The reviewer should therefore specify the type of replicate when preparing the monograph

The mean of the residues from replicate laboratory samples or replicate field samples should be taken as the single value for the trial, while the highest residue value from replicate plots or sub-plots or replicate trials should be taken as the single value for the purpose of identifying the STMR or HR value or recommending the maximum residue level

ROUNDING OF RESULTS

In identifying the STMR or HR value from a series of residue trials, the actual residue value should be used in the estimation of dietary intake without rounding up or down This would even be the case where the actual results were below the practical LOQ considered appropriate for enforcement purposes Rounding of residue values is inappropriate since the STMR and HR value are used at an intermediate stage in the dietary intake calculation

RESIDUE DEFINITION

The WHO Panel considers and indicates in its evaluations which metabolites should be included in the dietary risk assessment

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

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

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

In those cases where it is not possible to finalize the risk assessment at the JMPR (September, year 1), usually because of a change in residue definition, the MRLs would still be recommended to the CCPR (by way of Codex circular letter for comment at step 3) and the compound would be re-discussed at the following year's JMPR meeting (September, year 2) The recommended MRLs together with the conclusion of the risk assessment would be available for the next CCPR (April, year 3)

If two compounds for which STMRs can be calculated produce the same analyte in compliance monitoring (e g CS_2 for dithiocarbamates), it is possible to separate the dietary intake assessments, if required, because the dietary intake assessment is no longer based on the MRL but is based on residue data specific to the individual compounds

When the residue definition includes more than one component, the appraisal should include an explicit description of how the total residue is calculated from the components The explanation should show necessary molecular weight adjustments and how "less-than LOQ" residues are dealt with

Example fipronil

When one component of the fipronil residue is above and the other below the LOQ, the combined residue is assumed to be close to the residue of the measurable component plus the LOQ of the other To indicate that one of the residue results is a real measurement, express the sum of the values as a real figure (e g <0 002 + 0 004 mg/kg = 0 006 mg/kg) The method for calculating the total residue for various situations is illustrated below

Fipronil	Metabolite MB 46136 or MB 46513	Total
<0 002	<0 002	<0 004
<0 002	0 004	0 006
0 003	0 005	0 008

The residue concentrations for fipronil (437 2 g/mol) and the metabolites MB 46136 (453 1 g/mol, factor 0 965) and MB 46513 (389 02 g/mol, factor 1 1) are expressed in the evaluation tables as the individual compounds *per se*, but are calculated in the appraisal according to the respective residue definition (expressed as fipronil) The LOQs of the individual compounds are not adjusted by these factors

Example spinosad

The residue definition for spinosad requires the addition of spinosyns A and D residues Spinosyn A constitutes approximately 85% of the residue initially and in practice constitutes the majority of the spinosyn residue In this calculation where the residue of spinosyn D was <LOQ it was assumed to be zero except when both spinosyns A and D residues were <LOQ and in that case the total was taken as <LOQ These are reasonable assumptions since the spinosyn D level is usually much less than the spinosyn A level The method for calculating the total residue for various situations is illustrated below

spinosyn A	spinosyn D	Sum of spinosyns A and D
0 59	0 082	0 67
0 03	<0 01	0 03
<0 01	<0 01	<0 01

COMBINING OF POPULATIONS OF DATA FOR THE CALCULATION OF STMR VALUES

In estimating an STMR, the JMPR evaluates whether data sets for a given commodity or commodity group should be combined and whether residue data reflecting different countries' GAPs should be combined

In deciding whether the results of trials reflecting different countries' GAPs give rise to different populations of residues data, the size of the database reflecting the different countries' GAPs should be taken into account

The 2001 JMPR recommended the use of statistical calculations to assist with the estimation of STMRs The Mann-Whitney U-test was considered suitable for verifying whether residue populations reflecting different GAP or climatic conditions or derived from different crops may have similar median values

Test statistics (U_1 and U_2) are calculated using the individual results from both residue populations and then the smaller test statistic is compared to a tabulated critical value

(α_2=5%) Where the test statistic is less than or equal to the tabulated value, the two median values are considered to be similar

The JMPR agreed to combine residue populations where the U-test suggested their medians were similar and use the combined population for the estimation of maximum residue levels and STMR values Where the populations are different, only the population which contained the highest valid residue value for both estimates is used

Example tebufenozide

Residue populations of mandarin and orange flesh from Italy and Spain were compared using the Mann-Whitney U-test to determine whether the populations were similar or different

Residues in mandarin flesh 0 069, 0 076, 0 082, 0 092, 0 14, 0 18 mg/kg

Residues in orange flesh 0 021, 0 03, 0 04, 0 04, 0 05, 0 053, 0 11, 0 13, 0 13, 0 15 mg/kg

The test statistics, U_1 and U_2 values, are calculated as

$U_1 = n_1n_2 + [n_1(n_1+1)]/2 - \Sigma R_1$

$U_2 = n_1n_2 + [n_2(n_2+1)]/2 - \Sigma R_2$

Where

- n_1 and n_2 are the number of data points in populations 1 and 2 respectively (n_1 and ΣR_1 are assigned to the smaller when the sample sizes are different)
- ΣR is the sum of ranks of the corresponding values

The Mann-Whitney U-test

1 In a table, list all the measurements from lowest to highest Use bold or coloured fonts to distinguish between the data sets
2 In a column for each population, place the corresponding ranks next to each measurement For ties assign the average of the ranks (e g for 0 04, 0 04 the ranks are 3 5 and 3 5 instead of 3 and 4)
3 Calculate the sum of the ranks for each population
4 Calculate the U values using the above equations ($U_1 = 17$, $U_2 = 43$)
5 Check the correctness of the calculation ($U_1 + U_2 = n_1n_2$)
6 Compare the lower U value with the tabulated critical value The critical value is 11 ($n_1 = 6$, $n_2 = 10$ at α_2 =5%) Since U_1 is greater than 11, it is concluded that the samples probably came from populations with the same median

Residues (mg/kg)	Ranks for mandarins	Ranks for oranges
0 021		1
0 03		2
0 04		3 5
0 04		3 5
0 05		5
0 053		6
0 069	7	
0 076	8	
0 082	9	
0 092	10	
0 11		11
0 13		12 5
0 13		12 5
0 14	14	
0 15		15
0 18	16	
∑Rank	64	72
U values	$U_1 = 17$	$U_2 = 43$
Critical Value ($n_1 = 6$, $n_2 = 10$, $\alpha_2 = 5\%$)		11
$U_1 > 11$	Populations similar	

As the lower of U_1 and U_2 is greater than the critical value of 11 we conclude that the populations have similar distributions and the populations can be combined for the purposes of estimating an STMR value This conclusion has an effect on the calculation of the long-term intake of the residues, as the median values for the individual populations were 0 087 mg/kg for mandarin flesh and 0 0515 mg/kg for orange flesh instead of 0 079 mg/kg for the combined population

Reviewers should note that the test should be applied with caution when there are residues below the LOQ in the populations to be compared

Statistical tests are useful tools in the evaluation of pesticide residue trial data However due to the complexity of the task, which includes the consideration of several factors such as metabolism and rate of disappearance, such tests are not definitive and can only support the expert judgement

Treatment of apparent outliers

Residue values above the majority of the population have to be treated individually and should only be disregarded if experimental evidence raises doubt about their reliability At the time of evaluating the results, utmost care is required to decide that a result is not valid The exclusion of an apparent outlier must be justified by agricultural practice or other evidence deriving from the experimental set up or analytical conditions

RESIDUES BELOW LOQ

As a general rule, where all residue trials data are <LOQ, the STMR value would be assumed to be at the LOQ, unless there is scientific evidence that residues are "essentially zero" Such supporting evidence would include residues from related trials at shorter PHIs, exaggerated, but related application rates or a greater number of applications, expectations from metabolism studies or data from related commodities

Where there are two or more sets of trials with different LOQs, and no residues exceeding LOQ have been reported in the trials, the lowest LOQ should normally be used for the purpose of selection of the STMR value (unless the residues can be assumed to be essentially zero as given above) The size of the trials database supporting the lowest LOQ value should be taken into account in the decision

The HR value should also be assigned a level of 0 when there is evidence that the residues are "essentially zero"

PROCESSING, COOKING FACTORS AND EDIBLE PORTION RESIDUE DATA

In using data on the effects on residue levels of processing or cooking practices, the mean processing factor should be applied to the STMR value estimated for the raw agricultural commodity as already described The STMR value estimated in this way for the processed commodity should be referred to as the STMR-P

If data are available for the residues in the edible portion of the commodity (e g banana pulp), an STMR value should be estimated directly using the edible portion residue values from maximum registered use trials (as opposed to using pesticide values for the whole commodity)

If the processing factors from two trials are irreconcilable, e g 10-fold different, the mean is inappropriate because it would not represent either process In this case it is preferable to choose one of the values as being representative The highest processing factor should be chosen as the default (conservative) value if there is no other reason to choose one or the other

ESTIMATION OF STMR AND HR VALUES FOR COMMODITY GROUPS

Where there are adequate trials data the STMR values should, in principle, be identified for the individual commodities and these values used for the intake assessment However, where the MRL has been recommended for a group of commodities (e g pome fruit) a single STMR value should be calculated for the group of commodities

Large portion size and unit weights are available for single commodities, not for commodity groups Consequently, when an HR value is identified for a commodity group it can be used only on single commodities for IESTI calculation The IESTI calculation for a group HR should be applied to the major commodities of the group, and especially to those commodities with data supporting the MRL

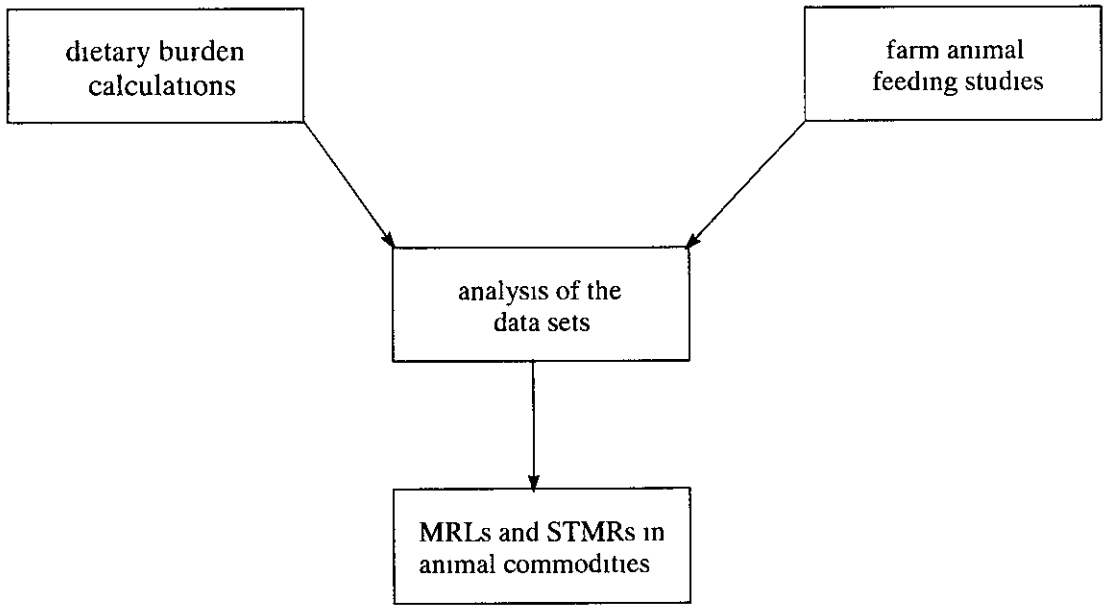
levels in animal commodities have been further developed in recent years and the explanations in reports have become more detailed

The situation is complex with many possible ways of using the data The exact procedure in a particular case may depend on availability of data The procedures described below are based on the experience with specific cases in the last few years and particularly on the compounds reviewed in 2001 Other cases with additional features may occur which may necessitate amendment of the current procedures

Residues arising from consumption of feed items

The 1986 JMPR explained the use of farm animal feeding studies in the estimation of MRL values in foods of animal origin It made the point that a sensible judgement of the expected ingestion level must be made The 1986 JMPR explained that it was unrealistic to assume that the theoretical maximum residue level would be achieved and maintained in the rations of food-producing animals receiving feeds produced on the farm or mixed feeds produced from commercially available ingredients

The estimation of residues that will arise in animal commodities is a two-pronged process involving farm animal feeding studies and dietary burden calculations These two independent sets of information are compiled and then combined in order to estimate the animal commodity residues that will arise in practice



In addition, the distinction should be made between those compounds where the plateau for residue levels in milk or eggs is reached rapidly in a repeat-dose study and those where it is reached slowly The following decision matrix is recommended for estimation of maximum residue levels and STMR values

Case	Estimation of residue levels in animal commodities	
	maximum residue level	STMR

Case	Estimation of residue levels in animal commodities	
	maximum residue level	STMR
when residue reaches plateau rapidly	choose • feed commodity MRL or STMR-P (for dietary burden calculation) • highest[1] residue level (from farm animal feeding study)	choose • feed commodity STMR or STMR-P (for dietary burden calculation) • mean[1] residue level (from farm animal feeding study)
when residue reaches plateau slowly	choose • feed commodity STMR or STMR-P (for dietary burden calculation) • highest[1] residue level (from farm animal feeding study)	choose • feed commodity STMR or STMR-P (for dietary burden calculation) • mean[1] residue level (from farm animal feeding study)

[1]Highest and mean refer to residue levels in the tissues and eggs of the relevant group of animals in the feeding study For milk, choose the mean residue in milk from the relevant group of animals in all cases

For compounds rapidly reaching the residue plateau in milk or eggs (plateau reached by 14 days) the residue contribution of a feed commodity for estimating maximum residue levels is calculated from the percent of the total diet and the estimated MRL or the highest residue (where no MRL is recommended) for raw agricultural commodity feed items For processed commodities, e g apple pomace, that are likely to originate from a number of farms, the STMR-P of the processed commodity is chosen as the likely highest residue to occur in practice

For compounds slowly reaching the residue plateau in milk or eggs (plateau not reached by 14 days) the residue contribution for the estimation of MRL values in commodities of animal origin is calculated from the percent of the total diet and from the STMR or STMR-P values for residues in animal feed items

The procedure illustrated in the above diagram is demonstrated in the following worked example for spinosad

Estimation of dietary burden of animals

Spinosad residues in milk reached a plateau after approximately 6 days, i e relatively rapidly Using the above decision matrix, animal commodity maximum residue levels are therefore derived from feed commodity MRLs and animal commodity STMRs are derived from feed commodity STMRs

In a table each for MRL and STMR estimation, all feed items, their Codex commodity group and the residue levels from the crop residue trials are listed The basis of the residue is provided, i e for the maximum residue level estimation, the basis is the MRL (for raw agricultural commodities) or the STMR-P (for processed commodities) The percent dry matter of the feeds is given using Appendix IX "Maximum proportion of agricultural commodities in animal feed", except where the trial data stipulated 100% dry matter The residue of each feed commodity on a dry weight basis is then calculated

Starting with the feed item with the highest residue, the percentage of livestock diet for each feed is allocated using Appendix IX One feed commodity only from each Codex Commodity Group is used or, occasionally more than one, but only up to the full % feed allocation for that

Group Feeds are allocated a percentage of the livestock diet for each animal until no more than 100% of the diet is used

The residue contribution of each feed (mg/kg) is then calculated using the residue on a dry weight basis and the corresponding percentage of the diet All residue contributions for each animal are then totalled to determine the total dietary burden

Maximum farm animal dietary burden estimation for spinosad example

						Feed allocation to total diets (%)			Residue contribution of feeds (mg/kg)		
Commodity	Codex commodity group	residue (mg/kg)	basis of residue	% dry matter	residue, on dry wt mg/kg	Beef cattle	Dairy cattle	Poultry	Beef cattle	Dairy cattle	Poultry
Apple pomace wet	AB	0 064	STMR-P	40	0 16	10			0 016		
Citrus pulp	AB	0 12	STMR-P	91	0 13						
Maize forage	AF	5	MRL	100	5 0	40	50		2 0	2 5	
Maize fodder	AS	5	MRL	100	5 0						
Wheat straw and fodder, dry	AS	1	MRL	100	1 0						
Sorghum	GC	1	MRL	86	1 2	40	40	80	0 47	0 47	0 93
Almond hulls	AM	2	MRL	90	2 2	10	10		0 22	0 22	
Cotton seed hulls		0 0020	STMR-P	90	0 0022						
Cotton seed meal		0 0017	STMR-P	88	0 0019			20			0 0004
					TOTAL	100	100	100			
						Maximum dietary burden			2 7	3 2	0 93

STMR farm animal dietary burden estimation for spinosad example

						Feed allocation to total diets (%)			Residue contribution of feeds (mg/kg)		
Commodity	Codex commodity group	residue (mg/kg)	basis	% dry matter	residue, on dry wt mg/kg	Beef cattle	Dairy cattle	Poultry	Beef cattle	Dairy cattle	Poultry
Apple pomace wet	AB	0 064	STMR-P	40	0 16	10			0 016		
Citrus pulp	AB	0 12	STMR-P	91	0 13						
Maize forage	AF	0 70	STMR	100	0 70	40	50		0 28	0 35	
Maize fodder	AS	0 46	STMR	100	0 46						
Wheat straw and fodder, dry	AS	0 215	STMR	100	0 22						
Sorghum	GC	0 165	STMR	86	0 19	40	40	80	0 08	0 08	0 15
Almond hulls	AM	0 56	STMR	90	0 62	10	10		0 062	0 062	
Cotton seed hulls	SO	0 0020	STMR-P	90	0 0022						
Cotton seed meal	SO	0 0017	STMR-P	88	0 0019			20			0 00039
					TOTAL	100	100	100			
						STMR dietary burden			0 43	0 49	0 15

The poultry dietary burdens will not be discussed further in this example

Use of the farm animal feeding study results and the dietary burden to estimate maximum residue levels and STMR values for commodities of animal origin

With the use of the following guidelines, the dietary burden calculations are compared to the feeding levels from the farm animal feeding studies to estimate the maximum residue levels and STMR values

- When a feeding level from the farm animal feeding study matches a dietary burden, the residue levels from the farm animal feeding study may be directly used as estimates of residues in tissues, milk and eggs resulting from the dietary burden
- When the feeding levels from the farm animal feeding study are different from the dietary burden, the resulting residues in tissues, milk and eggs may be estimated by interpolation between the closest feeding levels
- When the dietary burden is below the lowest feeding level in the farm animal feeding study, the resulting residues in tissues, milk and eggs may be estimated by applying the transfer factor (residue level in milk or tissue – residue level in diet) at the lowest feeding level to the dietary burden
- When the dietary burdens for beef and dairy cattle are different, the higher one should be used for calculation of the residues in muscle, liver and kidney
- For maximum residue level and HR estimation in meat, fat, liver, kidney and eggs, the highest residue from an animal in the relevant feeding group of the farm animal feeding study is used
- For STMR value estimation in meat, fat, liver, kidney and eggs, the mean residue from the animals in the relevant feeding group of the farm animal feeding study is used
- For maximum residue level and STMR estimation in milk the mean residue from the animals in the relevant feeding group of the farm animal feeding study is used
- It is not possible to extrapolate to a dietary burden more than approximately 30% above the highest feeding level

Continuing with the example of spinosad, the feeding levels from the farm animal feeding studies are entered into a table along with the dietary burden calculations and analysed using the above guidelines

The maximum dietary burdens for beef and dairy cattle are 2 7 and 3 2 mg/kg respectively, therefore the levels of residues in tissues and milk are taken directly from the 3 ppm feeding level in the farm animal feeding study without interpolation

The STMR dietary burdens (0 43 and 0 49 mg/kg) are below the lowest feeding level, 1 ppm, therefore the resulting residues in tissues and milk are calculated by applying the transfer factors at the lowest feeding level to those STMR dietary burdens (Transfer factor = residue level in milk or tissue – residue level in diet)

The highest individual tissue residue from the relevant feeding group was used in conjunction with the highest residue dietary burden to calculate the likely highest animal commodity residue level The mean tissue residue from the animals in the relevant feeding group was used in conjunction with the STMR dietary burden to estimate the animal commodity STMR values

For milk the mean milk residue at the plateau level from the relevant feeding group was used to estimate both the maximum residue level and the STMR

Dietary burden (mg/kg)[1] Feeding level [ppm][2]		Spinosad residues, mg/kg[3]								
		Milk	Fat		Muscle		Liver		Kidney	
		mean	high	mean	high	mean	high	mean	high	mean
MRL beef	(2 7) [3]									
MRL dairy	(3 2) [3]	*(0 13)* 0 13	*(1 7)* 1 7		*(0 069)* 0 069		*(0 44)* 0 44		*(0 26)* 0 26	
STMR beef	(0 43) [1]									
STMR dairy	(0 49) [1]	*(0 022)* 0 044		*(0 32)* 0 65		*(0 010)* 0 020		*(0 064)* 0 13		*(0 032)* 0 065

[1] Values in parentheses are the estimated dietary burdens
[2] Values in square brackets are the actual feeding levels in the transfer study
[3] Residue values in parentheses in italics are interpolated from the dietary burden, feeding levels in the transfer study and the residues found in the transfer study High is the highest individual animal tissue residue in the relevant feeding group Mean is mean animal tissue (or milk) residue in the relevant feeding group

The STMR burden for dairy cattle exceeds that for beef cattle, so is used for maximum residue level and STMR estimation on fat, muscle, liver and kidney

Highest residues expected in tissues and milk are fat 1 7 mg/kg, kidney 0 26 mg/kg, liver 0 44 mg/kg and milk 0 13 mg/kg Recommended maximum residue values (rounding to a suitable value) then become cattle meat 2 mg/kg (fat), cattle kidney 0 5 mg/kg, cattle liver 0 5 mg/kg and milk 0 2 mg/kg

Proposed STMR values are cattle meat 0 010 mg/kg, cattle kidney 0 032 mg/kg, cattle liver 0 064 mg/kg and milk 0 022 mg/kg

Residues arising from direct application to farm animals

Pesticides may be applied directly to farm animals for control of lice, flies, mites and ticks Application methods include dips, sprays, pour-ons and jetting Residue trials using the required method of application, dosage and withdrawal times are needed if residues may occur in animal commodities

The number of supervised trials on animals is, of necessity, far less than for crops

The conditions of a supervised residue trial on farm animals should match the maximum conditions described on the label If more than one application method is permitted (e g dip or pour-on treatment) residue data should be available for each method The evaluation should record the highest residue occurring in individual animal tissues resulting from the approved method, timing and dose For maximum residue level and HR estimation in meat, fat, liver and kidney, the highest residue is used The evaluation should record the average milk residues each day across the treatment group and the MRL recommendation will depend on the highest of these average milk residues on a day achieved within the conditions described

on the label It is assumed that morning and afternoon milkings are combined for any given day

The STMR concept is designed for supervised field trials on crops to obtain the typical residue value when a pesticide is used at maximum GAP The STMR methodology is not directly applicable to a single direct-animal treatment trial However, the idea of a typical residue value when a pesticide is used directly on animals (at maximum label conditions) is useful in long-term dietary intake estimations For this purpose the median of the residues in the tissues of animals slaughtered at the shortest interval after treatment (or later if residues were higher later) is taken to represent that typical value For estimation of the typical value in milk (needed for long- and short-term dietary intake) the mean residue from the relevant treatment group for the time of treatment should be used

Reconciliation of MRL recommendations and estimated residue levels resulting from direct treatment and from residues in animal feed

Where the maximum residue level recommendations from the two sources of residues do not agree, the higher recommendation will prevail Similarly, the estimates for typical residues from direct use at maximum label conditions or STMR values derived from the farm animal dietary burden and animal feeding studies, whichever is the higher, should be adopted for long-term intake estimation

CHAPTER 7

ESTIMATING DIETARY INTAKE OF PESTICIDE RESIDUES

CONTENTS

BACKGROUND

Available residue data are combined with cultural dietary information to make predictions of residue intake by consumers The consumer is considered to be adequately protected providing the intake of pesticide residues does not exceed the acceptable daily intake (ADI) or the acute reference dose (acute RfD)

The JMPR has, from the beginning, tried to arrive at predictions about the intake of pesticide residues on the basis of available data In taking the MRL as the residue level and using the dietary patterns for the quantity of food consumed, the JMPR arrived at the Theoretical Maximum Daily Intake or TMDI The JMPR was well aware of the fact that TMDI calculations result in a gross overestimation of the intake On the other hand, existing uses of the pesticide not brought to the attention of the JMPR could result in a minor underestimation of the residue intake

Until 1997 dietary intake calculations had been carried out according to the Guidelines for predicting dietary intake of pesticide residues[9] published by WHO in 1989 The dietary intake of any particular pesticide residue was obtained by multiplying the residue level in the food by the amount of commodity consumed from a "global" and five "cultural" diets, also called "regional" diets Total intake of the pesticide residue in each of the diet groups was then obtained by summing the intakes from all commodities containing the residue concerned Intake estimation could be refined by allowing for the residue level in the edible portion of the commodity, the reduction or increase of residue levels on commercial processing such as canning and milling, and the reduction or increase in the level of residue on preparation or cooking of the food

Based on the request of the CCPR a Joint FAO/WHO Consultation on Guidelines for Predicting the Dietary Intake of Pesticide Residues[10] in 1995 reviewed the existing guidelines and recommended feasible approaches for improving the reliability and accuracy of methods for predicting the dietary intake of pesticide residues The aim was to promote a greater acceptance of Codex MRLs by governments and, most importantly, by consumers The report

[9] WHO 1989 Guidelines for predicting dietary intake of pesticide residues GEMS/Food WHO, Geneva
[10] WHO 1995 Recommendations for the revision of the guidelines for predicting dietary intake of pesticide residues Report of the FAO/WHO Consultation, (WHO/FNU/FOS/95 11) Geneva

of the consultation contained recommendations for improving estimates of dietary intake, most notably the use of supervised trials median residue (STMR) levels in lieu of MRLs in the calculation of International Estimated Daily Intakes (IEDIs) and National Estimated Daily Intakes (NEDIs)

The IEDI incorporates those factors which can be applied at international level and which comprise a subset of the factors that might be considered at national level The factors to be considered for IEDI calculations are

- median residue data from sets of supervised trials,
- residue definitions, which include all metabolites and degradation products of toxicological concern,
- for residues at or below the limit of quantification (LOQ) (indicated with *), the median residue should be estimated to be the LOQ except when evidence from trials and supporting studies suggests that that residues are essentially zero,
- the edible portion,
- effects on residue levels due to storage, processing or cooking practices, and
- other known uses of the pesticide

The National Estimated Daily Intake (NEDI) should be based on the same factors as for the IEDI, but the following additional factors based on national use pattern of the pesticides and food consumption data should also be taken into consideration, which would result in a refinement of the NEDI

- proportion of crop or food commodity treated,
- proportion of crop domestically produced and imported,
- compliance monitoring and surveillance data,
- total diet (market basket) studies,
- food consumption data, including that of subgroups of the population

The revised guidelines also contained sections on the risk assessment of acute hazards posed by pesticide residues and predicting dietary intake of acutely toxic pesticide residues The guidelines have been further refined into operating procedures See the section in this chapter, "Short-term dietary intake "

The revised guidelines[11] were issued in 1997

LONG-TERM DIETARY INTAKE

Long-term dietary intakes are calculated by multiplying the residue concentrations (STMRs, STMR-Ps or recommended MRLs) by the average daily per capita consumption estimated for each commodity on the basis of the GEMS/Food diets[12] and summing the intakes for each food

[11] WHO 1997 Guidelines for predicting dietary intake of pesticide residues (revised) Prepared by the Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme (GEMS/Food) in collaboration with Codex Committee on Pesticide Residues (WHO/FSF/FOS/97 7)

[12] WHO 1998 GEMS/Food Regional Diets Regional per capita consumption of raw and semi-processed agricultural commodities Food Safety Unit WHO/FSF/FOS/98 3, Geneva

GEMS/Food Regional Diets, also referred to as cultural diets, are based on FAO food balance sheets from selected countries and expert knowledge Data are currently available for 5 regional diets Middle Eastern, Far Eastern, African, Latin American and European

International estimated daily intakes (IEDIs) are derived only where STMRs or STMR-Ps are used in the calculation Theoretical maximum daily intakes (TMDIs) use MRLs in the calculation

$$IEDI = \Sigma (STMR_i \times F_i)$$

$$TMDI = \Sigma (MRL_i \times F_i)$$

where

$STMR_i$ (or STMR-P_i) is	STMR (or STMR-P) for food commodity i
MRL_i is	MRL for food commodity i
F_i is	GEMS/Food regional consumption of food commodity i

The JMPR intake estimates take into account JMPR recommendations They may not always agree with a calculation that includes all current Codex MRLs because Codex MRLs whose withdrawal has been recommended by the JMPR are not included in the estimate

Long-term dietary intakes are expressed as percentage of the ADI for a 60 kg person The percentage of ADI is rounded to one significant figure for values up to and including 100% and to two significant figures for values above 100% When the percentage is higher than 100 for the compounds for which IEDIs are calculated, the information provided to the JMPR does not allow an estimate that the dietary intake would be below the ADI

At the National level, further refinements of the dietary intake calculations are possible, taking into account more detailed information on food consumption, monitoring and surveillance data, total diet or reliable data on the percentage of crop treated and percentage of crop imported

Long-term intake calculations are made in spreadsheets The spreadsheets were originally developed for TMDI calculations and were then modified to accommodate refinements as they were introduced The format provided in this manual is a simplification of the most recent spreadsheets because it is recognized that inserting data on the spreadsheet that are not needed in the intake calculation may be confusing for readers unfamiliar with the history of developments in this area

The format of a spreadsheet for calculating long-term intake is provided in Tables XI 4 and XI 5 (Appendix XI) The tables are completed for an IEDI estimation for parathion-methyl and for a mixed TMDI-IEDI calculation for myclobutanil

Notes for intake spreadsheets

- diets are expressed in g/day
- daily intakes are expressed in µg/person
- the MRL is not entered unless it is used in the calculation

- the STMR for meat is expressed on the muscle tissue for all compounds whether fat-soluble or non-fat-soluble MRLs for fat-soluble compounds are expressed on the fat

See Appendix X, section "Dietary risk assessment" for standard statements depending on the results of the IEDI calculations

SHORT-TERM DIETARY INTAKE

In 1994 the JMPR considered the assessment of acute dietary risk in response to the CCPR's reservations about MRLs proposed for acutely toxic pesticides The CCPR had suggested that the traditional ADI may not be appropriate for assessing risks reflecting short-term exposure to residues Revised guidelines[11] were published in 1997 by WHO and contained chapters on risk assessment of acute hazards and predicting dietary intake of acutely toxic pesticide residues Procedures and practical guidelines were subsequently developed and the 1999 JMPR commenced formal routine assessment of acute dietary risk for pesticide residues in food

High intake of a residue would occur when a large portion of a food with a high residue was consumed The large portion size was agreed as the 97 5th percentile daily consumption for eaters of that food Research in the UK and other countries had shown that the residue level in a unit of fruit or vegetable (i e a single apple or a single carrot) may be substantially higher than the residue in a composite sample representing the typical residue in the lot This concept provided the basis for assessment of short-term dietary intake of pesticide residues

The highest residue from the supervised residue trials at maximum GAP was generally seen as the better option than the MRL for short-term dietary intake calculations The MRL is expressed on commodity of trade rather than edible portion and the MRL compliance residue definition does not always match the dietary intake residue definition Estimation of an MRL usually involves "rounding up" to an accepted value, and rounding of values at an intermediate stage of a calculation is undesirable Furthermore, the use of the MRL in an intake calculation may give the impression that adjusting the MRL will change the intake, however there will be no real change of dietary intake if the MRL is changed but GAP and other factors remain the same

The highest residue in the composite sample of edible portion from the trials used for estimating the maximum residue level is defined as the HR, expressed as mg/kg In those cases where information is available only on the whole commodity and not on the edible portion, the HR expressed on whole commodity may be used in the dietary intake calculations, but as a less preferred option

A "high residue" is needed in the intake calculation for those processed commodities where bulking and blending are not influential, e g dried fruit or canned pineapple The preference was to apply the processing factor to the highest residue from the supervised residue trials at maximum GAP rather than to the MRL Similar arguments about rounding and residue definition apply here as for the HR case The high residue in a processed commodity is referred to as the HR-P (highest residue - processed commodity)

The HR-P is the residue in a processed commodity calculated from the highest residue of the raw agricultural commodity and the corresponding processing factor

Data on unit weights and edible portion percentages have been provided by France, the UK and the USA to WHO GEMS/Food

Large-portion consumption data have been provided by Australia, France, The Netherlands, Japan, the UK and the USA Mean body weights for adults and children aged 6 and under have been provided by Australia, France, The Netherlands, the UK and the USA

The values provided by WHO GEMS/Food for the highest large-portion diet with the associated body weight and country for children and general population are used in the IESTI calculations

Data on unit weights and large portion consumption (97 5 percentile diets) and the mean body weights for the populations associated with the food consumption data are provided on the WHO web site[13]

Calculations of intake recognize four different cases (1, 2a, 2b and 3) Case 1 is the simple case where the residue in a composite sample reflects the residue level in a meal-sized portion of the commodity Case 2 is the situation where the meal-sized portion as a single fruit or vegetable unit might have a higher residue than the composite Case 2 is further divided into case 2a and case 2b where the unit size is less than or greater than the large portion size respectively Case 3 allows for the likely bulking and blending of processed commodities such as flour, vegetable oils and fruit juices

LP	Highest large portion reported (97 5th percentile of eaters), kg food/day
HR	Highest residue in composite sample of edible portion found in the supervised trials used for estimating the maximum residue level, mg/kg
HR-P	Highest residue in a processed commodity, mg/kg, calculated by multiplying the highest residue in the raw commodity by the processing factor
bw	Mean body weight, kg, provided by the country from which the LP was reported
U	Unit weight of the edible portion, kg, provided by the country where the trials which gave the highest residue were carried out
v	Variability factor - the factor applied to the composite residue to estimate the residue level in a high-residue unit
STMR	Supervised trials median residue, mg/kg
STMR-P	Supervised trials median residue in processed commodity, mg/kg

See Appendix II, Glossary of Terms, for definitions of acute RfD, HR, HR-P, STMR and STMR-P

[13] http //www who int/fsf/Chemicalcontaminants/Acute_Haz_Exp_Ass htm

Case 1

The residue in a composite sample (raw or processed) reflects the residue level in a meal-sized portion of the commodity (unit weight is below 0 025 kg)

$$\text{IESTI} = \frac{\text{LP} \times (\text{HR or HR-P})}{\text{bw}}$$

Case 2

The meal-sized portion, such as a single fruit or vegetable unit might have a higher residue than the composite (whole fruit or vegetable unit weight is above 0 025 kg)

Case 2a

Unit edible weight of raw commodity is less than large portion weight

$$\text{IESTI} = \frac{\text{U} \times (\text{HR or HR-P}) \times v + (\text{LP-U}) \times (\text{HR or HR-P})}{\text{bw}}$$

The Case 2a formula is based on the assumption that the first unit contains residues at the [HR $\times$ *v*] level and the next ones contain residues at the HR level, which represents the residue in the composite from the same lot as the first one

Case 2b

Unit edible weight of raw commodity exceeds large portion weight

$$\text{IESTI} = \frac{\text{LP} \times (\text{HR or HR-P}) \times v}{\text{bw}}$$

The Case 2b formula is based on the assumption that there is only one consumed unit and it contains residues at the [HR $\times$ *v*] level

Case 3

Case 3 is for those processed commodities where bulking or blending means that the STMR-P represents the likely highest residue

$$\text{IESTI} = \frac{\text{LP} \times \text{STMR-P}}{\text{bw}}$$

Acute reference dose

The acute RfD (acute reference dose) of a chemical is the estimate of the amount of a substance in food or drinking-water, expressed on a body weight basis, that can be ingested over a short period of time, usually during one meal or one day, without appreciable health risk to the consumer on the basis of all the known facts at the time of the evaluation Acute RfDs are derived from toxicological data obtained from feeding studies on laboratory animals The estimated short-term dietary intake of a residue is compared with its acute RfD in the risk assessment

The JMPR WHO Core Assessment Group has already assessed many compounds and either assigned an acute RfD or decided that an acute RfD is unnecessary

The JMPR decided that it was inappropriate to use the ADI for a compound that has not yet been assessed for an acute RfD

In the short-term risk assessment of a compound, there are then 3 situations with respect to the acute RfD

1) an acute RfD is available
2) an acute RfD is unnecessary
3) the compound has not yet been evaluated for an acute RfD

When an acute RfD is available the calculated IESTI values may be expressed as % of acute RfD

When an acute RfD is unnecessary, IESTI calculations are not necessary In this case in the residue evaluations it is not necessary to estimate HR and HR-P values because they are not needed

When the compound has not yet been evaluated for an acute RfD, HR and HR-P values should be estimated and IESTI values calculated The acute RfD section in the table heading should state "may be necessary but has not yet been established" The final column in the IESTI tables cannot be completed (% acute RfD) and entries should be indicated by a dash "-"

IESTI tables

An acute risk assessment is carried out for each commodity-compound combination by assessing the IESTI as a percentage of the acute RfD of the compound If the percentage is higher than 100, the information provided to the JMPR does not allow an estimate that the acute dietary intake of the residue in that commodity would be below the acute reference dose See Appendix X, section "Dietary risk assessment" for standard statements depending on the results of the IESTI calculations

Tables XI 6 and XI 7 (Appendix XI) are examples of the format of IESTI calculation spreadsheets, the examples are for parathion-methyl For each compound, two tables are needed, one for the general population and one for children

The table heading should show the compound, IESTI, general population or children and acute RfD

The commodities and the STMR, STMR-P, HR and HR-P values are taken from the recommendations table Only those values needed in the calculations should be entered in the IESTI tables Note that STMR values are generally not used in IESTI calculations and should not be entered into the tables (exceptions STMR values are used for milk, STMR values for commodities like wheat are precursors to the STMR-P values for the processed commodities)

The percentages of the acute RfD are rounded to one significant figure for values up to and including 100% and to two significant figures for values above 100%

The IESTI values in the table are expressed as μg/kg bw in preference to the traditional mg/kg bw for more convenient reading, the % acute RfD is unchanged by the choice of units

Body weights

In selecting the appropriate body weight, an *ad hoc* meeting in 1999 recommended the use of 15 kg for children aged 6 and under and 60 kg for the general population Since it is necessary to express the IESTI as per kg bodyweight for comparison with the acute RfD, the JMPR recommended that body weights provided by the appropriate national Governments should be used in the calculation The JMPR agreed that where these were not available, default values of 15 or 60 kg should be used

Variability factors

The JMPR in 1999, after examining the available information, concluded that a variability factor (R97 5^{th} – mean) of 7 for medium sized units could be used on a temporary basis until the database was further refined The variability factor of 7 would not apply to granular soil treatments or leafy vegetables where the factor of 10 should be retained for medium sized units

Summary of variability factors

Commodity characteristic	*v*
Whole fruit or vegetable unit weight is <0 025 kg	Case 1
Whole fruit or vegetable unit weight is >0 25 kg	5
Whole fruit or vegetable unit weight is ≤0 25 kg but >0 025 kg	7
Leafy vegetables with unit weight ≤0 25 kg but >0 025 kg	10
Residue is derived from granular soil treatment with whole fruit or vegetable unit weight ≤0 25 kg but >0 025 kg	10

Food unit weights and % edible portion

Food unit weights are quite influential on Case 2 IESTI calculations Data on unit weights for a particular food provided to WHO GEMS/Food may cover a range

The JMPR decided to use the unit weight appropriate to the region where GAP had been used to recommend the MRL The JMPR agreed that in cases where no data had been supplied the calculation would not be carried out unless it could be concluded that a typical unit size was generally similar from region to region

National governments that supplied unit weight data also supplied % edible portion The unit weight on a whole commodity basis is used to decide the choice of variability factor, but the unit weight in Case 2 calculations is the edible portion unit weight For example, the avocado unit weight is 0 3 kg and 60% of its weight is edible Therefore the v for avocado is 5 (unit weight > 0 25 kg) and the unit weight edible portion (U) in Case 2 is 0 18 kg

Summary of choice of values in IESTI calculation spreadsheets

1 Commodity, STMR, STMR-P, HR and HR-P use values directly from the recommendations table

2 Large portion diet use the values provided by WHO GEMS/Food for the highest large-portion diet, body weight and country for children and general population

3 Unit weight choose the country, unit weight and edible portion weight from the values provided by WHO GEMS/Food[13] The country should be associated with the region where GAP had been used to recommend the MRL

4 Variability factor and case decide the variability factor and case from the unit weight, unit weight edible portion and large portion size

Animal commodities IESTI calculations

See also Chapter 6, section "Estimation of maximum residue levels and STMR values for commodities of animal origin "

According to the recommended sampling principles[14] (Pesticide Residues in Food, CODEX ALIMENTARIUS, 1993), "a lot would comply with the MRL if

a) the final sample (consisting of combined primary samples) of commodities other than meat and poultry products did not contain a residue above the MRL, or
b) none of the primary samples of meat and poultry products analyzed contained a residue above the MRL"

This implies that a variability factor should not be used in the IESTI calculation for animal commodities

The acute intake estimation from the consumption of animal commodities, except milk, should be performed using the Case 1 defined by the methodology For milk, Case 3 should be applied (bulking or blending large portion at STMR level)

WHEN JMPR ESTIMATES OF DIETARY INTAKE EXCEED THE ADI OR ACUTE RfD

After the procedures described in this chapter have been applied to pesticides evaluated as new compounds or under the periodic review program the results are the best estimates of dietary intake of those pesticides according to the available data and methods applicable at the international level The JMPR, by the use of footnotes, draws attention to those cases when intake estimates exceed the ADI or acute RfD

If the JMPR estimate of long-term intake of a new or periodic review compound still exceeds the ADI for one or more of the GEMS/Food regional diets a footnote will be attached to the compound in the recommendations table

> *"The information provided to the JMPR precludes an estimate that the dietary intake would be below the ADI - JMPR [year] "*

[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