness; Ataxia; Drunken behaviour	No information	Yes (presumed)	No information	Sedative; Hypnotic	Drunkenness; Coma	High if other depressants controlled and chloral derivatives available (presumed)	60, 145-150
S 75  (2,2,2-trichloro-1-hydroxyethyl)ethyl carbamate	Carbocloral	Drowsiness; Ataxia; Drunken behaviour	Possible but not established	Moderate (presumed)	No information	Hypnotic	Drunkenness; Coma	High if other depressants controlled and chloral derivatives available (presumed)	40
S 76 $HCONH \cdot CH(OH)C \cdot Cl_3$ *N*-(2,2,2-trichloro-1-hydroxyethyl) formamide	None; Chloral formamide (MI)	Drowsiness; Ataxia; Drunken behaviour	Probable but not established	Moderate (presumed)	Insomnia; Nervousness; Agitation; Convulsions; Delirium	Hypnotic; Herbicidal activity	Drunkenness; Coma	High if other depressants controlled and chloral derivatives available (presumed)	60, 145-150
S 77 $C \cdot Cl_3 \cdot CH \cdot (OH)_2$ 2,2,2-trichloro-1,1-ethanediol	None; Chloral hydrate (MI)	Drowsiness to coma; Ataxia; Drunken behaviour	Probable but not established	Moderate	Insomnia; Nervousness; Agitation; Convulsions; Delirium	Hypnotic	Drunkenness; Coma and death	High if other depressants controlled and chloral derivatives available	60, 145-150

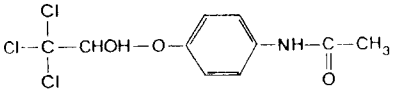
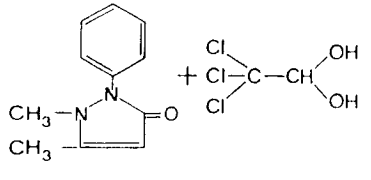
[a] International Nonproprietary Name proposed by the World Health Organization, if any, or other nonproprietary name, if any; if there is no nonproprietary name, the main entry in the *Subsidia Pharmaceutica Index Nominum* or in the *Merck Index* or other generally accepted name. " None " indicates that an International Nonproprietary Name has not been proposed so far. The following abbreviations show the source of the name used: BAN = British Approved Name; DCF = Dénomination commune française; IN = *Subsidia Pharmaceutica Index Nominum*; MI = *Merck Index*, 8th ed.; NFN = Nordisk Farmakopénaevn.

[b] Current therapeutic use and indications.

TABLE III. CENTRAL NERVOUS SYSTEM DEPRESSANTS

CHLORAL AND DERIVATIVES *(continued)*

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 78 $C \cdot Cl_3CH = NH$ Chloralimide, product of decomposition of chloral formamide (**S 76**)	None; Chloralimide	Drowsiness; Ataxia; Drunken behaviour	Probable but not established	Moderate (presumed)	Insomnia; Nervousness; Agitation; Convulsions; Delirium	Not used	Drunkenness; Coma	High if other depressants controlled and chloral derivatives available (presumed)	145-150
S 79  2-methyl-4-(2,2,2-trichloro-1-hydroxyethoxy)-2-pentanol	Chloralodol	Drowsiness	Probable but not established	Moderate (presumed)	Insomnia; Nervousness; Agitation; Convulsions; Delirium	Hypnotic (Hydrolysed to chloral hydrate in stomach)	Drunkenness; Coma	High if other depressants controlled and chloral derivatives available (presumed)	149, 150
S 80  α-mono-trichloraethyliden-D-glucose	None; Chloralose (DCF); α-Chloralose (MI)	Drowsiness; Ataxia; Drunken behaviour	Probable but not established	Moderate (presumed)	Insomnia; Nervousness; Agitation; Convulsions; Delirium	Hypnotic; Sedative; Laboratory anaesthetic	Drunkenness; Coma and death	High if other depressants controlled and chloral derivatives available (presumed)	60, 149, 150
S 81  1,1,1-trichloro-2-methyl-2-propanol	Chlorobutanol	Drowsiness; Ataxia	Probable but not established	No information	Not established	Hypnotic; Antiemetic; Bacteriostatic	Drunkenness; Coma	Low or non-existent	149, 150

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 82  β,β,β-trichloro-α-hydroxy-*p*-acetophenetidide	Cloracetadol	Drowsiness; Ataxia; Drunken behaviour	Probable but not established	Moderate (presumed)	Insomnia; Nervousness; Agitation; Convulsions; Delirium	Analgesic; Hypnotic; Sedative	Drunkenness; Coma	High if other depressants controlled and chloral derivatives available (presumed)	66
S 83 $C \cdot Cl_3 \cdot CH \cdot (OH)_2 \cdot COCH_2N(CH_3)_3O$ chloral hydrate compound with betaine	Cloral betaine	Drowsiness; Ataxia; Drunken behaviour	Probable but not established	Moderate (presumed)	Insomnia; Nervousness; Agitation; Convulsions; Delirium	Hypnotic (Hydrolysed to chloral hydrate in gastro-intestinal tract)	Drunkenness; Coma	High if other depressants controlled and chloral derivatives available (presumed)	149, 150
S 84 $CCl_3CH_2OCOOCH_2CCl_3$ bis(2,2,2-trichloroethyl)carbonate	Cloretate	Drowsiness; Ataxia; Drunken behaviour	Probable but not established	Moderate (presumed)	Insomnia; Nervousness; Agitation; Convulsions; Delirium	Sedative; Hypnotic	Drunkenness; Coma	High if other depressants controlled and chloral derivatives available (presumed)	40
S 85  Compound of 2,3-dimethyl-1-phenyl-3-pyrazolin-5-one with chloral hydrate	None; Dichloralphenazone (BAN)	Drowsiness; Ataxia; Drunken behaviour	Probable but not established	Moderate (presumed)	Unknown	Hypnotic	Drunkenness	High if other depressants controlled and chloral derivatives available (presumed)	40

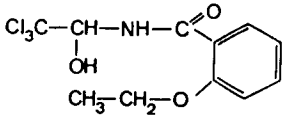
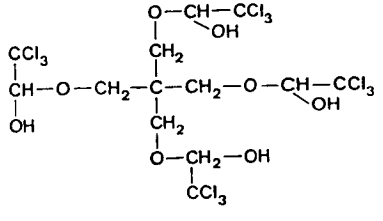
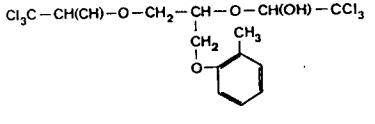
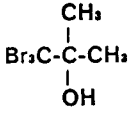
1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 86  *O*-ethyl-*N*-(2,2,2-trichloro-1-hydroxyethyl)salicylamide	None	Unknown	Probable but not established (presumed)	Moderate (presumed)	Unknown	Hypnotic	Unknown	High if other depressants controlled and chloral derivatives available (presumed)	40
S 87  1,1',1'',1'''-(neopentanetetryltetraoxy) tetrakis-(2,2,2-trichlorethanol)	Petrichloral	Drowsiness; Ataxia; Drunken behaviour	Probable but not established	Moderate (presumed)	Unknown	Hypnotic (Hydrolysed to chloral hydrate in gastro-intestinal tract)	Drunkenness; Coma	High if other depressants controlled and chloral derivatives available (presumed)	149, 150
S 88  1,1'-(3-*o*-tolyloxypropylenedioxy)-bis (2,2,2-trichloroethanol)	Toloxychlorinol	Drowsiness	Probable but not established	Moderate (presumed)	Insomnia; Nervousness; Agitation; Convulsions; Delirium	Hypnotic	Drunkenness; Coma	High if other depressants controlled and chloral derivatives available (presumed)	—
S 89  1,1,1-tribromo-2-methyl-2-propanol	None	Drowsiness; Ataxia; Drunken behaviour	Probable but not established (presumed)	Moderate (presumed)	Insomnia; Nervousness; Agitation; Convulsions; Delirium	Sedative	Drunkenness; Coma	High if other depressants controlled and chloral derivatives available (presumed)	40

TABLE III. CENTRAL NERVOUS SYSTEM DEPRESSANTS

CHLORAL AND DERIVATIVES *(concluded)*

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 90 $C \cdot Cl_3 \cdot CH_2 \cdot OH$ 2,2,2-trichlorethanol	None; Trichlorethanol	Drowsiness; Ataxia; Drunken behaviour	Probable but not established	Moderate (presumed)	Insomnia; Nervousness; Agitation; Convulsions; Delirium	Proposed as basal anaesthetic; Hypnotic (Is the active metabolite of chloral)	Drunkenness; Coma	High if other depressants controlled and chloral derivatives available (presumed)	145-150
S 91 $Cl_3C\text{-}CHOH\text{-}NH\text{-}C_6H_5\text{-}COOH$ *p*-(2,2,2-trichloro-1-hydroxyethylamino) benzoic acid	None	Unknown	Probable but not established (presumed)	Moderate (presumed)	Unknown	Hypnotic	Unknown	High if other depressants controlled and chloral derivatives available (presumed)	40
S 92 $Cl_3\text{-}C\text{-}CHOH\text{-}CH_3$ 1,1,1-trichloro-2-propanol	None	Drowsiness; Ataxia; Drunken behaviour	Probable but not established (presumed)	Moderate (presumed)	Insomnia; Nervousness; Agitation (presumed)	Hypnotic	Drunkenness; Coma	High if other depressants controlled and chloral derivatives available (presumed)	40
S 93 $C \cdot Cl_3CH_2 \cdot O \cdot P \cdot O \cdot (OH)_2$ 2,2,2-trichlorethyl dihydrogen phosphate	Triclofos	Drowsiness; Ataxia; Drunken behaviour	Probable but not established	Moderate (presumed)	Insomnia; Nervousness; Agitation; Convulsions; Delirium	Sedative; Hypnotic (Hydrolysed to trichlorethanol in body)	Drunkenness; Coma	High if other depressants controlled and chloral derivatives available (presumed)	145-150

TERTIARY ACETYLENIC ALCOHOLS

Only two compounds are listed (Table IV). Of these, methylpentynol (S 95) is a weak, short-acting hypnotic. Sales have been low and few instances of abuse have been reported.[155, 157] The other compound, ethchlorvynol (S 94) is more potent and instances of abuse are more frequent. There is strong clinical documentation for abrupt withdrawal of ethchlorvynol being followed by convulsions and delirium.[151-154, 156] Accordingly, ethchlorvynol must be judged to have moderate abuse potential and methylpentynol must, by analogy, be regarded as having dependence potential equivalent to that of ethchlorvynol.

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153. Essig, C. F. (1964) *Clin. Pharmacol.*, **5**, 334 (Addiction to sedatives and tranquilizers)
154. Government of the United States of America, US Food and Drug Administration (1965) Background material supplied to Advisory Committee on Abuse of Stimulant and Depressant Drugs, 27 December 1965, Washington, D.C.
155. Hitsche, B. & Herbst, A. (1967) *Psychiat. et Neurol. (Basel)*, **153**, 308-318 (Beobachtungen bei Missbrauch von Methylpentinol)
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CYCLIC ETHERS

The only compound in this group is paraldehyde (cyclic ether of acetaldehyde). Production is modest. Paraldehyde has little use except in the treatment of abstinence from alcohol. It is, of course, difficult to take because of its unpleasant odour and irritant properties. There is no question but that it can produce dependence of the barbiturate-alcohol type, and the clinical literature contains a number of case reports of paraldehyde dependence with convulsions and delirium occurring on withdrawal.[158-162] The number of cases of abuse of paraldehyde is low, and the cases generally involve alcoholics who use it to reinforce or substitute for alcohol. There is no known illicit traffic in paraldehyde. Paraldehyde has been shown to suppress abstinence from barbital in dogs physically dependent on barbital. The abuse potential of paraldehyde is low but definite.

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160. Mendelson, J., Wexler, D., Leiderman, P. H. & Solomon, P. (1957) *Quart. J. Stud. Alcohol*, **18**, 561 (A study of addiction to non-ethyl alcohols and other poisonous compounds)
161. Nothass (1920) *Allg. Z. Psychiat.*, **76**, 826 (Paraldehyd-psychosen)

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 94 $CH_3CH_2\text{-}C(OH)(C\equiv CH)\text{-}CH=CHCl$ ethyl-β-chlorovinylethinylcarbinol	None; Ethchlorvynol (BAN)	Drowsiness; Ataxia; Drunkenness; Stupor; Coma	Not proven	Yes	Yes; Convulsions and delirium	Hypnotic	Drunkenness; Dependence; Coma	Moderate	151-154, 156
S 95 $HC\equiv C\text{-}C(OH)(CH_3)\text{-}CH_2CH_3$ 3-methyl-1-pentyn-3-ol	Methylpentynol	Drowsiness; Ataxia; Drunkenness; Stupor; Coma	Not proven	Yes	Yes; Convulsions and delirium	Hypnotic	Drunkenness; Dependence; Coma	Moderate	155, 157

[a] International Nonproprietary Name proposed by the World Health Organization, if any, or other nonproprietary name, if any; if there is no nonproprietary name, the main entry in the *Subsidia Pharmaceutica Index Nominum* or in the *Merck Index* or other generally accepted name. " None " indicates that an International Nonproprietary Name has not been proposed so far. The following abbreviations show the source of the name used: BAN = British Approved Name; DCF = Dénomination commune française; IN = *Subsidia Pharmaceutica Index Nominum*; MI = *Merck Index*, 8th ed.; NFN = Nordisk Farmakopénaevn.

[b] Current therapeutic use and indications.

CARBAMIC ACID ESTERS OF MONOHYDROXY ALCOHOLS

Of the six compounds listed in Table V, only ethinamate (S 100) seems to have significant use at the present time. The fact that ethinamate can cause dependence of the barbiturate-alcohol type is well documented in the clinical literature.[163, 164] Ethinamate has not had an adequate evaluation for abuse liability in experimental animals. At present there seems to be little or no illicit traffic in the drug. Accordingly, ethinamate is rated as having moderate abuse potential.

The remainder of the group (S 96–S 99 and S 101) appear to be obsolete and out of production in most of the world. No documentation is available respecting their abuse potential. Compound S 101, urethan, is used only for animals. If compounds S 96 to S 99 were to be used again in significant amounts, they would, by chemical and pharmacological analogy, have to be suspected as probably having the same degree of abuse potential as ethinamate.

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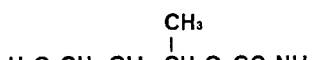
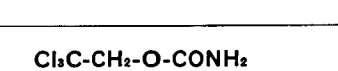
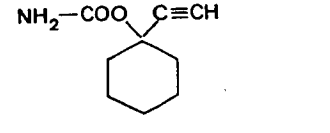
163. Ellinwood, E. H., Ewing, J. A. & Hoaken, P. C. S. (1962) *New Engl. J. Med.*, **266**, 185-186 (Habituation of ethinamate)

164. Essig, C. F. (1964) *Clin. Pharmacol. Therap.*, **5**, 334 (Addiction to nonbarbiturate sedative and tranquilizing drugs)

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 96 $H_2NCOOC(CH_3)_2C_2H_5$ Carbamic acid ester of 1,1-dimethylpropylalcohol	None; Amyl carbamate, tertiary (MI)	Drowsiness; Ataxia; Drunkenness; Stupor; Coma	Probable	Yes	Yes	Hypnotic; No use; No production	Intoxication; Death; Dependence	Moderate	60, 149, 150
S 97  Carbamic acid ester of methylpropylcarbinol	None	Drowsiness; Ataxia; Drunkenness; Stupor; Coma	Probable	Yes	Yes	Hypnotic	Intoxication; Death; Dependence	Moderate	149, 150
S 98 $Cl_3C\text{-}CH_2\text{-}O\text{-}CONH_2$ Carbamic acid ester of 2,2,2-trichlorethanol	None; Trichlorourethan (MI)	Drowsiness; Ataxia; Drunkenness; Stupor; Coma	Probable	Yes	Yes	Hypnotic	Intoxication; Death; Dependence	Moderate	60, 149, 150
S 99  Carbamic acid ester of 1,3-dichloropropanol	None	Drowsiness; Ataxia; Drunkenness; Stupor; Coma	Probable	Yes	Yes	Hypnotic	Intoxication; Death; Dependence	Moderate	149, 150
S 100  1-ethynylcyclohexanol carbamate	Ethinamate	Drowsiness; Stupor; Coma; Ataxia	Probable	Yes	Yes; Convulsions and delirium	Hypnotic	Intoxication; Death; Dependence	Moderate	162, 163, 164
S 101 $NH_2COOC_2H_5$ Ethyl carbamate	None; Urethan (MI)	Drowsiness; Narcosis; Coma	Probable	Yes	Yes	Hypnotic; No use, except in laboratory	Intoxication; Death; Dependence	Moderate	149, 150

[a] International Nonproprietary Name proposed by the World Health Organization, if any, or other nonproprietary name, if any; if there is no nonproprietary name, the main entry in the *Subsidia Pharmaceutica Index Nominum* or in the *Merck Index* or other generally accepted name. " None " indicates that an International Nonproprietary Name has not been proposed so far. The following abbreviations show the source of the name used: BAN = British Approved Name; DCF = Dénomination commune française; IN = *Subsidia Pharmaceutica Index Nominum*; MI = *Merck Index*, 8th ed.; NFN = Nordisk Farmakopénaevn.

[b] Current therapeutic use and indications.

CARBAMIC ACID ESTERS OF GLYCOLS

Of the drugs listed in Table VI, carisoprodol (S 103), emylcamate (S 104), mebutamate (S 107) and phenprobamate (S 110) are not used primarily as central nervous system depressants but are recommended either for hypertension (S 107) or as " muscle relaxants " (S 103, S 104 and S 110). Some newly introduced drugs, buramate (S 102) and pentabamate (S 109), have been marketed as " tranquillizers " and hexapropymate (S 105) and oxyfenamate (S 106) are used as sedatives. All these are weak drugs and have not been abused or shown to have abuse potential in animal or human experiments.

Tybamate (S 111) used as a sedative has had an especially good animal and experimental work-up for abuse potential.[167, 170, 174, 187] It appears to be a very weak, short-acting drug of no or very low dependence liability.

Meprobamate (S 108) is an entirely different case. It is a fairly potent central nervous system depressant which, pharmacologically, is similar to the barbiturates. Cases of dependence of the barbiturate-alcohol type were reported shortly after the drug was marketed and are still occurring. [168, 169, 172, 173, 175, 177-182, 185] Meprobamate has been shown to produce physical dependence in the dog [171] manifest by convulsions and canine " delirium " on withdrawal. Meprobamate has also been shown to suppress abstinence from barbital in dogs.

An extensive illicit traffic in meprobamate developed in the United States of America which was supplied by diversion from legal channels.

Accordingly meprobamate must be rated as having moderate to high potential for dependence of the barbiturate-alcohol type.

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167. Berger, F. M., Kletzkin, M. & Margolin, S. (1964) *Med. exp. (Basel)*, **10**, 327 (Pharmacologic properties of a new tranquilizing agent, 2-methyl-2-propyl-trimethylene butylcarbamate carbamate (tybamate))
168. Bulla, J. D., Ewing, J. A. & Buffaloe, W. J. (1959) *Amer. Practit.*, **10**, 1961 (Further controlled studies of meprobamate)
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170. Domino, E. F. (1965) In: DiPalma, J. R., ed., *Drill's pharmacology in medicine*, 3rd ed., pp. 356-364, McGraw-Hill, New York (Chapter 24: Psychosedative drugs. II. Meprobamate, chlordiazepoxide and miscellaneous agents)
171. Essig, C. F. (1958) *Arch. Neurol. Psychiat. (Chic.)*, **80**, 414-417 (Withdrawal convulsions in dog following chronic meprobamate intoxication)
172. Essig, C. F. & Ainslie, J. D. (1957) *J. Amer. med. Ass.*, **164**, 1382 (Addiction to meprobamate)
173. Ewing, J. A. & Haizlip, T. M. (1958) *Amer. J. Psychiat.*, **114**, 835-836 (A controlled study of the habit forming propensities of meprobamate)
174. Feldman, H. S. & Mulinos, M. G. (1966) *J. New Drugs*, **6**, 354 (Lack of addiction from high doses of tybamate)
175. Frangipane, M. (1963) *Friuli med.*, **18**, 737-741 (A case of toxicomania caused by meprobamate)
176. Fraser, H. F., Essig, C. F. & Wolbach, A. B. (1961) *Bull. Narcot.*, **13**, No. 4, 3-7 (Evaluation of carisoprodol and phenyramidol for addictiveness)
177. Haizlip, T. M. & Ewing, J. A. (1958) *New Engl. J. Med.*, **258**, 1181 (Meprobamate habituation. A controlled clinical study)
178. Held, H. & Oldershausen, H. F. V. (1969) *Klin. Wschr.*, **47**, 78-80 (Zur Pharmakokinetik von Meprobamat bei chronischer Hepatopatien und Arzneimittelsucht)
179. Hollister, L. E. & Glazener, F. S. (1960) *Psychopharmacologia (Berl.)*, **1**, 336 (Withdrawal reactions from meprobamate alone and combined with promazine)
180. Lemere, F. (1956) *Arch. Neurol. Psychiat. (Chic)*, **76**, 205 (Habit forming properties of meprobamate)
181. Phillips, R. M., Judy, F. R. & Judy, H. E. (1957) *Northw. Med. (Seattle)*, **56**, 453 (Meprobamate addiction)
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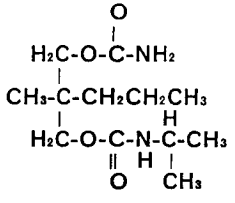
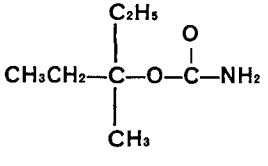
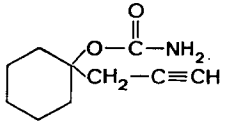
183. Shelton, J. & Hollister, L. E. (1967) *J. Amer. med. Ass.*, **199**, 338 (Simulated abuse of Tybamate in man. Failure to demonstrate withdrawal reactions)

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 102 $HO\text{-}CH_2\text{-}CH_2\text{-}O\text{-}CO\text{-}NH\text{-}CH_2$ Benzylcarbamic acid, 2-hydroxyethyl ester	Buramate	Drowsiness	No information	Unknown	No information	Tranquillizer; Antiepileptic (hyperkinesis, hypothalamic spasms)	No information	Very low	—
S 103  2-methyl-2-propyl-1,3-propanediol carbamate isopropylcarbamate	Carisoprodol	Drowsiness	Unknown	Unknown	Unknown	"Muscle relaxant"	Drowsiness	Very low	165, 176
S 104  3-methyl-3-pentanol carbamate	Emylcamate	Drowsiness	No information	Not reported	Unknown	Sedative; "Muscle relaxant"; Very little production	Drowsiness	Very low	170
S 105  Carbamic acid, 1-(1-propynyl)cyclohexyl ester	Hexapropymate	Drowsiness	No information	Unknown	No information	Tranquillizer	No information	Very low	—

[a] International Nonproprietary Name proposed by the World Health Organization, if any, or other nonproprietary name, if any; if there is no nonproprietary name, the main entry in the *Subsidia Pharmaceutica Index Nominum* or in the *Merck Index* or other generally accepted name. "None" indicates that an International Nonproprietary Name has not been proposed so far. The following abbreviations show the source of the name used: BAN = British Approved Name; DCF = Dénomination commune française; IN = *Subsidia Pharmaceutica Index Nominum*; MI = *Merck Index*, 8th ed.; NFN = Nordisk Farmakopénaevn; USAN = US Adopted Name.

[b] Current therapeutic use and indications.

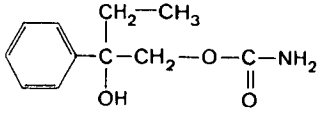
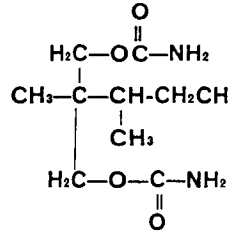
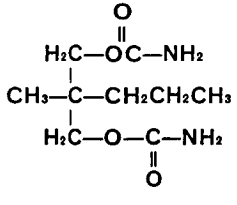
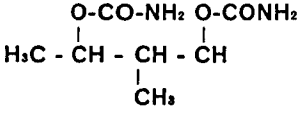
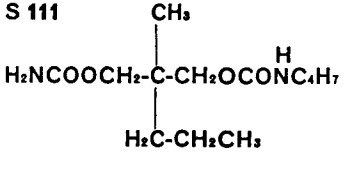
1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of inoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 106  β-ethyl, β-hydroxyphenethyl carbamate	Oxyfenamate; Hydroxyphenamate (USAN)	Drowsiness	No information	Unknown	No information	Sedative; Antidepressant	Drowsiness; Potentiation of CNS depressants	Very low	150, 170
S 107  2-*sec*-butyl-2-methyl-1,3-propanediol dicarbamate	Mebutamate	Drowsiness	Unknown	Unknown	Unknown	Hypertension; Only small-scale	Drowsiness; Very weak drug	Very low	170
S 108  2-methyl-2-propyl-1,3-propanediol dicarbamate	Meprobamate	Drowsiness; Stupor; Coma; Ataxia	Yes	Yes	Yes; Convulsions and delirium	"Minor tranquillizer"; Sedative	Drunkenness; Potentiation of other depressants; Death; Dependence	High	165, 166, 168-173, 175, 177-182, 184-186
S 109  3-methyl-2,4-pentanediol dicarbamate	Pentabamate	Drowsiness	No information	Unknown	No information	Tranquillizer	No information	Very low	—

TABLE VI. CENTRAL NERVOUS SYSTEM DEPRESSANTS

CARBAMIC ACID ESTERS OF GLYCOLS *(concluded)*

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 110 $C_5H_5(CH_2)_3$-O-$CONH_2$ 3-phenyl-1-propanol carbamate	Phenprobamate	Drowsiness	No information	Unknown	No information	"Muscle relaxant"; Tranquillizer	No information	Very low	—
S 111  2-methyl-2-propyltrimethylene butylcarbamate carbamate	Tybamate	Drowsiness; Ataxia	Unknown	Unknown	None proved	Sedation	Drowsiness; Potentiation of other depressants	Very low	167, 170, 174, 183, 187

184. Swanson, L. A. & Okada, T. (1963) *J. Amer. med. Ass.*, **184**, 780 (Death after withdrawal of meprobamate)
185. Taddei, J. & Parmi, E. (1959) *Boll. Soc. ital. Biol. sper.*, **35**, 211-214 (Pharmacological observation on the meprobamate habit)
186. Wilson, J. C. (1963) *Amer. J. Psychiat.*, **120**, 600-601 (Status epilepticus associated with withdrawal from deprol (meprobamate and benactyzine))
187. Veress, F., Major, V., Fink, M. & Freedman, A. M. (1969) *J. clin. Pharmacol.*, **9**, 232-238 (High dose tybamate therapy of heroin dependence)

PIPERIDINEDIONE DERIVATIVES

Of the seven drugs listed (Table VII), glutethimide (S 116) and methyprylon (S 117) have been marketed for the longest time. Originally, both glutethimide and methyprylon were advertised as being "non-barbiturate" hypnotics. Actually both drugs are pharmacologically quite similar to barbiturates and glutethimide is more toxic than barbiturates when taken in large doses. Shortly after both glutethimide and methyprylon became available, case reports began to appear in the literature indicating that the two drugs caused dependence of the barbiturate-alcohol type in man.[188-195] Glutethimide has been shown to induce dependence in dogs and monkeys and to suppress abstinence from barbital in physically dependent dogs and monkeys. Accordingly, glutethimide must be judged to have dependence potential of high degree equal to that of the barbiturate hypnotics. Although less well documented, methyprylon must be rated as having moderate or high abuse liability. The potential for dependence of aminoglutethimide (S 112), and cinperene (S 113) may, by chemical and pharmacological analogy, be assessed as being equal to that of methyprylon. Aminoglutethimide has been withdrawn from the market in the United States of America because of serious side-effects.

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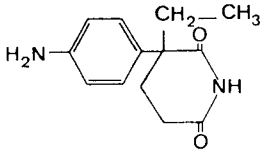
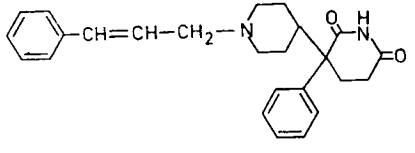
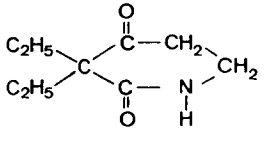
190. Jensen, R. (1960) *N. Z. med. J.*, **59**, 431 (Addiction to Nodular. A report of 2 cases)
191. Johnson, F. A. & VanBuren, H. C. (1962) *J. Amer. med. Ass.*, **180**, 1024 (Abstinence syndrome following glutethimide intoxication)
192. Lloyd, E. A. & Clark, L. D. (1959) *Dis. nerv. Syst.*, **20**, 1 (Convulsions and delirium incident to glutethimide (Doriden) withdrawal)
193. Luby, E. D. & Domino, E. F. (1962) *J. Amer. med. Ass.*, **181**, 46 (Additional evidence of addiction liability of glutethimide)
194. Ossenfort, W. F. (1957) *Dallas med. J.*, **43**, 229 (Drug addictions)
195. Sadwin, A. & Glen, R. S. (1958) *Amer. J. Psychiat.*, **115**, 469 (Addiction to glutethimide—Doriden)
196. World Health Organization (1966) *Drug Information* No. 56, Geneva (unpublished document)

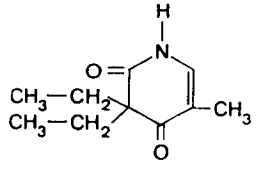
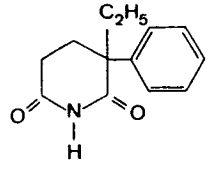
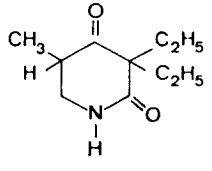
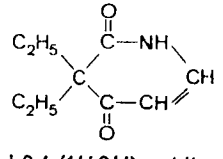
1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 112  2-(*p*-aminophenyl)-2-ethylglutarimide	Aminoglutethimide	Drowsiness	Yes (presumed)	Yes (presumed)	No information	Sedative; Serious side-effects	Drowsiness; Potentiation of other depressants	High (presumed)	196
S 113  2-(1-cinnamyl-4-piperidyl)-2-phenylglutarimide	Cinperene	No information	Yes (presumed)	Yes (presumed)	No information	Tranquillizer	Drowsiness; Potentiation of other depressants	No data	—
S 114  3,3-diethyl-2,4-piperidinedione	Dihyprylon	Drowsiness	Yes (presumed)	No information	No information	Hypnotic; Antitussive	No information	No data	—

[a] International Nonproprietary Name proposed by the World Health Organization, if any, or other nonproprietary name, if any; if there is no nonproprietary name, the main entry in the *Subsidia Pharmaceutica Index Nominum* or in the *Merck Index* or other generally accepted name. " None " indicates that an International Nonproprietary Name has not been proposed so far. The following abbreviations show the source of the name used: BAN = British Approved Name; DCF = Dénomination commune française; IN = *Subsidia Pharmaceutica Index Nominum*; MI = *Merck Index*, 8th ed.; NFN = Nordisk Farmakopénaevn.

[b] Current therapeutic use and indications.

TABLE VII. CENTRAL NERVOUS SYSTEM DEPRESSANTS

PIPERIDINEDIONE DERIVATIVES (*continued*)

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 115  3,3-diethyl-5-methyl-2,4-(1*H*,3*H*)-pyridinedione	Ethypicon	Drowsiness	No data	No information	No information	Hypnotic	No data	No data	—
S 116  2-ethyl-2-phenylglutarimide	Glutethimide	Drowsiness; Stupor; Coma; Drunkenness; Ataxia; Impaired cognition; etc.	Yes	Very marked	Marked convulsions and delirium	Hypnotic	Drunkenness; Potentiation of other CNS depressants; Coma; Death; Dependence	High	164, 191-195
S 117  3,3-diethyl-5-methyl-2,4-piperidinedione	Methyprylon	Drowsiness; Stupor; Coma; Drunkenness; Ataxia; Impaired cognition; etc.	Yes	Very marked	Convulsions and delirium	Hypnotic	Drunkenness; Potentiation of other CNS depressants; Coma; Death; Dependence	High	164, 188, 189, 190
S 118  3,3-diethyl-2,4-(1*H*,3*H*)pyridinedione	None; Pyrithyldion (MI)	Drowsiness	No data	No information	No information	Hypnotic	No data	No data	—

QUINAZOLINONES

Of the two compounds listed (Table VIII), methaqualone (S 120) has been marketed for the longest time. In Japan, many young persons abused methaqualone as long as that drug was available without prescription. The Japanese have also described convulsions and delirium following withdrawal of methaqualone, indicating that it produces dependence of the barbiturate-alcohol type. Only one report of dependence on methaqualone was found in the western literature.[204] Some evidence of abuse of a preparation (Mandrax) containing methaqualone and an antihistamine has been reported in British [197-199] and German [203] journals. Accordingly, methaqualone, pending the availability of more definitive information, must be regarded as having low to moderate potential for abuse. By chemical and pharmacological analogy, the abuse iability of mecloqualone (S 119) must be rated as equal to that of methaqualone.

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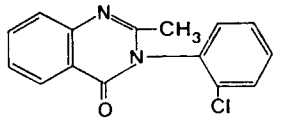
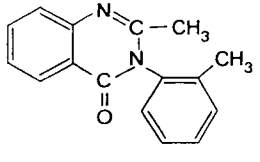
197. De Alarcon, R. (1969) *Brit. med. J.*, **1**, 122-123 (Methaqualone)
198. De Alarcon, R. (1969) *Brit. med. J.*, **1**, 319 (Mandrax and methaqualone)
199. Banady, D. R. (1969) *Brit. med. J.*, **1**, 577-578 (Mandrax)
200. Boissier, J. R. & Dumont, C. (1967) *Chem. Abstr.*, **67**, 8006, 84843W (Hypnotic)
201. Gitelson, S. (1967) *J. Amer. med. Ass.*, **201**, 977-979 (Methaqualone-meprobamate poisoning)
202. Grishina, V. M. (1967) *Chem. Abstr.*, **67**, 955, 10188q (Neurotropic properties of certain derivatives of 4-quinazolinone)
203. Ibe, K. (1965) *Arch. Toxikol.*, **21**, 179-198 (Acute methaqualone intoxication)
204. Madden, J. S. (1966) *Brit. med. J.*, **1**, 676 (Dependency on methaqualone hydrochloride—Melsedin)
205. Pfeiffer, C. C., Goldstein, L. & Murphree, H. B. (1968) *J. clin. Pharmacol.*, **8**, 235-244 (Quantitative analysis of the effect of methaqualone on the human EEG)

TABLE VIII. CENTRAL NERVOUS SYSTEM DEPRESSANTS

QUINAZOLINONES

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 119  3-(*o*-chlorophenyl)-2-methyl-4(3*H*)-quinazolinone	Mecloqualone	Drowsiness	No data	Probable	Not established	Hypnotic	Drunkenness	Low to moderate	200, 202
S 120  2-methyl-3-*o*-tolyl-4(3*H*)-quinazolinone	Methaqualone	Drowsiness; Drunkenness; Paraesthaesias; Stupor; Coma	No data	Probable	Not established	Hypnotic	Drunkenness; Potentiation of other CNS depressants; Suicide	Low to moderate	197-199, 201, 203-205

[a] International Nonproprietary Name proposed by the World Health Organization, if any, or other nonproprietary name, if any; if there is no nonproprietary name, the main entry in the *Subsidia Pharmaceutica Index Nominum* or in the *Merck Index* or other generally accepted name. "None" indicates that an International Nonproprietary Name has not been proposed so far. The following abbreviations show the source of the name used: BAN = British Approved Name; DCF = Dénomination commune française; IN = *Subsidia Pharmaceutica Index Nominum*; MI = *Merck Index*, 8th ed.; NFN = Nordisk Farmakopénaevn.

[b] Current therapeutic use and indications.

BENZODIAZEPINES

These drugs (Table IX) are pharmacologically similar to the barbiturates. Compound S 122, chlordiazepoxide, has enjoyed tremendous use in many countries as an " anti-anxiety " agent (sedative). Diazepam (S 126) has also had extensive sale for the same purpose as well as an antiepileptic drug. Chlordiazepoxide has been shown to produce physical dependence of the barbiturate-alcohol type in man [215] when given in very high doses of 300 mg or more daily. In addition, chlordiazepoxide has been shown to suppress abstinence from barbital in physically dependent dogs. An active illicit traffic in chlordiazepoxide supplied by diversion from licit sources developed in the USA. A number of papers describing cases of dependence on diazepam has been published.[206, 207, 210, 211, 214, 216, 218] Physical dependence on diazepam may be more severe than physical dependence on chlordiazepoxide since death has occurred during abstinence from diazepam. Accordingly, chlordiazepoxide and diazepam must be judged to have moderate abuse potential. The evidence of cases of dependence on these two substances, like that on phenobarbital, appears to be small in proportion to the large amounts used.

There is not sufficient information to assess accurately the abuse potentials of compounds S 121, S 123–S 125 and S 127–S 135. These drugs may, by chemical and pharmacological analogy, be tentatively suspected as having dependence liability similar to that of chlordiazepoxide and diazepam or possibly lower.

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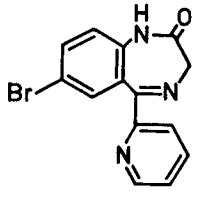
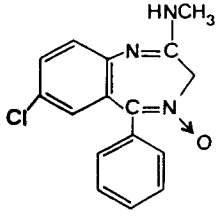
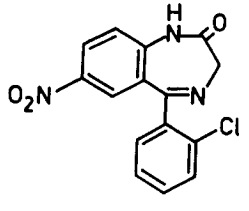
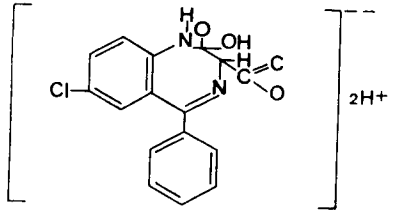
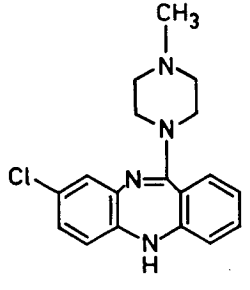
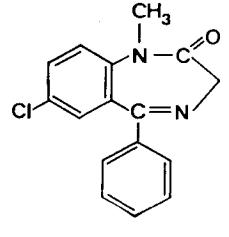
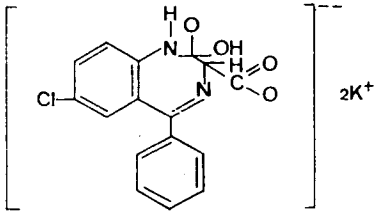
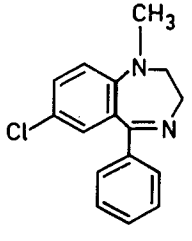
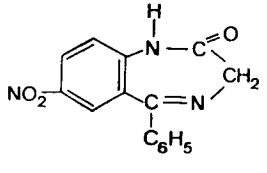
207. Barten, H. H. (1965) *Amer. J. Psychiat.*, **121**, 1210-1211, (Toxic psychoses with transient dysmnestic syndrome following withdrawal from Valium)
208. Bertolini, M. et al. (1969) *Arzneimittel-Forsch.*, **19**, 742-748 (On the anticonvulsant properties of oxazepam—Experimental study on the cat)
209. Berg, W. & Fleyel, H. (1969) *Arzneimittel-Forsch.*, **19**, No. 5, 740 (EEG Untersuchung mit Medazepam, einem neuen Benzodiazepin-Derivat)
210. Czerwenka-Wenkstetten, H., Hoffman, G. & Kryspin-Exner, K. (1966) *Wien. med. Wschr.*, **115**, 994 (Valium Entzugdelir)
211. Essig, C. F. (1966) *J. Amer. med. Ass.*, **196**, 714 (Newer sedative drugs that can cause states of intoxication and dependence)
212. Guile, L. E. (1963) *Med. J. Aust.*, **2**, 56-57 (Rapid habituation to chlordiazepoxide—Librium)
213. Halbert, R. J. et al. (1964) *Amer. J. Psychiat.*, **121**, 188 (Korsakoff-like psychosis associated with benzodiazepine overdosage)
214. Hollister, L. E., Bennett, J., Kimball, I., Savage, C. & Overall, J. E. (1963) *Dis. nerv. Syst.*, **24**, 746 (Diazepam in newly admitted schizophrenic patients)
215. Hollister, L. E., Motzenbecker, F. P. & Degan, R. O. (1961) *Psychopharmacologia*, **2**, 63-68 (Withdrawal reactions from chlordiazepoxide—Librium)
216. Lingjaerde, O. (1965) *Nord. psykiat. T.*, **19**, 73-78 (Acute and chronic overdosage of diazepam—Valium)
217. Randall, L. O., Schallek, W., Scheckell, C., Baneiger, R. & Moe, R. A. (1968) *Arzneimittel-Forsch.*, **18**, 1542-1545 (Zur Pharmakologie des neuen Psychopharmakons 7-chlor-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepin (Ro 5-4556))
218. Rilkin, R. (1966) *N. Y. St. J. Med.*, **66**, 1770 (Death following withdrawal of Diazepam)
219. Selig, J. W. (1966) *J. Amer. med. Ass.*, **198**, 951 (A possible Oxazepam abstinence syndrome)
220. Viscott, D. S. (1968) *Arch. gen. Psychiat.*, **19**, 370-376 (Chlordiazepoxide and hallucinations. Report of cases)

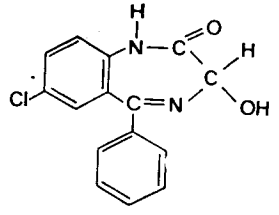
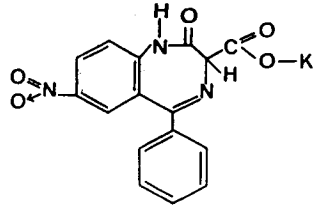
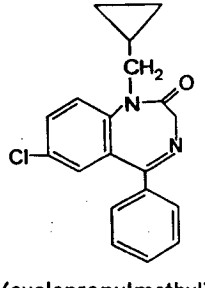
1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 121  7-bromo-1,3-dihydro-5-(2-pyridyl)-2*H*-1,4-benzodiazepin-2-one	Bromazepam	Drowsiness	Not established	Probable	Not proved	Tranquillizer	No data	Low (presumed)	—
S 122  7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine-4-oxide	Chlordiazepoxide	Drowsiness; Stupor; Coma; Drunkenness; Ataxia; Death (rare)	Yes	Yes, but usually mild	Yes, with high doses	Sedative; Production and sales very large	Drunkenness; Potentiation of other CNS depressants; Suicide; Dependence	Moderate	164, 212, 213, 215, 220
S 123  5-(*o*-chlorophenyl)-1,3-dihydro-7-nitro-2*H*-1,4-benzodiazepin-2-one	Clonazepam	Drowsiness	Not established	Probable	Not proved	Tranquillizer	No data	Low (presumed)	—

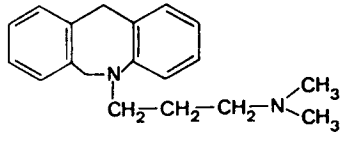
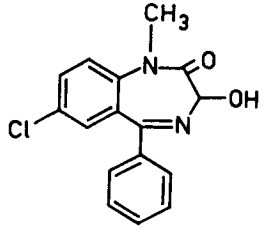
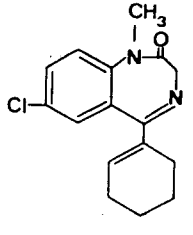
[a] International Nonproprietary Name proposed by the World Health Organization, if any, or other nonproprietary name, if any; if there is no nonproprietary name, the main entry in the *Subsidia Pharmaceutica Index Nominum* or in the *Merck Index* or other generally accepted name. "None" indicates that an International Nonproprietary Name has not been proposed so far. The following abbreviations show the source of the name used: BAN = British Approved Name; DCF = Dénomination commune française; IN = *Subsidia Pharmaceutica Index Nominum*; MI = *Merck Index*, 8th ed.; NFN = Nordisk Farmakopénaevn.

[b] Current therapeutic use and indications.

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 124  7-chloro-2,3-dihydro-2,2-dihydroxy-5-phenyl-1*H*-1,4-benzodiazepine-3-carboxylic acid	None; Clorazepic acid (BAN) (see Dipotassium clorazepate, **S 127**)	Drowsiness	No information	Probable	Not proved	Sedative	No data	Low (presumed)	—
S 125  8-chloro-11-(4-methyl-1-piperazinyl)-5*H*-dibenzo[*b*,*e*][1,4]diazepine	Clozapine	Drowsiness	Not established	Probable	Not proved	Tranquillizer	Low (presumed)	Low (presumed)	—
S 126  7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one	Diazepam	Drowsiness; Stupor; Coma; Drunkenness; Ataxia; Death (rare)	Yes	Yes	Not proved	Sedative; "Muscle relaxant"; Anticonvulsant	Drunkenness; Potentiation of other CNS depressants; Suicide	Moderate	149, 164, 206, 207, 210, 211, 214, 216, 218

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 127  [(3-carboxy-7-chloro-2,3-dihydro-2-hydroxy-5-phenyl-1*H*-1,4-benzodiazepin-2-yl)oxy]potassium	Dipotassium clorazepate	Drowsiness; Stupor; Coma; Drunkenness; Ataxia	Not established	Probable	Not proved	Sedative; Tranquillizer	Drunkenness; Potentiation of other CNS depressants	Low (presumed)	—
S 128  7-chloro-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine	Medazepam	Drowsiness; Stupor; Coma; Drunkenness; Ataxia	Not established	Probable	Not proved	Sedative	Drunkenness; Potentiation of other CNS depressants	Low (presumed)	209, 217
S 129  1,3-dihydro-7-nitro-5-phenyl-2*H*-1,4-benzodiazepin-2-one	Nitrazepam	Drowsiness; Stupor; Coma; Drunkenness; Ataxia	Not established	Probable	Not proved	Hypnotic; Anticonvulsant	Drunkenness; Potentiation of other CNS depressants	Low (presumed)	—

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 130  7-chloro-1,3-dihydro-3-hydroxy-5-phenyl-2*H*-1,4 benzodiazepin-2-one	Oxazepam	Drowsiness; Stupor; Coma; Drunkenness; Ataxia	Not established	Probable	Not proved	Sedative; Anti-epileptic	Drunkenness; Potentiation of other CNS depressants	Low	208, 219
S 131  potassium 2,3-dihydro-7-nitro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepine-3-carboxylate	Potassium nitrazepate	Drowsiness	Not established	Probable	Not proved	Tranquillizer	Drunkenness; Potentiation of other CNS depressants	Low (presumed)	—
S 132  7-chloro-1-(cyclopropylmethyl)-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one	Prazepam	Drowsiness	Not established	Probable	Not proved	Tranquillizer	Drunkenness; Potentiation of other CNS depressants	Low (presumed)	—

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 133  5,6-dihydro-*N*-[3-(dimethylamino)-propyl]-11*H*-dibenz[*b*,*e*]azepine	Prazepine	Drowsiness	Not established	Probable	Not proved	Psychotherapeutic	Drunkenness; Potentiation of other CNS depressants	Low (presumed)	—
S 134  7-chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one	Temazepam	Drowsiness	Not established	Probable	Not proved	Tranquillizer	No data	Low (presumed)	—
S 135  7-chloro-5-(cyclohexen-1-yl)-1,3-dihydro-1-methyl-2*H*-1,4-benzodiazepin-2-one	Tetrazepam	Drowsiness	Not established	Probable	Not proved	Tranquillizer	Drunkenness; Potentiation of other CNS depressants	Low (presumed)	—

SULFONMETHANES

The three compounds listed (S 136–S 138; Table X) constitute a group of old drugs that are quite toxic and relatively ineffective.[221, 222] There appears to be little production or use. The literature, all of which is old, concerning abuse of these drugs mostly deals with their direct toxic effects and not with dependence potential, which is rated as low. None of the three compounds has had adequate evaluation in experimental animals.

REFERENCES

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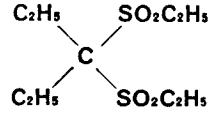
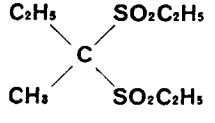
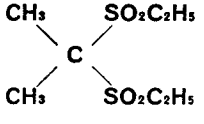
222. Shideman, F. E. (1958) In: Drill, V. A., ed. *Pharmacology in medicine*, 2nd ed., pp. 154-155 (Chapter 13, Sedatives and hypnotics. I. Bromides, chloral hydrate, paraldehyde, and miscellaneous agents).

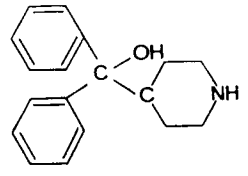
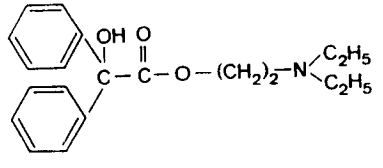
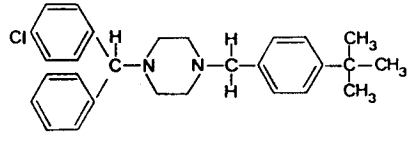
MISCELLANEOUS AGENTS

This is a heterogeneous group of agents of low efficacy as sedatives or hypnotics (S 139–S 158; Table XI). With the exception of hydroxyzine (S 146), production and sales have been quite low. No reports of abuse were found. None of these drugs has had a thorough examination for dependence potential, which must tentatively be regarded as quite low or non-existent for all members of the group.

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 136  2,2-bis(ethylsulfonyl)pentane	None	Drowsiness; Stupor; Coma; Ataxia; Skin rashes; Pigmentation; Peripheral neuropathy; Porphyrinuria	No data	Probable	No data	Hypnotic; Obsolete; No production	Chronic toxicity	Low	221, 222
S 137  2,2-bis(ethylsulfonyl)butane	None; Methylalfonalum (NFN); Trionalone (DCF); Sulfonethylmethane (MI)	Drowsiness; Stupor; Coma; Ataxia; Skin rashes; Pigmentation; Peripheral neuropathy; Porphyrinuria	No data	Probable	No data	Hypnotic; Obsolete; No production	Chronic toxicity	Low	221, 222
S 138  2,2-bis(ethylsulfonyl)propane	None; Sulfonalum (NFN); Sulfonalone (DCF); Sulfonmethane (MI)	Drowsiness; Stupor; Coma; Ataxia; Skin rashes; Pigmentation; Peripheral neuropathy; Porphyrinuria	No data	Probable	No data	Hypnotic; Obsolete; No production	Chronic toxicity	Low	221, 222

[a] International Nonproprietary Name proposed by the World Health Organization, if any, or other nonproprietary name, if any; if there is no nonproprietary name, the main entry in the *Subsidia Pharmaceutica Index Nominum* or in the *Merck Index* or other generally accepted name. "None" indicates that an International Nonproprietary Name has not been proposed so far. The following abbreviations show the source of the name used: BAN = British Approved Name; DCF = Dénomination commune française; IN = *Subsidia Pharmaceutica Index Nominum*; MI = *Merck Index*, 8th ed.; NFN = Nordisk Farmakopénaevn.

[b] Current therapeutic use and indications.

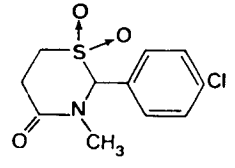
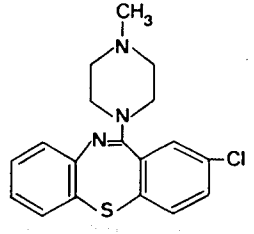
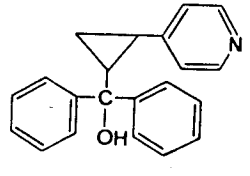
1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 139  α,α-diphenyl-4-piperidinemethanol	Azacyclonol	Slight drowsiness	No information	No information	No information	Anti-psychotic	Drowsiness	None	150, 170
S 140  2-diethylaminoethyl benzilate	Benactyzine	Drowsiness; Dizziness; Ataxia; Tachycardia; Dry skin; Delirium	No information	No information	No information	Sedative	Scopolamine-like psychosis	None	150, 170
S 141  1-*p*-*tert*-butylbenzyl-4-(*p*-chloro-α-phenylbenzyl)piperazine	Buclizine	Drowsiness; Dizziness; Potentiation of other CNS depressants; Antihistamic; Weak cholinergic blocker; Convulsions	No information	No information	No information	Sedative; Possible teratogen	Drowsiness; Poisoning	Very low	150, 170

[a] International Nonproprietary Name proposed by the World Health Organization, if any, or other nonproprietary name, if any; if there is no nonproprietary name, the main entry in the *Subsidia Pharmaceutica Index Nominum* or in the *Merck Index* or other generally accepted name. "None" indicates that an International Nonproprietary Name has not been proposed so far. The following abbreviations show the source of the name used: BAN = British Approved Name; DCF = Dénomination commune française; IN = *Subsidia Pharmaceutica Index Nominum*; MI = *Merck Index*, 8th ed.; NFN = Nordisk Farmakopénaevn.

[b] Current therapeutic use and indications.

TABLE XI. CENTRAL NERVOUS SYSTEM DEPRESSANTS

MISCELLANEOUS AGENTS *(continued)*

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 142  2-(*p*-chlorophenyl)tetrahydro-3-methyl-4*H*-1,3-thiazin-4-one 1,1-dioxide	Chlormezanone	Drowsiness; Headache; Dizziness; Nausea; Skin rash	No information	No information	No information	Sedative; "Muscle relaxant"	Drowsiness; Poisoning	Very low	150, 170
S 143  2-chloro-11-(4-methyl-1-piperazinyl)-dibenzo[*b*,*f*][1,4]thiazepine	Clotiapine	CNS depression	No information	No information	No information	Tranquillizer	Drowsiness	Unknown	—
S 144  diphenyl[2-(4-pyridyl)cyclopropyl]-methanol	Cyprolidol	Slight drowsiness	No information	No information	No information	Sedative; Psychotherapeutic; Related to azacyclonol and pipethanate	Drowsiness; Potentiation of CNS depression	Unknown	—

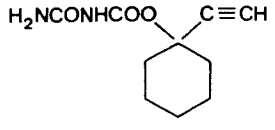
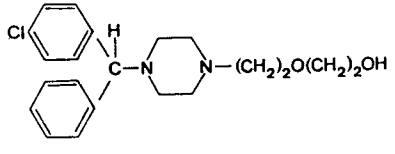
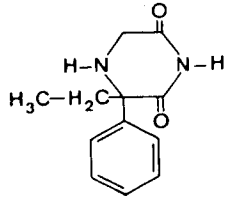
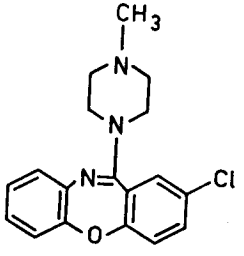
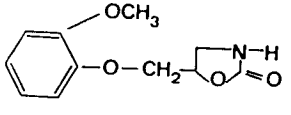
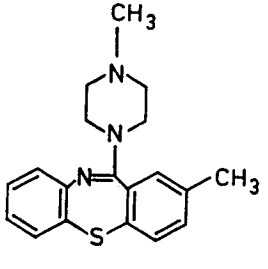
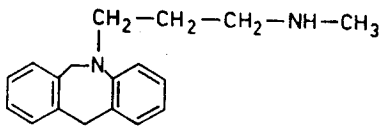
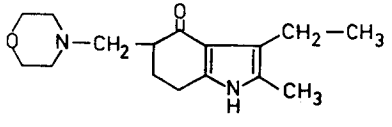
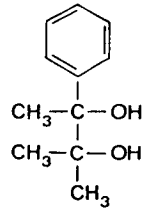
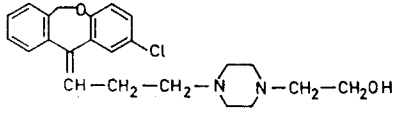
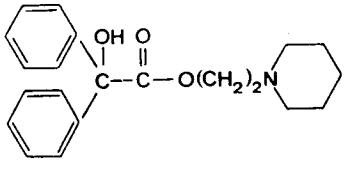
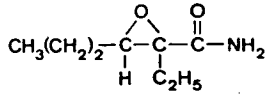
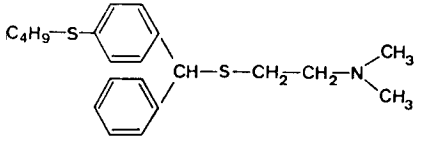
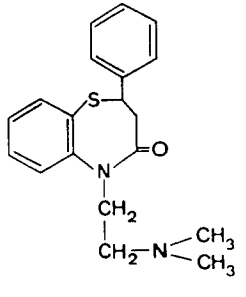
1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 145  1-ethynylcyclohexyl allophanate	None	CNS depression	No information	No information	No information	Hypnotic	Drowsiness	Unknown	—
S 146  2{2-[4-(p-chloro-α-phenylbenzyl)-1-piperazinyl]ethoxy}ethanol	Hydroxyzine	Drowsiness; Dizziness; Potentiation of other CNS depressants	No information	No information	No information	Sedative; Possible teratogen	Drowsiness; Poisoning	Very low	150, 170
S 147  3-ethyl-3-phenylpiperazine-2,6-dione	Imino-phenimide	CNS depression	No information	No information	No information	Hypnotic	Drowsiness	Unknown	—

TABLE XI. CENTRAL NERVOUS SYSTEM DEPRESSANTS

MISCELLANEOUS AGENTS *(continued)*

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 148  2-chloro-11-(4-methyl-1-piperazinyl)-dibenz[*b*,*f*][1,4]oxazepine	Loxapine	CNS depression	No information	No information	No information	Psychotherapeutic agent	No data	Unknown	—
S 149  5-[(*o*-methoxyphenoxy)methyl]-2-oxazolidinone	Mephenoxalone	Dizziness; Insomnia; Nausea; Skin rashes	No information	No information	No information	Sedative	Drowsiness; Poisoning; Potentiation of CNS depressants	Very low	150, 170
S 150  2-methyl-11-(4-methyl-1-piperazinyl)-dibenzo[*b*,*f*][1,4]thiazepine	Metiapine	CNS depression	No information	No information	No information	Psychotherapeutic agent	No data	Unknown	—

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 151  5,6-dihydro-5-[3(methylamino)propyl]-11*H*-dibenz[*b*,*e*]azepine	Mezepine	CNS depression	No information	No information	No information	Psychotherapeutic agent	No data	Unknown	—
S 152  3-ethyl-6,7-dihydro-2-methyl-5-(morpholinomethyl)indol-4(5*H*)-one	Molindone	CNS depression	No information	No information	No information	Antidepressant; Tranquillizer	Drowsiness	Unknown	—
S 153  2-(*p*-chlorophenyl)-3-methyl-2,3-butanediol	Phenaglycodol	Drowsiness	No Information	Not reported	Unknown	Sedative; Very little production	Drowsiness	Very low	170
S 154  *c*,*s*-4-[3-(2-chlorodibenz[*b*,*e*]oxepin-11(6*H*)-ylidene)propyl]-piperazinethanol	Pinoxepin	No information	No information	No information	No information	Tranquillizer	Drowsiness	Unknown	—

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 155  1-piperidineethanol benzilate	Pipethanate	Drowsiness; Dizziness; Ataxia; Delirium	No information	No information	No information	Sedative; Seems to be no longer produced	Scopolamine-like properties; Psychosis	Low	150, 170
S 156  2,3-epoxy-2-ethylhexanamide	Oxanamide	Drowsiness; Nausea; Skin rashes	No information	No information	No information	Sedative	Drowsiness; Potentiation of CNS depressants	Very low	150, 170
S 157  2-[*p*-(butylthio)-α-phenylbenzylthio]-*N*,*N*-dimethylethylamine	Captodiame	Drowsiness	No information	No information	No information	Sedative	Drowsiness; Potentiation of analgesics	Very low	5, 59, 150, 170
S 158  5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-phenyl-1,5-benzothiazepin-4[5*H*]-one	Tiazesim	CNS depression	No information	No information	No information	Tranquillizer; Antidepressant	Drowsiness	Unknown	—

CENTRAL NERVOUS SYSTEM STIMULANTS

GENERAL

This general group does not include the tricyclic antidepressants, the monoamine oxidase inhibitors or cocaine. The amphetamines are the most important drugs in this category.

Dependence of the amphetamine type [87] is characterized by the following: strong psychic dependence, a high degree of tolerance, and no readily evident physical dependence. However, a consistent syndrome manifested by a long period of marked rapid eye movement (REM) sleep, succeeded by ravenous appetite and then apathy and depression, has been described,[276] so possibly physical dependence as well as psychic dependence does occur.

As is the case with all forms of drug dependence, the spectrum of misuse and abuse of amphetamines varies markedly. Students may take one or two doses of amphetamines during one night in order to stay awake to study for examinations; other persons, usually young men, take huge doses of amphetamines intravenously in binges lasting days to weeks. Intravenous abuse is complicated by a high incidence of serious infections, marked inanition, sudden death (cardiac arrhythmias?) and suicide.

The most common problem of amphetamine dependence, regardless of the route of administration, is the development of a toxic psychosis of paranoid type which is difficult to distinguish from paranoid schizophrenia. An epidemic of this kind of reaction from methamphetamine occurred in Japan.[294] The amphetamine psychosis noted by the Japanese was confirmed in England by Connell [234] and by other authors in various countries.[244, 254, 259, 263, 272] All of the features of severe dependence of the amphetamine type have been reproduced in the monkey.

Abuse of amphetamine began to be noted soon after the introduction of the nasal inhalers containing DL-amphetamine. These were sold " across the counter " without prescription and were soon being smuggled into prisons where the containers were opened and the paper strips soaked in coffee or other drinks and swallowed. Soon after the introduction of D-amphetamine as an anorexigenic and antidepressant and after use of amphetamines as antifatigue drugs, abuse of amphetamines taken orally spread rapidly with the illicit market being supplied by diversion from legal sources. By 1965 the problem had reached huge proportions [283] in the USA, where intravenous abuse, which seems to have begun in California about 1960, is now a very serious problem on both the east and west coasts. The illicit market is now supplied partially by illegal synthesis of amphetamine and partly by diversions from legal sources.

In addition to Japan and the USA, Sweden has been heavily involved. The Swedes noticed the problem early and placed amphetamines under their narcotic law controls in 1938. Despite this, amphetamine abuse continued to spread in Sweden [244] until at present it is estimated that there are several thousand intravenous amphetamine abusers in that country. In Sweden, the favoured drug is phenmetrazine but all types of central stimulants are abused there, including amfepramone (S 166). The illicit market in Sweden has been supplied chiefly by smuggling from other countries.

Social damage from amphetamine dependence includes deterioration of work performance, impairment of family relationships, parasitic existence, poor judgement, and even assaultive behaviour toward other persons.

The symptoms observed in dependents abusing amphetamines intravenously is quite similar clinically to that observed in persons abusing cocaine intravenously.

EPHEDRINE AND DERIVATIVES

Ephedrine (S 159; Table XII) was included because of its historical interest, its chemical and pharmacological resemblance to the amphetamines, and its widespread use in medicine. It would seem strange if such a drug were not subject to some misuse and evidence of slight abuse was found in the literature.[223-226] Prokop [226] collected an extensive bibliography going back many years. There has been no thorough-going evaluation of the dependence-producing potential of ephedrine and its congeners in animals. No illicit market is known to exist.

Despite huge sales and easy availability, the incidence of abuse of ephedrine and its congeners (compounds S 160–S 162) is quite small. Therefore, the dependence liability of these drugs is judged to be low.

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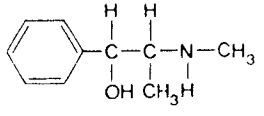
223. Innes, I. R. & Nickerson, M. (1965) In: Goodman, L. S. & Gilman, A., ed. *The pharmacological basis of therapeutics*, 3rd ed., Macmillan Co.' New York, pp. 477-520, (Drugs acting on postganglionic adrenergic nerve endings and structures innervated by them—sympathomimetic drugs)

224. Herridge, C. F. (1968) *Brit. med. J.*, **2**, 160 (Ephedrine psychoses)

225. Panse, F. & Klages, W. (1964) *Arch. Psychiat. Nervenkr.*, **206**, 69 (Klinisch-psychopathologische Beobachtungen bei chronischem Missbrauch von Ephedrin und verwandten Substanzen)

226. Prokop, H. (1968) *Nervenarzt*, **39**, 71-75 (Halluci-nose bei Ephedrinesucht)

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 159 (−)-2-methylamino-1-phenyl-1-propanol	None; (−)-ephedrine	As racephedrine	No information	Possible but mild	No information	Sympathomimetic; Nasal congestion; Asthma	Excessive stimulation	Low	223-226
S 160 (+)-2-methylamino-1-phenyl-1-propanol (pseuJo)	None; (+)-ephedrine	Relatively inert	No information	Unlikely	No information; Unlikely	Not produced	—	Low	223-226
S 161 2-methylamino-1-phenyl-1-propanol	None; Pseudo-ephedrine	—	No information	Unlikely	Unlikely	Said to have less pressor effect; Sympathomimetic	—	Low	223-226
S 162  (±)-2-methylamino-1-phenyl-1-propanol	None; Racephedrine	Increased blood pressure and pulse rate; Bronchial dilatation; Vaso-constriction; CNS stimulation	No information	Possible but mild	No information	Sympathomimetic; Nasal congestion; Asthma	Excessive stimulation	Low	223-226

[a] International Nonproprietary Name proposed by the World Health Organization, if any, or other nonproprietary name, if any; if there is no nonproprietary name, the main entry in the *Subsidia Pharmaceutica Index Nominum* or in the *Merck Index* or other generally accepted name. " None " indicates that an International Nonproprietary Name has not been proposed so far. The following abbreviations show the source of the name used: BAN = British Approved Name; DCF = Dénomination commune française; IN = *Subsidia Pharmaceutica Index Nominum*; MI = *Merck Index*, 8th ed.; NFN = Nordisk Farmakopénaevn.

[b] Current therapeutic use and indications.

AMPHETAMINES

This subgroup includes 31 different compounds with variable abuse potential (Table XIII). Four of the drugs, amphetamine (S 167), dexamphetamine (S 171), methamphetamine (S 180) and phenmetrazine (S 186), have been extensively abused in various countries (for references see Table XIII), both orally and intravenously. The dependence potential of these four compounds has to be regarded as very high. The great degree of risk also has to be considered in relation to the limited proven therapeutic usefulness of these compounds.

A small number of cases of abuse of amfepramone (S 166) has been reported in some countries,[231, 233, 260, 261, 275] and compound S 193 (SPA) was misused fairly extensively in Japan as long as it was available without prescription. Thus both amfepramone and SPA must be assessed as having moderate dependence potential which, however, is less than the abuse liability of the four compounds described in the preceding paragraph.

There is insufficient information concerning the dependence liability of some compounds sold as anorexiants: amfepentorex (S 165), amfecloral (S 164), benzphetamine (S 168), clobenzorex (S 170), chlorphentermine (S 169), fenfluramine (S 172), fludorex (S 173), furfenorex (S 174), mefenorex (S 177), mephentermine (S 178), metamfepramone (S 179), ortetamine (S 182), oxifentorex (S 183), pentorex (S 184), phendimetrazine (S 185), phentermine (S 188) and 1-phenyl-2-nicotinylaminopropion (S 189). All of these anorexiant drugs must, by chemical and pharmacological analogy, be suspected of being potentially capable of causing dependence of the amphetamine type.

Levamfetamine (S 176) is much less potent as a central stimulant than dexamphetamine but is as active as dexamphetamine as a peripheral sympathomimetic. No instance of abuse was found. The abuse potential of levamfetamine seems to be quite low. The remaining amphetamines (alfetamine, S 163; hydroxyamphetamine, S 175; methoxyphenamine, S 181; phenpromethamine, S 187; phenylpropanolamine, S 190; prenylamine, S 191 and propylhexedrine, S 192) have only feeble central nervous system stimulant properties and are used primarily for peripheral sympathomimetic effect. They are judged to have quite low or no dependence potential.

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237. Connell, P. H. (1968) *Practitioner*, **200**, 234-243 (The use and abuse of amphetamines)
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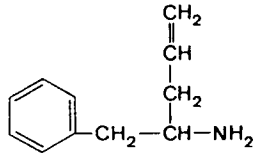
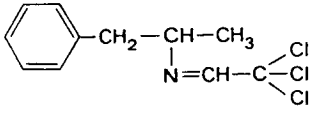
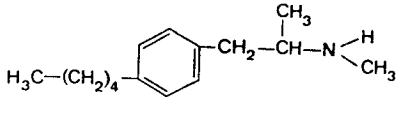
240. Edison, C. R. (1968) *J. Amer. med. Ass.*, **205**, 882-883 (Abuse of amphetamine)
241. Foxwell, M. H., Funderburk, W. H. & Ward, J. W. (1969) *J. Pharmacol. exp. Ther.*, **165**, 60-70 (Studies on the site of action of a new anorectic agent, fenfluramine)
242. Gagnon, M. A., Bordeleau, J. M. & Tétreault, L. (1969) *Int. Z. klin. Pharmakol. Ther. Toxikol.*, **2**, 74-82 (Fenfluramine: Study of its central action through its effects on sleep)
243. Glatt, M. M. (1968) *Lancet*, **2**, 215-216 (Abuse of methylamphetamine)
244. Goldberg, L. H. (1968) *Bull. Narcot.*, **20**, No. 1, 1-31, Part I; *Bull. Narcot.*, **20**, No. 2, 9-36, Part II (Drug abuse in Sweden)
245. Griffith, J. (1966) *Amer. J. Psychiat.*, **123**, 560 (A study of illicit amphetamine drug traffic in Oklahoma City)
246. Gylyp, J. A., Hart, J. J. D. & Warren, M. R. (1962) *J. Pharmacol. exp. Ther.*, **137**, 365-373 (Chlorphentermine, a new anorectic agent)

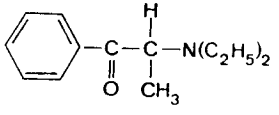
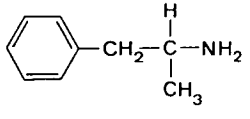
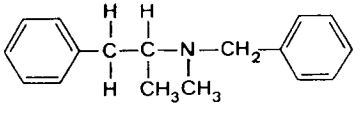
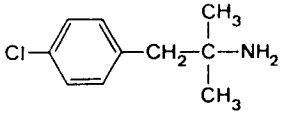
1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 163  α-allylphenethylamine	Alfetamine	No information	No information	No information	No information	Sympathomimetic	Unknown	Low	—
S 164  α-methyl-*N*-(2,2,2-trichloroethylidene) phenethylamine	Amfecloral	CNS excitation	Unknown	Yes (presumed)	No information	Anorexic; Sympathomimetic	CNS stimulation	Low	—
S 165  *N*,α-dimethyl-*p*-pentylphenethylamine	Amfepentorex	CNS stimulation	Unknown	Possible	No information	Anorexic	Unknown	Low	—

[a] International Nonproprietary Name proposed by the World Health Organization, if any, or other nonproprietary name, if any; if there is no nonproprietary name, the main entry in the *Subsidia Pharmaceutica Index Nominum* or in the *Merck Index* or other generally accepted name. " None " indicates that an International Nonproprietary Name has not been proposed so far. The following abbreviations show the source of the name used: BAN = British Approved Name; DCF = Dénomination commune française; IN = *Subsidia Pharmaceutica Index Nominum*; MI = *Merck Index*, 8th ed.; NFN = Nordisk Farmakopénaevn.

[b] Current therapeutic use and indications.

TABLE XIII. CENTRAL NERVOUS SYSTEM STIMULANTS

AMPHETAMINES *(continued)*

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 166  2-(diethylamino)propiophenone	Amfepramone	CNS excitation; Insomnia; Nervousness; Tachycardia; Arrhythmia	Unknown	Possible	Unknown	Anorexic	Insomnia; Inanition; Toxic psychosis	Moderate	231, 233, 259, 260, 275
S 167  (±)-α-methylphenethylamine	Amphetamine	CNS excitation; Insomnia; Anorexia; Nervousness; Increased blood pressure; Toxic psychosis	Yes	Marked	Probable, depending on definition	Vasoconstrictor; Analeptic; Anorexic; Mood elation; Narcolepsy	Insomnia; Toxic psychosis; Inanition; Dependence; Infections (if injected)	High	67, 227-230, 234-237, 239, 240, 244, 245, 247, 251, 253, 254-256, 259, 262-266, 269, 273, 276-280, 283-285, 287, 288, 294
S 168  *N*-benzyl-*N*,α-dimethylphenethylamine	Benzphetamine	CNS excitation; Insomnia; Nervousness	Unknown	Possible	Unknown	Anorexic	Unknown	Low	—
S 169  *p*-chloro-α,α-dimethylphenethylamine	Chlorphentermine	CNS excitation	No information	No information	No information	Anorexic; Minor stimulant; Possible sedative action; Pulmonary hypertension	CNS excitation	Low	227, 246

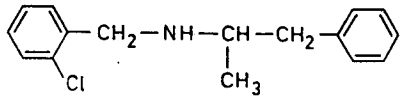
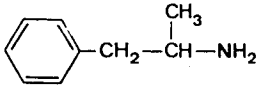
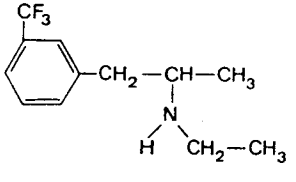
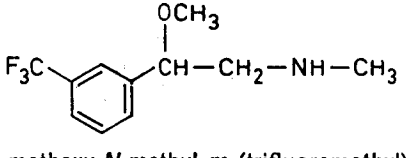
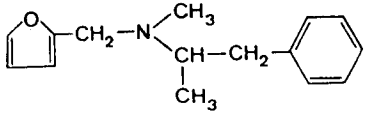
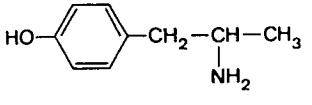
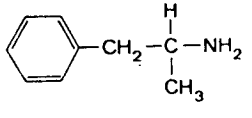
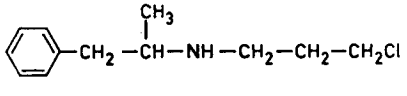
1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 170  (±)-*N*-(*o*-chlorobenzyl)-α-methylphenethylamine	Clobenzorex	CNS stimulation	No information	Possible	No information	Anorexic	CNS stimulation	Low	262
S 171  (+)-α-methylphenethylamine	Dexamphetamine	CNS excitation; Increased blood pressure; Insomnia; Anorexia; Toxic psychosis	Yes	Marked	Probable, depending on definition	Some uses; Has largely supplanted the racemate form, S 167	Insomnia; Toxic psychosis; Inanition; Dependence; Infections (if injected)	High	227-229, 234-237, 239, 240, 244, 245, 247, 251, 252, 253-256, 258, 262-266, 269, 272, 276-280, 283-288, 294, 295
S 172  3-(trifluoromethyl)-*N*-ethyl-α-methylphenethylamine	Fenfluramine	CNS stimulation	Unknown	No information	No information	Minor stimulant; Possibly sedative action	CNS stimulation	Low	227, 241, 242, 244, 250
S 173  β-methoxy-*N*-methyl-*m*-(trifluoromethyl) phenethylamine	Fludorex	CNS stimulation	Unknown	Possible	No information	Anorexic	CNS stimulation	Low	262

TABLE XIII. CENTRAL NERVOUS SYSTEM STIMULANTS

AMPHETAMINES *(continued)*

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 174  (+)-*N*-methyl-*N*-(α-methylphenethyl) furfurylamine	Furfenorex	CNS excitation	Unknown	Possible	Unknown	Anorexic	CNS excitation	Low	262
S 175  *o*-(2-aminopropyl)phenol; *p*-hydroxymethylphenethylamine	Hydroxyamphetamine	Increased blood pressure	Unknown	No information	No information	Sympathomimetic; Minor stimulant	Unknown	Low	255
S 176  (−)-α-methylphenethylamine	Levamfetamine	Very weak CNS excitation	Unknown	Very little	Unknown	Anorexic; Only ⅓ rd as potent as dextroamphetamine as central stimulant	Very little	Low	255
S 177  *N*-(3-chloropropyl)-α-methylphenethylamine	Mefenorex	Increased blood pressure; CNS stimulation	Unknown	Possible	No information	Anorexic	Unknown	Low	262

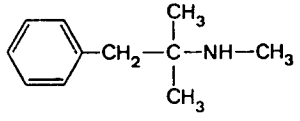
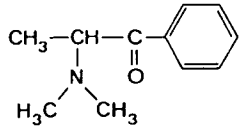
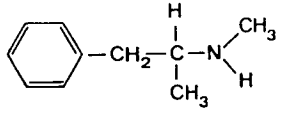
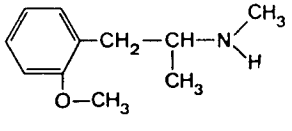
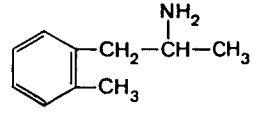
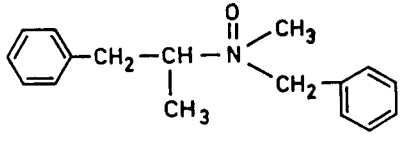
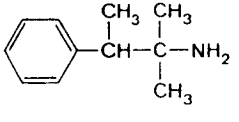
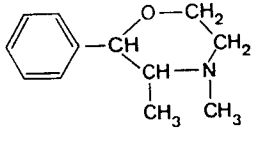
1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 178  *N*,α,α-trimethylphenethylamine	Mephentermine	CNS stimulation	Unknown	Possible	No information	Vasopressor; CNS stimulant	CNS excitation	Low	—
S 179  2-(dimethylamino)-propiophenone	Metamfepramone	CNS excitation; Insomnia; Nervousness	Unknown	Possible	Unknown	Anorexic	CNS excitation	Low	262
S 180  (±)-*N*,α-dimethylphenethylamine	Methamphetamine	CNS excitation; Increased blood pressure; Insomnia; Anorexia; Toxic psychosis	Yes	Yes	Probable, depending on definition	Vasoconstrictor; Analeptic; Mood elevator; Narcoleptic; Hyperkinetic children; Large illicit production	Insomnia; Toxic psychosis; Inanition; Dependence; Infections (if injected)	High	228-230, 234-237, 239, 240, 243-245, 248, 251-258, 262-264, 265, 266, 269, 272, 274, 277, 279-280, 283-285, 287-288, 290, 292, 294, 295
S 181  *o*-methoxy-*N*,α-dimethylphenethylamine	Methoxyphenamine	Minimal vasopressor; Cardiac and central side-effects	Unknown	Possible	No information	Bronchodilator	Unknown	Low	—

TABLE XIII. CENTRAL NERVOUS SYSTEM STIMULANTS

AMPHETAMINES *(continued*

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 182  *o*-α-dimethylphenethylamine	Ortetamine	CNS stimulation	Unknown	Possible	No information	Anorexic	Unknown	Low	—
S 183  *N*-benzyl-*N*,α-dimethylphenethylamine-*N*-oxide	Oxifentorex	CNS stimulation	Unknown	Possible	No information	Anorexic	CNS excitation	Low	262
S 184  α,α,β-trimethylphenethylamine	Pentorex	CNS stimulation	Unknown	Possible	No information	Anorexic	CNS stimulation	Low	262
S 185  (+)-3,4-dimethyl-2-phenylmorpholine	Phendimetrazine	CNS excitation; Insomnia; Nervousness	Unknown	Possible	Unknown	Anorexic	Unknown	Low	262

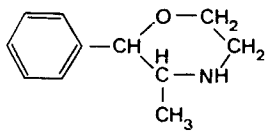
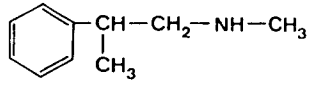
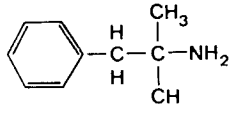
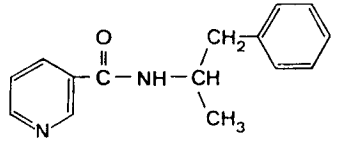
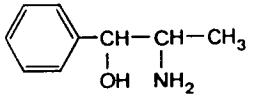
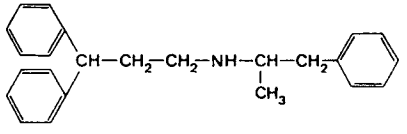
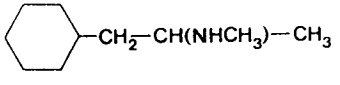
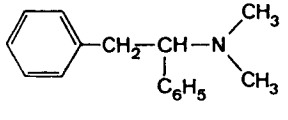
1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 186  3-methyl-2-phenylmorpholine	Phenmetrazine	CNS excitation; Increased blood pressure; Insomnia; Anorexia; Toxic psychosis	Yes	Yes	Probable, depending on definition	Analeptic; Anorexic; No illicit production known	Insomnia; Toxic psychosis; Inanition; Dependence; Infections (if injected)	High	229, 232, 235, 244, 245, 249, 251, 252, 255 256, 262, 267, 269, 273, 275, 276, 281-283, 287, 289, 293, 295
S 187  *N*,β-dimethylphenethylamine	Phenpromethamine	CNS stimulation	Unknown	No information	No information	Vasoconstrictor	Unknown	Low	—
S 188  α,α-dimethylphenethylamine	Phentermine	CNS excitation; Insomnia; Nervousness	Unknown	Possible	Unknown	Anorexic; Nasal decongestant	Unknown	Low	—
S 189  1-phenyl-2-nicotinylaminopropan	None; Phénatine (IN)	CNS excitation	Unknown	Possible	No information	CNS stimulant; Anorexic	Unknown	Low	—

TABLE XIII. CENTRAL NERVOUS SYSTEM STIMULANTS

AMPHETAMINES *(concluded)*

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 190  1-phenyl-2-aminopropanol	None; Phenylpropanolamine (BAN)	—	Unknown	No information	No information	Little CNS stimulative effect; Bronchodilator	Unknown	Low	—
S 191  *N*-(3,3-diphenylpropyl)-α-methylphenethylamine	Prenylamine	—	Unknown	Unlikely	No information	Coronary vasodilator	Unknown	Low	—
S 192  *N*,α-dimethylcyclohexane-ethylamine	Propylhexedrine	Increased blood pressure	Unknown	Possible	No information	Sympathomimetic; Anorexic	Unknown	Low	—
S 193  α-phenyl-*N*,*N*-dimethylphenethylamine	None; SPA	CNS stimulation; Increased blood pressure; Nervousness	Unknown	Probable	No information	CNS stimulant; Euphoric	CNS stimulation; Hallucinations	Moderate	287

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251. Herulf, B. & Sunesson, T. (1967) *Läk.-tidn.*, **64**, 1936-1942 (Young drug addicts in Stockholm)
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253. Jersild, T., Ott, C. & Thiede, J. (1967) *Yng. Laeg.*, **13**, 1664-1665 (Inoculation hepatitis in narco-maniacs and after tattooing)
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262. Lachnit, V. (1965) *Wien. Z. inn. Med.*, **46**, 248-254 (On the use of so-called anorexigenic drugs)
263. Ladewig, D., Battegay, R. & Labhardt, F. (1969) *Dtsch. med. Wschr.*, **94**, 101-107 (Stimulantien: Abhängigkeit und Psychosen)
264. *Lancet*, 1964, **2**, 452 (Amphetamine and delinquency)
265. *Lancet*, 1965, **1**, 1374 (Amphetamine)
266. Lemere, F. (1966) *Amer. J. Psychiat.*, **123**, 569 (The danger of amphetamine dependency)
267. Maffii, G. & Banfi, S. (1966) *Vrach. Delo.*, **9**, 739-745 (Experimental observations on addiction and abstinence phenomena in the rat treated with analgesics)
268. Maksimowska, M. (1966) *Pol. Tyg. Lek.*, **21**, 1938-1940 (Przypadek toksykomanii fenmetrazy-nowej—A case of phenmetrazine addiction)
269. Moorehead, N. C. (1968) *J. Irish med. Ass.*, **61**, 80-84 (Amphetamine consumption in Northern Ireland)
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272. Ney, P. S. (1967) *Canad. med. Ass. J.*, **97**, 1026-1029 (Psychosis in a child, associated with amphetamine administration)
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275. Oswald, I., Jones, H. S. & Mannerheim, J. E. (1968) *Brit. med. J.*, **1**, 796-799 (Effects of two slimming drugs on sleep)
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279. Rosenberg, C. M. (1968) *Med. J. Aust.*, **1**, 1031-1033 (Young drug addicts: addiction and its conse-quences)
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290. Teracka, A. (1967) *Psychiat. Neurol. jap.*, **69**, 597-619 (Prognostic and criminological studies on the mental disorder caused by the chronic methamphetamine intoxication)
291. Tolentino, I. & D'Avossa, B. (1957) *Arch. Psicol. Neurol. Psichiat.*, **18**, 127-168 (Psychotic reactions and psychosis due to phenylisopropylamine and sympatho-mimetic drugs—amphetamine group)
292. Utena, H. (1966) *Progr. Brain Res.*, **21B**, 192-207 (Behavioural aberrations in methamphetamine-intoxicated animals and chemical correlates in the brain)
293. Vencovsky, E. & Nevole, S. (1965) *Čs. Psychiat.*, **61**, 411-414 (The problem of phenmetrazine addiction)
294. Masaki, T. (1956) *The amphetamine problem in Japan.* In: *Wld Hlth Org. techn. Rep. Ser.*, No. 102, Geneva, pp. 14-21
295. Wilson, C. W. M. (1968) *Adolescent drug dependence*, Pergamon Press, Oxford

PIPERIDINE DERIVATIVES

Methylphenidate (S 195; Table XIV) is marketed as an antidepressant drug. It has limited usefulness in the treatment of narcolepsy. For many years cases of abuse were rare but recently abuse of methylphenidate has occurred in the USA, [297-299] the United Kingdom and Sweden.[244] When methylphenidate is taken intravenously in a high dose, it produces a clinical picture quite similar or identical to that caused by intravenous use of methamphetamine or phenmetrazine. Accordingly, it must be regarded as having high dependence liability coupled with limited proven therapeutic usefulness.

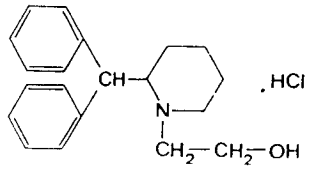
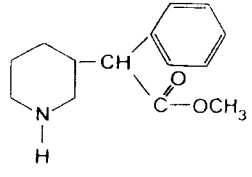
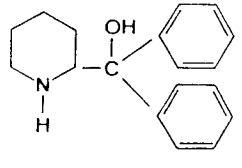
A few cases of abuse of pipradrol (S 196) occurred[244] a number of years ago, but in recent years no new cases have been reported. Thus it is difficult to rate the dependence potential of pipradrol but it must be judged, pending additional information, as being definite if somewhat less than that of methylphenidate.

REFERENCES

296. Ditman, K. S. et al. (1969) *Psychopharmacologia (Berl.)*, **14**, 1-11 (Dimensions of the LSD, methylphenidate and chlordiazepoxide experiences)
297. McCormick, T. C. & McNeel, T. W. (1963) *Texas State J. Med.*, **59**, 99 (Acute psychosis and Ritalin abuse)
298. Pollack, B. (1964) *Amer. J. Psychiat.*, **121**, 189 (Report of an unusually large dosage of methylphenidate hydrochloride)
299. Rioux, B. (1969) *Dis. nerv. Syst.*, **21**, 346-349 (Is Ritalin an addiction-producing drug?)

TABLE XIV. CENTRAL NERVOUS SYSTEM STIMULANTS

PIPERIDINE DERIVATIVES

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 194  2-(diphenylmethyl)-1-piperidine-methanol hydrochochloride	Diphemethoxidin (MI)	Restlessness	No information	No information	No information	Anorexigenic	Insomnia	Low	—
S 195  α-phenyl-2-piperidineacetic acid methyl ester	Methylphenidate	Restlessness; Agitation; Insomnia; Toxic psychosis	No information	Yes	No information	Analeptic; Antidepressant; Narcoleptic	Insomnia; Toxic psychosis	High	244, 296-299
S 196  α,α-diphenyl-2-piperidinemethanol	Pipradrol	Restlessness; Agitation	No information	No information	No information	CNS stimulant; Narcoleptic; Depression; Fatigue	Agitation; Insomnia	Low	244

[a] International Nonproprietary Name proposed by the World Health Organization, if any, or other nonproprietary name, if any; if there is no nonproprietary name the main entry in the *Subsidia Pharmaceutica Index Nominum* or in the *Merck Index* or other generally accepted name. "None" indicates that an International Nonproprietary Name has not been proposed so far. The following abbreviations show the source of the name used: BAN = British Approved Name; DCF = Dénomination commune française; IN = *Subsidia Pharmaceutica Index Nominum*; MI = *Merck Index*, 8th ed.; NFN = Nordisk Farmakopénaevn.

[b] Current therapeutic use and indications.

MISCELLANEOUS AGENTS

There are no reports of abuse available on any of the three compounds listed in Table XV. Aminorex (S 197) has been withdrawn from the market because of serious side-effects unrelated to abuse potential. Since all three drugs are used as psychic stimulants or anorexiants [11, 20, 300-303] they must be regarded tentatively as potentially having abuse liability equivalent to that of pipradrol.

REFERENCES

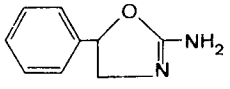
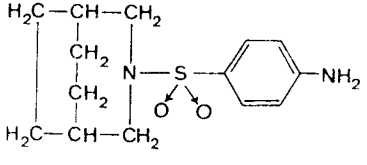
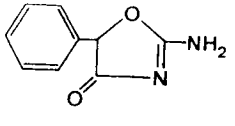
300. Boissier, J. R. et al. (1967) *Thérapie*, **23**, 1307-1316 (Pémoline et pémoline-magnesium. Action psychoanaleptique comparée)

301. Gelfant, S. et al. (1968) *Clin. Pharmacol. Ther.*, **9** 56-60 (Mg pemoline-stimulant effects on performance of fatigued subjects)

302. Herbert, E. W. et al. (1968) *Clin. Pharmacol. Ther.*, **9**, 578-582 (Mg-pemoline: Stimulant effects on performance in fatigued man)

303. Orzack, M. H., Taylor, C. L. & Kornetsky, C. (1968) *Psychopharmacologia (Berl.)*, **13**, 413-417 (A research report on the anti-fatigue effects of magnesium pemoline)

TABLE XV. CENTRAL NERVOUS SYSTEM STIMULANTS

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 197  2-amino-5-phenyl-2-oxazoline	Aminorex	CNS excitation	No information	No information	No information	Anorexic; Pulmonary hypertension	CNS stimulation	Low	11, 20
S 198  3-sulfanilyl-3-azabicyclo[3,2,2]nonane	Azabon	CNS excitation	No information	No information	No information	Psycho-stimulant	CNS stimulation	Low	—
S 199  2-imino-5-phenyl-4-oxazolidinone; phenylisohydantoine	Pemoline	CNS excitation	No information	No information	No information	Psycho-analeptic; Psychotonic; Comparable with caffeine or methyl-phenidate	Unknown	Low	300-303

[a] International Nonproprietary Name proposed by the World Health Organization, if any, or other nonproprietary name, if any; if there is no nonproprietary name, the main entry in the *Subsidia Pharmaceutica Index Nominum* or in the *Merck Index* or other generally accepted name. " None " indicates that an International Nonproprietary Name has not been proposed so far. The following abbreviations show the source of the name used: BAN = British Approved Name; DCF = Dénomination commune française; IN = *Subsidia Pharmaceutica Index Nominum*; MI = *Merck Index*, 8th ed.; NFN = Nordisk Farmakopénaevn.

[b] Current therapeutic use and indications.

HALLUCINOGENS

GENERAL

The most important chemical subgroups in this category are the indoles, the phenylalkylamines with methoxy- and/or methylenedioxy- substituents in the phenyl ring and the tetrahydrocannabinols.

The indoles and the phenyl-substituted phenylalkylamines (hallucinogenic amphetamines) are related pharmacologically, if not chemically. Many of the drugs in these two subgroups are hallucinogens that create dependence of the hallucinogen (LSD) type, which is characterized by moderate psychic dependence, quickly developing tolerance but no physical dependence. Drugs of this type cause central nervous system excitation, alterations in mood ranging from euphoria to dysphoria, anxiety, insomnia, anorexia, difficulty in concentrating, marked alterations in sensory perception, changes in body image and hallucinations. They are usually taken in the hope of inducing a mystical experience leading to a greater understanding of the users' personal problems and of the universe. These drugs appear to be particularly attractive to young people of bohemian habits who have rejected the usual goals and mores of their societies.

The dangers of these drugs include harm to the person himself or other people as a result of the drug-induced psychosis. In addition, the hallucinogens may solidify withdrawal from the mainstream of society and identification with a drug-taking subculture. Moreover, these compounds can precipitate psychotic states which are more severe and which may last longer than normally occurs.

Some persons have remained permanently psychotic after taking hallucinogens. These individuals are generally believed to have been persons who were " predisposed " to psychiatric disease and who were making only marginal personal adjustments in society. Even if this interpretation is correct, it must be admitted that the hallucinogen may have been a final and very important factor in precipitating permanent mental disorder in predisposed personalities.

The tetrahydrocannabinols include the most active materials found in marijuana [(—)-Δ^9-THC and (—)-Δ^8-THC]. These drugs can now be synthesized. Like LSD, they are psychotomimetic [383, 385, 394] but have sedative rather than stimulating effects, show no crossed tolerance to LSD, and are devoid of the autonomic effects of LSD.

These drugs are likely, if available, to produce dependence of the *Cannabis* (marijuana) type which is characterized by moderate to strong psychic dependence, little tolerance (?), and absence of physical dependence. The symptoms of intoxication with *Cannabis* include alterations in mood, perception and judgement, tachycardia, and sometimes psychotic symptoms. The dangers of the synthetic may be greater than those of *Cannabis*, because of greater potency and because psychotomimetic effects with the pure materials are dose-related.[383, 385, 394]

The hallucinogenic anticholinergics can be dismissed in a few words. Although the drugs are hallucinogenics they are not euphorigenic but dysphoric. The anticholinergics cause confusion, sedation, a delirium with frequently terrifying hallucinations, amnesia, and the usual peripheral autonomic signs of dilated and fixed pupils, tachycardia, flushing etc. The experience is unpleasant, and, even if persons prone to drug dependence try these drugs, they do so only once. The experience is, in the " hippie " jargon, strictly a " downer " (unpleasant feeling). There is no significant amount of abuse of these materials and no illicit traffic. In the USA, there are reports of a number of cases of adolescents smoking " Asthmador ", a proprietary preparation containing stramonium that was sold across the counter. As a rule these young people tried the drug once only.

INDOLES

The prototype drug in this subgroup (Table XVI) is compound S 219, lysergide (LSD), which produces dependence of the hallucinogen (LSD) type (see above). A tremendous literature on LSD exists which documents fully the dangers of abuse, which is now widespread in the USA, Canada, the United Kingdom, Australia and many western European countries (for references see Table XVI). LSD must be judged as a very dangerous substance which has no established therapeutic use.

Substances S 200–S 203, S 206, S 208, S 213–S 218 and S 220–S 222 are isomers or congeners of LSD. A number of these are much less potent than LSD in hallucinogenic effect or are not hallucinogenic at all (compounds S 203, S 213, S 216, S 217, S 220 and S 222) and accordingly carry a lesser degree of risk than LSD. None of these weak hallucinogens has been abused. Other compounds are all sufficiently potent to make it likely that they would be abused if available (S 200, S 201, S 206, S 208, S 214, S 218 and S 221).

Compounds S 202, S 207, S 209, S 223 and S 224 are derivatives of tryptamine. Dimethyltryptamine (S 209) is a short-acting hallucinogen which is effective only if smoked or injected. This compound has been extensively abused and an illicit market in dimethyltryptamine supplied by illegal synthesis has developed. Diethyltryptamine (S 207) is a similar drug but has not appeared in the illicit market. Psilocybine (S 224) and psilocin (S 223) are both potent hallucinogens that are effective orally as well as parenterally. Illicit traffic in psilocybine has occurred. Diethyltryptamine, psilocybine and psilocin accordingly must be judged to have high dependence potential.

Bufotenine (S 204) has been classed to be a hallucinogen but probably is not. Alpha-methyltryptamine (S 202) has been reported to have hallucinogenic properties but has not been abused. The dependence potential of these two compounds is therefore difficult to assess.

The remaining compounds, S 205, S 210, S 212 and S 225, are complex molecules that have been isolated from plants (see " Crude Plant Drugs ", below) many of which are used ritualistically by primitive peoples. Their animal and human pharmacology have not been studied sufficiently to permit a definite judgement as to their relative dependence potentials. Ibogaine (S 212) has appeared in the illicit market in the USA.

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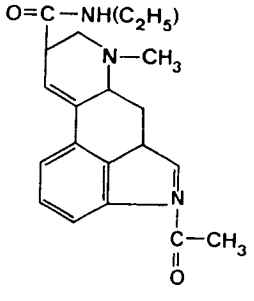
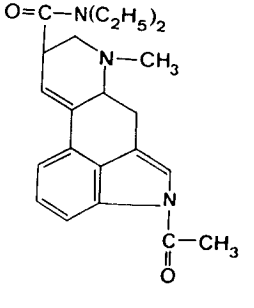
305. Cerletti, A. (1958) In: Heim, R. & Wasson, G. R., ed., *Les champignons hallucinogènes du Mexique*, pp. 268-271, Muséum national d'Histoire naturelle, Paris (Etude pharmacologique de la psilocybine)
306. Cohen, S. (1965) *The beyond within. The LSD story*. Atheneum, New York
307. Cohen, S. & Ditman, K. S. (1963) *Arch. gen. Psychiat.*, **8**, 475 (Prolonged adverse reactions to lysergic acid diethylamide)
308. DeJong, H. H. (1955) *Experimental catatonia. A general reaction form of the central nervous system and its implications for human etiology*, Williams & Wilkins, Baltimore
309. Delay, J. (1954) *Ann. méd.-psychol.*, **112**, N° 2, 1 (Les modifications de la personnalité, produites par la diethylamide de l'acide lysergique (LSD 25))
310. Delay, J., et al. (1959) *Ann. méd.-psychol.*, **117**, N° 1, 891-899 (Les effets somatiques de la psilocybine)
311. Delay, J., Pichot, P., Lempérière, Th., Nicolas-Charles, P. & Quétin, A. M. (1958) In: Heim, R. & Wasson, G. R., ed., *Les champignons hallucinogènes du Mexique*, Section 5, Ch. 7, Muséum national d'Histoire naturelle, Paris (Etude psycho-physiologique et clinique de la psilocybine)
312. Delay, J., Pichot, P., Lempérière, Th., Nicolas-Charles, P. (1958) *C.R. Acad. Sci. (Paris)*, **247**, 1235-1238 (Effets psycho-physiologiques de la psilocybine)
313. Delay, J., Lhermitte, F., Veridreaux, G. & Veridreaux, J. (1952) *Rev. neurol.*, **86**, 81-88 (Modifications de l'électrocorticogramme du lapin par la diéthylamine de l'acide *d*-lysergique (LSD-25))
314. Ditman, K. S., Tietz, W., Prince, B. S., Fargy, E. & Maas, T. (1967) *J. nerv. ment. Dis.*, **145**, 464 (Harmful effects of the LSD experience)
315. Draškoci, M. (1965) *Arch. farmac.*, **15**, 109-115 (Psichozomimetika)
316. Dubansky, B., Vyhnankova, M. & Setlik, L. (1968) *Čs. Neurol.*, **31**, 394-399 (Simultaneous occurrence of neurological symptoms and change of proprioceptive perception induced by psylocybine in patients with organic brain disorders)

TABLE XVI. HALLUCINOGENS

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 200  (+)-1-acetyl-*N*-monoethyl lysergic acid amide	None; ALA-10		No information	Possible	Improbable	No legitimate production; 1/15th as potent as LSD	Like LSD if dose high	High if available	64
S 201  (+)-1-acetyl-*N*,*N*-diethyl lysergic acid amide	None; ALD-52		No information	Probable	Improbable	No legitimate production; Equipotent with LSD; Same dangers	Like LSD if dose high	High if available	64

[a] International Nonproprietary Name proposed by the World Health Organization, if any, or other nonproprietary name, if any; if there is no nonproprietary name, the main entry in the *Subsidia Pharmaceutica Index Nominum* or in the *Merck Index* or other generally accepted name. " None " indicates that an International Nonproprietary Name has not been proposed so far. The following abbreviations show the source of the name used: BAN = British Approved Name; DCF = Dénomination commune française; IN = *Subsidia Pharmaceutica Index Nominum*; MI = *Merck Index*, 8th ed.; NFN = Nordisk Farmakopénaevn.

[b] Current therapeutic use and indications.

TABLE XVI. HALLUCINOGENS

INDOLE DERIVATIVES *(continued)*

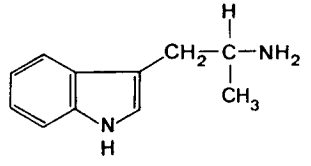
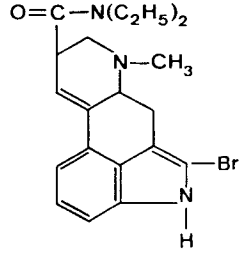
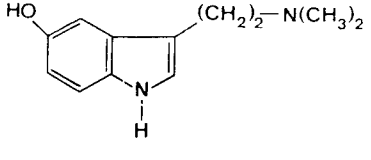
1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 202  α-methyltryptamine	None; AMT	Alterations in mood; Euphoria-dysphoria; Alterations in perception; Hallucinations; Depersonalization; Delayed onset	Unknown	Probable	Improbable	No legitimate production	Panic states; Schizophrenic reactions; Suicides; Precipitation of psychosis	High	—
S 203  (+)-2-bromo-*N,N*-diethyl lysergic acid amide	None; BOL-148		Confers cross-tolerance to LSD	Improbable	Improbable	No legitimate production; Less than 1/85th as potent as LSD	Weak drug; Short course	Low	—
S 204  3-[2(dimethylamino)ethyl]indol-5-ol; 5-hydroxydimethyltrytamine	None; Bufotenine (MI)	Probably not hallucinogenic; Cardiovascular effects	No information	Improbable	Improbable	Dangerous	Cardiac arrhythmia	Unknown	64, 319, 327

TABLE XVI. HALLUCINOGENS

INDOLE DERIVATIVES *(continued)*

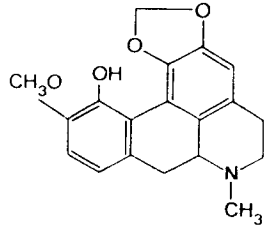
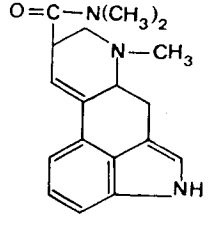
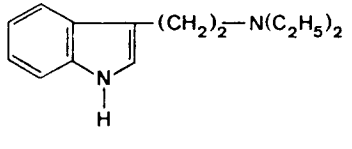
1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 205  6aα-aporphin-11-ol,10-methoxy-1,2 - (methylenedioxy)	None; Bulbocapnine (MI)	Not too well characterized; Said to be a hallucinogen	Unknown	Unknown	Unknown	No longer used	Unknown	Unknown	64, 326
S 206  (+)-*N,N*-dimethylamino lysergic acid amide	None; DAM-57		Unknown	Possible	Unknown	No legitimate production; 1/10th as potent as LSD	Could be like LSD if dose high	High if available	64, 304
S 207  *N,N*-diethyltryptamine	None; DET	Alterations in mood; Euphoria-dysphoria; Alterations in perception; Hallucinations; Depersonalization	Unknown	Yes	Improbable	No legitimate production	Panic states; Schizophreniform reactions; Suicides; Precipitation of psychosis	High	64

TABLE XVI. HALLUCINOGENS

INDOLE DERIVATIVES *(continued)*

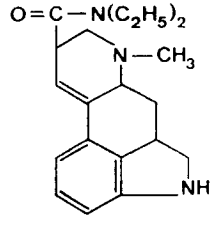
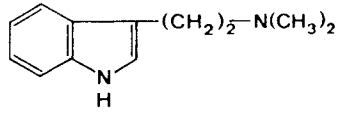
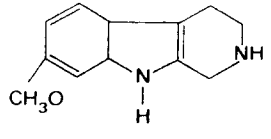
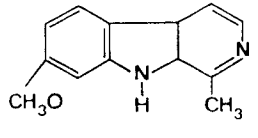
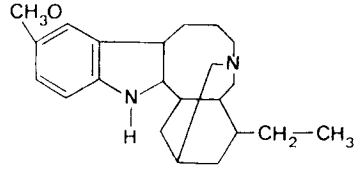
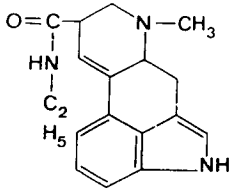
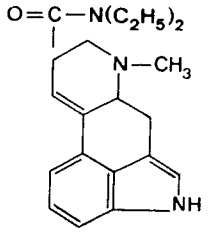
1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 208  (+)-2,3-dihydro-*N*,*N*-diethyl lysergic acid amide	None; 2,3-DH-LSD		No information	Possible	Improbable	No legitimate production; 1/6th as potent as LSD	Like LSD if dose high	High if available	322
S 209  *N*,*N*-dimethyltryptamine	None; DMT	Alterations in mood; Euphoria-dysphoria; Alterations in perception; Hallucinations; Depersonalization	Unknown; Cross-tolerance with LSD	Yes	No	None; No legitimate production	Panic states; Schizophreniform reactions; Suicides; Precipitation of psychosis	High	342, 343, 348
S 210  4,9-dihydro-7-methoxy-1-methyl-3*H*-pyrido[3,4b]indole	None; Harmaline		Unknown	Unknown	Unknown	Not well characterized; Said to be a hallucinogen	Unknown	Unknown	64, 338
S 211  7-methoxy-1-methyl-9*H*-pyrido [3,4-b]indole	None; Harmine (banisterine, yageine, etc.)	Drowsiness; Cyclical confused states	Unknown	Unknown	Unknown	No approved use; Not well characterized; MAO-inhibitor	Unknown	Unknown	64, 323, 340

TABLE XVI. HALLUCINOGENS

INDOLE DERIVATIVES *(continued)*

1 No. of compound and formula (or chemical name)	Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 212  6,9-methano-5*H*-pyrido[1′,2′ : 1,2] azepino[4,5b]indole	None; Ibogaine	Not well characterized; Excitation; Epilepsy-like states	Unknown	Unknown	Unknown	Not used; Said to be a hallucinogen	Unknown	Low	64, 327, 344
S 213 (+)-isolysergic acid amide	None; Isolysergamide	Fatigue; Drowsiness; Headache; Not hallucinatory	No information	Improbable	Improbable	No legitimate production	Drowsiness	Very low	332
S 214  (+)-*N*-monoethyl lysergic acid amide	None; LAE-32	As S 219	No information	Possible	Improbable	No legitimate production; 1/20th as potent as LSD	Like LSD if dose high	High if available	64, 304
S 215  **.Pyrrolidate** (+)-lysergic acid pyrrolidide; lysergic acid diethylamide pyrrolidate	None; LPD-824	As S 219	No information	Possible	Improbable	No legitimate production; 1/10th as potent as LSD	Like LSD if dose high	High if available	64, 304

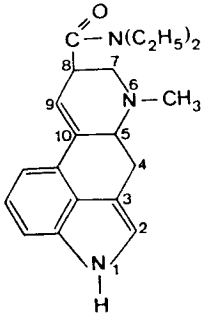
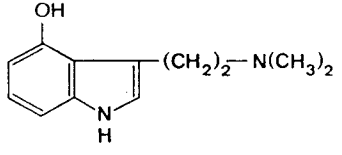
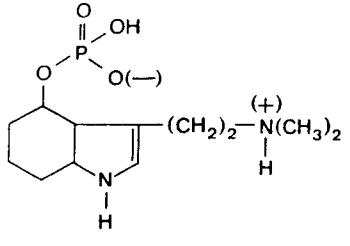
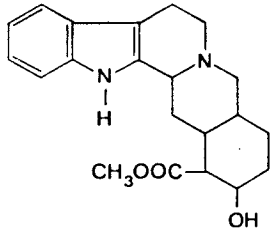
1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 216 (−)-*N,N*-diethyl lysergic acid amide	None; (−)-LSD	As S 219	Unknown	Improbable	Unknown	No legitimate production; Less than 1/70th as potent as D-form	—	Low	—
S 217 (+)-*N,N*-diethyl isolysergic acid amide	None; (+)-isoLSD	As S 219	Unknown	Improbable	Unknown	No legitimate production; Less than 1/50th as potent as LSD-25	—	Low	—
S 218 (+)-lysergic acid morpholide	None; LSM-775	As S 219	No information	Possible	Improbable	No legitimate production; 1/10th as potent as LSD	Like LSD if dose high	High if available	64, 304
S 219  (+)-ergoline-8β-carboxamide,9,10-didehydro-*N,N*-diethyl-6-methyl; (+)-*N,N*-diethyl lysergamide	Lysergide (Syn.: LSD, LSD-25)	Alterations in mood; Euphoria-dysphoria; Alterations in sensory perception; Depersonalization; Entoptic hallucinations; Time hallucinations; Dilated pupils; Hyperactive reflexes	Yes	Yes	No	No legitimate production	Panic states; Schizophreniform states; Suicide; Precipitation of permanent psychosis	High	64, 304, 306, 307, 309, 313-315, 318, 320-322, 326, 327, 330, 331, 333-337, 339, 341, 345, 346, 348, 351, 352, 369, 374
S 220 (+)-1-methyl-*N*-monoethyl lysergic acid amide	None; MLA-74	As S 219	No information	Improbable	Improbable	No legitimate production; Less than 1/25 as potent as LSD	Weak drug	Low	64, 304
S 221 (+)-1-methyl-*N,N*-diethyl lysergic acid amide	None; MLD-41	As S 219	No information	Probable	Improbable	No legitimate production; 1/3rd as potent as LSD	Like LSD if dose high	High if available	64, 304

TABLE XVI. HALLUCINOGENS

INDOLE DERIVATIVES *(concluded)*

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 222 (+)-1-methyl lysergic acid pyrrolidide	None; MPD-75	As S 219	No information	Possible	Improbable	No legitimate production; Less than 1/20th as potent as LSD	Weak drug; Short action	Low	64, 304
S 223  3-[2-dimethylamino)ethyl]indol-4-ol	None; Psilocin	Relatively non-toxic	No information	Probable	Improbable	LSD-like; 1/15th as potent (Dephosphorylated psilocybine; Probably the active metabolite)	Same as LSD and psilocybine	High	64, 352
S 224  3-(2-dimethylaminoethyl)-indol-4-yl-dihydrogen phosphate	Psilocybine	Relatively non-toxic	Yes; Cross-tolerance with LSD	Yes	No	No legitimate production; LSD-like; 1/15th as potent	Panic states; Schizophreniform reactions; Suicide; Precipitation of psychoses	High	64, 305, 310-312, 316-318, 325, 327, 329, 330, 334, 335, 341, 352, 368
S 225  Yohimban-16α-carboxylic acid, 17α-hydroxy-methylester	None; Yohimbine	Not well characterized;	Unknown	Unknown	Unknown	No legitimate production; Said to be a pure hallucinogen	Unknown	Unknown	64, 321, 328

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PHENYLALKYLAMINES WITH METHOXY- SUBSTITUENTS ON THE PHENYL RING

The prototype drug of this class (Table XVII) is mescaline (S 226), a close chemical relative of amphetamine. It is the most active material found in peyote and was the first of the hallucinogens to be isolated, synthesized and investigated.[353, 354, 356, 357, 366] Though less potent, its effects are identical to those of LSD and crossed tolerance between mescaline and LSD has been proved.[368, 369]

An active illicit market exists. Mescaline is a drug of high abuse potential with no established therapeutic use.

A large number of phenylalkylamines with methoxy- and/or methylenedioxy- substituents on the phenyl ring have been synthesized [356, 365] and many more could be made. There seemed to be little point in listing all of these potential hallucinogens at this time. Two of them, compounds S 228 (TMA) and S 227 (STP or DOM), have been sufficiently characterized as having mescaline-like effects in man [355, 358, 363-365] so that they must be rated as having high dependence potential. In addition, S 227 (STP) has appeared in the illicit market.

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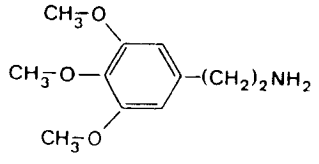
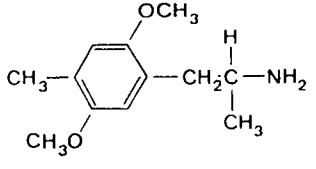
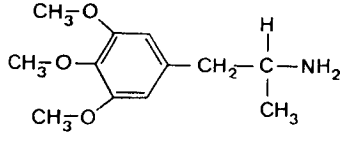
TABLE XVII. HALLUCINOGENS

PHENYLALKYLAMINES WITH METHOXY- SUBSTITUENTS ON PHENYL RING

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 226  3,4,5-trimethoxy-phenethylamine	None; Mescaline	Nausea; Vomiting; Change in mood; Euphoria-dysphoria; Alterations in sensory perception; Hallucinations	Yes; Also cross-tolerance to LSD-25	Yes	No	No legitimate production	Panic reactions; Suicide; Prolonged psychotic reaction	High	353, 354, 356, 357, 366-369
S 227  2,5-dimethoxy-4-methyl-amphetamine	None; STP; DOM	Mescaline-like	Unknown	Yes	Improbable	No legitimate production	Panic reactions; Suicide; Prolonged psychotic reaction	High	355, 358, 363-365
S 228  α-methylmescaline; 3,4,5-trimethoxy-isopropylamine	None; TMA	Mescaline-like; Twice as potent	No information	No information	No information	No legitimate production	Panic reactions; Schizophreniform states; Suicide; Prolonged psychotic reaction	High	359-362, 365

[a] International Nonproprietary Name proposed by the World Health Organization, if any, or other nonproprietary name, if any; if there is no nonproprietary name, the main entry in the *Subsidia Pharmaceutica Index Nominum* or in the *Merck Index* or other generally accepted name. "None" indicates that an International Nonproprietary Name has not been proposed so far. The following abbreviations show the source of the name used: BAN = British Approved Name; DCF = Dénomination commune française; IN = *Subsidia Pharmaceutica Index Nominum*; MI = *Merck Index*, 8th ed.; NFN = Nordisk Farmakopénaevn.

[b] Current therapeutic use and indications.

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HALLUCINOGENIC ANTICHOLINERGICS

As explained above, the subjective reaction to these drugs (Table XVIII) is dysphoric and not euphoric, and, although persons prone to drug dependence may try them once, they do not do so a second time. Accordingly, their abuse potential is very low or non-existent even though their psychotoxicity is quite high.

Some of the antihistamines and benactyzine can, in high dose or in very susceptible persons, cause an atropine-like psychosis.[64, 370, 371]

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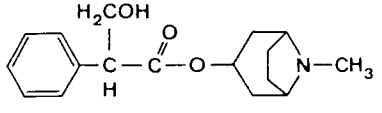
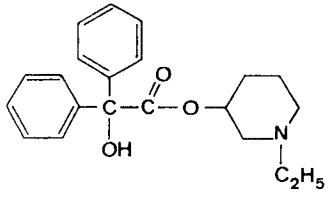
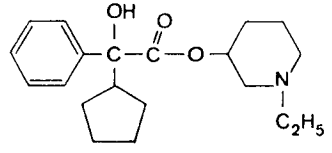
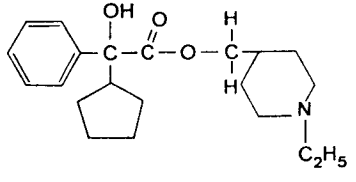
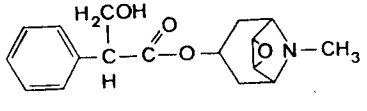
TABLE XVIII. HALLUCINOGENS

HALLUCINOGENIC ANTICHOLINERGICS

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 229  1α*H*,5α*H*-tropan-3α-ol(±)-tropate (ester); (±)-hyoscyamine	None; Atropine	Dry mouth; Dry skin; Hot skin; Tachycardia; Flushing; Diminished salivation; Dilated and fixed pupils; Disorientation; Confusion; Sedation; Hallucinations	Yes	No (in fact used as deterrent to abuse)	No	Cholinergic blocker	Poisoning; Toxic psychosis	None	370, 371, 373, 375-376
S 230  *N*-ethyl-3-piperidyl benzilate	None; JB-318	Like scopolamine	Yes	No (in fact used as deterrent to abuse)	No	No production	Poisoning; Toxic psychosis	None	374

[a] International Nonproprietary Name proposed by the World Health Organization, if any, or other nonproprietary name, if any; if there is no nonproprietary name, the main entry in the *Subsidia Pharmaceutica Index Nominum* or in the *Merck Index* or other generally accepted name. " None " indicates that an International Nonproprietary Name has not been proposed so far. The following abbreviations show the source of the name used: BAN = British Approved Name; DCF = Dénomination commune française; IN = *Subsidia Pharmaceutica Index Nominum*; MI = *Merck Index*, 8th ed.; NFN = Nordisk Farmakopénaevn.

[b] Current therapeutic use and indications.

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 231 *Mixture of:*  *N*-ethyl-2-pyridolidylmethylphenylcyclopentyl glycolate *and*  *N*-ethyl-3-piperidyl phenylcyclopentyl glycolate	None; JB-329	Typical atropine-like delirium [c]	Unknown	No	No	None	Poisoning; Toxic psychosis	None	329, 372
S 232  1α*H*,5α*H*-tropan-3α-ol,6β,7β-epoxy-(−)-tropate (ester); 6β,7β-epoxy-3α-tropanyl *s*-(−)-tropate; (−)-scopolamine, (−)-hyoscine	None; Scopolamine	Marked CNS effects; Less cholinergic blocking effect; Dry mouth; Dry skin; Tachycardia; Flushing; Diminished salivation; Dilated and fixed pupils; Confusion; Sedation; Hallucinations; Disorientation	Yes	No	No	Anaesthetic premedication; Amnesic	Poisoning; Toxic psychosis	None	370, 373, 374, 376

[c] There are a large number of other piperidyl benzilates with atropine-like effects. These can be found in reference 64.

TETRAHYDROCANNABINOLS

Only seven compounds of this type were selected for this review of more than a hundred that have been synthesized (S 233 to S 238; Table XIX). They were chosen because they have been made synthetically, are found in *Cannabis* (S 233 and S 235), are racemates or isomers (S 234, S 236 and S 237), or are chemical derivates of synthetic tetrahydrocannabinol that have been shown to induce effects similar to those of *Cannabis* in animals and in man. Many additional congeners will certainly be prepared in the future.

All of these tetrahydrocannabinols, while of great scientific interest and importance, have no proven therapeutic use. All are hallucinogens if taken in a sufficient dose. All must be rated as having high potential for producing dependence of the *Cannabis* type.

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383. Hollister, L. E., Richards, R. K. & Gillespie, H. K. (1968) *Clin. Pharmacol. Ther.*, **9**, 783 (Comparison of tetrahydrocannabinol and synhexyl in man)
384. Isbell, H. (1968) *Bull. Probl. drug depend.*, Addendum 1, pp. 1-32 (Substances occurring naturally in marihuana (*Cannabis sativa*) and identical or related semisynthetic or synthetic materials)
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386. Keeler, M. H. (1968) *Dis. nerv. Syst.*, **29**, 314-315 (Marihuana induced hallucinations)
387. Loewe, S. (1950) *Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak.*, **211**, 175-193 (Cannabiswirkstoffe und Pharmakologie der Cannabinole)
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389. Mechoulam, R. & Gaoni, Y. (1965) *J. Amer. chem. Soc.*, **87**, 3273 (The total synthesis of dl-Δ^1-tetrahydrocannabinol, the active constituent of hashish)
390. Mechoulam, R. & Gaoni, Y. (1967) *J. Amer. chem. Soc.*, **89**, 4552 (A stereoscopic synthesis of (—)-Δ^1 and $\Delta^{1(6)}$-tetrahydrocannabinols)
391. Petrzilka, T., Haefliger, W., Sikemeier, C., Dhloff, G. & Eschenmoser, A. (1967) *Helv. chim. Acta.*, **50**, 719 (Synthese und Aktivität des (—) Cannabidiols. Vorläufige Mitteilung)
392. Petrzilka, T. & Sikemeier, C. (1967) *Helv. chim. Acta.*, **50**, 1416 (Ueber Inhaltstoffe des Haschisch (2 Vorläufige Mitteilung). Synthese von (—)$\Delta^{6,1}$-3,4-*trans*-tetrahydrocannabinol sowie (±)-$\Delta^{6,1}$-3,4-*trans*-tetrahydrocannabinol)
393. Petrzilka, T. & Sikemeier, C. (1967) *Helv. chim. Acta.*, **50**, 2111 (Ueber Inhaltstoffe des Haschisch. III. (Conversion of (—)$\Delta^{6,1}$-3,4-*trans*-tetrahydrocannabinol to (1)-$\Delta^{1,2}$-3,4-*trans*-tetrahydrocannabinol)
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395. Williams, E. G., Himmelsback, C. K., Wikler, A., Ruble, D. C. & Lloyd, B. J. (1946) *Pub. Hlth Rep. (Wash.)*, **61**, 1059 (Studies on marihuana and pyrahexyl compounds)

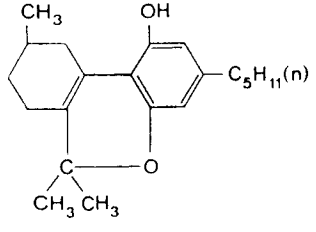
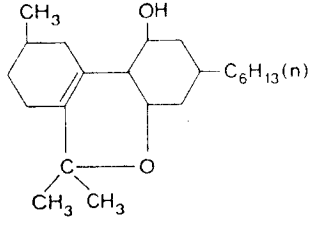
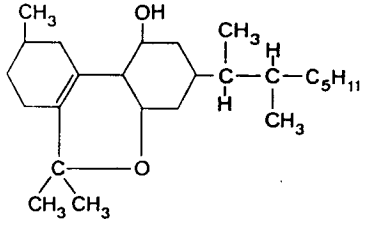
1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 236 (±)-Δ^8-*trans*-tetrahydrocannabinol; (±)-Δ^6-*trans*-tetrahydrocannabinol; (racemate of S 235)	None; (±)-Δ^8-THC (±)-Δ^6-THC	Not known in man; Marked alteration in behaviour of monkeys	No information	Probable	No information	—	Alterations in mood and judgement; Psychotic episodes	High	382, 384, 394
S 237  (+)-10a,6a-tetrahydrocannabinol; 6*H*-dibenzo[*b*,*d*]-pyran-1-ol-7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl	None; Synthetic THC		No information	Probable	No information	Marijuana-like in man and dog but very low potency	Alterations in mood and judgement; Psychotic episodes	High if available in large amounts	378, 384, 388
S 238  3-*n*-hexyl-tetrahydrocannabinol; 6*H*-dibenzo-[*b*,*d*]-pyran-1-ol-7,8,9,10-tetrahydro-6,6,9-trimethyl-3-hexyl	None; Parahexyl	Similar to S 233; Marked sedation	Probably some	Probable	Possible	None	Alterations in mood, judgement and attention; Psychosis	High	64, 379, 383, 387, 395

TABLE XIX. HALLUCINOGENS

TETRAHYDROCANNABINOLS *(concluded)*

1 No. of compound and formula (or chemical name)	2 Names [a]	3 Symptoms of intoxication	4 Tolerance	5 Psychic dependence	6 Physical dependence	7 Pharmacological notes [b]	8 Major dangers of abuse	9 Abuse-potential rating	10 References
S 239  6*H*-dibenzo-[*b*,*d*]-pyran-1-ol-7,8,9,10-tetrahydro-6,6,9-trimethyl-3-[1,2-dimethylheptyl]	None; DMHP	Similar to S 233; Marked sedation; Marked postural hypotension	No information	Probable	No information	The most potent tetrahydrocannabinol derivative yet known	Alterations in mood, judgement and attention; Psychosis; Postural hypotension	High	381, 384

MISCELLANEOUS HALLUCINOGENS

Only one compound is listed in this group, phencyclidine (1-(1-phenyl-cyclohexyl)-piperidine). This drug is marketed as an intravenous anaesthetic, for veterinary use only.[396-398] Phencyclidine is not used as an anaesthetic in man because it causes a severe psychotic reaction, which has not been well characterized, but which is manifested by marked depersonalization.[400] Although the effects of phencyclidine are believed to be dysphoric, it has appeared in the illicit market in the USA and is thought to have been illegally synthesized.[399] Accordingly it must be regarded as having moderate potential for abuse.

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398. Jaffe, M. H. (1964) *Anesth. Analg. Curr. Res.*, **43**, 221 (An anaesthetic for the chimpanzee: 1-(1-phenyl cyclohexyl) piperidine hydrochloride)

399. *J. Psychedelic Drugs*, 1968, **1**, No. 2, 146 (The peace pill)

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CRUDE PLANT DRUGS

This is a very interesting group of materials (Table XX) that pose some difficult problems. In most instances neither the animal nor the human pharmacology of the crude drugs has been well characterized. Many of them are used in religious rites by primitive peoples. Their effects can in several cases be attributed to the most potent drug that they are known to contain.

Anhalonium lewinii (S 242) or peyote contains mescaline and is used in sacramental fashion in the rites of the Native American Church. Even though peyote causes more nausea and vomiting than mescaline or LSD, a small illegal traffic in it has developed which is entirely unrelated to its religious use. It is a hallucinogen and has at least moderate potential for producing dependence. *Psilocybe mexicana* (S 248) is a small mushroom found in Mexico, which contains psilocybine and psilocin. It is used in religious and therapeutic rituals by Mexican Indians. It is hallucinogenic and illicit use and traffic in the mushroom has occurred. Like peyote, it must be judged to have definite dependence potential.

The bark, seeds and pods of several trees, *Anadenanthera peregrina* (S 241), *Mimosa hostilis* and *Virola calophylla*, are ground and used as snuff by Indians in South America and the Caribbean Islands. These materials contain principally dimethyltryptamine and congeners of dimethyltryptamine. No illicit traffic in these materials has yet occurred but they must be regarded as having some dependence potential if available.

Less is known about *Banisteropsis caapi* (S 244), *Amanita muscaria* (S 243) and *Tabernanthe iboga* (S 249) but all have been described as being hallucinogenic. No rating of dependence potential can be made.

Myristica fragrans (S 246) or nutmeg, is sometimes used as an intoxicant, but nutmeg seems to be only weakly hallucinogenic (if at all). Rather, nutmeg seems to cause primarily an unpleasant kind of drunkenness. The spice is abused most frequently by prisoners since it is relatively easy to obtain. Its abuse potential, in view of its great availability, must be rated as quite low. *Piper methysticum* (S 247) or *kava*, is used ritualistically by Polynesians in the South Pacific. The intoxication has not been well characterized but appears to be mild. Its dependence potential is low.

The seeds of the morning-glories, *Rivea corymbosa* and *Ipomea violacea* (S 250), contain compounds that are congeners of LSD but that are not truly hallucinogenic [407, 419] Many other varieties of morning-glory contain varying amounts of these drugs. The seeds are used ritualistically by Mexican Indians. Eating morning-glory seeds became popular for a time in the USA but the practice has spontaneously died out because of the low activity and unpleasant side-effects. The dependence potential of morning-glory seeds is regarded as being very low.

Datura stramonium (S 245) contains belladonna alkaloids and belongs to the group of anticholinergic hallucinogens. *Datura* has no or very low dependence potential because of the unpleasantness of its effects. It is sometimes used to adulterate *Cannabis*.

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405. Deulofeu, V. (1967) pp. 393-402 in ref. 318 (Chemical compounds isolated from Banisteriopsis and related species)
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TABLE XX

CRUDE PLANT DRUGS

	Scientific name of plant	Type of plant	Parts of plants used	Names commonly used	Active ingredients	Dangers of abuse	References
S 240	*Catha edulis*	Shrub	Fresh leaves	Khat	(+)-nor-pseudo-iso-ephedrine (cathine)	Stimulation	318, 408, 426, 427, 434
S 241	*Anadenanthera peregrina* (Syn. *Piptadenia peregrina*) Various varieties of above *Mimosa hostilis* *Virola calophylla*	Tree	Bark, seeds, seed pods	Cohoba, paricá, Epéna	Bufotenine (5-OH-DMT); Dimethyltryptamine; Dimethyltryptamine *N*-oxide; Bufotenine (5-OH-DMT) *N*-oxide; 5-methoxydimethyl-tryptamine	Psychoses	318, 401, 411, 420, 425, 426, 430
S 242	*Anhalonium lewinii* (Syn. *Lophophora williamsii*)	Cactus	Dried " buttons "	Peyote, peyotl	Mescaline	Psychoses	318, 375, 402, 414
S 243	*Amanita muscaria*	Mushroom	Entire mushroom	Fly agaric, panx	Muscarine; Muscimole; Ibotenic acid	Poorly characterized	318, 403, 406, 429, 431, 432
S 244	*Banisteropsis caapi*	Vine	Lower part	Ayahuasca, caapi, yagé	Various harmine and harmaline alkaloids	Psychoses	318, 338, 404, 411, 413
S 245	*Datura stramonium*	Herbaceous weed	Leaves	Asthmador, loco weed	Belladonna (atropine) alkaloids	Psychoses	318, 407, 418
S 246	*Myristica fragrans*	Tree	Kernel of seed, outside of seed shells (arillus)	Nutmeg, mace	Many terpines and aromatic compounds; Myristicin, etc.	Poorly characterized	318, 416, 419, 422, 423, 426, 428, 433, 435
S 247	*Piper methysticum*	Perennial shrub	Powdered roots of plants	Kava, kava-kava, kawa, cava	Contains many 5,6-dihydro-α-pyrones	Poorly characterized	318, 413, 410, 412 415, 417
S 248	*Psilocybe mexicana*	Mushroom	Entire mushroom		Psilocybine; psilocin	Psychoses	318, 404
S 249	*Tabernanthe iboga*	Shrub	Roots	—	Ibogaine	Poorly characterized in man	318, 405, 421
S 250	*Rivea corymbosa* *Ipomea violacea* Many other varieties	Climbing flowering vines, morning-glories	Seeds	Ololiqui; ololinqui	Various indoles such as D-lysergic acid amide, isolysergic amide, ergine, etc.	Sedation; Psychoses?	318, 332, 407, 419, 424

410. Holmes, L. D. (1967) pp. 107-125 in ref. 318 (The function of kava in modern Samoan culture)
411. Holmstedt, B. & Lindgren, J.-E. (1967) pp. 339-373 in ref. 318 (Chemical constituents and pharmacology of South American snuffs)
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417. Meyer, H. J. (1967) pp. 133-151 in ref. 318 (Pharmacology of kava)
418. Moreau, J. J. (de Tours) (1841) *Gazette Méd. de Paris, IX*, Nos. 41, 43 (Mémoire sur le traitement des hallucinations par le Datura Stramonium)
419. Payne, R. A. (1963) *New Engl. J. Med.*, **209**, 30 (Nutmeg intoxication)
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421. Schneider, J. A. & Sigg, E. B. (1956-57) *Ann. N.Y. Acad. Sci.*, **66**, 765 (Neuropharmacological studies on ibogaine, an indole alkaloid with stimulant properties)
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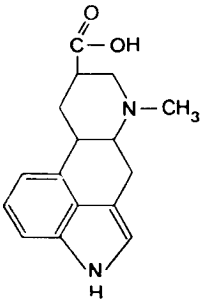
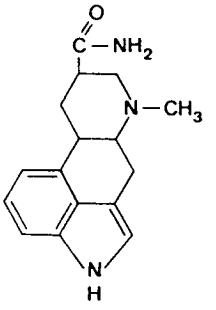
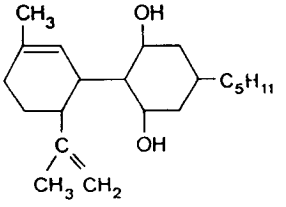
426. Schultes, R. E. (1969) *Bull. Narcot.*, **21**, No. 3, 3-16; No. 4, 15-28 (The plant kingdom and hallucinogens)
427. Trellu, M. (1959) *Bull. Narcot.*, **11**, 43-44 (The pharmacodynamics of Khat)
428. Truitt, E. B. (1967) pp. 215-222 in ref. 318 (The pharmacology of myristicin and nutmeg)
429. Waser, P. G. (1967) pp. 419-439 in ref. 318 (The pharmacology of Amanita Muscaria)
430. Wassen, S. H. (1967) pp. 233-289 in ref. 318 (Anthropological survey of the use of South American snuffs)
431. Wasson, R. G. (1967) pp. 405-414 in ref. 318 (Fly agaric and man)
432. Wasson, V. P. & Wasson, R. G. (1957) *Mushrooms, Russia and history*, Pantheon, New York
433. Weil, A. T. (1967) pp. 188-201 in ref. 318 (Nutmeg as a psychoactive drug)
434. WHO Expert Committee on Addiction-Producing Drugs (1962) *Twelfth report*, Geneva (*Wld Hlth Org. techn. Rep. Ser.*, No. 229)
435. Williams, E. Y. & West, F. (1968) *J. nat. med. Ass. (N.Y.)*, **60**, 289-290 (The use of nutmeg as a psychotropic drug)

PRECURSORS

Precursors (Table XXI) are chemicals which are not themselves highly active pharmacologically but which are readily convertible by simple chemical process into drugs of abuse. Precursors pose knotty problems. For example, lysergic acid (S 251) is a precursor for LSD; yet lysergic acid is also used for synthesis of the non-hallucinogenic ergot alkaloids that have great therapeutic use in medicine. LSD can be synthesized by coupling lysergic acid with ethylenediamine but ethylenediamine is a common chemical with great industrial use in the production of all sorts of compounds that are not used as drugs. Lysergamide (S 252) can also be used for the synthesis of LSD, but is not customarily employed for manufacture of ergot alkaloids. Cannabidiol (S 253) is a precursor to tetrahydrocannabinol and at the present time has no chemical use other than synthesis of tetrahydrocannabinol. These examples could be multiplied endlessly, Obviously, the dangers of a particular precursor have to be weighed against the kind and amount of its use as a chemical for purposes other than producing a drug of abuse, when considering the type of control measures that might be applied.

TABLE XXI

PRECURSORS

Formula and chemical name	Precursor to:
S 251  Lysergic acid; ergoline-8 β-carboxylic acid, 9,10-didehydro-6-methyl	Lysergide
S 252  Lysergamide; (+)-lysergic acid amide; ergoline-8 β-carboxamide, 9,10-didehydro-6-methyl	Lysergide
S 253  (±)- and (+)-cannabidiol; resorcinol, 2-*p*-mentha-1,8,dien-3-yl-5-pentyl	The tetrahydrocannabinols

RÉSUMÉ

APTITUDE DE MÉDICAMENTS «NON STUPÉFIANTS» À ENGENDRER LA DÉPENDANCE

Les auteurs présentent un ensemble de données cliniques et de laboratoire sur le risque de dépendance associé à l'usage de 253 médicaments et substances d'origine végétale psychotropes considérés comme capables, ou virtuellement capables, d'agir sur le système nerveux central (SNC) par stimulation, dépression ou création d'hallucinations, ou d'être à l'origine de troubles des fonctions perceptives, cognitives ou de jugement. Les substances ainsi étudiées comprennent 1) des médicaments qui, en raison de leur aptitude à susciter la dépendance, font déjà l'objet de mesures de contrôle dans plusieurs pays où la surveillance est particulièrement stricte; 2) des substances qui sont étroitement apparentées chimiquement à des médicaments soumis à un contrôle national, ou qui font preuve de propriétés très semblables; 3) d'autres substances qui ont déjà donné lieu à des abus, ou qui sont susceptibles d'être utilisées abusivement, à cause de leur similitude, du point de vue des caractéristiques chimiques et pharmacologiques, avec les substances mentionnées ci-dessus. Quelques précurseurs de certains hallucinogènes sont également passés en revue. Par contre, on n'a pas tenu compte dans cette étude des substances qui sont déjà placées sous contrôle international (comme les opiacés, la cocaïne, les feuilles de coca et le cannabis) ni de l'alcool.

Les substances étudiées ont été réparties en cinq grandes catégories: *a*) dépresseurs du SNC; *b*) stimulants du SNC; *c*) hallucinogènes; *d*) drogues végétales brutes; *e*) précurseurs. Certaines catégories ont été à leur tour subdivisées. C'est ainsi que les dépresseurs du SNC ont été classés en 13 groupes de composés: diuréides (barbituriques); mono-uréides; halogènes; chloral et ses dérivés; alcools acétyléniques tertiaires; éthers cycliques; hydrogéno-carbamates des monohydroxyalcools; hydrogéno-carbamates des glycols; dérivés de la pipéridione; quinazolinones; benzodiazépines; sulfométhanes; divers. Certains groupes de dépresseurs du SNC (réserpines, phénothiazines et butyrophénones), qui n'engendrent aucune pharmacodépendance ou abus, ne sont pas examinés.

Parmi les stimulants du SNC, quatre groupes ont été considérés: éphédrine et ses dérivés; amphétamines; dérivés de la pipéridine; agents divers. Les dibenzazépines à action antidépressive et les inhibiteurs de la monoamine-oxydase n'ont pas été retenus, aucun de ces deux groupes de substances ne donnant lieu à des abus fréquents.

Les hallucinogènes ont été répartis en indoles (LSD et substances du même type, dérivés de la tryptamine), phénylalcoylamines portant un substituant méthoxy sur le noyau phényle, anticholinergiques hallucinogènes, tétrahydrocannabinols, et hallucinogènes divers.

Le document donne une description générale des diverses catégories de médicaments psychotropes sous l'angle de leur aptitude à engendrer la dépendance. On y trouve également, pour chaque produit, des données, présentées sous forme de tableaux, concernant *a*) les dénominations communes et autres appellations; *b*) les formules de structure; *c*) les signes d'intoxication; *d*) la tolérance; *e*) la dépendance psychique (avec, dans certains cas, une appréciation qualitative de son degré); *f*) la dépendance physique et les principaux éléments du syndrome d'abstinence, quand il existe; *g*) certaines caractéristiques pharmacologiques; *h*) les principaux dangers résultant de l'abus; *i*) une évaluation qualitative du risque d'abus; *j*) de nombreuses références. Un index permet de s'orienter facilement, les substances étudiées y étant classées sous leur dénomination commune et sous leur nom chimique.

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