



# WORLD HEALTH ORGANIZATION

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## Report on meetings of expert committees and study groups

### Report by the Secretariat

Submitted to the Executive Board in accordance with the  
Regulations for Expert Advisory Panels and Committees<sup>1</sup>

#### EVALUATION OF CERTAIN VETERINARY DRUG RESIDUES IN FOOD

Joint FAO/WHO Expert Committee on Food Additives  
Forty-eighth report  
Geneva, 18-27 February 1997<sup>2</sup>

#### Main recommendations

1. The Committee made recommendations on residues in food of animal origin of several veterinary drugs. The report also contains general consideration of items relating, *inter alia*, to initiatives being undertaken by the Committee to promote transparency in the process of setting maximum residue limits (MRLs), standards that should be used for the generation of data, and the public health significance of residues of veterinary drugs at the injection site.

2. The Committee evaluated two anthelmintic agents (moxidectin and tiabendazole), eight antimicrobial agents (ceftiofur, danofloxacin, dihydrostreptomycin and streptomycin, enrofloxacin, flumequine, gentamicin, and spiramycin), one glucocorticosteroid (dexamethasone), and two insecticides (cyfluthrin and fluazuron). Acceptable daily intakes (ADIs) or temporary ADIs were established either at the current or previous meetings on all of these substances. Maximum residue limits were recommended

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<sup>1</sup> 4.23 *The Director-General shall submit to the Executive Board a report on meetings of expert committees held since the previous session of the Board. It shall contain his observations on the implications of the expert committee reports and his recommendations on the follow-up action to be taken, and the texts of the recommendations of the expert committee shall be annexed. The Executive Board shall consider the report submitted by the Director-General and address its comments to it.*

<sup>2</sup> WHO Technical Report Series, No. 879, 1998.

in appropriate tissues (muscle, liver, kidney and fat), milk and/or eggs for all substances except enrofloxacin and dexamethasone.

3. WHO has also published summaries of the toxicological and related information upon which the safety assessment of the veterinary drugs was made.<sup>1</sup> FAO has published<sup>2</sup> summaries of the residue information which formed the basis for the MRLs recommended.

### **Significance for public health policies**

4. The Committee noted the complexity of the risk assessment process, which required: assembling and analysing all the relevant data; interpreting studies of carcinogenicity, mutagenicity, reproductive toxicity, teratogenicity, antimicrobial activity, and other effects; extrapolating to humans effects observed in experimental animals; and assessing risks to humans based on available toxicological, epidemiological, and microbiological data.

5. Although the problem is universal, only a few scientific institutions can undertake such assessments at this stage. It is therefore important to provide all Member States with valid information both on the general aspects of risk assessment and on the specific veterinary drugs covered in this report.

6. The recommendations of the Committee are used by the Codex Alimentarius Commission for setting international standards, including standards on residues of veterinary drugs in foods. Such standards are established only for substances that have been evaluated by the Committee and have been allocated an ADI. This ensures that food commodities in international commerce meet strict safety standards.

### **Implications for the Organization's programmes**

7. The evaluation of chemicals in food by the Committee is an ongoing activity. Four meetings of the Joint FAO/WHO Expert Committee on Food Additives are scheduled in this biennium, two on residues of veterinary drugs in food and two on food additives and contaminants.

8. WHO cooperates with and contributes to the Joint FAO/WHO Food Standards Programme, which administers the Codex Alimentarius Commission. The Committee's evaluations are required for progress with proposed standards; its evaluations are critical to the work of the Codex Alimentarius Commission.

9. Regional offices and WHO Representatives in countries use the Committee's evaluations when advising Member States on food safety regulatory programmes.

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<sup>1</sup> *Toxicological evaluation of certain veterinary drug residues in food*. WHO Food Additives Series, No. 39, 1997.

<sup>2</sup> *Residues of some veterinary drugs in animals and foods*. FAO Food and Nutrition Paper 41/10, 1998.

## **WHO EXPERT COMMITTEE ON DRUG DEPENDENCE**

### **Thirty-first report**

**Geneva, 23-26 June 1998**

### **Main recommendations**

10. For the text of recommendations, see Annex.

### **Significance for public health policies**

11. In accordance with the established procedure, the United Nations Commission on Narcotic Drugs is expected in March 1999 to review and act on the four scheduling recommendations issued by this Expert Committee. These recommendations are of considerable significance for public health policies, if adopted, since the list of narcotic drugs and psychotropic substances under international control will be updated accordingly. Also of particular significance is the recommendation to clarify the ambiguities concerning the designation and scope of controlled substances, particularly in relation to their stereoisomers, through the development of suitable guidelines in collaboration with the International Narcotics Control Board.

12. The recommendation to review and modify the guidelines formulated in 1990 is of great significance for public health policies since this would enable the international drug control system to respond quickly to problems caused by the abuse of new drugs. Its implementation requires a decision by the Executive Board, as explained in paragraph 13 below.

### **Implications for the Organization's programmes**

13. The current two-step review procedure adopted by the Executive Board in 1990<sup>1</sup> has been criticized by the United Nations as overly time-consuming. The review procedure was revised once in 1994 in Executive Board decision EB93(16) to enable the Committee to pass the first step of review whenever there was a notification from a Party to the Single Convention on Narcotic Drugs, 1961, or to the Convention on Psychotropic Substances, 1971, or an explicit request from the United Nations Commission on Narcotic Drugs. The two-step review procedure is applied in all other cases. Further simplification of this procedure, as recommended by the Committee (see Annex, paragraph 4(1)), requires a modification of decision EB93(16). Document EB103/35 contains a draft decision for consideration by the Board.

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<sup>1</sup> Revised guidelines for the WHO review of dependence-producing psychoactive substances for international control. Document EB85/1990/REC/1, Annex 7.

ANNEX

**WHO EXPERT COMMITTEE ON DRUG DEPENDENCE:  
THIRTY-FIRST REPORT<sup>1</sup>**

**23-26 June 1998**

**CONCLUSIONS AND RECOMMENDATIONS**

**1. Scheduling recommendations<sup>2</sup>**

(1) **Dihydroetorphine.**<sup>3</sup> Dihydroetorphine is a potent  $\mu$ -opioid-receptor agonist. Based on its pharmacological properties and dependence potential as demonstrated in animal studies, as well as the pattern of abuse observed in China, it is assessed that dihydroetorphine is liable to similar abuse and productive of similar ill effects as drugs in Schedule I of the 1961 Convention. It is therefore recommended that dihydroetorphine be placed in Schedule I of the 1961 Single Convention on Narcotic Drugs.

(2) **Ephedrine.** On the basis of the available information concerning the pharmacological profile, dependence potential and likelihood of abuse of ephedrine, 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. The Committee therefore recommends that *l*-ephedrine and the racemate be placed in Schedule IV of the 1971 Convention on Psychotropic Substances. The *d*-isomer is significantly less potent than the *l*-isomer. The Committee noted, in making this recommendation, that, according to the 1971 Convention, ephedrine combination products would be eligible for exemption.

The Committee also noted that there are questions of overlapping jurisdiction concerning the 1971 Convention and the 1988 Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances that may make fully effective international regulation difficult. The interrelationship and interpretation of these conventions needs clarification by appropriate international bodies including the International Narcotics Control Board and WHO. In addition, the Committee recommends that WHO and the International Narcotics Control Board develop ways to alert Member States exporting pharmaceutical formulations of ephedrine that these preparations have the potential for abuse and for use as a precursor of illicit stimulants.

(3) **Remifentanil (INN).** On the basis of its pharmacological properties and dependence potential, it is assessed that remifentanil is liable to similar abuse and productive of similar ill effects as the drugs in Schedule I of the 1961 Convention. The Committee therefore recommends that remifentanil be placed in Schedule I of the 1961 Convention.

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<sup>1</sup> The full report of the Expert Committee is in preparation for publication in the WHO Technical Report Series.

<sup>2</sup> The scheduling recommendations have been communicated to the United Nations.

<sup>3</sup> In composite drug names containing both a chemical prefix and an INN, the INN is distinguished by being italicized.

(4) **Proposal of the Government of Spain.** In 1997, the Spanish Government submitted a proposal to the Secretary-General of the United Nations to amend the 1971 Convention by adding, to Schedules I and II, the isomers, esters and ethers of psychotropic substances already in these schedules, as well as any modified chemical compounds producing effects similar to those produced by the original substances (referred to here as “analogues”). The proposal was forwarded to the Expert Committee for its recommendations. The Committee did not recommend amending Schedules I and II of the 1971 Convention to extend international control collectively to esters, ethers and analogues of controlled substances. It was noted, however, that control can be applied to criminal activities involving analogues of scheduled substances at the national level, without extending unnecessary administrative and regulatory control to such substances when used for legitimate industrial and research purposes. In one country, this was achieved by applying criminal controls only to certain specified acts involving analogues. Governments that recognize the existence of problems with analogues in their countries should consider the desirability of adopting similar selective control measures, an option not available under the 1971 Convention once analogues have been scheduled.

In some countries, introducing national-level control for new analogues synthesized by clandestine laboratories is very difficult. Ideally, a combination of national and international control measures should be developed concurrently. WHO should therefore expedite the critical review of substances brought to its attention by governments.

With regard to the scheduling of isomers, the Committee recognized a need for clarification, and agreed that this could be achieved by modifying a qualifying phrase in the proposal of the Spanish Government regarding the substances to be included in Schedule I. The phrase would read as follows (modification underlined):

*The stereoisomers, except where expressly excluded, of psychotropic substances in this Schedule whenever the existence of such stereoisomers is possible within the specific chemical nomenclature in this Schedule.*

This modification renders the proposal chemically precise and consistent with the current interpretation of the Schedules. Thus modified, the proposal would provide explicit clarification of the scope of controlled isomers, including racemates.

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

## 2. Pre-review of psychoactive substances

(1) **Benzodiazepines.** Only diazepam meets the criterion for recommending critical review, namely whether WHO has information that may justify the substance’s rescheduling to Schedule III of the 1971 Convention. In the process of review, the Committee requested that Member States specifically be asked to comment on the impact of the scheduling of benzodiazepines on their use and abuse. Certain benzodiazepines, such as alprazolam and triazolam, may have greater potential to produce adverse effects than other benzodiazepines. However, information available at present is not sufficient to recommend their critical review.

(2) **Tobacco.** Smoking tobacco is dependence-producing, causes serious public health problems and has no therapeutic use. However, judging from the control measures provided for, the scheduling criteria specified and the substances already under control, existing international drug control measures for narcotic drugs and psychotropic substances appear to be unsuitable for controlling tobacco, a dependence-producing natural substance widely used for non-medical purposes at the time of adoption of the relevant conventions. Even though new information indicates health risks greater than those previously known, tobacco would not meet the criteria for scheduling under the existing international drug control treaties. Furthermore, once scheduled, total prohibition would be the only control measure applicable to tobacco, since the regulated supply of controlled substances is not allowed for non-medical and non-scientific purposes. The international framework convention for tobacco control would appear to achieve the result anticipated by the Committee in 1996 in requesting the pre-review of tobacco. Therefore, a critical review of tobacco is not recommended.

(3) **Gamma-hydroxybutyric acid (GHB).** Although results from preclinical studies of GHB do not uniformly predict it to have a high abuse liability, abuse of GHB has increased in the United States of America and has been reported in several European countries as well. A chemical derivative, gamma-butyrolactone (GBL) is also being abused. GHB and GBL have evident abuse liability, which may justify their being scheduled if more information about their abuse can be gathered from other countries. On this basis, the Committee recommends GHB and GBL for critical review.

(4) **4-bromo-2,5-dimethoxyphenethylamine (2C-B).** 2C-B is a centrally active hallucinogenic substance. It is structurally and pharmacologically similar to other phenethylamine hallucinogens and has been encountered in several countries. Its ease of clandestine synthesis and its popularity as a purported sexual “enhancer” are likely to encourage the production and abuse of 2C-B. On this basis, critical review of 4-bromo-2,5-dimethoxyphenethylamine (2C-B) is recommended.

(5) **N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (MBDB).** Although there is no information indicating significant abuse of MBDB at present, it is structurally and pharmacologically similar to MDMA and *N*-ethyl-MDA. Incidents involving MBDB have been reported in more than 10 countries in Asia, Europe and the United States of America. In view of this, there is a likelihood of MBDB being abused so as to produce similar public health problems as those produced by MDMA. Critical review of MBDB is therefore recommended.

(6) **Zolpidem (INN).** Although data obtained in studies in rodents suggest that zolpidem would have a lower abuse potential than benzodiazepines, baboon and human studies do not support the existence of a difference in abuse potential between zolpidem and benzodiazepine hypnotics. In general, when findings in animal and human studies are contradictory, greater weight should be given to the data obtained in human studies. There have been no reports of illicit activities concerning zolpidem. Spontaneous reports obtained through the drug safety monitoring system indicate that a few countries in Europe have experienced cases of adverse effects of zolpidem in clinical use. Although the cases of zolpidem discontinuation syndrome that have been reported to date do not appear to be serious enough to justify its international control, such reports were practically non-existent at the time of the last meeting of the Committee in 1996, and have increased in number along with the increasing medical use of zolpidem. The significance of the increases is unknown. It is likely that data addressing this will be available by the time of the 1999 Expert Committee meeting. Critical review of zolpidem is therefore recommended.

### 3. Substances for future pre-review

The Committee recommends that the following substances be subjected to pre-review: amfepramone (diethylpropion), carisoprodol, dronabinol and tramadol. A suggestion was made to consider pre-review of serotonin uptake inhibitors. After a brief discussion, the Committee did not recommend pre-review. At the request of the International Narcotics Control Board, the Committee recommended pre-review of poppy straw.

#### 4. Other issues

(1) **Guideline revision.** In an effort to provide timely advice and decisions, the Committee recommends that the guidelines formulated in 1990 be reviewed and modified so as to provide the Expert Committee latitude for proceeding more expeditiously and efficiently from identification of substances to their critical review and scheduling recommendations. This recommendation is made particularly with reference to clandestinely manufactured substances and substances of especially serious risk to public health and society and of no recognized therapeutic utility. Psychiatric and clinical data, wherever relevant, must be collected with the same care as chemical and pharmacological data.

(2) **Substance nomenclature.** The Committee has from time to time identified inconsistencies in substance nomenclature as reflected in the Schedules of the 1971 Convention. A question of possible confusion between acronyms used to designate substances in Schedule I of the 1971 Convention was raised in the discussion of the nomenclature of substances under control. It was noted that this latter issue had been raised by the International Conference on Drug Abuse and Illicit Trafficking held in 1987.<sup>1</sup> The lack of clarity arising from these two matters has led to conflicting interpretations of the Schedules and to varying degrees of precision in designating psychotropic substances for scheduling. To rectify this situation, the Committee recommends review of the nomenclature of all substances in the 1971 Convention by the appropriate international bodies. Such a review should take into account similar inconsistencies in the 1961 and 1988 Conventions.

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<sup>1</sup> Declaration of the International Conference on Drug Abuse and Illicit Trafficking and comprehensive multidisciplinary outline of future activities in drug abuse control. New York, United Nations, 1988.