CHAPTER 8: MAXIMUM RESIDUE LIMITS FOR PESTICIDES AND VETERINARY DRUGS

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8.1 Introduction

MRLs for pesticide residues and residues of veterinary drugs are the maximum concentrations of residues to be legally permitted in or on a food. MRLs for pesticides may also be applicable to animal feeds. MRLs are set by the CAC, acting as the risk manager. Draft MRLs for adoption by the CAC are elaborated by the relevant Codex committees, the CCPR and the CCRVDF, on the basis of scientific expert advice provided by the risk assessors—i.e. JMPR) and JECFA, respectively. The scientific advice developed by JMPR and JECFA aims to provide maximum residue levels for individual crops, plant and animal products, based on the results of scientific studies, so that these levels can be used by the relevant Codex committee to develop the draft MRLs, which may be adopted by the CAC.

In 2005, FAO, the National Institute for Public Health and the Environment of the Netherlands (RIVM) and WHO held a workshop entitled “Updating the Principles and Methods of Risk Assessment: Maximum Residue Levels (MRLs) for Pesticides and Veterinary Drugs” (FAO/WHO, 2006). This chapter is based on the outcome of that workshop.

8.2 Overview of current principles and practice of JMPR and JECFA for residue evaluation

8.2.1 JMPR assessment processes for pesticide residues

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 FAO Panel on Pesticide Residues in Food and the Environment evaluates pesticide residue data resulting from pesticide use according to GAP to estimate maximum residue levels in food and feed commodities. Under GAP, a pesticide is used for effective pest control, but leaves 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.

The substance of interest is identified by systematic and common names, CAS numbers and chemical formulae. 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 (livestock) and crop metabolism studies are the prime determinants of the residue definition in food and feed commodities. Radiolabelled substances are 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.

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 define 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.

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 used for monitoring and enforcement and for dietary intake estimates.
Pesticide residue definitions are established for MRL enforcement purposes and for dietary exposure assessment. Residues of parent substance and transformation products are usually expressed as equivalents of the parent substance.

For dietary exposure purposes, it is desirable to include pesticide metabolites and photolysis products that have toxicity properties similar to those of the parent substance. 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 they are 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; otherwise, anomalies in enforcement work will occur.

JMPR accepts national registered uses of pesticides as 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 preharvest 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 (i.e. median of the valid residue data, one point from each trial) and HR (i.e. 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 CCPR for use as an MRL. The STMR and HR are used in long-term and short-term dietary exposure estimates.

JMPR also requires data from food processing studies on pesticide residues to:

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

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 residue levels, HRs and STMRs are based on whichever is higher.

Food residues resulting from the use of external animal pesticide treatments may also need to be taken into account. Trials for these in livestock 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.
For chronic exposure assessment, estimates of likely pesticide residue levels in food are based on the STMRs from the supervised trials and food processing studies and long-term food consumption. Up until 2005, the JMPR used average daily per capita food consumption estimated for each commodity based on the five regional diets (Middle Eastern, Far Eastern, African, Latin American and European) from the GEMS/Food derived from FAO food balance sheets. From 2006, the five regional diets have been replaced by the GEMS/Food consumption cluster diets. The chronic intake is calculated as the sum of intakes for each food commodity (residue × food consumption) and compared with the ADI.

For short-term exposure assessment, 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 such 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 ARfD.

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

The JMPR procedures for recommending MRLs are summarized in Figure 8.1.

Figure 8.1. JMPR evaluation of residue data and recommendation of MRLs

8.2.2 JECFA assessment processes for veterinary drugs

The WHO publication Principles for the Safety Assessment of Food Additives and Contaminants in Food (WHO, 1987) describes the basic principles applied also in the assessment of veterinary drug residues in food. JECFA has been further developing its risk assessment principles for residues of veterinary drugs in foods since the first meeting devoted specifically to this topic in 1987 and has applied conservative approaches and principles to the assessment of residues of veterinary drugs. Veterinary drug MRLs (also called MRLVDs) are always derived with reference to the ADI. JECFA develops recommendations for MRLs, based on chronic intake estimates calculated from the median residue levels and a theoretical food basket (consisting of 300 g muscle, 100 g liver, 50 g kidney, 50 g fat, 1500 g milk, 100 g eggs and 20 g honey), to estimate a conservative daily intake of residues, known as the EDI. This estimate is then compared with the type and amount of residue considered to be without toxicological, pharmacological or microbiological hazard for human health, as expressed by the ADI. The formerly used TMDI utilized the MRL per se as the point estimate, which is a single value representing the upper limit of a high percentile of the distribution of residues. JECFA concluded at its sixty-sixth meeting (WHO, 2006) that this method was not realistic and that all concentrations in the distribution of residues should be considered in the estimation of intake.

In addition to specific residue data, JECFA also considers other factors, such as GVP and the availability of suitable analytical methods for determining residues in food animal tissues. Thus, recommended MRLs may be more conservative numerical values than those theoretically leading to the highest estimated daily intakes of residues compatible with the full ADI. If, for example, the levels of residues estimated from supervised trials, when the drug is administered according to good animal husbandry practice, are below those considered toxicologically acceptable, then the levels determined by good practice will dictate the acceptable residue level recommended by the Committee, provided that practical analytical methods are available for routine residue analysis. If the residues found in practice exceed those determined to be acceptable from the toxicological evaluation and consumption data, then drug use in the food-producing animals may need to be modified to reduce residue concentrations in edible tissues to acceptable levels. Possible modifications include extending
the withdrawal period and changing the drug dosage, form or method of delivery (WHO, 1988).

JECFA requests detailed pharmacological, toxicological, drug metabolism and other related studies to characterize the specific molecules for toxicological evaluation. Generally, identified metabolites that contribute 10% or more of the total residues are candidates for toxicological evaluation. However, in some instances, metabolites consisting of less than 10% of the total residues have been considered.

Microbiological risk has always been addressed by JECFA in its evaluations of substances with antimicrobial activity, and procedures for establishing an ADI on the basis of an antimicrobial NOEL have been developed. The assessment depends on whether or not residues of antimicrobial agents ingested via food of animal origin pose a danger to human health by selective pressure on the intestinal flora, thus favouring the growth of microorganisms with natural or acquired resistance. A decision-tree approach for the evaluation of antimicrobial veterinary drugs was introduced by JECFA at its forty-fifth meeting in 1995 (WHO, 1996) and later adopted at its fifty-second meeting in 1999 (WHO, 2000) (see section 4.12). Similar approaches have been subsequently developed and used by several regulatory authorities. In the interest of harmonization of methods, VICH developed a guideline, which was finalized in 2004 (VICH, 2004). The VICH guideline was a refinement of the JECFA approach, and, in recognition of the importance of international harmonization, the Committee agreed at its sixty-sixth meeting (WHO, 2006) to incorporate the VICH guideline in future assessments to ensure consistency and transparency in the determination of microbiological ADIs.

Additional specific data requirements for the consideration of MRLs on the basis of the ADI include authorized mode of administration, dose and formulation, toxicodynamic, toxicokinetic, metabolism and residue depletion studies. The above data are requested for at least a standard set of edible tissues of the food animal species for which MRLs are to be set, as well as for milk, eggs and honey, if applicable. JECFA also reviews the comparative metabolism between laboratory animals and food animals to determine qualitative or quantitative similarities or differences in metabolites across species.

JECFA uses residue depletion studies with radiolabelled parent drug as well as additional studies with unlabelled parent drug in intended target animal species for recommending MRLs in raw commodities of animal origin. The derived MRLs are defined on the basis of a marker residue substance (a substance with a known quantitative relationship to the total residue of concern). If MRLs cannot be recommended for every commodity of interest, JECFA attempts to include at least appropriate target tissues for regulatory residue analysis of both domestically marketed products and products moving in international trade. Dose treatments in such depletion studies should always include the maximum approved dose, administered in the commercial formulation and under the approved conditions of use. Residues are generally determined in several edible tissues and products, as appropriate for the intended use (e.g. in muscle, liver, kidney and fat of slaughter animals as well as in milk and eggs). These studies also have to provide the necessary information on all types of residues formed, such as free, conjugated and bound residues. For substances with an ADI derived from 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. Thus, the default assumption is that there may be dose additivity (see section 7.7). Similar considerations apply to substances with a microbiologically defined ADI.

JECFA may make full recommendations for MRLs of a veterinary drug in appropriate food animal species and tissues on the basis of a permanent ADI and adequate residue data. Where a suitable database is available, statistical approaches to estimate MRLs
may be used. Temporary MRLs may be recommended either when there is a full ADI but adequate residue and/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 also does not recommend MRLs when the required conditions of use would not be compatible with the GVP established by national authorities or when estimated chronic dietary intake of residues (see below) would substantially exceed the ADI.

In the context of recommending MRLs, JECFA carries out estimates of long-term (chronic) dietary exposures to residues of veterinary drugs using point estimates of the consumption of various commodities—depending on the use of the drug. These estimates are multiplied with a suitable point estimate of the concentration of total residue of concern in the given commodities, and the results are summed up for the relevant theoretical food basket. JECFA does not use acute dietary exposure estimates for residues of veterinary drugs. Assessment of dietary exposures to residues of veterinary drugs in food is discussed in detail in chapter 6 and will not be further discussed here. Similarly, the comparison of dietary exposure estimates with health-based guidance values such as the ADI (risk characterization) is discussed in chapter 7.

JECFA has noted on occasions that residues at injection sites may exceed the recommended MRL for the tissue(s) concerned at practical withdrawal times; however, 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 estimated daily intake. To assess the safety implications of residues at the injection site, JECFA requires information regarding drug dose, formulation, time elapsed since injection and concentrations of residues observed under standardized conditions of sampling. In order to facilitate the review of sponsor-generated dossiers, the Committee has accepted a sampling procedure laid down by both the European Medicines Agency (EMEA) and the USFDA. It was noted that the EMEA has recently modified its sampling procedure, which 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).

The JECFA procedures for recommending MRLs is summarized in Figure 8.2.
8.2.3 Comparison of JMPR and JECFA approaches
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
- GAP or GVP.

Table 8.1 compares the options used by JECFA and JMPR in recommending maximum residue levels.

Table 8.1: Options used for recommending maximum residue levels: a comparison of JECFA and JMPR evaluations

<table>
<thead>
<tr>
<th>JECFA</th>
<th>JMPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>recommended MRL (no request for additional data)</td>
<td>recommended MRL (no request for additional data)</td>
</tr>
<tr>
<td>- may be based on toxicological, microbiological or pharmacological ADI</td>
<td>- may be based on a sufficient number of supervised field trial data or adequate livestock feeding studies</td>
</tr>
<tr>
<td>temporary MRL</td>
<td>temporary MRL</td>
</tr>
<tr>
<td>- temporary ADI</td>
<td>- temporary ADI</td>
</tr>
<tr>
<td>- temporary due to residue or method deficiencies</td>
<td>- temporary due to residue or method deficiencies</td>
</tr>
</tbody>
</table>
JECFA  |  JMPR

- MRLs unnecessary or not specified
  (situations with a wide margin of safety or taking into consideration endogenous levels of the substance)

- 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.

The group of spices is a special case where the 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 of samples 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.

JMPR compares the long-term intake assessment, the IEDI, with the ADI, whereas the IESTI is compared with the ARfD (see also chapter 6 on dietary exposure assessment). JECFA compares the long-term intake assessment, the EDI, with the ADI and does not consider acute intakes.

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. In such cases, JECFA will not generally recommend MRLs to CCRVDF.

To summarize, 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, such as allergenicity, 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 GAP, 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.
8.3 Identification and description of residues and methods

8.3.1 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 CAC 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.

Thus, the definition of a pesticide residue and a veterinary drug residue are essentially the same. The definition for “pesticide residue” differs from the definition for “residues of veterinary drugs” by the addition of the phrase “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 or to carrier or delivery devices.

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 8.2.

### Table 8.2. Identity and physicochemical properties: data used to establish identity of substances by JECFA and JMPR

<table>
<thead>
<tr>
<th>JECFA</th>
<th>JMPR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Identity</strong></td>
<td><strong>Identity</strong></td>
</tr>
<tr>
<td>Chemical name</td>
<td>Chemical name</td>
</tr>
<tr>
<td>- IUPAC</td>
<td>- IUPAC</td>
</tr>
<tr>
<td>- CAS</td>
<td>- CAS</td>
</tr>
<tr>
<td>CAS registry number</td>
<td>CAS registry number</td>
</tr>
<tr>
<td>Synonyms (includes common and proprietary names)</td>
<td>Synonyms (includes common and proprietary names)</td>
</tr>
<tr>
<td>Structural formula</td>
<td>Structural formula</td>
</tr>
<tr>
<td>Molecular formula</td>
<td>Molecular formula</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>Molecular weight</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Physiochemical properties</strong></th>
<th><strong>Physiochemical properties</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical appearance (state, colour)</td>
<td>Physical appearance (state, colour)</td>
</tr>
<tr>
<td>Odour</td>
<td>Odour</td>
</tr>
<tr>
<td>Solubility in water</td>
<td>Solubility in water (including pH effects)</td>
</tr>
</tbody>
</table>
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 substance. 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 substance 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 stereoisomers are involved, where the relative proportions of the isomers should be given. 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 dibenzo furans, is also stated. Mass balance should typically be ≥98%. JECFA generally does not request identification of minor 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, particularly the information on volatility, partition coefficient, hydrolysis and photodegradation, not only helps 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.

8.3.1.1 Marker residue
The CAC (2003) 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”, 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 drug labelled with a radioactive isotope. The
results of the determinations of total residue (total radioactivity) are compared with the
concentrations of marker residue.

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
MRLVDs recommended by JECFA will not result in chronic intakes exceeding the ADI.

JMPR and the CCPR use an approach similar to that used by JECFA and the
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, degradation products 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 that can best indicate a
possible misuse of the pesticide and that also can be detected and measured by a broad base
of national laboratories. These analytes typically include residues that are easy to measure
(preferably using a multiresidue method) and that 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 to be referred to in establishing the MRLs for a pesticide based on the
criteria that it is simple (preferably a single substance) 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 substances. 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; a common MRL
is established for these parent substances, 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, 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 substances. 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).

8.3.1.2 Definition of residues for dietary intake

In 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 equivalents of the parent substance. For dietary exposure assessment purposes, it
is desirable to include metabolites and photolysis products that have toxicity properties
similar to those of 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 STMR and 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. Factors are derived to reflect the ratio between the marker residue and total residue. These factors are then used to adjust the concentrations of marker residue for each edible tissue to total residues of toxicological concern in the calculation of the EDI. The comparison of the EDI to the ADI is a risk assessment step that ensures that the ADI is not exceeded. If the EDI exceeds the ADI, the MRLs are adjusted in an iterative process to lower concentrations and the calculation is repeated to ensure that the corresponding EDI is below the ADI.

JECFA recognizes that the use of veterinary drugs in food-producing animals can result in residues that cannot be released from tissues using mild extraction procedures. Such bound residues can also frequently not be fully characterized. 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:

\[
\text{Residues} = \text{Free residues} + \text{bioavailable bound residues}
\]

\[
\text{Bound residue} = \text{Total residue} - (\text{extractable fraction} + \text{endogenous fraction})
\]

\[
\text{Residues} = P_0 + \sum_{n=n_1}^{n_x} (M_n \times A_n) + (\text{Bound residue} \times \text{fraction bioavailable} \times A_b)
\] (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 substance 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 substance 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.

8.3.2 Toxicokinetic 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 food commodities of plant origin are available on WHO and FAO websites. For JECFA, this information is in the call for data

8.3.2.1 Toxicokinetics 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 (see summary in Table 8.3). Metabolites obtained in these studies are qualitatively compared with metabolites identified in laboratory animals to ensure that substances occurring in significant amounts in edible commodities have been included in the toxicological evaluation or to determine 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.

**Table 8.3. Information used for residue definition: a comparison of JECFA and JMPR evaluations**

<table>
<thead>
<tr>
<th>JECFA</th>
<th>JMPR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total residue and metabolism study in livestock</strong></td>
<td></td>
</tr>
<tr>
<td>Study conducted in the target animal species only</td>
<td>Study conducted typically in lactating goats and laying hens or in related species.</td>
</tr>
<tr>
<td>Dosing levels sufficient to see total residue depletion and identify metabolites</td>
<td>Dosing levels sufficient to see total residue (but not necessarily depletion) and identify metabolites</td>
</tr>
<tr>
<td>Route of administration as indicated on the label</td>
<td>Mostly oral route of administration; other routes possible depending on the label use</td>
</tr>
<tr>
<td>Radiolabelled substances, typically 14C to show disposition and distribution of total residues in edible tissues</td>
<td>Radiolabelled substances, typically 14C to show disposition and distribution of total residues in edible and offal tissues</td>
</tr>
<tr>
<td>Same study or similar studies show metabolic profile of the distributed residues in edible tissues</td>
<td>Same study or similar studies show metabolic profile of the distributed residues in edible tissues and identity of metabolites</td>
</tr>
<tr>
<td>Comparative metabolism review to ensure residues in food animal adequately tested in toxicology</td>
<td>Comparative metabolism review to assure residues in food animal adequately tested in toxicology</td>
</tr>
<tr>
<td>Study intended to provide ratio of marker residue to total residues</td>
<td></td>
</tr>
</tbody>
</table>

**Plant metabolism studies**

Not relevant

Radiolabelled substances, typically 14C 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

**Toxicokinetics**

Studies may be conducted in laboratory animals, the target animal and humans

Not relevant
Studies are conducted to address the toxicokinetics 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. Results may be useful in explaining residue characteristics from sustained release (depot) formulations. May be useful in extrapolation of residue data to other species.

The metabolites, degradation and other transformation products have generally been identified and quantified in metabolism experiments with methods typically based on the use of radiolabelled substances. Metabolism studies in laboratory animals, usually in rats, serve to identify mammalian metabolites and to suggest possible times for residue clearance. Livestock metabolism and target animal metabolism studies provide the following information for the residue evaluators at JECFA and JMPR:

- time course of residue concentrations in edible tissues, milk and eggs;
- 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 suggest which metabolites need to be monitored. For some substances, residues in animal tissues, milk and eggs are not detectable even from the use of relatively high doses. In these cases, the metabolism studies may justify MRLs on animal commodities being set at the LOQ and may justify a decision that residue levels in tissues, milk or eggs are set to zero for dietary intake estimations.

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. For a fat-soluble substance, 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 with meat or muscle, which may contain 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 substance 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). The CCRVDF has recommended MRLs for both muscle and fat. This may be inappropriate, because laboratories could analyse both trimmable fat and muscle; however, the residues in meat are influenced by the intramuscular fat content, which 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 studies provide the background understanding for residue behaviour and support interpretation of the residue trials. For example, if the residue is essentially a surface residue, the edible portions of fruits like bananas and oranges should be relatively free of residues. 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, these substances 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.

8.3.2.2 Purpose of livestock metabolism studies for veterinary drug and pesticide evaluation

Metabolism studies in livestock are used to determine the qualitative and quantitative metabolism and degradation of the active ingredient.

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 toxicokinetics studies in the food-producing animals that simulate the conditions of use of the drug in animal husbandry are needed. Additionally, toxicokinetic and metabolic studies in the animal species used for toxicological investigation are required.

Livestock metabolism studies fulfil several major purposes:

- to provide an estimate of total residues (and residue depletion for JECFA) in the edible livestock commodities (muscle, fat, 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 exposure calculations and MRL enforcement or residue monitoring;
- to provide a quantitative estimation of the relative distribution of the parent substance 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 that in laboratory animals (such as the rat). JMPR in addition takes into account metabolites formed in plants and, where appropriate, soil.

Studies establish the toxicokinetics 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. Toxicokinetic parameters and variables including “flip-flop” toxicokinetics (situations where the rate of excretion exceeds the rate of absorption; Renwick, 2008), 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 both toxicokinetics and therapeutic activity. 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 toxicokinetics, toxicodynamics and toxicity may differ significantly for the enantiomers. In determining the toxicokinetic properties of a racemic mixture, it is essential to analyse for 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 and “flip-flop” blood kinetics. 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. Except for slow-release depot formulations, risk from exposure 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. JMPR experts have recently developed specific guidance on the setting of ARfDs, including a proposal for a single-dose study protocol suitable for this purpose (Solecki et al., 2005).

Livestock metabolism studies on pesticides should reflect feeding of one substance, 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 total radioactive residues (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.

8.3.2.3 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 TRR in the various 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, because the residue analyst testing a commodity in trade may not know whether the crop is transgenic or non-transgenic. 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 that 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) that have not been identified in laboratory animal metabolism studies are not covered by the initial toxicological database. Separate studies for these substances 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.

### 8.3.3 Analytical methods and residue stability in stored analytical samples

JECFA and JMPR have similar requirements for analytical method validation (see chapter 3). The primary distinction that is applied concerning use of suitable methods is that for methods used in toxicokinetic 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 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.

8.3.3.1 Method performance requirements
JECFA and JMPR have devoted a significant effort to evaluation of analytical methods performance because of the strong role it has in recommending MRLs and have developed analytical methods performance factors that can be used when 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. Adequate method performance testing for microbiological methods is required also. Guidance for analytical method performance factors has been described in individual reports. Based on JECFA and JMPR advice, the 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 made on a case-by-case basis.

For pesticide field trials, the analytes include parent substance 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. The LOQ of the analytical method is taken as the lowest residue level where analytical recoveries were tested and shown to be acceptable. Decisions for rejection of assay validation results due to low recovery are made on a case-by-case basis; in general, analytical recoveries are acceptable in the range 70–130%. 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.

For pesticides, the preferred regulatory method is a multiresidue procedure, even if its recoveries are not as good as those of a substance-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 JMPR uses analytical recovery to assess the acceptability of data, whereas 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).

8.3.3.2 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 the stability of pure standards as normally constituted and in solution and during sample processing. How the data are used can differ 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 should be 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 h prior to analysis, the stability of residues is 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 substances 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 $-20 \, ^\circ\text{C}$ 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. Decisions on acceptable stability criteria (usually $\geq 70\%$) are made 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 $-70 \, ^\circ\text{C}$, may be required. Since a positive result may lead to reanalysis, 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 that may elapse between an initial analysis and a subsequent reanalysis 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.

8.3.3.3 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 8.4.

**Table 8.4. Information on analytical methods and frozen storage stability: a comparison of JECFA and JMPR evaluations**

<table>
<thead>
<tr>
<th>JECFA</th>
<th>JMPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Validation and verification of marker residue methods</td>
<td>Validation and verification of enforcement residue methods</td>
</tr>
<tr>
<td>Usually single (marker) residue</td>
<td>Emphasis on multiresidue method for enforcement, single-residue methods for field trials</td>
</tr>
</tbody>
</table>
8.3.3.4 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.

JECFA also considers other factors when setting MRLs. For example, substances’ antimicrobial activity may interfere with fermentation processes in food production in foods of animal origin, and therefore the MRLs may be set at levels to avoid such interference. Such cases should be described explicitly and transparently in JECFA evaluation reports. It should be noted that MRLs accommodating fermentation processes are set by JECFA for technological reasons following a specific request from the 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 that 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 substance 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 breakdown 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 subsequent 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.

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 substances.
Partitioning of residues in milk into the fat is influenced by the molecular structure of the substance. Furthermore, the fat content of milk is variable. JECFA sets MRLs only on whole milk. JMPR recently decided to recommend two MRLs for fat-soluble substances, one on whole milk and one on milk fat. This is necessary to estimate residues in processed dairy commodities.

**8.3.4 Field study data used to identify the MRL**

**8.3.4.1 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 8.5.

**Table 8.5. Information on livestock feeding studies and animal treatments: a comparison of JECFA and JMPR evaluations**

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

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 3 and 10 times this dose. Veterinary drugs are administered at the maximum label dose and duration.

For pesticides, milk from dairy cows and eggs from poultry are collected daily during treatment and recovery. 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 8.6.

**Table 8.6. Information on direct treatment of livestock: a comparison of JECFA and JMPR evaluations**

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

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.

**8.4 Criteria for selecting data, species and commodities**

**8.4.1 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, as can be seen from comparison of the *Codex Classification of Foods and Animal Feeds* (CAC, 1993a) and the *Codex Glossary of Terms and Definitions* (Residues of Veterinary Drugs in Foods) (CAC, 2003). The relevant points of discussion on definitions are noted below.
8.4.1.1 Meat and muscle
JMPR (CAC, 1993b) 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, 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 does 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 carcases 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”.

8.4.1.2 Milk
The definitions used by JMPR and JECFA are substantially the same.

8.4.1.3 Egg
The definitions used by JMPR and JECFA for eggs are the same. The classification used by JMPR allows for specific commodities (e.g. duck eggs, goose eggs), whereas JECFA uses a wider species grouping for commodities (e.g. poultry eggs).

8.4.1.4 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.

8.4.1.5 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.

8.4.2 Data evaluation based on the application of GAP and GVP
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 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.
GAP and GVP 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 GVP 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 GAP. 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 GVP. In practice, this translates into the consideration of the following types of study data to recommend MRLs for appropriate commodities and species and uses. It should be noted that evaluations and recommended MRLs do not consider off-label use or potential misuses of the substance.

8.4.2.1 JMPR

Information requested and considered by JMPR is specified in the FAO manual (FAO, 2002a; http://www.fao.org/ag/agp/agpp/pesticid/JMPR/Download/FAOM2002.pdf) and comprises the following:

- identity, physical and chemical properties
- metabolism and environmental fate;
- residue analysis and stability of pesticide residues in stored samples;
- use pattern, including major pests or diseases to be controlled; crops and situations; formulations and type of treatment (route of application: e.g. foliar, dip, pour-on);
- number of treatments per season and interval between successive applications; application rate; preharvest interval in days;
- results from supervised trials on crops;
- results from farm animal feeding studies;
- fates of residues in storage and processing;
- residues in food in commerce and at consumption; and
- national MRLs.

8.4.2.2 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;
- toxicokinetic 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 non-radiolabelled 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; and
- 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).

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 JECFA and JMPR.

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

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

8.5 Extrapolation issues
8.5.1 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.

8.5.1.1 Pesticide residues
The term “minor crop” is not defined, although attempts have been made based on consumption and trade data (Harris & 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” (FAO, 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 residue levels on the “minor crop” similar 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 Animal Feeds are the basis for group maximum residue levels. Generally, in order for a group limit to be proposed, the 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 X, except for commodities Y, Z, etc......”.

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 & 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 United States and the EU (Table 8.7). 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 8.7. Extrapolations that can be used in situations of comparable GAP

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

Source: Harris & Gaston (2004)

8.5.1.2 Residues of veterinary drugs

JECFA has routinely recommended MRLs in animal species such as cattle, pigs, sheep, chicken and turkey. JECFA has recommended MRLs for 15 substances in minor species, including horse, goat, deer and rabbit (FAO/WHO, 2004). 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 3 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 TMDIs 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 EDI exceeding the exposure of residues permitted by the ADI for those species.

JECFA generally has based its recommendations on two situations:

- substances 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; and
- substances where MRLs were recommended only by extrapolation of information available for another relevant species.

8.5.1.3 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 in Table 8.8.

<table>
<thead>
<tr>
<th>Species with a full set of available data</th>
<th>Recommended extrapolations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruminant (muscle, liver, kidney, fat)</td>
<td>All ruminants</td>
</tr>
<tr>
<td>Non-ruminant mammals (muscle, liver, kidney, fat)</td>
<td>All non-ruminant mammals</td>
</tr>
<tr>
<td>Chicken and eggs</td>
<td>Poultry and poultry eggs</td>
</tr>
</tbody>
</table>

8.5.1.4 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.

8.5.2 Geographic extrapolation

8.5.2.1 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), which 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), whereas grapes are grown under a variety of conditions, such as crop height, leaf
numbers and plant density (multiple zones).

JMPR concluded that some of the recommendations of the York Workshop (Harris &
Pim, 1999) and Zoning Steering Group (Working Group on Pesticides, 2002) will continue to
be considered as auxiliary advice, but that substantial additional work would be required to
make the recommendations generally applicable as guidance.

8.5.2.2 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
are 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.

8.6 References
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