**Food and Agriculture Organization of the United Nations**

**World Health Organization**

**JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES**
**Sixty-sixth meeting (Residues of veterinary drugs)**
**Rome, 22 - 28 February 2006**

# SUMMARY AND CONCLUSIONS

*Issued 15 March 2006*

A meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) was held in Rome, Italy, from 22 to 28 February 2006. The purpose of the meeting was to evaluate residues of certain veterinary drugs in food.

Dr J.G. McLean, Camberwell, Victoria, Australia, served as Chairman, and Dr D. Arnold, Berlin, Germany served as Vice-Chairman.

Dr A. Wennberg, Nutrition and Consumer Protection Division, Food and Agriculture Organization of the United Nations, and Dr A. Tritscher, International Programme on Chemical Safety, World Health Organization, served as Joint Secretaries.

The present meeting was the sixty-sixth in a series of similar meetings and was the seventeenth meeting of JECFA convened to consider residues of veterinary drugs in food. The 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 recommend 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, comments on specific substances, and recommendations. The report will include an annex containing a detailed table (similar to Annex 1 in this summary) summarizing the conclusions reached by the Committee relating to ADIs and MRLs.

Items of a general nature that contain information that the Committee would like to disseminate quickly are included in Annex 2. The participants are listed in Annex 3.

Toxicological monographs summarizing the data that were considered by the Committee in establishing ADIs will be published in *WHO Food Additives Series No.57.* Residue monographs summarizing the data that were considered by the Committee in recommending MRLs will be published in *FAO JECFA Monograps No.2*.

More information on the work of JECFA is available at

www.fao.org/ag/agn/jecfa/index_en.stm and www.who.int/pcs/jecfa/jecfa.htm

***Annex 1***

***Recommendations on compounds on the agenda***

**Colistin** (antimicrobial agent)

Acceptable daily intake: The Committee established an ADI of 0–7 µg/kg body weight, on the basis of the $MIC_{50}$ of 1 µg /g of colistin base for *E. coli*.

Residue definition: Sum of colistin A and colistin B.

***Recommended maximum residue limits (MRLs)***

| Species | Fat[a] (µg/kg) | Kidney (µg/kg) | Liver (µg/kg) | Muscle (µg/kg) | Milk (µg/kg) | Eggs (µg/kg) |
|---|---|---|---|---|---|---|
| Cattle | 150 | 200 | 150 | 150 | 50 | |
| Sheep | 150 | 200 | 150 | 150 | 50 | |
| Goat | 150 | 200 | 150 | 150 | | |
| Pigs | 150 | 200 | 150 | 150 | | |
| Chicken | 150 | 200 | 150 | 150 | | 300 |
| Turkey | 150 | 200 | 150 | 150 | | |
| Rabbits | 150 | 200 | 150 | 150 | | |

[a]. The MRL includes skin + fat where appropriate.

**Erythromycin** (antimicrobial agent)

Acceptable daily intake: The Committee established an ADI of 0–0.7 µg/kg body weight, on the basis of the $MIC_{50}$ of 0.1 µg/g for *Bifidobacterium.*

Residue definition: Erythromycin A

***Recommended maximum residue limits (MRLs)***

| Species | Fat[a] (µg/kg) | Kidney (µg/kg) | Liver (µg/kg) | Muscle (µg/kg) | Eggs (µg/kg) |
|---|---|---|---|---|---|
| Chicken | 100 | 100 | 100 | 100 | 50 |
| Turkey | 100 | 100 | 100 | 100 | |

[a]. The MRL includes skin + fat where appropriate.

**Flumequine** (antimicrobial agent)

Acceptable daily intake: The Committee established an ADI of 0–30 µg/kg body weight at its 62nd meeting (WHO TRS No. 925, 2004).

Residue definition: Flumequine

***Recommended maximum residue limits (MRLs)***

| Species | Fat (µg/kg) | Kidney (µg/kg) | Liver (µg/kg) | Muscle (µg/kg) |
|---|---|---|---|---|
| Black tiger shrimp (*P. monodon*) | - | - | - | 500[a] |
| Shrimp | | | | 500[a, b] |

[a] The MRL is temporary. The following information is requested by the end of 2008: (1) Information on the approved dose for the treatment of diseases in shrimp and the results of residue depletion studies conducted at the recommended dose.
[b] The assignment of the temporary MRL applies to all freshwater and marine shrimp.

**Melengestrol acetate** (production aid)

Acceptable daily intake: The Committee established an ADI of 0-0.03 µg/kg body weight at its 54th meeting (WHO TRS No. 900, 2001).

Residues definition: Melengestrol acetate

***Recommended maximum residue limits (MRLs)***

| Species | Fat (µg/kg) | Liver (µg/kg) | Muscle (µg/kg) | Kidney (µg/kg) |
|---|---|---|---|---|
| Cattle | 18 | 10 | 1 | 2 |

**Ractopamine hydrochloride** (production aid)

Acceptable daily intake: The Committee established an ADI of 0–1 µg/kg body weight at its 62nd meeting (WHO TRS No. 925, 2004).

Residues definition: Ractopamine

***Recommended maximum residue limits (MRLs)***

The Committee maintained the MRLs recommended at its 62nd meeting (WHO TRS No. 925, 2004):

| Species | Fat (µg/kg) | Kidney (µg/kg) | Liver (µg/kg) | Muscle (µg/kg) |
|---|---|---|---|---|
| Cattle | 10 | 90 | 40 | 10 |
| Pigs | 10 | 90 | 40 | 10 |

**Trichlorfon (Metrifonate)** (insecticide)

Acceptable daily intake: The Committee confirmed the ADI of 0–2 µg/kg body weight established at its 60th meeting (WHO TRS No. 918, 2003).

Residues: The MRLs recommended by the 60th Committee were not reconsidered and were maintained.

**Triclabendazole** (anthelmintic)

Acceptable daily intake: The Committee established an ADI of 0–30 µg/kg body weight at its 40th meeting (WHO TRS No. 832, 1993).

Residues definition: Keto-triclabendazole

***Recommended maximum residue limits (MRLs)***

| Species | Fat (µg/kg) | Kidney (µg/kg) | Liver (µg/kg) | Muscle (µg/kg) |
|---|---|---|---|---|
| Cattle | 100 | 100 | 200 | 150 |
| Sheep | 100 | 100 | 200 | 150 |
| Goats | 100 | 100 | 200 | 150 |

***Annex 2***

***General considerations***

*An edited version of this section will appear in the report of the sixty-sixth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). It is reproduced here so that the information is disseminated quickly. This draft will be subject to extensive editing.*

**2.1. General principles regarding the evaluation of veterinary drugs within the terms of reference of JECFA, including compounds without ADI or MRL**

The Committee considered in detail the recommendation from the Bangkok workshop (Joint *FAO/WHO Technical Workshop on Residues of Veterinary Drugs without ADI/MRL, final report 2004)* and the draft paper prepared by the CCRVDF working group to address recommendations from this workshop in relation to veterinary drugs with no JECFA ADI or MRL (*Report of the working group on residues of veterinary drugs without AD/MRL, CX/RVDF 06/16/13, document for discussion at the 16th session of CCRVDF)*. In addition, other relevant parts of the 2005 Bilthoven MRL Workshop final report (*Updating the Principles and Methods of Risk Assessment: Maximum Residue Levels (MRLs) for Pesticides and Veterinary Drugs, final report of the joint FAO/RIVM/WHO workshop 2006*) were considered. In this context, the Committee discussed a number of closely linked issues, including data availability for compounds to be evaluated and the general terms of reference of the Committee, and are reported together because of the close linkage.

**Response to recommendations of the 2004 Bangkok meeting, and the 2005 report of the Codex Working Group on Residues of Veterinary Drugs on compounds without ADI/MRL**

Considering the recommendations of the 2004 *FAO/WHO Technical Workshop on Residues of Veterinary Drugs without ADI/MRL* the Committee noted that there existed a potential misunderstanding conveyed by the report of the data requirements for certain risk assessment tools. Mathematical modeling tools such as the Benchmark Dose offer alternative approaches to the traditional NOEL approach, but still require qualitatively similar dose-response data. The threshold of toxicological concern, while offering an alternative to the compound specific data needed for an ADI requires a significant amount of physico-chemical, pharmacological, and toxicological data about the compound class, and also chemical structure and exposure data about the compound of interest. Similarly, analysis of the risk presented to consumers by residues of a veterinary drug in the absence of an ADI calls for much the same kinds of data as are necessary to establish an ADI and MRL. The Committee also noted the usefulness of alternative approaches to the evaluation of veterinary drugs and the potential to provide meaningful information to risk managers responsible for mitigating this risk, particularly when it is not possible to set an ADI.

**The role and relationship of risk management and risk assessment in the evaluation process**

The risk analysis paradigm sets out specific roles for risk management and risk assessment. One of the roles of risk management is to formulate requests for specific information to be developed through a scientific risk assessment process. It is important that the specific information requests be clearly articulated to assure that the risk assessment response will properly address the problem identified by risk management. The evaluation of residues of veterinary drugs by the JECFA is designed to provide answers to a series of information

requests from the Codex risk managers. While seldom spelled out, these questions typically take the following form:

The JECFA is requested to develop the following scientific information regarding the veterinary drug.

1. A characterization of the hazard for human consumption presented by residues of the drug in edible tissues, milk and eggs.
2. Establishing an acceptable daily intake for residues of the drug
3. Recommend a maximum limit for residues of the drug in the edible tissues, milk and eggs of target species that will not result in an exposure to the human consumer in excess of the ADI.
4. In the event that an ADI or MRL cannot be determined:
    a. Define the scientific basis that prevents the determination of an ADI or MRL, identify the data gaps, and characterize the hazard for human consumption presented by the drug.
    b. Characterize the exposure to the human consumer of residues of the veterinary drug in the edible tissues, milk and eggs of treated animals.
    c. Recommend analytical methods and concentrations derived from the performance characteristics of the method that could be used to manage the risk presented by residues in food.
5. Advice on the characterization of the health risk of compounds from specific exposure scenarios.

The Committee further noted that the nature of the risk assessment determines the data needed for an adequate evaluation of the veterinary drug. In particular, it noted that the development of the MRL is dependant upon information related to, and developed in accordance with good practice in the use of the veterinary drug of interest. The critical impact of this veterinary drug use information underscores the need to have information provided resulting from the registration process in competent national authorities for the intended use of the veterinary drug.

**Criteria for compounds to come on the JECFA agenda**

The Committee considered the current criteria established by Codex for veterinary drugs to be evaluated by the JECFA. These criteria are:
In order to be placed on the CCRVDF priority list for the development of a maximum residue limit, the candidate veterinary drug, when used in accordance with good veterinary practices, should meet some, but not necessarily all, of the following criteria:

1. Use of the drug will have potential to cause public health and/or trade problems;
2. Drug available as commercial product;
3. Commitment that a dossier will be available

The Committee considered that the process of prioritization of veterinary drugs for evaluation by Codex, and the process of risk assessment of the veterinary drug by JECFA would be greatly improved by adherence to these criteria and provision of the information to the JECFA secretariat.

The Committee expressed concern regarding recent experience with veterinary drugs submitted for evaluation where data relevant to the risk assessment were either inadequate or not available to the Committee. The Committee suggested that the request for evaluation by a member country be accompanied by evidence of the nature and extent of the available data. While there are a number of ways to provide this information, the Committee suggested that a table of contents of the material to be provided would be a valuable tool in assessing the

availability of data for evaluation. In addition, the Committee noted that document CX/RVDF 06/16/10, dated October 2005 contains an annex "Template for the Establishment of a Preliminary Risk Profile" (see chapter 2.2.), which may be useful in this context. The information identified in this annex would be extremely useful in the risk assessment of veterinary drugs if provided to JECFA with the initial request for evaluation of the compound.

**Issues relating to data availability**

In reaching its conclusions on ADIs and MRLs, the Committee evaluates the available data, including that submitted by the sponsor and that identified in a search of the open literature. The Committee's decisions depend on consideration of the primary data. Limited reliance is placed on summary or review data alone, if not supported by relevant primary data. On a number of occasions, limited or at times no data are available for evaluation of compounds on the meeting agenda. Hence, in these instances, the Committee is unable to complete its evaluation because of significant gaps in the database. On such occasions, the Committee will identify the critical gaps and will suggest those additional data that should enable the evaluation to be concluded. The Committee is concerned that even after a reasonable time interval, appropriate data are either not being generated or submitted to the Committee. It is important to note, that JECFA is not a regulatory body and has no means to compel data submission. Hence, possible strategies to help resolve these issues were sought.

The Committee proposes that lists of veterinary drugs of public health concern be introduced. This would comprise two categories:

i) Veterinary drugs for which significant concerns had been identified, either because of incomplete information or pending resolution of a problem identified in the evaluation
ii) Veterinary drugs for which these concerns were not addressed, despite requests for data to resolve the outstanding issues. It is recommended that these compounds should not be used in food producing animals until outstanding data are provided and evaluated by JECFA.

Compounds would remain in category i) for a specified period and would then either be removed from the list because of resolution of the concerns, or would be moved to category ii). The Committee recommends that CCRVDF take an active role in establishing and supporting such lists, and should emphasize the need for Codex members and commercial entities to fulfill their responsibility in submitting relevant data in a timely manner.

**Considerations related to the terms of reference of JECFA**

*Information on approved uses*
Assessment of efficacy is not within the mandate of the Committee. However, since one of the criteria for scheduling a compound for JECFA evaluation is that the veterinary product containing the active compound is currently registered by a national or regional authority, confirmation of its authorisation, including approved dosages and conditions of use, should be provided in the data submission.

*Risk-benefit comparison*
The Committee recognizes that CCRVDF may use risk benefit considerations in prioritising compounds for evaluation. The number of veterinary drugs available and approved for certain therapeutic indications is very limited, and there is general concern that loss of a compound may have significant impact on food animals and derived products. Consideration of the relative

benefit provided by the availability of such a drug is outside the scope of the Committee, which has neither the mandate nor the expertise to address such questions. Hence, JECFA will continue to restrict its considerations to the human health risks of the compound.

**Considerations related to flexibility in the scientific process of the JECFA risk assessment**

The Committee discussed the rapid developments in science typified by the fields of genomics, proteomics, analytical chemistry, mathematical modeling, and new toxicological testing methods, together with the need to be able to bring to bear the most appropriate tools in the evaluation of veterinary drugs. The Committee recognized the continued need for flexibility in its approach and the importance of balancing this flexibility with consistency. The Committee also recognized that some of these new tools and technologies may require validation.

JECFA risk assessment should not be tied to specific approaches. JECFA will continue to apply the necessary flexibility to bring to bear the most appropriate science and risk assessment techniques.

**A decision tree approach in the evaluation of veterinary drugs by JECFA**

The Committee recommended that the JECFA Secretariat convenes a working group to develop a general decision tree for the evaluation of veterinary drugs which would identify different options for hazard identification, for hazard characterization and exposure assessment. The proposed approach will then be discussed at the next JECFA meeting dedicated to the assessment of veterinary drugs. The decision tree would be anticipated to provide a tool to assist in assessing different options in the evaluation of the veterinary drug, including the determination of a “traditional” ADI and recommended MRL. The decision tree is envisioned as a flexible document that will be adapted to advancement in science and in response to the nature of the compounds under evaluation. The working group will be expected to develop possible branches to the decision tree to make use of the best science available. Other options which may be considered are the use of a threshold of toxicological concern as an alternative to an ADI, and recommendations for analytical methods for the detection of residues of the drug in the absence of a formal MRL.

**2.2. Comments on the CCRVDF document ‘RISK MANAGEMENT METHODOLOGIES, INCLUDING RISK ASSESSMENT POLICIES IN THE CODEX COMMITTEES ON RESIDUES OF VETERINARY DRUGS IN FOODS’**

The Committee discussed the document, in particular Appendix 1, and provides the following comments to CX/RVDF/06/16/10:

**General Remarks**

The document has changed significantly from previous versions that JECFA had commented on, not only by title and content, but also by scope. The current title does not match the actual content, which covers both risk assessment and risk management within the context of Codex and the respective roles of CCRVDF and JECFA. Hence, it is recommended that the title be changed to reflect the fact that the document covers risk analysis principles: ‘Risk Analysis Principles Applied by the Codex Committee on Residues of Veterinary Drugs in Food’.

The current document introduces terminology, for example risk profile, level of protection, that is used in microbiological risk analysis and currently not used by JECFA and CCRVDF in the

evaluation of veterinary drug residues. Overall it is not clear if the document is describing current procedures, or is describing a way of working that should be achieved in the future.

It was brought to the Committee's attention by the secretariat that the corresponding document by CCPR is significantly different in level of detail and scope, as well as in the terminology used. The Committee noted that JECFA and JMPR have undertaken efforts to harmonize their procedures. Although JECFA and JMPR are independent scientific expert bodies, the main users for their scientific advice are the respective Codex Committees, CCRVDF and CCPR. It is therefore desirable that the Codex Committees also harmonize their procedures as appropriate.

**Specific Comments**

**Appendix 1**

1. Purpose – Scope

The current text does not give sufficient explanation of the purpose of the document.

3. Risk Management in CCRVDF

It is not clear if this part describes what CCRVDF understands to be current practice, or how risk management activities should be undertaken in the future. Once the responsibilities of risk assessors and risk managers are clearly defined in the document, the process in general as described would greatly facilitate the interaction between CCRVDF as the risk management body and JECFA as the risk assessment body.

In the current text under this chapter entitled 'Risk Management in CCRVDF' there is no clear description and separation of the roles and responsibilities of CCRVDF and JECFA. To this end, it would be useful to separate the roles of CCRVDF and JECFA, and to separate out risk management and risk assessment activities.

The need for a clear request from the risk manager, CCRVDF, to the risk assessor JECFA, is implicit in several places but should be stated more explicitly, as is the importance of dialogue between the two to ensure that the form of the risk assessment meets the requirements of the risk manager. As an example, JECFA might be asked to consider the consequences for human health for a number of risk management options.

Some of the suggestions have significant logistical and resource implications. Hence, some distinction needs to be made between what is desirable and what is essential. Some consideration needs to be given to how these logistical and resource limitations can be overcome.

Some of the proposals would require significant changes in risk assessment practice. Such changes would have implications far beyond the activities of JECFA. Hence, consideration should be given to the need to ensure harmonization, for example through IPCS.

The document should provide guidance as to the basis for requesting JECFA to reconsider an evaluation, to ensure the integrity of the process.

**Annex to Appendix 1: Template for the establishment of a preliminary risk profile**

The Committee concluded that this document would be very useful in the preliminary evaluation of veterinary drugs and in prioritizing the compounds for evaluation (although, as indicated above, the term “risk profile” should be reconsidered).

**Appendix 2: Proposed draft risk assessment policy for the setting of MRLVDS in food**

As above, this section needs to distinguish clearly between the roles of CCRVDF as risk manager and JECFA as risk assessor.

Consideration needs to be given as to how best to balance the scientific integrity and expertise of the risk assessment with other issues related to membership of JECFA, such as geographical distribution. In addition, to help development of capacity, the training of experts needs consideration.

The document should reflect and build upon previous international consensus, for example on core principles for the provision of scientific advice.

There is a lack of clarity with respect to the issue of intake assessment. It is not clear whether a major change in approach is being recommended, and if so, the feasibility of this needs to be considered.

### 2.3. Expression of the ADI and derivation of the MRL

#### Introduction

The CCRVDF at its 15th session discussed rounding practices when establishing ADIs and recommending MRLs for veterinary drug residues and requested JECFA to comment on certain practices suggested by CCRVDF.

The Committee considered the expression of the ADI at its thirty-sixth meeting in 1990. The Committee decided to express the ADI numerically to only one significant figure. If an ADI is calculated from a NOEL that has more than one significant figure, the ADI would therefore be rounded to one significant figure, consistent with accepted rounding procedures.

In the past, JECFA has applied its rounding practice to the derivation of ADIs for 25 veterinary drugs, resulting in 14 ADIs have been rounded down and 11 ADIs have been rounded up. Most of the veterinary drugs that have been reviewed by JECFA resulted in a calculated ADI of one significant figure without rounding.

The present Committee noted that the recommendation from the CCRVDF (report from the 15$^{th}$ session of CCRVDF Alinorm 05/28/31) suggests a misunderstanding of the relationship between the ADI and the derivation of the MRL.

#### General considerations at the current meeting

One of the functions of JECFA is to establish health-based guidance values for residues of veterinary drugs, most often an ADI. The ADI is an output of a risk assessment of the compound, following application of the first two steps of the risk assessment paradigm: hazard identification and hazard characterization. As such, it represents a health-based guidance value, where exposure is considered to represent a negligible risk to consumer if it does not exceed this value. The ADI has a number of uses in risk assessment and risk management, only one of which is in helping to derive the recommended MRLs.

The MRL and the ADI are separate outputs of the risk assessment process and serve different purposes.

The ADI is derived from the NOEL/LOEL from the appropriate toxicological studies, using a safety factor. Given that there are assumptions and uncertainties in deriving the ADI, such as the use of safety factors, the use of a range of doses in toxicological studies and normal biological variation, it is more meaningful to express the ADI to only one significant figure to avoid any inference of inappropriate precision.

The general rounding rule for mid-way values (x.5) is to round up, in line with common convention (see for example Australian Standard AS 2706-2003). Examples for rounding to one significant figure are as follows: 1.25 becomes 1, 0.73 becomes 0.7, and 1.5 becomes 2.

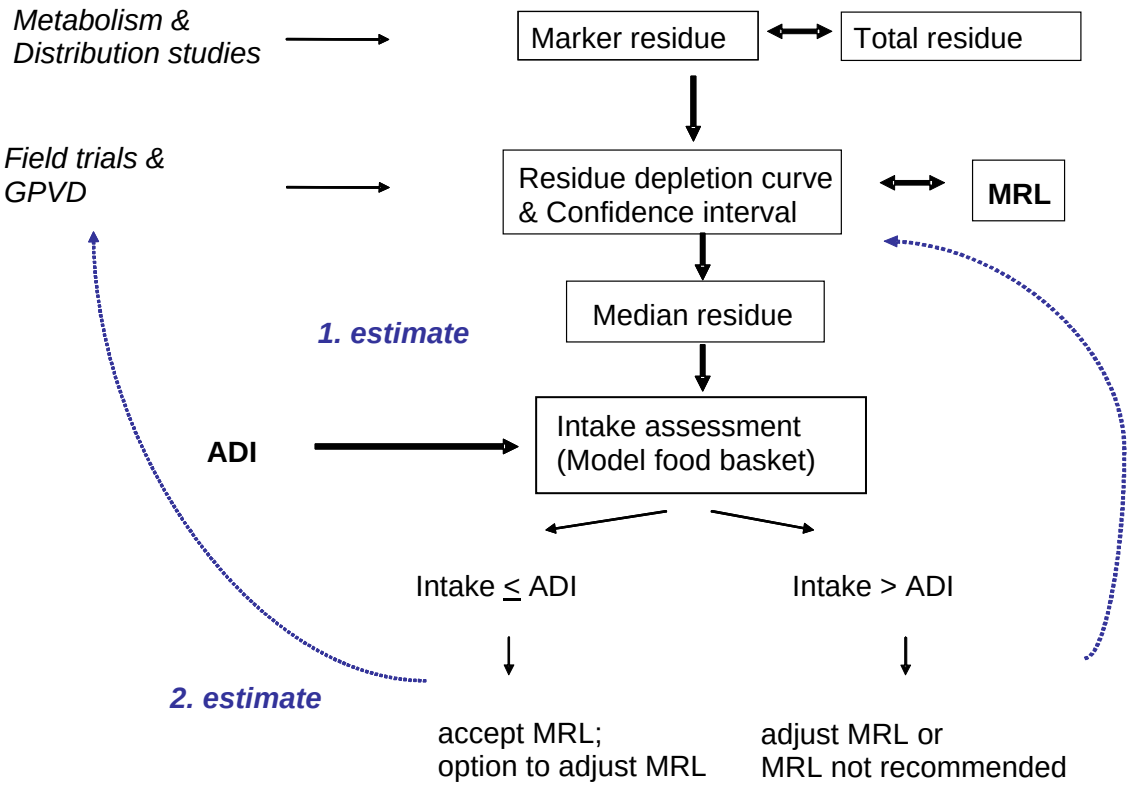
The MRL recommendation procedure is an iterative process. The MRL is not derived directly from the ADI. If the ADI is based on toxicological end-points, all residues of toxicological relevance are considered, if the ADI is based on microbiological end-points, all residues of microbiological relevance are considered. The MRL recommendation procedure also takes into account the conditions of use (e.g. use of the veterinary drug according to good practice in the use of veterinary drugs GPVD) and the residues that result from such use (e.g. residue depletion studies). It also considers results of radiolabel residue studies, the bioavailability of bound residues, the identification of target tissues and a marker residue, the availability of practical analytical methods, estimated exposure resulting from recommended MRLs and consideration of extension of the MRLs to tissues, eggs and milk of other species.

The initial consideration in recommending an MRL is whether it is sufficiently protective of human health. If the use of the veterinary drug yields an estimated intake of veterinary drug residues consistent with the ADI, the recommended MRLs may then be adjusted accordingly when taking into account the other factors noted above. As a general principle, the Committee will not normally recommend an MRL that results in residue levels that lead to dietary intake exceeding the ADI based on toxicological or microbiological considerations.

To protect consumers in all segments of the population, historically the Committee has based its recommendations on intakes estimated using a conservative model diet consisting of 300 g of muscle, 100 g of liver, 50 g of kidney and fat, 1.5 kg of milk and 100 g of eggs. Previously, the Committee estimated intakes by using MRLs to derive a Theoretical Maximum Daily Intake (TMDI). At the current meeting, the Committee modified this procedure and is now using the median residue levels to derive estimated daily intake (EDI) to better reflect estimates of chronic (lifetime) exposure (see section 2.4.1).

The following is an update of the figure prepared during the Bilthoven MRL workshop (*Updating the Principles and Methods of Risk Assessment: Maximum Residue Levels (MRLs) for Pesticides and Veterinary Drugs, final report of the joint FAO/RIVM/WHO workshop 2006*).

**JECFA Residue Evaluation**




**Conclusions**

The Committee confirmed that the rounding practices used in expressing the ADI are scientifically and mathematically sound. In addition, since the ADI is not directly used in the derivation of the MRL, the JECFA rounding practice has no direct consequence on the MRL.

### 2.4. Recommendations on principles and methods on derivation of MRLs

The Food and Agriculture Organization of the United Nations, the Netherlands National Institute for Public Health and the Environment and the World Health Organization (FAO/RIVM/WHO) organized a joint workshop on "Updating the Principles and Methods of Risk Assessment: Maximum Residue Levels (MRLs) for Pesticides and Veterinary Drugs", within the framework of the Project to Update the Principles and Methods for the Risk Assessment of Chemicals in Food. The main objective of this workshop was to review principles and procedures used by JECFA and JMPR in recommending MRLs and to reaffirm those that remain valid in view of current scientific knowledge; and harmonize to the extent appropriate.

The workshop resulted in a number of recommendations, several of them addressed to JECFA. The 66th JECFA considered these recommendations and the conclusions are listed below.

Recommendations and JECFA Comments and Conclusion

*The risk assessment framework for proposing MRLs*

1. JECFA should consider the use of the concept of the acute reference dose (ARfD) in addition to the ADI, when a veterinary drug being considered exhibits acute toxicity. JECFA should develop procedures to discriminate between ADI and ARfD for cases where it would be appropriate to estimate short-term (acute) intakes.

| |
|---|
| The Committee recommended that a paper should be prepared by an expert for the next meeting which considers compounds for which ARfD considerations are necessary, and propose a procedure for establishment of such values taking previous JECFA guidance and the ARfD guidance developed by JMPR into account. The paper also needs to consider the impact on intake assessment methods. |

*Identification and description of residues and methods*

2. The workshop concluded that the definition of a pesticide residue and a veterinary drug residue are essentially the same. The definition for “residues of veterinary drugs” could be made more consistent with the definition for “pesticide residue” by the addition of the phrase “considered to be of toxicological significance”.

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|---|
| The 66th Committee agreed to amend the definition of veterinary drug residues to: Parent compounds and/or their metabolites, including associated impurities of the veterinary drug concerned, in any edible portion of the animal product, which may be of significance to human health. |

3. The workshop recommended that FAO prepare a guidance manual to define, in detail, data needs and evaluation procedures for residue definitions and the derivation of MRLs for veterinary drugs.

| |
|---|
| The Committee recommends that FAO develop a guidance manual for submission and evaluation of data. |

4. JECFA should recommend MRLs for fat-soluble dual-use substances only for the trimmable fat from the meat.

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|---|
| JECFA has considered this in the past and the Committee reaffirmed the existing practice. |

5. Partitioning of residues in milk into the fat is influenced by the molecular structure of the compound. Furthermore, the fat content of milk is variable. JECFA proposes MRLs for whole milk. JMPR now recommends two MRLs for fat-soluble compounds, one on whole milk and one on milk fat. This is necessary to estimate residues in processed dairy commodities. The workshop recommended that JECFA and JMPR consider harmonizing this practice.

JECFA agrees to recommend MRLs for whole milk and for milk fat in the future. The Committee requested the Secretariat to reflect this in future calls for data.

*Criteria for selecting data, species, commodities*

6. For dual-use substances the evaluation of the application as a pesticide/drug to animals should be undertaken using the same principles. This can be achieved by several means that require co-ordination between JECFA and JMPR and also CCRVDF and CCPR (risk assessment policy) and will involve the adoption of mutual notification and co-ordination of procedures.

The Committee agreed on the importance of the coordination between JECFA and JMPR for dual-use substances and requested the Secretariat to take this into consideration when scheduling compounds for evaluation.

7. JMPR and JECFA should carry out a comprehensive review of all commodity and tissue definitions. As appropriate: harmonizing meat and muscle tissue definitions, combining definitions of poultry and poultry meat, avoid subdivision into specific commodities for milk and eggs, harmonize definition of animal fat to be equivalent and to exclude dairy milk, harmonize definitions for aquatic species, and consider whether JECFA MRLs for liver and kidney should include other offal. Subsequently, amending instructions on the portion of commodity to which the MRL applies is recommended.

The Committee recommended that the Secretariat convene a working group to address this issue.

*Extrapolation issues*

8. National governments are encouraged to submit GAP information particularly on ‘minor crops’ during the data and information call-in process for JMPR.

No action necessary.

9. JMPR should continue to evaluate extrapolation of pesticide residues data between geographic zones.

No action necessary.

10. JECFA should investigate a specific approach for MRLs in honey.

The Committee recommended that a paper be prepared by an expert with experience in beekeeping and honey production for the next meeting to consider if a separate approach for honey is warranted and in such case develop a draft recommendation for consideration at the next meeting.

11. Procedures for extrapolation from one species of animal having a full data set and recommended MRLs to another species need to be agreed upon and harmonized guidance documents prepared. This should be based on past experience with specific cases.

The Committee concluded that extrapolation may not be the appropriate term, but rather extension of the MRL. This was applied at this meeting to the MRL of flumequine for shrimps. The Committee noted that there is no formal procedure for extending MRLs, and further action on this is necessary.

12. A general principle on recommending Group MRLs in wider circumstances should be considered in an attempt to cover more uses where national authorizations exist.

The Committee has set group MRLs in the past and continues this practice, but the group MRL for JECFA needs to develop a definition of 'group-MRL'.

*Dietary risk assessment of residues*

13. To improve the international food consumption information data base, national governments should be encouraged to submit their consumption data to FAO and WHO.

No action necessary.

14. JECFA should consider using the median value of the distribution of residue concentrations from which the MRL is derived for the calculation of conservative estimates of long-term (chronic) intakes.

The Committee considered this recommendation and adopted the approach as described below in 2.4.1.

### 2.4.1 New Procedure for the Estimating of Chronic Dietary Intakes

The estimation of long-term (chronic) dietary intakes of residues of veterinary drugs by the Committee was in the past closely linked to the determination of the MRLs recommended by the Committee. The Committee used a calculated figure of total residue of toxicological or microbiological concern, the "Theoretical Maximum Daily Intake" (TMDI) for comparison with the ADI. The new procedure uses the same formula as used previously for the calculation of the TMDI including factors such as the ratio of marker to total residue concentrations - with the only exception that the median concentration replaces the MRL as point estimate of the residue concentration in the formula.

The MRL and the median concentration are derived from the same time point of the depletion data of the marker residue. The MRL is a point on the curve describing the upper one-sided 95% confidence limit over the $95^{th}$ percentile. The median is the corresponding point on the regression line for the same time point. Both figures are obtained from a statistical evaluation of the data (see figure 1).

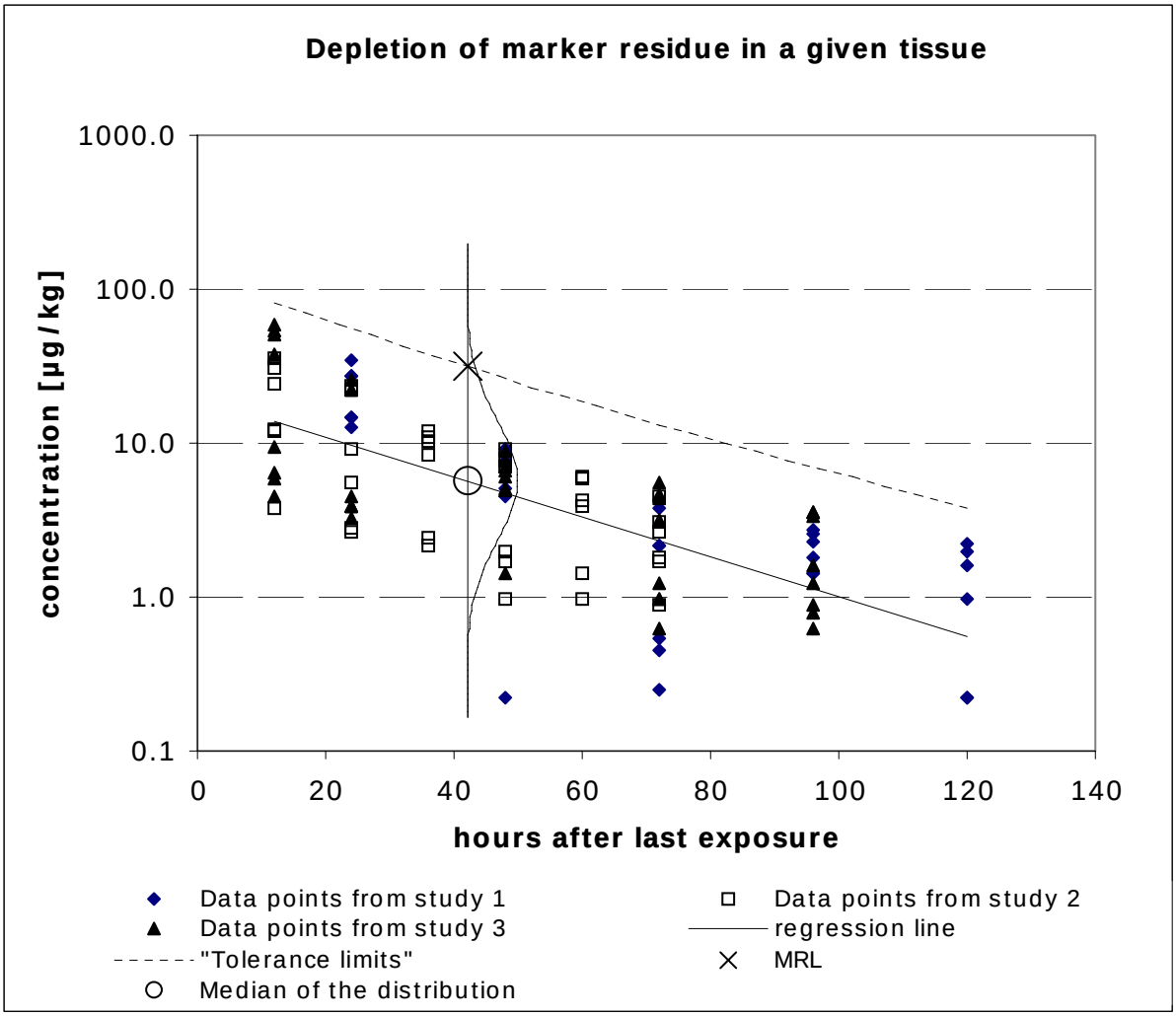


Figure 1 Explanation of the relationship between MRL and the median concentration used for the calculation of the Estimated Daily Intake

In developing this new calculation procedure, the present Committee concluded that the TMDI was no longer the most suitable estimate of chronic intake because the MRL was a single concentration representing the estimated upper limit of a high percentile of the distribution of marker residue present in a given tissue of the treated animals. The Committee concluded that it was not realistic to use an extreme value of the distribution in a scenario describing chronic intakes. In such a scenario all concentrations of the distribution of residues should be considered. The median concentration represents the best point estimate of a central tendency over a prolonged period of time, because the concentrations of residues in a given tissue consumed varies from day to day as reflected in the distribution. Therefore the Committee decided to use the median of the residue distribution to substitute for the MRL in the intake estimate. The new estimate of intake is called “Estimated Daily Intake”. In calculating the median from an array of results including values below the limit of quantification (LOQ) or below the limit of detection (LOD) half of the respective limit is used for the calculation of median concentrations of residues.

### 2.5. Use of spread sheet-based Procedure for Statistical Evaluation of Residue Depletion Data

The Committee has used on several occasions a statistical approach for the evaluation of marker residue depletion data when estimating MRLs. The approach is primarily based on linear regression analysis and statistical estimation of one-sided upper tolerance limits for the marker residue depletion in the individual target tissues (see also figure 1 of section 2.4.1 of the report). An iterative procedure is then used to calculate for different time points on the depletion curve the intake of residues of concern in the food basket. The calculated intake of residues is compared with the ADI and the time point of depletion below the ADI is selected to determine the MRLs.

At the 62nd meeting of JECFA the FAO Joint Secretariat proposed to the Committee an Excel-based workbook facilitating the complex calculations required to use this approach. The Committee investigated the workbook and recommended that the Secretariat should continue with its development. In order to take the necessary steps, the Secretariat requested comments from interested parties on both the features and the documentation of the tool. Comments were received from Canada, the EMEA, the IFAH and Argentina. The Committee reviewed all comments and noted that all respondents agreed that the mathematical/statistical approach was scientifically sound. Some comments analysed the advantages and the limitations of use of the workbook in a very objective manner. The comments from Canada, EMEA and Argentina supported the use of the statistical approach and of the tool in cases where it was appropriate. IFAH indicated that “IFAH does not support use of this programme by JECFA in any of its reviews of veterinary medicinal products” because the organization considered it was a tool to calculate withdrawal times which falls outside the terms of reference of JECFA. The Canadian comment suggested that JECFA should use the approach whenever possible and explain the reasons if it is not used.

The Committee concluded that the workbook would primarily be of value in assisting the experts to statistically evaluate available depletion data during the development of MRL recommendations. The Committee also concluded that it would use the statistical approach in future whenever it was appropriate and the experts drafting the working documents should explain to the Committee the reasons when not using it.

### 2.6. Revised approach for the derivation of a microbiological ADI

The Committee considered the VICH guideline entitled *Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Establish a Microbiological ADI*, dated May 2005 (VICH GL36). The document provides guidance on the assessment of human food safety for residues of antimicrobial veterinary drugs with regard to effects on the human intestinal microflora. The guideline provides recommendations for a harmonized approach for establishing microbiological ADIs. A decision-tree approach for the evaluation of antimicrobial veterinary drugs was introduced by JECFA at its 45$^{th}$ meeting in 1995 (WHO TRS No. 864, 1996) and later adopted at its 52nd meeting in 1999 (WHO TRS No. 893, 2000). Similar approaches have been subsequently developed and used by several regulatory authorities. In the interest of harmonization of methods, VICH developed a guideline which was recently finalized.

The VICH guideline is a refinement of the current JECFA approach. The Committee, in recognition of the importance of international harmonization, agreed to incorporate the VICH guideline in future assessments to ensure consistency and transparency in the determination of microbiological ADIs.

## *Annex 3*

### Sixty-sixth meeting of the Joint FAO/WHO Expert Committee on Food Additives

Rome, Italy, 22–28 February 2006

**Members**

Professor Arturo Anadón, Faculty of Veterinary Medicine, Universidad Complutense de Madrid, Spain

Dr Dieter Arnold, Berlin, Germany *(Vice-Chairman)*

Professor Alan R. Boobis, Faculty of Medicine, Imperial College, London, England

Dr Richard Ellis, Consultant, Myrtle Beach, South Carolina, USA

Dr Adriana Fernández Suárez, Instituto Nacional de Tecnología Agropecuaria, Buenos Aires, Argentina (unable to participate)

Dr Kevin Greenlees, Food and Drug Administration, Rockville, MD, USA

Dr James MacNeil, Canadian Food Inspection Agency, Saskatoon, Saskatchewan, Canada

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

Professor Joao Palermo-Neto, Faculty of Veterinary Medicine, University of São Paulo, São Paulo, Brazil

Dr José Luis Rojas Martínez, Ministerio de Agricultura y Ganadería, Heredia, Costa Rica

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

Professor G.E. Swan, Faculty of Veterinary Science, University of Pretoria, Pretoria, South Africa

Dr Janenuj Wongtavatchai, Faculty of Veterinary Science, Chulalongkorn University, Bangkok, Thailand (unable to participate)

**Secretariat**

Dr Carl E. Cerniglia, Food and Drug Administration, Jefferson, AR, USA (*WHO Temporary Adviser*)
Dr Maria de Lourdes Costarrica, Nutrition and Consumer Protection Division, Food and Agricultural Organization, Rome, Italy *(FAO Staff Member)*
Dr Lynn G. Friedlander, Food and Drug Administration, Rockville, MD, USA (*FAO Expert*)
Dr Sang-Hee Jeong, Ministry of Agriculture and Forestry, Anyang City, Republic of Korea *(WHO Temporary Adviser)*
Dr Jacek Lewicki, Faculty of Veterinary Medicine, Warsaw Agricultural University, Warsaw, Poland (*FAO Expert*)
Dr Phil T. Reeves, Australian Pesticides and Veterinary Medicines Authority, Kingston, ACT, Australia (*FAO Expert*)
Dr Scott McEwen, Ontario Veterinary College, University of Guelph, Guelph, Ontario, Canada (*WHO Temporary Adviser*)
Dr Shogo Ozawa, National Institute of Health Sciences, Tokyo, Japan (*WHO Temporary Adviser*) (unable to participate)
Professor Len Ritter, Department of Environmental Biology, University of Guelph, Ontario, Canada (*WHO Temporary Adviser*)
Dr Gladwin Roberts, Greenway, Australia (*WHO Temporary Adviser*)
Mrs Marla Scheffer, Orleans, Ontario, Canada *(WHO Editor)*
Dr Steven Sundlof, Food and Drug Administration, Rockville, MD, USA (*WHO Temporary Adviser*)
Dr Angelika Tritscher, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland (*WHO Joint Secretary*)
Dr Annika Wennberg, Nutrition and Consumer Protection Division, Food and Agriculture Organization, Rome, Italy *(FAO Joint Secretary)*