CHAPTER 5

JMPR PRACTICES IN EVALUATION OF PESTICIDE RESIDUE DATA

CONTENTS

5.1 INTRODUCTION

The Joint Meeting carries out a scientific evaluation and takes into account all information to which it has access. Better evaluations result from an understanding of the processes of residue behaviour rather than from only an empirical treatment of data. In addition, the available information varies to a great extent. Therefore, the JMPR does not follow rigid rules in its evaluations but considers the submitted information on a case-by-case basis. The basic principles outlined below are followed as far as practical and possible.

As part of the evaluation process the members of the FAO Panel prepare the monographs, including all relevant information concerning the pesticide, and the appraisal summarising the findings, conclusions and recommendations, and giving full explanation and reasoning for them. The monographs and appraisals are prepared in a uniform format, described in the FAO Panel Manual attached as Appendix X, to facilitate access to the required information by the reader. The monographs and appraisals are published by FAO in the series *Pesticide Residues in Food - Evaluations Part I. Residues*. In addition, a short summary of information evaluated and the recommendations for each compound are included in the Report of the JMPR.

The JMPR has recognized the need to explain the basis for its recommendations in full. Information on GAP and data on supervised residue trials are summarized in detail in the monograph and the reasoning behind the conclusions and recommendations is explained, i.e., data are provided in sufficient detail for the reader to understand the basis for the recommendations. The increased volume of the monographs since the early to mid 90s is largely due to the inclusion of more detailed explanations and reflects the increased resources required for the work.

5.2 PHYSICAL AND CHEMICAL PROPERTIES

Data submitted on physical and chemical properties of pure active ingredient are evaluated in order to recognize the influence of these properties on the behaviour of the pesticide during

and after its application on crops or animals. Data on physical and chemical properties are also needed for an understanding of analytical methods.

The volatility of the compound and its stability in water and after radiation from ultraviolet light may considerably affect the disappearance after application.

The solubility of the pesticide is especially of great interest, as the ability of the compound to penetrate plant and animal tissues is dependent on its solubility in water and organic materials, as is its behaviour during processing.

The designation of a residue as either 'fat-soluble' or non-fat soluble is important for MRL-setting purposes and for compliance with relevant standards. The 'fat-soluble' status determines the nature of a sample that should be taken for enforcement analysis.

The distribution of the residue between muscle and fat obtained from livestock metabolism and feeding studies should be the prime indicator of fat-solubility. In some cases the information available on distribution of the residue (parent compound and/or metabolites) from metabolism or feeding studies does not allow an assessment of fat solubility to be made. In the absence of other useful information, the physical property chosen by the JMPR to provide an indication of solubility in fat is the octanol-water partition coefficient, usually reported as log P_{ow}.

It should be noted that there are errors in estimates of log P_{ow} with differences of one unit for the same compound being reported. Different approaches to the development of these data often give different results. Interpretations must recognize these differences.

The partitioning of residues between fat and muscle as a function of P_{ow} can be predicted[24]. The fat tissue/blood partition coefficient refers to the ratio of chemical concentration or solubility in adipose tissue and blood. The solubility of a chemical in adipose tissue or whole blood is equal to the sum total of its solubility in lipid and water fractions of these matrices. The partition constant *k* for fat and muscle can be calculated assuming P_{ow} (octanol:water) has the same value as P_{lw}, the partition constant for lipid and water. Further, if it is assumed that muscle contains 5% lipid with the remainder water and that fat is 80% lipid then:

$$P_{lw} = [\text{lipid}]/[\text{water}] \approx P_{ow};$$

k = [partition coefficient residues in fat:blood]/[partition coefficient of residues in muscle:blood];

$$k = \frac{P_{ow}[\text{fraction lipid}]_{fat} + [\text{fraction water}]_{fat}}{P_{ow}[\text{fraction lipid}]_{muscle} + [\text{fraction water}]_{muscle}}$$

$$k = \frac{(P_{ow} \times 0.8) + 0.2}{(P_{ow} \times 0.1) + 0.9}$$

A plot of log P_{ow} versus predicted partitioning between fat and muscle (Figure 5.1) reveals that partitioning is essentially independent of log P_{ow} for compounds with values greater than 3.

The 2005 JMPR decided to revise the empirical limits recommended by the 1991 JMPR when considering log P_{ow} so that when no evidence is available to the contrary and log P_{ow} exceeds 3, the compound would be designated fat-soluble and when log P_{ow} is less than 3 it would not[25].

[24] Haddad S, Poulin P, Krishnan K. 2000. Relative lipid content as the sole mechanistic determinant of the adipose tissue:blood partition coefficients of highly lipophilic organic chemicals. Chemosphere 40:839-843.

[25] 2005 JMPR Report p. 28

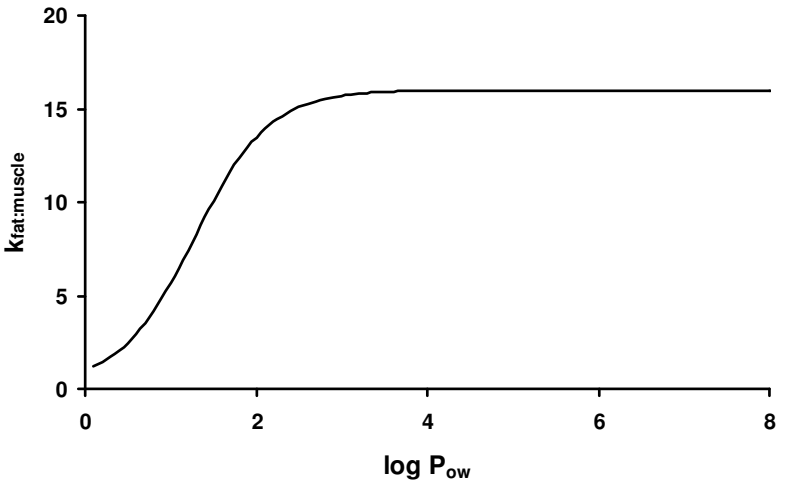

Figure 5.1 Plot of predicted partition of residue between meat and fat based on log P_{ow}
k = concentration ratio of residues in fat/muscle

The variable composition of some residues, e.g., where the residue is defined as a mixture of parent and metabolites, presents a problem since the fat-solubilities of the metabolites may be different from those of the parent compound. In this case, information on the log P_{ow} of each individual metabolite should be considered if available. The relative concentrations within the mixture are also subject to change and, as a result, the tendency of the mixture to partition into fat will also change. The JMPR recognized that many compounds which are neither clearly fat-soluble nor clearly water-soluble required special consideration.

Residue concentrations for the residue definition in both muscle and fat may be determined in the goat metabolism study, where the data allow. These values are compared to the residue concentrations found in the muscle and fat in the corresponding cattle feeding study. Data for milk and milk fat may also be considered as an additional factor regarding the fat solubility of a pesticide, although in some instances the residue may be designated fat soluble in meat but not in milk due to differences in partitioning of the individual components included in the residue definition.

Some worked examples are provided for recently reviewed compounds with log $P_{ow} > 3$ to illustrate different situations and the determinants that may be used to define a residue as being fat-soluble or not fat-soluble for the purposes of JMPR and the estimation of maximum residue levels for meat.

Cyprodinil has a log $P_{ow} = 4$, the residue is defined as parent compound. The residue in goat fat is 75× higher than the residue in muscle in the metabolism study, indicating greater solubility of the residue in fat versus muscle (2003 JMPR). On the basis of the data from the metabolism study, the residue is designated as being fat-soluble.

Flutolanil has a log $P_{ow} = 3.17$ and the residue is defined as the sum of flutolanil and trifluoromethyl benzoic acid for animal commodities. The cattle feeding study indicates that the residues in muscle and fat are comparable (2002 JMPR). On the basis of the data provided, the residue as defined for flutolanil is designated as not being fat-soluble.

Haloxyfop-R-methyl ester (active form) has log $P_{ow} = 4$; haloxyfop methyl (racemate) log $P_{ow} = 3.52$; haloxyfop acid log $P_{ow} = 1.32$; the residue of haloxyfop is defined as haloxyfop esters, haloxyfop and its conjugates expressed as haloxyfop. Results from two cattle feeding studies

have been reported by the JMPR (1996, 2001); the first by the 1996 JMPR showed residues in fat are higher than in muscle while the second reported by the 2001 JMPR showed residues in fat and muscle were comparable. The results can be explained by the analytical methods utilised in the two studies. Metabolism studies showed haloxyfop was present in fat as a non-polar conjugate that is easily hydrolysed under alkaline conditions to yield haloxyfop; in milk fat the conjugates were identified as conjugates of triacylglycerols. The cattle feeding study reported in the 1996 JMPR utilised an alkaline hydrolysis step to extract residues from all tissues while the later study utilised base extraction for muscle, kidney and liver but not fat. An alkaline extraction is an integral part of the analytical method for both plant and animal matrices and it is clear that the later study reported by the 2001 JMPR should be discounted. On the basis of the cattle feeding study where both fat and muscle samples were analysed using an appropriate residue method, the residue should be designated as fat-soluble.

Fipronil has a complex residue definition and the log P_{ow} for fipronil is 3.5 and log P_{ow} for a primary metabolite (MB 46136) is 3.8. The residue concentrations (parent + MB 46136) are 20 to 30× higher in goat fat compared to muscle in the metabolism study (2001 JMPR). In the cattle feeding study, residues (fipronil and MB 46136) were not detected in muscle (< 0.01 mg/kg) following dosing at the equivalent of 0.43 ppm. The individual components of the residue in fat were 3 to 4× higher for fipronil and were 40 to 50× higher for MB 46136 than those in muscle (< 0.01 mg/kg). Following combined dermal and oral administration to cattle, levels of fipronil and MB 46136 were < 0.01 mg/kg in muscle, however fipronil levels in fat were 4 to 6 × higher than the muscle LOQ and levels of MB 46136 ranged from 7 to 77× higher than the muscle LOQ over three fat depots sampled. The data clearly show that the residue as defined (fipronil and MB 46136) is fat-soluble. As is often the case, there are significant differences in residue levels in renal fat compared to abdominal fat illustrating the need for individual fat depots to be analysed in cattle feeding studies.

The above examples demonstrate that log P_{ow} of an individual component of a residue is an initial indicator, however it is not the only factor used to assess fat-solubility.

In order to apply these principles consistently, all residue definitions are re-examined during the periodic review of the compounds.

5.3 METABOLISM AND DEGRADATION OF PESTICIDES AFTER APPLICATION TO PLANTS, ANIMALS AND SOIL

Chemical degradation and metabolism are major mechanisms of disappearance of pesticides after application to plants, animals or soil. The rates of degradation and metabolism are dependent on the chemistry of the compounds and factors such as temperature, humidity, light, surface of the crops, pH of crop liquid and composition of soils. Metabolism studies provide fundamental information on the fate of the compound. Metabolites provide a qualitative or semi-quantitative picture of the composition of the residues, suggest probable residue behaviour, and indicate the distribution of residues within various tissues. The site and level of residues may also depend on whether the compound is absorbed by the leaves or roots of crops, whether it is mobile in the plant, and its persistence and mobility in soil.

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

the metabolite pattern is qualitatively and semi-quantitatively similar. If there are plant or farm animal metabolites which have not been identified as mammalian metabolites in experimental animals, these toxicological end points do not encompass those metabolites. Separate studies dosing with these metabolites may be necessary for assessment of their toxicological properties if significant residues occur in food items.

The information on the composition of the terminal residue is used to assess the suitability of the residue analytical methods for the development of residue data from supervised trials and to decide on the definition of residues.

5.4 ANALYTICAL METHODS

As part of the evaluation process the JMPR regularly assesses the validity of the analytical methods used in the supervised trials, food processing studies and farm animal feeding studies.

Each method is examined, based on its validation data and performance characteristics, for its overall suitability for the purpose intended, the compounds determined by the method and the substrates that may be analysed. Particularly important are the data for analytical recoveries. Method validation is needed on matrices representative of those in the trials and studies. The JMPR estimates the LOQ for the method as the lowest residue concentration where reliable recoveries (usually 70–120%) were achieved. The limit of detection provides an indication of presence of low level resides in various matrices, but as they do not provide quantitative data, they are not taken into account in estimation of residue levels. The JMPR, however, recognises that over time the LOQ may vary or change compared to the value estimated during method validation.

Where data are available the efficiency of the sample extraction steps used in the analytical methods are compared with radiolabel measurements on residue components in samples from the metabolism studies.

5.5 STABILITY OF PESTICIDE RESIDUES IN STORED ANALYTICAL SAMPLES

Residue samples from supervised trials, food processing studies and farm animal feeding studies are routinely stored under frozen conditions for a year or more before laboratory analysis. In such situations freezer storage stability studies are needed to provide assurance that the residues in the stored sample are essentially the same as in the fresh sample. If more than 30% of the residue is lost during storage before analysis, residues from studies involving similar storage periods may not be valid.

The results and conditions of the frozen stored sample testing should be compared with the duration and storage conditions of the analytical samples from the trials to help deciding on the validity of the trial residue data.

The following points are to be noted during evaluation of a freezer storage study (See also section **3**.3.4 "*Stability of residues during storage and sample processing*"):

- design of the study - (intended sampling intervals, replication, number of procedural recovery tests)
- storage vessels (size, material, sealed)
- nature of the samples being tested (commodity, unchopped, chopped or homogenised)

- nature of the residue (single compound or mixed)
- incurred or spiked residue (spiking levels)
- procedural recoveries and variability of procedural recoveries
- temperatures of storage (intended and actual record of temperature).

Procedural recoveries (samples spiked and analysed at the time a stored sample is analysed) should be used to decide on the validity of the batch of analyses. The analytical results for the stored sample should not be adjusted for the procedural recoveries.

In some storage stability study reports the term "% recovery" is used for "% analytical or procedural recovery" and also for "% remaining after storage." To avoid confusion, JMPR evaluations will report the concentration remaining or % remaining after storage for the stored samples and % procedural recovery for the analytical recovery tests.

In many cases simple inspection of the residue data can indicate whether the residues were stable for the intervals tested. Where the result is not so clear because of data scatter or because of marginal stability, further analysis of the data is warranted.

If a first-order decay is assumed, a plot of ln(conc) vs time will provide the disappearance half-life. Half-life = ln(0.5) ÷ slope.

Storage time for 30% loss of residue = 0.51 × half-life = approx 0.5 × half-life.

The validity of residue samples stored for intervals exceeding this time should be questioned.

5.6 INFORMATION ON GOOD AGRICULTURAL PRACTICES (GAP)

An essential element to enable the JMPR to estimate maximum residue levels of pesticides is information on Good Agricultural Practices. The FAO Panel relies on current registered labels for reliable GAP information. The FAO Panel uses the information on national GAPs to identify the likely scenarios which may lead to the highest residues in food or feed (often referred to as the 'critical GAP' or 'maximum GAP'), and relates these uses to the conditions prevailing in the execution of supervised trials. Therefore information on national GAP from those countries in which the supervised trials have been carried out, or from countries in close proximity with similar climatic conditions and agricultural practice is of the utmost importance.

With regard to the required presentation of adequate information on Good Agricultural Practice in the use of a pesticide in a country, the FAO Panel recognized that several countries may apply different pesticide use authorization systems. Some use a rigorous formal product-based registration scheme, while others use less formal authorization approaches. The "authorized safe use" or "approved uses" from the latter countries may still be included in the GAP table provided that the country involved supplies the information on nationally approved uses or authorized safe use. The terms "approved" and "authorized" are understood as GAP information from countries which do not have a full registration scheme, but where there is a form of authorization of use. This distinction recognizes the different terminologies and approaches to GAP authorizations at the national levels and does not imply that one national system is preferred over another.

Registered and approved use of a pesticide may vary considerably from country to country and the use patterns are often very different, especially in regions with great differences in climate. Growing conditions and, naturally, types of crops may also cause differences in the use pattern. According to the definition of Good Agricultural Practice, a pesticide should be

applied in such a way as to leave a residue which is the smallest amount practicable. Residue levels exceeding the smallest amount practicable, due to unnecessarily high application rates ("overdose") or unnecessarily short pre-harvest intervals (PHIs), are contrary to the concept of GAP.

5.7 RESULTS OF SUPERVISED TRIALS

Estimation of maximum residue levels is mainly based on reliable residue data from supervised trials carried out in such a way that treatments in the trials are equivalent to the uses which normally reflect the corresponding critical Good Agricultural Practice.

Where residues derived from the most critical GAP lead to acute intake concern, trials reflecting a less critical alternative GAP are considered for estimation of maximum residue levels.

The importance of reliable data has already been emphasized in the requirements for information and data from trials described in section **3**.5 'R*esidues resulting from supervised trials on crops*'.

The principles followed in evaluating supervised trial data are described in detail in the section in Chapter, 6 '*JMPR Practices in estimation of maximum residue levels*'.

5.8 PROCESSING STUDIES

"Processed food" in connection with Codex MRLs for pesticides refers to products resulting from the application of physical, chemical or biological processes to a "primary food commodity" whereas primary food commodities treated with ionising radiation, washed or submitted to similar treatments are not considered to be processed food in this context. The term "raw agricultural commodity (RAC)" is the same as "primary food commodity."

Originally the main interest for processed foods was on those important in international trade, such as milled cereal grains and other grain products, oil from oilseeds, juices and dried fruit. MRLs were established on these commodities. More recently interest has increased in obtaining better information about the residue levels in other types of processed food, e.g., primary food commodities which are peeled, cooked or baked. Some of those commodities are usually not moving in international trade, but information on the residue levels is essential to allow more refined dietary intake estimates to be conducted. As in the case of residue distributions between edible and non-edible parts of a food commodity, this may have the consequence that higher MRLs are acceptable when it is demonstrated that residues found in the whole commodity are destroyed or depleted through food processing. Experience has shown that residue levels usually decrease during processing, such as peeling, cooking and juicing. However, in other cases the residue level may increase during processing as in the case of oil from oilseeds and olives. Further, in some cases the active ingredient can be transformed during processing into metabolites that are more toxic than the parent compound.

The JMPR is aware that there is a considerable trade in manufactured foods based, for example, on fruits, vegetables, cereals and meat. However, the variety of forms under which the products are offered makes it impossible to recommend MRLs for all possible processed foods. For this reason the JMPR has agreed that in the case of processed foods where residues do not concentrate, MRLs will not be recommended, but for dietary intake purposes, residues present in the processed food are taken into account where possible.

The JMPR frequently estimates maximum residue levels for important processed foods and feeds moving in international trade when residues concentrate in these products at levels higher than in the RAC from which they are derived, e.g., oil, bran and peel. Even when the estimates are not recommended for use as maximum residue limits or when residues do not concentrate in the processed product, the JMPR will continue to record in its monographs the effect of processing on the level and fate of residues in food in order to allow better estimates of the dietary intake of pesticides.

Processing studies are among the critical supporting studies required for the evaluation of a new and periodic review compound. See Chapter 3 section 7, "*Fate of residues in storage and processing*", for the objectives and data requirements.

All the residues (parent and relevant metabolites) determined in the RAC also have to be determined in the processed products. In addition, any degradation products found in metabolism studies which require a separate dietary risk assessment also have to be considered. The residue has to be calculated according to the definition relevant for compliance with MRLs and the estimations of dietary intake.

As a result of the processing studies, it is possible to recognize residue reductions and concentrations and to calculate processing factors for important products.

The processing factor, *Pf*, is defined as the ratio of the residue found in the processed commodity to the residue in the raw commodity before processing.

$$Pf = \frac{\text{residue level [mg/kg] in processed product}}{\text{residue level [mg/kg] in RAC}}$$

Processing factors are very much affected and depend on the processing yield. The characteristics of pesticide residues such as water or fat solubility, the distribution of the pesticide on the commodity, e.g., surface or systemic, or its application in pre or post-harvest treatments are also relevant. Therefore, the processing factor should be considered as a combination of the process and the commodity.

Whenever more than two processing studies have been conducted for a particular pesticide in the same RAC, the median *Pf* would generally provide the best estimate for the processing factor, especially where studies may result in processing factors including both "less than" and real values, or some high unexplainable processing factors.

If the processing factors from two trials are irreconcilable, e.g., 10-fold different, the mean is inappropriate as it would represent neither process. In this case it is preferable to choose one of the values as being representative. The highest processing factor should be chosen as the default (conservative) value if there is no other reason to choose the alternative.

Processing factors may be determined from the RAC at various days after the last application. In this case the results from the shortest PHI, which closely reflects the critical GAP, onward should be taken into account. However, where the processing factors are not different all data can be considered as shown with the example of processing of grape treated with fenhexamid:

PHI (days)	14	21	28–35
Average PF	0.343	0.298	0.366
Median	0.355	0.32	0.36

When residues in the processed commodity are undetectable or < LOQ the calculated processing factor (residue level in RAC ÷ LOQ) should be reported with a "less than" (<) symbol. If residues in the processed commodity are undetectable or < LOQ in several processing studies it may mean that residues in the processed commodity are very low or essentially zero and the calculated processing factors are merely a reflection of the starting residue levels in the RAC. In this case the best estimate of the processing factor is the lowest "less than" value rather than the median of "less than" values.

When residues in the in the RAC are < LOQ but they are concentrated in the processed commodity (level > LOQ), the calculated processing factor (level in processed commodity/LOQ in RAC) should be reported with a "higher than" (>) symbol.

When residues in the processed commodity and in the RAC are both < LOQ (unquantifiable) the study is of no value for deriving a processing factor.

If several studies are available and a step that is routinely used in the processing of that RAC, e.g., cleaning or washing, is omitted in a study, it may be inappropriate to include that study in the calculation of the average processing factor.

5.9 RESULTS OF NATIONAL MONITORING PROGRAMMES

Data from national monitoring programmes are essential for estimation of EMRLs and maximum residue limits for spices. See also sections **6.**11.1 and **6**.11.2 in Chapter 6 on 'Estimation of maximum residue levels, HR and STMR values in spices' and 'Estimation of extraneous maximum residue levels'.

5.10 EVALUATION OF ADDITIONAL INFORMATION

Usually new information on GAP and related data from trials do not cause difficulties if the data received are of the same type and in agreement with data from earlier evaluations. However, information about new developments in the area of metabolism of the compound may be more problematic. Such information may require that the original residue definition be changed, which means that evaluation of old and new data together may be very complicated. Other than in exceptional circumstances, the evaluation of the results of additional metabolism studies, and of supervised trials revealing information on the proportions of the parent compound and significant metabolites can only be carried out at the time of a periodic review when all relevant information is available and taken into consideration in deciding on the definition of the residue.

In a similar way, problems may arise when a residue definition originally included two pesticides of which one of the compounds is also a metabolite of the other, and for toxicological or other reasons the decision is taken that the pesticides must subsequently be determined separately. In such a case old residue data are often inapplicable.

Improvements of analytical procedures may also cause difficulties. If the LOQ is lowered, the old residue data below the original LOQ are difficult to interpret and may be inapplicable and unavailable for later evaluations. In this context, as for new information on the metabolic profile of the compounds, the whole set of data on the compound has to be taken into consideration and decisions have to be taken by the JMPR on a case-by-case basis.

In most of such cases, however, all of the information required for the scientific re-evaluation is not available to the JMPR. Therefore, such complex problems are best and most efficiently handled during the periodic review of the compound for which all relevant original reports are required to be resubmitted and can be taken into consideration.

5.11 RE-EVALUATION OF COMPOUNDS IN THE CCPR PERIODIC REVIEW PROGRAMME

The periodic review programme requires different actions from those for the re-evaluation of additional information, called hereunder normal situation, and those compounds to be evaluated within the periodic review programme must be clearly identified in advance. See also Chapter 3 section 2 "*New and periodic review compounds*".

As discussed in detail in Chapter 3, data submitters should supply all relevant valid information at the time of the periodic review irrespective of whether it has been supplied previously.

The JMPR evaluates all relevant information on periodic review compounds in terms of identity, metabolism and environmental fate (methods of residue analysis, current use patterns (registered and officially authorized uses), supervised residue trials, farm animal feeding studies, and fate of residues in storage and processing, as in the case of a new compound. However, the conclusions and recommendations are somewhat different in periodic reviews and normal reviews.

A periodic review compound, unlike a new compound, already has existing MRL recommendations. Existing MRL recommendations are dealt with differently in a normal review and a periodic review.

Comparison of the data evaluation of a periodic review compound with normal re-evaluation (re-evaluation of some particular information made available to the JMPR) clarifies the major differences.

5.11.1 New and existing MRLs

If no MRL exists for the individual commodity or for the relevant commodity group, there is little difference in the treatment of information supplied for a normal evaluation or for a periodic review.

For an individual commodity subject to an evaluation, if new data are supplied where an MRL already exists the data are evaluated and the MRL may or may not require revision.

In a periodic review, where adequate information is supplied on an individual commodity, the MRL is either revised or confirmed to be relevant to modern GAP.

In a normal evaluation, when information on a single commodity included in a group commodity MRL is received, evaluation would either show that the group MRL could remain or that an individual MRL and a group (with specified exceptions) MRL could be recommended.

In a periodic review when information on only a single commodity included in a group commodity MRL is received it may be necessary to withdraw the group MRL and estimate a single-commodity MRL.

5.11.2 GAP information.

Under normal circumstances if no new GAP information is supplied the MRL would remain. New GAP information may allow previously recorded residue data to be reinterpreted to permit estimation of a new maximum residue level.

In the normal situation where new residue data are to be evaluated, judgement is required on a case-by-case basis to decide whether previously recorded GAP is still valid. GAP information recorded many years ago for some compounds may still be acceptable.

Under the periodic review programme the absence of GAP and residue information becomes significant. For example, if no GAP information is supplied for a particular commodity the JMPR reviewer can assume that there is no GAP for that commodity. Only GAP supplied for the purposes of re-evaluation is considered valid. If no GAP information is supplied, withdrawal of the MRL will be recommended. Similarly, if GAP information is available but insufficient supporting residue data are provided, the MRL may be recommended for withdrawal.

5.11.3 Supporting studies.

Critical supporting studies (metabolism, farm animal feeding, processing, analytical methods and storage stability of analytical samples) are evaluated to assist with the interpretation of data from supervised residue trials, to revise or confirm the residue definition, to validate residue and other trials and provide further information on residues in food as consumed. The FAO Panel may not recommend MRLs for new or periodic review compounds in the absence of critical supporting studies if their omission is not adequately justified.

5.12 DEFINITION OF RESIDUES

5.12.1 General principles

Residue definitions are required to clearly establish the compound or compounds of interest when estimating dietary intake risks associated with the presence of residues in food or feed commodities and also to provide the basis for monitoring of MRL compliance.

A pesticide residue is the combination of the pesticide and its metabolites, degradates, and other transformation products. Although metabolites, degradation products and impurities are included in the definition of pesticide residues, this does not necessarily mean that metabolites or degradation products should always be included in the residue definition for enforcement (MRLs) purposes or for estimation of dietary intake (STMR, HR).

The WHO Panel considers and indicates in its evaluations which metabolites are of toxicological significance and should be included in the dietary risk assessment.

FAO Panel reviewers and the respective reviewers on the Toxicological and Environmental Groups should communicate closely prior to the JMPR meeting on questions such as which metabolites are of toxicological significance.

In tabulating the residue trials data the FAO Panel reviewer should indicate the levels of relevant metabolites separately from those of the parent compound, but in a way which allows subsequent combination, in order to ensure that changes in the residue definition can be accommodated at the Joint Meeting.

If it is recommended that the residue definition for the risk assessment be different from that for enforcement this must be clearly stated in the appraisal.

These two requirements (intake risk assessment and MRL compliance) are sometimes not compatible and residue definitions that are the result of compromise between these competing requirements may sometimes appear arbitrary. For this reason, and because of the various purposes for which they are used, definitions of residues established by national governments often do not agree.

The basic requirements for the definition of residues are:

- The residue definition for MRL purposes should be
    - based on a single compound whenever possible
    - most suitable for *monitoring compliance* with GAP
    - the same for all commodities if possible
- Common moiety residues for MRL purposes should be avoided
- The residue definition for *dietary intake estimations and risk assessment* should include compounds of toxicological interest.

The requirements for the two residue definitions are sometimes not compatible and, as a compromise, various definitions of residues are possible. For some compounds it may be necessary to establish separate residue definitions for MRL enforcement and dietary intake estimation purposes. The residue definition for dietary intake purposes should include metabolites and degradation products of toxicological concern irrespective of their source, whereas the residue definition for compliance with MRLs needs to be a simple residue definition, i.e., indicator molecule, suitable for practical routine monitoring and enforcement of the MRL at a reasonable cost.

Although metabolites, degradation products and impurities are included in the definition of pesticide residues, this does not necessarily mean that metabolites or degradation products should always be included in the residue definition for enforcement (MRLs) purposes or for estimation of dietary intake (STMR). Inclusion of transformation products (metabolites and degradation products) in the residue definition depends on a number of factors, and the decision on whether they should be included is very complex and decisions have to be made on a case-by-case basis.

The metabolites and other transformation products have generally been identified and quantified in metabolism experiments with methods based on the use of labelled compounds. In some cases the methods used for supervised trials are complicated and or require specific extraction and cleanup procedures, sophisticated instrumentation, and consequently do not fit in multi-residue procedures, which increase the cost and limit their application for regulatory analytical work.

Furthermore, residue methods for incurred conjugated metabolites cannot be validated without labelled compound and having access to specialised laboratories, and some countries may experience extreme difficulty obtaining even ‘cold’ metabolites for use as standards in the analytical work. Therefore, inclusion of metabolites in the residue definition, particularly polar metabolites, is not practical for monitoring compliance with GAP. Complicated residue definitions typically require single-residue methods, thus lead to lower number of monitoring and/or enforcement analyses (*vs.* residues that can be analysed using multi-residue methods), as clearly indicated by the results of EU or US monitoring programmes.

It should be stressed that in choosing the appropriate analytes and the analytical method for the testing of the residue trials samples, the manufacturer or sponsor must consider the needs

of both risk assessment and compliance. In practice this will mean generating the data in such a way as to give the flexibility to establish two separate residue definitions where appropriate. In cases where it is likely that a multi-component residue definition will be required for risk assessment purposes, the manufacturer or sponsor should, in testing field trial samples, either:

a. analyse separately for the individual components of the residue, where analytical methods allow, rather than carrying out a total residue analysis,

or

b. if total residue methodology is used to produce data for risk assessment, and the suitable "indicator molecule" can be analysed with a multi-residue procedure, a second series of analyses of the field trial samples should be carried out for the indicator molecule, e.g., parent compound.

This approach allows the risk assessment to be carried out on the toxicologically significant residue components whilst ensuring that data are available to allow a different simple residue definition to be established, where appropriate, for compliance with the MRLs.

In cases where the manufacturer or sponsor has submitted residue trials data in which an analytical method for total residues has been used and it is not possible to identify a suitable simple residue definition for practical routine monitoring and enforcement of the MRL at reasonable cost, the FAO Panel may be unable to estimate MRLs for the compound.

The following examples further illustrate the complexity of the situation.

Several pesticides are metabolized to a compound, which itself is used as a pesticide (example: benomyl → carbendazim), and in some cases, the toxicology is substantially different for the pesticide and the metabolite (example: dimethoate → omethoate). Whenever possible, the parent pesticide and its metabolite(s) used as pesticides should be subject to separate MRLs. Analysing food commodities in trade for the metabolite may provide no information on which compound was used.

Where it is not possible to set separate MRLs because the parent pesticide is degraded rapidly or an analytical method is not available for measuring and distinguishing the parent compounds (examples: ethylene-bis-dithiocarbamates, benomyl → carbendazim, thiophanate-methyl → carbendazim), the MRLs applying to the pesticides concerned can only be determined in terms of the metabolite(s) or conversion products.

Another problem occurs when the metabolite from a pesticide may also originate from sources other than use of the pesticide. In this case, a residue of the metabolite present in a sample is of no use in determining GAP compliance, and the metabolite should not be included in the residue definition for MRL (example; cyromazine → melamine, also prometryn → melamine). Common metabolites for a certain group of pesticides, e.g., triazoles, should also be excluded from residue definitions of individual pesticides.

The JMPR considers the following factors when proposing or revising a residue definition:

- The composition of the residues found in animal and plant metabolism studies.
- The toxicological properties of metabolites and degradation products (for risk assessment).
- The nature of the residues determined in supervised residue trials.
- The fat-solubility.

- The practicality of regulatory analytical methods.
- Whether metabolites or analytes common to other pesticides are formed.
- Whether a metabolite of one pesticide is registered for use as another pesticide
- The definitions of residues already established by national governments and long-established and customarily accepted definitions.
- JECFA marker residue definitions already established for compounds that may leave pesticide residues in animal commodities.

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

Fat-solubility is a property of the residue and is primarily assessed from the partition of the residue between muscle and fat observed in metabolism and farm animal feeding studies. Should this information be insufficient, section 2 in this chapter, "*Physical and chemical properties*" provides guidelines for deciding whether a pesticide is fat-soluble based on the octanol-water partition coefficient. Sampling protocols for animal commodities depend on whether a residue is fat-soluble or not.

The JMPR has for many years included the qualification 'fat-soluble' in the definition of the residues of fat-soluble pesticides, using the expression:

"Definition of the residue: [pesticide] (fat-soluble)"

The 1996 JMPR recommended that 'fat-soluble' should no longer be included in the definition of the residue because 'fat-soluble' is a qualification of sampling instructions and is not relevant to the dietary intake residue definition. In order to avoid confusion while conveying the information that a residue is fat-soluble, the JMPR agreed that a separate sentence should indicate that the residue is fat-soluble.

JMPR policies on residue definitions have evolved over recent years and, therefore, all residue definitions are re-examined during the periodic review of the compounds.

An explanation of the residue definition for each compound is located in the monographs under the section, Residue Analysis. The residue definition should explicitly state if it applies to plant commodities or animal commodities or both.

5.12.2 Principles followed in defining residues for MRLs

The definition of residues for enforcement purposes should be as practical as possible and preferably based on a single residue component as an indicator of the total significant residue - the parent compound, a metabolite or a derivative produced in an analytical procedure. A residue definition for prothioconazole (JMPR 2008) may serve as a good example of a practical residue definition for MRL compliance, in which case the major metabolite, desthio-prothioconazole, (which can be recovered with several multi-residue procedures), was selected as a marker residue from a very complex residue composition. The selected residue component should reflect the application condition of the pesticide (dosage rate, pre-harvest interval) and it should be determined with a multi-residue procedure whenever possible. Monitoring for additional residue components only adds to the cost of analyses.

The advantage of this approach is appreciable as overall costs can be reduced and many more samples may be analysed by the regulatory laboratories. In addition, more laboratories can participate in regulatory monitoring of residues, since a relatively simple and rapid analytical procedure may not require the expensive equipment and time necessary for an extensive determination of all components of a residue. Nevertheless, the expression of residues with a single compound does not reduce the data requirement. Complete information on the total residue composition and the relative ratio of residue components is needed to determine whether a single compound can be used and is often needed for risk assessment purposes.

As far as possible the same definition of the residue should apply to all commodities, although there are exceptions. For example, if the major residue in animal commodities is a specific animal metabolite, a definition which includes that metabolite is needed for regulatory monitoring. However, the animal metabolite is not required in the residue definition for crop commodities if it is not found in the crops. Separate definitions would then be proposed for commodities of plant and animal origin.

Example: residue definition of thiabendazole:

> thiabendazole or, in the case of animal products, sum of thiabendazole and 5-hydroxythiabendazole.

It is generally preferable to express a residue in terms of the parent compound. Even if the residue consists mainly of a metabolite, the residue should be expressed in terms of the parent pesticide after molecular weight adjustment. Some examples are given to illustrate the practical application of the principle:

If the parent compound can exist as an acid or its salts, the residue is preferably expressed as the free acid.

Example: residue definition of 2,4-D:

> 2,4-D.

If metabolites are known to be present in significant amounts but the analytical method measures the total residue as a single compound, the residue is expressed as the parent compound. The metabolites included in the residue should be listed.

Example: residue definition of fenthion:

> sum of fenthion, its oxygen analogue and their sulphoxides and sulphones, expressed as fenthion.

Fenthion, its oxygen analogue and their sulphoxides and sulphones are all oxidised to a single compound (fenthion oxygen analogue sulphone) for measurement, but the residue is expressed as the parent fenthion.

There are exceptions:

Example: residue definition of amitraz:

> sum of amitraz and N-(2,4-dimethylphenyl)-N'-methylformamidine calculated as N-(2,4-dimethylphenyl)-N'-methylformamidine.

Ideally it should be possible to measure the residue as defined, with an LOQ adequate for proposed MRLs, with a high degree of specificity by a multi-residue regulatory analytical method. Although circumstances may warrant exceptions, the definition of a residue should not normally depend on a particular method of analysis, which means that the definition should not contain the words “determined as”. However, in the case of dithiocarbamates it is

necessary to describe the residue as ".... determined and expressed as ...." to produce a practical definition for residues.

Example: residue definition of thiram for compliance with MRLs:

> total dithiocarbamates, determined as CS_2 evolved during acid digestion and expressed as mg CS_2/kg.

Where the residue is defined as the sum of the parent compound and metabolites expressed as the parent, the concentrations of the metabolites should be adjusted according to their molecular weight before being added to produce the total residue. The words "expressed as" in the residue definition signify adjustment for molecular weight.

Example: residue definition of methiocarb:

> sum of methiocarb, its sulphoxide and its sulphone, expressed as methiocarb.

No allowance was made for molecular weights in the definitions of residues of some older compounds. Because such definitions are widely accepted the need for change should be carefully considered. The best time for the reconsideration of an existing residue definition is during a periodic review.

Examples: (no recalculation for molecular weight)

> residue definition of DDT:
>
> > sum of p,p'-DDT, o,p'-DDT, p,p'-DDE and p,p' TDE (DDD).
>
> residue definition of heptachlor:
>
> > sum of heptachlor and heptachlor epoxide

Metabolites arising from different sources should generally be excluded from definitions of residues for enforcement purposes unless the definition is a combined one covering the various sources. For example, p-nitrophenol arises from both parathion and parathion-methyl. It is often a major component of aged residues but is not included in the definitions of the residues.

Where a metabolite of one pesticide is registered for use as a second pesticide, separate MRLs would normally be established if the analytes of the two compounds were different. Preferably no compound, metabolite or analyte should appear in more than one residue definition.

Example: Triadimenol is a registered pesticide and a metabolite of triadimefon. The MRLs for triadimefon are for triadimefon only. The MRLs for triadimenol are for triadimenol only, but cover triadimenol residues arising from the use of either triadimefon or triadimenol.

There are cases of pesticides, however, where the chemical instability of the parent compound or the limitations of analytical methodology do not allow the application of the above principle. In such cases the residue definition has to be based on the stable common moiety. Benomyl and thiophanate-methyl both degrade to carbendazim.

Examples: residue definition of benomyl,: thiophanate-methyl and carbendazim.

> residue definition of benomyl:
>
> > sum of benomyl and carbendazim, expressed as carbendazim.
>
> residue definition of carbendazim:
>
> > carbendazim.

residue definition of thiophanate-methyl:

sum of thiophanate-methyl and carbendazim, expressed as carbendazim

Notes: *Benomyl*: Residues arising from the use of benomyl are covered by the MRLs for carbendazim.

Carbendazim: MRLs cover carbendazim residues occurring as a metabolic product of benomyl or thiophanate-methyl, or from direct use of carbendazim.

Thiophanate-methyl: Residues arising from the use of thiophanate-methyl are covered by the MRLs for carbendazim.

A major part of the residue of some pesticides is bound or conjugated, with the free residue disappearing very quickly. The bound or conjugated residue is therefore a better indicator for monitoring compliance with GAP. If the residue is defined as bound or conjugated there must be a clear instruction for the regulatory analyst as to how to measure it. The instruction could, for example, be to extract samples with a particular solvent under specified conditions, or perhaps to begin with a hydrolysis step. This option should be avoided as far as possible, as such a method cannot be validated without the use of incurred labelled residue in various sample matrices, and neither the labelled incurred residue nor facilities for detecting ^{14}C residues are available in all regulatory laboratories.

Example: residue definition of bendiocarb:

plant products: unconjugated bendiocarb;

animal products: sum of conjugated/unconjugated bendiocarb, 2,2 dimethyl-1,3-benzodioxol-4-ol/N-hydroxymethyl-bendiocarb, expressed as bendiocarb.