ISSN 1817-7077

FAO JECFA Monographs

6

RESIDUE EVALUATION OF CERTAIN VETERINARY DRUGS

Joint FAO/WHO Expert Committee on Food Additives

70th meeting 2008

World Health Organization

Food and Agriculture Organization of the United Nations

FAO JECFA Monographs 6

RESIDUE EVALUATION OF CERTAIN VETERINARY DRUGS

Joint FAO/WHO Expert Committee on Food Additives

70th meeting 2008

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS
Rome, 2009

ISBN 978-92-5-106213-5

SPECIAL NOTE

While the greatest care has been exercised in the preparation of this information, FAO expressly disclaims any liability to users of these procedures for consequential damages of any kind arising out of, or connected with, their use.

CORRIGENDA

RESIDUE EVALUATION OF CERTAIN VETERINARY DRUGS
FAO JECFA Monographs 6 (2009).

Page 4, last line: The word honey is corrected to residues.
Page 122, 3rd paragraph first line: The word boiler is corrected to broiler.
Page 288: The data for the veterinary drug Doramectin are missing and the information is inserted between the entries for Diminazene and Enrofloxacin as follows:

Substance	ADI (µg/kg bw)	ADI Status	JECFA	MRL (µg/kg)	Tissue	Species	Marker residue and other remarks
Doramectin	0-1	Full	62 (2004)	10 5 100 30 150 15	Muscle Muscle Liver Kidney Fat Milk	Cattle Pigs Cattle, Pigs Cattle	Doramectin

Page 290: The data for Lincomycin is corrected with respect to the number and year of the last meeting JECFA meeting at which the veterinary drug was on the agenda. The correct text is: 62 (2004).

Page 293: The data for Thiabendazole is corrected with respect to the tissues in the last line of the entry. The correct text for MRL 100 µg/kg for Cattle, goat is Milk as follows:

Substance	ADI (µg/kg bw)	ADI Status	JECFA	MRL (µg/kg)	Tissue	Species	Marker residue and other remarks
Tiabendazole (Thiabendazole)	0-100	Full	58 (2002)	100 100	Muscle, Liver, Kidney, Fat Milk	Cattle, Pigs, Goat, Sheep Cattle, Goat	Sum of tiabendazole + 5-hydroxy tiabendazole

TABLE OF CONTENTS

LIST OF PARTICIPANTS

JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES, 70TH MEETING
Geneva, Switzerland, 21 – 29 October, 2008

Members

Professor A. Anadón, Department of Toxicology and Pharmacology, Faculty of Veterinary Medicine, Universidad Complutense de Madrid, Madrid, Spain

Dr D. Arnold, Consultant, Berlin, Germany

Professor A.R. Boobis, Experimental Medicine & Toxicology, Division of Investigative Science, Faculty of Medicine, Imperial College London, London, England

Dr R. Ellis, Consultant, Myrtle Beach, SC, United States of America (USA) (*Joint Rapporteur*)

Dr A. Fernández Suárez, Food Protection Section, Food Technology Institute, National Institute of Agricultural Research, Buenos Aires, Argentina

Dr L.G. Friedlander, Office of New Animal Drug Evaluation, Center for Veterinary Medicine, Food and Drug Administration, Department of Health and Human Services, Rockville, MD, USA

Dr K. Greenlees, Office of New Animal Drug Evaluation, Center for Veterinary Medicine, Food and Drug Administration, Department of Health and Human Services, Rockville, MD, USA (*Joint Rapporteur*)

Dr J.C. Larsen, National Food Institute, Technical University of Denmark, Søborg, Denmark

Dr J.G. McLean, Professor Emeritus, Camberwell, Victoria, Australia (*Chairman*)

Professor J. Palermo-Neto, Department of Pathology, Faculty of Veterinary Medicine, University of São Paulo, São Paulo, Brazil

Dr P. Reeves, Veterinary Medicines and Residues, Australian Pesticides and Veterinary Medicines Authority, Kingston, ACT, Australia

Dr P. Sanders, Laboratoire d'Études et de Recherches sur les Médicaments Vétérinaires et les Désinfectants, Agence Française de Sécurité Sanitaire des Aliments, Fougères, France

Professor G.E. Swan, Faculty of Veterinary Science, University of Pretoria, Onderstepoort, South Africa (*Vice-Chairman*)

Secretariat

Dr S. Barlow, Consultant, Brighton, East Sussex, England (*WHO Temporary Adviser*)

Ms A. Bulder, Institute of Food Safety (RIKILT) – Wageningen UR, Wageningen, Netherlands (*WHO Temporary Adviser*)

Dr C.E. Cerniglia, Division of Microbiology, National Center for Toxicological Research, Food and Drug Administration, Department of Health and Human Services, Jefferson, AR, USA (*WHO Temporary Adviser*)
Dr P.L. Chamberlain, Covance Laboratories, Vienna, VA, USA (*WHO Temporary Adviser*)

Dr M. Choi, Department of Food Safety, Zoonoses and Foodborne Diseases, World Health Organization, Geneva, Switzerland (*WHO Staff Member*)

Dr B. Dunham, Chair Codex Committee on Residues of Veterinary Drugs in Food, Director, Center for Veterinary Medicine, Food and Drug Administration, Department of Health and Human Services, Rockville, MD, USA (*WHO Temporary Adviser, unable to participate*)

Dr D. Grant, Consultant, Ottawa, Ontario, Canada (*WHO Temporary Adviser*)

Dr T. Imai, Division of Pathology, Biological Safety Research Center, National Institute of Health Sciences, Tokyo, Japan (*WHO Temporary Adviser*)

Dr S.-H. Jeong, Toxicology Division, National Veterinary Research and Quarantine Service, Ministry for Food, Agriculture, Forestry and Fisheries, Anyang City, Republic of Korea (*WHO Temporary Adviser*)

Professor B. Le Bizec, Laboratoire d'Étude des Résidus et Contaminants dans les Aliments (LABERCA), École Nationale Vétérinaire de Nantes, Nantes, France (*FAO Expert*)

Dr J. Lewicki, Division of Pharmacology and Toxicology, Department of Preclinical Sciences, Faculty of Veterinary Medicine, Warsaw University of Life Sciences, Warsaw, Poland (*FAO Expert*)

Professor L. Ritter, Executive Director, Canadian Network of Toxicology Centres, Professor, Department of Environmental Biology, University of Guelph, Guelph, Ontario, Canada (*WHO Temporary Adviser*)

Dr G. Roberts, Consultant, Preston, Victoria, Australia (*WHO Temporary Adviser*)

Dra B. San Martín Nuñez, Laboratorio de Farmacología Veterinaria, Faculdad de Ciencias Veterinarias y Pecuarias, Universidad de Chile, Santa Rosa, La Pintana, Chile (*FAO Expert*)

Ms M. Sheffer, Orleans, Ontario, Canada (*WHO Editor*)

Dr A. Tritscher, Department of Food Safety, Zoonoses and Foodborne Diseases, World Health Organization, Geneva, Switzerland (*WHO Joint Secretary*)

Dr A. Wennberg, Nutrition and Consumer Protection Division, Food and Agriculture Organization of the United Nations, Rome, Italy (*FAO Joint Secretary*)

Professor Shi-Xin Xu, Division of Chemical and Pharmaceutical Evaluation, Center for Veterinary Drug Evaluation, China Institute of Veterinary Drugs Control, Beijing, China (*FAO Expert)*

ABBREVIATIONS

ADI	Acceptable daily intake
AOAC	AOAC International
AUC	Area under the curve
BW or bw	Body weight
CAC	Codex Alimentarius Commission
CAS	Chemical Abstracts Service
CCRVDF	Codex Committee on Residues of Veterinary Drugs in Foods
Cl	Clearance rate
Cmax	Maximum concentration
CR	Renal clearance
CV	Coefficient of variation
Cv_r	Repeatability
Cc_R	Reproducibility
ECD	Electron capture detector
EDI	Estimated daily intake
EFSA	European Food Safety Authority
EMEA	European Medicines Agency
FAO	Food and Agriculture Organization of the UN
FDA	US Food and Drug Administration
GC	Gas chromatography
GLP	Good laboratory practice
H or h	Hour
HPLC	High pressure liquid chromatography
IM	Intramuscular
IR	Infrared
IU	International Unit
IUPAC	International Union of Pure and Applied Chemistry
IV	Intravenous
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
Kg or kg	Kilogram (10^3grams)
LC	Liquid chromatography
LOD	Limit of detection
LOQ	Limit of quantitation
µg	microgram (10^{-6}grams)
mg	milligram (10^{-3}grams)
min	Minimum or minute
MGA	Melengestrol acetate
mL or ml	milliliter
MIC	Minimum Inhibitory Concentration
MRL	Maximum Residue Limit
MRM	Multiple reaction monitoring
MS	Mass spectrometry
MW or mw	Molecular weight
N	Negative
NA or na	Not analyzed or not applicable
NADA	New Animal Drug Application
NC or nc	Not calculated
ND	Not detected
NICI	Negative ion chemical ionization
NOEL	No effect level

NQ	Non quantifiable
P	Positive
QA	Quality assurance
QC	Quality control
RfD	Acute reference dose
RP	Reverse phase
SC	Subcutaneous (injection)
SD	Standard deviation
S/N	Signal to noise ratio
SPE	Solid phase extraction
SD	Standard deviation
s.e.	Standard error
$t_{½}$	Half life
TR	Total residue
TLC	Thin layer chromatography
TMDI	Theoretical maximum daily intake
TRR	Total radiolabelled residues
TRS	Technical Report Series
TSP	Thermospray
USP	United States Pharmacopoeia
UV	Ultraviolet
Vd	Volume of distribution
WHO	World Health Organization

INTRODUCTION

The monographs in this volume of the FAO JECFA Monographs on the residues of, statements on, or other parameters of the veterinary drugs on the agenda were prepared by the invited experts for the seventieth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) that was held in Geneva, Switzerland, 21-29 October, 2008. This was the eighteenth meeting of JECFA convened specifically to consider residues of veterinary drugs in food producing animal species. The Committee has evaluated residues of veterinary drugs at its 12th, 26th, 27th, 32nd, 34th, 36th, 38th, 40th, 42nd, 43rd, 45th, 47th, 48th, 50th, 52nd, 54th, 58th, 60th, 62nd and 66th meetings (ref. 1-15 and 18-22). The tasks for 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 recommend maximum residue limits (MRLs) for substances on the agenda when they are administered to food producing animals in accordance with good veterinary practice in the use of veterinary drugs. The enclosed monographs provided the scientific basis for the recommendations of MRLs.

There is an important feature to bring to the attention of readers. This volume of the FAO JECFA Monographs is the second in a new format for the presentation of monographs from meetings of the Committee. It was also the second meeting of JECFA subsequent to the completion of the workshop to update the principles and methods of risk assessment for MRLs for pesticides and veterinary drugs, held jointly by FAO/RIVM/WHO, in Bilthoven, The Netherlands, 7 - 11 November, 2005 (ref. 23). Specifically, the Committee continued to implement some of the more significant recommendations in the workshop report, including the concept of using median residue values to estimate daily intakes of residues of veterinary drugs in food for chronic exposure intake estimates and to consider a specific approach for recommending MRLs for substances used in apiculture.

Background

In response to the growing use of veterinary medicines in food animal production systems internationally and the potential implications for human health and fair trading practices, a Joint FAO/WHO Expert Consultation on Residues of Veterinary Drugs was convened in Rome, November 1984 (ref. 16). One of the major recommendations of this consultation was the establishment of the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) and the periodic convening of an appropriate expert body to provide independent scientific advice to this Committee and to member countries of FAO and WHO. At its first session in Washington, DC in November 1986, the CCRVDF reaffirmed the need for such a scientific body and made a number of recommendations and suggestions to be considered by JECFA (ref. 17). In response to these recommendations, the 32nd JECFA meeting was devoted entirely to the evaluation of residues of veterinary drugs in food – a new responsibility for the Joint FAO/WHO Expert Committee on Food Additives. Seventeen such meetings of JECFA have been held prior to this meeting of JECFA.

70th Meeting of JECFA

The present volume, in the new format, contains monographs of the residue data on eight of the substances scheduled for evaluation at the 70th meeting of the Committee. One substance, melengestrol acetate, was for review of toxicological data only and no residue monograph was prepared. In addition, a discussion paper and recommendations to CCRVDF was elaborated regarding specific approaches for MRLs in honey. The Committee was also asked to comment on use of malachite green in aquaculture. The monographs are prepared in a uniform format consistent with the data provided and the specific request for risk assessment by CCRVDF. The format includes identity of substance, residues in food and their evaluation, metabolism studies, tissue residue depletion studies, methods of residue analysis, a final appraisal of the study results, and if appropriate, recommendations on MRLs. A summary of the recommendations on compounds on the agenda and further information required is included in Annex 1. In addition, a summary of JECFA evaluations of residues of veterinary drugs in foods from the 32nd meeting to the present 70th meeting is found in Annex 2. **The monographs and general considerations on risk assessment principles of this**

volume must be considered in context of the full report of the meeting, which will be published in the WHO Technical Report Series.

On-line edition of Residues of some veterinary drugs in animals and foods (from FAO JECFA Monographs and FAO Food and Nutrition paper Number 41)

The monographs and statements that have been published in the FAO JECFA Monographs 2 and this volume as well as those published in FAO Food and Nutrition Paper Series 41 (sixteen volumes since 1988) are all available online at http://www.fao.org/ag/agn/jecfa-vetdrugs/search.html. The search interface is available in five languages (Arabic, Chinese, English, French and Spanish) and allows searching for compounds, functional classes, ADI and MRL status.

Contact and Feedback

More information on the work of the Committee is available from the FAO homepage of JECFA at http://www.fao.org/ag/agn/agns/jecfa_index_en.asp . Readers are invited to address comments and questions on this publication and other topics related to the work of JECFA to:

JECFA@fao.org

REFERENCES

1. Specifications for the Identity and Purity of Food Additives and their Toxicological Evaluation: Some antibiotics (Twelfth Report of the Joint FAO/WHO Expert Committee on Food Additives), FAO Nutrition Meetings Report Series No. 45, 1969; WHO Technical Report Series No. 430, 1969.
2. Evaluation of Certain Food Additives and Contaminants (Twenty-Sixth Report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series No. 683, 1982.
3. Evaluation of Certain Food Additives and Contaminants (Twenty-Seventh Report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series No. 696, 1983.
4. Evaluation of Certain Veterinary Drug Residues in Foods (Thirty-Second Report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series No. 763, 1988.
5. Evaluation of Certain Veterinary Drug Residues in Foods (Thirty-Fourth Report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series No. 788, 1989.
6. Evaluation of Certain Veterinary Drug Residues in Foods (Thirty-Sixth Report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series No. 799, 1990.
7. Evaluation of Certain Veterinary Drug Residues in Foods (Thirty-Eighth Report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series No. 815, 1991.
8. Evaluation of Certain Veterinary Drug Residues in Foods (Fortieth Report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series No. 832, 1993.
9. Evaluation of Certain Veterinary Drug Residues in Foods (Forty-second Report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series No. 851, 1995.
10. Evaluation of Certain Veterinary Drug Residues in Foods (Forty-third Report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series No. 855, 1995.
11. Evaluation of Certain Veterinary Drug Residues in Foods (Forty-fifth Report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series No. 864, 1996.
12. Evaluation of Certain Veterinary Drug Residues in Foods (Forty-seventh Report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series No. 876, 1998.
13. Evaluation of Certain Veterinary Drug Residues in Foods (Forty-eighth Report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series No. 879, 1998.
14. Evaluation of Certain Veterinary Drug Residues in Foods (Fiftieth Report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series No. 888, 1999.
15. Evaluation of Certain Veterinary Drug Residues in Foods (Fifty-second Report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series No. 893, 2000.
16. Residues of Veterinary Drugs in Foods, Report of a Joint FAO/WHO Consultation, Rome, 29 October - 5 November 1984. FAO Food and Nutrition Paper No. 32, 1985.
17. Report of the First Session of the Codex Committee on Residues of Veterinary Drugs in Foods. Washington, D.C., 27-31, October 1986.
18. Evaluation of Certain Veterinary Drug Residues in Foods (Fifty-fourth Report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series No. 900, 2001.
19. Evaluation of Certain Veterinary Drug Residues in Foods (Fifty-eighth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series No. 900, 2001.
20. Evaluation of Certain Veterinary Drug Residues in Foods (Sixtieth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 918, 2003.

21. Evaluation of Certain Veterinary Drug Residues in Animals and Foods (Sixty-second report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 925, 2004.

22. Evaluation of Certain Veterinary Drug Residues in Animals and Foods (Sixty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 939, 2006.

23. Final report from Workshop on Update of Principles and Methods of Risk Assessment – MRLs for pesticides and veterinary drugs. FAO/RIVM/WHO, Bilthoven, the Netherlands, 7-11 November, 2005. Available at the FAO JECFA website at: ftp://ftp.fao.org/ag/agn/jecfa/bilthoven_2005.pdf .