



Food and Agriculture  
Organization of the  
United Nations



World Health  
Organization

Module II: Scientific  
guidelines for the preparation  
of veterinary drug residue  
monographs, working papers  
and related summary  
documents for Joint  
FAO/WHO Expert  
Committee on Food Additives  
(JECFA) drafting experts and  
reviewers assigned by FAO

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## **Module II**

# **Scientific guidelines for the preparation of veterinary drug residue monographs, working papers and related summary documents for JECFA drafting experts and reviewers assigned by FAO**

## **1. Introduction to preparation of residue monographs**

### **1.1 Format**

A standard format has been developed by JECFA for monographs dealing with the evaluation of veterinary drug residues in foods. All residue monographs should have a common appearance, order of presentation and level of detail. While these issues are addressed in this guidance document, drafting experts are also advised to read monographs from recent meetings to ensure that the writing style and format that they use in drafting a monograph are consistent with the style and format currently used by the Committee. All JECFA residue evaluation monographs are available at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-publications/en/>.

### **1.2 Style, order and layout**

The writing style used in JECFA monographs and summary documents should be impersonal, as required in publications submitted to scientific journals. All studies should be properly referenced and opinions, where stated, should be identified as such. A more personal style may be used in the “Appraisal” section of the monograph, which provides an overview of the studies and an expert assessment of the information provided in the studies. The assessment must be objective and should avoid derogatory comments. If the drafting expert considers a particular study to be deficient, the specific deficiencies should be stated.

Authors should observe the following instructions in preparing a monograph and the accompanying summary:

- Use the appropriate Microsoft Word templates from Module III, which include the required font sizes for headings and body text.
- Pages should be in A4 format, numbered in the top right corner.
- Lines should be numbered. Re-start line numbers on each page of monographs; sequential line numbers may be used for the draft TRS summary documents.
- Tables and graphs should have a number, a title and if appropriate, a legend. They should be able to "stand alone" from the text. Graphs should elaborate and not duplicate other text or tables. Do not lock tables or figures in place on a page of text as this can cause problems in editing.
- Graphics should be compatible with the word processing language and clearly printable, in A4 format.
- Include a header with the names of the substance, authors and version number (e.g., draft 1) and date. Update the header with revised version numbers and dates each time

the document is revised and circulated to the Joint Secretary and other Committee members.

- Page numbers should be inserted as a header in the upper right corner of the page, beginning on page 2.

The monograph can take two forms, as a first time submission of the drug with a complete data package or as a subsequent review (addendum). An addendum typically includes a “Background” section outlining the previous Committee decisions and the reason for the current assessment. The same general format is used in both cases, but some headings may be omitted in an addendum or new headings may be required in some special cases, such as the review of potential environmental sources of chloramphenicol residues in foods conducted by the 62<sup>nd</sup> JECFA, published in the WHO compilation of toxicological monographs from the meeting.<sup>1</sup>

### 1.3 Objectives (what to include and how to present)

The objective is to provide a factual summary of all studies considered relevant by the drafting expert, reviewers and the Committee, whether provided by a Sponsor or obtained from other sources, such as literature reviews. The studies should enable the drafting expert and reviewer(s) to conduct a full evaluation of the nature and depletion of the residues of the substance, including a dietary exposure assessment, and to formulate **Maximum Residue Limits** (MRLs) which may be recommended by the Committee. The information should be presented clearly and transparently so that third parties can understand the basis of the JECFA decisions and recommendations.

### 1.4 Drafting expert and reviewer responsibilities

The purpose of the evaluation of the available residue information for a substance by the assigned drafting expert and reviewer(s) is to provide an independent scientific assessment of the quality of the available data and to determine whether MRL recommendations may be formulated for consideration by the Committee. Although a dossier from a Sponsor will usually include a summary report prepared by the Sponsor, this should not be used as a primary information source by the drafting expert. The drafting expert and assigned reviewer(s) should independently review each available study provided by the Sponsor, plus any other information obtained, such as publications from the peer-reviewed literature. The drafting expert and reviewer(s) should not rely on the summary tables contained in a report of a study provided by the Sponsor. Drafting experts and reviewers should prepare their own tables and figures following an analysis of the raw data provided in the annexes to the study to provide their own expert interpretation and analysis of the information. When the raw data are available for studies published in scientific journals, a similar approach should be taken to the evaluation of the data. When preparing the tables and figures for the monograph, the drafting expert and

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<sup>1</sup> WHO. (2004). *Toxicological evaluation of certain veterinary drug residues in food*, Sixty-second report of the Joint FAO/WHO Expert Committee on Food Additives, WHO Food Additives Series, No. 53, pp. 7-84; available at <http://www.who.int/foodsafety/publications/monographs/en/>.

reviewers should verify the means, medians and standard deviations and other quantities, such as elimination half-lives, that are reported. It is acceptable to use certain information contained in the Sponsor report, with permission from the Sponsor, such as chemical structures and metabolic pathway diagrams that may be included in the monograph.

As the Sponsor's submission includes an interpretation of the study results, differences of interpretation between the Committee and the Sponsor that have significant impact on MRL recommendations shall be discussed in the corresponding sections of the monograph.

All assigned experts should examine all studies that are included in the monograph and they should independently check each other's work before the draft monograph is forwarded to the FAO Joint Secretary for distribution to other residue experts participating in the Committee for their review and comment.

It is particularly important that the experts assigned to a substance agree on the content of the "Appraisal" section of the monograph and on any MRL recommendations which may be included in the first draft of the monograph. When agreement cannot be reached between the assigned experts, the opposing views should be presented to the Committee for discussion and decision by the Committee. Discussions with the experts assigned by WHO to prepare the toxicology monograph and to formulate an ADI/ARfD recommendation for the substance are essential, as this provides some preliminary indication of the potential ADI/ARfD recommendations as well as key issues to be considered in the evaluation.

### **1.5 Schedule and responsibilities for monograph preparation and distribution**

See Module I, Section 3.5 Schedule for participants a JECFA Meeting, for an outline of the typical schedule for monograph preparation and distribution. Note that revisions to the draft monograph typically will occur as a result of discussions and of new information which may be received during the JECFA meeting. Until the final changes are made by the drafting expert at the end of the meeting, the monograph is a draft document to support the discussion. It is therefore perfectly acceptable to include comment boxes or highlighted text that draws attention to potentially important or controversial aspects of the evaluation, as long as these are subsequently deleted.

## **2. General guidance on preparation and content of residue monograph**

The following sub-sections provide general guidance on the nature, quality and quantity of data which should be provided in a dossier for review by the drafting expert and reviewer(s), sources of data which may be accessed by the drafting expert in addition to information provided by a Sponsor. Additional sources of guidance on risk assessment and on study design and interpretation which may assist in the evaluation of data are also identified.

### **2.1 Sources of guidance on risk assessment and experimental design**

In addition to the guidance provided in this document, participants in JECFA evaluations of veterinary drug residues should be familiar with the content of the publications which are recommended below.



### **2.1.1 Risk assessment by JECFA (Environmental Health Criteria 240)**

A critical guidance document which should be used as an information source on best practices for risk assessment by drafting experts and reviewers is the publication *Environmental Health Criteria 240* (EHC 240).<sup>2</sup> Chapter 8 of EHC 240 is devoted to a discussion of the procedures used by JECFA and JMPR to assess residues of veterinary drugs and pesticides in foods. Other chapters provide an overview of topics such as risk assessment, risk characterization and the toxicological studies used to develop Acceptable Daily Intake (ADI) and Acute Reference Dose (ARfD) recommendations by expert committees such as JECFA. All members of JECFA are strongly encouraged to study this document to help them prepare for their role as a JECFA member.

### **2.1.2 Evaluation of experimental design and data quality for studies of veterinary drug residues**

A primary source of information on internationally accepted principles for design and interpretation of experiments to provide information for the registration of veterinary drugs for use in food producing animals is the series of guidelines produced by VICH, the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products, available at <http://www.vichsec.org/>. VICH guidelines are subject to periodic revision, so experts should ensure that they use the most recent version of any VICH guidelines for assessing submitted data.

The suitability of an analytical method proposed for regulatory use to support MRL recommendations made by the Committee is determined based on the criteria established by the CCRVDF for the validation of such methods, as contained in CAC/GL 71-2009, rev. 2012, 2014, *Guidelines for the Design and Implementation of National Regulatory Food Safety Assurance Programmes Associated with the Use of Veterinary Drugs in Food Producing Animals*.<sup>3</sup> Analytical terminology should be consistent with definitions in CAC/GL 72-2009, *Guideline on Analytical Terminology*.<sup>4</sup>

## **2.2 Initial assessment of dossier by drafting expert and reviewers**

When the data are received, it is important for the drafting expert and reviewer(s) to confirm receipt to the Sponsor and the FAO Joint Secretary. If the data submission does not arrive within a reasonable period of time, contact the Sponsor and the FAO Joint Secretary. On opening the package, it is recommended that the drafting expert and reviewer(s) perform some basic checks on the quality and usability of the documentation. If the drafting expert (or

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<sup>2</sup> Environmental Health Criteria 240, *Principles and Methods for the Risk Assessment of Chemicals in Food* (2009). A joint publication of the Food and Agriculture Organization of the United Nations and the World Health Organization, available at <http://www.who.int/foodsafety/publications/chemical-food/en/>.

<sup>3</sup> CAC/GL 71-2009, rev. 2012, 2014, *Guidelines for the Design and Implementation of National Regulatory Food Safety Assurance Programme Associated with the Use of Veterinary Drugs in Food Producing Animals*; available at <http://www.codexalimentarius.org/standards/list-standards>.

<sup>4</sup> CAC/GL 72-2009, *Guidelines on Analytical Terminology*, available at <http://www.codexalimentarius.org/standards/list-standards>.

reviewer) identifies any issues with the data submission where it is believed that the Sponsor could provide an improved submission, then the drafting expert (or reviewer) should inform the FAO Joint Secretary, who will contact the Sponsor with a detailed request for what is needed.

The typical dossier for a new substance includes an index of documents included in the dossier, copies of authorizations from national competent authorities and/or product labels, study reports with appendices of raw data and a summary report prepared for the Sponsor. The dossier may also include some scientific papers published in the peer-reviewed literature, but the drafting expert and reviewers should not assume that the inclusion of such papers represents the product of a comprehensive literature review. The following steps are recommended to be followed by the assigned drafting expert and reviewer(s) in preparation for the detailed review of a substance to which they have been assigned:

- Review the contents of the dossier to ensure that all studies listed in the index are included in the information provided by the Sponsor.
- Confirm that all electronic files open properly and are in a format that permits copying and pasting of metabolism schemes or other such material which may be included in the monograph.
- Determine if the information provided is for only major species, as defined by JECFA, or for additional species for which the JECFA procedures for MRLs for minor species apply (see “7. MRLs for Minor Species”). When a dossier includes data for fish, see “3.2.8.6. Special data requirements for drugs used in aquaculture”.
- Review the summary report provided by the Sponsor to ensure that all studies referenced in that report have been provided in the dossier and that all studies provided by the Sponsor are referenced in the summary report. If any studies referenced in the summary report have not been included, request copies of those studies from the Sponsor. If the dossier includes any studies not referenced in the Sponsor’s summary report, note this is an issue which may require further questions to the Sponsor. Further review may indicate that the study is not significant in the review of the substance and was therefore not cited in the Sponsor’s summary report.
- Check that all confidential studies provided by the Sponsor include raw data, usually provided in appendices to the study report. If raw data are missing, request these data from the Sponsor.
- Check that the dossier includes information on stability of residues and that this information was taken into account when pharmacokinetic, metabolism and depletion studies were conducted.
- Check to determine if the results provided in the depletion studies with non-radiolabelled drug have been corrected for recovery. If results are not corrected for recovery, these corrections must be identified in the monograph and the recommended MRLs should be based on residue concentrations that have been corrected for recovery.
- Check the limit of quantification and limit of detection of the different analytical methods used for the studies.

- Assess the requirements for a literature search for published papers. This may be of particular importance when the substance has a long history of use. At a minimum, a literature search covering the previous 5 years is recommended, with a literature search covering a much longer period recommended when assessing a drug with a long history of use. The drafting expert or reviewer with best access to library services and/or on-line search facilities should conduct the literature search.
- Check that the information provided by the Sponsor includes approved conditions of use (the Good Veterinary Practice, or GVP) and the names of countries which have established GVP for the substance.
- Check websites of regulatory authorities to obtain information on approved conditions of use, including regulatory limits and withdrawal periods, plus their assessment reports. Check to determine that all studies provided to these authorities are also contained in the dossier provided to JECFA by the Sponsor. This task should be undertaken by the assigned drafting expert or reviewer with the best access to on-line search facilities.
- Do not rely either on the assessment provided by the Sponsor in their summary report provided with the dossier or on assessments of national authorities in formulating your recommendations, but take them into account in your assessment.
- Sort all studies by category (pharmacokinetics, metabolism, residue depletion, etc.) in preparation to determine which headings typically included in a JECFA monograph are relevant to this monograph or addendum.

There have been instances in which no dossier has been submitted to JECFA by a Sponsor and the evaluation has been carried out primarily through extensive literature searches, combined with information that is publically available from regulatory agencies in member states. The drafting expert and reviewer(s) in such situations should follow such steps as are applicable in the above list.

**Example:** The 78th JECFA carried out an evaluation of emamectin benzoate in response to a request from the 20th Session of CCRVDF to establish an ADI and recommend MRLs in salmon and trout.<sup>5</sup> This evaluation was conducted using a recent evaluation conducted by the JMPR, combined with a detailed literature search and published reviews from national agencies, as no data were submitted by the sponsor. The 78th JECFA established an ADI and MRLs were recommended to CCRVDF. A monograph was published in the collection of residue monographs from JECFA 78.<sup>6</sup>

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<sup>5</sup> WHO. (2014). *Evaluation of certain veterinary drug residues in food*, Seventy-eight report of the Joint FAO/WHO Expert Committee on Food Additives, WHO Technical Report Series 988; available at <http://www.who.int/foodsafety/publications/jecfa-reports/en/>.

<sup>6</sup> FAO. (2014). "Emamectin benzoate" in *Residue evaluation of certain veterinary drugs*, FAO JECFA Monographs 15, pp. 23-37; available at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-publications/en/>.

## 2.3 Key JECFA policies for evaluation of studies submitted to JECFA

Sub-sections 2.3.1 – 2.3.6 provide general guidance on important JECFA evaluation policies.

### 2.3.1 Importance of GLP and GVP in evaluation of studies and data

Studies conducted according to Good Laboratory Practices (GLP) are expected to be the norm in dossiers submitted to JECFA, as noted in the report of the 48<sup>th</sup> JECFA.<sup>7</sup> A source of information for drafting experts and reviewers wishing to obtain information on GLP is the OECD Series on Principles of Good Laboratory Practice (GLP) and Compliance Monitoring provided by the Organisation for Economic Co-operation and Development (OECD).<sup>8</sup>

GVP, or Good Practice in the Use of Veterinary Drugs, “is the official recommended or authorized usage including withdrawal periods, approved by national authorities, of veterinary drugs under practical conditions”.<sup>9</sup>

### 2.3.2 Evaluation of non-GLP studies

For old drugs, which typically are no longer subject to patent, studies conducted to contemporary standards may not be available. A policy on the evaluation of such drugs was adopted by the 43<sup>rd</sup> Meeting of JECFA.<sup>10</sup> Available information may include studies conducted prior to the introduction of GLP by Sponsors seeking a national registration for the substance, studies conducted by government agencies or universities and papers published in the scientific literature. All reports must be considered based on their merits, which includes an assessment of the reputation of the organization that conducted the original study, the scientific reputation of the researchers who conducted the work, the reputation of the journal where the research has been published, the adequacy of the experimental design, the suitability of analytical methods used in the study and overall quality of the information presented. As when assessing dossiers for new drugs with studies conducted under GLP, MRLs should only be recommended if there are sufficient reliable residue depletion data to enable such a recommendation. Lack of GLP studies does not mean that all non-GLP information should be discounted, but rather that the Committee must determine that the available information is of acceptable quality and quantity to recommend MRLs.

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<sup>7</sup> WHO. (1998). *Evaluation of certain veterinary drug residues in food*, Forty-eight report of the Joint FAO/WHO Expert Committee on Food Additives, WHO Technical Report Series 879; available at <http://www.who.int/foodsafety/publications/jecfa-reports/en/>.

<sup>8</sup> OECD Series on Principles of Good Laboratory Practice (GLP) and Compliance Monitoring documents are available at <http://www.oecd.org/chemicalsafety/testing/oecdseriesonprinciplesofgoodlaboratorypracticeglpandcompliance-monitoring.htm>

<sup>9</sup> CAC. (2015) *Codex Alimentarius Commission Procedural Manual*, 24<sup>th</sup> edition; available at <http://www.codexalimentarius.org/procedures-strategies/procedural-manual/en/>.

<sup>10</sup> WHO. (1995) *Evaluation of certain veterinary drug residues in food*, Forty-third report of the Joint FAO/WHO Expert Committee on Food Additives, WHO Technical Report Series 855; available at <http://www.who.int/foodsafety/publications/jecfa-reports/en/>.

### 2.3.3 Use of information on analytical recovery

The MRLs recommended by JECFA are based on an assumption of 100% recovery of the marker residue, as stated in the report of the 45th JECFA, “it should be recognized that the assignment of an MRL to an analyte in a particular tissue sample is based on the assumption that there is complete (i.e. 100%) recovery of the analyte. Where complete recovery is not achieved by a particular method, the analytical results should be corrected to 100% to determine whether the residue is within, or exceeds, the MRL.”<sup>11</sup>

Recovery data are expected to be reported for each analytical run and the results for the samples included in that analytical run should be corrected for the recovery determined for that run. When recovery data are not available for each analytical run and only an average recovery for the analytical method is available, this may instead be used to correct the individual results for recovery, but it should be stated in the monograph that this was the procedure that was used.

The recovery of methods using radiolabel detection is usually assumed to be 100%, so recovery information should focus on methods for parent compound and/or metabolites using other methods of detection. Recovery information may not be provided when analytical methods use an internal standard and results are assumed to be recovery corrected by the internal standard. In such cases, it should be clearly stated in the monograph that the method of analysis used an internal standard.

### 2.3.4 Major and minor species designations

The 52<sup>nd</sup> JECFA designated cattle, pig, sheep and chickens as major species, with all other species, such as goat, deer, rabbit and turkey, designated as “minor species” (see).<sup>12</sup> The CCRVDF has also used the term “additional species” when referring to minor species. Details on the evaluation procedures to be used in response to requests from CCRVDF for the recommendation of MRLs for minor species are found in “7. MRLs for Minor Species”.

### 2.3.5 Bound residues

The 34<sup>th</sup> Meeting of JECFA established policies regarding the evaluation of bound residues.<sup>13</sup> The Committee defined the terms “total residues”, “extractable residues”, “non-extractable residues”, “bioavailable residues” and “marker residue” and stated that “in the absence of other information, a bound residue should be considered of no greater toxicological concern than the compound for which the ADI was set”. This approach has been consistently followed by subsequent meetings of the Committee when assessing the potential dietary intake of the

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<sup>11</sup> WHO. (1996). *Evaluation of certain veterinary drug residues in food*, Forty-fifth report of the Joint FAO/WHO Expert Committee on Food Additives, WHO Technical Report Series, No. 864; available at <http://www.who.int/foodsafety/publications/jecfa-reports/en/>

<sup>12</sup> WHO. (2000). *Evaluation of certain veterinary drug residues in food*, Fifty-second report of the Joint FAO/WHO Expert Committee on Food Additives, WHO Technical Report Series, No. 893; available at <http://www.who.int/foodsafety/publications/jecfa-reports/en/>

<sup>13</sup> WHO. (1989) *Evaluation of certain veterinary drug residues in food*, Thirty-fourth report of the Joint FAO/WHO Expert Committee on Food Additives, WHO Technical Report Series 788; available at <http://www.who.int/foodsafety/publications/jecfa-reports/en/>.

residues of a substance, as reflected in the determination of the marker-to-total residue ratio for use in dietary intake calculations. See also “3.2.4.8.4 Bound residues and bioavailability”.

### **2.3.6 Bioavailability**

The 34<sup>th</sup> Meeting of JECFA established policy for consideration of information on the bioavailability of residues, particularly with respect to their use in dietary intake calculations.<sup>13</sup> The Committee determined that “in the absence of relevant residue data, it should be assumed that the entire residue is bioavailable and that its potency is equal to that of the most toxic component of the residue”. The Committee adopted a procedure which follows the Gallo-Torres Model<sup>14</sup> for incorporation of a bioavailability factor in the dietary exposure calculation. The Meeting Report describes the types of experiments which may generate relevant information on bioavailability of residues and when such information should be used in the dietary intake calculation. A procedure for calculation of daily intake which takes into account the toxicological potency and bioavailability was included as Annex 3 of the meeting report. This approach was re-affirmed by the 81<sup>st</sup> Meeting of JECFA in its evaluation of zilpaterol hydrochloride.<sup>15</sup> The Committee has generally taken a conservative approach in determining when it is appropriate to include a bioavailability factor in the dietary intake calculation. See also “3.2.4.8.4 Bound residues and bioavailability”.

## **2.4 Guidance on other issues related to data assessment and presentation**

Sub-sections 2.4.1 – 2.4.4 provide guidance on general issues related to the presentation of information in a monograph, which includes the use of tables, figures abbreviations and units of measure and the procedures to be followed for the use of copyright materials.

### **2.4.1 Tables and graphs**

All relevant data should be included in the monograph, using tables and figures when appropriate. For example, the results of a metabolism or residue depletion study involving multiple tissues and/or timepoints are usually most clearly provided in tables or figures, rather than as long lists of data embedded in the text describing a study. Tables are a preferred form of data presentation, as these are more useful should a future JECFA need to re-consider some of the studies from an evaluation. The original data files reviewed by the earlier meeting of JECFA may not be available for re-assessment and the data provided in the original monograph may therefore be the only available source of such information.

The source (author, year) should be included in the table heading. Tables should be placed in the text immediately following the paragraph in which they are first cited, or as near to this as

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<sup>14</sup> Gallo-Torres, H.E. (1977). Methodology for the determination of bioavailability of labeled residues. *J. Toxicol. Environ. Health.* 2(4): 827-45.

<sup>15</sup> WHO. (2016) *Evaluation of certain veterinary drug residues in food*, Eighty-first report of the Joint FAO/WHO Expert Committee on Food Additives, WHO Technical Report Series available at <http://www.who.int/foodsafety/publications/jecfa-reports/en/>.

is practical. Repeating header rows may be used where the table extends over more than one page.

### 2.4.2 Units of measure

The FAO general guidance on style for FAO publications specifies that SI units should be used, such as cm, g, and °C, with a space between the number and the unit.<sup>16</sup> The concentration unit used for Codex Alimentarius Commission MRLs is the µg/kg and this should be used in the monograph to report concentrations of residues, including in milk. The preferred unit for reporting bodyweight of experimental animals is the kilogram (kg), while temperatures should be reported in degrees Celsius (°C).

Times between the administration of a dose of a substance or sample collection intervals are usually expressed in hours (h) or days (d), as appropriate or, when experiments include much longer intervals between treatment or between collection of samples, in weeks (w). For drugs which are rapidly absorbed or eliminated, particularly in reporting on pharmacokinetic experiments, it may be appropriate to report times in minutes (m). The drafting expert should choose the appropriate time units.

### 2.4.3 Use of abbreviations

Abbreviations should always be defined in full the first time they are used in a document.<sup>16</sup> Avoid the use of abbreviations as a form of short notation; such abbreviations may already have another accepted usage in the literature and may cause confusion for readers. Abbreviations used in the monograph and summary should be those which are well recognized and used in the relevant literature, such as LC for liquid chromatography and µg for microgram. Please use abbreviations which are from recognized sources, such as *Guidelines on analytical terminology*, CAC/GL 72-2009<sup>3</sup>, and the “Gold Book” from the International Union of Pure and Applied Chemistry.<sup>17</sup> Experts and reviewers should also consult also recent publications of the FAO JECFA Monographs, which each contain a list of abbreviations used in the monographs for that meeting.<sup>18</sup>

### 2.4.4 Copyright issues

Unless informed otherwise, the drafting experts and reviewers may assume that they are free to use all information and data provided by the Sponsor in the monograph without further attribution or permission than inclusion of a reference to each study. However, if chemical structure diagrams, metabolic pathway diagrams, figures or tables from the reports provided by the Sponsor are re-produced in the monograph, permission should be sought from the Sponsor. When tables, diagrams or figures are re-produced from a literature publication, permission must be sought from the publisher. Any such materials should be clearly identified

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<sup>16</sup> FAOSTYLE, available at <http://www.fao.org/docrep/004/ac339e/AC339E00.htm>.

<sup>17</sup> IUPAC (2014). *IUPAC Compendium of Chemical Terminology - the Gold Book*, available at <http://www.iupac.org/home/publications/e-resources.html>.

<sup>18</sup> FAO JECFA Residue Monographs are available at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-publications/en/>.

in the draft monograph and a detailed list of the re-produced materials should be provided to the FAO Joint Secretary, whose office will assist in obtaining the required permissions prior to publication of the FAO JECFA Monograph for the meeting.

### **3. Specific guidance on monograph preparation**

#### **3.1 Monograph title and authors**

The monograph begins with a first page title heading giving the name of the substance and the names and addresses of the drafting expert and reviewers.

##### **3.1.1 Name of substance (Monograph title)**

The name of the substance used in the monograph title should be the same as used in the request for review to JECFA from the CCRVDF and as used in the Call for Data issued by the JECFA Secretariat.<sup>19</sup>

##### **3.1.2 Authors**

List the name, city and country of the lead reviewer first, followed by the name, city and country of any other reviewers who participated in the preparation of the monograph. The order should reflect the relative contributions of the reviewers to the drafting of the monograph.

##### **3.1.3 Additional information**

When the monograph is for a re-assessment of a substance or the assessment of new information on a substance which has previously been reviewed by the Committee, a note is included under the author identification indicating that this monograph is an addendum to a report or reports issued by previous meetings of the Committee. (See example template, Module III).

#### **3.2 Monograph structure and format**

The body of the monograph typically includes the headings and sub-headings which are provided in Sections 3.2.1–3.2.7 (except those sub-sections identified as guidance for experts). Some may be excluded, as appropriate, when the monograph is an addendum to a previous review. Typically, all these headings and sub-headings will be included when there has been a significant time gap between an initial assessment and a further assessment of a substance by the Committee. When the monograph is to review only a limited number of studies, such as may be provided when the Committee has requested an additional depletion study or a method validation, then the sections “Identity” and “Other information on identity and properties” are usually omitted and only headings relevant to the information provided for review are included in the monograph.

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<sup>19</sup> The JECFA Call for Data may be accessed at <http://www.fao.org/food/food-safety-quality/scientific-advice/calls-data-experts/en/>.



### 3.2.1 Identity

Under this heading, nomenclature for the substance which is the subject of the risk assessment is presented. The nomenclature used for the substance must be clearly presented, so that there can be no misunderstanding as to the identity of the substance which has been evaluated by JECFA. Include the following information, using these sub-headings and in this order, to identify the compound:

- International Non-proprietary Name (INN)
- Synonyms (common and trade names)
- IUPAC name(s)
- Chemical Abstract Service Number
- Structural formula of main component(s)
- Molecular formula
- Molecular weight

Indicate whether the structure and associated information is for a salt form used in the commercial product or a free form of the active substance and if the product contains an isomer mixture. Drafting experts are requested not to create a table to present the information in this section as that can create problems in formatting the final document for publication.

### 3.2.2 Other information on identity and properties

This information provides key properties by which the substance being evaluated can be chemically identified and differentiated from other compounds. Properties which may be used in residue analysis, such as absorbance wavelengths and molecular weight, should be identified, as well as information on isomeric forms of the substance. The information should provide unequivocal identification of the substance under review. When the formulated substance is in salt form, it is critically important to distinguish in references to the substance in the monograph whether the discussion involves the salt or a free form of the active substance. Most of the required information should be found in the dossier provided by the Sponsor. Additional information may be found in reference materials such as the Merck Index, chemical handbooks, peer-reviewed publications and information from chemical suppliers. Use of less authoritative sources, such as some Internet websites, is not recommended, unless information can be verified from additional sources.

This section provides additional information on the physical and chemical properties of the substance. It typically includes the following sub-headings, as appropriate:

- Pure active ingredient
- Appearance
- Impurities
- Melting point
- Solubility
- Log  $K_o/w$  or Partition Coefficient

- pH
- Optical rotation
- $UV_{\max}$
- Stability (particularly important to indicate if exposure to light, acidic or basic conditions can cause degradation, as this may be critical in residue analysis for the substance)

### 3.2.3 Background

This section is only included when the monograph is identified as an addendum to a previous monograph.

The “Background” section should:

- Identify the meeting or meetings at which the substance was previously considered.
- State what decisions were taken at each previous meeting where the substance was considered by JECFA.
- Identify any requests for additional data which were made in the report of a previous JECFA meeting and the date by which such data were requested, using the precise wording of the earlier report.
- When the substance is on the agenda for further review as a result of a specific request from CCRVDF or as a decision of the JECFA Secretariat, state the specific reason(s) for the referral, using the precise language of the referral.
- State what information has been received from the Sponsor or other sources for review by JECFA in response to the Call for Data.

Reports from previous JECFA Meetings may be accessed at <http://www.who.int/foodsafety/publications/jecfa-reports/en/>, while reports of CCRVDF Meetings may be accessed at <http://www.codexalimentarius.org/meetings-reports/en/>.

### 3.2.4 Residues in food and their evaluation

#### 3.2.4.1 Conditions of use

Under this sub-heading, provide information on the approved conditions of use in member states of the Codex Alimentarius Commission. General information on the nature of the substance should be included, such as the activity of the substance (i.e., state whether the substance is used as an anti-bacterial, a coccidiostat, etc.) and the species against which the substance is active or the condition for which it is used as a therapeutic treatment. For agents approved for other uses, such as use as a production aid, state the nature of such approved use. The information in this section should include the species and class of food-producing animals for which the substance is approved and may also include withdrawal periods imposed by national authorities. Any restrictions on the use should be noted.

### 3.2.4.2 Dosage

Under this sub-heading, provide information on the approved formulation(s), approved route(s) of administration and dosage(s) and the food-producing animals to which they apply. This information, along with the conditions of use given under the previous sub-heading, constitutes the Good Veterinary Practice for the substance and MRL recommendations are made based only on usage consistent with the GVP information provided to the Committee for review. A study conducted using the recommended dose of the commercial formulation of a drug is generally considered to be a more reliable study for recommendation of MRLs than studies conducted with experimental formulations that are not equivalent to the commercial product or studies conducted at doses other than those recommended under GVP for the drug. When a substance has approved uses in multiple species and information on GVP is available for a number of countries, a summary table may be included to present this information.

*Example:* See “Table 1: Conditions of registered uses of tilmicosin in selected countries”, Tilmicosin monograph prepared for the 70<sup>th</sup> JECFA.<sup>20</sup>

### 3.2.4.3 Pharmacokinetics and metabolism

This section provides information on the pharmacokinetic behaviour of the substance in both laboratory and food producing animals, such as the rates of absorption and elimination, half-life in plasma and tissue, elimination pathways and metabolism. The pharmacokinetic data provide the first indication of the potential for persistent residues and the tissues in which they may occur. Indeed these may be important factors in Committee decisions on MRLs for minor species when limited depletion data are available for those species. Similarly, when it is demonstrated that metabolism is similar across all species for which data are available, this can be a key factor in decisions on MRLs for minor species. Metabolic data also typically are used to identify the marker residue and target tissues, which are discussed in more detail in “3.2.4.3.7.1. Identification of marker residue and target tissues”.

The section deals, in order, with pharmacokinetic studies in laboratory animals, pharmacokinetic studies in food producing animals, metabolism studies in laboratory animals and metabolism studies in food producing animals. Summarize each study and its results, making sure that the following information is included:

- The objective of the study, the GLP status of the study and reference information.
- The breed of animals used in the study, their sex, age and weight and the number of animals used.
- The duration of the study and sampling times.
- The nature of the formulation used in the study, the dose, the route of administration and the frequency of administration.

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<sup>20</sup> FAO. (2008). “Tilmicosin” in *Residue evaluation of certain veterinary drugs*, FAO JECFA Monographs 6, pp. 159-195; available at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-publications/en/>.

- A comment on the method performance and method validation data provided for the method(s) used in the study.
- Any additional information which may have had an impact on the study results.
- For pharmacokinetic studies, the results, including any pharmacokinetic data calculated. Include a table or tables with pharmacokinetic parameters, when appropriate.

**Example:** See “Table 1.3. Comparative description of important pharmacokinetic parameters in pigs after i.v. or i.m. administrations of different formulations of amoxicillin at different doses” in the Amoxicillin monograph prepared for the 75<sup>th</sup> JECFA.<sup>21</sup>

- For metabolism studies, the results, including which metabolites were identified in specific tissues, urine and faeces and any information on bound residues. Use tables if there are multiple metabolites and tissues. For simple metabolic pathways involving only one or two compounds, it may be more appropriate to simply identify them in the text discussing the study results.

When pharmacokinetic data are provided for a number of laboratory and food producing-animal species, the drafting expert may find it useful to end the pharmacokinetics section of the monograph with the sub-heading “Summary of pharmacokinetic studies”. This should include a short paragraph summarizing the findings.

**Example:** See the Apramycin monograph prepared by the 75th JECFA.<sup>22</sup>

When there are comparative metabolism studies involving multiple species or *in vitro* metabolism studies using tissues from multiple species, an additional sub-heading, “Comparative metabolism” may be included at the end of the metabolism section (see “3.2.4.3.6. Comparative metabolism”).

#### **3.2.4.3.1 Pharmacokinetics in laboratory animals**

This information is also typically reviewed in the Toxicology monograph, so discussion should focus on key information of relevance to the behaviour of residues and the recommendation of MRLs. Typically, information is provided on one or more species, most commonly rats and/or mice, with other species used in these studies most commonly being dogs. When a substance has hormonal activity, studies using monkeys may also be provided. The usual order of presentation is rat, then mice, dog, monkey and any other laboratory species. A separate sub-heading should be used for each laboratory animal species for which information is available.

When there are multiple studies for a species, these are usually presented in chronological order. However, if one study is considered more significant or more reliable than other studies

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<sup>21</sup> FAO. (2012). “Amoxicillin” in *Residue evaluation of certain veterinary drugs*, FAO JECFA Monographs 12, pp. 1-35; available at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-publications/en/>.

<sup>22</sup> FAO. (2012). “Apramycin” in *Residue evaluation of certain veterinary drugs*, FAO JECFA Monographs 12, pp. 37-71; available <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-publications/en/>.

considered by the Committee, this one may be discussed first and in greater detail, with the others following as additional information or supporting studies. In some cases, a table summarizing pharmacokinetic results from all the studies in the food producing animal species for which information was evaluated may be useful. This may be more important for inclusion in the “Appraisal” section to highlight similarities or differences in the behaviour of the substance in different species or when the results of different studies in a species yield conflicting results.

#### **3.2.4.3.2 Pharmacokinetics in food-producing animals**

As in the previous section, sub-headings are used for each species of food-producing animal for which information has been provided. The usual order of presentation is cow, then pig, sheep, other mammals, such as horse or goat, then chicken, other poultry, rabbit and fish. This information is not typically included in the toxicology monograph and the inclusion of greater detail may therefore be appropriate. The focus of evaluation and discussion should be on the absorption and elimination of the drug in food producing animal species and the associated pharmacokinetic parameters. Issues related to residues at injection or application sites should be noted if observed, and similarities or differences in absorption or elimination between species should be discussed. Drug bioavailability according to routes of administration and drug formulations should be reported. When pharmacokinetic information is available for multiple food producing animal species, it may be appropriate to include a summary paragraph and table at the end of the section. However, it may be more appropriate to include such an evaluation in the “Appraisal” section of the monograph.

#### **3.2.4.3.3 Predictive approaches using structure activity relationships or in silico tools to predict ADME properties**

This sub-heading is included when data from such studies are provided in the dossier. In response to a question posed to JECFA by the 20<sup>th</sup> Meeting of the CCRVDF on the use of such data, JECFA provided the following response:

“JECFA also continues to assess developing approaches, such as the use of *in silico* and *in vitro* approaches for investigation of adsorption, metabolism, excretion and distribution (ADME) and to use data from such studies, when available. For example, data from *in silico* studies were included in the toxicological evaluation of derquantel by the 75th JECFA. However, caution must be taken in interpretation as *in vitro* studies may provide very different metabolic profiles from *in vivo* experiments, as the experimental conditions differ, and this could have marked influences in the observed metabolism.”<sup>23</sup>

To date, reports in the peer-reviewed scientific literature on the use of models which predict residue distribution and concentrations in edible tissues based on pharmacokinetic data are limited. However, any dossier containing such modelling approaches should be considered on

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<sup>23</sup> FAO. (2014). “Annex 4. Response from JECFA to nine questions posed by CCRVDF 20 ” in *Residue evaluation of certain veterinary drugs*, FAO JECFA Monographs 15, pp. 205-210; available at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-publications/en/>.

its merits. Should a drafting expert encounter such an approach in a dossier, it is suggested that they notify the FAO Joint Secretary so that additional reviewers with specialized expertise in pharmacokinetics may be assigned to assist with the evaluation of that study and to prepare a briefing on the issues involved for discussion by the full Committee. In the meantime, the drafting expert should prepare text which will be included in the draft monograph summarizing the study and study results. The final monograph should reflect the Committee decision on the validity of the approach for this particular substance.

#### **3.2.4.3.4 Metabolism in laboratory animals**

The purpose of this section is to identify the metabolites found in laboratory animal species. These studies are usually conducted prior to studies in food producing animals, but may include additional studies conducted when apparent differences in metabolism are observed in studies with food producing animals. While *in vivo* studies are commonly provided, information from *in vitro* studies may be provided for some species.

*Example:* The 70th Meeting of the Committee determined the metabolism of monensin in rats and dogs from *in vitro* studies using incubation in liver microsomes from these laboratory animal species.<sup>24</sup>

As for pharmacokinetics studies, summarize each metabolic study provided for laboratory animals, by species, discussing the study results, providing a sub-heading for each species. Studies are usually reviewed in chronological order when there are multiple studies for a species unless one study is considered more significant or more reliable than other studies by the reviewers.

#### **3.2.4.3.5 Metabolism in food-producing animals**

Studies should be provided which define the metabolites found in any major food-producing animal species {cattle (bovine), pig (porcine), sheep (ovine) and chicken} for which MRLs are to be recommended. This information may be derived from *in vivo* studies conducted with representative animals of the target species or with suitable *in vitro* systems, such as liver microsomes. For major species, dossiers should typically include studies conducted with radiolabelled drug to ensure that all administered product is accounted for and to aid in the separation and identification of the metabolites.

Contemporary studies usually provide mass spectral identification of the metabolites after chromatographic separation. Once data are available from a radiolabelled study for one major species, studies in additional species using non-radiolabelled drug or using *in vitro* systems may be appropriate, using chromatographic separation and mass spectral identification to confirm the metabolic pattern in the other species. However, if significant differences in metabolic profile are observed in these studies in the additional species, particularly if there are unidentified metabolites, this should be clearly identified in the monograph as an issue

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<sup>24</sup> FAO. (2008). "Monensin" in *Residue evaluation of certain veterinary drugs*, FAO JECFA Monographs 6, pp. 109-135; available at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/guidelines0/en/>.

requiring discussion by the Committee. The significance of such unidentified metabolites should be discussed with the toxicology experts and the final monograph is modified to reflect the Committee decision on the issue.

Review the available studies by species, under sub-headings identifying the species. The usual order of presentation is cow, then pig, sheep, other mammals, such as horse or goat, then chicken, other poultry, rabbit and fish. Identify metabolites and tissues and excreta in which they are found. As previously noted, the metabolism section should include a figure defining the metabolic pathway(s) for the species for which the metabolites have been identified.

*Example:* See “Figure 1. Metabolic pathway for cyhalothrin (or lambda-cyhalothrin) in rats, dogs and cattle” in the Cyhalothrin monograph prepared for the 58<sup>th</sup> JECFA.<sup>25</sup>

A summary table may be informative when the metabolic information is more complex, with different metabolites found in tissues and excreta of different species.

*Example:* See “Table 2: Summary of monensin metabolites isolated from animal tissues and excreta” in the Monensin monograph prepared for the 70<sup>th</sup> JECFA.<sup>24</sup>

When the metabolism is complex and involves different metabolites in different species, it may be appropriate to provide a metabolic pathway diagram for each species.

#### **3.2.4.3.6 Comparative metabolism**

When metabolic data are provided for a number of food-producing animals and laboratory animals, the drafting experts may find it useful to end the metabolism section of the monograph with the sub-heading “Comparative Metabolism”. This should include a paragraph summarizing the findings from the studies reported in various species, plus paragraphs summarizing any *in vitro* or other comparative metabolism studies. The metabolic pathway figure and/or summary table may be included as part of this section to provide more detailed information, when required.

The availability of comparative metabolism information may be of particular importance when determining if MRLs can be harmonized across multiple species or in considering the extension or extrapolation of MRLs from major species to minor species. The available data on comparative metabolism should also be summarized in the Appraisal section.

#### **3.2.4.3.7 Additional information for drafting experts and reviewers**

*The following sub-headings are not typically included in the monograph. The information provided under these sub-headings is intended to assist the drafting experts and reviewers in ensuring that all necessary information and analysis are included in the Pharmacokinetics and Metabolism section of the monograph.*

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<sup>25</sup> FAO. (2000) “Cyhalothrin” in *Residues of some veterinary drugs in animals and foods*, FAO Food and Nutrition Paper 41/13, pp.1-17; monograph available from the Online Edition: "Residues of some veterinary drugs in foods and animals" at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-vetdrugs/en/>.

### 3.2.4.3.7.1 Identification of marker residue and target tissues

From the metabolic information provided, a marker residue should be identified and this identification should be clearly stated in the section of the monograph dealing with metabolism in food-producing animals. The MRL is usually expressed in terms of the marker residue, which is the target compound for analysis of residue of the substance. The marker residue is defined as follows:

**“Marker Residue:** A residue whose concentration decreases in a known relationship to the level of total residues in tissues, eggs, milk or other animal tissues. A specific quantitative analytical method for measuring the concentration of the residue with the required sensitivity must be available.”<sup>26</sup>

A marker residue may be:

- the parent compound;
- a major metabolite;
- the sum of the parent compound and/or a metabolite or metabolites; or
- a derivative formed during analysis by chemical reaction of the parent drug and/or metabolites.

In addition, a recommendation is usually made for a target tissue or tissues for regulatory programmes, based on information obtained from the metabolic and residue depletion studies. The initial indications of suitable target tissues may come from the metabolic studies and be confirmed in later sections of the monograph dealing with the depletion studies. The intention of this recommendation is that edible tissues will be identified for regulatory monitoring which are most likely to be available for testing and also which are likely to contain higher concentrations of the residues than other edible tissues which might be available for testing. The concept of “target tissue” is discussed in Section “15.1.3 Target Tissue” of CAC/GL 71-2009, rev. 2012, 2014, Guidelines for the design and implementation of national food safety assurance programme associated with the use of veterinary drugs in food-producing animals:

“The usual target tissue selected by competent authorities to be tested for veterinary drug residues in a residue control programme is the edible tissue in which residues of the marker residue occur at the highest concentrations and are most persistent. For lipophilic substances, the usual target tissue is fat. For most other substances, the target tissue is liver or kidney, depending on the primary route of elimination. One of these tissues is usually the target tissue designated for use in testing of domestically produced foods of animal origin. The organ tissues may not be available for testing imported products, so muscle tissue may be the target tissue for testing of these commodities. In some cases, such as drugs which are normally administered as injectable formulations, testing of muscle tissue from suspected injection sites may be required.”<sup>3</sup>

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<sup>26</sup> CAC/MISC 5-1993, Glossary of Terms and Definitions (Residues of Veterinary Drugs in Foods); available at <http://www.codexalimentarius.org/standards/en/>.



There may be instances when tissues other than muscle, liver, kidney and fat or skin with fat may need to be considered for the establishment of MRLs and these may also be considered as target tissues by national authorities.

**Example:** The 32<sup>nd</sup> Session of the Codex Alimentarius Commission requested in 2009 that JECFA “undertake a review of new data on residues of ractopamine in pig tissues, a summary of which was submitted to the eighteenth session of the Codex Committee on Residues of Veterinary Drugs in Food by the People’s Republic of China”.<sup>27</sup> The JECFA Secretariat published a Call for Data in response to this request from the CAC and, “due to the urgency and specificity of the request for scientific advice from the 32<sup>nd</sup> CAC, and in view of the lack of time and resources to convene a regular JECFA meeting”. A meeting of JECFA experts was held in electronic format.<sup>28</sup> The report noted that “Substituting specific organ tissue data in the model diet employed by the Committee for liver and kidney would result in dietary intakes that are still below the upper bound of the ADI, with the exception of lung tissue, where specific risk management measures may need to be considered. International food consumption data on offal and other organ tissues such as lung are lacking and further work should be undertaken to address this issue.”

Following a request from the 22<sup>nd</sup> Session of the CCRVDF that JECFA consider the recommendation of MRLs for zilpaterol hydrochloride in “offal”, the 81<sup>st</sup> JECFA requested that CCRVDF provide a definition of “offal” as JECFA noted that “the definitions of the tissues comprising offal were not consistent to identify between countries”.<sup>15</sup> Until further policy is developed by JECFA to deal with edible tissues other muscle, liver, kidney and fat (or skin with fat), such requests should be evaluated by drafting experts and reviewers on a case-by-case basis.

#### **3.2.4.3.7.2 Guidance on experimental design and representative species**

See *VICH GL46 (MRK), Metabolism and Residue Kinetics - Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: metabolism study to determine the quantity and identify the nature of residues.*<sup>29</sup> This VICH document provides guidance on the experimental design for metabolism studies, including the nature of the formulation to be used, the requirement that the animals used should be representative of the population to which the drug is typically administered, the number of animals to be used, sampling intervals and suitable test methods. This guidance may be used in assessing the adequacy of experimental design in metabolic studies under review. Studies which do not meet the criteria recommended in this guidance should be reviewed on their merits, but may be

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<sup>27</sup> FAO/WHO. (2009) ALINORM 09/32/REP , Report of the Thirty-Second Session of The Codex Alimentarius Commission, Rome, Italy, 29 June - 4 July 2009; available at <http://www.codexalimentarius.org/meetings-reports/en/?y=2009>

<sup>28</sup> FAO. (2010). “Ractopamine hydrochloride” in Residue evaluation of certain veterinary drugs, FAO JECFA Monographs 9, pp. 1-40; available at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/guidelines0/en/>.

<sup>29</sup> Available at <http://www.vichsec.org/>.

considered after review to be less reliable for decision-making due to a lower number of animals used, use of an inappropriate formulation of drug or route of administration, inadequate sampling or less reliable means of metabolite separation and identification than those recommended in the guidance document.

See also *VICH GL 47 (MRK), Metabolism and Residue Kinetics - Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: laboratory animal comparative metabolism studies*.<sup>29</sup> This document provides similar guidance on the criteria which should be applied in the evaluation of metabolic studies with laboratory animals. This guidance document discusses suitable test formulations, criteria for in vitro and in vivo experiments, sampling and analytical requirements, particularly for comparative metabolism studies. A reviewer may use this guidance document as a “best practices” tool for assessment of the quality of studies provided for review. Any deficiencies in design and conduct of a study should be noted in the expert review.

#### **3.2.4.3.8 Tissue residue depletion studies**

This section of the monograph reviews the available information on residue depletion in food-producing animals and provides the data on which MRL recommendations will be based. It is presented using two main sub-headings, one dealing with studies using formulations containing radiolabelled substance and the other containing studies with the non-radiolabelled drug, usually the commercial formulation. For guidance on acceptable study design, consult *VICH GL 48 (MRK), Metabolism and Residue Kinetics – Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: Marker residue depletion studies to establish product withdrawal periods*.<sup>29</sup> An additional sub-heading may be included when there is information in the dossier on the bioavailability of bound residues in animal-derived foods.

For each study, include the following information:

- The objective of the study, the GLP status of the study and the study reference.
- The breed and number of animals used in the study, their sex, age and weight.
- The duration of the study, the sampling times and the number of animals sacrificed at each sampling time.
- The nature of the formulation used in the study, the dose, the route of administration and the frequency of administration (preferably consistent with GVP for the commercial product).
- Any additional information which may have had an impact on the study results, including stability of analyte during storage.
- The results, including which residues were identified in specific tissues, urine and faeces.
- The analytical method(s) general description and an assessment of the extent of method validation information provided for review.
- The LOD and/or LOQ of the method(s) used in the study.

- The analytical recovery, where appropriate. The recovery of methods using radiolabel detection is usually assumed to be 100%, so recovery information should focus on methods for parent compound and/or metabolites using other methods of detection. Recovery information may not be provided when analytical methods use an internal standard and results are assumed to be recovery corrected by the internal standard.

#### 3.2.4.3.8.1 Radiolabelled residue depletion studies

The radiolabel depletion study data provide key information on the total residues found in various tissues and excreta. The information on the proportion of residues which are present as parent compound, metabolites or bound residues obtained from these studies is used in the risk assessment to formulate MRL recommendations and to determine the marker-to-total residue conversion factors used in dietary intake calculations for the exposure assessment.

For many compounds under evaluation, the marker residue (MR) may only represent a portion of the total residue of toxic concern (TR). A primary purpose of the review of the data should be to determine if marker-to-total residue (MR:TR) ratios can be established for the edible tissues and milk or eggs, when these are required for the dietary intake calculation. The data also provide information on the relative distribution of the drug residues in the various edible tissues and MRL recommendations should reflect the relative distribution of the residues in the edible tissues (liver, L; kidney, K; muscle, M; fat, F).

In general, when the toxicity of the metabolites is not experimentally established, the assumption is made that all residues, including bound residues, share the same toxicity as the parent drug<sup>13</sup>, as discussed in Section 2.3.5. However, approaches such as (Quantitative) Structure-Activity Relationship [(Q)SAR] may also be used by the toxicology reviewers to predict the toxicological significance of some metabolites when experimental evidence is not available. [(Q)SAR] models the behaviour of a chemical based on the behaviour of other chemicals which share elements of the chemical structure of the compound under evaluation. The Organization for Economic Co-operation and Development (OECD) has published guidelines for the validation of [(Q)SAR] models, but recommended that the validation of such models for regulatory use should be carried out by “the regulatory authorities of the member countries.”<sup>30</sup>

In some cases, a portion of the total residue may be determined to be of no toxic concern and in such cases the MR:TR ratio reflects the relationship between the marker residue and the portion of the total residue that is considered to be of toxic concern. The decision on the proportion of the residues that are of toxic concern is made in consultation with the toxicology reviewers. This information should be discussed with these reviewers during the preparation of MRL recommendations as it is an important consideration in the dietary intake calculation for the exposure assessment. It is always wise to assume that the marker-to-total residue factors

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<sup>30</sup> OECD. (2007). Guidance Document on the Validation of (Quantitative) Structure-Activity Relationships [(Q)SAR] Models, NO(2007)2, available at <http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?doclanguage=en&cote=env/jm/mono%282007%292>

will be required for the dietary intake calculations when there is extensive metabolism of the parent drug and to ensure that this information is available from the data provided in the dossier.

It is critical that the MR:TR ratio is determined at the timepoint which coincides with the concentrations used as a basis for the MRLs and the dietary intake calculations. The MR:TR ratios typically vary over time, usually becoming larger as the marker residue depletes and bound residues remain unchanged in the tissues. Ideally, these data are provided from a radiolabel depletion study where both total residues and marker residue are determined at each sampling time in each tissue. In the review of derquantel, the 78th JECFA stated in the residue monograph that “the Committee concluded that determining the MR:TR ratio from a radiolabel study was the customary and preferred practice.”<sup>31</sup>

Most contemporary studies with labeled drug will include both results of radiochemical analysis using a scintillation counter to measure the total residue (TR) concentrations and also marker residue (MR) concentrations obtained by analysis with a potential regulatory method for the marker residues. Ideally, the radiochemical analysis will also include a chromatographic separation so that residues of the marker residue (when chemical derivatization is not required) can be determined from this assay and compared with the results of the conventional marker residue assay. However, some dossiers may contain studies which provide only total radioactive residues or only radiochemical analysis after chromatographic separation. These can be problematic, as it becomes more difficult to establish a reliable link between the total residues and the results of a marker residue analysis for non-radiolabelled drug. When such a situation is encountered, the drafting expert and reviewers should consider the total information available from the radiolabel depletion studies and the studies with non-radiolabelled drug to determine if the total data set from these studies can provide the necessary information to provide a basis for MRL recommendations. If there are equivalent studies contained in the dossier using both the radiolabelled and non-radiolabelled drug, it may be possible to establish the required linkage with sufficient confidence to recommend factors for conversion of marker residue to total residues from the two studies.

**Example:** See the monograph on diminazene prepared by the 42<sup>nd</sup> JECFA.<sup>32</sup> Data from a radiolabelled residue depletion study (Table 1 of monograph) were compared with data from a residue depletion study using non-radiolabelled drug (Table 2 of monograph). In both experiment approximately the same dose of drug was administered to calves by intramuscular (i.m.) injection. Residues in tissues were determined in the study with radiolabel drug at 20 days post-treatment, while residues in the study with non-radiolabelled drug were determined in tissues at 21 days post-treatment. In this case, the Committee determined that there were sufficient similarities in the conditions

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<sup>31</sup> FAO. (2014). “Derquantel” in *Residue evaluation of certain veterinary drugs*, FAO JECFA Monographs 15, pp. 13-21; available at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-publications/en/>.

<sup>32</sup> FAO. (1994). “Diminazine” in *Residues of some veterinary drugs in animals and foods*, FAO Food and Nutrition Paper 41/6, pp.33-38; monograph available from the Online Edition: "Residues of some veterinary drugs in foods and animals" at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-vetdrugs/en/>.

of the two experiments that the results could be used to derive the marker-to-total residue relationships for liver, kidney and muscle.

When the concentration of median total residue remains higher than the ADI according to the data available, this means that the marker residue corresponding to the MRL is reached after the final timepoint for which data were provided. In such cases, reliable estimates of the marker-to-total residue ratio cannot be made. These ratios should not be determined by extrapolation unless the Committee can determine from the available data that both marker and total residues have achieved a steady state, where no further changes in ratio are anticipated.

Questions to consider when assessing such studies include:

- Were the animals used in the studies with labeled and non-radiolabelled drug equivalent (similar age, sex, bodyweight)?
- Were the formulations, doses and routes of administration used in the studies the same or equivalent?
- Were the environmental conditions similar for both studies?
- Were the time period and timepoints used for sampling similar in the studies?
- Were the concentrations of marker residue expressed for the same chemical entities if marker residue was determined by scintillation counting in the radiolabel study and the marker residue method in the non-radiolabelled study?
- Did the radiochemical measurement method used in the radiolabel study and the marker residue assay method used in the study with non-radiolabelled drug have similar LOD's, LOQ's and analytical ranges so that the results of the two studies yield results for total residues that can be compared with results for marker residue?

When there are differences in the animals, product formulations, dosage, environmental conditions, sampling times or analytical method performance, comparison of results of the studies becomes difficult. JECFA has typically avoided the use of factors to “correct” results so that comparisons can be made between the results of two studies, with the exception of adjusting residue concentrations to reflect differences in dosage. This should only be done when there are data to indicate a clear linear relationship exists between dose and resulting residue concentrations.

There are situations where radiolabel depletion studies in food-producing animal species may not be available, particularly with older, off-patent substances. In such situations, the reviewer should present the available residue depletion information in the draft monograph for review and decision by the Committee. When there is sufficient information to indicate that either there is minimal metabolism, with only one major product (typically parent compound), it may be possible to recommend MRLs based on the depletion data for the marker residue.

**Example:** See the amoxicillin residue monograph prepared for the 75<sup>th</sup> JECFA.<sup>21</sup>

In other cases, when there is evidence that the compound is extensively metabolized or when there are no detectable residues in tissues, it may be possible to recommend MRLs using the

available residue depletion data from studies with non-radiolabelled drug and the LOQs of the analytical method.

**Example:** See the monograph on colistin prepared by the 66<sup>th</sup> JECFA.<sup>33</sup>

When depletion studies using radiolabelled drug are not available, this should be clearly stated in the monograph under the sub-heading “Radiolabelled residue depletion studies”.

There are also cases where it may not be necessary that the analysis of the marker residue is included in the total residue study, as it has been demonstrated that the only residue of toxicological concern is the marker residue, usually the parent compound. In such situations where conversion factors from marker to total residues are not required, the total residue study is of value in assessing the relative distribution of residues in the edible tissues, in determining when there are detectable radiolabelled residues present below the LOQ of the method for the marker residue and in assessing the presence of bound residues.

**Example:** See the monograph on sarafloxacin prepared by the 50<sup>th</sup> JECFA.<sup>34</sup>

Under the heading “Radiolabelled residue depletion studies”, summarize the available studies under sub-headings for each species for which information is provided.

#### **3.2.4.3.8.1.1 Marker-to-total residue conversion factors**

*This is not a monograph sub-heading, but is included here to provide additional guidance for drafting experts.*

The “Radiolabelled Residue Depletion Studies” section should include a clear statement of the factors for conversion of marker to total residues (MR:TR) for each species when these can be determined. These should be determined at the withdrawal time corresponding to the MRL for use in the dietary intake calculation. When the data are insufficient to make such a determination, a statement should be made that they could not be determined or the process used to derive the factors from the available data should be clearly explained (e.g., MR:TR ratios from another major species were used as surrogates, with the scientific justification for this decision). When the conversion factors are not deemed relevant to the dietary exposure calculation, this should also be stated. This information should also be discussed in the “Appraisal” section of the monograph, along with its relevance to the development of MRL recommendations.

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<sup>33</sup> FAO. (2006). “Colistin” in *Residue evaluation of certain veterinary drugs*, FAO JECFA Monographs 2, pp. 7-28; available at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-publications/en/>.

<sup>34</sup> FAO. (1999). “Sarafloxacin” in *Residues of some veterinary drugs in animals and foods*, FAO Food and Nutrition Paper 41/11, pp.107-117; monograph available from the Online Edition: "Residues of some veterinary drugs in foods and animals" at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-vetdrugs/en/>.

Use tables to summarize the data. Include a table which compares total and marker residues and the MR:TR ratios at various sampling times when both marker and total residues are determined in a study.

*Example:* See Table 7.2 in the monograph for lasalocid sodium prepared for the 78<sup>th</sup> JECFA.<sup>35</sup>

#### **3.2.4.3.8.1.2 Residues at the injection site**

Depending on routes of administration used in the pharmacokinetic and metabolism studies, there may be information suggesting that persistent residues at the injection site require consideration. The definitive information on this issue will typically come from the depletion studies with labelled drug carried out with a route of administration and dose typical of those used in treatment of animals with the commercial product or from studies using the commercial formulation and analysis for the parent drug or marker residue. When there are concerns about persistent residues at the injection site, include a paragraph with the sub-heading “Residues at the injection site”.

*Examples:* See the Moxidectin monograph prepared by the 45<sup>th</sup> JECFA<sup>36</sup> and the Addendum to the Doramectin monograph prepared by the 52<sup>nd</sup> JECFA.<sup>37</sup>

#### **3.2.4.3.8.2 Residue depletion studies with non-radiolabelled drug**

*Note: In monographs and meeting reports issued prior to the 81<sup>st</sup> meeting of the Committee, the term “unlabelled drug” was used to refer to studies with non-radiolabelled drug.*

This section should include only data from studies in food-producing animals. As with the previous sections of the monograph, sub-headings are used for each species, starting with the major species designated by JECFA (cattle, pig, sheep and chicken) and then progressing to minor (additional) species. These studies provide data on residues of the marker residue in the edible tissues, eggs and milk (or honey) and are therefore critical for the recommendation of MRLs. As noted in “2.3.3 Use of information on analytical recovery”, MRLs are established based on an assumption of 100% recovery of the marker residue.<sup>11</sup> Therefore, it is critical to state whether the residue concentrations reported in the studies under review have been corrected for recovery and whether this has been taken into account in the MRL recommendation.

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<sup>35</sup> FAO. (2014). “Lasalocid sodium” in *Residue evaluation of certain veterinary drugs*, FAO JECFA Monographs 15, pp. 65-87; available at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-publications/en/>.

<sup>36</sup> FAO. (1996). “Moxidectin” in *Residues of some veterinary drugs in animals and foods*, FAO Food and Nutrition Paper 41/8, pp.107-124; monograph available from the Online Edition: "Residues of some veterinary drugs in foods and animals" at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-vetdrugs/en/>.

<sup>37</sup> FAO. (2000). “Doramectin” in *Residues of some veterinary drugs in animals and foods*, FAO Food and Nutrition Paper 41/12, pp.27-36; monograph available from the Online Edition: "Residues of some veterinary drugs in foods and animals" at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-vetdrugs/en/>.

Before conducting the depletion studies, the company or individuals conducting the study should have demonstrated that the analytical method used in the study was suitably validated [see *VICH GL 49 (MRK), Method used in residue depletion studies: Guidelines for the validation of analytical methods used in residue depletion studies*<sup>29</sup> for guidance on appropriate validation criteria] and that the stability of residues in the tissues (or eggs, milk or honey) during storage pending analysis has been demonstrated.

Data reviewed in this section must be clearly presented, as these residue depletion data are of particular importance in the development of the MRL recommendations. There must be an adequate number of data points to plot a depletion curve in each matrix (fat, kidney, liver, muscle, egg, milk or honey) for which an MRL recommendation is to be made or it must be clearly demonstrated that there are no quantifiable or no detectable residues present in a specific tissue at the timepoint corresponding to the concentrations used as a basis for MRL recommendations in other tissues containing quantifiable residues. The depletion data are usually presented in tables in this section of the monograph.

**Examples:** See the monographs for amoxicillin<sup>21</sup> and apramycin<sup>22</sup> prepared for the 75<sup>th</sup> JECFA.

As for the preceding section, studies are summarized by species, under a sub-heading for the species (see templates in Module III).

When the results of a particular study with non-radiolabelled drug can be directly compared with the results of a study with radiolabelled drug (same age, class and bodyweight of animals, same dose of drug and route of administration, same or similar sampling times), it is appropriate to discuss the comparability of results of the two studies. This may be done as a final paragraph to the section when there are multiple studies in one or more species to compare or it may be discussed in the Appraisal section. The summary paragraph can also point out any deficiencies in the available data and may include a statement as to whether the data provided are sufficient to support MRL recommendations.

At a minimum, residue data from a depletion study under the established GVP, with data extending to or beyond the longest withdrawal period set by a Codex member state on which the Committee has information, plus marker-to total residue ratios (when these are required for the dietary intake calculation) are required if MRL recommendations based on the depletion data are to be considered by the Committee. The Committee will also consider other factors, such as the availability of a suitable residue method for regulatory use, when considering such recommendations.

#### **3.2.4.3.8.3 Relationship of data from studies with non-radiolabelled drug to MRL recommendations**

*This is not a monograph sub-heading, but is included here to provide additional guidance for drafting experts.*

The data from the studies with non-radiolabelled drug are usually the basis for MRL recommendations. In assessing the available data, the drafting expert should determine if these



data are sufficient to support MRL recommendations and whether the dietary intake calculation used will be the Estimated Daily Intake, EDI, or the Theoretical Maximum Daily Intake, TMDI, which are discussed in “3.2.7 Exposure Assessment”. In the EDI approach, the median concentration and the MRL are determined for the same timepoint from the depletion curve using the JECFA Statistical Tool<sup>38</sup> or an equivalent method of calculation. Since the EDI calculation is based on median concentrations, there should be quantifiable residues present in the majority of tissues or other matrices (eggs, milk, honey) from which median residues for the EDI calculation may be determined and from which an MRL can be assigned. When data are insufficient to calculate median concentrations, the Committee uses the TMDI calculation to assess potential dietary intake of residues. MRL recommendations by JECFA for tissues (or eggs, milk or honey) containing no quantifiable residues (or no detectable residues) are typically based on 2 x LOQ of a suitable analytical method.<sup>2</sup> This approach was first used by the 43<sup>rd</sup> JECFA in recommending MRLs for spiramycin<sup>10</sup> and has been used at subsequent meetings of the Committee.

There are instances where the Committee has also used total residue data from a study with radiolabelled drug in the development of MRL recommendations.

*Examples:* The 40<sup>th</sup> JECFA, in recommending a revised MRL for closantel in sheep kidney, based this decision on data from a radiolabel study.<sup>39</sup> The 62<sup>nd</sup> JECFA used marker residue data from a radiolabel study in cattle in making MRL recommendations for alpha-cypermethrin.<sup>40</sup>

Data from radiolabel depletion studies are also frequently used by drafting experts to develop a better understanding of the depletion of a substance when the detection of radiolabelled residues permits the detection of residues that are below the LOQ or LOD of the analytical method for the marker residue used in depletion studies.

Common problems in the conduct of depletion studies are the use of analytical methods which do not have a sufficiently low LOQ to detect residues which may be present and failure to use equivalent formulations of the drug or the same sampling intervals in the studies with labelled and non-radiolabelled drug. When such issues are noted, comment should be included in the monograph and these should be significant factors in the bullet points which provide the basis for recommendations regarding MRLs.

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<sup>38</sup> FAO. (2003). Software-based workbook for statistical evaluation of residue depletion data for veterinary drugs; available at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/guidelines0/residue-depletion/en/>.

<sup>39</sup> FAO. (1993). “Closantel” in *Residues of some veterinary drugs in animals and foods*, FAO Food and Nutrition Paper 41/5, pp.1-19; monograph available from the Online Edition: “Residues of some veterinary drugs in foods and animals” at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-vetdrugs/en/>.

<sup>40</sup> FAO. (2004). “Alpha-cypermethrin and cypermethrin” in *Residues of some veterinary drugs in animals and foods*, FAO Food and Nutrition Paper 41/16, pp.11-24; monograph available from the Online Edition: “Residues of some veterinary drugs in foods and animals” at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-vetdrugs/en/>.

#### 3.2.4.3.8.4 Bound residues and bioavailability

As discussed in “2.3.6 Bioavailability”, the bioavailability of the residues in food to consumers may be a factor in the intake calculation. A section on bioavailability of bound residues is only included in the monograph when data are provided by the Sponsor and this heading usually appears after the section dealing with depletion studies with non-radiolabelled drug. A dossier may include studies where laboratory animals received a diet of edible tissues from a food-producing animal containing residues of radiolabelled drug. The use of the term “bioavailability” with respect to the bioavailability of incurred residues in tissues (residues resulting from administration of the drug to the animal) should not be confused with the use of the term with respect to the portion of a dose of the formulated product that is “bioavailable” to the treated animals. The term has been used in both contexts in monographs, so it must be clearly stated in the monograph which type of study is being described. A bioavailability correction factor is not applied in the dietary intake calculations based on the bioavailability of the formulated product to treated animals. It has only been applied in a limited number of cases where there were data for the bioavailability of incurred residues in edible tissues and where this bioavailability was not included in the establishment of the ADI or ARfD.

*Example:* See the monograph on zilpaterol hydrochloride prepared for the 81<sup>st</sup> meeting of JECFA.<sup>41</sup>

While it may be assumed that the bioavailability of residues in foods relates in large measure to the bioavailability of bound residues, not all dossiers that contain information on bound residues also contain the specific studies related to the bioavailability of such residues. In cases where there is significant information on bound residues, the proportion of the total residue that they comprise and the nature and extractability of the bound residues (see 2.3.5 Bound residues), it may be appropriate to include a separate heading “Bound Residues/Bioavailability” in the monograph, again usually after the section dealing with depletion studies with non-radiolabelled drug.

*Example:* See “Bound Residues/Bioavailability” in the danofloxacin monograph prepared for the 48<sup>th</sup> Meeting of JECFA.<sup>42</sup>

#### 3.2.5 Methods of Analysis for Residues in Tissues

In this section of the monograph, analytical methods which are candidates for regulatory use are reviewed for acceptability using the analytical method validation criteria established by the CCRVDF, as contained in in CAC/GL 71-2009, rev. 2012, 2014, Sections 13-19.<sup>3</sup> The objective of the review is to identify a method or methods suitable for use in national regulatory testing programmes to support the MRLs recommended for residues of the substance in animal

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<sup>41</sup> FAO. (2016). “Zilpaterol hydrochloride” in *Residue evaluation of certain veterinary drugs*, FAO JECFA Monographs 18; available at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-publications/en/>.

<sup>42</sup> FAO (1998). “Danofloxacin” in *Residues of some veterinary drugs in animals and foods*, FOA Food and Nutrition Paper 41/10, pp. 23-37; monograph available at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-vetdrugs/en/>.

derived foods. In addition to the typical method validation criteria (method range, recovery, selectivity, measurement uncertainty, etc.), criteria for method suitability include the availability of necessary reagents and equipment and the accessibility of the method for a routine regulatory laboratory. Methods using reagents that are not commercially available, unless these can be prepared in a routine laboratory, or methods using prototype (or obsolete) instruments are not considered suitable. The method should use equipment that is expected to be found in a laboratory that does routine testing for veterinary drug residues in foods.

**Example:** In recommending MRLs for pirlimycin residues, the 62<sup>nd</sup> JECFA made the following comment to CCRVDF:

“For the maximum residue limits for pirlimycin, the Committee noted that the analytical method submitted by the sponsor had been validated suitably, however, the mass spectrometry interface used was no longer commercially available and therefore the method would not comply with all Codex requirements for a Regulatory Analytical Method. Since the Committee received information that verification of this method using different equipment was in progress, it recommended that CCRVDF should propose the MRL for adoption by the Codex Alimentarius Commission only if this work has been completed and made available to the Working Group Methods of Analysis and Sampling in the CCRVDF.”<sup>43</sup>

### 3.2.5.1 Guidance on method validation requirements

The 78<sup>th</sup> JECFA “agreed that the method selection and validation criteria contained in CAC/GL 71-2009 and subsequent revisions to these guidelines will be applied when assessing the suitability of methods”.<sup>5</sup> CAC/GL 71-2009, rev. 2012, 2014,<sup>3</sup> should be interpreted with reference to other Codex guidance on method validation, available at <http://www.codexalimentarius.org/standards/en/>, including:

- CAC/GL 27-1997: Guidelines for the Assessment of the Competence of Testing Laboratories Involved in the Import and Export Control of Foods.
- CAC/GL 28-1995, Rev.1-1997: International Harmonized Protocol for the Proficiency Testing of (Chemical) Analytical Laboratories.
- CAC/GL 37-2001: Harmonised IUPAC Guidelines for the Use of Recovery Information in Analytical Measurement.
- CAC/GL 49-2003: Harmonized IUPAC Guidelines for Single-Laboratory Validation of Methods of Analysis.
- CAC/GL 54-2004: Guidelines on Measurement Uncertainty.
- CAC/GL 64-1995: Protocol for the Design, Conduct and Interpretation of Method Performance Studies.

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<sup>43</sup> WHO. (2004). “Annex 2. Recommendations on compounds on the agenda: Pirlimycin” in *Evaluation of certain veterinary drug residues in food*, Sixty-second report of the Joint FAO/WHO Expert Committee on Food Additives, WHO Technical Report Series 925, pg. 69; available at <http://www.who.int/foodsafety/publications/jecfa-reports/en/>.

- CAC/GL 65-1997: Harmonized Guidelines for Internal Quality Control in Analytical Chemistry Laboratories.
- CAC/GL 72-2009: Guideline on Analytical Terminology.

When a term used in analytical measurement is not defined in CAC/GL 72-2009, the drafting expert should consult JCGM 200:2012, the International Vocabulary of Metrology – Basic and general concepts and associated terms (VIM), 3<sup>rd</sup> edition (or any subsequent revised edition), available at <http://www.bipm.org/en/publications/guides/#vim>, to ensure correct use of scientific terminology in their review of an analytical method.

### 3.2.5.2 Preparing the method evaluation

The following steps are recommended to be followed by the drafting expert in preparing an evaluation of available methods for residues of the substance under review:

**Step 1. Identification of available methods.** In addition to information in the dossier provided by the Sponsor, the drafting expert may also receive validation packages submitted by member states for methods used by their residue control laboratories in response to the Call for Data. The drafting expert may also identify potential methods through a literature search or from personal knowledge of methods used in expert laboratories. In such situations, drafting experts may contact scientists in expert laboratories to request the methods and the accompanying method validation packages for assessment when these are available for distribution. The FAO Joint Secretary should be informed in advance of any such contacts and it is preferable that such requests should be discussed in advance with the FAO Joint Secretary.

**Step 2. Initial review of available data.** There are two primary issues to address in review of the data provided:

1. The completeness of the method validation package - assess all method performance data provided and state if all required criteria are met, indicating any deficiencies.
2. For a validation package with results from a single laboratory, the validation work should be performed under GLP or the method should be included within the scope of an ISO-17025 accreditation (or equivalent) of the laboratory providing the data, consistent with the requirements of CAC/GL 49-2003, Harmonized IUPAC Guidelines for Single-Laboratory Validation of Methods of Analysis.<sup>44</sup>

When data are provided from a collaborative study, the criteria referenced in CAC/GL 64-1995: *Protocol for the Design, Conduct and Interpretation of Method Performance Studies*<sup>45</sup> should be applied in conjunction with the criteria contained in CAC/GL 71-2009, rev. 2012,

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<sup>44</sup> Available at <http://www.codexalimentarius.org/standards/en/>; see also: Thompson, M., Ellison, S.L.R., Wood, R. (2002) Harmonized Guidelines For Single-Laboratory Validation Of Methods Of Analysis. *Pure Appl. Chem.*, 74, (5) 835 – 855; available at <http://pac.iupac.org/publications/pac/pdf/2002/pdf/7405x0835.pdf>

<sup>45</sup> Available at <http://www.codexalimentarius.org/standards/en/>; see also Horwitz, W. (1995). Protocol for the design, conduct and interpretation of method performance studies. *Pure & Appl. Chem.* 67 (2):331-343, available at <http://pac.iupac.org/publications/pac/pdf/1995/pdf/6702x0331.pdf>

2014. Multi-laboratory studies which do not meet the requirements of CAC/GL 64-1995 should be assessed using the criteria in CAC/GL 71-2009, rev. 2012, 2014,<sup>3</sup> or subsequent revisions.

**Step 3. Classification of available methods.** The initial assessment of the method(s) provided should determine the category into which the method best fits and this will then determine the appropriate criteria to be applied in assessing the suitability of the analytical method for residue control (CAC/GL 71-2009, rev. 2012, 2014, sections 13-15) and the quality of the validation data (CAC/GL 71-2009, rev. 2012, 2014, sections 16-19). CAC/GL 71-2009, rev. 2012, 2014, identifies three categories of analytical methods and the validation criteria to be applied for each category:

- **Screening methods:** These methods provide results which are qualitative or semi-quantitative in nature and are used as to identify the presence (or absence) of residues which may exceed an MRL in an analytical sample.
- **Quantitative methods:** These methods provide a quantitative result which may be used to determine if residues in a particular sample exceed an MRL, but do not provide unequivocal confirmation of the identity of the residue.”
- **Confirmatory method:** These methods provide unequivocal confirmation of the identity of the residue. Some confirmatory methods and may also confirm the quantity of the analyte which is present in a sample.

When the dossier includes screening and/or confirmatory methods in addition to quantitative methods, the usual order of review is to begin with screening methods, then quantitative methods and finally confirmatory methods. Review the methods which are assigned to each category under the three sub-headings:

- Screening methods
- Quantitative methods
- Confirmatory methods

When a dossier includes only quantitative methods, these sub-headings are not required, but a comment may be inserted that no methods suitable for screening or confirmation were provided for review. Additional sub-headings may be used for each category of methods to classify methods by techniques, such as liquid chromatography.

*Example:* See the “Methods of Analysis” in the monograph on Narasin prepared by the 70<sup>th</sup> JECFA.<sup>46</sup>

**Step 4. Review each method proposed for regulatory use according to the appropriate criteria for the category of method as stated in CAC/GL 71-2009, rev. 2012, 2014.** The review should include a reference citing the source of the method, the species/matrices to which the method is applicable, a description of the sample preparation, extraction and clean-up and the analyte separation method used for analysis. This information should also include the

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<sup>46</sup> FAO. (2009). “Narasin” in *Residue evaluation of certain veterinary drugs*, FAO JECFA Monographs 6, pp. 137-158; available at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-publications/en/>.

identification of grades of solvents or reagents used, quantities specified, solid phase extraction cartridges or other separation media used, details of chromatographic columns (length, diameter and chromatographic media), temperature of separation, details of mobile phases or carrier gases used in chromatographic systems and detector requirements and settings.

Note that some Sponsors have objected in some instances to the inclusion of detail in the review which would enable an analyst to implement the method from the information in the review, citing confidentiality of proprietary information. If this should occur, remove some details from the review, such as reagent quantities or specific identification of chromatographic media (e.g., column manufacturer and product name). In such situations, state that the competent national authorities should request a copy of the method from the Sponsor. If the method under review is from the peer-reviewed literature, any direct reproduction of text from the original publication should be clearly identified as such and any necessary permission for use of text, figures, tables or other materials from such copyright materials must be obtained. The FAO Joint Secretary should be contacted in order to facilitate this process. It is, in most cases, simpler to provide a summary of material in the drafting expert's own words, including their expert opinions on the proposed method.

Method recovery, coefficient of variation and trueness for the marker residue should meet the target ranges identified in Table 3, "Performance criteria which should be met by methods suitable for use as quantitative analytical methods to support MRLVDs for residues of veterinary drugs in foods" in CAC/GL 71-2009, rev. 2012, 2014.<sup>3</sup> In cases where internal standard procedures, such as addition of isotope-labelled drug, are used to provide an internal correction for recovery to an assumed value of 100%, absolute recovery information may not be available. In such cases, instead of assessing method recovery, assess the suitability of the internal standard procedure used and the reliability of the results obtained.

For methods used to support Codex Maximum Residue Limits for Veterinary Drugs (MRLVDs), method selectivity should be assessed consistent with the direction provided in CAC/GL 71-2009, rev. 2013, 2014.<sup>3</sup> The following general guidance is provided:

"Quantitative methods provide quantitative information which may be used to determine if residues in a particular sample exceed an MRLVD or other regulatory action limit, but do not provide unequivocal confirmation of the identity of the residue. Such methods which provide quantitative results must perform in good statistical control within the analytical range that brackets the MRLVD or regulatory action limit." (Section 14. Integrating Analytical Methods for Residue Control, CAC/GL 71-2009, rev. 2012, 2014<sup>3</sup>).

Additional specific guidance on method selectivity requirements for each of the three categories of methods is provided in CAC/GL 71-2009, rev. 2013, 2014<sup>3</sup>, as follows:

- For screening methods, see Section 18.1 Performance Characteristics of Screening Methods.
- For quantitative methods, see Section 18.2 Performance Characteristics for Quantitative Methods,

- For confirmatory methods, see Section 18.3 Performance Characteristics for Confirmatory Methods.

The drafting expert should identify the appropriate criteria to be applied in the assessment of each method for which validation data are available (screening, quantitative or confirmatory) and should present the information in a format which is well organized and informative. This may include the use of a table, with supporting text, or a short paragraph summarizing the information available to address each of the applicable criteria. When the method provided for consideration is a multi-analyte or multi-residue method, it should be assessed according to the criteria contained in Appendix C – Performance Characteristics for Multi-Residue Methods (MRMs) for Veterinary Drugs, CAC/GL 71-20090, rev. 2012, 2014.<sup>3</sup>

Analyte stability is of particular importance. This should include both an assessment of the stability of the analyte during typical conditions of storage while awaiting analysis, preferably using representative sample material containing incurred residues, and of stability of analyte during analysis. CAC/GL 70-2009, *Guidelines for settling disputes over analytical (test) results* states that “reserve samples should be kept in a satisfactory condition for the appropriate length of time”.<sup>47</sup> The reserve sample material is intended to be maintained under conditions “which should not adversely affect the quality”. While no specific times are specified, a typical storage time for which analyte stability should be demonstrated in animal-derived foods under frozen storage would be in the range of 3-6 months. CAC/GL 71-2009, rev. 2012, 2014<sup>3</sup>, states that it is “prudent to conduct the storage study for a period which extends to at least 90 days beyond the expected time for all screening, quantitative, and confirmatory analyses to be completed and the results reported in case there is a challenge and a request for re-analysis”. When information on stability of the analyte during storage provided in the dossier is for shorter time periods, this should be noted in the review, which should also state the recommended conditions for sample storage. Stability data, where there is evidence of degradation and multiple data points, may be given in a table or in a figure. When no evidence of degradation has been observed, a simple statement in the text is sufficient.

Stability of the analyte during preparation and analysis is a critical issue which should be addressed. Some analytes may degrade under exposure to light, heat or certain chemical treatments and any such issues should be identified. Many modern analytical instruments include autosamplers with capacity for large numbers of samples, so there is a potential that a final extract of a sample may sit for hours in a vial in the autosampler prior to analysis. Information on the stability under such conditions should be provided in the method validation information.

The review of the method should include the status of the laboratory providing the validation data (accredited or work conducted under GLP), an assessment by the drafting experts of the quality of the information provided and the suitability of the method for support of the MRL or MRLs proposed by the Committee. When none of the methods provided are deemed by the

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<sup>47</sup> CAC/GL 70-2009, *Guidelines for settling disputes over analytical (test) results*; available at <http://www.codexalimentarius.org/standards/en/>.

drafting experts to meet the minimum validation criteria as required by CAC/GL 71-2009, rev. 2012, 2014, this should be clearly stated.

For substances for which an MRL is not recommended or for which JECFA determines that an ADI cannot be recommended because the substance exhibits toxicity which renders it not suitable for use in food-producing animals, an assessment of method performance is also of value to competent authorities in Codex member states, particularly for those substances for which the CCRVDF is considering the formulation of Risk Management Recommendations (RMRs).

*Examples:* For recent reviews of analytical methods, see the residue monographs prepared by the 75<sup>th</sup> and 78<sup>th</sup> meetings of JECFA, published in FAO JECFA Monographs 12<sup>48</sup> and 15.<sup>49</sup>

Tables summarizing information for individual methods as well as more extensive tables summarizing the performance of a number of methods can be used to supplement information in the text of the monograph. Figures depicting calibration plots should generally be avoided.

### 3.2.5.3 Criteria for recommending methods as suitable for support of MRLs

The following questions may be used by drafting experts to help assess the suitability of methods and these can best be addressed in preparing the Appraisal section of the monograph: Does the method address all matrices (species and tissues, eggs, milk or honey) for which MRLs are to be recommended?

- Are the validation data complete for each matrix for which an MRL will be recommended? If not, what is missing?
- Do method recoveries, coefficients of variation and trueness meet the requirements given in CAC/GL 71-2009, rev. 2012, 2014, for each matrix for which an MRL will be recommended?
- Is there adequate information on analyte stability in all matrices for which MRLs will be recommended?
- For single laboratory validations, was the validation conducted under GLP or in a laboratory where the method is accredited under ISO-17025 or equivalent? If not, does the drafting expert have another basis to judge the reliability of the work?
- Does the method meet practical requirements so that it is suitable for implementation in a routine residue control laboratory in most Codex member states?

This latter requirement can pose a problem for some quantitative confirmatory methods using “state of the art” technologies that may not yet be available to many routine laboratories. This has been raised as an issue by national delegations at meetings of CCRVDF. The issue was of

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<sup>48</sup> FAO. (2012). *Residue evaluation of certain veterinary drugs*, FAO JECFA Monographs 12; available at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-publications/en/>.

<sup>49</sup> FAO. (2014). *Residue evaluation of certain veterinary drugs*, FAO JECFA Monographs 15; available at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-publications/en/>.



particular concern for advanced methods used in the detection of substances without an ADI or MRL, such as chloramphenicol and the nitrofurans. It was noted in the report of the Joint FAO/WHO Technical Workshop on Residues of Veterinary Drugs without ADI/MRL held in Bangkok in 2004 that:

“Development of analytical methods does not consider the technical and resource limitations of developing countries frequently responsible for assuring the quality of exported food products derived from animals (including aquatic animals) treated with veterinary drugs. State of the art methodologies such as LC-MS are expensive to develop and maintain, particularly in the absence of the necessary technological infrastructure.”<sup>50</sup>

This issue remains of concern and should be considered when assessing the practicality of analytical methods for use in regulatory programs to support Codex MRLs for veterinary drugs.

Any deficiencies in the data provided for each method should be noted in the review of that method.

### **3.2.6 Appraisal**

The “Appraisal” section of the monograph is where the drafting expert and reviewer(s) summarize the key facts which have been established from their evaluation of the dossier, with their assessments on the quality and completeness of the studies. In this section, the focus should be on the studies which are critical to the decisions taken by the Committee. The final section of the monograph on MRL recommendations is built on the foundation laid in the “Appraisal” section, so any considerations cited in formulating the MRL recommendations should be supported by the information and assessment provided in the “Appraisal”.

The drafting expert and reviewer(s) must systematically review the information presented in the preceding sections of the monograph, establishing the basis on which MRL recommendations are formulated. The “Appraisal” section should be relatively short and concise, reviewing the available information for each key element, noting deficiencies in information provided for review and giving expert opinion, thus providing the basis for MRL recommendations. It is not necessary to repeat tables or figures from other sections of the monograph in this section. In some cases, particularly when there are a large number of studies to discuss, it may be helpful to prepare a summary table which incorporates key information from multiple studies. Discuss the studies in order of importance rather than in chronological order unless it is more logical to introduce a key study with a brief discussion of an earlier study. Some dossiers, for example, contain pilot studies which provide results used in the design of a subsequent pivotal study. The drafting experts should determine how best to present the information, keeping in mind that this section of the monograph will be used by readers

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<sup>50</sup> FAO.(2004). Report of the Joint FAO/WHO Technical Workshop on Residues of Veterinary Drugs without ADI/MRL, Bangkok, Thailand, August 24-26, 2004; available at <http://www.fao.org/3/contents/f25f1bdd-8d87-5c34-b1b4-814a60bb1a2e/y5723e00.htm>

who wish to understand the basis for the MRL recommendations, but may not be residue experts themselves.

### **3.2.6.1 Order of presentation and content**

The opening paragraph of the “Appraisal” should summarize the key information on the conditions of use for the substance, with information on the GVP (approved dose, mode of administration, species/classes for which there is an approved use). Additional information on GVP in member states, such as withdrawal times, may also be included here, as this is relevant to subsequent MRL recommendations. Note also if the product is approved for use in human medicine.

The second paragraph should summarize the pharmacokinetic information available for the substance, both in laboratory animals and food-producing animals. If information is available for humans, this should be included. The summary should include information on rates of absorption and elimination, particularly in food-producing animal species, especially if the available information suggests a slow release of residues from sites of administration or from other tissues.

The third paragraph should review the information available on metabolism, particularly if there are comparative metabolism studies. Identify any metabolites of toxic concern that must be considered in setting the MRL and also provide information on bound residues. Information on the relative distribution of the residues in the various edible tissues, milk or eggs (or honey) should be provided. The marker residue is typically identified in this paragraph. When there is limited information available on pharmacokinetics and/or metabolism, the two paragraphs may be combined. When there is information on multiple species that is relevant to the MRL recommendations, the information on pharmacokinetics and/or metabolism may be split into several paragraphs to improve readability and the text should include a discussion of comparative metabolism in the species for which data are available.

The next topic to review is the depletion studies with radiolabelled drug. The key information to summarize includes the total residues and their relationship to the marker residue when a conversion factor from marker to total residues must be included in the intake calculation. Any additional information that may be contained in these studies on bound residues or information that may be in the data from the studies concerning the persistence of residues at sites of administration should also be reviewed. When there is evidence, for example, that residues may persist in injection site muscle at concentrations above the MRL for muscle at the withdrawal times established under the GVP in member states, this should be noted and considered in making the MRL recommendations.

The subsequent paragraph should summarize the information on residue distribution and depletion obtained from the depletion studies with non-radiolabelled drug and identify the primary study or studies providing the data on which MRL recommendations will be based.

A paragraph should follow those on the depletion studies which include any studies in laboratory animals fed tissues or other treated animal derived foods to determine the

bioavailability of those residues. If a factor for bioavailability is to be included in the dietary intake calculation, it should be stated here.

The next paragraph should provide an overview of the available analytical methods and include a clear statement as to whether a suitable method or methods was identified to support the MRL recommendations. A closing paragraph may be included to provide an overall assessment of the quality and quantity of data available for the evaluation.

### **3.2.6.2 Identification of deficiencies**

A key element of the “Appraisal” section is to provide expert opinion, noting any deficiencies in the data (pharmacokinetics, metabolism, depletion or analytical methods) which may prevent the recommendation of MRLs or which may raise issues to be considered by national authorities in establishing GVP for the substance. The Appraisal should also include a global assessment of the quality and completeness of the data submitted and of the impact this may have on MRL recommendations by the Committee. When the deficiencies are significant in nature, the Committee will usually determine that MRLs cannot be recommended and request additional studies to be conducted, so the background for such recommendations must be clear to readers from the evaluation provided by the drafting experts in the Appraisal section.

### **3.2.6.3 Basis for recommendations in the MRL section**

The Appraisal section must clearly state the following:

- The species and matrices for which data were provided and for which MRLs have been requested by the CCRVDF;
- The adequacy of the pharmacokinetic data provided;
- The adequacy of metabolic information provided and whether a marker residue was identified;
- The adequacy of radiolabelled depletion studies and whether data were sufficient to calculate ratios of marker to total residues if these are required for the dietary intake calculations;
- The adequacy of depletion data to enable the Committee to formulate MRL recommendations; and
- The availability of suitably validated analytical methods to support the MRL recommendations;
- Any other issues, such as bound residues, bioavailability of residues or persistent residues at injection sites, which may be relevant to the MRL recommendations and/or dietary intake calculations.
- The dietary intake model to be used in the assessment and the reasons for use of this model.

### **3.2.7 Dietary exposure assessment**

It was decided at the 81<sup>st</sup> Meeting of JECFA that a section of exposure assessment should follow the Appraisal.<sup>15</sup> The drafting expert should include in this section information on which

type of exposure assessment was used (EDI, TMDI or other), the reason this type of assessment was chosen, the data used and the outcome. A table detailing the intake calculation should be included. It is appropriate in this section to include figures showing the tolerance limit plots on which the MRL is based and the corresponding median concentrations used in the EDI (or other) calculations of dietary exposure. When there are limited depletion data, as is the case when residues are below the LOQ at most timepoints in the tissues (or milk, eggs or honey), such plots may serve little value and the information can be summarized in the text. When other information is used in the intake calculations, such as food quantities used in a GECDE or GEADE calculation, these should be clearly stated and the source of the information should be identified and referenced.

As discussed in EHC 240<sup>2</sup>, exposure assessment is an essential step in the risk assessment process. The MRLs recommended by JECFA are based on “estimates of long-term (chronic) dietary exposures to residues of veterinary drugs in which point estimates of both the amounts of food commodities consumed and the residue concentrations are used”. The numerical result of the exposure estimate is “then compared with the type and amount of residue considered to be without toxicological, pharmacological or microbiological hazard for human health, as expressed by the ADI”. This comparison is reported in each residue monograph for the information of the risk managers, the CCRVDF, and other interested parties. Based on the results of the exposure assessment provided in the monograph, CCRVDF can then determine that the MRLs recommended by JECFA are consistent with the mission statement of the Codex Alimentarius Commission, “to ensure safe, good food for everyone, everywhere”.<sup>51</sup>

### **3.2.7.1 Exposure calculations based on the model diet**

JECFA has to date adopted two dietary exposure calculation approaches based on a standard food basket containing specific quantities of muscle, liver, kidney, fat, eggs, milk and honey, the Theoretical Maximum Daily Intake, or TMDI, and the Estimated Dietary Intake, or EDI.

#### **3.2.7.1.1 Theoretical Maximum Daily Intake (TMDI) approach**

The 34th Meeting of JECFA adopted the Theoretical Maximum Daily Intake, or TMDI, as the standard dietary exposure calculation to be used by the Committee.<sup>13</sup> This was applied to all substances until the 66<sup>th</sup> Meeting of JECFA, but is now used only when residue data are too limited to calculate an EDI for substances with an ADI based on a chronic toxicological endpoint.

Residue concentrations used in the TMDI calculation are the MRLs established for the substance. The calculation may include factors to adjust from marker residue to total residue concentrations, to correct for bioavailability of the residue in the food to the consumer or to adjust for the difference in the masses of parent substance and marker residue when the MRL is expressed as the concentration of parent compound.

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<sup>51</sup> CAC. (2015) .Home page, Codex Alimentarius Commission; available at <http://www.codexalimentarius.org/>

The TMDI for all types of food items assigned an MRL is then summed, using the highest MRL for each individual food item. For example, if there are MRLs for a substance in beef, pork and sheep muscle, with the highest MRL being for pork muscle, the MRL for pork muscle is used in the calculation. The resultant TMDI for all food items must not exceed the upper limit of the ADI. Examples of the TMDI calculation are found in “3.2.7.1.4 Performing dietary intake calculations using the model diet.”

### **3.2.7.1.2 Estimated Daily Intake (EDI) approach**

The Estimated Daily Intake, or EDI, was adopted by the 66th Meeting of JECFA<sup>52</sup> to be used when:

- The ADI is based on chronic exposure, and
- There are sufficient residue data for all food basket items at the timepoint associated with the MRL to provide median concentrations to use in the calculation.

The calculation is essentially the same as that used for the TMDI, except that the median residue concentration associated with the MRL is used in the calculation instead of the MRL. JECFA considers that the median residue is more representative of potential exposure than the upper limit represented by the MRL, a view accepted by the CCRVDF at its 18th Session in 2009.<sup>53</sup> When the residue data are insufficient to calculate the EDI, the TMDI calculation is used instead. Examples of the EDI calculation are found in “3.2.7.1.4 Performing dietary intake calculations using the model diet.”

### **3.2.7.1.3 Dietary consumption factors used in the model diet**

The TMDI and EDI calculations use a standard food basket to represent the daily consumption of animal-derived foods by a typical consumer, who is assigned a lifetime body mass of 60 kg. The basic dietary intake factors (food basket items) which are used in the dietary intake calculations based on a standard food basket (EDI or TMDI) are:<sup>2</sup>

- 300 g of muscle
- 100 g of liver
- 50 g of kidney
- 50 g of tissue fat
- 100 g of eggs
- 1500 g of milk
- 50 g of honey

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<sup>52</sup> WHO. (2006). *Evaluation of certain veterinary drug residues in food*, Sixty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives, WHO Technical Report Series 939; available at <http://www.who.int/foodsafety/publications/jecfa-reports/en/>.

<sup>53</sup> FAO/WHO. (2009) Report of the Eighteenth Session of the Codex Committee on Residues of Veterinary Drugs in Foods, Natal, Brazil, 11-15 May 2009, ALINORM 09/32/31; available at <http://www.codexalimentarius.org/meetings-reports/en/>.

The intake factors for tissues, milk and eggs were first used by the 34<sup>th</sup> JECFA<sup>13</sup>, based on dietary survey and food balanced sheet information, and the approach was confirmed following a review by the 40<sup>th</sup> JECFA.<sup>54</sup> Honey was later added to the food basket items, adjusted from 20 to 50 g daily consumption following a review by the 60<sup>th</sup> JECFA.<sup>55</sup>

The intake calculation should include the intake from each food basket item for which a MRL is recommended. When the MRL recommendation is for muscle of fish, 300 g of fish (fillet or muscle with adhering skin in normal proportions) should be used in the intake calculations. When there are MRLs recommended for multiple species and different MRLs are recommended for different species, select the MRL from those recommended for the various species for each food basket item which will result in the highest intake estimate.

#### **3.2.7.1.4 Performing dietary intake calculations using the model diet**

A table showing the dietary intake estimate made by the Committee for the substance should be included in the “Exposure Assessment”. The caption should clearly state whether the basis for the dietary intake estimates is an EDI or the TMDI. In the EDI and TMDI calculations, a standard body mass of 60 kg is used, representing the average bodyweight (bw) of an individual over a lifetime.<sup>56</sup> Intake of residues by a consumer is usually expressed in units of µg/kg bw/day.

*Calculation based on bodyweight:* Total intake (µg) ÷ standard body weight (60 kg) = daily intake per kg bw per day.

The preferred approach is to use the EDI calculation and this is used when the ADI is based on a chronic toxicological end-point and there are sufficient data points to calculate median residue concentrations {see 3.2.7.1.2 Estimated Daily Intake (EDI) approach}. When the ADI is based a chronic end-point, but the data are insufficient to allow the calculation of median concentrations for the residues, the TMDI is used (see 3.2.7.1.1 Theoretical Maximum Daily Intake (TMDI) approach). When the ADI/ARfD is based on an acute exposure toxicological endpoint the GEADE is calculated and this does not use the model diet {see 3.2.7.3.2 The Global Estimate of Acute Dietary Exposure (GEADE)}.

The next consideration is to determine whether guidance MRLs based on analytical method limits of quantification should be included in the dietary intake calculation. As a general approach, the following is suggested:

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<sup>54</sup> WHO. (1993). “Food consumption surveys” in *Evaluation of certain veterinary drug residues in food*, Fortieth report of the Joint FAO/WHO Expert Committee on Food Additives, WHO Technical Report Series, No. 832, pg. 6; available at <http://www.who.int/foodsafety/publications/jecfa-reports/en>

<sup>55</sup> WHO. (2009). “*Evaluation of certain veterinary drug residues in food*”, Seventieth report of the Joint FAO/WHO Expert Committee on Food Additives, WHO Technical Report Series, No. 954; available at <http://www.who.int/foodsafety/publications/jecfa-reports/en>

<sup>56</sup> WHO. (2012) Joint FAO/WHO Expert Meeting on Dietary Exposure Assessment Methodologies for Residues of Veterinary Drugs, Final Report including Report of Stakeholder Meeting, 7–11 November 2011, Rome; available at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/en/>.

- When there are no detectable residues in the depletion studies with radiolabelled and non-radiolabelled drug in the tissue at the timepoint on the depletion curve corresponding to the MRL recommendations, the drafting expert should recommend to the Committee that the guidance MRLs based on 2xLOQ should not be included in the TMDI calculation.
- When there are detectable residues in the some individual tissues in the depletion studies with radiolabelled and/or non-radiolabelled drug at the timepoint on the depletion curve corresponding to the MRL recommendations, the 66<sup>th</sup> Meeting of JECFA recommended the following calculation procedure for the EDI: “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”.<sup>52</sup>
- When the ADI/ARfD is based on an acute toxic response, a conservative approach should be taken and the drafting expert should recommend that the procedure recommended by the 66<sup>th</sup> Meeting of JECFA<sup>52</sup> (bullet 2) be included in the dietary intake calculation, as appropriate.

Determine which of the following factors apply for the dietary intake calculation to be used for the substance.

#### 3.2.7.1.4.1 Dietary intake factors only

This calculation uses only the dietary intake factors and marker residue median concentrations (EDI) or MRLs (TMDI).

**Example.** TMDI calculation based on data for tylosin from FAO JECFA Residues Monograph 6, prepared for the 70<sup>th</sup> JECFA.<sup>57</sup>

Tissue	MRL (µg/kg)	Standard Food Basket (kg)	Daily intake (µg)
Liver	100	0.1	10
Kidney	100	0.05	5
Muscle	100	0.3	30
Fat	100	0.05	5
Milk	100	1.5	150
Eggs	300	0.1	30
Total			230

*Calculation for each food basket item in above table:* MRL (µg/kg) x Food basket item (kg) = Daily intake (µg)

When the EDI calculation is to be performed, the same format is used, but substituting the median residue concentrations for the MRLs.

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<sup>57</sup> FAO. (2009). “Tylosin” in *Residue evaluation of certain veterinary drugs*, FAO JECFA Monographs 6, pp. 243-279; available at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-publications/en/>.

### 3.2.7.1.4.2 Marker-to-total residue (MR/TR) ratio

An additional column for the ratio of marker-to-total residues is added to the table showing the dietary intake calculations when an adjustment from marker-to-total residues is required (i.e., the total residue is considered to be of toxicological concern and assigned the same pharmacological activity as the marker residue).

*Example.* EDI calculation based on data for ractopamine hydrochloride contained in FAO JECFA Residues Monograph 2, prepared for the 66<sup>th</sup> JECFA.<sup>58</sup>

Tissue	Median residue concentration (µg/kg)	Standard Food Basket (kg)	MR:TR ratio	Daily intake (µg)
Liver	8.14	0.1	0.16	5.1
Kidney	14.97	0.05	0.33	2.3
Muscle	5.00	0.3	1.0	1.5
Fat	2.50	0.05	1.0	0.1
Total				9.0

*Calculation for each food basket item in above table:* Median residue (µg/kg) x Food basket item (kg) ÷ MR:TR ratio = Daily intake (µg)

When the TMDI calculation is to be performed, the same format is used, but substituting the MRLs for the median residue concentrations.

### 3.2.7.1.4.3 Bioavailability factor

The 34<sup>th</sup> JECFA described a procedure in which the quantity of residues of toxicological concern (i.e., the pharmacologically active residues) is calculated in both the extractable and the bound fractions of the total residue in the liver, kidney, muscle and fat. When appropriate, the calculation is also done for milk and/or eggs.<sup>13</sup> The following general formula is the used for the calculation of the residue of concern.

$$\begin{aligned}
 & \text{Total pharmacologically active residue} \\
 &= \text{Free residue} + \text{Bioavailable bound residue} \\
 &= \sum_{i=1}^n (M_i \times A_i) + (\text{Bound residue} \times \text{Fraction bioavailable} \times A_b)
 \end{aligned}$$

Where  $M_i$  is the concentration of metabolite I (including parent drug/marker residue),  $A_i$  its pharmacological potency, bound residue is total residue – extractable residue and  $A_b$  the pharmacological potency applied for the bound residue. Table 1 of Annex 3 of the report of the 34<sup>th</sup> meeting of the Committee provides an example calculation for trenbolone acetate.<sup>13</sup>

<sup>58</sup> FAO. (2006). "Ractopamine hydrochloride" in *Residue evaluation of certain veterinary drugs*, FAO JECFA Monographs 2, pp. 65-69; available at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-publications/en/>.



**Example:** Total trenbolone acetate equivalents in various tissues (TMDI calculation): adapted from table 1, Annex 3, TRS 788.<sup>13</sup>

Tissue	Total residue (µg/kg)	Free residue			Bound residue (µg β-TBOH/TBA equivalent per kg)		Total TBA equivalent per kg tissue (µg)	Standard Food Basket (kg)	Total maximum daily intake of TBA equivalents (µg)
		TBA (µg/kg)	β-TBOH (µg/kg)	α-TBOH (µg β-TBOH/TBA equivalent per kg)	Total bound	Amount bioavailable			
		II	III	IV	V	VI			
Liver (0.1 kg)	50	0	1.4	0.35	4.8	0.72	2.5	0.1	0.25
Kidney (0.05 kg)	22	0	0.71	0.06	2.1	0.31	1.1	0.05	0.06
Muscle (0.3 kg)	3.2	0	0.72	0.02	2.5	0.37	1.1	0.3	0.33
Fat (0.05 kg)	2.5	0	1.1	0.02	0.14	0.02	1.1		0.06
<b>Total</b>									<b>0.70</b>

II, III, IV – data obtained from residue depletion studies; V – amount equal to 10% of actual α-TBOH concentration, assuming a toxicological potency equal to 10% of the toxicological potency of β-TBOH; VI – total bound residue for muscle equals total residue (II) minus free residues, expressed as β-TBOH (IV + V), while for liver, kidney and fat the amount bioavailable is calculated as for muscle, then multiplied by 0.1 on the assumption that the bound residues in these tissues are α-TBOH, with a toxicological potency of 0.1 that of as β-TBOH; VII is obtained by multiplying the amounts in column VI by 0.15, the amount of the total bound residue which was considered to be bioavailable; VIII is calculated by adding IV, V and VII; I is the quantity from the standard food basket; IX is VIII multiplied by I.

When a bioavailability factor is applied to a substance for which the ADI is based on a chronic endpoint, the EDI is calculated as described in section 3.2.7.1.4.1 Dietary intake factors only (above), using the median residue, adjusted to include all pharmacologically active residues, at the timepoint at which the MRLs are established. When the TMDI calculation is to be performed, the same format is used, but substituting the MRLs, adjusted to reflect total active residues, for the adjusted median residue concentrations.

#### 3.2.7.1.4.4 Factor converting marker residue to parent drug

In some cases, including the preceding example, the Committee may decide to express the MRLs in terms of the parent drug, not the marker residue. When this approach is taken, a factor is required in the dietary intake calculation to convert the concentrations of marker residue to parent drug.

**Example:** EDI calculation based on data for monepantel contained in FAO JECFA Residues Monograph 15, prepared for the 78<sup>th</sup> JECFA.<sup>59</sup>

The Committee designated the metabolite monepantel sulfone as the marker residue, but expressed the MRLs in terms of monepantel, measured as monepantel sulfone, requiring a factor of 0.94 to convert residues of monepantel sulfone to monepantel equivalents in the dietary intake calculation. This factor is used in addition to the factors to convert marker residue to total residues.

#### Calculation of EDI for monepantel, measured as monepantel sulfone.

Tissue	Median residue concentration (µg/kg)	Standard Food Basket (kg)	MR:TR ratio	Monepantel parent: Monepantel sulfone ratio	Daily intake (µg)
Muscle	152	0.3	1	0.94	43
Kidney	1295	0.05	0.66	0.94	184
Liver	406	0.1	0.66	0.94	29
Fat	2620	0.05	0.66	0.94	187
Total					443

*Calculation for each food basket item in above table:* Median residue (µg/kg) x Food basket item (kg) ÷ MR:TR ratio x parent/marker ratio = Daily intake (µg)

When the TMDI calculation is to be performed, the same format is used, but substituting the MRLs for the median residue concentrations.

<sup>59</sup> FAO. (2014). "Monepantel" in Residue evaluation of certain veterinary drugs, FAO JECFA Monographs 15, pp. 89-92; available at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-publications/en/>.

### 3.2.7.2 Exposure calculations based on food consumption data

Two new approaches to dietary exposure calculation using actual food consumption data, the Global Estimate of Chronic Dietary Exposure (GECDE) and the Global Estimate of Acute Dietary Exposure (GEADE), were proposed by the Joint FAO/WHO Expert Meeting on Dietary Exposure Assessment Methodologies for Residues of Veterinary Drugs in 2011 as alternatives to the current model diet approach.<sup>56</sup> These new approaches were tested in a pilot study by the 78<sup>th</sup> Meeting of JECFA.<sup>5,60</sup> The report of the 78<sup>th</sup> JECFA noted that there “has been an ongoing need to improve the approaches used to estimate dietary exposure to veterinary drug residues” and included the results of a pilot project to evaluate “new methods for acute and chronic dietary exposure assessment for veterinary drug residues in foods” recommended by an expert consultation convened by FAO and WHO in 2011.<sup>5</sup> The Committee agreed that the new calculations should be “used in parallel with the model diet approach until more experience has been obtained in the interpretation of the results with the new approach”. Subsequently the 81<sup>st</sup> Meeting of JECFA decided that the GEADE calculation should be used to assess the dietary exposure to substances for which the ADI/ARfD is based on an acute toxicological end-point.<sup>15</sup> The Committee also compared the GECDE with the EDI (or TMDI) for compounds with an ADI based on a chronic toxicological end-point and agreed to continue to the evaluation of this approach for such substances.

The same basic formula is used for calculation of the GECDE and the GEADE, with exposure expressed on a daily intake/bodyweight ( $\mu\text{g}/\text{kg}$ ) basis, as for the EDI and TMDI:

$$\text{Dietary exposure} = \sum \frac{\text{Concentration of chemical in food} \times \text{Food consumption (g)}}{\text{Body weight (kg)}}$$

As in the EDI and TMDI calculation, the concentration of chemical in the food is adjusted from the concentration of marker residue by any factors required to provide the concentration of total pharmacologically active residues.

#### 3.2.7.2.1 The Global Estimate of Chronic Dietary Exposure (GECDE)

The monograph prepared for the 78<sup>th</sup> JECFA to describe the pilot study of new approaches to estimates of dietary exposure states that “the GECDE is the highest exposure calculated using the 97.5th percentile consumption figure for a single food selected from all the foods, plus the mean dietary exposure from all the other relevant foods”.<sup>60</sup> It is calculated as:

“GECDE = Highest exposure from one animal product + Total mean exposure from all other products”

The GECDE is reported in  $\mu\text{g}/\text{kg}$  of bodyweight per day, using 60 kg as the bodyweight for an adult, 15 kg as the bodyweight for a child and 5 kg as the bodyweight for an infant.

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<sup>60</sup> FAO. (2014) Annex 3 – Pilot of new approaches to estimate dietary exposure to veterinary drug residues, *FAO JECFA Monographs 15*, pp. 175-205, available at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-publications/en/>.

The monograph contains the following description of the process by which the GECDE is determined:

“The Global Estimated Chronic Dietary Exposure (GECDE) uses median residues combined with two different types of consumption data to estimate chronic dietary exposure. Firstly, the highest exposure at the 97.5<sup>th</sup> percentile of consumption is selected from all the foods relevant to exposure. This value is derived from chronic consumers of the food; that is, the percentile consumption is calculated from consumers of the food only and is different from the 97.5<sup>th</sup> percentile of consumption used in acute exposure, which reflects a single eating occasion (acute). Secondly, the mean dietary exposures from all the other relevant foods are then added to estimate total exposure. The mean dietary exposure is derived from the total population; in other words, non-consumers of the food are included in the mean calculation. In addition to the general population and children, dietary exposure of infants can also be estimated.

The GECDE assumes that, in the longer term, an individual would be a high-level consumer of only one category of food and that their consumption of other foods containing the residue would remain at the population average (total population). Therefore, the 97.5<sup>th</sup> percentile food consumption amount for consumers of the food only should be used, to be derived from surveys with individual records of two or more days' duration, by first calculating the average food consumption amount per day per person, preferably expressed on a per kilogram bodyweight basis for each individual. The choice of a high percentile, such as the 97.5<sup>th</sup>, is justified by its application for a single commodity (instead of two, as applied for other food chemicals). The 97.5<sup>th</sup> percentile is used because it was more commonly reported in the data submitted. It is essential to document information on the number of consumers on which the percentile is based to demonstrate that the data are truly representative of the population of interest.”<sup>60</sup>

**Examples:** See Annex 3 – Pilot of new approaches to estimate dietary exposure to veterinary drug residues for sample calculations.<sup>60</sup>

To calculate the GECDE, the following steps are followed:

- **Step 1.** Calculate the high-level exposure from each animal product = 97.5<sup>th</sup> percentile consumption × Median residue (General population).
- **Step 2.** Calculate the median exposure from the other food items, mean consumption x Median residue (General population), adjusted when required to the median total concentration of pharmacologically active residues.
- **Step 3.** Calculate the GECDE by summing the high exposure result for liver (offal) calculated in Step with and the median exposure calculated for the other food items (in this case muscle and fat/skin).
- **Step 4.** Round off the result to 0.1 µg.
- **Step 5.** Calculate the GECDE for children and infants from the available data as calculated for the general population.

### 3.2.7.2.2 The Global Estimate of Acute Dietary Exposure (GEADE)

The Global Estimate of Acute Dietary Exposure, or GEADE, is used instead of the EDI or TMDI when there is concern that an acute exposure may occur for a consumer.<sup>15</sup> As stated in the monograph prepared for the 78<sup>th</sup> JECFA:<sup>60</sup>

“The GEADE considers high-level exposure from each relevant food of animal origin individually. The concurrent occurrence of the selected high residue concentration in each food to which a consumer might be exposed (e.g. an MRL or high residue concentration derived from depletion studies, such as the upper one-sided 95% confidence limit over the 95th percentile residue concentration) is combined with a high daily consumption (97.5th percentile) of that food (meat, offal, milk, others). The 97.5th percentile food consumption amount (consumers only) was selected as being a more statistically robust value than the maximum food consumption amount because it represents an actual distribution of values.”

The GEADE is calculated in a similar fashion to the GECDE and is based on the establishment of an acute reference dose, ARfD, by the Committee. The GEADE is reported in  $\mu\text{g}/\text{kg}$  of bodyweight per day, using 60 kg as the bodyweight for an adult, 15 kg as the bodyweight for a child and 5 kg as the bodyweight for an infant. When the Committee recommends an Acute Reference Dose, the drafting expert should include a calculation of the GEADE in the draft monograph for consideration by the Committee. The following steps are to be followed for the calculation:

- **Step 1.** Calculate the high-level exposure from each animal product = 97.5th percentile consumption (kg consumed per kg bodyweight  $\times$  95th percentile residue for the general population, adjusted to total pharmacologically active residues (when required).
- **Step 2.** Calculate the GEADE for the general population, assuming all food items for which an MRL has been established are consumed at the 97.5th percentile for consumption and that each food item contains residues at the 95th percentile for concentration, adjusted to total pharmacologically active residues.
- **Step 3.** Calculate the GEADE values for children and for infants, following the calculations procedure used for the general population.

**Example:** See the monograph on zilpaterol hydrochloride prepared by the 81<sup>st</sup> meeting of the Committee.<sup>41</sup>

Since the ADI and ArfD were determined for zilpaterol hydrochloride based on an acute toxicological response, the Committee determined that the GEADE was the appropriate estimate of potential dietary exposure of consumers to residues of zilpaterol hydrochloride. To calculate the dietary intake of zilpaterol residues, all residues from the study with radiolabelled drug in cattle were converted to total pharmacologically active residues, expressed as zilpaterol hydrochloride equivalents. The GEADE was calculated to be 1.9  $\mu\text{g}/\text{day}$  for adults and 0.57  $\mu\text{g}/\text{day}$  for children, which represents 80% and 94% of the ArfD for adults and children, respectively.<sup>41</sup>

GEADE (adults) =  $\sum (\text{Concentration of chemical in food} \times \text{Food consumption (g)}) / (60 \text{ kg})$

GEADE (children) =  $\sum (\text{Concentration of chemical in food} \times \text{Food consumption (g)}) / (15 \text{ kg})$

For zilpaterol hydrochloride, the concentrations used in the calculation were the 95/95 UTLs derived at 77 hours post-dose: 3.3 µg/kg in kidney, 3.5 µg/kg in liver, and 0.5 µg/kg in muscle. Consumption factors used in the calculations were from the following table (Table 8.20 in the zilpaterol hydrochloride monograph<sup>41</sup>).

**Consumer statistics calculated from 97.5<sup>th</sup> tissue consumptions (expressed in grams tissue/kg bw/day).**

Cattle Tissue	97.5 <sup>th</sup> General population consumption			97.5 <sup>th</sup> Children consumption		
	max	p97.5	Median	max	p97.5	Median
Muscle	7.7	6.6	3.9	12.7	12.0	7.1
Liver	6.4	5.8	2.0	8.3*	7.5	2.8
Kidney	3.2*	3.0	1.5	12.9*	12.3*	2.1

### 3.2.7.3 Acute Reference Dose (ARfD) and exposure calculation

An acute reference dose is defined as “the estimate of the amount of a substance in food or drinking-water, expressed on a body weight basis that can be ingested in a period of 24 hours or less without appreciable health risk to the consumer”.<sup>2</sup> JECFA has not typically dealt with compounds for which it has been deemed necessary to establish an acute reference dose, or ARfD, but does consider the establishment of an ARfD on a case-by-case basis. The 52nd JECFA established an ARfD for carazolol, based on the potential that residues at the injection site could exceed the ARfD for several hours post-injection in pigs.<sup>12</sup> The ARfD, in this case, was set as the upper limit of the ADI. The exposure calculation was made using consumption of 300 g of muscle (injection site muscle) from the model diet and the actual concentrations of carazolol residues found 2 hours post-treatment in the injection site muscle of pigs injected with the approved dose of carazolol.

More recently, the 81<sup>st</sup> JECFA agreed to principles to be used by a working group to further develop guidance on “when and how to establish ARfDs for veterinary drugs” and established an ArfD for two substances, ivermectin and zilpaterol hydrochloride.<sup>15</sup> The Committee also noted in the evaluation of lasalocid sodium “the need to develop an approach for establishing a microbiological ARfD”. For substances which have been assigned an ARfD, the GEADE is compared with the ARfD, not the ADI.<sup>15</sup>

When there is a decision by JECFA to establish an Acute Reference Dose, this recommendation will come from the toxicology drafting experts, typically when the dietary intake calculations made by the drafting experts for residues indicate that there is a potential for the ADI to be exceeded by the consumption of a single serving of a food basket item, such as muscle or liver, by a consumer.

### 3.2.8 Maximum Residue Limits

This section of the monograph begins with either a simple statement that the Committee has recommended MRLs based on a set of considerations which follow in bullet points or a statement that the Committee did not recommend MRLs, with the reason(s) for this decision. The MRL recommendations are developed from an evaluation of the depletion data associated with use according to Good Veterinary Practice for the substance and should result in a dietary intake calculation that is consistent with the ADI (or ARfD). The basic consideration is that whichever dietary exposure calculation is used for a particular substance, that calculation should not yield a result which exceeds the upper limit of the ADI or the ARfD. The ADI is expressed as a range, from 0 to an upper limit, such as 0 – 2 µg/kg bodyweight, with the upper limit of the ADI in this example for a 60 kg individual being 120 µg. The ARfD is a single value, expressed in µg/kg bodyweight, which should not be exceeded when the dietary intake is calculated using the GEADE.

#### 3.2.8.1 Importance of GVP as basis for MRL recommendations

CCRVDF has requested that JECFA provide recommendations for MRLs that are consistent with the approved use of a substance in Codex member states, referred to as the Good Veterinary Practice, or GVP.<sup>61</sup> When the studies submitted use different dosages than those which have been approved or animals in the studies are not representative of the typical animals receiving treatment, this must be noted and should be a major factor when the Committee considers MRL recommendations.

MRLs should not be recommended by JECFA if the data provided do not reflect the actual use of the drug in member states. A recommendation of MRLs from JECFA to CCRVDF which is not consistent with the MRLs and/or withdrawal times established in the member states will usually result in the recommendations being referred back to JECFA for further consideration. There are instances where JECFA has established a lower ADI than that established in member states. When MRLs consistent with the GVP in the Codex member states cannot be recommended by JECFA, the scientific basis should be clearly explained in the considerations associated with the MRL recommendations in the monograph and the meeting report.

#### 3.2.8.2 Drafting the bullet points

Typically, the bullet points would include the following:

- The ADI (state the range) established by the Committee and the upper bound of the ADI (in µg) for a 60 kg person.
- The ARfD, if established by the Committee.
- Information on the GVP in member states, including species for which the drug is approved, dose rates and withdrawal times.

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<sup>61</sup> FAO/WHO. (1989) Report of the Second Session of the Codex Committee on Residues of Veterinary Drugs in Foods, ALINORM 89/31, Washington D.C., 30 November-4 December 1987; available at <http://www.codexalimentarius.org/meetings-reports/en/>.

- A statement on the pharmacokinetics, particularly when these data may be critical to the MRL recommendations.
- A statement on the metabolism, which may include information on the extent of metabolic breakdown.
- Identification of the marker residue.
- Identification of target tissues for monitoring of domestic production and imported products.
- Identification of marker-to-total residue ratios; when ratios differ between species, clearly identify which are used in the dietary intake calculation.
- If a correction for marker-to-total residues is not required in the dietary intake calculations, this should be stated; in such cases, identify the species/matrices used in the dietary intake calculation when MRLs have been recommended for multiple species.
- A statement regarding any other considerations which may apply, when needed, such as the inclusion of a factor for bioavailability in the dietary intake calculation.
- A statement on the availability of suitable analytical methods to support the MRL recommendations.
- If the residue concentrations reported in the depletion studies have not been recovery corrected, this correction should be applied when formulating MRL recommendations and this should be clearly stated in the bullet points.
- State which MRLs, if any, are based on method LOQ.

*Example:* See the bullet points in the monograph on Emamectin benzoate prepared for the 78th JECFA.<sup>6</sup>

### 3.2.8.3 Presenting the MRL recommendations

A paragraph which provides the MRL recommendations and a summary of the basis for these recommendations usually follows the bullet points. The MRL recommendations for fat, liver, kidney and muscle and the species to which these recommendations apply are stated, along with any MRL recommendations for milk and/or eggs, again with species identified, and/or MRL recommendations for honey. The Committee will usually use the adjective “full” when the recommendations also include a recommendation for a “temporary” MRL to prevent confusion, or when there has previously been a recommendation for temporary MRLs for the substance.

The initial MRL recommendations should be prepared by the drafting expert prior to the meeting of the Committee and then finalized once a final decision on the ADI/ARfD has been made by the Committee. General guidance on the process for development of MRL recommendations was provided in the report of the 66<sup>th</sup> JECFA.<sup>52</sup> For the drafting expert, development of the MRL recommendations can be the most stressful part of their assignment, as a final decision on the ADI/ARfD typically comes in the final days of the JECFA meeting. While there is no guarantee that MRLs drafted prior to the meeting will prove to be the final MRL recommendations once the final decision on the ADI/ARfD has been made, this does not mean that it is impossible to prepare potential MRL recommendations. Prior to the Committee



meeting, the drafting expert can use sources such as the ADI/ARfD proposed by the Sponsor, ADIs/ARfDs established by the competent authorities in member states and discussions with the drafting experts for the toxicology monograph to identify potential values for the ADI/ARfD.

- **Step 1.** Develop a short list of potential ADI/ARfD values which might be established by the Committee, based on information from the Sponsor, information on ADIs/ARfDs set by national or regional authorities and preliminary evaluation of the toxicological data by the drafting experts for the toxicology monograph.
- **Step 2.** Establish whether the decisions on ADI/ARfD by competent authorities in member states and/or the probable basis for an ADI/ARfD to be recommended by the drafting experts for the toxicology monograph will be a chronic endpoint or an acute endpoint. When the basis for the ADI is a chronic endpoint and sufficient residue data are available to determine median residue concentrations, then the EDI is used to estimate intake and MRLs can be recommended consistent with this calculation. If sufficient data are not available to calculate an EDI, then the TMDI is used to estimate dietary intake when the ADI is based on a chronic endpoint. If the basis for the ADI is an acute endpoint, the 81<sup>st</sup> JECFA determined that the GEADE should be used to estimate the dietary intake.<sup>15</sup> When the ADI is based on an acute toxicological endpoint, the drafting expert should anticipate that it is probable that an ARfD will also be recommended, based on the toxicological evaluation. MRL recommendations should be consistent with the exposure calculation that is used and should result in an estimated intake below the ADI (or ARfD).
- **Step 3.** Identify any additional factors to be included in the intake calculation. Most commonly, these will be factors for conversion of marker residue to total residue. The Committee will only make a decision on these factors based on recommendations from the drafting expert, so the drafting expert is in the best position to assess what factors should be used in the preliminary dietary intake calculations while developing potential MRL recommendations.
- **Step 4.** Review the information on GVP for the substance in member states, particularly the highest dose approved and the associated withdrawal time for that treatment. The target then is to develop MRL recommendations which are consistent with the upper limit of dietary intake associated with the probable ADI (or ARfD) and also with the withdrawal times established in the member state(s).
- **Step 5.** Using the JECFA Statistical Tool<sup>38</sup> or an equivalent method of calculation, develop potential MRL recommendations based on the appropriate exposure calculation (EDI, TMDI or GEADE).

If the intake calculations produce a result in excess of the ADI (or ARfD), then move to the next timepoint on the depletion curve and repeat the calculations until a result is achieved which results in an estimated intake lower than the ADI (or ARfD). If it is necessary to recommend MRLs which require a longer withdrawal time than has been established by competent authorities in member states, this should be noted with the recommendations.

The drafting expert can reduce the stress associated with having to prepare MRL recommendations late in the Committee meeting when a final decision has been taken on the ADI (or ARfD) by having MRL recommendations prepared for several timepoints, based on the depletion data and potential values for the ADI (or ARfD) proposed by the toxicology reviewers. If no proposal on the ADI (or ARfD) is available prior to the meeting from the toxicology reviewers, ADIs (or ARfDs) already established in Codex member states and/or the ADI (or ARfD) proposed by Sponsor may be used to generate initial proposals for MRLs. The depletion data will not change, so it is simply a matter of having the depletion data entered into the Statistical Tool, then modelling the recommendation for MRLs that are consistent with the potential ADI (or ARfD) decision from the Committee and secondly, if possible, that are consistent with the withdrawal time(s) established by member states. Focus on the GVP. For a typical residue evaluation, this may involve preparing MRL recommendations for 2-3 timepoints on the depletion curve. If none of these results prove consistent with the ADI (or ARfD), this preparative work will at least provide a clear indication of the timepoint on the depletion curve that is likely to provide MRL recommendations consistent with the ADI (or ARfD). It is not necessary to include all potential MRL recommendations in the draft monograph, but experts should simply have the calculations performed so that they can be introduced, discussed and modified, if necessary, by the Committee once a final decision on the ADI (or ARfD) is reached. The MRL recommendations in the monograph are then finalized once the Committee has established an ADI (or ARfD).

When all residues in a tissue, eggs, milk or honey at a sampling time are below the LOQ, MRLs are usually recommended at a concentration twice the LOQ (2 x LOQ). These MRLs are intended as guidance limits, as discussed in EHC 240<sup>2</sup>, and the intent is that there should be no quantifiable residues in the matrix specified.

In recommending MRLs, the following principles are typically applied by the drafting expert:

1. The MRLs should, whenever possible, be consistent with the GVP established for the substance in the Codex member states.
2. The MRLs recommended for the tissues should be consistent with the distribution of residues in those tissues.
3. The MRLs are usually derived from the UTL 95/95 residue concentration determined from the depletion plot using the JECFA Statistical Tool or an equivalent method of calculation.
4. MRL recommendations are typically multiples of 5, 10 or 100 µg/kg, rounded up from the UTL 95/95 residue concentration to a value consistent with the sensitivity of the proposed regulatory analytical method. The sensitivity of a quantitative method is the ability of the method to discriminate between concentrations, so the method sensitivity should be, for example, 0.1 µg/kg when MRLs are less than 1 µg/kg and 1 µg/kg when MRL recommendations are in the 1 – 10 µg/kg.
5. MRLs recommended based on 2 x LOQ are not rounded.
6. The dietary intake calculation associated with the recommended MRLs should not exceed the ADI (or ARfD).

#### 3.2.8.4 Special considerations such as persistent residues at injection sites

For some compounds, there may be issues which make the recommendation of MRLs more difficult. The most common of these is the persistence of residues at an injection site or site of application, such that residues in that muscle tissue may exceed the MRL recommended for muscle tissue at the withdrawal time which has been established as part of the GVP in member states. In such cases, the Committee has recommended a MRL for muscle to CCRVDF, but with the additional advice that there may be a problem with residues at the injection site exceeding the MRL recommended for muscle tissue under the approved conditions of use in Codex member states.

*Example:* In recommending MRLs for doramectin in muscle, the 45<sup>th</sup> JECFA stated: <sup>62</sup>

“The Committee also notes the high concentrations of residues at the injection sites during the 35 day period after parenteral administration of the non-radiolabelled recommended dose.”

The MRLs for doramectin in cattle muscle or fat subsequently established by the Codex Alimentarius Commission carry the following cautionary note: <sup>63</sup>

“High concentration of residues at the injection site over a 35 day period after subcutaneous or intramuscular administration of the drug at the recommended dose.”

#### 3.2.8.5 Substances with a long history of use

Situations have arisen during the evaluation of drugs which fall under JECFA policies for “drugs with a long history of use” which have resulted in the Committee developing a procedure for the recommendation of MRLs for such substances. In discussing statistical approaches to the development of MRL recommendations, the 52<sup>nd</sup> JECFA noted that when the data are limited for the depletion of residues resulting from the use of a drug with a long history of use, specifically citing the example of when the available studies include only 3 animals per sampling time, “the Committee has agreed in principle to use mean values and to consider incorporating three standard deviations for determining the upper limits of residue concentrations at a particular time”.<sup>12</sup>

#### 3.2.8.6 Special data requirements for drugs used in aquaculture

When reporting on experiments to assess residue concentrations in fish, it is important that the mean water temperature and number of days of exposure (sometimes referred to as the degree days) are included in summarizing the data, as rates of absorption and elimination of drugs used in aquaculture are affected by the water temperature over the time in which the experiment was conducted. While the Committee has not issued specific guidance on the requirements of

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<sup>62</sup> FAO. (1996). “Doramectin” in *Residues of some veterinary drugs in animals and foods*, FAO Food and Nutrition Paper 41/8, pp.85-98; monograph available from the Online Edition: "Residues of some veterinary drugs in foods and animals" at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-vetdrugs/en/>.

<sup>63</sup> CAC/MRL 2 – 2012, Codex Alimentarius Commission Maximum Residue Limits for Veterinary Drugs in Foods; available at <http://www.codexalimentarius.org/standards/en/>.

pharmacokinetic, metabolism and residue depletion studies in fish, the following general guidance may be implied from the past JECFA evaluations of substances used as veterinary drugs in aquaculture:

- Studies should preferably be conducted under GLP.
- The dossier should include information on the GVP in one or more member states.
- The small size (body mass) of most aquaculture fish species relative to food-producing animals and the method of treatment (large numbers of fish in a confined pond or in an enclosure in fresh or salt water) requires a larger number of individual animals to be sampled than are required for such studies with large land animals to provide representative results.
- Studies, particularly the depletion studies, should be conducted under conditions representative of typical conditions in the aquaculture industry (method of feeding, environmental factors), using fish which are either near market weight or at a weight representative of when the treatment is typically applied.

Some guidance on the design of residue depletion studies for species raised in aquaculture is currently available from the United States Food & Drug Administration guidance for products in minor use or used in minor species, which recommends for products used in aquaculture that “the number of animals per time period should be increased to at least 15 to 20 animals per time period”.<sup>64</sup> Guidance from the European Medicines Agency (EMA) for medicinal products approved for minor use or minor species includes use in fish and requires a minimum of 10 animals per timepoint for the establishment of MRLs and a minimum of 3 sampling times for the establishment of withdrawal times.<sup>65</sup> An additional EMA guideline provides some further general instruction on the establishment of MRLs for fish.<sup>66</sup> A project to develop harmonized guidance was in progress at Step 1 in VICH at the time of preparation of this guidance document. JECFA drafting experts and reviewers are encouraged to be aware of any further developments in international organizations and national regulatory authorities concerning the development of guidance for residue studies related to the establishment of MRLs in species raised in aquaculture.

Drafting experts and reviewers are also encouraged to read previous JECFA monographs and meeting reports dealing with drugs used in aquaculture to gain a better understanding of how

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<sup>64</sup> U.S.F.D.A. (2008). *GFI#61, Guidance for Industry: FDA Approval of New Animal Drugs for Minor Uses and for Minor Species*; available at:

<http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm042450.htm>

<sup>65</sup> E.M.A. (2006) Guideline on safety and residue data requirements for veterinary medicinal products intended for minor uses or minor species, EMEA/CVMP/SWP/66781/2005; available at [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000383.jsp&mid=WC0b01ac058002dd38](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000383.jsp&mid=WC0b01ac058002dd38)

<sup>66</sup> E.M.A. (1998) Note for guidance on the establishment of maximum residue limits for *Salmonidae* and other finfish, EMEA/CVMP/153b/97-Final; available at [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000383.jsp&mid=WC0b01ac058002dd38](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000383.jsp&mid=WC0b01ac058002dd38)

previous meetings of JECFA have dealt with the data available for review of products used in aquaculture by those meetings.

### **3.2.8.7 Identification of any additional studies required to support MRL recommendations**

When the available data do not lead to a MRL recommendation or when the MRLs recommended are designated as temporary due to some gaps or deficiencies in the available data, the closing paragraph(s) of the Maximum Residue Limits section identify the deficiencies, the data required to complete the MRL evaluation and the deadline by which these data should be provided to JECFA.

*Example:* Only temporary MRLs were recommended for cattle by the 70<sup>th</sup> JECFA in the review of narasin due to insufficient data.<sup>46</sup>

“Before re-evaluation of narasin with the aim of recommending permanent MRLs in tissues of cattle, the Committee would require a detailed description of a regulatory method, including its performance characteristics and validation data. This information is required by the end of 2010.”

### **3.2.9 References**

Reference citations should follow the standard format used in the FAO JECFA Monograph series.

#### **3.2.9.1 Citation format**

All information on references cited in the monograph is provided under the heading “References” at the end of the monograph, using the citation format described in the guide “FAO STYLE”.<sup>16</sup> The references are listed in this section in alphabetical order, with author name(s) in bold, and followed by the year of publication. The full name of the report or publication is given, followed by the source. For publications from the scientific literature, the full name of the journal (no abbreviations) or book is in italics. For books, include the publisher name, city and country. If a publication is not in English, include the language of publication in brackets at the end of the citation. A typical monograph will predominantly list references to confidential reports provided by the Sponsor, with additional references to published papers, JECFA and Codex Alimentarius documents and other communications. Examples of the format for each type of citation are provided below.

*Example 1: Confidential research reports provided by a Sponsor* (Source: Narasin monograph prepared for the 75<sup>th</sup> JECFA.<sup>67</sup>)

**Handy, P.R., Thomson, T.D. & Tamura, R.N.** 1985. Determination of the depletion of narasin residues in broiler chickens. *Agricultural Analytical Chemistry*, Lilly

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<sup>67</sup> FAO. (2012). “Narasin” in *Residue evaluation of certain veterinary drugs*, FAO JECFA Monographs 12, pp. 135-153; available at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-publications/en/>.

Research Laboratories, Division of Eli Lilly and Company, Report Number AAC-8408. Sponsor submitted.

**Example 2: Publication from the peer-reviewed scientific literature** (Source: Gentian violet monograph prepared for the 78<sup>th</sup> JECFA.<sup>68</sup>)

**Roybal, J.E., Munns, R.K., Hurlbut, J.A. & Shimoda, W.** 1990. Determination of gentian violet, its demethylated metabolites, and leucogentian violet in chicken tissue by liquid chromatography with electrochemical detection. *Journal of the Association of Official Analytical Chemists*, 73: 940–946.

**Example 3: Previous JECFA report** (Source: Tilmicosin addendum monograph prepared for the 70<sup>th</sup> JECFA.<sup>69</sup>)

**FAO/WHO** (1998). 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.

**Example 4: Codex Alimentarius Commission document** (Source: Derquantel monograph prepared for the 78<sup>th</sup> JECFA.<sup>31</sup>)

**FAO/WHO.** 2013. Report of the Twenty-first Session of the Codex Committee on Residues of Veterinary Drugs in Foods, Minneapolis, United States of America, 26–30 August 2013. CAC doc. REP14/RVDF. Available at: [http://www.codexalimentarius.org/download/report/802/REP14\\_RVe.pdf](http://www.codexalimentarius.org/download/report/802/REP14_RVe.pdf). Accessed 2014-05-29.

**Example 5: Other studies and reports** (Source: Emamectin benzoate monograph prepared for the 78<sup>th</sup> JECFA.<sup>6</sup>)

**EMA [European Agency for the Evaluation of Medicinal Products].** 1999. Committee for Veterinary Medicinal Products. Emamectin. Summary Report (1). Doc. EMEA/MRL/546/99-FINAL. Available at [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Maximum\\_Residue\\_Limits\\_-\\_Report/2009/11/WC500014125.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Maximum_Residue_Limits_-_Report/2009/11/WC500014125.pdf). Accessed 2014-05-07.

**Example 6: Other communications to JECFA** (Source: Derquantel monograph prepared for the 78<sup>th</sup> JECFA.<sup>31</sup>)

**Concerns from a Member State.** 2012. Submitted by the Delegation of Australia, includes one attachment with TMDI scenarios.

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<sup>68</sup> FAO. (2014). “Gentian violet” in *Residue evaluation of certain veterinary drugs*, FAO JECFA Monographs 15, pp. 39-59; available at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-publications/en/>.

<sup>69</sup> FAO. (2009). “Tilmicosin addendum” in *Residue evaluation of certain veterinary drugs*, FAO JECFA Monographs 6, pp. 159-195; available at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-publications/en/>.

**Example 7. Publication language is not English** (Source: Recombinant bovine somatotrophins monograph prepared for the 78th JECFA<sup>70</sup>).

**Campos, B.G., Coelho, S.G., Quintão, A.M.L., Rabelo, E., Machado, T. & Silper, B.** 2011. [Use of bovine somatotrophin (bST) 500 mg in crossbred *Bos taurus* × *Bos indicus* cows every 12 or 14 days.] *A Hora Veterinária*, 179: 8–13 (in Portuguese).

### 3.2.9.2 Placement in text

The reference citation should appear in the monograph text in the first sentence in which it is cited, in the format (author, year).

**Example 1: Report with authors identified** (Source: Gentian violet monograph prepared for the 78th JECFA.<sup>68</sup>)

“As part of method development for determination of gentian violet, its demethylated metabolites and leucogentian violet, gentian violet residues were measured in livers and muscle from chickens treated with a standard broiler diet containing 30 mg/kg gentian violet for 3 weeks (Roybal et al., 1990).”

**Example 2: Reports from committees or organizations** (Source: Derquantel monograph prepared for the 78th JECFA.<sup>31</sup>)

“Derquantel was previously reviewed by the Committee at its 75th meeting (FAO, 2012), which assigned an ADI of 0–0.3 µg/kg corresponding to an upper bound of acceptable intakes of 18 µg/day for a 60 kg person.”

### 3.2.9.3 Conventions (order of citation)

When there are multiple citations from the same author or authors, they are listed in the Reference section in order of publication, starting with the earliest. If there are multiple publications by the author or authors within the same year, a letter is added after the year for identification purposes, beginning with “a” and proceeding alphabetically.

**Example:** (Source: Gentian violet monograph prepared for the 78th JECFA.<sup>68</sup>)

**McDonald, J.J., Breeden, C.R., North, B.M. & Roth, R.W.** 1984a. Species and strain comparison of the metabolism of gentian violet by liver microsomes. *Journal of Agricultural and Food Chemistry*, 32: 596–600.

**McDonald, J.J., North, C.R., Breeden, C.R., Lai, C.C. & Roth, R.W.** 1984b. Synthesis and disposition of 14C-labelled gentian violet in F344 rats and B6C3F1 mice. *Food Chemistry & Toxicology*, 22: 331–336.

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<sup>70</sup> FAO. (2014). “Recombinant bovine somatotrophins” in *Residue evaluation of certain veterinary drugs*, FAO JECFA Monographs 15, pp. 93-132; available at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-publications/en/>.

The text citations are “McDonald *et al*, 1984a” and “McDonald *et al*, 1984b”, respectively.

### **3.2.10 Final revisions (post-meeting)**

Before submission of the final version of the monograph, the drafting experts should:

- Check to ensure that all corrections/revisions from other members of the Committee have been incorporated.
- Ensure that the text of the Maximum Residue Limits Section of the monograph is consistent with the text of the meeting report (the summary) for the substance. The introduction to this section should be the same in both documents. The bullet points leading to the MRL recommendations and the paragraph containing MRL recommendations and dietary intake estimates should be identical. If there is a paragraph dealing with data gaps or deficiencies and a request for additional studies, the wording should also be identical in both documents. The table showing the dietary intake calculations is included in the monograph, but not in the Summary for the TRS Report of the Meeting.
- Check the document for typographical errors, missing references, missing or incorrect table and figure captions and review the text to ensure that the content of the monograph is consistent with the content of the Summary contained in the TRS Report of the Meeting. In particular, check to ensure that any observations or opinions expressed in the Appraisal Section of the original draft are consistent with the evaluation and decisions of the Committee contained in the TRS Report of the Meeting.

## **4. Preparation of Technical Report Series Summary (Meeting Report)**

This section provides guidance for drafting experts on the preparation of the draft summary for inclusion in the Report of the Meeting published in the WHO Technical Report Series.

### **4.1 Overview**

The drafting expert assigned to prepare each monograph by FAO (and WHO) is also responsible for preparing a draft summary document for consideration by the Committee during the JECFA Meeting. While the monograph is written as a document for residue experts, containing extensive technical details on the studies conducted and on data provided, the summary is written for a more general audience who have a general understanding of the material, but not at the expert level. The summary contains the text to be included in the JECFA Meeting Report.

Draft summary documents are required for distribution to all Committee members and the JECFA Secretariat prior to the start of a JECFA Meeting, with revisions made promptly by the drafting expert during the meeting (see Module I, “3.5 Schedule for participants a JECFA Meeting” and “5.3.3 Role of drafting expert”). As the specifics of arrangements for providing the revised summary to the rapporteur and for document distribution may change from meeting to meeting, all Committee members should ensure that they obtain information on document management at the beginning of the JECFA Meeting and adhere to these procedures.



## 4.2 Sections of summary for substances under review

The headings and content typically used in the preparation of the Summary are described under the following sub-headings.

### 4.2.1 Explanation

This opening section of the Summary provides a brief review of the nature of the referral of substance to JECFA and the registered uses provided.

*Example:* (Source: “Emamectin benzoate” in the Seventy-eighth report of the Joint FAO/WHO Expert Committee on Food Additives<sup>5</sup>):

“Emamectin benzoate (CAS No. 155569-91-8) is a macrocyclic lactone insecticide derived from the avermectin series isolated from fermentation of *Streptomyces avermitilis*. Emamectin benzoate contains a mixture of at least 90% emamectin B1a benzoate and at most 10% emamectin B1b benzoate. Emamectin benzoate acts by stimulating the release of  $\gamma$ -aminobutyric acid, an inhibitory neurotransmitter, thus causing insect paralysis within hours of ingestion and subsequent insect death 2–4 days later.

Emamectin benzoate is authorized for use as a pesticide on fruits, vegetables, cereals, tree nuts, oilseeds, herbs and tea. It is also registered for use as a veterinary drug in the treatment of sealice infestations in Salmonidae and other finfish in several countries. Emamectin benzoate is used as a premix coated onto non-medicated fish feed pellets to achieve an intended dose of 50  $\mu\text{g}/\text{kg}$  of fish biomass per day for 7 days. It can be used up to 3 times per year with a maximum of five treatments in any 2-year growth cycle.

Emamectin benzoate has not previously been evaluated by the Committee. The Committee evaluated emamectin benzoate at the present meeting at the request of the Twentieth Session of CCRVDF (2), with a view to establishing an ADI and recommending MRLs in salmon and trout. Other avermectins, such as ivermectin, eprinomectin and doramectin, have previously been evaluated by JECFA (Annex 1, references 92, 105, 120, 135 and 158). Although no data were submitted to JECFA by the sponsor for the evaluation of emamectin benzoate, JECFA decided to undertake an evaluation based on the recent JMPR evaluation and published literature.”

### 4.2.2 Toxicology evaluation

This section is prepared by the toxicology experts, under the heading “Toxicological evaluation” or “Toxicological and microbiological evaluation”. It typically includes a brief paragraph identifying sources of toxicological information used by the Committee and results of any previous toxicological reviews by JECFA. This is followed by the heading “Biochemical data”, under which a summary of all relevant biochemical data, with emphasis on studies leading to ADI/ARfD decision, is provided. The final part of the toxicology section is under the heading “Evaluation” and this section of the Summary contains a concise assessment of the

key toxicological information reviewed by the Committee and the resulting decision on an ADI/ARfD.

### **4.2.3 Residue evaluation**

This portion of the final Summary for a substance is prepared by the drafting expert assigned by FAO. However, as noted in the preceding section, all members of the Committee and the Secretariat are expected to question the content during discussions held throughout the Meeting.

#### **4.2.3.1 Opening paragraph(s)**

This material appears directly under the heading “Residue evaluation” and provides a basic overview of the residue information provided for review to the Committee.

*Example:* (Source: “Emamectin benzoate” in the Seventy-eighth report of the Joint FAO/WHO Expert Committee on Food Additives<sup>5</sup>):

“The present evaluation was performed on the basis of available published peer-reviewed scientific papers, evaluations from national agencies and the JMPR evaluation. Despite the request of the Committee, the sponsor of a marketed authorized emamectin benzoate formulation for sealice control did not send the dossier used by national authorities for risk assessment.

The Committee reviewed studies on the pharmacokinetics and metabolism of emamectin benzoate and residue studies on emamectin benzoate in the relevant species of finfish.”

#### **4.2.3.2 Data on pharmacokinetics and metabolism**

This section should be brief and relate to residue issues to avoid extensive overlap with the summary of pharmacokinetics prepared by the toxicology expert from content of the toxicological monograph. Typically, the dossiers received for the toxicological review and the residue review will both contain studies on the pharmacokinetics and metabolism of the substance in laboratory animals. The summary documents prepared both by the toxicology experts and the residue experts should contain summaries of the relevant studies provided in the dossiers they received. As the meeting progresses, the contents of the residue and toxicology summaries dealing with pharmacokinetics in laboratory animals are compared and, when the two documents are merged, the Committee will usually choose the text which best summarizes these studies from either from the toxicology summary or the residue summary for inclusion in the merged document. Studies of the pharmacokinetics and metabolism of the substance in food-producing animals are typically only included in the dossier provided for residue review. Studies on comparative metabolism may be of particular importance when assessing MRL recommendations for multiple species, particularly for the extension or extrapolation of MRLs to minor species.

The main objective is to focus on the studies which provide the information used by the Committee to recommend MRLs, so this includes rate of absorption and rate and route of elimination, metabolism and tissue distribution, with identification of marker residue and target tissues. When studies on bioavailability of incurred residues are included in the dossier, they are summarized in this section. Less detail is usually provided than in the monograph and tables and figures are used in the summary only when alternatives for data presentation are cumbersome or could lead to confusion.

The studies in this section are summarized by species, following the same order used in the monograph.

#### 4.2.3.3 Residue data

In this section, the focus is on the key residue-related studies which contain the data leading to the decision on MRLs. Key elements include the identification of the depletion profile and summaries of the pivotal studies used in recommending MRLs. As in the preceding section, less detail is provided than in the monograph and use of tables and figures is avoided, whenever possible. Again, studies in this section are summarized under sub-headings by species, following the same order used in the monograph.

**Example 1: Description of a residue depletion study in a monograph** (from Amoxicillin monograph prepared by the 75<sup>th</sup> JECFA<sup>21</sup>).

“In a GLP-compliant study, twenty randomly selected dairy cows received five daily i.m. injections of 7 mg amoxicillin equivalents/kg bw at 24-hour intervals (Connolly, Prough and Lesman, 2006b). Pre-dose samples were collected for analytical control purposes from all animals. Raw milk samples were collected at 12-hour intervals for a period of 8 days (16 milkings). The mean amoxicillin concentrations were 9.42 µg/kg at 12 h post-dose, declining to 3.17 µg/kg at 24 h post-dose. Mean residues increased after each of the remaining 4 doses, and subsequently declined rapidly to below 4 µg/kg by 24 h after each respective dose. There was no evidence of bio-accumulation upon repeated dosing. At 12 h following the 5<sup>th</sup> dose, amoxicillin concentrations averaged 5.84 µg/kg and declined to concentrations below 4 µg/kg at 36 h after the fifth dose, and all samples obtained after 72 h presented concentrations of approximately 0.46 µg/kg. Table 1.23 summarizes the data.”

**Example 2: Description of the same study** (from the Seventy-fifth report of the Joint FAO/WHO Expert Committee on Food Additives<sup>71</sup>).

“Lactating dairy cows: In a GLP-compliant study, cows were treated intramuscularly at 7 mg amoxicillin per kilogram of body weight once daily for 5 days. There was no evidence of significant excretion in milk (LOQ = 1 µg/kg) and, following cessation of

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<sup>71</sup> WHO. (2012) *Evaluation of certain veterinary drug residues in food*, Seventy-fifth report of the Joint FAO/WHO Expert Committee on Food Additives, WHO Technical Report Series 969; available at <http://www.who.int/foodsafety/publications/jecfa-reports/en/>.

treatment, amoxicillin residues in milk declined from an average (n = 4) of 5.8 µg/kg at 12 hours to 0.46 µg/kg at 156 hours post-treatment.”

#### 4.2.3.4 Analytical methods

The primary focus in this section of the Summary is to confirm that a validated analytical method suitable for regulatory purposes is available to support the MRL recommendations made by the Committee. When a suitable analytical method has not been identified, or when a method appears to meet the requirements but lacks adequate validation data, this information is provided in the summary. The same level of detail on analytical methods that is contained in the monograph is not required in the summary. Typically, a brief description of the principle of the method is given to provide assurance that the method meets the requirement that it is suitable to be used in a typically equipped residue control laboratory, including the information that the method was validated in a collaborative study, in a GLP study or that it was provided by a laboratory under ISO-17025 accreditation (or equivalent). Basic information is then given on the method validation, typically including information on such critical parameters as the LOQ, precision and the analytical range.

When the Committee is dealing with an issue such as information received in response for a request for a suitably validated analytical method, a more detailed description may be provided of the method validation, since this was the primary focus of the review.

*Examples:* For typical sections on analytical methods where the criteria contained in CAC/GL 71-2009 have been applied in the evaluation, see the reports of the 75<sup>th</sup> and 78<sup>th</sup> Meetings of JECFA, TRS 969<sup>71</sup> and TRS 988<sup>5</sup>.

#### 4.2.3.5 Maximum residue limits

This section of the Summary provides the Committee recommendations on MRLs for the substance. It usually consists of an introductory sentence, followed by the decision points (in bullet form) from the Maximum Residue Limits section of the monograph. **The wording of the bullet points must be the same in both the final version of the Summary and the final version of the monograph.** Following the bullet points, there is usually a paragraph which gives the MRL recommendations.

*Example:* **Typical MRL recommendations section from a Summary where recommendations are for full MRLs** (See the Amoxicillin summary from the Seventy-fifth report of the Joint FAO/WHO Expert Committee on Food Additives.<sup>71</sup>)

In instances where temporary MRLs are recommended, the decision points are again usually placed in bullet points, followed by paragraphs giving the temporary MRL recommendations and estimated dietary intake, and then followed by a final paragraph detailing the additional studies required, with a timeframe for submission of the additional information requested by the Committee. The additional studies that are requested may appear in standard text, as in the following example, or as bullet points.

**Example:** Typical text from a Summary where recommendations include temporary MRLs (See the Apramycin Summary from the Seventy-fifth report of the Joint FAO/WHO Expert Committee on Food Additives.<sup>71</sup>)

When MRLs are not recommended, the reasons leading to this decision may be provided in bullet points. However, a simple statement that MRLs were not recommended is more common.

**Example:** See the Gentian violet Summary from the Seventy-eighth report of the Joint FAO/WHO Expert Committee on Food Additives.<sup>5</sup>

In some situations where the Committee has been asked to review the status of previous recommendations, the final section may appear under the heading ‘Conclusions’ or ‘Evaluation’ instead of ‘Maximum residue limits’.

**Example:** See the Flumequine Summary in the report of the 66<sup>th</sup> JECFA.<sup>52</sup>

#### **4.2.3.6 Dietary Exposure assessment**

A separate section summarizing the results of the dietary exposure assessment was introduced in the Report of the 81<sup>st</sup> Meeting of JECFA.<sup>15</sup> In previous meeting reports, this information was included in ‘Maximum residue limits’, as in the examples noted above. This section should be included when MRLs are proposed or in situations where the exposure assessment based on the available depletion data indicates that MRLs cannot be recommended within the timeframe covered by the residue depletion studies. The basis for the assessment (chronic effects or acute effects) and the type of exposure assessment used (EDI, TMDI, GEADE or other) should be stated, along with the outcome of the exposure assessment. When both chronic and acute exposure assessments have been conducted as part of the evaluation, these should be summarized, using the headings ‘Chronic dietary exposure assessment’ and ‘Acute dietary exposure assessment’.

**Example:** See the reviews of substances contained in the Report of the 81<sup>st</sup> Meeting of JECFA.<sup>15</sup>

#### **4.2.3.7 References**

Summary documents as published in the TRS Meeting Report have not usually included references to the studies discussed in an evaluation of a substance. References have been included to past JECFA evaluations, CCRVDF meeting reports, reports of expert consultations and other such documents. Information on references to be included in a summary and the format to be used will be provided by the Secretariat prior to a JECFA Meeting or by the WHO editor for the TRS publication during the meeting. Drafting experts and reviewers should consult the TRS publication from the previous meeting to see examples of current practice.

### 4.3 General considerations

This section of the guidance provides information on the content and preparation of documents which appear in meeting report in the TRS publication under the heading “General considerations”.

#### 4.3.1. Introduction to “General considerations”

Items which appear in meeting reports under the heading “General considerations” usually deal with matters of JECFA policy and/or procedure, particularly with requirements for data submission and with evaluation procedures used by the Committee. Work on a topic may be initiated as a result of questions from CCRVDF, as a result of discussions within JECFA or by a request from the JECFA Secretariat. Items which appear under this heading in a Meeting Report may:

- inform the Committee on an issue of interest, such as the report of a recent meeting of CCRVDF or a recent expert consultation; or
- clarify the position of the Committee on an issue; or
- describe a matter that is receiving on-going consideration in the Committee; or
- clarify data submission requirements for Sponsors; or
- provide information about a new or revised approach to the evaluation of data; or
- provide comment on an issue of interest to JECFA.

*Example 1:* Clarify the position of the Committee on an issue. (Excerpt from the Seventy-fifth report of the Joint FAO/WHO Expert Committee on Food Additives.<sup>71</sup>)

#### *“JECFA considerations for chronic dietary exposure assessments*

Chronic dietary exposure estimates cover food consumption over the long term and are intended to be used for comparison with a health-based guidance value based on chronic toxicity, such as an ADI, in a risk assessment process. At its seventieth meeting, the Committee confirmed the use of the median residue level from depletion studies, with a correction for marker residue to total residue, instead of the MRL for long-term dietary exposure estimates, when supported by the available data.”

*Example 2:* Clarify data submission requirements for Sponsors. (Excerpt from the Seventy-fifth report of the Joint FAO/WHO Expert Committee on Food Additives.<sup>71</sup>)

#### *“Information on registration/approval status of veterinary drugs*

Nationally approved good practices in the use of veterinary drugs make an important contribution to the risk profile of a drug. For JECFA, it is important that all related information relevant for the risk assessment is available to the Committee when it evaluates substances with a view to recommending MRLs. In the past, information on registration/approval status of veterinary drugs and on approved conditions of use was not always available to the Committee in time, leading to unnecessary difficulties in its discussions. The Committee therefore requests:

- that CCRVDF provide the Secretariat with information on registration/approval status and the use pattern of veterinary drugs whenever it requests an evaluation by JECFA;
- that the JECFA Secretariat always include a request for submission of such information by the sponsors of the data into future calls for data.

The Secretariat should also verify that such information is contained in the data submission of sponsors before it gives work assignments to the experts of the Committee.”

#### **4.3.2 Process of development**

For some issues, such as a summary report of the activities of CCRVDF or another expert committee (such as JMPR), the issue will be raised in plenary session when JECFA meets, usually by a member of the Secretariat. When issues are simply to provide information to JECFA, the summary will usually be prepared by the Secretariat. This may include a summary of discussion of the matter by JECFA. For matters requiring a response from JECFA or more discussion by the Committee, a summary document may be drafted for further discussion within JECFA by the Secretariat or members of the Committee.

For issues involving JECFA policy or requiring more detailed discussion, it is not uncommon for such assignments to stretch over several meetings, with an initial working paper prepared by a drafting expert for consideration at a first meeting. This may lead to a decision that further development of the working paper will be required, which may include a request for comments from the CCRVDF or another expert committee. A revised working paper may then be presented at a subsequent meeting and formally adopted by the Committee after further discussion. The Committee may also decide in some cases to suspend work pending further development of a scientific consensus within the greater scientific community. When adopted, working papers on these issues typically become part of the risk assessment procedures of JECFA.

##### **4.3.2.1 Assignment to a drafting expert or electronic working group**

When an issue involves significant questions of JECFA risk assessment policy, such as the further development of policy or responding to questions on assessment policy from CCRVDF which require detailed preparation, a drafting expert or FAO consultant may be assigned to prepare a working paper for consideration at a future JECFA Meeting or to work with an electronic working group of JECFA members between scheduled JECFA Meetings to prepare a response to CCRVDF from the JECFA Secretariat.

*Example:* Drafting expert or consultant working with electronic working group.

Questions on JECFA risk assessment policy from the 20<sup>th</sup> Session of the CCRVDF were dealt with between scheduled JECFA Meetings so that a response to the questions could be provided to the 21<sup>st</sup> Session of the CCRVDF. To formulate the responses, a FAO consultant prepared a background paper and drafted answers to the questions. These were then considered by members of an electronic working group and the final response to each question, as agreed by

the electronic working group, was provided to the JECFA Secretariat, which then issued the JECFA response to the CCRVDF. The response to the questions was provided to the 78<sup>th</sup> JECFA Meeting and published as an Annex in the FAO JECFA Monographs 15<sup>23</sup> and documented in the Report of the 78<sup>th</sup> JECFA.<sup>5</sup>

*Example:* Drafting expert preparing paper for discussion at JECFA Meeting.

The 78<sup>th</sup> JECFA conducted a pilot study of several new approaches to calculations of dietary exposure to residues of veterinary drugs in foods. An expert on dietary exposure was assigned to prepare a working paper explaining the new procedures and using data from substances under review to prepare sample calculations using the new procedures. This drafting expert worked with the FAO drafting experts assigned to the various substances under evaluation at the 78<sup>th</sup> JECFA, both in preparation for the 78<sup>th</sup> JECFA and during the meeting, to adjust the dietary intake calculations to reflect decisions on MRLs. The Committee was fully informed on the new procedures in discussions during the meeting. A summary of the pilot study, prepared by the drafting expert, was included in the General Considerations section of the Report of the 78<sup>th</sup> JECFA<sup>5</sup> and the final version of the working paper was published as Annex 3 in FAO JECFA Residue Monographs 15.<sup>60</sup>

#### **4.3.2.2 Matters arising during a JECFA Meeting**

A matter may arise in the course of discussions of a substance or assessment policy during a JECFA meeting which results in a decision by the Committee that must be included in the meeting report. This may be in the form of a comment to highlight the matter or a statement to indicate a new interpretation or application of JECFA risk assessment policy has taken place or is required. In such cases, a drafting expert familiar with the topic may be asked to prepare a statement on the issue for the Committee. These are typically one or two paragraphs in length, giving a brief summary of the issue and the decision taken by the Committee. As with all other Committee decisions included in the meeting report, the content of the document is reviewed and approved by the Committee.

*Example:* The 78<sup>th</sup> JECFA, in evaluating analytical methods, recognized that the procedures adopted by the 52<sup>nd</sup> JECFA in 1999 to assess method validation required up-dating to reflect current international guidance on this issue. See: “2.10, JECFA analytical method validation requirements” in the Report of the 78<sup>th</sup> JECFA.<sup>5</sup>

#### **4.3.2.3 Decision process**

Whether a topic included in General Considerations results from an issue which arose at the Meeting or is the result of a pre-meeting assignment of a working paper, the process is the same as for other materials included in the JECFA Meeting Report:

- A JECFA member or a member of the JECFA Secretariat is assigned to prepare the summary document for inclusion in the Meeting Report.
- The issue is raised as a matter to be discussed by the Committee and time is scheduled for discussion.



- Initial discussion of the draft occurs, usually with suggestions for revision.
- Further discussion is scheduled, as needed, until all Committee members are in agreement with the content.
- A final version of the document is considered during the review of all documents to be included in the Meeting Report.
- The final approved text is given to the rapporteur and the editor.

#### **4.4 Schedule for preparation of materials to include in TRS**

Drafting experts should adhere to the following schedule for the preparation of summary documents for inclusion in the Meeting Report which is published in the WHO Technical Report Series.

##### **4.4.1 First drafts**

For topics assigned to a drafting expert for preparation of a working paper (usually a topic to be published under General Considerations), the assigned drafting experts are expected to provide a first draft of the working paper for the to the FAO Joint Secretary 6-8 weeks prior to a JECFA Meeting so that copies can be provided to all meeting attendees at the opening of the JECFA Meeting (preferably available for distribution prior to the meeting). A summary version for inclusion in the meeting report should be prepared for distribution at the start of the JECFA Meeting if the full paper is not intended to be published in the meeting report (drafting experts should seek advice from the FAO Joint Secretary if clarification on publication intentions is required).

When a matter arises during a JECFA Meeting requires the preparation of text for inclusion in the Meeting Report, the assigned drafting expert typically will have 1-2 days for preparation of draft text for matters which arise during the first week of the Meeting. Should a matter arise during the second week of the Meeting, the drafting expert should excuse themselves from the Committee discussions at the earliest opportunity and prepare the draft text immediately for consideration by the Committee.

##### **4.4.2 Amendment of summary drafts during meeting**

A drafting expert should expect that the initial draft will go through several rounds of discussion and amendment to reflect on-going discussions and decisions by the Committee. The schedule for discussion, preparation of an amended draft by the drafting expert and further consideration by the Committee can become quite compacted as a JECFA Meeting moves into the final days. In general, summary documents should be in approved final draft by the second (preferably third) day prior to the close of the meeting, with only minor revisions made when the Committee meets in the final plenary session on the closing day to do a final review and approval of all documents for inclusion in the Meeting Report. All required revisions moving to the final draft should be prepared as expeditiously as possible by the drafting expert to meet the schedule for discussion of topics during the both the plenary sessions of the full Committee and also the working sessions of the FAO experts.

In general, a draft (initial or revised) will be discussed first within the FAO expert group and, once they are satisfied with the content, by the full Committee. During discussions with the Committee, drafting experts must be careful to record all amendments to the text so that these changes appear in the next version of the document provided to Committee members. Each draft must be provided to the appropriate rapporteur (usually the FAO rapporteur until the discussion of the final draft) before it is circulated to the Committee. Drafting experts should consult with the FAO chair if they do not have a clear understanding of when the next discussion of their assignment is planned and should ensure that they can meet the planned timelines.

#### **4.4.3 Role of rapporteur(s)**

A rapporteur is appointed for the FAO group at each meeting, along with a rapporteur for the WHO group. One of these individuals also serves as the Committee rapporteur. The rapporteurs are responsible for maintaining document control during the meeting, and for ensuring that any revisions made to documents by the Committee during the final plenary session to approve the content of the Meeting Report are included in the final text.

#### **4.4.4 Role of committee chairperson(s)**

Both the FAO and WHO groups appoint a Chairperson to facilitate discussions within their respective groups. One of these individuals will also usually serve as the Committee Chairperson, with the other as Vice-Chairperson. Their primary responsibility during a JECFA Meeting is to schedule the work on each agenda item so that all work is completed to be included in the Meeting Report. They are assisted in this work by the FAO and WHO Joint Secretaries. A Chairperson moderates the discussions, recognizing speakers during plenary sessions, making sure that all opinions are heard and understood and setting schedules for further discussion of each topic. The Chairpersons also usually carry a full workload of Committee assignments, including being a drafting expert for one or more substances and/or topics. While they may be among the most experienced members of the Committee, other drafting experts should recognize the workload that goes with the assignment as Chairperson and not make additional demands on their time if this can be avoided.

#### **4.4.5 Final draft**

The final text of a summary document for inclusion in the JECFA Meeting Report is agreed by the Committee at the closing plenary session where the text of the Meeting Report is approved. Any changes in the final draft approved by the Committee at the closing plenary session are usually the responsibility of the rapporteur, assisted by the editor of the Meeting Report. A drafting expert should only become involved in revisions of a draft during the closing session of a JECFA Meeting if requested to do so by the rapporteur and/or the editor.

## **5. Overview presentation by drafting expert for opening of JECFA Meeting**

The drafting expert for each assigned substance (or topic) should prepare a brief PowerPoint presentation to provide an overview to the Committee of the issues associated with the topic on the first day of the JECFA meeting before general discussions begin.

### **5.1 Objective of Presentation**

The objective of the presentation is to inform the Committee of key issues which may require discussion, the overall data completeness and quality, deficiencies which may require the formulation of questions to be sent to the Sponsor during the meeting and potential Committee recommendations on MRLs. The presentation should help focus discussions when the Committee begins the review of the content of the summary documents prepared for inclusion in the JECFA Meeting Report.

### **5.2 Format and content**

In the presentation, the drafting expert should:

- Inform the Committee of the species for which MRLs have been requested by CCRVDF (slide 1).
- State for which species data were available for review (slide 1).
- Summarize the key elements of the data on residue pharmacokinetics, metabolism and depletions, including the identification of a marker residue and target tissues (slides 2-4, add 1 slide if needed).
- Comment on the availability of validated analytical methods (slide 5 or 6).
- Provide an opinion as to whether the data appear adequate to recommend MRLs and identify any concerns, data gaps and challenges in interpretation of the data (slide 6 or 7).
- Identify any issues on which the Committee may wish to pose a question to the Sponsor (slide 7 or 8).

The presentation should be for 5-10 minutes, using 6-8 slides (maximum). When the assignment relates to the development of JECFA risk assessment procedures or other such issues, the drafting expert should prepare a presentation which outlines the issue, key considerations, sources of information and recommendations.

## **6. Questions to sponsors**

Questions for the Sponsor should preferably be agreed by the drafting expert and reviewer and sent well in advance to the meeting – always keeping the FAO Joint Secretary copied and informed on any correspondence and communication with the Sponsor. However, it is common that issues will be identified during the initial discussions of a substance by the Committee which may result in a decision to ask a Sponsor if they have any additional data relevant to the issue or if they wish to provide any additional comment or interpretation on particular results or data interpretations which may be included in the dossier. Questions are usually sent by the

Committee within the first week of a JECFA meeting with a request for response by early in the second week of the meeting at the very latest. When assigned by the Committee to draft a question for a Sponsor on an issue, a drafting expert should ensure that the timelines established at the meeting for preparation of questions to a Sponsor are met.

## **7. MRLs for Minor Species**

The 78<sup>th</sup> JECFA adopted the following definitions, data requirements and risk assessment procedures for the assessment of requests for the extension or extrapolation of MRLs from major species to minor species.<sup>5</sup>

### **7.1 Definitions of extension and extrapolation**

The 78<sup>th</sup> JECFA stated that:

“JECFA will use the term extension when sufficient depletion data are available for the minor species to permit the derivation of MRLs for tissues of that species from the depletion curves. The term extrapolation will be used when insufficient depletion data are available in that species to derive MRLs for tissues from that species.”<sup>5</sup>

Drafting experts should take care that the terms “extension” and “extrapolation” are used as defined when making MRL recommendations in monographs and summary documents.

### **7.2 Data requirements and assessment procedures**

The 78<sup>th</sup> JECFA stated the principles that are to be applied when assessing the extrapolation of MRLs from major species to minor species.<sup>5</sup> In addition to the usual requirements for all substances that are evaluated by JECFA, such as evidence of GVP in a member state, the principles to be used in extrapolation provide more flexibility than is accepted by JECFA for the evaluation of substances used in major species. These principles are summarized in a decision tree for extrapolation of MRLs from major species (cattle, sheep, pigs, chickens) to minor species included in the report of the 78th JECFA.<sup>5</sup> Drafting experts should consult the report of the 78<sup>th</sup> JECFA<sup>5</sup> and “Annex 5 – JECFA Guidelines for the Extrapolation of MRLs to Minor Species” in FAO JECFA Monographs 15<sup>72</sup> for further information and guidance on the extrapolation of MRLs from major species to minor species.

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<sup>72</sup> FAO. (2014). “Annex 5 – JECFA Guidelines for the Extrapolation of MRLs to Minor Species” in *Residue evaluation of certain veterinary drugs*, FAO JECFA Monographs 15, pp. 211-228; available at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-publications/en/>.

### 7.3 Decision tree for extrapolation of MRLs from major species (cattle, sheep, pigs, chickens) to minor species<sup>5,72</sup>

There is an approved use for the drug in a minor species in a Codex member State.	NO →	Evidence of an approved use in a Codex member state must be provided.
YES ↓		
An ADI and MRLs for use of the drug in a relevant species have been recommended.	NO →	A full evaluation to establish an ADI and MRLs is required.
YES ↓		
Metabolism information for a relevant species and the minor species are available.	NO →	Comparative metabolism information must be provided for the relevant and minor species.
YES ↓		
Metabolites and bound residues of toxic concern are qualitatively and quantitatively similar.	NO →	Additional toxicological evaluation and a residue depletion study in the minor species may be required.
YES ↓		
The marker residue from the relevant species is also applicable for the minor species.	NO →	Studies are required to identify the marker residue for the minor species, plus depletion data using this marker residue in the minor species and data to adjust marker-to-total residue when this factor is required for the dietary exposure calculation.
YES ↓		
A suitable analytical method for the marker residue is available, preferably with data on application to the minor species.	NO →	A suitable validated analytical method applicable to tissues from the minor species is required.
YES ↓		
Marker-to-total residue relationship and bioavailability is similar in both species or not required for exposure calculation.	NO →	Data to establish marker-to-total residue relationships and/or bioavailability in edible tissues of minor species may be required when needed in dietary exposure calculations.
YES ↓		
Available data indicate similar distribution and depletion patterns in major and minor species (data may be from metabolism, pharmacokinetic and/or residue depletion studies).	NO →	Additional residue depletion data are required for the minor species.
YES ↓		
MRLs may be extrapolated from the relevant species to the minor species.		

## 7.4 Examples of past decisions

**Example 1: Large mammal** - The 45<sup>th</sup> JECFA reviewed data on moxidectin residues which included pharmacokinetic studies in rats, sheep and cattle, metabolic studies in rats, sheep and cattle, depletion studies with radiolabelled moxidectin in cattle and sheep and depletion studies using non-radiolabelled drug in cattle, sheep and deer.<sup>36</sup> Data were also provided on analytical methodology for tissues from cattle, sheep and deer. The Committee recommended MRLs for tissues from cattle and sheep and temporary MRLs for tissues from deer, requesting “further information on the marker compound for deer tissues”. Data from an *in vitro* metabolic study using liver tissues from deer, cattle, sheep and goats provided to the 50<sup>th</sup> JECFA showed that metabolism was similar in cattle, sheep and deer.<sup>73</sup> Based on these results, the Committee recommended MRLs for deer tissues, removing the “temporary” designation. This is one of the earliest examples of JECFA accepting data from an *in vitro* study to provide the necessary metabolic information for a minor species and fits the definition of extension currently used by JECFA.

**Example: Poultry, rabbit** - The 70<sup>th</sup> JECFA established MRLs for avilamycin, used as a veterinary medicine in chickens, turkeys, pigs and rabbits.<sup>74</sup> Pharmacokinetic data were provided for chickens, but not for turkeys and rabbits. Metabolism was similar in rats and pigs, but no metabolic data were available for chickens, turkeys or rabbits. Depletion data were available from studies in pigs and chickens using radiolabelled drug, but not for turkeys and rabbits. Depletion data using non-radiolabelled avilamycin were available from studies in pigs, chicken, turkeys and rabbits and a validated analytical method was available for tissues from all four species. Marker residue is non-detectable in muscle, kidney and fat at zero withdrawal and is not detectable in liver at 24 hours post-treatment. A marker-to-total residue ratio could only be calculated for pig liver (0.5) and a conservative factor of 0.1 was applied to all other species/tissues. MRLs for chicken tissues were established using a conservative approach of 10 x LOQ and the same MRLs were established for pig tissues. The Committee stated that the MRLs for chicken “may be extended to turkeys based on similarity between the species” and “as a minor species, MRLs were harmonized based on the existing recommended MRLs in major species” for rabbits. In this example, the Committee formally used the term “extension” and gave an explanation of the basis for the extension.

**Example 3: Fish** - The 52<sup>nd</sup> JECFA reviewed pharmacokinetic and total residue studies using <sup>14</sup>C-deltamethrin in cattle, chickens and salmon, *in vitro* metabolic studies using

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<sup>73</sup> FAO. (1999). “Moxidectin” in *Residues of some veterinary drugs in animals and foods*, FAO Food and Nutrition Paper 41/11, pp.79-82; monograph available from the Online Edition: "Residues of some veterinary drugs in foods and animals" at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-vetdrugs/en/>.

<sup>74</sup> FAO. (2009). “Avilamycin” in *Residue evaluation of certain veterinary drug*, FAO JECFA Monographs 6, pp.29-53; monograph available from the Online Edition: "Residues of some veterinary drugs in foods and animals" at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-vetdrugs/en/>.

liver enzyme preparations (bovine and chicken), metabolic studies using <sup>14</sup>C-deltamethrin in cattle and chickens and depletion studies using non-radiolabelled deltamethrin in cattle, sheep and chickens.<sup>75</sup> Analytical methods were reviewed for tissues from cattle, chicken and salmon. Based on the data provided, the Committee established MRLs for tissues from cattle and chickens and the MRLs were “extended to sheep for muscle, liver, kidney and fat and salmon muscle tissue”.

## **8. MRLs for honey for the establishment of MRLs for veterinary drug residues in honey**

The 78<sup>th</sup> JECFA established principles for the evaluation of requests for the establishment of MRLs for honey.<sup>5</sup> These are expected to evolve as experience is gained with evaluations of such requests and also as a result of on-going work in a VICH working group.

### **8.1 Overview**

As of 2015, there are no Codex MRLs for residues of veterinary drugs in honey and no pending recommendations for such MRLs from JECFA. The Report of the 52<sup>nd</sup> JECFA noted that JECFA had begun the development of guidelines for the establishment of MRLs for honey and requested comment from the CCRVDF.<sup>12</sup> Subsequently, CCRVDF established a working group which worked on the topic over a number of meetings, leading to a recommendation to the 66<sup>th</sup> JECFA by a FAO/WHO/RIVM Workshop held in 2005 that JECFA should investigate a specific approach to the establishment of MRLs for honey.<sup>76</sup>

A working paper was considered at the 70<sup>th</sup> JECFA on possible approaches to the establishment of MRLs for residues of veterinary drugs in honey.<sup>77</sup> A number of points which JECFA considered relevant to the establishment of MRLs for veterinary drug residues in honey were noted in the Report of the 70<sup>th</sup> JECFA, including a recommendation to use 50 g as the quantity of honey in dietary intake calculations, replacing the amount of 20 g previously identified.<sup>55</sup> The 21<sup>st</sup> Session of the CCRFVDF adopted this recommendation from JECFA.<sup>78</sup> The 78<sup>th</sup> JECFA subsequently established principles to be used in the establishment of MRLs for veterinary drug residues in honey, as documented in the Report of the 78<sup>th</sup> JECFA<sup>5</sup> and in FAO JECFA Monographs 15.<sup>79</sup>

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<sup>75</sup> FAO. (2000). “Deltamethrin” in *Residues of some veterinary drugs in animals and foods*, FAO Food and Nutrition Paper 41/12, pp.1-20; monograph available from the Online Edition: "Residues of some veterinary drugs in foods and animals" at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-vetdrugs/en/>.

<sup>76</sup> FAO (2006) *Updating the Principles and Methods of Risk Assessment: Maximum Residue Levels (MRLs) for Pesticides and Veterinary Drugs*; available at [ftp://ftp.fao.org/ag/agn/jecfa/bilthoven\\_2005.pdf](ftp://ftp.fao.org/ag/agn/jecfa/bilthoven_2005.pdf)

<sup>77</sup> FAO. (2009). “Residues of veterinary drugs in honey and possible approaches to derive MRLs for this commodity” in *Residue evaluation of certain veterinary drug*, FAO JECFA Monographs 6, pp.1-28; available at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-publications/en/>.

<sup>78</sup> CAC. (2014) Report of the twenty-first session of the Codex Committee on Residues of veterinary Drugs in Foods, REP14/RVDF; available at <http://www.codexalimentarius.org/meetings-reports/en/>.

<sup>79</sup> FAO. (2014). “Annex 6 – JECFA guidance for the establishment of MRLs in honey” in *Residue evaluation of certain veterinary drugs*, FAO JECFA Monographs 15, pp. 229-232; available at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-publications/en/>.

## 8.2 Special issues related to honey

The following guidance is contained in “Annex 6 - JECFA guidance for the establishment of MRLs in honey”, published in FAO JECFA Monographs 15:<sup>79</sup>

“Extensive variability can be observed in the concentrations of the residue found in samples collected from different areas of the same hive or from different hives. For large-scale production, where products from various sources are blended in bulk, samples from multiple hives at multiple locations and times may be required to derive a representative picture for the typical bulk product in international trade. In addition, any reduction in residue concentration is typically a result of dilution or chemical degradation of the parent drug over time from sources such as moisture, heat and light exposure, rather than from metabolic processes. Furthermore, as the depletion pathway in honey is different from the typical metabolic pathways in animals treated with drugs, the marker residue designated for tissues, milk and/or eggs may not be appropriate for honey.”

## 8.3 Minimum data requirements

The 78<sup>th</sup> JECFA identified the following data requirements to enable the establishment of MRLs for residues of veterinary drugs in honey:<sup>5</sup>

- “all available information on approved uses in a Codex Member State;
- an existing ADI or the availability of toxicological data to establish an ADI;
- data to establish a marker residue in honey;
- evidence of a validated analytical method for the determination of residues in honey;
- and
- data on the nature of residues in honey, typical concentrations found and the stability of these residues.”

The Committee also noted that there are no pharmacokinetic or metabolic data to consider for the use of veterinary drugs in honey, but data on degradation of the residue from environmental factors and dilution as honey is produced in the hive must be considered when assessing residues.

In considering the establishment of MRLs for veterinary drug residues in honey, the CCRVDF and JECFA have recognized three potential situations:

1. The establishment of an MRL for honey for substances with an existing ADI and/or a Codex MRL in a food-producing animal or food commodity.

- Information on GVP must be provided.
- Residue depletion data related to the GVP use must be available;
- A marker residue must be identified for the depletion study and a validated analytical method must be available.

2. The establishment of an MRL for honey for substances for which an ADI has not previously been established by JECFA or JMPR.



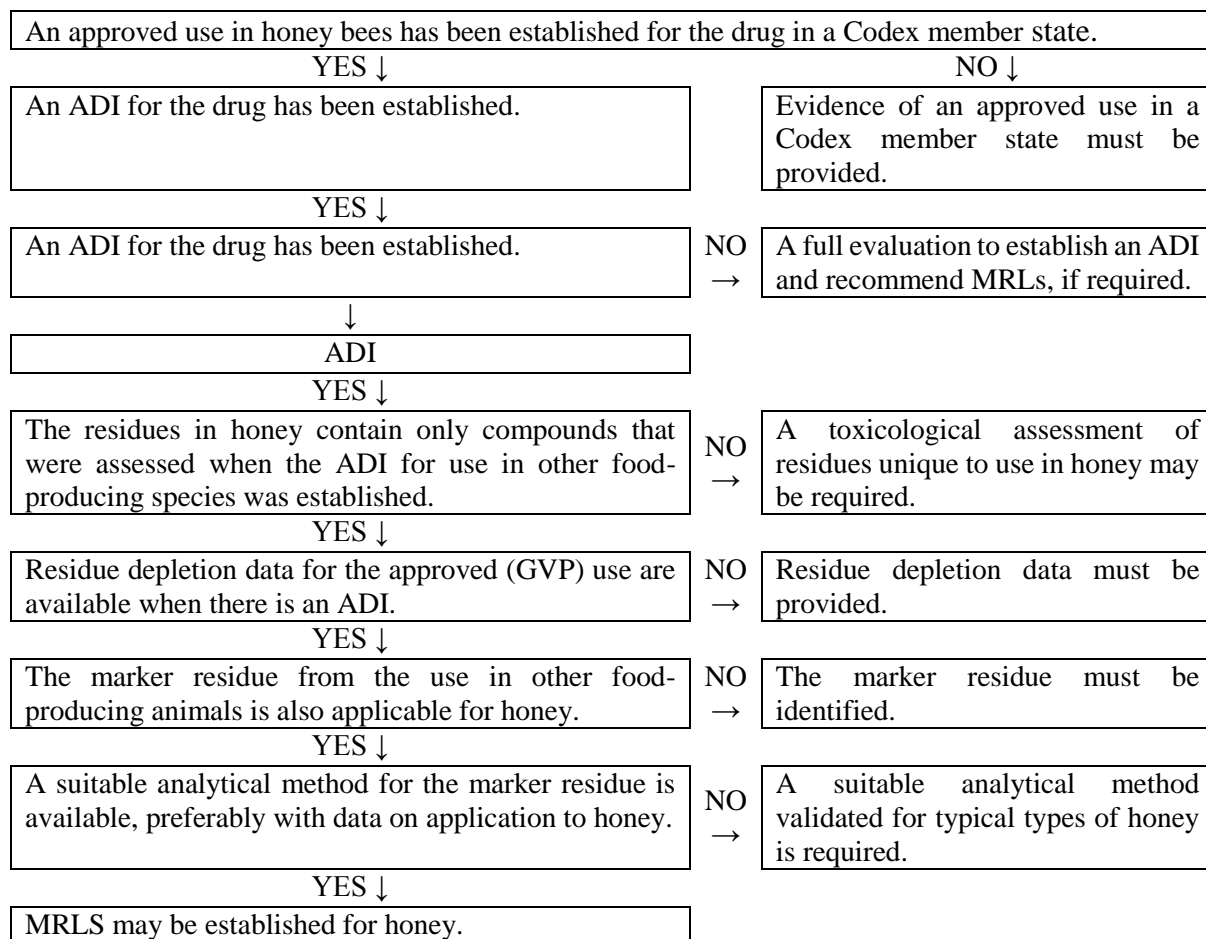
- Such substances would have to be evaluated as new animal drugs or pesticides and be subject to a full food safety risk assessment.

3. The establishment of an MRL for honey for substances that are not approved for use in food-producing animals.

- When the Committee has previously made such a decision based on the risk assessment for a substance, there would be no exception for use of the substance in honey.

#### 8.4 Decision tree for the establishment of MRLs for veterinary drug residues in honey.<sup>5,79</sup>

The 78<sup>th</sup> JECFA approved a decision tree which will assist drafting experts in the evaluation of a dossier for the establishment of MRLs for veterinary drug residues in honey.



## 9. Preparation of JECFA Policy Papers

As noted in Section 5.3, “General considerations”, assignments to a drafting expert may include the development of a policy statement for inclusion in a Meeting Report. For major revisions or additions to JECFA risk assessment policies, an assignment may last over several JECFA Meetings and may involve several drafting experts or an electronic working group. In this section, some general guidance is provided on the process that is typically followed and the consultations which should be anticipated to occur as part of that process.

### 9.1 Overview

From its earliest work on the development of standards for the safety of veterinary drug residues in foods, JECFA has recognized the importance of the transparency of the work done by the Committee. In particular, JECFA has recognized that risk assessment policies and procedures followed by the Committee should be understood by the Codex Committees for which it serves as risk assessor, the Sponsors who provide the information required to conduct risk assessments and all interested parties.

The 12<sup>th</sup> JECFA, held in 1968, was the first meeting of the Committee to consider residues of veterinary drugs in foods.<sup>80</sup> The 32<sup>nd</sup> JECFA in 1987, the first meeting devoted exclusively to veterinary drug residues, began to more formally elaborate principles governing the safety evaluation of residues of veterinary drugs in foods and developed a list of information that Sponsors should provide to enable the evaluation of a substance.<sup>81</sup> The 34<sup>th</sup> JECFA, meeting in 1989, stated the specific tasks before the Committee were<sup>82</sup>:

- a. To establish principles for evaluating the safety of residues of veterinary drugs in foods and for determining acceptable and safe levels for such residues when the drugs in question are administered to food-producing animals in accordance with good practice in the use of veterinary drugs;
- b. To evaluate or re-evaluate the safety of the residues of certain veterinary drugs;
- c. To consider the biological impact of veterinary drug residues bound to cellular constituents in animal tissues; and
- d. To discuss and provide advice on matters arising from the report of the CCRVDF.

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<sup>80</sup> WHO. (1969) *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, WHO Technical Report Series 430; available at <http://www.who.int/foodsafety/publications/jecfa-reports/en/>.

<sup>81</sup> WHO. (1988). Evaluation of certain food additives and contaminants, Thirty-second Report of the Joint FAO/WHO Expert Committee on Food Additives, WHO Technical Report Series 763 ; available at <http://www.who.int/foodsafety/publications/jecfa-reports/en/>.

<sup>82</sup> WHO. (1989). Evaluation of certain food additives and contaminants, Thirty-fourth Report of the Joint FAO/WHO Expert Committee on Food Additives, WHO Technical Report Series 788; available at <http://www.who.int/foodsafety/publications/jecfa-reports/en/>.

The 36<sup>th</sup> JECFA expanded on this work, laying out a decision process with a flow diagram for the establishment of MRLs.<sup>83</sup>

Procedures have continued to evolve, with meetings such as the 52<sup>nd</sup> JECFA<sup>12</sup> and the 78<sup>th</sup> JECFA<sup>5</sup>, devoting considerable time to the further elaboration of risk assessment policy. Typically, a matter for the further development of JECFA risk assessment policy and/or procedures will be identified in a JECFA meeting report, following which the FAO Joint Secretary will identify a drafting expert to prepare a working paper. This paper is discussed at the next JECFA Meeting, after which it may be referred to the CCRVDF for comment. The working paper may evolve over several JECFA and CCRVDF meetings before a final version is adopted by JECFA.

## **9.2 Style, format and content of working paper**

The working paper should contain an Introduction section which states the nature of the work assignment, followed by a Background section which provides a review of relevant work on the topic by past meetings of JECFA and of any working papers or guidance documents from CCRVDF. The next section (with an appropriate heading) reviews the available knowledge and policies or procedures of other organizations or committees that may inform the decision. This includes work on the topic such as reports of expert consultations, work by JMPR, VICH or other international committees and organizations and guidance documents on evaluation procedures, data requirements or other topics relevant to the working paper from national or regional authorities. If there has been a request for submissions on the topic in a Call for Data, these should also be summarized and discussed. An expert analysis of the materials follows, with preliminary recommendations for consideration by the Committee.

As the work progresses, the draft working paper may be amended into a monograph or annex for inclusion in the FAO JECFA Monographs publication for the JECFA meeting and a summary document is included in the meeting report.

## **9.3 Consultative process**

While the development of a policy or procedural guidance document is typically assigned to one or more drafting experts, there may be instances where a larger electronic working group is established. Depending on the nature and scope of the work, development of the document may require that it be forwarded to CCRVDF, other Codex Committees or other expert committees, such as JMPR, for comment. This is done by the JECFA Secretariat after the initial consideration of the document at a JECFA Meeting. As the work progresses, the document evolves from an initial draft reflecting the analysis and opinions of the drafting expert(s) to a document which incorporates the analysis and decisions of the Committee.

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<sup>83</sup> WHO. (1990). Evaluation of certain food additives and contaminants, Thirty-sixth Report of the Joint FAO/WHO Expert Committee on Food Additives, WHO Technical Report Series 799; available at <http://www.who.int/foodsafety/publications/jecfa-reports/en>

#### 9.4 Style and format of final documents

The drafting expert should consult examples of such documents from the 78<sup>th</sup> JECFA published as Annexes in FAO JECFA Monographs 15<sup>84</sup> and in the General Considerations section of TRS 988<sup>5</sup> to find examples which are similar to their assignment. These include the reports on the pilot study for new approaches to dietary exposure, procedures for the extrapolation of MRLs to minor species and procedures for the establishment of MRLs for honey. Additional examples may be found in the work of the 70<sup>th</sup> JECFA on issues related to the establishment of MRLs for veterinary drug residues in honey<sup>77</sup> and the work conducted by the 62<sup>nd</sup> and 66<sup>th</sup> Meetings of JECFA on the development of the JECFA Statistical Tool<sup>38</sup> and the Estimated Dietary Intake calculation<sup>52</sup>, respectively.

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<sup>84</sup> FAO (2014) *Residue evaluation of certain veterinary drugs*, FAO JECFA Monographs 15; available at <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-publications/en/>.