CHAPTER 3

DATA AND INFORMATION REQUIRED FOR JMPR EVALUATIONS

CONTENTS

3.1 INTRODUCTION

The JMPR is not a regulatory body and therefore cannot "require" (in the strict sense of the word) submission of data. However, it can and does refrain from estimating maximum residue levels when data are inadequate. In such cases, the data inadequacies are identified in the Report. For residue evaluations, the Meeting considers all aspects of the use and the fate of a pesticide and its residues, which implies that all studies that provide such information are necessary. It is solely for the JMPR to decide which data are relevant and which are not. The JMPR publishes lists of those data which it considers "desirable" when these are found to be lacking or if areas are insufficiently addressed in data submissions.

Data submitters are advised to follow the guidelines in this chapter when compiling their data package.

3.2 NEW AND PERIODIC REVIEW COMPOUNDS

The data and information needed for the evaluation of pesticide residues of new compounds and compounds evaluated within the periodic review programme are outlined in this section.

An objective of the periodic review is to make the best use of the existing database, regardless of the age of the studies. Consequently, countries and industry are requested to provide all relevant information irrespective of whether it had been previously supplied. However, experience has shown that some periodic review submissions contain data that are of limited use for estimating maximum residue levels. For example:

- Residue data that do not relate to current good agricultural practice (GAP) and are not accompanied by adequate details of the conduct of the field trial, the handling of the samples or details of the analysis (including associated recovery data).
- Residue data developed with non-selective analytical methods, e.g., colorimetric analysis or bioassay.

- Lack of information on specifics and conditions of sampling, sample transportation, sample storage and intervals from sampling until storage and storage until analysis.
- Omission of critical supporting studies, such as metabolism, farm animal feeding, processing, analytical methods and freezer storage stability studies.

Residue data or studies with obvious deficiencies submitted even as supplementary data can be judged only on a case-by-case basis when considered in the context of the available database.

In preparing product monographs (working papers) the data submitters should consider the relevance of residue data in the light of current use practices, residue definitions, analytical methods etc., and that only data pertinent to commodities with current or proposed uses should be provided. If critical supporting studies are not provided, the submission must include an explanation of why specific critical supporting studies, e.g., processing information, were not provided. Studies which fulfil the requirements of modern national registration systems will generally meet the needs of the JMPR.

The content and format of a submission (data package) should follow the format of the JMPR evaluations.

3.2.1 Identity

ISO common name
Chemical name
(IUPAC)
(Chemical Abstract)
CAS Registry. No.
CIPAC No.
Synonyms
Structural formula
Molecular formula
Molecular weight

3.2.2 Physical and chemical properties

Provide a detailed physical and chemical characterization for new and periodic review compounds as guidance for the interpretation of available test data.

Pure active ingredient
Appearance
Vapour pressure (in mPa at stated temperature)
Melting point
Octanol-water partition coefficient (at stated pH and temperature)
Solubility (Water and organic solvents at stated temperatures)
Specific gravity (... g/cm^3 at ...stated temperature)
Hydrolysis (at stated pH and temperature)
Photolysis
Dissociation constant
Thermal stability

Technical material
Minimum purity (in %)

Main impurities (range of amounts; confidential information will not be presented as such in the JMPR monographs)
Melting range
Stability
Reference to FAO specifications for TC or TK (TC, technical material; TK, technical concentrate).

Formulations
Provide a list of commercially available formulations.
Reference to FAO specifications for formulations

3.2.3 Metabolism and environmental fate

Information is required on:

- Animal metabolism
- Plant metabolism
- Environmental fate in soil
- Environmental fate in water-sediment systems.

In addition, *in vitro* data are useful to show if the pesticide is likely to undergo hydrolysis (acid, base, or enzymatic), oxidation or reduction, photolysis, or other changes.

The dose level and criteria for identification and characterization of residue components, including non-extracted residues, are similar to those described in guidelines of registration authorities. In order to guide data submitters and assist the evaluation of experimental results, the most important principles are summarised below.

Metabolism studies are conducted to determine the qualitative metabolic fate of the active ingredient and elucidate its metabolic pathway. Many pesticides undergo change during and after application to plants, soil, water and livestock. The composition of the terminal residue must, therefore, be determined before the residue analytical methodology can be developed and residues quantified.

Radiolabelled active ingredients are required to allow quantification of the total, extractable and unextracted radiolabel residues. The active ingredient should be labelled so that the degradation pathway can be traced as far as possible. The radiolabel should be positioned in the molecule so that all significant moieties or degradation products can be tracked. If multiple ring structures or significant side chains are present, separate studies reflecting labelling of each ring or side chain will normally be required if it is anticipated that cleavage between these moieties may occur. A scientifically based rationale may be submitted in lieu of conducting studies with multiple radiolabels if no cleavage is anticipated.

In choosing the position to be labelled, assurance is needed that a stable position is selected. The preferred isotope is ^{14}C, although ^{32}P, ^{35}S, or other radioisotopes may be more appropriate if no carbon or only labile carbon side chains exist in the molecule. The use of tritium (^{3}H) as a label is strongly discouraged due to the possibility of hydrogen exchange with endogenous materials. If a potentially labile side chain or tritium labelling is chosen, a metabolism study will be considered adequate if all significant radioactivity in the crop is identified and found to be associated with the active ingredient, and not related to loss of the label from the basic structure of the active ingredient molecule.

The specific activity of the radiolabelled active ingredient should be adequate to meet the general data requirements of the metabolism study (quantification of 0.01 mg/kg total radioactive residue (TRR) in edible tissues, milk, eggs or crop matrices). Studies with 1× application rates are generally necessary for the decision of exceeding or not exceeding the threshold levels. However, dosing with an exaggerated rate, e.g., 5×, is recommended when low residue levels are anticipated, which in turn may result in a lack of data to define the metabolic pathways from the 1× treatment.

The desired goal of a metabolism study is the identification and characterization of at least 90% of the TRR in edible tissues, milk, eggs and in each raw agricultural commodity (RAC) of the treated crop. In many cases it may not be possible to identify significant portions of the TRRs especially when low total amounts of residue are present, when incorporated into biomolecules, or when the active ingredient is extensively metabolised to numerous low level components. In the latter case it is important for the applicants to demonstrate clearly the presence and levels of the components, and if possible, attempt to characterise them. Studies should utilize state-of-the-art techniques and include citations of such techniques when used. Table 3.1 provides guidance on strategy for identification and characterization of extractable residues.

Table 3.1 Strategy for Identification and Characterization of Extractable Residues from Metabolism in Crops

Relative amount (%)	Concentration (mg/kg)	Required Action
< 10	< 0.01	No action if no toxicological concern
< 10	0.01 – 0.05	Characterize. Only attempt to confirm identity if straightforward, e.g., a reference compound is available or the identification is known from a previous study.
< 10	> 0.05	Characterization/identification needs to be decided on a case-by-case basis taking into account how much has been identified.
> 10	< 0.01	Characterize. Only attempt to confirm identity if straightforward, e.g., a reference compound is available or the identification is known from a previous study.
> 10	0.01 – 0.05	Significant attempts to identify should be made especially if needed to establish a pathway, ultimately characterization might be accepted.
> 10	> 0.05	Identify using all possible means.
> 10	> 0.05 unextracted radiolabel	See notes

Notes: The extracted solid material should be assayed and, if radioactivity is present in the unextracted radiolabel fraction down to the trigger values of 0.05 mg/kg or 10% of the TRR, whichever is greater, release of the radioactivity should be attempted for further identification.

Treatments of extracted solids materials may be performed sequentially or in parallel. Types of treatments suggested include addition of dilute acid and alkaline at 37 °C, use of surfactants, enzymes, and 6N acid and/or 10N alkali with reflux. It should be kept in mind that the milder procedures provide more accurate assignments of metabolite structures released. Exhaustive extraction such as acid/alkaline reflux would probably release moieties as their final hydrolysis products, which may have little structural relationship to the original unextracted radiolabel. Further details on the recommended procedures for performing metabolism studies (test site and conditions, sampling, analysis, identification and characterization of residues, etc.) are given in the OECD Guidelines for the Testing of Chemicals, Test No. 501: Metabolism in Crops, and Test No. 503: Metabolism in Livestock[3].

[3] OECD Guidelines for the Testing of Chemicals, Test No. 501: Metabolism in Crops; Test No. 503: Metabolism in Livestock http://puck.sourceoecd.org/vl=3615016/cl=46/nw=1/rpsv/cw/vhosts/oecdjournals/1607310x/v1n7/contp1-1.htm

During the conduct of the metabolism studies, it may be helpful to retain radiolabelled samples for future analyses by the subsequently developed analytical methods (for enforcement, data collection or dietary risk assessment) in order to assess the extraction efficiency of these methods (sometimes referred to as "radiovalidation" of methods). Samples retained should include representative portions of crops, muscle, liver milk and eggs. If specific metabolites accumulate in specific organs, samples of these organs should also be retained. However, if the analytical methods mirror those used in the radiolabelled studies, such data would generally not be necessary. The radiovalidation of the extraction process of analytical methods should be submitted as part of the report on the analytical method, or it may stand by itself as a report, or in the metabolism report itself. The cover letter or summary of the full data package should indicate where it has been placed.

The information provided for evaluation should include documentation on the proposed metabolic pathway, including a table with associated chemical structures and names (Chemical Abstract Service (CAS) and International Union of Pure and Applied Chemistry (IUPAC) as available), the quantities of the metabolites in the different parts of the plants (surface, leaves, stems and edible root), in different animal tissues (fat, muscles, kidneys, liver, eggs and milk) and in different soil types. Any postulated intermediates/metabolites should also be indicated in the pathway. The rate of the formation and disappearance of metabolites in plants, animals and soil must also be investigated. Where the structure of a metabolite or alteration product is identical to that of another registered pesticide and the information is in the public domain, the data submission should state this fact.

The capability of the analytical methods utilized in the metabolism study to determine the components of the residue, whether free, conjugated, or unextracted, should be clearly specified.

It is emphasised that all data on animal metabolism have to be provided to both the WHO Core Assessment Group and the FAO Panel of Experts. Normally the WHO Group will include detailed discussion on the metabolism of small experimental laboratory animals, e.g., rats, mice, guinea pigs, rabbits and dogs, in their monographs and the FAO Panel will include detailed discussion of the metabolism of farm animals, e.g., cattle, goats, sheep, pigs and chickens, in their monographs. The required data on plant metabolism should be submitted to the FAO Panel, while the WHO Group wishes to receive only schemes of plant metabolism.

The metabolism studies on farm animals and crops should provide the basic evidence to support proposed residue definition(s) for food commodities, and provide evidence as to whether or not a residue should be classified as fat soluble.

3.2.3.1 Farm animal metabolism

These studies are required whenever a pesticide is applied directly to livestock, to animal premises or housing, or where significant residues remain in crops or commodities used in animal feed, in forage crops, or in any plant parts that could be used in animal feeds.

Separate animal feeding studies (farm animal feeding studies) are required for ruminants and poultry. Except in special cases, it is not necessary to carry out metabolism studies with pigs since information on metabolism in a monogastric animal is available from studies with rats. If metabolism in the rat is different from that in the cow, goat and chicken, pig metabolism studies may be necessary. Such differences may include (but are not limited to) the following:

- differences in the extent of the metabolism

- differences in the nature of the observed residue
- the appearance of metabolites with sub-structures, which are of known potential toxicological concern.

Usually the most important metabolism studies are those involving ruminants and poultry. Lactating goats or cows and in the case of poultry, chickens are the preferred animals.

For each set of experimental conditions for pesticides (dermal *vs.* oral application or for each radiolabelled position), the following number of animals should be used. A ruminant metabolism study can be carried out on a single animal. For poultry, the use of ten birds per experiments (or dose) is recommended. Additional animals may be included if it is scientifically required. It is not necessary to include control animals in livestock metabolism studies. The minimum dosage used in livestock oral metabolism studies should approximate the level of exposure expected from the feeding of treated crops with the highest observed residues. However, for oral studies, livestock should be dosed at least at a level of 10 mg/kg in the diet. In the case of dermal application the minimum dose should be the maximum concentration from the label. Exaggerated dosages are usually needed to obtain sufficient residue in the tissues for characterization and/or identification. Ruminants and swine should be dosed daily for at least five days, and poultry for at least seven days.

If the metabolism study is intended to be used in place of a separate livestock feeding study with unlabelled compound, inclusion of a second animal (or group of animals in the case of poultry) treated with a realistic dose and extended dosing period is strongly recommended, if it is suspected that a plateau is not likely to be reached. Such a study may allow JMPR to propose maximum residue levels for animal tissues in the absence of livestock feeding studies. Use of a metabolism study in place of a feeding study would require fully adequate scientific reasoning, especially if a plateau has not been reached in milk or eggs in the metabolism study.

All estimates of relative dose used in animal metabolism studies should be based on a feed dry weight basis. It should be noted that the use of percent crop treated information and median residue values are not acceptable to determine the dose level in these experiments.

3.2.3.2 Plant metabolism

Plant metabolism studies should be designed in such a way as to represent the composition of the residues when the pesticide use matches maximum GAP conditions. When low residue levels in crops are expected from the maximum application rate, experiments at exaggerated rates may be needed to aid metabolite identification. The crop should be treated with radiolabelled active ingredient, preferably containing formulation ingredients typical of an end-use product as applied in the field.

A metabolism study should be submitted for each type of crop group for which use is proposed. Crops can be considered to belong to one of five categories for crop metabolism studies:

- root crops (root and tuber vegetables, bulb vegetables)
- leafy crops (Brassica vegetables, leafy vegetables, stem vegetables, hops)
- fruits (citrus fruit, pome fruit, stone fruit small fruits, berries, grapes, banana, tree nuts, fruiting vegetables, persimmon)
- pulses and oilseeds (legume vegetables, pulses, oilseeds, peanuts, legume fodder crops, cacao beans, coffee beans)

- cereals (cereals, grass and forage crops).

One crop from a group will cover the entire group for purposes of metabolism in those crops within the group. In order to extrapolate metabolism of a pesticide to all crop groupings, metabolism studies on a minimum of three representative crops (from the five different crop categories) should be conducted. If the results of these three studies indicate a comparable metabolic route, then additional studies will not be needed on crops in the other two groups.

The studies should reflect the intended use pattern of the active ingredient such as foliar, soil/seed, or post-harvest treatments. If, for instance, three studies have been conducted using foliar application and at a later date the authorised uses also include soil application, e.g., seed treatment, granular, or soil drench, then an additional study reflecting soil application should be carried out.

On the other hand, if different metabolic routes are observed among the representative crops from studies conducted in a similar manner, e.g., foliar spray with similar pre-harvest interval (PHI) and growth stages, further studies should be conducted for uses on crops in the remaining categories for which MRLs are being requested. Differences in the quantities of metabolites belonging to the same pathway will not trigger the need for additional studies.

There are situations where an *authorised use is unique*, in terms of the crop and/or its growing conditions, for which a metabolism study would be necessary, in addition to the three representative crops. For example, if a use exists on paddy rice, a metabolism study should be submitted for paddy rice, regardless of other available metabolism studies.

Metabolism in rotational crops studies are conducted to determine the nature and amount of pesticide residue uptake in rotational crops that are used as human food or as livestock feed. Such studies are generally not required for uses of pesticides on permanent or semi-permanent crops including, but not limited to, the following commodities or crop groups: asparagus, avocado, banana, berries crop group, citrus fruit crop group, coconut, cranberry, dates, fig, ginseng, globe artichoke, grapes, guava, kiwi fruit, mango, mushrooms, olives, papaya, passion fruit, pineapple, plantain, the pome fruits crop group, rhubarb, the stone fruits crop group, and the tree nuts crop group[4].

Specifically the studies fulfil these purposes:

- Provide an estimate of total radioactive residues (TRRs) in the various raw agricultural commodities (RACs) via soil uptake.
- Identify the major components of the terminal residue in the various RACs, thus indicating the components to be analysed for in residue quantification studies, i.e., the residue definition(s) for both risk assessment and enforcement.
- Elucidate the degradation pathway of the active ingredient in rotated crops.
- Provide data to determine rotational crop restrictions based on residue uptake levels. This information is mainly used by national regulators.)
- Provide information for determining if limited field trials for rotational crops (see section **3**.5.2) should be submitted.

The study should normally be performed using a sandy loam soil that has been treated with the radiolabelled test substance applied at a rate equivalent to the maximum seasonal rate

[4] OECD Guidelines for the Testing of Chemicals, Test No. 502: Metabolism in Rotational Crops

(1×), unless the label limits its use to one soil type other than sandy loam. In either case, the soil should not be sterilized. Where the label allows nine applications at weekly intervals of 1 kg active ingredient *per* hectare, the maximum seasonal application rate may be obtained, for instance, with one application of 9 kg active ingredient *per* hectare or three applications of 3 kg active ingredient *per* hectare or other application scheme as long as the maximum seasonal rate was met. In all such cases, the aging period for the soil will be considered to start at the last application. The soil should be treated with radiolabelled pesticide active ingredient, preferably containing formulation ingredients typical of an end use product as applied in the field. Following application to the soil, the pesticide may be incorporated into the soil if this represents typical agricultural practice.

Rotational crops should be representative of each of the following crop groupings:

- root and tuber vegetable, e.g., radish, beets or carrots
- small grain, e.g., wheat, barley, oats or rye
- leafy vegetable, e.g., spinach or lettuce.

Where possible, crops should include those expected in the rotational schedule on the label, if known.

Representative rotational crops should be planted at three appropriate rotational intervals, e.g., 7–30 days for assessing circumstances of crop failure or closely rotated crops, 60–270 days to reflect a typical rotation after harvest of the primary crop and 270–365 days for crops rotated the following year. The rotational intervals selected should be based on the expected agricultural use for the pesticide and typical rotational practices. In cases where the pesticide applied, e.g., certain herbicides, results in excessive phytotoxicity to rotational crops at 7–30 days, an alternative timing for the first rotational interval should be studied. Information regarding planting restrictions due to phytotoxicity should be provided.

The study may be performed either in a greenhouse or in an outdoor plot or container or a combination of the two, e.g., rotated crops can be grown under greenhouse conditions in soils that were treated and aged under outdoor or field conditions.

Post-harvest uses require at least one study if no other appropriate foliar metabolism study is available. A foliar study can substitute for a post-harvest study if the mature commodity was present and exposed at application. If there are post-harvest uses on a number of commodities from different crop groupings, then up to three additional studies should be submitted.

These studies provide information on the approximate level of total residues, identify the major components of the total terminal residue, indicate the route of distribution of residues and its mobility (uptake from soil, absorption by plants or surface residue) and show the efficiency of extraction procedures for various components of the residue.

Transgenic and non-transgenic crops may metabolize the pesticide differently. Full and detailed information will be required for a transgenic crop with metabolism differences from the non-transgenic crop. For genetically modified crops that do not involve the insertion of a gene conveying resistance by means of metabolism, no additional metabolism studies are needed. However, the rationale for concluding that the gene does not alter metabolism should be detailed. When a gene is inserted that conveys active ingredient resistance due to pesticide metabolism, then a crop metabolism study should be conducted for each crop grouping to which the genetically modified crops belong. If one such study shows a similar metabolism to conventional crops, however, no additional studies would be needed. If a different metabolic route is observed, then two additional studies should be submitted.

3.2.3.3 Environmental fate in soil, water and water-sediment systems

The FAO Panel does not evaluate data on environmental toxicology, but does require studies on environmental fate relevant to the potential for uptake of residues by food and feed crops.

These studies are normally required for all pesticides except those with a specific restricted use, e.g., seed treatment, post-harvest application in storage. The availability of relevant studies is essential for the assessment of the potential for residues in food and feeds.

The FAO Panel reviewed the various types of environmental fate studies as related to the process of estimating residues in commodities and concluded that some of the studies included in previous evaluations do not assist significantly in defining the residue of concern or estimating residue levels. It should be noted that the studies required are in some cases dependent upon the use pattern (soil, foliar, seed treatment) and that paddy rice presents a unique situation. The data requirements on environmental fate are summarized in Table 3.2.

Table 3.2: Requirements for submission of data on environmental fate for the JMPR

Type of study	Type of use and requirement (yes/no/conditional)						Comments
	Foliar	Soil	Plants of root, tuber, bulb, or peanut (at/after pegging)	Seed dressing (including seed potato)	Herbicide (for weeds in crop)	Paddy rice	
Physical and chemical properties	Condi-tional	Condi-tional	Conditional	Conditional	Conditional	Condi-tional	Only to the extent not provided for the technical material, e.g., hydrolysis and photolysis.
Degradation in soil (aerobic)	No	Yes	Yes	Yes	Yes	No	May be part of confined rotational crop.
Soil photolysis	No	Yes	Yes	Yes	Yes	No	
Degradation in soil (anaerobic)	No	No	No	No	No	No	
Persistence in soil	No	No	No	No	No	No	
Mobility/leaching in soil	No	No	No	No	No	No	
Adsorption by soil types	No	No	No	No	No	No	
Hydrolysis rate and products	Yes	Yes	Yes	Yes	Yes	Yes	Hydrolysis in sterile aqueous buffers. Abiotic epimerization should be provided as appropriate (e.g., pyrethroids)
Photolysis-plant surface	Conditional	No	See foliar	No	No	See foliar	Plant metabolism may suffice. Needed for special cases (e.g., abamectin)
Photolysis-natural pond water	No	No	No	No	No	Conditional	Plant metabolism may be adequate for rice. Useful for GAP involving application to water surface.
Crop uptake and bioavailability (see rotational crops)	No	No	No	No	No	No	

Type of study	Type of use and requirement (yes/no/conditional)						Comments
	Foliar	Soil	Plants of root, tuber, bulb, or peanut (at/after pegging)	Seed dressing (including seed potato)	Herbicide (for weeds in crop)	Paddy rice	
Rotational crops-confined	Yes	Yes	Yes	Yes	Yes	No	Not required where no crop rotation (e.g., orchard crops). Soil and crop should be analysed for radiolabelled residues.
Rotational crops-field	Condi-tional	Condi-tional	Conditional	Conditional	Conditional	No	Requirement conditional on results of confined rotational crop study.
Field dissipation studies	Condi-tional	Condi-tional	Conditional	Conditional	Conditional	No	Requirement conditional on results of confined rotational crop study.
Residue degradation (biodegradability) in water-sediment systems	No	No	No	No	No	Conditional	Metabolism study for paddy rice may be adequate. In other cases, metabolism/degradation needed, e.g., application to pond water.

3.3 SAMPLING AND RESIDUE ANALYSIS

3.3.1 Sampling

Reliable results can only be obtained from samples taken according to the objectives of the study. Utmost attention should be given to the selection of sampling methods, handling (packing, labelling, shipping and storage) of samples. The study should be designed to assure the integrity of the whole chain of activities. The sampling method and the selection of the objects of sampling depend on the purpose of the study.

In crop metabolism studies, samples of all raw agricultural commodities should be obtained for characterization and/or identification of residues. In commodities with inedible peel such as oranges, melons, and bananas, the distribution of the residue between peel and pulp should be determined. For crops that are sometimes consumed at an immature stage, such as baby corn or leafy salads, samples should also be taken of such commodities for analysis. Where mature inedible crop parts, e.g., apple leaves, potato foliage, are used to help identify residues, the edible parts must also be sampled and analysed to demonstrate the similarity of metabolic profiles. If more than one use pattern is involved, extra samples need to be taken to reflect, for example, the different PHIs.

In rotational crop studies the selected representative rotated crops should be harvested and the appropriate plant parts of raw agricultural commodities (RAC) for human and livestock feed sampled. Samples should also be collected on selected crops at multiple intervals if both immature and mature crops are normally harvested as part of normal agricultural practices. Harvested samples should include forage, hay, straw and grain for cereal crops; an immature and mature leafy vegetable sample and both the root or tuber and the leafy (aerial) portion of the root crop, even if the leafy portion is not a RAC of the actual root crop planted. Data from the leafy portion of the root crop and the immature leafy vegetable are needed as these crops can be used as models to extrapolate to wider ranges of food crops. In addition, due to the increase in the culinary use of immature greens, an immature leafy vegetable sample is

needed. Immature leafy vegetables are defined as the crop stage representing approximately 50% of the normal time period for the plant to reach full maturity. Sampling of the soil is not required, but may be performed depending on the specific objectives of the study.

In livestock metabolism studies excreta, milk and eggs should be collected twice daily (if applicable). Tissues to be collected should include at least muscle (loin and flank muscles in ruminant and leg and breast muscle in poultry), liver (whole organ for the goat and poultry and representative parts of the different lobes of the liver if cattle or swine are used), kidney (ruminants only), and fat (renal, omental and subcutaneous). The TRR should be quantified for all tissues, excreta, milk, and eggs. For milk the fat fraction should be separated from the aqueous portion by physical means and the TRR in each fraction quantified[5].

In supervised field trials the whole RAC should be sampled as it moves in commerce. For some crops, there may be more than one RAC. For example, the RACs for field corn include the grain (seed), fodder (stover), and forage. One sample from each RAC should normally be taken from treated plots at each sampling interval.

Some crops may be shipped without having been stripped, trimmed or washed; therefore these procedures should only be used on residue samples to the extent that these are commercial practices prior to shipment. Of course, data on trimmed or washed samples may be generated optionally for use in risk assessments. The recommended sampling method for supervised trials is described in Appendix V.

In selective field surveys and monitoring programmes the Codex standard method of sampling for the determination of pesticide residues for compliance with MRLs[6] should be used. The method of sampling, handling and storage condition of samples should be described in detail in all studies. In the case of supervised trials, field surveys and monitoring programmes the information provided should also include the method for selecting the timing of primary samples (sample increments), the number of primary samples in the composite sample and the total weight of the composite sample.

3.3.2 Sample preparation and processing

To provide residue data for estimation of the MRLs, samples of commodities should be prepared according to the Codex standard to obtain the portion of commodity to which the Codex MRLs apply[7]. The guidance for sample preparation is given in Appendix VI.

Edible portion residue data are required for dietary intake estimation. For commodities where the RAC differs from the edible portion, e.g., bananas, samples should be further prepared to separate the edible and inedible portions for separate analysis.

3.3.3 Analytical methods

Analytical methods are used to generate the data for estimating dietary exposure, to establish Maximum Residue Limits (MRLs), and to determine processing factors. Analytical methods are also used in enforcement of any MRLs that may be established. It is important to note that the methods should be able to determine all analytes included in the residue definition for the particular pesticide. The residue definition used for dietary risk assessment purposes may

[5] OECD Guidelines for the Testing of Chemicals Test No. 503: Metabolism in Livestock

[6] Codex Alimentarius Commission, Recommended method of sampling for the determination of pesticide residues for compliance with MRLs, ftp://ftp.fao.org/codex/standard/en/cxg_033e.pdf

[7] FAO, Portion of Commodities to which Codex Maximum Residue Limits Apply and which is Analyzed. In Joint FAO/WHO Food Standards Programme Codex Alimentarius Vol. 2A, Part I. Section 2. Analysis of Pesticide Residues , FAO, Rome, 2000, 27-36. www.codexalimentarius.net/download/standards/43/CXG_041e.pdf

differ from that used for MRL enforcement purposes, thereby requiring different analytical methods. In the event one analytical method cannot cover all compounds included in a particular residue definition, more than one method may be necessary.

The major residue components should be determined individually as far as technically possible. The use of non-specific methods is generally discouraged. For some analytes, specific residue analytical methods might be unavailable or difficult to perform. In these cases, conversion to a common moiety is valid when all components containing that moiety are considered toxicologically important and when no single component is an adequate marker of residue concentration. Under these circumstances, a "common moiety method" may be used.

For enforcement methods surveillance laboratories prefer multi-residue methods, which could include a large number of analytes, as the laboratories generally do not have sufficient capacity to apply individual methods for all compounds possibly present. Despite potentially lower recovery rates associated with multi-residue methods. This fact is clearly demonstrated by the published results of national monitoring studies which indicate that compounds recoverable with multi-residue procedures are much more frequently analysed than those requiring individual methods. When the analyte is not amenable to the multi-residue method techniques, a single residue method may be provided.

In practice, data may have to be generated in such a way as to provide the flexibility to establish two separate residue definitions where appropriate, one for risk assessment and a second for MRL compliance monitoring. In such cases, where possible, applicants should either separately analyse for the individual components of the residue definition, rather than carrying out a common moiety method; or carry out first analyses according to a common moiety approach and a second series of analyses of the field trial samples for a suitable indicator molecule in parallel, if the common moiety methodology is unsuitable for practical routine monitoring and enforcement of the MRL at reasonable cost. The availability of appropriate methods for monitoring purposes should be considered.

The method(s) should:

- have the ability to determine all of the likely analytes that may be included in the residue definition (both for risk assessment and enforcement) in the presence of the sample matrix
- distinguish between individual isomers/analogues when necessary for the conduct of dietary risk assessments
- be sufficiently selective so that interfering substances never exceed 30% of the limit of analytical quantification (LOQ)
- demonstrate acceptable recovery and repeatability
- cover all crops, animals, and feed items being treated. If significant residues occur, cover processing fractions and drinking water
- cover all edible animal commodities if animals are likely to consume treated crops.

Enforcement methods should be suitable, where technically possible, to quantify residues at or below 0.01 mg/kg.

The methods used in various studies should be validated to demonstrate that they are fit for the purpose of the study. During the analyses of the samples the performance of the methods should be verified with appropriate quality control tests. Details of method validation

procedures, including testing the efficiency of extraction and confirmation, the criteria for acceptable performance parameters and format for reporting the method are given for pre- and post-registration studies in the OECD Guidance document on analytical methods[8] and in the Good Laboratory Practice elaborated by the CCPR[9].

Analytical methods provided should include:

- specialised methods used in the supervised trials and environmental fate studies which were submitted for evaluation, and
- enforcement methods.

The methods should be summarised including a clear outline of the compounds determined and the commodities for which the method is recommended. In addition, the specificity, repeatability of the method, the limit of quantification and the range of residue levels for which the method has been validated, the mean recovery and the relative standard deviation of recoveries at each fortification level, including the limit of quantification, etc should be given.

Information should be submitted to the JMPR not only on the principles of analytical methods used in the supervised trials and experiments but also the whole analytical procedure in detail including a precise description of the portion of sample analysed, stability of residues during sample processing, tests to prove the efficiency of extraction, recoveries at various levels, limits of quantification, limits of detection, chromatograms of samples and controls and a description of how the limit of quantification and detection were derived.

In addition to the methods developed by the manufacturers, published methods suitable for use by regulatory authorities should also be provided. The CCPR may not proceed with an MRL if no published regulatory method is available.

3.3.3.1 Extraction efficiency of residue analytical methods

Extraction efficiency is regarded as key for the development of methods, and data should be provided for the solvents and conditions (temperature, pH, time) typically used. Extraction efficiency may significantly influence the accuracy of the analytical results as poor extraction efficiency can be a major source of bias in a method. However, it cannot be checked by traditional recovery studies carried out with samples fortified shortly before analysis. The rigorous validation of the efficient extraction of all residues included in the residue definition can only be performed with samples that have incurred the analyte(s) through the route by which they would normally reach the sample. This is generally the case in metabolism studies, where the efficiency of extraction can be determined by means of radiolabelled analytes.

An IUPAC report[10] on bound xenobiotic residues in food commodities of plant and animal origin has recommended that “the extraction procedures used in residue analytical methods should be validated using samples from radiolabelled studies where the chemical has been applied in a manner consistent with the label and Good Agricultural Practices”.

Ideally, the commodities of interest from the metabolism and rotational crop studies should be retained for determining the extraction efficiency of the regulatory methods and methods used in supervised field trials and rotational crop studies. Justification for the commodities selected

[8] OECD Guidance Document on Pesticide Residue Analytical Methods, Series on Pesticides Number 39, Series on Testing And Assessment Number 72, 2007

[9] Codex Secretariat (2003) Revised Guidelines on Good Laboratory Practice in Residue Analysis CAC/GL 40 1993, Rev.1-2003, http://www.codexalimentarius.net/download/standards/378/cxg_040e.pdf

[10] Skidmore, M.W., Paulson, G.D., Kuiper, H.A., Ohlin, B. and Reynolds, S. 1998. Bound xenobiotic residues in food commodities of plant and animal origin. Pure & Applied Chemistry, 70, 1423–1447.

should be included in the study report. The retained commodities should be subjected to the extraction procedures from the analytical methods of interest so the extraction efficiency can be readily determined using radiochemical procedures (combustion analysis, liquid scintillation counting and chromatographic analyses using a radio detector). The efficiency can be compared to the relative amount extracted from the metabolism study, wherein the commodities are subjected to rigorous extraction procedures designed to remove most, if not all, of the potential analytes of interest. This comparison is known as radio-validation and should be conducted for the extraction schemes from all methods, if possible.

Alternatively, comparative extraction efficiency studies including the frequently used extraction solvents, such as acetone + water, ethyl acetate, and acetonitrile, can be conducted on samples from metabolism studies for compounds expected to be included in the residue definition(s). Information should be provided on the efficiency of extraction with the solvents used in relevant regulatory methods.

In cases where samples from metabolism studies are no longer available for development of a new analytical method, it is possible to "bridge" between two solvent systems. Incurred residues obtained, e.g., during supervised field trials, might be extracted using as a first step the solvent system under the conditions applied during the metabolism studies and then, in a second step, by using the solvent under consideration. Information on extractability can be obtained by direct comparison of the analytical results.

The testing of extraction efficiency can be either part of the metabolism study or the method development study. In any case, the results of the investigations should be cited in the relevant method validation studies since they are essential for the development of both types of methods (pre-registration and post-registration).

3.3.4 Stability of residues during storage and sample processing

Ideally samples for metabolism studies and residue analysis should be stored at/or below –18 °C. Storage under any other conditions needs to be recorded and justified. Storage stability studies are required because many routes of degradation and dissipation can occur, even under cold storage conditions.

In most residue studies, samples are stored for a period of time prior to analysis. During this storage period residues of the pesticide and/or its metabolites included in the residue definitions may decline due to processes such as volatilization or enzymatic degradation. Therefore, in order to be certain that the level of residues that were present in samples at the time of their collection are the same at the time of analysis, controlled studies are needed to assess the effect of storage on residue levels. Storage stability studies are performed to demonstrate that pesticide residues are stable during frozen storage of the samples to be analysed or show the degree to which residues decline in that period of time.

Storage stability studies should be designed in such a way that the stability of residues in the stored samples can be definitely determined. When the analytical method determines a ”total residue”, storage stability studies should include not only the total residue, but also separate analyses of all compounds which may be included in the residue definitions.

Normally, samples should be frozen within 24 hours of sampling or harvest. However, where this is not the case, the period of ambient or cooled storage should be considered in the planning of the freezer storage stability study.

It is preferred that the form of the commodity e.g., homogenate, coarse chop, whole commodity, extract, in a freezer storage stability study should be, as far as possible, the same

as that in the corresponding residue studies. In some cases the freezer storage stability study may need to reflect storage of more than one of the above forms. For example, if the trial samples are stored as homogenates for several months, extracted, and then these extracts stored for several weeks prior to final analysis, the freezer storage stability commodities should be handled in the same manner.

Where residues are considered to be stable, typical sampling intervals of 0, 1, 3, 6 and 12 months could be employed, which can be extended if the samples are stored for longer periods e.g., up to 2 years. In contrast, if relatively rapid decline of residues is suspected, sampling intervals such as 0, 2, 4, 8 and 16 weeks could be chosen. If there is no prior knowledge then the choice of intervals could be a combination of the above[11].

Duplicate samples of every commodity at each time point for all components of the residue definitions need to be analysed. However, if a significant difference (greater than 20%) exists between the results for the duplicate samples from the same time point, judgement should be applied and consideration given to analysing additional samples of the commodity from that time point.

If the freezer storage stability study uses incurred residues, then it should be established that all components of the residue definitions are present in the samples and at sufficient levels to allow any decline to be observed. In this case it is important that the sample is analysed fresh, i.e., immediately after sampling, and at appropriate storage periods thereafter. An old, i.e., frozen, sample with incurred residues may already have degraded to a stable level and when storage stability studies are conducted on an old sample, this may not reflect storage stability behaviour on fresh samples.

If test substances are added to untreated commodities in the laboratory, it is usually the active substance and/or relevant identified metabolites that are added. Where the residue definitions contain more than one component studies need to be designed to demonstrate stability of each component. Consequently, the use of mixed spiking solutions is not recommended as it could mask potential transformations from one compound to another. Therefore, the freezer storage stability study should be conducted with separate samples of each commodity under investigation spiked with the individual components of the residue definitions.

Samples should be spiked at 10×LOQ, the limit of quantification of the method for each analyte in order to adequately determine the stability of the residues under storage conditions. This will make it less likely that highly variable recoveries would prevent the determination of the stability of the residues. Spiking procedures should be undertaken in the same way as the spiking of the samples in the validation of the analytical methods e.g., for the recovery data. Where this is not possible, then a full rationale/ justification for the applicability of the data should be provided. In instances where no detectable residues are found in field treated commodities, or residue levels are close to the analytical method's LOQ, spiked control commodities should be employed in the freezer storage stability studies rather than incurred residues.

Residue storage stability studies in animal tissues, milk and eggs should be provided in the event animal commodity MRLs are needed.

In the case of studies involving crop commodities, the principles of extrapolation between commodities within specific commodity categories is supported .The commodity categories are as follows:

[11] OECD Guidelines for the Testing of Chemicals, Test No 506: Stability of Pesticide Residues in Stored Commodities

- commodities with high water content
- commodities with high acid content
- commodities with high oil content
- commodities with high protein content
- commodities with high starch content.

If residues are shown to be stable in all commodities studied, a study on one commodity from each of the five commodity categories is acceptable. In such cases, residues in all other commodities would be assumed to be stable for the same duration of time under the same storage conditions.

If MRLs are sought in just one of the five commodity categories, the stability of the test substance in 2–3 diverse commodities within the desired category should be tested. If the stability of analytes is confirmed, further studies with other crops in that category are not required.

If there is no observed decline of residues across the range of the five different commodity categories then specific freezer storage stability data for processed foods will not be needed. However, if instability is shown after a certain length of storage, any commodities (RAC or processed commodity) should be analysed within the demonstrated time period for stable storage.

Determinations as to whether sample integrity was maintained during collection, sample preparation, and storage should be made. The study conditions should reflect those to which the samples from the residue trials have been subjected. Where sample extracts have been stored for more than 24 hours prior to analysis, the stability of residues should be demonstrated with recovery studies performed under similar conditions.

In case of metabolism studies, the tests should show that the basic profile of radiolabelled residues has not changed throughout the duration of the study. It is impossible to spike samples before the identity of the residue and the length of time needed for metabolism studies are known. Storage stability data are not normally necessary for samples analysed within six months of collection, provided evidence is given that attempts were made to limit degradation of residues by appropriate storage of matrices and extracts during the analytical portion of the study.

If instability of the active ingredient is suspected or observed, based on other information, steps should be taken to safeguard the integrity of the study. In those cases where a metabolism study cannot be completed within six months of sample collection, evidence should be provided that the identity of residues did not change during the period between collection and final analysis. This can be done by analyses of representative substrates early in the study and at its completion. The substrate should be the item stored, i.e., if the matrix extract is used throughout the study and the matrix is not extracted later in the study, the stability of the extract should be shown.

If changes are observed, e.g., disappearance of a particular HPLC peak or TLC spot, additional analyses or another metabolism study with a shorter collection to analysis interval may be necessary

The residue concentration present in the intact sample material may also significantly change during the sample homogenization process (mincing, chopping grinding). The decomposition, evaporation of residues cannot always be observed with the usual recovery studies performed

by adding known amount of analytical standards to the homogenised test portion shortly before extraction. Acceptable recoveries may be obtained even if substantial portion of the test material 'disappeared' during homogenization. Systematic studies, performed with fruits and vegetables applying test substance mixtures containing a stabile and several other compounds with unknown stability, revealed that the decomposition of residues can be substantially reduced or eliminated under cryogenic processing of deep-frozen sample materials[12, 13].

Detailed reports should be submitted on stability of residues during storage and sample processing.

If trial supervised trial samples are always analysed within 30 days of their storage in frozen conditions, applicants can omit conducting a freezer storage stability study provided justification is given e.g., basic physical chemical properties data show residues are not volatile or labile.

3.4 USE PATTERN

Current GAP information on pesticides under consideration must be made available to the JMPR. The essential GAP is the set of current registered uses involving the highest rates and shortest PHIs for the same pesticide on the same crop in the same country and the use patterns in the supervised field trials should reflect this essential (often referred to as critical) GAP. The GAP information should be presented in a systematic manner according to the standardized format(s) given in this Manual. Formats are available for applications on agricultural and horticultural crops, post-harvest uses and direct animal treatments; other formats may be necessary for other types of use. The information should be presented in such a way as to facilitate comparison with supervised trial conditions.

GAP summaries are intended as an aid to the evaluation of submitted data and are to be provided in addition to certified labels. It is emphasised that copies of original labels have to be provided by the manufacturer(s) (or other data submitters) in addition to the summary information. Furthermore, the original label should be accompanied by an English translation of the relevant sections, e.g., dosage specifying if the concentration of spray or the kg/ha rate is primarily defined, application methods, growth stage of plants at the time of application of the pesticide, use conditions, and any restriction of use, if it is printed in a language other than English.

The summary should not include any use information which is not specifically given on the label, e.g., not kg ai/hL if only kg ai/ha is specified; not calculated PHI if application at a specific growth stage is authorized, not number of applications calculated from specified intervals and PHI. Crops included in groups, e.g., leafy vegetables, or fruits, should be individually named, unless they correspond with the commodities of the commodity groups in

[12] Fussell R.J., Jackson-Addie K., Reynolds S.L. and Wilson M.F., (2002): Assessment of the stability of pesticides during cryogenic sample processing, J. Agric. Food Chem., 50, 441.

[13] Fussell, R.J., Hetmanski, M.T., Macarthur, R., Findlay, D. Smith, F., Ambrus Á. and Brodesser J.P. (2007): Measurement Uncertainty Associated with Sample Processing of Oranges and Tomatoes for Pesticide Residue Analysis. J. Agric. Food Chem., 55, 1062-1070.

the actual Codex Commodity Classification[14]. The specific uses of a compound will not be evaluated if the relevant labels have not been provided.

Labels reflecting current GAP should be clearly distinguished from "proposed" labels. Furthermore, indexing of labels in such a manner to allow easy cross-reference to GAP summaries and supervised field trials would facilitate the evaluation. The specific uses of a compound will not be evaluated if the relevant labels have not been provided.

If GAP information is provided by responsible national regulatory authorities the above detailed information is required and the submission of the label is desirable. The submission of GAP information by national authorities is especially important in case of a generic pesticide produced by several manufacturers. In the latter case information on the chemical composition of technical products and their formulations used in the reporting country would also be desirable.

The use patterns should be summarised by the data submitters from two aspects, (1) biological efficacy and (2) formulation and application. The biological efficacy may be described by listing the major pests or diseases controlled, or it can be given in tabular form. In the latter case, the table should contain the commodities, pests controlled and the growth stage of crop when the application(s) is (are) likely to be required (see an example in Table 3.3).

Table 3.3 Information on pests and diseases controlled by terbufos (JMPR 1989)

Crop	Pests/diseases controlled	Timing of application(s)
Banana	Aphids, corm borer, corm weevil, nematodes	2-4 times per year
Cotton	Soil pests, wireworms	Furrow treatment at planting
Potato	Black maize beetle, wireworm	Furrow treatment at planting
Sugar cane	Nematodes, pink spittlebug, sugarcane froghopper, West Indian canefly, white grubs, wireworm	Furrow treatment, at planting or side dressing, 4 months PHI

Information on formulations, application methods and active ingredient dosage rates should be summarised in tabular form (see Tables 3.4–3.6). Specific information relevant to the use according to GAP (such as dosage depending on the pest; specified minimum intervals between repeated applications; total amount of active ingredient which may be applied during the growing season; restrictions on irrigation or aerial application) should be added as a comment or footnote(s).

Table 3.4 Registered uses of folpet on vegetables and cereals.

Crop	Country	Formulation	Application [a]		Spray			PHI, days
			Method	Rate kg ai/ha	Conc., kg ai/hL	Number	Interval [b]	
Barley	France			1.5				21
Beans	Greece	WP 800 g/kg	foliar	0.6–1.5	0.1-0.25	3–4		7
Beans	Portugal	WP 800 g/kg	foliar		0.13	1–2		7
Beans, green	Spain	WP 800 g/kg	foliar	1.6	0.16			21
Brassica vegetables	Italy	WP 800 g/kg	foliar	0.35–0.40				10

[14] FAO/WHO. 1993. Codex Classification of Foods and Animal Feeds in Codex Alimentarius, 2nd ed., Volume 2. Pesticide Residues, Section 2. Joint FAO/WHO Food Standard Programme. FAO, Rome. Note: the CCPR currently is working on the revision of classification of commodities. The reader is advised to check which groups have been finalised and enforced BY the Committee/CAC

Crop	Country	Formulation	Application [a]		Spray			PHI, days
			Method	Rate kg ai/ha	Conc., kg ai/hL	Number	Interval [b]	
Lettuce	France	WP 800 g/kg	foliar	0.64				21-41 [a]
Lettuce	Israel[3]	WP 800 g/kg	foliar	2.0		weekly		11

[a] summer PHI 21 days, winter PHI 41 days
[b] in days or weeks

Table 3.5 Post-harvest GAP uses of .... on fruit.

Crop	Country	Formulation	Application			Notes [d]
			Method [a]	Conc. kg ai/hL [b]	Contact time [c]	
Apples	Australia	EC 310 g/l	dip	0.05-0.36	minimum 10-30 secs	
Apples	France		dip	0.04-0.20	30 secs	
Apples	France		drench	0.04-0.20	30 secs to 2 mins	
Pears	Turkey		dip, drench or fog	0.075	max 2 mins	

[a] Examples of method: dip, drench, spray, fog

[b] Concentration of dip, drench, spray, etc

[c] Contact time or other requirement, as specified on the label

[d] Explain if treatment is variety dependent, if commodity is not to be consumed or sold for an interval after treatment, etc, as specified on the label.

Table 3.6 Registered uses of .... for direct external animal treatment.

Animal [a]	Country	Formulation	Application			WHP slaughter [e]	WHP milk [f]
			Method [b]	Rate [c]	Conc. [d]	days	days
Beef cattle	USA	SC 25	pour-on	2 mg ai/kg bw	25 g/L		
Dairy cattle, non-lactating	USA	SC 25	pour-on	2 mg ai/kg bw	25 g/L		
Dairy cattle, lactating	USA	SC 25	pour-on	2 mg ai/kg bw	25 g/L		
Sheep	Australia	25	jetting	0.5 L fluid per month of wool growth	25 mg/L	0	

[a] Farm animal as stated on the label.

[b] Methods include pour-on, dip, ear-tag, jetting, spraying.

[c] The rate or dose may be expressed per animal or per kg bodyweight. State explicitly if the dose is expressed on active ingredient, formulation or spray solution.

[d] The concentration of the spray or dip, etc., applied to the animal. The application concentration for a pour-on is the same as the formulation concentration.

[e] With-holding period. Label instruction on interval between animal treatment and slaughter for human consumption.

[f] Label instruction on interval between animal treatment and milking.

When different formats are used to report GAP data on special uses, e.g., seed dressings, they should always include details on the following aspects of the use pattern:

- Responsible reporting body
- Pesticide names
- ISO-E common name. For other international code names, indicate the Standards organisation between brackets-, e.g., (British Standards Institute: BSI), (American National Standards Institute: ANSI), (Japanese Ministry for Agriculture, Forestry

and Fisheries: JMAF). Proprietary name(s) or trade name(s) can also be given if relevant.

- CCPR number of pesticide, if available
- Information on the use pattern as described on the approved label. Use rates and concentrations must be explicitly expressed in terms of active ingredient.

If GAP information is provided by responsible national regulatory authorities the above detailed information is required and the submission of the label is desirable. The submission of GAP information by national authorities is especially important in case of a generic pesticide produced by several manufacturers. In the latter case, information on the chemical composition of technical products and their formulations used in the reporting country would also be desirable. Governments or responsible national organisations are requested to summarise the GAP information, as shown in Table XI.2 (Appendix XI). The entry required under "Country" is the name of the country whose GAP is listed in the table, which is not necessarily the same as that of the country submitting the information. The table should strictly reflect the information contained on the label. In the case of extensions of use that do not appear on the product label, i.e., off-label approvals, a copy of the 'regulatory approval' document or its English translation should be provided.

The following GAP information requirements are re-emphasised:

- The summary should not include any information on use that is not given on the label.
- Valid copies of current labels must be provided, together with English translations of the relevant sections.
- Crops included in crop groups should be named individually unless they correspond with the actual Codex Commodity Classification of Food and Animal Feed[15].
- Individual commodities should preferably be referenced to the Codex Classification of Food and Animal Feed.
- Labels reflecting current GAP should be clearly distinguished from 'proposed' labels.
- Summary information on GAP relevant to the submitted supervised trials and current GAP with higher rates or smaller PHIs, etc for the same pesticide on the same crop in the same country should be submitted. However, to avoid unnecessary costs for the translation of labels by industry and to avoid unnecessary extra work on uses that are inadequately supported by residue data, copies of the original labels (and if necessary the translations) need be provided only for those uses that are adequately supported by residue data according to FAO requirements.

3.4.1 Periodic review compounds undergoing re-registration by national authorities

In national review programmes, current uses are frequently revised to meet new requirements for the safety of human health and the environment. The data submitted to JMPR therefore often include both current registered uses and labels awaiting approval by national authorities. Data from field trials, however, usually relate to new uses. In such cases, the JMPR cannot amend or recommend maintenance of existing MRLs.

[15] FAO/WHO. 1993. Codex Classification of Foods and Animal Feeds in Codex Alimentarius, 2nd ed., Volume 2. Pesticide Residues, Section 2. Joint FAO/WHO Food Standard Programme. FAO, Rome.

Furthermore, for some compounds, both old labels and revised labels stipulating lower rates exist simultaneously, and MRLs reflecting the adjusted uses cannot be established.

In order to ensure the best review of data on residues, the following information on periodic review compounds undergoing national re-registration should be submitted to the FAO Joint Secretary to the JMPR:

- current registered uses
- current registered uses that will be supported
- envisaged new or amended uses
- the status of the registration and an estimate of the date on which new or amended uses will become GAP
- an estimate of the date on which old registered uses will be revoked
- a clear description of the uses (new, amended, or current but not to be supported) to which the data from supervised trials of residues relate.

Reviews of such compounds should focus on new or amended uses or current uses that will be supported, giving full details of the evaluation. MRLs will be recommended only for current uses.

MRLs will be recommended for new and amended uses only when those uses have become GAP.

3.4.2 Presentation of GAP information

All information should be presented in English and must come directly from approved labels.

Crops and situations should be described exactly as on the approved label. If the approved label is for use on crop groups, e.g., "citrus" or "orchard trees", this should be the entry in the GAP table. Individual crops included in national grouping should be identified by their English names (local varieties in brackets) in Table endnotes, preferably using crops associated with the commodity descriptions given in the Codex Classification of Foods and Animal Feeds.

Pest information can be given in the form of the English name of a specific pest or in the form of a "broader" group of related pest species, e.g., powdery mildews, spider mites, lepidopterous insects, yeasts, etc. The use of a Latin name (between brackets) may often provide clarification. Avoid the use of very broad classes of pest organisms, such as fungus diseases, insect pests or similar indications, as this generally provides insufficient information.

Present the formulation of the pesticide product using the two-letter coding system developed by GIFAP and adopted by FAO and CIPAC. The codes are given in Appendix III. The definition of the terms can be found in the FAO Manual on the Development and Use of FAO Specifications for Plant Protection Products (2006)[16].

The concentration of active ingredient in the formulated product has to be presented for liquid formulations in g/L, such as EC (emulsifiable concentrate) or SC (suspension concentrate, also called flowable concentrate) provided that the label instructions give the dosage rate in litres of the formulated product per ha or per 100 litres spray liquid (or in similar measures).

[16] FAO. 2006. Manual on the development and use of FAO specifications for pesticides. 1st edition.. http://www.fao.org/agriculture/crops/core-themes/theme/pests/pm/jmps/manual/en/

The concentration of active ingredient in solid formulations is expressed on a w/w basis as g/kg or % of active ingredient in the solid product.

The type of treatment must be given in sufficient detail, e.g., the type of apparatus used and its output, such as ULV, high volume sprayer, etc. There is often a link between the type of treatment and specific formulations developed for such applications. It has to be recognised that the residue deposit from different types of treatment may differ considerably, e.g., a ULV application may give rise to a larger residue deposit than a high volume application, both with the same amount of active ingredient per hectare.

The greater part of the residue at harvest consists of the residue deposit applied at the last application. Since the persistence of the pesticide residue may be different in different times of the season, the growing stage at the last application should be recorded. For example, in moderate climate zones the residue decrease of several pesticides in autumn is in general less than in high summer, due to the higher light intensity (UV) and the higher temperature in the latter period. Code numbers (preferably BBCH) used to describe growth stages should be fully explained.

State the number of treatments per season only if specified on the label. Since the treatment intervals, and thus the number of treatments, are often linked to dosage rates, the recommended alternative situations should be clearly indicated, e.g., for scab control on apples dosage A is applied for preventive treatments at 7–8 days intervals or a higher dosage B (approximately1.5×A) with an interval of 10–14 days. The interval between successive applications may have a considerable impact on the amount of residue deposit at a certain time since residues from earlier applications of the pesticides may still be present at the time of a successive treatment. Some labels specify the maximum total application rate per season. This information should be included preferably as a footnote.

The application rate should always be expressed in metric units. See Appendix X, section "General" for non-metric to metric unit conversion factors. The dosage rates should also be expressed as amounts of active ingredient in g or kg/ha. When indicated on the label, the maximum amount of active ingredient which can be applied within a growing season should also be provided as such, and not calculated as a maximum number of applications.

In cases where the indications on the label are given in g/hL or kg/hL (spray concentration), state this spray concentration but do not calculate the kg ai/ha equivalent with the average amount of spray liquid used per hectare. If prior compilations included calculated kg ai/ha values, this fact should be clearly distinguished from label instructions.

The pre-harvest interval (PHI) in days prescribed or recommended and stated on the label should be presented for the commodities concerned. If different PHIs are recommended for the same or similar commodity, e.g., for glasshouse or outdoor grown crops, or in the case of higher dosage rates, the particular circumstances should be clearly indicated. Sometimes the timing is indicated in terms of crop growth stage, e.g., when the pesticide is recommended for use at a very early stage of the crop development, such as bud burst in apple and pears, pre- and post-emergence applications for weed control, etc. In such cases the reference to the growth stage of last application can be extremely helpful to clarify GAP. PHIs included in the GAP table should only be taken from explicit PHI statements on approved labels.

In the case of direct treatment of animals, the withdrawal or withholding period between treatment and slaughter for human consumption or treatment and collection of milk or eggs should be stated. For application of pesticide to forage and fodder crops, the subsequent grazing restrictions for food-producing animals should also be indicated.

3.5 RESIDUES RESULTING FROM SUPERVISED TRIALS ON CROPS

Supervised field trials (crop field trials) are conducted to determine pesticide residue levels in or on raw agricultural commodities, including feed items, and should be designed to reflect pesticide use patterns that lead to the highest possible residues. Objectives of crop field trials are to:

- quantify the expected range of residue(s) in crop commodities following treatment according to the proposed or established good agricultural practice (GAP)
- determine, when appropriate, the rate of decline of the residue(s) of plant protection product(s) on commodities of interest
- determine residue values such as the Supervised Trial Median Residue (STMR) and Highest Residue (HR) for conducting dietary risk assessment
- derive maximum residue limits (MRLs).

Crop field trials may also be useful for selecting residue definitions by providing information on the relative and absolute amounts of parent pesticide and metabolites.

The term "supervised trials" covers the application of a pesticide approximating targeted or authorised use including studies for residues in crops grown in fields, e.g., outdoor, in greenhouses (glass or plastic covering) and in crops treated after harvest, e.g., stored grains, wax or dip treatment of fruits, and involves careful management of the trial procedure and reliable experimental design and sampling. Residue trials performed along the lines described in the OECD Test Guideline[17,18] are considered by the JMPR as supervised trials. New supervised trials should be planned, implemented, documented and reported according to the OECD (or comparable) GLP principles (OECD, 1995–2002) or in compliance with national regulations which ensure the quality of residue data.

Maximum Residue Limits are largely derived from residue data obtained from supervised trials designed to determine the nature and level of residues resulting from the registered or approved use of the pesticide. Since this work will usually have been done before registration is obtained, in many cases the trials should be based on the intended registered use. Since the compounds are evaluated by the JMPR after they have been registered by national authorities (see Chapter 2 "*Selection of compounds for evaluation*") some of the trial data may not be relevant for JMPR evaluations. Therefore normally only supervised trial data reflecting the current GAPs should be submitted. Note however, that in cases with a limited number of trials at GAP, results from other supervised trials can provide supporting information, such as residue decline study to indicate rate of concentration decrease or trials with higher rates leading to residues below LOQ. Residue data should be presented primarily for mature crops at normal harvest. However, where a significant part of the consumable crop is present at the time of application, some residue dissipation studies are required to complement the residue data obtained at normal harvest.

Residue decline data are necessary for uses where the pesticide is applied when the edible portion (human food or animal feed) of the crop has formed or it is expected that residues may occur on the food or feed commodities at, or close to, the earliest harvest time. Residue decline data are used in residue evaluation for purposes such as:

[17] OECD Draft Test Guideline: Crop Field Trial 19-Feb-2009

[18] Draft Revised Guidance Document on Overview of Residue Chemistry Studies, (Series on Testing And Assessment No.64) 18-Feb-2009

- determining if residues are higher at longer PHIs than requested;
- estimating the half-life of the residues
- determining whether alteration of the PHI to levels represented in the decline trials around the GAP PHI affects the residue levels
- allowing for a degree of interpolation to support use patterns, including PHIs, not directly equivalent to those used in the trials on a case-by-case basis
- determining the profile of the residue over time to add to the understanding of metabolism of the pesticide under conditions more applicable to GAP and to assist in appropriate selection of residue definitions
- determining the time interval to reach maximum residues for a systemic compound applied to crops such as potatoes or peanuts.

For estimating maximum residue levels of pesticide residues in commodities moving in international trade, results of supervised trials representing the typical agriculture practices, growing and climatic conditions prevailing in all exporting countries should ideally be considered. Therefore, it is in the interests of national governments and the responsibility of data submitters to provide all relevant valid supervised trial data and supplementary information to the FAO Panel in order to ensure that the recommended limits cover the maximum residues arising from the authorised use of a pesticide and a realistic estimate can be made for the long-and short-term dietary intake of residues.

It is emphasised, however, that the JMPR performs the evaluation of the submitted information and estimates maximum residue levels if the database is considered sufficient, regardless of whether it represents worldwide use or is limited to a region. The number of trials (generally minimum 6–10) and samples is dependent on the variability of use conditions, the consequent scatter of the residue data, and the importance of the commodity in terms of production, trade and dietary consumption. Residue data should be available from trials, preferably carried out in at least two separate years or at least representative of different weather conditions in accordance, or approximately in accordance, with Good Agricultural Practice. If uses are authorised in regions with substantially different climatic conditions, trials should also be carried out in each region. Residue data from only one season may be considered sufficient provided that crop field trials are located in a wide range of crop production areas such that a variety of climatic conditions and crop production systems are taken into account.

3.5.1 Planning and implementation of supervised trials

The general principles which should be considered in planning, conducting and reporting supervised trials are briefly described hereunder. Detailed guidance can be found in the referred documents.

Field trials should be conducted in regions where the crops are predominantly grown commercially and should reflect the main types of crop maintenance and agricultural practice, especially those which can significantly impact residues, e.g., bagged and unbagged bananas, furrow and overhead irrigation, pruning of grape leaves. Soil type, e.g., sand, loam, sandy loam, should be identified and reported for all crop field trial sites. If the product is directly applied to soil, the field trials should include field sites with different soil types.

Post-harvest treatments on stored products such as potatoes, grains and seeds are often carried out in a number of storage locations with variable conditions in regard to temperature,

humidity, aeration, etc. Information should be available on the use practice and all the conditions under which the treated commodities are kept. How commodities are stored during application can vary from commodities stacked in sacks, box stores and heaps to automated systems in large-scale silos or automated systems for fruit treatment.

Crop variety may influence the uptake of the active ingredient and the metabolism capability. Residue trial reports should identify which crop varieties were utilized. In a set of residue trials, a selection of commercially important varieties of a crop, e.g., table and wine grapes, seasonal variations, e.g., winter wheat vs. spring wheat, vegetation period of different varieties, different maturation periods, e.g., early and late maturing fruit varieties, and morphologic variability, e.g., cherry tomatoes, should be considered. This will provide a range of conditions of use that are representative of actual agricultural situations.

Plot size may vary from crop to crop. However, plots should be large enough to allow application of the test substance in a manner which reflects or simulates routine use and such that sufficient representative sample(s) can be obtained without bias, generally at least 10 m^2 for row crops and typically four trees or eight vines for orchard and vineyard crops. Plots should also be large enough to avoid contamination during mechanical sampling or harvesting if applicable. Control (untreated) plots should be located in the immediate vicinity of the treated plot(s) so that cultivation and cropping take place under similar/identical conditions. It is also important to ensure that plots are adequately buffered or separated to avoid cross contamination.

Application of the test substance may be made with hand-held or commercial equipment as long as the equipment can be calibrated. Hand-held equipment used to make test substance applications in crop field trials should do so in a manner that simulates commercial practice. Where water is used for preparing the spray solution for aerial application and the label rate specifies spray volumes $\geq$ 18.7 litre/ha (2 gallons/acre) for row crops and $\geq$ 93.5 litre/ha (10 gallons/acre) for tree and orchard crops, the field trials can be performed with ground equipment instead of aerial application.

The *maximum label rate* of the active ingredient with maximum number of applications and minimum re-treatment interval (according to the critical GAP, *c*GAP) should be used when applying the test substance for crop trials.

Application timing is governed by requirements to control pest and plant growth stage, e.g., pre-bloom or 50% head emergence, and/or as number of days prior to harvest. Any time that a specific PHI is indicated on the label, e.g., “Do not apply this product less than 14 days prior to harvest.”, that specific PHI must be used in the crop field trials as a component of the *c*GAP, whereas the growth stage at application is of minor importance. Inversely, there are cases where the growth stage is a critical component of the GAP, e.g., pre-emergence, at planting, pre-bloom, flag leaf or head emergence, while the PHI is of secondary importance. In these cases it is important to include as many varieties of the crop as possible in order to evaluate an appropriate range of PHIs, e.g., shorter and longer intervals from planting to maturity in the case of pre-emergence application to an annual crop. Basically in all trials both the growth stage at application (preferably as BBCH code) and PHI should be recorded.

For all *pre-harvest applications*, the *application rate* should be expressed in terms of amount of product and/or active ingredient per unit area, e.g., kg ai per hectare, and where appropriate, the concentration, e.g., kg ai/100 litres, at which it is applied.

Row crops (potatoes, wheat, soya beans, etc.) are typically treated with broadcast sprays for which plot area (length × width) is a key consideration. In contrast, for some crops such as tree nuts, tree fruits, trellised vegetables and vines, the crop height, crown height or tree

height, i.e., treated foliage height, should be recorded in order to allow crop row volume or tree row volume estimations or rate per unit area calculation as needed. Special consideration may be needed for foliar applications to '*tall' crops,* e.g., orchard and vine crops, hops, greenhouse tomatoes, where flat boom spraying is not common practice and (air assisted) mist blowing equipment is often used. It is important to consider and report both the spray concentration, e.g., kg ai/100 litres, and spray volumes, e.g., litres spray mixture/ha, at the various crop growth stages when planning and conducting crop field trials in these crops.

Application rates for *seed treatments* are normally expressed as amount of active ingredient per unit of seed weight, e.g., g ai/1000 kg seed, and seeding rate, e.g., kg seed/hectare.

In case of post-harvest dip or drench treatment of fruit, concentration of the active ingredient in spray liquid should be recorded, e.g., kg ai/100 litres or hL, as well as the amount of fruit treated per volume and contact time in seconds. Where dips are replenished to maintain the active ingredient concentration during treatment, i.e., where residue stripping occurs, the additional 'top-up' treatments should also be recorded. For powdering, fogging or spraying of stored goods, e.g., potatoes or grains, the application rate should be recorded, e.g., kg ai/ton or 1000 kg. The application rate for gases and aerosols used in *fumigation* should be expressed as amount per unit volume of treated bulk good, e.g., g ai/m^3.

The design of *residue decline studies* should include 3 to 5 sampling intervals in addition to the target PHI (if practical, include 0 day sampling). These sampling intervals should be spaced somewhat equally and, where possible, sampling should occur at shorter and longer time points relative to the target PHI, when such is permitted by the window of commercial maturity. When multiple applications are involved, a sampling point immediately prior to the final application is desirable to determine the contribution of earlier applications and the effect on residual half-life.

Another acceptable residue decline study design option, referred to as "reverse decline," involves applications being made to separate plots at different time intervals from the targeted commercial harvest date. All plots are then harvested on the same day, the commercial harvest date, resulting in different intervals from last application to harvest. Such a design may be appropriate for situations where the commodity is likely to be harvested within a narrow time window. For example, such a study could examine the use of a pre-harvest desiccant close to maturity where harvest must occur within a short time frame after application.

When residue decline studies are conducted, sampling of more than one commodity or matrix per crop may be needed. This will be the case whenever different commodities are used as food or feed at different growth stages of the crop, e.g., cereal forage, cereal fodder, cereal grain and straw. This will result in two or more sets of sampling dates within one residue decline trial.

The *formulation tested* in crop field trials should be as close as possible to the commercially available end-use product for the crop or commodity.

Adjuvants such as wetting agents, spreader-stickers, non-ionic surfactants, and crop oil concentrates may result in better deposition, penetration, or persistence of pesticide residues in or on the plant. Therefore, for a test substance which has a label allowance for the use of an unspecified adjuvant, crop field trials must include an adjuvant (any locally-available adjuvant), applied according to the label recommendation of the adjuvant. For a test substance which has a label recommendation for the use of a specific adjuvant, crop field trials must include the adjuvant, or another adjuvant with similar properties, applied according to the label recommendation of the adjuvant.

Additional plant protection measures, which are not the subject of crop field trials, are often required for crop management during the course of a study to control weeds, disease or other pests (could also include fertilizers, plant tonics or plant growth regulators). These crop and plot maintenance products should be chosen from among those products which do not affect, i.e., interfere with, residue analyses for the components of the relevant residue definition. Additionally, these maintenance products should be applied to both the control and treated plots in the same manner, i.e., rate and timing.

In many cases, active ingredients may be applied in combination, i.e., tank mix, pre-mix or sequential, in crop field trials to a single treated plot as long as there is clear analytical separation, i.e., no analytical interference, of active ingredients and any relevant metabolites. A single sample may then be collected from the treated plot and prepared for residue analysis for two or more active ingredients. The exception to the combination of active ingredients in this manner would be those that are known to be synergistic, but will not be formulated together in registered products.

3.5.1.1 Number of trials

Currently there is no international agreement on the minimum number of trials to be provided for the estimation of STMR, HR and MRL. Different countries have determined the minimum number of crop field trials required for registration of a use on a crop and establishment of a suitable MRL. Geographic distribution of field trials within a country or region serves to ensure that data will be available for trials in key crop production areas, and a sufficient variety of horticultural practices may be represented in a crop field trial data set.

The JMPR has not specified the minimum number of trials required for estimation of maximum residue levels, high (HR) and supervised trial median residues (STMR). The evaluation of the experience gained with the application of statistical methods for supporting the estimation of maximum residue levels (see section **6**.10) indicated, however, that a minimum of 15 valid residue data would be required to obtain a realistic estimate for maximum residue level using the statistical method.

The OECD Working Group on Pesticides elaborated guidance on the minimum number of trials[19] which should be generated for registration of a pesticide in all OECD countries where the target GAP is uniform, i.e., maximum 25% deviation in one of the key parameters. The number of supervised trials required in various OECD countries and the number of trials recommended for a comprehensive submission is described in Appendix XII. Though, the JMPR does not require specified number of trials, adherence to the OECD guidance may be a safe way to decide on the minimum number of outdoor field trials to be submitted for evaluation.

3.5.1.2 Consideration of various types of formulations and derivatives of active ingredient

Data needed to cover *additional formulation types* or classes shall be addressed on a case-by-case basis.

Controlled release formulations, e.g., certain microencapsulated products, normally require a complete data set tailored to that particular use. Since these formulations are designed to control the release rate of the active ingredient, increased residues are possible compared to other formulation types.

[19] Draft Revised Guidance Document on Overview of Residue Chemistry Studies (Series on Testing And Assessment No.64) 18 Feb 2009

Granular formulations applied intact will generally require a complete data set regardless of what data are already available for other formulation types. No residue data will be required for dusts if data are available at the *c*GAP for a formulation of the active ingredient applied as a wetting spray, e.g., emulsifiable concentrates (EC), wettable powders (WP).

The most common formulation types which are diluted in water prior to application include EC, WP, water dispersible granules (WG), suspension concentrates (SC) (also called flowable concentrates), and soluble concentrates (SL). Residue data may be translated among these formulation types for applications that are made to seeds, prior to crop emergence, i.e., pre-plant, at-planting, and pre-emergence applications, just after crop emergence or directed to the soil, such as row middle or post-directed applications (as opposed to foliar treatments).

Some active ingredients, e.g., phenoxy herbicides, can be applied as one or more salts and/or esters. Different salts of an active ingredient may be considered equivalent for residue purposes in most cases regardless of the timing of the application. However, examples for which additional data may be needed for a new salt include the presence of counter ions that impart surfactant properties, significantly change the degree of dissociation, or chelate with the active ingredient ion. If the PHI is less than or equal to 7 days, the different esters are considered as new formulations of that active ingredient for the purposes of determining data needs, and bridging studies would be required as for different formulations.

In the case of up to 25% increases or decreases of the nominal active ingredient application rate, the number of applications, or the PHI, under otherwise identical conditions, the residue results can be assumed to be comparable. Tolerances on the parameters should be those that would result in ±25% change in the residue concentration, not ±25% changes in the parameters themselves. It is ±25% for application rate because application rate is directly proportional to residue concentration (see also section **6**.2). When combining field trials for a complete data set for a crop use, this "25% rule" may be applied to any one of the critical GAP components; however it is not acceptable to apply the rule to more than one *c*GAP component listed here at a time. The same principle may be applied for judging the equivalency of residue data where a specific formulation type with different active ingredient content was used in the trials, provided that the *c*GAP is not changed significantly as a result, e.g., no more than 25% increase in amount of active ingredient per unit area.

Bridging studies (see also **6**.2 Formulations) are an essential extrapolation tool to make the best use of existing data to support minor changes or variations to existing uses. A bridging study normally involves a comparison of different formulations or application methods for the purpose of data extrapolation, but may or may not involve side-by-side comparisons. If bridging trials are deemed necessary and a pesticide is used on a wide range of crops, data should be generated for at least three major crop groups (one crop per crop group), e.g., a leafy crop, a root crop, a tree fruit, a cereal grain, an oilseed with a minimum of four trials per crop. The trials should be carried out on crops that would be expected to show high levels of residue (often those with applications at or near harvest). If a bridging study is conducted and residues are significantly higher with a new formulation or different application method, or the combined residue data set obtained with different formulations would lead to a higher MRL, generation of a complete new data set may be necessary.

3.5.2 Rotational crop studies (limited field study)

Metabolism and residue studies conducted in rotational crops (sometimes referred to as follow up, following, succeeding crops) are typically required for uses of pesticides where it is reasonable that a food or livestock feed crop may be planted after the harvest of a pesticide treated crop (or in some cases replanting of crops after failure of the pesticide treated crop).

Residues in rotational crops are determined to verify if and at what levels residues detected in the rotational crop metabolism study (see section **3**.2.3.2) may be found under field conditions. The data generated are used to determine if MRLs in rotational crops will be required or to establish appropriate rotational restrictions at the national level, i.e., the time from application to a time when rotation crops can be planted where there will be no residues of toxicological significance in rotational crops.

The residues in rotational crops are usually composed of various metabolites in low concentrations and the compounds included in the residue definition are generally below the LOQ and do not require any further action. Rotational crop studies are normally not required for pesticide uses in permanent crops, e.g., various tree and vine crops, or semi-permanent crops, such as asparagus, where rotations are not part of the normal agricultural practices.

In cases where the TRRs exceed the trigger value (0.01 mg/kg) in a RAC from crops in the confined rotational crop metabolism studies, then the nature of the residues in those test crops having a TRR greater than 0.01 mg/kg will normally need to be determined and submitted.

If the relative toxicity of the components found in the rotational crop metabolism study is considered to be less than that for the primary crops residue definition, then rotational crop studies may not be needed, even if residues above 0.01 mg/kg could be expected. In such cases, a reasoned argument should be provided to support the decision.

If there are particular toxicological concerns, it may be necessary to require residues in rotational crops (limited field) study in circumstances where residues could be expected below 0.01 mg/kg.

Field rotational crop studies are conducted with a non-radiolabelled pesticide applied under the agronomic use practices at the maximum seasonal application rates in at least two diverse agricultural regions representative of the use. The study design should seek to address situations where the potential uptake of pesticide soil residues in rotational crops is the highest, either due to mode of application, soil type and soil temperatures, pesticide persistence or other environmental or cultural practices.

Studies involving a root/tuber crop, a small grain crop, and a leafy vegetable crop are normally sufficient to represent all possible rotational crops. If there is no uptake of significant residues in one or two of the representative crops in the metabolism in rotational crop study, a limited field study is still required for three different representative crops[20]. If the pesticide is to be applied primarily to paddy rice, an alternative study design, such as aging the pesticide under flood conditions prior to rotation to field crops, may be required.

3.5.3 Sampling and analytical methods

The basic requirements concerning sampling and analysis are described in section **3**.3 of this chapter. The sampling methods are given in Appendix V.

Analysis should include all residues significant for both residue definitions (MRL compliance and dietary intake assessment). The concentration of residue components should be determined individually as far as technically possible.

[20] OECD Guidelines for the Testing of Chemicals, Test No. 504: Residues in Rotational Crops (Limited Field Studies)

3.5.4 Reporting the results of trials

To ensure the availability of all detailed information necessary for evaluation, copies of the complete original reports on the supervised trials have to be submitted, preferably in English or with sufficient keys or translation to facilitate review. In addition, the results of supervised trials should be summarised in the form given in Table XI.3 (Appendix XI). The explanations for the entries in the table are the same as those given under section **3**.4 "*Use pattern*" in this chapter. The location of trials should be given by country and region within that country. Names of countries should preferably be recorded in English. An acceptable, but less preferred, alternative is to use the ISO alpha 3 code made up of 3 capital letters (ISO, 1993).

If more than one analyte is measured, the concentrations of individual residues should be reported separately. The total residue may be calculated additionally. In the latter case the conversion factors used for the calculation should also be reported.

The residue values should be reported taking into account the uncertainty of analytical measurement. In view of the performance of current analytical techniques, that would correspond to two significant figures. E.g. 0.0012; 0.012; 0.12; 1.2; 12 up to 99 mg/kg. For convenience residues ≥100 may be expressed with three figures.

The recovery values obtained at different concentration levels should be reported, but the residues measured should not be corrected for recovery. If the correction was done by the laboratory, this fact should be specifically mentioned together with the reasons for the correction and the method used for correction.

The analytical replicates (obtained by analysing replicate portions of the same laboratory sample) should be distinguished from results of replicate samples. The average value of the analytical replicates should be included in the summary table (Table XI.3, Appendix XI).

- Samples taken from replicate plots (in close vicinity and treated on the same day with the same equipment using the same formulation at the same nominal rate) and replicate samples taken from a single plot should be clearly distinguished. For each trial, result from each replicate plot should be listed separately.

When primary samples are analysed, the weight of the primary samples should be included in the report.

The method of expression of residues should be clearly indicated including, for instance, conversion factors applied, correction for blank or control samples, or recoveries. Uncorrected (or unadjusted) residue data should always be included in the report.

The residues in animal feed should be reported on a dry weight basis (see also **6**.13 Expression of Maximum Residue Limits). If it is not expressed on a dry weight basis this should be clearly stated, together with any information on the moisture content.

Based on the experience of the FAO Panel, the presentation of the following information in the summary of supervised trials is often insufficient or ambiguous, and needs special attention. The supplementary information and explanation of trial conditions can be given as remarks or footnotes.

- Description of crop – other names (varieties or cultivars) can be given in brackets.
- Dates of application in relation to growth stage and intervals between applications and between last application and sampling. Clear indication of the related dates of multiple applications and sequential sampling is of special importance. Especially important is information on the intervals of handling and storage conditions from

sampling to sample storage, and intervals and conditions of sample storage prior to analysis.

- Method of application in relation to GAP. Application rate in metric units.
- Sampling method should be described in detail, including the number of primary samples in the composite sample and the total weight of composite sample, and the method of preparation of subsamples from a bulk sample. In the case of new trials, the sample sizes given in the FAO Guidelines on Producing Pesticide Residues Data from Supervised Trials should be followed as far as possible (Appendix V).
- Sample preparation should be carried out according to the Codex Guide on "Portion of Commodities to which Codex MRLs Apply" (Appendix VI). The portion of the commodity which is analysed should be unambiguously described.

When the residues in edible and inedible portions are analysed separately the mass ratios of the two portions should be reported for each sample, for example, residue data measured in citrus pulp alone are useful for estimating dietary intake but cannot be used for estimating a maximum residue level.

The JMPR must be able to clearly identify the portion of commodity in which the residues were determined.

In the case of cereal grains, some grains and seeds are still in the husks, and for rice results are often reported on polished rice. (The residue levels are usually considerably different for those sorts of commodities. Furthermore, the rice commodities analysed should be in the form in which they may enter international trade.)

Stone fruit data should clearly indicate whether the residue is expressed on the whole commodity without stem or with stone and stem removed. In the latter case the proportion of stone in whole fruit (% w/w) should be given at each sampling interval.

In animal products, for fat-soluble pesticides, the data for meat should indicate whether it is expressed on the whole trimmable fat basis or on extracted or rendered fat and the types of fat involved.

The requirements described in this chapter should be applied for all trials, including those performed by government institutions, irrespective of their sponsor

3.6 SUBMISSION OF INFORMATION FOR ESTIMATION OF MRLs OF PESTICIDE RESIDUES IN/ON SPICES

The 35th Session of the CCPR decided to elaborate MRLs based on monitoring data. Monitoring data had previously been used by the JMPR for estimating EMRLs; however, more detailed information is required for estimating MRLs for pesticides which may be used according to the current agricultural practice.

Registered or permitted uses of pesticides on specific spices may not be generally available, and farmers may use a range of available pesticides to protect their spice crops from pests and diseases that have been found to be effective against pests and diseases on vegetables. In addition, the spices may be indirectly exposed to pesticides applied to the primary crops within which spice-producing plants are also grown, i.e., as an inter-crop. Therefore, supervised residue trial data on spices may not be readily available. Residue monitoring data can be a source of information in the estimation of MRLs for these commodities.

Post-harvest treatment is usually made on a spice that has been aggregated from several different cropping areas. The original crops may have been exposed to different pesticides, which may increase the number of pesticide residues for which analysis should be undertaken when spice samples are investigated.

3.6.1 Submission of monitoring data

Spices are usually difficult substrates for the determination of trace organic contaminants. Reliable identification and quantitative determination of pesticide residues in spice samples of unknown origin can be a very laborious and complicated task, especially where access to GC-MS and LC-MS-MS techniques is limited. More commonly multi-residue methods are used for analysis of samples in such situations. However, MRLs may only be estimated for pesticides for which analysis was specifically targeted and positive results were confirmed with an appropriate method.

As the spice commodity is usually aggregated from several sources (fields) and not blended, it cannot be considered a single lot, as with samples from supervised trials. Consequently, the sampling procedure involved in the provision of residue data for the estimation of MRLs should be performed with utmost care. Primary samples should be taken from as many randomly selected positions as technically possible (preferably > 25) and the mass of laboratory sample should be ≥1 kg. Where a large amount of material (> 5 tons) is involved it is preferable that more than one independent sample be taken to obtain information on the residue distribution.

The evaluation of monitoring data submitted to the JMPR indicated that the distributions of residues were scattered or skewed upwards, and no distribution fitting appeared to be appropriate. The 2004 JMPR concluded that the analyses of at least 58 samples are required for a given pesticide commodity combination to estimate a maximum residue level based on monitoring data alone.

The submission for supporting the estimation of a MRL in a spice commodity should contain:

a. the scientific and English name of the spice producing plant and its Codex Classification (Para 199, ALINORM 03/24A, 2003) if available.
b. description of the agricultural practice for growing the spice producing plant including:
    - cultivation as a main crop or as an inter-crop;
    - pesticides authorised on the main crop and their likely use in relation to the harvest of the spice-crop (if relevant);
    - likely direct pesticide applications to the spice-crop and their timing in relation to harvest;
    - frequency of harvest and harvesting method;
    - information on the processing of the spice-crop to obtain the spice commodity; and
    - storage conditions and need for post-harvest protection.
c. a detailed description of sampling and sample processing methods
d. a description of the analytical method, or reference to a well established procedure, used for quantitative determination and confirmation together with its validation data and performance characteristics [Residue components included in the reported result (residue definition); LOQ, mean recovery and its CV at various fortification

levels (if reported results were adjusted for recovery, the method of adjustment)] for individual pesticide residues recovered by the method. The actual LOQ values should be reported which were verified during the analyses of the samples. For further details on basic requirements for analytical methods see sections **3**.3**.**

e. The summary table of results presented for individual spice×pesticide residue combinations as shown in section **3**.13. "Data requirements for EMRL estimation".
f. Any other information considered relevant for the evaluation of residue data.

3.6.2 Designing of selective field surveys and reporting data for obtaining residue data in/on spices

Selective field surveys are an alternative approach to generate residue data to support the elaboration of MRLs for spices, as monitoring results have limited use in estimating maximum residue levels mainly because of the lack of information on the pesticide treatment history of the sampled commodity. In such situations pesticide residues present in the samples may not be detected precluding the estimation of suitable MRLs, which could lead to trade problems. The analysts should, therefore, have as much information as possible on the actual or possible use of pesticides on the spices to be analysed.

In a selective field survey samples are taken from fields where the crop is grown, treated directly or indirectly with pesticides, and harvested according to the local agricultural practice. The essential feature of the selective field survey is that all pesticide applications, the growth stage of the crop and post-harvest treatment of spices are recorded and are attached to the sampling report. This allows the laboratory to identify for analysis all pesticides applied, in addition to environmental contaminants such as organochlorine pesticides, which may be taken up from soil.

For MRL estimation the selective field survey is a better data source as the pesticides used are known rather than pesticide monitoring data involving the testing for pesticide residues in samples of unknown origin.

The following aspects should be considered in planning and conducting selective field surveys:

- A successful survey requires the full co-operation of the growers who should understand that it is being undertaken to help facilitate their production and that the correct information is essential for success.
- Sites for surveys should be selected to represent typical growing conditions of the particular spice. The more information and residue data provided the more accurate the maximum residue level that can be estimated.
- The minimum number of fields surveyed and samples collected depends on the diversity of the growing conditions. As an initial step, a minimum of 10 reliable residue results representing the typical growing or processing conditions with supplementary information are required for each spice×pesticide combination. Field samples are taken with 12 primary samples sufficient for preparing one laboratory sample.
- In the case of post-harvest application a minimum of 10 lots, treated independently, should be sampled, preferably from different processing or storage facilities. The laboratory samples should consist of a minimum of 25 primary samples.

The following details should be reported in addition to those listed in section **3**. 7.1.

- Person and organization responsible for organizing, supervising and reporting on the selective field survey.
- Typical agricultural practice (see details under section **3**. 7.1)
- Description of growing conditions of the plant producing the spice, e.g., main or intermediate crop, the growth stage at harvest, date of harvest and harvested part of the plant.
- Where the plant is grown as an intercrop between rows of a major crop, the registered or permitted uses of pesticides on the major crop.
- The date and method of application, and dosage of pesticides actually applied on the main crop and intercrop, for treatments carried out on the fields where the samples are taken directly from the fields
- Details of post-harvest application together with information on pre-harvest treatments where available.
- Description of any processing of the spice and its storage conditions.
- Storage conditions of samples until analysis.
- Portion of sample analysed
- Residues of ai and metabolites (mg/kg) found in the samples. The results should be tabulated as shown in Table 3.7.

Table 3.7 Summary of selective field survey results

Commodity name with Codex Number (if available)

Pesticide application			Date of		Analysis			
ai [a]	kg ai/ha kg ai/hL	Date(s)	Harvest	Sampling	Date	Residues mg/kg		Method

[a] indicate whether the application was direct or indirect.

3.7 FATE OF RESIDUES IN STORAGE AND FOOD PROCESSING

Once the residue has been identified, information on its fate during storage and processing should be included.

Processing studies are among the critical supporting studies required for the evaluation of a new or periodic review compound. The effects of industrial processing and household preparation on residues have to be studied to estimate residue levels in processed products.

Objectives of processing studies

Processing studies have the following objectives.

- To obtain information about breakdown or reaction products which require a separate risk assessment.

- To determine the quantitative distribution of residues in the various processed products, allowing the estimation of processing factors for products which may be consumed.
- To allow more realistic estimates to be made of the chronic or acute dietary intake of pesticide residues.

Need for processing studies

Studies are not normally required if:

- the plant or plant product is normally only eaten raw, e.g., head lettuce
- only simple physical operations such as washing and cleaning are involved
- no residues above the limit of quantification occur.

Studies are necessary if significant residues occur in plants or plant products which are processed. "Significant residues" normally means residues above 0.1 mg/kg in RAC. If the pesticide concerned has a low ARfD or ADI consideration has to be given to conducting processing studies with analyses for residues below 0.1 mg/kg. In the case of hops this level should be 5 mg/kg (residues in beer are then < 0.01 mg/kg because of the dilution factor). For residues of a fat-soluble pesticide in oilseeds, the possibility of concentration in the oil has to be taken into account.

Determinations of the nature of pesticide residues in processed products are basic to processing studies. They make it possible to confirm the definition of the residue for processed products or to define extra breakdown products to be determined in further studies.

3.7.1 Guidelines for the conduct of processing studies on the nature of the residues

The objective of studies of the nature of residues is to establish whether or not breakdown or reaction products of residues in the raw commodities are formed during processing which may require a separate risk assessment.

On examining the effects of processing on pesticide residues one will find that the main procedures, e.g., preparation of fruit juices, preserves, wine, will be mainly hydrolytic, because processes involving heating would generally inactivate enzymes present in the commodity. Studies of hydrolysis are therefore chosen as the model for degradation in processing. Since the substrate itself is not likely to have a major effect, the presence of the commodity during such studies is not required. Studies of hydrolysis are not required if the water solubility of the substance is ≤ 0.01 mg/L.

Hydrolysis data (required as part of the physical-chemical properties of an active ingredient) are normally generated at temperatures between 0 °C and 40 °C for a time chosen to allow observance of degradation up to at least 70% at pH 4, 7 and 9. The objective of these studies is primarily related to environmental conditions. Therefore, they are not interchangeable with the required data needed to assess residue behaviour during processing, where higher temperatures but normally much shorter periods and, in some cases, at more extreme pH values are typically involved. Reactions are therefore faster and may lead to the formation of different degradation products.

Table 3.8 summarises typical conditions (temperature, time and pH) which prevail for each of the processing operations[21].

Table 3.8 Typical parameters during processing operations

Type of process	Critical operation	Temperature (°C)	Time (min)	pH
Cooking vegetables, cereals	Boiling	100[a]	15–50[b]	4.5–7
Fruit preserves	Pasteurisation	90–95[c]	1–20[d]	3–4.5
Vegetable preserves	Sterilisation	118–125[e]	5–20[f]	4.5–7
Fruit Juice	Pasteurisation	82–90[g]	1–2[h]	3–4.5
Oil	Raffination	190–270[i]	20–360[j]	6–7
Beer	Brewing	100	60–120	4.1–4.7
Red wine [k]	Heating of grape mash	60	2[l]	2.8–3.8
Bread	Baking	100–120[m]	20–40[n]	4–6
Instant noodle	Steam and dehydration (by frying or hot air)	100 140–150 (frying) • 80 (air)	1–2 1–2(frying) 120(air)	9[o]

[a] Temperature of the vegetables during cooking
[b] Time the vegetables or cereals are kept at 100 °C
[c] Temperature within the fruit preserves during pasteurisation
[d] Time the fruit preserves are kept at 90–95 °C
[e] Temperature within the vegetable preserves during sterilisation
[f] Time the preserves are kept at 118–125 °C
[g] Temperature of the fruit juice during pasteurisation
[h] Time the fruit juice is kept at 82–90 °C
[i] Temperature of the deodorization during raffination
[j] Time of the deodorization
[k] White wine is not heated
[l] Subsequently either chilled quickly or allowed to cool slowly (overnight)
[m] Temperature within the loaf and on the surface during 20–40 minutes
[n] Time the loaf and the surface is kept at 100–120 °C
[o] Wheat flour is kneaded with 0.1–0.6% *Kansui* (alkaline water containing 20% K2CO3 and 3.3% Na2CO3)

Based on the details given in Table 3.8 three representative sets of hydrolytic conditions can be considered appropriate to investigate the effects of hydrolysis for the relevant processing operations. These are defined in Table 3.9.

Table 3.9: The hydrolysis conditions listed below are selected to cover most processing procedures.

Temperature, °C	Time, min	pH	Processes represented
90	20	4	Pasteurisation
100	60	5	Baking, brewing, boiling
120[a]	20	6	Sterilization

[a] Closed system under pressure (e.g. Autoclave or similar)

For other processing practices involving more extreme conditions (deodorization during raffination, high pH of instant noodles (Table 3.8), the temperature and time for preparation of meat and fish) specific studies should be considered on a case-by-case basis.

[21] OECD Guidelines for the Testing of Chemicals, Test No. 507: Nature of the Pesticide Residues in Processed Commodities - High Temperature Hydrolysis

The effects of processes other than hydrolysis, e.g., oxidation, reduction, enzymic or thermal degradation, may also have to be investigated if the properties of the pesticide or its metabolites indicate that such processes may produce toxicologically significant degradation products.

Depending upon the potential range of pesticide uses, one or more of the representative hydrolysis situations should be investigated. The studies are normally conducted with a radiolabelled form of the active substance or the residue in question. The desired goal of such a study is the identification and characterization of at least 90% of the remaining TRR. The principles for selecting position for labelling, identification and or characterization of residue components and basic requirements for performing and reporting the studies are the same as or very similar to those described under metabolism studies (Section **3.**2.3).

The JMPR will take into account the nature of the major products in the hydrolysis study, dilution or concentration factors during processing, and the initial residue levels in the raw agricultural commodity when evaluating the results of the studies.

3.7.2 Guidelines for the conduct of processing studies on effects on residue levels

Processed products can be classified according to certain types of process. The studies have to take into account the importance of the processed product in human or animal diets. Degradation products of toxicological significance occurring in the hydrolysis studies have to be taken into consideration as well as residues of concern found in plant metabolism studies.

For a core set of data on an active ingredient the processing studies should be conducted on representative commodities such as citrus fruits, apples, grapes, tomatoes, potatoes, cereals and oilseeds. By using core processing procedures and selected crops it should be possible to extrapolate to other crops processed by the same procedure. Only in cases where it is not possible to derive consistent processing factors or where a very low ADI is established would it be necessary to conduct processing studies on every crop[22].

In some cases further trials may be necessary to cover particular circumstances. Examples are the determination of residues in oil produced from oilseeds with no significant residues where the active substance has a log P_{ow} above 4, and extended studies on active substances with a very low ADI.

3.7.2.1. Test conditions for processing procedures

The procedures to be used in processing studies should always correspond as closely as possible to those that normally occur in practice. Thus products of household preparation, e.g., cooked vegetables, should be produced using the equipment and preparation techniques normally used in households, whereas industrial items such as cereal products, preserves, fruit juices or sugar should be produced by procedures representative of commercial food technology.

In some cases more than one commercial process may be routinely used, e.g., the different UK and US commercial practices in the production of potato chips; see the 1998 JMPR evaluation of maleic hydrazide. Reasons should be provided for the chosen process.

[22] OECD Guidelines for the Testing of Chemicals, Test No. 508: Magnitude of the Pesticide Residues in Processed Commodities

Importance should be attached to carrying out processing studies for commodities included in GEMS/Food diets and for animal feedstuffs derived from crops, e.g., products of cereals, oilseeds, apples, citrus and tomatoes.

3.7.2.2 Nature of the processing studies

The studies should be designed so that processing factors can be derived and MRLs recommended for processed foods and feed important in international trade. For consistent processing factors the results of more than one study are necessary.

Processing studies should simulate commercial or household practices as closely as possible. The RAC used in the studies should be a field-treated commodity containing quantifiable residues, so that processing factors for the processed products can be determined. This may require field treatment at an exaggerated application rate to obtain sufficiently high residue levels. Processing studies with spiked samples are not acceptable unless it can be demonstrated that the residue in the RAC is entirely on the surface.

3.8 INFORMATION AND DATA FROM TRIALS ON STORED PRODUCTS

When residue data are submitted to the JMPR from treatment of stored products such as grains and seeds, the treatments are often carried out in a number of stores with variable conditions with regard to temperature, humidity, aeration, etc. Information should be available on the use practice and all the conditions under which the products are kept.

Treatments of grain and other products in store give rise to particular difficulties. Pesticides used for storage vary considerably in stability. The rate of disappearance can be influenced by variations in ambient temperatures, e.g., tropical compared to temperate, moisture content and aeration. Application of pesticides can vary from commodities stacked in sacks to automated systems in large-scale silos. In addition, the variability of residues within a store, i.e., intra-store variability, can be particularly high, for instance in situations such as fogged potatoes in box stores. For this reason sampling procedures must be designed to obtain a sample, representative of the lot.

3.9 INFORMATION AND DATA FROM FARM ANIMAL FEEDING AND EXTERNAL ANIMAL TREATMENT STUDIES

The results of livestock feeding studies are used for estimating MRLs in food of animal origin and to assess the dietary exposure of pesticides due to consumption of such foods.

Feeding studies are generally required where significant residues occur in crops or commodities fed to animals and metabolism studies indicate that significant residues (> 0.01 mg/kg) may occur in edible tissues or that the potential for bioaccumulation exists.

Residues in livestock studies are typically conducted in ruminants (dairy cattle) and poultry (laying hen). In general, the results of cattle feeding studies may be extrapolated to other domestic animals (ruminants, horses, pigs, rabbits and others) and laying hen feeding studies to other types of poultry (turkey, goose, duck and others).

Except in special cases, it is not necessary to carry out metabolism studies with pigs since information on metabolism in a monogastric animal is available from studies with rats. If metabolism in the rat is different from that in the cow, goat and chicken, pig metabolism studies may be necessary. In such circumstances, if the metabolic pathways in the pig study

are different from those in the ruminant study, a pig feeding study should be conducted unless the expected intake by pigs is not significant[23].

Farm animal feeding studies are not necessary when residues levels are below the limit of quantification in feed items from crop field trials that reflect the proposed critical GAP of the pesticide, i.e., maximum rate, maximum number of applications, minimum pre-harvest interval), unless the livestock metabolism study shows a potential for significant bioaccumulation of the pesticide in animal commodities. However, when quantifiable residues are present in the feed items, it will be necessary to consider the anticipated dietary burden and the results of the livestock metabolism study.

In cases where a metabolism study with dosing at the equivalent of 10×, where 1× is the anticipated dietary burden, results in levels of the residues of concern below the limit of quantification (LOQ) (typically 0.01 mg/kg) in all edible commodities, then no quantifiable residues would be anticipated in livestock commodities as a result of the proposed use. In such situations, the metabolism study can also serve as a feeding study.

3.9.1 Animal feeding study

Farm animal feeding studies use unlabelled compounds to establish the relationship between levels in feed and likely residues in tissues, milk and eggs.

Animal feeding studies should be designed to provide clear information on the fat solubility of the residues. Therefore, the likely fat solubility of residues with log P_{ow} > 3 should be taken into account in preparing the study plan including sampling.

The test substance used in the study should be representative of the residue in the crop or feed. Livestock are dosed with the representative component(s) of the residue as defined in the feed, which is derived from crop metabolism, confined rotational crop and processing studies. The residue definition of a pesticide might consist of parent compound plus one or more metabolites, or a single or several metabolites or degradation products. If the parent compound is the major residue in feeds/plants, and when it is metabolised by livestock similarly as in plants, it is appropriate to dose the animals with the parent compound only. If a unique plant metabolite is the predominant residue in the feeds and plants, then it may be appropriate to dose with the metabolite only. Generally the feeding of mixtures is not recommended and needs a specific rationale. In some cases the use of field aged residues is preferable.

The test substance(s) should be applied in a suitable form, preferably by capsule to simulate the residue concentrations in feed and to ensure consistent exposure over the duration of the study. If the substance is applied to the feed, it must be thoroughly mixed with the feed and regular analytical checks must be made to ensure the consistency and stability of the chemical in the feed over the study duration.

Once acclimatized, which is indicated, for example, by normal feed consumption, body weight stability, or the production of average quantities of milk or eggs, the animals should be dosed daily for a minimum of 28 days or until residues plateau in milk or eggs, if they have not done so in 28 days.

It is important that the study period is long enough to reach plateau levels for residues in meat, milk and eggs and to observe the rates of decline of the residue levels when the intake

[23] OECD Guidelines for the Testing of Chemicals, Test No. 505: Residues in Livestock

of feed with pesticides has ceased and quantifiable residues are present in milk, meat, fat or eggs after the terminal dose at the nominal 1× dose level. A depuration phase conducted with the highest dose group is sufficient to cover all feeding levels associated with GAP, as the objective of the depuration phase is to provide information on the decline rate. At least three time points following cessation of dosing at the highest dose level should be included, i.e., practical zero withdrawal and three other time points, with at least one ruminant and three hens to be slaughtered per time point. An adequate number of time points should be chosen to be able to estimate a half-life of depuration in meat/fat, milk or eggs. In some circumstances, such as the cases of compounds that preferentially accumulate in fat as opposed to milk, registrants may consider conducting a separate depuration study using beef rather than lactating cattle, as the rates of depuration may be different where milk becomes an additional route of elimination for the chemical. Typically, three animals should be included at each depuration time point. Livestock are typically fed at 1×, 3× (or 5×), and 10×, where 1× is a level based on the lowest expected regional dietary burden, as estimated from the highest residue levels in individual feedstuffs (median residues in processed feedstuffs) and the percentage of each feedstuff in the regional livestock diets. Additional dose levels may be added as necessary, for example, to refine dietary risk assessments. As the basic assumption is that all feedstuff that make up the total livestock diet will be pesticide treated, the dietary burden reflects the reasonable worst case that may occur in practice.

The 10X dose will allow an estimate of what will happen if the normal level is exceeded, will indicate whether residues are proportionate to the intake and will provide additional data if new uses of the product are introduced.

For studies with ruminants and monogastrics one untreated (control) animal per study and three (3) animals per dose groups are required. In the case of bioaccumulating substances, the highest dose group will comprise a minimum of 3 additional animals. For studies with poultry one untreated (control) animal per dose level (3 to 4 per study) and 9–10 animals per dose group are normally used. In the case of bioaccumulating substances, the highest dose group will comprise a minimum of nine (9) additional animals. Cows should be in mid-lactation producing an average milk yield, and chickens should be in full egg production before dosing is started. The condition of the animals, both during the acclimatisation and dosing phases should be recorded throughout the study period, together with information on the age and individual bodyweights, daily feed consumption (individual or mean group basis), milk production or egg production. The physical condition of the animals can provide important information on rates of absorption and depuration of the administered chemical. Any health problems, abnormal behaviour, low feed consumption or unusual treatment of the animals should be reported and the effect of these on the study results should be discussed where relevant.

3.9.2 Direct treatment of animals or premises

For pesticides that are directly applied to livestock or are used in agricultural premises and label restrictions cannot preclude the possibility of residues in meat, milk or eggs, residue studies to determine residues levels in edible livestock commodities should be provided. The studies should reflect the maximum exposure conditions and all possible residue transfer routes such as direct absorption, direct consumption or direct contamination, e.g., contamination of milk from milking equipment.

Separate studies are required for each application type, e.g., ruminants (cattle), non-ruminants (swine) and poultry (chicken). Extrapolation based on direct animal treatment is generally not justified. Dermal treatments on cattle cannot be extrapolated to dermal treatment of sheep.

MRLs are set only for sheep if application is on sheep. For direct treatments, the formulation might also be important and therefore separate studies might be required for different formulation types.

Each study should include a treatment at the highest exposure (treatment) rate, and at 1.5 to 2 times that rate, using the proposed methods as indicated on the label in two separate premises, or in two isolated areas of the same premises. In a third separate area animals should be kept as control animals. The animals in all three areas should be of the same breed and sex and of the same general age, weight and body condition. In the study, adequate details of the nature of the housing and application of the treatment should be reported. Where multiple treatments are proposed, the trials should be carried out accordingly and the animals slaughtered or eggs/milk collected after all treatments are completed.

There may be specific situations where data are needed to simulate exposure from direct application of a product to livestock in addition to exposure through feeding of treated crops. In such cases, the residue study should reflect the level of residues to be expected from the combined exposure scenarios. If separate feeding and direct treatment studies have been conducted, it is normally acceptable to add the residues from these studies to determine the appropriate maximum residue levels. However, this may result in higher than necessary MRLs for animal commodities.

3.9.3 Documentation of animal feeding studies

Information should be provided on:

- number of animals per feeding group
- weight of each animal
- nature of the residue or compound being dosed (pure compound, aged residue, mixture of parent and metabolite)
- dose rates per day (mg compound/kg bw/day or mg compound/animal/day)
- equivalent feeding levels (ppm in feed on a dry weight basis)
- feed intake (dry weight basis)
- description of the feed
- milk or egg production
- duration of dosing and withdrawal, times for milk or egg collection and animal slaughter
- residue levels in tissues and milk (and milk fat for fat soluble pesticides) or eggs.

Tissues to be analysed should include, as a minimum, skeletal muscle, perirenal fat, subcutaneous fat or backfat, liver and kidney. Special care should be taken to ensure that residues on the skin or wool do not contaminate the tissue samples during sample collection. Individual animal residue data should be reported. In the case of fat-soluble chemicals fat depots should not be pooled, but analysed separately. However, if there is insufficient backfat for analysis, the backfat should be supplemented with other subcutaneous fats, preferably brisket fat, and its source reported in the study.

3.9.3.1 Nature of fat samples in studies on fat-soluble compounds

The information obtained from feeding and direct treatment studies must allow an MRL to be recommended to cover residues in the various types of fat which may be subsequently sampled by regulatory authorities. It is sometimes assumed that the levels of residues are approximately the same in the different fat depots within an animal (except at the site of a direct treatment), but this is not necessarily the case.

Farm animal feeding and external animal treatment studies for fat-soluble compounds should provide information on the highest residue levels likely to occur in any fat depot when directions for registered uses of the pesticide are followed. The highest levels would be the basis for an MRL recommendation. In such studies fat samples from the various fat depots need to be analysed separately.

The description of "fat" in some studies has not always been totally 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, mesenterial, subcutaneous,
- location in the animal body (if more than one possibility)
- 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 of the animal, which should also be recorded.

3.9.4 Information on direct treatment of animals and animal housing

When a compound is used both as a pesticide on crops and for direct animal or animal housing treatments 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 FAO Panel will not recommend MRLs covering direct animal or animal housing treatments for new compounds and will recommend withdrawal of the old MRLs which were based on such uses.

3.10 RESIDUES IN FOOD IN COMMERCE AND AT CONSUMPTION

Monitoring data are the basis for establishing EMRLs for pesticides which have become environmental contaminants (see Chapter 5, Estimating extraneous maximum residue levels), and in the case of spices. The spice monitoring data shall be provided in the formats specified in section **3**.6.1).

3.11 NATIONAL RESIDUE DEFINITIONS

Information on national residue definitions is needed for new and periodic review compounds. This background information assists decision making on residue definitions.

3.12 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 new information, additions or corrections must be presented.

The new information and data will mainly be related to additional GAP and new data from supervised trials, which enable the JMPR to estimate maximum residue levels and eventually propose MRLs for additional commodities, change of 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; improved analytical methods with lower limits of quantification and improved ability to differentiate between parent compound and metabolites.

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

It is emphasised that recommendations of the FAO Panel can only be based on information available to the JMPR, 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.

The experience of the meeting shows that often the information available to national governments has not been provided to the JMPR. The full documentation available to governments should be provided to resolve any 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 calculating the revised international estimated daily intake, IEDI, value may not, as it would require consideration of all residue data evaluated previously.

3.13 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 of the compound from the market.

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.
- Analytical method used together with its performance characteristics (see basic requirements for reporting methods in section **3**.5.4). In addition, indicate each LOQ level reported by the laboratories, e.g., LOQ: 0.05 mg/kg, 0.02 mg/kg or 0.01 mg/kg.
- The detectable residues should be reported individually in order to facilitate the application of statistical methods for estimation of maximum residue level.

The detailed residue data should be presented in an Excel workbook in tabular form shown hereunder.

Standard format for reporting pesticide residues monitoring data
Country:
Pesticide:
Residue components measured by the method:
Commodity:
National MRL:
LOQ or limit of reporting (mg/kg):

LOQ or limit of reporting [mg/kg]	Commodity [a,b]	No of samples [c]	Year
0.01	GC0640 Barley grain	52	2000-2006
0.02	MM0812 Cattle meat	23	2000-2003
0.01	MM0812 Cattle meat	34	2004-2006

[a] Describe the commodity according to Codex Commodity Classification together with the portion of commodity analysed.
[b] List different commodities under each other
[c] The table contains example for reporting LOQ values

Detected residues [a] [mg/kg]:

Year	Commodities [b, c]			
	Barley grain	Cattle meat		
2000	0.012	0.02		
	0.012	0.021		
	0.013	0.021		

[a] Replicate samples taken from the same stored commodity should be marked
[b] Describe the commodity according to Codex Commodity Classification together with the portion of commodity analysed.
[c] Insert additional columns to the table as needed.