



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



Programme of Food Safety and Food Aid
World Health Organization
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IPCS

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY



This document is issued under the umbrella of the **International Programme on Chemical Safety** (IPCS) which was established in 1980 as a joint venture of the United Nations Environment Programme, the International Labour Organization, and the World Health Organization. The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer-review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

IOMC

INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS

A cooperative agreement among ILO, WHO, UNIDO and OECD

This document is a contribution to the **Inter-Organization Programme for the Sound Management of Chemicals** (IOMC) which was established in 1995 by UNEP, ILO, FAO, WHO, UNIDO and OECD, (Participating Organizations) following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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List of abbreviations

ADI	acceptable daily intake
acute RfD	acute reference dose
CAC	Codex Alimentarius Commission
CCPR	Codex Committee on Pesticide Residues
FAO	Food and Agriculture Organization of the United Nations
GAP	good agricultural practice(s)
GEMS/Food	Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme
IEDI	International Estimated Daily Intake
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LOD	limit of determination
MRL	Maximum Residue Limit
NEDI	National Estimated Daily Intake
NTMDI	National Theoretical Maximum Daily Intake
NOAEL	no-observed-adverse-effect level
PHI	pre-harvest interval
STMR	Supervised Trials Median Residue
STMR-P	STMR corrected for processing
TMDI	Theoretical Maximum Daily Intake
WHO	World Health Organization

1 Introduction

The Codex Committee on Pesticide Residues (CCPR) is a subsidiary body of the Codex Alimentarius Commission (CAC) that advises on all matters related to pesticide residues. Its primary objective is to develop Maximum Residue Limits (MRLs), in order to protect the health of the consumer while facilitating international trade. Public health considerations are taken into account by establishing the MRLs at levels not higher than those resulting from use of the pesticide in accordance with Good Agricultural Practices (GAP). However, explicit consideration of possible exposure to residues of a pesticide is an integral part of the risk assessment process to ensure that the Acceptable Daily Intake (ADI) of the pesticide is not exceeded. The best assurance that exposure to residues are within safe limits is obtained from dietary intake studies which can provide detailed food consumption data and accurate and reliable pesticide residue data. When such studies are not feasible or the pesticide is not yet being used or has only recently been approved for use, pesticide residue intake must be predicted on the basis of the available data.

In 1989, guidelines for predicting dietary intake of pesticide residues were prepared by the Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme (GEMS/Food) in collaboration with the CCPR (WHO, 1989). Based on these guidelines, GEMS/Food routinely provided international dietary exposure assessment calculations for pesticides considered by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) and the CCPR. The guidelines were effective in resolving concerns for dietary intake for most pesticides; however, exposure assessments for a number of pesticides indicated that more accurate methods for estimating intake of pesticide residues were required. On the request of the CCPR and consistent with a recommendation of the FAO/WHO expert consultation on risk analysis (FAO/WHO, 1995a), a joint FAO/WHO consultation was convened 2-6 May 1995 in York, United Kingdom to revise the 1989 guidelines. Based on the report of this consultation (FAO/WHO, 1995b), the present revised guidelines have been prepared by GEMS/Food.

The revised guidelines address methods for exposure assessment of long-term hazards posed by pesticide residues to be conducted at the international and national levels. The procedures described for the international level are used, in part, by the CCPR in considering the acceptability of MRLs being developed by that committee. The guidelines also cover the exposure assessment of acute hazards which are of particular concern for certain pesticides. Worked examples of various intake calculations are also included to illustrate the best use of data in assessing exposure and characterizing risk. The present guidelines are intended to assist national authorities in their considerations on the acceptability of Codex MRLs and in making national decisions on granting of pesticide registration. The approaches described here are designed to provide reasonable assurance that use of Codex MRLs will not result in a dietary intake of a pesticide that exceeds its ADI, or acute Reference Dose (acute RfD) when appropriate.

For the purpose of these guidelines, the terms “dietary exposure” and “dietary intake” are considered synonymous. A glossary of various terms used in this document is presented in Annex 1.

2 Risk assessment of long-term hazards posed by pesticide residues

2.1 Acceptable Daily Intakes

The ADI of a pesticide is established by JMPR on the basis of a complete review of the available information, including data on the biochemical, metabolic, pharmacological, and toxicological properties of the pesticide derived from studies of experimental animals and observations in humans. The no-observed-adverse-effect level (NOAEL) for the most sensitive toxicological parameter, normally in the most sensitive species of experimental animal, is used as the starting-point. A safety factor that takes into consideration the type of effect, the severity or reversibility of the effect, and the problems of inter- and intraspecies variability is applied to the NOAEL to determine the ADI for humans. If available, pertinent data on humans may be used in estimating the ADI for humans, usually with a reduced safety factor. This evaluation is the hazard characterization step in the risk assessment of long-term hazards posed by pesticide residues.

Concern has been occasionally expressed that adverse health effects might arise from exposure to the residues of more than one pesticide in food. The significance of interactions of pesticides was considered by the 1981 JMPR (FAO/WHO, 1982), which concluded that there was no compelling evidence to warrant alteration in the general approach for estimating ADIs. In 1996, JMPR revisited the issue (FAO/WHO, 1997a) and concluded that interactions between pesticide residues, other dietary constituents, and environmental contaminants could occur, but that such interactions depend on many factors, including the chemical and physical nature of the substances, the dose, and conditions of exposure. Furthermore, the outcome, which cannot be predicted reliably, may be enhanced, mitigated, or additive toxicity. In view of these uncertainties, the JMPR concluded that the safety factors that are used for establishing ADIs should provide a sufficient margin of safety to account for potential synergism.

2.2 Residue levels

Several indices of residue levels can be used to predict pesticide residue intake. The MRL is one such index and represents the maximum concentration of a pesticide residue (expressed as mg/kg) that the CAC recommends be legally permitted in food commodities and animal feeds. Pesticide residue levels that would be expected from the use of GAP are estimated from a collection of nationally generated data. The MRLs recommended by the JMPR, on which the Codex MRLs are usually based, reflect the considered decision of the experts present at the meeting after examination of all pertinent data. Factors that may be taken into consideration when choosing an index to be used in predicting pesticide residue intake include the residue levels found in practice, their distribution in the commodity, and the effect on residues of the various processes used in the preparation of food.

Neither the MRL nor the ADI is permanently fixed. Both the MRL and ADI are determined according to the best judgement of a group of internationally recognized experts on the data available to them at the time of the evaluation.

The data are summarized in JMPR reports and evaluations. As new data become available, the ADI or MRL may be reconsidered by JMPR. In addition, pesticides may be scheduled for re-evaluation by JMPR under the on-going periodic review process.

2.3 Exposure assessment

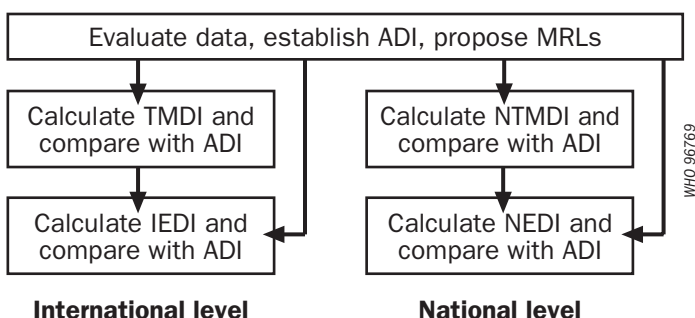
An exposure assessment is necessary in order to reach a conclusion on the acceptability of proposed MRLs and the underlying GAP from a public health point of view. The dietary intake of a pesticide residue in a given food is obtained by multiplying the residue level in the food by the amount of that food consumed. The total dietary intake of the pesticide residue is then obtained by summing the intakes of all foods containing the residue. Exposure to a pesticide residue present, or likely to be present, in drinking water or in a food for which no MRL has been established should be taken into consideration when such information is available. The estimated dietary intake of pesticide residues resulting from application of a pesticide and other sources should be less than its established ADI. However, short-term intake above the ADI should not necessarily be considered a health hazard (see Section 5.2).

2.4 Risk characterization

At the international level, the Theoretical Maximum Daily Intake (TMDI) is used as a convenient screening tool for assessing dietary intake. When information is available, the International Estimated Daily Intake (IEDI) is used to obtain a better estimate of dietary exposure. For the TMDI and IEDI, the risk characterization is based on an average adult weighing 60 kg. For some regions and especially for some countries, the correct average body weight should be used to more accurately reflect the acceptable intake per person. The National Theoretical Maximum Daily Intake (NTMDI) and the National Estimated Daily Intake (NEDI) may be used for similar purposes at the national level. The recommended approach to dietary intake assessments at the international and national levels is presented schematically in Figure 1 below.

Figure 1

Scheme for the assessment of dietary intake of pesticide residues for long-term hazards



The results of TMDI and IEDI calculations are expressed as a percent of the ADI and presented as a range of values corresponding to the representative diets for various regions of the world (see Section 3.1.2). In view of the uncertainties and variability inherent to calculations of dietary intake, values

up to and including 100% are rounded to one significant figure and those over 100%, are rounded to two significant figures (e.g. 3%, 70%, 110%, 360%, 1200%, etc. where the zeros are not considered significant).

Experience in applying the original guidelines (WHO, 1989) indicated that the approach may have been misinterpreted because many countries did not take full advantage of all the available data to refine the dietary intake estimate, particularly in cases when the estimated intake exceeded the ADI. These revised guidelines for assessing dietary intake therefore place emphasis on making the best use of the available data at any level.

3 Predicting dietary intake of pesticide residues at the international level (long-term hazards)

At the international level, estimates of dietary intake play an important role in ensuring safe food for consumers throughout the world. Such assessments can be conducted centrally with minimal resources. This chapter presents the international method used for assessing the potential long-term (chronic) hazards resulting from ingestion of low levels of pesticide residues in the diet over a life-time. Long-term hazard exposure assessment at the national level is presented in Chapter 4.

3.1 Theoretical Maximum Daily Intake

Codex MRLs are convenient for making a first estimate of pesticide residue intake which is referred to as the *Theoretical Maximum Daily Intake* (TMDI). Because the actual levels found in most foods are well below the corresponding MRLs, this estimate should be used only to separate those pesticides for which there are no concerns for long-term intake from those that require further consideration.

The TMDI is calculated by multiplying the established or proposed Codex MRLs by the estimated average daily regional consumption for each food commodity and then summing the products:

$$\text{TMDI} = \sum \text{MRL}_i \times F_i$$

where

MRL_i = Maximum Residue Limit for a given food commodity

F_i = Per capita GEMS/Food regional consumption of that food commodity

The TMDI is compared to the ADI of the pesticide, calculated for a 60 kg person and expressed as a percent of the ADI. For certain regions, the average body weight of the population may differ significantly from 60 kg. More precise average body weights will be taken into consideration during the development of future regional diets.

The TMDI is an overestimate of the true pesticide residue intake because, among other things: only a portion of a specific crop is treated with a pesticide; most treated crops contain residues well below the MRL at harvest; residues are usually reduced during storage, preparation, commercial processing, and cooking; and, it is unlikely that every food for which an MRL is proposed will have been treated with the pesticide over the lifetime of the consumer. Therefore, it should not be concluded that the proposed MRLs for a pesticide are unacceptable when the TMDI exceeds the ADI. If the TMDI does not exceed the ADI, however, it is highly unlikely that the ADI would be exceeded, even for high intake consumers, provided that the main uses of the pesticide are covered by Codex MRLs.

3.1.1 Estimates of residue levels

The MRL represents the maximum residue level that is expected to occur in a commodity following the application of a pesticide according to GAP. Therefore, the use of the MRL in the prediction of pesticide residue intake will lead to an overestimation of actual pesticide residue intake. Supervised field trials of some pesticide uses result in MRLs that are at or below the limit of determination (LOD) of the analytical method. In such cases, the MRL is set at or about the LOD and an asterisk (*) is placed after the MRL in the Codex Alimentarius. The previous guidelines considered MRLs established at or about the LOD as equal to zero. To promote a consistent approach of overestimating intake at this early stage, however, the TMDI is always calculated using the MRL. In using the MRL in TMDI calculations, however, the MRL should generally be representative of residues of toxicological concern. It is recognized that, in some cases, the definition of a residue established for setting the MRL may not be appropriate for assessing dietary intake. (See Section 3.2.1)

3.1.2 Estimates of food consumption

There are several possible indices of food consumption. A commonly used index is average daily consumption; others include average portion sizes, percentile consumption values, and the average consumption of people who actually eat the commodity. In predicting pesticide residue intake, long-term food consumption habits and not day-to-day variations should be reflected to permit valid comparison with the ADI, which is based on intake over a lifetime. Thus, average daily food consumption values are used in predicting pesticide residue intake for long-term hazards.

Food consumption patterns vary considerably from country to country and even within a country; thus, to a large extent, individual countries must estimate their own consumption pattern(s). For predicting pesticide residue intake at the international level, average food consumption data given in the food balance sheets compiled by FAO are used. These are generally based on a country's annual food production, imports, and exports; waste at the household or individual level and subsistence farming are not taken into account. Although the food consumption data derived from such food balance sheets are subject to many uncertainties and limitations, they represent the best available source of data for international comparison and are adequate for predicting pesticide residue intake, given the inherent uncertainties in the residue estimates and ADIs.

The GEMS/Food global and five regional diets based on FAO food balance sheet data have been used previously. While the global diet approach has been discontinued, the five regional diets (Middle Eastern, Far Eastern, African, Latin American, and European) are retained. If data from food balance sheets are not available for a commodity, the consumption level for a similar food is used. If data on a similar food is unavailable, a default value of 0.1 g/day is assigned which is the lowest quantified value in the current GEMS/Food diets. In order to predict pesticide residue intake at the international level more accurately, the regional diets will be revised and expanded by WHO to ensure better representation of the cultures and regions of the world. Copies of the current GEMS/Food regional diets can be obtained on request from WHO.

For pesticides that are fat-soluble, MRLs are specified for the fat portion of animal products. Consumption figures for mammalian and poultry meat are corrected based on the assumptions that mammalian meat contains 20% fat and poultry meat (with adhering skin) contains 10% fat. In cases when residues in milk are expressed on a fat basis, GEMS/Food assumes that whole milk contains 4% fat unless it is otherwise stated.

3.2 International Estimated Daily Intake

The *International Estimated Daily Intake* (IEDI) incorporates correction factors for application at the international level. When information is available, the IEDI is calculated to refine the intake estimate on the basis of all available information, providing a “best estimate” of dietary intake. In order to estimate the actual residue intake from the food supply, a number of factors must be applied that are described in detail below. These factors are summarized in Table 1.

Table 1

Factors for refining estimates of residue levels for predicting long-term dietary intake of pesticide residues at the international level

-
- Median residue levels from supervised trials, including residue definition (see Section 3.2.1)
 - Residues in edible portions (see Section 3.2.2)
 - Effects of processing and cooking on residue levels (see Section 3.2.3)
 - Other known uses of the pesticide (see Section 3.2.4)
-

The IEDI may be derived from the following equation:

$$\text{IEDI} = \sum \text{STMR}_i \times E_i \times P_i \times F_i$$

where

- STMR_i = Supervised trials median residue level for a given food commodity
- E_i = Edible portion factor for that food commodity¹
- P_i = Processing factor for that food commodity
- F_i = GEMS/Food regional consumption of that food commodity

If the ADI is exceeded by the IEDI after all of the factors are applied, additional relevant data provided by governments, industry and other sources should be considered. If the ADI is still exceeded, concern about dietary intake becomes an issue for risk management to be considered by the CCPR.

3.2.1 Median residue levels from supervised trials, including residue definition

While the MRL has been used in the past, a more appropriate starting point for estimating long-term dietary intake is the most likely residue level (i.e. the mean or median level) resulting from use of the pesticide at the maximal conditions officially approved. The mean and median levels in supervised trials are usually considerably lower than the maximum observed. Although the use of the median or the mean generally gives similar results, the median is preferred because it simplifies calculations for residue levels below the LOD. For assessing exposure to pesticide residues, the *Supervised Trials Median Residue Level* (STMR) is therefore used by WHO to calculate the IEDI whenever STMRs have been determined by the JMPR. Beginning in 1996, the JMPR has routinely established STMRs at the same time that MRLs are recommended. On the

¹ For some commodities, such as banana, STMR levels may be determined directly from levels measured in the edible portion.

basis of procedures used by the JMPR in determining STMRs, guidance to experts evaluating residue data in the estimation of the dietary intake of pesticide residues is given in Annex 2.

When JMPR evaluates residue data, it also explicitly defines the residue for estimation of dietary intake. For the purpose of assessing dietary intake, all metabolites and degradation products of toxicological concern must be included in supervised trials and studies of processing. This issue may be of special significance where the parent compound has disappeared but metabolites or degradation products are still detectable. Therefore, the composition of residues is considered for the purposes of both dietary intake estimates and compliance with MRLs and, if necessary, separate definitions of the residues are developed.

If the median residue level is at or below the LOD, the STMR for dietary intake purposes is established at the LOD even if all measurements of residues in a set of trials within the specified conditions are at or below the LOD. The STMR is estimated to be zero when data from the trials and supporting evidence suggest that levels are essentially zero. Supporting evidence includes data from related trials at shorter preharvest intervals, exaggerated application rates, or a greater number of applications, data from metabolic studies, and data on related commodities (see No 3.6, Annex 2).

Direct comparison of pesticide use patterns in different countries is difficult because only rarely do the application rates, numbers of applications, and preharvest interval correspond. Trial data are included in the evaluation if they correspond to the maximum registered use in either the country in which the trial was conducted or in a country with comparable climatic, geographic, and growing conditions. Judgement must be used in deciding whether the conditions of a trial comply with the approved GAP. Because the same issue arises for MRL estimations, the same trial conditions relative to application rate, number of applications, and preharvest intervals are used. It should be noted that the STMR should represent all metabolites and degradation products of toxicological concern (see Section 3.2.3.2).

3.2.2 Residues in edible portions

MRLs are established for residues present in the whole commodity, including the inedible portions. For commodities with inedible peel, the outer inedible portion of a commodity will often contain most of the residue. Therefore, the level of residues in the edible portion of a food commodity is used in estimating dietary intakes. Residue data should quantify the distribution of residue in the whole and the edible portion of a commodity. There is no universal distribution ratio because the amount of residue in the edible portion varies from pesticide to pesticide. In the case of fruits with inedible skins, such as bananas, citrus and melons, supervised trials commonly include data on edible portion, skin and whole commodity. In practice, the STMR is estimated directly from residue data on the edible portion.

Residue data on the edible portions should be obtained to refine estimates of dietary intake for the following commodities: citrus fruits, bananas, pineapples, kiwifruits, and other fruits with inedible peel; cereals; oilseeds; and cucurbits with inedible peel, such as melons. In some countries edible portions of some food commodities may vary, and consequently, national governments should consider local dietary habits when using such data.

3.2.3 Residues after processing

As noted in the previous guidelines (WHO, 1989), residues on raw commodities are normally dissipated during storage, transport, preparation, commercial processing, and cooking. In some cases, however, residues may be concentrated in processed fractions, resulting in higher levels than in raw commodities. Some pesticides are destroyed by food preparation processes, such as heating and boiling, but toxic degradation products may be formed in some cases. The knowledge that residues of such pesticides are not expected to occur in canned food and juices and other thermally treated products can be used in interpreting data from trials and extrapolating them to other commodities.

Many primary products are consumed only after processing. Washing and cleaning, which are the initial steps in most processing procedures, frequently reduce residue levels, particularly for nonsystemic pesticides. Many other types of processing (e.g. the milling of cereals to flour and the polishing of rice) result in a significant lowering of residue levels. However, other types (e.g. the conversion of fruits to pomace and the extraction of oil from oilseeds) may result in concentration of residues. Data are often available on the fate of the original residues, but are not consistently provided for evaluation.

Some commodities are always processed (e.g. cereals to flour, bran and bread; oilseeds to oil) and processing data for these commodities should be evaluated at the international level. For other commodities, only a portion of the crop is processed (e.g. fruits to juices and dried fruits). Because many of these processed commodities are well defined, the data may be usefully evaluated at the international level. For some processed products, data on residues and consumption data must be obtained (e.g. for grapes used to make wine and hops used to make beer). Some processed commodities are prepared specially from only one type of the raw commodity; e.g. raisins are produced from seedless grapes in climates that allow sun drying. Residues in those grapes rather than in all grapes should then be used in estimating likely residues in raisins. When a process is unique to a region or country (e.g. peeling potatoes and other vegetables; methods of cooking), governments should use available relevant data or, if necessary, obtain specific data on residues and consumption to reflect regional or national characteristics.

The following processing methods are widely used by industry and often by consumers:

- drying (e.g. dates, figs, grapes)
- canning (e.g. vegetables, pineapples)
- juicing (e.g. citrus fruits, tomato juice)
- milling (e.g. wheat, rice, other cereals)
- baking of bread
- brewing (e.g. hops, soya beans)
- wine-making (e.g. grapes)
- oil extraction and refining (e.g. olive oil, rapeseed oil)
- cooking in water (e.g. potatoes, rice, vegetables)
- refining (e.g. sugar)

Data on the effects of storage, processing and cooking on residues have not been consistently provided, and such data should be developed, particularly at the international level, in order to allow more realistic estimates of dietary intakes of pesticides.

3.2.3.1 *Development and use of data on processing*

Available studies of processing should be reviewed comprehensively at international and national levels to identify and characterize the main practices used to process food before consumption. Data on the effects of processing on residues should be generated under the following conditions:

- Crops used for the study should contain residues incurred from treatment under label-prescribed conditions of time and method.
- Ideally, initial residue levels should result in levels above the LOD in most processed fractions and by-products, allowing a mass-balance calculation to be performed. Exaggerated field or post-harvest application rates can be used when feasible to ensure that the residues in raw agricultural commodities are sufficient to allow measurable levels in processed commodities.
- Representative agricultural and food processing facilities should be used. If laboratory experiments are conducted, conditions characteristic of the commercial process should be closely simulated with particular attention to scale. Details of processes and specifications of operating conditions should be well documented.

After appropriate processing studies have been performed and evaluated, reduction or concentration factors (also known as processing factors) should be determined as follows:

- For risk assessments of long-term hazards, the STMR (or another appropriate residue level index) should be used together with mean reduction or mean concentration factors. When corrected for processing, the STMR is referred to as the STMR-P.
- For risk assessments of acute hazards (see Chapter 6), the MRL (or highest reasonable level of residues in the set of relevant residue data) should be used together with lowest reduction or highest concentration factors.

3.2.3.2 *Metabolites and degradation products*

The potential for producing metabolites or degradation products of toxicological concern should be taken into account in the design of a processing study and in the risk assessment. In many cases, the initial steps in processing, such as washing, reduce the amount of parent compound and, subsequently, the amount(s) of metabolite(s) and degradation product(s) formed; however, some metabolites and degradation products of toxicological concern (e.g. ethylenethiourea, propylenethiourea, and oxygen analogues of phosphorothiolates), can be produced or persist in processed food. MRLs are not usually established for such substances, but separate ADIs might have to be established for potentially toxic metabolites and degradation products.

Information is often available on the conversion of a parent compound to a metabolite or degradation product during processing. Estimates of dietary intake can be made at the national level on the basis of information on the consumption of processed commodities; however, this approach is useful only if an ADI or other assessment of the toxicological properties of the metabolite or degradation product has been performed.

3.2.4 Other known uses of the pesticide

In estimating dietary intake of pesticide residues, consideration should be given to sources of residues other than those arising from agricultural and external animal treatment uses of a pesticide. Estimated intakes of pesticides that are also used as veterinary drugs should include the contributions of residues from both sources. Coordination between the CCPR and the Codex Committee on Residues of Veterinary Drugs in Foods has been established for this purpose.

3.2.5 Estimates of food consumption

GEMS/Food regional diets based on food balance sheets include commodities that contain inedible or non-eaten portions. The consumption of the edible portion of food commodities should be used in estimating intakes rather than that of entire commodities. Correction factors currently used for the weight of the edible portion include a 30% reduction for both citrus fruits and banana; factors for other foods (see Section 3.2.2) must be developed.

4 Predicting dietary intake of pesticide residues at the national level (long-term hazards)

4.1 National Theoretical Maximum Daily Intake

The *National Theoretical Maximum Daily Intake* (NTMDI) can be used at the national level to confirm the TMDI and incorporates factors available only at the national level. Although it is a gross overestimate of exposure, the NTMDI can be a useful screening tool for estimating dietary intake of pesticide residues on the basis of national maximum limits and for evaluating the acceptability of Codex MRLs. When the NTMDI incorporating Codex MRLs is below the ADI, national authorities may accept these MRLs because the NTMDI is a conservative but scientifically sound exposure assessment method. It must be emphasized, however, that countries should make use of all available relevant data to refine dietary intake estimates, particularly when the NTMDI exceeds the ADI.

While countries may have different approaches, the following formula is often used:

$$\text{NTMDI} = \sum \text{MRL}_i \times F_i$$

where

MRL_i = Maximum Residue Limit (or national maximum limit) for a given food commodity

F_i = National consumption of that food commodity per person

4.1.1 Estimates of residue levels

National maximum limits for pesticide residues should normally be used in estimating national dietary intakes of pesticide residues. When evaluating the acceptability of Codex MRLs, existing or draft Codex MRLs that are being considered for adoption by the national authority should be used in calculating NTMDIs. When there is no Codex MRL for a food commodity, the national maximum limit should be used to estimate the intake from that commodity.

4.1.2 Estimates of food consumption

National food balance sheets may be used to make a first estimate of per capita national food consumption. Corrections for wastage and home production can improve this data. Because food balance sheets are thought to overestimate consumption of most commodities, the use of the per capita food consumption based on these sheets is generally thought to accommodate high percentile consumers. However, when more accurate data on food consumption are available, these should be used (see Section 4.2.2).

4.2 National Estimated Daily Intake

The National Estimated Daily Intake (NEDI) represents a refinement of the IEDI, as it can be based on more realistic estimates of the levels of pesticide residues in food and the corresponding amounts of food consumed. Factors for refining estimates of residue levels that should be taken into account in

making such estimates are given in Table 2. Some are applicable at both the international and national levels and were discussed above in connection with the IEDI (see Section 3.2); however, data at the national level may be more precise and culturally relevant, as in the case of edible portions and processing and cooking practices. In other cases, certain factors are only available at the national level and are discussed in more detail below in Table 2.

4.2.1 Estimates of residue levels available only at the national level

4.2.1.1 Proportion of crop or commodity treated

When reliable data are available on the proportion of a crop treated, better estimates can be made of dietary intake of residues from commodities that are made sufficiently homogeneous in the food supply through centralised processing and distribution (e.g. cereal grains and canned or frozen vegetables). If a treated crop or commodity is uniformly distributed in the food supply, the residues for estimating dietary intake can be reduced proportionately. This approach is limited to chronic exposure estimates.

4.2.1.2 Proportions of crop or commodity produced domestically and imported

Information on the proportions of a crop or commodity that is produced domestically and also imported can be useful in estimating dietary intake when consumption by the consumer can be assumed to reflect these proportions. Information on the treatment regime in the exporting country is particularly useful, although such data are not normally available. When the pesticide is not used on the crop or commodity in the exporting country, the imported proportion of the food supply can be assumed to contain no residues. This approach is limited to chronic exposure estimates.

Table 2

Factors for refining estimates of residue levels for predicting long-term dietary intake of pesticide residues at the national level

National and International	National Only
➤ Median residue levels from supervised trials, including residue definition (see Section 3.2.1)	➤ Proportion of crop or commodity treated (see Section 4.2.1.1)
➤ Residues in edible portions (see Section 3.2.2)	➤ Proportions of crop or commodity produced domestically and imported (see Section 4.2.1.2)
➤ Effects of processing and cooking on residue levels (see Section 3.2.3)	➤ Monitoring and surveillance data (see Section 4.2.1.3)
➤ Other known uses of the pesticide (see Section 3.2.4)	➤ Total diet (market basket) studies (see Section 4.2.1.4)
	➤ Food consumption data, including for subgroups of the population (see Section 4.2.2)

4.2.1.3 Monitoring and surveillance data

Food contamination monitoring and surveillance programmes play an important role in promoting the safety of the food supply when properly implemented (WHO, 1979). Considerable information is available from national monitoring and surveillance programmes which indicate that most pesticide residues are

either not detected in foods moving in international trade or occur at levels generally well below the established MRLs. This finding must be interpreted cautiously. The samples may not have been sufficiently representative of the food supply, the results may not include all components of the residue definition, and the pesticide residues of interest may not be detected by the methods of analysis used. Some countries are in the process of reviewing their monitoring programmes to address these concerns.

When it is determined that the dietary intake estimate of a pesticide may exceed the ADI, representative monitoring data might be used to assess potential residue levels in foods available on the market. With the precautions noted above, some countries are using such information in refining their calculations of dietary intakes based on data from two or more years. The number of samples of a given commodity ranges from 50 to 400, depending on its dietary significance. Mean, median and higher percentile (e.g. 90th) residue levels are generally determined and used in dietary intake assessments as in supervised trials. Some countries have reported using higher percentile food consumption data when estimating dietary intakes on the basis of monitoring data. The refinements described above for the IEDI (i.e. edible portions and processing factors) generally apply to residue data derived from monitoring and surveillance programmes.

4.2.1.4 Total diet studies

Total diet (market basket) studies and other measured estimates of pesticide residue intake are considered to represent more accurate records of dietary intake than calculated intakes (WHO, 1987). Such studies have consistently demonstrated that exposure to pesticide residues in food is well within established reference levels, i.e. ADIs. These studies are, however, difficult and expensive to perform. They are also not applicable to compounds recently registered for agricultural and food uses.

4.2.3 Estimates of food consumption

Additional sources of information on food consumption data can be used nationally to supplement national food balance sheet data. Food supply surveys (including food balance sheets) are generally based on a country's food production, imports and exports. As waste at the household or individual level is not considered, food balance sheets are usually overestimates of average food consumption over a long period of time. In developing countries, subsistence farming may need to be considered as this production is not included in food balance sheet data. The foods are not necessarily in the forms that people consume, but rather in raw or semi-processed forms. If information on residue concentrations in processed food commodities is available, food consumption data for those processed food commodities must also be available in order to use these data to refine intake assessments.

Improved estimates of pesticide residues by the population at the national level should include consideration of relevant subgroups who may be more sensitive to certain toxic effects, such as children, pregnant women and the elderly. In addition, authorities may wish to consider possible risks to subgroups of the population which habitually consume greater quantities of individual foods than are shown on food balance sheets.

The best available food consumption data should be used for predictions of pesticide residue intake at the national level. Countries should use only average food consumption values if use of other values results in a hypothetical level

of consumption that would not be attained in practice. In predicting the pesticide residue intake of identified subgroups relevant average food consumption data for such subgroups should be used. Subgroups, such as pregnant women, infants and children, high consumers and vegetarians, may require separate consideration.

In addition to data from food balance sheets, information can be obtained from at least four other suitable methods at the national level for estimating food consumption. These methods are: household budget, diary food records, 24-hour recalls, and food frequency questionnaires. Some of the data from surveys using such methods can be used to increase the flexibility and sensitivity of analyses without significantly increasing the resources required for evaluation. Often, household budget surveys may help to refine estimates of consumption from food balance sheets since they are collected at the household level. These surveys provide estimates that reflect food intended for human consumption and are therefore more realistic.

5 Risk assessment of acute hazards posed by pesticide residues

5.1 Derivation of the Acute Reference Dose

Concerns have been expressed that acute toxic effects may sometimes be elicited following consumption of food containing residues of certain pesticides. In responding to reservations expressed by the CCPR, the 1994 JMPR (FAO/WHO, 1994) considered situations in which the ADI derived from short- or long-term studies was probably not an appropriate toxicological benchmark for assessing risks posed by short-term exposure to acutely toxic residues. The acute reference dose (acute RfD) was developed to assess acute hazards using the same basic principles and methods used to derive the ADI. A no-observed-adverse-effect level (NOAEL) is identified from the database for acute effects (e.g. developmental effects, blood dyscrasias and neurotoxic effects such as delayed neuropathy and cholinesterase inhibition), and an appropriate safety factor is then applied. As part of this assessment JMPR specifies the subgroups of the population who are at risk on the basis of the acute toxicity endpoint(s) used to establish the acute RfD(s) so that the appropriate food consumption and body weight can be used in the risk assessment.

5.2 Transient exposures over the acute RfD

As established by the JMPR, an ADI typically includes a safety factor of 100 that is applied to a NOAEL from animal studies to take into account the potential greater sensitivity of humans and possible variations in sensitivity within the human population. Because the ADI incorporates a 100-fold safety factor and is often based on NOAELs from lifespan studies in animals and because the gaps between doses can introduce an additional safety margin, short-term intake of levels above the ADI for a day or several days should not represent a human health hazard.

With regard to the acute toxicity of pesticides, however, short-term intakes above the acute RfD are of more concern because toxicity might be observed after one or only a few doses. Because the acute RfD will incorporate a safety factor, however, adverse health effects should not be assumed to ensue if the acute RfD is marginally exceeded.

5.3 Single and multiple exposures

Dietary intake of specific foods can occur at a single sitting (one meal or serving) or be spread over one day. Intake should be compared with the toxicological effects that are of concern from short-term exposures. For example, if a food commodity containing a carbamate pesticide residue is consumed in a single meal or serving, greater concern is roused than if the same total residue is consumed in smaller increments throughout one day. The single total dose may not permit rapid reversibility of cholinesterase inhibition, and subsequently elicit adverse effect(s), whereas such effects may not be evident when small doses permit the reversibility of cholinesterase inhibition before subsequent exposure occurs.

6 Predicting dietary intake of acutely toxic pesticide residues

6.1 Residue considerations

Risk assessment of acute hazards relates to the maximum residue expected in food as consumed when the pesticide is used according to approved label conditions. Because the residue value for assessing dietary exposure for acute hazards is generally selected in the same way as the MRL, the MRL can be used in these calculations, especially for foods that are consumed raw. National MRLs, however, are occasionally based on statistical procedures, and certain values used for assessing dietary intake of acutely toxic pesticides may differ from the national MRL.

With regard to acute hazards, significant variation in the residue levels can occur in individual commodity units (e.g. one carrot or one potato) that comprise the larger composite samples used in field trials to establish the MRL (MAFF, 1995). Additional field trial data may need to be obtained, therefore, on individual commodity units and the results at the high end of the residue distribution extrapolated to estimate the appropriate level for assessing dietary intake. Large-scale mixing in commercial processing results in levels in individual units of processed commodities that are much lower than the MRL.

Dietary intake estimates for acute hazards should be based on the residue levels in the edible portions of food. Information on residues in processed fractions should be used only when none of the commodity is consumed raw. The use of median residue levels is not appropriate for short-term exposure estimates.

6.2 Exposure assessment at the international level

It is considered unlikely that an individual will consume two different commodities in large portion weights within a short period of time, and the presence on those commodities of the same pesticide at its MRL is considered even less likely. Therefore, calculations of dietary exposure for assessing an acute hazard can generally be based on consumption of a large portion of a single commodity containing residues assumed to be at the MRL. If the short-term exposure assessment based on one commodity does not exceed the acute RfD, it is highly unlikely that the acute RfD would be exceeded in practice; however, this procedure may be modified to reflect the toxicological findings accurately.

In order to assess exposure to acute hazards at the international level, a database of large portion weights of fruits, vegetables and other selected commodities is being developed by WHO. Depending on the commodity, these weights may represent individual units, e.g. one large apple or one large potato, or quantities consumed on a single occasion. Portion weights must be adjusted to reflect information about the edible portion.

6.3 Exposure assessment at the national level

At the national level, exposure assessment of acute hazards can be refined for certain commodities by determining the distribution of portion weights for

consumers of such foods. The actual residue levels in these commodities – preferably at the point of consumption – can also be better defined at the national level. Separate portion weight distributions should be determined for subgroups at particular risk (e.g. children and pregnant women). Special studies are required to assess exposure of farmers and other persons who may be subject to additional exposure to pesticide residues through air, water and dermal contact.

When high residue levels are likely to be found in more than one commodity, a total intake estimate for acute hazards may be necessary. For reasons stated earlier, it would be inappropriate to sum the intake derived from estimates based on large portion weights with residues present at their MRLs to obtain a total estimate. In such cases, more sophisticated models that can incorporate the probability of selecting foods with different residue levels will give better estimates of dietary exposure. If data on food consumption are collected for individual portions, those data should be used; they must therefore be available in a format that permits computation of the potential pesticide intake for individuals rather than households or populations. These results can then be compiled to describe the intake of appropriate subgroups. Additional guidance is available which addresses this problem (FAO/WHO, 1997b).

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Annex 1 **Glossary**

Acceptable Daily Intake (ADI)

The ADI 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 daily over a lifetime without appreciable health risk to the consumer on the basis of all the known facts at the time of the evaluation. It is expressed in milligrams of the chemical per kilogram of body weight.

Acute Reference Dose (acute RfD)

The acute RfD 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. It is expressed in milligrams of the chemical per kilogram of body weight.

Codex Committee on Pesticide Residues (CCPR)

The CCPR is a subsidiary body established by the Codex Alimentarius Commission. The CCPR is responsible for establishing maximum residue limits for pesticides in food and feed, preparing lists of pesticides by priority for evaluation by the JMPR, and considering methods of sampling and analysis for the determination of pesticide residues in food and feed that contain pesticide residues. Membership of the CCPR is open to all Member States and Associate Members of FAO and WHO. Representatives of international organizations that have formal relations with either FAO or WHO may attend meetings as observers. The CCPR is hosted by the Government of the Netherlands and has met annually since 1966.

Codex Maximum Residue Limit (MRL)

A Codex MRL for pesticide residues is the maximum concentration of a pesticide residue (expressed as mg/kg), recommended by the Codex Alimentarius Commission to be legally permitted in or on food commodities and animal feed. MRLs are based on good agricultural practice data and food derived from commodities that comply with the respective MRLs are intended to be toxicologically acceptable. Consideration of the various dietary residue intake estimates and determinations, both at the national and international level in comparison with the Acceptable Daily Intake, should indicate that foods complying with Codex MRLs are safe for human consumption.

Exposure Assessment

The qualitative and/or quantitative evaluation of the likely intake of biological, chemical or physical agents via food as well as exposure from other sources if relevant.

Food consumption

For assessing long-term hazards, food consumption is an estimate of the daily average per capita quantity of a food or group of foods consumed by a specified

population. Food consumption is expressed in grammes of food per person per day.

Good Agricultural Practice Good Agricultural Practice (GAP) in the use of pesticide includes the nationally authorized safe uses of pesticides under actual conditions necessary for effective and reliable pest control. It encompasses a range of levels of pesticide applications up to the highest authorised use, applied in a manner which leaves a residue which is the smallest amount practicable.

Hazard A biological, chemical, or physical agent in, or condition of, food with the potential to cause harm.

Hazard Characterisation The qualitative and/or quantitative evaluation of the nature of the adverse health effects associated with biological, chemical and physical agents which may be present in food. For chemical agents, a dose-response assessment should be performed. For biological and physical agents, a dose-response assessment should be performed if the data is obtainable.

Hazard Identification The identification of biological, chemical and physical agents capable of causing adverse health effects and which may be present in a particular food or groups of foods.

International Estimated Daily Intake (IEDI)

The IEDI is a prediction of the long-term daily intake of a pesticide residue on the basis of the assumptions of average daily food consumption per person and median residues from supervised trials, allowing for residues in the edible portion of a commodity and including residue components defined by the JMPR for estimation of dietary intake. Changes in residue levels resulting from preparation, cooking, or commercial processing are included. When information is available, dietary intake of residues resulting from other sources should be included. The IEDI is expressed in milligrams of residue per person.

Joint FAO/WHO Meeting on Pesticide Residues (JMPR)

JMPR is the abbreviated title for the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group. Their meetings are normally convened annually. The FAO Panel of Experts is responsible for reviewing residue and analytical aspects of the pesticides considered, including data on their metabolism, fate in the environment, and use patterns and for estimating the maximum residue levels and supervised trials median residue levels that might occur as a result of the use of the pesticide according to good agricultural practice. The WHO Core Assessment Group is responsible for reviewing toxicological and related data on the pesticides and, when possible, for estimating acceptable daily intakes (ADIs) and long-term dietary intakes of residues. As necessary, acute reference doses (acute RfDs) for pesticides are estimated along with appropriate estimates of short-term dietary intake.

Limit of Determination (LOD)

The LOD is the lowest concentration of a pesticide residue or contaminant that can be identified and quantitatively measured in a specified food, agricultural commodity, or animal feed with an acceptable degree of certainty by a regulatory method of analysis.

National Theoretical Maximum Daily Intake (NTMDI)

The NTMDI is a prediction of the long-term daily intake of a pesticide residue, assuming that residues of the pesticide are present at national maximum residue levels or at Codex MRLs and that average daily consumption of foods per person is represented by national food balance sheets. The NTMDI is expressed in milligrams of residue per person.

National Estimated Daily Intake (NEDI)

The NEDI is a prediction of the daily intake of a pesticide residue which is based on the most realistic estimate of residue levels in food and the best available data on food consumption for a specific population. The residue levels may be estimated based on median residues from supervised trials and allowing for residues in edible portion of a commodity. The residue includes the parent, metabolites and degradation products considered to be toxicologically significant. Changes in residues resulting from processing and cooking may be included. The proportion of the commodity treated or imported may be used to correct residue estimates. When adequate information is available, monitoring and surveillance data or total diet studies may also be used. When appropriate, dietary intake of residues from other known uses are assessed. The NEDI is expressed in milligrams of the residue per person.

No-observed-adverse-effect level (NOAEL)

The NOAEL is the highest dose of a substance that does not cause any detectable toxic effects in experimental animals and is usually expressed in milligrams per kilogram of body weight per day.

Pesticide

Pesticide means any substance or mixture of substances intended for preventing, destroying, attracting, repelling, or controlling any pest including unwanted species of plants or animals during the production, storage, transport, distribution and processing of food, agricultural commodities, or animal feeds or which may be administered to animals for the control of ectoparasites. The term includes substances intended for use as a plant-growth regulator, defoliant, desiccant, fruit thinning agent, or sprouting inhibitor and substances applied to crops either before or after transport. The term normally excludes fertilizers, plant and animal nutrients, food additives, and animal drugs.

Pesticide residue

A pesticide residue is any specified substance in food, agricultural commodities, or animal feed resulting from the use of a pesticide. The term includes any derivatives of a pesticide, such as conversion products, metabolites, reaction products, and impurities that are considered to be of toxicological significance.

Processing Factor

The processing factor is the residue level in the processed commodity divided by the residue level in the initial commodity.

Regional Diet

In the context of this publication, a regional diet is a hypothetical diet prepared by GEMS/Food to represent a regional group of countries in which the quantitative intake of food commodities is similar based on data derived from FAO Food Balance Sheets. Regional diets can also represent cultural groups and thus populations that share the same regional diet need not be in the same geographical region.

Risk Analysis	A process consisting of three components: risk assessment, risk management and risk communication.
Risk Assessment	A scientifically based process consisting of the following steps: (i) hazard identification, (ii) hazard characterisation, (iii) exposure assessment, and (iv) risk characterisation.
Risk Characterisation	The qualitative and/or quantitative estimation, including attendant uncertainties, of the probability of occurrence and severity of known or potential adverse health effects in a given population based on hazard identification, hazard characterization and exposure assessment.
Risk Communication	The interactive exchange of information and opinions concerning risks among risk assessors, risk managers, consumers and other interested parties.
Risk Management	The process of weighing policy alternatives in the light of the results of risk assessment and, if required, selecting and implementing appropriate control options, including regulatory measures.
Supervised Trials	Scientific studies in which pesticides are applied to crops or animals according to specified conditions intended to reflect commercial practice after which harvested crops or tissues of slaughtered animals are analysed for pesticide residues. Usually specified conditions are those which approximate existing or proposed GAP.
Supervised Trials Median Residue (STMR)	The supervised trials median residue (STMR) is the expected residue level in the food commodity (expressed in milligrams of residue per kilogram of commodity) when a pesticide has been used according to maximum GAP conditions. The STMR is estimated as the median of the residue values (one from each trial) from supervised trials conducted according to maximum GAP conditions and includes residue components defined by the JMPR for estimation of dietary intake. For some commodities, such as banana, STMR levels may be determined directly from levels measured in the edible portion when data are available.
Supervised Trials Median Residue – Processing (STMR-P)	The supervised trials median residue – processing (STMR-P) is the expected residue level in the food commodity (expressed in milligrams of residue per kilogram of commodity) when a pesticide has been used according to maximum GAP conditions and the commodity is processed according to the main practice used to prepare the food prior to consumption.
Theoretical maximum daily intake (TMDI)	The TMDI is a prediction of the maximum daily intake of a pesticide residue, assuming that residues are present at the MRLs and that average daily consumption of foods per person is represented by regional diets. The TMDI is calculated for the various regional diets and is expressed in milligrams of residue per person.

Annex 2 **Guidance to experts in the evaluation and estimation of supervised trials median residue levels for predicting dietary intake of pesticide residues**

1 Introduction

The 1996 Joint FAO/WHO Meeting on Pesticide Residues (JMPR) reviewed and endorsed, in principle, the recommendations that were addressed to the JMPR in the report “Revision of guidelines for predicting dietary intake of pesticide residues” (WHO, 1995). In order to implement the recommendations related to residue data, the FAO Panel of the 1996 JMPR developed practical guidance for its expert reviewers in evaluating and estimating supervised trials median residue (STMR) levels on the basis of a report by an ad hoc working group of the FAO Panel. The 1996 JMPR agreed to support the FAO Panel’s general and specific recommendations, while recognising that data evaluation is evolving. The full recommendations are attached as an annex to the report of the 1996 JMPR.

The following recommendations are based on those adopted by the 1996 JMPR. A few minor amendments have been introduced in the text, but the meaning and intent of the original JMPR recommendations have been retained. For example, recommendations of the 1996 JMPR that are specific to the Codex and JMPR process have not been included. Two recommendations, one on dietary intake of acutely toxic pesticides and the other on estimating maximum residue limits (MRLs) for products of animal origin, have also not been included. Both of these topics are complex and procedures are still being developed by the JMPR to address them.

2 General Recommendations

The 1996 JMPR made a number of general recommendations. Of these, the following are relevant to experts evaluating residue data in the estimation of the dietary intake of pesticide residues:

- 2.1** The abbreviation “STMR” should be used in written evaluations, monographs and reports to mean Supervised Trials Median Residue.
- 2.2** Residue reviewers should routinely identify STMR levels for each commodity as part of their evaluation of compounds in order to facilitate more realistic estimates of long-term dietary intake.

3 Specific Recommendations

The following specific recommendations arising from the 1996 JMPR should be used as guidance by experts evaluating residue data for the estimation of the dietary intake of pesticide residues:

3.1 Comparability

- 3.1.1** In comparing residue trials data to good agricultural practice (GAP), residue trials data from neighbouring countries with similar climate and cultural practices should be considered, together with residue trials data from the country with GAP.
-

- 3.1.2** In identifying the STMR, the trials values selected should be comparable with the maximum registered use (i.e. maximum application rate, maximum number of treatments, and minimum pre-harvest interval (PHI)) on which the MRL is based.
- 3.1.3** In establishing comparability of uses in the residue trials to the maximum registered use, the application rates in the trials should generally be no more than 25 to 30% of the maximum application rate. Deviations from this range should be fully explained. Similarly, 25 to 30% should also be used as a guide for establishing comparability of PHI; however, in this case the latitude of acceptable PHIs will also depend on the rate of decline of residues of the compound under evaluation. Consideration as to whether the number of treatments reported in trials are comparable to the registered maximum number of treatments will depend on the persistence of the compound and the interval between applications. Nevertheless, when a large number of treatments are made in the trials (more than 5 or 6) the residue level should be considered to be influenced very little by further treatments unless the compound is persistent or the treatments are made with unusually short intervals.
- 3.1.4** In establishing comparability of residue trials data in which more than one parameter (i.e. application rate, number of treatments, and PHI) deviate from the maximum registered use, consideration should be given to the combination effect on the residue value which may lead to an underestimation or overestimation of the STMR. For example, a trial result should not normally be selected for the estimation of the STMR if both the application rate is lower (perhaps 0.75 kg/ha in the trial and 1 kg/ha under GAP) than the maximum rate registered and the PHI is longer (perhaps 18 days in the trial and 14 days under GAP) than the minimum registered PHI, since these parameters would combine to underestimate the residue. When results are selected for the estimation of STMRs, despite combination effects, the reasons should be fully explained.
- 3.1.5** If the residue value arising from a use considered comparable with the maximum registered use is lower than another residue value from the same trial which is within GAP, then the higher residue value should be selected in identifying the STMR. For example, if the GAP specified a minimum PHI of 21 days and the residue levels in a trial reflecting GAP were 0.7, 0.6 and 0.9 mg/kg at 21, 28 and 35 days respectively, then the residue value of 0.9 mg/kg would be selected.

3.2 Trials with more than one residue value

- 3.2.1** In identifying the STMR, only one data point should be taken from each trial (i.e. site location).
- 3.2.2** Where several residue values have been reported from replicate plots from a single trial (i.e. site location), the highest residue should be selected for the purpose of identifying the STMR.
- 3.2.3** Where several residue values have been reported from replicate analyses of the same field sample, the mean residue should be selected for the purpose of identifying the STMR.

3.3 Rounding of results

In identifying the STMR from a residue trial, 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 limit

of determination considered appropriate for enforcement purposes. Rounding of residue values is inappropriate since the STMRs are used at an intermediate stage in the dietary intake calculation.

3.4 Residue definition

- 3.4.1 Consideration should routinely be given to which metabolites should be included in the dietary risk assessment and if necessary the residue definition for the risk assessment should be different from that for enforcement.
- 3.4.2 Close communication should be established between residue reviewers of a pesticide and their respective toxicological counterparts on such issues as the identification of metabolites and degradation products that are of toxicological significance.
- 3.4.3 In tabulating the residue trials data, the residue reviewer should consider indicating the levels of relevant metabolites separately from those of the parent compound, but in a way which would allow subsequent combination, in order to ensure that subsequent changes in the residue definition can be accommodated.
- 3.4.4 If two compounds for which STMRs are to be calculated produce the same residue used for compliance monitoring (e.g. almost all MRLs for dithiocarbamates are based on the determination of CS₂), it is possible to separate the intake assessments, if required, because the intake assessment is no longer based on the MRL but rather is based on residue data specific to the individual compounds.

3.5 Combining of populations of data for the calculation of STMRs

In identifying the STMR for situations where residue trials data are being evaluated against more than one country's GAP, residue data reflecting different countries' GAPs would normally be combined; however, if the trials data reflecting different countries' GAPs appear to give rise to different populations of data, then these data sets should not be combined. In these cases the STMR should be calculated from the population(s) of data which is (are) used for the MRL. 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.

3.6 Residues below the limit of determination

- 3.6.1 As a general rule, when all residue trials data are below the limit of determination (LOD), the STMR should be assumed to be at the LOD, unless there is scientific evidence that residues are "essentially zero". Such supporting evidence includes residue levels from related trials at shorter PHIs, exaggerated application rates, greater number of applications, expectations from metabolic studies and data from related commodities.
 - 3.6.2 When two or more sets of trials have different LODs, and no determinable residues are reported in the trials, then the lowest LOD should normally be used for the purpose of STMR selection (unless the residues can be assumed to be essentially zero as discussed above). The size of the trials database supporting the lowest LOD value should be taken into account in the decision.
-

3.7 Processing and cooking factors and edible portion residue data

- 3.7.1** In using data on the effects on residue levels during processing and cooking, the mean reduction or concentration factor should be applied to the STMR that should then be referred to as the STMR-P for the commodity.
- 3.7.2** If data are available for the residues levels in the edible portion of the commodity (e.g. banana pulp), the STMR 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).

3.8 Estimation of STMRs for commodity groups

When adequate trials data are available, the STMRs should, in principle, be identified for the individual commodities and these values used for the intake assessment; however, when the MRL has been established for a group of commodities (e.g. pome fruit), a single STMR should be calculated for the group of commodities.

3.9 Presentation of STMRs in written evaluations and monographs

- 3.9.1** The GAP(s) on which trials data have been selected for the purpose of identifying the STMR should be clearly identified.
- 3.9.2** In tabulating trials data, the residue reviewer should identify those residue values that result from treatments according to GAP (and that therefore have been used for the MRL evaluation) by underlining and those residue values selected for the estimation of the STMR by double underlining.
- 3.9.3** The range for application rates and PHIs used in the selection of residue values for STMR should be clearly identified (e.g. “trials data with application rates from 1.8–3.0 kg active ingredient per hectre have been selected”).
-

Annex 3 Examples of dietary intake calculations

1 Theoretical Maximum Daily Intake (TMDI) for 2,4-D (2,4-dichlorophenoxyacetic acid)

The TMDIs for the five regional diets are calculated for 2,4-D from current MRLs for comparison with its ADI of 0.01 mg/kg body weight established by the 1996 JMPR. This is equivalent to 0.6 mg per day for a person weighing 60 kg. Sixteen MRLs for a variety of commodities have previously been recommended by JMPR and adopted by Codex. Seven of these MRLs are established at the LOD but the MRLs are used for all commodities in calculating the TMDIs (see Section 3.1.1). The calculated TMDIs are expressed as percentages of the ADI and then rounded off to one significant figure. TMDIs are presented as a range of values from 7% to 50% of the ADI (see Section 2.4). Details of these calculations are provided in Appendix 1.

2 International Estimated Daily Intake (IEDI) for Parathion-methyl

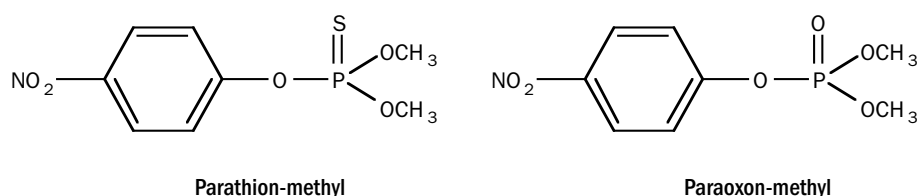
The following example illustrates procedures for determining the STMR for residues of parathion-methyl on wheat and the evaluation of processing data for the conversion of wheat to flour and bran. These procedures are the same as those used by the JMPR in determining STMRs and processing factors (see Section 3.2.1). GEMS/Food uses these STMRs and processing factors to calculate the IEDI. These procedures can also be applied by national authorities in calculating the NEDI. Guidance in this regard is provided in Annex 2.

2.1 Consideration of Residue Definition

The main toxic effect of parathion-methyl and its metabolite paraoxon-methyl (Figure A3-1 below) is the inhibition of cholinesterase. The only other major metabolite, 4-nitrophenol, has no such activity. For estimating dietary intake, the residue definition will be the sum of parathion-methyl and paraoxon-methyl. The definition used for MRL purposes is parathion-methyl only. Estimates of intake of the combined residues will be compared with the ADI for parathion-methyl.

Figure A3-1

Residue definition for STMR for parathion-methyl on wheat



2.2 Determination of STMR for parathion-methyl on wheat

Parathion-methyl is approved for use on wheat in the United States of America (USA) with application rates of 0.28-1.4 kg ai/ha and with the final application no later than 15 days prior to harvest. A total of twelve field trials in the USA were available for evaluation which are summarized in Table A3-1 below.

Table A3-1

Results of field trials with parathion-methyl on wheat

Commodity	Use pattern		Number of trials	Residues (mg/kg) parathion-methyl + paraoxon-methyl
	Applic. rate (kg ai/ha)	PHI* (days)		
Wheat (USA GAP)	0.28-1.4	15		
Wheat (USA trial)	1.4	13	1	0.78
Wheat (USA trials)	1.4	14	11	<0.05 (3 results), 0.15, 0.22, <u>0.33</u> , <u>0.35</u> , 0.78, 0.93, 1.1, 1.6, 5.6

* PHI: pre-harvest interval

In the twelve supervised trials on wheat, parathion-methyl was applied at 1.4 kg ai/ha and the wheat was harvested 13 days (1 trial) or 14 days (11 trials) after the final application (trial conditions agree in practical terms with GAP). Residues of parathion-methyl + paraoxon-methyl in the wheat in rank order (median underlined) were: <0.05 (3 results), 0.15, 0.22, 0.33, 0.35, 0.78, 0.93, 1.1, 1.6 and 5.6 mg/kg. Because the median residue from the twelve valid trials on wheat is between 0.33 and 0.35 mg/kg, the STMR for parathion-methyl on wheat is established at 0.34 mg/kg.

2.3 Processing studies for parathion-methyl on wheat

In two milling studies carried out in the USA, parathion-methyl was applied at an exaggerated rate (7.0 kg ai/ha). The wheat was harvested 13 and 14 days after final treatment and was milled into bran, flour and other fractions. Residue data are summarised in Table A3-2 below.

Table A3-2

Results of milling studies of parathion-methyl on wheat

Commodity	Parathion-methyl + paraoxon-methyl residues (mg/kg)	
	Study 1	Study 2
Wheat grain	6.33	9.95
Bran	15.19	19.26
Flour	2.1	2.89

The residue level in the processed commodity divided by the residue level in the initial commodity is the processing factor as shown in Table 3. In the processing of wheat to bran the mean processing factor for parathion-methyl +

paraoxon-methyl levels is 2.17. In the processing of wheat to flour the mean processing factor for parathion-methyl + paraoxon-methyl levels is 0.31 as shown below in Table A3-3.

Table A3-3

Calculated processing factors for parathion-methyl on wheat

Process	Calculated processing factors		
	Study 1	Study 2	Mean
Wheat to bran	2.40	1.94	2.17
Wheat to flour	0.33	0.29	0.31

The STMR for parathion-methyl on wheat can therefore be corrected for processing which is designated as STMR-P as shown in Table A3-4. The contribution to dietary intake of pesticide residues from wheat flour and bran may be calculated using the appropriate STMR-P and consumption data for these commodities.

Table A3-4

SMTR-Ps for parathion-methyl on wheat flour and bran

Commodity	STMR (mg/kg)	Processing factor	STMR-P (mg/kg)
Wheat	0.34		
Bran		2.17	0.74
Flour		0.31	0.105

3 National Theoretical Maximum Daily Intake (NTMDI) for Tebufenozide

This example illustrates the use of the NTMDI in assessing whether draft MLRs would be acceptable on the basis of public health considerations. In this case, a national authority is considering the adoption of the Codex proposed uses of tebufenozide on grapes, rice (husked), pome fruits and walnuts. The country already has an existing use for tebufenozide on potatoes at a maximum residue limit of 0.5 mg/kg. Details of the NTMDI calculation are presented in Appendix 2. Note that the ADI is calculated using the average adult body weight for the country of 55 kg. Because the NTMDI was well below the ADI, the proposed Codex MRLs do not pose a risk to public health.

If the NTMDI had exceeded the ADI, however, a further refinement of the dietary intake must be conducted including the determination of STMR levels and other factors to improve the estimate of residues in food as consumed.

4 National Estimated Daily Intake (NEDI) for Parathion-methyl

The example given above for calculating the IEDI is also relevant for estimating the STMR and STMR-P in the calculation of the NEDI; however, national practices and preferences should be considered in applying these correction factors.

The following example illustrates the use of information on the proportions of domestic and imported foods in refining estimates of residues (see Section 4.2.1.2).

In this instance, a country had information that 25% of the wheat consumed in the country was imported from another country which did not permit the use of parathion-methyl on wheat. Imported wheat was stored at a central elevator and distributed throughout the country. For domestic production, the country used the Codex MRL of 5 mg/kg for wheat which was wholly consumed in the form of flour. Based on the STMR-P for residues of parathion-methyl in flour of 0.105 mg/kg, the residue level for estimating dietary intake as corrected for import considerations is calculated to be 0.076 mg/kg using the formula:

$$(0.105 \text{ mg/kg}) \times (75\%) + (0.0 \text{ mg/kg}) \times (25\%) = 0.076 \text{ mg/kg}$$

A similar reduction may be possible when the proportion of treated and non-treated domestically-produced wheat is known (see Section 4.2.1.1).

Appendix 1 Example of detailed Theoretical Maximum Daily Intake (TMDI) calculation for 2,4-D (2,4-dichlorophenoxyacetic acid)

Theoretical Maximum Daily Intake (TMDI)

Pesticide Code - 20
 Name - 2,4-D
 ADI = 0.01 mg/kg bodyweight or 0.600 mg/person

Commodity	MRL mg/kg	Note	Step	Middle Eastern		Far Eastern		African		Latin American		European	
				Diet g/day	TMDI mg/day	Diet g/day	TMDI mg/day	Diet g/day	TMDI mg/day	Diet g/day	TMDI mg/day	Diet g/day	TMDI mg/day
GC 640 Barley	0.5		CXL	1.00	0.0005	3.50	0.0018	1.75	0.0009	6.50	0.0033	19.75	0.0099
FB 264 Blackberries	0.1		CXL	0.00	0.0000	0.00	0.0000	0.00	0.0000	0.00	0.0000	0.50	0.0001
FC 1 Citrus fruits	2		CXL	54.25	0.1085	6.33	0.0127	5.08	0.0102	54.75	0.1095	49.00	0.0980
PE 112 Eggs	0.05	(*)	CXL	14.50	0.0007	13.00	0.0007	3.58	0.0002	11.75	0.0006	37.50	0.0019
GC 645 Maize	0.05	(*)	CXL	48.25	0.0024	31.17	0.0016	106.17	0.0053	41.75	0.0021	8.75	0.0004
MM 95 Meat	0.05	(*)	CXL	37.00	0.0019	32.83	0.0016	23.83	0.0012	47.00	0.0024	155.50	0.0078
A03 1 Milk products	0.05	(*)	CXL	15.50	0.0008	0.70	0.0000	0.40	0.0000	7.80	0.0004	43.80	0.0022
ML 106 Milks	0.05	(*)	CXL	116.75	0.0058	32.00	0.0016	41.75	0.0021	160.00	0.0080	294.00	0.0147
GC 647 Oats	0.5		CXL	0.00	0.0000	0.00	0.0000	0.17	0.0001	0.75	0.0004	2.00	0.0010
VR 589 Potato	0.2		CXL	59.00	0.0118	19.17	0.0038	20.58	0.0041	40.75	0.0082	240.75	0.0482
FB 272 Raspberries, red, black	0.1		CXL	0.00	0.0000	0.00	0.0000	0.00	0.0000	0.00	0.0000	0.50	0.0001
GC 649 Rice	0.05	(*)	CXL	48.75	0.0024	279.33	0.0140	103.42	0.0052	86.50	0.0043	11.75	0.0006
GC 650 Rye	0.5		CXL	0.00	0.0000	1.00	0.0005	0.00	0.0000	0.00	0.0000	1.50	0.0008
GC 651 Sorghum	0.05	(*)	CXL	2.00	0.0001	9.67	0.0005	26.58	0.0013	0.00	0.0000	0.00	0.0000
FB 19 Vaccinium berries, including bearberry	0.1		CXL	0.00	0.0000	0.00	0.0000	0.00	0.0000	0.00	0.0000	0.00	0.0000
GC 654 Wheat	0.5		CXL	327.25	0.1636	114.83	0.0574	28.33	0.0142	116.75	0.0584	178.00	0.0890
				TOTAL =	0.29856		0.0961		0.0447		0.19739		0.2744
				% ADI =	50%		16%		7%		33%		46%
				(Rounded) % ADI =	50%		20%		7%		30%		50%
				Reported Range =	7-50% of ADI								

* MRL is established at the limit of determination

Appendix 2 **Example of detailed National Theoretical Maximum Daily Intake (NTMDI) calculation for tebufenozide**

National Theoretical Maximum Daily Intake (NTMDI)

Pesticide Code - 196
 Name - Tebufenozide
 ADI = 0.02 mg/kg bodyweight or 1.1 mg/person (55 kg)

		National			
Commodity Code	Name	MRL mg/kg	Note	Diet g/day	NTMDI mg/day
FB 269	Grapes	0.5		18.00	0.0090
CM 649	Rice, Husked	0.1		12.00	0.0012
FP 9	Pome fruits	1		45.00	0.0450
VR 589	Potato	0.5	1/	240.00	0.1200
TN 678	Walnuts	0.05		1.00	0.0001

TOTAL = 0.18

% ADI = 16%

(Rounded) % ADI = 20%

1/ National maximum limit

These guidelines describe procedures that can be used by national authorities to predict the dietary intake of pesticide residues and thus reach conclusions concerning the acceptability of Codex Maximum Residue Limits from a public health point of view. Prepared in collaboration with the Codex Committee on Pesticide Residues, the guidelines respond to the need for a method of reaching reasonable assurance that the intakes of pesticide residues for different populations do not exceed safety limits.

The book opens with background information on methods used to establish daily intake and maximum residue limits for pesticides. Methods for predicting the dietary intake of pesticide residues are then introduced in terms of general considerations, indices of residue levels, and indices of food consumption, including those appropriate for use in predicting intake at international and national levels.

Now in its second edition, the book reflects several improvements in methods for estimating levels of residues in food. Readers are given details for calculating intake levels using theoretical maximum daily intake, and estimated daily intake. To illustrate the use of these guidelines, the book features sample calculations of theoretical maximum daily intake, and international estimated daily intake values as well as estimates of exposure performed at the national level. The book concludes with a glossary of key terms and a series of notes on the correct use of the guidelines

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