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CONTENTS

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Geneva, 17–22 April 1989

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WHO EXPERT COMMITTEE ON DRUG DEPENDENCE

Twenty-sixth Report

1. INTRODUCTION

The WHO Expert Committee on Drug Dependence met in Geneva from 17 to 22 April 1989. The meeting was opened on behalf of the Director-General by Dr Hu Ching-Li, Assistant Director-General, who drew attention to the important work of the Expert Committee in making recommendations for the international control of narcotic drugs and psychotropic substances.

Under two of the three existing international treaties for drug control, namely the Single Convention on Narcotic Drugs, 1961 (as amended by the 1972 protocol) and the Convention on Psychotropic Substances, 1971, WHO has been assigned and will continue to have the important function of recommending to the Secretary-General of the United Nations, on the basis of the evidence available to WHO, which narcotic drugs and psychotropic substances should be considered for international control at an appropriate level under one or other of the treaties.

Over the last six years, this activity has been carried out in accordance with the *Guidelines for the WHO Review of Dependence-producing Psychoactive Substances for International Control* (*1*). The sixth Programme Planning Working Group (*2*), which met early in 1989, considered that the time had come both to revise these guidelines in the light of the experience gained and to include the criteria for the selection of psychoactive substances for international control to be met when WHO initiates a notification based on the information available to it.

2. PREPARATION FOR THE MEETING AND FORMAT OF THIS REPORT

Prior to the meeting of the Expert Committee, the WHO Secretariat carried out a detailed assessment of all the drugs to be

reviewed by the Committee and compiled all the relevant information in a critical review document (*3*), which was then submitted to the Committee. An addendum to this document was subsequently prepared, based on the discussions during the sixth Programme Planning Working Group (*2*).

In response to suggestions from the United Nations Commission on Narcotic Drugs and the WHO Executive Board, the Programme Planning Working Group at its third meeting (*4*) proposed a format for the Expert Committee on Drug Dependence to use in reporting the outcome of its review of each substance. The Expert Committee used this format in its twenty-third (*5*), twenty-fourth (*6*) and twenty-fifth reports (*7*), and it has been followed again in the present one.

3. BENZODIAZEPINES

3.1 Brotizolam

3.1.1 *Substance identification*

Brotizolam (INN, CAS 57801-81-7), chemically 2-bromo-4-(*o*-chlorophenyl)-9-methyl-6*H*-thieno[3,2-*f*]triazolo-[4,3-*a*][1,4]diazepine, is also known as Lendormin, Lindormin, Ladormin and Lendorm. No stereoisomers are possible.

3.1.2 *Similarity to already known substances and effects on the central nervous system*

Brotizolam is a benzodiazepine possessing the full range of group-specific CNS-depressant effects of these compounds, so that it is an anxiolytic, anticonvulsant, sedative–hypnotic, muscle relaxant, etc. In animal experiments, brotizolam is as efficacious as diazepam in most of its pharmacological effects. Clinical studies of the hypnotic effects suggest that brotizolam is approximately 20–40 times as potent as diazepam. Brotizolam is freely soluble in chloroform and slightly soluble in water. It is rapidly absorbed and has an elimination half-life of approximately 5–10 hours in humans. Case reports of overdosage suggest qualitative similarity to diazepam.

3.1.3 *Dependence potential*

Brotizolam has been demonstrated to be reinforcing in animal studies. Drug-discrimination studies in monkeys indicated that it had pentobarbital-like effects. The subjective effects of brotizolam in humans have been found to be similar to those of nitrazepam and flurazepam. In physical-dependence studies in animals, brotizolam substituted for barbital and produced barbiturate-like withdrawal signs.

Comparative human studies on physical dependence are not available, but rebound-insomnia has been reported in sleep studies. Furthermore, a few cases of dependence/withdrawal syndrome have been reported.

3.1.4 *Actual abuse and/or abuse liability (likelihood of abuse)*

There is at present no direct evidence of actual abuse of brotizolam. The Committee noted the relatively low level of production reported and the short period of time since it was introduced into the market.

There are currently no reports of illicit trafficking or diversion of brotizolam. There are some suspicions of possible abuse, as indicated by cases of an unspecified infraction of a national drug law, an incident of theft of brotizolam and an attempted suicide.

3.1.5 *Therapeutic usefulness*

Brotizolam is currently available in 15 countries and marketed in tablet strengths of 0.125 and 0.25 mg for the treatment of sleep disturbances.

3.1.6 *Recommendation*

On the basis of the available data concerning its pharmacological profile, dependence potential and possible abuse, the Committee rated the abuse liability of brotizolam as moderate and the therapeutic usefulness as moderate to high. Few public health and social problems are currently associated with its use. Since it is planned to carry out an intensive review of the 33 benzodiazepines already scheduled, to be conducted in 1990 at the 27th meeting of the Expert Committee, and in view of the lack of clear-cut abuse and of public health and social problems associated with the substance, the

Committee was unable to come to a firm decision concerning the scheduling of brotizolam. It therefore recommended that a decision be deferred to the 27th meeting of the Expert Committee, at which brotizolam could be reviewed, together with the 33 benzodiazepines currently controlled and already on its agenda.

3.2 Etizolam

3.2.1 *Substance identification*

Etizolam (INN, CAS 40054-69-1), chemically 4-(*o*-chlorophenyl)-2-ethyl-9-methyl-6*H*-thieno[3,2-*f*]-*s*-triazolo-[4,3-*a*][1,4]diazepine, is also known as Depas, Y-7131 and AHR-3219. No stereoisomers are possible.

3.2.2 *Similarity to already known substances and effects on the central nervous system*

Etizolam is a benzodiazepine possessing the full range of group-specific CNS-depressant effects of these compounds, so that it is an anxiolytic, anticonvulsant, sedative–hypnotic, muscle relaxant, etc. Unlike diazepam, it has the imipramine-like effect of blocking norepinephrine uptake. In animal experiments, etizolam is 6–10 times more potent than diazepam in most of its pharmacological effects. Clinical studies of the hypnotic effects suggest that etizolam is approximately 10 times as potent as diazepam. It is freely soluble in chloroform but practically insoluble in water, and has an elimination half-life of approximately 6–16 hours in humans.

3.2.3 *Dependence potential*

Etizolam has been demonstrated to be reinforcing in animal studies. In physical-dependence studies in animals, it substituted for barbital and produced barbiturate-like withdrawal signs. Drug-discrimination studies in monkeys indicated that it had pentobarbital-like effects.

In clinical observations of physical dependence, one case of mild withdrawal manifestations was reported.

3.2.4 *Actual abuse and/or abuse liability (likelihood of abuse)*

There is at present no direct evidence of actual abuse of etizolam. The Committee noted the relatively limited distribution of the drug and the short period of time since it was introduced into the market.

There are currently no reports of illicit trafficking, production or diversion of etizolam. Three cases of attempted suicide have been reported in patients.

3.2.5 *Therapeutic usefulness*

Etizolam is currently in use in Japan, where it is marketed in tablet strengths of 0.5 and 1.0 mg for the treatment of anxiety disorders and some forms of sleep disturbance.

3.2.6 *Recommendation*

On the basis of the available data concerning its pharmacological profile and dependence potential, the Committee rated the abuse liability of etizolam as moderate and the therapeutic usefulness as moderate to high. Few public health and social problems are currently associated with the use of etizolam. Since it is planned to carry out an intensive review of the 33 benzodiazepines already scheduled, to be conducted in 1990 at the 27th meeting of the Expert Committee, and in view of the lack of clear-cut abuse and of public health and social problems associated with the substance, the Committee was unable to come to a firm decision concerning the scheduling of etizolam. It therefore recommended that a decision be deferred to the 27th meeting of the Expert Committee, at which etizolam could be reviewed, together with the 33 benzodiazepines currently controlled and already on its agenda.

3.3 Midazolam

3.3.1 *Substance identification*

Midazolam (INN, CAS 59467-70-8), chemically 8-chloro-6-(*o*-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]-benzodiazepine, is also known as Dormicum, Dormoniol, Hypnovel, Versed, Dormonid, and Flormidal. No stereoisomers are possible.

3.3.2 *Similarity to already known substances and effects on the central nervous system*

Midazolam is a benzodiazepine possessing the full range of group-specific CNS-depressant effects of these compounds, so that it is an anxiolytic, anticonvulsant, sedative–hypnotic, muscle relaxant, etc. In animal experiments, midazolam is as efficacious as diazepam in most of its pharmacological effects, but has a more rapid onset and shorter duration of action. Clinical studies suggest that it is twice as potent as diazepam in its sedative–hypnotic effects. Midazolam itself is insoluble in water, but its salts are soluble. It has an elimination half-life of approximately 2–2.5 hours in humans. Therapeutic use of midazolam, particularly at higher doses or in the elderly, may result in cardiopulmonary disturbances.

3.3.3 *Dependence potential*

Midazolam has been demonstrated to be reinforcing in animal studies. In physical-dependence studies in animals, it substituted for phenobarbital and produced barbiturate-like withdrawal signs.

3.3.4 *Actual abuse and/or abuse liability (likelihood of abuse)*

Abuse of midazolam, together with evidence of illicit trafficking and diversions, have been reported from a number of countries. The Committee noted reports of severe adverse cardiopulmonary effects and some deaths.

3.3.5 *Therapeutic usefulness*

Midazolam is currently available in at least 33 countries. It is marketed in the form of tablets for use in sleep disturbances and as a parenteral preparation for use as an adjunct to anaesthesia.

3.3.6 *Recommendation*

On the basis of the available data concerning its pharmacological profile, dependence potential and actual abuse, the Committee rated the abuse liability of midazolam as moderate and the therapeutic usefulness as moderate to high. Some public health and social problems are currently associated with the use of midazolam. As with all benzodiazepine agonists studied to date, it can be inferred

from the preclinical studies that midazolam is capable of producing a state of dependence in human subjects similar to that observed with diazepam. In addition, the Committee noted that the availability of the substance in an injectable form enhances the likelihood of abuse. The Committee therefore considered that midazolam is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control. In the light of this assessment, the Committee recommended the placing of the drug in Schedule IV of the Convention on Psychotropic Substances, 1971.

3.4 Quazepam

3.4.1 *Substance identification*

Quazepam (INN, CAS 36735-22-5), chemically 7-chloro-5-(*o*-fluorophenyl)-1,3-dihydro-1-(2,2,2-trifluoroethyl)-2*H*-1,4-benzodiazepine-2-thione, is also known as Oniria, Quazium, Selepam, Prosedar, Dormalin and Temodol. No stereoisomers are possible.

3.4.2 *Similarity to already known substances and effects on the central nervous system*

Quazepam is a benzodiazepine possessing the full range of group-specific, CNS-depressant effects of these compounds, so that it is an anxiolytic, anticonvulsant, sedative–hypnotic, muscle relaxant, etc. In animal experiments, quazepam is as efficacious as diazepam in most of its pharmacological effects. Clinical studies suggest that the hypnotic effects of quazepam are approximately equivalent to those of flurazepam. Quazepam is soluble in methylene chloride and hexane, but insoluble in water. It has an elimination half-life of approximately 40 hours in humans. Case reports of overdosage suggest qualitative similarity to diazepam.

3.4.3 *Dependence potential*

Quazepam has been demonstrated to be reinforcing in animal studies. In physical-dependence studies in animals, it substituted for barbital and produced barbiturate-like withdrawal signs. Drug-discrimination studies in monkeys indicated pentobarbital-like effects with quazepam. Human studies on dependence potential are not available.

3.4.4 *Actual abuse and/or abuse liability (likelihood of abuse)*

There is at present no direct evidence of actual abuse or of illicit trafficking, diversion or production of quazepam. The Committee noted the relatively short period of time since the drug was introduced into the market.

3.4.5 *Therapeutic usefulness*

Quazepam is currently available in 9 countries in 15-mg tablets for the treatment of sleep disturbances.

3.4.6 *Recommendation*

On the basis of the available data concerning its pharmacological profile and dependence potential, the Committee rated the abuse liability of quazepam as moderate and the therapeutic usefulness as moderate to high. No public health and social problems are currently associated with the use of quazepam. Since it is planned to carry out an intensive review of the 33 benzodiazepines already scheduled, to be conducted in 1990 at the 27th meeting of the Expert Committee, and in view of the lack of clear-cut abuse and of public health and social problems associated with the substance, the Committee was unable to come to a firm decision concerning the scheduling of quazepam. It therefore recommended that a decision be deferred to the 27th meeting of the Expert Committee, at which quazepam could be reviewed, together with the 33 benzodiazepines currently controlled and already on its agenda.

4. ANALOGUES OF CONTROLLED SUBSTANCES (DESIGNER DRUGS)

4.1 Fentanyl analogues

It should be noted that the compounds described in this section are chemically very similar to substances already controlled in Schedules I and IV of the Single Convention on Narcotic Drugs, 1961, as amended by the 1972 protocol. These "designer drugs" represent a potentially serious international public health problem because of their relative ease of synthesis and, in some cases, their extreme potency, which makes them effective in very small amounts.

4.1.1 Alpha-*methylthio*fentanyl

4.1.1.1 *Substance identification.* *Alpha*-methylthio*fentanyl*[1] (CAS 103963-66-2), chemically *N*-[1-[1-methyl-2-(2-thienyl)ethyl]-4-piperidyl]propionanilide, is also known as NIH 10538 and MCV 4583. There is one chiral carbon atom in the molecule, so that two stereoisomers and one racemate are possible.

4.1.1.2 *Similarity to already known substances and effects on the central nervous system.* *Alpha*-methylthio*fentanyl* has been classified pharmacologically as a relatively selective mu-type opioid-receptor agonist with a profile similar to that of fentanyl. Its analgesic potency in rodents is at least the same as that of fentanyl and 450–600 times that of morphine. Its analgesic effect has a rapid onset but a longer duration than that of fentanyl.

4.1.1.3 *Dependence potential.* *Alpha*-methylthio*fentanyl* substitutes completely for morphine in morphine-dependent withdrawn monkeys and is about 100 times more potent than morphine in this regard.

No human studies are available concerning the dependence potential of *alpha*-methylthio*fentanyl.*

4.1.1.4 *Actual abuse and/or abuse liability (likelihood of abuse).* *Alpha*-methylthio*fentanyl* is one of the fentanyl analogues that have appeared in the illicit drug traffic since late 1979. It has been identified in drug seizures in the USA by a Drug Enforcement Administration laboratory, and clandestine production has been demonstrated.

4.1.1.5 *Therapeutic usefulness.* At present, *alpha*-methylthio-*fentanyl* has no known therapeutic use.

4.1.1.6 *Recommendation.* The Committee found that there was sufficient evidence to indicate that *alpha*-methylthio*fentanyl* is liable to similar abuse to, and produces ill-effects similar to those seen with, drugs in Schedule I of the Single Convention on Narcotic Drugs, 1961, and that Convention as amended by the 1972 protocol. The Committee rated the abuse liability of the substance as high. The public health and social problems associated with the substance are

[1] In composite drug names containing both chemical prefixes and INNs, the INN is distinguished by being italicized.

extremely serious and there is no known therapeutic use. Therefore, the Committee recommended that *alpha*-methylthio*fentanyl* be controlled in Schedules I and IV of the Single Convention on Narcotic Drugs, 1961, and that Convention as amended by the 1972 protocol.

4.1.2 Para-*fluoro*fentanyl

4.1.2.1 *Substance identification.* *Para*-fluoro*fentanyl*[1] (CAS 90736-23-5), chemically 4′-fluoro-*N*-(1-phenethyl-4-piperidyl)propionanilide, is also known as NIH 10022, NIH 10491 and MCV 4323. No stereoisomers are possible.

4.1.2.2 *Similarity to already known substances and effects on the central nervous system.* *Para*-fluoro*fentanyl* has been classified pharmacologically as a relatively selective mu-type opioid-receptor agonist with a profile similar to that of fentanyl. Its analgesic potency in rodents is estimated to be 100 times that of morphine.

4.1.2.3 *Dependence potential.* *Para*-fluoro*fentanyl* substitutes completely for morphine in morphine-dependent withdrawn monkeys and is about 50–75 times more potent than morphine in this regard. No human studies are available concerning the dependence potential of *para*-fluoro*fentanyl.*

4.1.2.4 *Actual abuse and/or abuse liability (likelihood of abuse).* *Para*-fluoro*fentanyl* is one of the fentanyl analogues that have appeared in the illicit drug traffic since late 1979. It has been identified in drug seizures in the USA by a Drug Enforcement Agency laboratory, and clandestine production has been demonstrated.

4.1.2.5 *Therapeutic usefulness.* At present, *para*-fluoro*fentanyl* has no known therapeutic use.

4.1.2.6 *Recommendation.* The Committee found that there was sufficient evidence to indicate that *para*-fluoro*fentanyl* is liable to similar abuse to, and produces ill-effects similar to those seen with, drugs in Schedule I of the Single Convention on Narcotic Drugs, 1961, and that Convention as amended by the 1972 protocol. The

[1] See footnote 1, page 15.

Committee rated the abuse liability of the substance as high. The public health and social problems associated with the substance are extremely serious and there is no known therapeutic use. Therefore, the Committee recommended that *para*-fluoro*fentanyl* be controlled in Schedules I and IV of the Single Convention on Narcotic Drugs, 1961, and that Convention as amended by the 1972 protocol.

4.1.3 Beta-*hydroxy*fentanyl

4.1.3.1 *Substance identification. Beta*-hydroxy*fentanyl*[1] (CAS 78995-10-5), chemically *N*-[1-(*beta*-hydroxyphenethyl)-4-piperidyl]-propionanilide, is also known as NIH 10506 and MCV 4568. There is one chiral carbon atom in the molecule, so that two stereoisomers and one racemate are possible.

4.1.3.2 *Similarity to already known substances and effects on the central nervous system. Beta*-hydroxy*fentanyl* has been classified pharmacologically as a relatively selective mu-type opioid-receptor agonist with a profile similar to that of fentanyl. Its analgesic potency in rodents is estimated to be about 50 times that of morphine. In the rhesus monkey, *beta*-hydroxy*fentanyl* acts promptly and its duration of action (120–150 minutes) is shorter than that of morphine.

4.1.3.3 *Dependence potential. Beta*-hydroxy*fentanyl* substitutes completely for morphine in morphine-dependent withdrawn monkeys and is 50 times more potent than morphine in this regard. No human studies are available concerning the dependence potential of *beta*-hydroxy*fentanyl.*

4.1.3.4 *Actual abuse and/or abuse liability (likelihood of abuse). Beta*-hydroxy*fentanyl* is one of the fentanyl analogues that have appeared in the illicit drug traffic since late 1979. It has been identified in drug seizures in the USA by a Drug Enforcement Administration laboratory, and clandestine production has been demonstrated.

4.1.3.5 *Therapeutic usefulness.* At present, *beta*-hydroxy*fentanyl* has no known therapeutic use.

[1] See footnote 1, page 15.

4.1.3.6 *Recommendation.* The Committee found that there was sufficient evidence to indicate that *beta*-hydroxy*fentanyl* is liable to similar abuse to, and produces ill-effects similar to those seen with, drugs in Schedule I of the Single Convention on Narcotic Drugs, 1961, and that Convention as amended by the 1972 protocol. The Committee rated the abuse liability of the substance as high. The public health and social problems associated with the substance are extremely serious and there is no known therapeutic use. Therefore, the Committee recommended that *beta*-hydroxy*fentanyl* be controlled in Schedules I and IV of the Single Convention on Narcotic Drugs, 1961, and that Convention as amended by the 1972 protocol.

4.1.4 Beta-*hydroxy-3-methyl*fentanyl

4.1.4.1 *Substance identification. Beta*-hydroxy-3-methyl*fentanyl*[1] (CAS 78995-14-9), chemically *N*-[1-(*beta*-hydroxyphenethyl)-3-methyl-4-piperidyl]propionanilide, is also known as ohmefentanyl, F 7302, NIH 10551 and OMF. The molecule has three chiral centres, and eight stereoisomers and four pairs of racemates are possible.

4.1.4.2 *Similarity to already known substances and effects on the central nervous system. Beta*-hydroxy-3-methyl*fentanyl* has been classified as a relatively selective mu-type opioid-receptor agonist with a profile similar to that of fentanyl. Its analgesic potency in rodents is estimated to be 25 000 times that of morphine. The drug has a rapid onset of action and a duration of about 90 minutes. Like other mu-opioids, *beta*-hydroxy-3-methyl*fentanyl* depresses respiration but to a lesser extent than fentanyl. The respiratory depression is reversible by nalorphine.

4.1.4.3 *Dependence potential. Beta*-hydroxy-3-methyl*fentanyl* substitutes completely for morphine in morphine-dependent withdrawn monkeys and is 25 000 times more potent than morphine in this regard. No human studies are available concerning the dependence potential of *beta*-hydroxy-3-methyl*fentanyl.*

4.1.4.4 *Actual abuse and/or abuse liability (likelihood of abuse). Beta*-hydroxy-3-methyl*fentanyl* is one of the fentanyl analogues that have appeared in the illicit drug traffic since late 1979. It has been

[1] See footnote 1, page 15.

identified in drug seizures in the USA by a Drug Enforcement Administration laboratory, and clandestine production has been demonstrated.

4.1.4.5 *Therapeutic usefulness.* At present, *beta*-hydroxy-3-methyl*fentanyl* has no known therapeutic use.

4.1.4.6 *Recommendation.* The Committee found that there was sufficient evidence to indicate that *beta*-hydroxy-3-methyl*fentanyl* is liable to similar abuse to, and produces ill-effects similar to those seen with, drugs in Schedule I of the Single Convention on Narcotic Drugs, 1961, and that Convention as amended by the 1972 protocol. The Committee rated the abuse liability of the substance as high. The public health and social problems associated with the substance are extremely serious and there is no known therapeutic use. Therefore, the Committee recommended that *beta*-hydroxy-3-methyl*fentanyl* be controlled in Schedules I and IV of the Single Convention on Narcotic Drugs, 1961, and that Convention as amended by the 1972 protocol.

4.1.5 *Thio*fentanyl

4.1.5.1 *Substance identification.* Thio*fentanyl*[1] (CAS 1165-22-6), chemically *N*-[1-[2-(2-thienyl)ethyl]-4-piperidyl]propionanilide, is also known as NIH 10505 and MCV 4567. No stereoisomers are possible.

4.1.5.2 *Similarity to already known substances and effects on the central nervous system.* Thio*fentanyl* has been classified pharmacologically as a relatively selective mu-type opioid-receptor agonist with a profile similar to that of fentanyl. Its analgesic potency in rodents is estimated to be 60–100 times that of morphine.

4.1.5.3 *Dependence potential.* Thio*fentanyl* substitutes completely for morphine in morphine-dependent withdrawn monkeys and is about 60 times more potent than morphine in this regard. No human studies are available concerning the dependence potential of thio*fentanyl.*

4.1.5.4 *Actual abuse and/or abuse liability (likelihood of abuse).* Thio*fentanyl* is one of the fentanyl analogues that have appeared in

[1] See footnote 1, page 15.

the illicit drug traffic since late 1979. It has been identified in drug seizures in the USA by a Drug Enforcement Administration laboratory, and clandestine production has been demonstrated.

4.1.5.5 *Therapeutic usefulness.* At present, thio*fentanyl* has no known therapeutic use.

4.1.5.6 *Recommendation.* The Committee found that there was sufficient evidence to indicate that thio*fentanyl* is liable to similar abuse to, and produces ill-effects similar to those seen with, drugs in Schedule I of the Single Convention on Narcotic Drugs, 1961, and that Convention as amended by the 1972 protocol. The Committee rated the abuse liability of the substance as high. The public health and social problems associated with the substance are extremely serious and there is no known therapeutic use. Therefore, the Committee recommended that thio*fentanyl* be controlled in Schedules I and IV of the Single Convention on Narcotic Drugs, 1961, and that Convention as amended by the 1972 protocol.

4.1.6 *3-Methylthio*fentanyl

4.1.6.1 *Substance identification.* 3-Methylthio*fentanyl*[1] (CAS 86052-04-2), chemically *N*-[3-methyl-1-[2-(2-thienyl)ethyl]-4-piperidyl]-propionanilide, is also known as NIH 10546 and MCV 4591. There are two chiral carbon atoms in the molecule so that four stereoisomers and two racemates are possible.

4.1.6.2 *Similarity to already known substances and effects on the central nervous system.* The pharmacological profile of only one of the two racemates of 3-methylthio*fentanyl* ((±)-*cis*-3-methylthio*fentanyl*) has been examined. This racemate behaves as a relatively selective mu-type opioid-receptor agonist. In rodent analgesic tests the substance is about 1000 times more potent than morphine.

4.1.6.3 *Dependence potential.* 3-Methylthio*fentanyl* substitutes completely for morphine in morphine-dependent withdrawn monkeys and is about 1000 times more potent than morphine in this regard. No human studies are available concerning the dependence potential of 3-methylthio*fentanyl.*

[1] See footnote 1, page 15.

4.1.6.4 *Actual abuse and/or abuse liability (likelihood of abuse).* 3-Methylthio*fentanyl* is one of the fentanyl analogues that have appeared in the illicit drug traffic since late 1979. It has been identified in drug seizures in the USA by a Drug Enforcement Administration laboratory, and clandestine production has been demonstrated.

4.1.6.5 *Therapeutic usefulness.* At present, 3-methylthio*fentanyl* has no known therapeutic use.

4.1.6.6 *Recommendation.* The Committee found that there was sufficient evidence to indicate that 3-methylthio*fentanyl* is liable to similar abuse to, and produces ill-effects similar to those seen with, drugs in Schedule I of the Single Convention on Narcotic Drugs, 1961, and that Convention as amended by the 1972 protocol. The Committee rated the abuse liability of the substance as high. The public health and social problems associated with the substance are extremely serious and there is no known therapeutic use. Therefore, the Committee recommended that 3-methylthio*fentanyl* be controlled in Schedules I and IV of the Single Convention on Narcotic Drugs, 1961, and that Convention as amended by the 1972 protocol.

4.2 Analogues of tenamfetamine (MDA)

4.2.1 N-*Hydroxy*tenamfetamine

4.2.1.1 *Substance identification.* (±)-*N*-Hydroxy*tenamfetamine*[1] (CAS 74698-47-8), chemically *N*-[*alpha*-methyl-3,4-(methylenedioxy)phenethyl]hydroxylamine, is also known as *N*-hydroxy MDA, 3,4-methylenedioxy-*N*-hydroxyamphetamine, *N*-hydroxy-3,4-methylenedioxyamphetamine, *N*-OH-MDA, *N*-hydroxy-3,4-methylenedioxyphenylisopropylamine and 1-(3,4-methylenedioxyphenyl)-2-hydroxyaminopropane. There is one chiral carbon atom in the molecule so that two stereoisomers and one racemate are possible.

4.2.1.2 *Similarity to already known substances and effects on the central nervous system.* In rodent studies, (±)-*N*-hydroxy*tenamfetamine* was shown to be a psychomotor stimulant. In drug-

[1] See footnote 1, page 15.

discrimination studies in rats, the substance did not generalize to either *d*-amfetamine or (±)-1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM). In humans, it was reported to have psychotomimetic activity at relatively high doses.

4.2.1.3 *Dependence potential.* In self-administration studies in the baboon, (±)-*N*-hydroxy*tenamfetamine* was reinforcing. The substance produced an amfetamine-like pattern of intake. The laboratory that carried out these studies previously reported that (±)-*N*-methyl-*alpha*-methyl-3,4-(methylenedioxy)phenethylamine (MDMA) was self-administered by baboons in a similar experiment.

4.2.1.4 *Actual abuse and/or abuse liability (likelihood of abuse).* No data are available on actual abuse, but (±)-*N*-hydroxy*tenamfetamine* has been identified in illicit traffic in both the USA and Europe. Clandestine production has been reported.

4.2.1.5 *Therapeutic usefulness.* There is no known therapeutic use for (±)-*N*-hydroxy*tenamfetamine.*

4.2.1.6 *Recommendation.* On the basis of the data concerning its pharmacological profile, dependence potential and actual abuse, the Committee rated the likelihood of abuse of (±)-*N*-hydroxy-*tenamfetamine* as moderate. The public health and social problems associated with the substance are not serious at the present time; it has no known therapeutic use.

The Committee found that there was sufficient evidence that (±)-*N*-hydroxy*tenamfetamine* is being, or is likely to be, abused so as to constitute a public health and social problem warranting the placing of the substance under international control.

In the light of this assessment, the Committee recommended that (±)-*N*-hydroxy*tenamfetamine* be controlled under Schedule I of the Convention on Psychotropic Substances, 1971.

4.2.2 N-*Ethyl*tenamfetamine *(MDE)*

4.2.2.1 *Substance identification.* (±)-*N*-Ethyl*tenamfetamine*[1] (MDE) (CAS 14089-52-2), chemically *N*-ethyl-*alpha*-methyl-3,4-(methylenedioxy)phenethylamine, is also known as *N*-ethyl MDA, 3,4-methylenedioxy-*N*-ethylamphetamine, *N*-ethyl-3,4-methylene-

[1] See footnote 1, page 15.

dioxyamphetamine, Eve, MDEA, *N*-ethyl-3,4-methylenedioxyphenylisopropylamine, 1-(3,4-methylenedioxyphenyl)-2-ethylaminopropane and 3,4-methylenedioxyethamphetamine. There is one chiral carbon atom so that two stereoisomers and one racemate are possible.

4.2.2.2 *Similarity to already known substances and effects on the central nervous system.* (±)-*N*-Ethyl*tenamfetamine* has psychomotor stimulating properties in rodents and is neurotoxic through its damaging effects on serotonergic systems in the brain. In discrimination studies in rats, (±)-*N*-ethyl*tenamfetamine* generalizes to MDMA but not to *d*-amfetamine or DOM. Psychotomimetic effects have been observed in humans. Thus, (±)-*N*-ethyl-*tenamfetamine* has a pharmacological profile similar to that of MDMA.

4.2.2.3 *Dependence potential.* In a baboon self-administration study, (±)-*N*-ethyl*tenamfetamine* was found to have reinforcing properties. No studies are available on the dependence potential in human subjects.

4.2.2.4 *Actual abuse and/or abuse liability (likelihood of abuse).* There is evidence of abuse from the Drug Abuse Warning Network (DAWN) in the USA, and two deaths have been reported in which (±)-*N*-ethyl*tenamfetamine* was detected in body fluids, together with other drugs. The substance has been identified in drug seizures in Canada, the Federal Republic of Germany, and the USA. Clandestine production has been demonstrated. There is some evidence that (±)-*N*-ethyl*tenamfetamine* may pose a significant risk to public health owing to its neurotoxicity.

4.2.2.5 *Therapeutic usefulness.* There is no known therapeutic use for (±)-*N*-ethyl*tenamfetamine.*

4.2.2.6 *Recommendation.* On the basis of the available data concerning its pharmacological profile, dependence potential and actual abuse, the Committee rated the likelihood of abuse of (±)-*N*-ethyl*tenamfetamine* as moderate. The public health and social problems associated with the substance are extremely serious and it has no known therapeutic use.

In the light of this assessment, the Committee recommended that (±)-*N*-ethyl*tenamfetamine* be controlled under Schedule I of the Convention on Psychotropic Substances, 1971.

4.3 Analogue of aminorex

4.3.1 *4-Methyl*aminorex

4.3.1.1 *Substance identification.* 4-Methyl*aminorex*[1] (CAS 3568-94-3), chemically 2-amino-4-methyl-5-phenyl-2-oxazoline, is also known as McN-822, euphoria, U4Euh, ICE, *d,l-cis*-2-amino-4-methyl-5-phenyl-2-oxazoline, *d,l-erythro*-2-amino-4-methyl-5-phenyl-2-oxazoline, (±)-*cis*-2-amino-4-methyl-5-phenyl-2-oxazoline and (±)-*erythro*-2-amino-4-methyl-5-phenyl-2-oxazoline. There are two chiral carbon atoms so that four stereoisomers and two racemates are possible.

4.3.1.2 *Similarity to already known substances and effects on the central nervous system.* 4-Methyl*aminorex* (*cis* racemate) is a potent psychomotor stimulant. Its actions are similar to those produced by amfetamine. It stimulates spontaneous activity in mice, and has sympathomimetic and central stimulating effects in dogs. In discrimination studies in rats, it generalized to *d*-amfetamine. Its potency is about one-half that of *d*-amfetamine and it produces a lower degree of stimulation.

4.3.1.3 *Dependence potential.* In self-administration studies in rhesus monkeys, 4-methyl*aminorex* (*cis* racemate) had potent reinforcing activity. All animals self-administered the substance at rates comparable to that of cocaine. No human studies are available concerning the dependence liability of 4-methyl*aminorex* (*cis* racemate).

4.3.1.4 *Actual abuse and/or abuse liability (likelihood of abuse).* No epidemiological data on actual abuse are available but there have been individual case reports. One death has been reported in which significant blood levels of 4-methyl*aminorex* (*cis* racemate) and diazepam were found in the body. There is evidence of illicit traffic in the USA and clandestine production has been demonstrated.

[1] See footnote 1, page 15.

4.3.1.5 *Therapeutic usefulness.* There is no known therapeutic use for 4-methyl*aminorex* (*cis* racemate).

4.3.1.6 *Recommendation.* On the basis of available data concerning its pharmacological profile, dependence potential and actual abuse, the Committee rated the likelihood of abuse of 4-methyl*aminorex* (*cis* racemate) as moderate to high. The public health and social problems associated with the substance are moderately serious and it has no therapeutic use.

The Committee found that there was sufficient evidence that 4-methyl*aminorex* is currently being, or is likely to be, abused so as to constitute a public health and social problem warranting the placing of the substance under international control.

In the light of this assessment, the Committee recommended that 4-methyl*aminorex* (*cis* racemate) be controlled under Schedule I of the Convention on Psychotropic Substances, 1971.

5. DRONABINOL

On 1 December 1987, the Government of the United States of America sent a notification to the Secretary-General of the United Nations, pursuant to Article 2, paragraph 1, of the Convention on Psychotropic Substances, 1971, requesting the transfer of *delta*-9-tetrahydrocannabinol (*delta*-9-THC) from Schedule I to Schedule II of the Convention (*8*). The Secretary-General of the United Nations, in a note verbale (*8*), requested a recommendation by the Director-General of WHO.

The generic term *delta*-9-THC in the Convention refers to two racemates and four stereoisomers. However, both the data presented by the United States of America together with its notification and the material presented in the Critical Review concern a single stereochemical variant of *delta*-9-THC, namely dronabinol. Since little or no data exist on the racemates and other stereoisomers, and since the pharmaceutical preparation marketed in the USA contains only this particular stereochemical variant, the Expert Committee reviewed only dronabinol, and it is to this substance alone that the recommendation given below thus refers.

5.1 Substance identification

Dronabinol (CAS 1972-08-3), chemically (6a*R*,10a*R*)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]-pyran-1-ol, is also known as (6a*R-trans*)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]-pyran-1-ol, (−)-*trans-delta*-9-THC, (−)-*trans-delta*-1-tetrahydrocannabinol, and (−)-*trans-delta*-1-THC. Two trade names are known, Marinol and Deltanyne.

Two racemates and four stereochemical variants of the parent substance, *delta*-9-tetrahydrocannabinol, are possible. However, this review and recommendation apply solely to (−)-*trans-delta*-9-tetrahydrocannabinol, i.e., dronabinol.

5.2 Similarity to already known substances and effects on the central nervous system

Dronabinol is identical with the major active principle of cannabis and cannabis resin, which are listed in Schedules I and IV of the Single Convention on Narcotic Drugs, 1961. It is listed in Schedule I of the Convention on Psychotropic Substances, 1971. It produces complex effects on the central nervous system. In small doses, it produces stimulation, followed by sedation, while in high ones it produces hallucinogenic effects. The non-therapeutic effects of dronabinol may be considered as essentially identical with those of marijuana and other centrally active cannabinoids. It produces significant decreases in a number of performance measures, including those of psychomotor performance.

5.3 Dependence potential

A number of animal studies on dronabinol have been conducted to date but most of them, with the exception of one in monkeys, have failed to demonstrate any reinforcing effects. In studies of the subjective effects in humans, the substance was reported to be moderately euphorigenic. Chronically administered high doses of dronabinol apparently produce a state of physical dependence in rats. Withdrawal of dronabinol causes a disruption of operant behaviour in monkeys maintained on the drug; this does not occur until the second day of withdrawal and often lasts for over a week. This disruption of behaviour can be reversed by readministration of the drug. After abrupt discontinuation of high doses of dronabinol given for 10 days or longer, human subjects exhibited some evidence

of a withdrawal syndrome characterized by irritability, insomnia, restlessness, "hot flushes", diaphoresis, rhinorrhoea, "loose stools", hiccoughs and anorexia.

Evidence of the development of tolerance to the behavioural and cardiovascular effects of the substance has been found in human subjects. Animal studies have also confirmed a marked tolerance to the behavioural and hypothermic effects.

5.4 Actual abuse and/or abuse liability (likelihood of abuse)

Dronabinol has been available for scientific and very limited medical use under close supervision for more than 15 years. The pharmaceutical product (a solution in sesame oil for oral use) was marketed in 1986 in the USA. A number of cases of theft and one case of "illicit purchase" have been reported. One attempt to synthesize the substance clandestinely was reported in the United Kingdom. Data from the Drug Abuse Warning Network (DAWN) in the USA have indicated a small number of reports from emergency rooms or medical examiners. Although the actual abuse of the marketed product is very limited, dronabinol has a high abuse liability, as inferred from the abuse of cannabis and its products, with consequent public health and social hazards.

5.5 Therapeutic usefulness

Dronabinol is being used in the USA and has been approved for marketing in Canada as an antiemetic for use in cancer chemotherapy. It is effective in some cases in relieving severe nausea and vomiting refractory to the currently available antiemetics. It may make possible treatment with anti-cancer drugs in some patients who might otherwise refuse chemotherapy. When applied in selected cases as an adjunct to cancer chemotherapy, dronabinol has a moderate to high therapeutic usefulness, but has otherwise no therapeutic role. It may produce a high incidence of transient side-effects involving the central nervous system, depending on the dose used.

5.6 Recommendation

On the basis of the available data concerning its pharmacological profile, dependence potential and actual abuse, the Committee rated

the abuse liability of dronabinol as high and its therapeutic usefulness as moderate to high as an antiemetic adjunct to cancer chemotherapy in selected cases; however, it has otherwise no therapeutic role. Although few public health and social problems are currently associated with the therapeutic use of dronabinol, this substance is the active principle of cannabis and is capable of producing the same effects as the plant material. Thus, the Committee considered that dronabinol is likely to be abused so as to constitute a public health and social problem. In the light of this assessment, the Committee recommended rescheduling of the drug from Schedule I to Schedule II of the Convention on Psychotropic Substances, 1971.[1]

6. GENERAL RECOMMENDATIONS AND CONCLUSIONS

1. The Expert Committee was informed that, at times, some essential information is not provided in the documents received by WHO, which uses the format outlined in an unpublished document concerning information required for decision-making for the international control of psychoactive substances (*9*). The Committee therefore recommended that the quality of the data should be improved by further specifying and clarifying the types of information to be collected on individual substances in respect of the following:

(*a*) *Solubility*. This is an important factor in possible diversion of a substance for use by the parenteral route. Solubility data are therefore important in deciding whether a substance needs to be placed under control.

(*b*) *General pharmacology*. The information needed under this heading includes a comparison of the substance's pharmacodynamic profile with those of prototypic substances that are already scheduled, the potency ratio based on a comparison with these substances, and the efficacy of the substance in terms of its maximum effect.

[1] Two members of the Committee, Professor M. Mubbashar and Professor G. Lagier, took a different view and felt that a decision on the recommendation should be deferred until further convincing data are available concerning the therapeutic usefulness of dronabinol. Moreover, they considered that the recommendation might be misinterpreted and promote the abuse of cannabis and its extracts.

(*c*) *Toxicity*. Many of the results obtained in preclinical safety studies may not be relevant to an assessment of the extent of abuse-related public health and social problems. Instead, what is required is information on the acute toxicity and on toxic manifestations and organ toxicity at the dose regimen that might be involved when the substance is abused.

(*d*) *Clinical documents*. Information on human pharmacodynamic effects, overdose manifestations, and pharmacokinetics, and particularly on the rate of onset and duration of the effects, is very important in assessing abuse liability and the extent of possible abuse-related public health problems. These human observations are also of particular importance for the validation of the preclinical data. When additional comparative data on prototypic drugs are available, they should also be included in the material supplied to WHO.

(*e*) *Dependence potential*. Data on the dependence potential in animals and humans are essential in assessing the abuse liability of a substance under review. The data should include the reinforcing properties in animals and, if available, in humans, the drug discriminative properties in animals, and the subjective effects in healthy volunteers with or without a previous history of abuse. Data on withdrawal observations in patients and abusers, together with the dose regimen under which the observations were made, are also indispensable.

(*f*) *Epidemiology of use and abuse*. In the assessment of the abuse of a substance, the availability of information on any actual abuse is very important. This may consist of both direct and indirect evidence of abuse, the latter including Drug Abuse Warning Network data, and data on seizures, attempted suicides and abuse-related deaths. Criminal use should also be considered when data on it are available. These data can be obtained not only from epidemiological studies but also from clinical case reports of dependence or abuse.

Such information is also indispensable in assessing the seriousness of the abuse-related public health and social problems. When epidemiological data are available, it is particularly important that a brief description should be given of the methods used in the study, together with an indication of the size of the study population.

(*g*) *Nature and magnitude of public health and social problems*. The magnitude of the abuse-related public health and social problems forms part of WHO's assessment, based on the data provided by a

number of related organizations. When public health and social problems do exist, it is sometimes difficult to decide whether they are associated with abuse or not. The degree of reliability of the information should therefore be indicated.

(*h*) *Therapeutic usefulness.* Data on therapeutic usefulness, as required for the assessment of psychotropic substances under the 1971 Convention, are important in reaching a decision on a particular drug. In this connection, it is not sufficient merely to mention the number of countries where the drug in question is on the market. The provision of comparative data on drugs belonging to the same therapeutic group would make it possible to evaluate its advantages, if any, in relation to those drugs.

2. The Expert Committee noted that the application of consistent guidelines and evaluation criteria had brought to light certain difficulties in the acquisition of systematic and consistent preclinical data from animal studies, especially on specific psychotropic substances giving rise to important public health and social problems. The Committee was informed that generating such data by means of studies conducted in established complex testing systems would require either the voluntary participation of collaborating testing laboratories or arranging for these laboratories to carry out the necessary studies under contract.

The Committee recommended that WHO should explore both methods of ensuring timely and consistent evaluation of problem drugs. In this respect, it was suggested that WHO should seek the support of the United Nations Commission on Narcotic Drugs in February 1990, since the issue may affect future scheduling processes and decisions.

3. The Committee recognized that, in addition to assessing the benefit/risk ratio of psychoactive substances with dependence liability, it was also important to encourage doctors, pharmacists, nurses and primary health care personnel to become familiar with the rational use of psychoactive drugs. In this context, the Committee appreciated the recent WHO publication on psychoactive drugs (*10*) and recommended that the number of languages into which it is translated should be increased so as to ensure its wider circulation. The Committee also recommended that WHO should continue providing technical assistance to national activities in this area.

4. While recommending midazolam for scheduling under Schedule IV of the Convention on Psychotropic Substances, 1971, the Committee noted the scarcity of information on the abuse of brotizolam, etizolam and quazepam. Therefore, the Committee considered it appropriate to defer a decision on the scheduling of these three substances. However, in view of the planned review of the 33 benzodiazepines already scheduled, to be conducted at the 27th meeting of the Expert Committee in 1990, the Committee recommended that midazolam, as well as brotizolam, etizolam and quazepam, be included in that review.

The Committee noted that benzodiazepines are often marketed primarily either as anxiolytics or as hypnotics. In view of certain differences in pharmacokinetics, metabolism, etc., the Committee recommended that, in addition to diazepam, other benzodiazepine reference substances—e.g., triazolam, flunitrazepam, etc.—should be selected so as to reflect relevant pharmacological differences.

5. The Expert Committee urged WHO and other United Nations agencies with responsibilities in the international control of narcotic drugs and psychotropic substances to assist national authorities in their efforts to implement and interpret the Conventions.

6. The Committee recommended that WHO should consider collecting information on the way that scheduling is currently being interpreted in developing countries and the extent to which this affects the availability of phenobarbital for the medical treatment of convulsive disorders, and should recommend ways of dealing with any difficulties in this respect in a report to the Commission on Narcotic Drugs.

7. The Committee commended WHO for its positive response to the International Conference on Drug Abuse and Illicit Trafficking (ICDAIT). The Organization's document *Controlling Psychoactive Substance Abuse* (*11*) presents an excellent and ambitious plan that will require cooperation among many United Nations, governmental and nongovernmental agencies. The Committee urged all these bodies to assist in implementing the plan.

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[1] WHO unpublished documents prefixed "DMP" and "MNH": a limited number of copies may be available to interested persons from the Division of Drug Management and Policies, World Health Organization, 1211 Geneva 27, Switzerland.