



**WORLD HEALTH ORGANIZATION  
ORGANISATION MONDIALE DE LA SANTE**

**31ST EXPERT COMMITTEE ON DRUG DEPENDENCE**  
M605, WHO/HQ, Geneva  
23-26 June 1998

**LIST OF DOCUMENTS**

<u>Divider Number</u>	<u>Document Number</u>
1. Draft agenda	PND/ECDD31/1
2. List of participants and addresses	PND/ECDD31/2a & 2b
3. WHO Review Procedure	PND/ECDD31/3
4. Critical Review of Psychoactive Substances	PND/ECDD31/4
<b>Annex 1 - Dihydroetorphine</b>	
<b>Annex 2 - Ephedrine</b>	
<b>Annex 3 - Remifentanil</b>	
<b>Annex 4 - Proposal of the Government of Spain</b>	
5. Pre-Review Data Sheets	PND/ECDD31/5
<b>Benzodiazepines</b>	
<b>Tobacco</b>	
<b>Gammahydroxybutyrate (GHB)</b>	
<b>4-Bromo-2,5-dimethoxyphenethylamine (2-CB)</b>	
<b>N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (MBDB)</b>	
<b>Zolpidem (INN)</b>	
6. Other documents	

ND/ECD31/1



**WORLD HEALTH ORGANIZATION  
ORGANISATION MONDIALE DE LA SANTE**

**31ST EXPERT COMMITTEE ON DRUG DEPENDENCE**  
M605, WHO/HQ, Geneva  
23-26 June 1998

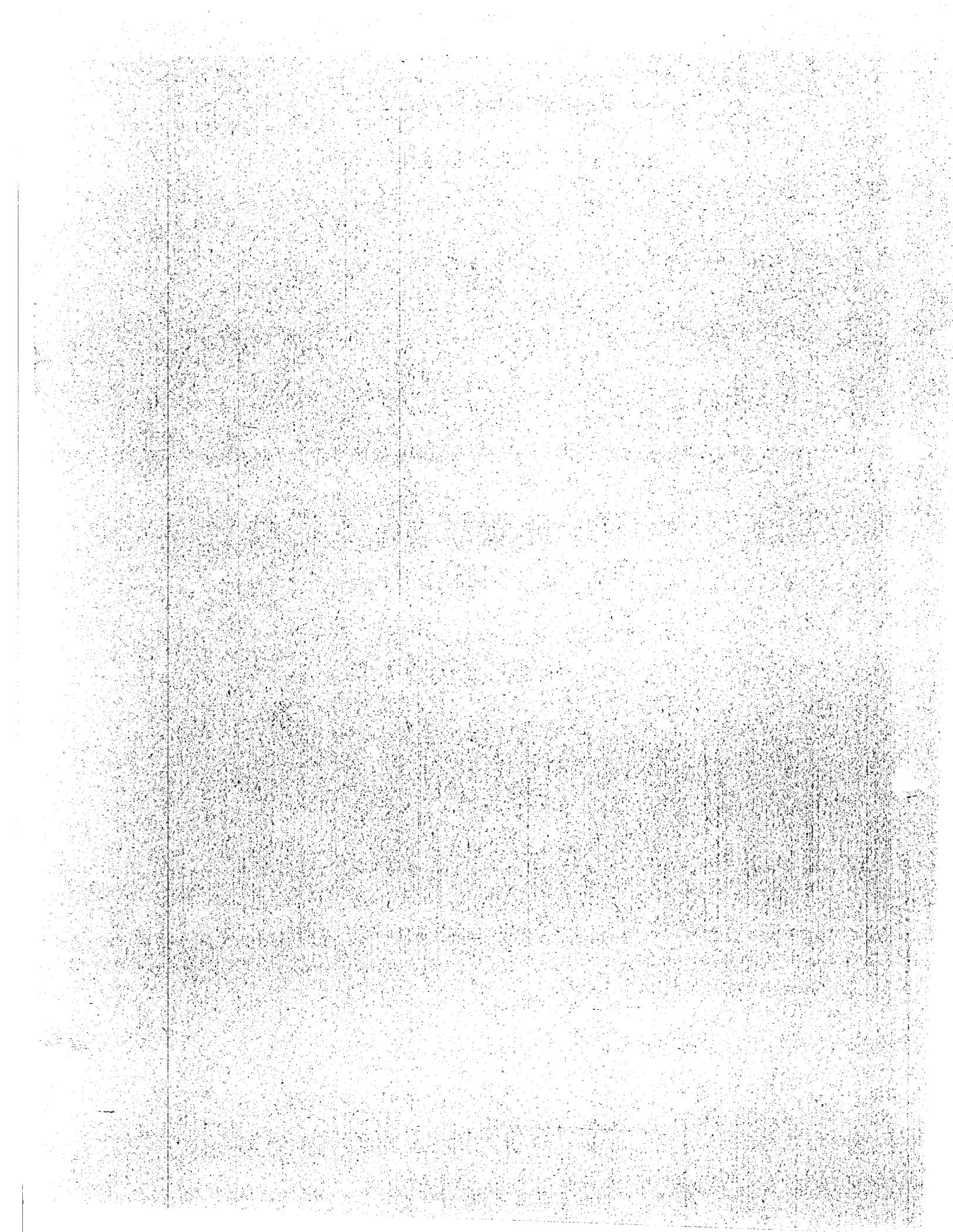
**PND/ECDD31/1**

**DRAFT AGENDA**

1. Opening
  2. Election of Chairperson and Rapporteur
  3. Approval of agenda
  4. Critical review of:
    - (i) Dihydroetorphine
    - (ii) Ephedrine
    - (iii) Remifentanil
    - (iv) With regard to all substances in Schedules I and II of the Convention on Psychotropic Substances, 1971:
      - (a) their isomers, except where expressly excluded, whenever the existence of such isomers is possible,
      - (b) their esters and ethers, except where included in another schedule, whenever the existence of such esters and ethers is possible,
      - (c) salts of those esters, ethers and isomers, under the conditions stated above, whenever the formation of such salts is possible,
      - (d) a substance resulting from modification of the chemical structure of a substance already in these schedules and which produces pharmacological effects similar to those produced by the original substance.
  5. Pre-review of:
    - (i) Benzodiazepines
    - (ii) Tobacco
    - (iii) Gammahydroxybutyrate (GHB)
    - (iv) 4-Bromo-2,5-dimethoxyphenethylamine (2C-B)
    - (v) N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (MBDB)
    - (vi) Zolpidem (INN)
  6. Adoption of report
-



PN01ECDD31/2





**WORLD HEALTH ORGANIZATION  
ORGANISATION MONDIALE DE LA SANTE**

**31ST EXPERT COMMITTEE ON DRUG DEPENDENCE**

**PND/ECDD31/2A**

M605, WHO/HQ Geneva

23-26 June 1998

**PARTICIPANTS**

**Members**

Professor Cai Zhi-Ji, National Institute of Drug Dependence, Beijing Medical University,  
Beijing, People's Republic of China

Dr P. Das Gupta, Drugs Controller (India), Ministry of Health & Family Welfare, New  
Delhi, India

Dr S. Haghghi, Director General, Food Drug and Clinical Laboratories, Tehran, Islamic  
Republic of Iran

Dr E. Medina-Mora, Instituto Mexicano de Psiquiatria, Mexico D.F., Mexico

Professor U. Rydberg, Department of Clinical Neuroscience, Clinical Alcohol and Drug  
Addiction Research, Magnus Huss Clinic, Karolinska Hospital, Stockholm, Sweden

Dr P.O. Emafo, 24 Oghosa Crescent, off Ihama Road, GRA Benin City, Nigeria

Professor E.M. Sellers, Departments of Pharmacology, Medicine and Psychiatry, Centre for  
Research in Women's Health, Women's College Hospital, University of Toronto,  
Toronto, Ontario, Canada

Professor W. Wieniawski, Chairman, Polish Pharmacopoeia Commission, Warsaw, Poland

**Representatives of UN and other organizations**

Joint United Nations Programme on HIV/AIDS, (UNAIDS) Geneva, Switzerland

United Nations International Drug Control Programme (UNDCP), Vienna, Austria

International Narcotics Control Board (INCB), Vienna, Austria

International Criminal Police Organisation (ICPO/Interpol), Lyon, France

International Organization of Consumers Unions (IOCU), London, UK

International Federation of Pharmaceutical Manufacturers Associations (IFPMA), Geneva

World Self-Medication Industry (WSMI), London, UK

World Psychiatric Association (WPA), New York, USA

International Council on Alcohol and Addictions (ICAA), Lausanne, Switzerland

**Secretariat**

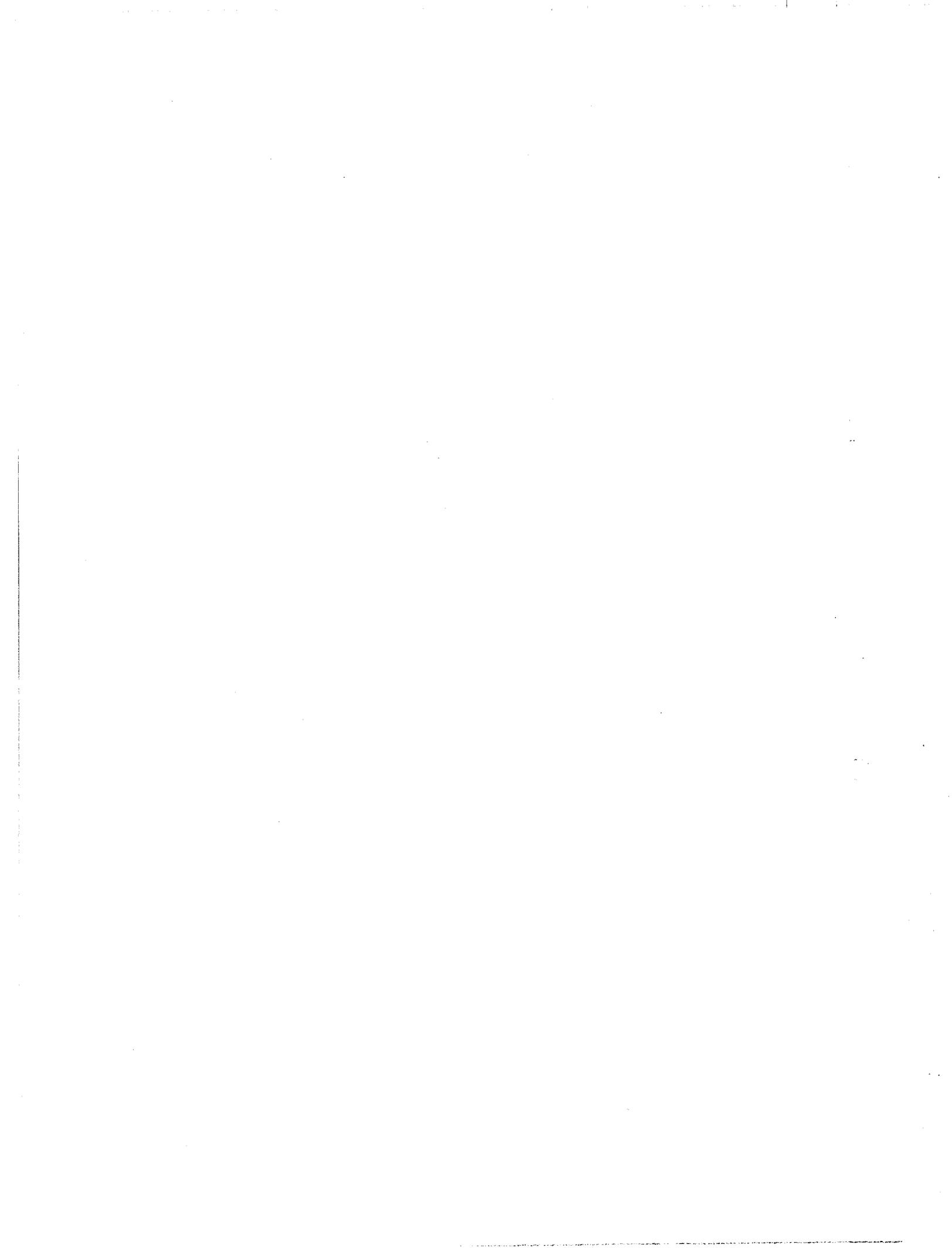
Dr J. Idänpään-Heikkilä, Director DMP

Mr T. Yoshida, DMP/PND (Secretary)

Dr K.D. Hutchinson (Temporary Adviser)

Dr M. Klein (Temporary Adviser)

Dr K. Szendrei (Temporary Adviser)





**WORLD HEALTH ORGANIZATION  
ORGANIZATION MONDIALE DE LA SANTE**

**31ST EXPERT COMMITTEE ON DRUG DEPENDENCE**  
M605, WHO/HQ, Geneva  
23-26 June 1998

**PND/ECDD31/2B**

**ADDRESSES**

Professor Cai Zhi-Ji, National Institute of Drug Dependence, Beijing Medical University,  
38, Xue Yuan Road, Haidan District, Beijing, People's Republic of China.  
Tel: +86. Fax: +86.10.6975.2538

Dr P. das Gupta, Drugs Controller (India), Ministry of Health & Family Welfare, 342-A Norman  
Bhaven, New Delhi-110 011, India. Tel: +91.11.301.8806; fax: +91.11.301.7924

Dr S. Haghighi, Director General, Food, Drug and Clinical Laboratories (FDCL), No. 31  
Emam Khomeini Avenue, Tehran 11136, Islamic Republic of Iran. Fax: +98.21.6404330

Dr E. Medina-Mora, Instituto Mexicano de Psiquiatria, Calzada Mexico-Xochimilco No. 101,  
Col San Lorenzo Huipulco, 14370 Mexico, D.F., Mexico. Tel: +52.5.655.4268; fax:  
+52.5.513.3446

Professor U. Rydberg, Department of Clinical Neuroscience, Clinical Alcohol and Drug  
Addiction Research Section, Magnus Huss Clinic, Karolinska Hospital, 171 76 Stockholm,  
Sweden. Tel: +46.8.517.70000; fax: +46.8.32.63.69

Dr P.O. Emafo, 24 Oghosa Crescent, off Ihama Road, GRA Benin City, Edo State, Nigeria.  
Tel: +23.4.52.250.592; fax: +23.4.52.250.668

Professor E.M. Sellers, Departments of Pharmacology, Medicine and Psychiatry, Centre  
for Research in Women's Health, Women's College Hospital, University of Toronto,  
76, Greenville Street (Room 947), Toronto, Ontario M5S 1B2, Canada. Tel: +1.416.323.7552;  
fax: +1.416.323.7553.

Professor W. Wieniawski, Chairman, Polish Pharmacopoeia Commission, 30/34 Chelmska Str.,  
00-725 Warsaw, Poland. Fax: +48.22.41.06.52





**WORLD HEALTH ORGANIZATION  
ORGANISATION MONDIALE DE LA SANTE**

**31ST EXPERT COMMITTEE ON DRUG DEPENDENCE**  
M605, WHO/HQ, Geneva  
23-26 June 1998

**PND/ECDD31/3**

**WHO REVIEW PROCEDURE**

**(Provisional Agenda Items: 4 & 5)**

The review of psychoactive substances by the Expert Committee on Drug Dependence is to be carried out in accordance with the established procedures. This short document provides an outline of these procedures.

## WHO REVIEW PROCEDURE

### 1. Outline of the review procedure

Since 1990, WHO's review of psychoactive substances has been carried out in two steps, in accordance with the Revised Guidelines for the WHO Review of Dependence-Producing Psychoactive Substances for International Control adopted by the Executive Board that same year. The first step is referred to as "pre-review" which is a preliminary review carried out to determine whether or not a fully documented review ("critical review") of the substance is required. Critical review is conducted only when WHO "has information that may justify the scheduling" of a substance. Both pre-review and critical review are carried out by the Expert Committee on Drug Dependence (ECDD).

The first step, pre-review, is unnecessary if there has been an official notification to the United Nations by a Party, or an explicit request from the UN Commission on Narcotic Drugs. The two-step review procedure applies only to WHO-initiated reviews. In such cases, at least two meetings of the ECDD are required for WHO to formulate a scheduling recommendation to the United Nations.

This review procedure applies not only to new substances but to the re-scheduling of substances already under international control.

### 2. Scheduling criteria

#### 2.1 **Narcotic drugs**

The Revised Guidelines indicate that the ECDD should first decide whether the substance under review has morphine-like, cocaine-like, or cannabis-like effects, or is convertible into a scheduled substance having such effects. If so, the ECDD should then determine if the substance:

- (1) is liable to similar abuse and productive of similar ill effects as the substances in Schedule I or Schedule II;
- (2) is convertible into a substance already in Schedule I or Schedule II.

This is because the 1961 Single Convention on Narcotic Drugs indicates that the similarity in both "abuse liability" and "ill effects" to those already in these Schedules is the criterion, as follows.

Schedule I or II	If a substance is liable to similar abuse and productive of similar ill effects as the drugs in Schedule I or Schedule II, or is convertible into a drug ...
------------------	--

Some drugs in Schedule I can also be placed in Schedule IV if they meet the following criteria:

**Schedule IV**            If a drug in Schedule I is particularly liable to abuse and to produce ill effects, and such liability is not offset by substantial therapeutic advantages not possessed by substances other than drugs in Schedule IV ...

**Schedule III** only contains exempt preparations of specified compositions containing drugs in Schedules I or II.

Examples of narcotic drugs in the three Schedules are:

**Schedule I**    Morphine, heroin, pethidine, cocaine, cannabis (106 substances)

**Schedule II**    Codeine, dihydrocodeine, pholcodine (10 substances)

**Schedule IV**    Cannabis, heroin (17 substances)

## 2.2 Psychotropic substances

The Convention on Psychotropic Substances, 1971, defines WHO's role in the scheduling process as follows:

If the World Health Organization finds:

- (a) That the substance has the capacity to produce
  - (i) (1) A state of dependence, and
  - (2) Central nervous system stimulation or depression, resulting in hallucinations or disturbances in motor function or thinking or behaviour or perception or mood, or
  - (ii) Similar abuse and similar ill effects as a substance in Schedule I, II, III or IV, and
- (b) That there is sufficient evidence that the substance is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control,

the World Health Organization shall communicate to the Commission an assessment of the substance, including the extent or likelihood of abuse, the degree of seriousness of the public health and social problem and the degree of usefulness of the substance in medical therapy, together with recommendations on control measures, if any, that would be appropriate in the light of its assessment.

With regard to the selection of a particular Schedule, WHO has been using the following additional criteria. These criteria were first developed by the ECDD at its 17th meeting

in 1969, when it discussed the “then-new” international drug control system for psychotropic substances.

- Schedule I Substances whose liability to abuse constitutes an especially serious risk to public health and which have very limited, if any, therapeutic usefulness.
- Schedule II Substances whose liability to abuse constitutes a substantial risk to public health and which have little to moderate therapeutic usefulness.
- Schedule III Substances whose liability to abuse constitutes a substantial risk to public health and which have moderate to great therapeutic usefulness.
- Schedule IV Substances whose liability to abuse constitutes a smaller but still significant risk to public health and which have a therapeutic usefulness from little to great.

The ECDD reconfirmed these criteria at its 29th meeting in 1994, but worked out the following supplementary guidelines;

- In cases where the 1969 criteria apply only in part, the scheduling recommendation should be made with a higher regard to the risk to public health than to therapeutic usefulness.
- Notwithstanding the above, recommendations for inclusion in Schedule I should be made only when the 1969 criteria are fully met, with respect to both therapeutic usefulness and the risk to public health.

Thus, when the abuse liability of a psychotropic substance constitutes a “significant” risk to public health, it would go to Schedule IV, regardless of its therapeutic usefulness. If the degree of risk to public health is “substantial”, it would go either to Schedule II or III, depending on its therapeutic usefulness. Theoretically, the possibility of a therapeutically useful substance meeting the criteria for Schedule I is ruled out. Also, the lack of therapeutic usefulness should not be used to justify a recommendation for inclusion in Schedule I, if its abuse liability does not constitute “an especially serious risk” to public health and society.

Examples of psychotropic substances in the four Schedules are:

- Schedule I (+)-lysergide (LSD), MDMA, mescaline, psilocine (27 substances)
- Schedule II Amphetamines, methylphenidate, secobarbital (15 substances)
- Schedule III Amobarbital, pentobarbital, flunitrazepam (9 substances)
- Schedule IV Most benzodiazepines, phenobarbital, pemoline (60 substances)

PND/ECD/31/14



WORLD HEALTH ORGANIZATION  
ORGANISATION MONDIALE DE LA SANTE

31ST EXPERT COMMITTEE ON DRUG DEPENDENCE  
M605, WHO/HQ, Geneva  
23-26 June 1998

PND/ECDD31/4

## CRITICAL REVIEW OF PSYCHOACTIVE SUBSTANCES

(Provisional Agenda Item: 4)

This document provides an in-depth review of the following three substances - dihydrotorphine, ephedrine and remifentanil - as well as the proposal of the Government of Spain concerning the scheduling of isomers, esters, ethers and analogues of the substances in Schedules I and II of the 1971 Convention on Psychotropic Substances. This document has been prepared by the Secretariat, with the assistance of external experts, for use by the participants of the 31st Session of the WHO Expert Committee on Drug Dependence (ECDD).

## TABLE OF CONTENTS

	<u>Page</u>
1. Introduction	1
2. Abbreviations used:	
A. Names of countries	1 - 6
B. Other abbreviations	6
3. Information gathering	7
4. Organization of information & contributors	7
5. Format of review of substance	8

### ANNEXES

Dihydroetorphine .....	ANNEX 1
Ephedrine .....	ANNEX 2
Remifentanil .....	ANNEX 3
Proposal of the Government of Spain .....	ANNEX 4

## 1. INTRODUCTION

This document has been prepared for evaluation by the 31st Expert Committee on Drug Dependence (ECDD) which will meet from 23 to 26 June 1998. This ECDD will review the following three substances: **Dihydroetorphine**; **Ephedrine**; and **Remifentanil**. In addition, the ECDD will also review the **proposal of the Government of Spain** concerning the scheduling of isomers, esters, ethers and analogues of all substances in Schedules I and II of the Convention on Psychotropic Substances, 1971. Specific details on these substances and the Spanish proposal are given in the four Annexes to this document. The review has been prepared consistent with the Revised Guidelines for the WHO Review of Dependence-Producing Psychoactive Substances for International Control.

## 2. ABBREVIATIONS USED IN THIS REVIEW

### A. Names of countries

WHO codes for Member States (WHO Manual III.4, Annex) was used for country name abbreviations.

<u>Code</u>	<u>Country</u>
AFG	Afghanistan
ALB	Albania
ALG	Algeria
AMS	American Samoa
ANG	Angola
ANI	Antigua and Barbuda
ARG	Argentina
ARM	Armenia
AUS	Australia
AUT	Austria
AZE	Azerbaijan
BAH	Bahamas
BAA	Bahrain
BAN	Bangladesh
BAR	Barbados
BLR	Belarus
BEL	Belgium
BLZ	Belize
BEN	Benin
BER	Bermuda
BHU	Bhutan
BOL	Bolivia
BIH	Bosnia & Herzegovina
BOT	Botswana
BRA	Brazil
VIB	British Virgin Islands

BRU	Brunei Darussalam
BUL	Bulgaria
BFA	Burkina Faso
BUU	Burundi
CAM	Cambodia
CAE	Cameroon
CAN	Canada
CAV	Cape Verde
CAR	Caribbean
CAY	Cayman Islands
CAF	Central African Republic
CHA	Chad
CHI	Chile
CHN	China
COL	Colombia
COM	Comoros
CNG	Congo
COK	Cook Islands
COR	Costa Rica
IVC	Côte d'Ivoire
CRO	Croatia
CUB	Cuba
CUR	Curaçao (AMRO)
CYP	Cyprus
CZH	Czech Republic
COD	Democratic Republic of Congo
KRD	Democratic People's Republic of Korea
DEN	Denmark
DJI	Djibouti
DOM	Dominica
DOR	Dominican Republic
ECA	Eastern Caribbean
ECU	Ecuador
EGY	Egypt
ELS	El Salvador
EQG	Equatorial Guinea
ERI	Eritrea
EST	Estonia
ETH	Ethiopia
FIJ	Fiji
FIN	Finland
FRA	France
FRG	French Guiana
FRP	French Polynesia
GAB	Gabon
GAM	Gambia
GEO	Georgia

DEU	Germany
GHA	Ghana
GRE	Greece
GRA	Grenada
GUA	Guadeloupe
GUM	Guam
GUT	Guatemala
GUI	Guinea
GUB	Guinea-Bissau
GUY	Guyana
HAI	Haiti
HON	Honduras
HOK	Hong Kong
HUN	Hungary
ICE	Iceland
IND	India
INO	Indonesia
IRA	Iran, Islamic Republic of
IRQ	Iraq
IRE	Ireland
ISR	Israel
ITA	Italy
JAM	Jamaica
JPN	Japan
JOR	Jordan
KAZ	Kazakstan
KEN	Kenya
KIR	Kiribati
KUW	Kuwait
KGZ	Kyrgyzstan
LAO	Lao People's Democratic Republic
LVA	Latvia
LEB	Lebanon
LES	Lesotho
LIB	Liberia
LIY	Libyan Arab Jamahiriya
LTU	Lithuania
LUX	Luxembourg
MAC	Macao
MAD	Madagascar
MAL	Malawi
MAA	Malaysia
MAV	Maldives
MAI	Mali
MAT	Malta
MSI	Marshall Islands
MAR	Martinique

MAU	Mauritania
MAS	Mauritius
MEX	Mexico
MIC	Micronesia
MON	Monaco
MOG	Mongolia
MOT	Montserrat
MOR	Morocco
MOZ	Mozambique
MMR	Myanmar
NAM	Namibia
NRU	Nauru
NEP	Nepal
NET	Netherlands
NEA	Netherlands Antilles
NEC	New Caledonia
NEZ	New Zealand
NIC	Nicaragua
NIG	Niger
NIE	Nigeria
NIU	Niue
NCA	Northern Caribbean
NMI	Northern Mariana Islands
NOR	Norway
OMA	Oman
PAK	Pakistan
BLA	Palau
PAN	Panama
PNG	Papua New Guinea
PAR	Paraguay
PER	Peru
PHL	Philippines
POL	Poland
POR	Portugal
PUR	Puerto Rico
QAT	Qatar
KOR	Republic of Korea
MDA	Republic of Moldova
REU	Reunion
ROM	Romania
RUS	Russian Federation
RWA	Rwanda
SCN	St Kitts and Nevis
SAH	St Helena
SAL	St Lucia
SAV	St Vincent and the Grenadines
SMA	Samoa

SMR	San Marino
STP	Sao Tome and Principe
SAA	Saudi Arabia
SEN	Senegal
SEY	Seychelles
SIL	Sierra Leone
SIN	Singapore
SVK	Slovakia
SVN	Slovenia
SOL	Solomon Islands
SOM	Somalia
SOA	South Africa
SPA	Spain
SRL	Sri Lanka
SUD	Sudan
SUR	Suriname
SWZ	Swaziland
SWE	Sweden
SWI	Switzerland
SYR	Syrian Arab Republic
TJK	Tajikistan
THA	Thailand
MKD	The former Yugoslav Republic of Macedonia
TOG	Togo
TOK	Tokelau
TON	Tonga
TRT	Trinidad and Tobago
TUN	Tunisia
TUR	Turkey
TKM	Turkmenistan
TCA	Turks and Caicos Islands
TUV	Tuvalu
UGA	Uganda
UKR	Ukraine
UAE	United Arab Emirates
UNK	United Kingdom of Great Britain and Northern Ireland
TAN	United Republic of Tanzania
USA	United States of America
URU	Uruguay
UZB	Uzbekistan
VAN	Vanuatu
VEN	Venezuela
VTN	Viet Nam
VUS	Virgin Islands (United States)
WAF	Wallis and Futuna
WIN	West Indies

YEM	Yemen, Republic of
YUG	Yugoslavia
ZAM	Zambia
ZIM	Zimbabwe

B. Other abbreviations

<u>Abbreviation</u>	<u>Description</u>
1961 Convention	Single Convention on Narcotic Drugs, 1961
1971 Convention	Convention on Psychotropic Substances, 1971
1988 Convention	UN Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, 1988
ARC	Addiction Research Centre of NIDA, USA
BAN	British Approved Name
BKA	Federal Criminal Investigation Office of Germany
CL	Circular Letter
CND	United Nations Commission on Narcotic Drugs
CPDD	College on Problems of Drug Dependence, Inc
CSA	Controlled Substances Act of the USA
CSM	Committee on Safety of Medicine, UNK
DAWN	Drug Abuse Warning Network
DCF	Denomination Commune Française (French approved nonproprietary name)
DEA	Drug Enforcement Administration of the USA
DMP	Division of Drug Management and Policies
ECDD	Expert Committee on Drug Dependence
EEG	Electroencephalography
FDA	Food and Drug Administration of the USA
GAPM	German Association for Pharmaceutical Manufacturers
HQ	Headquarters
ICPO (INTERPOL)	International Criminal Police Organization
IMS	International Medical Systems
INCB	International Narcotics Control Board
MAO	Monoamine oxidase
NFN	Nordiska Farmakopenamder (Nordic Pharmacopoeic Council Approved Name)
NGO	Nongovernmental organization
NIDA	National Institute on Drug Abuse of the USA
OTC	Over-the-counter (no prescription required)
STRIDE	System to Retrieve Information from Drug Evidence of the USA
UN	United Nations
UNDCP	United Nations International Drug Control Programme
WHO	World Health Organization

### 3. INFORMATION GATHERING

This section summarizes the WHO procedures for the review of dependence-producing substances, according to the Revised Guidelines for the WHO Review of Dependence-Producing Psychoactive Substances for International Control.

#### Data collection

Literature review was the main source of information for data collection. In addition, a Circular Letter (C.L.) was issued in December 1997 by the Director-General of WHO for gathering the information required for the Critical Review of dihydroetorphine, ephedrine and remifentanil. In order to avoid unnecessary duplication with a similar questionnaire issued by the United Nations, WHO's questionnaire excluded the proposal of the Government of Spain, which was the subject of the UN questionnaire.

This C.L. was translated into all six official WHO languages and addressed to the Ministries of Health of WHO Member States. Fifty Member States have returned the completed questionnaire to the WHO focal point as of 1 May 1998. This C.L. and questionnaire was also sent to WHO Collaborating Centres on Research and Training in Drug Dependence. The input received from the College on Problems of Drug Dependence concerning the abuse liability of ephedrine will be presented to the participants separately as additional information.

WHO also invited concerned pharmaceutical industries to provide additional information.

### 4. ORGANIZATION OF INFORMATION & CONTRIBUTORS

The first draft of the Critical Review was prepared in February-May 1998 by the Secretariat with the technical assistance of the following external experts: Professor Cai Zhi-Ji, National Institute on Drug Dependence, China; Professor Donald Jasinski, Johns Hopkins University, USA; Dr Kira Hutchinson, US Drug Enforcement Administration; and Dr Michael Klein, US Food and Drug Administration.

The documents on **ephedrine** and **remifentanil** were sent to the concerned pharmaceutical industries who had contributed information on them. Comments received from the pharmaceutical industry before the ECDD meeting will be presented separately to the participants as additional information.

### 5. FORMAT OF REVIEW OF SUBSTANCES

The following format is used for presentation of relevant data on the three substances under review. The review document on the proposal of the Government of Spain is structured differently, each discussion point presented on the basis of relevance to the overall question to be addressed by the Expert Committee.

1. Substance Identification
  - A. International Nonproprietary Name (INN)
  - B. Chemical Abstract Service (CAS) Registry Number
  - C. Other Names
  - D. Trade Names
  - E. Identification Characteristics
  - F. WHO Review History
2. Chemistry
  - A. Chemical Name. IUPAC Name. CA Name.
  - B. Chemical Structure
  - C. Stereoisomers
3. General Pharmacology
4. Toxicology - Including Adverse Reactions in Man
5. Pharmacokinetics
6. Dependence and Abuse
  - A. Preclinical studies
  - B. Clinical studies
7. Epidemiology of Drug and Abuse with an Estimate of the Abuse Potential
8. Nature and Magnitude of Public Health Problems
9. National Control
10. Therapeutic and Industrial Use
11. Production, Consumption and International Trade
12. Illicit Manufacture, Illicit Traffic, and Related Information
13. Bibliography

## DIHYDROETORPHINE

### 1. Substance Identification

- A. Name: *Dihydroetorphine*<sup>1</sup>
- B. Chemical Abstract Service (CAS) Registry Number:  
(base): 14357-76-7
- C. Other Names: None
- D. Trade Names: None
- E. Identification Characteristics:

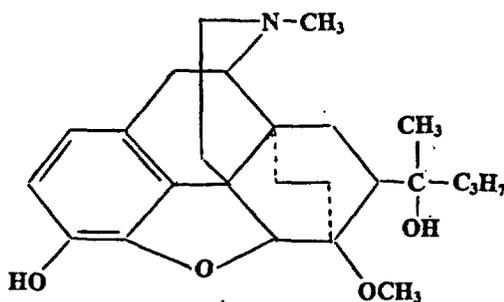
DHE is a white, crystalline powder with a melting point of 217-219°C.  
Dihydroetorphine hydrochloride dissolves in water.

- F. WHO Review History:

In 1996, after a pre-review, the 30<sup>th</sup> WHO Expert Committee on Drug Dependence recommended the critical review of dihydroetorphine.

### 2. Chemistry

- A. Chemical Name: 7,8-Dihydro-7  $\alpha$ -[1-(*R*)-hydroxy-1-methylbutyl]-6,14-endo-ethanotetrahydrooripavine
- B. Chemical Structure:



<sup>1</sup>In composite drug names containing both chemical prefixes and INNs, the INN is distinguished by being italicized.

Molecular Formula:  $C_{23}H_{28}N_1O_3$  (Dihydroetorphine)  
 $C_{23}H_{28}N_1O_3HCl$  (Dihydroetorphine Hydrochloride)

Molecular Weight: 450.02 (Dihydroetorphine)

### 3. General Pharmacology

*In this section, both preclinical and clinical studies are described to evaluate the pharmacological actions of DHE. These studies include those tests commonly used to evaluate the pharmacological profile of drugs. On the whole, these studies show that DHE produces effects that are characteristic of morphine-like substances.*

#### Analgesic Effect

Results from studies indicate that DHE is a highly potent analgesic. Huang and Qin (1982) reported that the analgesic ED<sub>50</sub> of DHE in mice and rabbits were  $0.47 \pm 0.11$   $\mu\text{g}/\text{kg}$  (hot plate test) and  $0.43 \pm 0.08$   $\mu\text{g}/\text{kg}$  ( $K^+$  iontophoresis method), respectively, compared with those of morphine ( $2.95 \pm 0.54$  and  $4.9 \pm 0.39$   $\text{mg}/\text{kg}$ , respectively), showing that its analgesic efficacy was 6,277 (in mice) and 11,488 (in rabbits) times as potent as those of morphine; in monkey experiments ( $K^+$  iontophoresis method), the pain thresholds raised from  $0.84 \pm 0.45$  mA to  $1.9 \pm 0.9$  mA ( $P < 0.02$ ). In mice and rabbits, the peak analgesic effect was attained 15 minutes after subcutaneous injection of DHE, and the duration of analgesic effect lasted 60-90 minutes, which was shorter than that of morphine (120-150 minutes). It was shown by hot plate test in mice that DHE was similar to morphine in exhibiting its analgesic effect as a pure agonist of opioid receptor by the fact that when the effective rate of analgesia produced by DHE reached 100%, the analgesic rate did not decrease after continuous increases in dose. In case of partial agonist as buprenorphine, when it reached the maximum effective rate of analgesia, the increase in doses caused a decrease in the effective rate.

The report of Tokuyama et al (1996) showed that DHE, by different routes of administration such as intraperitoneal (i.p.), subcutaneous (s.c.), intravenous (i.v.), oral (p.o.), intracerebroventricular (i.c.v.) and intrathecal (i.t.), exerted an antinociceptive effect in mice in a dose-dependent manner as measured by the tail pinch method. In comparison with morphine, the efficacy ratio of the antinociceptive effect between DHE and morphine was approximately 1,000 to 1,500: 1 by parenteral administration (i.p., s.c. or i.v.), and about 100:1 by oral route. However, the antinociceptive effect of DHE was only 10 to 20 times as potent as that of morphine when administered by direct application into CNS (i.c.v. or i.t.). The duration of the antinociceptive effect of DHE was shorter than that of morphine.

Wang, Huang and Qin (1991), Wang and Qin (1996a), using radioligand binding assay for studying the binding characteristics of DHE to opioid receptors in rat brain, concluded that DHE is a  $\mu$ -receptor selective ligand; the relative affinity ratio of DHE to  $\mu$ -,  $\delta$ - and  $\kappa$ -opioid receptors in mouse brain was 333:1:1, the analgesic effect caused by i.c.v. injection of DHE was antagonized by  $\beta$ -funaltrexamine, a  $\mu$ -receptor

antagonist, but could not be antagonized by  $\delta$ - and  $\kappa$ -selective antagonists naltrindole and norbinaltorphimine (Wang, Lu and Qin, 1995). Wang and Qin (1996b), tested the mRNA levels of  $\mu$ -opioid receptors in rat midbrain, hippocampus and striatum after DHE and morphine treatment by solution hybridization. Results showed that mRNA levels of  $\mu$ -receptors in the above-mentioned brain regions decreased after DHE or morphine treatment. It was suggested that the down-regulation of mRNA levels of  $\mu$ -receptors may correlate to DHE or morphine tolerance.

#### Other Effects

Bian, Xing and Xu (1986) studied the interactions between DHE, L-tetrahydropalmatine (L-THP), B-7601 (a diphenylhydroxyacetic acid derivative with anticholinergic activity) and diazepam. Results showed that the analgesic and CNS inhibitory effects were enhanced by the combination of DHE, L-THP and B-7601; DHE alone caused respiratory inhibition and bradycardia, L-THP attenuated the respiratory inhibition but not bradycardia induced by DHE, bradycardia was antagonized by B-7601; i.v. injection of the combination of DHE, L-THP, B-7601 and diazepam immediately caused general anesthesia in dogs and the operation can be done without evident change in ECG but respiration changed variably.

#### Clinical Studies

DHE is a domestically developed narcotic analgesic. Clinical trials were carried out solely in China. Results of the clinical studies conducted in the 1980s by a number of clinicians on 1,578 patients with pain were summarized by Huang in 1991. An additional 43 clinical reports with a total of 3,685 patients under clinical studies were published in medical journals in the 1990s. All of the above data indicated that DHE is effective for relieving pain in various diseases or clinical situations. The efficacy of DHE in relieving cancer pain was reported in a number of papers: (Huang, 1987; Wu and Sun, 1991; Chen, Lin and Tan 1994; Wei, Liu and Yang, 1994; Tao and Hua, 1994; Xu, 1994; Yang, Hong, Li, Qian, Chen and Chen, 1995; Wang, Huang, Zhang and Wu, 1995; Ma, Wu and Zhang, 1995; Liu, Wang, Wei, Guo, Han and Li, 1995; Li and Hao, 1996; Lu, Cheng, Tang and He, 1996; Li, Li and Qu, 1996; Liu, Guo and Zheng, 1996; Sheng, Chen, Kang, Li and Liu 1996). A total number of 1,754 cancer patients were under clinical studies.

According to Wu and Sun (1991), among 103 cancer patients, 77 cases (74.8%) suffered from severe pain and 26 (25.2%) from moderate pain. DHE given sublingually, 20-100 $\mu$ g/dose, produced complete relief of pain in 39 cases (37.9%) and moderate relief of pain in 53 cases (51.5%). The total effective rate was 89.3%, and the average relief time was 3.9 hours. The average time for initiating pain relief after drug administration was 20 minutes. Yang, Hong, Li, Qian, Chen and Chen (1995) conducted a large scale clinical study on 1,116 cancer patients for assessing the pain relief efficacy of DHE. 875 cases (78.4%) among 1,116 patients suffered from severe pain and 241 cases (21.6%) from moderate pain. DHE 20 $\mu$ g/dose was given sublingually; 668 in 875 cases with severe pain (3%) and 198 in 241 cases with moderate pain (82.1%), (in total of 1,116 cases), 866 cases (77.6%) got complete pain

relief, 214 cases (19.2%) got moderate pain relief. The total effective rate was 96.8%. The time for initiating pain relief after drug administration was 30-120 minutes and the duration of pain relief lasted 3-11 hours.

DHE was effective in relieving pain during operation and postoperative pain (Lin, Jin and Piao, 1994; Wang, Huang, Sun, Liu and Hou, 1994; Wang, Shi and Guo, 1994; Zhao and Lin, 1994; Ye and Ji, 1996); DHE also showed its analgesic efficacy when used for the induction and maintenance of general anesthesia (Zhou, Jin, Sun, He and Li, 1987; Song, Jiang and Wu, 1991; Wang, Geng and Hua, 1994; Mi and Jin, 1994; Jin, Li, Jin, Zheng and Liu, 1996; Cheng and Sun, 1996). DHE was used for relieving labour pain and pain caused by induced abortion (Yan, Song, Pan and Zhang, 1994; Zhong, Peng, Liu and Jin, 1994; Cheng, Cheng, Li, Sun and Chen, 1995; Li and Weng, 1995; Chen, Liu, Zhang, Tang and Cheng, 1995; Ma, Gao, Su, Guo and Li, 1995; Yang, 1996; Zhao, Zhang, Liu, Wu and Li, 1996; Wu and Xu, 1996; Li, Luo, Lu, Zhou and Fang, 1996; Zhang, 1996; Shangguan, 1996).

The analgesic properties of DHE were shown in the treatment of pain in various diseases, i.e., angina pectoris, fracture, trauma, cholelithiasis, cholecystitis, renal calculus, gastrospasm, duodenal ulcer (Ren, Gao, Xu and Liang, 1993; Zhang and Wu, 1994), thromboangiitis obliterans (Lu and Tang, 1995).

During the years 1991-1995, attempts have been made to use DHE for suppressing withdrawal syndromes of heroin. Preclinical studies in rats and monkeys (Wang, Liu and Qin, 1992) and clinical studies (Wang, Yan, Yang, Qin, Wei and Li, 1992; Su, Lin, Shen, Zhang and Huang, 1992; Sha, Zhu, Liu, Wang and Zhang, 1993; Lin, 1994; Su, Lin, Deng, He, Wang and Huang, 1994; Su, Deng, He, Wang and Sha, 1994; Yang, Yang, Li, Lu, Dong and Qin, 1994; Yuan, Tang, Li and Zhang, 1994; Sha, Liu, Zhang, Cheng and Chen, 1994; Qin, Yang, Sha, Liu, Su, Yang, Li, Lu, Deng, He and Luo, 1995; Li, Liang, Liu and Liang, 1995; Sha, Zhang, Cheng and Liu, 1997) showed that DHE exerted a withdrawal syndrome suppressing effect in heroin addicts. However, because of widespread DHE abuse in this country, the clinical use of DHE for the detoxification of heroin addicts was prohibited by the health authorities.

#### **4. Toxicology - Including Adverse Reactions in Man**

*This section describes animal studies and human studies of the possible toxicity effects of DHE. These studies collectively suggest that DHE produces adverse effects similar to those produced by opioids.*

##### Animal Studies

Huang and Qin (1982) reported respiratory inhibition caused by DHE, the s.c. respiratory inhibition ED<sub>50</sub> of DHE, morphine and etorphine in rabbits were 0.86±0.18µg/kg, 5.15±0.08mg/kg and 1.36±0.18µg/kg, respectively; the margin of safety among analgesic ED<sub>50</sub> and respiratory inhibition ED<sub>50</sub> of DHE, morphine and etorphine were 2.0, 1.0 and 1.2, respectively; 30 minutes after s.c. injection of DHE and 45 minutes after s.c. injection of morphine, the volume of ventilation decreased

most significantly and recovered to the level before drug administration within 3 to 4 hours; DHE 10µg/kg i.m. in dogs, or 2.86µg/kg s.c. in monkeys, the respiratory rates of dogs or monkeys decreased by 30-50%. It was shown in the same report that DHE exerted an immobilizing effect in mice, dogs and monkeys, the s.c. and i.c.v. ED<sub>50</sub> of DHE causing the loss of righting reflex in mice were 50±7 and 0.35±0.05µg/kg, respectively.

The s.c. LD<sub>50</sub> of DHE in mice and rabbits were 82±17µg/kg and 0.047±0.016mg/kg. The therapeutic indices of DHE in mice and rabbits were 174 and 109, respectively.

Animal experiments indicated that DHE inhibited the immune function (Xu, Guo and Su, 1993; Wu, Li, Zhang and Li, 1997). Experiments undertaken by Xu, Guo and Su (1993) showed that DHE administered s.c. to mice in a dose equal to 1-40 times of analgesic ED<sub>50</sub> in a gradually increasing manner within 15 days caused a decrease in phagocytosis function of peritoneal macrophages, a reduction of the capability of both splenocyte proliferation and antibody-producing cells and inhibition of the production and activity of both IL-1 and IL-2. However, the immune-inhibitory effect was weaker than that of morphine.

According to Wang, Zhang, Huang and Wang (1996a), when 4µg/kg of DHE was injected intramuscularly into pregnant mice before parturition, the incidence of cyanosis in the newborn mice was 13.8% compared with 7.4% in the control group, showing a statistically significant difference (P<0.05). The same authors (1996b) reported that 4µg/kg of DHE injected i.m. into the pregnant mice before parturition caused a decrease in the weights of spleen and thymus in male F1 mice on postnatal day 21.

The effect of DHE on neurobehavioral teratology in offspring of mice was studied by Yin, Duan and Li (1996). High (50µg/kg), medium (0.5µg/kg) and low (0.05µg/kg) dosage levels of DHE were given subcutaneously. Results showed that some indices were inhibited by DHE when compared with the control group (P<0.05). Namely, reflex development such as visual placing, movement coordination, learning and memory function, and locomotor activity.

### Clinical Studies

According to the clinical trial conducted by Wu and Sun (1991), the main adverse drug reactions (ADRs) in 103 patients were dizziness (72%), somnolence (60%), nausea (30%), vomiting (16.5%), shortness of breath (8%) and constipation (5%). The major adverse drug reaction of DHE when used for anesthesia was respiratory inhibition (Huang, 1982). After intravenous injection of 0.3µg/kg of DHE, respiration became superficial and the respiratory rate slowed down; DHE caused an accumulation of CO<sub>2</sub> in blood and a decrease in partial pressure of oxygen. Three in 188 cases (1.6%) showed apnoea.

There were 22 reports published in medical literature during 1992 and 1997 with a total number of 152 patients intoxicated from DHE (Zhao, 1992; Cao and Li, 1992;

Zhang and Ye, 1993; Luo, Ma and An, 1993; Ni, 1994; Wang, 1994; Wu, 1994; Yang and Lin, 1994; Cao and Hua, 1994; Wang, Zhao, Zhang and Yang, 1994; Zhang, Liu, Zhang and Wang, 1994; Li, Yang, Zhang and Tan, 1994; Huang, Li, He and Gu, 1994; Yu and Guo, 1995; Zhao, Zhao, Zhang, Jin, Wu and Li, 1995; Jiao, 1995; Yang and Qiao, 1995; Liu and Sheng, 1995; Han, 1995; Ai, Xu, Ren and Xu, 1996; Wang and Wang, 1996; Cai, Qiao, Yang and Wu, 1997). The major symptom was respiratory inhibition. The emergency treatment in 132 patients was successful and 20 patients died of respiratory paralysis.

Li, Yao, Li, Li and Zhong (1997) reported the morphological study of 60 cases of opiate addicts' cadavers which were divided into 3 groups, namely, 20 cases who abused DHE only (group D), 20 cases who abused DHE with anileridine (group D+A) and 20 cases who abused heroin only (group H). Results showed that significant cadaveric ecchymosis, foamy secretion of mouth and nose, cyanosis of lips, fingernails and toenails, obsolete and newly infected loci at injected sites, appeared in all 3 groups of which the changes in group D and group D+A were more remarkable than those in group H ( $P < 0.01$ ). Stiff eminence in musculus gastrocnemius and musculus masseter appeared only in group D and group D+A which could be considered as the characteristic morphological change of cadaver of DHE addicts; drug-induced myosis has not been found in all of the three groups.

Several adverse drug reactions induced by DHE in cardiovascular systems such as bradycardia (Chang and Hu, 1995), shock syndromes (Liu, 1994; Tang and Zhang, 1994), angina pectoris (Liu, 1996) and atrial fibrillation (Tian and Zhang, 1996) were reported. Furthermore, some authors reported that DHE induced anaphylactic reactions (Fu, 1994; He, Zheng and Lu, 1994; Huang and Wang, 1995; Sheng, 1996; Zhang, Wang and Wang, 1996), of which the symptoms included skin rash, hypotension, dyspnea, dizziness, nausea, excessive sweating, pallor and palpitation.

In a few cases, DHE induced syncope (Wang, 1996), comatose state in a patient with liver disease (Jia, Liu, Tan, Zhang and Xu, 1996), convulsion in an epileptic patient (Jin and Wang, 1995), shivers in four limbs (Liu, Yang and Lin, 1995), ageusia (Li, 1994), Dong and Long (1993) all reported local irritation caused by DHE (ulcer, edema and severe pain at local site of injection) in 15 patients after v.injection, Jin, Liu, Li and Dai (1996) reported the severe damage of enamel in 5 patients caused by sublingual administration of DHE. Furthermore, Qiu, Huang, Zhang and Qin (1994) reported a DEA-induced erosion of gingiva in one addict who took DHE sublingually over a long period of time. Song, Xu, Wang and Zhou (1997) found that among 60 cases of DHE addicts, there were 5 cases (8.2%) with hepatitis B complications.

## 5. Pharmacokinetics

Pharmacokinetics of DHE were studied in mice (Huang, Wang, Yuan and Qin, 1988). After sublingual (s.l.) administration of  $2.36 \mu\text{g}/\text{kg}$  of  $[15,16-^3\text{H}]$  DHE ( $1/2$  analgesic  $\text{ED}_{50}$ ) in mice, the pharmacokinetic parameters in blood and brain were:  $C_0$  321 and 621 pg/ml or g,  $K$  0.0166 and  $0.0243 \text{min}^{-1}$ ,  $t_{1/2}$  41.7 and 28.5 min,  $K_a$  0.273 and  $0.095 \text{min}^{-1}$ ,  $t_{1/2}$  (a) 2.5 and 7.3 min,  $t_{\text{max}}$  10.9 and 19.2 min,  $C_{\text{max}}$  252 and 290 pg/ml or

g,  $AUC_{0-180\text{min}}$  18.2 and 20.5  $\text{ng} \cdot \text{min} \cdot \text{ml}^{-1}$ , Vd 7.4 and 3.80L/kg, CL 122 and 92  $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , respectively. After s.c. injection of 1.0  $\mu\text{g}/\text{kg}$  of [15,16- $^3\text{H}$ ] DHE in mice, the pharmacokinetic parameters in blood were  $C_0$  492  $\text{pg}/\text{ml}$  or g,  $K$  0.0252  $\text{min}^{-1}$ ,  $t_{1/2}$  27.7 min,  $K_a$  0.262  $\text{min}^{-1}$ ,  $t_{1/2}$  (a) 2.7 min,  $t_{\text{max}}$  9.9 min,  $C_{\text{max}}$  334  $\text{pg}/\text{ml}$  or g,  $AUC_{0-180\text{min}}$  17.1  $\text{ng} \cdot \text{min} \cdot \text{ml}^{-1}$ , Vd 2.0L/kg, CL 75  $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . After s.c. injection of [15,16- $^3\text{H}$ ] DHE,  $t_{1/2}$  (min) and  $AUC_{0-180\text{min}}$  ( $\text{ng} \cdot \text{min} \cdot \text{ml}^{-1}$ ) of different doses (1, 2, 4, 8, 16  $\mu\text{g}/\text{kg}$ ) were 27.7 and 17.10, 38.5 and 40.69, 28.9 and 106.43, 22.4 and 185.97, 25.7 and 83, respectively. The calculated relative bioavailability of DHE s.l. was 29.2% of that by s.c. injection. The distribution of [ $^3\text{H}$ ] DHE in rat brain by *in vitro* quantitative autoradiography was studied by Yuan, Yu and Zhang (1995). The high density of binding sites was in patches of striatum, nucleus accumbens, I and III laminae of cerebral cortex, thalamus, habenula, amygdaloid complex, interpeduncular nucleus and locus coeruleus. The mediate density of binding sites was in olfactory bulb, other parts of cerebral cortex, superior and inferior colliculus. The low density was in septum, hypothalamus and central grey.

## 6. Dependence and Abuse

*Studies described in this section indicate that DHE is able to be abused by the human population. Animal experiments indicated that DHE produces effects similar to those produced by heroin, and its psychological dependence is even higher, as shown by self-administration (SA), drug discrimination (DD) and conditioned place preference (CPP) studies. Abuse of DHE occurred in China in the early 1990s and DHE is now strictly controlled by the health authorities.*

### Psychological Dependence Potential

Studies aimed to evaluate the psychological dependence potential of DHE by SA, DD and CPP experiments have been undertaken. SA experiments were carried out in monkeys and rats (Cao, Chen and Cai, 1990; Wang, Ha, Wang and Zheng, 1995; Chen, Zheng, Xie, Wang and Cai, 1996; Wang, Wang, Ha and Zheng, 1996; Wang, Wang, Ha and Zheng, 1997; Martin, Kim, Harris and Smith, 1997). DD experiments were undertaken in rats (Chen, Zheng, Xie, Wang and Cai, 1996). CPP experiments were undertaken in rats and mice (Wang, Deng and Cai, 1993; Tokuyama, Nakamura, Nakao, Takahashi and Kaneto, 1996; Liu and Zhang (1977)). Most of the above studies were conducted at the National Institute on Drug Dependence (NIDD) of Beijing Medical University. All of the results, except those obtained by Tokuyama et al (1997), indicated that DHE possessed a strong psychological dependence potential. Zheng, Zhang and Cai (1995), Zheng and Zhang (1995) in comparisons of results obtained by their colleagues in NIDD, pointed out that the potency of psychological dependence potential of DHE was 5,000-10,000 times more than morphine in SA experiments in rats, 500 and 100 times more than morphine and heroin in SA experiments in monkeys, 8,125 and 1,188 times more than morphine and heroin in DD experiments in rats, respectively, and 5,000 times more than morphine in CPP experiments. According to Martin, Kim, Harris and Smith (1997), the potency of the reinforcing effect of DHE in rats was roughly 1,500-3,000 times more than morphine.

### Physical Dependence Potential

The physical dependence-producing properties of DHE were studied. All of the studies showed that the physical dependence-producing properties of DHE were relatively low. Huang and Qin (1982) reported that the withdrawal syndromes caused by DHE in mice jumping tests were weaker than morphine. In monkey precipitation tests and abrupt withdrawal tests, withdrawal syndromes of DHE were significantly weaker than morphine. Cao, Chen and Cai, (1990) compared the physical dependence potential of DHE, AP-237 (a domestic developed analgesic), morphine and pethidine in mice jumping tests and precipitation tests in rats, results showed that the potencies of physical dependence potential were: morphine at the top, followed by pethidine, and DHE or AP-237 at the end. In the experiment undertaken by Tao, Zhang, Shi, Ning and Cai (1992), DHE was given to rats and mice by drug-admixed-food method, and by sublingual administration in mice, the results also showed the low physical dependence potential of DHE. Zhang and Qin in rat experiments observed the physical dependence potential of DHE when given by continuously intravenous infusion. It was shown that the potency of DHE in producing physical dependence at equivalent analgesic doses was lower than morphine, and the efficacy of DHE in producing physical dependence at sufficiently large doses was also lower than morphine. Results obtained by Tokuyama, Nakamura, Takanashi and Kaneto (1994) in mice jumping tests also showed the weak potency of DHE in producing physical dependence. Zhang and Qin (1995) in rat and mice jumping tests compared the potency of etorphine, DHE and morphine in producing physical dependence. Subcutaneous injection of 31 and 62 times of analgesic ED<sub>50</sub> in mice and rats respectively caused no evident withdrawal syndromes after precipitation by naloxone. When 124 times of analgesic ED<sub>50</sub> of etorphine were used, the withdrawal syndromes appeared, but they were weaker than those induced by 62 times of ED<sub>50</sub> of morphine. In rat precipitation tests, drugs were given by continuous intravenous infusion, 10-20 times of analgesic ED<sub>50</sub> of etorphine and DHE produced evident withdrawal syndromes after naloxone precipitation, but they were still weaker than those induced by equivalent analgesic ED<sub>50</sub> of morphine.

### Clinical Studies

Clinical signs of DHE dependence were reported by a number of clinicians who worked in the treatment units for detoxification of opioid-dependent patients. Wang (1993), Cui (1993), He, Lu and Zheng (1993), Wang, Qin, Zhang and Qiu (1994), Yue and Wan (1994), Yu, Tian and Shen (1994), Zhang, Dong, Wang and Li (1994), Zhou (1994), Qiu, Huang, Zhang and Qin (1994), Wang, Zhao, Zhang, Bai, Xia, Zhao, Yang and Han (1995), Wang, Zhang, Zhao, Yang and Chen (1995), Cao, Sun, Xing, Wang and Gao (1995), Xu and Qu (1995), Sun Fan (1995), Shi, (1995), Deng, Li, Li, Fang, Li, Deng and Yuan (1996), Yang, Li, Shi and Wu (1997), Zhao and Feng (1997) and Ning and Li (1997) have made observations on a total number of 1,267 cases of DHE addicts. There were two reasons for starting to abuse DHE - iatrogenic and social. A number of DHE addicts started to use DHE for medical purposes. DHE is highly effective for relieving severe pain and the patients increased the doses because tolerance developed quickly. However, psychological dependence also

developed quickly and the potent dependence-producing properties of DHE played a dominant role in compelling the patients to start abusing the drug. Another reason was a social one. DHE was used to replace heroin by opiate addicts because of its stronger psychological dependence-producing properties, cheaper price, and less strict control than heroin. Results of the above clinical studies can be summarized as follows:

The withdrawal syndromes of DHE were similar to those of heroin, such as dysphoria, craving, general malaise, anxiety, insomnia, intolerance of cold, chill, salivation, lacrimation, perspiration, gooseflesh, yawning, pain in bone, muscle, joint or abdomen, nausea, vomiting, diarrhea and palpitation. Usually the withdrawal signs were weaker than for heroin, but in a few cases delirium, hallucination especially visual hallucinations or convulsion may occur. According to Wang, Zhao, Zhang, Bai, Xia, Zhao, Yang and Han (1995), the rates of appearance of withdrawal syndromes of DHE were: perspiration, dysphoria, insomnia and craving (100%), nausea, vomiting and diarrhea (75%), gooseflesh (72%), hyperventilation (62%), chill (58%). In comparison with heroin, perspiration was more evident than that for heroin ( $P < 0.01$ ), insomnia and craving were close to heroin ( $P > 0.05$ ). Total scores of withdrawal syndromes of DHE ( $21 \pm 10$ ) were less than those of heroin ( $29 \pm 5$ ) ( $P < 0.01$ ).

The period for establishing DHE dependence varied individually, as shown in seven reports. The short period ranged from 10 days to one month (Yue and Wan, 1994; He, Lu and Zheng, 1993; Yu, Tian and Shen, 1994; Shi, 1995), the medium period ranged from 3-6 months (Qiu, Huang, Zhang and Qin, 1994; Cui, 1993; Wang, Qin, Zhang and Qiu, 1994) and the long period was 11 months (Wang, Qin, Zhang and Qiu, 1994). Data in 17 reports showed that the daily dose of DHE for maintaining the abuse varied markedly, ranging from  $60 \mu\text{g}$  (Yue and Wan, 1994) to  $24,000 \mu\text{g}$  (Qiu, Huang, Zhang and Qin, 1994).

DHE developed significant tolerance. Data in 7 reports showed the variation of latent periods of beginning tolerance, ranging from 3 days (Cao, Sun, Xing, Wang and Gao, 1995) to 4 months (Cui, 1993). The development of tolerance was usually earlier than dependence. Qiu, Huang, Zhang and Qin (1994) reported two cases of DHE addicts and one of them showed the order of starting times of tolerance and dependence development. The patient took  $20-40 \mu\text{g}$  of sublingual tablets of DHE at bedtime to prevent insomnia - 15 days later the dose increased to  $60-80 \mu\text{g}$ . Three months after commencing DHE medication, the dose increased to  $300 \mu\text{g}$ . Withdrawal syndromes, including intolerance of cold, abdominal pain, nausea, vomiting, fatigue, yawning, craving, occurred after stopping drug use. Dosage continued to increase and reached  $16,000 \mu\text{g}$  six months after the first dose, which had increased 800 times the original dose.

In a study of Li, Nie, Zhu and Pang (1995), the comparison of pathopsychological characteristics of two groups of addicts (DHE group with 32 cases; heroin group with 23 cases) was made. HAMD (Hamilton Depression Scale) and HAMA (Hamilton Anxiety Scale) were used. Results showed that the scores of HAMD and HAMA of

both drugs were higher than in normal people, indicating that abuse of DHE or heroin both produced pathopsychological damage to the addicts; results also showed that the scores of HAMD on the first day (HAMD d1), the seventh day (HAMD d7) and HAMA on the seventh day (HAMA d7) of the DHE group were higher than the heroin group ( $P<0.05$ ,  $P<0.01$  and  $P<0.01$ , respectively). The difference of scores of HAMA on the first day (HAMA d1) between both groups was not significant ( $P>0.05$ ), indicating that DHE produced more severe depression and anxiety than heroin. The authors suggested that besides the use of anxiolytics and antidepressants in the treatment of drug dependence, psychotherapy should be strengthened.

The influence of DHE and heroin on the endocrine system was studied by Wang, Zhao, Zhao, Han, Yang, Fu, Li and Zhang (1996). Results of the DHE group (11 cases) in comparison with the normal group (26 cases) showed that, blood concentrations of TSH and  $T_3$  decreased ( $P<0.01$ ), C peptide and insulin increased ( $P<0.01$ ),  $T_4$  decreased, testosterone increased, but the difference was not significant ( $P>0.05$ ). In the DHE group, when compared with heroin group (29 cases), blood concentrations of TSH and  $T_4$  were lower ( $P<0.01$ ); no difference in those of  $T_3$  ( $P>0.05$ ). Those of C peptide, insulin and testosterone were higher ( $P<0.01$ ). They came to the conclusion that the pituitary-thyroid functions of DHE addicts were inhibited and abuse of DHE raised the pancreatic and testicular functions.

## 7. Epidemiology of Drug Use and Abuse with an Estimate of the Abuse Potential

DHE was registered in China in December of 1992 and used effectively for relieving severe pain. Abuse of DHE happened soon after it was introduced for use as an opiate withdrawal syndrome suppressing agent in the early 1990s. DHE abuse spread very quickly in the country and a number of epidemiological studies have been conducted with the purpose of revealing the demographic characteristics of DHE abuse, situation and reasons of abuse, relapse and poly-drug abuse, lifestyle of DHE abusers and the consumption of DHE (Wang, 1993; Zhang, Feng, Yang, Li, Zhu and Wan, 1993; Chen, Yang, Liu, Jiao, Xiao and Ai, 1995; Cao, Sun, Xing, Wang and Gao, 1995; Liu, Cao, Shi and Cai, 1995; Deng, Li, Li, Fang, Li, Deng and Yuan, 1996; Liu, Wang, Ge, Zhang, Sun, Sun, Zhao and Cai, 1996; Li and Wang, 1996; Zhao, Li, Zhao and Feng, 1996; Cao, Sun, Xing, He, Wang, Gao and Liu, 1996; Cao, Liu, Lian and Mu, 1997; Sun, Ren and Gao, 1997; Teng, Jiao, Gu and Han, 1997; Yang, Li, Shi and Wu, 1997; Liu, Cao, Zhu, Teng, Ren, Lian, Mu, Yang and Cai, 1997).

Liu, Cao, Shi and Cai (1995) conducted a survey on 297 DHE addicts. Data were obtained from five provinces located in the north-east (Heilongjiang), north (Neimonggu and Shanxi), north-west (Shaanxi) and south-west (Yunnan) parts of China. The demographic characteristics which were similar to those of heroin abusers were summarized as follows: males occupied the major part of DHE abusers (82.1%), the mean age of addicts was  $28.14 \pm 4.92$  years, the ethnicity of the abusers was mainly Han (85%); the education of the majority of DHE addicts was at the lower levels, i.e., secondary and primary school (88.8% and 7.7%, respectively); the self-employed (45.8%) and unemployed (15.1%) occupied 60.9% of DHE abusers. The main reasons for initial use of DHE were: curiosity (53.9%), heroin substitution and

avoidance of withdrawal syndromes (53,5%); influence by others (26.3%). For current use: avoidance of withdrawal (82.8%), seeking euphoria (25.3%), relief of trouble (20.2%).

Liu, Cao, Zhu, Teng, Ren, Lian, Mu, Yang, Jiao and Cai (1997) found that the relapse rate of DHE addicts was high (80.2%), the frequency of times of relapse influenced the relapse rate of DHE addicts; the high frequency raised the relapse rate. Psychological factors played the most important role on relapse.

DHE is a potent  $\mu$ -opioid agonist. Based on its pharmacological properties and dependence potential demonstrated in animal studies, as well as its actual abuse observed in China, it is estimated that DHE is liable to similar abuse and productive of similar ill effects as the drugs in Schedule I of the 1961 Convention.

#### **8. Nature and Magnitude of Public Health Problems**

DHE is available only in China. Once abuse of DHE occurred, it spread out widely, but only for a short period, and now DHE abuse has reduced due to the strict controls introduced by the health authorities, and also because the production of DHE was temporarily terminated in 1996 and 1997.

#### **9. National Control**

DHE is controlled in China as a narcotic drug.

#### **10. Therapeutic and Industrial Use**

DHE is used as an analgesic for relieving acute severe pain. No industrial use.

#### **11. Production, Consumption and International Trade**

The production rate of DHE in 1995 (the year before the temporary termination of its production) was 589 grams.

Consumption of DHE in 1995 was 596 grams.

The stock held of DHE at the end of 1995 was 46 grams.

#### **12. Illicit Manufacture, Illicit traffic and Related Information**

There are no clandestine laboratories in China. Raw materials and preparations of DHE (sublingual tablets, injections) are produced in one pharmaceutical factory only, namely, the Si Huan Pharmaceutical Factory.

DHE was diverted from licit into illicit channels.

#### **13. Bibliography**

Ai Yu-Hang, Xu Dao-Miao Ren Fei and Xu Qi-Ming. Severe respiratory inhibition in an old patient caused by sublingual administration of DHE. *Mod Diag Treat*, 7(1):50-51,1996.

Bian Chun-Fu, Xing Shu-Hua and Xu Peng-Cheng. The interactions between dihydroetorphine, L-tetrahydropalmatine, B-7601 and diazepam. *Acta Pharmaceutica Sinica*, 21(8):561-565,1986.

Cai Jin, Qiao Yu-Huai, Yang Yu-Xia and Wu Xiu-Ying. Nursing in the rescue process of acute intoxication with DHE hydrochloride in 20 cases. Abstracts of the Fourth National Conference on Drug Dependence, 1997:113-114.

Cao Gui-Hua, Chen Hong and Cai Zhi-Ji. Drug dependence on dihydroetorphine. *Chin J Clin Pharmacol*, 6(1):54-59,1990.

Cao Jia-Qi, Liu Zhi-Min, Lian Zhi and Mu Yue. An survey of the life-style of drug abusers. Abstract of the Fourth National Conference on Drug Dependence, 1997:43.

Cao Jing-Luan and Li Yong-Sheng. DHE hydrochloride-induced one case of respiratory inhibition. *Chin J New Drugs*, 1(5):49,1992.

Cao Yong-Xiao and Hua Jian-Feng. Successful rescue of one case intoxicated severely by DHE. *North-West Pharm J*, 9(4):161, 1994.

Cao Yong-Xiao, Sun Yan-Ling, Xing Fu, Wang Nai-Yao and Gao Wen-Xi. A survey of 185 DHE hydrochloride abusers. *Chin Bull Drug Depend*, 4(1):21-24,1995.

Cao Yong-Xiao, Sun Yan-Ling, Xing Fu, He De-Ming, Wang Nai-Yao, Gao Wen-Xi and Liu Zhi-Min. A retrospective survey of 50 dihydroetorphine abusers. *Chin Bull Drug Depend*, 5(4):234-237,1996.

Chang Xiu-Lan and Hu Dao-Ping. A case of bradycardia caused by DHE hydrochloride. *Chin Pharm Aff*, 9(5):313,1995.

Chen Bing-Xue, Lin Zhi-Hua and Tan Jie-Fang. The therapeutic effect of dihydroetorphine hydrochloride on chronic stubborn pain, *J Clin Anesthesiol*, 10(4):210-211,1994.

Chen Jun, Zheng Ji-Wang, Xie Lu, Wang Wei-Ping and Cai Zhi-Ji. Application and comparison of three methods in evaluating the potency of psychic dependence. *Chin Pharmacol Bull*, 12(3):235-238,1996.

Chen Qi-Meng, Liu De-Min, Zhang Wei, Tang Xin-Zhi and Cheng Man-Li. Analgesic effect of DHE hydrochloride in obstetric. *Chin Vill Med*, 23(6):50-51,1995.

Cheng Man-Li, Cheng Dai-Li, Li Hong, Sun Yue and Chen Jian-Ping. Analgesic effects of sublingual dihydroetorphine hydrochloride during labor. *Chin J Anesthesiol*, 15(2):82-84,1995.

- Cheng Man-Li and Sun Yue. The use of dihydroetorphine hydrochloride in intravenous combination anesthesia. *Tianjin Med Pharm*, 24(8):511-512,1996.
- Chen Yuan-Ning, Yang Yu-Zhang, Liu Ying-Hua, Jiao Xiao-Lan, Xiao Yue-Ping and Ai Min. A survey on and analysis of dihydroetorphine utilization *Chin Bull Drug Depend*, 4(1):16-20,1995.
- Cui Yu-Hua. A report of one case of addict induced by dihydroetorphine hydrochloride tablet. *Chin Bull Drug Depend*, 2(3):215-216,1993.
- Deng Jun-Lin, Li Jiang-Zhong, Li Jiu-Gui, Fang Mei, Li Wen-Jun, Deng Zheng-Quan and Yuan Ze-Qiong.. A clinical analysis of 638 cases of opiate physical dependence. *Chin Magaz Drug Abuse Prev Treat*, 2:21-24,1996.
- Dong Fei-Yun and Long You-Hua. Treatment of 15 cases of dihydroetorphine hydrochloride-induced body surface ulcer by combination of traditional Chinese and western medicine. *J Yunnan Trad Chin Med*, 14:49,1993.
- Fan Ping. One case of DHE addiction due to intravenous injection of excessive doses of solution with dissolved tablets of the drug. *Chin Bull Drug Depend*, 4(3):192,1995.
- Fu Yi-Ling. DHE hydrochloride-induced severe anaphylactic reaction in two cases after using sublingual tablets of the drug. *Beijing Clin Pharm*, 7(2):27,1994.
- Han Kang-Sheng. Report of one case with respiratory inhibition caused by DHE. *Jiangsu Med Pharm*, 21(10):702,1995.
- He Zhen-Feng, Lu Yun-Lan and Zheng Gui-Feng. A report of one case of DHE-induced addiction. *Chin Bull Drug Depend*, 2(3):216,1993.
- He Zhen-Feng, Zheng Gui-Feng and Lu Yun-Lan. DHE-induced rash in one case. *Chin J New Drugs*, 3(2):38,1994.
- Huang Chang-Xia. The use of dihydroetorphine in clinical digestive system. *Med J Lib Army*, 12(2):132-133,1987.
- Huang Mao and Qin Bo-Yi. Analgesic and other central nervous system inhibitory effects of dihydroetorphine. *Acta Pharmacol Sin*, 3(1):9-13,1982.
- Huang Mao and Qin Bo-Yi. Physical dependence on DHE in mice and monkeys. *Acta Pharmacol Sin*, 3(2):81-84,1982.
- Huang Mao, Wang Mei-Ying, Yuan Shu-Lan and Qin Bo-Yi. Pharmacodynamics and pharmacokinetics of dihydroetorphine hydrochloride administered sublingually in mice and rats. *Acta Pharmacol Sin*, 9(4):308-312,1988.
- Huang Mao. Preliminary clinical studies of DHE hydrochloride tablets and injections.

Monograph of Research of Dihydroetorphine Hydrochloride: a Potent Analgesic, 1991:27-34.

Huang Rong-Hua, Li Jin-Chang, He Qi-Zhi and Gu Hong-Qin. Recognition of successful rescue in one case with apnea caused by DHE. *New Med*, 25(10):533,1994.

Huang Yue-Rong and Wang Wei. One case of patient with rash induced by DHE hydrochloride. *Chin J Pharmacoepidemiol*, 4(4):252,1995.

Jia Xue-Ke, Liu Xiao-Rong, Tan Xin-Jin, Zhang Mei and Xu Ping. DHE-induced coma in terminal liver cancer patients after administration of drug. *New Drugs and Clin Rem*, 15(1):60-61,1996.

Jiao Ji-Tai. A report of rescue of one case intoxicated by DHE. *Industr Med J*, 8(1):55-56,1995.

Jin Feng-Ling and Wang Chong. Report of a case of epileptic convulsion induced by DHE. *J Beijing Med Univ*, 27(6):418,1995.

Jin Feng-Ling, Li Zhao, Jin Qing-Chen, Zheng Qing and Liu Xiao-Hong. The use of dihydroetorphine in general anesthesia. *Chin J Anesthesiol*, 16(7):320-322,1996.

Jin Xiao-Mei, Liu Bao-Chun, Li Zong-Tong and Dai Jun-Zhou. Severe damage of hard tissue of teeth in 15 cases caused by sublingual administration of DHE. *J Oral Med Cross*, 12(2):126-127,1996.

Li E and Weng Li-Ju. Influence of dihydroetorphine hydrochloride and tramadol on labor pain and umbilical blood gas. *Chin J Obstet Gynecol*, 30(6):345-348,1995.

Li Hong-Ying. DHE-induced ageusia in one case. *Med J NDFSC*, 4(2):67,1994.

Li Hong-Wei and Wang You-De. An analysis of epidemiological survey on 540 cases of drug abusers. *Chin J Drug Abuse Prev Treatm*, 2:7-9,1996.

Li Jian-Guo, Liang Wan-Qiang, Liu Xia-Ling and Liang Biao. A clinical study of the treatment of heroin dependence by DHE hydrochloride. *Chin J Neurol Psychiatry*, 28(4):208,1995.

Li Jing-Mei, Yang Shu-Zhen, Zhang Li-Ping and Tan Wen. An analysis of rescue of sudden respiratory arrest induced by DHE hydrochloride in 8 cases. *Chin J Appl Int Med*, 14(9):557,1994.

Li Lan, Luo Yue-Xi, Lu Shu-Lan, Zhou Yun-Fang and Fang Ming. The use of DHE hydrochloride in artificial abortion. *Reprod Contracept*, 6:462,1996

Li Ping and Hao De-Zhi. A clinical study of DHE injection for moderate to severe cancer pain treatment in 55 advanced patients. *Huaxi Med*, 11(3):350-352,1996.

Li Wei-Min, Nie Bing, Zhu Ze-Liang and Pang Yu-Tai. Comparison of the characteristics of pathophysiology between the DHE and heroin addicts. *Chin Bull Drug Depend*, 4(2):114-116,1995.

Li Yu-Sheng, Li Jun-Ling and Qu Feng-Lian. Using dihydroetorphine to control cancer pain. *Chin J New Drugs*, 5(2):122-123,1996.

Li Zhen, Yao Feng-Sheng, Li Yong-Chun, Li Wan-Li and Zhong Cheng. Morphological study on the cadavers of DHE and Heroin addicts. *Chin Bull Drug Depend*, 6(1):47-50,1997.

Lin Hui. Clinical study on DHE and buprenorphine and their combination in the treatment of heroin addicts. *Chin bull Drug Depend*, 3(1):30-31,1994.

Lin Song-Yue, Jin Ri-Tian and Piao Zhe-Hong. An approach to observe epidural injection of DHE for postoperative analgesia. *J Clin Anesthesiol*, 10(4):226,1994.

Liu Guo-Long and Sheng Xin-Xiu. Report of one case of severe respiratory inhibition induced by ordinary dose of DHE hydrochloride. *J First Mil Med Univ*, 15(2):179, 1995.

Liu Qiao-Qin. DHE hydrochloride-induced shock in one case. *Chin J Hosp Pharm*, 15(6):280,1995.

Liu Shang-Yi, Wang Fu-Gui, Wei Rong, Guo Xiu-Lan, Han Yan-Ping and Li Li. A comparative observation on the clinical analgesic effect of Ai-Tong-Ling ointment, pethidine and DHE. *Guiyang Chin Trad Med J*, 17(4):62,1995.

Liu Xiao-Lin, Guo Ren-Hong and Zheng Xiu-Li. A report of 36 cases of old patients with cancer pain treated by DHE hydrochloride. *Appl Ger Med*, 10(1):41,1996.

Liu Ying, Yang Zhong-Dong and Lin Li-Qin. One case of DHE-induced adverse drug reactions. *Chin J Clin Pharmacol*, 11(3):145,1995.

Liu Zhi-Min, Cao Jia-Qi, Shi Fan and Cai Zhi-Ji. An epidemiological study on DHE abuse. *Chin Bull Drug Depen*, 4(4):223-231,1995.

Liu Zhi-Min, Wang Xiao-Ping, Ge Yun, Zhang Xue-Bin, Sun Wen Lin, Sun Gui-Kuan, Zhao Dong and Cai Zhi-Ji. A preliminary study on the psychic dependence of dihydroetorphine by using Addiction Research Center Inventory-Chinese Version (ARCI-CV). *Chin Bull Drug Depend*, 5(4):229-233,1996.

Liu Zhi-Min, Cao Jia-Qi, Zhu Guang-Rong, Teng Ying-Qun, Ren Zheng-Hong, Lian Zhi, Mu Yue, Yang Xiao-Song and Cai Zhi-Ji. A survey on poly-drug abuse of opiate addicts in two areas: Yunnan and Heilongjiang, Abstracts of the Fourth National Conference on Drug Dependence, 1997:43-44.

Liu Zhi-Min, Cao Jia-Qi, Zhu Guang-Rong, Teng Ying-Qun, Ren Zheng-Hong, Lian Zhi, Mu Yue, Yang Xiao-Song, Jiao Jie and Cai Zhi-Ji. Epidemiological study on the relapse of opiate addicts. *Chin Bull Drug Depend*, 6(3):169-174,1997.

Liu Zhi-Rong. Report of DHE-induced angina pectoris in one case. *Interm Med J*, 31(8):58,1996.

Liu Zhong-Hua and Zhang Kai-Gao. Neural mechanism of conditioned place preference effect of DHE hydrochloride. Abstracts of the Fourth National Conference on Drug Dependence,1997:25.

Lu Xia, Cheng Chu, Tang Guo-Jiao and He Yan-Ling. Three-step ladder approach to analgesia for pain in patients with advanced cancer: a clinical analysis of 62 cases. *Med Diag Treat*, 7(4):205,1996.

Lu Xin-Liang and Tang Jing-Hua. An observation of therapeutic efficacy of DHE hydrochloride in the treatment of pain due to thromboangiitis obliterans. *J Appl Comb Trad Chin Modern Med*, 8(10):614,1995.

Luo Fang, Ma Jian-Fang and An Yi-Ming. Rescue of two cases of DHE intoxication. *Chin J Clin Pharmacol*, 9(4):246,1993.

Ma Xue-Jin, Gao Ai-Ling, Su Qing, Guo Yi-Li and Li Zhi-Qing. An analysis of analgesic effect of DHE in 80 cases during labor. *Shandong Med Pharm*, 35(6):41,1995.

Ma Yun-Qing, Wu Dong-Ke and Zhang Pei-Wei. A clinical observation of the analgesic effect of dihydroetorphine hydrochloride with excessive high dose on terminal cancer pain. *Acta Acad Med Jiangxi*, 35(3):75-77,1995.

Martin TJ, Kim SA, Harris LS and Smith JE. Potent reinforcing effects of dihydroetorphine in rats. *Eur J Pharmacol*, 324:141-145,1997.

Mi Wei-Dong and Jin Bing. The effects of potent narcotics on haemodynamics during induction of anesthesia. *J Clin Anesthesiol*, 10(4):193-196,1994.

Ni Zhi-Quan. Death of one case caused by overdose of DHE hydrochloride. *Appl J Oncol*, 9(1):50,1994.

Ning Li-Xin and Li Dong-Mei. A clinical study of DHE dependence and its detoxification. Abstracts of the Fourth National Conference on Drug Dependence, 1997:98.

Qin Bo-Yi, Yang Zheng, Sha Li-Jun, Liu Ze-Yuan, Su Mu-Jin, Yang Jie-Wen, Li Jin, Lu Xin-Qiang, Deng Bian-Ming, He Zhi-Qi and Luo Xiao-Yun. Effectiveness of combined therapy with dihydroetorphine and methadone in detoxification of heroin addicts. *Chin Bull Drug Depend*, 4(2):77-83,1995.

Qiu Ze-Wu, Huang Shao-Qing, Zhang Li-Ying and Qin Bo-Yi. A report of DHE hydrochloride-induced dependence in 2 cases with excessive doses of the drug. *Chin Bull Drug Depend*, 3(4):249-250,1994.

Ren Bao-Shui, Gao Yu-Mei, Xu Zhen-Wei and Liang Xin-Chun. The use of DHE tablets for

clinical analgesia. *New Drugs Clin Rem*, 12(5):299,1993.

Sha Li-Jun, Zhu Hui, Liu Ze-Yuan, Wang Ling and Zhang Zhi-Xiang. Dihydroetorphine on heroinism withdrawal. *New Drugs Clin Rem*, 12(1):27-30,1993.

Sha Li-Jun, Liu Ze-Yuan, Zhang Zhi-Xiang, Cheng Lin-Xia and Chen Hong. DHE hydrochloride combined with methadone on heroinism withdrawal. *New Drugs Clin Rem*, 13(6):337-339,1994.

Sha Li-Jun, Zhang Zhi-Xiang, Cheng Lin-Xia and Liu Ze-Yuan. Colonic dialysis therapy of Chinese herbal medicine in abstinence of heroin addicts. *Chin J Comb Trad Chin Modern Med*, 17(2):76-78,1997.

Shanguan Xue-Hong. The use of DHE hydrochloride for analgesia during parturition and the influence on the foetus and the newborn. *Hebei Med* 2(6):598-599,1996.

Sheng Xin-Xiu, Chen Bi-Jun, Kang Shi-Jun, Li Jin-Han and Liu Guo-Long. A clinical observation on the treatment of cancer pain by DHE injection. *J First Mil Med Univ*, 16(4):373,1996.

Sheng Yan-Xing. Report of DHE-induced anaphylactic rash in one case. *New Med*, 27(3):129,1996.

Shi Le-Hua. Detoxification of 2 cases of DHE hydrochloride addicts. *Lan Hou Health*, 16(4):294, 1995.

Song Da-Jun, Jiang Hao and Wu Jue. Clinical comparison of DHE, phenoperidine, fentanyl and morphine in combination of intravenous general anesthesia. *Chin J Anesthesiol*, 11(5):268-271,1991.

Song Jing-Li, Xu Ya-Qin, Wang Yan-Yi and Zhou Chun-Rong. A clinical observation of hepatitis B complicated with chasing of DHE. Abstracts of the Fourth National Conference on Drug Dependence, 1997:59.

Su Mu-Jin, Lin Yun, Shen Tian-Guang, Zhang Lei and Huang Hua. Clinical efficacy of small dosage of DHE hydrochloride combined with anisodamine in the treatment of 40 cases of heroin addicts. *Chin Bull Drug Depend*, 2(1):48-51,1992.

Su Mu-Jun, Lin Yun, Deng Bian-Ming, He Zhi-Qi, Wang Ai-Lan and Huang Hua. Combining usage of dihydroetorphine hydrochloride and buprenorphine hydrochloride in detoxification of heroin addicts: Analysis of clinical curative effect in 57 cases. *Chin Bull Drug Depend*, 3(1):12-16,1994.

Su Mu-Jin, Deng Bian-Ming, He Zhi-Qi, Wang Jue and Sha Li. A clinical study on the treatment of heroin addicts by dihydroetorphine hydrochloride combined with methadone. *Chin Bull Drug Depend*, 3(2):99-102,1994.

Sun Jian. One case of DHE hydrochloride dependence. *Chin J Clin Pharmacol*,

11(3):160,1995.

Sun Yan-Hui, Ren Yu-Wei and Gao Pei-Lan. An epidemiological investigation on poly-drug abuse of 500 cases of opiate addicts in Shanxi province. Abstracts of the Fourth National Conference on Drug Dependence, 1997:48-49.

Tang Shu-Fang and Zhang Ming-Qiong. DHE hydrochloride-induced shock syndromes in 3 cases. Chin J Hosp Pharm, 15(11):522,1995.

Tao Mo and Hua Jin-Nian. Report of the treatment of terminal cancer pain by sublingual tablets of dihydroetorphine in 72 cases. Res Tumor Prev Treatm, 21(4):246,1994..

Tao Qing, Zhang Kai-Gao, Shi Shu-Guang, Ning Ya-Qing and Cai Zhi-Ji. Further explorations of physical dependence potential of dihydroetorphine. Chin J Pharmacol Toxicol, 6(3):196-200,1992.

Teng Ying-Qun, Jiao Jie, Gu Chun-Jiang and Han Jun. An epidemiological investigation of poly-drug abuse in Harbin area. Abstracts of the Fourth National Conference on Drug Dependence, 1997:50.

Tian Jia-Zhong and Zhang Xiu-Ying. One case of atrial fibrillation caused by sublingual administration of DHE hydrochloride. Chin J Cardiovasc Dis, 24(6):475,1996.

Tokuyama S, Nakamura F, Takahashi M and Kaneto H. Physical dependence produced by dihydroetorphine in mice. Bio Pharm Bull, 17(8):1056-1059,1994.

Tokuyama S, Nakamura F, Nakao K, Takahashi M and Kaneto H. A potent Mu-opioid receptor agonist, dihydroetorphine, fails to produce the conditioned place preference in mice. Jpn J pharmacol, 71:357-360,1996.

Tokuyama S, Nakamura F, Takahashi M and Kaneto H. Antinociceptive effect of dihydroetorphine following various routes of administration: a comparative study with morphine. Bio Pharm Bull, 19(3):477-479,1996.

Wang Ai-Ping, Zhang Qing-Lin, Huang Chun-Qian and Wang Zhi-Qiao. Effect of DHE hydrochloride on mice parturition. Chin J Obstetrics,31(5):299-301,1996.

Wang Ai-Ping, Zhang Qing-Lin, Huang Chun-Qian and Wang Zhi-Qiao. Effect of DHE hydrochloride on F<sub>1</sub> mice growth. Bull Acad Mil Sci, 20(2):113-116,1996.

Wang Dan-Xin, Huang Mao and Qin Bo-Yi. Binding characteristics of DHE to opioid receptors in rat brain. Chin J Pharmacol Toxicol, 5(3):161-163,1991.

Wang Dan-Xin, Liu Yong-Shao and Qin Bo-Yi. Experimental therapeutic effects of DHE in morphine-dependent rats and monkeys. Chin J Pharmacol Toxicol, 6(1):36-40,1992.

Wang Dan-Xin, Lu Xin-Qiang and Qin Bo-Yi. Dihydroetorphine is a -receptor ligand. J

Pharm Pharmacol, 47:669-673,1995.

Wang Dan-Xin and Qin Bo-Yi. Binding of [<sup>3</sup>H] dihydroetorphine to opioid receptor in rat brain membrane. Acta Pharmacol Sin, 17(3):281-283,1996a.

Wang Dan-Xin and Qin Bo-Yi. Effects of DHE treatment on regulation of opioid receptor mRNA level in rat brain region. Chin J Pharmacol Toxicol, 10(4):247-250,1996b.

Wang Gui-Lin, Wang Wei-Ping, Ha Ying and Zheng Ji-Wang. Intravenous self-administration of DHE in rats. Chin Bull Drug Depend, 5(3): 167-169,1996.

Wang Hai, Huang Bao-Xing, Sun Hui-Ming, Liu Xiong-Hua and Hou Hui-Rong. Clinical observation of epidural DHE analgesia in postoperative patients. J Curr Oncol, 1(1):66-68,1994.

Wang Hui-Kai, Geng Zhi-Long and Hua Chuan-Bao. An exploration on the use of DHE for anesthesia in cardiac operation. Lan Hou Health, 15(1):23-24,1994.

Wang Nian-Sheng, Deng Hong-Bing and Cai Zhi-Ji. Evaluation of psychic dependence potential of DHE by conditioned place preference method. Chin Bull Drug Depend, 2(4):271-273,1993.

Wang Shu-Fan, Yan De-Kuan, Yang Zheng, Qin Bo-Yi, Wei Yu-Jun and Li Fu-Yu. Clinical investigation on detoxification of heroin addiction with DHE hydrochloride. Chin J Clin Pharmacol, 8(2):106-112,1992.

Wang Shu-Fan, Qin Bo-Yi, Zhang Yu and Qiu Ze-Wu. DHE hydrochloride-induced dependence in two cases. New Drugs Clin Rem, 13(1): 60, 1994.

Wang Wei-Ping, Wang Gui-Lin, Ha Ying and Zheng Ji-Wang. Psychological dependence potential of DHE in rhesus monkeys. Chin Bull Drug Depend, 6(1):8-12,1997.

Wang Xiao-Hong. DHE hydrochloride-induced syncope in one case. Chin J Hosp Pharm, 16(7):332,1996.

Wang Xiao-Jia, Huang Jian-Jin, Zhang Shu-Zhan and Wu Jin-Min. Clinical observation of therapeutic effect of DHE on cancer pain. Henan J Oncol, 8(1):48-49,1995.

Wang Xiao-Ping. A survey on status of DHE abuse. Chin Bull Drug Depend, 2(2):105,1993.

Wang Yan-Ping and Wang Jian. Nursing of patients with respiratory failure caused by acute DHE intoxication and treated with naloxone. Chin J Nursing, 31(10):591-592,1996.

Wang Zhi-Gang, Zhao Zhu-Lin, Zhang Xian-Wu and Yang Yu-Zhang. Analysis of 9 mortal cases caused by DHE hydrochloride abuse. Chin Bull Drug Depend, 3(3):176-178,1994.

Wang Zhi-Gang, Zhang Xian-Wu, Zhao Zhu-Lin, Yang Yu-Zhang and Chen Wei-Guo. Clinical study of clonidine in the detoxification of DHE addicts. Chin Bull Drug Depend,

4(3):159-162, 1995.

Wang Zhi-Gang, Zhao Zhu-Lin, Zhang Xian-Wu, Bai Yong-Gui, Xia Yan-Min and Zhao Jin-Shuan. Abstinence syndromes in 40 DHE addicts vs 40 heroin addicts. *New Drugs Clin Rem*, 14(1):23-26,1995.

Wang Zhi-Gang, Zhao Jin-Shuan, Zhao Zhu-Lin, Han Yan-Qiu, Yang Yu-Zhang, Fu Jing-Chun, Li Xiu-Lian and Zhang Xian-Wu. Thyroid gland function, pancreas secretion, and testosterone concentrations in DHE addicts. *New Drugs Clin Rem*, 15(6):322-324,1996.

Wang Zhi-You. Successful rescue of one case intoxicated with excessive doses of DHE hydrochloride by using naloxone hydrochloride. *Chin J Pharmacoepidemiol*, 3(2):98-103,1994.

Wang Zuo-Jun, Shi Zhi-Zhen and Guo Ling-En. Recognition of the use of sublingual tablets of DHE hydrochloride in appendectomy. *J Clin Anesthesiol* 10:228,1994.

Wei Chang-Yuan, Liu Jian-Lun and Yang Nan-Wu. Clinical observation on the therapeutic effect of dihydroetorphine hydrochloride tablets on terminal cancer pain. *Guangxi Med*, 16(6):514-515,1994.

Wu Guan-Qing and Sun Yan. Dihydroetorphine hydrochloride for moderate and severe cancer pain. *Chin J Oncol*, 13(1):64-67,1991.

Wu Shi-Qi and Xu Ling. The use of DHE for relief of labor pain. *New Drugs Clin Rem*, 15(1):53-54,1996.

Wu Wei-Ran, Li Ying, Zhang Wen-Ren and Li Feng-Yuan. Influence of DHE on immune function of mice. *Abstracts of the Fourth National Conference on Drug Dependence*, 1997:36.

Wu Yan-Shan. A Report of one case of respiratory inhibition caused by sublingual administration of DHE hydrochloride. *Appl Med J*, 10(5):512.

Xu Jiang-Ping, Guo Qing-Fu and Su Jun-Feng. Effect of DHE, ohmefentanyl and etonitazene on immune function in mice. *Chin J Pharmacol Toxicol*, 7(4):290-293,1993.

Xu Mei-Qin. Observation of the analgesic efficacy of dihydroetorphine hydrochloride tablets on cancer pain. *Railway Med*, 22(6):366,1994.

Xu Shi-Zhen and Qu Li-Rong. Clinical analysis of 38 cases of DHE dependence. *Chin Bull Drug Depend*. 4(3):163-164,1995.

Yan Hong-Yun, Song Yue-Qing, Pan Feng-Ju and Zhang Guo-Qing. The use of DHE hydrochloride in artificial abortion. *Hebei Med Pharm*, 16(1):40,1994.

Yang Li-Ping and Lin Li, Rescue of one case of respiratory inhibition caused by DHE tablets. *Shaanxi Med J*,23(5):320,1994.

Yang Liang, Li Hong, Shi Qing-Zhen and Wu Ya-Wei. An analysis of drug dependence

characteristics of DHE in 116 cases in Kunming city. Abstracts of the Fourth National Conference on Drug Dependence, 1997:52.

Yang Ru-Chang, Hong Chuan-Ying, Li Xian-Ying, Qian Yi-Ping, Chen Dai-Chun and Chen Zheng-Zhong. Clinical use of DHE hydrochloride in terminal cancer pain. *New Med*, 26(3):135,1995.

Yang Yu-Lan. The use of DHE and tetracaine in artificial abortion. *J Bengbu Med Coll*, 21(4):223,1996.

Yang Yu-Xia and Qiao Yu-Huai. A report on rescue of 20 cases of DHE intoxication. Abstracts of the Third National Conference on Drug Dependence, 1995:62.

Yang Zheng, Yang Jie-Wen, Li Jin, Lu Xin-Qiang, Dong Chun-Xiang and Qin Bo-Yi. Evaluation on detoxification effects of DHE combined with methadone in heroin addicts. *Chin J New Drugs*, 3(4):23-27,1994.

Ye Zhao-Chuan and Ji Meng. A clinical observation on the effect of sublingual administration of DHE supplement to analgesia in local operation. *J Clin Anesthesiol*, 12(4):202,1996.

Yin Hong, Duan Jun-Jiang and Li Xiu-Qin. The effect of DHE on neurobehavioral teratology in offsprings of mice. *Chin Bull Drug Depend*, 5(3):145-150,1996.

Yu Fang and Guo Yan-Rong. A report of DHE hydrochloride-induced respiratory failure. *Clin Misdiagn Mistreatm*, 3(1):32,1995.

Yu Xin, Tian Yun-Hua and Shen Yu-Chun. Four cases of DHE dependence. *Chin Med J*, 74(9):547,1994.

Yuan Ben-Li, Yu Shou-Zhong and Zhang Zhi. Distribution of [<sup>3</sup>H] DHE in rat brain observed by *in vitro* quantitative autoradiography. *Chin J Pharmacol Toxicol*, 9(1):61-64,1995.

Yuan De-Fa, Tang Xiang-Xian, Li Li-Hua and Zhang Mao-Yun. Dihydroetorphine combined with buprenorphine on heroinism withdrawal. *New Drugs Clin Rem*, 13(5):283-284,1994.

Yue Zhong-Ying and Wan Yong-De. DHE-induced addiction in 78 cases. *Chin J Hosp Pharm*, 14(7):327,1994.

Zhang Da-Zhuang and Wu Ying-Chuan. DHE used for effectively relieving severe abdominal pain in 20 cases. *J Clin Anesthesiol*, 10(4):226-227,1994.

Zhang Min and Ye Jin-Zhao. DHE-induced severe respiratory inhibition in one case. *Chin J Pharmacoepidemiol*, 2:38,1993.

Zhang Rui-Min, Feng Zai-Kun, Yang Mao-Bin, Li Jian-Hua, Zhu Hua and Wan Wen-Peng. An analysis of the survey of 102 cases of heroin addicts abusing DHE. *Chin J Neurol*

Psychiatry, 19(6):367-368,1993.

Zhang Xi-Mei, Wang Xian-Mei and Wang Chun-Hua. DHE hydrochloride-induced severe anaphylactic reaction in one case. Chin J Comb Trad Chin Med Oto-Rhino-Laryngol, 4(4):183,1996.

Zhang Xiao-Xiu, Dong Xing-Fang, Wang Fei-Fei and Li Bing. DHE hydrochloride-induced addiction in 40 cases. Mod Appl Pharm, 11(1):50,1994.

Zhang Ying-Ge and Qin Bo-Yi. Physical dependence of DHE produced by continuous intravenous infusion in rats. Chin Bull Drug Depend, 3(4):218-222,1994.

Zhang Ying-Ge and Qin Bo-yi. Re-evaluation of physical dependence of etorphine. Abstracts of the Third National Conference on Drug Dependence, 1995:19-20.

Zhang Yong, Liu Xiao-Ling, Zhang Mei-Sheng and Wang Xiao-Xia. Acute DHE intoxication in 3 cases by injecting excessive doses of solution of dissolved tablets. Chin Bull Drug Depend, 3(3):190,1994.

Zhang Yu-Hua. An observation of therapeutic efficacy of DHE hydrochloride for relieving labor pain in 100 cases. J Luzhou Med Col, 19(2):135-137,1996.

Zhao Guang-Jun, Zhang Qi-Lan, Liu Xue-Jun, Wu Xi-Xiang and Li Gui-Feng. A clinical study on the use of DHE for analgesia during parturition. Adv Mod Gynecol, 5(1):44-45,1996.

Zhao Guo-Hou, Zhao Huai-Bi, Zhang Zai-Heng, Jin Wei-Qiu, Wu Peng-Lan and Li Qing. The diagnosis and treatment of 28 cases of acute intoxication caused by intravenous DHE administration. Acad J Kunming Med Coll, 16(1):26-28,1995.

Zhao Huai-Bi. A report of 11 cases of acute intoxication caused by DHE hydrochloride. Chin Bull Drug Depend, 2(1):56,1992.

Zhao Huai-Bi, Li Yu-Ping, Zhao Guo-Hou and Feng Yong-Qian. Clinical analysis and survey of DHE abuse. Chin J new Drugs, 5(2):124,1996.

Zhao Jian-Ying and Lin Jian-Dong. A clinical observation of analgesic effect of DHE during operation. J Fujian Med Coll, 28(2):187-188,1994.

Zhao Shu-Yun and Feng An-Hua. A report of drug dependence produced by DHE in 10 cases of cancer patients. Abstracts of the Fourth National Conference on Drug Dependence, 1997:70-71.

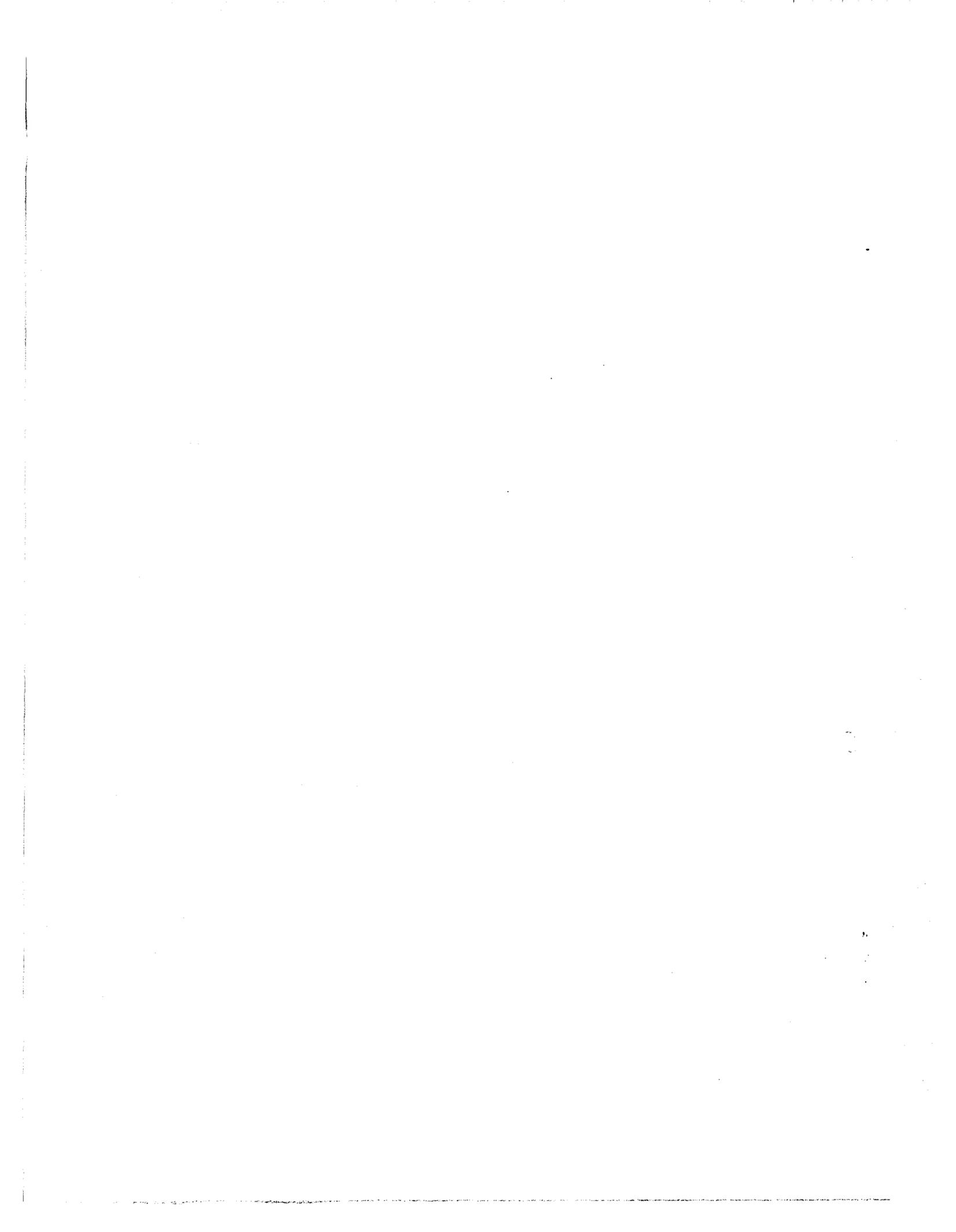
Zheng Ji-Wang, Zhang Kai-Gao and Cai Zhi-Ji. Evaluation of psychological dependence and the psychic dependence potential of DHE. Abstracts of the Fourth National Conference on Drug Dependence, 1997:9-10.

Zheng Ji-Wang and Zhang Kai-Gao. Psychic dependence potential of dihydroetorphine hydrochloride. Chin Bull Drug Depend, 4(2):65-69,1995.

Zhong Mei, Peng Cai-E, Liu Guo-Bing and Jin Zhi-Kui. The use of DHE hydrochloride tablets and tramadol drips in artificial abortion. *Chin J Appl Gynecol Obstet*, 10(4):246,1994.

Zhou Fu-Min, Jin Bing, Sun Qi-Fan, He Bo-Lin and Li Hui. Preliminary exploration of anesthesia caused by intra-tracheal administration of DHE. *Chin J Anesthesiol*, 7(3):147-149,1987.

Zhou Si-Tan. Addiction of DHE hydrochloride. *Sichuan Med.*, 15(6):336,1994.



**EPHEDRINE****1. Substance Identification**

**A. International Nonproprietary Name (INN):** NA

Other Nonproprietary Name: Ephedrine

**B. Chemical Abstract Service (CAS) Registry Number**

299-42-3 Anhydrous ephedrine  
50906-05-03 Ephedrine hemihydrate  
50-98-6 Ephedrine hydrochloride  
134-72-5 Ephedrine sulfate

**C. Other Names**

Racephedrine, Ephetonin (*dl*-form); Biophedrin, Ephedral, Ephedrosst, Sanedrine (*l*-form hydrochloride)

**D. Trade Names**

Ephedrine and its salts are available in a variety of dosage forms, frequently in combination with antitussives, expectorants, sedatives and/or antihistamines. Various formularies list over 200 trade names for *l*-ephedrine, *d,l*-ephedrine, and combination products.

**E. Identification Characteristics**

Ephedrine is obtained from plants of the *Ephedra* genus (*l*-ephedrine) or prepared synthetically (*d,l*-ephedrine).

Anhydrous ephedrine or ephedrine hemihydrate exists as colourless crystals or white crystalline powder. The anhydrous form has a melting point of 36 °C and the hydrated 42 °C. Both forms are soluble 1 to 20 in water and 1 in 0.2 alcohol. Highly soluble in ether. Solution decomposes on light exposure.

Ephedrine sulfate is soluble 1 in 1.3 of water and 1 in 90 of alcohol. Ephedrine hydrochloride is soluble 1 in 3 of water and 1 in 14 of alcohol and insoluble in ether. Solution decomposes in light.

## F. WHO Review History

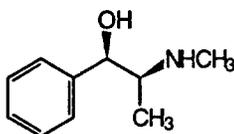
Ephedrine was pre-reviewed at the 30th ECDD in 1996, which recommended critical review.

## 2. Chemistry

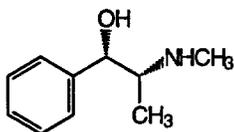
### A. Chemical Name. IUPAC Name. CA Name.

(1R\*,2S\*)-2-methylamino-1-phenylpropan-1-ol

### B. Chemical Structure



*l*-ephedrine



*d*-ephedrine

### C. Stereoisomers

The methyl substitution at the  $\alpha$  position and the hydroxyl substitution at the  $\beta$  position result in two asymmetric carbon atoms in ephedrine, yielding four stereoisomers. All have been prepared synthetically. They are designated *l*-ephedrine, *d*-ephedrine and *l*-pseudoephedrine, *d*-pseudoephedrine. Only *l*-ephedrine and *d*-pseudoephedrine are found in the plant. In ephedrine (*erythro-form*), the OH on the  $\alpha$ -carbon and the NHCH<sub>3</sub> on the  $\beta$ -carbon are close to each other. In pseudoephedrine (*threo-form*), they are remote from each other.

## 3. General Pharmacology

*This section describes the pharmacology of ephedrine. It is shown that ephedrine shares*

*pharmacological similarity with amphetamine, being a less potent CNS stimulating agent and a more potent bronchodilator.*

This section is compiled from reviews of ephedrine and sympathomimetic amines that include Anonymous, 1996; Goodman and Gilman, 1996; Hoffman and Lefkowitz, 1996; Gunne, 1977; Kawasuji et al, 1996; Lewander, 1977; Love, 1995; McEvoy, 1996; and White et al, 1997. Ephedrine is an alkaloid in plants of the genus *Ephedra*. These plants are found in temperate and sub-tropical latitudes of Europe, Asia and America, and grow especially in northern and western China, northern India, and Spain. Ma Huang (yellow astringent) is a Chinese herb containing ephedrine and has been employed as a medicinal product for over 5,000 years. In Western medicine, the properties of ephedrine and its introduction to therapeutics occurred in the early 1920s. Ephedrine was recognized to have pharmacological properties similar to those of epinephrine, and numerous clinical and experimental studies have compared the drug to epinephrine. Synthetic ephedrine as a racemic mixture was prepared in 1927 and marketed under the name Ephetonin. In contrast to epinephrine, ephedrine lacks the hydroxyl groups on the benzene ring and contains a methyl group in the  $\alpha$  position. These differences account for the greater stability, oral efficacy, and the central nervous stimulation of ephedrine when compared to epinephrine. The free carbon aliphatic chain in ephedrine was concluded to increase duration and oral efficacy (see Chemistry). Methyl substitution on the  $\alpha$  carbon led to the development of similar free carbon aliphatic chain compounds. The earliest were amphetamine (INN: amfetamine) and methamphetamine (INN: metamfetamine).

Consequently, ephedrine shares pharmacological similarity with amphetamine, the prototype of the centrally active sympathomimetic amines. Ephedrine is both an  $\alpha$ - and a  $\beta$ -adrenergic agonist and enhances the release of norepinephrine from sympathetic neurons. Classically the hydroxyl group on the  $\beta$  position is held to reduce the central activity of ephedrine. In general, ephedrine is viewed as being a less potent CNS agent but a more effective bronchodilator.

The pharmacology of epinephrine is related to its actions both peripherally and within the CNS. Ephedrine relaxes bronchial smooth muscle by stimulation of  $\beta_2$ -adrenergic receptors. Epinephrine acts on  $\beta_1$ -adrenergic receptors in the heart, producing a positive inotropic effect when low doses are administered. Epinephrine also produces a positive chronotropic effect through the sinoatrial node. This effect is overcome by increased vagal activity as a reflex with increased arterial blood pressure, resulting in bradycardia. Thus, depending upon the dose and circumstances, bradycardia, tachycardia or unchanged heart rate may occur. Ephedrine increases the autorhythmicity of the idioventricular or nodal pacemaker. This action prevents or stops arrhythmias of some types. Ephedrine increases the irritability of the heart muscle such that the rhythmic function of the ventricles can be altered. Consequently, ventricular tachycardia, extrasystoles, and fibrillation may occur. The direct cardiac stimulatory effect of ephedrine produces increased cardiac metabolism which results in dilation of coronary blood vessels. Increased coronary artery blood flow results. Under certain conditions, coronary blood flow may be decreased. The  $\beta_2$ -adrenergic actions of ephedrine result in vasodilation, and

action at  $\alpha$ -adrenergic receptors results in vasoconstriction. Arterioles in skeletal muscle are dilated, and arterioles in the skin, mucous membranes and viscera are constricted. Pulmonary and cerebral vessels may constrict or dilate. Peripheral vascular resistance may be increased, decreased, or unchanged. Systolic and diastolic pressure are increased as a result of vasoconstriction and cardiac stimulation. Peripheral venous pressure is increased. Circulating plasma volume may decrease. Vasoconstriction of renal vessels results in decreased renal blood flow. Dilated blood vessels in nasal mucosa are constricted by ephedrine, resulting in nasal decongestion following topical application.

The CNS actions of ephedrine are similar to those of amphetamine and other centrally active sympathomimetic amines. The actions of ephedrine and amphetamine on peripheral structures is related to release of norepinephrine from storage in adrenergic terminals and a direct action on both  $\alpha$ - and  $\beta$ -receptor sites; however, a central vasomotor effect is recognized. The central effect of the drugs is not completely understood. For example, *d*-amphetamine (INN: dexamphetamine) has central noradrenergic, dopaminergic and serotonergic actions. The main sites of action are the cerebral cortex and possibly the reticular activating system. Ephedrine and amphetamines cause an increase in motor activity, mental alertness, diminished sense of fatigue, enhanced mood, and euphoria. Ephedrine decreases appetite and promotes weight loss. A thermogenic action of ephedrine at  $\beta_3$  receptor in brown fat is described. With larger doses, there is psychic stimulation and excitability.

Amphetamines in general are not believed to facilitate mental and physical performance. Amphetamine and ephedrine do appear to improve performance when performance has been reduced by fatigue or sleep deprivation. Depression and fatigue follow the psychic stimulation produced by amphetamines. Ephedrine produces an anorexigenic effect leading to loss of weight (Norregaard et al, 1996).

Ephedrine relaxes the smooth muscle of the GI tract, contracts the urinary bladder trigone and sphincter, and relaxes the detrusor muscle. Urinary retention can result. Ephedrine decreases the activity of the uterus or, on occasions, an excitatory effect. Liver glycogenolysis occurs resulting in increases in blood glucose; however, hyperglycemia does not usually occur. Oxygen consumption and metabolic rate are increased by ephedrine. Ephedrine increases muscle strength in patients with myasthenia gravis.

#### **4. Toxicology - Including Adverse Reactions in Man**

*This section describes both the physical and psychiatric adverse effects of ephedrine. Physical adverse effects include hypotension accompanied by either tachycardia or bradycardia, as well as arrhythmias, edema, hemorrhage, focal myocarditis, subpericardial hemorrhage, necrosis of the intestine, and hepatic and renal necrosis after prolonged administration. Large doses can result in anxiety, nervousness, insomnia, muscle tremor, seizures, altered mental status and cerebral hemorrhage, and toxic psychosis.*

This section is compiled from reviews by others that include Anonymous, 1996; Anonymous, 1998; Derlet, 1989; Doyle and Kargin, 1996; Gunne, 1977; Lewander, 1977; Love, 1995; Lustik et al, 1997; Mack, 1997; McEvoy, 1996; Nadir et al, 1996; and Theoharides, 1997. The adverse effects of ephedrine are related to its peripheral actions at  $\alpha$ - and  $\beta$ -receptors and may vary according to the physiologic state of the individual. The other toxic effects relate to the activity of ephedrine centrally.

Hypotension may occur which can be accompanied by either tachycardia or bradycardia. Norepinephrine stores in sympathetic nerve endings may be depleted, resulting in tachyphylaxis to the cardiac and pressor effects. After several doses of ephedrine, hypotension more severe than the original illness being treated may result from the direct cardiac depression and vasodilation that are produced by ephedrine. Prolonged administration of ephedrine, like all pressor agents, has been reported to cause edema, hemorrhage, focal myocarditis, subpericardial hemorrhage, necrosis of the intestine, and hepatic and renal necrosis. Frequently, these effects have been reported in patients with severe shock, and it is unclear whether it is the shock or the ephedrine responsible for the toxicity. However, hemorrhagic strokes and myocardial infarcts have been reported in individuals taking therapeutic doses of ephedrine alkaloids. Ephedrine prolongs bleeding time and may inhibit platelet aggregation produced by epinephrine. Ephedrine increases the excitability of the heart muscle and is able to alter rhythmic function of the ventricles. Consequently, palpitations and tachycardia, extrasystoles, and potentially fatal arrhythmias including ventricular fibrillation may occur. Acute urinary retention or difficult urination may occur in patients receiving ephedrine. Ephedrine, especially after parenteral use, may constrict renal blood vessels and decrease urine formation. Other consequences of sympathomimetic activity are elevations in body temperature, hyperventilation and bronchodilation. Pulmonary edema has been reported. Large doses of ephedrine have been reported to produce anorexia, nausea and vomiting. Rhabdomyolysis can occur in overdose and result in renal failure. Excessive use or overdoses of ephedrine can result in anxiety, nervousness, insomnia, muscle tremor, seizures, altered mental status, and cerebral hemorrhage. Like amphetamine, a toxic psychosis may follow acute or chronic overdose.

Fatal intoxications with ephedrine are rare (Backer et al, 1997). Usually these fatalities occur when ephedrine is taken in conjunction with other stimulants. The estimated lethal dose in man is 2 grams. In animals, fatal doses produce cardiac and respiratory failure. Convulsions from direct stimulation or asphyxia occur in animals.

Certain drug interactions with ephedrine are clearly recognized. Ephedrine should not be administered with other sympathomimetic medications because of additive effects and increased toxicity.  $\alpha$ -adrenergic blocking drugs reduce the vasopressor response to ephedrine; however, this combination can cause vasodilation. The cardiac stimulating effects of ephedrine may result in increased cardiac output and a pressor response with sufficient dose.  $\beta$ -adrenergic blocking drugs such as propranolol block the cardiac and bronchodilating effects of ephedrine. Like epinephrine and other sympathomimetic amines, ephedrine increases cardiac irritability and may result in arrhythmias in patients

who have received cyclopropane or halogenated hydrocarbon general anesthetics. As an indirectly acting sympathomimetic drug, the effects of ephedrine are potentiated in the presence of monoamine oxidase inhibitors. Hypertensive crises and subarachnoid hemorrhages have occurred in patients who have taken ephedrine after MAO inhibitors. Drugs such as reserpine and methyldopa block the pressor response to ephedrine by reducing the quantity of norepinephrine in sympathetic nerve endings. On the other hand, ephedrine may antagonize blockage produced by guanethidine, resulting in loss of antihypertensive action. The pressor response to ephedrine is enhanced after atropine which blocks the reflex bradycardia. Theophylline derivatives in conjunction with ephedrine have been reported with a greater incidence of adverse effects. The cardiac glycosides can sensitize the myocardium to the effects of ephedrine. Finally, the administration of diuretics decreases arterial responsiveness to ephedrine.

## 5. Pharmacokinetics

*This section describes pharmacokinetics of ephedrine, which is largely excreted unchanged in the urine. Ephedrine is slowly metabolized in the liver by oxidative deamination, demethylation, aromatic hydroxylation and conjugation. Elimination half-life varies between 3 to 6 hours, depending on the acidity of the urine.*

This section is compiled from reviews of others that include Ångård, 1977; Love, 1995; and McEvoy, 1996. After oral, IM, or subcutaneous administration, ephedrine is distributed throughout the body. Ephedrine accumulates in liver, kidneys, spleen and brain. Ephedrine is slowly metabolized in the liver by oxidative deamination, demethylation, aromatic hydroxylation, and conjugation. Metabolites are  $\beta$ -hydroxyephedrine, *p*-hydroxynorephedrine, norephedrine, and conjugates of these compounds. Ephedrine and the metabolites are excreted in urine (95% in 24 hours), usually with the majority of the drug (55 to 75%) unchanged. Urinary excretion of ephedrine and the metabolites is dependent upon urinary pH. In general, acidifying the urine increases the excretion. The elimination half-life of ephedrine is about three hours when the urine is acidified and about six hours when urinary pH is about 6.3. Renal impairment results in increased half-life.

## 6. Dependence Potential

*This section summarizes animal and human studies on the dependence potential of ephedrine. Ephedrine has been found to generalize to cocaine and amphetamine in drug discrimination studies in rats. In monkeys, ephedrine racemate and the *d*- and *l*-isomers generalized to amphetamine with *d*-ephedrine indicating a lower potency than the *l*-isomer. They were all found to have reinforcing properties in self-administration studies in monkeys. In humans with histories of substance abuse, ephedrine is estimated to have amphetamine-like subjective effects several times less potent than *d*-amphetamine.*

### A. Preclinical Studies

In three rhesus monkeys trained to self-administer cocaine, *l*-ephedrine maintained responding rates greater than saline in substitution tests (Gold and Balster, 1996). In rats trained to discriminate cocaine from placebo, *l*-ephedrine generalized to cocaine - though at a slightly lower rate than *d*-amphetamine (Gold and Balster, 1996). Other discrimination studies in rats have found that ephedrine generalizes to cocaine and *d*-amphetamine (Gauvin et al, 1993; Huang and Ho, 1974). NIDA-sponsored CPDD test results showed that in two of the three amphetamine-trained monkeys, an oral dose of 10 mg p.o. of racemic ephedrine was discriminated as amphetamine. At 30 mg p.o. these two monkeys responded only 50% on the drug-appropriate lever but showed stimulatory signs. Two of the three monkeys discriminated *l*-ephedrine as amphetamine at oral doses of 10-30 mg. At higher doses stimulation was noted in all monkeys. In monkeys trained to self-administer cocaine *l*- and racemic ephedrine had definite reinforcing properties. *d*-Ephedrine was both less efficacious and potent than the *l*-isomer in its ability to generalize to amphetamine. In the case of pseudoephedrine, only 1/3 monkeys discriminated *d*- and *l*-isomers as amphetamine. However, *d*-pseudoephedrine was clearly self-administered while the *l*-isomer was not when tested between doses ranging from 0.03 to 0.3 mg/kg/injection (Harris, 1998).

### B. Clinical Studies

In humans with histories of substance abuse, *l*-ephedrine, *d*-amphetamine, *d*-methamphetamine, phenmetrazine, and methylphenidate injected subcutaneously produced similar increases in respiratory rate and blood pressure and similar types of subjective changes, including euphoria (Martin et al, 1971). The agents differed only in mg-for-mg relative potency with a concordance of potency estimates across measures. Subsequently, ephedrine was studied orally (Jasinski et al, 1976). In general, *l*-amphetamine and other amphetamine-like drugs differed only in mg-for-mg potencies.

Shown below is an estimate of relative potency of amphetamine-like drugs in producing amphetamine-like subjective and physiologic effects in substance abusers. Potencies are expressed as mg of the drug equivalent to 1 mg of *d*-amphetamine (Jasinski et al, 1976).

**Subcutaneous administration  
mg equivalent to 1 mg  
*d*-amphetamine**

<i>d</i> -amphetamine	1
<i>d</i> -methamphetamine	1
methylphenidate	2
phenmetrazine	4
<i>l</i> -ephedrine	5
diethylpropion	14
<i>d</i> -amphetamine (oral)	1

### Oral administration

<i>d</i> -amphetamine	1
phentermine	2
benzphetamine	5
l-ephedrine	5
diethylpropion	7

It is noted that ephedrine, like *d*-amphetamine, has similar potencies either by the oral or subcutaneous route. This is consistent with their complete absorption and slow metabolism. Diethylpropion is a pro-drug more potent orally since a greater amount of the active metabolite is formed.

In human volunteers with no drug dependence histories, *l*-ephedrine produced euphoria, was liked and was judged to have amphetamine-like reinforcing effects (Chait, 1994).

#### 7. Epidemiology of Use and Abuse with an Estimate of the Abuse Potential

Of the 50 countries which have returned the questionnaire to WHO, ephedrine is available for medical use in the following 46 countries: AUS, BAA, BEL, BFA, BLR, BRA, CHN, COK, COL, COR, CZH, DEU, FIN, FRA, GRE, HUN, IRE, ISR, JOR, JPN, KIR, LTU, LUX, MAD, MAT, MSI, NET, NEZ, NRU, OMA, PAN, PER, PHL, POL, QAT, SAA, SIN, SPA, SVK, SVN, SWE, SWI, THA, TVL, UAE, USA. Of these 46 countries, the following 12 countries have indicated present or past ephedrine abuse:

**BEL:** Sporadic reports on ephedrine abuse. The view of the competent authority is that this level of abuse does not justify controlling ephedrine as a narcotic or psychotropic drug.

**BFA:** Three preparations are available on prescription. Though no information is provided on ephedrine abuse, BFA reported seizures of ephedrine tablets smuggled from neighbouring countries.

**CHN:** Oral dosage forms are available. Ephedrine was abused in the past and resulting health problems stopped after it was placed under national control as a psychotropic drug.

**COR:** Ephedrine abused as a doping agent.

**DEU:** 16 preparations are registered, some as prescription drugs and others are OTCs. Abused by drug addicts in the past, which decreased after withdrawal of many of the preparations from the market.

**FIN:** Available on prescription. Some misuse exists, as indicated by a few abusers visiting treatment centres. A few cases of diversion on falsified prescriptions and

illegal importations were discovered.

- FRA: 24 preparations of different dosage forms are available, of which 18 are OTC. A few cases of ephedrine abuse are reported in the capital region. Though a significant increase in seizures of ephedrine was reported, there was no clear indication of the purpose of use.
- IRE: Tablets are available on prescription. Seized MDMA samples were found to contain ephedrine, suggesting some abuse as a substitute for MDMA.
- SUD: Ephedrine importation was stopped because of its abuse as a stimulant.
- SVK: Seven preparations of different dosage forms are sold. A few cases of misuse, and significant amounts of seizures in connection with clandestine manufacturing of stimulants.
- THA: Approximately 40 kg/year is used as a nasal decongestant. A few cases of abuse are known to the police, as well as illicit trafficking as a precursor in border areas.
- USA: Ephedrine is sold as a single entity or in combination with multiple ingredients, both as a prescription and OTC medication. In addition, Ma Huang and extracts are sold as dietary supplements. DAWN data indicate an increase in drug abuse episodes of ephedrine and pseudoephedrine. Subsequent analyses indicated that the incidence with pseudoephedrine was higher than for ephedrine. STRIDE data for the 6-year period 1992-1997 indicated about 700 exhibits involving small quantities (200 tablets or less) of ephedrine, representing about 300 cases, were likely to have been associated with ephedrine abuse.

Adverse events tabulated for ephedrine products sold as food supplements for the State of Texas were reported by the Centers for Disease Control (CDC).

### **Estimate of the abuse potential**

Ephedrine's abuse potential as a stimulant has been demonstrated in animal and human studies. Ephedrine is abused in some countries. However, it is difficult to evaluate the likelihood of its abuse and the seriousness of the resultant public health problems, because of the long history of generalized safe use of the ephedrine alkaloids in OTC preparations. Although the response rate was rather low, three-fourths of the countries which responded having therapeutic use of ephedrine (34/46) were unaware of ephedrine abuse in their countries. Of the 12 countries which reported present or past ephedrine abuse, one country was of the opinion that the low level of abuse would not justify its control as a controlled drug. Other countries did not express their views concerning the seriousness of the problem. Four countries have responded to the problem of ephedrine abuse with a regulatory action. It would be useful to analyse these examples since it is likely that the authorities of these countries considered the abuse of ephedrine as a

significant public health problem. China applied tighter national controls and the problem apparently stopped. Germany reduced the number of ephedrine preparations and the problem of ephedrine abuse reduced. It should be noted, however, that Germany still has 16 ephedrine preparations, including some OTC products, and consumes large quantities of ephedrine (88 tonnes imported, with some re-exportation). Sudan had to stop ephedrine importation because of its abuse as a stimulant. In the USA, the abuse of dietary supplements containing Ma Huang prompted the FDA to set threshold levels of ephedrine ingestion through the use of Ma Huang.

Taking the above into consideration, the ECDD would be requested to assess whether "ephedrine is liable to be abused so as to constitute a significant (for Schedule IV) or substantial (for Schedule II or III) public health and social problem warranting the placing of ephedrine under international control".

## **8. Nature and Magnitude of Public Health Problems**

There are four areas of public health and social concern regarding ephedrine abuse and misuse. These are: (1) dependence on ephedrine itself, (2) the use of ephedrine as a look alike drug, (3) the misuse of Ma Huang, and (4) the use of ephedrine as a precursor. However, (4) is not discussed in this document as this is irrelevant to the assessment of ephedrine's abuse liability and there is a separate control system based on the 1988 Convention to deal with the problem of precursors.

### **(1) Abuse of Ephedrine itself**

World literature documents cases of ephedrine abuse which have primarily manifested themselves as developments of typical amphetamine-like psychosis (Griffith, 1977). Hallucinations, paranoid behaviour, aggressiveness, or other schizophrenic-like behaviour has been reported following daily use of large doses of ephedrine. In general, ephedrine dependence has all the characteristics of an amphetamine-like dependence except the incidence of abuse and psychosis is significantly less for ephedrine than with amphetamine or methamphetamine.

### **(2) Use as Look Alike Drug**

Though only Ireland indicated in the WHO questionnaire the detection of ephedrine in illicit preparations claimed to be MDMA, such fake MDMA preparations containing ephedrine and hallucinogenic substances have been encountered in other countries as well. Licit ephedrine preparations are also used as a substitute for amphetamines. In the USA, a number of OTC medications were deliberately advertised and sold as bogus drugs of abuse (Chase, 1996; Nightingale, 1996; Hecht, 1998; Klatt et al, 1986). For stimulants, these included ephedrine, caffeine, and phenylpropanolamine. These were formulated to resemble licit amphetamine.

### (3) The Use and Abuse of Ma Huang

Abuse of Ma Huang is not well known except in the USA, where vitamins, minerals, and herbs are classified as food supplements rather than pharmaceutical products. This has allowed manufacturers to promote known effects of the drugs on structure and function of the body, and they can be sold under various names. Unlike drugs, the resulting products were sold as Ma Huang and extracts from Ma Huang. Ma Huang contains six naturally occurring ephedrine alkaloids - *l*-ephedrine, *d*-pseudoephedrine, *l*-N-methylephedrine, *d*-N-methylpseudoephedrine, *l*-norephedrine, and *d*-norpseudoephedrine. A huge number of products have been sold as food supplements. The most common ingredient is Ma Huang or Ephedra (*Ephedra sinica*, or Chinese Ephedra) which contains botanical sources of ephedrine and related alkaloids. The labels on the products identifies them as Ma Huang or Ma Huang extract. Other names which are common are Ephedra extract, Ephedra concentrate, Ephedra herb powder, and Epitonin.

Many of these products were mixed with other ingredients including methylxanthines such as caffeine, theophylline, and theobromine; salicin from white willow; and chromium. The products were also combined with various amino acids or other ingredients. Reports of adverse events associated with these products resulted in the FDA attempting to review these products in an attempt to limit their distribution and use. These products were advertised to promote weight loss, enhance muscular strength, produce psychic energy, and increase endurance.

## 9. National Control

The 46 countries which have indicated the therapeutic use of ephedrine are grouped as follows:

### Distribution control of ephedrine as pharmaceuticals

Prescription: AUS, BAA, BFA, FIN, GRE, IRE, MSI, NEZ (pharmacy only), PER, QAT, SVK, SVN, SWE

OTC: BRA, LUX, PAN, SWI

Both: DEU, FRA, HUN, JOR, JPN, MAT, NET, PHL, SIN, USA

Unspecified: BEL, BLR, CHN, COK, COL, COR, CZH, ISR, KIR, LTU, MAD, NRU, OMA, POL, SAA, SPA, THA, TVL, UAE

### Control of Ma Huang as dietary supplements

USA In 1997 the FDA proposed a measure that would prohibit companies from marketing dietary supplements that contained 8 mg or more of ephedrine alkaloids per serving (Nightingale, 1997). These measures would also

prohibit the inclusion of other stimulants such as caffeine in supplements that contained ephedrine alkaloids. The proposal also requires substantial labelling and marketing changes. The labelling could not suggest conditions of use that would result in ingestion of 8 mg or more of ephedrine alkaloids in a 6-hour period or 24 mg in a day. Consumers would be cautioned against using the product for longer than seven days. Claims that require longer periods of use to achieve intended effects such as weight lifting or body building would be prohibited. Products with label claims that encourage short-term excessive use such as energy enhancement would be required to state that "taking more than the recommended serving may result in heart attack, stroke, seizure, or death." These dietary supplements are also required to contain a label which includes a statement warning of the potential risk of ephedrine. This proposal did not extend to non-prescription drug products.

#### **10. Therapeutic and Industrial Use**

92 % of the countries which responded to the WHO questionnaire (46/50) indicated therapeutic use of ephedrine. Although the response rate was rather low (50/191), this figure suggests that ephedrine is used therapeutically in a large majority of the countries in the world. Some of these countries have indicated a large number of pharmaceutical products containing ephedrine on the market, e.g., 68 products in Brazil, 69 products in Singapore, and 52 products in Jordan. Even in Europe, France, Germany and Spain reported 24, 16 and 36 ephedrine preparations, respectively. Reported dosage forms include tablets, powders, syrups, ampoules for injection, suppositories, nasal drops and nasal sprays.

Ephedrine is used widely as a bronchodilator in the symptomatic treatment of reversible bronchospasm which may occur in association with asthma, bronchitis, emphysema, and other obstructive pulmonary diseases. Injectable ephedrine has been used in moderate to severe asthma attacks, acute asthma attacks, or anaphylactic reactions, including anaphylactic shock, although it is not as effective as epinephrine. A sedative or tranquillizer may be admixed with ephedrine to minimize the CNS stimulating effects of ephedrine. At times, ephedrine is combined with antitussives or expectorants for the management of cough associated with asthma. Tolerance develops to the bronchodilatory effects of ephedrine. Ephedrine has been used both orally and topically as a nasal decongestant. Like other sympathomimetic amines, rebound congestion and tachyphylaxis may occur. Hypotension and shock have been treated with parenteral ephedrine through its actions producing cardiac stimulation and vasoconstriction. A recognized use of ephedrine is to treat hypotension during spinal anesthesia. In obstetrical patients, ephedrine is used to correct the maternal hypotension from spinal anesthesia, and it is suggested that this corrects the consequences of maternal hypotension to the fetus. Ephedrine is used to increase ventricular rate in bradycardic patients and in syncope caused by atrioventricular nodal block. The drug is used to treat carotid sinus syndrome or Adams-Stokes disease. Most of these uses have been replaced by other

drugs such as isoproterenol or electrical cardiac pacemakers. Ephedrine has enjoyed some use as an anti-obesity agent. Other uses of ephedrine have been to reduce edema in patients with diabetic neuropathy. There is some use to combat motion sickness. Ephedrine is used to increase muscle strength in patients with myasthenia gravis with poor response to neostigmine or other anticholinesterase drugs. Ephedrine is used to relieve dysmenorrhea by decreasing uterine contractions. The effects on the urinary bladder and sphincter and the detrusor muscle allows use of ephedrine to treat urinary incontinence and enuresis. The CNS stimulant effects of ephedrine were used originally to treat narcolepsy or depressive states; however, this use has been supplanted by other amphetamine-like drugs such as amphetamine, methamphetamine, and methylphenidate.

### 11. Production, Consumption and International Trade

Only about half the responding countries (24/50) indicated estimated quantities of production or importation of ephedrine, as follows.

Importation, > 1,000 kg/yr	DEU (88 t, including re-exportation), FRA (14 t), MAD (14.7 t)
Importation, 100 - 1,000 kg/y	AUS, BLR, COL, HUN, MAT, PER, PHL, SPA, SVK, SWE
Importation, < 100 kg/yr	GRE, LTU, MSI, NEZ, QAT, SIN, SVN, THA, UAE
Manufacture	CHN (500 t), CZH (140 t), MAT (291 kg for re-exportation)

### 12. Illicit Manufacture, Illicit Traffic, and Related Information

The INCB report on precursors describes recent cases of diversion and attempted diversion of ephedrine. Consignments of ephedrine were ordered from different manufacturing countries, in particular the Czech Republic and India, by brokers in Switzerland, were shipped eventually to Mexico. However, when tighter controls over ephedrine were introduced in the supplier countries, traffickers appeared to quickly change their tactics. It is also stated that China appears to be the source of ephedrine used in the illicit manufacture of methamphetamine in south-east Asia. In 1996, a total of 12 tonnes of ephedrine diversion attempts were prevented and shipments of 4.5 tonnes were stopped because of suspicious circumstances (United Nations, 1998).

### 13. Bibliography

Allen, A.C. and Kiser, W.O. Methamphetamine from ephedrine: 1. Chloephedrine and aziridines. *Journal of Forensic Science* 32:953-962, 1987.

Ängård, E. General Pharmacology of Amphetamine-like Drugs A. Pharmacokinetics and Metabolism. In: *Drug Addiction II*, edited by Martin, W.R. Berlin: Springer-Verlag, 1977, p. 3-32.

Anonymous Ephedrine in **Martindale: The Extra Pharmacopeia**. Royal Pharmaceutical Soc. of Great Britain. Micromedex, Inc. (Vol. 95 1974-1978), 1998.

Anonymous From the Centers for Disease Control and Prevention. Adverse events associated with ephedrine-containing products--Texas, December 1993-September 1995. *JAMA* 276(21):1711-1712, 1996.

Backer, R., Tautman, D., Lowry, S., Harvey, C.M., and Poklis, A. Fatal ephedrine intoxication. *J. Forensic Sci.* 42(1):157-159, 1997.

Chait, L. Factors influencing the reinforcing and subjective effects of ephedrine in humans. *Psychopharmacology* 113:381-387, 1994.

Chase, S.L. The FDA warns of the dangers of ephedrine. *RN.* 59(12):67, 1996.

Cho, A.K. Ice: a new dosage form of an old drug. *Science* 249(4969):631-633, 1990.

Derlet, R.W., Rice, P., Horwitz, B.Z., and Lord, R.V. Amphetamine toxicity: Experience with 127 cases. *Journal of Emergency Medicine* 7(2):157-161, 1989.

Doyle, H. and Kargin, M. Herbal stimulant containing ephedrine has also caused psychosis [letter; comment]. *BMJ.* 313(7059):756, 1996.

Gauvin, D., Moore, K.R., Youngblood, B., and Holloway, F.A. The discriminative stimulus properties of legal, over-the-counter stimulants administered singly and in binary and ternary combinations. *Psychopharmacology* 110:309-319, 1993.

Gold, L.H. and Balster, R.L. Evaluation of the cocaine-like discriminative stimulus effects and reinforcing effects of modafinil. *Psychopharmacology (Berl)* 126(4):286-292, 1996.

Goodman, L.S. and Gilman, A. Drugs Stimulating Structures Innervated by Adrenergic Nerves. In: *The Pharmacological Basis of Therapeutics*, Anonymous 1956, p. 476-540.

Griffith, J.D. Amphetamine Dependence; Clinical Features. In: *Drug Addiction II*, edited by Martin, W.R. Berlin: Springer-Verlag, 1977, p. 277-304.

Gunne, L.M. General Pharmacology of Amphetamine-like Drugs C. Effects of Amphetamines in Humans. In: *Drug Addiction II*, edited by Martin, W.R. Springer-Verlag, 1977, p. 247-266.

Harris, L.S. Summary of CPDD test results. *Personal communication*, 1998

Hecht, A. Shutting down a major source of deadly 'look-alike' drugs. *FDA Consumer* 20:33,

1998.

Hoffman, B.B. and Leefkowitz, R.J. Catecholamines, Sympathomimetic Drug and Adrenergic Receptor Agonists. In: *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, edited by Hardman, J.G. and Limbird, L.E. New York: The McGraw Hill Companies, Inc, 1996, p. 199-248.

Huang, J. and Ho, B.T. Discriminative stimulus properties of legal, over-the-counter stimulants administered singly and in binary and ternary combinations. *Pharmacology Biochemistry Behavior* 2:669-673, 1974.

Jasinski, D.R., Pevnick, J.S., Griffith, J.D., Gorodetzky, C.D., and Cone, E.J. Progress Report on Studies from the Clinical Pharmacology Section of the Addiction Research Center. *Minutes, Committee on Problems of Drug Dependence, National Research Council, Richmond Va.* 38th Meeting: 112-148, 1976.

Jones, T.L. Dangerously revved. Ephedrine misuse poses health hazards. *Tex. Med.* 92(5):52-53, 1996.

Kawasuji, T., Koike, K., and Saito, H. Chronotropic effects of optical isomers of ephedrine and methylephedrine in the isolated rat right atria and in vitro assessment of direct and indirect actions on beta 1-adrenoceptors. *Biol. Pharm. Bull.* 19(11):1423-1428, 1996.

Klatt, E.C., Montgomery, S., Namiki, T., and Noguchi, T.T. Misrepresentation of stimulant street drug: a decade of experience in an analysis program. *Journal of Toxicology - Clinical Toxicology* 24(5):441-450, 1986.

Lewander, T. General Pharmacology of Amphetamine-like Drugs B. Effects of Amphetamines in Animals. In: *Drug Addiction II*, edited by Martin, W.R. Springer-Verlag, 1977, p. 33-246.

Love, L.A. Evaluation of the Safety of Food Products Containing Sources of Ephedrine Alkaloids, Briefing Materials for Food Advisory Committee Special Working Group on Foods Containing Ephedrine Alkaloids. Anonymous Food and Drug Administration. p. 1-51, 1995.

Lustik, S.J., Chhibber, A.K., van Vliet, M., and Pomerantz, R.M. Ephedrine-induced coronary artery vasospasm in a patient with prior cocaine use. *Anesth. Analg.* 84(4):931-933, 1997.

Mack, R.B. "All but death, can be adjusted". Ma Huang (ephedrine) adversities. *N.C. Med. J.* 58(1):68-70, 1997.

Martin, W.R., Sloan, J.W., Sapira, J.D., and Jasinski, D.R. Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine, and methylphenidate in man... *Clinical Pharmacology & Therapeutics.* 12(2):245-58X<79>X, 1971.

Martyr, J.W. and Orlikowski, C.E. Epidural anaesthesia, ephedrine and phenylephrine in a patient taking moclobemide, a new monoamine oxidase inhibitor. *Anaesthesia*

51(12):1150-1152, 1996.

McEvoy, G.K. Drug Information American Hospital Formulary Service. Anonymous Bethesda, MD USA: American Society of Health System Pharmacists. p. 872-876, 1996. 1-879907-61-5.

Nadir, A., Agrawal, S., King, P.D., and Marshall, J.B. Acute hepatitis associated with the use of a Chinese herbal product, ma-huang [see comments]. [Review] [20 refs]. *Am.J.Gastroenterol.* 91(7):1436-1438, 1996.

Nightingale, S.L. From the Food and Drug Administration. *JAMA* 275(20):1534, 1996.

Nightingale, S.L. From the Food and Drug Administration. *JAMA* 278(1):15, 1997.

Norregaard, J., Jorgensen, S., Mikkelsen, K.L., Tonnesen, P., Iversen, E., Sorensen, T., Soeberg, B., and Jakobsen, H.B. The effect of ephedrine plus caffeine on smoking cessation and postcessation weight gain. *Clin.Pharmacol.Ther.* 60(6):679-686, 1996.

Shearer, V.E., Ramin, S.M., Wallace, D.H., Dax, J.S., and Gilstrap, L.C., 3rd. Fetal effects of prophylactic ephedrine and maternal hypotension during regional anesthesia for cesarean section. *J.Matern.Fetal Med.* 5(2):79-84, 1996.

Theoharides, T.C. Sudden death of a healthy college student related to ephedrine toxicity from a ma huang-containing drink [letter]. *Journal of Clinical Psychopharmacology* 17(5):437-439, 1997.

United Nations *Precursors and chemicals frequently used in the illicit manufacture of narcotic drugs and psychotropic substances: Report of the International Narcotics Control Board for 1997 on the Implementation of Article 12 of the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988*, New York, 1998

White, L.M., Gardner, S.F., Gurley, B.J., Marx, M.A., Wang, P.L., and Estes, M. Pharmacokinetics and cardiovascular effects of ma-huang (*Ephedra sinica*) in normotensive adults. *J.Clin.Pharmacol.* 37(2):116-122, 1997.

**REMIFENTANIL****1. Substance Identification**

**A. International Non-Proprietary Name (INN): Remifentanil**

**B. Chemical Abstract Service (CAS) Registry Number:**  
CAS-132539-07-2; CAS-132875-61-7 (base).

**C. Other Names:**

Also known by code name GI87084B (and GI87084X for the corresponding base).

**D. Trade Names: ULTIVA®**

**E. Identification Characteristics:**

Remifentanil hydrochloride is a white to off-white solid. The pH value of a 1% w/w solution is approximately 5. pKa was determined to be 7.07. The Distribution Coefficient between n-octanol and an aqueous buffer (pH 7.3) measured to be 17.9 by HPLC. Solubility in aqueous solvents is: 150 mg/mL in water, unbuffered and in 5% Dextrose Injection USP and 120 mg/mL in 0.9% Sodium Chloride Injection USP; in organic solvents, 130 mg/mL (methanol), 12.5 mg/mL (acetonitrile), 10 mg/mL (ethanol), and <1 mg/mL (isopropanol, ethyl acetate). Examination of infrared and x-ray diffraction spectra of the salt provide no evidence of polymorphism or solvates. Its hydrochloride salt is chemically stable when stored at 30°C for 5 years.

ULTIVA® is a sterile, nonpyrogenic, preservative-free, lyophilized powder for intravenous administration after reconstitution and dilution. Each vial contains 1, 2, or 5 mg of remifentanil base, in 3, 5, and 10 mL vials, respectively (each in cartons of 10); 15 mg glycine; and hydrochloric acid to buffer the solutions to pH of 3 after reconstitution. After reconstitution, ULTIVA® solution is clear and colorless and contains equivalent of 1 mg/mL remifentanil base.

**F. WHO Review History:** Remifentanil was pre-reviewed by the 30th meeting of the ECDD which recommended critical review.

**2. Chemistry:**

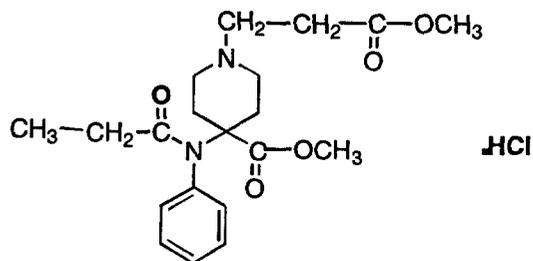
**A. Chemical Name**

**IUPAC Name:** 1-(2-methoxycarbonyl-ethyl)-4-(phenyl-propionylamino)-piperidine-4-carboxylic acid methyl ester hydrochloride.

**CA Index Name:** 3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]propanoic acid methyl ester, hydrochloride salt.

**Others:** 4-(Methoxycarbonyl)-4-[(1-oxopropyl) phenylamino]-1-piperidinepropanoic acid, methyl ester, monohydrochloride; 4-carboxy-4-(N-phenylpropionamide)-1-piperidine propionic acid, dimethyl ester, monohydrochloride.

**B. Chemical Structure**



**Molecular Formula:**  $C_{20}H_{28}N_2O_5 \cdot HCl$

**Molecular Weight:** 412.9

**C. Stereoisomers:** Remifentanil has no optical activity.

**3. General Pharmacology**

*This section reviews preclinical and clinical pharmacology studies documenting that remifentanil is a short-acting mu-opioid receptor agonist activity of remifentanil. In most of these studies, remifentanil exhibits greater potency as a mu-opioid than morphine or pethidine, and is comparable to fentanyl.*

Fentanyl, sufentanil, and alfentanil for use during anesthesia are more potent than morphine and meperidine, do not cause histamine release, and produce fewer cardiovascular changes (Meuldermans *et al.*, 1982). Alfentanil was introduced to provide a rapid-onset, rapid-recovery opioid. This rapid recovery was predicted owing to its much shorter terminal elimination half-life. Because of the ester linkage, remifentanil is susceptible to metabolism by esterases in blood and other tissues (Grosse *et al.*, 1994). Initial studies in dogs demonstrated its rapid and extensive metabolism by ester

hydrolysis, with a terminal half-life of 3.8-8.3 minutes. The pharmacodynamic properties of remifentanil in animals, compared with equipotent doses of both alfentanil and sufentanil, were similar (Glass, 1995; Egan, 1995). Remifentanil produced minimal effects on the cardiovascular system, with an expected mild bradycardia and a 15-20% decrease in arterial blood pressure at larger doses, which was similar to that seen with equipotent doses of alfentanil.

### Preclinical Pharmacology:

Remifentanil's pharmacological profile is characteristic of other selective  $\mu$ -opioids. Preclinical studies demonstrate its analgesic, hemodynamic, respiratory depressant effects and physical dependence-producing properties.

The  $\mu$ -opioid receptor is recognized as the site of analgesia, anesthesia, and addiction. Both isolated tissue studies and *in vitro* binding assays have demonstrated that remifentanil exhibits a  $\mu$ -opioid receptor selectivity profile. James *et al.* (1991) demonstrated that remifentanil potently inhibits electrically-evoked contraction in the guinea pig ileum (GPI) in a concentration-dependent fashion. The  $EC_{50}$  for remifentanil was similar to the marketed 4-anilidopiperidines (TABLE 1). In contrast, GR90291, the major metabolite of remifentanil, was approximately 800-fold less potent than remifentanil.

**TABLE 1. COMPARISON OF POTENCY OF REMIFENTANIL WITH OTHER OPIOID AGONISTS IN THE GUINEA PIG ILEUM (GPI) PREPARATION**

COMPOUND	$EC_{50}$ in GPI (nM)	$EC_{50}$ in GPI [ng(base)/mL]
Remifentanil	2.4 $\pm$ 0.6	0.9 $\pm$ 0.23
Alfentanil	20.1 $\pm$ 1.2	8.4 $\pm$ 0.5
Fentanyl	1.8 $\pm$ 0.4	0.60 $\pm$ 0.13
Sufentanil	0.3 $\pm$ 0.09	0.12 $\pm$ 0.04
GR90291	1900 $\pm$ 100	656 $\pm$ 34

Mouse vas deferens (MVD) and rat vas deferens (RVD) studies ( $EC_{50}$  = 39.5 $\pm$ 7.4 nM, equivalent to 14.9 $\pm$  2.8 ng/mL, and  $EC_{50}$  = 387 $\pm$ 44 nM, equivalent to 146 ng/mL, respectively) with remifentanil demonstrated potent opioid activity (James *et al.*, 1991). Naloxone antagonism of remifentanil in all three tissues (GPI, MVD, RVD) was consistent with remifentanil activity mediated through  $\mu$ -opioid receptors.

The above studies indicate selectivity for the  $\mu$ -opioid receptors. The lack of activity of remifentanyl at other opioid receptor subtypes was confirmed with the use of the  $\delta$ -opioid selective antagonist, ICI-174864 and the  $\kappa$ -opioid selective antagonist, nor-binaltorphimine. The latter antagonists had no effect on activity of remifentanyl in MVD (which has  $\delta$ - and  $\mu$ -opioid receptors, and GPI which possesses  $\kappa$ - and  $\mu$ -opioid receptors). The lack of activity of the selective  $\delta$ - and  $\kappa$ -opioid receptor antagonists on remifentanyl in these tissues suggests that the actions of remifentanyl are mediated through  $\mu$ -opioid receptors. In other isolated tissue studies, remifentanyl was found devoid of activity on  $\alpha_1$ -adrenoceptors, calcium channels and 5HT<sub>2</sub> receptors in rabbit aortic rings, and M<sub>2</sub> muscarinic and H<sub>1</sub> histaminergic receptors in GPI longitudinal muscle strips, and on catecholamine uptake in spontaneously beating guinea pig left atria. Remifentanyl produced a 28% increase in contractile force in the electrically paced guinea pig left atria at 100  $\mu$ M.

Affinity to a number of different receptor and ion channel systems was investigated by radioligand binding assays. Systems investigated were  $\alpha_1$ ,  $\alpha_2$ , and  $\beta$  (non-selective) adrenergic, dopamine (non-selective), GABA<sub>A</sub>, GABA<sub>B</sub>, H<sub>3</sub>-histamine, serotonin (non-selective), central muscarinic (non-selective), P<sub>2</sub> $\gamma$  purinergic receptors. Ion channels tested were ATP-modulated, low conductance CA<sup>+2</sup> activated and voltage dependent K<sup>+</sup> channels, and site 1 and site 2 on Na<sup>+</sup> channels. Data confirms that remifentanyl has no significant binding affinity for any receptors or ion channels tested other than opioid receptors.

Among opioid receptors, remifentanyl has greater affinity for  $\mu$ -opioid receptors ( $EC_{50}$ =2.6 nM) than  $\delta$ -opioid ( $EC_{50}$ =67 nM) or  $\kappa$ -opioid receptors ( $EC_{50}$ =6.1  $\mu$ M). GR90291 had a similar profile, but was considerably less potent than remifentanyl.  $EC_{50}$  values for GR90291 were 1.4  $\mu$ M, 12  $\mu$ M, >10  $\mu$ M for  $\mu$ ,  $\delta$ , and  $\kappa$ -opioid receptors, respectively. Although remifentanyl has affinity for the  $\delta$ - and  $\kappa$ -opioid receptors, it apparently lacks the intrinsic efficacy to produce significant activation of these receptors.

Remifentanyl was studied in rats, mice and dogs for potential analgesic activity. Antinociceptive activity of remifentanyl has been demonstrated in the rat tail withdrawal assay (Schuster *et al.*, 1991; Lutz *et al.*, 1994). Remifentanyl hydrochloride intravenous, over a wide dose range of 3.0  $\mu$ g/kg to 3.0 mg/kg, was shown to be a potent, short-acting analgesic. The potency was similar to that observed for fentanyl, alfentanil, and sufentanil. The major metabolite, designated GR90291, was 400 times less potent than the parent molecule (Schuster *et al.*, 1991; Lutz *et al.*, 1994). A rate constant ( $\lambda$ ) for disappearance of antinociceptive response of each was calculated from these results. The rate constants are inversely proportional to the durations of action of these compounds. Remifentanyl had the shortest duration of action. Alfentanil, fentanyl, and

sufentanil had significantly longer durations of action than remifentanil. The metabolite had a longer duration of action than the parent molecule (TABLE 2).

**TABLE 2. COMPARISON OF ANTINOCICEPTIVE EFFECTS OF REMIFENTANIL WITH OTHER OPIOID AGONISTS IN RAT TAIL WITHDRAWAL ASSAY (Lutz *et al.*, 1994).**

COMPOUND	ED <sub>50</sub> nmoles/kg (95% CL)	ED <sub>50</sub> µg/kg(95% CL)	λ (min <sup>-1</sup> ) [mean ± s.d.] <sup>+</sup>
Remifentanil HCl	6.5 (1.9-23.5)	2.7 (0.8-9.7)	0.23±0.06
Alfentanil HCl	4.6 (1.0-23.1)	1.9 (0.4-9.6)	0.13±0.09
Fentanyl citrate	8.1 (4.0-16.5)	4.3 (2.1-8.7)	0.05±0.01
Sufentanil citrate	2.1 (1.3-3.2)	0.98 (0.63-1.5)	0.04±0.01
GR90291A*	2460(2230-2710)	1070 (970-1180)	0.04±0.01

\* GR90291A is the trifluoroacetic acid salt.

+ Calculated using a pharmacokinetic-pharmacodynamic model.

Lozito *et al.* (1994) evaluated loss of righting (LOR) in rats of a series of opioid anesthetics; LOR is predictive of clinical anesthesia. Following bolus i.v. administration of fentanyl, sufentanil, alfentanil, and remifentanil, ED<sub>100</sub> doses for LOR were 0.035, 0.003, 0.05, and 0.020 mg/kg, respectively. For EEG infusion studies, rats were implanted with jugular catheters and 5 cortical electrodes on the surface of the dura mater. Each agent was infused at a rate of 0.02 ml/min.; each animal received the ED<sub>100</sub> dose every 60 seconds until LOR was observed. Following single infusion to LOR, the difference in time from return of righting (ROR) to baseline EEG for fentanyl, sufentanil, alfentanil, and remifentanil was 30.9, 35.3, 14.9, and 1.3 minutes, respectively. Following a 3 hour washout period, multiple infusions (3 successive infusions to LOR) were administered. Following ROR (after the third LOR) the return to baseline EEG for fentanyl, sufentanil, alfentanil, and remifentanil was 56.1, 58.5, 13.6, and 2.9 minutes, respectively. There were no statistically significant differences between the single and multiple infusions for the return to baseline EEG for alfentanil and remifentanil, but there were significant increases in time to return to baseline following multiple infusions of fentanyl and sufentanil. These results show that there was no cumulation of alfentanil and remifentanil with respect to EEG effects but cumulation was observed for fentanyl and sufentanil.

Bolus intravenous administration of anesthetic agents (fentanyl, alfentanil, remifentanil, sufentanil, etomidate and propofol) produced anesthesia in rats as measured by loss of righting (LOR) with calculated ED<sub>150</sub> doses of 0.06, 0.09, 0.037, 0.007, 2.51, and 6.12 mg/kg, respectively (La Marca *et al.*, 1995). Animals

trained in an 8 arm radial maze (RAM) were assessed for cognitive recovery, as measured by response efficiency (percentage of correct arm entered within 10 minutes), immediately, 15 minutes and 30 minutes following iv administration of the calculated ED<sub>150</sub> dose of each of these agents, and subsequent return of righting (ROR). Animals administered fentanyl or sufentanil were unable to successfully complete the maze throughout the testing periods. Animals receiving remifentanil showed cognitive recovery within the first testing interval (immediately after return of righting), while animals receiving alfentanil, etomidate or propofol showed recovery at the 15-minute testing interval following ROR. In another experiment, bolus iv administration of the ED<sub>150</sub> dose of these agents was evaluated in an acute rat EEG model. After ROR, return to baseline EEG levels occurred at 0.30, 2.88, 5.06, 16.25, 31.29 and 43.98 minutes for remifentanil, propofol, alfentanil, etomidate, fentanyl and sufentanil, respectively. Data show that the return to efficient cognitive functioning corresponds to the return to normal baseline EEG waveforms.

Remifentanil was also tested for antinociceptive activity in conscious dogs. Metabolism in dog blood was slower than that observed in rat blood. In humans, the metabolic profile of remifentanil was more likely to be like that of the dog, since duration of action of the drug in dogs and man were similar. In a paw pinch test in dogs, remifentanil was found to produce potent antinociceptive effects of short duration (TABLE 3). Remifentanil was eleven-fold less potent than sufentanil and had a much shorter duration of action (4.5 fold). In dogs lightly anesthetized with isoflurane (0.8-1%) and nitrous oxide (50%), remifentanil hydrochloride (0.05-5.0 mg/kg/min., intravenous) produced an EEG pattern characteristic of deepening anesthesia (Hoffman *et al.*, 1993). The EEG showed a decrease in the high frequency low amplitude ( $\beta$ ) activity and 50% spectral edge frequency, and an increase in low frequency high amplitude ( $\delta$ ) activity.

**TABLE 3. COMPARISON OF ANTINOCICEPTIVE EFFECTS OF REMIFENTANIL AND SUFENTANIL IN DOG PAW PINCH ASSAY.**

COMPOUND	ED <sub>50</sub> nmoles/kg	ED <sub>50</sub> $\mu$ g/kg	$\lambda$ (min <sup>-1</sup> )
Remifentanil HCl	9.1 $\pm$ 1.9	3.4 $\pm$ 0.71	0.18 $\pm$ 0.02
Sufentanil citrate	0.85 $\pm$ 0.13	0.33 $\pm$ 0.05	0.04 $\pm$ 0.003

The Maximum Non-Lethal Dose (single i.v.) was 5 mg/kg in rats, 70 mg/kg in mice, and 80 mg/kg in dogs.

**Clinical Pharmacology:****Analgesic and anaesthetic effects:**

In early analgesic studies, remifentanyl was administered by bolus dose to treat pain (Schuster *et al.*, 1991). In analgesic studies using a bolus dose in the analgesic phase, a higher incidence of respiratory depression, apnea, muscle rigidity, hypertension, hypotension, shivering, and pruritus was seen compared to studies employing continuous infusion remifentanyl regimen only (Schuttler *et al.*, 1997). Thus, studies used a continuous infusion dosing regimen with no bolus dosing, with pain responses treated with an infusion rate increase of 0.025 mcg/kg/min. Remifentanyl produced a dose dependent change in auditory evoked response data, indicating increasing depth of anesthesia with increasing remifentanyl infusion. Changes also occurred in somatosensory evoked responses indicating increasing analgesic effect with increasing dose.

Based on total number of patients in general anesthesia studies, the incidence of awareness in the clinical programme was 0.9% for remifentanyl patients (19/2070) and 0.9% for alfentanil patients (5/530).

Jhaveri *et al.* (1997) demonstrated that remifentanyl is 15 times more potent than alfentanil, based on the ED<sub>50</sub> (median effective dose for loss of consciousness) to achieve loss of response to a verbal command and 20 times more potent than alfentanil based on the EC<sub>50</sub> (median effective concentration). Remifentanyl and alfentanil were administered iv over 2 minutes in ascending doses (remifentanyl 2-20 µg/kg; alfentanil 40-200 µg/kg) to unpremedicated healthy patients. Patients were observed for rigidity and loss of consciousness, 2 mg/g/min thiopental was administered until loss of consciousness was achieved. Arterial blood samples, obtained at specified time intervals, were analyzed for remifentanyl and alfentanil whole-blood concentration. Blood pressure and heart rate were also recorded at preset time intervals. Neither drug could reliably produce loss of consciousness. With both drugs, there was a dose dependent decrease in thiopental requirements and a dose dependent increase in incidence and severity of rigidity (P < 0.05). ED<sub>50</sub> for loss of consciousness with remifentanyl was 12 µg/kg, and for alfentanil it was 176 microg/kg. EC<sub>50</sub> (whole blood concentration) of remifentanyl was 53.8 ng/mL and for alfentanil it was 1.012 ng/mL.

**Effects on the circulatory system**

Remifentanyl exhibited dose dependent decreases in systolic blood pressure (Sebel *et al.*, 1997), up to bolus doses of 2 mcg/kg when administered without a premedicant or up to 15 mcg/kg in the presence of glycopyrrolate. However, across the dose range used for induction of general anesthesia in clinical trials,

mean systolic BP and heart rate reductions after remifentanyl were relatively similar. The mean hemodynamic profile was similar across nitrous oxide and isoflurane studies (Baker *et al.*, 1997). Systolic BP reductions in the propofol studies were of greater magnitude (approximately 20-30% reduction upon induction of anesthesia) and were similar to those reported for propofol alone. Overall, systolic BP and heart rate remained relatively stable (i.e., did not increase above baseline values). With a remifentanyl infusion rate of 0.1-0.5mcg/kg/min, the percentage of patients with a reduction in systolic BP to <80 mm Hg was 11-51% in inpatient studies and 3-11% in outpatient studies. In the inpatient studies, systolic BP reductions of this magnitude were more frequent when remifentanyl was administered with isoflurane or propofol (32-51%) compared with nitrous oxide (11%). Postoperative tachycardia or hypertension are not related to the anesthetic or analgesic regimen employed.

**Cerebrovascular Effects:** Neurosurgical patients often have reduced intracranial compliance and are therefore more susceptible to increases in cerebral blood volume (CBV) due to increased cerebral blood flow. An increase in CBV results in an increase in intracranial pressure (ICP), which may result in herniation of the brain or significantly reduce cerebral perfusion pressure (CPP), resulting in ischemia. Bolus doses of remifentanyl (0.5 or 1 mcg/kg over 1 minute) or alfentanil (10 or 20 mcg/kg over 1 minute) did not significantly change ICP in neurosurgical patients with intracranial mass lesions anesthetized with thiopental and maintained with N<sub>2</sub>O and isoflurane. CPP decreased significantly after the high dose infusions of remifentanyl (1 mcg/kg) and alfentanil (20 mcg/kg), which was secondary to the transient, dose-dependent decrease in mean arterial pressure (Baker *et al.*, 1997).

A remifentanyl/N<sub>2</sub>O regimen was evaluated in patients undergoing surgical removal of an intracranial mass lesion. Remifentanyl was administered in a continuous infusion, first as an induction infusion (1.0 mcg/kg/min), then by maintenance infusion (0.4 mcg/kg/min) with N<sub>2</sub>O/O<sub>2</sub> (2:1). Cerebral blood flow reactivity remained intact with the combination.

### **Effects on the respiratory system**

In monitored anesthesia care studies, mean respiratory rate decreased by 20%, although mean SPO<sub>2</sub> remained unchanged. After remifentanyl infusions of 0.1 mcg/kg/min in the period before or during local anesthetic injection, 5-14% of patients had a respiratory rate decrease to <8 breaths per minute. After this period of stimulation, a higher incidence of patients with respiratory rate decreases was seen (up to 37%) with a continuing infusion rate of 0.1 mcg/kg/min. Based on these findings, the remifentanyl rate should be decreased after the period of initial stimulation to avoid respiratory rate decreases <8 breaths per minute (Gold *et al.*,

1997).

Respiratory depressant effects of low dose remifentanil (0.025 mcg/kg/min) were reversed by naloxone (6 mcg/kg). High dose remifentanil (0.1 mcg/kg/min) also depressed respiration leading to hypoxia. However, the same dose of naloxone did not reverse the respiratory effect of high dose remifentanil. Alfentanil (0.5 mcg/kg/min) induced a significant reduction in ventilatory response to hypoxia, and this effect was significantly reversed by naloxone. Spontaneous recovery from alfentanil was clearly slower than for remifentanil (Amin *et al.*, 1995).

When remifentanil was used at the recommended starting dose (0.1 mcg/kg/min) for placement of a regional block or instillation of a local anesthetic, the incidence of respiratory depression was 6% compared with 8% in all monitored anesthesia care studies.

### **Other effects**

**Pupillary Response:** Remifentanil caused maximum pupil constriction within 2-5 minutes that returned to baseline in less than 15-30 minutes.

### **Attenuation of effects in special population groups**

In studies involving more than 3,000 patients and volunteer subjects, elderly patients were approximately twice as sensitive as younger patients to the  $\mu$ -opioid activity of remifentanil. Age and obesity ( $\geq 1.3$  times ideal body weight) were the only demographic factors that consistently influenced the results of remifentanil therapeutic use in anesthesia and analgesia.

**Obesity:** Hypotension and bradycardia were more frequently observed in obese patients (>80% over ideal body weight) compared to controls after administration of 7.5 or 10 mcg/kg boluses of remifentanil over 60 seconds. Blood concentrations of remifentanil were higher in obese patients compared to controls when the drug was dosed based upon total body weight. The pharmacokinetic parameters of remifentanil are better correlated with ideal body weight.

**Elderly Patients:** In general anesthesia studies, only age was statistically significant when the incidence of adverse events was analyzed with respect to demographic factors (Minto, Schnider, Egan *et al.*, 1997; Minto, Schnider, Shafer, 1997). Elderly patients (>65 years) were four times more likely to experience an adverse event in the remifentanil group. No statistically significant difference was seen in the other opioid group with respect to age, perhaps reflecting the relatively lower doses used in the other opioid group compared with those used in the remifentanil group. Hypotension contributed largely to the increased incidence of

adverse events in the elderly which was greater than seen with alfentanil and fentanyl. Therefore, reduced initial and maintenance dosing (50% reduction) with careful titration has been recommended for the elderly (>65 years).

**Renal Impairment:** Remifentanil pharmacokinetics were unchanged in patients with end-stage renal disease (creatinine clearance <10 mL/min). Although the pharmacokinetics of remifentanil were not altered in subjects with severe renal impairment, the elimination of the principal metabolite of remifentanil (GR90291) was markedly reduced in subjects with renal impairment (ie, half life of approximately 30 hours) compared with controls (half life of approximately 2 hours) (Shlugman *et al.*, 1994). The half life of the main metabolite of remifentanil increased from 2 to 24 hours in anephric patients. An approximately 15-20 fold increase in  $t_{1/2}$  is expected in subjects with severe renal impairment. Based on relative potency data collected in anaesthetized dogs, the concentration of GR90291 that could be achieved during a long term high dose infusion of remifentanil (1 mcg/kg/min for 12 hours) in renal impairment subjects is not likely to elicit any significant  $\mu$ -opioid effects. The pharmacodynamics of remifentanil were unchanged in renal impairment subjects based upon the  $EC_{50}$  for reduction in  $CO_2$ -stimulated minute ventilation.

**Hepatic Impairment:** The pharmacokinetics of remifentanil and its main metabolite (GR90291) were not altered in hepatic impairment patients awaiting liver transplants. The pharmacokinetics of remifentanil in anhepatic patients were similar to that of healthy patients (Derschwitz *et al.*, 1994).

**Pediatric Use:** The pharmacokinetics, safety, and hemodynamic response to remifentanil (5 mcg/kg over 1 minute) were evaluated in pediatric patients undergoing elective surgery or diagnostic procedures requiring general anesthesia. The pharmacokinetics of remifentanil were similar for pediatric patients (2-12 years) and adults. Hemodynamic responses to remifentanil were typical of those seen after opioid administration; as compared with alfentanil, there was greater post-surgical pain with remifentanil, but fewer incidents of greater hypoxia (Davis *et al.*, 1997).

**Cholinesterase Deficiency:** Remifentanil hydrolysis was studied in blood from cholinesterase deficient individuals (and normal controls). Whole blood, plasma, and reconstituted erythrocytes from these individuals were studied. Cholinesterase activity measured in the plasma of the deficient subjects was significantly lower than in normal controls, confirming their prior phenotypic classification. There were no differences in half life or mean residence time between cholinesterase deficient individuals and normal controls.

**Contraindications:**

Due to the presence of glycine in the formulation, remifentanyl is contraindicated for epidural and intrathecal administration. Remifentanyl is also contraindicated in patients with known hypersensitivity to fentanyl analogs.

**4. Toxicology - Including Adverse Effects in Man**

*This section reviews the human toxicology of remifentanyl, excluding adverse effects associated with drug withdrawal which are discussed in section 6. The available data do not provide a basis for distinguishing the toxicological profile of remifentanyl from other classic mu-opioid receptor agonists. The occurrence of brain microhemorrhages observed in a dog study is a noteworthy toxicologic event that provides a potential warning in humans.*

**Comparison of Animal Pharmacology and Toxicological findings With Adverse Drug Events (ADEs) Observed in Humans:**

**Exposure to Drug:** The highest bolus dose given was 3 mg (47.6 mcg/kg). This was recorded as an overdose. The highest infusion rate given to a volunteer subject was 8 mcg/kg/min (20 minute infusion), and the highest infusion rate given to a patient was 15 mcg/kg/min; this patient had no associated ADE). The longest infusion given to a patient lasted 15.5 hours.

**Premature Discontinuations and Serious Adverse Events (Including Death) in Clinical Trials:** A total of 92 patients were withdrawn from clinical trials due to an ADE (excluding death), and 86 of these patients received remifentanyl; 83 patients were withdrawn for reasons other than an ADE.

A total of 121 volunteers and patients who participated in a remifentanyl clinical trial had one or more ADEs that were considered serious (excluding death). Of these 121 patients, 101 received remifentanyl, 18 received other opioids, 2 received other anesthetics, and 0 received placebo.

Most serious ADEs reported involved peri- or postoperative complications or were attributable to  $\mu$ -opioid effects such as hypotension, bradycardia, muscle rigidity, or respiratory depression (Schuttler *et al.*, 1997). Known or suspected accidental overdoses that met the criteria for serious ADEs were reported for 14 patients. Of these cases, 8 involved remifentanyl, 4 with alfentanil, 1 with isoflurane and propofol, and 1 with lidocaine and bupivacaine. Reasons given for accidental overdoses with remifentanyl included misreading bolus dose preparation instructions, flushing remifentanyl infusion lines, and faulty infusion pump.

The remifentanil toxicological profile is consistent with that expected of a potent  $\mu$ -opioid agonist. The major toxicological findings with remifentanil include: i) brain microhemorrhages found in dogs; ii) reduction in male fertility in rats with associated macroscopic and microscopic changes in male sexual organs; and iii) a positive mouse result in the *in vitro* lymphoma assay with metabolic activation. These distinctive opioid toxicities in animals have not been correlated in man.

The most common ADEs (>5%) were nausea, hypotension, vomiting, bradycardia, headache, pruritus, sweating, respiratory depression, apnea, and muscle rigidity. Of these, nausea in the remifentanil group was experienced with a statistically significantly higher frequency compared with other opioids and propofol. Pruritus, sweating, and muscle rigidity were experienced in a statistically significantly higher frequency in the remifentanil group compared with propofol. Although statistical testing could not be performed, respiratory depression, apnea, shivering, and bradycardia occurred in the remifentanil group but in no patients in the comparator groups. A higher comparative incidence of these events in the remifentanil group vs. the other opioid group may have occurred due to the low number of alfentanil patients studied (n=49).

When patients at risk were analyzed by treatment, there was a statistically significant higher incidence of ADEs in the remifentanil group compared with the other opioid patients. This difference was attributable to the increased incidence of hypotension in the remifentanil patients. The risk factors that were significantly associated with an increased incidence of ADEs were age >65 years and cardiac medications (primarily antihypertensives). This analysis demonstrated a consistent picture with that seen previously; namely, the risk of experiencing an ADE with remifentanil is likely to increase in the elderly. In addition, patients taking antihypertensives are known to experience greater decreases in blood pressure under anesthesia.

**TABLE 4. Adverse Events Reported in  $\geq 1\%$  of Patients in General Anesthesia Studies at the Recommended Doses of ULTIVA.**

Adverse Event	Induction/Maintenance		Postoperative Analgesia		After Discontinuation	
	ULTIVA (n=921)	Alfentanil/ Fentanyl (n=466)	ULTIVA (n=281)	Morphine (n=98)	ULTIVA (n = 929)	Alfentanil/ Fentanyl (n =466)
Nausea	8 (<1%)	0	61 (22%)	15 (15%)	339 (36%)	202 (43%)
Hypotension	178 (19%)	30 (6%)	0	0	16 (2%)	9 (2%)
Vomiting	4 (<1%)	1 (<1%)	22 (8%)	5 (5%)	150 (16%)	91 (20%)
Muscle rigidity	98 (11%)	37 (8%)	7 (2%)	0	2 (<1%)	1 (<1%)
Bradycardia	62 (7%)	24 (5%)	3 (1%)	3 (3%)	11 (1%)	6 (1%)

The overdoses attributed to alfentanil were attributed to prolonged anesthesia maintenance periods and accumulation effect. In addition to serious ADEs reported from completed studies, 5 serious ADEs (3 postoperatively after treatment with remifentanil and 2 postoperatively after treatment with fentanyl) have been reported in patients from 2 ongoing remifentanil studies.

Seven patients randomized to remifentanil died during or shortly after the conduct of 5 clinical trials. Each of the patients developed either peri- or postoperative complications or had pre-existing conditions that led to death. All 7 deaths were classified in the investigators' judgment as unrelated to remifentanil. In addition, 3 poststudy deaths were reported to the sponsor by the investigator(s) after an extended period of time following each patient's discharge from the study. None of the deaths was considered related to study drug treatment.

**General Anesthesia:** In general anesthesia studies, remifentanil had an ADE profile consistent with  $\mu$ -opioid pharmacological profile (Schuttler *et al.*, 1997). For all general anesthesia studies, excluding the cardiac anesthesia studies, most common ADEs (>5%) were nausea, hypotension, vomiting, muscle rigidity, hypertension, shivering, bradycardia, tachycardia, and respiratory depression. Of these, hypotension, bradycardia, muscle rigidity, and shivering occurred with a statistically significantly higher frequency in the remifentanil group compared with the other opioid group.

Muscle rigidity was primarily seen during the induction phase. Severity of muscle rigidity was related to bolus dose: severe muscle rigidity was seen following remifentanil  $\geq 4 \mu\text{g}/\text{kg}$ . The incidence of chest-wall rigidity was approximately 1/3rd of the overall incidence of muscle rigidity (6%).

Shivering, a common event resulting from a fall in body core temperature during surgery and anesthesia, is effectively treated with opioid agonists. The increased incidence in the remifentanil group primarily result from the absence of  $\mu$ -opioid effects after discontinuation of remifentanil (Wilhelm *et al.*, 1997).

Hypotension and bradycardia are dose related ADEs of opioid administration (Schuttler *et al.*, 1997). The higher comparative incidence of these ADEs may be due to the higher relative dose of remifentanil administered in the clinical programme.

Most serious ADEs in the monitored anesthesia care studies occurred in studies employing a higher infusion scheme for remifentanil (ie, up to  $0.2 \mu\text{g}/\text{kg}/\text{min}$ ) than has been recommended in the label. One serious event occurred with a starting dose of  $0.1 \mu\text{g}/\text{kg}/\text{min}$ .

Shivering	3 (<1%)	0	15 (5%)	9 (9%)	49 (5%)	10 (2%)
Fever	1 (<1%)	0	2 (<1%)	0	44 (5%)	9 (2%)
Dizziness	0	0	1 (<1%)	1 (1%)	27 (3%)	9 (2%)
Visual disturb.	0	0	0	0	24 (3%)	14 (3%)
Headache	0	0	1 (<1%)	1 (1%)	21 (2%)	8 (2%)
Respir. depress.	1 (<1%)	0	19 (7%)	4 (4%)	17 (2%)	20 (4%)
Apnea	0	1 (<1%)	9 (3%)	2 (2%)	2 (<1%)	1 (<1%)
Pruritus	2 (<1%)	0	7 (2%)	1 (1%)	22 (2%)	7 (2%)
Tachycardia	6 (<1%)	7 (2%)	0	0	10 (1%)	8 (2%)
Postoper. pain	0	0	7 (2%)	0	4 (<1%)	5 (1%)
Hypertension	10 (1%)	7 (2%)	5 (2%)	3 (3%)	12 (1%)	8 (2%)
Agitation	2 (<1%)	0	3 (1%)	1 (1%)	6 (<1%)	1 (<1%)
Hypoxia	0	0	1 (<1%)	0	10 (1%)	7 (2%)

## 5. Pharmacokinetics

*This section reviews the pharmacokinetics of remifentanyl. The available data indicate that remifentanyl is ultra-short acting because of its rapid hydrolysis by esterases in the blood and tissues into inactive metabolites.*

The ultra-short duration of action of remifentanyl compared with alfentanil, sufentanil and fentanyl results from the following. The propanoic acid methyl ester moiety of remifentanyl is rapidly hydrolyzed by esterases in the blood and tissues to yield the major metabolite (a de-esterified carboxylic acid of remifentanyl, designated GR90291), which was 4213-4637 times less potent as a  $\mu$ -agonist than remifentanyl in a pharmacokinetics-pharmacodynamics study in dogs, using an EEG spectral edge model. Remifentanyl was 7.7-8.5 times more potent than alfentanil. Hoke *et al.* (1997) determined these relative potencies in anesthetized dogs by electroencephalogram evaluation using a periodic analysis of estimated concentration that elicits 50% of maximum response ( $EC_{50}$ ) for delta EEG activity and spectral edge 95. Each dog received a 5 minute infusion of 0.5  $\mu$ g/kg/min remifentanyl, 500  $\mu$ g/kg/min GR90291 and 1.6 mg/kg/min alfentanil in random order, separated by 1 week. Serial blood samples were collected during and after the infusion. Blood-brain equilibration half-life was 2.3-5.2 minutes for remifentanyl, 0.39-0.41 min for GR 90291 and 3.1-3.7 minutes for alfentanil. These EEG pharmacodynamic responses are ten times greater than the predicted potencies from the in vitro mu-opioid receptor binding described above.

Remifentanil's pharmacokinetics in beagle dogs and metabolism and excretion in mice, rats, rabbits and dogs are similar to those in humans. Remifentanil does not accumulate upon repeated administration in any animal species studied (Vuyk, 1997; Schraag and Georgieff, 1995; Westmoreland *et al.*, 1993; Nigrovic *et al.*, 1997; Rushton and Sneyd, 1997).

After infusion of remifentanil, pharmacokinetics in dogs are linear between 0.4  $\mu\text{g}/\text{kg}/\text{minute}$  and the highest rate tested, 40  $\mu\text{g}/\text{kg}/\text{minute}$ . GR90291 is primarily eliminated in urine in all species. The only other metabolite was the product of N-dealkylation from the piperidine ring, designated GR94219, the occurrence of which was 2% of the dose in urine or feces of mice, rats, and dogs. Approximately 16-18% of total systemic clearance of remifentanil could be accounted for in liver, kidney, blood, muscle, brain and lung. Of these, muscle contributed most to clearance (5-9%), and liver and kidney contributed only 0-3%.

The lack of remifentanil accumulation even after prolonged intravenous infusions results in rapid, predictable recovery without delayed respiratory depression in all surgical settings (ie, there is no increase in context-sensitive half-time of remifentanil, even with long infusions) (Duthie *et al.*, 1997). Esterase metabolism makes remifentanil independent of hepatic or renal function for its elimination, and therefore dose adjustments are not required in patients with hepatic or renal impairment (Derschwitz *et al.*, 1994; Shlugman *et al.*, 1994).

After intravenous administration of remifentanil, the pharmacokinetic profile of remifentanil can be characterized by a three-compartment model with a rapid distribution half-life of 0.9 minutes, a slower phase with a half-life of 6.4 minutes, and a terminal elimination half-life of 10 to 20 minutes. Since the third compartment contributes to less than 1% of the total area-under-the-curve (AUC), the effective biological half life of remifentanil is less than 5 minutes (Egan, 1995; Egan *et al.*, 1993; Glass *et al.*, 1993).

The pharmacokinetics of remifentanil during hypothermic cardiopulmonary bypass demonstrated a 20-30% reduction in clearance, an observation consistent with the expected effects of hypothermia on an enzymatic hydrolytic process. Elderly patients had 25% reduction in clearance and 50% reduction in volume of distribution.

No difference in the pharmacokinetics and pharmacodynamics of remifentanil was observed between males and females from 18-39 years old. In subjects from 40-64 and >65 years, a significant difference was observed for remifentanil central compartment volume, with females exhibiting a lower volume distribution compared with males. However, no difference was observed for remifentanil clearance or steady-state volume of distribution in these two age groups after correcting for weight differences (Minto, Schnider, Egan *et al.*, 1997; Minto, Schnider, Shafer, 1997).

## 6. Dependence Potential

### A. Preclinical Studies of Abuse Liability

*This sub-section reviews preclinical studies which provide information about the capacity of the drug to produce physical withdrawal signs upon cessation of repeated administration of the drug, the capacity of the drug to suppress morphine withdrawal signs, and the capacity of the drug to reinforce self-administration. Data on rats and monkeys indicate that the potency of remifentanil to produce withdrawal or suppress morphine withdrawal is comparable to pentazocine or codeine, or significantly weaker than would suggest its pharmacological potency. However, remifentanil is shown to have a significantly stronger reinforcing efficacy in monkeys in comparison to pentazocine. The opiates that were selected for comparison with remifentanil were likely not the best comparator agents*

*Most of the findings used in this and the next sub-sections are based on studies sponsored by the manufacturer of remifentanil. Many of these studies have not been published yet but are summarized in "Basis for the Recommendation for Controlling Remifentanil and its Salts in Schedule II of the Controlled Substances Act" (US Government, 1996).*

#### Physical Dependence - Preclinical

A study to test for physical dependency potential of remifentanil in rats was conducted. Remifentanil (8 or 15 mg/kg every 10 minutes), saline, or pentazocine (4 mg/kg hourly) was administered intermittently via catheter for 3 or 7 days. At the end of the infusion period and after a brief acclimation period, treatment was withdrawn. Compared with the pentazocine group, withdrawal signs in the remifentanil group at 15 mg/kg/infusion were clearly weaker in the 3-day infusion experiment but about the same in the 7-day infusion experiment. These results indicate that the physical dependence-producing potential of remifentanil is about the same or weaker than pentazocine. The relatively weak demonstration of physical dependence in rats may likely be due to its short duration of  $\mu$ -agonist activity and the poor comparator selected.

Two studies were performed in rhesus monkeys to investigate the ability of remifentanil to suppress morphine withdrawal signs. In the first study, groups of 3 rhesus monkeys were made dependent on morphine by receiving 3 mg/kg subcutaneously every 6 hours for at least 3 months. Remifentanil (0.25 and 1.0 mg/kg, sc) or control agents (morphine 3 mg/kg sc as a positive control or saline as a negative control) were given to monkeys who had not received morphine for 14-15 hours and were showing definite signs of withdrawal. Remifentanil suppressed withdrawal signs at both doses administered. The suppression was greater at the 1.0 mg/kg dose than at 0.25 mg/kg dose, although the 1.0 mg/kg dose did not completely suppress some withdrawal signs as did the positive control (morphine). Higher doses of remifentanil might completely suppress withdrawal.

Onset of remifentanil in suppressing withdrawal was immediate, and the offset was similar to that of morphine.

In the second study, six rhesus monkeys were repeatedly used in four tests. The monkeys were first made physically dependent on morphine by repeated, gradually increasing, subcutaneous administration of morphine over a 12-week period, beginning at 3 mg/kg/day and ending at 6 mg/kg twice daily. At 19 hours after the last administration of morphine, when nearly all animals were showing intermediate to severe signs of morphine withdrawal, one or two animals received saline and the others received a single sc dose of remifentanil (45 and 60 mg/kg) or codeine (16 and 24 mg/kg). Remifentanil and codeine produced dose-dependent suppression of the morphine withdrawal signs, with maximum effects at 15-30 minutes and 0.5-1 hour after administration, respectively. Marked suppression of withdrawal was seen in all animals with both drugs at the highest doses tested. The dose-dependent suppression of morphine withdrawal effects in this study demonstrates the substitution potential of remifentanil for morphine. The ability of a 60 mg/kg dose of remifentanil to markedly suppress withdrawal demonstrates the potency of this compound compared with morphine and codeine.

#### **Reinforcing Efficacy - Preclinical**

**Self Administration in Monkeys:** Six rhesus monkeys (4 with previous experience administering drugs and 2 drug naive) were tested in a drug self-administration paradigm. The average daily number of saline intakes in the drug experienced monkeys ranged from 0.3 to 3.3 during the first self-administration period. When 0.25 mg/kg infusion pentazocine was made available, however, the average number of daily intakes rose to 28.7 to 69.7. When pentazocine was replaced with saline, the number of daily intakes rapidly decreased. Introduction of 0.25 mg/kg infusion remifentanil hydrochloride for 2 weeks rapidly increased the number of daily intakes in all 4 animals, ranging from 270.6 to 607.9 in Week 1 and 522.4 to 850.7 in Week 2. The daily number of intakes rapidly decreased when saline was introduced for 2 days, but increased again when remifentanil was again made available for another 2 weeks, ranging from 734.1 to 1069.1 intakes during the final week of remifentanil. In the final period of saline administration, the daily number of intakes rapidly decreased in all of the animals. The 2 drug naive monkeys began by self administering saline, which was followed by 0.25 mg/kg/infusion remifentanil for 3 weeks, saline for 2 days, remifentanil for 2 weeks, and finally saline for 1 week. After an initially slow administration rate, the inexperienced monkeys were enticed with raisins to push the levers more frequently. This produced a gradually increasing tendency for remifentanil, and mean daily intakes during the final week of treatment were 892.7 and 906.1 with a lower rate for saline infusions .

#### **B. Clinical Studies of Abuse Liability**

*This section reviews information available on the drug's subjective effects related to*

*dependence-producing capacity, cases of abuse or dependence and toxicity in humans. There have been no experimental clinical studies on withdrawal substitution in opioid-dependent subjects or reinforcing effects. Data indicate that remifentanyl has an abuse potential that is greater than placebo and equal to fentanyl in its peak effects. Although remifentanyl is short-acting (1/2 hrs), one case of its abuse that occurred during the clinical trial has demonstrated that its abuse potential can become a reality, with the associated risk of overdose.*

**Subjective Effects:**

A subjective effects clinical study was carried out in 12 opiate experienced nondependent users. A pilot phase included two single blind pilot studies to confirm the remifentanyl and fentanyl doses to be used in a second phase and timing of measurements. Remifentanyl doses were 0.6, 1.2, 1.8, 2.4, 3.0 and 3.6 µg/kg as 1 minute i.v. infusions; each dose was separated from the previous dose by a minimum of 1 hour. Fentanyl was administered as a one minute i.v. infusion in ascending doses of 0.4, 0.8, 1.3, 2.0, 3.0 and 4.5 µg/kg; on each treatment day, subjects received two doses separated by six hours. Administrations were stopped when any dose approached or exceeded the subjects' clinical tolerance. Measurements of subjective and pupillary effects were taken at 1 and 3 minutes post-infusion in order to attempt to capture extremely rapid effects. The second phase, a comparator study was a randomized, double-blind, crossover comparison of the abuse liability of remifentanyl and fentanyl, occurring over up to nine consecutive days, with subjective reports of drug effects as the primary dependent variables. The study included a negative (placebo) as well as a positive (fentanyl) control. Study results showed clear objective effects typical of all opioid drugs (decrease in pupil diameter, oxygen saturation) for the two drugs. Results also showed a spectrum of subjective effects and observer ratings consistent with the subjects' liking these drugs. The few differences in magnitude of subjective peak effects between the two drugs occurred only for those measures that could not be obtained earlier than five minutes after infusion. The very rapid peak effects of remifentanyl were not significantly different from those of fentanyl; however, significant differences in the duration of most subjective effects, reflecting the differences in the half-lives, were observed. Although no differences between fentanyl and remifentanyl peak effects were measured in this study, it is possible that such differences would appear, with the fentanyl peaks being larger, if both drugs were taken in doses leading to equal respiratory depression.

In another study involving healthy subjects, who were conscious and able to report subjective feelings while receiving remifentanyl by bolus or continuous infusion, indicated that CNS effects such as relaxation occurred in 28 of 81 (35%) subjects who received reference opioids (alfentanil and fentanyl), about twice the incidence compared with remifentanyl (38 of 244; 16%). Euphoria occurred at about the same incidence for reference opioids (10/81; 12%) and remifentanyl (26/244; 11%).

**Actual abuse:**

One case of remifentanyl abuse by intranasal administration occurred during the clinical study of the drug. In this case, an emergency room physician reported an apparent overdose in which the patient was treated and recovered. The patient was found unconscious, tachycardic, cyanotic and having seizure activity. Patient reported that he had administered 25 mg remifentanyl via the intranasal route and that he had been taking the drug for a period of 6 to 8 weeks.

As a drug of abuse, fentanyl has a history of abuse by health care professionals, most commonly being anesthesia room personnel. When abused, the most common route of administration for fentanyl derivatives is intravenous, although it can be smoked, taken orally, transmucosally or intranasally. Remifentanyl has been developed to be administered by the i.v. route. No studies examining alternative routes of remifentanyl administration (s.c., intradermally, im, po, or transdermally) have been completed in humans. Animal studies indicate that remifentanyl is poorly absorbed by the oral and dermal routes, but was well absorbed following intratracheal inhalation or ocular application.

**Drug Overdose:**

In clinical trials involving 3,024 subjects, there have been 8 reported occurrences of overdosage. No deaths were reported, and all subjects recovered with no serious sequelae. In all cases, subjects were in a monitored care setting and symptoms were rapidly recognized and treated. All of the 8 overdose cases resulted from excessive bolus administration of remifentanyl due to investigator error (2 cases), dilutional error (1 case), pump failure (1 case), and inappropriate flushing of the intravenous line containing remifentanyl when a second medication was given (4 cases). Of the 8 cases, 7 resolved within 21 minutes. In the remaining case, the patient received 100 times the recommended bolus dose of remifentanyl as a result of a dilutional error. The patient developed respiratory arrest which required intubation and mechanical ventilation. Remifentanyl was withdrawn; however, surgery continued under general anesthesia. The respiratory arrest was considered resolved 1.75 hours later when the patient extubated following general anesthesia.

**7. Epidemiology of Drug Use and Abuse, with an Estimate of Abuse Potential**

As indicated in Section 11, the quantity of remifentanyl being distributed for medical use is still very limited, although 17 countries have reported its marketing approval. There are no epidemiological data concerning illicit activities involving the drug. There has been only one case of remifentanyl abuse by the intranasal route of administration. In this case, an emergency room physician reported an apparent overdose in which the patient was treated and recovered. The patient was found unconscious, tachycardic, cyanotic and

having seizure activity. The patient reported that he had administered 25 mg remifentanyl via the intranasal route and that he had been taking the drug for a period of 6 to 8 weeks. In the absence of epidemiological information, this case report and the experimental study results are the only basis available for a rough estimation of the abuse liability of this drug.

Remifentanyl is a potent  $\mu$ -opioid receptor agonist similar to fentanyl, except that it is ultra-short acting due to a rapid transformation by esterases into an inactive metabolite. The abuse potential of remifentanyl appears to be comparable to the class of other  $\mu$ -opioid agonists such as fentanyl, in both animal tests under unrestricted drug availability as well as in clinical tests on subjective peak effects in opioid-experienced humans. The short duration of the peak effects does not appear to reduce the abuse potential of remifentanyl observed under such experimental conditions. The case of remifentanyl abuse via the intranasal route has also demonstrated the abuse potential this drug possesses.

This would not necessarily signify that remifentanyl's abuse liability is comparable to that of fentanyl. Abuse liability (the likelihood of abuse) is dependent not only on the abuse potential of the drug but also on the likelihood that the conditions required for the drug to exert that abuse potential can be realized. For remifentanyl to exert similar abuse potential as fentanyl, more frequent ingestion of the drug via effective route of administration is required because of its shorter half-life. Only when this condition is met will remifentanyl have a comparable abuse liability to fentanyl. With respect to the route of administration, at least animal tests have indicated that remifentanyl is poorly absorbed by the oral and dermal routes. In terms of the effective route of administration, remifentanyl has more restrictions than fentanyl. Because of these additional requirements, it is reasonable to estimate that remifentanyl has an abuse liability smaller than that of fentanyl.

It is very difficult, however, to estimate how much smaller its abuse liability is than fentanyl. If it were similar to that of codeine rather than morphine, inclusion in Schedule II of the 1961 Convention could be considered. In terms of "ill effects" (toxicity/adverse effects), remifentanyl is much more potent than codeine as an opioid agonist. Had it been made as readily accessible as codeine, its high potency might contribute to the risk of overdose.

As a whole, it would be safe to assess that remifentanyl has similar abuse liability and ill effects as other opioids in Schedule I of the 1961 Convention.

#### **8. Nature and Magnitude of Public Health Problems**

No report on public health problems.

## 9. National Control

Of the 17 countries which reported marketing of remifentanil, DEU, FRA, GRE, NEZ, USA and UZB indicated controls as a narcotic. Other countries indicated prescription requirements without further elaboration.

## 10. Therapeutic and Industrial Use

Remifentanil hydrochloride is used for medical purposes as an analgesic, (i) for use during induction and maintenance of general anesthesia for inpatient and outpatient procedures, and (ii) for continuation into the immediate postoperative period under the direct supervision of an anesthesia practitioner in a postoperative anesthesia care unit or intensive care setting (Cartwright *et al.*, 1997; Derschwitz *et al.*, 1995; Bowdle *et al.*, 1997; Baker *et al.*, 2007; Amin *et al.*, 1997; Guy *et al.*, 1997; Philip *et al.*, 1997; Yarmush *et al.*, 1997). It is also used as an analgesic component of monitored anesthesia care (Pandit and Green, 1994; Wilhelm *et al.*, 1997; Smith *et al.*, 1997; Servin 1997; Gold *et al.*, 1997; Kovac *et al.*, 1997).

There is no known industrial use of remifentanil.

## 11. Production, Consumption and International Trade.

Of the 50 Member States which responded to the WHO questionnaire by 1 May 1998, the following 17 have reported marketing approval of remifentanil injections: AUS, BEL, COL, DEU, FRA, GRE, ISR, LUX, NET, NEZ, PHL, SIN, SPA, SWE, SWI, USA, UZB. Only three countries reported the quantity of remifentanil imported, which totalled half a kilogramme in terms of weight.

## 12. Illicit Manufacture, Illicit Traffic and Related Information

### A. Reports of Illicit Activity:

Although at least 17 countries have approved marketing of remifentanil injections as of May 1998, it has been on the market only since 1996. Its distribution and use is still very limited in quantity. There have been no reports of illicit activities involving remifentanil.

No epidemiologic information is therefore available on history and current pattern of abuse. One case of remifentanil abuse by intranasal administration was reported. In this case, an emergency room physician reported an apparent overdose in which the patient was treated and recovered. The physician reported that the patient was found by his wife unconscious, tachycardic, cyanotic, and having seizure activity. The patient reported that he had administered 25 mg remifentanil via the intranasal route, and that he had been taking the drug for a period of 6 to 8 weeks.

**B. Analysis of Reports of Illicit Activity: N/A**

**13. Bibliography**

Abbadie, C., Taylor, B. K., Peterson, M. A., Basbaum, A. I., "Differential contribution of the two phases of the formalin test to the pattern of c-fos expression in the rat spinal cord: Studies with remifentanil and lidocaine," *Pain*, 69(1-2): 101-10, 1997.

Amin, H. M.; Sopchak, A. M.; Esposito, B. F.; Henson, L. G.; Batenhorst, R. L.; Fox, A. W.; Camporesi, E. M., "Naloxone-induced and spontaneous reversal of depressed ventilatory responses to hypoxia during and after continuous infusion of remifentanil or alfentanil," *J. Pharmacol. Exp. Ther.*, 274(1): 34-9, 1995.

Bacon, R.; Chandrasekan, V.; Haigh, A.; Royston, D.; Sundt, T., "Early extubation after open-heart surgery with total intravenous anaesthetic technique [letter]," *Lancet*, 345(8942): 133-4, 1995.

Baker, K. Z., Ostapkovich, N., Sisti, M. B., Warner, D. S., Young, W. L., "Intact cerebral blood flow reactivity during remifentanil/nitrous oxide anesthesia," *J. Neurosurg. Anesthesiol.*, 9(2): 134-40, 1997.

Bowdle, T. A.; Ready, L. B.; Kharasch, E. D.; Nichols, W. W.; Cox, K.; "Transition to post-operative epidural or patient-controlled intravenous analgesia following total intravenous anesthesia with remifentanil and propofol for abdominal surgery," *Eur J. Anesthesiol.*, 14(4): 374-9, 1997.

Cartwright D. P., Kvalsvik, O., Cassuto, J., Jansen, J. P., Wall, C., Remy, B., Knape, J. T., Noronho, D., Upadhyaya, B. K., "A randomized, blind comparison of remifentanil and alfentanil during anesthesia for outpatient surgery," *Anesth.-Analg.*, 1997, 85(5): 1014-9.

Davis, P. J., Lerman, J., Suresh, S., McGowan, F. X., Cote, C. J., Landsman, I., Henson, L. G., "A randomized multicenter study of remifentanil compared with alfentanil, isoflurane, or propofol in anesthetized pediatric patients undergoing elective strabismus surgery," *Anesth.-Analg.*, 84 (5): 982-9, 1997.

Derschwitz, M., Rosow, C. E., Michalowski, P., Connors, P. M., Hoke, J. F., Muir, K. T., Dienstag, J. L., "Pharmacokinetics and pharmacodynamics of remifentanil in volunteer subjects with severe liver disease compared with normal subjects," *Anesthesiol.*, 81(3A):A377, 1994.

Derschwitz, M.; Randel, G. I.; Rosow, C. E.; Fragen, R. J.; Connors, P. M.; Librojo, E. S.; Shaw, D. L.; Peng, A. W.; Jamerson, B. D., "Initial clinical experience with remifentanil, a new opioid metabolized by esterases," *Anesth-Analg.*, 81(3): 619-23, 1995.

DeSouza G., Lewis M.C.; TerRiet M. F.; "Severe bradycardia after remifentanil," [letter],

Anesthesiology, 87(4): 1019-1020, 1997.

Drummond, J.C., "Are the data missing? [letter]" Anesthesiology, 79(6): 1451, 1993.

Duthie, D. J.; Stevens, J. J.; Doyle, a. R.; Baddoo, H. H.; Gupta, S. K.; Muir, K. T.; Kirkham, A. J., "Remifentanil and pulmonary extraction during and after cardiac anesthesia," Anesth-Analg., 84(4):740-4, 1997.

Duthie, D. J., Stevens, J. J., Doyle, A. R., Baddoo, H. H., "Remifentanil and coronary artery surgery," [letter; comment], Lancet, 345(895): 649-50, 1995.

Egan, T. D., "Remifentanil: an esterase-metabolized opioid," West. J. Med., 166(3): 202, 1997.

Egan, T. D., "Remifentanil pharmacokinetics and pharmacodynamics. A preliminary appraisal," Clin. Pharmacokinet., 29(2): 80-94, 1995.

Egan, T. D., Lemmens, H. J. M., Fiset, P., Hermann, D. J., Muir, K. T., Stanski, D. R., Shafer, S. L., "The pharmacokinetics of the new short-acting opioid remifentanil (GI87084B) in healthy adult male volunteers," Anesthesiology, 79(5): 881-92, 1993.

Egan, T.D., Lemmens, H.J.M., Fiset, P., Stanski, D.R., Shafer, S.L., "Pharmacokinetic-dynamic fingerprinting in the early development of GI87084B," Clin. Pharmacol. & Therap., 53(2):209, 1994.

Egan, T.D., Minto, C., Lemmens, H.J.M., Muir, K.T., Hermann, D.J., Shafer, S.L., "Remifentanil versus alfentanil: comparative pharmacokinetics," Anesthesiology, 81(3A):A373-4, 1994.

Egan, T.D., Lemmens, H.J., Fiset, P., "The pharmacokinetics of the new short-acting opioid remifentanil (GI87084B) in healthy adult male volunteers [see comments]," Anesthesiology, 79(5): 881-92, 1993.

Evans, T. N., Gunning, K. E., Park, G. R., "Remifentanil for major abdominal surgery [letter]," Anaesthesia, 52(6): 606, 1997.

Glass, P. S., "Remifentanil: a new opioid," J. Clin. Anesth., 7(7): 558-63, 1995.

Glass, P. S.; Gan, T. J.; Howell, S.; Ginsburg, B.; "Drug interactions: volatile anesthetics and opioids," J. Clin. Anesth., 9(6 Suppl): 18S-22S, 1997.

Glass, P. S.; Hardman, D.; Kamiyama, Y.; Quill, T. J.; Marton, G.; Donn, K. H.; Grosse, C. M.; Hermann, D.; "Preliminary pharmacokinetics and pharmacodynamics of an ultra-short-acting opioid: remifentanil (GI87084B)," Anesth.-Analg, 77(5): 1031-40, 1993.

ANNEX 3 (Page 24)

Gold, M. I.; Watkins, W. D.; Sung, Y. F.; Yarmush, J.; Chung, F.; Uy, N. T.; Maurer, W.; Clarke, M. Y.; Jamerson, B. D.; "Remifentanil versus remifentanil/midazolam for ambulatory surgery during monitored anesthesia care," *Anesthesiology*, 87(1): 51-7, 1997.

Grosse, C. M., Davis, I. M., Arrendale, R. F., Jersey, J., Amin, J., "Determination of remifentanil in human blood by liquid-liquid extraction and capillary GC-HRMS-SIM using a deuterated internal standard," *J. Pharm. Biomed. Anal.*, 12(2): 195-203, 1994.

Guy, J.; Hindman, B. J.; Baker, K. Z.; Borel, C. O.; Maktabi, M.; Ostapkovick, N.; Kirchner, J.; Todd, M. M.; Fogarty-Mack, P.; Yancy, V.; Sokoll, M. D.; McAllister, A.; Roland, C.; Young, W. L.; Warner, D. S., "Comparison of remifentanil and fentanyl in patients undergoing craniotomy for supratentorial space-occupying lesions," *Anesthesiology*, 86(3): 514-24, 1997.

Hanel, F., Werner, C., "Remifentanil," *Anaesthesist*. 1997, 46(10): 897-908.

Haidar, S. H.; Moreton, J. E., Liang, Z., Hoke, J. F., Muir, K. T., Eddington, N. D., "Evaluating a possible pharmacokinetic interaction between remifentanil and esmolol in the rat," *J. Pharm. Sci.*, 86(11): 1278-82, 1997.

Hoffman, W. E., Cunningham, F., James, M. K., Baughman, V. L., and Albrecht, R. F., "Effects of remifentanil, a new short-acting opioid, on cerebral blood flow, brain electrical activity and intracranial pressure in dogs anesthetized with isoflurane and nitrous oxide," *Anesthesiology* 79(1):107-13, 1993.

Hoke, J. F.; Cunningham, F.; James, M. K.; Muir, K. T.; Hoffman, W. E., "Comparative pharmacokinetics and pharmacodynamics of remifentanil, its principle metabolite (GR90291) and alfentanil in dogs," *J. Pharmacol. Exp. Ther.*, 281(1): 226-32, 1997.

Hoke, J. F., Muir, K. T., Glass, P. S. A., Shlugman, D., Rosow, C. E., Dershwitz, M., Michalowski, P., "Pharmacokinetics (PK) of remifentanil (R) and its metabolite (GR90291) in subjects with renal disease," *Clin. Pharm. and Therap.*, PI-55, 1995.

Hoke, J. F., Shlugman, D., Dershwitz, M., Michalowski, P., Malthouse, D. S., "Pharmacokinetics and pharmacodynamics of remifentanil in persons with renal failure compared with healthy volunteers," *Anesthesiology*, 87(3): 533-41, 1997.

Hughes, M. A., Glass, P. S. A., Jacobs, J. R., "Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs," *Anesthesiology*, 74:53-63, 1991.

Jaeger K., Andre M, Scheinichen D., Heine J., Kleine H.D., Leuwer M., Piepenbrock S., "Effect of remifentanil on respiratory burst of human neutrophilic granulocytes in vitro," *Anaesthesiol-Reanim.* 22(5): 121-4, 1997.

James, M. K., Feldman, P. L., Schuster, S. V., Bilotta, J. M., Brackeen, M. F., and Leighton, H. J., "Opioid receptor activity of GI87084B, a novel ultra-short acting analgesic, in isolated tissues," *J. Pharmacol. Exp. Ther.*, 259(2):712-8, 1991.

James, M. K., Vuong, A., Grizzle, M. K., Schuster, S. V., and Shaffer, J. E., "Hemodynamic effects of GI87084B, an ultra-short acting mu-opioid analgesic, in anesthetized dogs," *J. Pharmacol. Exp. Ther.*, 263(1):84-91, 1992.

Jhaveri, R.; Joshi, P.; Batenhorst, R.; Baughman, V.; Glass, P. S., "Dose comparison of remifentanil and alfentanil for loss of consciousness," *Anesthesiology*, 87(2): 253-9, 1997.

Kapila, A.; Glass, P. S.; Jacobs, J. R.; Muir, K. T.; Hermann, D. J.; Shiraishi, M.; Howell, S.; Smith, R. L.; "Measured context-sensitive half-times of remifentanil and alfentanil," *Anesthesiology*, 83(5): 968-75, 1995.

Kapila, A., Muir, K. T., Hermann, D. J., Shiraishi, M., Leonard, M. D., Glass, P. S. A., "Measured context sensitive half times of remifentanil and alfentanil," *Anesthesiology*, 79:A377, 1993.

Kovac, A. L., Azad, S. S., Steer, P., Witkowski, T., Batenhorst, R., McNeal, S., "Remifentanil versus alfentanil in a balanced anesthetic technique for total abdominal hysterectomy," *J. Clin. Anesth.*, 9(7): 532-41, 1997.

La Marca, S.; Lozito, R. J.; Dun, R. W., "Cognitive and EEG recovery following bolus intravenous administration of anesthetic agents," *Psychopharmacology-Berl.*, 120(4): 426-32, 1995.

Lennens, H. J., "Pharmacokinetic-pharmacodynamic relationships for opioids in balanced anaesthesia," *Clin. Pharmacokinet.*, 29(4): 231-42, 1995.

Lozito, R. J., La Marca, S., Dunn, R. W., Jerussi, T. P., "Single versus multiple infusions of fentanyl analogues in a rat EEG model," *Life Sci.*, 55(17): 1337-42, 1994.

Lutz, M.W., Morgan, P.H., James, M.K., Feldman, P.L., Brackeen, M.F., Lahey, A.P., James, S.V., Bilotta, J.M., Pressley, J.C., "A pharmacodynamic model to investigate the structure-activity profile of a series of novel opioid analgesics," *J. Pharmacol. Exp. Ther.*, 271(2):795-803, 1994.

Meuldermans W., Hurkmans, R., Heykants, J., "Plasma protein binding and distribution of fentanyl, sufentanil, alfentanil and lofentanil in blood," *Arch. Int. Pharmacodyn.*, 257:4-19, 1982.

Minto, C. F.; Schnider, T. W.; Egan, T. D.; Youngs, E.; Lemmens, H. J.; Gambus, P. L.; Billard, V.; Hoke, J. F.; Moore, K. H.; Hermann, D. J.; Muir, K. T.; Mandema, J. W.; Shafer, S. L.;

ANNEX 3 (Page 26)

Anesthesiology, 86(1): 10-23, 1997.

Minto, C. F.; Schnider, T. W.; Shafer, S. L. "Pharmacokinetics and pharmacodynamics of remifentanyl. II. Model application," *Anesthesiology*, 86(1): 24-33, 1997.

Nigrovic, V.; Diefenback, C.; Mellinshoff, H., "Esters and stereoisomers," *Anaesthesist*. 46(4): 282-6, 1997.

Pandit, S. K.; Green, C. R., "General anesthetic techniques," *Int. Anesthesiol. Clin.*, 32(3): 55-79, 1994.

Philip, B. K.; Scuderi, P. E.; Chung, F.; Conahan, T. J.; Maurer, W.; Angel, J. J.; Kallar, S. K.; Skinner, E. P.; Jamerson, B. D.; "Remifentanyl compared with alfentanil for ambulatory surgery using total intravenous anesthesia. The remifentanyl/alfentanil outpatient TIVA Group," *Anesth.-Analg.*, 84(3): 515-21, 1997.

Ramsay M.A.; Flanders D., "Nalbuphine and pruritus," [letter], *Anaesthesia*, 52(10): 1023, 1997.

Rizzi, R. R., "No difference between remifentanyl and fentanyl in patients undergoing craniotomy" [letter], *Anesthesiology*, 88(1): 271-2, 1998.

Royston, D., "Remifentanyl in cardiac surgery," *Eur. J. Anaesthesiol-Suppl.* 10:77-9, 1995.

Rushton, A. R., Sneyd, J. R., "Opioid analgesics," *Br. J. Hosp. Med.*, 57(3): 105-6, 1997.

Russell, D., Royston, D., Rees, P. H., Gupta, S. K., Kenny, G. N., "Effect of temperature and cardiopulmonary bypass on the pharmacokinetics of remifentanyl," *Br. J. Anaesth.*, 79(4): 456-9, 1997.

Schraag, S.; Georgieff, M., "Intravenous anesthesia -- current aspects," *Anesthesiol-Intensivmed-Notfallmed-Schmerzther.*, 30(8): 469-78, 1995.

Schuster, S. V., Bilotta, J. M., Lutz, M. W., and James, M. K., "Analgesic activity of the ultra-short acting opioid, GI87084B," *FASEB J.* 5, A\*60 (No. 2846), 1991.

Schuttler, J.; Albrecht, S.; Breivik, H.; Osnes, S.; Prys-Roberts, C.; Holder, K.; Chauvin, M.; Viby-Mogensen, J.; Mogensen, T.; Gustafson, I.; Lof, L.; Noronha, D.; Kirkham, A. J., "A comparison of remifentanyl and alfentanil in patients undergoing major abdominal surgery [see comments]," *Anaesthesia*, 52(4): 307-17, 1997.

Sebel, P. S.; Hoke, J. F.; Westmoreland, C.; Hug, c. C.; Muir, K. T.; Szlam, F., "Histamine concentrations and hemodynamic responses after remifentanyl," *Anesth.-Analg.*, 80(5):990-3, 1995.

Selinger, K., Lanzo, C., Sekut, A., "Determination of remifentanyl in human and dog blood by HPLC with UV detection," *J. Pharm. Biomed. Anal.*, 12(2): 243-8, 1994.

Servin, F., "Remifentanyl: when and how to use it," *Eur. J. Anaesthesiol Suppl.*, 15:41-4, 1997.

Shlugman, D., Dufore, S., Dershwitz, M., Michalowski, P., Hoke, J., Muir, K. T., Rosow, C., Glass, P. S. A., "Respiratory effects of remifentanyl in subjects with severe renal impairment compared to matched controls," *Anesthesiology*, 81(3A), A1417, 1994.

Smith, I., Avramov, M. N., White, P. F., "A comparison of propofol and remifentanyl during monitored anesthesia care," *J. Clin. Anesth.*, 9(2): 148-54, 1997.

Smith, M.A.; Morgan, M., "Remifentanyl [editorial;comment], *Anaesthesia*, 52(4): 291-3, 1997.

Stevens, J. B., Wheatley, L., "Tracheal intubation in ambulatory surgery patients: using remifentanyl and propofol without muscle relaxants," *Anesth.-Analg.*, 86(1): 45-9, 1998.

Taylor, B. K.; Peterson, M. A.; Basbaum, A. I., "Early nociceptive events influence the temporal profile, but not the magnitude, of the tonic response to subcutaneous formalin: effects with remifentanyl," *J. Pharmacol. Exp. Ther.*, 280(2): 876-83, 1997.

Todd, M. M., "Anesthesiology," *JAMA*, 277(23): 1842-3, 1997.

Trissel, L.A., Gilbert, D. L., Martinez, J. F., Kim, M. C., "Compatibility of remifentanyl hydrochloride with selected drugs during simulated Y-site administration," *Am. J. Health Syst. Pharm.*, 54(19): 2192-6, 1997.

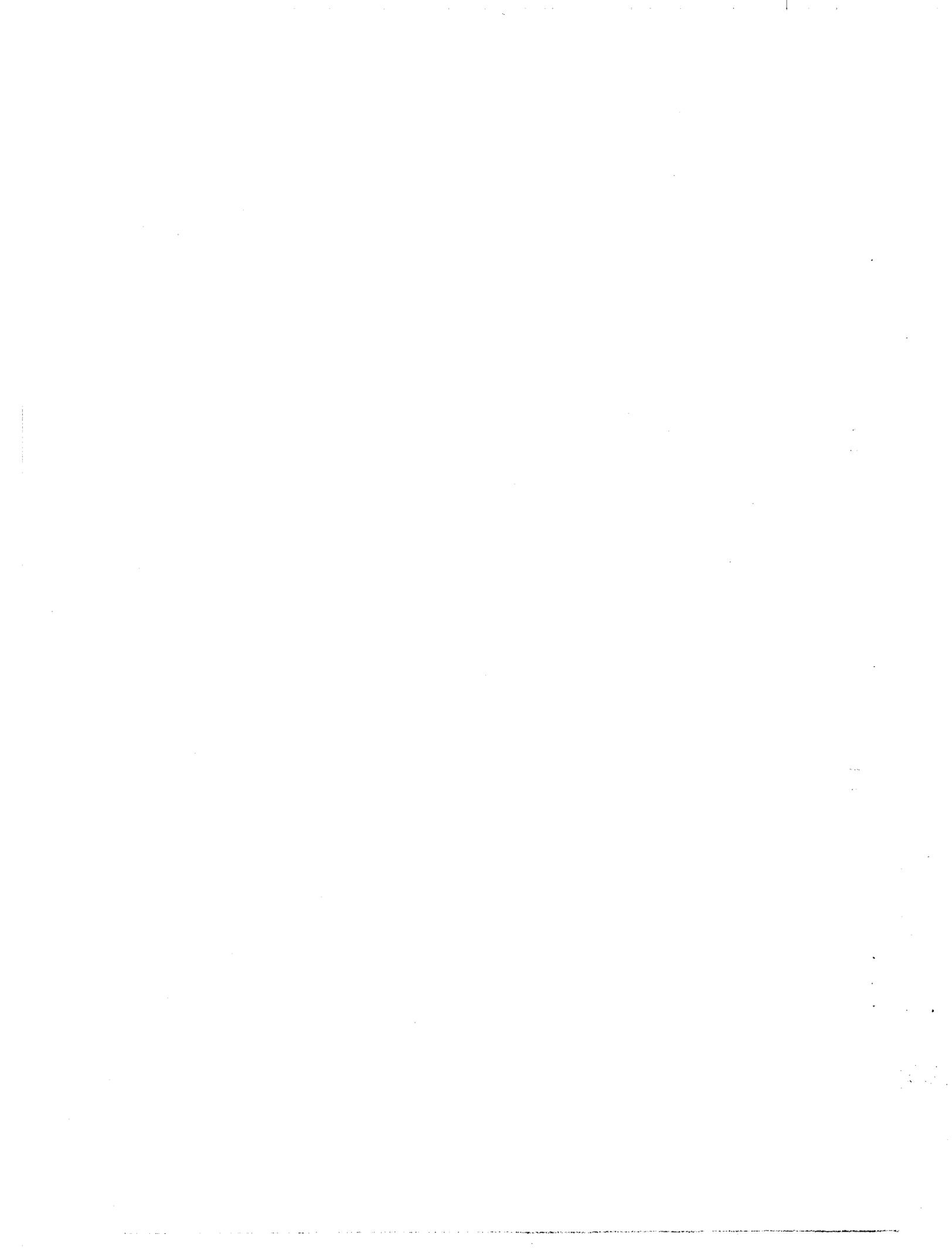
US Government, "Basis for the Recommendation for Controlling Remifentanyl and its Salts in Schedule II of Controlled Substances Act", *Federal Register*, 61(180): 48655-48656, 1996

Vuyk, J., "Pharmacokinetic and pharmacodynamic interactions between opioids and propofol," *J. Clin. Anesth.*, 9(6 Suppl): 23S-26S, 1997.

Westmoreland, C. L., Hoke, JF, Sebel, PS, Hug CC, Muir KT, "Pharmacokinetics of remifentanyl (GI87084B) and its major metabolite (GI90291) in patients undergoing elective inpatient surgery [see comments]," *Anesthesiology* 79(5):893-903, 1993.

Wilhelm, W.; Huppert, A.; Brun, K.; Gruness, V.; Larsen, R.; "Remifentanyl with propofol or isoflurane. A comparison of the recovery times after arthroscopic surgery," *Anaesthesist.*, 46(4): 335-8, 1997.

Yarmush, J., D'Angelo, R., Kirkhart, B., O'Leary, C., Pitts, MC., Graf, G., "A comparison of remifentanyl and morphine sulfate for acute postoperative analgesia after total intravenous anesthesia with remifentanyl and propofol," *Anesthesiology*, 87(2): 235-43, 1997.



## Proposal of the Government of Spain

### 1. INTRODUCTION

In April 1997, the Spanish Government submitted a proposal to the Secretary General of the United Nations to amend the Convention on Psychotropic Substances, 1971 (hereinafter referred to as "the 1971 Convention") by adding to Schedules I and II, the chemical compositions of the isomers, esters and ethers of the psychotropic substances already in these schedules, as well as any modified chemical compounds producing effects similar to those produced by the original substances (hereinafter referred to as "analogues"). An English translation of the Spanish proposal is attached as Appendix 1. The purpose of this document is to provide an in depth analysis of the impact on the 1971 Convention if the Spanish proposal were adopted.

### 2. WHO REVIEW HISTORY

In the past, the Expert Committee on Drug Dependence (ECDD) discussed problems of chemically generic extensions to the list of scheduled substances at its 21st meeting in 1977 (hereinafter referred to as "the 1977 Committee"). The Committee discussed, among other things, salts, esters and ethers, isomers and generic descriptions of drugs (1). Later in 1986, another WHO meeting (hereinafter referred to as "the 1986 meeting") reviewed the chemical and pharmaceutical specifications of substances again (2). In this discussion paper, reference will be made to the conclusions of these meetings as appropriate.

### 3. TERMINOLOGY AND SCOPE OF DISCUSSION

Within the standard chemical lexicon, terms such as isomers, esters and ethers have specific meanings which may be too general for the purposes of the international treaties. To avoid undesirable broadening of the scope of control, the Spanish proposal qualifies some of these terms. It will be useful to confirm "working definitions" of the above terms for the purpose of this paper.

The Spanish proposal also recommends the modification of the 1971 convention to include the salts of isomers, esters, and ethers of Schedule I and II psychotropic substances. Since the salts of the substances listed in these Schedules are already under international control, they will not be addressed independently.

There is some overlap in the definition of some of the terms. For example, in some circumstances, an ester, or an ether or a positional isomer of a psychotropic substance could also be defined as an analogue of a psychotropic substance.

#### *Isomer*

For the purposes of this document, the term "isomer" will imply **stereoisomer** (meaning specifically enantiomers and/or diastereomers) and **geometric isomer**.

## ANNEX 4 (Page 2)

The reason for this working definition is the qualifying phrase in the Spanish proposal "whenever the existence of such isomers is possible within the specific chemical nomenclature in this Schedule". This is also consistent with the Schedules of the 1961 Convention, as well as the position of the 1977 Committee, and will exclude other types of isomerism (1).

### *Ester*

The term "ester" is defined in various chemistry reference texts as well as by IUPAC as a substance that is "formally" derived from the reaction of a carboxylic acid and an alcohol with the loss of water. Under the 1961 Convention, esters and salts of esters of substances listed in Schedule I are treated as Schedule I substances, whenever "the existence of such esters is possible". Although not stated, it is implied that that substance possesses the necessary functional groups to form an ester via the formal (or most obvious) process. Therefore, the discussion of esters of psychotropic substances is restrained to those which specifically possess a hydroxyl group or a carboxylic acid functional group.

Thus, esters made via manipulation of a carboxylic acid functional group are not considered, although it may be possible to convert any psychotropic substance into an ester via a multi-step reaction scheme, resulting in an unending number of esters to be considered.

### *Ether*

For purposes of this paper, "ether" will refer to a substance that contains at least one oxygen atom linked to two carbon atoms (IUPAC definition). Although ethers can be formed via a wide range of functional group transformations, this paper will examine ethers of substances in Schedules I and II of the Psychotropic Convention made by alkylation of a psychotropic substance which possesses a hydroxyl functional group. Thus, esters made via manipulation of a carboxylic acid functional group are not relevant. This limitation was imposed for logical and practical purposes as it may be possible to convert any psychotropic substance into an ester of that psychotropic substance via a multi step reaction scheme, resulting in an unending number of esters to be considered.

This paper will not explore ethers made via functional group manipulation (conversion of other ethers, ketones, or alkenes or the conversion of any other functional group) of any psychotropic substance.

### *Analogue*

For the sake of simplicity, the term "analogue" is used in this document to mean "a substance resulting from modification of the chemical structure of a substance already in these schedules (I and II) and which produces pharmacological effects similar to those produced by the original substance" in the Spanish proposal. Examples of analogues will be presented that differ from psychotropic substances by a single functional group of similar valence, although this is not necessarily the limitation implied within the proposal. Some positional isomers, as well as esters and ethers, could be regarded as analogues. Furthermore, the definition of analogue applies only to those substances which are not included in either the 1971 or the 1961 Convention.

For the purposes of this paper, "similar" pharmacological activity could be interpreted as a stimulant, depressant or hallucinogenic effect resembling that produced by a Schedule I or II psychotropic substance.

#### 4. IMPLICATIONS OF ADOPTING THE SPANISH PROPOSAL

##### 4.1 Isomers

##### 4.1.1 Strict interpretation of the Spanish proposal

The Spanish proposal qualifies "isomers" by "whenever the existence of such isomers is possible within the specific chemical nomenclature in this Schedule". If strictly interpreted, this would mean that, when the chemical name of a substance in the Schedule refers to a particular stereoisomer, no other stereoisomers would be included. Isomers would be controlled only when the existing chemical name in the Schedule is non-stereospecific. For example, since the chemical name of cathinone in Schedule I refers only to the *levo*- isomer, (-)-*S*-2-aminopropiophenone, the *dextro*- isomer of cathinone, (+)-*R*-2-aminopropiophenone, would remain uncontrolled even if the Spanish proposal on isomers were adopted.

If there were no discrepancy between the current interpretation of the listing of the substances in the Schedules and the Spanish proposal, the addition of isomers would not change the scope of substances under control. In this case, this proposal would only provide a clarification without extending controls to yet uncontrolled isomers. The discussion paper will now examine this question.

The reports of the relevant WHO meetings have been reviewed in order to determine the interpretation of the current listing of substances in the Schedule with regard to stereospecificity. The 1977 Committee already noted obvious inconsistencies in the Schedule; it observed that no particular stereoisomer was specified for a number of substances listed in the original schedules even though they were capable of existing in stereoisomers, whereas other chemical names contained stereochemical information, such as (+) or (±) (1). The 1986 meeting, noting the same inconsistencies, pointed out further a specific problem encountered in implementing the 1971 Convention - the assumption by some manufacturers that any unlisted enantiomer or racemic mixture of a scheduled drug was not scheduled (2). Subsequently, the *levo*-isomers of amphetamine (levamfetamine) and methamphetamine, as well as methamphetamine racemate, were added to Schedule II. The 24th meeting of the ECDD, in recommending the addition of methamphetamine racemate in 1987, noted that the control status of the racemate was "open to possible misinterpretation" (3).

It would become clear from these discussions that all isomers, whenever the existence of such isomers is possible within the chemical nomenclature of the substance, were considered included. This principle, however, was not explicitly expressed anywhere. The absence of written clarification led to misinterpretation, with respect to amphetamine and methamphetamine, that unlisted stereoisomers would not be controlled. These stereoisomers were subsequently added to the relevant schedule in order to make this interpretation crystal clear.

On the basis of the above, one could conclude that the Spanish proposal concerning isomers, if strictly interpreted, would explicitly state the current interpretation of the Schedules without changing the scope of substances under control.

The INN<sup>1</sup> names for amphetamine (INN: *amfetamine*) and methamphetamine (INN: *metamfetamine*) may have been associated with such misinterpretations; in addition to *amfetamine*, INNs were also selected, in accordance with the rules, for the two stereoisomers of *amfetamine*, i.e. *dexamfetamine* and *levamfetamine*. In the case of *metamfetamine*, the INN has been defined for one specific isomer, whereas Schedule II includes two isomers, i.e. *metamfetamine* (as the INN for the specific isomer) and *metamfetamine racemate*.

*Amfetamine* (racemate) and *dexamfetamine* (*dextro*-isomer) were already listed separately in the original Schedule. According to the current interpretation as described above, the separate scheduling of *dexamfetamine* would have been unnecessary if the scheduling of racemate also covered *dextro*- or *levo*- form of the substance. The most likely reason for the scheduling of *dexamfetamine* in addition to *amfetamine* is to prevent the misinterpretation that the control of *amfetamine* would not extend to *dexamfetamine* because, in terms of INN, it is a different pharmaceutical substance from *amfetamine*. It is ironical that the addition of *dexamfetamine* had exactly the opposite effect. This has in fact aggravated the confusion instead of minimizing it.

#### 4.1.2 Expanded interpretation of the Spanish proposal

Though contradictory to the qualifying phrase, there appears to be room to interpret the Spanish proposal on isomers differently, namely as a proposal to include yet uncontrolled isomers. The overall intention, rather than the wording of the proposal, would support such an interpretation. From the entire text of the Spanish proposal, it is clear that the overall objective of the proposal is to change the current substance-by-substance scheduling into "preventive" group scheduling.

Seen from this point of view, the proposal could be interpreted so as to include all possible stereo- and geometric- isomers, except where expressly excluded, regardless of whether the existing chemical nomenclature is stereospecific or not. In order to determine the scope of isomers which would be included if this proposal were adopted, the chemical names of the psychotropic substances listed in Schedules I and II were examined for stereospecificity, applying the current interpretation guide described in the preceding subsection.

There are 47 substances listed in Schedules I and II of the 1971 Convention (See Table 1). The listing has several redundancies. For example, both amphetamine and methamphetamine are listed three times in Schedule II because of the separate listing of *d*- and *l*- isomers as well as their racemates. When stereoisomers are ignored, there are 43 substances in the two Schedules of which 36 have possible enantiomers. Of these 36 substances, only 23 have enantiomeric isomers possible by virtue of a single asymmetric centre in the molecular structure (See Appendix 2). Thirteen substances have both diastereomeric and enantiomeric isomers possible

---

<sup>1</sup>International Nonproprietary Names for pharmaceutical substances. After the adoption of the 1971 Convention, the INN name *amphetamine* has been changed to *amfetamine*, and *methamphetamine* to *metamfetamine*.

by virtue of two or more asymmetric centres in the molecular structure. The six tetrahydrocannabinols (five in Schedule I and one in Schedule II with possible diastereomeric isomers) specifically include their stereochemical variants. The structures of the remaining seven substances which possess both diastereomeric and enantiomeric isomers are shown in Appendix 3.

None of the 43 substances have possible geometric (“*cis-trans*”/double bond) isomers. It is therefore unnecessary to consider geometric isomers in this section. Isomers of psychotropic substances possessing *cis-trans* isomers about a ring fusion, such as the tetrahydrocannabinols, or possessing *cis-trans* isomers by virtue of a plane of symmetry imposed by a cyclic structure, such as *cis-* and *trans*-4-methylaminorex, will be treated as diastereomers within this document. Seven of the 43 substances in Schedules I and II are devoid of stereoisomers.

The inclusion of enantiomers of psychotropic substances in Schedules I and II would therefore increase the number of controlled substances by two, specifically adding (+)-cathinone and (-)-lysergide (Appendix 2). The inclusion of both enantiomers and diastereomers would add the following six substances: (+)-cathinone, (-)-lysergic acid diethylamide; (±)-isolysergic acid diethylamide (2 substances); (±)-*trans*-4-methylaminorex (2 substances). The chemical structures of these substances are indicated in Appendix 3.

There are two ways of introducing the Spanish proposal on isomers into the Schedules. One is not to change the current listing of individual substances but add isomers at the end of the two Schedules, after modifying the qualifying phrase in the proposal. Changes are minimal this way, but the apparent inconsistencies with regard to stereospecificity in the current listing will also remain unchanged. Furthermore, it is not so simple to modify the qualifying phrase to make it accurate yet readily understandable.

The other solution would be to rewrite the list by changing stereospecific chemical names to non-stereospecific names and adding isomers at the end of the two Schedules together with the qualifying phrases. Separate stereospecific listing of certain substances, such as amphetamine, could be eliminated and the inconsistencies removed. This would serve to simplify the two Schedules. If national schedules were modified the same way, the burden of forensic laboratories might be reduced since stereospecific identification of controlled substances in seized samples would no longer be required for criminal justice procedures.

However, such a significant rewriting of the current schedules might create a different kind of confusion. For example, three substances by INN, *amfetamine*, *dexamfetamine* and *levamfetamine*, would be listed under just one trivial name *amphetamine* and one non-stereospecific chemical name to cover all possible stereoisomers. Two other entries of this substance (*dexamfetamine* and *levamfetamine*) would be deleted. This change might give rise to a misunderstanding that *dexamfetamine* and *levamfetamine* would no longer be under control in the minds of those who are used to recognizing drugs primarily by INNs. It is also possible that changing two of the four Schedules of the Convention may confuse the interpretation of the remaining Schedules III and IV.

In fact, most of the inconsistencies with regard to stereospecificity in the current Schedules originate from the rigid linkage with the INN system. The INN system is developed for

Schedules is rigidly linked to the INN system, it would be very difficult to completely solve the problem of inconsistencies in chemical names.

In terms of the real impact on the effectiveness of drug control, the advantages of adding enantiomers would be slight, pertaining only to two substances. The inclusion of both diastereomers and enantiomers of Schedule I and II psychotropic substances would have a slightly greater, yet insignificant impact, since only six substances would be added. These newly added substances would include *l*-lysergic acid diethylamide which is a substance of low abuse potential as it does not possess the psychoactive potency of its enantiomer; (+)-cathinone possesses CNS stimulant activity similar to (-)-cathinone and amphetamine, but is significantly less potent (4); *trans*-4-methylaminorex is rarely encountered on the illicit drug market, if at all.

In terms of regulatory compliance, the inclusion of isomers would have certain implications at the national level. Although WHO has no information at present concerning the extent of use of these newly controlled isomers, the possibility of some of them being used for legitimate purposes is not ruled out. In the absence of evidence of abuse, some governments would have difficulty in placing isomers under national control, even if an international decision to add isomers were adopted by the Commission on Narcotic Drugs.

#### 4.2 Ethers and esters

Eleven of the 43 substances in Schedules I and II of the 1971 Convention could be transformed into both ethers and/or esters as defined in the first section of this document. Nine of these substances are benzopyran derivatives ( $\Delta^9$ -THC and related compounds). The remaining two compounds are psilocine and zipeprol.

There is little evidence in the scientific literature to support the international control of ethers of  $\Delta^9$ -THC. In a study on the synthesis and pharmacological evaluation of ether and related analogues of  $\Delta^8$ -,  $\Delta^9$ - and  $\Delta^{9,11}$ -THC, ether analogues of cannabinoids were found to possess limited pharmacological activity relative to  $\Delta^9$ -THC. The phenolic hydroxyl was found to be important for receptor recognition and *in vivo* potency (5). There is no indication that esters or ethers of THC are encountered in the illicit drug market. There is no indication that esters or ethers of psilocine or zipeprol are currently encountered on the illicit drug market. Furthermore, the manufacture of a nonpsychotropic substance (such as an ether or ester of a psychotropic substance) from a psychotropic substance is subject to the controls required by the 1971 Convention until the psychotropic substances come to be in such a condition that it will not, in practice, be abused or recovered (Article 4 paragraph (b)). Hence, the manufacture of ethers and esters of psychotropic substances from psychotropic substances is already under control. Advantages in terms of additional controls would therefore be partial and limited, if any.

In terms of regulatory compliance, the inclusion of esters and ethers of psychotropic substances would have a certain impact on legitimate industry. Although WHO has no information at present concerning the extent of use of esters and ethers, the possibility of some of them being used for legitimate purposes is not ruled out. In the absence of evidence of abuse, some governments would have difficulty in placing such substances under national control, even if an international decision to control esters and ethers were adopted by the Commission on Narcotic Drugs.

National drug control legislation may not always provide for the kind of flexibility which would allow governments to automatically update national schedules in conformity with international scheduling decisions. If the existing legislation cannot accommodate collective scheduling of a group of unspecified substances such as “esters” or “ethers”, such governments would not be able to comply with the international scheduling decision.

Though difficult to assess, the regulatory burden on legitimate industry and research would be potentially significant, and might adversely affect drug discovery and development.

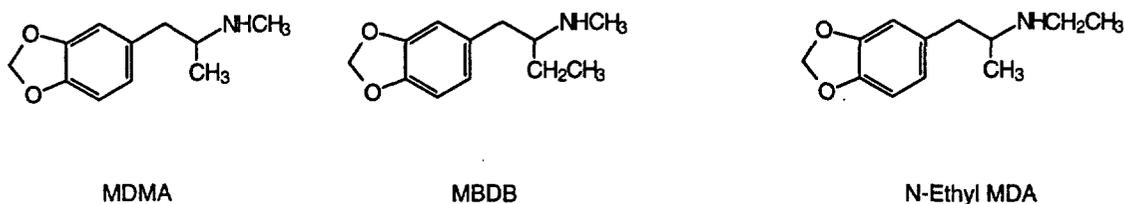
Some ethers and esters of psychotropic substances could be considered as analogues of psychotropic substances if they have similar pharmacological activities to those under control.

### 4.3 Analogues

#### 4.3.1 Implications of controlling analogues

Controlling analogues under the 1971 Convention would potentially result in the international control of a number of compounds. For example, MBDB could be considered an analogue of MDMA by virtue of extending the aliphatic carbon chain by one carbon atom (homologation), as shown in Figure 1. MBDB is not currently a psychotropic substance nor is it listed in any schedule of the 1961 Convention. In some countries, the abuse of MBDB has resulted in a public or social problem and has pharmacological effects that may be considered similar to those produced by MDMA.

**Figure 1 MBDB as a Potential Analogue of MDMA**

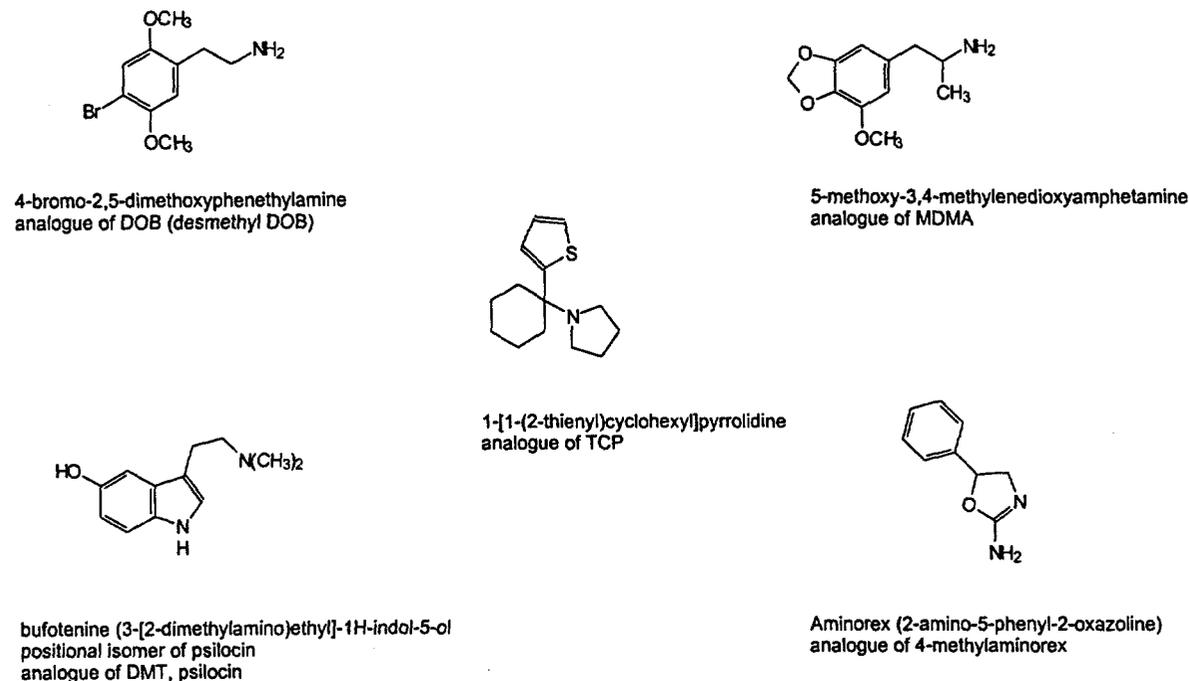


The chemical structures of several substances which might be considered analogues of Schedule I and II psychotropic substances are shown below in Figure 2. None of the substances shown in Figure 2 are listed in any of the schedules of the 1961 nor the 1971 Convention. These substances also possess pharmacological activity that could be classified as “similar” to psychotropic substances in Schedules I or II of the 1971 Convention.

**Figure 2**

psychotropic substances in Schedules I or II of the 1971 Convention.

Figure 2



Many of the substances in Figure 2 are amphetamine-like stimulants. Amphetamine-like substances are relatively easy to synthesize and are often illicitly produced in clandestine laboratories. The abuse of illicitly produced amphetamine-type stimulants is currently a drug abuse problem of global dimensions. Unlike the inclusion of isomers, esters and ethers, controlling analogues of Schedule I and II substances could have a significant impact in terms of thwarting international trafficking in amphetamine-type substances. Also, the tryptamines, or indole alkaloids related to psilocine and psilocybin are a class of compounds for which an analogue provision might have some merit. There are numerous possible analogues of the indole alkaloids listed in Schedules I and II of the 1971 Convention. Thus, analogues control would have a clear advantage in terms of coverage. Unfortunately, this advantage would not extend to the 1961 Convention. More specifically, new fentanyl and pethidine analogues which are not their isomers, esters or ethers, would be outside the scope of the Spanish proposal.

Controlling analogues would require a drastic departure from the way the Schedules have been updated until now. It is very questionable whether such a substantive modification of the Schedules is compatible with Article 2 of the 1971 Convention, which stipulates the scheduling procedure and criteria. Under this provision, WHO's assessment of individual psychoactive substances is required. For WHO to communicate a scheduling recommendation to the UN, it is required that WHO finds:

- (a) that the substance has the capacity to produce similar abuse and similar ill effects as a substance in Schedule I, II, III or IV, and
- (b) that there is sufficient evidence that the substance is being or is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control.

The proposed inclusion of analogues, which may satisfy requirement (a) above only by definition, ignores requirement (b). Furthermore, even (a) has to be judged by WHO under this Article, whereas the Spanish proposal does not specify who makes this judgement.

In effect, the inclusion of analogues would require major amendments to Article 2 of the 1971 Convention.

Even if the 1971 Convention could be amended such that analogues with similar pharmacological activity were added to Schedules I and II, the control of nonspecific chemical entities might lead to many new problems. The Parties would be obligated to 1) require licences for the manufacture, trade and distribution of analogues; 2) require medical prescriptions for the dispensing of analogues; 3) comply with the obligations relating to export and import of analogues, including prohibition and restrictions; 4) furnish statistical reports of analogues and; 5) adopt measures to repress acts contrary to laws and regulations adopted pursuant to foregoing obligations. Thus, any legitimate manufacturer of a psychotropic substance analogue would have to register with the appropriate authorities. There would be potential restrictions on the import and export of a wide range of substances.

A practical problem in implementing these regulations would be the difficulty in determining whether a particular substance having certain similarities to controlled drugs is a controlled analogue or not. If the competent national authorities make such a judgement without delay, the confusion could be minimized at the national level. However, in case of dispute between different national authorities, it would be very difficult to apply trade-related provisions.

The impact of controlling analogues on legitimate industrial and academic activities is difficult to assess. However, compared with esters and ethers, the scope of analogues that could be controlled would be larger in number and more difficult to determine. In this connection, it should be noted that much of the research work on some hallucinogenic substances in Schedule I had in fact been carried out in laboratories of pharmaceutical companies. Although the plan to develop them as new medicines was subsequently abandoned, it would be fair to say that even such research would not have taken place had it been known at that time that these substances would be controlled anyway. Ketamine, for example, has some chemical and pharmacological similarity to phencyclidine in Schedule II. Although ketamine has hallucinogenic side-effects, it has some value as an injectable anaesthetic which can be used in hospitals having no modern equipment for anaesthesia. It is not difficult to imagine that analogues control would discourage research and development activities on these types of drugs.

Both the 1977 Committee (1) and the 1986 meeting (2) did not recommend the generic extension of international controls to analogues.

#### 4.3.2 National experiences

The mandate of the ECDD is limited to making international scheduling recommendations in accordance with the relevant Conventions. Reviewing national control measures is, strictly speaking, outside the mandate given to it. In this particular case, it may nevertheless be useful to consider one or two examples of national approaches. As discussed in the preceding subsection, applying all the control measures of the 1971 Convention to analogues might lead to certain difficulties even at the national level. Without prejudice to other approaches, the US experience with analogues control is outlined below for reasons of a clear separation between regulatory and criminal controls.

During the 1960s-1980s, the United States experienced problems with the illicit manufacture and distribution of so-called "designer drugs" or analogues of controlled substances under the United States Controlled Substances Act. At this time the drug laws were based on specific chemical substances and thus it was easy to defeat drug control measures via a simple alteration to the chemical structure that did not greatly impact the pharmacological activity of the substance. Hence, the altered chemical substance was not subject to controls and the process of scheduling this new substance such that it would be subject to controls utilizing traditional scheduling procedures required several years. The United States Government then enacted emergency scheduling provisions to the Controlled Substances Act which allowed the U.S. Attorney General to emergently schedule, for a period of one year, any substance that was determined to be an immediate hazard to the public health and safety. During this time, the substance could be controlled either through a formal administrative or legislative process. However, the emergency scheduling provisions were still insufficient to combat the problem of designer drugs. Emergency scheduling required several months to be put into place. Shortly thereafter, the United States Congress passed the Controlled Substances Analogue Act of 1985 which amended the Controlled Substances Act to allow for the criminal prosecution of those persons who intentionally marketed a controlled substances analogue for the purposes of avoiding controlled substances laws. This provided the drug law enforcement officials with a proactive response to the problem of designer-drug trafficking.

The Controlled Substances Analogues Act is effective in that it imposes criminal sanctions on the activity of manufacturing and distributing analogues intended for human consumption. All other uses of analogues are exempt from the provisions of this Act. The analogue intended for human consumption is treated as a Schedule I controlled substance if it has a chemical structure similar to that of a controlled substance in Schedule I or II. It must produce a stimulant, depressant or hallucinogenic effect substantially similar to or greater than that produced by a Schedule I or II controlled substance. It must be presented by an individual to produce such an effect. Legitimately marketed substances or those under investigation are exempt from such provisions. Analogues are controlled under the criminal but not the regulatory aspects of the Controlled Substances Act. Therefore legitimate research and development are not impeded.

There is no list of Controlled Substances Analogues. Substances are determined to be analogues during the course of criminal proceedings on a case by case basis. The United States Government has successfully prosecuted a number of individuals who have manufactured and distributed analogues of controlled substances such as MDA, amphetamines, pethidine, and fentanyl. Challenges to the analogue provisions of the Controlled Substances Act have been unsuccessful in courts of law. Since the passage of the Act, there has been a dramatic decrease

unsuccessful in courts of law. Since the passage of the Act, there has been a dramatic decrease in the number of analogues encountered on the illicit drug market in the United States. Since 1990, only four substances have been placed under emergency control. There are currently no controlled substance analogues under review in the United States for emergency or permanent control. The analogue provision of the Controlled Substances Act has proven to be a successful instrument for attacking the problem of analogues. Similar legislation that is in accord with individual legal systems could be considered by other countries.

## 5. TENTATIVE CONCLUSION AND RECOMMENDATIONS

In 1997, the Spanish Government submitted a proposal to the Secretary General of the United Nations to amend the 1971 Convention by adding to Schedules I and II, the chemical compositions of the isomers, salts, esters and ethers of the psychotropic substances, as well as any modified chemical compounds producing effects similar to those produced by the original substances. An in-depth analysis of potential advantages and disadvantages of this proposal has led to the following conclusions.

With regard to the scheduling of analogues or "any modified chemical compounds producing effects similar to those produced by the original substances", the Committee was of the opinion that there would be a significant advantage in terms of extending the scope of control. However, extending controls collectively to these groups of substances which are related to, but different from, the substances in the two Schedules may contradict the scheduling procedure stipulated in Article 2 of the Convention which requires WHO to evaluate individual substances.

Furthermore, the lack of specificity in such group designations may lead to new problems, such as disagreements among Parties concerning the precise scope of substances under control. With regard to the scheduling of esters and ethers, the same question would arise with regard to the conformity with Article 2 of the 1971 Convention. In addition, the advantages in terms of extended scope of control would be rather limited. Though difficult to evaluate, controlling analogues, esters and ethers is likely to have a negative impact on legitimate industrial and research activities involving these substances.

For these reasons, it is not recommended to amend Schedule I and II of the 1971 Convention to extend international controls collectively to esters, ethers and analogues of controlled substances. It is noted, however, that criminal activities involving analogues of controlled substances can be controlled at the national level, without extending unnecessary administrative and regulatory controls to these substances used for legitimate industrial and research purposes. In one country, this was achieved by applying only criminal controls to certain specified acts involving analogues. Governments having problems with analogues should consider the desirability of adopting similar selective control measures, an option which is not available under the 1971 Convention once analogues have been scheduled.

With regard to the scheduling of isomers, the qualifying phrase in the proposal that this would only apply "whenever the existence of such isomers is possible within the specific chemical nomenclature in this Schedule", renders the proposal consistent with the current interpretation of the Schedules. Hence the proposal would provide an explicit clarification of the scope of controlled isomers without changing it. Even if the real intention of the proposal were to add enantiomers, diastereoisomers and geometric isomers of all the substances in the two Schedules regardless of whether they are possible within the existing chemical nomenclature, the

advantages in terms of extended scope of control would be insignificant, involving only six isomers of limited abuse liability. Although the existing inconsistencies in listing substances in the Schedules could be partially reduced, the potential benefits of the proposal are uncertain. Adding isomers to the schedules alone would not solve the problem of inconsistency in the current listing of substances with respect to stereospecificity. Since this inconsistency is linked to the same inconsistency in INNs, it is difficult to solve this problem without a major rewriting of the schedules. Whichever approach is taken, the advantages in terms of expanded scope of control are very slight, involving only six isomers of insignificant abuse liability. It is questionable whether there is any need or justification to extend international controls to these substances at present. If there is a confusion arising from the inconsistencies in the present chemical designations of the Schedules, clarification could be provided by means of interpretation guidelines adopted by an appropriate body, such as the International Narcotics Control Board (INCB). If this approach is agreeable to the INCB, WHO should collaborate with it in developing such guidelines.

With regard to future scheduling recommendations, non-stereospecific designation should be used whenever there is no need to exclude a particular stereoisomer, since this approach has a clear advantage over stereospecific designation in terms of simplicity in criminal justice procedures against illicit activities.

Table I. Substances in Schedule I

Chemical Name	Other Names <sup>(1)</sup>
(±)-4-bromo-2,5-dimethoxy- $\alpha$ -methylphenethylamine	DOB
(-)-(S)-2-aminopropiophenone	Cathinone
3-[2-(diethylamino)ethyl]indole	DET
(±)-2,5-dimethoxy- $\alpha$ -methylphenethylamine	DMA
3-(1,2-dimethylheptyl)-7,8,9,10-tetrahydro-6,6,9-trimethyl-6H-dibenzo[b,d]pyran-1-ol	DMHP
3-[2-(dimethylamino)ethyl]indole	DMT
(±)-4-ethyl-2,5-dimethoxy- $\alpha$ -phenethylamine	DOET
<i>N</i> -ethyl-1-phenylcyclohexylamine	PCE, Eticyclidine
3-(2-aminobutyl)indole	Etryptamine
9,10-didehydro- <i>N,N</i> -diethyl-6-methylergoline-8b-carboxamine	Lysergide, LSD
(±)- <i>N</i> , $\alpha$ -dimethyl-3,4-(methylenedioxy)phenethylamine	MDMA
3,4,5-trimethoxyphenethylamine	Mescaline
2-(methylamino)-1-phenylpropan-1-one	Methcathinone
(±)- <i>cis</i> -2-amino-4-methyl-5-phenyl-2-oxazoline	4-methylaminorex
2-methoxy- $\alpha$ -methyl-4,5-(methylenedioxy)phenethylamine	MMDA
(±)- <i>N</i> -ethyl- $\alpha$ -methyl-3,4-(methylenedioxy)phenethylamine	<i>N</i> -ethyl MDA
(±)- <i>N</i> -[ $\alpha$ -methyl-3,4-(methylenedioxy)phenethyl]hydroxylamine	<i>N</i> -hydroxy MDA

<i>p</i> -methoxy- $\alpha$ -methylphenethylamine	PMA
3-hexyl-7,8,9,10-tetrahydro-6,6,9-trimethyl-6 <i>H</i> -dibenzo[ <i>b,d</i> ]pyran-1-ol	Parahexyl
3-[2-(dimethylamino)ethyl]indol-4-ol	Psilocine
3-[2-(dimethylamino)ethyl]indol-4-yl dihydrogen phosphate	Psilocybine
1-(1-phenylcyclohexyl)pyrrolidine	PHP, PCPY
2,5-dimethoxy- $\alpha$ ,4-dimethylphenethylamine	STP, DOM
$\alpha$ -methyl-3,4-(methylenedioxy)phenethylamine	MDA
1-[1-(2-thienyl)cyclohexyl]piperidine	TCP, Tenocyclidine
7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6 <i>H</i> -dibenzo[ <i>b,d</i> ]pyran-1-ol	isomer of THC
(9 <i>R</i> , 10 <i>aR</i> )-8,9,10,10 <i>a</i> -tetrahydro-6,6,9-trimethyl-3-pentyl-6 <i>H</i> -dibenzo[ <i>b,d</i> ]pyran-1-ol	isomer of THC
(6 <i>aR</i> , 9 <i>R</i> , 10 <i>aR</i> )-6 <i>a</i> ,9,10,10 <i>a</i> -tetrahydro-6,6,9-trimethyl-3-pentyl-6 <i>H</i> -dibenzo[ <i>b,d</i> ]pyran-1-ol	isomer of THC
(6 <i>aR</i> , 10 <i>aR</i> )-6 <i>a</i> ,7,10,10 <i>a</i> -tetrahydro-6,6,9-trimethyl-3-pentyl-6 <i>H</i> -dibenzo[ <i>b,d</i> ]pyran-1-ol	isomer of THC
6 <i>a</i> ,7,8,9-tetrahydro-6,6,9-trimethyl-3-pentyl-6 <i>H</i> -dibenzo[ <i>b,d</i> ]pyran-1-ol	isomer of THC
(6 <i>aR</i> , 10 <i>aR</i> )-6 <i>a</i> ,7,8,9,10,10 <i>a</i> -hexahydro-6,6-dimethyl-9-methylene-3-pentyl-6 <i>H</i> -dibenzo[ <i>b,d</i> ]pyran-1-ol	isomer of THC
( $\pm$ )-3,4,5-trimethoxy- $\alpha$ -methylphenethylamine	TMA

(1) Only one or two names are listed, without preference to INN.

Table II. Psychotropic Substances in Schedule II

Chemical Name	Other Names <sup>(1)</sup>
( $\pm$ )- $\alpha$ -methylphenethylamine	Amphetamine, Amfetamine
(+)- $\alpha$ -methylphenethylamine	Amphetamine, Dexamphetamine
7-[2-[( $\alpha$ -methylphenethyl)amino]ethyl]theophylline	Fenetylline
(-)-( <i>R</i> )- $\alpha$ -methylphenethylamine	Levamphetamine
(-)- <i>N</i> , $\alpha$ -dimethylphenethylamine	Levomethamphetamine
3-( <i>o</i> -chlorophenyl)-2-methyl-4(3 <i>H</i> )-quinazolinone	Mecloqualone
(+)-( <i>S</i> )- <i>N</i> , $\alpha$ -dimethylphenethylamine	Methamphetamine
( $\pm$ )- <i>N</i> , $\alpha$ -dimethylphenethylamine	Methamphetamine racemate
2-methyl-3- <i>o</i> -tolyl-4(3 <i>H</i> )-quinazolinone	Methaqualone
Methyl $\alpha$ -phenyl-2-piperidineacetate	Methylphenidate
1-(1-phenylcyclohexyl)piperidine	Phencyclidine, PCP
3-methyl-2-phenylmorpholine	Phenmetrazine

5-allyl-5-(1-methylbutyl)barbituric acid	Secobarbital
(6aR, 10aR)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol	$\Delta$ -9-tetrahydrocannabinol and its stereochemical variants
$\alpha$ -( $\alpha$ -methoxybenzyl)-4-(b-methoxyphenethyl)-1-piperazineethanol	Zipeprol

(1) Only one or two names are listed, without preference to INN.

## References

1. WHO Expert Committee on Drug Dependence. *Twenty-first report*. Geneva, World Health Organization, 1978 (WHO Technical Report Series, No. 618)
2. *Chemical and Pharmacological Specifications of Substances for Control Under the International Drug Control Treaties. Report of the WHO Meeting*. Geneva, World Health Organization, 1986
3. WHO Expert Committee on Drug Dependence. *Twenty-fourth report*. Geneva, World Health Organization, 1988 (WHO Technical Report Series, No. 761)
4. Gugelmann, R.; Von Allmen, M.; Brenneisen, R.; Porzig, H. "Quantitative differences in the pharmacological effects of (+)- and (-)-cathinone." *Experientia* 1985, 41, 1568-1571.
5. Compton, D.R.; Prescott, W.R.; Martin, B.R.K.; Siegel, C.; Gordon, P.M.; Razdan, R.K.; "Synthesis and pharmacological evaluation of ether and related analogues of  $\Delta^8$ -,  $\Delta^9$ - and  $\Delta^{9,11}$ -tetrahydrocannabinol." *J. Med. Chem.* 1991, 34, 3310-3316.

Appendix 1

**Letter addressed to the UN Secretary-General communicating the proposal of the Government of Spain**

Sir,

Recent years have witnessed an alarming phenomenon in the field of production, trafficking and illicit use of drugs, namely the sudden spread of synthetic drugs.

This phenomenon, which affects a large number of countries and has international ramifications, is developing extensively, so much so that prevention mechanisms need to be urgently created within the framework of international law in order to forestall its further spread.

Synthetic drugs are easy to produce. It is sufficient to modify the chemical structure of an amphetamine-type stimulant in order to obtain the new final product, which is then introduced into the illicit drug market, predominantly among young people. It is chemically possible to obtain a large number of modified structures in which the basic composition of the amphetamine is maintained unchanged.

Although some derivatives are subject to control under the United Nations Convention on Psychotropic Substances of 1971 (for example, MDMA, MDA, MDE and DOB), others are still not subject to such control (for example, MBDB).

It is the view of Spain that, as a matter of urgency, the 1971 Convention should generate mechanisms to prevent the appearance of new psychotropic substances.

It has been noted that the individual inclusion of substances in the Schedules is a slow process which does not prevent new substances being created on the basis of similar chemical compounds.

The Government of Spain considers that it would be advisable to open up discussion on the control of synthetic drugs through the Convention's Schedules with the aim of achieving tighter control over the production and traffic of this type of substance.

Consequently, convinced of the need to open up the system of Schedules to all psychotropic substances liable to engender a serious problem of addiction, the Government of Spain seeks, by means of the text given below, the addition to Schedules I and II of the 1971 Convention of the chemical compositions of the isomers, salts, esters and ethers of the psychotropic substances, as well as any modified chemical compounds producing effects similar to those produced by the original substance:

*“The isomers, except where expressly excluded, of psychotropic substances listed in this Schedule whenever the existence of such isomers is possible within the specific chemical*

*nomenclature in this Schedule;*

*The esters and ethers of psychotropic substances listed in this Schedule, except where included in a different Schedule, whenever the existence of such esters or ethers is possible;*

*The salts of psychotropic substances listed in this Schedule, including the salts of esters, ethers and isomers under the conditions stated above, whenever the formation of such salts is possible;*

*Any other modified chemical compound which produces effects on the organism similar to those produced by the original controlled substance”.*

In addition to the arguments put forward above, I should like to make a number of further points in support of this proposal:

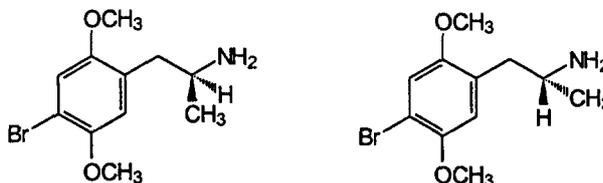
1. It would mean the acquisition of a legal instrument which would reinforce action against drug organizations and traffickers by preventing them for evading the controls on existing substances by creating altered forms of those substances with similar effects.
2. Courts of justice would be furnished with the scientific and legal foundations they require to make an effective judicial response to the new amphetamine-type stimulants being introduced into the market.
3. The use would be averted of conflicting criteria for action by Governments in their campaigns directed at prevention, treatment and law enforcement in relation to the new synthetic drugs.
4. The health systems of the United Nations Member States would be provided with a legal response enabling them to formulate specific treatment strategies with respect to the use of synthetic drugs appearing in future.
5. This proposed text would forestall the possibility of illicit substances being processed by illicit drug trafficking organizations in such a way that the chemical substance obtained produces the same effects as those sought but through a slight chemical alteration of the molecular structure or through the use of optical, positional or other isomers.

By means of this text, as provided for in article 2 of the United Nations Convention on Psychotropic Substances of 1971, the Government of Spain seeks to set in motion the process of amending Schedules I and II through the inclusion of this proposal.

I look forward to receiving your reply and remain,

Yours sincerely,

(Signed) Gonzalo Robles Orozco

**Appendix 2****Substances in Schedules I and II which Possess Only Enantiomeric Stereoisomers****Brolamphetamine, DOB ((±)-4-bromo-2,5-dimethoxy-α-methylphenethylamine)**

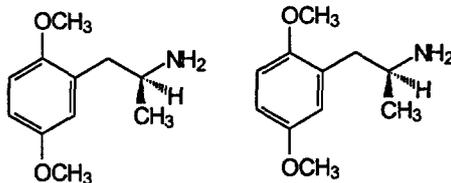
Both enantiomers of DOB fall under the controls specified by the 1971 Convention for Schedule I psychotropic substances.

**Cathinone ((-)-(S)-2-aminopropiophenone)**

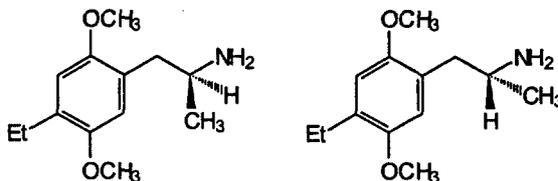
(S)-(-)-Cathinone

(R)-(+)-Cathinone

The control of isomers (enantiomers) of Schedule I and II psychotropic substances would result in the additional control of (+)-cathinone.

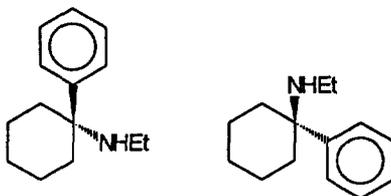
**DMA ((±)-2,5-dimethoxy-α-methylphenethylamine)**

Both enantiomers of DMA fall under the controls specified by the 1971 Convention for Schedule I psychotropic substances.

**DOET ((±)-4-ethyl-2,5-dimethoxy-α-phenethylamine)**

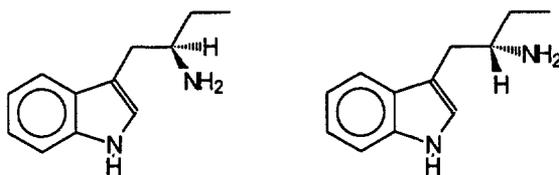
Both enantiomers of DOET fall under the controls specified by the 1971 Convention for Schedule I psychotropic substances.

**PCE, Eticyclidine ( N-ethyl-1-phenylcyclohexamine)**



Both enantiomers of eticyclidine fall under the controls specified for psychotropic substances (in absence of more specific stereochemical information).

**Etryptamine (3-(2-aminobutyl)indole)**



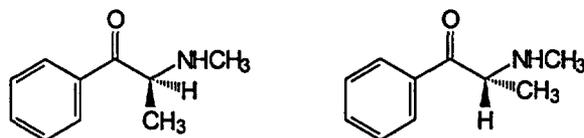
Both enantiomers of the above substance fall under the controls specified for psychotropic substances (in absence of more specific stereochemical information).

**MDMA ((±)-N,α-dimethyl-3,4-(methylenedioxy)phenethylamine)**



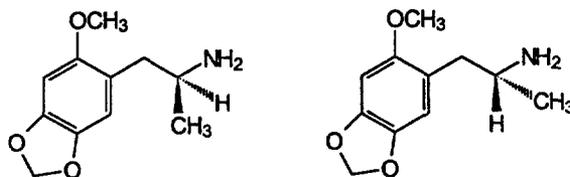
Both enantiomers of MDMA fall under the controls specified by the 1971 Convention for Schedule I psychotropic substances.

**Methcathinone (2-(methylamino)-1-phenylpropan-1-one)**

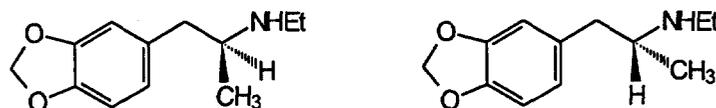


Both enantiomers of methcathinone are under the controls specified for psychotropic substances (in absence of more specific stereochemical information).

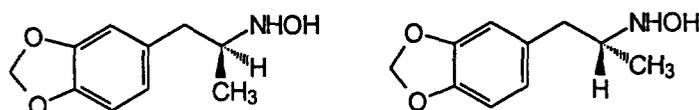
**MMDA (2-methoxy-α-methyl-4,5-(methylenedioxy)phenethylamine)**



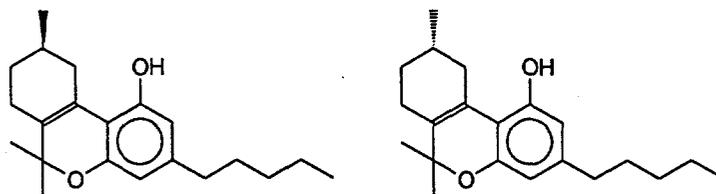
Both enantiomers of the above substance fall under the controls specified for psychotropic substances (in absence of more specific stereochemical information).

**N-Ethyl MDA ((±)-N-ethyl-α-methyl-3,4-(methylenedioxy)phenethylamine)**

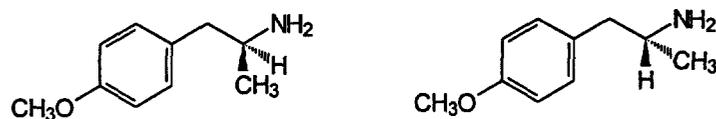
Both enantiomers of N-Ethyl MDA fall under the controls specified by the 1971 Convention for Schedule I psychotropic substances.

**N-hydroxy MDA ((±)-N-[α-methyl-3,4-(methylenedioxy)phenethyl]hydroxylamine)**

Both enantiomers of N-hydroxy MDA fall under the controls specified by the 1971 Convention for Schedule I psychotropic substances.

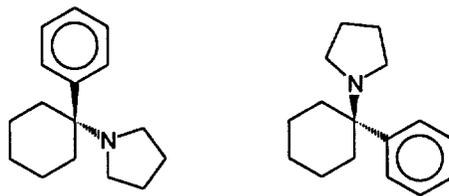
**Parahexyl (3-hexyl-7,8,9,10-tetrahydro-6,6,9-trimethyl-6H-dibenzo[b,d]pyran-1-ol)**

Both enantiomers of parahexyl fall under the controls specified for psychotropic substances (in absence of more specific stereochemical information).

**PMA (p-methoxy-α-methylphenethylamine)**

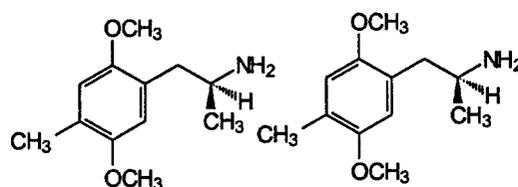
Both enantiomers of PMA fall under the controls specified for psychotropic substances (in absence of more specific stereochemical information).

**PHP, PCPY, Rolicyclidine (1-(1-phenylcyclohexyl)pyrrolidine)**



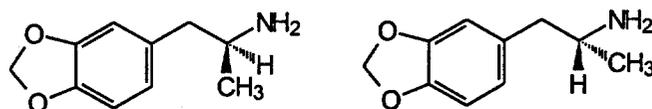
Both enantiomers of PHP fall under the controls specified for psychotropic substances (in absence of more specific stereochemical information).

**STP, DOM (2,5-dimethoxy- $\alpha$ ,4-dimethylphenethylamine)**



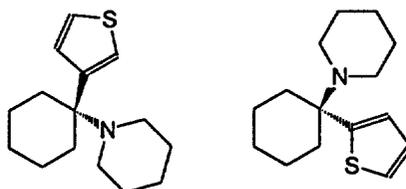
Both enantiomers of STP fall under the controls specified for psychotropic substances (in absence of more specific stereochemical information).

**MDA, Tenamfetamine ( $\alpha$ -methyl-3,4-(methylenedioxy)phenethylamine)**

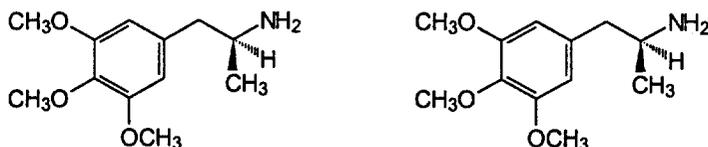


Both enantiomers of the above substance fall under the controls specified for psychotropic substances (in absence of more specific stereochemical information).

**TCP 1-[1-(2-thienyl)cyclohexyl]piperidine)**



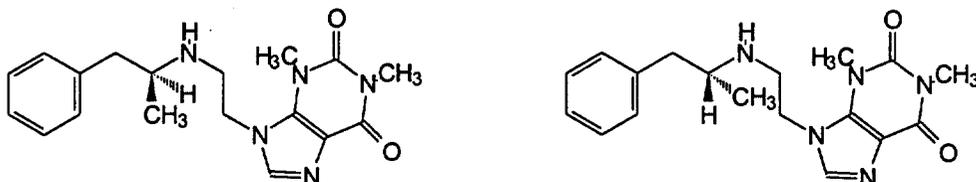
Both enantiomers of the above substance fall under the controls specified for psychotropic substances (in absence of more specific stereochemical information).

**TMA ((±)-3,4,5-trimethoxy-α-methylphenethylamine)**

Both enantiomers of TMA fall under the controls specified by the 1971 Convention for Schedule I psychotropic substances.

**Amphetamine ((±)-α-methylphenethylamine)**

Both enantiomers of amphetamine are specifically under international control.

**Fenetylline (7-[2-[(α-methylphenethyl)amino]ethyl]theophylline)**

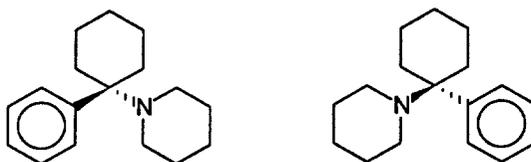
Both enantiomers of fenetylline fall under the controls specified for psychotropic substances (in absence of more specific stereochemical information).

**Methamphetamine ((±)-N,α-dimethylphenethylamine)**

(S)-(+)-methamphetamine

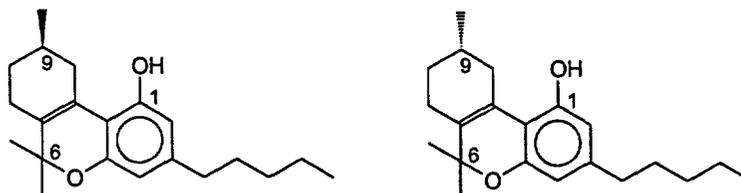
(R)-(-)-methamphetamine

Both enantiomers of methamphetamine are currently under international control.

**Phencyclidine, PCP (1-(1-phenylcyclohexyl)piperidine)**

Both enantiomers of PCP fall under the controls specified for psychotropic substances (in absence of more specific stereochemical information).

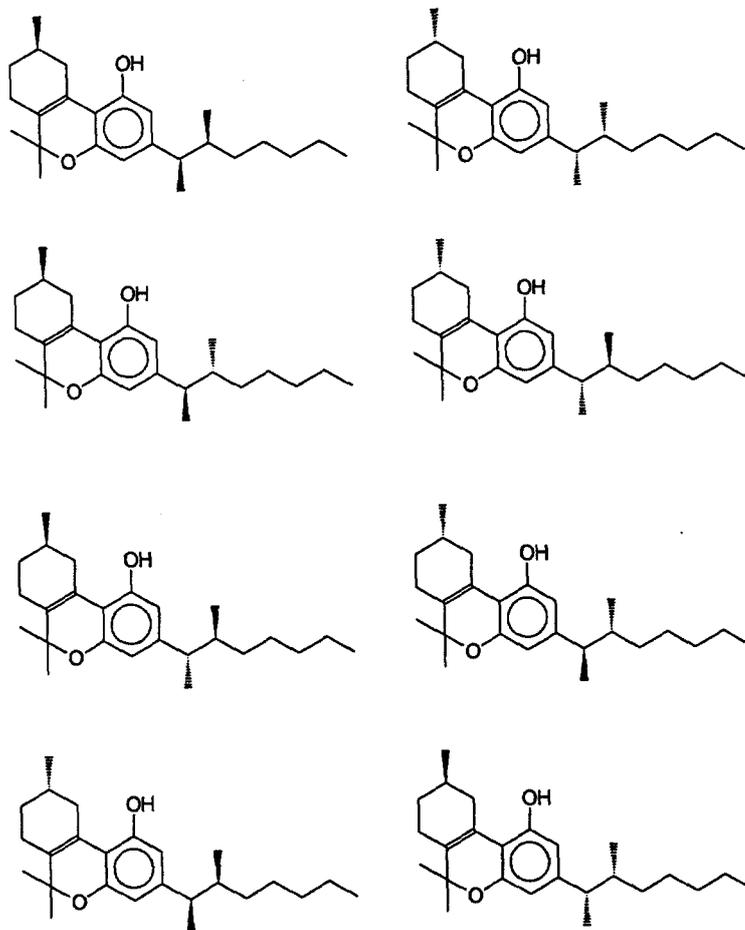
**7,8,9,10-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol**

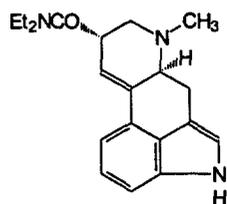
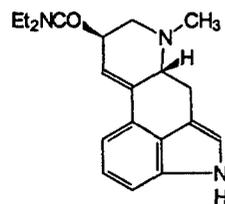
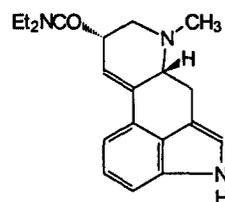


All stereochemical variants of listed tetrahydrocannabinol isomers are under international control.

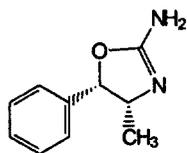
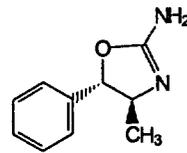
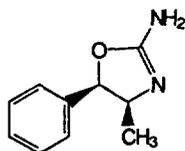
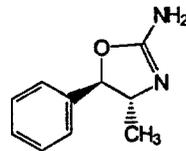
**Appendix 3****Substances in Schedules I and II Which Possess Enantiomeric and Diastereomeric Stereoisomers****DMHP (3-(1,2-dimethylheptyl)-7,8,9,10-tetrahydro-6,6,9-trimethyl-6H-dibenzo[b,d]pyran-1-ol)**

There are eight possible diastereomeric isomers of DMHP by virtue of its three chiral carbon centers in the molecular structure. All eight diastereomers fall under the controls specified for Schedule I psychotropic substances (in absence of more specific stereochemical information). Hence the control of either diastereomers or enantiomers of DMHP would have no net effect in terms of additional substances controlled under the 1971 Convention.

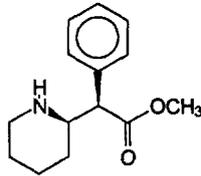


***d*-Lysergic acid diethylamide (9,10-didehydro-*N,N*-diethyl-6-methylergoline-8 $\beta$ -carboxamide)***d*-lysergic acid diethylamide*l*-lysergic acid diethylamide*d*-isolysergic acid diethylamide*l*-isolysergic acid diethylamide

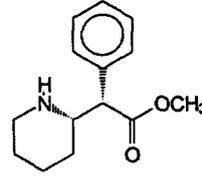
There are four possible diastereomeric isomers of *d*-lysergic acid diethylamide by virtue of the two asymmetric centers in the molecular structure. One enantiomer (*d*-lysergic acid diethylamide) is currently controlled. The inclusion of diastereomers of this substance would result in additional control of *l*-lysergic acid diethylamide, *d*-isolysergic acid diethylamide and *l*-isolysergic acid diethylamide. The control of enantiomers of *d*-lysergic acid diethylamide would result in the additional control of *l*-lysergic acid diethylamide only.

**4-Methylaminorex (( $\pm$ )-*cis*-2-amino-4-methyl-5-phenyl-2-oxazoline)***cis*-4-methylaminorex*trans*-4-methylaminorex*cis*-4-methylaminorex*trans*-4-methylaminorex

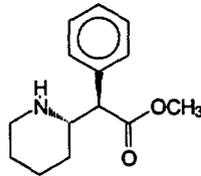
There are four possible diastereomers of 4-methylaminorex. Both *cis* diastereomers are currently controlled. The control of diastereomers of 4-methylaminorex would result in additional control of the two additional (*trans*) diastereomers. The control of enantiomers of 4-methylaminorex would have no net effect in terms of additional substances controlled under the 1971 Convention.

**Methylphenidate ((R\*,R\*)-(±)-methyl α-phenyl-2-piperidineacetate)**

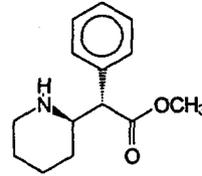
(R,R)-methylphenidate



(S,S)-methylphenidate

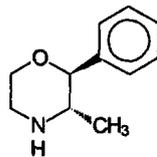


(S,R)-methylphenidate

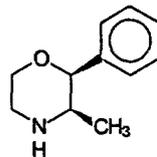
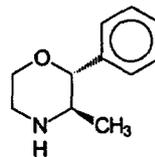


(R,S)-methylphenidate

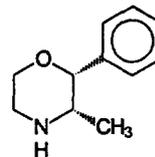
There are four possible diastereomers of methylphenidate by virtue of two asymmetric centers in the molecular structure. All four diastereomers fall under the controls specified for Schedule I psychotropic substances (in absence of more specific stereochemical information). Hence the control of either diastereomers or enantiomers of methylphenidate would have no net effect in terms of additional substances controlled under the 1971 Convention.

**Phenmetrazine (3-methyl-2-phenylmorpholine)**

trans-phenmetrazine

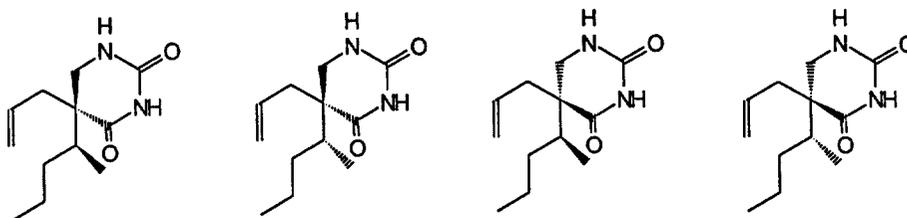


cis-phenmetrazine



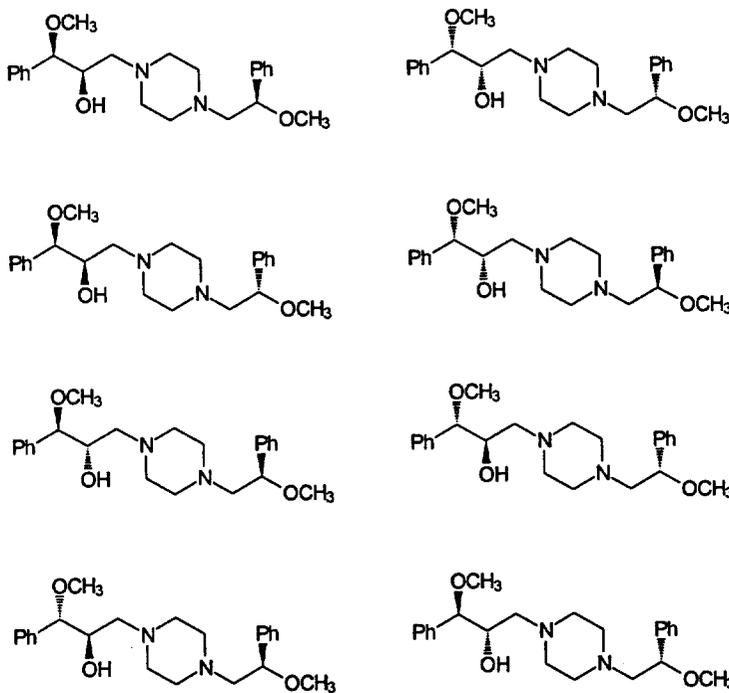
There are four possible diastereomers of phenmetrazine by virtue of two asymmetric centers in the molecular structure. All four diastereomers fall under the controls specified for Schedule I psychotropic substances (in absence of more specific stereochemical information). Hence the control of either diastereomers or enantiomers of phenmetrazine would have no net effect in terms of additional substances controlled under the 1971 Convention.

**Secobarbital (5-allyl-5-(1-methylbutyl)barbituric acid)**



All diastereomers of secobarbital fall under the controls specified for psychotropic substances (in absence of more specific stereochemical information).

**Zipeprol ( $\alpha$ -( $\alpha$ -methoxybenzyl)-4-( $\beta$ -methoxyphenethyl)-piperazineethanol)**



There are eight possible diastereomers of zipeprol by virtue of three asymmetric centers in the molecular structure. It is assumed that all eight diastereomers fall under the controls specified for Schedule II Psychotropic Substances (in absence of more specific stereochemical information). The control of either diastereomers or enantiomers of this substance would result in no change to the 1971 Convention.





**WORLD HEALTH ORGANIZATION  
ORGANISATION MONDIALE DE LA SANTE**

**31ST EXPERT COMMITTEE ON DRUG DEPENDENCE**  
M605, WHO/HQ, Geneva  
23-26 June 1998

**PND/ECDD31/5**

**PRE-REVIEW DATA SHEETS**

**(Provisional Agenda Item: 5)**

Since 1990, WHO's review of psychoactive substances has been carried out in two steps. The first step is referred to as "pre-review" which is a preliminary review carried out to determine whether or not a fully documented review ("critical review") of the substance is required. The judgement criterion to use is whether or not "WHO has information that may justify the scheduling" of the substance. Both pre-review and critical review are carried out by the Expert Committee on Drug Dependence (ECDD). This review procedure applies not only to new substances but to the re-scheduling of substances already under international control, such as the majority of benzodiazepines which are currently in Schedule IV of the Convention on Psychotropic Substances.

## TABLE OF CONTENTS

	<u>Page</u>
1. Benzodiazepines .....	1
2. Tobacco .....	12
3. Gammahydroxybutyrate (GHB) .....	16
4. 4-Bromo-2,5-dimethoxyphenethylamine (2-CB) .....	20
5. N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (MBDB) ....	24
6. Zolpidem (INN) .....	27

## LIST OF CONTRIBUTORS

This document has been prepared by the Secretariat with the technical support of the following experts:

Dr P.M. Bearsley, Dept. of Pharmacology, Medical College of Virginia, USA  
Dr G. Feussner, Drug & Chemical Evaluation Section, US Drug Enforcement Administration  
Dr J. Roache, Mental Sciences Institute, Houston, USA

## BENZODIAZEPINES

### 1. PREVIOUS REVIEW

Until 1994, most of the benzodiazepines were placed in Schedule IV. At its 29th meeting, the ECDD recommended the re-scheduling of flunitrazepam to Schedule III, and recommended pre-review of alprazolam and diazepam. However, the ECDD was of the opinion, at its 30th meeting in 1996, that it would be preferable to consider benzodiazepines as a class. On this basis, the 1996 ECDD recommended a pre-review of several benzodiazepines for the next meeting, including alprazolam, bromazepam, chlordiazepoxide, diazepam, temazepam, and other benzodiazepines to be identified by the Secretariat in accordance with certain criteria - increases in abuse, illicit trafficking or criminal activity involving the drug.

### 2. DIFFERENTIAL SCHEDULING OF BARBITURATES

Internationally, most of the benzodiazepines on the market have been placed in Schedule IV. Flunitrazepam is the only benzodiazepine which has been re-scheduled to Schedule III. Some benzodiazepines are uncontrolled, as well as non-benzodiazepines which are pharmacologically similar to benzodiazepines, such as zopiclone and zolpidem. In accordance with the scheduling criteria, this differentiation is to be based on whether the abuse liability (likelihood of abuse) of the substance in question constitutes a "substantial risk", "significant risk" or a smaller risk to public health. The scheduling criteria in use are discussed in more detail in document PND/ECDD31/3.

In the absence of concrete criteria for differentiating a "substantial" risk from a "significant" risk, the assessment by the ECDD would have to be guided by past scheduling decisions. In view of the pharmacological similarity, the best example would be the differential scheduling of barbiturates in the original schedules of the Convention adopted in 1971. There, barbiturates were grouped into three categories. Amobarbital, cyclobarbital, pentobarbital and scobarbital were placed in Schedule III and methylphenobarbital and phenobarbital in Schedule IV, while the other barbiturates were unscheduled. Of the three barbiturates, secobarbital was rescheduled later to Schedule II for reasons of increased abuse.

Therefore, a comparison of benzodiazepines with barbiturates would provide a reasonable basis for the differential scheduling of benzodiazepines.

### 3. DIFFERENTIAL ABUSE LIABILITY OF BENZODIAZEPINES

#### 3.1 Assessment of Abuse Liability

Methods to assess the abuse liability of sedative drugs, including barbiturates and benzodiazepines, have been well established and are described elsewhere (Roache and Griffiths, 1989; deWit and Griffiths, 1991; Roache and Meisch, 1991; Griffiths and

Weerts, 1997). The likelihood of drug abuse involves many factors including social-cultural as well as pharmacological variables. The data utilized to assess likelihood of abuse include experimental studies of the behavioural effects of benzodiazepines in humans and animals, critical review of epidemiological data on the prevalence of benzodiazepine abuse, and systematic clinical assessment of the incidence or extent of the current abuse problem.

### 3.2 Data Sources for Differential Abuse Liability Assessment

There are several sources of data that contribute to an abuse liability assessment as described below.

#### **Pharmacological Profile**

Pharmacokinetic data identify which compounds have rapid onset and/or short durations, which are characteristics shared by most drugs of abuse. Dosage formulation plays a key role here as shown by the experience with temazepam (Ruben and Morrison, 1992; Griffiths and Weerts, 1997). Intravenous drug abuse with temazepam was a substantial problem when it was first formulated as a soft capsule permitting the extraction of an injectable liquid. However, reformulation of the product into a hard capsule reduced the prevalence of its intravenous abuse. Based on recent experimental findings there is good evidence to suggest that a slow-onset, sustained release form of diazepam (de Wit et al, 1993) and alprazolam (Mumford et al., 1995a) would reduce their abuse potentials if the dosage forms could be made resistant to tampering which could bypass the delayed release mechanisms. Pharmacodynamic data demonstrating differential receptor subtype binding or partial agonist profiles may be a basis for observed differences in abuse liability. Both human and animal research has shown that abecarnil, a beta-carboline whose actions are mediated at the benzodiazepine receptor, has little to no abuse potential (Sannerud et al., 1992; Mumford et al., 1995b), presumably because it is a partial and/or selective agonist at the benzodiazepine receptor. Zolpidem is an imidazopyridine having agonist selectivity for the Type I (omega) benzodiazepine receptor. Although this drug exhibits a differential receptor binding profile and can be behaviourally distinguished from other benzodiazepines, it does not clearly show a reduced abuse potential in comparison to triazolam (Evans et al., 1990; Griffiths et al., 1992). Whereas pharmacological variables undoubtedly account for most of the observed differences among individual benzodiazepine receptor ligands, chemical and biochemical data alone do not provide sufficient information for differential scheduling decisions. Rather, these data predict or explain differences that must be observed behaviourally as described below.

#### **Preclinical Data on Abuse Potential**

The reinforcing effects of a drug are probably the most essential aspect of drug action that predicts a likelihood of abuse. Thus far, most of the benzodiazepines studied have been shown to maintain self-administration behaviour and thus exert reinforcing effects predicting some potential for abuse (Griffiths and Weerts, 1997; Weerts et al.,

1998; Woods et al., 1987, 1992). Procedures for distinguishing quantitative differences in reinforcing effects among individual drugs are technically difficult (Roache and Meisch, 1991, 1995) and have not been well-studied for the benzodiazepines as a class. This makes it difficult to determine whether there are meaningful differences amongst individual agents (Woods et al., 1992; Woods and Winger, 1997).

Physical dependence can also be assessed in the animal laboratory where controlled dosing regimens have clearly shown that most benzodiazepine receptor ligands possess the capacity to produce physical dependence and withdrawal (Woods et al., 1987, 1992). The differences, where they exist, relate to reduced dependence potential for partial agonists and more rapid onset of withdrawal symptoms for quickly eliminated compounds. Whereas physical dependence potential rightfully is considered in abuse liability assessment, it should be noted that physical dependence, in and of itself, is neither necessary nor sufficient for the maintenance of self-administration or drug abuse behaviour (Roache and Meisch, 1991, 1995).

These preclinical data sources are extremely important to abuse liability assessment because they use reasonably valid experimental models to systematically investigate pharmacological variables to an extent not possible in humans. However, there are species differences in pharmacodynamic and behavioural parameters and it is not always possible to directly extrapolate animal findings to humans. To the extent that preclinical data sources support and amplify human and clinical observations, then these data are invaluable aids to abuse liability assessment. However, when contradictory findings exist, then greater weight should be given to the human data source. For example, rodent data suggested that zolpidem would have a lesser abuse potential than other benzodiazepines; however, baboon (Griffiths et al., 1992) and human (Evans et al., 1990) studies did not support a difference between this and other benzodiazepine hypnotics (Lobo and Greene, 1997).

### **Human Laboratory and Experimental Assessments**

Experimental and laboratory methods for benzodiazepine abuse potential assessment in humans have been established (Roache and Griffiths, 1989; de Wit and Griffiths, 1991; Griffiths and Weerts, 1997) including self-administration procedures to directly assess reinforcing effects (Spiga and Roache, 1997). Using self-administration procedures, benzodiazepines have been shown to function as reinforcers for drug abusers and for social drinkers of alcohol (Evans et al., 1996; Griffiths and Weerts, 1997). However, these procedures are not sufficiently developed to provide much quantitative differentiation of individual drugs (Roache and Meisch, 1995). The best evidence for differential reinforcing effects is seen in comparisons of diazepam and oxazepam (Roache and Griffiths, 1989; Griffiths and Weerts, 1997) wherein diazepam has been shown to be more reinforcing. Behavioural questionnaire ratings by drug abusers can also be used to predict and quantify the likelihood of abuse. Self-rated subjective mood, euphoria, drug liking, and drug preference have been used in human laboratory abuse liability assessment (Roache and Griffiths, 1989; Griffiths and Wolf, 1990). More recent studies have permitted drug abusers to receive the consequence of

their choices between drugs and designated amounts of money (Griffiths et al., 1996). To the extent that their choice for drugs ultimately involves a probability that the drug will be received, they appear to reflect drug reinforcement processes (Spiga and Roache, 1997). Such procedures have demonstrated the reduced abuse liability of the partial/selective agonists abecarnil and pazinaclone relative to classic benzodiazepine agonists (Mumford et al., 1995b, 1995c).

The self-reports of street drug experience among drug abusers, patients, and clinicians treating substance abusers also adds important data on differences in the abuse liability of benzodiazepines. Using this methodology, a study has demonstrated that diazepam's abuse liability is comparable to that of pentobarbital, which is significantly higher than that of oxazepam and phenobarbital (Griffiths and Wolf, 1990). Extensive data from subjective mood ratings, drug liking, and self-reported drug preference have consistently identified rapid onset benzodiazepines such as diazepam to have a greater abuse liability than slower onset benzodiazepines such as oxazepam. Finally, many human laboratory studies have provided data on the adverse effects of benzodiazepines in terms of performance impairment (Hindmarch, 1990; Griffiths and Weerts, 1997; Rush et al., 1998; Woods et al., 1992). These data suggest there may be differences amongst individual agents. In particular, triazolam has often been reported to have a greater amnestic potential. However, more recent, systematic comparisons have questioned this assertion (Rothschild, 1992; Rush et al., 1998; Lobo and Greene, 1997).

Human laboratory research with subjects with histories of drug abuse provides one of the best data sources for abuse liability assessment because the findings have a direct relevance to the behaviour of the target population. This is especially true when drug abusers are asked about their drug preferences in a confidential and non-threatening environment where double-blind, placebo-controlled designs are employed. Thus, human laboratory procedures provide a unique combination of experimental assessment and etiological validity. Consequently, these data should have a great influence on regulatory decisions especially when they are consistent with pre-existing preclinical and pharmacological profile data. If there are conflicts between various data sources, greater weight may be given to the human laboratory data except where flaws in the research design could lead to erroneous conclusions.

### **Community Surveys and Case Records Data**

The final type of data that are important to abuse liability assessment are statistics estimating the prevalence, incidence, and actual records of drug abuse. In fact, laboratory tests, whether in animals or humans, produce data on abuse potential rather than abuse liability, because these tests can only measure substance-dependent properties. In contrast, data from statistically-valid random population samples or community-based surveys often involve record reviews of drug abuse cases from hospital, public health, or law enforcement agencies. The data representing instances of benzodiazepine abuse are most meaningfully interpreted by relating the abuse frequency counts with estimates of drug availability based upon prescription drug audits or sales data. General population surveys often note that the frequency of

benzodiazepine abuse is relatively rare compared to their widespread use (Griffiths and Weerts, 1997; Woods et al., 1987, 1992). However, the prevalence of benzodiazepine abuse is much higher in selected community samples of specific populations such as surveys of methadone maintenance patients. Many of these databases do not provide data on individual benzodiazepines. However, when estimates of the frequency of abuse of individual agents are adjusted for their prescription frequency, then differences among benzodiazepines can emerge (Griffiths and Wolf, 1990; Woods and Winger, 1997; Bergman and Griffiths, 1986). Case records of abuse provide the most definitive documentation of an actual abuse episode. These data include law enforcement arrest or diversion reports, hospital or medical examiner records of drug overdose, or even clinical case reports of abusing patients. However, there is no valid way to estimate population prevalence from case reports which certainly undercount the actual prevalence of abuse. Survey and case record data (see Griffiths and Weerts, 1997; Woods and Winger, 1997; Woods et al., 1992) clearly show that selected benzodiazepines have been abused more frequently than others; among those are diazepam, flunitrazepam, and injectable temazepam.

It is suggested that statistically-valid survey data provide the best data on abuse liability, or estimates of actual prevalence of drug abuse, while incident or case reports provide the most definitive evidence that a real problem exists. However, it should be recognized that the reasons for a particular episode of abuse may have less to do with the pharmacology of the drug than with cultural or historical factors. In comparison to the other data sources, we believe that positive evidence of abuse on epidemiological and incidence report measures provides the strongest basis for tighter regulatory control of identified agents; even in the absence of experimental data predicting that abuse. However, the lack of drug abuse prevalence studies or case reports could be a consequence of non-pharmacological factors and does not necessarily indicate a low abuse potential. Therefore, in the absence positive indices of actual abuse, we believe the experimental data derived from animal and especially human studies provide the strongest scientific basis for regulatory decisions.

### 3.3 Summary of Conclusions for Differences in the Likelihood of Abuse

Based on a review of the current literature from the above-specified databases certain conclusions can be drawn regarding the differential abuse liability of selected individual benzodiazepines.

**Flunitrazepam.** The Commission on Narcotic Drugs has placed flunitrazepam into Schedule III reflecting the judgement that it has a "substantial" risk which is quantitatively greater than the other benzodiazepine ligands which are in Schedule IV or unscheduled. We agree that flunitrazepam appears to have a greater abuse liability than a number of other benzodiazepines. Pharmacological profile data identify it as a rapid-onset, short to intermediate duration compound (Woods and Winger, 1997; Mintzer and Griffiths, 1998) all of which would predict a higher abuse liability. Preclinical data have demonstrated reinforcing effects and physical dependence potential (Woods and Winger, 1997), although it is not remarkably different from other benzodiazepine receptor agonists in these features. Human laboratory and

experimental data with flunitrazepam are relatively sparse and inconclusive (Woods and Winger, 1997) but recent studies have suggested a relatively greater abuse liability for this compound (Mintzer and Griffiths, 1998). The most compelling data are from the epidemiological and case reports showing a greater frequency of flunitrazepam use among drug abusers than most other benzodiazepines (Woods and Winger, 1997), especially after adjustment for its relative sales or prescription frequency. Worldwide, many arrest reports and clinical impressions have suggested this drug to be a particular abuse problem. Data compiled by the US Drug Enforcement Administration (DEA) show that there were a large number of encounters of flunitrazepam (i.e., seizures or undercover purchases) by law enforcement agencies in the last three years (James Tolliver, personal communication, cited in Mintzer and Griffiths, 1998). These reports are even more significant given the fact that flunitrazepam is not legally available on the US market.

**Diazepam.** Many human experimental and clinical studies have identified diazepam as having a greater abuse liability than other benzodiazepines (Roache and Griffiths, 1989; Roache and Meisch, 1995; Griffiths and Wolf, 1990; Griffiths and Weerts, 1997). This conclusion is based upon systematic research examining diazepam-induced subjective effects and self-administration (Griffiths et al., 1984), surveys of drug abusers and clinician scientists in the field (Griffiths and Wolf, 1990) and epidemiological data adjusted for prescription frequency from the United States (Tolliver, 1997; Griffiths et al., 1984) and Sweden (Bergman and Griffiths, 1986). The best-documented differences among members of the benzodiazepine class are based upon comparisons of diazepam and oxazepam (Roache and Griffiths, 1989) wherein the rapid onset characteristics of diazepam are thought to explain its greater abuse liability than the slow onset oxazepam. In comparison with barbiturates, diazepam's abuse liability is similar to pentobarbital (Schedule III) and that of oxazepam is comparable to that of phenobarbital (Schedule IV). The evidence for a high abuse liability for diazepam is greater and more complete than it is for any other benzodiazepine. There are no direct experimental comparisons between diazepam and flunitrazepam. However, abuse reports and the self-reported preferences of drug abusers (reported by Woods and Winger, 1997) suggest that abuse potential for diazepam is second only to flunitrazepam.

**Temazepam.** Temazepam does not frequently show up in U.S. surveys of drug abuse records (Woods et al., 1987, 1992). However, a few countries around the world have found evidence for temazepam abuse occurring at a higher frequency than with other benzodiazepines. Temazepam abuse has occurred primarily amongst intravenous drug abusers who were injecting temazepam as well as other injectable benzodiazepines (Strang et al., 1993, 1994; Darke et al., 1995). In part, the higher frequency of temazepam abuse in those countries appears to be related to the availability of a soft gelatin capsule formulation of temazepam which permitted extraction of the injectable liquid filling (Griffiths and Weerts, 1997). Reformulation of temazepam into a hard capsule preparation appears to have been somewhat successful at reducing the intravenous abuse of this drug in the United Kingdom (Rubin and Morrison, 1992; Strang et al., 1994).

### 3.4 Consequence of Abuse

Although benzodiazepines are widely known for their safety, they have some potential for harm. First, all benzodiazepines exert some degree of sedative and muscle relaxant effect. As a consequence, memory impairment, risk of accidents, falls and hip fractures in the elderly are potential risks associated with both short-term and long-term use of these drugs (Hindmarch, 1990; Griffiths and Weerts, 1997). Second, chronic use of benzodiazepines is well known to result in neuroadaptational changes resulting in physical dependence manifested by withdrawal symptoms upon abrupt discontinuation of chronic dosing (Woods et al., 1987; 1992). Finally, due to their reinforcing effects and physical dependence-producing effects, benzodiazepines can engender a pattern of non-therapeutic long-term, low-dose use in patients for whom they have been prescribed (Griffiths and Weerts, 1997). This appears to be a particular problem in the elderly and in chronic pain patients (Griffiths and Weerts, 1997).

Comparison within the same group indicates that benzodiazepine agonists differ in their potential to produce various adverse effects including sedation, behavioural or cognitive disturbances.

**Triazolam.** Triazolam often has been considered to have a greater adverse effect profile than other benzodiazepines. Putative problems include anterograde amnesia, induction of bizarre behavioural or psychotic-like behavioural abnormalities, as well as rebound phenomena causing early morning insomnia (Rothschild, 1992). However, the scientific basis for this has been controversial and many scientists have argued that triazolam is not fundamentally different from other short-acting hypnotics (Rothschild, 1992; Lobo and Greene, 1997). Systemic characterization of dose-response functions generally have shown that triazolam is not different from similarly-acting hypnotics (Woods, 1997; Mintzer and Griffiths, 1998; Rush et al., 1998). To the extent that bizarre or psychotic behavioural abnormalities have occurred due to chronic triazolam use, these quite likely could be explained by iatrogenic interdose-rebound phenomena which should be lessened by the short-term therapies recommended by the U.S. FDA.

**Alprazolam.** Alprazolam is a short to intermediate duration benzodiazepine anxiolytic that potentially can produce more severe withdrawal or discontinuation difficulties than slowly eliminated acting agents upon discontinuation following chronic use (Juergens, 1991; Sellers et al., 1993). There is also data suggesting that interdose rebound phenomena can perpetuate continued use and diminish therapeutic efficacy for some patients (Juergens, 1991). These phenomena lie in the realm of iatrogenic prescription dependence and appear to be characteristics found with other quickly eliminated benzodiazepine anxiolytics.

## 4. PROVISIONAL SUMMARY

A review of the literature provides sufficient data to suggest that a few individual benzodiazepines or benzodiazepine preparations have a greater abuse liability than the

other members of the same class. The strongest cases could be made that flunitrazepam, diazepam, and injectable dosage forms of temazepam have greater abuse liabilities than other benzodiazepines. Diazepam has been shown to have an abuse liability comparable to pentobarbital, which is in Schedule III of the 1971 Convention, in human studies with subjects with histories of drug abuse.

Of these three benzodiazepines, flunitrazepam has already been re-scheduled to Schedule III. In the case of temazepam, the higher abuse liability applies only to its injectable preparation, the availability and abuse of which are geographically limited at present. For this reason, it is estimated that only diazepam meets the criterion for recommending critical review, namely the availability of information that may justify its rescheduling to Schedule III of the 1971 Convention.

Existing data suggest that some other benzodiazepines, such as alprazolam and triazolam, may have greater potential to produce adverse effects than other benzodiazepines. However, the overall information available at present is not sufficient to recommend their critical review.

#### References

- Bergman, U and Griffiths, RR (1986) Relative abuse of diazepam and oxazepam: Prescription forgeries and theft/loss reports in Sweden. *Drug Alc Depend* 16:293-301.
- Darke SG, Ross JE, Hall WD (1995) Benzodiazepine use among injecting heroin users. *Medical J Australia* 162: 645-647
- de Wit, H, Dudish, S, and Ambre, J (1993) Subjective and behavioural effects of diazepam depend on its rate of onset. *Psychopharmacology* 112:324-330.
- de Wit, H and Griffiths, RR (1991) Testing the abuse liability of anxiolytic and hypnotic drugs in humans. *Drug Alc Depend* 28:83-111.
- Evans, SM, Funderburk, FR, and Griffiths, RR (1990) Zolpidem and triazolam in humans: Behavioural and subjective effects and abuse liability. *J Pharmacol Exp Ther* 255:1246-1255.
- Evans, SM, Griffiths, RR, and deWit, H (1996) Preference for diazepam, but not buspirone, in moderate drinkers. *Psychopharmacology* 123:154-163.
- Fraser, HF, and Jasinski, DR (1977) In: *Handbook of Experimental Pharmacology*, Vol 45, edited by WR Martin, pp. 589-612, Springer-Verlag, New York.
- Griffiths, RR, Lamb, RJ, Sannerud, CA, Ator, NA, and Brady, JV (1991). Self-injection of barbiturates, benzodiazepines and other sedative-anxiolytics in baboons. *Psychopharmacology*, 103:154-161.
- Griffiths RR, Lukas SE, Bradford D, Brady JV, Snell JD (1981) Self-injection of barbiturates and benzodiazepines in baboons. *Psychopharmacology* 75:101-109

- Griffiths, RR, McLeod, DR, Bigelow, GE, Liebson, IA, Roache, JD, and Nowowieski, P (1984) Comparison of diazepam and oxazepam: Preference, liking, and extent of abuse. *J Pharmacol Exp Ther* 229:501-508.
- Griffiths, RR, Rush, CR, and Puhall, KA (1996) Validation of the multiple-choice procedure for investigating drug reinforcement in humans. *Exper Clin Pharmacol* 4:97-106.
- Griffiths, RR, Sannerud, CA, Ator, NA, and Brady, JV (1992) Zolpidem behavioural pharmacology in baboons: Self-injection, discrimination, tolerance, and withdrawal. *J Pharmacol Exp Ther* 260:1199-1208.
- Griffiths, RR and Weerts, EM (1997) Benzodiazepine self-administration in humans and laboratory animals - implications for problems of long-term use and abuse. *Psychopharmacology* 134:1-37.
- Griffiths, RR and Wolf, B (1990) Relative abuse liability of different benzodiazepines in drug abusers. *J Clin Psychopharmacol* 10:237-243.
- Hindmarch, I (1990) Human psychopharmacological differences between benzodiazepines. In: *Benzodiazepines: Current Concepts*. Hindmarch, I, Beaumont, G, Brandon, S, and Leonard, BE (eds) Chichester: John Wiley & Sons, Ltd., pp.73-93
- Juergens, S (1991) Alprazolam and diazepam: Addiction Potential. *J Subst Abuse Treatment* 8:43-51.
- Lobo BL and Greene WL (1997) Zolpidem: Distinct from triazolam? *Ann Pharmacother* 31:625-632.
- Mintzer, MZ and Griffiths, RR (1998) Flunitrazepam and triazolam: A comparison of psychomotor, cognitive, and subjective effects in sedative drug abusers. (unpublished manuscript, submitted)
- Mumford, GK, Evans, SM, Fleishaker, JC, Griffiths, RR (1995a) Alprazolam absorption kinetics affects abuse liability. *Clin Pharmacol Ther* 57:356-365.
- Mumford, GK, Rush, CR, and Griffiths, RR (1995b) Abecarnil and alprazolam in humans: Behavioural, subjective, and reinforcing effects. *J Pharmacol Exp Ther* 272:570-580.
- Mumford, GK, Rush, CR, and Griffiths, RR (1995c) Alprazolam and DN-2327 (Pazinaclone) in humans: psychomotor, memory, subjective, and reinforcing effects. *Exp Clinical Psychopharmacology* 3:39-48.
- Roache JD and Griffiths, RR (1989) Abuse liability of anxiolytics and sedative/hypnotics: Methods assessing the likelihood of abuse. In: *Testing for abuse liability of drugs in humans*. Fischman MW and Mello NK (eds), National Institute on Drug Abuse Research Monograph No. 92:123-146.

Roache, JD and Meisch, RA (1991) Drug self-administration research in drug and alcohol addiction. In: Miller, N (ed) *Comprehensive Handbook of Drug and Alcohol Addiction*. New York: Marcel Dekker, Inc. pp.625-638.

Roache, JD and Meisch, RA (1995) Findings from self-administration research on the addiction potential of benzodiazepines. *Psychiat Ann* 25:153-157.

Rothschild, AJ (1992) Disinhibition, amnestic reactions, and other adverse reactions secondary to triazolam: A review of the literature. *J Clin Psychiatr* 53:69-79.

Ruben SM and Morrison, CL (1992) Temazepam misuse in a group of injecting drug users. *Br J Addict* 87:1387-1392.

Rush, CR, Armstrong, DL, Ali, JA, and Pazzaglia, PJ (1998, in press) Benzodiazepine-receptor ligands in humans: Acute performance-impairing, subject-rated, and observer-rated effects. *J Clin Psychopharmacology*

Sannerud, CA, Ator, NA, and Griffiths, RR (1992) Behavioural pharmacology of abecarnil in baboons: Self-injection, drug discrimination, and physical dependence. *Behav Pharmacol* 3:507-516.

Sellers, EM, Ciraulo, DA, DuPont, RL, Griffiths, RR, Kosten, TR, Romach, MK, and Woody, GE (1993) Alprazolam and benzodiazepine dependence. *J Clin Psychiatr* 54:64-77.

Spiga R and Roache, JD (1997) Human drug self-administration: A review and methodological critique. In: *Drug Addiction and its Treatment: Nexus of Neuroscience and Behaviour*, Johnson, BA and Roache, JD (eds) Philadelphia: Lippencott-Raven pp.39-71.

Strang J, Griffiths P, Abbey J, Gossop M (1994) Survey of use of injected benzodiazepines among drug users in Britain. *Br Med J* 308: 1082

Strang J, Seivewright N, Farrell M (1993) Oral and intravenous abuse of benzodiazepines. In: Hallström C (Ed) *Benzodiazepine Dependence*. Oxford University Press, Oxford pp 128-142

Tolliver, J. (1997) Number of benzodiazepine dosage units seized by DEA per million dosage units dispensed in the United States: Data presented at the FDA hearings on benzodiazepines, September 11, 1997, Washington D.C.

Weerts, EM, Kaminski, BJ and Griffiths, RR (1998) Stable low-rate midazolam self-injection with concurrent physical dependence under conditions of long-term continuous availability in baboons. *Psychopharmacology* 135:70-81.

Wesson, DR and Smith, DE (1977) *Barbiturates: Their Use, Misuse, and Abuse*. Human Sciences Press, New York.

Woods, JH, Katz, JL, and Winger, G (1987) Abuse liability of benzodiazepines. *Pharmacol Rev* 39:251-413.

Woods, JH, Katz, JL, and Winger, G (1992) Benzodiazepines: Use, abuse, and consequences. *Pharmacol Rev* 44:151-347.

Woods, JH and Winger, G (1997) Abuse liability of flunitrazepam. *J Clin Psychopharmacol* 17(Suppl.2):1s-57s.

## TOBACCO

### 1. PREVIOUS REVIEW

When the ECDD pre-reviewed nicotine at its 30th meeting, it did not recommend a critical review because when existing nicotine preparations were used, it was found that the blood level of nicotine did not reach a high enough level to produce the psychotropic effect the 1971 Convention is concerned with, and there was no evidence of significant abuse of such preparations. However, the ECDD recommended tobacco for pre-review because of the potential for a higher blood concentration of nicotine when tobacco is smoked, resulting in a greater liability for abuse and associated public health problems.

### 2. ISSUES FOR DISCUSSION

According to the adopted procedures, a substance is selected for critical review "when WHO has information that may justify the scheduling of a substance". This judgement would have to be based on a careful examination of not only the public health and social problems associated with tobacco, but also the nature of the existing drug control treaties, to determine whether these treaties are suitable for controlling tobacco.

### 3. APPROPRIATENESS OF EXISTING DRUG CONTROL TREATIES FOR TOBACCO CONTROL

#### 3.1 The original intention of the Conventions

Tobacco and alcohol use and abuse were prevalent at the time the drug control treaties (the 1961 Single Convention on Narcotic Drugs and the 1971 Convention on Psychotropic Substances) were drafted. The conferees who drafted the Convention on Psychotropic Substances noted that tobacco "is not suitable for the kind of controls for which the (treaties) provide.... The problem, however serious, therefore does not 'warrant' the placing of tobacco 'under international' control i.e. under the Vienna Convention. Tobacco was not considered by the 1971 Conference to be a suitable object for control by that treaty" (*Commentary on the Convention on Psychotropic Substances*. New York, United Nations, 1976, p48, para 11, hereinafter referred to as "the Commentary").

The 1971 Convention was a "new" legal instrument developed for the purpose of controlling "new" types of drugs of abuse for which the 1961 Convention was considered unsuitable. The fact that the drafters of the 1971 Convention gave some consideration to tobacco would imply that they did not think that tobacco could be controlled by the 1961 Convention. Thus, it would be fair to conclude that the drafters of the two Conventions did not have any intention to control tobacco under these Conventions.

#### 3.2 Appropriateness of the control system for tobacco control

The original intention of the Conventions may not provide absolute guidance for the interpretation of Conventions. However, a careful examination of the control system set forth by the treaties, as well as the scheduling criteria, would also support the same conclusion as explained below.

### *Control system*

Both the 1961 and the 1971 Conventions require parties to limit the manufacture, export, import, distribution and possession of the scheduled substances "to medical and scientific purposes". Moreover, substances controlled in Schedule I (e.g. substances with "very limited, if any, therapeutic usefulness") of the 1971 Convention are restricted to scientific and "very limited medical purposes".

Since smoking tobacco is neither medical nor scientific use, a total ban would be the consequence of controlling tobacco under these treaties. Unless this is the intention, these treaties are not suitable for controlling tobacco.

### *Scheduling criteria*

1961 Convention: In order to be controlled under this international treaty, substances must be similar to drugs already controlled in terms of both "ill effects" and "abuse".

Accordingly, under the current guidelines, the ECDD must determine whether the substance has morphine-like, cocaine-like, or cannabis-like effects" (*Revised Guidelines for the WHO Review of Dependence-Producing Psychoactive Substances for International Control*, WHO, Geneva, p51, hereinafter referred to as "the Guidelines"). With regard to the similarity in "ill effects", of these three groups, cannabis is closer to tobacco than the other two groups of drugs (coca alkaloids and opioids). It would, however, be difficult to establish the similarity in ill effects between tobacco and cannabis, in view of the clear pharmacological difference between the two active ingredients (nicotine and THC).

With regard to "abuse", it is clear that usual smoking of tobacco was not considered as "abuse of tobacco" at the time of adoption of this Convention. The term "abuse" was used widely to mean unusual or abnormal use or treatment of things (not only drugs but other things such as people, power or authority). While no perfect definition of "abuse" was available, it clearly excluded intended and well-known uses of things. Smoking cigarettes, like drinking beer or coffee, was the intended use of tobacco. Thus, smoking cigarettes was not considered as "abuse" of tobacco, unless there was an element of abnormality (e.g. consumption of unusually large quantities).

Since the term is not defined in the Convention itself, there may be room to change the interpretation of "abuse" in accordance with changing social norms. What was normal during the 1960s could be perceived as abnormal today. For example, smoking in aeroplanes could already be seen as an abnormal or unusual use of tobacco in some countries. Globally, however, recent changes in societal norms are not significant enough to consider usual smoking as "abuse" of tobacco.

1971 Convention: In order to be controlled under this treaty, the substance must meet the following two conditions:

(1) capacity to produce:

(a) similar "abuse" and "ill effects" to those already under control, or (b)(i) "dependence" and (ii) central nervous system stimulation or depression, resulting in hallucinations, or disturbances in motor function or thinking or behaviour or perception of mood, **and**

(2) likelihood of "abuse" so as to constitute a public health and social problem warranting the placing of the substance under international control.

With regard to the similarity criterion (1)(a), there is no natural product like tobacco in the current list of controlled psychotropic substances. In 1985, WHO recommended control of cathinone and cathine, the principle active ingredients in khat leaves, a "natural product", which in some parts of the world are chewed as part of social norms. WHO did not recommend control of Khat itself. Furthermore, none of the controlled psychotropic substances belong to the same pharmacological group as nicotine. Thus, there is no possibility of tobacco meeting the "similarity" criterion. This finding is consistent with the commentary which states "nor does (tobacco) have the capacity to produce 'similar abuse and ill effects' similar to those of a substance in a schedule of the Vienna Convention" (p48, para. 11 of the Commentary).

With respect to criterion (1)(b), half of the requirement, namely dependence-producing capacity, is adequately met. As already pointed out by the 20th ECDD in 1973, tobacco is clearly a dependence-producing substance.

It is not clear, however, the extent to which the remaining half of the requirement concerning the nature of the psychotropic effect is met. As rightly pointed out by the same ECDD, and as noted in the Commentary itself, it produces relatively little stimulation or depression of the central nervous system, or disturbances in perception, mood, thinking, behaviour or motor function. Any such psychotoxic effects produced by tobacco, even when it is used in large amounts, are dissimilar to other substances under control.

Concerning criterion (2) regarding the likelihood of abuse, the term "abuse" needs to be clarified first, as discussed earlier. Applying a general notion of "abuse" being "unusual or abnormal use", it is clear that smoking tobacco constitutes a public health problem, regardless of whether it is abused or not. This public health problem, however serious, therefore does not 'warrant' the placing of tobacco 'under international' control. Tobacco was not considered by the 1971 conference to be a suitable object for control by that treaty" (p48, para. 11 of the Commentary).

In conclusion, tobacco cannot be considered to meet the scheduling criteria of either the 1961 or the 1971 Convention.

4. PROVISIONAL SUMMARY

Smoking tobacco is dependence-producing and causes serious public health problems. However, judging from the control measures provided for, the scheduling criteria specified and the substances already under control, it is clear that the existing international drug control measures for narcotic drugs and psychotropic substances are unsuitable for controlling tobacco, a dependence-producing substance which was widely used for non-medical purposes at the time of adoption of the relevant conventions. Even though new information indicates greater health risks than previously known, tobacco would not meet the scheduling criteria under the existing international drug control conventions. Furthermore, once scheduled, total prohibition would be the only control measure applicable to tobacco, since the regulated supply of controlled substances is not allowed for non-medical and non-scientific purposes.

References

*Commentary on the Convention on Psychotropic Substances.* United Nations, New York, 1976

*Revised Guidelines for the WHO Review of Dependence-Producing Psychoactive Substances for International Control.* WHO, Geneva, 1990

## Gamma-Hydroxybutyrate (GHB)

### Substance

Chemical Name:  $\gamma$ -Hydroxybutyric acid

Group/Chemical Relatives: Gamma-aminobutyric acid (GABA) derivative  
CAS 502-85-2 (sodium salt) Sodium Oxybate

Chemical Structure:



### Previous review

GHB has not been reviewed.

### Pharmacology

Gamma-hydroxybutyrate (GHB) is a short-chain fatty acid derivative of gamma-aminobutyric acid (GABA) and is naturally found in the human brain (Bessman and Fishbein, 1963). GHB has affinity for at least two binding sites in the brain, a GHB-specific binding site and the GABAB receptor (Benavides et al., 1982; Mathivet et al., 1997). There is approximately a 1000-fold greater affinity for GHB at its specific binding site than for the GABAB receptor, where its affinity is poor with an  $K_D$  of 100 nM. GHB and its specific binding site have several properties characteristic of a neurotransmitter acting through a specific CNS receptor including endogenous synthesis, a saturable neuronal binding site with selective brain distribution, affiliation with an active transport system into plasma membrane vesicles, and whose pharmacological effects can be reversibly blocked with specific antagonists (Benavides, et al., 1982; Hechler et al., 1991; Maitre et al., 1990; Snead and Liu, 1984; Vayer et al., 1988).

GHB can affect several neurotransmitter systems. It can increase acetylcholine and 5-hydroxytryptamine levels (Giarman and Schmidt, 1963; Waldmeier and Fehr, 1978) and decrease noradrenergic concentrations (Miguez et al., 1988) in select brain areas. GHB can produce opiate-like effects and some of its effects are antagonizable by naloxone, but naloxone neither binds to the GHB-selective binding site nor does GHB bind to  $\mu$ -,  $\delta$ -, or  $\kappa$ -opioid receptors (Feigenbaum and Simantov, 1996). GHB's effects on the dopaminergic system is complex. Inhibition of dopamine release can occur resulting in an increase in dopamine concentration in the nerve terminals, which is augmented by stimulation of tyrosine hydroxylase, the rate limiting enzyme of dopamine's synthesis (reviewed, Tunnicliff 1997).

GHB has CNS depressant effects. Increasing the oral dose from 10, to 20-30, to over 50 mg/kg results in amnesia and hypotonia, progressing to somnolence, and ultimately to loss of consciousness and coma. GHB has been used as an anesthetic or anesthetic adjuvant, but its lack of analgesia and its reported ability to produce absence-like (Snead, 1988) and grand-mal (Winters and Spooner, 1965) seizure activity in laboratory animals has threatened and limited this indication. In balanced, randomized, double-blind studies in levorphanol-maintained opiate addicts, 30 mg/kg GHB produced effects causing subjects to report being "sluggish", "spaced", "carefree", and in a "good mood".

GHB has not been shown to completely produce the discriminative stimulus effects of any CNS-active agents thus far tested, at least not in a typical dose-dependent fashion. Rats trained to discriminate 200 mg/kg GHB from saline did not completely generalize their response to phencyclidine (PCP), apomorphine, morphine, LSD, chlordiazepoxide, muscimol, baclofen, or 3-aminopropane sulfonic acid (Winter 1981). Additionally, rats trained to discriminate heroin or PCP from vehicle did not generalize to GHB doses up to 300 mg/kg (Beardsley et al., 1996). In another study, 300 mg/kg GHB, but neither higher nor lower doses, generalized from a 1.0 g/kg ethanol stimulus, and GHB did not generalize from ethanol at any dose if the ethanol training dose was increased to 2.0 g/kg (Colombo et al., 1995a). When rats were trained to discriminate 300 mg/kg GHB, only 1.0 g/kg ethanol, but neither higher nor lower doses generalized from the GHB stimulus (Colombo et al., 1995b). Additionally, GHB failed to reliably produce either amphetamine-like, pentobarbital-like, triazolam-like or benzodiazepine antagonist discriminative effects in rhesus monkeys (France et al., 1998).

#### Metabolism, Pharmacokinetics

GHB is endogenously produced by the biotransformation of succinic semialdehyde via succinic semialdehyde reductase. Succinic semialdehyde is a metabolite of GABA. Metabolism of GHB in adults entails its oxidative re-conversion to succinic semialdehyde via GHB-ketoacidtranshydrogenase and subsequent entry into the Krebs cycle via succinate (Tunnicliff, 1997).

Bioavailability of GHB, estimated in rats, is no greater than 65% following oral dosing, and is likely limited by first-pass metabolism (Lettieri and Fung, 1976). Peak blood levels in humans following oral administration occur within two hours following doses up to 100 mg/kg (Hoes et al., 1980). The  $t_{1/2}$  is 27 min following a 25 mg/kg dose and increases with increases in dose accompanied by little change in  $C_{max}$  (Ferrara et al., 1992). Distribution into tissues follows a two-compartment model, with an apparent volume of distribution in the first compartment of 0.4 L/kg and in the second compartment of 0.58 L/kg (Dyer, 1991). Following doses of 75 or 100 mg/kg, GHB is undetectable in blood 8 h, and in urine, 12 h following administration (Hoes, et al., 1980).

#### Therapeutic use

General anesthetic and anesthetic adjuvant in France (Gamma-OH), Germany and the Netherlands (Somsanit) and for the treatment of alcohol dependence in Italy (Alcover). Potential indications for the treatment of narcolepsy. No medical use in the USA.

#### Geographic availability

Available as a medicine in several countries in Europe (France, Hungary, Italy, the Netherlands), Dominican Republic, New Zealand and Morocco. Also available as an "unauthorized" product for use by bodybuilders and misuse by drug abusers both in the USA and Europe. It can be produced easily from butyrolactone. Until 1990, it was sold as a food supplement in health food stores in the USA.

#### Adverse effects

There have been many reports of toxicity attributable to GHB use. Many of the signs of toxicity are consistent with a sedative-hypnotic like profile. Drowsiness, ataxia, dizziness, headache, nausea, emesis, diarrhea, coma, tonic-clonic seizure like activity, depressed respiration, bradycardia, and emergence delirium have all been reported (Chin et al., 1992; Dyer, 1991; Stephens and Basalt, 1994; Still and Ryan, 1996; Thomas et al., 1997). Symptoms typically resolve upon drug discontinuation. Chronic GAB use has also been associated with one case of Wernicke-Korsakoff syndrome (Friedman et al., 1996) as well as an ability to induce physical dependence (Galloway, et al., 1997). A fatality has been reported attributable to the presence of GHB under heroin intoxication (Ferrara et al., 1995), but fatalities solely attributable to GHB have not been reported.

#### Dependence/abuse potential

**Preclinical:** The overall preclinical profile of GHB is not consistent with a robust drug of abuse. GHB does not reliably produce the discriminative stimulus effects of representatives from several drug abuse classes including amphetamine, heroin, morphine, phencyclidine, LSD, pentobarbital, and triazolam (Beardsley et al., 1996; France et al., 1998; Winter 1981). Its ability to cross-generalize with ethanol is dose-irregular (Columbo et al., 1995a, 1995b). Additionally, in two separate studies primates failed to self-administer GHB intravenously (Beardsley et al., 1996; France et al., 1998). Oral self-administration of GHB and conditioned place preference induced by GHB, however, have been reported in rats (Colombo et al., 1995; Martellotta et al., 1997).

**Clinical:** In the USA, there have been several documented cases of GHB use for its reported euphorogenic effects (e.g., Chin et al., 1992; Galloway et al., 1997). Long-term use of GHB has also been reported to induce physical dependence with a withdrawal syndrome characterized by insomnia, anxiety and tremor resolving within 3-12 days (Galloway et al., 1997).

Actual abuse

**Abuse pattern:** Abused by bodybuilders for its alleged effect as a growth hormone releasing agent, and by young poly-drug abusers ("clubbers" and "ravers") as a depressant for its ability to produce euphoric and hallucinatory states, often in combination with amphetamine-type stimulants, in Europe and the USA. The extent of GHB abuse in Europe is not well documented but several countries (e.g. France, UK, Sweden) have reported its abuse. In the USA, approximately 500 encounters with GHB have been documented by information gathered from law enforcement, poison control centres and hospitals. There have been many overdose cases attributed to GHB abuse. In addition, 19 cases in which GHB was found in the biological fluids of deceased individuals.

Illicit traffic:

Since GHB is not yet controlled in many countries, little information is available on "illicit" activities.

Preliminary assessment

GHB has therapeutic indications in anaesthesia in several countries in Europe, and has a potential usefulness for the treatment of narcolepsy and drug abuse disorders. Although GHB gained early favour with health enthusiasts as a safe and "natural" food supplement sold in health food stores in the USA, the medical community soon became aware of overdoses and other problems caused by its abuse. GHB produces drowsiness, dizziness, nausea, visual disturbances, unconsciousness, hypotension, bradycardia, seizures, severe respiratory depression and coma, and a withdrawal syndrome has been described following discontinuation of its long-term use. Severe cases of overdose required emergency medical treatment, including intensive care. GHB is produced in illicit laboratories using a relatively simple synthesis and inexpensive starting materials. Although results from preclinical studies of GHB would not uniformly predict it to have high abuse liability, its abuse has increased in the USA and has also been reported in several European countries. GHB has evident abuse liability, which may justify its scheduling if more information about its abuse can be gathered from other countries. On this basis, the Committee recommends GHB for critical review.

### 4-Bromo-2,5-dimethoxyphenethylamine (2-CB)

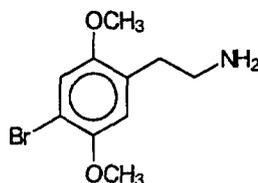
#### Substance

Known Source: small research quantities only

Chemical Name: 2-(4-bromo-2,5-dimethoxyphenyl)-1-aminoethane

Group/Chemical Relatives: substituted phenethylamine; structural analogue of 4-bromo-2,5-dimethoxyamphetamine (DOB) and 4-methyl-2,5-dimethoxyamphetamine (DOM)

Chemical Structure:



#### Previous review

4-Bromo-2,5-dimethoxyphenethylamine (2C-B) has not been reviewed by WHO

#### Metabolism, pharmacokinetics

Unknown

#### Pharmacology

4-Bromo-2,5-dimethoxyphenethylamine (4-bromo-2,5-DMPEA) displays high affinity and selectivity to central serotonin receptors. Radioligand binding assays have been conducted on the frontal cortices, striata and hippocampi of Sprague-Dawley rats. Results suggest that 4-bromo-2,5-DMPEA is a 5-HT<sub>2</sub> agonist with high affinity but less selectivity than DOB for 5-HT<sub>2</sub> receptors. The affinities of 4-bromo-2,5-DMPEA for 5-HT<sub>1A</sub>, 5-HT<sub>1B</sub>, and 5-HT<sub>1C</sub> sites were 10, 30, and 2 times that of DOB, respectively. Further, in drug discrimination studies in rats trained to discriminate either DOM or R-(-)-DOB from saline, stimulus generalization was observed in both groups of animals. 4-Bromo-2,5-DMPEA appears slightly less potent (ED<sub>50</sub> = 0.67 mg/kg) than DOM (ED<sub>50</sub> = 0.44 mg/kg) and about seven times less potent than R-(-)-DOB.

In human subjects, 4-bromo-2,5-DMPEA was found to have a threshold psychotomimetic dose of about 4 mg orally and an effective oral dose range of 8 to 10 mg. At fully effective dose, 4-bromo-2,5-DMPEA produces considerable euphoria with increased body awareness and increased receptiveness to visual, auditory, olfactory and tactile stimuli. Higher doses (20 to 40 mg) are likely to produce overt LSD-like hallucinations. Doses greater than 50 mg have produced extremely fearful hallucinations and morbid delusions.

#### Therapeutic use

4-Bromo-2,5-DMPEA has never been developed as a pharmaceutical product for medical application.

#### Adverse effects

4-Bromo-2,5-DMPEA shares important chemical and pharmacological properties with other phenethylamine hallucinogens and is likely to produce similar public health risks. Sensory distortion and impaired judgement can lead to serious consequences for both the user and the general public.

#### Dependence potential

**Preclinical:** Self administration data in baboons indicate that 4-bromo-2,5-DMPEA, like most hallucinogenic substances, is not robustly reinforcing. However, 4-bromo-2,5-DMPEA did maintain low rates of self-injection.

**Clinical:** No data available

#### Actual abuse

4-Bromo-2,5-DMPEA abuse was first reported in the United States in Louisiana in 1978. Over the next several years, it was sporadically encountered by law enforcement personnel in Pennsylvania, Iowa, Texas, California, Oregon and Arizona. Clandestine laboratories have been seized in California (1986 and 1994) and Arizona (1992). In 1993, the pattern and extent of abuse changed drastically. 4-Bromo-2,5-DMPEA, under the name of Nexus, started being supplied in kilogram quantities from a South African source. A sophisticated promotional and distribution campaign was initiated in Florida. Records seized from members of this distribution network indicated that several thousand dosage units (5 and 10 mg tablets and capsules) were distributed to individuals in 23 different states and 67 cities in the US. Promotional materials provided with the tablets and capsules claimed that this substance was "all natural" and could alleviate impotence, frigidity and diminished libido. The extensive distribution and abuse of this substance led to emergency scheduling procedures (January 1994) and final Schedule I classification (June 1995) under the US Controlled Substances Act.

4-Bromo-2,5-DMPEA has been encountered in other countries. Both Germany and Great Britain have placed this substance under control equivalent to the US Schedule I rating. In August 1993, the National Criminal Intelligence Service (NCIS) reported the seizure of 4-bromo-2,5-DMPEA clandestine laboratory in Essex, England. The Drug Analytical Services Drug Laboratories, Quebec City, Canada reported two encounters with this substance in 1993. Intelligence information reported that Nexus products containing 4-bromo-2,5-DMPEA have been shipped to Taiwan, Korea and Australia in kilogram quantities.

#### Preliminary assessment

4-Bromo-2,5-dimethoxyphenethylamine (2-CB) is a centrally active hallucinogenic substance. It is structurally and pharmacologically similar to other phenethylamine hallucinogens and has been encountered in several countries. Its ease of clandestine synthesis and its popularity as a purported sexual enhancer are likely to encourage the production and use of this substance. On this basis, it may be appropriate to conduct a critical review of 4-bromo-2,5-dimethoxy-phenethylamine.

#### References

- Glennon, RA, Kier, LB and Shulgin, AT (1979) Molecular connectivity analysis of hallucinogens. *J Pharmaceutical Sciences*. 68: 906-907.
- Glennon, RA, Titeler, M and Lyon, RA (1987) A preliminary investigation of the psychoactive agent 4-bromo-2,5-dimethoxyphenethylamine: a potential drug of abuse. *Pharmacology, Biochemistry and Behavior*. 30: 597-601.
- Gupta, SP, Bindal MC and Singh, P. (1982) Quantitative structure-activity studies on hallucinogenic mescaline analogs using modified first order valence connectivity. *Arzneim.-Forsch./ Drug Res*. 32: 1223-1225.
- Johnson, MP, Mathis, CA, Shulgin, AT, Hoffman, AJ and Nichols, DE (1990) [<sup>125</sup>I]-2-(2,5-dimethoxy-4-iodophenyl)aminoethan ([<sup>125</sup>I] 2C-I) as a label for 5HT<sub>2</sub> receptor in the rat frontal cortex. *Pharmacol Biochem Behav*. 35: 211-217.
- Kier, LB and Glennon, RA (1978) Progress with several models for study of the SRA of hallucinogenic agents. In *QuaSAR Research Monograph* 22. G Barnett, M Trsic R Willette Eds. National Institute on Drug Abuse, Washington D.C. 159-175.
- Noggle, FA, DeRuiter, J and Clark, CR (1994) Analytical profile for 4-bromo-2,5-dimethoxy-phenethylamine (Nexus) and related precursor chemicals. *Microgram*. 27: 343-355.
- Ragan, FA, Hite, SA, Samuels, MS and Garey, RE (1985) 4-Bromo-2,5-dimethoxyphenethylamine: Identification of a new street drug. *J Anal Tox*. 9: 91-93.

Sannerud, CA, Kaminski, BJ and Griffiths, RR (1996) Intravenous self-administration of four novel phenethylamine in baboons. *Behavioral Pharmacol.* 7: 315-323.

Shulgin, AT and Carter, MF (1975) Centrally active phenethylamines. *Psychopharmacol Comm.* 1: 93-98.

Shulgin, A and Shulgin, S (1991) 2C-B: 4-bromo-2,5 dimethoxyphenethylamine. *Pikal: A chemical love story.* 503-50.

## N-Methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (MBDB)

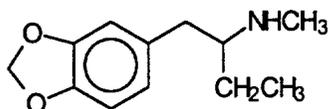
### Substance

Known Source: small research quantities only

Chemical Name: N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine; N-methyl-1-(3,4-benzodioxol-5-yl)-2-butanamine

Group/Chemical Relatives: positional isomer of MDE

Chemical Structure:



### Previous review

N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine has not been reviewed by WHO

### Metabolism, pharmacokinetics

Unknown

### Pharmacology

The psychoactive effects of N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (MBDB) have been described as different from classical hallucinogens like LSD and generally similar to the effects of MDMA.

Preclinical studies using discriminative stimulus techniques suggest that MBDB does not produce LSD-like effects in rats but both MDMA and MDA will fully substitute for MBDB.

Using rat hippocampal synaptosomes, MBDB was examined for its ability to block the reuptake of neurotransmitters into the nerve terminal (Nichols, 1986). MBDB was found to be a poor dopamine uptake inhibitor, a moderately potent norepinephrine uptake inhibitor and a potent serotonin uptake inhibitor. Comparing the  $IC_{50}$  values for uptake inhibition with other structurally similar compounds (MDA, MDMA and DOM), MBDB values were almost identical to MDMA except norepinephrine uptake inhibition was about half that of MDMA. In both compounds, the S-(+) (dextro) isomers were more potent inhibitors.

The psychoactive effects of MBDB have been described by Shulgin (1991). An oral dose of 210 mg of MBDB produces intense euphoria and considerable intoxication. Effects develop rapidly, peak at about 30 minutes and last about 4 to 6 hours. MDMA-like visual effects and stimulant-like activity were judged to be significantly less pronounced for MBDB otherwise Shulgin noted that he would have difficulty distinguishing MDMA from MBDB in a blinded test.

#### Therapeutic use

N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine has never been developed as a pharmaceutical product for medical application.

#### Adverse effects

N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine shares important chemical and pharmacological properties with MDMA and is likely to produce similar public health risks.

#### Dependence potential

Preclinical: No data available

Clinical: No data available

#### Actual abuse

As a positional isomer of MDE, MBDB is a Schedule I substance in the USA. The following seizures have been reported: forty-four capsules were seized by local police in Cape Coral, Florida in 1994; in 1996, seven tablets were seized at JFK Airport and 2 tablets were seized by US Customs in Florida in 1997. MBDB has been encountered also in Austria, Belgium, Denmark, Finland, Germany, Ireland, Italy, Spain, Thailand and the UK. However, there is no information indicating significant abuse of this substance.

#### Preliminary assessment

Although there is no information indicating significant abuse of MBDB at present, it is structurally and pharmacologically similar to MDMA. MBDB has been encountered in more than 10 countries in Europe, Asia and the USA. In view of the above, there is a likelihood of MBDB being abused so as to produce similar public health problems as MDMA. Critical review is recommended.

#### References

Nichols, DE (1986) Differences between the mechanism of MDMA, MBDB and classic hallucinogens: Identification of a new therapeutic class: Entactogens. *J Psychoactive Drugs*.

PND/ECDD31/5 (page 26)

18: 303-313

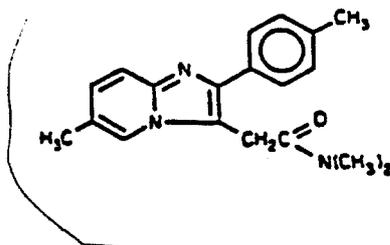
Nichols, D.E. and Oberlender, R. (1989) Structure-activity relationships of MDMA and related compounds: A new class of Psychoactive Drugs. *Ann NY Acad Sci.* 600: 613-623.

Shulgin, A and Shulgin, A (1991) *Pihkal - A Chemical Love Story*. D. Joy, Ed. Transform Press, Berkeley, California

**Zolpidem (INN)**Substance**Chemical Name:** N,N,6-Trimethyl-2-*p*-tolylimidazo[1,2- $\alpha$ ]pyridin-3-acetamide**Group/Chemical Relatives:** Imidazopyridine derivative

CAS 82626-48-0

CAS 99294-93-4 (tertarate)

**Trade Names:** Stilnox, Ambien, Somno, Sanval, Ivadal**Chemical Structure:**Previous review

Zolpidem was pre-reviewed at the 29th meeting of the ECDD, which recommended continued surveillance but did not recommend critical review.

Pharmacology

Zolpidem is a novel short-acting hypnotic launched first in France in 1988. Zolpidem possesses an imidazopyridine structure and differs from classical benzodiazepines in terms of binding profile to benzodiazepine receptors (Arbilla S., Depoortere H. and George P., 1985).

Zolpidem enhances the function of GABAergic synapses like diazepam, however, with an efficacy qualitatively and quantitatively different from that of diazepam, suggesting that zolpidem is a partial agonist at the benzodiazepine recognition site (Biggio G *et al.*, 1989).

Zolpidem has greater affinity with  $\omega_1$  sites than  $\omega_2$  sites (Dennis T *et al.*, 1988). The sedative action of zolpidem can be evidenced at a much lower recognition site occupancy rate than that needed for myorelaxant or anticonvulsant effects (Benavides J *et al.*, 1988). 20 mg zolpidem was somnogenically comparable with 0.5 mg triazolam in healthy male subjects but had milder effects on performance than triazolam (Balkin TJ *et al.*, 1992). In a double-blind study comparing the effect of 10 mg zolpidem and placebo, no significant differences were found between zolpidem and placebo in relation to sleep patterns and cardiovascular parameters (heart rate, systolic diastolic and mean blood pressures) (McCann CC *et al.*, 1993). However, a

review of the literature that compares zolpidem with triazolam concluded that zolpidem offered no distinct therapeutic advantage over triazolam for the treatment of insomnia (Lobo BL and Greene WL, 1997).

#### Metabolism, pharmacokinetics

After i.v. administration of zolpidem, the disappearance of zolpidem from plasma is biphasic in rats, with a rapid phase of 0.2 to 0.3 hours and a slower phase of 1.3 to 1.5 hours. After p.o. administration, peak plasma concentrations were reached at 15 min (first sampling time). Regardless of the route of administration, the concentrations of zolpidem in the brain were 30 to 50 per cent of those of the plasma values in the early phase. The rate of disappearance from the brain paralleled that of plasma. Metabolites of zolpidem have no significant hypnotic activity. No alteration of the sleep pattern was observed (Garrigou GD *et al.*, 1989).

#### Therapeutic use

Zolpidem is a short-acting hypnotic used to induce sleep. It is marketed in a number of countries in Europe, the Americas and elsewhere.

#### Toxicology including adverse effects in humans

The toxic response to zolpidem included respiratory depression, which was corrected by flumazenil, a benzodiazepine antagonist (Dabailleul G *et al.*, 1991).

A fatality due to ingestion of zolpidem and acepromazine, a phenothiazine sedative used in veterinary practice, was reported. Zolpidem and acepromazine blood concentrations were 3.29 and 2.40 µg/ml, respectively. It is the first report of a death involving either of these two drugs. The results suggest a reciprocal potentiation of the toxic effects of zolpidem and phenothiazines (Tracqui A, Kintz P and Mangin P, 1993).

Out of 344 cases of intentional acute overdoses, 105 cases showed signs of intoxication attributable to zolpidem. At doses of 140 - 440 mg, drowsiness occurred most frequently (N=89), but 4 cases of coma and one case of respiratory failure were also reported. Fatalities were reported for 6% but could not be directly linked to zolpidem (Garnier R *et al.*, 1994).

#### Dependence/abuse potential

**Preclinical:** In rats trained to discriminate a dose of 5 mg/kg chlordiazepoxide from saline, zolpidem failed to produce high levels of response on the chlordiazepoxide-associated level, except at a dose which greatly reduced rates of lever pressing (Sanger DJ, 1988). In mice, both tolerance and withdrawal symptoms upon discontinuation occurred after repeated administration of midazolam for 10 consecutive days, but this did not occur with zolpidem (Perrault G *et al.*, 1992). However, in baboons, zolpidem

developed tolerance, withdrawal syndromes and maintained high levels of self-injection (Griffiths RR *et al.*, 1992).

**Clinical:** Like the studies in baboons, human abuse liability studies did not show a difference between zolpidem and triazolam in experimental conditions (Evans EM, Funderburk FR and Griffiths RR, 1990). However, several authors wrote that zolpidem, being a selective (omega 1) benzodiazepine agonist, posed a smaller risk of tolerance and dependence than benzodiazepines (Schoch P *et al.*, 1993; Sanger DJ *et al.*, 1994; Plaznik A, 1995; Ohta T, 1996).

Despite such a general perception, cases of zolpidem dependence began to be reported in the literature, in the form of a letter to the editor (Unden M, 1993; Sanchez LG, Sanchez JM, Lopez-Moreno J, 1996; Chamorro-Garcia L, Martin M, de Dios-Molina J, 1996) as well as case reports. Of the three cases reported in Denmark, withdrawal symptoms and ultimately psychosis developed in two cases following cessation of zolpidem. Two cases involved dependence upon and abuse of the drugs; in one, a well known alcoholic, zolpidem was abused in combination with alcohol. The other had prior well-known dependence on sedative-hypnotics (Bruun TG, 1993). In a patient with a history of substance abuse, the observed tolerance-related event and withdrawal symptoms were comparable to those maintained by benzodiazepines (Bottlender R *et al.*, 1997). In Germany, a 75 years-old patient of chronic senile depression, who had no history of benzodiazepine or alcohol dependence, was reported to have fulfilled the criteria for zolpidem dependence (Thome J *et al.*, 1995).

Until recently, withdrawal symptoms, dependence and abuse had not been reported and zolpidem was thought to be less dependence-producing than benzodiazepines. With increasing clinical use, cases of withdrawal symptoms and dependence began to be reported under the national post-marketing surveillance programme in a few countries. Germany reported 19 cases of dependence and 11 cases of withdrawal syndromes by December 1997. In response to a WHO questionnaire, Sweden reported 9 cases of dependence and Armenia one. Switzerland informed WHO that some cases of dependence were reported but not confirmed. 16 other countries reported marketing of zolpidem with no report of dependence or abuse.

### Preliminary assessment

Although rodent data suggested that zolpidem would have a lesser abuse potential than benzodiazepines, baboon and human studies did not support a difference between this and benzodiazepine hypnotics. In general, when contradictory findings exist between animal and human studies, then greater weight should be given to the human data. Furthermore, spontaneous reports obtained through the drug safety monitoring system indicate that a few countries in Europe have encountered cases of zolpidem dependence in clinical use. Although cases of zolpidem dependence reported to date do not appear to be serious enough to justify its international control, it is noted that such reports were practically non-existent at the time of the last meeting in 1996, but have increased in number along with the increasing medical use of zolpidem

afterwards. In view of this trend, it is not unlikely that much more data that may justify the scheduling of zolpidem may become available by the time of the next meeting in 2,000. Critical review is recommended on this basis.

### References

Arbilla S, Depootere H and George P. Pharmacological profile of the imidazopyridine zolpidem at benzodiazepine receptors and electrocorticogram in rats. *Maunyn. Schmiedebergs Arch. Pharmacol.*, 1985, 330(3): 248-251

Balking TJ *et al.* Comparison of the daytime sleep and performance effects of zolpidem versus triazolam. *Psychopharmacology Berl.*, 1992, 107(1): 83-88

Benavides J *et al.* In vivo interaction of zolpidem with central benzodiazepine (BZD) binding sites (as labeled by [3H]Ro 15-1788) in the mouse brain. Preferential affinity of zolpidem for the omega 1 (BZD1) subtype. *J. Pharmacol. Exp. Ther.*, 1988, 245(3): 1033-1041

Biggio G *et al.* Enhancement of GABAergic transmission by zolpidem, and imidazopyridine with preferential affinity for type I benzodiazepine receptors. *Eur. J. Pharmacol.*, 1989, 161(2-3): 173-180

Bottlender R, Schuz C, Moller HJ, Soyka M. Zolpidem dependence in a patient with former polysubstance abuse. *Pharmacopsychiatry*, 1997, 30(3): 108

Bruun TG. [Abuse potential during use and withdrawal psychosis after treatment with the hypnotic zolpidem (Stilnoct)], *Ugeskr. Laeger*, 1993, 155(35):2711-2713

Chamorro-Garcia L, Martin M, de Dios-Molina J. [Zolpidem dependence (letter)], *Med. Clin. Barc.*, 1996, 106(12): 478-479

Debailleul G *et al.* HPLC quantification of zolpidem and prothipendyl in a voluntary intoxication. *J. Anal. Toxicol.*, 1991, 15(1): 35-37

Dennis T *et al.* Distribution of central omega 1 (benzodiazepine 1) and omega 2 (benzodiazepine 2) receptor subtypes in the monkey and human brain. An autoradiographic study with [3H]flunitrazepam and the omega 1 selective ligand [3H]zolpidem. *J. Pharmacol. Exp. Ther.*, 1988, 247(1): 309-322

Evans SM, Funderburk FR and Griffiths RR. Zolpidem and triazolam in humans: Behavioural and subjective effects and abuse liability. *J. Pharmacol. Exp. Ther.*, 1990, 255: 1246-1255

Garnier R, Guerault E, Muzard D, Azoyan P, Chaumet -Riffaud AE, Efthymiou M. Acute zolpidem poisoning - analysis of 344 cases. *J. Toxicol. Clin. Toxicol.*, 1994, 32(4): 391-404

Garrigou GD *et al.* Pharmacokinetics, brain distribution and pharmaco-electrocorticographic profile of zolpidem, a new hypnotic, in the rat. *J. Pharmacol. Exp. Ther.*, 1989, 248(3): 1283-

1288

- Lobo BL & Green WL. Zolpidem: distinct from triazolam? *Ann. Pharmacolther.*, 1997, 31(5): 625-632
- McCann CC *et al.* Effect of zolpidem during sleep on ventilation and cardiovascular variables in normal subjects. *Fundam. Clin. Pharmacol.*, 1993, 7(6): 305-310
- Ohta T. [Recent progress in development of psychotropic drugs (5) - Hypnotics], *Nihon Shinkei Seishin Yakurigaku Zassi*, 1996, 16(5): 161-170
- Perrault G *et al.* Lack of tolerance and physical dependence upon repeated treatment with the novel hypnotic zolpidem. *J. Pharmacol. Exp. Ther.*, 1992, 263(1): 298-303
- Plaznik A. Pharmacology of tolerance to benzodiazepine receptor ligands. *Pol. J. Pharmacol.*, 1995, 47(6): 489-499
- Sanger DJ. Discriminative stimulus properties of anxiolytic and sedative drugs: pharmacological specificity. *Psychopharmacol. Ser.*, 1988, 4:73-84
- Sanger DJ *et al.* Recent developments in the behavioural pharmacology of benzodiazepine (omega) receptors: evidence for the functional significance of receptor subtypes. *Neurosci. Biobehav. Rev.*, 1994, 18(3): 355-372
- Sanchez LG, Sanchez JM, Lopez-Moreno J. Dependence and tolerance with zolpidem [letter], *Am. J. Health Syst. Pharm.*, 1996, 53(21): 2638
- Schoch P *et al.* Aspects of benzodiazepine receptor structure and function with relevance to drug tolerance and dependence. *Biochem. Soc. Symp.*, 1993, 59: 121-134
- Tracqui A, Kintz P, Mangin P. A fatality involving two unusual compounds - zolpidem and acepromazine. *Am. J. Forensic Med. Pathol.*, 1993, 14(4): 309-312
- Thome J *et al.* [Zolpidem dependence and depression in the elderly], *Psychiatr. Prax.*, 1995, 22(4): 165-166
- Uden M. [Significance of the sedative zolpidem in combination with alcohol and benzodiazepines in patients with physical dependence (letter, comment)], *Ugenskr. Laeger.*, 1993, 155(51): 4194-4195