

# **JMPR Review and MRL Recommendations**

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# Outline

- Structure and operation of JMPR
- Type of evaluations
- Data and information required for JMPR evaluations
- JMPR practices in estimating maximum residue levels and proposing maximum residue limits
- Definition of residues
- Estimation of group MRLs, and MRLs for minor crops

# JMPR

- The “Joint Meeting on Pesticide Residues” (JMPR) is an independent expert ad-hoc body, administered jointly by FAO and WHO, consists of two groups:
  - WHO Core Assessment Group.
  - FAO Panel on Pesticide Residues in Food and the Environment

# WHO Core Assessment Group

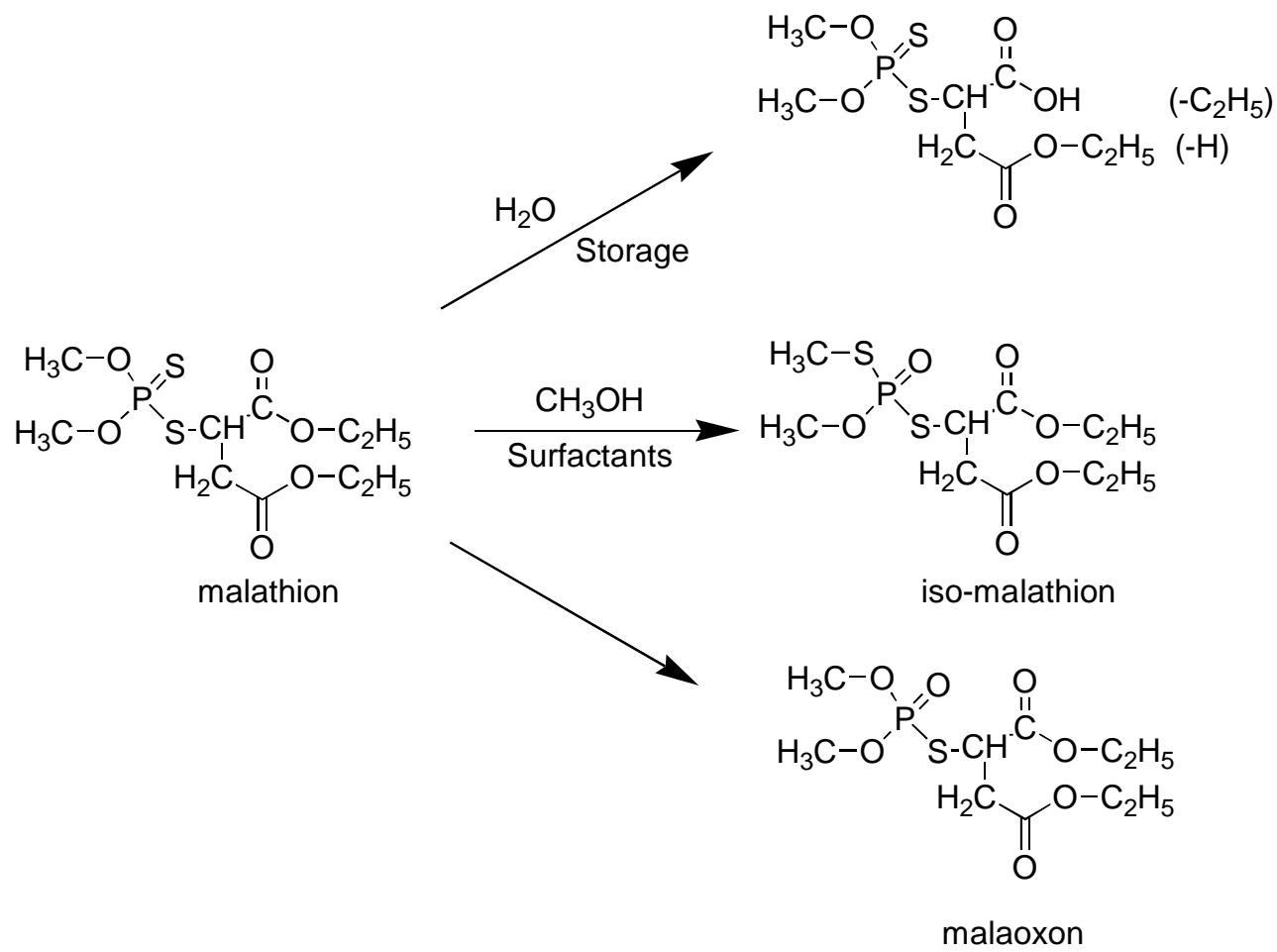
is responsible for reviewing pesticide toxicological and related data for:

- determining no observed adverse effect levels (NOAELs);
- establishing Acceptable Daily Intakes (ADI) of pesticide residues in food, acute reference doses (acute RfDs), where necessary, and
- characterising other toxicological criteria such as non-dietary exposures.

# Toxicological evaluation

- It is based on tests performed with substances of known composition.
- Technical grade pesticides may contain a complex mixture of impurities derived from starting materials, products of side reactions, decomposition products and impurities in starting materials.
- The toxicity of the pesticide may be influenced by some impurities, which may vary depending on the manufacturing process and the materials used for the synthesis.

# Toxic impurities of malathion



# Malathion LD<sub>50</sub> 12500 mg/kg

- $(\text{CH}_3\text{O})_3\text{P}=\text{S}$
  - $(\text{CH}_3\text{O})_2\text{P}(\text{S})\text{SCH}_3$
  - Isomalathion
  - Malaoxon
- 15 mg/kg, rat
  - 1515 mg/kg, rat
  - 0.05% in pure malathion:  
LD<sub>50</sub>, rat:4400 mg/kg
  - 0.5% in pure malathion  
LD<sub>50</sub>, rat:2000 mg/kg  
LD<sub>50</sub>, mice: 215 mg/kg

# Toxicological evaluation

- The results of toxicological evaluation (e.g. NOEL, LD<sub>50</sub>, EC<sub>50</sub>, ADI, etc.) are valid only for products of similar or improved composition, and should not be used for assessing the safety of pesticides manufactured under different conditions.
- FAO and WHO decided to align the programme of pesticide specifications (JMPS) and JMPR, to assure that technical products with known impurity profile and physico-chemical properties will be evaluated by the JMPR.

# Evaluation of pesticide residues

The FAO Panel is responsible for reviewing :

- pesticide use patterns (GAPs),
- data on the chemistry and composition of pesticides,
- environmental fate,
- metabolism in farm animals and crops,
- methods of analysis for pesticide residues, and
- estimating maximum residue levels, supervised trials median residue values (STMRs), and high residues (HR) of pesticides in food and feed commodities.

# The FAO and WHO Expert Groups

- coordinate their activities, discuss chemical and toxicological aspects (e.g. metabolism patterns, level and toxicological significance of metabolites, definition of residues, evaluation of the estimated long- and short- term intakes),
- issue a joint Report containing the conclusions and recommendations of the Meeting.

The maximum residue levels are recommended to the Codex Committee on Pesticide Residues (CCPR) as suitable for consideration as Codex Maximum Residue Limits (Codex MRLs) to be adopted by the Codex Alimentarius Commission (CAC).

# The JMPR

- evaluated pesticides over the last 40 years by applying the best scientific knowledge available and continuously reviewing and updating its evaluation procedures,
- performed the evaluations based on the experimental data provided primarily by the pesticide manufacturers and the Member States,
- The available information varies to a great extent. Therefore the JMPR does not follow rigid rules in its evaluations, but considers the submitted information on a case-by-case basis.

# FAO manual

on the submission and evaluation of pesticide residues data for the estimation of maximum residue levels in food and feed

- incorporates all relevant information and principles which are used by the JMPR to estimate maximum residue levels, high residues and supervised trials median residue levels;
- defines and provides guidance on the type, amount, quality and format of data submissions required for the estimation of maximum residue levels on which the Codex MRLs are based;
- serves as a source of information and instruction for all those directly involved in the activities of the FAO Panel,
- assist member countries in evaluating residue data for the registration of pesticides and in developing their national evaluation systems.

# JMPR Evaluations include

- review of **new compounds** (compounds evaluated by the JMPR for the first time);
- review of compounds under the **periodic review** programme;
- **re-evaluation of new information** relating to compounds other than new or periodic review chemicals.

# Data and Information Required for JMPR Evaluations

New and periodic review  
compounds

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

Codex MRLs cover residues derived from authorized uses worldwide and therefore reflect a variety of agricultural practices and environmental conditions.

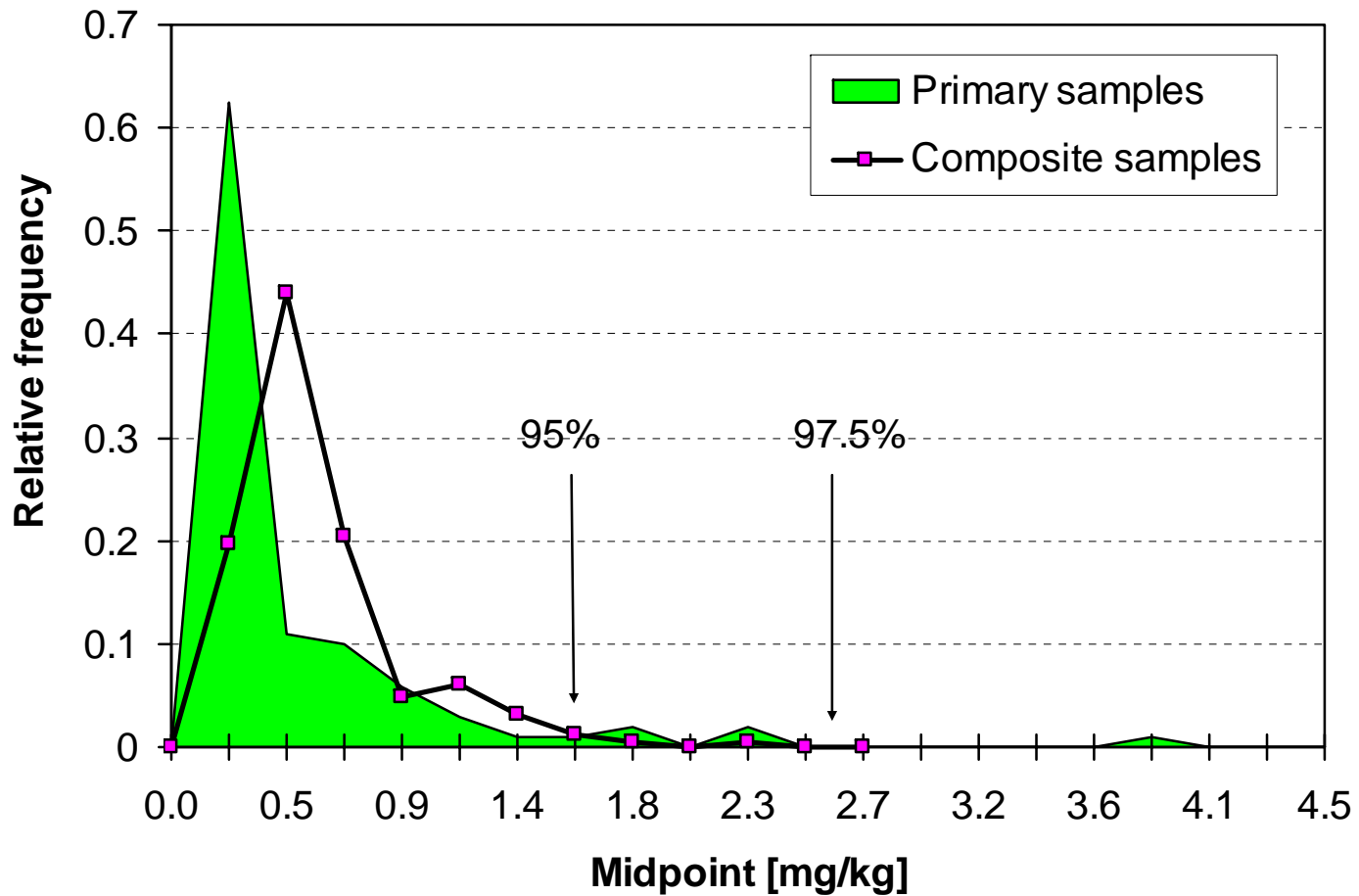
# Plant commodities

- Maximum residue levels are estimated for residues on a whole commodity basis in or on the portion of the primary and some processed food commodities and feed to which Codex MRLs apply. (Reports on supervised trials and monitoring programmes should clearly describe the size of sample and portion of commodity analysed.)
- **Median** and **high residues** are estimated on the edible portion of the commodity **for dietary intake purposes**.
- The maximum residue level estimation is based either on all approved uses or on only those which lead to the highest residues (critical GAP), provided that sufficient number of data are available.

# Definition and purpose of MRL

- The MRL is the maximum concentration of a pesticide residue (expressed as mg/kg), to be legally permitted in or on food commodities and animal feeds.
- MRLs are based on GAP data, and foods derived from commodities that comply with the respective MRLs are intended to be toxicologically acceptable.
- The definition of MRL includes the residue components and the portion of commodity to which the MRL applies.
- The Codex MRL refers to the average residue in a sample taken according to the specified Codex sampling procedure.
- MRL provides the objective means for controlling compliance with GAP, but **it is not a health limit.**

# MRL – residue distribution



# Data base for estimation of residue levels

- FAO Panel takes into account all relevant information and **especially the residues arising from supervised trials** where the trial conditions reflect the established GAP.
- The estimation of STMR and HR values relies on the selection of residue data from trials within GAP. **One data point for each value** is selected from each trial. A sufficient number of trials are needed to represent field and cultural practice variability.

# Data requirements

- The JMPR considers all aspects of available information on residue distribution and magnitude of residues in deciding on the suitability of data base for estimation of residue levels.
- The estimation of maximum residue levels is assisted by statistical methods, such as the *NAFTA Method for Calculating Pesticide Maximum Residue Limits from Field Trial Data*, or the Mann-Whitney U Test for comparing the medians of data sets reflecting different GAPs.

Distribution of residues among fields

	Residue (%) in median ranges					
	$R_i \leq 1 < 3$	$3 < R_i < 4$	$4 < R_i < 5$	$5 < R_i < 6$	$6 < R_i < 7$	$R_i > 7$
Aple	72.99	9.98	9.00	2.19	1.22	4.62
Pear	72.03	14.69	4.90	1.40	0.70	6.29
Citrus	79.40	5.03	7.04	1.51	2.51	4.02
Stone fruits	72.47	9.55	5.62	2.81	2.81	6.74
Grape	72.20	11.53	3.39	4.75	1.36	6.78
Berries	86.90	6.90	2.76	2.76	0.00	0.69
Average %	<b>75</b>	<b>86</b>	<b>91</b>	<b>94</b>	<b>96</b>	

# Recommendations for minimum number of trials from a Scientific Workshop (PSD, UK, 1999)

	<b>Number of zones where GAP exists</b>	<b>Insignificant in diet</b>	<b>Significant in diet</b>
<b>Insignificant in trade</b>	1 zone	3	6
	2-3 zones	4	8
	> 3 zones	5	10
<b>Significant in trade</b>	1 zone	6	8
	2-3 zones	8	12
	> 3 zones	10	16

There is no internationally agreed minimum data requirement.

# Selection of trial conditions

- The trials should be carried out with the same crops as those specified in the national GAPs.
- The dosage rate and pre-harvest intervals should preferably reflect the maximum GAP. Trials performed within  $\pm 30\%$  maximum dose and minimum PHI are acceptable.
- The results obtained at a number of places over some years likely better represent the commercial practice and the variation of residues among areas of widely differing conditions.

# Supervised trials considered independent:

- trials at different geographic locations and sites, dates of planting (annual crops) and treatments,
- two trials with different formulations,
- trials at significantly different application rates and spray concentrations,
- different types of treatment (foliar, directed application), on different plots at the same site,
- crop varieties – some varieties may be sufficiently different to influence the residue,
- trials with and without the addition of surfactant may be sufficiently different.

# Selection of residue data from not independent supervised trials

One residue data from :

- replicate laboratory samples taken from a field sample,
- replicate field samples (each sample is taken randomly through a whole sprayed plot),
- samples from replicate plots or sub or split-plots (the whole trial is subject to the same spraying operation, but it is divided into 2 or more areas that are sampled separately),
- samples from replicate trials, which are not independent.

The 2007 Meeting decided to use in future evaluations the highest residues measured in replicate field samples, and continue to use the average of the analysis results of replicate test portions or replicate laboratory samples as the single value for the purpose of identifying the STMR or HR value or recommending the maximum residue level.

# Definition of residues

- Based on the composition and distribution of residues, and taking into account the available analytical methodology as well as the toxicological significance of metabolites and degradation products, the FAO Panel recommends the definitions of residues for enforcement purposes and for dietary intake calculations.
- The basic requirements for the definition of residues are that it should:
  - be most suitable for *monitoring compliance* with GAP, and
  - include compounds of toxicological interest for *dietary intake estimations and risk assessment*.

# Definition of residues for enforcement

- The definition of residues for enforcement purposes should be as practical as possible and preferably based on a single residue component as an indicator of the total significant residue - the parent compound, a metabolite or a derivative produced in an analytical procedure.
- The selected residue component should reflect the application condition of the pesticide (dosage rate, pre-harvest interval) and it should be determined with a multi-residue procedure whenever possible.
- Simple residue definition enables the control of wider range of residues in increased number of samples, and consequently better protection of consumer health.

# Residue data from supervised trials

- The manufacturer or sponsor must consider the needs of both risk assessment and compliance monitoring when choosing the appropriate analytes and the analytical method for the testing of the residue trials samples.
- Complete information on the total residue composition and the relative ratio of residue components is needed.
- The individual components of the residue should be determined separately, where analytical methods allow, rather than carrying out a total residue analysis.
- If total residue methodology is used to produce data for risk assessment, and the suitable “indicator molecule” can be analysed with a multi-residue procedure, a second series of analyses of the field trial samples should be carried out for the indicator molecule (e.g. parent compound).

## Residue data from supervised trials (2)

- The above approach allows the risk assessment to be carried out on the toxicologically significant residue components whilst ensuring that data are available to allow a different simple residue definition to be established, where appropriate, for compliance with the MRLs.
- In cases where the manufacturer or sponsor has submitted residue trials data in which an analytical method for total residues has been used and it is not possible to identify a suitable simple residue definition for practical routine monitoring and enforcement of the MRL at reasonable cost, the FAO Panel may be unable to estimate MRLs for the compound.

# Reporting residue data

- The concentration of residue components should be determined individually, as far as technically possible, and reported separately.
  - The total residue may be calculated additionally.
  - The recovery values obtained at different concentration levels should be reported, but the residues measured should not be corrected for recovery.
  - 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 average value of the analytical replicates should be reported, and should be distinguished from replicate samples.
- The residues in animal feed should be reported on a dry weight basis (If not, that should be clearly stated, together with any information on the moisture content.)

# Food safety assessment of use pattern

- Chronic exposure
- **TMDI, NEDI, IEDI**  $\Rightarrow$  ADI
- Acute exposure
- **NESTI, IESTI**  $\Rightarrow$  Acute Reference Dose
- **JMPR can only perform deterministic estimate of intakes at international level due to lack of suitable data-base for probabilistic modelling. Substantial refinement may be possible at national level.**

# TMDI, IEDI

- $TMDI = \sum MRL_i * F_i$

- $EDI = \sum STMRI_i * E_i * P_i * F_i$

- STMRI: supervised trial median residue
- $E_i$ : proportion of residue in edible portion
- $P_i$ : processing factor
- $F_i$ : food intake

# Refinement of residue intake

- EDI may provide more realistic estimates if one can consider:
  - Proportion of area treated with a pesticide
  - Monitoring data reflecting actual use
  - National intake figures
  - Portion of commodities imported

# Short term intake: ESTI

- The residue ingested within a short period of time (24 hours or less)
- The maximum residue which may occur in individual crop units may have to be taken into account.
- **Variability factor:** the 97.5<sup>th</sup> percentile of residues present in individual crop units divided by the average residue in the lot:.

$$v = R_{P0.975} / \mu \rightarrow R_{0.975} / R_j$$

# IESTI

Case 2: Weight of crop unit is smaller than the large portion size:  $U < LP$

IESTI=

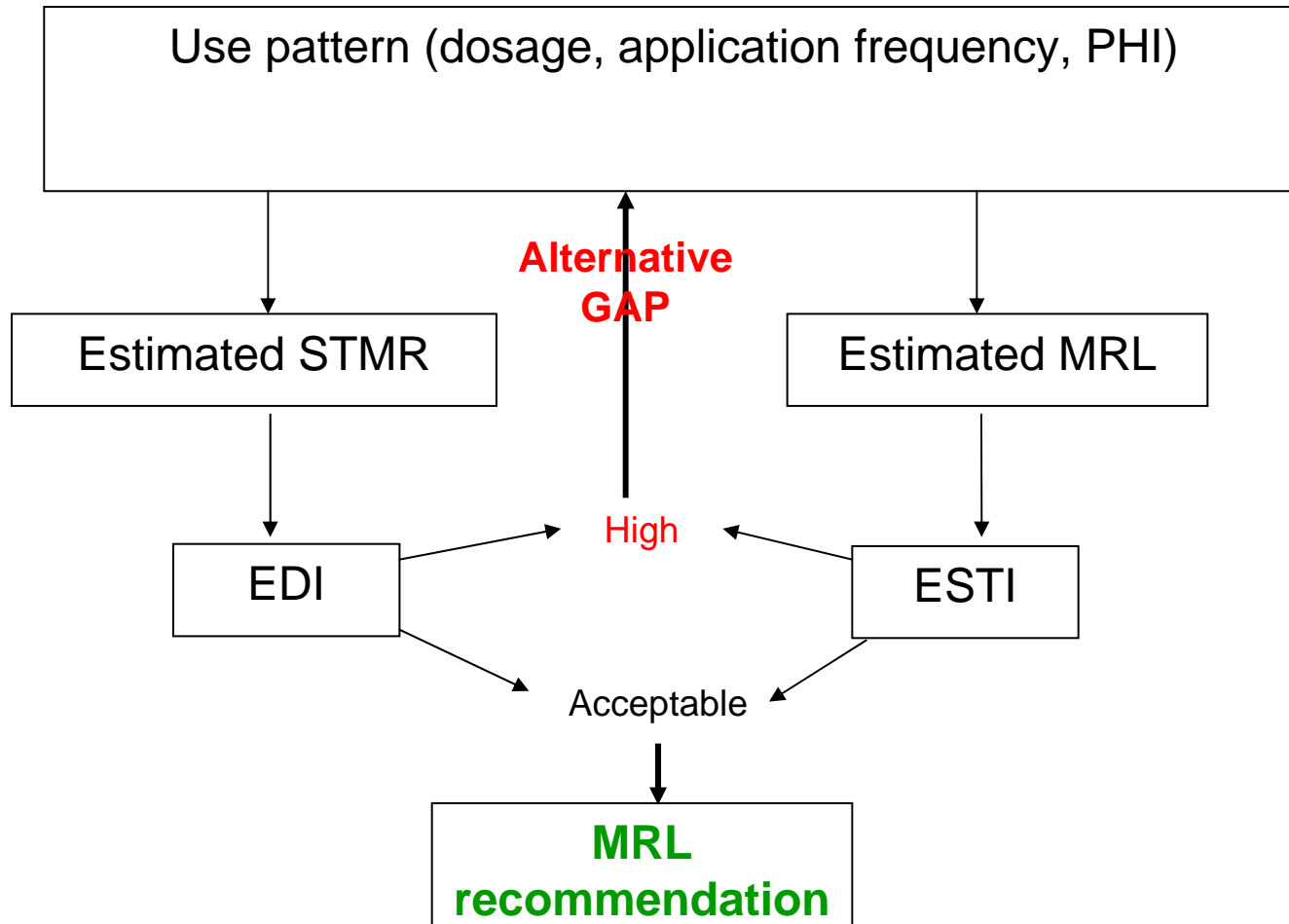
$$\frac{[U * (HR_{or}HR - P) * \nu] + [LP - U) * (HR_{or}HR - P)}{bw}$$

The JMPR is using a default variability factor of  $\nu=3$ , which is based on large number of field trials.

# Sources of uncertainties in estimating acute intake

- $IESTI = (U \times HR \times v + (LP-U) \times HR) / bw$
- $IESTI = (LP \times STMR - P) / bw$
- $v$  is estimated with about 95% probability
- **What is the probability of finding the HR or STMR in supervised trials???**
- **What is the reliability of the estimated large portion and unit crop sizes???**
- **Further refinement of  $v = 3$  will not improve the accuracy of IESTI.**

# Acceptability of recommended use pattern



# Estimation of group maximum residue levels

- The establishment of commodity group MRLs has long been considered as an acceptable procedure at both the national and international levels.
- The approach recognizes that adequate data for the major crops of a group may be sufficient to estimate maximum residue levels for the whole group.
- It is not possible currently to define precisely those commodities on which trials will always provide data that can lead to a group MRL.
- If the “highest residue” situation can be identified, however, the relevant data can be extrapolated to other crops with confidence.

# Practice of the JMPR for estimating group MRLs

- The JMPR relies on the Codex Classification of Foods and Feeds as the primary basis for recommending MRLs for individual or grouped commodities.
- Generally the JMPR refrains from estimating maximum residue levels for large Codex 'classes' of foods or feeds such as fruits, vegetables, grasses, nuts and seeds, herbs and spices, or mammalian products.
- Residue data and approved uses are usually more likely to refer to smaller Codex 'groups' such as pome fruits, citrus fruits, cereal grains, cucurbit fruiting vegetables, milks, meat of cattle, pigs and sheep, etc., with specified exceptions (e.g. cereal grains except rice and maize).
- In the latter case, separate MRLs are estimated for exceptional commodities.

# Situations where JMPR does not estimate group MRLs

- When adequate residue data are available for only a few primary commodities in a food group, separate MRLs should generally be recommended for each commodity on which the data are considered adequate.
- A group limit cannot be established where the variability of the residue levels is too great, even though data on the major crops within the group are available.
- The registration document or label does not specify the group(s) on which the pesticide can be used.

# Main limitations for recommending group MRLs

- There is unfortunately no consensus at the international level on the selection of representative commodities for estimating maximum residue levels for groups.
- The Codex Classification of Foods and Feeds has not been fully adopted at the national level in most countries, and crop grouping can be quite different.

# Inclusion of minor crops in group MRLs

- Adequate data on residues in all or most of the major commodities with the potential for high residues within a group may allow estimates of maximum residue levels to be extrapolated to minor crops in the group. (e.g. triticale if residue data on wheat and rye are available).
- Where residues in/on minor crops fit in the residue pattern of major crop (e.g. chilli peppers and sweet peppers → MRL on peppers).

# Information and data required to support extrapolation to minor crops

- The importance and extent of the use of the pesticide in terms of pests controlled, and the nature of the problems or potential problems for international trade.
- A description of the cultural practices for the production of the major and minor crops and the approved or registered uses of the pesticide on the major crop from which extrapolation is proposed, 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.

# Data required to support extrapolation to minor crops (2)

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

# Possible future actions for facilitating estimation of MRLs for minor crops

- Preparation of science based background information covering all aspects that support extrapolation from major crops to minor crops.
- Revision of national use patterns and specification of minor crops on which the pesticide use is authorised.
- Design and implement supervised trials to demonstrate similarity of residue pattern in/on major and minor crops with
  - contribution of all stake holders at national (and possibly at international level),
  - determining residues included in the JMPR residue definition.

Thank you for your attention

# Review of new compounds

The criteria for inclusion in the priority list:

(a) the pesticide must be available for use as a commercial product;

(b) the use of the pesticide must:

- give rise to residues in or on a food or feed commodity moving in international trade,
- the presence of residues is (or may be) a matter of public health concern, or
- create (or have the potential to create) problems in international trade.

# The periodic review programme

Need for periodic re-evaluation:

- Codex MRLs established several years ago may not reflect current use patterns.
- Some of the old toxicological studies and residue trials may not meet the current standards.

An objective of the periodic review is to make the best use of the existing database, regardless of the age of the studies:

- Countries and industry are requested to provide all relevant information irrespective of whether it had been previously supplied.
- Studies which fulfil the requirements of modern national registration systems will generally meet the needs of the JMPR.

Reviews of such compounds should focus on new or amended uses or current uses that will be supported.

# Re-evaluation of new information

- 1 Clarification of a single question raised by the Codex Committee on Pesticide Residues..
2. New information related to the use of a pesticide:
  - change in the use or new use patterns,
  - data on metabolism, residue behaviour, etc.
  - additional toxicological data have become available (Where a serious public health concern exists in relation to a particular pesticide, governments should notify the WHO Joint Secretary of the JMPR promptly and provide appropriate data.)

# Data and Information Required for JMPR Evaluations

New and periodic review  
compounds

# New and periodic review compounds

- Identity
- Physical and chemical properties of pure active ingredient and technical material
- Metabolism and environmental fate
  - Animal metabolism
  - Plant metabolism
  - Environmental fate in soil
  - Environmental fate in water-sediment systems

# Methods of residue analysis

- Methods used in the supervised trials and environmental fate studies which were submitted for evaluation,
- Enforcement 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
- Information on efficiency of extraction  
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).

# Use pattern

## **Provide only**

- use information which is specifically given on the label,
- essential GAP (highest rates or smallest PHIs, for the same pesticide on the same crop in the same country)
  - crops included in crop groups should be named individually.
- valid copies of current labels for uses adequately supported by residue data

# 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 or Short-term Intakes.
- Results of supervised trials representing the typical agriculture practices, growing and climatic conditions prevailing in all exporting countries should ideally be considered.

# Fate of residues in storage and processing

Processing studies are required if significant residue ( $> 0.1$  mg/kg) occur in plants or pesticide concerned has a low acute RfD or ADI :

- to obtain information on the nature of residues,
- to estimate the processing factors for products which may be consumed (effect on residue levels),
- to allow more realistic estimates to be made of the chronic or acute dietary intake of pesticide residues.

Studies are not generally 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 above the limit of determination occur.

# Farm animal feeding studies

- Feeding studies with poultry, lactating cows (or goats) and pigs are generally required where significant residues ( $>0.1$  mg/kg) 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.
- Farm animal feeding studies use unlabelled compounds to establish the relationship between levels in feed and likely residues in tissues, milk and eggs.

# Residues in Food in Commerce and at Consumption

- Monitoring data are the basis for establishing EMRLs for pesticides which have become environmental contaminants.
- Monitoring data was used to estimate and recommend maximum residue levels for spices for a number of commodities and pesticide residues, based on the decision of CCPR as the risk manager body.

## Distribution of residues among fields

	A.I.	Trial #	Residue range		Ave. CV
			Average	Median	
Aple	29	805	0.037-2.53	0.01-2.4	83
Pear	18	279	0.028-14.3	0.015-14.5	82
Citrus	27	389	0.053-4.26	0.02-3.4	80
Stone fruits	20	351	0.029-4.96	0.02-2.9	91
Grape	22	583	0.025-3.16	0.02-2.85	94
Berries	14	288	0.05-7.99	0.06-6.15	71

# Residue data from supervised trials

- The manufacturer or sponsor must consider the needs of both risk assessment and compliance monitoring when choosing the appropriate analytes and the analytical method for the testing of the residue trials samples.
- Complete information on the total residue composition and the relative ratio of residue components is needed.
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