The description of "fat" in some studies has not always been completely clear It could be taken to mean "trimmable fat" containing moisture and possibly some other tissue or it could mean the lipid portion Residue levels of fat-soluble pesticides should be expressed on the lipid portion

For fat-soluble pesticides in both feeding and direct animal treatment trials, the fat samples analysed should be fully described because residue levels may vary in fat from several fat depots within the body of the same animal The fat description should include

- the nature of the fat (e g peri-renal, subcutaneous),
- location in the animal body (if more than one possibility), and
- lipid content (rendered or extracted fat may be assumed as 100% lipid)

In external animal treatment studies a sample of the fat at the treatment site, e g the site of a pour-on treatment, should also be taken for analysis

Residue levels of fat-soluble pesticides may depend on the condition (degree of fatness) of an animal, which should also be recorded

Information on veterinary uses

When a compound is used both as a pesticide on crops and for direct animal treatments (veterinary uses), full information on approved uses for both purposes and data from residue trials according to the approved uses, together with metabolism data in animals, should be included in the submission to the FAO Panel

In the case of the first evaluation of a compound or re-evaluation within the periodic review, veterinary uses will be treated in the same way as all other uses If information is not supplied, the JMPR will not recommend MRLs covering veterinary uses for new compounds and will recommend withdrawal of the old MRLs which were based on veterinary uses

RESIDUES IN FOOD IN COMMERCE AND AT CONSUMPTION

Summarize any available monitoring data (including total diet studies, market basket studies, etc) relevant to the pesticide under review This information is of particular interest for further refining of the dietary intake estimates

Monitoring data are the basis for establishing EMRLs for pesticides which have become environmental contaminants (see Chapter 5 section, "Estimating extraneous maximum residue levels")

NATIONAL MAXIMUM RESIDUE LIMITS

Information on national MRLs must be reliable and up-to-date Up-to-date MRLs should be supplied by national governments or the company preparing the submission Include a document reference and date for the source of the information Do not report MRLs from a secondary source or from non-validated information

Report national MRLs exactly as they are published The English translation of the commodity description should be as accurate as possible and must not be converted to the presumably equivalent Codex descriptions The portion of the commodity to which the MRL applies should be specified if it is different from that recommended by the Codex Guide[3]

Provide national residue definitions

RECONSIDERATION OF PREVIOUS RECOMMENDATIONS

In the light of new uses of a compound or additional information on its residues the compound may have to be re-evaluated, in which case all relevant new information must be presented See also Chapter 5 section, "Re-evaluation of additional information "

The new information and data will be mainly related to additional GAP information and new data from supervised trials, which enable the JMPR to estimate maximum residue levels and eventually propose MRLs for additional commodities, changes to established MRLs or confirm existing MRLs Other types of information may also be submitted, such as reports about additional metabolites which were unknown at the time when the pesticide was first evaluated, ratio and magnitude of the parent compound and the metabolites in additional matrices, new reports about animal feeding studies, and improved analytical methods with lower limits of quantification and improved ability to differentiate between parent compound and metabolites

When transgenic crops are developed for herbicide tolerance, additional information on metabolism and analytical methods will be needed as well as the usual data requirements for new uses

It is emphasized that recommendations of the JMPR can only be based on information provided, and requests or suggestions from the CCPR for changes of recommendations should always be accompanied by a clear statement of the reason for the referral, and must be supported by the data necessary for the JMPR to (re)consider the issue

In the past the information available to national governments has not always been provided to the JMPR The full documentation available to the governments should be provided to resolve questions referred to the JMPR

It is only possible to obtain STMR and HR values when all the relevant data for a particular compound are available A complete dossier of information is available for new and periodic review compounds For other evaluations related to new uses of a compound or additional information on its residues, estimation of a revised maximum residue level may be possible, but obtaining STMR and HR values may not

DATA REQUIREMENTS FOR EMRL ESTIMATION

The Extraneous Maximum Residue Limit (EMRL), for JMPR purposes, refers to a pesticide residue arising from environmental sources (including former agricultural uses) other than the use of a pesticide directly or indirectly on the commodity (see Appendix II, Glossary of Terms) EMRLs are estimated from residue data generated in food monitoring programmes

In any proposal for EMRLs a clear statement that the pesticide (or any precursor) has no permitted uses on the crop, the animal or animal feeds is required If former uses have been discontinued, provide the date of the withdrawal

Include the following monitoring data and supporting information for evaluation

- Country
- Year or years
- Commodity description (Codex Classification of Foods and Animal Feeds) and portion analysed
- Pesticide, and residue definition
- Sample classification as import, export or domestic production and consumption
- Statement whether the samples derive from random monitoring or are aimed at a particular problem or situation

If the number of samples monitored is large, the information should be summarized in categories For each pesticide/commodity/year, etc combination, the summary should show the following three categories

- Number of samples analysed
- Number of samples with residues below the LOQ or the limit of reporting
- Number of samples exceeding current MRL or proposed EMRL and, in this category, the individual residue values

The detailed residue data should be presented in tabular form shown in Table 3 5 to allow comparison with other data or combination with data from other reports (Hamilton *et al* , 1997)

The results of monitoring programmes where no residues were detected should also be reported to help develop a more complete picture of the extraneous residue situation

Table 3 5 Standard format for reporting pesticide residues monitoring data

Country Residue definition
Commodity Limit of reporting (LOQ, mg/kg)
Codex or National MRL

Year	No of samples analysed	No of residues detected	No of residues < LOQ	Number of samples in residue range (mg/kg)										
				≤0 005	>0 005 ≤0 01	>0 01 ≤0 02	>0 02 ≤0 05	>0 05 ≤0 1	>0 1 ≤0 2	>0 2 ≤0 5	>0 5 ≤1	>1 ≤2	>2 ≤5	>5 ≤10

Note * The residue ranges are to be selected according to the residue levels detected

CHAPTER 4

PREPARATION OF DATA DOSSIERS FOR THE CONSIDERATION OF THE FAO PANEL OF THE JMPR

CONTENTS

ORGANIZATION OF THE DOSSIER

Before a pesticide can be considered for JMPR evaluation it must already be available for use as a commercial product, which means that scientific studies have been prepared and then evaluated in national registration systems. Such studies are generally suitable for JMPR purposes, therefore dossiers of reports prepared for modern registration systems may be submitted However, JMPR does not review some topics, e g efficacy and ecotoxicology, and they should not be included in the dossier submitted to JMPR

The dossier to be submitted to the FAO Panel of JMPR should be arranged within the following topics It comprises the technical reports provided in support of the working paper or monograph (see below)

0 Data directory (see below, also Appendix VII)
1 Background information
2 Metabolism and environmental fate
3 Residue analysis
4 Use patterns
5 Residues resulting from supervised trials on crops
6 Fate of residues in storage and processing
7 Residues in animal commodities
8 Residues in food in commerce or at consumption
9 National maximum residue limits and residue definitions

A table of contents should be included at the beginning of each volume Each volume should be clearly labelled as per the example below

- Company name
- Date
- Common name of the active ingredient
- Number of the volume and total number of volumes in the submission
- Title of the section
- A list of commodities dealt with in that volume (for residue trials, farm animal feeding, processing and storage stability) and a list of animals, crops, soil and water (for metabolism)

Example

- Bayer AG
- November 1992
- Fenthion
- Volume 15 of 18

  Section 5 Residues resulting from supervised trials

- Citrus fruits
  lemons, oranges, tangelos

- Pome fruits
  apples, pears

Data submission

A hard copy of the data is to be submitted directly to the reviewer, together with an electronic copy where available A copy on CD-ROM or diskette should be provided to the FAO Joint Secretary for reference and storage The directory should indicate the form in which the copies of reports are provided The preferred format for electronic copies is pdf files or Word files

Working papers, summaries of GAP information and residue data should be provided in Word format and diagrams of metabolism pathways should be prepared using a commercial chemical structure drawing programme for inclusion as graphics in the document

DATA DIRECTORY

See also Appendix VII, "Standardized format for organizing the data directory (index) of information to be submitted for evaluation "

Manufacturers are required to supply to the FAO Joint Secretary a detailed index or directory of the information to be provided for the residue evaluation by November of the year preceding the scheduled review

The directory provides an opportunity for data submitters to conduct a brief overview of the data package and identify gaps or omit studies which are not up to current standards It ensures that an acceptable data package will be available for the consideration of the FAO Panel

A review of the directory prior to submission of the actual data facilitates planning for the JMPR and helps ensure an equitable distribution of work among the Panel members A comprehensive data directory makes it easier for reviewers to find relevant sections or studies during the evaluation, particularly in a large submission In addition, these directories provide a permanent record of the data submitted

It is not possible for the FAO Joint Secretary to determine from the directory the acceptability of residue data in relation to the use pattern, the availability of critical supporting studies or the monograph, etc This initially remains the responsibility of the data submitter and ultimately the task of the FAO Panel

The detailed reports submitted to the FAO Panel in support of the monograph must be organized according to the standardized format of the directory (Appendix VII) Reports or submissions developed for national regulatory authorities should be collated according to this format

An electronic copy of the directory should be supplied in Word format to allow document searches and for incorporation of the references into the Evaluation

The JMPR manual for FAO Panel members (Appendix X) may also be useful to those preparing data submissions for review

WORKING PAPER OR MONOGRAPH

Manufacturers are required to submit a working paper or monograph summarizing the results of the trials and the conclusions drawn from them, together with copies of original reports, by 28 February of the year of the scheduled review

The working paper should, where appropriate, relate the residue data to the residue definition, analytical methods, GAP information, dose levels in animal studies etc, and clearly demonstrate the basis for a proposed MRL The sub-sections describing supervised trials should follow the sequence of the Codex Commodity Classification and conclude with an evaluation of the information provided

In the case of submissions (non-periodic-review) provided in support of a new or existing MRL, the evaluation may be limited to a brief discussion of the available residue data and GAP information In the latter case, new critical supporting studies are valuable information and should be submitted The re-submission of previously evaluated studies is not necessary

The preparation of a draft working paper is expected to facilitate the evaluation of the data by the reviewer and the overall operation of the Panel It is not intended as a substitute for the FAO Panel review of the individual study reports

Reports (in English) prepared by companies for submission to authorities in USA, Europe etc, are likely to be considered generally acceptable Where such reports are not in the format specified below, a directory must be provided which permits the reviewer ready access to the individual technical reports There may also be the need for additions to such submissions, for example

- commodity descriptions in Codex terms
- summaries of good agricultural practices
- summaries of residue data from supervised trials

The data and information required for the JMPR evaluation and the formats recommended for preparing the summary information are described in detail in Chapter 3 "Data and information required for JMPR evaluation" The information from the individual studies should be organized according to the suggested subheadings in the directory with an evaluation of the available data in each subsection Under the various subheadings, explain any trial details relevant to the assessment of the data that might be considered to influence the residues or the validity of the trials

Include schematic diagrams of metabolism pathways in electronic form

Processing studies should be grouped according to the commodity or substrate of interest Summarize the data in tabular format Such tables should be set out carefully so that it is absolutely clear which sample is derived from which product in the processing phase The scale of the processing by the weight of commodity processed should be indicated The review of each study should describe the field treatments and state the application rate in the study

Include flow diagrams to explain any complex commercial processes

Summarize information on national MRLs in tabular format The typical column headings include country, commodity and MRL Footnotes or an extra column will be necessary if countries use different residue definitions or the limits were set on a portion of the commodity which is different from that recommended by the CAC

CHAPTER 5

JMPR PRACTICES IN ESTIMATING MAXIMUM RESIDUE LEVELS AND PROPOSING MAXIMUM RESIDUE LIMITS

CONTENTS

INTRODUCTION

The JMPR carries out a scientific evaluation of the data provided and takes into account all available information 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 draft evaluations, 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 draft evaluations and appraisals are prepared in a uniform format, described in Appendix X, JMPR Manual for FAO Panel Members, to facilitate access to the required information by the reader The monographs (combined evaluation and appraisal documents) 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 therefore information on GAP and data on supervised residue trials are summarized in detail in the monograph and the reasoning behind the evaluation 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 that occurred in the early to mid 90s is largely due to the inclusion of more detailed explanations and reflects the increased resources required for the work

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

The volatility of the compound, its stability in water and sensitivity to irradiation with ultraviolet light may considerably affect its 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

The physical property chosen by the JMPR to represent 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 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 recommended that the octanol-water partition coefficient should be the prime indicator of fat-solubility, supplemented by inferences which may be drawn from the distribution of residues between muscle and fat tissues

The JMPR recognized that many compounds which are neither clearly fat-soluble nor clearly water-soluble required special consideration

In general, when log P_{OW} exceeds 4 the compound would be designated fat-soluble and when log P_{OW} is less than 3 it would not be so designated Pesticides with intermediate log P_{OW} would be considered on a case-by-case basis using the evidence of residue distribution between muscle and fat tissues

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 and suggest probable residue behaviour The results of metabolism studies suggest target tissues in animals 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 estimate, based on toxicological studies in experimental mammalian animals, is 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, the ADI does 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

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 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 validation data for analytical recoveries The JMPR estimates the LOQ for the method as the lowest residue concentration where reliable recoveries (usually 70-120%) were achieved Method validation is needed on substrates representative of those in the trials and studies

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

STABILITY OF PESTICIDE RESIDUES IN STORED ANALYTICAL SAMPLES

Residue samples from the supervised trials, food processing studies and farm animal feeding studies are routinely stored under frozen conditions for a year or more before laboratory analysis 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 The aim is to decide if no more than 30% of the residue was lost during storage before analysis

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

The following points are to be noted during evaluation of a freezer storage study

- design of the study - (intended sampling intervals, replication, number of procedural recovery tests)
- longest duration of storage tested
- storage vessels (size, material, sealed or open)
- nature of the samples being tested (commodity, unchopped, chopped or homogenized)
- 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 shows that 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 or the longest duration of storage in the tests should be questioned

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, 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 uses 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

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 according to Good Agricultural Practice The importance of reliable data has already been emphasized in the requirements for information and data from trials (Chapter 3 section "Residues resulting from supervised trials on crops")

The principles followed in evaluating supervised trial data are described in detail in the section in this chapter, "Estimation of maximum residue levels "

PROCESSING STUDIES

In relation to Codex MRLs for pesticides "processed food" refers to products resulting from the application of physical, chemical or biological processes to a "primary food commodity" Primary food commodities treated with ionizing 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 obtain knowledge about the real intake of pesticides from food commodities for which MRLs have been established 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 in food processing Experience has shown that residue levels usually decrease during processing, such as peeling, cooking and juicing In other cases the residue level may increase during processing as it often does in the case of oil from oilseeds and olives Further, in some cases the active ingredient can be transformed during processing into degradation products 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 specified that, in the case of processed foods for which no MRLs have been recommended, the maximum residue permitted in the processed food should not be greater than the maximum residue permitted in the equivalent weight of the raw agricultural commodity The JMPR frequently estimates maximum residue levels for important processed foods and feeds in international trade when residues concentrate in these products at levels higher than in the raw agricultural commodities from which they are derived (e g oil, bran, peel, etc) 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 This has been found to be critical for better estimates of dietary intake of pesticides

Processing studies are among the critical supporting studies required for the evaluation of a new or periodic review compound See Chapter 3 section, "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 studies of the nature of the residue which require a separate dietary risk assessment also have to be considered The residue must be calculated according to the definition relevant for compliance with MRLs and for the estimations of dietary intake

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

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

If more than one processing study has been conducted for a particular pesticide in the same RAC, the average processing factor for each type of process should be used for each processed commodity If the processing factors from two trials are irreconcilable, e g 10-fold different, the mean is inappropriate because it would not represent either 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 one or the other

When residues in the processed commodity are undetectable or <LOQ the calculated processing factor (LOQ – residue level in RAC) 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 mean of "less than" values Reported processing factors should be rounded to 2 significant figures

When residues in the processed commodity and in the RAC are both undetectable 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, washing) is omitted in a study, it may be inappropriate to include that study in the calculation of the average processing factor

To estimate a maximum residue level for a processed product the MRL or maximum residue level of the RAC is multiplied by the processing factor For the purpose of IEDI estimation, the STMR of the RAC is multiplied by the processing factor to give the STMR-P of the processed product

If data are available for the residues in the edible portion of the commodity (e g in banana pulp), an STMR should be estimated directly from the residues in the edible portion found in supervised trials at the maximum registered rate of use

RESULTS OF NATIONAL MONITORING PROGRAMMES

The results of national monitoring programmes are considered as supporting information for confirmation of practical applicability of estimated maximum residue levels They are also useful for estimating dietary intake at national level Data from national monitoring programmes are essential for recommending EMRLs See section in this chapter, "Estimation of extraneous maximum residue levels "

RE-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 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 the changes in the metabolism 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

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 (i e other than in the periodic review programme), consequently, those compounds to be evaluated within the periodic

review programme must be clearly identified in advance See also Chapter 3 section, "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 (animal and plant metabolism, environmental fate in soil and in water-sediment systems), residue analysis (analytical methods, stability of residues in stored analytical samples, residue definition), current use patterns (registered and officially authorized uses), supervised residue trials, farm animal feeding studies, fate of residues in storage and processing, residues in food in commerce or at consumption and national maximum residue limits, as in the case of a new compound However, the conclusions and recommendations are somewhat different in periodic 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

New 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 normally or under the periodic review programme

Existing MRLs

For an individual commodity in the normal situation, if new data are supplied where an MRL already exists the data are evaluated and the MRL may or may not require revision

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

In the normal situation, 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

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

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, influence the residue definition, validate residue and other trials and provide further information on residues in food as consumed The JMPR may not recommend MRLs for new or periodic review compounds in the absence of critical supporting studies if their omission is not adequately justified

DEFINITION OF RESIDUES

For the purposes of an MRL or STMR, a pesticide residue is defined as the combination of the pesticide and its metabolites, derivatives and related compounds to which the MRL or STMR apply (See Appendix II, Glossary of Terms)

Residue definitions that are the result of compromise between 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 that it should

- be most suitable for monitoring compliance with GAP, and
- include compounds of toxicological interest for dietary intake estimations and risk assessment

The two requirements 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 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 other cases the methods used for supervised trials are complicated or require sophisticated instrumentation and hence are unsuitable for regulatory analytical work Furthermore, some countries may experience extreme difficulty obtaining 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

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

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

or

(ii) if total residue methodology is used to produce data for risk assessment, and the suitable "indicator molecule" can be analysed with a multi-reside 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 as proof of illegal use of the pesticide, and the metabolite should not be included in the residue definition for MRL (example, cyromazine □ melamine, also prometryne □ melamine)

The JMPR considers the following factors when proposing 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 of the compound and relevant transformation products
- 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

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 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 oxidized 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