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**FOOD AND AGRICULTURE ORGANIZATION  
OF THE UNITED NATIONS**

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**JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES  
Forty-third meeting, Geneva, 15-24 November 1994**

**SUMMARY AND CONCLUSIONS**

A Joint FAO/WHO Expert Committee on Food Additives (JECFA) meeting was held in Geneva, Switzerland, from 15 to 24 November 1994. Professor J.G. McLean, Pro Vice-Chancellor, Swinburne University of Technology, Hawthorn, Victoria, Australia, served as Chairman and Dr J. Boisseau, Director, National Laboratory of Veterinary Drugs, Fougères, France, served as Vice-Chairman.

Dr J. Paakkanen, Food Quality Liaison Group, Food and Nutrition Division, Food and Agriculture Organization of the United Nations, and Dr J.L. Herrman, International Programme on Chemical Safety, World Health Organization, served as Joint Secretaries.

The present meeting was the forty-third in a series of such meetings and was the seventh JECFA meeting convened to deal exclusively with residues of veterinary drugs in food. The primary tasks before the Committee were to further elaborate principles for evaluating the safety of residues of veterinary drugs in food and for establishing acceptable daily intakes (ADIs) and maximum residue limits (MRLs) for certain drugs when they are administered to food-producing animals in accordance with good practice in the use of veterinary drugs.

The report of the meeting will appear in the WHO Technical Report Series. Its presentation will be similar to that of previous reports, namely, general considerations, specific comments on substances on the agenda, and recommendations. The report will include annexes containing a detailed table (similar to Table 1 in this report) summarizing the conclusions reached by the Committee after its evaluations of the substances on the agenda.

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Toxicological monographs summarizing the data that were considered by the Committee in assessing the safety of the substances on the agenda will be published in WHO Food Additives Series No. 34. Residues monographs summarizing the data that were considered by the Committee in establishing MRLs will be published in FAO Food and Nutrition Paper Series No. 41/7.

**NOTE**

This document has been published prior to the publication of the full report of the forty-third meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) to ensure the fast dissemination of information, in particular to the Codex Alimentarius Commission, to which JECFA is the scientific advisory body on matters relating to residues of veterinary drugs in food.

The FAO and WHO Joint Secretaries of JECFA request that further inquiries regarding the compounds evaluated at the forty-third meeting be made only **after** the full official report has been published and distributed by WHO in the name of both sponsoring Organizations, FAO and WHO. Your cooperation is very much appreciated.

Table 1: Recommendations on compounds on the agenda

Substance	Acceptable daily intake (ADI) and other toxicological recommendations	Recommended maximum residue limit (MRL)
<b><math>\beta</math>-Adrenoceptor-blocking agent</b>		
Carazolol	0-0.1 $\mu\text{g}$ per kg of body weight	Muscle & fat/skin (pigs): 5 $\mu\text{g}/\text{kg}^{\text{a,b}}$ Liver & kidney (pigs): 25 $\mu\text{g}/\text{kg}^{\text{a,b}}$
<b>Antimicrobial agents</b>		
Dihydrostreptomycin & streptomycin	0-30 $\mu\text{g}$ per kg of body weight <sup>c,d</sup>	Muscle, liver & fat (cattle, pigs, chickens & sheep): 500 $\mu\text{g}/\text{kg}^{\text{e,f}}$ Kidney (cattle, pigs, chickens & sheep): 1000 $\mu\text{g}/\text{kg}^{\text{e,f}}$ Milk (cattle): 200 $\mu\text{g}/\text{l}^{\text{e,f}}$
Enrofloxacin	0-0.6 $\mu\text{g}$ per kg of body weight <sup>e</sup>	No MRLs recommended <sup>g</sup>
Gentamicin	0-4 $\mu\text{g}$ per kg of body weight <sup>e</sup>	Muscle & fat (cattle & pigs): 100 $\mu\text{g}/\text{kg}^{\text{a,e}}$ Liver (cattle & pigs): 200 $\mu\text{g}/\text{kg}^{\text{a,e}}$ Kidney (cattle & pigs): 1000 $\mu\text{g}/\text{kg}^{\text{a,e}}$ Milk (cattle): 100 $\mu\text{g}/\text{l}^{\text{a,e}}$
Neomycin	0-30 $\mu\text{g}$ per kg of body weight <sup>e</sup>	Muscle, liver & fat (cattle, chickens, ducks, goats, pigs, sheep & turkeys): 500 $\mu\text{g}/\text{kg}^{\text{a,h}}$ Kidney (cattle, chickens, ducks, goats, pigs, sheep & turkeys): 5000 $\mu\text{g}/\text{kg}^{\text{a,h}}$ Eggs (chickens): 500 $\mu\text{g}/\text{kg}^{\text{a,h}}$ Milk (cattle): 500 $\mu\text{g}/\text{kg}^{\text{a,h}}$
Oxolinic acid	No ADI allocated <sup>i</sup>	No MRLs recommended <sup>i</sup>
Spiramycin	0-50 $\mu\text{g}$ per kg of body weight	Muscle (cattle): 100 $\mu\text{g}/\text{kg}^{\text{k}}$ Muscle (pigs & chickens): 200 $\mu\text{g}/\text{kg}^{\text{k}}$ Liver (cattle): 300 $\mu\text{g}/\text{kg}^{\text{k}}$ Liver (pigs): 600 $\mu\text{g}/\text{kg}^{\text{a,k}}$ Liver (chickens): 800 $\mu\text{g}/\text{kg}^{\text{k}}$ Kidney (cattle): 200 $\mu\text{g}/\text{kg}^{\text{k}}$ Kidney (pigs): 300 $\mu\text{g}/\text{kg}^{\text{a,k}}$ Kidney (chickens): 1600 $\mu\text{g}/\text{kg}^{\text{k}}$ Fat (cattle): 300 $\mu\text{g}/\text{kg}^{\text{k}}$ Fat (pigs): 200 $\mu\text{g}/\text{kg}^{\text{a,k}}$ Fat (chickens): 600 $\mu\text{g}/\text{kg}^{\text{k}}$ Milk (cattle): 100 $\mu\text{g}/\text{l}^{\text{k}}$
<b>Glucocorticosteroid</b>		
Dexamethasone	0-0.015 $\mu\text{g}$ per kg of body weight <sup>l</sup>	Muscle & kidney (cattle, horses & pigs): 0.5 $\mu\text{g}/\text{kg}^{\text{a,e,m}}$ Liver (cattle, horses & pigs): 2.5 $\mu\text{g}/\text{kg}^{\text{a,e,m}}$ Milk (cattle): 0.3 $\mu\text{g}/\text{l}^{\text{a,e,m}}$

Substance	Acceptable daily intake (ADI) and other toxicological recommendations	Recommended maximum residue limit (MRL)
Tranquilizer		
Azaperone	0-3 µg per kg of body weight <sup>e</sup>	Muscle & fat (pigs): 60 µg/kg <sup>h,n</sup> Liver & kidney (pigs): 100 µg/kg <sup>h,n</sup>

#### NOTES

- a. Expressed as parent drug.
- b. The Committee noted that the concentration of carazolol at the injection site may exceed the ADI, which is based on the acute pharmacological effects of carazolol.
- c. Temporary ADI (see Table 2).
- d. Group temporary ADI for dihydrostreptomycin and streptomycin, either singly or in combination.
- e. Temporary MRL (see Table 2).
- f. Expressed as the sum of dihydrostreptomycin and streptomycin.
- g. The ADI for enrofloxacin is based on antimicrobial activity. MRLs were not recommended because the relationship between total antimicrobial activity and residues of enrofloxacin and ciprofloxacin could not be determined.
- h. Temporary MRLs were recommended because the ADI is temporary.
- i. An ADI could not be established for oxolinic acid because of major reporting and protocol deficiencies in the available studies and because a clear no-observed-effect level (NOEL) could not be identified for arthropathy in dogs.
- j. MRLs were not recommended for oxolinic acid because an ADI was not established.
- k. Expressed as the sum of spiramycin and neospiramycin. MRLs in pig muscle and temporary MRLs in pig liver, kidney, and fat are based on total antimicrobially-active residues.
- l. The ADI for dexamethasone was established at the forty-second meeting of the Committee.
- m. The MRLs for dexamethasone in cattle and pigs were recommended at the forty-second meeting of the Committee.
- n. Expressed as the sum of azaperone and azaperol.

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**Table 2: Further toxicological studies and other information required or desired**

***Antimicrobial agents***

**Dihydrostreptomycin and streptomycin**

The following information is required for evaluation in 1997:

1. Information to assess the potential for effects on fertility and peri-/postnatal toxicity.
2. An evaluation report or results of experimental studies on the metabolism of dihydrostreptomycin and streptomycin.
3. Residue data on eggs.
4. Results of studies to determine the relationship between the antimicrobial activity of the residues and the measurement of the residues by specific chemical methods.

**Enrofloxacin**

The following information is required for evaluation in 1997:

1. Detailed reports of the studies referenced in the summary tables that were available on MIC (minimum inhibitory concentration) values for enrofloxacin.
2. Information on the effects of enrofloxacin and ciprofloxacin on specific genera of microorganisms obtained from the human intestine.

The following required information will be reviewed as soon as possible after it becomes available:

- Results of studies to determine the antimicrobial activity of the residues other than enrofloxacin and ciprofloxacin.

**Gentamicin**

The following information is required for evaluation in 1997:

1. Information on the effects of gentamicin on specific genera of microorganisms obtained from the human intestine.
  2. Information to assist in the assessment of carcinogenic potential, including:
    - a. the results of genotoxicity assays for gene mutations in mammalian cells and chromosomal aberrations *in vitro* and *in vivo*.
    - b. details of an investigation on possible structural similarities between gentamicin and known carcinogens.
  3. A validated chemical method with a limit of quantification below the MRL recommended for milk.
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### **Neomycin**

The following information is required for evaluation in 1996:

1. The results of gene mutation studies, in particular in eukaryotic cells.
2. A study on chromosomal aberrations *in vivo*.

### **Oxolinic acid**

Before reviewing the compound again, the Committee would wish to have the following:

1. Resolution of the protocol and reporting deficiencies encountered in the toxicological studies that were reviewed at the meeting.
2. Results of a study to identify a NOEL for arthropathy in the dog.
3. An examination of the significance of the increased incidence of Leydig cell lesions observed in rats in a recent carcinogenicity study.
4. *Either* a detailed report, including individual animal data, of the recent carcinogenicity study in rats *or* genotoxicity studies to assess point mutation and chromosomal aberrations.

### **Spiramycin**

The following information is required for evaluation in 1996:

1. A validated analytical method for spiramycin and neospiramycin in pig tissues.
2. Residue data to estimate the percentage of the total antimicrobial activity represented by spiramycin and neospiramycin in pig liver, kidney and fat.

### ***Tranquillizing agent***

#### **Azaperone**

The following information is required for evaluation in 1998:

1. Results of studies to resolve the genotoxic potential of the metabolites of azaperone, which have been reported to be mutagenic in *Salmonella spp.*
  2. Evidence to support the claim that azaperone or its degradation products are not structurally similar to known carcinogens.
  3. Results of a study to assess the effects of azaperone on reproduction and fertility in male laboratory animals.
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