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Principles and Methods for the Risk Assessment of Chemicals in Food

Chapter 8
MAXIMUM RESIDUE LIMITS FOR PESTICIDES AND VETERINARY DRUGS

A joint publication of the Food and Agriculture Organization of the United Nations and the World Health Organization

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The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organization (ILO) and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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8. MAXIMUM RESIDUE LIMITS FOR PESTICIDES AND VETERINARY DRUGS

For acronyms and abbreviations used in the text, the reader may refer to the list of acronyms and abbreviations at the front of this monograph. Definitions of select terms may be found in the glossary at the end of the monograph.

8.1 Introduction

Maximum residue limits (MRLs) for pesticide residues and residues of veterinary drugs are the maximum concentrations of residues to be permitted in or on a food by national or regional legislation. MRLs for pesticide residues may also in certain cases be applicable to animal feeds. MRLs are set by the Codex Alimentarius Commission (CAC), acting as the risk manager. Draft MRLs for adoption by CAC are elaborated by the relevant Codex committees, the Codex Committee on Pesticide Residues (CCPR) and the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF), on the basis of scientific expert advice, including recommendations on MRLs, provided by the risk assessors—i.e. the Joint Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO) Expert Meeting on Pesticide Residues (JMPR) and the Joint FAO/WHO Expert Committee on Food Additives (JECFA), respectively.

JMPR evaluates pesticide residue data resulting from pesticide use according to Good Agricultural Practice (GAP) to estimate maximum residue levels[1] in food and feed commodities. Under GAP, a pesticide is used for effective pest control, but leaves a residue that is the

[1] JMPR distinguishes between a "maximum residue level", which is a scientific estimate with its attendant uncertainty, and a "maximum residue limit", or MRL, which is equivalent to a legal limit.

smallest amount practicable. Estimated maximum residue levels are recommended to CCPR (the risk managers) for use as MRLs. If the estimated chronic dietary exposure for a pesticide residue exceeds the acceptable daily intake (ADI) or an estimated short-term exposure exceeds the acute reference dose (ARfD), JMPR flags this situation to CCPR, indicating the type of data that may be useful in refining the dietary intake estimates.

JECFA recommends MRLs for veterinary drugs[1] to CCRVDF. The veterinary drugs proposed for evaluation by JECFA should be registered by national or regional authorities, commercially available and used according to the Good Practice in the Use of Veterinary Drugs (GPVD) approved by the registration authorities. CAC defines GPVD as the "official recommended or authorized usage including withdrawal periods, approved by national authorities, of veterinary drugs under practical conditions" (FAO/WHO, 2008b). If MRLs cannot be proposed such that the estimated chronic dietary exposure to a veterinary drug residue remains below the ADI, JECFA does not recommend MRLs.

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: MRLs for Pesticides and Veterinary Drugs" (FAO/WHO, 2006a). This chapter is based on the outcome of that workshop and subsequent considerations by JECFA and JMPR.

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 an understanding of residue behaviour. Residue data requirements

[1] Both JECFA and CCRVDF use the acronym MRL for this limit throughout its stepwise elaboration; however, MRLVD is the acronym of the final standard adopted by CAC on the recommendation of CCRVDF.

and evaluation for JMPR are described in the FAO manual on the submission and evaluation of pesticide residue data for the estimation of maximum residue levels in food and feed (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. 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, Chemical Abstracts Service (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. Substances labelled with radioactive isotopes 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 or other degradation 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 or 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 a supervised trials median residue (STMR) (i.e. median of the valid residue data, one point from each trial) and highest residue (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 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 by a margin sufficient to require an MRL higher than the RAC MRL, it is necessary for JMPR to estimate a maximum residue level for the processed commodity (FAO/WHO, 2004b).

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 HRs and STMRs for feed commodities multiplied by standard animal diets based on Organisation for Economic Co-operation and Development (OECD) livestock feed tables since 2007 (FAO/WHO, 2008a). 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. 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.

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 values are higher from this comparison.

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. Until 2005, 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 Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme (GEMS/Food) derived from FAO food

balance sheets. Since 2006, the five regional diets have been replaced by the 13 GEMS/Food consumption cluster diets. Information on these diets is available on the WHO web site (http://www.who.int/foodsafety/chem/gems/en/index1.html). 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 (see chapter 6, appendix 6.1).

When an estimate of short-term exposure for a pesticide residue in a food commodity exceeds the ARfD, JMPR examines residue data from supervised trials with alternative GAPs to compare those alternative short-term exposures with the ARfD. If an estimated alternative short-term exposure does not exceed the ARfD, JMPR recommends a maximum residue level based on the alternative GAP.

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 (after examination of alternative GAPs).

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

8.2.2 JECFA assessment processes for residues of veterinary drugs

JECFA has developed risk assessment principles for residues of veterinary drugs in foods since the first meeting devoted specifically to this topic in 1987 (FAO/WHO, 1988) and has applied conservative approaches and principles to the assessment of residues of veterinary drugs. 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 estimated daily intake (EDI). The formerly

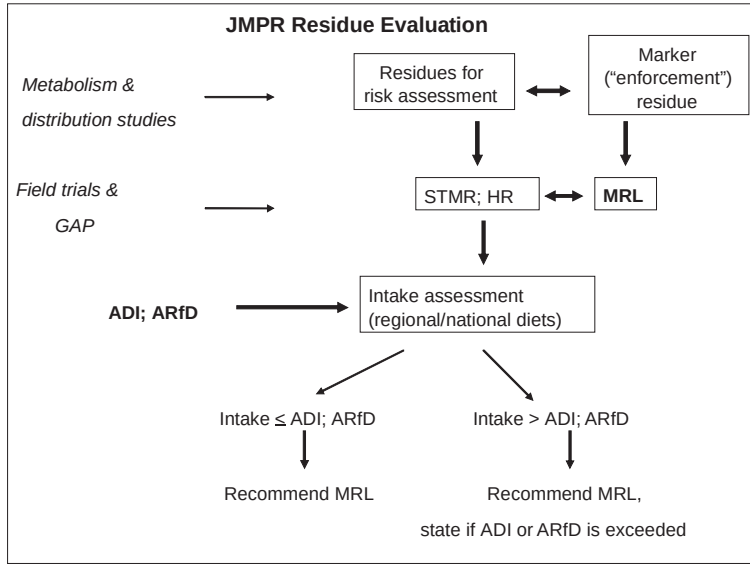

Fig. 8.1. JMPR evaluation of residue data and recommendation of MRLs

used theoretical maximum daily intake (TMDI) utilized the MRL per se as the point estimate for acceptable levels in food, which is a single value representing the upper limit of a high percentile of the distribution of residues, normally the 95th percentile. JECFA concluded at its sixty-sixth meeting (FAO/WHO, 2006b) that this method was not realistic and that all concentrations in the distribution of residues should be considered in the estimation of intake.

In the context of recommending MRLs, JECFA carries out estimates of long-term (chronic) dietary exposures to residues of veterinary drugs in which point estimates of both the amounts of food commodities consumed and the residue concentrations are used (for details, see chapter 6, section 6.3.4.1). The numerical result of this estimation, the EDI, 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 (for details, see chapter 7). JECFA, at its seventieth meeting (FAO/WHO, 2009), confirmed the utility of the EDI as a tool to ensure that intakes of residues resulting from use of veterinary drugs in accordance with GPVD and the recommended MRLs do not exceed the ADI.

The use of the EDI is currently applicable only to the evaluation of chronic toxicity of, and chronic exposure to, residues as reflected by the ADI. JECFA does not yet use acute dietary exposure estimates for residues of veterinary drugs, but the development of such estimates is under consideration.

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 first type of study serves to estimate the time course of the concentration of the total residue of concern and to determine a marker residue substance (a substance with a known quantitative relationship between its concentration and the concentration of the total residue of concern; see section 8.3.1.1). The derived MRLs are defined on the basis of the marker residue substance. The second type of study provides information on the time course of the concentration of the marker residue in raw commodities of animal origin under approved practical conditions of use. Information from these studies is used in the derivation of MRLs and for the estimation of dietary exposure using suitable time points on the residue depletion curve. Thus, MRLs are expressed as *concentrations of a marker residue*. However, daily intakes are estimated as *amounts of total residue* of concern ingested by a person. Therefore, the selected point estimate of marker residue concentration has to be converted to equivalents of total residue and multiplied by the point estimate of the amount of the commodity consumed. The details are described in section 6.3.4.1 in chapter 6. The relationships among empirical residue depletion data, MRL, depletion/withdrawal times and EDI are illustrated in Figure 8.2.

MRLs are generally recommended for several edible tissues and products, as appropriate for the intended use—for example, for muscle, liver, kidney and fat of slaughter animals, for fat and skin of poultry (and, where appropriate, of pigs) in natural proportions, for muscle and skin of fish in natural proportions, as well as for milk, eggs and honey. 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

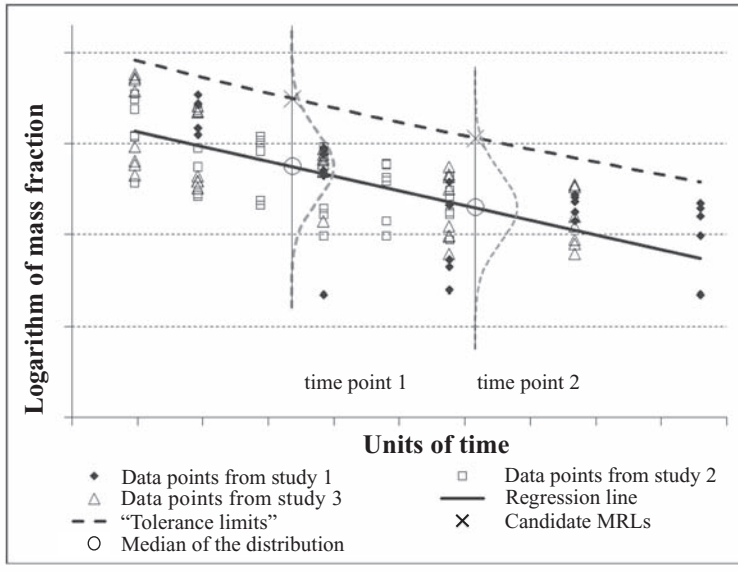

Fig. 8.2. Basic model for the determination of the MRL and of a point estimate of residue concentration used for the dietary exposure estimate

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 or data show that a metabolite has greater toxicity than the parent drug and therefore needs to be addressed separately. Thus, the default assumption is that there may be dose additivity (see chapter 7, section 7.3). Similar considerations apply to substances with a microbiologically defined ADI (see chapter 5).

In addition to specific residue data, JECFA also considers other factors, such as GPVD and the availability of suitable analytical methods for determining residues in food animal tissues. Thus, recommended MRLs may be numerically lower than the theoretical maximum values compatible with the ADI. If, for example, the

concentrations of residues in edible tissues or products estimated from residue depletion studies, when the drug is administered according to GPVD, are *below* those considered toxicologically or microbiologically maximally acceptable, then the levels observed under GPVD will determine the recommended MRLs, provided that practical analytical methods are available for routine compliance monitoring. If the residue exposure estimates found following GPVD *exceed* those compatible with the ADI, then drug use in the food-producing animals may need to be modified to reduce residue concentrations in edible tissues to acceptable concentrations before JECFA can recommend MRLs. Possible modifications include extending the withdrawal period and changing the drug dosage, form or method of delivery (FAO/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 no-observed-adverse-effect level (NOAEL) 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 (FAO/WHO, 1996) and later adopted at its fifty-second meeting in 1999 (FAO/WHO, 2000) (see chapter 4, section 4.12). In the interest of harmonization of methods, the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) developed a guideline (VICH, 2004) that was a refinement of the JECFA approach, and the Committee agreed at its sixty-sixth meeting (FAO/WHO, 2006b) to incorporate the VICH guideline in future assessments to ensure consistency and transparency in the determination of microbiological ADIs (for details, see chapter 5).

Additional specific data requirements for the consideration of MRLs on the basis of the ADI include authorized mode of administration, dose and formulation, and 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.

The data requirements of JECFA flow from the above summarized requirements of the MRL and include information on authorized conditions of use (e.g. mode of administration, dose and formulation of the commercial product, withdrawal times for edible tissues, discard times for eggs and milk), precise identification and properties of the substance under review and used in tests and studies, detailed pharmacological and toxicological studies in laboratory animals, other special studies as necessary on a case-by-case basis (e.g. microbiological studies) and pharmacokinetic and residue depletion studies in the target species of animal. Typically, a dossier of primary data and descriptions of studies conducted with the drug is provided by a sponsor (the manufacturer) or occasionally by a national authority for review by JECFA. In reaching its conclusions on MRLs, JECFA evaluates all data available to it, including those submitted by the sponsor and those identified in a search of the open literature. The Committee's decisions depend largely on consideration of the primary detailed data. Limited reliance is placed on summary or review data alone, if not supported by relevant primary data (FAO/WHO, 2006a).

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, the above-described statistical approaches to estimate MRLs may be used. In cases where the basic model is not applicable, JECFA uses other approaches on a case-by-case basis to ensure that, if the recommended MRLs are applied, dietary exposure remains within acceptable limits. These may include using the model diet and the ratio of marker to total residues to perform a check that the MRLs recommended would not exceed the ADI. If the dietary exposure estimate exceeds the ADI, the MRLs are adjusted in an iterative process to

lower concentrations, and the calculation is repeated to ensure that the corresponding dietary exposure estimate is below the ADI.

Temporary MRLs may be recommended either when there is a full ADI but adequate residue or analytical method performance data are lacking or when the ADI is temporary. The Committee may recommend MRLs "not specified" or "unnecessary" when there is a very wide margin of safety between dietary exposure to residues and the ADI, also taking into consideration endogenous levels of the substance, where applicable. 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 for uses incompatible with the GPVD established by national authorities.

JECFA has noted on occasions that residues at injection sites may exceed the recommended MRL for the tissue or tissues concerned at practical withdrawal times. To assess the safety implications of residues at the injection site, JECFA requires information on concentrations of residues observed in injection sites sampled under standardized conditions. The Committee has accepted a sampling procedure required by both the European Medicines Agency (EMEA) and the United States Food and Drug Administration (USFDA). It was noted that the EMEA has recently modified its sampling procedure, which now requires, in addition to a core sample of 500 g, a second sample of tissue surrounding the core sample in order to confirm the quality and correctness of the original sampling (EMEA, 2004). JECFA assesses the safety of injection site residues by comparison with an ARfD (e.g. carazolol in injection sites, evaluated at the fifty-second meeting of JECFA; FAO/WHO, 2000), although JECFA has not yet determined consumption figures for estimating acute intakes. Therefore, the consumption figure for muscle normally used for estimates of chronic intake is also used in these cases, and injection site tissue replaces muscle tissue for the estimation of acute intakes. 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 (chronic) daily intake expressed by the EDI.

The JECFA procedures for recommending MRLs are summarized in Figure 8.3.

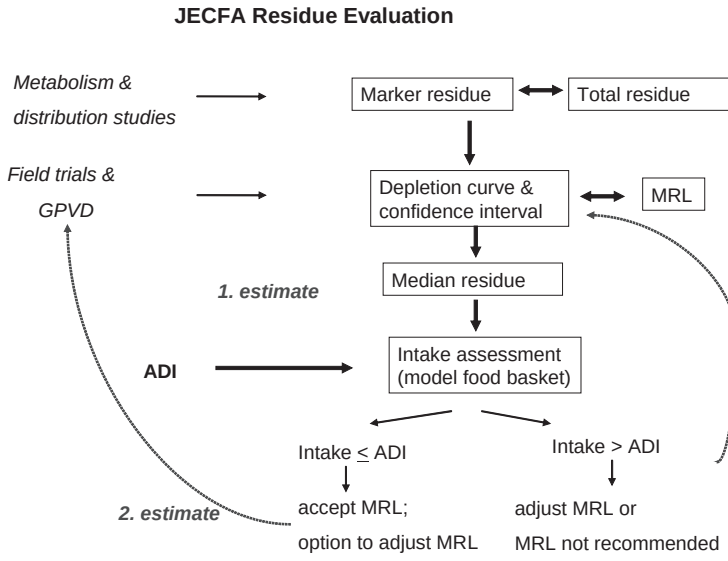

Fig. 8.3. JECFA evaluation of residue data and recommendation of MRLs

8.2.3 Comparison of JMPR and JECFA approaches

The factors considered for the establishment of MRLs include:

- residue definitions;
- animal species or crop;
- commodities (significance in trade and consumption);
- adequacy of the methods used in all studies and tests;
- analytical methods suitable for enforcement purposes; and
- GAP or GPVD.

Table 8.1 compares the options used by JECFA and JMPR in recommending MRLs.

When an ADI has been established but no residues have been detected in a commodity in any of the residue studies using validated methodology, JECFA and JMPR may establish MRLs based on the limit of quantification (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.

Table 8.1. Options used for recommending MRLs: a comparison of JECFA and JMPR evaluations

JECFA	JMPR
• recommended MRL (no request for additional data) - may be based on suitable residue depletion studies, GPVD or requirements of food technological processes, and compatible with toxicological, microbiological or pharmacological ADI	• recommended MRL (no request for additional data) - may be based on a sufficient number of supervised field trial data or adequate livestock feeding studies
• temporary MRL due to: - temporary ADI - deficiencies in residue studies or in analytical methods	• temporary MRL due to: - temporary ADI - deficiencies in residue trials or in analytical methods
• MRLs “unnecessary” or “not specified” (situations with a very wide margin of safety or taking into consideration endogenous levels of the substance)	
• MRLs as guidance limits (in situations where residue concentrations in tissues are below the LOQ of the validated analytical method)	
	• EMRL relating to contamination 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 due to: - no ADI established - significant deficiencies in residue or analytical method data	• no MRL recommended due to: - no ADI established - significant deficiencies in residue or analytical method data

DDT, dichlorodiphenyltrichloroethane; EMRL, extraneous maximum residue limit; LOQ, limit of quantification.

The group of spices is a special case where CCPR agreed to consider MRLs estimated from monitoring data (FAO/WHO, 2004a). The 2004 JMPR used spice 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 (FAO/WHO, 2004c). Such an MRL has no direct relation to a registered or approved use of the pesticide.

JMPR compares the long-term intake assessment, the international estimated daily intake (IEDI), with the ADI, whereas the short-term intake assessment, the international estimated short-term intake (IESTI), is compared with the ARfD (see also chapter 6 on dietary exposure assessment). In cases where the predicted chronic exposure exceeds the ADI or the short-term exposure exceeds the ARfD, even after consideration of alternative GAPs, JMPR will report this fact to CCPR and may, if possible, indicate the data necessary to allow refinement of the risk characterization. In similar cases, JECFA will not generally recommend MRLs to CCRVDF.

To summarize, JMPR recommends MRLs based on evaluation of residue data to estimate likely maximum residue levels in food commodities resulting from pesticide use according to GAP—that is, 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 residue levels must be safe for the consumer. JMPR estimates long-term and short-term dietary exposures and compares these with the ADI or the ARfD, respectively.

JECFA recommends MRLs based on evaluation of residues resulting from drug use according to GPVD and estimates dietary exposure to residues. It also takes into account other relevant public health risks, such as allergenicity, as well as food technological aspects. MRLs are recommended only if they are compatible with GPVD and do not cause chronic dietary exposure in excess of the ADI.

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 (FAO/WHO, 2008b) 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….
>
> *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….
>
> *Residues of veterinary drugs* include the parent compounds and/or their metabolites in any edible portion of the animal product, and include residues of associated impurities of the veterinary drug concerned.

Thus, the definition of a pesticide residue and a veterinary drug residue are essentially equivalent. 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 as 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.

Most of the differences in requirements for physicochemical properties reflect the concern with environmental fate, which is addressed only 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 certain cases, parameters such as dissociation constant, *n*-octanol–water partition coefficient and photochemical degradation may be relevant for JECFA assessments. In specific cases,

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

JECFA	JMPR
Identity	
Chemical name	Chemical name
- IUPAC	- IUPAC
- CAS	- 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
Physicochemical 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	
Ultraviolet absorbance maximum	
	Vapour pressure
	Volatility (Henry's Law constant)
	Dissociation constant
	n-Octanol–water partition coefficient
	Hydrolysis rate
	Photochemical degradation
	Relative density

IUPAC, International Union of Pure and Applied Chemistry.

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 dibenzofurans, is also stated. Mass balance should typically be ≥98%. JECFA generally does not request identification of minor impurities. However, identification of residue components that represent 10% or more of the total residues of the veterinary drug in the edible tissues is generally required. 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 for 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

CAC (FAO/WHO, 2003b) 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 the 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 concentrations of

total residues (total radioactivity expressed as equivalents of the parent drug) are compared with the concentrations of the marker residue, and the ratio of the concentration of the marker residue to that of total residues can be calculated.

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 to be released for analysis. Not only parent drug, but several metabolites, including releasable bound residues, may possess significant pharmacological, toxicological or antimicrobial properties. However, the marker residue is not necessarily a residue of toxicological or microbiological concern. MRLs recommended by JECFA are expressed as concentrations of the marker residue. The relationship between the marker residue and total residues is used for the conversion of concentrations of the marker residue into concentrations of total residues of concern for the purpose of estimation of dietary exposure.

JMPR and CCPR use an approach similar 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, 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 in which multiple metabolites and degradation or transformation products are present. For each pesticide used on food or feed commodities, JMPR selects the residues 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.

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.

There are rare situations for both veterinary drugs and pesticides in which the same metabolite is formed from several closely related parent substances and could be used as marker residue for all of them. In such cases, JECFA or JMPR may establish individual ADIs for the parent drugs or a group ADI for these substances, as appropriate. However, MRLs recommended for the parent substances are then expressed in terms of a common "marker residue".

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). 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.

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 or other degradation products that have toxicity properties similar to those of the parent substance.

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 their 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 residues at each time point. 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.

JECFA recognizes that the use of veterinary drugs in food-producing animals can result in residues that cannot be extracted from tissues using mild procedures. In certain cases, non-extractable residues may be releasable using more specific or vigorous methods, such as the application of procedures for the release of conjugated residue components, without destroying the compounds of interest. The remaining fraction of the bound radioactivity may partly consist of fragments of the drug incorporated into endogenous compounds (endogenous fraction) that would be of no toxicological concern. Bound residues can frequently not be fully characterized. JECFA has developed a procedure to estimate the dietary exposure to residues of a drug that has a bound residue component (FAO/WHO, 1989). It takes into account the toxicological potency and bioavailability of the residues. Using the parenthetical definitions for residues and bound residues (Residues = free residues + bioavailable bound residues; Bound residue = total residue − (extractable fraction + endogenous fraction), the following equation describes the calculation of the total residue of (toxicological) concern for a given tissue:

$$\text{Residue} = P_0 + \sum_{n=n_1}^{n_x} (M_n * A_n) + (\text{Bound residues} * \text{fraction bioavailable} * A_b)$$

where:

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

Where the endogenous fraction is not known, it should be given a value equal to zero. If the bioavailable fraction of the residues is not known, JECFA considers that a bound residue is of no greater concern than the substance for which the ADI was established, and

therefore this fraction is taken to be equal to 1. In considering the safety of bound residues, JECFA acknowledges that a suitable extractable residue component may be selected as the marker residue used for recommending an MRL if bound residues make up an insignificant portion of the total residue. In these cases, it is not necessary to apply the above calculations. However, where bound residues become a significant portion of the total residues of concern, then the procedure described may be used to assess their safety.

8.3.2 Pharmacokinetic, toxicokinetic and metabolic data used to determine the residue definition

The data requirements for JECFA and JMPR determinations of the residue definition in target species, livestock and food commodities of plant origin are available on WHO and FAO web sites. For JECFA, this information is provided in the call for data for the individual meetings. For JMPR evaluation, detailed guidance is available in chapter 3 of the FAO manual on the submission and evaluation of pesticide residue data for the estimation of maximum residue levels in food and feed (FAO, 2002a).

8.3.2.1 *Pharmacokinetics, 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). The metabolites, degradation products and other transformation products are typically identified and quantified with methods based on the use of substances labelled with radioactive isotopes. Metabolites obtained in these studies are qualitatively compared with metabolites identified in laboratory animals, usually rats, to ensure that substances occurring in significant amounts in edible commodities have been included in the toxicological testing or to determine whether additional testing of individual metabolites is necessary. Metabolism studies in laboratory animals also serve to identify mammalian metabolites and to suggest possible time courses for clearance of residues.

For pesticides, a residue definition in food and feed of plant origin is obtained from plant metabolism, confined rotational crop and soil metabolism studies. Soil 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

JECFA	JMPR
Total residue and metabolism study in livestock	
Kinetic study conducted in the target animal species only	Study conducted typically in lactating goats and laying hens or in related species
Dosing levels sufficient to see total residue depletion and identify metabolites (normally at recommended dosing levels)	Dosing levels sufficient to see total residue (but not necessarily depletion) and identify metabolites
Route of administration as indicated on the label	Mostly oral route of administration; other routes possible depending on the label use
Radiolabelled substances, typically ^{14}C (^{3}H if higher sensitivity is required), to show disposition and distribution of total residues in edible tissues (including milk and eggs as appropriate), body fluids and excreta	Radiolabelled substances, typically ^{14}C, to show disposition and distribution of total residues in edible tissues (including milk and eggs, as appropriate)
Same study or similar studies show metabolic profile of the distributed residues in edible tissues	Same study or similar studies show metabolic profile of the distributed residues in edible tissues and identity of metabolites
Comparative metabolism review to ensure that residues in food animal are adequately tested in toxicology	Comparative metabolism review to ensure that residues in food animal are adequately tested in toxicology
Study intended to provide ratio of marker residue to total residues	Not relevant
Plant metabolism studies	
Not relevant	Radiolabelled substances, typically ^{14}C, to show disposition and distribution of total residues in edible commodities
Not relevant	Same study or similar studies show metabolic profile of the distributed residues in edible tissues and identity of metabolites
Not relevant	Comparative metabolism review to ensure that residues in plants are included in mammalian toxicology testing

Table 8.3. ***(Continued)***

JECFA	JMPR
Pharmacokinetics	
Studies may be conducted in laboratory animal species and target animals; if available, data from studies in humans are also considered	Metabolism studies are conducted in lactating ruminants and laying hens
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 in laboratory animal species	Metabolism studies provide information on the identity and disposition of residues in edible tissues, milk and eggs
Results are informative for assessment of differences in residue profiles depending on formulation, route of administration, dosing regimen and species specificity	For external treatment of animals, studies with formulated products used according to approved label instructions provide information on resulting residue levels
Results may be useful in explaining residue characteristics from sustained release (depot) formulations	Not relevant
May be useful in extrapolation of residue data to other species	Results from feeding studies in cattle and hens are extrapolated to mammalian and poultry livestock, respectively

In summary, livestock metabolism and target animal metabolism studies provide the following information for the residue evaluations by JECFA and JMPR:

- nature of the residue in edible tissues, milk and eggs;
- residue distribution in edible tissues, milk and eggs;
- time course of residue concentrations in edible tissues, milk and eggs; and
- information on fat solubility of residues.

JECFA and JMPR consider the results of the animal metabolism studies to be the prime determinant of residue definition in animal commodities and use the results to 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 edible 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 basis of 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). JECFA may recommend MRLs for both muscle (without trimmable fat) and fat (for details on definitions, see section 8.4.1.1). These residue definitions for muscle and fat were maintained at the sixty-sixth meeting of JECFA (FAO/WHO, 2006b). The residue control systems should take the differences between the JMPR definition of meat (may contain adhering fat) and the JECFA definition of muscle (which does not contain trimmable fat) into account. However, even if trimmable fat is removed, the residues of fat-soluble substances in muscle are influenced mainly 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 treatment.

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

Metabolism studies in livestock are used to qualitatively and quantitatively determine the 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 veterinary drugs in food by JECFA, appropriate metabolism and toxicokinetic studies in the food-producing animals that simulate the conditions of use of the drug in animal husbandry are needed. Additionally, toxicokinetic and metabolism studies in the animal species used for toxicological investigation are required.

Livestock metabolism studies fulfil several major purposes:

- to estimate total residues and their major components (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 residues to be considered for both dietary exposure calculations and MRL enforcement or residue monitoring;
- to estimate 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.

Toxicokinetic studies with the formulated drug product in healthy animals of each of the target species should be designed to determine the rate and extent of absorption of the active substance and its distribution, metabolism and excretion, including identification and quantification of major metabolites. The proportion of the administered dose eliminated by metabolism (usually by liver) and excretion (in urine and faeces) is also determined. Kinetic parameters, including "flip-flop" kinetics (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 or populations based on compartmental or non-compartmental analyses.

Chirality may have a marked impact on both pharmacokinetic behaviour and pharmacodynamic activity. A drug with a single chiral centre exists in two enantiomeric forms, and these enantiomers may have distinct pharmacokinetic and pharmacodynamic properties in vivo. Most registered chiral drugs contain a racemic mixture (50:50) of the two enantiomers. In determining the kinetic properties of such a mixture, it is essential to analyse each enantiomer separately. For both veterinary drugs and pesticides, JECFA and JMPR (respectively) consider it important to consider the possible different properties of enantiomers in the safety assessment and in the process for recommending MRLs.

Injectable sustained-release formulations frequently lead to 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. Hence, the marker residue (if it is not the parent drug molecule) is unlikely to be appropriate for determining residues at the injection site. Risk from exposure to injection site residues is primarily considered short term (acute) in nature (FAO/WHO, 2000), and JECFA has for certain substances established ARfDs based on pharmacological end-points. JMPR has 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 individual substances, usually the parent compound. 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 the plant metabolism studies show that a plant metabolite comprises a major portion of the total radioactive residues on a feed item or that 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 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—that is, to identify the metabolism and degradation products when a pesticide is applied to a plant directly or indirectly, including the relative quantity of metabolites and degradation products in extracts and non-extractable material.

Crop metabolism studies serve the following major purposes:

- to provide an estimate of total radioactive residues 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 serve 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. However, the principles for deciding residue definition remain the same. 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 crop that is planted following the harvest of the target 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). For methods used in pharmacokinetic or 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 analysts involved in that specific study. Most contemporary studies are conducted according to Good Laboratory Practice (GLP) and provide detailed records of the data provided for assessment. JECFA and JMPR always perform an independent review of the validation data for the methods used in the studies. When a method is assessed for its suitability to support MRL enforcement and monitoring of residues, the practicability of use of the method in a routine setting is additionally an important consideration.

Although the requirements for analytical methods and analyte stability determinations are very similar for both JECFA and JMPR, there are some differences in how they evaluate the submitted data. The comparison is summarized in Table 8.4. More details are provided in the following sections.

8.3.3.1 *Method performance requirements*

JECFA and JMPR have devoted significant efforts to evaluating the performance of analytical methods because of the influence it has in recommending MRLs. Both have adopted performance criteria that are used when evaluating methods proposed for monitoring of compliance of commodities with a recommended MRL. Major considerations include accuracy (frequently estimated from analyte recoveries), precision (repeatability and reproducibility), sensitivity (slope of the calibration curve) and selectivity. Use of commonly—usually commercially—available laboratory instruments and use of solvents that do not pose potential environmental or human health risks are

Table 8.4. Information on analytical methods and stability of residues in frozen storage prior to analysis: 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 multiresidue method for enforcement, single-residue methods for field trials
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

also important factors to consider. In addition, adequate method performance testing for specific techniques (e.g. microbiological detection) is required. Guidance for analytical method performance factors has been described in individual reports. Based on JECFA and JMPR advice, CCRVDF and CCPR have established performance criteria for analytical methods for controlling compliance with MRLs (FAO, 2002b; FAO/WHO, 2003a). Target values for method precision and recovery have been established for the residue concentrations typically required to support MRLs.

Evaluations 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. Low recoveries may occasionally be acceptable if the concentration of an internal standard is used as a reference point for quantification of the analyte.

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 accepts adjustments of analytical results for analytical recovery. This is consistent with analytical practices in the respective areas of veterinary drugs and pesticides and with International Union of Pure and Applied Chemistry (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.

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 materials containing predominantly water, oil, protein or starch. 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 those in the fresh sample (FAO, 2002a). When the analytical method determines the "total residues", storage stability studies include not only the total residues, 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 ensure 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 °C over a period of at least 6 weeks to reflect the typical period of time for which a survey sample may be stored awaiting regulatory analysis. Decisions on acceptable stability criteria (usually ≥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 °C, may be required. As a positive result may lead to reanalysis, possibly by a second laboratory, it is preferable that stability is investigated over a prolonged 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 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 residues 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 or dairy commodities.

JECFA also considers other factors when setting MRLs. For example, the antimicrobial activity of substances 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 are described explicitly and transparently in JECFA evaluation reports. It should be noted that MRLs accommodating food technological requirements are set by JECFA following a specific request from CCRVDF.

JMPR evaluates changes in the nature of the residues during commercial food processing and levels occurring in processed plant commodities. It evaluates food processing data on residue behaviour where significant residues occur in plants 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 residue concentrations below 0.1 mg/kg in case residues concentrate in further processing steps (see chapter 3 of FAO, 2002a). The FAO manual (FAO, 2002a) gives general advice on planning and conducting food processing studies.

Effects on the nature of the residues 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 the processing effects of pasteurization, boiling (also baking and brewing) and sterilization. The hydrolysis studies are the basis for the subsequent studies on the levels of residues in processed products. They make it possible to confirm the definition of the marker 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 level in the processed commodity than in the raw product for fat-soluble substances. Partitioning of residues into the fat in milk is influenced by the molecular structure of the substance. Furthermore, the fat content of milk is variable. JMPR decided to recommend two MRLs for fat-soluble substances, one on whole milk and one on milk fat (FAO/WHO, 2004c). This is necessary to estimate residues in processed dairy commodities. Until its sixty-sixth meeting (FAO/WHO, 2006b), JECFA had recommended MRLs only on a whole milk basis, but at that meeting it adopted the JMPR approach. For this purpose, residue depletion studies involving milk should include analysis of the marker residue in both whole milk and the fat portion of the milk.

8.3.4 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 8.5.

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. For pesticides, milk from dairy cows and eggs from poultry are collected daily during treatment and recovery. Collection of residue depletion data in fat is particularly useful for persistent pesticides with slow depletion rates.

Veterinary drugs are administered at the maximum label dose and duration. Sampling of edible tissues, milk and eggs may be appropriate during treatment, depending on the type of product and treatment, but is typically performed less frequently than sampling after the cessation of treatment for veterinary drugs.

Although JECFA (for direct drug treatment) requires only that a veterinary drug is administered according to the approved label instructions, both JECFA (for chronic feed and water treatments) and JMPR consider it important for studies to continue at least until residue levels reach a plateau in relevant tissues and products, such as 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 approaches to these types of studies is presented in Table 8.6.

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

Table 8.5. 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 1×, 3× and 10× expected dietary burden
For chronic feed and water treatment, duration sufficient to reach plateau concentrations of residue in edible tissues and in milk and eggs	Duration typically 28 days with 5- to 7-day recovery period; target is to reach plateau concentrations of residue in milk and eggs
Slaughter intervals and number of animals slaughtered for tissue collection sufficient to estimate maximum concentrations of residues and time of occurrence of maximum residue concentrations and kinetic parameters of subsequent depletion	
Measure residue levels in muscle, fat, liver and kidney (whole milk and eggs, if applicable)	Measure residue levels in the four edible tissues at end of treatment and recovery
Measure residue levels in milk and eggs regularly during and after cessation of treatment	Measure residue levels in milk and eggs collected daily during treatment and recovery period
Residues to be measured are the marker residues, used to derive the MRLs, to estimate the exposure to residues and for the 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

Table 8.6. 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 and method of application at the 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 course to the maximum concentration of residues and subsequent depletion	Slaughter intervals to demonstrate time to and duration of maximum residue concentrations and subsequent depletion
Trials to cover typical breeds in commercial production	Trials to cover typical breeds in commercial production
Measure residues in muscle, fat, liver and kidney (whole milk, eggs and honey, if applicable)	Measure residues in muscle, fat, liver and kidney (whole milk, milk fat for fat-soluble substances and eggs)
Sample muscle and, where applicable, fat from the treatment site	Sample fat from the 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

8.4 Criteria for selecting data, species and commodities

8.4.1 Comparability of definitions for species, tissues and commodities of foods of animal origin

The evaluation of pesticide and veterinary drug residues is similar conceptually in a number of areas, but some details and assumptions are at variance, as can be seen from a comparison of the Codex Classification of Foods and Animal Feeds (FAO/WHO, 2006c) with

the Codex Glossary of Terms and Definitions (Residues of Veterinary Drugs in Foods) (FAO/WHO, 2003b). The relevant points of discussion on definitions are noted below.

8.4.1.1 Meat and muscle

JMPR (FAO/WHO, 2006c) 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 (FAO/WHO, 2003b) 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 (FAO/WHO, 2006c) 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 analysed and MRLs apply to the poultry fat".

JECFA (FAO/WHO, 2003b) refers to *poultry* as "domesticated birds including chickens, turkeys, ducks, geese, guinea-fowls or pigeons".

8.4.1.2 Milk

The definitions for *milk* used by JMPR and JECFA are substantially the same (FAO/WHO, 2003b, 2006c).

8.4.1.3 Eggs

The definitions used by JMPR and JECFA for *eggs* are the same. The classification used by JMPR and JECFA allows for specific commodities (e.g. duck eggs, goose eggs); JECFA may use a wider species grouping for commodities, depending on the available data (e.g. poultry eggs) (FAO/WHO, 2003b, 2006c).

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 the term may also apply in certain cases to invertebrates. Some differences may be in relation to the portion of the commodity to which the MRL applies. For JMPR, the portion of fish is the whole commodity in general after removal of the digestive tract; for JECFA, the portion of aquatic species refers to muscle tissue or muscle and skin in natural proportions (FAO/WHO, 2003b, 2006c).

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 the definition of edible offal considered by JECFA (i.e. liver and kidney). Specific species/food categories for liver and kidney that correspond with the JECFA species/tissue combination also exist in the Codex Classification of Foods and Animal Feeds used by JMPR (FAO/WHO, 2003b, 2006c).

8.4.2 Data evaluation based on the application of GLP, 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 GLP. The principles of GLP define a set of rules and criteria for a quality system applied to the processes and conditions under which non-clinical health and safety studies are planned, performed, monitored, recorded, archived and reported.

GAP and GPVD refer to those uses that are authorized by national registration authorities and 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 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 GPVD. In practice, this translates into the consideration of the types of study data given in the following sections 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 on the submission and evaluation of pesticide residue data for the estimation of maximum residue levels in food and feed (FAO, 2002a) and comprises the following:

- identity and 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, and formulations and type of treatment (route of application: e.g. foliar, dip, pour-on);
- 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;
- direct treatment of animals, if applicable (not covered by animal feeding studies; this refers to a dermal treatment);
- labels of the commercial products authorized, confirming the above use patterns; and
- national residue definitions.

8.4.2.2 JECFA

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

- chemical identity and properties;
- use and dosage forms;
- pharmacokinetic/toxicokinetic and metabolism studies in experimental and target animals;
- residue depletion studies in target animals using substances labelled with radioactive isotopes (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;
- labels of the commercial products authorized, confirming the above use patterns; 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).

8.4.3 Direct external animal treatment—dossier submissions to JMPR and JECFA

Residue studies relating to substances with ectoparasiticidal 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 pesticidal 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

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/WHO, 1997). No definition of "minor crop" is widely accepted, although attempts to produce an acceptable definition have been made based on consumption and trade data (Harris & Gaston, 2004). 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" to be 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 on the submission and evaluation of pesticide residue data for the estimation of maximum residue levels in food and feed (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 (FAO/WHO, 2006c) are the basis for group maximum residue levels.

The approach was amended by JMPR in 2006 (FAO/WHO, 2007) in responding to recommendations from a workshop (FAO/WHO, 2006a). Commodity group MRLs may be proposed on the basis of the following minimum conditions: the pesticide is registered or authorized on the crop group, and relevant and adequate residue data are available for at least one major commodity of the group. However, all relevant data for the commodities of the group should be taken into account.

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, for example, group X, except for commodities Y and Z.

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 of America (USA) and the European Union (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.

8.5.1.2 *Residues of veterinary drugs*

JECFA has routinely recommended MRLs in animal species such as cattle, pigs, sheep, chickens and turkeys. JECFA has recommended MRLs for at least 15 substances in some species, including horses, goats, deer and rabbits, on the basis of data from related species (FAO, 2004). This extension of MRLs from one species with a comprehensive data set to another species without such a data set has been based

Table 8.7. Extrapolations that can be used in situations of comparable GAP[a]

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 subgroup
	Sweet potato or yam to tuber and corm excluding potato subgroup
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 subgroup
Pulses	Any dried bean and dried pea to whole group
Oilseeds	Any three oilseeds to whole group
Cereals	Rice plus any two other cereals to whole group including rice

[a] From Harris & Gaston (2004).

on considerations such as the choice of a marker residue and how similar the MRLs are for the species for which recommendations on MRLs have already been made based on data.

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. When these differences in the ratios exist, harmonization of the MRLs across species could result in the EDI exceeding the exposure to residues permitted by the ADI for those species.

JECFA has based its recommendations on two situations:

- substances with a residue depletion study using unlabelled drug 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 extension of MRLs to other 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 so that the most complete set of MRLs can be recommended.

For substances that have MRLs recommended in one or more species, MRLs could be extended to a related species provided that the metabolic profile is comparable, the marker residue is present in the species for which the extension is considered at sufficient levels for monitoring by validated analytical methods and there is an approved use. Extension of MRLs from one species to another may be reviewed on a case-by-case basis; however, possible examples are shown in Table 8.8.

Table 8.8. Possible extrapolations between animal species

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

8.5.1.4 Honey

It is not appropriate to consider honey as a candidate for extension of MRLs from one species to another because of the difficulty in extrapolating from mammals, birds or fish to bees, as the treatment modalities are not comparable. The factors likely to influence the extent of formation and the kinetic behaviour of residues in honey are more numerous than those for the foods derived from other animal species. The main groups of substances that typically leave residues in edible bee products are antibiotics (residues mainly in honey and royal jelly) and persistent lipophilic acaricides (residues mainly in wax and propolis). The stability of some of these substances in honey may be limited; however, a decrease in concentration over time will be a factor mainly of dilution as more honey is produced. Furthermore, the marker residue concept is not normally or easily applicable.

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 (FAO/WHO, 2004d) assessed the results of work carried out by an OECD/FAO project (OECD, 2003), which reviewed supervised residue trials on a given crop conducted under 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. It was 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. 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 number and plant density (multiple zones). JMPR concluded that some of the recommendations of a workshop examining these issues (Harris & Pim, 1999) and the project steering group (OECD, 2003) would 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 different animal breeds to adequately adapt to different climates, and these animal breeds may have different metabolic profiles. In addition, different climates may result in different 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.

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