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Updating the Principles and Methods of Risk Assessment:

MRLs for Pesticides and Veterinary Drugs

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MRLs for Pesticides and Veterinary Drugs

Contents

I. PREFACE AND INTRODUCTION

The Joint Food and Agriculture Organization of the United Nations/The Netherlands National Institute for Public Health and the Environment/World Health Organization (FAO/RIVM/WHO) Workshop: "Updating the Principles and Methods of Risk Assessment: Maximum Residue Levels (MRLs) for Pesticides and Veterinary Drugs" was organized within the framework of the *Project to Update the Principles and Methods for the Risk Assessment of Chemicals in Food* which was launched by FAO and WHO in 2002 with the following objectives:

1. Assure the continuation of transparent and sound expert evaluations of scientific data for risk assessments of chemicals in food;
2. Review principles and procedures used by JECFA and JMPR and reaffirm those that remain valid in view of current scientific knowledge;
3. Facilitate the incorporation of new scientific tools, approaches and knowledge in the implementation of risk assessment of food chemicals (e.g., regional diets, dose-response modelling, and biomarkers, including genomics, proteomics);
4. Harmonize, to the extent possible, risk assessment procedures for different classes of chemicals in food (e.g., additives, contaminants, pesticide residues, veterinary drug residues, and natural toxicants); and
5. Harmonize, to the extent appropriate, approaches to risk assessment by JECFA and JMPR with those of other scientific groups (including national, regional, other public health and environmental).

The experts invited for the present workshop (7-10 November 2005, Bilthoven, The Netherlands) were asked to review the scientific principles and procedures used by JECFA and JMPR for recommending MRLs and to harmonize their approaches to the extent useful and possible with emphasis on the general principles applied by both scientific bodies. In addition, the workshop was asked to identify appropriate follow-up activities and recommend to FAO and WHO what practical steps in the work of JECFA and JMPR should be undertaken in order to update, improve and harmonize the existing sets of guidelines.

The experts were selected by FAO and WHO based upon their scientific and technical expertise related to the work of JECFA and JMPR and experts affiliated with organizations whose activities contribute to the evaluation of pesticides and veterinary drugs.

Dr Bernadette Ossendorp opened the workshop at the Centre for Substances and Integrated Risk Assessments, RIVM, and introduced Dr Henken, Director, Nutrition, Medicines and Consumer Safety, RIVM, who welcomed the participants on behalf of RIVM. Dr Henken explained the sphere of action of RIVM and drew attention to the overall importance of the Update Project and the need for harmonization between pesticide and veterinary drug risk assessments. On behalf of FAO and WHO, Dr Manfred Lützow thanked the organizing institution and Dr Bernadette Ossendorp for the skilful preparation of this expert workshop.

The workshop appointed Dr Dieter Arnold, Germany, as Chairperson, and Dr Bernadette Ossendorp, Netherlands, as Co-Chairperson. The Joint Secretariat nominated as rapporteurs Dr Richard Ellis, USA, and Mr Denis Hamilton, Australia.

During the meeting three working groups discussed the framework and the scientific aspects of the process that leads to the recommendation of maximum residue levels for pesticides by JMPR and maximum residue limits for veterinary drugs by JECFA:

- Working group I: Identifying and defining residues for risk assessment and enforcement (Chair: Mr Denis Hamilton, Australia - Rapporteur: Dr Kevin Greenlees, USA).
- Working group II: Species and commodities for MRL setting - Role of GAP and GPVD in MRL setting (Chair: Dr Gudrun Gallhoff, European Commission - Rapporteur: Dr Caroline Harris, UK).

- Working group III: Role of science in the derivation and application of the MRL (Chair: Dr Steve Funk, USA - Rapporteur: Dr Dugald MacLachlan, Australia).

In preparation for these discussions, a number of participants were asked to prepare working papers on the various aspects of the assessment of residue data and the recommendation of MRLs. These papers were circulated to all participants before the meeting. The workshop participants were not asked to revise the working papers in detail but used them as a basis for the discussion and the development of this workshop report.

The draft sections of this report were adopted by the plenary meeting of the workshop. The draft report of the workshop was subsequently edited by the meeting rapporteurs and a draft-for-comment was sent to all participants. The rapporteurs prepared a final report taking into account suggested edits and comments.

II. CURRENT PRINCIPLES AND PRACTICE OF JECFA AND JMPR (SHORT OVERVIEW)

JMPR assessment processes for pesticide residues

The "Joint Meeting on Pesticide Residues" (JMPR) is an international scientific expert body administered jointly by FAO and WHO. The JMPR WHO Core Assessment Group evaluates toxicology data for establishing acceptable daily intakes (ADIs) and acute reference doses (ARfDs) and the FAO Panel on Pesticide Residues in Food and the Environment evaluates pesticide residue data resulting from pesticide use according to good agricultural practice (GAP) to estimate maximum residue levels in food and feed commodities. Under GAP a pesticide is used for effective pest control, but leaving a residue that is the smallest amount practicable. The use must be safe for the user and the environment and residues in food must be safe for the consumer.

Unlike most national pesticide authorities, which approve and register pesticide uses, Codex and JMPR have no such registration function. The objective of a JMPR evaluation is to recommend suitable standards for pesticide residues in food commodities. Residue evaluation is complex and the available information should be used in the context of understanding residue behaviour. Residue data requirements and evaluation for JMPR are described in the FAO Manual (FAO, 2002a).

The compound of interest is identified by systematic and common names, Chemical Abstracts Service (CAS) numbers and chemical formulas. Information on physicochemical properties such as melting point, water solubility, octanol-water partition coefficient, vapour pressure and hydrolysis is provided to assist with understanding the stability of the formulated product and the fate and movement of its residues.

The results of animal and crop metabolism studies are the prime determinants of the residue definition in food and feed commodities.

Radiolabelled compound (usually ^{14}C) is used in metabolism studies so that the disposition of the residue can be followed and to help with identification of metabolites.

Laboratory animal, usually rat, metabolism studies serve to identify animal metabolites and to suggest times for residue clearance.

Livestock metabolism studies (usually lactating goat and laying hen) with repeated oral dosing provide the following information for the residue evaluator:

- rates of residue accumulation in milk and eggs;
- residue distribution in tissues, milk and eggs;
- metabolite identity;
- nature of the residue in tissues, milk and eggs; and

- residue fat solubility.

Plant metabolism studies provide the following information for the pesticide residue evaluator:

- nature of the metabolites (and photolysis products);
- plant metabolites not appearing in animals;
- composition of residue at normal harvest;
- surface or absorbed residue;
- foliar absorption;
- root absorption;
- translocation to seeds, fruits or other edible portion;
- absorption of soil metabolites; and
- differences in metabolism in transgenic crops.

A pesticide metabolite identified in plants but not in animals will necessitate an additional toxicology assessment.

The fate of pesticide residues in soil may influence the nature and level of residues in crops, particularly for soil or seed treatments. Rotational crop studies are designed to answer questions about the nature and level of pesticide residues that might occur in a crop sowed or planted subsequent to the original crop that received the pesticide treatment.

Transgenic crops may have a metabolite pattern different from that of non-transgenic crops and the pesticide residue definition should cover both situations because the residue analyst testing a commodity in trade may not know whether the crop is transgenic or non-transgenic.

Analytical methods used in the supervised trials and processing studies must be validated for the substrates and analytes. Analytes will include relevant metabolites that need to be measured in the trials and processing studies as specified in the residue definitions (enforcement and dietary intake). Analytical recoveries are acceptable in the range 70-130%. The limit of quantification (LOQ) of the analytical method is taken as the lowest residue level where analytical recoveries were tested and shown to be acceptable.

Extractability of the residue should be tested by analysis of samples from the metabolism studies, where concentrations of parent and metabolites are already known from radiolabel (usually ^{14}C) measurement.

Validated analytical methods are also needed for monitoring and enforcement. These methods apply to the enforcement residue definition. Ideally, enforcement analysis can be achieved in a multiresidue method.

Experimental data are needed to show that residues of parent pesticide and relevant metabolites were stable during freezer storage at least for the intervals that samples were stored in the residue trials and in the processing, livestock feeding and metabolism studies. The substrates tested for storage should represent the range of substrates in the studies. Supervised trials and studies where conditions and intervals of storage would have produced more than 30% decline in residues are generally unacceptable.

Pesticide residue definitions are established for MRL enforcement purposes and for dietary intake assessment. Residues of parent compound and transformation products are usually expressed as parent compound.

For dietary intake purposes it is desirable to include pesticide metabolites and photolysis products that have similar toxicity properties to the parent. For enforcement purposes (testing of food consignments for compliance with MRLs) it is not desirable to include metabolites in the residue definition if they are present as only a minor part of the residue, or if difficult and expensive to analyse. Metabolites or analytes common to other pesticides are generally avoided in residue definitions if the pesticides are to have separate sets of MRLs because anomalies in enforcement work will occur.

Pesticide residues are described as fat-soluble or not on the basis of their distribution between fat and other tissues in animal metabolism and livestock feeding studies with support from the octanol-water partition coefficient.

JMPR accepts national registered uses of pesticides as Good Agricultural Practice (GAP). The recommended maximum residue levels depend mainly on the data from supervised residue trials conducted in line with maximum registered uses (highest application rate, minimum pre-harvest interval, etc) within GAP. The trials should cover the range of conditions expected to occur in practice including application methods, seasons, cultural practices and crop varieties.

When the number of trials is sufficient, JMPR estimates a maximum pesticide residue level for the commodity of trade and an STMR (median of the valid residue data, one point from each trial) and HR (highest of the valid residue data, one point from each trial) for the edible portion of the commodity.

The estimated maximum residue level is recommended to the Codex Committee on Pesticide Residues (CCPR) for use as an MRL (maximum residue limit). The STMR and HR are used in long-term and short-term dietary exposure estimates.

The aim of food processing studies on residues is:

- to identify breakdown or reaction products generated by the process;
- to relate the levels of residue in processed products to levels in the raw agricultural commodity (RAC) and to calculate processing factors from trials that simulate or are equivalent to commercial processes; and
- to support dietary exposure calculations.

If residue levels in the processed commodity exceed the residue levels in the RAC, it is necessary for JMPR to estimate a maximum residue level for the processed commodity.

The aim of livestock feeding studies is to find the levels of pesticide residue likely to occur in animal tissues, milk and eggs from repeated daily dosing of the animals over a few weeks. The nominal feeding levels (equivalent to the doses expressed as concentrations in the feed dry matter) should be close to expected residue level burdens in feed commodities.

Trials with direct external animal treatments should employ the recommended formulated product with the dose rate, method of application and timing as required for the registered product. Evaluation of external animal treatments should take into account the disposition and nature of the residues found in a dermal metabolism study.

The pesticide residue dietary burdens for livestock are derived from highest residues and STMRs for feed commodities multiplied by standard animal diets. The dietary burdens are then related to the feeding levels for the pesticide in the livestock feeding studies to estimate animal commodity maximum residue levels. Estimated maximum residue levels, HRs and STMRs derived from external animal treatments are compared with those derived from exposure through the feed. The recommended maximum residues levels, HRs and STMRs are based on whichever is the higher.

For chronic intake, estimates of likely pesticide residue levels in food are based on the STMRs from the supervised trials and food processing studies. The diets are the five regional diets (Middle Eastern, Far Eastern, African, Latin American and European) from Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme (GEMS/Food) derived from FAO food balance sheets. The chronic intake is calculated as the sum of intakes for each food commodity (residue × food consumption) and compared with the ADI. A revision of these regional diets is under preparation and is expected to be implemented in 2006.

For short-term intake, estimates of high intake of pesticide residue on a single day are based on the HRs from the supervised trials. Large portion sizes and fruit and vegetable unit weights have been provided by a number of countries, but more data are needed. The short-term intake is calculated for

each food separately (large portion size × HR × a variability factor for some cases) and compared with the acute reference dose (ARfD).

JMPR, by the use of footnotes to the recommended maximum residue levels, draws attention to those cases when estimates of pesticide residue intake exceed the ADI or ARfD.

The JMPR procedures for recommending MRLs are summarized in Figure 1.

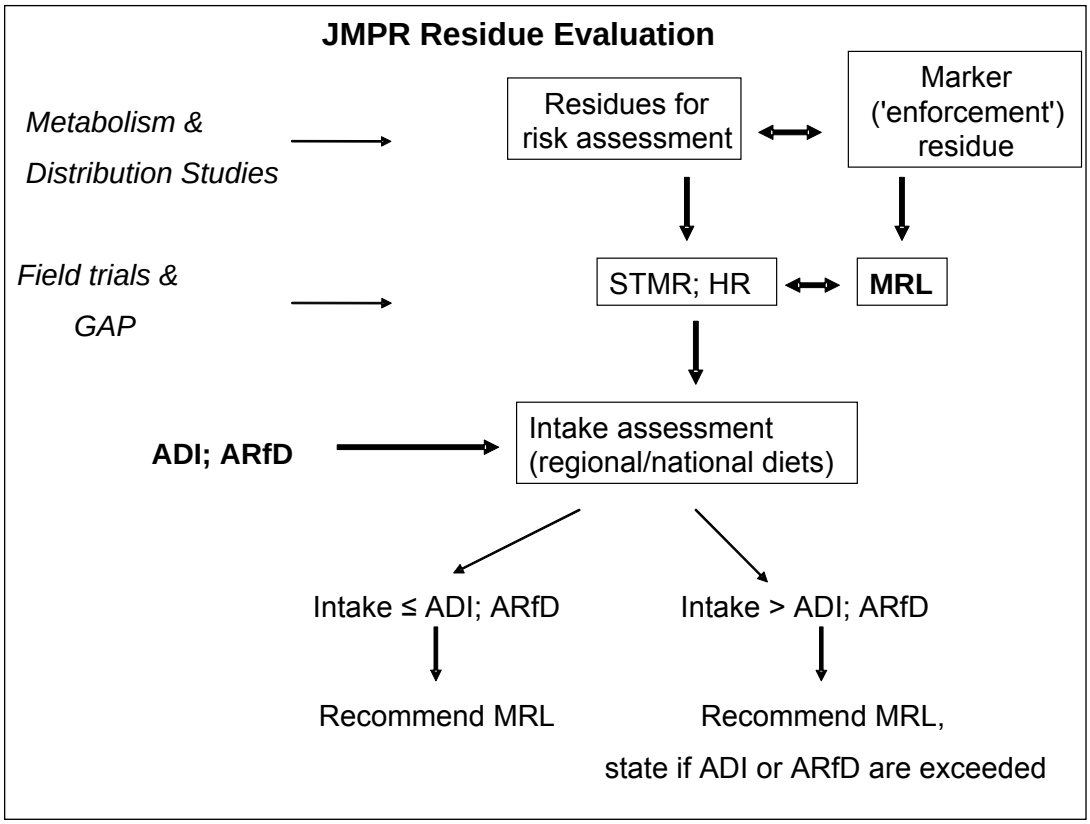

Figure 1. JMPR evaluation of residue data and recommendation of MRLs.

JECFA assessment processes for veterinary drugs

General risk assessment principles

The WHO publication *Principles for the Safety Assessment of Food Additives and Contaminants in Food*, (WHO, 1987) in part, describes many of the basic principles applied in the hazard identification and hazard characterization used by JECFA (It also contains a chapter on chemical composition and specifications, for example). In addition, JECFA has been developing its risk assessment principles since the first meeting devoted specifically to residues of veterinary drugs in foods in 1987, published in the WHO Technical Report Series prepared for each meeting devoted specifically to residues of veterinary drugs in food. The workshop noted that all JECFA meetings for residues of veterinary drugs in food have been held subsequent to the publication of the EHC-70 document. A complete list of the relevant documents and references is provided in the bibliography. In these monographs, conservative approaches and principles have been applied to the assessment of residues of veterinary drugs. For example, MRLs are linked to the ADI, although there is some flexibility to recommend MRLs depending on factors such as consumption, veterinary use practices and availability of suitable analytical methods for determining residues in food animal tissues. Thus, recommended MRLs may be reduced to more conservative values than full use of the ADI. While JECFA has specific, documented scientific principles to guide assessments, each compound is assessed on its own merits after considering the data provided or available in the public scientific literature. The Committee has

carried out quantitative risk assessments in situations when the quantity and quality of the data are adequate for this purpose.

JECFA requests detailed pharmacology data, drug metabolism and other related studies to identify the specific molecules for toxicological evaluation. Generally, identified metabolites that contribute ten percent or more of the total residues are candidates for toxicological evaluation. However, in some instances metabolites consisting of less than ten percent of the total residues have been considered. Typical toxicology requests, including individual animal data in relevant studies, include short-term and long-term carcinogenicity, reproduction and developmental (including fetal development and multi-generation) studies in experimental animals, genotoxicity, neurotoxicity, pharmacological effects and evaluation of microbial risk. Microbial risk has been addressed several times by JECFA and procedures for evaluating a microbiological basis for establishing an ADI have been developed. While a toxicological based ADI requires consideration of total residues, an ADI based on microbiological endpoint study requires consideration of microbiological residues of concern. Details of the acceptable daily intake assessment, however, are beyond the scope of this chapter.

Residue evaluation: MRL considerations

Data requirements are intended to adequately identify and characterize the veterinary drug being evaluated for toxicology and residue considerations. Specific information includes mode of administration, dose and formulation, pharmacokinetic, metabolic and pharmacodynamic studies, residue depletion studies with radiolabelled drug and non-radiolabelled drug in target animals at appropriate times of withdrawal, information on major residue components for determining a marker residue and target tissue. In addition, information is requested regarding free and bound residues (including bioavailability), routine analytical methods and appropriate method performance factors and information on antimicrobial assays for those compounds for MRL considerations on antimicrobial end points. The above data are requested for all relevant food animal species and tissues, as well as milk, eggs and honey using good veterinary practice. The JECFA has developed a mathematical model to account for bound residues in tissue. In consideration of MRLs, the JECFA also reviews the comparative metabolism between laboratory animals and food animals to determine qualitative or quantitative similarities or differences in metabolites across species.

The JECFA does not recommend MRLs when the theoretical maximum daily intake (TMDI) of residues substantially exceeds the ADI. The TMDI is the upper limit consideration in recommending MRLs. For purposes of recommending MRLs, the JECFA uses a theoretical food basket that consists of 300 g muscle, 100 g liver, 50 g kidney, 50 g fat, 1500 g milk, 100 g for eggs and 20 g for honey. Considerations in MRLs are based on the adequacy of the data. Where a large database is available, statistical approaches to MRLs may be used.

JECFA uses radiolabelled parent drug studies in intended host animal species as well as additional studies with non-radiolabelled parent drug for recommending MRLs and a marker residue compound and appropriate target tissues for residue analysis. Dose treatments preferably considered are those conducted at the maximum approved dose. Residues are generally determined in all four edible tissues – muscle, liver, kidney and fat as well as milk and eggs, where the data are sufficient. JECFA identifies the appropriate stable compound that can be used as the marker residue and indicates the most appropriate tissues for analysis, considering needs of national authorities for domestic residue control programmes and product intended for international trade. These studies also provide the necessary information to determine consideration of bound residues and relationships between the marker residue and total residues of concern as determined by the ADI (e.g., a toxicological or microbiological end-point). For substances with a toxicological end-point, all residues are considered to have the same toxicological significance as the parent drug unless data are provided to permit JECFA to discard them from consideration. For substances with a microbiological end-point, only those residues with significant antimicrobial activity are considered for residue analysis.

JECFA recognized that the use of veterinary drugs in food producing animals can result in residues that are neither extractable from tissue nor readily characterized using mild extraction procedures. The Committee has developed a procedure to estimate the maximum daily intake of residues of a drug that

has a bound residue component. It takes into account the toxicological potency and bioavailability of the residues.

Residues = Free residues + Bioavailable bound residues.
Bound residue = Total residue - (extractable fraction + endogenous fraction).

$$\text{Residues} = P_0 + \sum_{n=n_1}^{n_X} (M_n \times A_n) + (\text{Bound residue} \times \text{fraction bioavailable} \times A_b) \quad \ldots\ldots (1)$$

where

P_0 = amount of parent drug per kg of tissue.
$n_1..n_x$ = different metabolites of the parent drug.
M_n = amount of (unbound) parent drug metabolite n per kg of tissue.
A_n = toxicological potency of n relative to that of parent drug.
A_b = estimated relative toxicological potency of the metabolites in the bound residue (when no information is available, use $A_b = 1$)

JECFA considers that in the absence of other data, a bound residue should be considered of no greater toxicological concern than the compound for which the ADI was established. In considering the safety of bound residues, JECFA acknowledges that a suitable extractable residue analyte may be selected as a marker compound and used for recommending an MRL if bound residues make up an insignificant portion of the total residue. Where bound residues become a significant portion of the total residues of toxicological significance, then the procedure described may be used to assess their safety. The use of residue data for the purpose of safety assessment is evaluated on a case-by-case basis.

JECFA may make full recommendations for MRLs of a veterinary drug in appropriate food animal species and tissues when there are adequate data to do so and in accord with the ADI. Temporary MRLs may be recommended when there is a full ADI yet adequate residue or method performance data are lacking or when the ADI is temporary. The Committee may recommend MRLs "not specified" or "unnecessary" when there is a wide margin of safety of residues when compared with the ADI). Finally, JECFA may determine that MRLs cannot be recommended because of significant deficiencies in either residue data or available analytical methods or when an ADI is not established.

JECFA does not include residues that persist at or near the injection site in assessing the contribution of drug residues in edible tissues to the total daily intake. To assess the safety implications of residues at the injection site, JECFA requires information regarding drug dose, formulation and time elapsed since injection. JECFA has noted on occasions that residues may exceed the recommended MRL at practical withdrawal times. The Committee has recommended a sampling procedure currently utilized by both the Committee for Veterinary Medicinal Products (CVMP) of the European Medicines Agency (EMEA) and the U.S. Food and Drug Administration (FDA). The intention of the Committee was to standardize sampling of injection sites for results provided for review in sponsor-generated dossiers. It was noted that the CVMP has recently modified its sampling procedure that now requires a second “surrounding” sample (tissue surrounding the core 500 g sample) to confirm the quality and correctness of the original sampling (EMEA 2003).

JECFA has devoted a significant effort to analytical methods performance because of the strong role it has in recommending MRLs. JECFA has developed analytical methods performance factors for consideration as suitable for determining compliance with a recommended MRL. Major considerations include accuracy (recovery), precision, reproducibility, sensitivity (dose-response), and selectivity, among others. Use of common laboratory instruments and solvents that do not have environmental or health considerations are important factors. Guidance for analytical method performance factors has been described in individual reports. Methods are considered in cooperation with the Codex Committee on Residues of Veterinary Drugs in Food (CCRVDF) *ad hoc* Working Group on Methods of Analysis and Sampling. Adequate method performance testing for microbiological methods is required also.

JECFA has devoted efforts recently to develop statistical tools for data analysis to derive MRLs. A JECFA paper has been prepared as well as a set of proposed statistical tools for JECFA experts to

apply for recommending a set of MRLs. The approach has to meet two specific criteria: 1) the time point selected to recommend the MRLs is compatible with registered uses (Good Practice in the Use of Veterinary Drugs), and 2) that it does not result in a theoretical residue exposure in excess of the ADI.

A summary of the JECFA procedures for recommending MRLs is described in Figure 2.

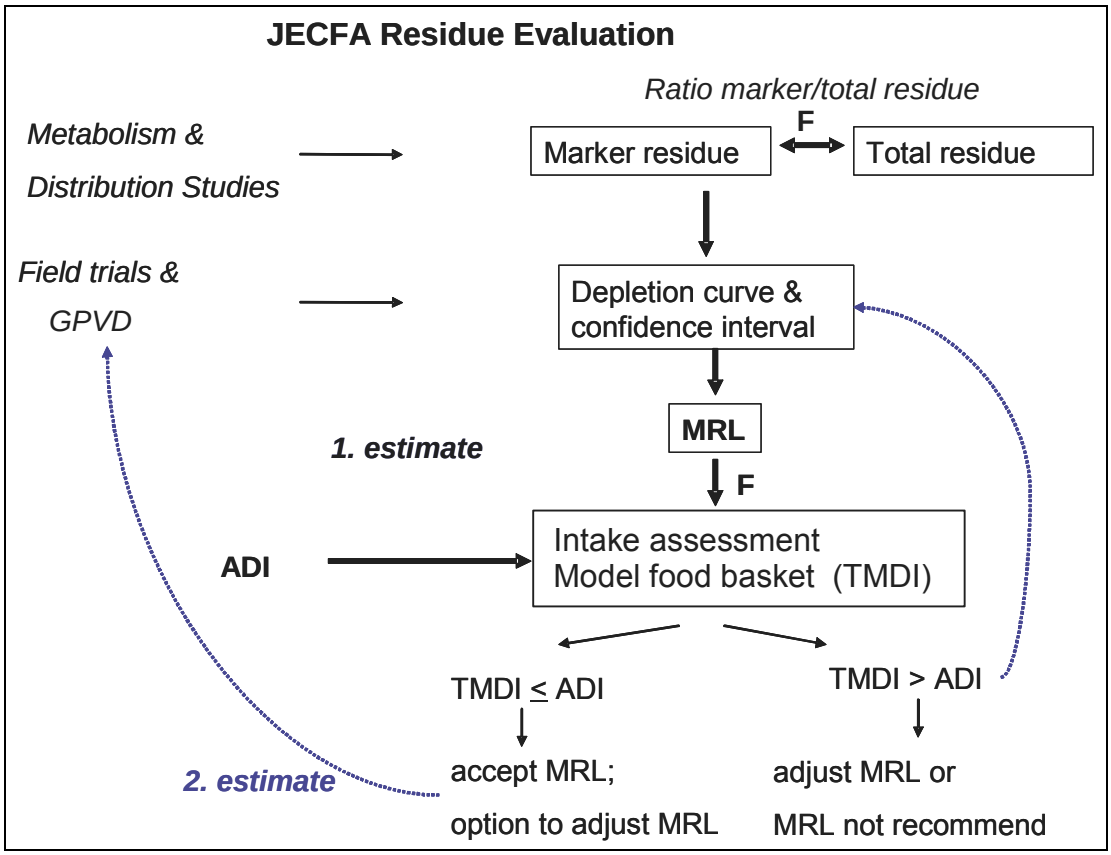

Figure 2. JECFA evaluation of residue data and recommendation of MRLs.
(F = ratio of marker residue to total residue)

III. THE RISK ASSESSMENT FRAMEWORK FOR PROPOSING MRLs

Much of the framework of MRL estimation and risk assessment is mandated by the respective Codex Committee (CCPR and CCRVDF), either through historical tradition or specific directives and preceded the development of the risk analysis paradigm.

Risk analysis is a process consisting of three components: risk assessment, risk management and risk communication. It is a structured, systematic process that examines the potential adverse effect consequential to a hazard or condition of a food and exposure to the hazard and that develops options for mitigating the risk. Risk analysis includes interactive communication amongst all interested parties involved in the process. This includes problem formulation and defining the questions to be addressed by the risk assessors.

> For veterinary drugs, CCRVDF acts as the risk manager, while JECFA acts as the risk assessor. For pesticides, CCPR and JMPR respectively perform those functions.

Risk assessment is the scientific evaluation of known or potential adverse effects resulting from human exposure to food borne hazards.

Risk Assessment consists of four steps:

- Hazard identification
- Hazard characterization
- Exposure assessment
- Risk characterization

Hazard identification - Residues of veterinary drugs and pesticides which may be present in a particular food or group of foods are derived from active substances that are capable of causing adverse health effects in humans. After the initial concern raised by the risk manager and the commissioning of a risk assessment (CCPR or CCRVDF), the risk assessors (JECFA or JMPR) perform a detailed hazard identification, thereby identifying all possible adverse effect that can be caused by the substance.

Hazard characterization - JECFA and JMPR evaluate toxicological studies in order to determine an ADI and, if considered necessary, an ARfD. JMPR considers on a routine basis whether an ARfD is necessary. JECFA has done this only on a case-by-case basis. Normally, JECFA will consider both chronic and acute effects and if the acute effects represent the most relevant endpoint, the ADI will be based on this effect.

Exposure assessment - To assess the exposure resulting from commodities treated with the pesticide under consideration, JMPR uses the supervised trials median residue level (STMR) and the GEMS/Food regional diets (based on FAO food balance sheets) to assess the chronic intake (IEDI). JMPR uses the highest residue found in supervised trials (HR) and the GEMS/Food database on the highest 97.5^{th} percentiles of consumption derived from a limited number of national food consumption surveys to assess the acute intake (IESTI). STMR and HR relate to the residue definition for dietary risk assessment, which includes all toxicologically relevant residues, and they relate to the edible portion of the food commodities. The MRL on the other hand relates to the residue definition for enforcement and to the Codex Commodity Classification of Foods and Feeds.

JECFA uses the draft MRLs to take account of total amount of potentially active residues and a conservative theoretical food basket that consists of 300 g muscle, 100 g liver, 50 g kidney, 50 g fat, 1500 g milk, 100 g for eggs and 20 g for honey to estimate a theoretical maximum daily intake (TMDI) of residues. JECFA uses the same food basket for both chronic and acute intake assessments. The conservative assumption is that all the tissues in the basket would contain residues at concentrations equivalent to the MRLs. An iterative process may be followed in recommending the MRLs.

Risk characterization – Risk characterization is the qualitative and quantitative estimation, including attendant uncertainties, of the probability of occurrence and severity of known or potential adverse health effects in a given population based on hazard identification, hazard characterization and exposure assessment. Risk characterization involves integration of the hazard characterization and exposure assessment.

The aim of the risk assessment process relating to residues of pesticides and veterinary drugs in foods is to develop maximum levels based on the results of scientific studies for consideration by the respective Codex Committee. In essence, JMPR estimates maximum residue levels that may be used by CCPR to recommend MRLs to the Codex Alimentarius Commission. JECFA recommends draft maximum residue limits for veterinary drugs (MRLVDs) for consideration by CCRVDF. CCRVDF then recommends these MRLVDs that meet its approval to the Codex Alimentarius Commission.

The factors considered for the establishment of MRLs include:

- residue definitions;
- species or crop;
- commodities (significance in trade and consumption);
- analytical methods suitable for enforcement purposes; and
- Good Agricultural Practice or Good Practice in the Use of Veterinary Drugs.

These factors will be discussed elsewhere in this report.

Table 1 compares the options used by JECFA and JMPR in recommending maximum residue levels.

Table 1. Options used for recommending maximum residue levels, a comparison of JECFA and JMPR evaluations.

JECFA	JMPR
• recommended MRL (no request for additional data). - may be based on toxicological, microbiological or pharmacological ADI	• recommended MRL (no request for additional data). - may be based on a sufficient amount of supervised field trial data or adequate livestock feeding studies.
• temporary MRL. - temporary ADI - temporary due to residue or method deficiencies	• temporary MRL - temporary ADI - temporary due to residue or method deficiencies
• MRLs unnecessary or not specified (situations with a wide margin of safety or taking into consideration endogenous levels of the compound)	
• MRLs as guidance limits (situations where tissue residue concentrations are below analytical method limits)	
	• EMRL (extraneous MRL) relating to contaminants resulting from former use of the pesticide and based on monitoring data (e.g. DDT).
	• MRL relating to spices based on monitoring data.
• no MRL recommended - no ADI - significant deficiencies in residue or method data	• no MRL recommended - no ADI - significant deficiencies in residue or method data

When an ADI has been established but no residues have been detected in a commodity in any of the residue studies, JECFA and JMPR may establish MRLs based on the LOQ of the proposed control method. In such cases it is considered that these MRLs afford the necessary protection for consumers and adjustment to reflect subsequent developments in analytical methods performance is not required.

When an ADI cannot be established for a veterinary drug, MRLs have not been proposed. The workshop noted that there are several reasons for not establishing an ADI (e.g., lack of sufficient data, use, etc.). The Workshop noted the recommendation made at the Bangkok Workshop (FAO/WHO, 2004a) regarding the development of alternative approaches of toxicological evaluation which could provide additional risk management options for such substances, including the establishment of action limits based on analytical limit of detection (LOD) or limit of quantification (LOQ), for example. In situations when no detectable residues are considered acceptable, confirmation of residue identity may be more important than quantification.

The group of spices is a special case where CCPR agreed to consider MRLs estimated from monitoring data (CCPR, 2004). The 2004 JMPR used spices monitoring data to estimate a 95th percentile value for the population for which residues were detected at the 95% confidence level, which became the basis for an MRL recommendation (JMPR, 2004b). Such an MRL has no direct relation to a registered or approved use of the pesticide.

As indicated previously, JMPR compares the long-term intake assessment (IEDI) to the ADI, while the short-term intake assessment (IESTI) is compared to the ARfD. JECFA compares the TMDI to the ADI.

In cases where the predicted intakes exceed the ADI or ARfD, JMPR will report this fact to the CCPR and may, if possible, indicate the data necessary to allow refinement of the risk characterization. JECFA will in such cases not generally recommend MRLs to CCRVDF.

Summary of risk assessment process employed by JECFA and JMPR

JECFA recommends MRLs based on the type and amount of residue considered to be without toxicological, pharmacological or microbiological hazard for human health as expressed by the ADI. It also takes into account other relevant public health risks as well as food technological aspects and estimated food intakes.

JMPR evaluates residue data to estimate likely maximum residue levels in food commodities resulting from pesticide use according to good agricultural practice, i.e. with pesticide use for effective pest control, but leaving a residue that is the smallest amount practicable. The use must be safe for the user and the environment and residues must be safe for the consumer.

As noted previously, the schematic approaches used by JMPR and JECFA are described in Figures 1 and 2, respectively.

Risk management – Risk management is the process of weighing policy alternatives in the light of the results of risk assessment and, if required selecting and implementing appropriate control options.

The determination of risk assessment policy is the responsibility of the risk management. Both JECFA and JMPR may use or develop new risk assessment principles and methodologies during their meetings. These are summarized as General considerations in the Reports of the meetings. In their subsequent meetings, CCRVDF and CCPR will discuss these changes and provide comments.

IV. IDENTIFICATION AND DESCRIPTION OF RESIDUES AND METHODS

Residue definition, chemical identity, and physicochemical properties

A residue, defined in the simplest terms, results when a drug or pesticide is deliberately applied to a food producing animal or plant. This differentiates "residues" from "contaminants". The Codex Procedural Manual (CAC, 2005) provides the following definitions:

Contaminant means any substance not intentionally added to food, which is present in such food as a result of the production (including operations carried out in crop husbandry, animal husbandry and veterinary medicine), manufacture, processing, preparation, treatment, packing, packaging, transport or holding of such food or as a result of environmental contamination. The term does not include insect fragments, rodent hairs and other extraneous matter.

Residues of veterinary drugs include the parent compounds and/or their metabolites in any edible portion of the animal product, and include associated impurities of the veterinary drug concerned.

Pesticide residue means any specified substance in food, agricultural commodities, or animal feed resulting from the use of a pesticide. The term includes any derivatives of a pesticide, such as conversion products, metabolites, reaction products, and impurities considered to be of toxicological significance.

Neither of these definitions of residues includes reference to other substances that may be present as adjuvants in the formulated products, nor to carrier or delivery devices.

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

Both JECFA and JMPR have similar requirements for the identification and characterization of a substance that is under review for the establishment of an ADI and MRLs. A comparison of the data used for these purposes by JECFA and JMPR is given in Table 2.

Table 2. Identity and physicochemical properties: data used to establish identity of substances by JECFA and JMPR.

JECFA	JMPR
IDENTITY	
Chemical name IUPAC CAS	Chemical name IUPAC CAS
CAS Registry Number	CAS Registry Number
Synonyms (includes common and proprietary names)	Synonyms (includes common and proprietary names)
• Structural formula	• Structural formula
• Molecular formula	• Molecular formula
• Molecular weight	• Molecular weight
PHYSICO-CHEMICAL PROPERTIES	
• Physical appearance (state, colour)	• Physical appearance (state, colour)
	• Odour
• Solubility in water	• Solubility in water (including pH effects)
• Solubility in organic solvents	• Solubility in organic solvents
• Stability of pure material	
• Melting point	• Melting point
• Optical rotation	
• UV absorbance maximum	
	• Vapour pressure
	• Volatility (Henry's Law constant)
	• Dissociation constant
	• n-Octanol–water partition coefficient
	• Hydrolysis rate
	• Photochemical degradation
	• Relative density

Most of the differences in requirements for physicochemical properties reflect the concern with environmental fate, which is only addressed for pesticides by JMPR. However, there are some additional differences in the respective situations. JMPR considers the properties and relative toxicities of both the pure and the technical forms of the pesticide under review. In specific cases, a veterinary drug referred to JECFA or a pesticide referred to JMPR for review may be formulated as a salt (or readily hydrolysable ester), which is rapidly dissociated into the pure active compound. It must be clearly stated in the description of the drug or pesticide in the monographs whether the description and properties given refer to the pure active compound or to the salt (or ester).

It is very important also to specify the composition of the active substance, whether it is a pesticide or a veterinary drug, especially when stereo-isomers are involved. In some cases, only one isomer is active, or one may be significantly more biologically active than others.

JMPR requires information on the route of synthesis, composition of the technical grade material and the representative batches used for the toxicological tests to interpret the results of the studies on toxicity. In general, impurities present at 0.1% or greater in a pesticide are identified, but any presence of highly toxic impurities, such as dioxins or dibenzofurans, is also stated. Mass balance should typically be ≥98%. JECFA generally does not request identification of impurities and seeks identification for residues that represent 10% or more of the total residues of the veterinary drug in the edible tissues.

The information on appearance and physical properties may be used to establish purity of analytical standards used in a control laboratory. The information required by JMPR on solubilities, and particularly the information on volatility, partition coefficient, hydrolysis and photodegradation, helps not only to establish the stability of standards, but also is critical to predicting the behaviour and fate of pesticides when applied under various typical conditions of field use and during commercial food processing.

Marker residue

The Codex defines a marker residue for veterinary drugs as a "residue whose concentration decreases in a known relationship to the level of total residues in tissues, eggs, milk or other animal tissues" (CAC/MISC 5-1993 (Amended 2003)), based on a definition used by JECFA. The relationship between the concentrations of marker residue and total residues is usually established at representative time points during depletion in a study using radiolabelled drug. The results of the determinations of total residue (total radioactivity) are compared to the concentrations of marker residue measured using a suitable chemical method.

Ideally, the marker residue provides unequivocal evidence of exposure to a specific drug. It may be the parent drug, a major metabolite, a sum of parent drug and metabolites or a reaction product formed from the drug residues during analysis. In some cases, the marker residue is present as a bound residue and requires chemical or enzymatic treatment or incubation to be released for analysis. The marker residue is not necessarily a residue of toxicological or microbiological concern. Not only parent drug, but several metabolites, including releasable bound residue, may possess significant toxicological or antimicrobial properties. The relationship between the marker and total residues is used in verifying that the MRLs recommended by JECFA will not result in the theoretical maximum daily intake exceeding the ADI.

JMPR and CCPR use a similar approach to that used by JECFA and CCRVDF to designate the residue resulting from application of a pesticide that will be used in the establishment of MRLs, referred to as "the definition of residue for enforcement purposes". A pesticide residue typically may include not only the pesticide, but also its metabolites, degradates, and other transformation products. The situation may vary, from those in which only the parent pesticide is found on treated commodities, to situations where multiple metabolites and degradation or transformation products are present. For each pesticide used on food or feed commodities, JMPR selects the residue(s) to be used for dietary risk assessment and those on which MRLs will be expressed. The term "definition of the residue" or "residue definition" may be used in reference to either of these two purposes.

MRLs for pesticides are expressed in terms of those analytes which can best indicate a possible misuse of the pesticide and which also can be detected and measured by a broad base of national laboratories. These analytes typically include residues which are easy to measure (preferably using a multi-residue method), and which normally occur as a significant part of the residue and are common to the commodities in which residues are expected to occur. JMPR selects the residue referred to in establishing the MRLs for a pesticide based on the criteria that it is simple (preferably a single compound) and suitable for practical routine monitoring and enforcement of the MRL at a reasonable cost. Similar considerations are applied by JECFA in designating the marker residue for a veterinary drug.

There are rare situations for both veterinary drugs and pesticides where a single marker residue is common to several related parent compounds. In such cases, JECFA assumes that all metabolites have the same toxicity as the parent drug unless data are provided to indicate otherwise and establishes the ADI on the parent drug, and a common MRL is established for these parent compounds, expressed in terms of a common "marker residue". Similar toxicity is not necessarily the case for pesticides with MRLs based on a common "residue for enforcement purposes". For example, the JMPR has found it possible in the case of the dithiocarbamates to separate the dietary intake assessments, because the dietary intake assessment does not rely on the common MRL but is based on residue data from supervised trials specific to the individual compounds. JECFA uses the same approach for the dietary intake assessment of veterinary drugs with a common marker residue as for individual veterinary drugs (see discussion below).

Definition of residues for dietary intake

In the JMPR, residue definitions are established for purposes of enforcement of the MRL and for dietary intake assessment. Residues of parent and transformation products are usually expressed as parent compound. For dietary intake purposes it is desirable to include metabolites and photolysis products that have similar toxicity properties to the parent.

The definition of a residue (for estimation of dietary intake) used by JMPR is that combination of the pesticide and its metabolites, impurities and degradation products to which the supervised trials median residue (STMR) and high residue (HR) apply. The residue definition for estimation of dietary intake depends on the results of metabolism and toxicology studies and its general suitability for estimating dietary intake of the residue for comparison with the ADI and ARfD (FAO, 2002a).

In JECFA, data from a study with the radiolabelled drug are assessed to follow the distribution and depletion of the total residues in the edible tissues. The relationships between the total and marker residues are established for each tissue at each time point from analytical data on marker residue and the radiolabel data on total residue. Factors are derived to reflect the ratio between the marker residue and total residue. These factors are then used to adjust the proposed MRLs for each edible tissue to total residues of toxicological concern in the calculation of the TMDI. The comparison of the TMDI to the ADI is a risk assessment step that assures that the acceptable daily intake is not exceeded. If the TMDI exceeds the ADI, the MRLs are adjusted in an iterative process to lower concentrations and the calculation is repeated to ensure that the TMDI is below the ADI.

Pharmacokinetic and metabolism data used for residue definition evaluation

The data requirements for JECFA and JMPR evaluations of the residue definition in target species, livestock and in food commodities of plant origin are available in WHO and FAO websites.

For JECFA this information is in the call for data.
(http://www.who.int/ipcs/food/jecfa/data/en/index.html).

For JMPR evaluation, detailed guidance is available in Chapter 3 of the *FAO Manual on Submission and evaluation of pesticide residues data for the estimation of maximum residue levels in food and feed* (FAO, 2002a).

Pharmacokinetics and metabolism

The residue definition for veterinary drugs and pesticides in edible commodities of animal origin is obtained from metabolism studies conducted in target species and livestock animals. Metabolites obtained in these studies are qualitatively compared with metabolites identified in laboratory animals to ensure that compounds occurring in significant amounts in edible commodities have been included in the toxicological evaluation or whether information on additional metabolites needs to be evaluated. For pesticides a residue definition in food and feed of plant origin is obtained from plant metabolism studies, confined rotational crop and soil metabolism studies. Metabolites or degradation products might be taken up by plants and occur in edible commodities.

The metabolites, degradates, and other transformation products have generally been identified and quantified in metabolism experiments with methods typically based on the use of radiolabelled compounds.

Laboratory animal, usually rat, metabolism studies serve to identify animal metabolites and to suggest times for residue clearance.

Livestock metabolism and target animal metabolism studies provide the following information for the residue evaluator at JECFA and JMPR:

- time course of residue concentration increase in milk and eggs (and rates of depletion, JECFA);
- residue distribution in edible tissues, milk and eggs;
- metabolite identity;
- nature of the residue in tissues, milk and eggs; and
- residue fat solubility.

JECFA and JMPR consider the results of the animal metabolism studies to be the prime determinant of residue definition in animal commodities and will suggest which metabolites need to be monitored. For some compounds residues in animal tissues, milk and eggs do not result even from relatively high doses. In these cases the metabolism studies may justify MRLs on animal commodities being set at LOQ (limit of quantification) and may justify a decision that residue levels in tissues, milk or eggs are set to zero for dietary intake estimations.

For a fat-soluble compound, it is better to regulate on the residue in the fat component of the meat, as the residue will be more consistent in fat, compared to meat or muscle containing varying levels of fat. Therefore the 'fat-soluble' status determines the nature of a sample that should be taken for enforcement analysis.

For a fat-soluble compound in meat, JMPR estimates residue levels for both muscle and fat for dietary intake estimation based on dietary consumption of meat and recommends an MRL for the trimmable fat from the meat, i.e. on the fat tissue. CCRVDF has recommended MRLs for both muscle and fat. This may be inappropriate because laboratories could analyze both trimmable fat and muscle. The workshop indicated that JECFA should recommend MRLs for fat-soluble compounds only for the trimmable fat from the meat, as the residues in meat are influenced by the intramuscular fat content that can have considerable variability.

Plant metabolism studies provide the following information for the residue evaluator (JMPR):

- nature of the metabolites and photolysis products;
- plant metabolites not appearing in animals;
- composition of residue at normal harvest;
- surface or absorbed residue;
- foliar absorption;
- root absorption;
- translocation to seeds, fruits or other edible portion;
- absorption of soil metabolites; and
- differences in metabolism in transgenic crops.

Plant metabolism provides the background understanding for residue behaviour and supports interpretation of the residue trials, e.g. if the residue is essentially a surface residue, the edible portions of fruits like bananas and oranges should be relatively free of residues. Transgenic crops may have a metabolite pattern different from that of non-transgenic crops. If residues translocate from treated foliage to seeds, fruits, roots or other edible portion residue levels might be expected to increase for a time after treatment.

Photolysis products may constitute part of the residue when a pesticide is used on crops in the field. Because photolysis products are generated by a non-biological mechanism, one might expect that these compounds are less likely than plant metabolites to be animal metabolites also.

The fate of the pesticide in soil may influence the residues in crops, particularly for soil or seed treatments. Rotational crop studies are designed to answer questions about the nature and level of pesticide residues that might occur in a crop following the treated crop.

Table 3. Information used for residue definition, a comparison of JECFA and JMPR evaluations.

JECFA	JMPR
TOTAL RESIDUE AND METABOLISM STUDY IN LIVESTOCK	
• Study conducted in the target animal species only. • Dosing levels sufficient to see total residue depletion and identify metabolites. • Route of administration as indicated on the label. • Radiolabelled compounds, typically ^{14}C to show disposition and distribution of total residues in edible tissues. • Same study or similar studies show metabolic profile of the distributed residues in edible tissues. • Comparative metabolism review to assure residues in food animal adequately tested in toxicology. • Study intended to provide ratio of marker residue to total residues.	• Study conducted typically in lactating goats and laying hens or in related species. • Dosing levels sufficient to see total residue (but not necessarily depletion) and identify metabolites. • Mostly oral route of administration – other routes possible depending on the label use. • Radiolabelled compounds, typically ^{14}C to show disposition and distribution of total residues in edible and offal tissues. • Same study or similar studies show metabolic profile of the distributed residues in edible tissues and identity of metabolites. • Comparative metabolism review to assure residues in food animal adequately tested in toxicology.
PLANT METABOLISM STUDIES	
Not relevant	• Radiolabelled compounds, typically ^{14}C to show disposition and distribution of total residues in edible commodities. • Same study or similar studies show metabolic profile of the distributed residues in edible tissues and identity of metabolites. • Comparative metabolism review to assure residues in plants are included in mammalian toxicology testing.
PHARMACOKINETICS	
• Studies may be conducted in laboratory animals, the target animal, and in humans. • Studies are conducted to address the pharmacokinetics and relative bioavailability of the veterinary drug by the intended route of administration and to establish oral bioavailability of residues • Results are informative in addressing differences in formulation, route of administration, dose, duration of dosing and species.	Not relevant

JECFA	JMPR
• Results may be useful in explaining residue characteristics from sustained release (depot) formulations. • May be useful in extrapolation of residue data to other species	

Purpose of livestock metabolism studies for veterinary drug and pesticide evaluation

Livestock metabolism studies are used to determine the qualitative and quantitative metabolism and degradation of the active ingredient.

Livestock metabolism studies conducted on target species using the recommended route of administration are assessed for veterinary drugs. For assessments by JMPR, metabolism studies with oral dosing of dairy livestock or laying hens provide information on the fate of residues resulting from pesticide use in the production of feedstuffs, or pesticide treatment of animal housing. For direct animal treatment dermal application studies are conducted.

For the evaluation of certain veterinary drugs in food by JECFA, appropriate metabolic and pharmacokinetics studies in the food-producing animals that simulate the conditions of use of the drug in animal husbandry are needed. Additionally, pharmacokinetic and metabolic studies in the animal species used for toxicological investigation are required.

Livestock metabolism studies fulfill several major purposes:

- to provide an estimate of total residues (and residue depletion for JECFA) in the edible livestock commodities (muscle, fat, offal (offal = liver and kidney for JECFA), eggs, milk), as well as the excreta;
- to identify the major components of the terminal residue in the edible commodities, thus indicating the components to be considered in defining the residue for both dietary intake calculations and MRL enforcement or residue monitoring;
- to provide a quantitative estimation of the relative distribution of the parent compound and metabolites in muscle and fat;
- to show the efficiency of extraction procedures for various components of the residue, an element of analytical method validation; and
- to provide the basis for a metabolic profile or degradation pathway.

JECFA and JMPR compare the metabolism in target species and livestock with laboratory animals (such as the rat) metabolism. JMPR in addition takes plant metabolites and, where appropriate, soil metabolites into account.

Pharmacokinetic data are not typically evaluated for pesticides. Studies establish the pharmacokinetics of a veterinary drug conducted with the formulated drug product in healthy animals of each of the target species. The studies are designed to establish the rate and extent of absorption of the active substance, its distribution, metabolism and excretion profiles including identification and quantification of major metabolites. Ideally the proportion of the administered dose eliminated by metabolism (usually by liver) and excretion (in urine and faeces) is determined. Pharmacokinetic parameters and variables including *flip-flop* pharmacokinetics when present are derived from plasma concentration time data in individual animals based on compartmental or non-compartmental analyses.

For some drugs, chirality has a marked impact on pharmacokinetics. A drug with a single chiral centre exists in two enantiomeric forms. Most chiral drugs are licensed in products containing the racemic mixture (50:50) of the two enantiomers. Because the body is a chiral environment, drug pharmacokinetics, pharmacodynamics and toxicity may differ significantly for the enantiomers. In determining the pharmacokinetic properties of a racemic mixture, it is essential to analyse and then characterize each enantiomer separately.

JECFA and JMPR consider it important for both veterinary drugs and pesticides to consider the differing properties of enantiomers when setting MRLs.

Depot formulations (sustained release formulations) commonly lead to relatively prolonged persistence of drug at the injection site. Injection site residues vary markedly between animals in magnitude of concentration and persistence. They usually comprise a very high proportion of unchanged drug, as post-absorption metabolism has not occurred. Hence, the marker residue (if it is not the parent drug molecule) is unlikely to be appropriate for determining residues at the injection site. Exposure risk to injection site residues is primarily considered short-term (acute) in nature. The acute toxicity approach to injection site residues of veterinary drugs used by JECFA is consistent with the ARfD approach used by JMPR for pesticides. The most appropriate study to establish an ARfD is still under discussion. JMPR experts have recently developed more specific guidance including a proposal for a single dose study protocol (Solecki et al. 2005).

Livestock metabolism studies on pesticides should reflect feeding of one compound, usually the parent. The dosing material for oral studies should not be a mixture of active ingredient and plant metabolites. If the plant metabolites are also found to be animal metabolites, then additional livestock metabolism experiments that involve dosing with plant metabolites need not be considered. If a plant metabolite comprises a major portion of the TRR on a feed item (from plant metabolism studies), or it is not also an animal metabolite, a livestock metabolism study involving dosing with that metabolite might be necessary.

Purpose of plant metabolism studies

Plant metabolism studies are not relevant for the evaluation of veterinary drugs. Plant metabolism studies are conducted for pesticides to determine the qualitative metabolic (or degradation) fate of the active ingredient. The composition of the terminal residue must be determined before the residue definition is decided and before analytical methods can be developed for monitoring and for MRL enforcement purposes. Crop metabolism studies are used to elucidate the degradation pathway of the active ingredient, i.e., to identify the metabolism and degradation products when a pesticide is applied to a plant directly or indirectly, including the relative quantity of degradation products in extracts and non-extractable material.

Crop metabolism studies serve the following major purposes:

- to provide an estimate of total radioactive residues (TRR) in the various raw agricultural commodities (RACs) of treated crops;
- to determine the distribution and movement of residues within the plant, e.g. to determine whether the pesticide is absorbed through roots or foliage or whether translocation occurs;
- to identify the components of the terminal residue, which serves as part of the basis for setting the residue definition, thereby defining the components to be quantified by the residue analytical methodology; and
- to demonstrate the efficiency of the extraction procedures for the various components of the residue.

Transgenic and non-transgenic crops may metabolize the pesticide differently. The principles for deciding residue definition do not change and depend strongly on metabolism and analytical methods. When a commodity produced by a non-transgenic crop cannot be readily distinguished from the transgenic crop commodity, the residue definition should be the same for both. No single approach is applicable to all situations and a case-by-case approach is needed at present

Data on metabolism are used in evaluating both the toxicological and residue profiles of pesticides. JMPR examines the metabolism in experimental animals and compares it with both that in food-producing livestock and in plant species on which the pesticide is used. This is required to decide upon the relevance of the toxicological studies to humans, and to define the residues in plants and livestock products. The ADI estimate, based on toxicological studies in experimental mammalian animals, is relevant for residues in foodstuffs only if the metabolite pattern is qualitatively similar.

Plant metabolites, or degradation products e.g. from photolysis, which have not been identified in laboratory animal metabolism, are not covered by the initial toxicological database. Separate studies for these compounds may be necessary if significant residues occur in food and feed items.

For pesticide evaluation by JMPR, soil metabolism and rotational crop studies provide information on metabolites or degradation products produced in the soil that may be taken up in the target crop or a following crop. If metabolites occur that had not been previously identified in crops or animals, further information on their toxicological significance is needed.

For paddy rice, grown in a water-sediment environment, studies such as photolysis in natural pond water and residue degradation in water-sediment systems are relevant. However, the necessary information on the nature of the residue may be obtained from a paddy rice metabolism study.

Analytical methods and residue stability in stored analytical samples

JECFA and JMPR have similar requirements for analytical method validation. The primary distinction that is applied concerning use of suitable methods is that for methods used in pharmacokinetic studies, residue depletion studies, supervised field trials and processing studies, the emphasis is on demonstrating that the method performed reliably in the hands of the analyst or analysts involved in that specific study. Most contemporary studies are conducted according to Good Laboratory Practices (GLP) and provide such assurance through the detailed records of the work that are provided for assessment. In addition, when a method is assessed for its suitability for support of marker residue MRLs, monitoring and MRL enforcement, demonstration of successful transfer of the method between analysts, as well as the practicality of use of the method in a routine setting, become significant considerations.

Method performance requirements

JECFA and JMPR expect that the analytical methods used in the pharmacokinetic, metabolism, sample storage stability and residue depletion studies provided for review are clearly and fully described and have explicitly stated performance characteristics (such as analyte recovery and precision). The methods used in field trials should include the parent compounds and the relevant metabolites or degradation products. Decisions for rejection of assay validation results due to low recovery are handled on a case-by-case basis.

CCRVDF and CCPR have established performance criteria for analytical methods for controlling the compliance with MRLs (FAO, 2002b; CCPR, 2003). Target values for method precision and recovery have been established for the residue concentrations typically required to support MRLs. Evaluation of analytical assays for veterinary drugs and pesticides are arrived at using similar procedures, but the interpretation of the results is different.

For veterinary drugs, the analyte is the marker residue and all validation and stability requirements are directed towards that molecule. Results are corrected for recovery. Decisions for rejection of assay validation results due to low recovery are handled on a case-by-case basis.

For pesticides, the analytes include parent compound and all relevant metabolites. Analytical methods are required to determine all residue components needed for the residue definitions for compliance with the MRL and for estimation of dietary intake. The major residue components are determined individually as far as technically possible.

For pesticides, the regulatory method is preferably a multi-residue procedure even if its recoveries are not as good as those of a specific individual method. Where the residue definition for dietary exposure assessment is different from that for regulatory purposes, analytical methods specially developed for determination of specified metabolites are also required.

In summary, the main difference in the procedures is that the JMPR uses analytical recovery to assess the acceptability of data, while the JECFA adjusts analytical data for analytical recovery. This is

consistent with analytical practices in the respective areas of veterinary drugs and pesticides, and with IUPAC guidance on recovery correction (Thompson *et al., 1999)*.

Analyte stability

The purpose of the stability studies is to show that the analyte is stable under conditions of analysis and storage. Similar analyte stability information is evaluated by JECFA and JMPR, including both the stability of pure standards, as normally constituted and in solution, and during sample processing. How the data are used can be different between JECFA and JMPR.

Stability studies are conducted to determine if pesticide levels in stored analytical samples remain stable during the period of storage under controlled freezer conditions. The results of storage stability tests conducted on residue samples held in storage from representative substrates are provided. For plant materials, the number of crops depends on the uses of the pesticide. Typical matrices are selected to include predominantly water, oil, protein or starch-containing materials. Animal tissues, milk and eggs are tested for residue storage stability when animal commodity MRLs are needed. The study conditions reflect those to which the samples from the residue trials have been subjected (often with storage for a year or more). Where sample extracts have been stored for more than 24 hours prior to analysis, the stability of residues are demonstrated with recovery studies performed under similar conditions.

Freezer storage stability studies are needed to provide assurance that the residues in the stored sample are essentially the same as in the fresh sample (FAO, 2002a). When the analytical method determines a "total residue", storage stability studies include not only the total residue, but also separate analyses of all compounds that may be included in the residue definitions.

JMPR considers that residue data from supervised trials and other studies would generally not be valid when the samples have been stored in conditions and for a time shown by the frozen storage stability studies to result in more than 30% reduction of residue concentration. JMPR does not adjust residue data for possible losses during frozen storage.

For veterinary drugs, the stability of the analyte under normal conditions of storage is investigated to demonstrate the period for which the marker residue remains stable in target tissues to assure the accuracy of the analytical result obtained in the residue depletion studies and for validation of the regulatory assays. For example, in a veterinary drug, stability is demonstrated during frozen storage at -20^{o}C over a period of at least 6 weeks to reflect the typical period of time that a survey sample may be stored awaiting regulatory analysis. Acceptable stability criteria (usually ≥ 70%) are handled on a case-by-case basis. If the analyte is not stable in tissues under these conditions of storage, other conditions, such as storage at -70^{o}C, may be required. Since a positive result may lead to re-analysis, possibly by a second laboratory, it is preferable that stability is investigated over a prolonged time period of 3-6 months to represent the potential time which may elapse between an initial analysis and a subsequent re-analysis of a regulatory sample. Preferably, such studies are conducted with both fortified blank matrix and incurred materials, as the behaviour of residues in fortified matrix may not be the same as observed when incurred residues are investigated.

Summary – analytical methods and analyte stability

The requirements for analytical methods and analyte stability determinations are very similar for both JECFA and JMPR, but there are some differences in how they evaluate the submitted data. The comparison is summarized in Table 4.

Table 4. Information on analytical methods and frozen storage stability, a comparison of JECFA and JMPR evaluations.

JECFA	JMPR
• Validation and verification of marker residue methods	• Validation and verification of enforcement residue methods
• Usually single (marker) residue	• Emphasis on multi-residue method for enforcement, single residue methods for field trials

JECFA	JMPR
• Recovery correction used	• No recovery correction used, but monitored (also no correction for loss of analyte during frozen storage of samples)
• Stability of marker residue in matrices	• Stability of parent and relevant metabolites in representative matrices
• Raw commodities only	• Includes assay validation for processed food studies

Fate of residues during commercial food processing

The aim of food processing studies on pesticide residues is to identify breakdown or reaction products generated by the process, to find the levels of residue in processed products and to support dietary exposure calculations. JECFA does not consider processing and evaluates residues of veterinary drugs only in the raw product. Also JMPR does not require any processing data for meat and dairy commodities.

It is current practice for JECFA to accommodate for fermentation processes in animal products in food production by setting the MRLs for substances with antimicrobial activity accordingly. The Workshop confirmed its agreement with this practice. JECFA should describe such cases explicitly and transparently in its evaluation reports. It should be noted that MRLs accommodating fermentation processes are set by JECFA for technological reasons following a specific request from CCFAC.

JMPR evaluates changes in the nature of the residues during commercial food processing and levels occurring in processed plant commodities. JMPR evaluates food processing data on residue behaviour where significant residues occur in plant or plant products which are processed into food. For example, information on the fate of pesticide residues in wheat during milling is needed because residue levels in bran and flour are likely to be higher and lower respectively than those in the wheat, necessitating the recommendation of an MRL for bran. "Significant residues" are generally defined as >0.1 mg/kg, unless the compound has a high acute or chronic toxicity. Special attention should be given to residues less than 0.1 mg/kg in case residues concentrate in further processing steps (Chapter 3 of the FAO Manual: FAO, 2002a).

Two types of processing studies are evaluated: investigations to determine the effect on the nature and level of the residues. The FAO Manual (FAO, 2002a) gives general advice on planning and conducting such studies.

Effects on the nature of the residue during processing and the identification of alteration products, are commonly determined by in-vitro hydrolysis procedures. Therefore a concept is adopted of selecting three different hydrolytic conditions to represent these effects. The hydrolysis studies are the basis for the following studies on the level of residues in processed products. They make it possible to confirm the definition of the residue for processed products or to define extra breakdown products to be analysed in further studies. The ethylene bisdithiocarbamate fungicides (EBDC) are a much studied example to illustrate the formation of degradation products of toxicological concern.

Based on the effect on residue levels and the disposition of the residues in the various processed products, processing factors are calculated and considered by JMPR as follows:

$$\text{Processing factor} = \frac{\text{residue level in processed commodity}}{\text{residue level in raw commodity}}$$

Processing factors assist in the dietary intake assessment of processed commodities. They are also used in recommending MRLs for processed products with an existing Codex commodity code, but only if the processing leads to an increase of the residue level.

Residues in processed dairy commodities with higher fat content than milk will have a higher residue in the processed commodity than in the raw product for fat-soluble compounds. Partitioning of residues in milk into the fat is influenced by the molecular structure of the compound. Furthermore the fat content of milk is variable. JECFA sets MRLs on whole milk. JMPR recently decided to recommend two MRLs for fat-soluble compounds, one on whole milk and one on milk fat. This is necessary to estimate residues in processed dairy commodities. The working group recommended that JECFA and JMPR consider harmonizing this practice.

Field study data used to identify the MRL

Livestock feeding studies and animal treatments

The aim of livestock feeding studies for pesticides is to find the levels of residue likely to occur in animal tissues, milk and eggs from repeated daily dosing of the animals over a few weeks. This is comparable to the residue depletion studies conducted for veterinary drugs chronically administered in feed or in drinking water. The JMPR and JECFA approaches to these study types are presented in Table 5.

Table 5. Information on livestock feeding studies and animal treatments, a comparison of JECFA and JMPR evaluations.

JECFA	JMPR
• Use of veterinary drug in line with label instructions – (use of veterinary drug in medicated feed or drinking water products) • Trials in typical breeds in commercial production and conditions	
• Study conducted in target animal species	• Lactating dairy cows to represent mammals, laying hens to represent poultry.
• Use of approved formulation at maximum label dose and duration under typical field conditions	• Dosing daily via capsule at approximately 1x, 3x, and 10x expected dietary burden
• For chronic feed and water treatment duration sufficient to reach residue plateau concentrations in edible tissues and in milk and eggs	• Duration typically 28 days with 5-7 day recovery period. Target is to reach plateau residues in milk and eggs
• Slaughter intervals for tissue collection to demonstrate concentrations and time of maximum residues and subsequent depletion.	
• Measure residues in muscle, fat, liver and kidney (whole milk and eggs)	• Measure residues in the four edible tissues at end of treatment and recovery
• Milk sampling at cessation of treatment.	• Measure residues in milk and eggs collected daily during treatment and recovery period
• Residues to be measured are the marker residues, used to establish the MRL and for risk assessment	• Residues to be measured include the components of the residue definitions for MRL enforcement and risk assessment
• Residue depletion study	
• Conduct under GLP	• Conduct under GLP

The nominal lowest feeding level for pesticides (equivalent to the doses expressed as concentrations in the feed dry matter) should be close to the expected residue level burdens in feed commodities. Additionally, animals are fed levels of 3x and 10x this dose. Veterinary drugs are administered at the maximum label dose and duration.

Milk from dairy cows and eggs from poultry are collected daily during treatment and recovery for pesticides. Milk and egg sampling is done at the cessation of treatment for veterinary drugs, and for some period of depletion. Collection of depletion data in the fat is useful for pesticides with persistent residues. Both JECFA and JMPR consider it important for studies to continue at least until plateau residue levels are reached in milk and eggs.

Both pesticides and veterinary drugs may result in residues in the food animal as a result of direct treatments. A comparison of the JECFA and JMPR approach to these types of studies is presented in Table 6.

Table 6. Information on direct treatment of livestock, a comparison of JECFA and JMPR evaluations.

JECFA	JMPR
• Use of veterinary drug in line with label instructions – all treatments.	• Use of pesticide in line with label instructions - external treatment only.
• Trials in typical commercial animals and conditions.	• Trials in animals expected to generate highest residue (preferred).
• Study conducted in target animal species using approved formulation at maximum label dose and duration under typical field conditions.	• Study conducted in target animal species using approved formulation at maximum label dose and duration under typical field conditions.
• Slaughter intervals to demonstrate time and duration of maximum residues and subsequent depletion.	• Slaughter intervals to demonstrate time and duration of maximum residues and subsequent depletion.
• Trials to cover typical breed(s) in commercial production.	• Trials to cover typical breed(s) in commercial production.
• Measure residues in muscle, fat, liver and kidney (whole milk and eggs).	• Measure residues in muscle, fat, liver and kidney (whole milk, milk fat for fat-soluble compounds and eggs).
• Sample muscle and included fat of treatment site.	• Sample of fat at treatment site.
• Residues to be measured are the marker residues, used to establish the MRL and for risk assessment.	• Residues to be measured to cover enforcement and risk assessment residue definitions.
• Depletion study.	• Depletion study.
• Conduct under GLP.	• Conduct under GLP not stressed.

Trials with external animal treatments of pesticides and veterinary drugs should employ the recommended formulated product with the dose rate, method of application and timing as required for the registered product. Evaluation of external animal treatments should take into account the disposition and nature of the residues found in a metabolism study based on the same route of exposure.

Both JECFA and JMPR consider it important that these studies result in the maximum concentration of residues in the edible tissues that might occur with approved uses of a registered product.

V. CRITERIA FOR SELECTING DATA, SPECIES, COMMODITIES

Comparability of definitions for species tissue and commodity, food of animal origin

The evaluation of pesticide and veterinary drug residues is similar conceptually in a number of areas, but the details and assumptions are at variance for historical or other reasons. The workshop made a side by side comparison of the *Codex Classification of Foods and Animal Feeds* (CAC, 1993) and the *Codex Glossary of Terms and Definitions* (Residues of Veterinary Drugs in Foods) CAC/MISC 5-1993, Amended 2003. The relevant points of discussion on definitions are noted below.

Meat and Muscle

JMPR (CAC, 1993) refers to **Meats** (from mammals other than marine mammals) as "*muscular tissues, including adhering fatty tissues such as intramuscular, intermuscular and subcutaneous fat from animal carcases or cuts of these as prepared for wholesale or retail distribution in a fresh state*".

JECFA (CAC/MISC 5-2003) refers to **Muscle** as "*skeletal tissue of an animal carcass or cuts of these tissues from an animal carcass that contains interstitial and intramuscular fat*". This includes "*bone, connective tissue, tendons as well as nerves and lymph nodes in natural portions*" but not include edible offal or trimmable fat. **Meat** is considered the edible part of any mammal.

JMPR refers to **Poultry meats** as "*the muscular tissues including adhering fat and skin from poultry carcasses as prepared for wholesale or retail distribution*." and specifies that "*for fat-soluble pesticides a portion of adhering fat is analyzed and MRLs apply to the poultry fat*".

JECFA refers to **Poultry** as "*domesticated birds including chickens, turkeys, ducks, geese, guinea-fowls or pigeons*".

Milk

The definitions used by JMPR and JECFA are substantially the same. The classification used by JMPR allows for specific commodity (e.g. buffalo milk, cattle milk) identification while JECFA uses a combination of species and commodity (e.g. sheep milk) approach.

Egg

The definitions used by JMPR and JECFA for eggs are the same. The classification used by JMPR allows for specific commodity (e.g. duck eggs, goose eggs) while JECFA uses a combination species and commodity (e.g. poultry eggs) approach.

Aquatic species

JMPR uses definitions for fish that range from general category to specific species (e.g. trout). JECFA uses a definition that allows for inclusion of several aquatic species, and in certain cases, invertebrates. Some differences may be in relation to the portion of the commodity to which the MRL applies. For JMPR, it includes all commodities in general after removal of the digestive tract; for JECFA, it refers to muscle tissue and skin in natural proportion and includes certain other invertebrates, particularly cephalopods.

Edible offal

The definition used by JMPR for ***edible offal*** includes a much broader list of organs (e.g., liver, kidney, tongue, heart, stomach, thymus gland, brain) than considered by JECFA as edible offal (i.e. liver and kidney). When referring to a specific commodity reference of cattle liver, JMPR applies a specific food category (e.g., MO 1281 "cattle liver") that corresponds with the JECFA species tissue combination.

Data evaluation based on the application of GAP[*] and GPVD[†]

JECFA and JMPR consider all the relevant information on the uses of the substance as it is authorized in commercial products by national authorities. Many national governments have established data quality requirements for substances intended for new uses and new registrations. This is generally referred to as consideration of data from studies conducted according to good laboratory practice (GLP). The principles of GLP define a set of rules and criteria for which a quality system concerned with the organizational process and the conditions under which non-clinical health and safety studies are planned, performed, monitored, recorded, archived, and reported.

Good agricultural practice and good practice in the use of veterinary drugs, GAP and GPVD, refer to those uses authorized by national registration authorities and which are issued as directions for use and printed on pesticide product and veterinary drug preparation labels. The GAP and GPVD authorizations may vary among national governments to satisfy the practical needs of plant production and animal husbandry and relevant national legislation.

MRLs for residues of pesticides and veterinary drugs are recommended based on the results of analysis of residue trials reflecting the registered or authorized uses of the substance and available analytical methods. In order to identify whether a specific study and its data are suitable for recommending an MRL, JMPR considers the approved product label that describes the registered or authorized uses reflecting Good Agriculture Practice. Similarly, JECFA reviews information from residue and metabolism studies from the approved uses of commercial products as guidance to determine whether data from studies were conducted according to GPVD. In practice this translates into the consideration of the following types of study data to recommend MRLs for appropriate commodities and species and uses.

JMPR

Information requested and considered by JMPR is specified in the FAO Manual (FAO, 2002a) and comprises the following:

- major pests or diseases to be controlled;
- crops and situations;
- formulation of the pesticide product;
- concentration of active ingredient;
- type of treatment (route of application, e.g. foliar, dip, pour-on);
- number of treatments per season;
- interval between successive applications;
- application rate;
- pre-harvest interval (PHI) in days;
- direct treatment of animals if applicable (i.e. withdrawal or withholding period between treatment and slaughter for human consumption or treatment and collection of milk or eggs); and
- labels of the commercial products authorized confirming the above.

JECFA

JECFA considers the conditions of use of commercial products authorized. In its call for data, the FAO secretariat requests

- Chemical identity and properties
- Use and dosage forms
- Pharmacokinetic and metabolic studies in experimental and target animals
- Radiolabelled residue depletion studies in target animals (to provide information on total residues and major residue components)
- Residue depletion studies with unlabelled drug for analysis of marker residue in target animals, eggs milk and honey, as appropriate
- A description of the analytical procedures for detection and determination of residues

[*] GAP: Good Agricultural Practice in the Use of Pesticides – see Glossary of Terms.
[†] GPVD: Good Practice in the Use of Veterinary Drugs – see Glossary of Terms.

- A review of the routine analytical procedures for determination of residues, including quality assurance systems

Registered and approved veterinary uses may vary from country to country because, among other reasons, the efficacious use patterns may be different, especially in regions with great differences in disease distribution, predominant parasites, production methods (e.g., extensive or intensive), predominant animal breeds, climate and water temperature (e.g., aquaculture). It should be reiterated, that evaluations and recommended MRLs do not consider off-label use or potential misuses of the substance.

The JECFA and JMPR recommendations are based on the approved use conditions resulting in the highest residues and cover all known uses that have been evaluated. Details regarding the recommended MRLs are published in the Reports and Monographs of the JECFA and JMPR.

Direct external animal treatment – dossier submissions to JMPR and JECFA

Residue studies relating to ectoparasiticide uses may be submitted to JMPR or JECFA for evaluation and MRL recommendations. The majority of such dossier submissions regarding direct external animal treatment are provided to JECFA.

Where the compound primarily has pesticide uses on food crops, the data submission for direct external animal treatments is likely to be included as part of the pesticide dossier submission to JMPR.

If the compound has been developed by a company whose business is primarily animal health, it is likely that the dossier will be sent to JECFA.

The Workshop noted that the route of submission was probably a matter of efficiency. From this review of the procedures the Workshop concluded that the results of the assessments by either JECFA or JMPR would be expected to be similar.

VI. EXTRAPOLATION ISSUES

Proposal for expanding the scope of MRLs

Both JECFA and JMPR have no fixed rules on extrapolation of MRLs to other crops and species or between regions but have extrapolated data on a case-by-case basis.

Pesticide residues

The term 'minor crop' is not defined although attempts have been made based on consumption and trade data (Harris and Gaston, 2004).

JMPR relies on the registrations of national authorities. Consequently, JMPR does not recommend separate MRLs unless there are nationally registered or approved uses. In order to make recommendations for any MRL, JMPR would expect to receive information on the national registered uses and data from appropriate residue trials.

Where residue data are unavailable or are very limited, JMPR will consider extrapolating from one crop with relevant data to another crop where relevant data are incomplete. The 1997 JMPR listed the information needed for extrapolation to additional crops including 'minor crops' (JMPR, 1997). In particular the information requested includes the description of the cultural practices for the production, the approved or registered uses of the pesticide and the reasons for expecting similar residue levels on the 'minor crop' to those on the major crop. Information on the potential problems in international trade is also useful.

The current JMPR approach to the estimation of group maximum residue levels is explained in the FAO Manual (FAO, 2002a). Group tolerances may be proposed where data are available on a number of crops within that crop group or at least two species are included in products of animal origin.

Commodity groupings described in the Codex Classification of Foods and Feeds are the basis for group maximum residue levels. Generally, for a group limit to be proposed, residue levels in the main commodities of the group should not be too divergent and registered uses should be similar. In some cases where the residues on one or a few commodities in the group are quite different from the rest, it may be possible to recommend a limit for "group, except …..".

A general principle on recommending Group MRLs in wider circumstances should be considered in an attempt to cover more uses where national authorizations exist. Overall, to facilitate international trade and protect consumer health, it may be better to recommend these MRLs rather than to have no standards at all.

In an FAO sponsored project on minimum data requirements, Harris and Gaston (2004) recommended a number of possibilities for plant commodity group tolerances and extrapolations that were based on a comparison of the national rules from Australia, the USA and the European Union. It was proposed that these extrapolations were most likely to be acceptable from a risk management perspective as these minimum data requirements were already routinely applied in these countries.

Table 7. Extrapolations that can be used in situations of comparable GAP (Harris and Gaston, 2004).

Crop	Recommended extrapolations
Citrus fruit	Oranges and a small citrus to whole group.
Tree nuts	Almonds plus one other nut (except coconuts) to whole group.
Pome fruit	Apples and pears to whole group.
Stone fruit	Peaches, nectarine and cherry or peaches, plum and cherry to whole group.
Berries and other small fruit	Any berry and currant to whole group (excluding grapes).
Root and tuber vegetables	Potato, carrot and one other root crop to whole group. Potato to tuber and corm sub group. Sweet potato or yam to tuber and corm excluding potato sub group.
Bulb vegetables	Onions green and dry to whole group.
Fruiting vegetables (non-cucurbits)	Tomato and peppers to whole group.
Fruiting vegetables (cucurbits)	Cucumber, melon and other cucurbits to whole group.
Brassicas	Cauliflower or broccoli and cabbage and one other Brassica to whole group.
Leafy vegetables (also see stem vegetables)	Head and leafy lettuce and spinach to leafy vegetables. Cos lettuce to leafy Asian vegetables.
Herbs	Two leafy herbs to whole group.
Legume vegetables (fresh)	Beans green and peas green to whole group.
Stem vegetables	Celery to leafy petioles sub group.
Pulses	Any dried bean and dried pea to whole group.
Oilseeds	Any 3 oilseeds to whole group.
Cereals	Rice plus any two other cereals to whole group including rice

Residues of veterinary drugs

The JECFA has routinely recommended MRLs in animal species such as cattle, pigs, sheep, chicken and turkey. JECFA has recommended MRLs for 15 substances in species including horse, goat, deer, rabbit, etc. (FAO/WHO, 2004b). This extension of MRLs from one species with a comprehensive data set to another species without such a data set has been based on considerations such as the choice of a marker residue and the similarity in the MRLs from one or more species to another.

For the majority of substances with MRLs for more than one species, the same marker residue has been identified. For products such as eggs and milk, the marker residue is not different from those defined for edible tissues including liver and kidney. The parent drug has been chosen as the marker residue in almost all cases.

The range of variation of the MRLs between species has routinely been a factor of three or less (e.g. cattle and pig muscle 300 μg/kg, poultry muscle 800 μg/kg). From the examination of the variations of MRLs between species, most of the differences can be explained by variations in ratios of the marker residue to total residues. These differences in the ratio of marker residue to total residue in different species are a limiting factor when calculating theoretical maximum daily intakes for adjustment of the MRLs so that they are harmonized across species. When these differences in the ratios exist, harmonization of the MRLs across species could result in the TMDI exceeding the exposure of residues permitted by the ADI for those species.

JECFA generally has based its recommendations on two situations:

- Compounds with a non-radiolabelled residue depletion study in the specific species in conjunction with data on comparative metabolism or relevant data on metabolism in another species;
- Compounds where MRLs were recommended only by extrapolation of information available for another relevant species.

Possible extrapolations between animal species

For substances that have no MRLs recommended in any species, a full set of residue data in all relevant species and tissues should be provided to recommend the most complete set of MRLs.

For substances that have MRLs recommended in one or more species, MRLs could be extrapolated to another species provided that the metabolic profile is comparable, the marker residue is present in the extrapolated species at sufficient levels for monitoring by validated analytical methods and there is an approved use. Extrapolations for food producing species should be reviewed on a case-by-case basis; however, possible examples are shown below.

Species with a full set of available data	Recommended extrapolations
Ruminant (muscle, liver, kidney, fat)	All ruminants
Non-ruminant mammals (muscle, liver, kidney, fat)	All non-ruminant mammals
Chicken and eggs	Poultry and poultry eggs

Honey

It is not appropriate to consider honey as a candidate for extrapolation because of the difficulty in extrapolating from animals, birds or fish to bees. Therefore JECFA should attempt to elaborate specific approaches to derive MRLs for honey.

Geographic extrapolation

Pesticide residues

Residue data from countries are compared with national registered uses in the country of the trials or in a neighbouring country with similar climate and cultural practices.

The 2004 JMPR (JMPR, 2004a) assessed the results of work carried out by the Zoning Steering Group (Working Group on Pesticides, 2002), who reviewed supervised residue trials on a given crop conducted at the same GAP with the commodity harvested on day zero after the final pesticide application and showed that residue levels were at least as variable within geographic zones as between geographic zones. The Zoning Steering Group suggested that application method, crop type and local agricultural practices were major contributors to differences in residue levels among trials conducted under the same GAP. Climate had only a minor direct effect. The JMPR suggested, therefore, that hypothetical zones (not geographical zones) could be developed on the basis of crop type and variations in agricultural practice. For example, wheat is grown in a relatively uniform manner worldwide (one zone), while grapes are grown under a variety of conditions (e.g., crop height, leaf numbers and plant density; multiple zones).

The JMPR concluded that some of the recommendations of the York Workshop (Harris and Pim, 1999) and Zoning Steering Group used by the JMPR will continue to be considered as auxiliary advice but that substantial additional work was required to make the recommendations generally applicable as guidance.

Veterinary drug residues

There are very few examples in JECFA where climate may have had an effect on residue levels of veterinary drugs and therefore additional data to address geographic extrapolation is not justified. JECFA is aware, however, that climate (e.g., tropical versus temperate) may require differing animal breeds to adequately adapt to differing climates and these animal breeds may have different metabolic profiles. In addition, differing climates may result in differing insect infestations in food animals such that approved uses in temperate climates may not be effective in tropical climates. More data are necessary to clarify these types of situations.

VII. DIETARY RISK ASSESSMENT OF RESIDUES

Assessment of dietary exposure to pesticide and veterinary drug residues integrates data on residues in food with food consumption data. The resulting dietary exposure estimate is then compared with the relevant toxicological parameter to assess the potential risk from exposure – ADI (acceptable daily intake) for long term exposure and ARfD (acute reference dose) for short-term exposure. This latter process is called risk characterization.

The ADI and ARfD are established on the basis of a review of the available information, including data on the biochemical, metabolic, pharmacological, microbiological and toxicological properties of the chemicals derived from studies of experimental animals and, where available, appropriate observations in humans. For the purpose of this report, the terms "dietary exposure" and "dietary intake" are considered synonymous. Additional information on dietary exposure assessment can be found in Chapter 7 of this project (*Updating the principles and methods of risk assessment*, Chapter 7: *Exposure/intake assessment for chemicals in food*).

Currently, both JECFA and the JMPR conduct long term (chronic) dietary intake assessments, while short-term (acute) intake assessments are conducted routinely by JMPR and on a case-by-case basis by JECFA. Both expert bodies use a deterministic, point estimate approach, which is considered to be suitable at the international level to assess the exposure to pesticide and veterinary drug residues in connection with the establishment of Codex MRLs.

JECFA and JMPR use different internationally established food consumption data. Consumption data used by JMPR are reported by GEMS/Food (Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme) while JECFA uses a theoretical food basket that was developed during the first committee meetings. Residue data used by both expert bodies are derived from crop and animal studies submitted by sponsors.

In assessing the chronic exposure to pesticides, the JMPR uses primarily the supervised trials median residue (STMR) measured as the residues of toxicological concern on the edible portion of the food commodity. JECFA uses the MRL adjusted by a factor describing the ratio between the total residue of toxicological or microbiological concern and the marker residues, on which the MRL is based. The short term exposure is calculated by the JMPR using the highest residue value in edible portion (HR) from the supervised trials or the STMR for blended commodities, both for the residues of toxicological concern.

Pesticide residue intake assessment

Chronic or long-term exposure

The deterministic method initially recommended to estimate the chronic exposure to pesticides (WHO, 1989) relied on the calculation of the Theoretical Maximum Daily Intake, in which the concentration of residues for each crop-pesticide combination was considered to be at the MRL. Since 1996, the JMPR has used a revised approach (WHO, 1995, 1997a) with the supervised trials median residue (STMR) level replacing the MRL in the calculation, for the estimation of the International Estimated Daily Intake (IEDI). The STMR aims to better represent the residue level that one might be exposed for a long period when consuming commodities treated according to GAP.

In predicting pesticide chronic residue intake, long-term food consumption habits and not day-to-day variations should be reflected to permit valid comparison with the ADI. Thus, average daily food consumption values are used in the calculation. Until now (2005), the JMPR has used average daily per capita consumption estimated for each commodity on the basis of the GEMS/Food 5 regional diets. Beginning in 2006, the 5 regional diets will be replaced by the GEMS/Food 13 cluster diet, which is based on the food balance sheets compiled by FAO for the period 1997-2001. The data are available on the WHO Website (http://www.who.int/foodsafety/chem/gems/en/).

The IEDI for each pesticide and for each GEMS/Food regional diet is calculated by multiplying the STMR for a given raw or processed food commodity (in mg/kg) by the daily consumption of that food commodity. The individual intakes are summed up for all the food for which there is available residue and food consumption data, divided by the relevant body weight for the regional diet, and expressed as a percentage of the ADI.

Whenever STMR data are not available (e.g., for old compounds within the Codex system), an assessment can still be conducted using MRL values (TMDI) or a mixture of STMR and MRL values. Ideally, the residue values should be for the edible portion of the commodity, e.g., banana without peel. JMPR Reports include summaries of the chronic assessments as well as spreadsheet details for each compound JMPR evaluations and reports, from 1991 to the present, 2005, can be found at the FAO website: http://www.fao.org/ag/AGP/AGPP/Pesticid/Default.htm (FAO, 1991-2005).

Acute or short-term exposure

Short-term exposure of pesticides should be conducted for pesticides of acute hazard for which an acute reference dose has been established by the JMPR.

The intake of residues in a single meal or over the course of day may be somewhat higher than the long-term or typical daily average for two reasons. First, the consumer may eat a larger than average amount of that food on a particular day and secondly, the food may contain higher residues than the average. The extreme situation occurs when the two situations coincide. Therefore, in estimating short-term risk for pesticide residues, data on large portion consumption and the occurrence of the high residue are needed.

As it is considered unlikely that an individual will consume two or more different commodities in large portion weights within a short period of time, and that those commodities will have the highest level of the same pesticide, the acute assessment is conducted for each commodity separately.

The procedures for calculating the short-term intake of pesticides were defined primarily in 1997 at the FAO/WHO Geneva Consultation (WHO, 1997b), refined at the International Conference in 1999 (Harris *et al*., 2000) and at subsequent JMPR Meetings. In this approach, the International Estimate of Short-Term Intake (IESTI) is calculated for each crop-pesticide combination taking into account the large portion (LP) of a certain food consumed, which represents the 97.5th percentile of eaters, the unit weight (U) of the food in edible portion and, in some cases, the variability of residues in individual units of a composite sample. This variability expressed as the variability factor, is defined as "the 97.5th percentile of the residues present in crop units divided by the mean of the residue population of the sampled lot".

At its 37th Session (2005), the CCPR stated that "food containing residues at the level of the adopted Codex MRL must be safe for the consumers" (ALINORM 05/28/24 para 76). The present workshop discussed whether using the HR in the acute intake calculations (the current JMPR methodology) instead of the MRL adjusted for toxicologically relevant residues to estimate the IESTI complies with this risk management definition. The workshop concluded that the total IESTI calculation (all parameters in the equation considered) is sufficiently conservative to ensure consumer safety, but invited JMPR to discuss this issue again in more detail at its next meeting.

The highest residue value in edible portion or the STMR found in supervised trials are used as the residue concentration in the food. Depending on food large portion and unit weights (LP and U) and whether the food commodity is blended or not blended the IESTI for each commodity is calculated using different equations. A detailed description of the methods currently used by the JMPR is described in Chapter 3 of the 2003 JMPR Report. (JMPR, 2003).

Data on the consumption of large portions, unit weight and body weight used currently by the JMPR were provided by the governments of Australia, France, The Netherlands, Japan, Sweden, South Africa, the UK and the USA and were compiled by GEMS/Food. These data are available on the WHO Website (http://www.who.int/foodsafety/chem/gems/en/). Two estimations are conducted, one for children and one for the general population. The results of intake assessments by JMPR are summarized each year in Chapter 3 of JMPR Reports, while the intake spreadsheets with detailed information for each compound are included in Annex 4 of JMPR Reports.

Residues of veterinary drugs

Assessment of long-term (chronic) intake

The estimation of long-term (chronic) dietary intakes of residues of veterinary drugs by JECFA is closely linked to the determination of the MRLVDs recommended by the Committee. In this context JECFA uses a calculated estimate of long term (chronic) intake of residues of toxicological or microbiological concern - called the "Theoretical Maximum Daily Intake" (TMDI) – for comparison with the ADI. (Note that allowance is made for body weight in the comparison because the ADI is expressed per kg of body weight and the TMDI is expressed per person).

In the calculation of the TMDI:

- it is assumed that a person with a body weight of 60 kg may consume daily 500 g of mammalian or poultry meat (300 g muscle, 100 g liver, 50 g kidney, 50 g fat) plus 1500 g milk, 100 g egg and 20 g honey. Meat can be substituted by 300 g fish (muscle and skin in natural proportions). In the cases of pigs and poultry and depending on the disposition of the substance, fat may be replaced by the same amount of fat and skin in natural proportions; and
- furthermore it is assumed that all animals of the target species are treated with the drug and that upon consumption the concentrations of marker residue in the above "standard edible tissues" obtained from these animals are equal to the corresponding recommended MRLVDs.

The contribution to the TMDI of the consumption of the individual tissues is calculated by multiplying: the amount of tissue consumed with the concentration of marker residue corresponding to the MRLVD of the tissue with the ratio of the concentrations of the total residue of concern and the marker residue. The intake resulting from 100 g (0.1 kg) liver would, for example, be calculated as follows:

$$Intake_{\text{total residue from liver}}\,[\text{mg/person/day}] = 0.1\,[\text{kg}] * MRLVD_{\text{liver}}\,[\text{mg/kg}] * ratio_{\text{liver}}$$

The TMDI itself is then the sum of the individual intakes resulting from similar calculations for all tissues with their corresponding recommended MRLVDs.

Figure 3 illustrates a procedure being evaluated by JECFA for determining MRLVDs and the role of the withdrawal time (Good Practice in the use of Veterinary Drugs) in this process.

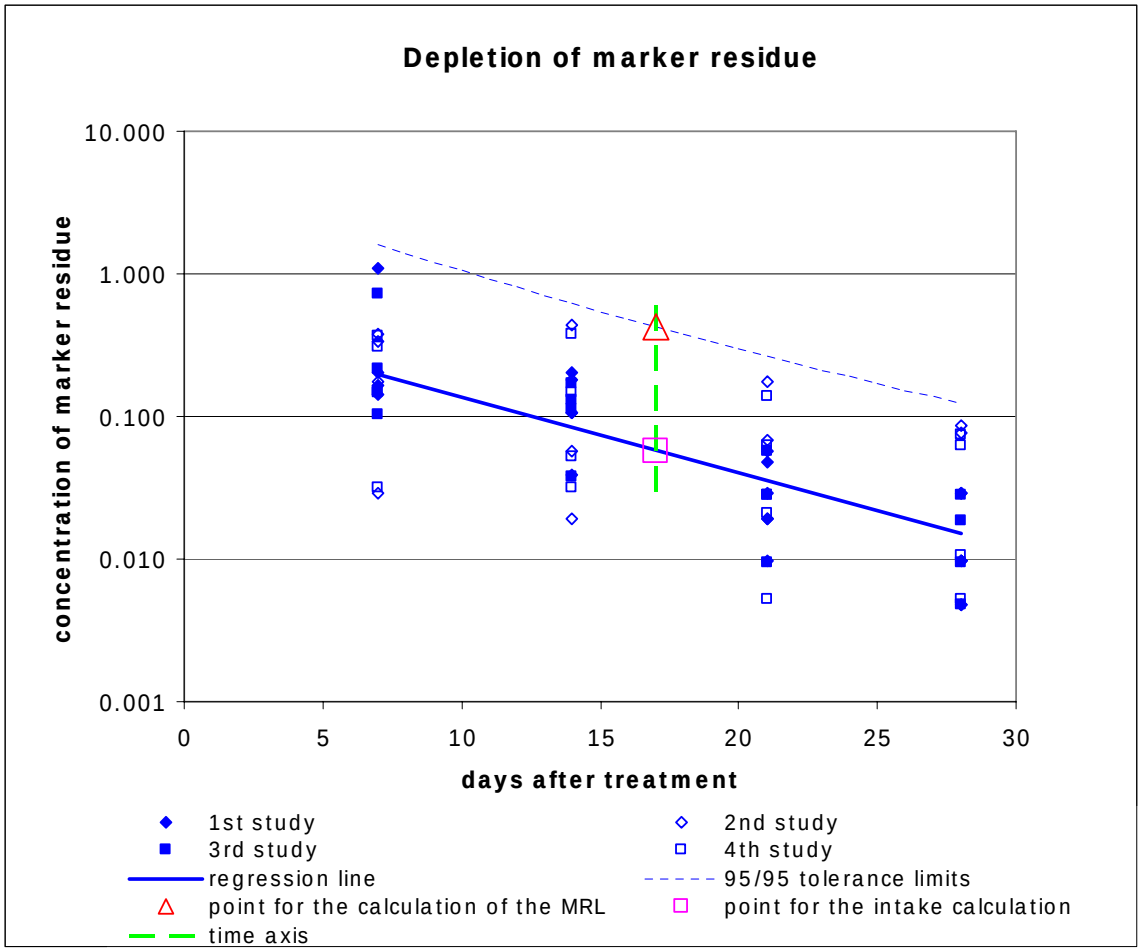

Figure 3. Use of depletion data for deriving MRLVDs and for point estimates of long-term intakes.

Figure 3 presents kinetic depletion data of marker residue in a tissue obtained in four different studies on a semi-log scale, where concentrations are accepted as log-normally distributed and a first-order depletion rate would produce a straight line. The solid line is the regression line calculated by linear regression using the logarithmically transformed concentration data. The dotted line shows the upper 95% confidence interval over the 95th percentile of all predicted values resulting from similar treatments of the same species and breed of animals under the same conditions. These limits are called "tolerance limits" in statistics. The MRLVD is a point on this line. In order to determine the most appropriate point on this line the resulting TMDI is calculated and compared to the ADI, the point on the time axis (days after treatment) is compared with the withdrawal time and the MRLVD itself is compared with the performance characteristics of the proposed regulatory analytical method. Figure 3 shows the MRLVD as a triangle on the dotted line and the corresponding median as a square on the solid line.

Short-term (acute) intakes

In a considerable number of cases the ADI allocated by JECFA for a veterinary drug was based on a no-observed-effect-level for an acute effect. However, JECFA has currently no established procedure

to calculate acute intake estimates. When it has been necessary, JECFA has done so on the basis of the data available.

Limitations of the data currently available and of procedures

Food consumption

The current food consumption data used by JMPR (GEMS/Food regional diets) to conduct chronic exposure assessment are based on food balance information provided by member countries to FAO. Food balance is the country's annual food production plus imports and minus loss and exports. Waste at the household or individual level and subsistence farming are not taken into account. Ideally, food consumption data should be based on actual food consumption surveys, i.e. what is eaten. To improve the international food consumption information data-base, national governments should be encouraged to submit their food consumption data to FAO and WHO.

The current data provided by GEMS/Food to conduct short-term intake assessments lack the detailed information needed for optimal assessment. For example, those situations in which the number of consumers is insufficient to estimate the 97.5th percentile value used to derive the large portion value (LP) are not indicated. Ideally, the GEMS/Food large portion data base should contain the number of person-days in the food survey that was used to derive the large portion (LP), the percentile and more information on the distribution of consumption. It is also suggested that GEMS/Food, in reporting the large portion values, separate food consumed "as is" from processed foods (e.g. raw apple from apple juice, milk from cheese etc). In addition, only a limited number of countries provided the data, which could compromise the assessment conducted at international level. National governments are also encouraged to submit relevant data for short-term exposure calculations to GEMS/Food.

The current food consumption values used by JECFA (theoretical food basket) are derived from very limited information on consumption habits in a small number of countries. Nevertheless, the theoretical food basket approach leads, in combination with the MRL, to over conservative estimates of the long-term exposure to veterinary drugs of "average eaters" and highly conservative estimates for the "preferential eaters". Although the JECFA food basket is very conservative when compared to the GEMS/Food regional diets used by JMPR to assess the long-term exposure, these values are lower than those in the GEMS/Food database on the highest 97.5th percentiles of consumption used by JMPR to assess the short-term exposure.

A proposal for a new approach to estimate the chronic and acute dietary exposure to veterinary drugs

To make chronic intake estimates conducted by JECFA more realistic, a new approach is proposed. The concentrations corresponding to the MRLVD and the median frequently differ by a factor exceeding 5 (see Figure 3). Theoretical considerations and probabilistic simulations clearly show that – if a consumer eats this tissue or product over a life time – the concentration in the tissue of a given day will vary largely between several standard deviations below and above the median, however the long term daily intake observed over a sufficient time period will equal the median and not the MRLVD or tolerance limit. Therefore, the MRLVD is not a suitable point estimate of the concentration to be used in assessments of long-term (chronic) intakes of residues of veterinary drugs. The most suitable value is the median. The value of the median is not influenced by the logarithmic transformation used in its determination. However, the only estimate of intake used by JECFA is currently the TMDI. There was only one exception to the use of the TMDI: in the assessment of the nature-identical hormone growth promoting substances estradiol-17-beta, testosterone and progesterone by the 52nd Meeting of the Committee the median was used (in the absence of MRLVDs). Thus, in principle, JECFA has not ruled out this possibility.

As explained above, the TMDI is not a suitable estimate of long-term (chronic) dietary intakes. It is even more problematic to use this figure if the TMDI exceeds the ADI with the consequence that JECFA does not propose MRLs for the substance under review. JECFA should consider using the median value of the distribution of residue concentrations from which the MRL is derived for the calculation of conservative estimates of long-term (chronic) intakes.

JECFA should develop methods to perform an acute intake assessment for compounds where an ARfD is established. For cases where it would be appropriate to estimate short-term (acute) intakes JECFA currently has not a full set of adequate consumption figures.

National or regional dietary exposure assessment to pesticides conducted by governments and other bodies

National governments are encouraged to conduct their own national dietary risk assessments to assist with national decisions on granting of pesticide registration. At the national level, the possible availability of additional data may facilitate a tiered approach. For example, in the first tier, a deterministic model could be used. When the dietary exposure to a given pesticide exceeds the ADI or ARfD, a more refined estimation could be conducted, applying deterministic or probabilistic methods. Refinements that may be considered could include the following: percent crop treated; residue surveillance or monitoring data; market basket survey data; processing and food preparation data.

National dietary intake estimates should be based on national consumption data. These data can be obtained through food consumption surveys at the level of the individual person, including records and diaries, food frequency questionnaires and dietary recall, or at the household level, including a household budget survey. Detailed descriptions of various food surveys can be found in another part of this project (*Updating the principles and methods of risk assessment*, Chapter 7: *Exposure/intake assessment for chemicals in food*). Ideally, these data should discriminate between the consumption by individual groups of the population, such as children, from consumption by the general population. National governments are encouraged to submit their consumption data to GEMS/Food.

VIII. RECOMMENDATIONS

Recommendations are arranged according to the section of the document from which they originated.

III. The risk assessment framework for proposing MRLs

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

IV. Identification and description of residues and methods

2. The workshop concluded that the definition of a pesticide residue and a veterinary drug residue are essentially the same. The definition for “residues of veterinary drugs” could be made more consistent with the definition for “pesticide residue” by the addition of the phrase “considered to be of toxicological significance”.
3. The workshop recommended that FAO prepare a guidance manual to define, in detail, data needs and evaluation procedures for residue definitions and the derivation of MRLs for veterinary drugs.
4. JECFA should recommend MRLs for fat-soluble dual-use substances only for the trimmable fat from the meat.
5. Partitioning of residues in milk into the fat is influenced by the molecular structure of the compound. Furthermore, the fat content of milk is variable. JECFA proposes MRLs for whole milk. JMPR now recommends two MRLs for fat-soluble compounds, one on whole milk and one on milk fat. This is necessary to estimate residues in processed dairy commodities. The workshop recommended that JECFA and JMPR consider harmonizing this practice.

V. Criteria for selecting data, species, commodities

6. For dual-use substances the evaluation of the application as a pesticide/drug to animals should be undertaken using the same principles. This can be achieved by several means that require co-

ordination between JECFA and JMPR and also CCRVDF and CCPR (risk assessment policy) and will involve the adoption of mutual notification and co-ordination of procedures.

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

VI. Extrapolation issues

8. National governments are encouraged to submit GAP information particularly on 'minor crops' during the data and information call-in process for JMPR.
9. JMPR should continue to evaluate extrapolation of pesticide residues data between geographic zones.
10. JECFA should investigate a specific approach for MRLs in honey.
11. Procedures for extrapolation from one species of animal having a full data set and recommended MRLs to another species need to be agreed upon and harmonized guidance documents prepared. This should be based on past experience with specific cases.
12. A general principle on recommending Group MRLs in wider circumstances should be considered in an attempt to cover more uses where national authorizations exist.

VII. Dietary risk assessment of residues

13. To improve the international food consumption information data base, national governments should be encouraged to submit their consumption data to FAO and WHO.
14. JECFA should consider using the median value of the distribution of residue concentrations from which the MRL is derived for the calculation of conservative estimates of long-term (chronic) intakes.

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Glossary of terms

Acceptable Daily Intake (ADI). An estimate of the total residues of a veterinary drug, expressed on a body weight basis, that can be ingested daily over a lifetime without any appreciable health risk.

Acceptable daily intake (ADI). The ADI of a chemical is the estimate of the amount of a substance in food or drinking-water, expressed on a body-weight basis, that can be ingested daily over a lifetime without appreciable health risk to the consumer on the basis of all the known facts at the time of the evaluation. It is expressed in milligrams of the chemical per kilogram of body weight. (WHO, 1997a).

Acute Reference Dose (ARfD). The ARfD of a chemical is 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 h or less, without appreciable health risk to the consumer on the basis of all the known facts at the time of evaluation. It is expressed in milligrams of the chemical per kilogram of body weight. (JMPR, 2002).

Definition of residues. The definition of a residue for compliance with MRLs is that combination of the pesticide and its metabolites, derivatives and related compounds to which the MRL applies (FAO, 2002a).

Definition of residues. The definition of a residue for estimation of dietary intake is that combination of the pesticide and its metabolites, impurities and degradation products to which the STMR and HR apply (FAO, 2002a).

Estimated Acute Intake (EAI). An estimate of the maximum intake of a veterinary drug residue during one meal or one day, which assumes that residues are present at the highest levels reported in residue trials, as occurring in injection sites.

Estimated Short-term Intake (ESTI). An alternative term for EAI (see above) used by some licensing authorities.

Extraneous Maximum Residue Limit (EMRL). The EMRL refers to a pesticide residue or a contaminant arising from environmental sources (including former agricultural uses) other than the use of the pesticide or contaminant substance directly or indirectly on the commodity. It is the maximum concentration of a pesticide residue that is recommended by the Codex Alimentarius Commission to be legally permitted or recognized as acceptable in or on a food, agricultural commodity or animal feed. The concentration is expressed in milligrams of pesticide residue or contaminant per kilogram of the commodity. (CAC, 1993, amended 2001).

Good Agricultural Practice (GAP) in the use of pesticides. GAP includes the nationally authorized safe uses of pesticides under actual conditions necessary for effective and reliable pest control. It encompasses a range of levels of pesticide applications up to the highest authorised use, applied in a manner which leaves a residue which is the smallest amount practicable. Authorized safe uses are determined at the national level and include nationally registered or recommended uses, which take into account public and occupational health and environmental safety considerations. Actual conditions include any stage in the production, storage, transport, distribution and processing of food commodities and animal feed. (CAC, 2005).

Good experimental field practice The formalised process for designing and recording the practices used in the performance of field investigations with pesticides, and which assure the reliability and integrity of the data. See GLP. (Holland, 1996).

Good laboratory practice (GLP). The formalised process and conditions under which laboratory studies on pesticides are planned, performed, monitored, recorded, reported and audited. Studies performed under GLP are based on the national regulations of a country and are designed to assure the reliability and integrity of the studies and associated data. The US-EPA GLP definition also covers field experiments (see Good experimental field practice). (After OECD, 1992) (Holland, 1996).

Good Practice in the Use of Veterinary Drugs (GPVD). GPVD is the official recommended or authorized usage including withdrawal periods, approved by national authorities, of veterinary drugs under practical conditions (CAC, 2005).

Highest residue (HR). The HR is the highest residue level (expressed as mg/kg) in a composite sample of the edible portion of a food commodity when a pesticide has been used according to maximum GAP conditions. The HR is estimated as the highest of the residue values (one from each trial) from supervised trials conducted according to maximum GAP conditions, and includes residue components defined by the JMPR for estimation of dietary intake (FAO, 2002a).

International estimated daily intake (IEDI). The IEDI is a prediction of the long-term daily intake of a pesticide residue on the basis of the assumptions of average daily food consumption per person and median residues from supervised trials, allowing for residues in the edible portion of a commodity and including residue components defined by the JMPR for estimation of dietary intake. Changes in residue levels resulting from preparation, cooking, or commercial processing are included. When information is available, dietary intake of residues resulting from other sources should be included. The IEDI is expressed in milligrams of residue per person (WHO, 1997a).

International estimated short-term intake (IESTI). The IESTI is a prediction of the short-term intake of a pesticide residue on the basis of the assumptions of high daily food consumption per person and highest residues from supervised trials, allowing for residues in the edible portion of a commodity and including residue components defined by the JMPR for estimation of

dietary intake. The IESTI is expressed in milligrams of residue per kg body weight. (FAO, 2002a).

Marker residue. The parent drug, or any of its metabolites, or a combination of any of these, with a known relationship to the concentration of the total residue in each of the various edible tissues at any time between administration of the drug and the depletion of residues to safe levels.

Marker residue. The substance that is, or is representative of, the residue of toxicological concern in the target tissue and/or milk/eggs. Identification of a marker residue is extremely important as it is the substance determined for control purposes in the enforcement of MRLs by national governments and industry (WHO, 1993).

Maximum residue level*) The maximum residue level is estimated by the JMPR as the maximum concentration of residues (expressed as mg/kg) which may occur in a food or feed commodity following Good Agricultural Practices. The estimated maximum residue level is considered by the JMPR to be suitable for establishing Codex MRLs. (FAO, 2002a).

Maximum Residue Limit*) The MRL is the maximum concentration of a pesticide residue (expressed as mg/kg), recommended by the Codex Alimentarius Commission to be legally permitted in or on food commodities and animal feeds. MRLs are based on GAP data and foods derived from commodities that comply with the respective MRLs are intended to be toxicologically acceptable. (CAC, 1993).

Maximum Residue Limit*) The maximum concentration of residue resulting from the use of a veterinary drug (expressed in mg/kg or µg/kg on a fresh weight basis) that is recommended by the Codex Alimentarius Commission to be legally permitted or recognized as acceptable in or on a food. It is based on the type and amount of residue considered to be without toxicological hazard for human health as expressed by the Acceptable Daily Intake (ADI), or on the basis of a temporary ADI that utilizes an additional safety factor. It also takes into account other relevant public health risks as well as food technological aspects and estimated food intakes (WHO, 1989).

No Observable Effect Level (NOEL). The highest dose of a substance which causes no changes distinguishable from those in normal (control) animals. (WHO, 1990).

Pesticide. Any substance or mixture of substances intended for preventing, destroying or controlling any pest, including vectors of human or animal disease, unwanted species of plants or animals causing harm during or otherwise interfering with the production, processing, storage, transport or marketing of food, agricultural commodities, wood and wood products or animal feedstuffs, or substances which may be administered to animals for the control of insects, arachnids or other pests in or on their bodies. The term includes substances intended for use as a plant growth regulator, defoliant, desiccant or agent for thinning fruit or preventing the premature fall of fruit, and substances applied to crops either before or after harvest to protect the commodity from deterioration during storage or transport (FAO, 2003).

Primary food commodity. For the purposes of the Codex Alimentarius, the term "primary food commodity" means the product in or nearly in its natural state intended for processing into food for sale to the consumer or as a food without further processing. It includes irradiated primary food commodities and products after removal of certain parts of the plant or parts of animal tissue." (JMPR Report 1979, Annex 3). Explanatory note: The term "raw agricultural commodity (RAC)" means the same as "primary food commodity."

Processing factor. The processing factor for a specified pesticide residue, commodity and food process is the residue level in the processed product divided by the residue level in the starting commodity, usually a raw agricultural commodity (FAO, 2002a).

Regulatory method of analysis. A regulatory method of analysis is a method suitable for the determination of a pesticide residue in connection with the enforcement of legislation. (JMPR Report 1975, Annex 3).

Residue. Any specified substances in or on food, agricultural commodities or animal feed resulting from the use of a pesticide. The term includes any derivatives of a pesticide, such as

*) It should be noted that all three terms are frequently abbreviated using the same acronym MRL irrespective of the different meaning and context in which they are used.

conversion products, metabolites, reaction products, and impurities considered to be of toxicological significance. The term "pesticide residue" includes residues from unknown or unavoidable sources (e.g. environmental) as well as known uses of the chemical (FAO, 2003).

Supervised trials for estimating maximum residue levels. Scientific studies in which pesticides are applied to crops or animals according to specified conditions intended to reflect commercial practice after which harvested crops or tissues of slaughtered animals are analysed for pesticide residues (FAO, 2002a).

Supervised trials median residue – processed (STMR-P). The STMR-P is the expected residue in a processed commodity calculated by multiplying the STMR of the raw agricultural commodity by the corresponding processing factor, or derived directly from a series of processing trials. The STMR-P is expressed in units of mg/kg (FAO, 2002a).

Supervised trials median residue (STMR). The STMR is the expected residue level (expressed as mg/kg) in the edible portion of a food commodity when a pesticide has been used according to maximum GAP conditions. The STMR is estimated as the median of the residue values (one from each trial) from supervised trials conducted according to maximum GAP conditions (FAO, 2002a).

Target tissue. The edible animal tissue (muscle, fat, liver or kidney) selected to monitor for the total residue in the target animal. It is usually but not necessarily the tissue with the slowest depletion rate of residues.

Theoretical Maximum Daily Intake (TMDI). The TMDI is a prediction of the maximum daily intake of a pesticide residue, assuming that residues are present at the MRLs and that average daily consumption of foods per person is represented by regional diets. The TMDI is calculated for the various regional diets and is expressed in milligrams of residue per person. (WHO, 1997a).

Use pattern. The combination of all factors involved in the use of a pesticide, including the concentration of active ingredient in the preparation being applied, rate of application, time of treatment, number of treatments, use of adjuvants and methods and sites of application which determine the quantity applied, timing of treatment and interval before harvest (FAO, 2003).

Veterinary drug. Any substance applied or administered to any food producing animal, such as meat or milk-producing animals, poultry, fish or bees, whether used for therapeutic, prophylactic or diagnostic purposes or for modification of physiological functions or behaviour (FAO/WHO, 2000).

Withdrawal Period. The interval between the time of the last administration of a veterinary drug and the time when the animal can be safely slaughtered for food, or milk or eggs can be safely consumed.

Glossary of abbreviations

ADI	acceptable daily intake
ai	active ingredient
ARfD	acute reference dose
bw	body weight
CAC	Codex Alimentarius Commission
CAS	Chemical Abstracts Service
CCN	Codex classification number (for compounds or commodities)
CCPR	Codex Committee on Pesticide Residues
CCRVDF	Codex Committee on Residues of Veterinary Drugs in Food
CVMP	Committee for Veterinary Medicinal Products – European Medicines Agency
CXL	Codex level
DT_{50}	time to 50% decomposition
DT_{90}	time to 90% decomposition
EBDC	ethylene bisdithiocarbamate
EMEA	European Medicines Agency
EMRL	extraneous maximum residue limit
FAO	Food and Agricultural Organization of the United Nations

FDA	US Food and Drug Administration
GAP	good agricultural practice
GC	gas chromatography
GEMS/Food	Global Environment Monitoring System–Food Contamination Monitoring and Assessment Programme
GLP	good laboratory practice
GPVD	good practice in the use of veterinary drugs
HPLC	high-performance liquid chromatography
HR	highest level of residue in the edible portion of a commodity found in trials to estimate a maximum residue limit in the commodity
HR-P	highest residue in a processed commodity calculated by multiplying the HR of the raw commodity by the corresponding processing factor
IEDI	international estimated daily intake
IESTI	international estimated short-term dietary intake
ISO	International Standards Organization
IUPAC	International Union of Pure and Applied Chemistry
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
LOQ	limit of quantification
MRL	maximum residue limit
MRLP	Maximum Residue Limit for Pesticides
MRLVD	Maximum Residue Limit for Veterinary Drugs
NOAEC	no-observed-adverse-effect concentration
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
OECD	Organisation for Economic Co-operation and Development
PHI	pre-harvest interval
P_{ow}	octanol–water partition coefficient
ppm	parts per million
RAC	raw agricultural commodity
RIVM	Netherlands National Institute for Public Health and the Environment
STMR	supervised trials median residue
STMR-P	supervised trials median residue in a processed commodity calculated by multiplying the STMR of the raw commodity by the corresponding processing factor
TMDI	theoretical maximum daily intake
TRR	total radiolabelled residue, total radioactive residues
UNEP	United Nations Environment Programme
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
WHO	World Health Organization

ANNEX
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