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### Commission on Narcotic Drugs

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**Implementation of the international drug control treaties:  
changes in the scope of control of substances**

### Changes in the scope of control of substances

#### Report of the Secretary-General

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## I. Consideration of notifications recommending scheduling under the Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol

### Inclusion of dihydroetorphine and remifentanil in Schedule I

1. Pursuant to article 3, paragraphs 1 and 3 (iii), of the Single Convention on Narcotic Drugs of 1961,<sup>1</sup> and of that Convention as amended by the 1972 Protocol,<sup>2</sup> the Director-General of the World Health Organization (WHO) notified the Secretary-General, by a note dated 30 September 1998, that WHO was of the opinion that two substances, 7,8-dihydro-7-*a*-[1-(*R*)-hydroxy-1-methylbutyl]-6,14-*endo*-ethanotetrahydrooripavine (also known as dihydroetorphine) and 1-(2-methoxycarbonyl-

ethyl)-4-(phenylpropionylamino)-piperidine-4-carboxylic acid methyl ester (also known as remifentanil), should be included in Schedule I of that Convention. The text of those notifications, as well as the substantiating evidence in support of the recommendations contained in the report of the thirty-first session of the WHO Expert Committee on Drug Dependence, held from 23 to 26 June 1998, which reviewed the two substances, *inter alia*, for possible international control, are reproduced in annex I to the present document.

2. In accordance with the provisions of article 3, paragraph 2, of the 1961 Convention, the Secretary-General transmitted to all Governments, by a note dated 11 November 1998, the texts of the notification. As at 15 February 1999, 10 Governments had responded to the note. The Governments of China, Japan, Italy, Mexico, the Netherlands, Spain, Tunisia and the United Kingdom of Great Britain and Northern Ireland concurred or had no objection to the recommendation by WHO of the inclusion of the substances known as dihydroetorphine and remifentanil in Schedule I of the 1961 Convention. The

Government of Bulgaria expressed support for the inclusion of the substance known as remifentanyl in Schedule I.

3. The notifications by the Director-General of WHO will be before the Commission on Narcotic Drugs, in accordance with article 3, paragraph 3 (iii), of the 1961 Convention. Article 3, paragraph 3 (iii), reads as follows:

“If the World Health Organization finds that the 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, it shall communicate that finding to the Commission which may, in accordance with the recommendation of the World Health Organization, decide that the substance shall be added to Schedule I or Schedule II.”

4. At the present stage, the Commission should therefore decide whether or not it wishes to include 7,8-dihydro-7-*a*-[1-(*R*)-hydroxy-1-methylbutyl]-6,14-endo-ethanotetrahydrooripavine (also known as dihydroetorphine) and that 1-(2-methoxycarbonylethyl)-4-(phenylpropionylamino)-piperidine-4-carboxylic acid methyl ester (also known as remifentanyl), in Schedule I of the 1961 Convention, as amended by the 1972 Protocol, or, if not, what other action, if any, is required.

## **II. Notifications recommending scheduling or amendment to the Schedules under the Convention on Psychotropic Substances of 1971**

### **A. The proposal of the Government of Spain to amend Schedules I and II related, in particular, to the inclusion of isomers, esters and ethers, and salts of those esters, ethers and isomers**

5. Pursuant to article 2, paragraph 1, of the Convention on Psychotropic Substances of 1971,<sup>3</sup> the Government of Spain notified the Secretary-General that it was of the opinion that Schedules I and II of the 1971 Convention should be amended to include:

(a) Isomers, except where expressly excluded, of substances listed in those Schedules, whenever the existence of such isomers was possible;

(b) Esters and ethers of substances in those Schedules, except where included in another Schedule, whenever the existence of such esters or 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 Schedule I or II and which produces pharmacological effects similar to those produced by the original substances.

6. In accordance with article 2, paragraph 2, of the 1971 Convention, the Secretary-General transmitted to all Governments, by a note verbale dated 28 May 1997, the notification received from the Government of Spain. The Secretary-General also transmitted a copy of that notification to WHO, in accordance with the provisions of article 2, paragraph 2, of the Convention, for consideration by the WHO Expert Committee on Drug Dependence at its thirty-first session, in 1998.

7. In accordance with the provisions of article 2, paragraph 4, of the 1971 Convention, WHO transmitted to the Secretary-General, by a note dated 30 September 1998, its assessments and recommendations in response to the proposal made by the Government of Spain. Those recommendations are as follows:

(a) WHO does not recommend the amendment of Schedules I and II of the 1971 Convention to extend international controls collectively to esters, ethers and analogues of controlled substances;

(b) With regard to isomers, WHO recommends that a phrase could be added for substances in Schedule I of the 1971 Convention. That phrase would read:

“The stereoisomers, unless specifically excepted, of substances in this Schedule, whenever the existence of such stereoisomers is possible within the specific chemical designation;”

(c) With regard to stereoisomers of the substances in Schedules II, III and IV of the 1971 Convention, WHO recommends that interpretation guidelines be developed by the International Narcotics Control Board in collaboration with WHO in order to eliminate the confusion arising from inconsistencies in the present nomenclature of the Schedules in the 1971 Convention.

8. In accordance with the provisions of article 2, paragraph 2, of the 1971 Convention, the Secretary-General transmitted to all Governments the assessments

and recommendations of WHO, reproduced in annex II to the present document, by a note dated 11 November 1998. In response to that note, as at 15 February 1999, 18 Governments had provided their comments on the recommendations made by WHO in response to the proposal made by the Government of Spain. The manufacture, processing, marketing, import and export of esters, ethers and analogues of substances in Schedules I and II of the 1971 Convention is banned in Bulgaria. The Governments of Bulgaria, Tunisia and Turkey expressed support for the proposal of the Government of Spain. The Governments of China, Finland, Italy, Japan and Switzerland were not in favour of the proposal and supported the recommendations of WHO concerning the proposal by the Government of Spain. The Government of China indicated that it was not desirable to extend controls collectively to the isomers, esters, ethers and analogues of psychotropic substances already listed in Schedules I and II of the 1971 Convention because they did not all have the same potential dependence property and abuse tendency. The Government of Thailand did not have any objection to extending international control collectively to isomers, esters and ethers of substances covered in the Spanish proposal, which were already under control in Thailand. The inclusion of chemical compounds resulting from the modification of substances already included in Schedules I and II should be done selectively. The Government of India indicated that there was no known abuse of isomers, ethers, esters, salts or any other substances resulting from the modifications of the chemical structure of substances included in Schedules I and II. They were not a cause of serious public health problems.

9. With regard to isomers, the Government of China supported the proposal of WHO to introduce a qualifying phrase to be added for substances in Schedule I. The phrase as amended should read (additions in italics):

“The stereoisomers, unless specifically excepted, of *psychotropic* substances in this Schedule, whenever the existence of such stereoisomers is possible within the specific chemical designation *in this Schedule*.”

The Government of the United Kingdom also supported the qualifying phrase with the words “in this Schedule” added at the end of the phrase proposed by WHO. Stereoisomers of substances in Schedule I are already controlled under the drug legislation of the United Kingdom.

10. The Government of Spain submitted the following in response to the note by the Secretary-General:

“A trend emerging in Europe, and specifically in Spain, in connection with what are termed ‘synthetic’ drugs is the regular appearance on the illicit drug market of substances already scheduled under the Convention on Psychotropic Substances of 1971, but with a modified molecular structure, a phenomenon that confronts the judicial authorities and forensic experts with a legal loophole allowing drug traffickers to go unpunished and that places the medical community in a situation of uncertainty.

“For this reason, Spain is urging the United Nations to take a decision regarding the inclusion, in the schedules of controlled substances, of any modified molecular structure of substances already under international control (various salts, different isomers, modifications involving the addition or removal of chemical radicals and, generally, any alteration whose effects are similar to those produced by the classic drugs of abuse falling within the category of ‘synthetic’ substances).

“The inclusion of this amendment submitted by Spain would provide international legal coverage for such modified substances and enable specific biomedical and forensic studies to be made of them, and would also allow the adoption of a flexible approach to the coordination of international efforts to curb the changes continually taking place in the illicit drug market in line with variations in market supply and demand.

“The measure should be a global one, in order to prevent the movement of these modified synthetic substances from countries having more soundly based legislative systems to countries whose legal regime is weaker and which are therefore more vulnerable.

“With regard to isomers, Spain wishes to urge that consideration be given to the inclusion of all types of isomerism—optical isomerism (stereoisomers), positional isomerism (the same radicals but in different positions) and so on—since this would

encompass all chemical possibilities of isomeric modification.

“Finally, Spain regards the inclusion of this amendment in the 1971 Convention as an important step since it would place the international community in an advantageous position with regard to the illicit market in synthetic substances and would make for a very rapid response time in the implementation of legal, criminological, assistance and preventive measures, which would otherwise have to await the ultimate incorporation of individual additions, with all this means in terms of human suffering and powerlessness of States.”

11. The Government of the Netherlands provided the following observations:

“Firstly, the Netherlands fully recognizes the need to maintain a viable and flexible international legal framework to counter the production of synthetic drugs, which both satisfies the need for appropriate responses to newly emerging substances that threaten public health and safety and the need for careful examination of substances so as to establish the precise level of danger that they may pose to public health and safety. The Convention on Psychotropic Substances of 1971 perfectly meets those demands. The system of scheduling individual substances is at the core of this Convention. Article 2 of the Convention, *inter alia*, prescribes that new substances should first be carefully examined by WHO and then could be added to one of four Schedules if deemed necessary. The Netherlands agrees with WHO that this system may be weakened by unconditionally scheduling analogues of scheduled substances, as suggested in the Spanish proposal. An amendment of the system in such a manner could possibly lead to an extension of Schedules I and II by literally hundreds of thousands of substances.

“After careful consideration of the proposal, the Netherlands cannot avoid the impression that the proposed amendment affects the nature and scope of the Convention itself rather than being an addition of

substances to Schedules I and II. Therefore, the Netherlands concurs with WHO that the proposal, as it stands, may contradict the scheduling procedure stipulated in article 2, paragraph 2, of the 1971 Convention. Consequently, it seems that the proposal, as it stands, constitutes a proposed amendment of the Convention, subject to article 30 of the 1971 Convention.

“Secondly, the automatic addition of all analogues of substances in Schedules I and II to Schedules I and II only would be contrary to the principle of the differentiated approach of using four schedules to reflect varying degrees of pharmacological potency, health hazards and other relevant factors. The Netherlands attaches great importance to a balanced and thorough expert opinion on health and social risks created by new substances before they are included in a schedule. As indicated above, WHO is required by the Convention to examine and evaluate each individual substance. Applying unconditional analogue scheduling would, however, substantially diminish the importance of this WHO task. In the opinion of the Netherlands, this would be a loss of expertise and negatively affect the scientific basis of the decision-making process within the Commission on Narcotic Drugs.

“Thirdly, unconditional scheduling of analogues could give rise to a number of controlled substances that would make it difficult for policy makers and law enforcement officials to concentrate on the most harmful substances. Finally, the legal and chemical construction of analogues is likely to cause interpretation difficulties in both national and international law enforcement practice and could lead to possibly diverging interpretations of the Convention in various States parties.

“In conclusion, therefore, the Netherlands is of the opinion that in regarding the amendment proposal put forward by the Government of Spain there should be clarity as to whether the amendment has been put forward in conformity with the provisions of the Convention. Secondly, further thought should be given to the implications of the proposal for the nature of the control regime as embodied in the 1971 Convention.”

12. At its thirty-first session, the WHO Expert Committee on Drug Dependence examined the proposal of the Government of Spain. The assessments and recommendations of WHO are reproduced in annex II.

13. In accordance with the provisions of article 2, paragraph 2, of the 1971 Convention, the Commission has before it the notifications from the Government of Spain and from WHO. The Commission may wish to take any action or decision with respect to this notification, pursuant to article 2, paragraph 5, of the Convention. Article 2, paragraph 5, reads as follows:

“The Commission, taking into account the communication from the World Health Organization, whose assessments shall be determinative as to medical and scientific matters, and bearing in mind the economic, social, legal, administrative and other factors it may consider relevant, may add the substance to Schedule I, II, III or IV. The Commission may seek further information from the World Health Organization or from other appropriate sources.”

At the present stage, the Commission should therefore decide whether or not it wishes, given the assessment and recommendations of WHO, to amend Schedules I and II of the 1971 Convention as per the notification of the Government of Spain or, if not, what other action, if any, is required.

### **B. Inclusion of *l*-ephedrine and the racemate *d,l*-ephedrine in Schedule IV**

14. Pursuant to article 2, paragraphs 1 and 4, of the 1971 Convention, the Director-General of WHO notified the Secretary-General, by a note dated 30 September 1998, that WHO was of the opinion that (1*R*,2*S*)-2-methylamino-1-phenylpropan-1-ol (also known as *l*-ephedrine) and the racemate (1*R*,2*SR*)-2-methylamino-1-phenylpropan-1-ol (also known as *d,l*-ephedrine) should be included in Schedule IV of that Convention.

15. In accordance with the provisions of article 2, paragraphs 1 and 4, of the 1971 Convention, the Secretary-General transmitted to all Governments, by a note dated 11 November 1998, the text of the notification. In response to that note, 18 Governments had provided, as at 15 February 1999, economic, social, legal, administrative or other factors relevant to the possible scheduling of *l*-ephedrine and the racemate. The

Governments of Bulgaria, China, Finland, India, Italy, Mexico, Spain, Thailand, Tunisia and Turkey supported or had no objection to the inclusion of *l*-ephedrine and the racemate in Schedule IV of the 1971 Convention.

16. The Government of Switzerland supported the WHO proposal, with the following reservations:

(a) As ephedrine is already subject to the control measures related to precursors, it would be necessary to remove it from Table I of the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988.<sup>4</sup> In effect, one substance should not be subject to different control regimes (in one case as a precursor and in the other as a psychotropic substance). If ephedrine continues to be listed as a precursor, difficulties of application will inevitably arise;

(b) Pharmaceutical preparations containing a concentration of ephedrine of less than 1 per cent should not be subject to control measures.

17. The Government of the United Kingdom made the following observations:

“Ephedrine is already controlled under the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988. The WHO recommendation would also bring it under the control of the Convention of Psychotropic Substances of 1971, resulting in a dual regime of controls that would impose additional burdens on the pharmaceutical industry. In view of the low level of ephedrine misuse in the United Kingdom and the potential burden that additional controls would impose on the pharmaceutical industry, we have reservation about the WHO recommendation and consider that further controls are unnecessary.”

18. The Government of the Netherlands submitted the following observations:

“WHO rightly points out that the fact that both substances are already covered by the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988 would create overlapping jurisdictions regarding ephedrine control. The substance regime under the 1971 Convention differs considerably from that of the 1988 Convention, in particular in that the 1971 Convention is much more restrictive. Including ephedrine in the 1971 schedules would thus have far-reaching consequences on licensing regimes for industrial and pharmacological

purposes. It is unclear how inclusion in the 1971 Convention would affect the implementation of the relevant provisions of the 1988 Convention.

“Moreover, the Netherlands has some doubts as to the potential value of inclusion of ephedrine in Schedule IV of the 1971 Convention, considering the broad exemption clauses applicable to Schedule IV in relation to combination products.

“In conclusion, the Netherlands would support the recommendation of WHO to let appropriate international bodies clarify the interrelationship of the 1971 and the 1988 Conventions as regards the consequences of including substances in both Conventions. Also, the Netherlands would like to have further clarification of the potential value of including *l*-ephedrine and *d,l*-ephedrine in the 1971 Convention in view of the exemption of combination products.”

19. The Government of Japan submitted the following observations:

“We support the recommendation that ephedrine be placed in Schedule IV of the Convention on Psychotropic Substances of 1971. However, pharmaceutical preparations containing no more than 10 per cent of ephedrine are licensed and widely used as antitussives and remedies for common colds without prescription (“over-the-counter drugs”). Thus we believe that these products should be exempt from certain regulations in accordance with article 3, paragraph 2, of the Convention on Psychotropic Substances in Japan.”

20. The Government of Singapore submitted the following comments:

“(a) *Legal factors*. In Singapore, preparations containing less than 1 per cent of ephedrine are exempted from licensing. These generally include herbal and health supplements. Therefore, there are substantial numbers of preparations in our local market that are not subject to control. To institute the controls suggested by WHO effectively would inevitably lead to licensing of all traders, including those dealing in herbal and health supplements;

“(b) *Economic factors*. Placing ephedrine under the Convention on Psychotropic Substances of 1971 would impose trade barriers, which could hinder the legitimate availability of ephedrine in medicinal products and health supplements. Since

some of the preparations are currently not controlled in Singapore, we are unable to estimate the number of traders who would be affected.

“(c) *Administrative factors*. Singapore would have to employ additional staff to manage the records, in order to comply effectively with more stringent requirements;

“(d) *Social factors*. Singapore is encouraging self-medication of common illnesses to reduce healthcare costs. Self-medication with ephedrine would inevitably be restricted if it were controlled as a psychotropic substance.

“We have not found any abuse of ephedrine in Singapore. In view of the implications listed in paragraph 3, we are of the opinion that ephedrine need not be placed in Schedule IV of the Convention on Psychotropic Substances of 1971.”

21. At its thirty-first session, the WHO Expert Committee on Drug Dependence reviewed the substance with a view, *inter alia*, to possible international control. The assessments and recommendations of WHO are reproduced in annex III.

22. In accordance with the provisions of article 2, paragraph 2, of the 1971 Convention, the notification from WHO is brought to the attention of the Commission on Narcotic Drugs. The Commission may wish to take any action or decision with respect to this notification, pursuant to article 2, paragraph 5, of the Convention. Article 2, paragraph 5, reads as follows:

“The Commission, taking into account the communication from the World Health Organization, whose assessments shall be determinative as to medical and scientific matters, and bearing in mind the economic, social, legal, administrative and other factors it may consider relevant, may add the substance to Schedule I, II, III or IV. The Commission may seek further information from the World Health Organization or from other appropriate sources.”

23. The Commission on Narcotic Drugs should therefore decide whether or not it wishes (1*R*,2*S*)-2-methylamino-1-phenylpropan-1-ol (also known as *l*-ephedrine) and the racemate (1*R*,2*SR*)-2-methylamino-1-phenylpropan-1-ol (also known as *d,l*-ephedrine) to be included in Schedule IV of the 1971 Convention.

*Notes*

- <sup>1</sup> United Nations, *Treaty Series*, vol. 520, No. 7515.
- <sup>2</sup> *Ibid.*, vol. 976, No. 14152.
- <sup>3</sup> *Ibid.*, vol. 1019, No. 14956.
- <sup>4</sup> *Official Records of the United Nations Conference for the Adoption of a Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, Vienna, 25 November-20 December 1988*, vol. I (United Nations publication, Sales No. E.94.XI.5).

## **Annex I**

### **Note verbale dated 30 September 1998 from the Director-General of the World Health Organization to the Secretary-General concerning dihydroetorphine and remifentanil**

The Director-General of the World Health Organization presents her compliments to the Secretary-General of the United Nations and has the honour to transmit, in accordance with article 3, paragraphs 1 and 3 (iii), of the Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol, assessments and recommendations of the World Health Organization concerning the proposed inclusion of dihydroetorphine and remifentanil in Schedule I of the Convention (see appendix).

## Appendix

### Assessments and recommendations of the World Health Organization

#### A. Dihydroetorphine

##### 1. Substance identification

1. Dihydroetorphine (CAS 14357-76-7) is chemically 7,8-dihydro-7-*a*-[1-(*R*)-hydroxy-1-methylbutyl]-6,14-*endo*-ethanotetrahydrooripavine.

##### 2. Similarity to known substances and effects on the central nervous system

2. Dihydroetorphine is chemically similar to etorphine, which is in Schedule I of the Single Convention on Narcotic Drugs of 1961.<sup>1</sup> Pharmacologically, animal studies indicate that dihydroetorphine is a highly potent analgesic, with an analgesic efficacy of 6,000 and 11,000 times as potent as morphine in mice and rabbits, respectively. In mice and rabbits, the peak analgesic effect was attained 15 minutes after subcutaneous injection of dihydroetorphine and the duration of analgesic effect lasted 60-90 minutes, which was shorter than that of morphine (120-150 minutes). Radioligand binding assay indicated that dihydroetorphine is a selective mu-type opioid-receptor agonist.

##### 3. Dependence potential

3. Animal studies indicated that dihydroetorphine possessed a strong psychological dependence potential, 5,000-10,000 times more potent than morphine in self-administration tests in rats, 500 and 100 times more potent than morphine and heroin in self-administration studies in monkeys, 8,000 and 1,000 times more potent than morphine and heroin in drug discrimination studies in rats, respectively. However, animal studies showed that the physical dependence-producing properties of dihydroetorphine were relatively low. The withdrawal syndromes caused by dihydroetorphine in mice jumping tests were weaker than morphine. In monkey withdrawal precipitation tests and abrupt withdrawal tests, withdrawal syndromes of dihydroetorphine were significantly weaker than those of morphine.

##### 4. Actual abuse and/or evidence of likelihood of abuse

4. Abuse of dihydroetorphine began soon after it was marketed in China in 1992. Although indicated as an analgesic, it was also used as an opiate withdrawal syndrome suppressing agent. Its abuse spread very quickly in the country. Epidemiological studies have shown that there were two reasons for starting to abuse dihydroetorphine—iatrogenic and social. One group of abusers began to use the drug for medical purposes but increased the doses because tolerance developed quickly, and the potent dependence-producing properties of dihydroetorphine played a dominant role in compelling the patients to start abusing the drug. Opiate abusers were another group of people who took the drug as a substitute for heroin because of its stronger psychological dependence-producing properties, cheaper price and less strict control than heroin.

## 5. Therapeutic usefulness

5. Dihydroetorphine was registered in China in December 1992 for the relief of acute severe pain. However, it is not useful as a drug for substitution treatment of opioid withdrawal because of the short duration of its action.

## 6. Recommendation

6. Dihydroetorphine is a potent mu-type opioid-receptor 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 dihydroetorphine is liable to similar abuse and productive of similar ill effects as the drugs in Schedule I of the Single Convention on Narcotic Drugs of 1961. It is therefore recommended that dihydroetorphine be placed in Schedule I of the Convention.

## B. Remifentanil

### 1. Substance identification

7. Remifentanil (CAS-132875-61-7), chemically 1-(2-methoxycarbonyl-ethyl)-4-(phenylpropionylamino)-piperidine-4-carboxylic acid methyl ester, is also known as GI 87084X. Remifentanil hydrochloride (CAS-132539-07-2) is also known as GI 87084B. There are no chiral carbon atoms in the molecule; no stereoisomers or racemates are possible.

### 2. Similarity to known substances and effects on the central nervous system

8. Remifentanil is classified as a relatively selective mu-type opioid-receptor agonist with a profile similar to fentanyl, alfentanil and sufentanil, but with an ultra-short duration of action. Comparison of potency in *in vitro* binding assays specific for the mu-type opioid receptor has demonstrated similar potencies of remifentanil and fentanyl. Remifentanil's analgesic potency was found to be similar to fentanyl, alfentanil and sufentanil in rats, mice and dogs.

9. In clinical pharmacology studies, remifentanil exhibited properties (including adverse effects) that were similar to other fentanyl analogues. The most serious adverse effects were attributable to its mu-type opioid-receptor agonist properties and included hypotension, bradycardia, muscle rigidity and respiratory depression.

### 3. Dependence potential

10. Withdrawal signs developed in rats following cessation of remifentanil administration. Remifentanil substituted for morphine in morphine-dependent withdrawn monkeys. Remifentanil was found reinforcing in self-administration studies in monkeys.

11. In opiate-experienced non-dependent human subjects, the very rapid subjective peak effects of remifentanil were not significantly different from those of fentanyl. In another study involving healthy subjects, euphoria occurred at about the same incidence for remifentanil as for fentanyl and alfentanil.

### 4. Actual abuse and/or evidence of likelihood of abuse

12. One case of remifentanil abuse and overdose by intra-nasal administration occurred during the clinical study of the drug. Remifentanil had been administered over a period

of several weeks, leading to an overdose resulting in loss of consciousness, tachycardia, depressed respiration and seizures. Following emergency room treatment, the patient recovered.

**5. Therapeutic usefulness**

13. Remifentanyl is used as an analgesic during induction and maintenance of general anaesthesia, in post-operative anaesthesia, and in monitored anaesthesia care. It has been approved for marketing in 17 countries.

**6. Recommendation**

14. Remifentanyl is a short-acting mu-type opioid-receptor agonist. Based on its pharmacological properties and dependence potential, it is estimated that remifentanyl is liable to similar abuse and productive of similar ill effects as the drugs in Schedule I of the Single Convention on Narcotic Drugs of 1961. It is therefore recommended that remifentanyl be placed in Schedule I of the Convention.

*Notes*

<sup>1</sup>United Nations, *Treaty Series*, vol. 520, No. 7515

## **Annex II**

### **Note verbale dated 28 September 1998 from the Director-General of the World Health Organization to the Secretary-General concerning the proposal of the Government of Spain**

The Director-General of the World Health Organization presents her compliments to the Secretary-General of the United Nations and has the honour to submit, in accordance with article 2, paragraph 4, of the Convention on Psychotropic Substances of 1971, assessments and recommendations of the World Health Organization, in response to his note verbale of 15 May 1997 concerning the proposal by the Government of Spain (see appendix).

## Appendix

### **Assessments and recommendations of the World Health Organization concerning the proposal of the Government of Spain**

#### **1. Outline of the proposal**

1. In 1997, the Government of Spain submitted a proposal to the Secretary-General of the United Nations to amend the Convention on Psychotropic Substances of 1971 by adding to Schedules I and II<sup>1</sup> the chemical compositions of the isomers, esters and ethers of the psychotropic substances already in those schedules, as well as any modified chemical compounds producing effects similar to those produced by the original substances (hereinafter referred to as “analogues”). The Spanish proposal also recommended the inclusion of the salts of those substances. However, the question of salts is not addressed in the section below since the salts of the substances listed in Schedules I and II are already under international control. An in-depth analysis of potential advantages and disadvantages of the proposal has led to the conclusions below.

#### **2. Assessment and recommendation**

2. With regard to the scheduling of analogues or “any modified chemical compounds producing effects similar to those produced by the original substances”, extending controls collectively to those groups of substances which are related to, but potentially pharmacologically different from, the substances in the two Schedules may contradict the scheduling procedure stipulated in article 2 of the Convention on Psychotropic Substances of 1971, which requires the World Health Organization (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. The same questions may arise concerning the scheduling of esters and ethers. 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 those substances.

3. For these reasons, it is not recommend to amend Schedules I and II of the 1971 Convention to extend international controls collectively to esters, ethers and analogues of controlled substances. It has been 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 those 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 that is not available under the 1971 Convention once analogues have been scheduled.

4. In some countries, introducing national controls for new analogues synthesized by clandestine laboratories is very difficult. Ideally, a combination of national and international controls should be developed concurrently. There is a need to expedite the critical review of substances brought to the attention of WHO by Governments.

5. With regard to isomers, a useful clarification could be provided by introducing a modified qualifying phrase in the proposal of the Government of Spain into Schedule I. The revised phrase to be added to Schedule I would read (additions in italics):

“The *stereoisomers*, unless specifically excepted, of psychotropic substances in this Schedule, whenever the existence of such *stereoisomers* is possible within the specific chemical designation in this Schedule.”

6. This renders the proposal chemically precise and consistent with the current interpretation of the Schedule. The proposal could thus provide an explicit clarification of the scope of controlled isomers, including racemates.

7. With regard to stereoisomers of the substances in Schedules II, III and IV, the confusion arising from the inconsistencies in the present nomenclature of those Schedules should be clarified by means of interpretation guidelines to be developed by an appropriate international body, such as the International Narcotics Control Board, in collaboration with WHO.

*Notes*

<sup>1</sup> United Nations, *Treaty Series*, vol. 1019, No. 14956.

### **Annex III**

#### **Note verbale dated 30 September 1998 from the Director-General of the World Health Organization to the Secretary-General concerning the proposed inclusion of ephedrine (*l*-ephedrine and the racemate) in Schedule IV of the Convention on Psychotropic Substances of 1971**

The Director-General of the World Health Organization presents her compliments to the United Nations and has the honour to transmit, in accordance with article 2, paragraphs 1 and 4, of the Convention on Psychotropic Substances of 1971, assessments and recommendations of the World Health Organization concerning the proposed inclusion of ephedrine (*l*-ephedrine and the racemate, known as *d,l*-ephedrine) in Schedule IV of the Convention (see appendix).

## Appendix

### Assessments and recommendations of the World Health Organization

#### Ephedrine

##### 1. Substance identification

1. Ephedrine (2-methylamino-1-phenylpropan-1-ol) exists in four stereoisomeric forms and two corresponding racemic mixtures. They are designated traditionally *l*-ephedrine, *d*-ephedrine and *l*-pseudoephedrine and *d*-pseudoephedrine. *l*-ephedrine, also designated (-)-ephedrine, is chemically (1*R*,2*S*)-2-methylamino-1-phenylpropan-1-ol. Racemic ephedrine, also designated as *d,l*-ephedrine or (±)-ephedrine, is chemically (1*RS*,2*SR*)-2-methylamino-1-phenylpropan-1-ol.

##### 2. Similarity to known substances and effects on the central nervous system

2. Ephedrine is chemically and pharmacologically similar to amphetamines. It is also similar to cathine, which is (+)-norpseudoephedrine. Ephedrine is both an α- and a β-adrenergic agonist and enhances the release of norepinephrine from sympathetic neurons. In general, ephedrine is viewed as being a less potent central nervous system stimulating agent but a more effective bronchodilator. Ephedrine increases motor activity and mental alertness and diminishes the sense of fatigue. Ephedrine decreases appetite and promotes weight loss.

##### 3. Dependence potential

3. In humans with histories of substance abuse, *l*-ephedrine, *d*-amphetamine (international non-proprietary name (INN): dexamphetamine), *d*-methamphetamine (INN: metamphetamine), phenmetrazine and methylphenidate injected subcutaneously produced similar increases in respiratory rate and blood pressure and similar types of subjective changes, including euphoria. The agents differed in relative potency. In general, amphetamine-like stimulants differed only in relative potencies when given orally. *l*-ephedrine was five times less potent than amphetamine in producing amphetamine-like subjective and physiologic effects in substance abusers, but was more potent than amfepramone (diethylpropion).

4. In monkeys trained to self-administer cocaine, *l*-ephedrine maintained responding rates greater than saline in substitution tests. In rats trained to discriminate cocaine from placebo, *l*-ephedrine generalized to cocaine—though at a slightly lower rate than *d*-amphetamine. Ephedrine generalized to cocaine and *d*-amphetamine in other drug discrimination studies in rats. In amphetamine-trained monkeys, an oral dose of 10 mg racemic ephedrine was discriminated as amphetamine. In monkeys trained to self-administer cocaine, *l*- and racemic ephedrine had definite reinforcing effects. *d*-ephedrine was both less efficacious and potent than the *l*-isomer in its ability to generalize to amphetamine.

#### **4. Actual abuse and/or evidence of likelihood of abuse**

5. Of the 50 countries that have returned the questionnaire to the World Health Organization (WHO), ephedrine was available for medical use in 46 countries. Of those 46 countries, the following 12 countries have indicated present or past ephedrine abuse or illicit traffic in ephedrine, presumably associated with its abuse: Belgium, Burkina Faso, China, Costa Rica, Finland, France, Germany, Ireland, Slovakia, Sudan, Thailand and United States of America. Although quantitative information is difficult to obtain, the extent of ephedrine abuse was significant enough for some Governments to implement various regulatory controls. The current problem of abuse seems to be particularly serious in certain African countries. When abuse exists, it seems to involve ephedrine single-entity products. In addition, in the United States, combination products containing ephedrine in herbal preparations have been abused.

6. The problem of ephedrine diversion was reported in the material provided by the International Narcotics Control Board, which indicated that a few countries served as major suppliers of ephedrine to other countries. Often, there is a large gap between the amount required for legitimate use and the amount imported into those countries, reflecting diversion for abuse. Some ephedrine, traded in dosage forms, is used as a precursor to synthesize methamphetamine.

#### **5. Therapeutic usefulness**

7. 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. Hypotension and shock have been treated with parenteral ephedrine through its actions producing cardiac stimulation and vasoconstriction. Less common indications include obesity, motion sickness and enuresis.

8. The commonality of ephedrine use as a medicine is indicated by the fact that 92 per cent of the countries that responded to the WHO questionnaire (46 out of 50) indicated therapeutic use of ephedrine. That figure suggests that ephedrine is used therapeutically in many countries in the world. Some of the countries have indicated a large number of pharmaceutical products containing ephedrine on the market, often as combination products.

#### **6. Recommendation**

9. On the basis of the available information concerning its pharmacological profile, dependence potential and actual abuse, the public health and social problems associated with the abuse of ephedrine are assessed to be significant. The current problem appears to be particularly serious in certain African countries. On this basis, it is recommended that *l*-ephedrine and the racemate be placed in Schedule IV of the Convention on Psychotropic Substances of 1971.<sup>1</sup> The *d*-isomer, which is significantly less potent than the *l*-isomer, need not be controlled. In making this recommendation, it is noted that ephedrine combination products would be eligible for exemption according to the 1971 Convention.

10. It is further noted that there are overlapping jurisdictions concerning the 1971 Convention and the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988,<sup>2</sup> which may make fully effective international regulation of ephedrine difficult. The interrelationship and interpretation

of the two Conventions needs clarification by appropriate international bodies, including the International Narcotics Control Board and WHO. In addition, it is recommended that those bodies develop ways to alert Member States that export pharmaceutical formulations of ephedrine to the fact that these preparations have the potential for abuse and use as a precursor.

*Notes*

<sup>1</sup>United Nations, *Treaty Series*, vol. 1019, No. 14956.

<sup>2</sup>See *Officials Records of the United Nations Conference for the Adoption of a Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, Vienna, 25 November-20 December 1988*, vol. I (United Nations publication, Sales No. E.94.XI.5).