Residues of veterinary drugs in food

FAO Guidelines for the preparation of JECFA monographs and summaries for veterinary drug residues

Rome, September 2002

1 Introduction

1.1 Preface

This edition of the guidelines* for the preparation of monographs and summaries for residues of veterinary drugs replaces the guidelines issued in 1998 for the Joint FAO/WHO Expert Committee on Food Additives (JECFA). They are intended primarily for drafting experts who prepare draft monographs for JECFA and for those Members who have been assigned to peer review them. The guidelines are also useful to sponsors who intend to prepare summaries of the data that they provide. The FAO Secretariat encourages the submission of such summaries by sponsors.

Major changes to the previous edition of the guidelines are the following:

1.2 Background

These notes are designed to guide JECFA experts in the preparation of the first draft of the monograph on residues of veterinary drugs for consideration at meetings of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). The drafting expert and the reviewer should work together to prepare a consolidated first draft that contains all relevant sections, which is submitted to the FAO Secretariat in sufficient time before the meeting for distribution to other members. They should also consult the experts for the toxicity who are assigned by WHO whilst preparing the draft.

Most monographs are published after meetings of the Expert Committee in the *FAO Food and Nutrition Papers*. To facilitate their editing and to avoid delays in their publication, the FAO Secretariat would appreciate close adherence by drafting experts to the standard style described in these guidelines.

The monograph structure is outlined below , which shows the order in which items appear and numbering style. Boldfacing should be used with all titles and headings. Working papers should be submitted in *single spacing*. They should be provided in electronic format on diskettes at the time of the meeting. If a Macintosh computer is used, the file should be converted to a format that can be used in DOS or Windows.

Two types of residue monographs are published after the meeting, full monographs and monograph addenda. Full monographs are published on veterinary drugs that are reviewed by the Committee for the first time. When re-evaluations are performed, monograph addenda are often prepared, which summarize the relevant

* These guidelines are available from the FAO Joint Secretary, Joint FAO/WHO Expert Committee on Food Additives, Nutrition Division, Food and Agriculture Organization of the United Nations, Rome, Italy.

safety data that have become available since the most recent evaluation; they do not contain the summaries included in earlier monographs. The same pattern is followed with both, although addenda usually contain fewer sections than do full monographs.

2 Timetable*

The FAO Joint Secretary will arrange for dispatch of data package from the sponsors six months before the meeting. During the following four months the drafting expert has the main responsibility for preparing working documents (e.g. draft monograph) using these guidelines. The draft monograph is sent to the FAO Secretary who forwards copies (without appraisal section) to the submitters of the data and the other assigned experts (FAO and WHO) at least one month before the JECFA meeting.

The drafting expert edits the draft monograph following the comments received from the sponsor and the reviewer. This version will be used by the JECFA as a working document for the meeting, it is distributed to all participants (members, FAO Consultants, WHO Temporary Advisers).

The drafting expert prepares a draft summary document (see below guideline on preparation of summaries) for presentation to JECFA. This will form the basis of the text to be added to the report of the Committee. This report is be published in the WHO Technical Report Series following the conclusion of the meeting.

All experts assigned to a specific compound will collaborate to identify draft questions for data submitters prior to the meeting if possible, regarding explanation of or deficiencies in the information supplied that are to be answered at the informal session the JECFA meeting.

After the JECFA meeting the drafting expert or primary author revises the working monograph as necessary following the Committee's review and recommendations. This shall include a section on MRLs and the requests for additional information for further review by the Committee if needed. This is the basis of the final version of the FAO residue monograph to be published in the *FAO Food and Nutrition Papers 41/xx* prepared in collaboration with "A" author and the JECFA Secretary. This may take several months depending on the size and complexity of the data in the monograph.

3 Preparation of monograph

3.1 General comments, layout

Authors are asked to use the following in preparing the papers:

- The Joint Secretariat is currently using Microsoft Word 97. Please use a compatible text processing system. In case of doubt: send a test file to the Joint Secretary.
- The font for the monographs should be Times Roman or Times New Roman preferably font size 10 pt.
- Graphics should be compatible with the word processing language and clearly printable.
- Pages should be numbered in the top right corner.
- Lines should be numbered.
- Tables and graphs should have a number, a title and if appropriate, a legend. They should be able to "stand alone" from the text. Graphics should be to elaborate and not duplicate other text or tables.
- Check each part of the report for accuracy and completeness (e.g. is the work done to GLP?).

The monograph can take two forms, as a first time submission of the drug with a complete data package or it is a subsequent review for consideration based on new information submitted by the submitters of data following a previous evaluation and list of specific requests by JECFA.

* See also the *FAO procedural guidelines for residues of veterinary drugs (Rome 2002), available at* www.fao.org/es/esn/jecfa

3.2 Structure of the draft monograph for a new drug (first time evaluation)

The next pages set out the titles and their format as used for monographs as agreed to by previous Committees. Each section is expanded on subsequently.

TITLE

Name of the drug in boldfaced capital letters, centered). Note: The common name should be used. Specific product names should be used only when absolutely necessary.

IDENTITY

Chemical:

Synonyms:

Structural formula:

Structure:

Molecular formula:

Molecular weight:

OTHER INFORMATION ON IDENTITY AND PROPERTIES

Pure active ingredient:

Appearance:

Melting point:

Solubility:

Optical rotation:

Ultraviolet maxima:

Stability to acids, bases, etc.:

RESIDUES IN FOOD AND THEIR EVALUATION

Conditions of Use

General

Dosage

METABOLISM

Pharmacokinetics

Toxicological Test Species

Rats

Mice

Dogs
Others (specify)

Metabolism in Food Animals (Note: animal species given as examples only):
Cattle
Swine
Sheep
Chickens/Turkeys
Others (specify)

TISSUE RESIDUE DEPLETION STUDIES

Radiolabeled Residue Depletion Studies
Cattle
Swine
Sheep
Chickens/Turkeys
Others (specify)

Other Residue Depletion Studies (with unlabeled drug)
Cattle
Swine
Sheep
Chickens/Turkeys
Others (specify)

Bound Residues/Bioavailability

METHODS OF ANALYSIS FOR RESIDUES IN TISSUES

Appraisal of Analytical Method(s) Performance

APPRAISAL

MAXIMUM RESIDUE LIMITS

REFERENCES

3.3 Structure of the draft addendum to a monograph (re-evaluation)

This is often a shorter manuscript that specifically addresses the requested studies by JECFA and the information provided. It should include a brief background of previous assessments and decisions of the Committee. Detailed guidance noted below for the monograph presentation applies as well to evaluations of new substances.

Identity and other information on identity and properties. This section is best written by reference to previous monographs. It contains straightforward factual information.

Residues in food and their evaluation. Title only.

Conditions of use. Brief review of use(s). It may contain information where submitters of data propose additional uses.

General. The use of the drug with reference to the species, age, sex and the conditions for either therapeutic or prophylactic uses. The use of the drug at a specific geographic location (e.g. in the tropics) or timeframe for age of animals or birds, etc., could be highlighted. Indicate whether the drug is used on single/few or large groups of animals. Give contraindications (e.g., not recommended for use in lactating animals).

Dosage. Give the type of formulation(s) of the drug (e.g. implant, suspension, bolus, in feed), the dosage (size and number) and the route(s) of administration.

Metabolism. A title only - with two sections.

Pharmacokinetics. This section previously overlapped with the WHO monograph. **The Committee agreed that all the information must be provided by the FAO expert(s).** It will include:

1. The absorption of the drug with respect to the route/site of administration in the toxicological test species and target food animals (e.g., the blood parameters for maximum concentration, the time to maximum concentration and the half life).

2. The excretion in the toxicological test species and target food animals into the urine, faeces, milk and eggs, giving information on the percentage distribution and the times.

Metabolism. This section will overlap with the WHO monograph. Comment on the metabolism in the species in the same order as presented in the species used in the titles. Follow this with a comparison of the metabolism in the target animals with that of the laboratory animals and primates. The purpose is to identify the metabolites that the consumer will be exposed to and whether these metabolites have been evaluated for their toxicological potency. Where possible it is more relevant to compare metabolism in the tissues, (e.g., muscle or liver, rather than in the excreta). One possible way of presenting the data is to prepare a table listing species against metabolites using either quantitative or semi-quantitative (e.g., ++, +, -, ?) indicators. Identify the major metabolites that are >10% of the total residues and comment on the proof of the identity of these metabolites.

Tissue residue depletion studies. Title only - two sections (radiolabel and unlabelled drug).

Radiolabeled Residue Depletion Studies: A data package should contain most of the following information and conditions. Absence of any of the following should be noted.

1. Proof that the use of a radiolabel is not exchanged nor easily removed from the molecule.

2. The dose used relative to the maximum recommended in field use and administered by the recommended route.

3. The period of investigation should extend at least to the proposed withdrawal times.

4. The number of animals used. This may be limited by cost but ideally there should be at least four per time point. Data derived from one or two animals should be addressed with caution and reported as a range.

5. The results for individual animals on the total residues in each edible tissue (muscle, liver, kidney and fat) and where appropriate, for milk, eggs and at the injection site.

6. The results for the concentrations of the parent drug and the main metabolites in each edible tissue and where appropriate for milk, eggs and at the injection site.

7. Pertinent details of the analytical methods used for steps 5 and 6 above (e.g., limits of detection or quantitation).

8. Information on the quantity and nature of bound residues, if any.

Given the above data the author can present for each target species:

1. A summary of the animal experiments. **The information is presented for each species in turn.**
2. The depletion of total residues (e.g., the concentrations, is the rate exponential and what is the half-life) in the separate tissues.

3. The depletion of the parent drug and the main metabolites in tissues.

4. The mathematical relationship between the parent drug and/or the main metabolites and the total residues at different time points. This will be important in the choice of a possible marker residue.

The use of tables and graphs is recommended where it will simplify the presentation. It is advisable to use a consistent format if the same type of information is presented for more than one species. The results for concentrations of residues (radiolabelled and unlabelled studies) should include the mean value and either the standard deviation (SD) or the range. The maximum concentration and mean value plus 3 times the SD observed at a given time point may be important when considering the MRLs.

Other Residue Depletion Studies (with Unlabeled Drug): The author should comment on whether the information meets with some of the following requirements. The information should be collected from target animal experiments in which the drug was administered at its highest recommended dose by the recommended route. The period of investigation should extend beyond the sponsors proposed withdrawal times. The number of animals should be sufficient to allow a statistical analysis of the data and in particular the mean and SD of residues. The analyte measured must be the expected marker residue and the analytical method(s) must be suitable. The data may best be presented for each time point as a range for 3 or less animals and as the mean and SD for 4 or more values. Where available, all the residue data should be corrected for recovery. Each species should be covered separately, giving information on the animal experiment, the collection of samples, the analytical method and the results.

Bound Residues/Bioavailability. The information on the nature and quantity of the bound residues in the edible tissues should be presented. If the bound residues are a very low fraction (<10%) of the total residues then they may be thought of as not of toxicological concern. On the other hand if they are a high fraction of the residues then the information on the nature and bioavailability of the bound residues must be discussed.

Methods of analysis for residues in tissues. This section should discuss and present information on the analytical methods available for the possible control of the drug at the regulatory level. The methods may be submitted by the sponsor or in the open literature. The author needs to assess whether the method is suitable for the analysis but remember that the method will be further evaluated by the CCRVDF. The method(s) should be summarised and the performance criteria checked and summarised against Table 1.

Table 1. Checklist for Analytical Method(s).

Criteria	Comment	Acceptable (Y/N)
QA system	GLP, in-house, etc.	
Matrices	M, L, K, F, etc.	
Accuracy	Is it suitable for the proposed MRL?	
Recovery	Values for fortified and actual	
Linearity	Spread (dispersion) around MRL and r^2 /r	
Calibration curve		
LOD	How was it derived?	
LOQ	How was it derived? Is it <50% of recommended MRL?	
Repeatability		
Reproducibility		
Specificity from blank	. Is there interference on calibration curves, for example?	
Specificity to related drugs and metabolites	List those tested and results	
Ruggedness testing	If it was done, how?	
Confirmation method	Is there one? (Not obligatory)	
Proficiency testing	Not obligatory	
Publication	Preferred but not obligatory	

How these criteria were derived from the data may need comment. It is probably advisable at the present time to avoid using the phrase "validated method". It is better at this stage to say that the method is "suitable, suggested or recommended". Whether the method is valid may be decided at a later evaluation by CCRVDF. The methods should be suitable for each species and tissue investigated.

Appraisal. This section is the appraisal by the JECFA experts (the "A" author in consultation with the "B" author) of the information package. The Committee at the JECFA meeting will undertake a full appraisal. If an ADI is likely to be established (check with Toxicology authors) then the primary question to be answered is "Are the data adequate to establish an MRL for a marker residue in target tissues of target animals?"

Discuss whether the information in the sections for each target species is sufficient to make an estimate of the total residues and a possible marker residue. The marker residue is discussed as an indicator of the residues that are of toxicological concern. Where no information is available on the toxicological potency of the metabolites or the bound residues then all the residues are considered of equal toxicity to the parent drug. In this situation the marker residue is a means to measure the total residues. There may be information on the toxicological potency of the metabolites and the bioavailability of the bound residues. Often this will show that these residues are of no toxicological concern and can be discarded from the total residues, this in turn would permit a higher MRL for the marker residue to be calculated.

If there is sufficient information the expert should suggest at least two possible target tissues. They must include muscle or fat (for international trade control) and either liver or kidney (for national regulatory control). For poultry and fish a combination of muscle and skin (in natural proportions) may serve as a target tissue. Where it is relevant milk, eggs and honey may be target tissues. The analytical method should

be suitable for the proposed target tissues and species. Evaluation of the method should be based on the findings in Table 1.

Discuss whether the information is adequate for each target species. It may be possible to recommend temporary MRLs for species where there data are limited, particularly if it can be shown that there are good grounds for extrapolating the data for that species (e.g., from veal calves to adult cattle) or from one species to another (e.g., extrapolation between ruminants).

Some data packages will be inadequate and the expert should indicate the deficiencies in the information necessary to assess recommending MRLs.

The toxicological information may be good enough for the Toxicology authors to make a judgement of the probable range of the ADI. Using this hypothetical value it may be possible to give an idea of possible MRLs which would be compatible with the recommended usage of the drug. To the extent the data permit, recommendations on MRLs should be harmonised for an individual tissue (e.g., muscle) in all target species. For substances used as veterinary drugs and as pesticides, reviewers should consult on any recommended MRLs by the Joint Committee on Pesticide Residues (JMPR) to harmonise MRLs when ever possible.

This appraisal section will form the basis of the section in the final monograph and the Blue Book Summary discussing MRLs.

References. Authors are recommended to follow the examples given in previous FAO/JECFA publications in series Nos. 41.

Editorial note:

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The Joint FAO/WHO Expert Committee on Food Additives (JECFA) is an international expert scientific committee that is administered jointly by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO). It has been meeting since 1956, initially to evaluate the safety of food additives. Its work now also includes the evaluation of contaminants, naturally occurring toxicants and residues of veterinary drugs in food.

More information on the work of JECFA is available at

www.fao.org/es/esn/jecfa/ /index_en.stm

www.who.int/pcs/jecfa/jecfa.htm