CHAPTER 3

DATA AND INFORMATION REQUIRED FOR JMPR EVALUATIONS

CONTENTS

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 addition, the JMPR publishes lists of those data which it considers "desirable" when these are found to be lacking or insufficiently addressed in data submissions Data submitters are advised to follow the guidelines in this chapter when compiling their data package

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 has 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 monograph 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 headings of this section follow the format of the JMPR evaluations

IDENTITY

- ISO common name
- Chemical name
  - IUPAC
  - CAS
- CAS Registry No
- CIPAC No
- Synonyms and trade names
- Structural formula
- Molecular formula
- Molecular weight

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)
- Relative density (at stated temperature)
- Hydrolysis (at stated pH and temperature)
- Photolysis
- Dissociation constant

Technical material

- Minimum purity (in %)
- Main impurities (range of amounts, confidential information will not be presented as such in the JMPR monographs)
- Appearance
- Density
- 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

METABOLISM AND ENVIRONMENTAL FATE

Information is required on

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

Metabolism studies are conducted to determine the qualitative metabolic fate of the active ingredient 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 data can be developed and residues can be quantified The dose level and criteria for identification and characterization of residue components, including non-extractable residues, are similar to those described in guidelines of registration authorities

The information should include documentation on the identity of the metabolites and the quantities present Attention should be paid to the presence of metabolites in the different parts of the plants (surface, leaves, stems, fruits and edible root crops), in different animal tissues (fat, muscle, kidneys, liver, eggs and milk) and in different soil types The rate of the formation and disappearance of metabolites in plants, animals and soil must also be investigated

It is emphasized 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, dogs, etc) 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

Farm animal metabolism

Farm animal metabolism 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 a ruminant and poultry (and sometimes pigs) whenever significant residues (>0 1 mg/kg dry weight) occur in items of feed for these animals and the farm animal metabolism studies indicate that residues may occur above the limit of quantification (LOQ) of residue analytical methods carried out with unlabelled compounds (see this chapter section, "Information and data from farm animal feeding and external animal treatment studies")

Usually the most important metabolism studies are those involving ruminants (using lactating goats or cows) and poultry,where chickens are the preferred animals 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

A high percentage of the administered dose as radiolabelled tracer should be accountable in animal metabolism studies

Plant metabolism

Plant metabolism studies are usually required for a minimum of three diverse plants (unless the pesticide is to be used on only one or two crops) If the metabolism in three diverse (dissimilar) crops is similar, then the metabolism in other crops is normally assumed to be similar However, if the metabolism is different in different types of plants, a metabolism study is required for each type of crop group (e g root vegetables, leafy crops, fruits, pulses and oilseed, cereals) for which use is proposed

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 mobility (uptake from soil, absorption by plants or surface residue) and show the efficiency of extraction procedures for various components of the residue

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

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

Environmental fate in soil and water-sediment systems

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 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

The submitted data should include

- physical and chemical properties
- metabolism and degradation in soil, identification of metabolites and degradation products, and an indication of their levels
- persistence of the parent compound and its metabolites or degradation products in soil under aerobic and anaerobic conditions
- mobility of the parent compound and its transformation products in soil
- adsorption by various soils
- hydrolysis rate and products
- photolysis on soil and plant surfaces
- crop uptake and bioavailability of parent compound and its major transformation products
- residues in rotational crops
- soil dissipation
- residue degradation and disposition in water-sediment systems

RESIDUE ANALYSIS AND STABILITY OF PESTICIDE RESIDUES IN STORED ANALYTICAL SAMPLES

Analytical methods

Analytical methods should include (1) specialized methods used in the supervised trials and environmental fate studies which were submitted for evaluation, and (2) enforcement methods

Analytical methods are required to determine all residue components needed for the residue definitions for compliance with the MRL and for estimation of dietary intake The major residue components should be determined individually as far as technically possible

The individual studies should be summarized and clearly outline the compounds determined, the commodities for which the method is recommended, specificity, repeatability of the method, the LOQ 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 LOQ, etc

Information should be submitted to the JMPR not only on the analytical principles 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, tests to prove the efficiency of extraction, recoveries at various levels, LOQs, limits of detection, chromatograms of samples and controls and a description of how the limits of quantification and detection were derived

When specific techniques and methods have been used to determine residues in supervised trials which are not readily available in average regulatory laboratories (bearing in mind the laboratories in developing countries), alternative methods suitable for regulatory control of residues should also be provided The regulatory method should be validated by comparative analyses of samples of typical field treated commodities with both methods

The regulatory method should be preferably a multi-residue procedure even if its recovery is not as good as that of a specific individual method as, generally, the laboratories do not have sufficient capacity to apply individual methods to look for compounds possibly present 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

In addition to the company methods, 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

Extraction efficiency of residue analytical methods

Information should be provided on the efficiency of extraction with the solvents used in relevant regulatory methods

As part of the evaluation process the JMPR regularly assesses the suitability of analytical methods for regulatory purposes, and when possible concludes that specific methods used in supervised trials can be adapted for use in regulatory and monitoring analysis However information is not normally available on the efficiency of extraction of the regulatory method

Extraction efficiency may significantly influence the accuracy of the analytical results 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[1] on bound xenobiotic residues in food commodities of plant and animal origin has recommended

> *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*

The use of metabolism studies for directly assessing the efficiency of extraction procedures in regulatory monitoring methods is rarely possible, because the extraction procedures in such studies are usually much more rigorous than those which are generally used for monitoring purposes Consequently, comparative extraction efficiency studies including the frequently used extraction solvents, such as acetone+water, ethyl acetate, and acetonitrile should be carried out on samples from metabolism studies for the compounds which are expected to be included in the residue definition(s)

Storage stability tests

The results of storage stability tests for residues in stored analytical samples of representative substrates should be provided for samples held in storage before analysis For plant materials, the number of different crop samples depends on the uses of the pesticide Typical matrices should be selected to include predominantly water, oil, protein or starch-containing materials Animal tissues, milk and eggs should be tested for residue storage stability when animal commodity MRLs are needed The study conditions should reflect those to which the samples

[1] 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

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

Storage stability studies are required because many routes of degradation and dissipation can occur, even under cold storage conditions Guidance on proper storage is given in the FAO Guidelines on Pesticide Residue Trials to Provide Data for the Registration of Pesticides and Establishment of MRLs[2] 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

USE PATTERN

Current GAP information on pesticides under consideration must be made available to the JMPR The essential GAP information is the set of current registered uses related to the use patterns in the supervised field trials and current registered higher rates or smaller pre-harvest intervals (PHIs), etc for the same pesticide on the same crop in the same country The GAP information should be presented in a systematic manner according to the standardized format(s) provided in Appendix X section, "Use pattern" 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 emphasized that copies of original labels have to be provided by the manufacturer(s) (or other data submitters) in addition to the GAP summaries Furthermore, the original label should be accompanied by an English translation of the relevant sections (e g dosage, including specification if the concentration of spray or the kg/ha rate is primarily defined, application methods, growing stage of plants at the time of application, 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

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

[2] FAO Guidelines on Pesticide Residue Trials to Provide Data for the Registration of Pesticides and Establishment of MRLs

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 the case of a generic pesticide produced by several manufacturers In such cases 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 summarized by the manufacturers 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 Table 3 1)

Table 3 1 Information on pests and diseases controlled by [pesticide]

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, whitegrubs, wireworm	Furrow treatment, at planting or side dressing, 4 months PHI

Information on formulations, application methods and dosage rates should be summarized in tabular form (see Table 3 2) 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 formats are also provided for post-harvest and direct external animal treatments in Table 3 3 and Table 3 4 respectively

Table 3 2 Registered uses of [pesticide] on vegetables and cereals

Crop	Country	Formulation	Application				PHI, days
			Method	Rate kg ai/ha	Spray conc , kg ai/hl	Number	
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
Lettuce	France	WP 800 g/kg	foliar	0 64			21-41[1]
Lettuce	Israel[2]	WP 800 g/kg	foliar	2 0		weekly	11

[1] summer PHI 21 days, winter PHI 41 days
[2] proposed registration

Table 3 3 Post-harvest GAP uses of [pesticide] on fruit

Crop	Country	Formulation	Application			Notes[4]
			Method[1]	Conc kg ai/hl[2]	Contact time[3]	
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	

[1] Examples of method dip, drench, spray, fog
[2] Concentration of dip, drench, spray, etc
[3] Contact time or other requirement, as specified on the label
[4] 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 4 Registered uses of [pesticide] for direct external animal treatment

Animal[1]	Country	Formulation	Application			whp slaughter[5]	whp milk[6]
			Method[2]	Rate[3]	Conc [4]	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	

[1] Farm animal as stated on the label
[2] Methods include pour-on, dip, ear-tag, jetting, spraying
[3] 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
[4] 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
[5] Withholding period Label instruction on interval between animal treatment and slaughter for human consumption
[6] Label instruction on interval between animal treatment and milking for human consumption

When different formats are used to report GAP data on special uses (e g seed dressing, etc), they should always include details on the following aspects of the use pattern

(i) Responsible reporting body

(ii) Pesticide names ISO-E common name For other international code names, indicate the Standards organization 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

(iii) CCPR number of pesticide, if available

(iv) Information on the use pattern as described on the approved label Use rates and concentrations must be explicitly expressed in terms of active ingredient or product

Governments or responsible national organizations are requested to summarize 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 registrations), a copy of the registration document or its English translation should be provided

The following GAP information requirements are re-emphasized

- 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
- 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

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 the 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

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

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 a 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[3]

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 (1995)[4]

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) 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 recognized 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

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[3] 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

[4] FAO 1995 Manual on the development and use of FAO specifications for plant protection products 4th edition FAO Plant Production and Protection Paper No 128 FAO, Rome

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 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 (~ 1.5 x 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

Application rate should always be presented in metric units See Appendix X, section "General" for non-metric to metric unit conversion factors Express dosage rates of 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 commodities, 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 bud burst in apples 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

RESIDUES RESULTING FROM SUPERVISED TRIALS ON CROPS

Supervised trials serve as the primary source of information for estimating maximum residue levels and calculating International Estimated Daily Intake (see Appendix II for definition of supervised trials)

The term "supervised trials" includes the application of a pesticide approximating targeted or authorized use methods with the use of reliable experimental design and sampling and where

care is taken in the whole procedure Residue trials performed along the lines described in the FAO Guidelines on Producing Residues Data from Supervised Trials[5] 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, 1992, 1993) 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 section, "Selection of compounds for evaluation") some of the trial data may not be relevant for JMPR evaluations Therefore only supervised trial data reflecting the current GAPs should be submitted 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

At present there is no internationally agreed minimum data base required for estimating maximum residue levels The subject is being discussed and elaborated under the auspices of the OECD Pesticide Working Group[6]

For estimating maximum residue levels of pesticide residues in commodities moving in international trade, results of supervised trials representing the typical agriculture practices and 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 manufacturers 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 authorized use of a pesticide and a realistic estimate can be made for the long- term intake of residues

It is emphasized, 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 a minimum of 6-10) and samples required 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 Several 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 GAP If uses are authorized in regions with substantially different climatic conditions, trials should also be carried out in each region

To ensure the availability of all detailed information necessary for evaluation, copies of the complete original reports on the supervised trials must be submitted, preferably in English or

[5] FAO 1990 Guidelines on Producing Pesticide Residues Data from Supervised Trials FAO Rome

[6] Harris, C and Pim, J 1999 Minimum data requirements for establishing maximum residue limits (MRLs) including import tolerances Recommendations from the Scientific Workshop held at the Pesticides Safety Directorate, York, UK on 6-8 September 1999 Document 2734/SANCO/99

with sufficient keys or translation to facilitate review In addition, the results of supervised trials should be summarized 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 "Use pattern" in the previous section 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)

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

Analysis of samples

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 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 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)

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

The residues in animal feed should be reported on dry weight (see Chapter 5 section, "Expression of Maximum Residue Limits") If it is not expressed on dry weight this should be clearly stated, together with any information on the moisture content

Data required for extrapolation to minor crops

The data submitted to support extrapolation to a minor crop must include the following information See also Chapter 5 section, "Extrapolation of residue data to minor crops "

- Background information on the reasons for describing the crop as minor, the importance of the use of the pesticide in terms of pests controlled, the extent of its use on the minor crop, and the nature of the problems or potential problems for international trade
- A description of the cultural practices for the production of the major crop and the approved or registered uses of the pesticide on the major crop from which extrapolation is proposed
- A description of the cultural practices for the production of the minor crop, the approved or registered uses of the pesticide on the minor crop, and the reasons for expecting similar residue levels on the minor crop to those on the major crop
- Supervised residue trials on the major crop supporting the MRL or reference to the JMPR Evaluations if trials data have already been reviewed by the JMPR

The data submission should also include the following supporting information where available

- Data on supervised trials with approved or registered uses on the minor crop
- A copy of the label describing the registered or approved uses and an English translation of the instructions for use
- Monitoring data from selective surveys on the minor crop produced under typical commercial conditions where the pesticide is known to have been used

Note that this section deals with minor crops, not minor uses, which may apply to major or minor crops JMPR evaluation of data for minor uses is the same as for other uses

FATE OF RESIDUES IN STORAGE AND 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 Requirements on this point are set out in guidelines such as EPA OPPTS 860 1520 and the EU Council Directive 91/414/EEC (explained in detail in European Commission guideline 1607/VI/97 rev 2, Appendix E Doc 7035/VI/95 rev 5)

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, or
- no residues occur above the LOQ

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 If the pesticide concerned has a low acute RfD 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

Guidelines for the conduct of processing studies - nature of the residue

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

The hydrolysis conditions listed below are selected to cover most processing procedures

Temperature, °C	Time, min	Processes represented
90	20	Pasteurization
100	60	Baking, brewing, boiling
120	20	Sterilization

Depending upon the potential range of uses of the pesticide, 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 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

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

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

Processed products can be classified according to certain types of processing 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 In cases where it is not possible to derive consistent processing factors or where a very low ADI is established it may be necessary to conduct processing studies on every crop

In some cases further trials may be necessary to cover particular circumstances, for example, 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

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

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) are important and should be a priority

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 raw agricultural commodity (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

Generally, processing studies should be conducted on crops harvested at a reasonable interval (comparable with PHI) after the last application to allow aging of the residue as expected in normal commercial practice

Information and data from trials on stored products

When residue data are submitted to the JMPR from treatment on 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 *c f* 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

Information and data on residues in the edible portions of food commodities

Include all the information on residues in the edible portion of commodities for estimating dietary intake This information is especially important in the case of crops for which maximum residue levels are estimated for the whole commodity as marketed and whose outer parts, e g the peel of bananas, citrus fruits and melons, are normally discarded before consumption or processing This section should thus represent a summary and conclusions of the information on storage and processing, also taking into account the likely residues in the residue trials

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

Farm animal feeding studies use unlabelled compounds to establish the relationship between levels in feed and likely residues in tissues, milk and eggs (see also Chapter 6 section, "Estimation of maximum residue levels and STMR values for commodities of animal origin ")

Feeding studies with poultry, lactating cows (or goats) and pigs are generally required where significant residues (>0 1 mg/kg dry weight) 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 Feeding studies are usually carried out using the parent compound, which is normally the residue of greatest significance on the treated crop In cases where this is not so, the farm animal feeding studies should be carried out using a metabolite or a realistic crop residue mixture In some cases the use of field incurred residues is preferable

When only low levels (<0 1 mg/kg dry weight) of residues are found in feed items the anticipated animal dietary burden and the results of the metabolism studies must be considered The latter may indicate that residues in animal commodities would be well below detection limits and thus farm animal feeding studies are not necessary

Where external treatment of animals is needed, this must be carried out with the formulated product in a manner which reflects the proposed use When a pesticide may be applied in more than one type of formulation or by more than one mode of treatment, separate studies reflecting the usage or combination of usages are required

When the use of a pesticide in agricultural buildings is such that restrictions cannot preclude the possibility of residues in meat, milk, poultry or eggs, residue studies should be carried out reflecting the maximum conditions of exposure Separate studies are required for ruminants (cattle), non-ruminants (swine) and poultry (chicken) The studies should reflect all possible residue transfer routes such as direct absorption, direct consumption or direct contamination, e g contamination of milk from milking equipment

General guidance with respect to the role of livestock metabolism and feeding studies in the estimation of Maximum Residue Limits by the JMPR may be found in the FAO Guidelines on

Producing Residues Data from Supervised Trials[5] These guidelines (or future updates) should be followed in performing farm animal feeding (animal transfer) studies

According to the above-mentioned FAO Guidelines the feeding study should include a control group, a group fed at the level of expected intake and a group dosed with an exaggerated level (3-5x, occasionally a higher level, 10x, may be needed) The latter 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 these studies, the number of animals in each treated group should be at least 3 for larger animals (cows and goats) and 5-10 for poultry (laying hens) Cows should be in mid-lactation producing an average milk yield, and chickens should be in full egg production before dosing is started

It is also 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 of feed with pesticides has ceased

The documentation of animal feeding studies should include information 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, etc),
- 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, and
- residue levels in tissues and milk or eggs

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 suitable for 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