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INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

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Principles and Methods for the Risk Assessment of Chemicals in Food

Chapter 6
DIETARY EXPOSURE ASSESSMENT OF CHEMICALS IN FOOD

A joint publication of the Food and Agriculture Organization of the United Nations and the World Health Organization

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The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organization (ILO) and the World Health Organization (WHO). 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.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research and the Organisation for Economic Co-operation and Development (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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6. DIETARY EXPOSURE ASSESSMENT OF CHEMICALS IN FOOD

For acronyms and abbreviations used in the text, the reader may refer to the list of acronyms and abbreviations at the front of this monograph. Definitions of select terms may be found in the glossary at the end of the monograph.

6.1 Introduction

Exposure assessment is an essential element for quantifying risk. The role of dietary exposure assessment has been central to the work of the Joint Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO) Expert Committee on Food Additives (JECFA) and the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) in performing risk assessments on chemicals in foods.

The Codex Alimentarius Commission's (CAC) Procedural Manual (FAO/WHO, 2008a) defines exposure assessment as "the qualitative and/or quantitative evaluation of the likely intake of biological, chemical, and physical agents via food as well as exposures from other sources if relevant". This chapter deals with the assessment of dietary exposure to chemicals present in food (i.e. food additives, contaminants, processing aids, nutrients and residues of pesticides and veterinary drugs). However, some of the principles and approaches described here are also applicable to biological agents in food.

Dietary exposure assessment combines food consumption data with data on the concentration of chemicals in food. The resulting dietary exposure estimate may then be compared with the relevant health-based guidance value for the food chemical of concern, if available, as part of the risk characterization. Assessments may be undertaken for acute or chronic exposures, where acute exposure covers a period of up to 24 h and long-term exposure covers average daily exposure over

the entire lifetime. Dietary exposure assessments of nutrients have default assumptions that are different from those for other food chemicals owing to the specific need to look at both nutrient adequacy and potential to exceed upper safety levels (see chapter 9, section 9.2.2).

The general equation for both acute and chronic dietary exposure is:

$$\text{Dietary exposure} = \frac{\Sigma\ (\text{Concentration of chemical in food} \times \text{Food consumption})}{\text{Body weight (kg)}}$$

The use of standard terminology is recommended to ensure consistent application and understanding. It is recommended that "consumption" be used to refer to the amount of food consumed and "dietary exposure" to the amount of chemical ingested via food. The term "dietary exposure" is used synonymously with the term "dietary intake", depending upon existing regulatory frameworks or other related considerations. In this chapter, the term "food" also includes beverages, drinking-water and food supplements.

This chapter updates and expands the report of the FAO/WHO Consultation on Food Consumption and Exposure Assessment of Chemicals (FAO/WHO, 1997). It was developed by an FAO/WHO Workshop on Exposure Assessment for Chemicals in Food held in May 2005 (FAO/WHO, 2008b). Its aim was to provide guidance to WHO and FAO and their expert advisory bodies, CAC, national governments and the risk analysis community at large on how to perform and interpret dietary exposure assessments at the international, regional, national and local levels.

6.1.1 General considerations

The following points are basic general principles and considerations when undertaking dietary exposure assessments:

- The objective of the dietary exposure assessment must be clearly identified before the appropriate food consumption and concentration data may be selected. For example, preregulation (i.e. before approval for use) and post-regulation (i.e. after approval for use)

dietary exposure assessments are undertaken for different purposes and may have different data sources and default assumptions.

- As stated in the FAO/WHO consultation on risk assessment analysis (FAO/WHO, 1995a), CAC should ensure harmonized approaches to the risk assessment of food chemicals. In this chapter, harmonization is understood to result in equivalence, which does not necessarily mean that all dietary exposure assessment procedures across food chemicals need to be the same. Rather, such procedures should aim at providing equivalent levels of consumer protection.

- Irrespective of the severity of toxicological end-point, type of chemical in food, possible population subgroups of concern or reasons for performing the dietary exposure assessment, the most appropriate data and method should be used, harmonizing the approach to dietary exposure assessments where possible.

- International dietary exposure assessments should provide exposure estimates that are equal to or greater than (or lower than, in the case of nutrient deficiency) the best available estimates carried out at the national level. It is assumed that the international estimate covers potential dietary exposure in countries for which no data were available.

- Dietary exposure assessments should cover the general population, as well as critical groups that are vulnerable or are expected to have exposures that are significantly different from those of the general population (e.g. infants, children, pregnant women or elderly).

- If international dietary exposure assessments exceed a health-based guidance value, then national authorities should be asked to submit their national exposure estimates through CAC or its technical committees or directly to JMPR or JECFA.

- It is recommended that national authorities that wish to perform their own dietary exposure assessments use national food consumption and concentration data, but international nutritional and toxicological reference values. It would be helpful for the

Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme (GEMS/Food), JECFA and JMPR to receive data from national and regional authorities on food consumption and chemical concentrations, as well as the results of their dietary exposure assessments.

- If the estimated international dietary exposure to a chemical does not exceed its relevant health-based guidance value (or is not below the nutritional reference value), then the level of exposure should be acceptable at the national level, because the level of overestimation for international dietary exposure assessments for any region would tend to be greater than that for national estimates. This applies to both acute and chronic exposure assessments.

6.1.2 Dietary exposure assessment methods

The following points are basic general principles and considerations with respect to the methods used for dietary exposure assessment:

- In principle, international dietary exposure assessments need to be performed for all identified chemicals present in the diet that are subject to risk assessment. Similar methods are appropriate for contaminants, pesticide and veterinary drug residues, food additives (including flavourings), processing aids and other chemicals in foods. The methods used may also be applied to estimating nutrient intakes, noting that these assessments are more often undertaken at a national rather than at an international level (see chapter 9, section 9.2.2).

- A stepwise approach is recommended, in which screening methods can be applied to identify, among the large number of chemicals that may be present, those of no safety concern, using minimal resources in the shortest possible time. A refined exposure assessment is not needed for such substances.

- Screening methods, if used, need to overestimate exposure of high consumers using conservative assumptions in terms of food consumption and chemical concentration (see section 6.3.4.1). This is to avoid situations where the exposure estimated with

the screening would erroneously indicate that no safety concern existed (i.e. exposure is below a health-based guidance value) and that no further refined dietary exposure assessment is necessary.

- In order to effectively screen chemical substances and establish risk assessment priorities, the screening procedure should not use unsustainable diets to estimate consumption. Rather, physiological limits of consumption should be taken into account.

- Further steps to allow the refinement of the dietary exposure assessment should be designed in such a way that potential high dietary exposure to a specific chemical is not underestimated. The methodologies should take into consideration non-average individuals, such as those who consume large portions of specific food items. Some consumers may also be loyal to those foods or brands of food containing the highest concentrations of the chemical of interest or may occasionally consume foods with very high concentrations of the chemical.

6.1.3 *Presentation of results of dietary exposure assessment*

The following points are general considerations with respect to the presentation of the results of the dietary exposure assessment:

- The method applied should be clearly described. Information about the model and data sources used, assumptions, limitations and uncertainties should also be documented (see section 6.3.3).

- Any assumptions concerning concentrations of the chemical in foods and food consumption patterns upon which dietary exposure estimates are based need to be transparent (see sections 6.2.1 and 6.2.2).

- The percentiles (e.g. 90th, 95th or 97.5th) used to represent highly exposed consumers should be clearly stated and their derivation described (see section 6.2.2.3).

6.2 Data sources

The data required for assessing dietary exposure are determined by the objective of the assessment. Dietary exposure can be assessed for a chemical 1) before it has been approved for use (preregulation), 2) after

it has potentially been in the food supply for years (post-regulation) or 3) that is present naturally in foods or as a result of contamination. In the first case, chemical concentration data are available or estimated from the manufacturer or food processor. In the other two cases, additional chemical concentration data could be obtained from food in the marketplace. For each assessment, the suitability of the available data should be assessed (e.g. some market data may not be sufficient for acute exposure assessments).

6.2.1 Data on concentrations of chemicals in food, including water

In dietary exposure assessments, it is important to obtain accurate information on both the concentrations of chemicals in food and food consumption. The selection of the sampling, analysis and reporting procedures is critical for obtaining consistent and comparable data on chemical concentrations in food (WHO, 1985; Petersen et al., 1994). The selection of data based on consistent procedures is particularly important at the international level, where data from several countries may be compared or combined. Possible sources of chemical concentration data are summarized in Table 6.1.

Appropriate data sources and levels of food chemicals to use in dietary exposure assessments at an international level may be determined by the relevant Codex committee based on the advice of JECFA or JMPR.

6.2.1.1 *Use of maximum levels (MLs) or maximum residue limits (MRLs) in dietary exposure assessments (preregulation)*

It is important to understand the method of derivation of Codex MLs or MRLs for various food chemicals when considering the potential uncertainties in the data if they are to be used in dietary exposure assessments. In the case of pesticide residues, MRLs are proposed by JMPR based on field trial studies performed under Good Agricultural Practice (GAP), then considered and recommended to CAC by the Codex Committee on Pesticide Residues (CCPR). For veterinary drugs, the MRLs are derived by JECFA from controlled residue depletion studies carried out in compliance with Good Practice in the Use of Veterinary Drugs (GPVD), then considered and recommended to CAC by the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF).

Table 6.1. Sources of chemical concentration data

Chemical type	Preregulation dietary exposure assessments	Post-regulation dietary exposure assessments[a]
Food additives Packaging materials	Proposed MLs Proposed manufacturers' use levels Migration data (for packaging materials)	Reported manufacturers' use levels Food industry surveys Monitoring and surveillance data TDS Scientific literature
Contaminants, including natural toxicants	Proposed MLs Monitoring and surveillance data TDS GEMS/Food database (see section 6.2.1.8) Scientific literature	
Pesticide residues	Proposed MRLs HR STMR	Monitoring and surveillance data TDS GEMS/Food database on chemical concentrations Scientific literature
Veterinary drug residues	Residue depletion studies	Monitoring and surveillance data TDS Scientific literature
Nutrients	Proposed MLs for fortification Food composition data	Monitoring and surveillance data TDS Scientific literature

HR, highest residue level from trial; ML, maximum level; MRL, maximum residue limit; STMR, supervised trial median residue level; TDS, total diet study.

[a] In addition to all preregulation data sources.

In the case of pesticide residues and food additives, maximum levels/limits (i.e. MRLs and MLs) are usually based on good practice considerations, even if a consideration of consumer safety might allow higher levels than these. For veterinary drugs, good practice considerations are also taken into account. However, the determining criterion is that dietary exposure estimates should be below the acceptable daily intake (ADI). In the preregulation phase when proposed maximum levels/limits based on good practice result in potential chronic or acute

dietary exposures that exceed relevant health-based guidance values, the refinement of dietary exposure estimates with more accurate data may be possible before a final decision on the MRL or ML is taken. For veterinary drug residues, the current practice by JECFA is to use a set "food basket" to derive an estimate of potential dietary exposure; at an international level, this estimate cannot be refined, although at a national level, further refinement may be possible.

In the case of chemical contaminants, MLs are established by the Codex Committee on Contaminants in Food (CCCF), following advice from JECFA. MLs need to be compatible with tolerable intake levels and are based on the lowest level of contamination that can be reasonably achieved without removing the food from the food supply. For contaminants having a chronic toxic effect, the setting of an ML for the chemical in the food in which it occurs is unlikely to have direct and immediate impact on the exposure of the population unless a significant proportion of the food is withdrawn from the market. In addition, when the overall exposure to a chemical is below the health-based guidance value, MLs in food contributing to the exposure are unlikely to have any impact in terms of public health.

Codex standards for nutrients may reflect typical levels in foods. Sometimes these levels apply to raw commodities, which require processing before being consumed.

6.2.1.2 Use of other concentration data sources for dietary exposure assessments (preregulation and post-regulation)

Maximum levels/limits are convenient values to use to assess dietary exposure for preregulation purposes, but it is recognized that a person would not always consume foods containing chemicals at their corresponding maximum levels/limits. Analytical data on concentrations of chemicals in food are needed to more accurately estimate the levels likely to be found in the diet as consumed. These data can be derived from crop and animal trial data (pesticide and veterinary drug residues) or monitoring and surveillance data on food (all chemicals). It may be appropriate to select different data sources in international and national assessments. Certain foods are widely blended across many individual units (e.g. orange juice); in these cases, it may be appropriate to estimate concentrations in blended commodities by

using the arithmetic mean of the concentrations in the individual or composite samples.

When using data provided by national governments as well as other sources in international exposure assessments, it is important, wherever possible, to have detailed information on the data source, survey type or design, sampling procedures, sample preparation, analytical method, limit of detection (LOD) or limit of quantification (LOQ), and quality assurance procedures.

For acute dietary exposure assessments, it should be recognized that although aggregated monitoring data may provide a reliable estimate of mean residue level, such data do not provide reliable estimates of the highest residue levels in single units, as required for these estimates.

6.2.1.3 *Approaches for obtaining food chemical concentration data*

(a) Supervised trials and residue depletion studies (pesticide and veterinary drug residues only)

Traditionally, the primary source of preregulation residue data in foods has been supervised trial data for pesticides and residue depletion studies for veterinary drugs that must be submitted in support of the registration of a pesticide or veterinary drug, respectively.

For pesticides, the trials are usually performed by a manufacturer or other parties. In the trials, a maximum registered use scenario (with respect to application rates, number of applications, preharvest or withdrawal intervals, etc.) is simulated. The trials are designed to determine the maximum residue concentrations that may be present in food and feed of animal or plant origin at the earliest point at which these food commodities could enter commerce and are used to establish legally enforceable residue limits. These data often overestimate the residue concentrations that are likely to occur in food as actually consumed, because they reflect the maximum application rate and shortest preharvest interval. Therefore, these data should not be the first choice when assessing actual dietary exposure, but are the first choice for assessing the safety implications for consumers of a proposed MRL calculated on the basis of GAP.

For veterinary drugs, the residue depletion studies are usually performed by the manufacturer or other commercial entities, using the commercial formulation and recommended dose regimens in the target animal species. The doses chosen should represent the upper end of registered doses. The studies are designed to estimate the formation and depletion of residues (determined as the marker residue) of the veterinary drug in edible tissues and products and serve as the basis for the derivation of the MRLs and estimation of exposure (see chapter 8). MRLs are derived to represent the upper 95th confidence limit of the 95th percentile of the residue concentrations at the chosen time point on the residue depletion curve. Using the MRLs for estimation of exposure would overestimate the residue concentrations that are likely to occur in food products of animal origin, as it would assume that all animals of a target species would be treated and that the products are obtained exactly when 95% of the residue concentrations had depleted to the MRL. Therefore, the MRL values should not be considered as a first choice when assessing dietary exposure. However, the MRLs may be used for a conservative assessment of exposure in the case where low or non-detectable residue levels are measured in the depletion studies or when the MRLs are based on other considerations, such as the LOQ of the analytical method.

Supervised trial data and the results of residue depletion studies do not account for residue degradation that sometimes occurs during the interval between the farm and the market or the home or subsequent residue losses when food is processed and prepared for consumption.

(b) Monitoring and surveillance data

Data that reflect concentrations of chemicals in food are often available from monitoring and surveillance programmes in which food samples are obtained closer to the point of consumption in the chain of commerce. These data generally provide a better characterization of chemicals in foods as purchased by consumers (EC, 2004; USFDA, 2004b; USDA, 2008).

There are two types of monitoring and surveillance data: random and targeted. Targeted data are often collected for enforcement purposes in response to specific problems and should be used with caution in dietary exposure assessments, as they may not be representative

of all the food available for sale. Truly representative residue data are scarce, and the source of residue data used in dietary exposure assessments should always be carefully described and evaluated.

For post-regulation chronic dietary exposure assessments of pesticide and veterinary drug residues, suitable monitoring and surveillance data are preferred over data from supervised trials and depletion studies, as these in principle more closely represent what is consumed. The samples are usually collected on a random basis close to the point of consumption, at terminal markets and large-chain store distribution centres immediately prior to distribution to supermarkets and grocery stores. Such sampling therefore accounts for residue degradation during transit and storage and, in the case of pesticides, may also provide data on residues resulting from post-harvest applications of fungicides and growth regulators used as preservatives during food delivery. However, some monitoring programmes are designed to measure compliance with a given standard and may not use the most sensitive methods of analysis or may not describe concentrations in the food as consumed because marker organs have been used—for example, levels of heavy metal contamination only in the liver may be analysed.

For acute dietary exposure assessments, the fact that only a small proportion of any commodity entering the food-chain is monitored means that there are significant limitations in using monitoring data.

(c) Refinement of concentration data by use of correction factors

Concentration data for food chemicals may be refined by applying correction factors to the concentration data when based on raw commodities to reflect changes due to processing or to account for the portion that is actually consumed. Processing factors can be routinely incorporated into dietary exposure assessments to make the results more reflective of actual exposures. Specifically, processing of agricultural commodities can increase or decrease chemical concentrations or alter the nature of chemicals in foods. Processing studies are usually regarded as specific for the food, the active substance and the process. In cases where processing studies are not available, standard mass balance assumptions, based on general information on the effects of some processing operations, such as drying of grapes to make raisins, may sometimes be used (USEPA, 1996).

In some cases, the risk assessor may refine estimates of dietary exposure to pesticide residues by taking into account the proportions of crop or food commodity produced domestically and imported. In many cases, only a fraction of the total food or crop supply may be anticipated to contain the substance being evaluated. Where data exist to quantify the percentage affected, these values can be incorporated as an adjustment factor to be applied to concentration data in order to more accurately estimate chronic dietary exposures. There is no international consensus on using this type of information in the context of dietary exposure estimates in the process for setting MRLs for pesticide residues. Some of these factors are country or region specific and may be appropriate to use only when undertaking national dietary exposure assessments.

(d) Total diet studies

Total diet studies (TDSs) in principle provide the most accurate measure of the average concentrations of pesticide residues, contaminants, nutrients and other chemicals actually ingested in foods by the population living in a country and, if possible, population subgroups. However, the accuracy of some TDSs is lowered by using limited sample sizes and survey durations. Therefore, when using a TDS in a dietary exposure assessment, it should be checked whether the TDS is fit for purpose.

Concentration data from TDSs differ from data obtained from other chemical surveillance or monitoring programmes, because concentrations of chemicals are measured in foods after they have been prepared for normal consumption. Concentration data in a TDS are not based on historical composition data, and processing factors for raw food commodities (FAO/WHO, 1997) do not need to be applied, because estimated dietary exposures are based on the edible portions of the food—for example, bananas are peeled and the skin discarded along with any associated chemical residues. A TDS also incorporates the impact of cooking on less stable chemicals and on the formation of new ones.

Analytical methods used in a TDS should be capable of measuring concentrations of chemicals in foods at appropriate levels. Typically, methods with LODs or LOQs 10–1000 times lower than those needed for enforcement purposes are used for TDSs.

The broad scope of a TDS may necessitate significant compositing of samples if resources are limited (see also section 6.2.1.4). Compositing may be on either an individual food basis or a food group basis. Such compositing will not prevent the estimation of total exposure but will limit the ability to identify the specific sources of the food chemical. Owing to resource considerations, TDSs usually have a small number of mean concentration data (usually n = 1–8) for each individual food or food group, in contrast to data usually generated through surveillance or monitoring of individual food commodities (where n = 30–50 or more).

6.2.1.4 *Sampling*

(a) Sample collection

When undertaking programmes to generate data on concentrations of chemicals in food, the sampling procedure selected and how it is carried out are critical to the validity of the results obtained. Different sampling plans and methods are required, depending on the objectives of the studies.

The following questions should be addressed when the sampling plan is designed (WHO, 1985, 2002a,b, 2005a; Kroes et al., 2002):

- Is the food list representative of the foods normally consumed by the population or the specific age/sex groups to be investigated?
- Are foods with very low consumption but of potential concern regarding chemical content included?
- How many sampling sites are involved, and are they representative?
- Should the sampling be representative of commercial food processing or of homemade foodstuffs?
- Does sampling account for regional differences in soil content, climate, pest vectors and GAP, as well as those foods extensively distributed on a national basis, including imported foods?
- Are seasonal differences also considered?

- Are the main brands/cultivars covered for each food?
- Is sample size sufficient to cope with localized analytes, such as aflatoxins?
- Have standard operating procedures (SOPs) been established to standardize sampling?

For an acute exposure assessment, additional information is required on residues in single samples or individual unit crops. If such detailed data are not available, concentrations in single samples can also be derived from composite samples taken from a lot by applying a variability factor (see sections 6.2.1.5 and 6.3.6.2) to take into account the differences in chemical concentrations in sample increments or unit crops.

(b) Sample preparation and processing

Sample preparation includes actions taken to prepare the analytical sample from the laboratory (bulk) sample—for example, reducing the size of a large bulk sample by subsampling and removing foreign materials or parts of the sample material that are not analysed (e.g. stones, withered leaves, stone of fruits, bones of meat). For generating data to be used in dietary exposure assessment, the chemical concentrations in the edible portion of the commodities are of interest; for enforcement, the portion of the commodity specified in the relevant regulation should be prepared for analysis. Sample preparation may include, for instance, washing, peeling, cooking, etc., so that foods are prepared as for normal consumption (i.e. table ready). In such cases, cooking of foods needs to be based on one or more recipes or methods for each food item, in order to account for food habits. Sample preparation might also involve compositing of food samples taken from different regions, brands and even food types (e.g. milks and milk products), before homogenization and analysis. Such preparation will provide an estimate closer to the true average.

Sample processing includes physical operations performed to prepare a well-mixed or homogeneous matrix to form the analytical sample, from which the test portions for the analysis are taken. Some labile and volatile compounds may be lost during these processes, so special handling, including cryogenic processing, may be required.

Special care should also be taken to ensure that the size of the test portion is representative and sufficient for the accurate and reproducible determination of the average chemical or residue content of the analytical sample (FAO/WHO, 2003).

(c) Specific design approaches for generating concentration data

A good study design is the most important element of any exposure study (FAO/WHO, 2000). There are two main approaches to analysing foods when generating analytical data from surveys, including TDSs, and both can impact significantly, but differently, on the estimated dietary exposures. These two approaches are 1) analysis of food group composites and 2) analysis of individual foods (either as single samples or as composites).

In the *food group composite approach*, samples of similar foods (e.g. milk, cheese, butter, cream) are prepared and then combined to form a composite for a food group (e.g. dairy products). The basis for the relative proportions of foods contributing to the food group composite needs to be defined, but the proportions are generally based on food consumption data for an average consumer in the population.

The advantage of the food group composite approach relates primarily to the ability to determine the approximate dietary exposure to chemicals by analysis of a relatively small number of samples. By analysis of perhaps 10–20 representative food group composites that are carefully prepared to represent the national, socioeconomic, regional or ethnic dietary habits of a population, an approximation of chemical dietary exposure can be obtained.

The main disadvantage of the food group composite approach is that it restricts calculating chemical exposures to only that segment of the population upon which the proportional contribution of foods was based. If, for example, it was based on an adult male diet, this can only roughly approximate an adolescent or child or adult female diet, as types of foods and proportions of each consumed may differ substantially between age/sex groups.

The food group composites approach is often used when undertaking a TDS. As an example, the United Kingdom TDS has 20 food group composites (Ysart et al., 1999; FSA, 2004). Separate groups

have been established for foods consumed in large amounts (e.g. staples, such as bread, milk and potatoes) and also for food groups that may make a significant contribution to dietary exposure because they are known to be susceptible to contamination (e.g. offal and fish). This combined approach can facilitate the identification of sources of exposure while conserving resources.

In the *individual food approach*, each food is prepared and analysed separately. Often multiple samples of the same food purchased across the country are composited so as to get as representative a sample across the diet as possible. Each individual food composite may, depending on available resources, be composited in a targeted manner across brands, retail outlets, cities/regions or seasons for that food.

The major advantages of the individual food approach over the food group composite approach for analyses are the ability to estimate the contribution of individual foods to exposures as well as the greater flexibility in calculating dietary exposures for various segments of the population, provided appropriate food consumption information is available (WHO, 1985). The major disadvantage of the individual foods approach is the larger number of samples that need to be analysed in order to represent all foods consumed by the population. If the individual foods are also composited, then the principal disadvantage, which also applies to food group composites, is the so-called "dilution effect" inherent in the use of composites. For example, the concentration of one food in the composite may well be significantly in excess of the LOD or LOQ, but diluted to below the LOD or LOQ by other foods in the composite, such that the overall composite has a "not detected" (ND) result. This dilution effect can lead to significant underestimation or overestimation of dietary exposures, depending on the protocol used for assigning values to the samples with ND or "not quantified" (NQ) results (see section 6.2.1.5). In addition, unusual sources of elevated concentrations could be masked in the composite.

Some countries have used the individual foods approach in their TDSs. The associated number of individual foods specified are as follows: Canada, 135 foods (Dabeka et al., 2003); the Czech Republic, 220 foods (WHO, 2005a); France, 338 foods (Leblanc et al., 2005); Ireland, 107 foods (WHO, 2005a); New Zealand, 121

foods (Vannoort, 2003, 2004a,b,c); and the United States of America (USA), 286 foods (USFDA, 2004a). Australia has tended to use a more limited range of individual foods (70 foods; FSANZ, 2003), but this has occasionally presented problems for dietary exposure estimates (e.g. when lead was detected in honey, and honey was mapped to represent sugar-containing products, including highly consumed soft drinks that were not likely to contain lead) (FSANZ, 2001). Such grouping or mapping can lead to significant overestimation of actual dietary exposure and illustrates the need for a full description of any assumptions inherent in a dietary exposure assessment.

6.2.1.5 *Analysis*

There are a number of important differences in analytical methodology depending on whether the samples are analysed to provide data for dietary exposure assessment (e.g. TDSs) or for enforcement of MRLs or MLs. For instance, some veterinary drug residue metabolites that are of toxicological concern and are important for dietary exposure assessment are not analysed in monitoring programmes for enforcement purposes, as they are not part of the relevant residue definition. Method sensitivity can also differ. Generally, for accurate dietary exposure assessments, the LOD or LOQ should be as low as technically possible, because most foods will not contain detectable residues, and the value assigned to those samples will affect the estimated dietary exposures (see below). Most TDSs utilize sensitive methods, whereas monitoring or surveillance programmes typically use less sensitive methods, if the purpose is to confirm that residue concentrations are below the legal limits. In any case, residue data generated for enforcement purposes can be used for dietary exposure assessment provided the appropriate assumptions for samples below the LOD or LOQ are applied and numerical data are reported, not just pass or fail results.

(a) Quality assurance

Obtaining best estimates for dietary exposure is critically dependent on the quality of the concentration data. Concentration data should be obtained using validated methods where possible (see chapter 3) that are fit for the purpose of the assessment. Key aspects of data quality include:

- suitability of the sampling plan in order to obtain representative samples of food (e.g. early identification of the foods contributing most to the estimated dietary exposures can assist in directing resources to the most important foods);
- basing the number of samples determined on the statistical characteristics of each data set;
- appropriateness of sample handling procedures;
- selection and validation of the analytical method; and
- use of analytical quality control programmes.

Analytical quality control programmes include employing properly trained personnel familiar with the specific objectives of the tasks performed, regular testing of the performance parameters of the analytical methods by use of reference materials where available and applicable, and testing the bias/accuracy, reproducibility and sensitivity of the procedures. Participation in proficiency tests provides objective means to verify the capability of the laboratory and comparability of the results obtained in different laboratories. The established quality system and capability of the laboratory should be demonstrated by appropriate accreditation. Relevant detailed information can be obtained from a number of sources (Keith et al., 1983; USNRC, 1993; Hughes in WHO, 2002a; Kroes et al., 2002; Sack in WHO, 2002a; Vannoort in WHO, 2002b; FAO/WHO, 2003; IANZ, 2004).

(b) Handling non-detects or non-quantified results

The protocol for assigning concentration values to ND or NQ results is critical to the dietary exposure estimate. Concentrations should err on the side of nutritional or toxicological caution, while remaining scientifically defensible. This issue has been extensively considered (USNRC, 1993; WHO, 1994, 1995c; USEPA, 2000b; Vannoort et al., 2000; Egan et al., 2002; Kroes et al., 2002; Renwick et al., 2003; Tressou et al., 2004; Counil et al., 2005; Sinha et al., 2006; Jain et al., 2008). There are no international guidelines on the need to report both the LOD and LOQ in a standardized manner. Inconsistent reporting of LODs or LOQs may lead to differences in the numerical value that should be assigned to ND or NQ results for use in dietary exposure estimates. It is therefore important to recognize that this is currently considered on a case-by-case basis, so all assumptions made need to be recorded.

Unless there is reason to assume that a food does not contain a chemical of interest (e.g. foods for which a pesticide is not registered for use or for which a food additive is not permitted, or foods that undergo extensive processing during which a chemical is likely to be completely removed), it should be assumed that samples without detectable (or quantifiable) concentrations may contain the chemical below the LOD or LOQ. The risk assessor must decide what value to assign to such samples. One common, albeit arbitrary, option is to assign a value of one half the LOD or LOQ to these samples. If the number of samples with ND or NQ residues is large, such replacement would distort the calculated mean and chemical variability values. It should be noted that the median concentration derived from data sets with over 50% of results below the LOD or LOQ will not be influenced at all by the magnitude of the positive results, whereas the mean can be heavily influenced by a cluster of very high results.

Another option is to use lower-bound or upper-bound values (e.g. zero and the LOD). In general, for chemicals likely to be present in the food (e.g. naturally occurring contaminants, nutrients and mycotoxins), both lower and upper bounds should be calculated for the mean food concentration. The lower bound is obtained by assigning a zero value to those samples in which the chemical was ND or NQ and using these values to estimate dietary exposure. An upper-bound dietary exposure is estimated by assigning the LOD to all samples with ND results and the LOQ to all samples with less than the LOQ but more than the LOD. In some cases, the LOD may equal the LOQ.

In cases where different chemicals are considered as a group for dietary exposure assessment purposes (e.g. dioxins or aflatoxins), the assignment of numerical values to ND or NQ results can be complex when different LODs or LOQs were used for the analysis of each individual chemical in the group. The simple summation of the LODs or LOQs is not feasible, as this will tend to result in an overestimation of dietary exposure, and rules for how to deal with these results need to be developed and recorded.

The impact of these assumptions on the concentration selected for the dietary exposure estimate should be presented in the dietary exposure assessment and also in any associated risk assessment. Some

guidance has been provided (Helsel, 1990; WHO, 1995). For example, GEMS/Food Europe has suggested that if fewer than 60% of results are less than the LOD or LOQ, then a reasonable estimate of the mean can probably be obtained by setting all ND or NQ results to LOD/2 or LOQ/2, respectively (WHO, 1995). Some experts have suggested that additional considerations should be undertaken if more than 10–15% of the samples are below the LOD. In general, when data sets have a large number of samples that are less than the LOD or LOQ, it may be advisable to perform sensitivity analyses by first assigning all ND or NQ results to zero, setting these values to the full LOD or LOQ and then evaluating how the exposure estimates change. The assignment of different values to ND results may have a significant impact on estimated dietary exposures, the effect being greater for less sensitive analytical methods with higher LODs. Alternatively, more sophisticated methods such as maximum likelihood estimation or regression on order statistics can be used to evaluate the impact of the values assigned to ND or NQ results. For chemicals unlikely to be present unless specifically added (i.e. pesticide and veterinary drug residues, additives), using a lower-bound mean concentration only is generally the norm.

In field trial residue data, the occurrence of samples in which no pesticide residue was detected requires a decision about how to include a precise quantitative value in the residue data file if it is to be used for probabilistic analysis. Unlike non-treated crops, it can be assumed that there is a finite residue present, but that it is merely below the LOD. The USEPA (1998) has chosen to use a value of LOD/2 or LOQ/2 as a reasonable means to address such findings. When residues from a set of supervised trials are all below the LOQ, JMPR assumes that the median and high residues are equal to the LOQ unless there is scientific evidence that residues are "essentially zero". This is clearly distinguished from consideration of non-treated crops (above), in which the pesticide residue is properly assigned as "zero".

6.2.1.6 *Deriving concentration data for use in estimating dietary exposures*

This is an important issue, where the choice of concentration data to use in a dietary exposure estimate depends on the purpose of the modelling exercise. For a probabilistic approach, an empirical, parametric or non-parametric distribution of available concentration data is used (see section 6.3.5.2). For a deterministic or point estimate approach, a statistic such as the mean or median may be derived

from the whole data set. The approach taken and underlying reasoning should be clearly stated in the dietary exposure assessment.

For contaminants, the mean food concentration value derived from monitoring or surveillance data is often used in dietary exposure estimates. However, depending upon the anticipated profiles of contamination or the sampling design, in some situations a median or geometric mean may be a more appropriate measure of the concentration—for example, when there is a highly skewed distribution of concentration data or where a significant proportion of results are below the LOD or LOQ (WHO, 1994, 1995; FAO/WHO, 2000). For TDSs and nutrients, the mean is generally used, as there are usually insufficient concentration data to justify use of the median, especially for the individual food composite approach, where often only a few results for each food may be available. For chemicals that are intentionally added to foods, the mean concentration is often used to reflect the expected concentration in food over time and may be derived from manufacturers' use data (food additives, including flavours) and monitoring or surveillance data (food additives, including flavours, pesticide and veterinary drug residues). The highest or median residue levels from supervised trials (highest residue level found in trials [HR]; supervised trials median residue [STMR]) or the MRL may be used to represent pesticide and veterinary drug residue levels, depending on the dietary exposure scenario and whether an acute or chronic dietary exposure estimate is required.

6.2.1.7 *Uncertainty in food chemical concentration data*

The use of maximum food chemical concentrations (MLs and MRLs) in dietary exposure estimates substantially overestimates the amount of chemicals present, and these data therefore have the greatest uncertainty if used other than for a worst-case analysis. Data from direct measurements after use of or treatment with pesticides or veterinary drugs, from a supervised field trial or manufacturer use levels for food additives, have less associated uncertainty. Although these data provide a more accurate estimate of exposure compared with maximum concentrations of the chemical in or on the food commodity as it enters the food distribution system, they do not reflect the impact of storage, transportation or preparation of the food. Still more accurate information on concentrations of chemicals in food is available from national monitoring and surveillance data. The most accurate

data are obtained from the measurement of chemical concentrations in foods as consumed. Although this approach would provide the least uncertainty, it is typically the most resource intensive.

A common method for describing uncertainty in food chemical concentration data is to repeat the analysis using 1) bounding "high-end" estimates for all parameters, 2) bounding "low-end" estimates for all parameters and 3) central tendency estimates (mean or median) for all parameters. Based on the implied uncertainty, the risk manager can then determine if the expenditure of time and resources necessary to gather additional information about these parameters to further refine the dietary exposure estimate is warranted. The handling of non-detects in the data set of chemical concentrations is of importance in determining the high-end and low-end estimates, as is the treatment of censored values, as assumptions about those values and their treatment may influence the result of the assessment.

Uncertainties in data on concentrations of chemicals in food can be reduced by improving the quality of the data available (see section 6.2.1.5). Uncertainty in dietary exposure assessments has been discussed elsewhere (EFSA, 2006; IPCS, 2008; see also chapter 7, section 7.2.2).

Indicators of data quality need to be clearly defined and provided to users of the data. This information should be sufficiently complete to enable critical decisions to be made concerning the appropriateness of the available data for the specific use.

(a) Errors in analytical measurements

Three types of error can be distinguished in most measurements:

- *Gross errors* refer to unintentional or unpredictable errors that occur while generating the analytical result. Errors of this type invalidate the measurement. It is not possible or desirable to statistically evaluate and include the data with gross errors in the estimation of uncertainty. Laboratory quality assurance procedures should minimize gross errors.

- *Random errors* are present in all measurements and cause replicate results to fall on either side of the mean value. The random

error of a measurement cannot be compensated for, but increasing the number of observations and training of the analyst may reduce such errors.

- *Systematic errors* occur in most experiments, but their effects are quite different. The sum of all the systematic errors in an experiment is referred to as the bias. As they do not sum to zero over a large number of measurements, individual systematic errors cannot be detected directly by replicate analyses. The problem with systematic errors is that they may go undetected unless appropriate precautions are taken. For example, systematic errors in an analysis can be identified only if the analytical technique is applied to a reference material, the sample is analysed by another analyst or preferably in another laboratory, or the sample is reanalysed by another analytical method. However, only if the reference material matches identically in terms of analyte, matrix and concentration does it meet the ideal conditions for determining the bias of the method. The bias of a method may also be investigated by recovery studies. However, recovery studies assess only the effects of analysis and do not necessarily apply to naturally incurred samples or components of the bias that may be introduced prior to the analytical step. In pesticide residue analysis, results are not normally corrected for recovery. If the result has been corrected for recovery, the uncertainty associated with recovery should be incorporated in the uncertainty estimation of the measurement.

Some examples of sources of errors are illustrated in Table 6.2. It should be noted that not all sources mentioned have to be evaluated in the uncertainty estimation. Some sources are already incorporated in the overall uncertainty, whereas others are negligible and may be disregarded. However, it is important to recognize and assess all sources before elimination. Further information may be obtained from published documents (Eurachem, 1999; FAO, 2002).

(b) Procedures for estimating measurement uncertainty

Although there are a number of options available to laboratories for the estimation of measurement uncertainty, there are two preferred procedures, commonly described as the “bottom up” approach and the

Table 6.2. Sources of error in sampling, sample preparation and analysis

Procedure	Sources of systematic error	Sources of random error
Sampling	Selection of sampling position	Large variation of food chemical concentration in food or on treated crops
		Small number of primary samples taken (sample size)
	Incorrect labelling	
	Contamination of sample	
Shipping and storage	Decomposition of analytes	
Sample preparation	The portion of sample to be analysed (analytical sample) may be incorrectly selected	The analytical sample is in contact with and contaminated by other portions of the sample
		Rinsing and brushing are performed to varying extents, stalks and stones may be differentially removed
		Is food for analysis raw or cooked? If cooked, how is it cooked?
Sample processing	Decomposition of analyte during sample processing, cross-contamination of the samples	Non-homogeneity of the analyte in single units of the analytical sample
		Non-homogeneity of the analyte in the ground or chopped analytical sample
		Variation of temperature during the homogenization process
		Texture (maturity) of foods or plant materials affecting the efficiency of the homogenization process
Extraction/ cleanup	Incomplete recovery of analyte	Variation in the composition (e.g. water, fat and sugar content) of sample materials taken from a commodity
	Interference of co-extracted materials (load of the adsorbent)	Temperature and composition of sample/solvent matrix

Table 6.2. ***(Continued)***

Procedure	Sources of systematic error	Sources of random error
Quantitative determination	Interference of co-extracted compounds	Variation of nominal volume of devices within the permitted tolerance intervals
	Incorrect purity of analytical standard	Precision and linearity of balances
	Biased weight/volume measurements	Incomplete and variable derivatization reactions
	Operator bias in reading analogue instruments, equipment	Changing of laboratory environmental conditions during analysis
	Determination of substance that does not originate from the sample (e.g. contamination from the packing material)	Varying injection, chromatographic and detection conditions (matrix effect, system inertness, detector response, signal to noise variation, etc.)
	Determination of substance differing from the residue definition	Operator effects (lack of attention)
	Biased calibration	Calibration

"top down" approach. The bottom up or component-by-component approach breaks down all the analytical operations into primary activities. These are then combined or grouped into common activities, and an estimate is made of the contribution of these activities to the combined uncertainty value of the measurement process. The top down approach is based on method validation and long-term precision data derived from laboratory control samples, proficiency testing results, published literature data and interlaboratory collaborative trials. Uncertainty estimates based on interlaboratory studies may also take into account the between-laboratory variability of the data and provide a reliable estimate of the method performance and the uncertainty associated with its application. It is important to acknowledge, however, that collaborative studies are designed to evaluate the performance of a specific method and participating laboratories. They normally do not evaluate imprecision due to sample preparation or processing, as the samples generally tend to be highly homogenized.

6.2.1.8 Available food composition databases

(a) Food composition data for nutrients

Food composition databases contain information on the nutrient content of various foods and beverages. They are based on chemical analysis of nutrients in foods, which are complemented with calculated and imputed values. Most food composition databases are compiled at a national level, whereas some exist at a regional level. Most national databases report nutrient values that are not readily comparable at an international level owing to differences in foods from different countries (e.g. variety, soil, processing and fortification), but also artificial differences as a result of component identification, food description and nomenclature, analytical methods, mode of expression and units used (Deharveng et al., 1999).

International efforts are under way to harmonize these issues under the International Network of Food Data Systems (INFOODS) (http://www.fao.org/infoods/index_en.stm) of the United Nations University or, at the European level, under the European Food Information Resource Network (EuroFIR) (http://www.EuroFir.net), in order to be able to generate and compile high-quality nutrient values that are more comparable among countries. Generally, the exchange of nutrient values on the basis of food names alone is not sufficient to use and evaluate these data. Standardized vocabularies for foods and components will facilitate international use of the data. Some work has already been completed, including standardized vocabulary (http://www.fao.org/infoods/nomenclature_en.stm), component identification (Klensin et al., 1989; http://www.fao.org/infoods/tagnames_en.stm) and interchange formats and procedures (Klensin, 1992; http://www.fao.org/infoods/interchange_en.stm). Guidelines on interchange of food composition data have been proposed since 1992 and have been enlarged or updated since (see above web pages plus http://www.fao.org/infoods/index_en.stm).

Increasingly, in many nations, voluntary fortification of a wide array of foods creates an almost insurmountable challenge to managers of food composition databases. To portray the nutrient content in foods accurately, food composition databases should be updated frequently and be specific enough to accommodate many different formulations of the same foods. To improve the accuracy of estimates of nutrient intake, food consumption assessments should include the

collection of sufficient information for processed foods to ensure that food composition data match the foods consumed.

(b) GEMS/Food database

One of the activities of the WHO GEMS/Food Programme is the maintenance of databases of information collected by contributing institutions on contaminant and pesticide residue levels in foods and estimated dietary exposures to food chemicals from TDSs and duplicate diet studies based on internationally recommended procedures (WHO, 1979, 1985, 1997; FAO/WHO, 1997).

GEMS/Food international databases include individual and aggregated data on contaminants and pesticide residues in foods. GEMS/Food has provided information to assist in understanding the terminology used and how to submit data (EC, 2004; WHO, 2005b). GEMS/Food has also developed core, intermediate and comprehensive lists of priority contaminant/commodity combinations that should be considered for monitoring for public health reasons. These lists are periodically updated (see Annex V of WHO, 2002a).

In addition to protocols for electronic data submission, WHO has developed a computer system to allow the direct entry of data into the GEMS/Food database as well as the retrieval of data and creation of reports from the database. The system, Operating Program for Analytical Laboratories for data on individual and aggregate contaminant levels in foods (OPAL I), is available on request (foodsafety@who.int). OPAL II, for submitting data on dietary exposures to contaminants from TDSs and duplicate diet studies, is also available.

The GEMS/Food database is accessible through the Internet at http://www.who.int/foodsafety/chem/gems/en/. In this regard, data deemed confidential by the data submitter will not be made public without the expressed permission of the data submitter. In these cases, the database will display only the name of the country, the contaminant and the number of records.

Examples of national food chemical concentration data can be accessed on the Internet from various sources, including Australia (FSANZ, 2003), New Zealand (Vannoort, 2003, 2004a,b,c), the USA (USFDA, 2004a,b; USDA, 2008) and Europe (EC, 2004).

6.2.2 Food consumption data

Food consumption data reflect what individuals or groups consume in terms of solid foods, beverages, including drinking-water, and dietary supplements. Food consumption can be estimated through food consumption surveys at an individual or household level or approximated through food production statistics. Food consumption surveys include records/diaries, food frequency questionnaires (FFQs), dietary recall and TDSs. The quality of data from food consumption surveys depends on the survey design, the method and tools used, the motivation and memory of the respondents, the statistical treatment and the presentation (foods as purchased versus as consumed) of the data. Food production statistics by definition represent foods available for consumption by the whole population, typically in the raw form as produced.

6.2.2.1 Food consumption data requirements

Ideally, food consumption data used at the international level should take into account the differences in food consumption patterns in different regions. To the extent possible, consumption data used in dietary exposure assessments should include information on factors that may influence dietary exposure (those that may either increase or decrease risk). Such factors include demographic characteristics of the population sampled (age, sex, ethnicity, socioeconomic group), body weight, the geographic region, day of the week and the season in which the data are collected. Consideration of food consumption patterns for sensitive subpopulations (e.g. young children, women of childbearing age, the elderly) and consumption patterns for individuals at the extreme ends of the distributions is also important. Given that the design of consumption studies can have a critical impact on the results of any dietary exposure assessment, harmonization of study design should be achieved to the extent possible. All food consumption surveys should preferably include data on foods, beverages (including drinking-water) and food supplements. Ideally, all countries, including developing countries, should conduct food consumption surveys on a periodic basis, preferably with individual dietary records.

Individual record data will generally provide the most precise estimates of food consumption. Broad surveys, covering the food consumption patterns of the whole population, may not be needed if the food in which the chemical of interest is found is consumed by

only a subset of the population. If resources are limited, small-scale studies are appropriate and may cover specific foods or target population subgroups (e.g. children, nursing women, ethnic minorities or vegetarians). This approach can improve the precision of estimates of dietary exposure for specific population subgroups or specific food chemicals.

6.2.2.2 *Approaches for food consumption data collection*

(a) Population-based methods

Food supply data at the national level, such as food balance sheets or food disappearance data, provide gross annual estimates of the national availability of food commodities. These data may also be used to calculate the average per capita availability of energy and macronutrients and exposure to chemicals (e.g. pesticides and contaminants). Because consumption is expressed in terms of raw and semiprocessed commodities, these data are not generally useful for estimating dietary exposure to food additives. The major limitation of national food supply data is that they reflect food availability rather than food consumption. Losses due to cooking or processing, spoilage and other sources of waste and additions from subsistence practices cannot easily be assessed. According to FAO/WHO (1997), food balance sheet consumption estimates tend to be about 15% higher than the consumption estimates derived from household surveys or national dietary surveys. These data do not include water consumption. Where water consumption data are not available, a default water consumption value of 2 litres per adult may be used as per the WHO drinking-water guidelines (WHO, 2008).

Despite these limitations, food balance sheet data are useful for tracking trends in the food supply, for determining the availability of foods that are potentially important sources of nutrients or chemicals and for monitoring food groups targeted for control. Food supply data are not useful for either evaluating individual nutritional intake or food chemical dietary exposure or identifying subgroups of the population at risk.

(b) Household-based methods

A variety of information regarding food availability or consumption at the household level may be collected, including data on foodstuffs purchased by a household, follow-up of consumed foods or

changes in food stocks. Such data are useful for comparing food availability among different communities, geographic areas and socioeconomic groups and for tracking dietary changes in the total population. However, these data do not provide information on the distribution of food consumption among individual members of the household.

(c) Individual-based methods

Data collected by individual-based methods provide detailed information on food consumption patterns; however, as with other food consumption surveys, they may be prone to bias. For instance, several studies have found that nutrient intakes derived from 24 h recalls tend to underestimate true intakes of some macronutrients for some subjects (Madden et al., 1976; Carter et al., 1981; Karvetti & Knutts, 1985). Regression analyses between recall and actual intakes exhibited the "flat-slope syndrome", whereby individuals tend to overestimate food amounts when consumption is low and underestimate food amounts when consumption is high. In some cases, individuals may overestimate consumption of foods perceived as "good foods" and underestimate consumption of foods perceived as "bad foods".

The *food record*, or food diary, requires that the subject (or observer) report all foods consumed during a specified period (usually 7 days or less). These surveys generally collect information not only about the types of food consumed, but also about the source of the foods and the time of day when and place where foods are consumed. The amounts consumed should be measured as accurately as possible. Amounts may be determined by weighing or measuring volume.

The *24 h dietary recall* consists of listing of foods and beverages (including drinking-water and sometimes dietary supplements) consumed during the previous day or during the 24 h prior to the recall interview. Such surveys generally collect information not only about the types and amounts of food consumed, but also about the source of the foods and the time of day when and place where foods are consumed. Foods and drinks are recalled from memory with the aid of an interviewer who has been trained in methods for soliciting dietary information, without the introduction of interviewer bias. The interview is usually conducted in person, but may be conducted by telephone or via the Internet. In some situations, the recall is self-administered by the subject, but this approach results in less reliable

data. Researchers have developed multipass methods that guide the respondent through the 24 h reference period several times, providing opportunity for the respondent to remember food details and additional foods (Slimani et al., 1999; Raper et al., 2004).

The *FFQ*, sometimes referred to as a "list-based diet history", consists of a structured listing of individual foods or food groups. For each item on the food list, the respondent is asked to estimate the number of times the food is usually consumed per day, week, month or year. The number and types of food items may vary, as well as the number and types of frequency categories. FFQs may be unquantified, semiquantified or completely quantified. The unquantified questionnaire does not specify serving sizes, whereas the semiquantified tool provides a typical serving size. A completely quantified FFQ allows the respondent to indicate any amount of food typically consumed. Some FFQs include questions regarding the usual food preparation methods, trimming of meats, use of dietary supplements and identification of the most common brand of certain types of foods consumed.

The validity of dietary patterns assessed with FFQs depends on the representativeness of the foods listed in the questionnaire. Whereas some authors (Rimm et al., 1992; Green et al., 1998; Thompson et al., 2000; Brunner et al., 2001) have concluded that FFQs produce valid data for dietary exposure assessments, others (Kroke et al., 1999; Schaefer et al., 2000) have found that FFQs do not produce reliable estimates of some macronutrients.

FFQs are commonly used to rank individuals by consumption of selected foods or nutrients. Although FFQs are not designed to be used to measure absolute dietary exposure, the method may be more accurate than other methods for use in estimating average dietary exposure to those chemicals having large day-to-day variability and for which there are relatively few significant food sources. Brief FFQs may focus on one or several specific nutrients or food chemicals and include a limited number of food items. In addition, FFQs can be used in the identification of absolute non-consumers of certain foods.

The meal-based *diet history survey* is designed to assess usual individual food consumption. It consists of a detailed listing of the types of foods and beverages commonly consumed at each eating occasion

over a defined time period, which is often a "typical week". A trained interviewer probes for the respondent's customary pattern of food consumption on each day of the typical week and may use software designed for this type of interview (e.g. Mensink et al., 2001). The reference time frame is often over the past month or the past several months or may reflect seasonal differences if the reference time frame is the past year.

The *food habit questionnaire* may be designed to collect either general or specific types of information, such as food perceptions and beliefs, food likes and dislikes, methods of preparing foods, use of dietary supplements and social settings surrounding eating occasions. These types of information are frequently included along with the other four methods, but may also be used as the sole basis for data collection. These approaches are commonly used in rapid assessment procedures. The questionnaire may be open-ended or structured and self-administered or interviewer-administered and may include any number of questions, depending on the information desired.

(d) Combined methods

Consumption data obtained by different collection methods may be combined to improve accuracy and facilitate validity of the dietary data and for other practical reasons. For example, the food record has been combined with the 24 h recall. The FFQ that focused on selected nutrients has been used in addition to the 24 h recall. The 24 h recall is frequently used to help establish the typical meal plan. This information can be used to obtain better information from the diet history method. The FFQ may also be used as a cross-check for the other three types of methods.

An example of a recommendation to use two methods of collecting food consumption data is that of the European Food Consumption Survey Method (EFCOSUM) project, where the most cost-effective method for harmonizing food consumption data between European Union (EU) member countries was determined as follows: at least two 24 h recalls should be performed for each subject on non-consecutive days taking working and non-working days into account, in combination with a questionnaire on habitual consumption of infrequently consumed foods, to get insights into the proportion of non-consumers

(Brussard et al., 2002). The collection of repeated non-consecutive recalls allows for the estimation of usual food consumption by a modelling technique that separates intraindividual and interindividual differences in consumption (see section 6.2.2.4). Other combinations of consumption data from different sources may be appropriate, depending on the purpose of the dietary exposure assessment.

6.2.2.3 *Data reporting and use*

(a) Mapping

Food consumption data should be available in a format that allows matching of the consumption data with the concentration data used in the dietary exposure assessment. For example, for raw agricultural commodities and some semiprocessed commodities (e.g. polished rice and flour), the GEMS/Food format (see section 6.2.1.8) uses the Codex Classification System for Food and Feeds. This system was established by CCPR to specify foods for which pesticide MRLs are applicable. The system includes the common name of the food in English, French and Spanish, as well as the Latin name or names. This coding is also used by CCCF for identifying foods subject to MLs for contaminants. The system is being revised and expanded to include more foods, including processed foods. In the case of acrylamide, which occurs only in processed foods, additional fields have been included to more accurately describe the analysed food. These include four fields for ingredients (in order of predominance), the Codex code for processed foods, the method of heating and the processing method (FAO/WHO Acrylamide in Food Network: http://www.acrylamide-food.org/).

Foods may be consumed as such or as an ingredient as part of a recipe or food mixtures. For example, ground beef may be consumed as a single food item or as a component of a beef casserole. When modelling food consumption, it is important to know whether the consumption estimate includes all sources of the food. Recipes can be broken down into their ingredients, which can then be mapped to the corresponding individual food and added to the total consumption of that food from all sources (e.g. whether “apples” includes the apple in a baked apple pie and apple juice; whether “potatoes” includes potatoes fried as in french fries or potato chips/crisps: if potatoes and french fries are considered separate foods, then this should be stated). The recipe mapping approach needs to be documented.

The use of standard recipes and the attribution of the ingredients to individual foods introduce some uncertainty into consumption data (e.g. assuming that, on average, 70% of bread is flour). The error would be significantly higher if the contribution of mixed foods were omitted. Using standardized recipes results in reduced variability that may underestimate or overestimate the amount of individual foods or food ingredients consumed for high-percentile consumers, depending on the relative quantity of the ingredient in the recipe. Another potential source of error lies in the decisions taken in mapping foods from food consumption surveys to foods with concentration data, because in many cases the food and the food description do not correspond exactly (Slimani et al., 2000).

(b) Data format/modelling

Data collected using *population-based methods* are generally compiled and reported for raw or semiprocessed agricultural commodities, and they represent the total annual amount of a commodity available for domestic consumption per year. The amount may be for the entire population or at the per capita level. A daily consumption amount may be estimated by dividing the total annual amount by 365. It is not possible to estimate the consumption amount per eating occasion or only for consumers of the foods from these data alone.

Data from *individual food consumption surveys* are often not publicly available in raw format (i.e. at the individual respondent level), and risk assessors have to rely on published summary statistics. When the raw data are available, they can be used to estimate dietary exposures from multiple foods, to estimate dietary exposures by specific population subgroups or to estimate distributions of food consumption, rather than just mean consumption.

When only summary data are available, it is important to know and document the commodity, the type of commodity (e.g. raw juice, juice concentrate), how the statistics are aggregated and whether they refer to typical or high-end consumers, how a typical consumer is defined (e.g. median or mean food consumption or dietary exposure level), whether they refer to consumers only or to the total population (all survey respondents, per capita estimates), whether they represent daily consumption, consumption per eating occasion or per meal or averages across survey days (in the case of multiday surveys), as well

as the data requirements listed in section 6.2.2.1. When comparing food consumption data among countries or surveys, caution should be exercised even if the same methods are used, because the results may not be readily comparable owing to differences in study design, tools, statistical analysis and reporting of results (Slimani et al., 2000; Brussard et al., 2002).

Market share corrections can be applied to food consumption data for processed foods or percentage of treated crops. The approach is used mainly when the substance being evaluated has been deliberately added to the food. The maximum or mean concentration of a chemical is assigned only to the proportion of the market in which the additive is used or the proportion of the crop in which a pesticide is used, not to the consumption data for the whole food category. This technique may refine the estimate of mean dietary exposure, but it does not refine the dietary exposure estimate for the most exposed section of the population (i.e. consumers who are loyal to the food products containing the additive or the pesticide), as it may underestimate their actual dietary exposure. When assessing dietary exposure to additives or flavourings, market share data should consider brand loyalty, where feasible. For pesticides, correction for the percentage of crop treated can be taken into account when setting MRLs; in post-regulation situations, however, at a national level, consideration should be given to the possibility that a section of the population may systematically consume foods derived from treated crops only.

(c) Food portion sizes

Unit weights represent weights of typical commodity units (e.g. a single apple or a single banana) and are used in the calculation of acute dietary exposure estimates, such as the international estimated short-term intake (IESTI). Unit weights may also be used to convert reports of food consumption by single units in an FFQ or 24 h recall survey to gram weights. Estimates of mean or median unit weights of raw agricultural commodities and the per cent edible portion (e.g. one orange and the percentage of orange pulp) have been provided by France, Japan, Sweden, the United Kingdom and the USA and compiled by GEMS/Food (http://www.who.int/foodsafety/chem/acute_data/en/).

Standard portion sizes are used to assess the consumption of foods and beverages in a large number of food surveys. That is, a standard

weight will be assigned to a banana, a cookie or a glass of soft drink. These portions can be more or less detailed (with, for example, differing weights for different glass sizes). However, standard portion sizes do not usually describe the full variability in the weights of portions as consumed in the population. Their use can lead to an overestimate of low portions and an underestimate of high portions and thus to overestimates and underestimates of dietary exposure. They are a very useful and pragmatic tool, but the uncertainty that they introduce in food consumption data must be kept in mind—specifically, the impact on the estimate of high levels of dietary exposure to food chemicals and low levels of intake for nutrients.

Large portion (LP) sizes have been used for a variety of risk assessments in Europe and by JMPR. For these purposes, the LP values have been based on the 97.5th percentile of food consumption derived from records of individual consumer days (i.e. survey days on which the food or foods of interest were consumed). For use in an acute dietary exposure assessment for pesticide residues (see section 6.3.6.2), the LP value should be matched to the raw Codex commodity to which the residue data relate. In the case of commodities that are eaten predominantly fresh, such as fruits and vegetables, the LP value should be derived for the raw commodity. When a high proportion of the commodity, such as cereal grains, is consumed in a processed form, the LP value should relate to the processed commodity (e.g. bread, flour), provided matching residue concentration data are also available for the processed food.

Upper-percentile and lower-percentile food consumption amounts should be defined based on individual consumer days. For surveys collecting multiple days of consumption data per person, the individual consumer days are assumed to be independent observations in the derivation of upper and lower percentiles as follows:

- If the survey includes multiple days per participant, only the valid consumer days on which consumption of the food of interest occurs should be used.

- If a survey participant has multiple valid consumer days, these consumer days should be considered as independent observations in the database and not averaged.

- The number of consumer days on which the percentile is based should be explicitly stated, as the purpose of the assessment may determine how these records are treated. For example, multiple consumer days for each participant would be treated separately in an acute dietary exposure estimate, but may be combined or adjusted by a mathematical formula to represent "usual" consumption in a chronic dietary exposure estimate (see section 6.2.2.4).

In estimating acute dietary exposures to chemical residues in a single commodity or food, it is appropriate to use food consumption data for only those people who consume the single food (consumers only). Estimations of acute dietary exposures to chemical residues in multiple commodities or foods should be conducted for both consumers only and all respondents in the survey (total survey population).

LP (97.5th percentile) consumption values as well as body weights and ages are compiled by GEMS/Food and are available at http://www.who.int/foodsafety/chem/acute_data/en/. These data were provided by Australia, France, the Netherlands, Japan, South Africa, the United Kingdom and the USA, along with body weights of the general population and children aged 6 years and under.

Ideally, the food consumption values in the GEMS/Food LP database should be based on the 97.5th percentile of individual consumer days from national surveys. This database needs to be expanded to include data from additional countries to better represent all member countries. When data are provided, additional information is desirable that fully describes the underlying data, food groups used and assumptions that were made in preparing the estimates of the LP values.

If individual records are not available, the risk assessor can estimate a high-percentile food consumption value by multiplying a central estimate by an inflation factor. If the approximate shape of the distribution for a particular parameter is known, better high-percentile estimates can be developed.

6.2.2.4 *Usual food consumption patterns*

For a probabilistic exposure assessment, the readily available distributions of food consumption data are not representative of true long-term consumption; for example, consumption data are usually

collected over a period of a few days, but are often used to represent food consumption during a lifetime. It is difficult from the methodological point of view to obtain representative data from single subjects to represent the lifetime exposure of consumers. Nevertheless, food consumption data on a national or group level reported across a range of age groups at one point in time or over a short time period can be used to model lifetime consumption.

Approaches that have been used to estimate long-term consumption have included methods combining food frequency data with consumption amount information (e.g. IEFS, 1998; Tran et al., 2004) and statistical models that use the correlations among the days of consumption to estimate the "usual" intake of nutrients or contaminants using short-term consumption data (e.g. USNRC, 1986; Slob, 1993, 1996; Carriquiry et al., 1995; Nusser et al., 1996). These models are most appropriate when the chemical of interest occurs in various basic food products, resulting in a nutrient intake or chemical dietary exposure different from zero for virtually every individual each day. Parametric and non-parametric methods are needed in order to better simulate the frequency of consumption for occasionally eaten food on a long-term basis.

Application of such methods results in a distribution of long-term nutrient intakes or food chemical dietary exposures that shows less variability than the distribution of dietary exposures directly derived from short-term food consumption data (Carriquiry, 2003).

Lambe & Kearney (1999) warned against using short-term consumption data for estimating long-term or usual consumption and showed that survey duration affects estimates of the per cent consumers, the mean and high consumption of foods and the classification of individuals as high or low consumers of foods or nutrients. Thus, data from such surveys need to be adjusted for use in the estimation of long-term consumption for chronic dietary exposure assessments.

6.2.2.5 Food consumption databases

(a) Databases collected through population-based methods

Food balance sheet data include the amounts of foods available for human consumption derived from national statistics on food

production, disappearance or utilization. They are generally available for most countries. Examples include those compiled by the United States Department of Agriculture's (USDA) Economic Research Service (Putnam & Allshouse, 1999) and the Australian Bureau of Statistics (2000). The FAO's statistical database (FAOSTAT) is a compilation of similar statistics for more than 250 countries. When official data from Member countries are missing, the data are estimated from national food production and utilization statistics (http://faostat.fao.org/).

The GEMS/Food consumption cluster diets developed by WHO are based on selected FAO food balance sheets and represent average per capita food consumption. Using a cluster analysis approach where countries with similar patterns of consumption of 20 key foods were grouped together and then sorted by geographic location, 13 consumption cluster diets were produced based on all available FAO food balance sheet data for the period 1997–2001 (http://www.who.int/foodsafety/chem/gems/en/index1.html). The consumption cluster diets were last revised in 2006, incorporating country comments on the first version; although they are still based on the 1997–2001 data, identified data gaps were filled where possible. Further details on these diets are available on the WHO web site (http://www.who.int/foodsafety/chem/ClusterDietsAug06.xls). The consumption cluster diets are expected to be updated every 10 years. The 13 GEMS/Food consumption cluster diets are now used as a tool for international chronic dietary exposure assessments by JMPR and JECFA. The consumption cluster diets replace the five regional diets previously developed by WHO (1998, 2003).

(b) Databases collected through individual-based methods

Many countries now collect food consumption data at an individual level. Some examples of these food consumption databases are listed below:

- The 1994–1996 and 1998 USDA Continuing Survey of Food Intakes by Individuals (CSFII) (USDA, 2000) and, since 1999, the National Health and Nutrition Examination Survey (NHANES) (http://www.cdc.gov/nchs/nhanes.htm) provide 2-day (CSFII) and 1- or 2-day (NHANES) food consumption data for individuals in

the USA, along with corresponding demographic and anthropometric data (age, sex, race, ethnicity, body weight and height, etc.) for each individual.

- Many European countries have national dietary surveys (Verger et al., 2002). Data from 17 European food consumption surveys were published in 2008 in the European Food Safety Authority's (EFSA) Concise European Food Consumption Database (http://www.efsa.europa.eu/en/datex/datexfooddb.htm).

- The 1995 Australian National Nutrition Survey collected data from one 24 h food recall for 13 858 individuals aged 2 years and older (McLennan & Podger, 1997, 1998, 1999), and the Australian National Children's Nutrition and Physical Activity Survey collected data from two 24 h recalls for children 5–16 years of age (Commonwealth of Australia, 2008).

- The 1997 New Zealand National Nutrition Survey collected data on one 24 h food recall for 4636 individuals aged 15 years and older (New Zealand Ministry of Health, 1999), and the 2002 National Children's Nutrition Survey collected data from two 24 h recalls for individuals aged 5–14 years (New Zealand Ministry of Health, 2003).

- The 2002–2003 Brazilian Household Budget Survey (Pesquisa de Orcamentos Familiares) provides the amount of food acquired during 7 consecutive days by 48 470 households in all 27 Brazilian states (http://www.ibge.gov.br).

6.3 Estimating dietary exposure

6.3.1 Introduction

The most appropriate method to use in estimating dietary exposure will depend upon a variety of factors. The following sections discuss the range of options, highlight some methods that are currently used and summarize the advantages and disadvantages of those methods.

The method applied in any dietary exposure assessment should be clearly stated and reproducible. Information about the model and data

sources used, assumptions, limitations and uncertainties should also be documented.

A framework for conducting exposure assessments should be established that will allow the analyst to select the most appropriate method for the intended use of the assessment. A framework that includes a stepwise approach is recommended, noting that the "best estimate" in terms of the "most realistic" dietary exposure assessment may not always be the "best estimate" in terms of the "most appropriate" one to suit the purpose of the dietary exposure exercise. In general, the early steps of the framework will include screening methods that use minimal resources and the shortest possible time (see Figure 6.1) to identify, among the large number of chemicals, those of no safety concern. No further (refined) exposure assessment is needed for substances that do not present safety concerns when analysed using screening methods that include conservative assumptions.

For the purposes of dietary exposure estimates, food consumption data should be presented such that individual consumer body weights are applied to the consumption figures for each consumer. If individual body weight data are not available or if the individual body weights have not been correlated to the food consumption figures, average body weights for the target population should be used. Average body weights of 60 kg for adults and 15 kg for children are assumed for most populations in the world; however, for certain regions, the average body weight of the population may differ significantly from 60 kg. For the adult Asian population, an average body weight of 55 kg is assumed. Actual average body weights in a country may vary significantly from 60 kg. If the default 60 kg adult body weight underestimates the actual individual body weights, the dietary exposure estimate on a per kilogram body weight basis will be overestimated. Likewise, if the default 60 kg adult body weight overestimates the actual individual body weights, the dietary exposure estimate on a per kilogram body weight basis will be underestimated.

6.3.2 Considerations when undertaking an exposure assessment

The specific approach that is most appropriate for estimating dietary exposure depends on several considerations, including 1) the type of substance being evaluated (food additive, including flavouring,

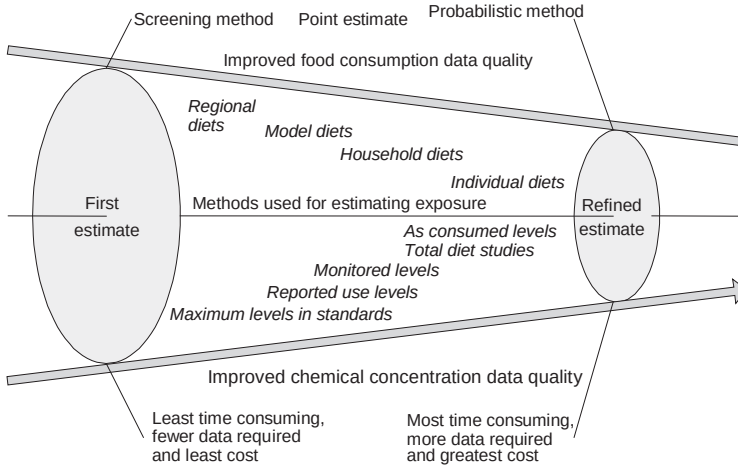

Fig. 6.1. Stepwise approach to obtaining realistic dietary exposure assessments

pesticide, veterinary drug, contaminant or nutrient) and whether the concern is the potential for too much or, for nutrients, too little intake, 2) the duration of exposure required to produce the toxic or beneficial effect, 3) the potential for different exposures in different subgroups or individuals within the population of consumers and 4) the type of estimate needed (point estimate or probabilistic characterization of the distribution of exposures). These considerations are further elaborated below in conjunction with each of the methods discussed.

6.3.3 Stepwise approach to exposure assessment

Ideally, exposure assessments should aim to identify substances that may be of safety concern with the minimum expenditure of resources. Therefore, most exposure assessment frameworks employ a stepwise or tiered approach in which the initial steps rely on conservative screening methods. If no safety concerns are identified, no additional exposure assessment is required. Where potential safety concerns are identified, the subsequent steps of the framework provide methods that incorporate increasingly specific or refined data (and require more resources).

At step (tier) 1, dietary exposure can be assessed by using screening methods based on conservative assumptions. If the estimated dietary

exposure to a given chemical substance exceeds its health-based guidance value (e.g. ADI, provisional maximum tolerable daily intake [PMTDI] or, for nutrients, the upper level of intake [UL]; see FAO/WHO, 2006b), a more accurate method of dietary exposure assessment should be applied. A stepwise approach is being used by JECFA for additives (including flavourings), contaminants and nutrients.

In the sections that follow, examples of the available methods have been organized (somewhat arbitrarily) into categories to assist the reader in selecting the most appropriate framework and the desired methods for each step of the framework. The methods are divided into those that provide single (point) estimates and those that characterize the full distribution of consumer exposures.

Point estimates include 1) screening methods, 2) exposure methods that rely on crude estimates of consumption (default factors based on physiological limits, food production data or usage/poundage data), such as the theoretical added maximum daily intake (TAMDI) and other model diets (for veterinary drug residues and packaging materials), and 3) more refined exposure methods based on actual consumption data and chemical concentration data, such as TDSs, selective studies of individual foods and duplicate portion diets (see sections 6.3.4.1 and 6.3.4.2).

Characterizing the full distribution of consumer exposures is the most resource-intensive assessment, as data are required that characterize the range of food consumption practices as well as the range of chemical concentrations in the foods that are eaten. Therefore, such methods are usually reserved for later steps. When such methods are employed, appropriate statistical models are used to evaluate the data and to describe the range of consumer exposures and the associated probabilities of consumers having each level of exposure. These exposure assessments are generally referred to as probabilistic exposure estimates. Examples of probabilistic assessments are the Monte Carlo assessments that have been conducted to assess consumer exposure to acrylamide (FAO/WHO Acrylamide in Food Network: http://www.acrylamide-food.org). The possibility of using probabilistic modelling has also been discussed at meetings of JMPR and CCPR, and some preliminary investigations of its use at an international level have been undertaken.

6.3.4 Deterministic/point estimates of dietary exposure

A deterministic or point estimate of dietary exposure is simply a single value that describes some parameter of consumer exposure (e.g. the average exposure of a population). For example, an average dietary exposure is calculated as the product of the average consumption of the foods of interest and the average residues of the substance of interest in those foods. A point estimate of a high-consumer exposure (e.g. the upper 90th-percentile consumer) can also be calculated, provided the appropriate data are available.

A point estimate is not inherently "conservative" or "realistic". The conservatism incorporated into the analysis is determined by the data and assumptions that are used in calculating the estimate. Point estimates can range from initial screening methods that use very few data and generally include very conservative assumptions to refined exposure assessments that include extensive underlying data in order to realistically calculate the desired exposure estimates.

6.3.4.1 Screening methods

Screening methods should be designed to reflect the particulars of the exposures that are to be considered. The screening assessments currently performed by international organizations, such as those conducted by JECFA and JMPR, are different for food additives, pesticides and veterinary drugs.

The screening method that is selected should be easy to use and pragmatic. Screening methods should overestimate dietary exposure of high consumers using conservative assumptions in terms of food consumption and chemical concentration (e.g. budget methods). This will avoid situations where the dietary exposure estimated by the screening process would erroneously indicate no safety concern (i.e. understate exposure). However, in order to effectively screen chemical substances and establish risk assessment priorities, the first steps of the procedure should not consider unsustainable diets, or the results will be too unrealistic to be useful. At a minimum, physiological limits of consumption should be taken into account.

Although screening methods are sometimes criticized as being "too conservative", it must be borne in mind that their aim is not to

assess true dietary exposure but to identify food chemicals for which a more comprehensive dietary exposure assessment is necessary. This must be made clear when results are presented, as should all assumptions made. For example, the budget method (see below) was used to screen intakes of 58 additives in Europe. For 22 of the additives, the potential dietary exposure calculated with the budget method was lower than the relevant ADI (EC, 1998), whereas 36 of these additives did not "pass" the budget method. For the 36 that did not pass, it was recommended that more refined exposure assessments be conducted.

Different screening methods are described below, together with a critical analysis of the assumptions on which they are based and of their fitness for purpose. There is a need for harmonization, where possible, of these methods.

Screening methods can be created that are appropriate for a worst-case assessment of compounds that are toxic for both acute and chronic exposures, as well as for specific subpopulations of interest.

(a) Poundage data (food additives, including flavours)

Poundage data provide estimates of the amount of a chemical substance available per capita for use in food manufacturing in a country during a period of time, usually over 1 year. The estimated dietary exposure that is provided with such a calculation is based neither on observed consumption patterns nor on data on the actual concentration of the chemical substance in foods. These estimates may take into account the import or export of the chemical and of foods containing it. They may also include non-food uses. Surveys of poundage data are usually performed by producer associations that ask single producers to report their volumes of production. A very large year-to-year variability in poundage data may occur, especially for substances produced in low quantities. This limits the usefulness of poundage data surveyed on a single-year basis.

Exposure estimates based on poundage data may be adjusted by the proportion of the population likely to consume the food (per cent consumers) in which the chemical may be present, as well as for under-reporting of the amount of chemical produced. Nonetheless, there is a very large uncertainty in a mean dietary exposure derived from

poundage data, as typically no information is available that allows the user to identify the precise foods in which the substance is consumed, who is consuming the food or how much of the substance is discarded without being consumed. Poundage data and derivative methods do not adequately describe highly exposed consumers and are therefore not sufficient to determine if their dietary exposure is within health-based guidance values. Additional methods based on use level data should be used in the first step of the screening (e.g. budget method). Poundage data can be used to provide an indication of the historical and geographical trends in the use of a substance or as a comparative measure of overall population dietary exposure relative to other substances.

(b) Budget method

A screening method referred to as the "budget method" has been used to assess the theoretical maximum daily dietary exposure to some food additives. The results are compared with the ADI for the substance. The budget method has been used at an early stage in assessing additives by JECFA (FAO/WHO, 2001) and for assessments within the EU.

The method relies on assumptions regarding 1) the level of consumption of foods and of non-milk beverages, 2) the concentration of the additive in foods and in non-milk beverages and 3) the proportion of foods and of non-milk beverages that may contain it. More specifically, the levels of consumption of foods and beverages considered are maximum physiological levels of consumption—i.e. the daily consumption of 0.1 litre of non-milk beverages per kilogram of body weight and the daily consumption of 100 kcal/kg body weight from foods (equivalent to 0.05 kg/kg body weight based on an estimated energy density of 2 kcal/g) (Hansen, 1979). In a 60 kg person, these levels correspond to the daily consumption of 6 litres of non-milk beverages and 3 kg of food.

The levels contained in foods and beverages are assumed to be the highest maximum levels of the additive reported in any category for foods and for beverages, respectively. When the level of an additive is particularly high in a very specific category of food or beverage (e.g. chewing gum), the additive level considered is the highest maximum

level among the other categories that are more "representative", in order to provide somewhat more realistic estimates. The proportions of solid foods and beverages that may contain the substance are set arbitrarily. In the case of food additives, a default proportion that is often used for European assessments is 12.5% for solid foods and 25% for beverages (EC, 1998). For additives used in a wide range of foods, the proportion of solid foods may be set at 25%.

The overall theoretical maximum daily exposure to an additive is calculated by summing the potential exposure from beverages and from foods, as shown below:

Overall theoretical maximum daily exposure	=	[maximum level of the additive in beverages (mg/l) × 0.1 (litre/kg body weight) × percentage of beverages that may contain the substance] + [maximum level of the chemical in solid foods (mg/kg) × 0.05 (kg/kg body weight) × percentage of solid foods that may contain the substance]

The potential dietary exposure to the additive is expressed in milligrams per kilogram body weight per day.

For example, if an additive may be present at up to 350 mg/l in beverages and up to 1000 mg/kg in foods and if the proportions of beverages and foods that may contain it are assumed to be, respectively, 25% and 12.5%, the theoretical maximum daily exposure to this substance will be:

$$[350 \times 0.1 \times 0.25] + [1000 \times 0.05 \times 0.125] = 15 \text{ mg/kg body weight}$$

In a 60 kg person, this daily exposure corresponds to 900 mg of the food additive deriving from the consumption of 1.5 litres of beverages and 375 g of food containing the substance at the maximum level.

The budget method may need to be applied to different food consumption levels to provide similar levels of conservatism for adults and for children. For example, when the budget method was applied to consider exposures to food additives authorized for use in the EU (EC, 1998), a specific budget calculation was performed for children by setting the proportion of beverages that could contain the additives

at 100%. The level of consumption of beverages considered was therefore 0.1 litre/kg body weight (i.e. 1.5 litres in a typical 3-year-old child weighing 15 kg). This is a conservative assumption according to the results of a survey in the United Kingdom, which reported that the 97.5th percentile of consumption of beverages containing additives was 0.07–0.08 litre/kg body weight in children aged 1.5–4.5 years (Gregory et al., 1995).

The budget method has the advantage of requiring virtually no product-specific data and of being very simple and rapid to perform. A disadvantage of the budget method is that the results depend largely on the proportions of foods and beverages that are assumed to contain the substance, and typically those proportions are set arbitrarily. The usefulness of the method can be improved if the proportions are chosen with an understanding of the impact on the conservativeness of the method.

Another arbitrary assumption of the budget method is the identification of categories of foods and beverages with very high use levels that are considered not "representative", such as chewing gums. When such items are identified, assessment of the quantity of the specific food item that would lead to exposure in excess of the toxicity reference value should be performed in parallel with the budget method in order to determine if the consumption of the specific item can lead to exposure in excess of the health-based guidance value.

The assumptions of the budget method with respect to energy have been examined in a case-study of food additives, applying the assumptions used for EU assessments (Douglass et al., 1997). The assumptions for the energy density of foods were found to be only a slight overestimate, which would detract from the overall conservatism of the method. On the other hand, the assumptions regarding energy intake and beverage consumption were overestimates of even high levels of consumption. Overall, the exposure to additives estimated with the budget method was found to be higher than the survey-based 95th-percentile exposure to additives (Douglass et al., 1997).

In summary, the budget method is a simple, inexpensive and conservative screening method that can easily be applied to all chemicals intentionally added to food (additives, including flavourings,

processing aids, etc.) for comparison with their relevant toxicological reference values, provided the maximum concentrations of the chemical in foods and beverages can be ascertained.

(c) Model diets

Model diets are constructed from available information on food consumption and are designed to represent a typical diet for the population whose exposure is to be considered. A model diet can be constructed that reflects the diet of the general population or a specified subpopulation. For example, it may be of interest to evaluate the subgroup of the population that has the highest consumption of foods of interest or high consumption in relation to body weight.

Although model diets can be extremely useful, the models are only as good as the underlying data and assumptions, which should be stated for each model. Some examples of model diets that have been used to evaluate consumer exposure are summarized below.

TAMDI model diet for flavourings. The TAMDI model diet was designed to provide a conservative estimate of potential exposure to specific flavouring substances on the basis of allowed maximum (upper use) levels (UUL) in the different categories of foods and beverages that could be flavoured. The resulting exposure estimate is for a hypothetical consumer who consumes a fixed amount of flavoured foods and beverages every day, and those foods always contain the specific flavouring at its specified UUL (Cadby, 1996). The TAMDI is calculated by summing the exposures estimated for each individual food category (see Table 6.3).

The consumption levels considered are aimed at representing typical portions of flavoured foods and beverages (e.g. a glass of non-alcoholic beverage, a piece of bakery ware). The portion sizes are twice those that were used by CAC to estimate exposure to intense sweeteners in the absence of sufficient data relevant to the consumption of sugar-free products (FAO/WHO, 1989a).

The TAMDI was used by the European Scientific Committee on Food (SCF) to assess potential exposure to single flavourings (EC, 2003). A modified TAMDI, in which typical use levels have been used instead of UULs, has been applied in the evaluations of groups of

Table 6.3. Food consumption and concentration levels used in the TAMDI calculations[a]

Foods and beverages	Consumption (g/day)	Concentration (mg/g)
Beverages (not alcoholic)	324	UUL1
Foods	133	UUL2
Exceptions:		
- Candy, confectionery	27	UUL3
- Condiments, seasonings	20	UUL4
- Alcoholic beverages	20	UUL5
- Soups, savouries	20	UUL6
- Other exceptions (e.g. chewing gum)	2	UUL7

[a] TAMDI (mg/day) = (324 × UUL1) + (133 × UUL2) + (27 × UUL3) + (20 × UUL4) + (20 × UUL5) + (20 × UUL6) + (2 × UUL7).

chemically defined flavourings published by EFSA since 2004 (EFSA, 2004). The selection of a typical use level instead of a UUL, as a general principle in a screening process, may not be representative of the highest daily intakes, as consumers could be loyal to flavoured products containing a UUL.

The consumption levels considered in the TAMDI calculation may underestimate the average consumption of flavoured foods by some consumers. On the other hand, the assumption that all flavoured foods consumed each day will contain the same flavouring at its UUL is obviously conservative.

A major disadvantage of the TAMDI model is the arbitrary choice of food categories and portion size. The method cannot differentiate between different types of products that are grouped in the same category in Table 6.3. Also, the TAMDI model does not specify whether it is assessing the exposure at the upper 90th, 95th or some other percentile of exposure.

The advantages of TAMDI are that it is very easy to apply and that the hypotheses on which it is based are transparent in terms of consumption levels and concentrations. On the basis of some limited case-studies, the TAMDI appears to provide a conservative estimate

of high exposure to flavourings (Lambe et al., 2002). It can therefore be considered as a tool to prioritize dietary exposure assessments provided the underlying assumptions are clearly delineated. The TAMDI method may need to be supplemented with dietary exposure assessments targeted to high consumers of single categories of flavoured foods and beverages.

An alternative, less conservative, estimate for dietary exposures to flavouring agents was recently developed by JECFA (FAO/WHO, 2009a), using the single portion exposure technique (SPET). The use of the SPET estimate in the JECFA screening procedure for flavouring agents is further described in chapter 9.

Model diet for veterinary drug residues. A model diet intended to cover high consumers of animal products is used by JECFA to check that proposed MRLs for veterinary drug residues in foods of animal origin would not result in the ADI being exceeded. The model assumes that the amounts of foods are consumed daily by a person weighing 60 kg, and it is intended to cover the consumption of all processed foods with these foods as ingredients (Table 6.4). The consumption of meat and fish in 1 day is considered mutually exclusive. As the skin of pigs, poultry and certain fish species may be consumed, the residues in this associated tissue also have to be taken into account.

JECFA considered the consumption estimate for honey to be used in the model diet at its seventieth meeting (FAO, 2009; FAO/WHO, 2009b). It was noted that honey is widely used as a sweetener and glazing agent in confectionery products, breakfast cereal and baked goods, in addition to direct consumption of liquid and set honey, and that such uses must be taken into account for dietary exposure estimates. Based on limited data from two European countries, the Committee concluded that a consumption amount of 20 g per day was between the median and up to the 95th percentile of daily consumption for honey eaters. Based on the limited data, consumption of 50 g honey per person per day would be expected to cover all consumers of honey, but further data are necessary to determine the accuracy of this figure, in particular whether this figure would also cover consumption of products containing honey. In the case where residues are found in both honey and wax, this would need to be considered in dietary exposure estimates, where a ratio of honey to wax of 9:1 will be used.

Table 6.4. Model diet for exposure assessment of veterinary drug residues (FAO/WHO, 1989b, 1995c, 2009b)

Category of food of animal origin	Tissue or product	Consumption (g/day)	Remarks
Meat tissues (500 g in total)	Muscle	300	a) For definitions of meat and muscle, see chapter 8, section 8.4.1
	Liver	100	
	Kidney	50	b) For pigs and poultry, muscle may be replaced by fat and skin in natural proportions
	Fat	50	
Fish	Muscle	300	May be replaced by muscle and skin in natural proportions
Milk	Whole milk	1500	
Eggs	Egg content, excluding shell	100	
Honey		20	

JECFA has in the past calculated MRLs such that the dietary exposure estimated was lower than the relevant ADI, using the MRL as the point estimate of concentration for the exposure estimate. The MRL is a point concentration of the marker residue on the residue depletion curve describing the upper one-sided 95% confidence limit over the 95th percentile (see section 6.2.1.3 for derivation and food amounts from the model diet). Such a model clearly corresponds to a non-sustainable diet but was used to provide a conservative dietary exposure estimate, known as the theoretical maximum daily intake (TMDI).

For estimating chronic dietary exposures to veterinary drug residues, JECFA decided in 2006 to use the median of the residue distribution to substitute for the MRL in the dietary exposure estimate (FAO/WHO, 2006a). The new estimate of dietary exposure is called the estimated daily intake (EDI). In calculating the median from an array of results, results below the LOQ or LOD are assigned a value of half of the respective limit for the calculation of the median concentration of residues. Definitions of the foods in the model were also revised. The contribution to the EDI due to the consumption of the individual

tissues is calculated by multiplying the amount of tissue in the model diet by the median concentration of marker residue corresponding to the MRL of the tissue and by the ratio of the concentrations of the total residue of concern and the marker residue. The dietary exposure resulting from consuming 100 g (0.1 kg) of liver would, for example, be calculated as follows:

$$\text{Intake}_{\text{total residue from liver}} \text{ (mg/person per day)} = 0.1 \text{ (kg)} \times \text{median residue}_{\text{liver}} \text{ (mg/kg)} \times \text{ratio}_{\text{liver}}$$

The EDI itself is then the sum of the individual intakes resulting from similar calculations for all tissues.

Model diet for chemical substances migrating from packaging materials. Currently, the EU and the USA each have methods for assessing substances migrating from food packaging materials. The models are described below.

The *EU model diet* for chemical substances migrating from packaging materials is used to establish a maximum limit of migration, the so-called specific migration limit, or SML (Barlow, 1994; EC, 2002).

The maximum limit of migration is determined by assuming that a person weighing 60 kg could ingest daily up to 1 kg of foodstuffs in contact with a plastic article (600 cm^2 contact surface) that would always contain the substance under consideration at a concentration corresponding to the SML without exceeding the relevant health-based guidance value (i.e. TDI).

The assumption of repeated daily exposure to the same type of packaging material is conservative, but in some cases the other assumptions are not. For example, individuals may consume daily more than 1 kg of packaged food, especially if beverages are considered. Moreover, the default ratio of surface to mass (600 cm^2/1 kg) is that of a cube of 10 cm side width (total area 6 × 100 cm^2) containing 1 kg food; this ratio is low in comparison with that of foods in small packages (e.g. single portions, food in slices, some baby foods).

The *United States model diet* used to evaluate food contact substances assumes a consumption of 3 kg of packaged foods and beverages and employs consumption factors that describe the fraction of

the daily diet expected to be in contact with specific packaging material types (e.g. glass, plastic, paper) (http://www.cfsan.fda.gov/~lrd/foodadd.html). Migration levels are then assigned according to the nature of the food likely to be in contact with the packaging material (aqueous, acidic, alcoholic and fatty).

6.3.4.2 *More refined deterministic/point estimates*

Point estimate modelling may also be appropriate as a second step in a tiered approach. The model selected can be more or less conservative, depending upon the purpose and the available information.

As noted above, deterministic models use a single point estimate for each model parameter. For concentration data, the point estimate typically consists of the mean, the median, a high percentile of all observed values or even the ML proposed by national or international food authorities. Concentrations can be further modified using additional correction factors as appropriate (see section 6.2.1.2). For food consumption data, the point estimate typically consists of the mean or a high percentile of all the consumption values of a considered food in a population of interest.

This type of deterministic modelling has the advantage of being relatively simple to implement. Models can often be "developed" by using tools such as spreadsheet or database programs. However, because such models generally contain limited information, interpretation of the results can be problematic. The results are dependent on the input data and their appropriate treatment, but the impact may not be readily apparent (e.g. if the chosen input value used is not representative of the underlying distribution, then the result is likewise not representative). If "conservative" values (e.g. high concentration and high consumption values) are used in the model, the resulting exposure estimates will overstate typical exposures. For this reason, use of point estimate modelling with conservative parameter values may be appropriate for screening-level assessments. Nonetheless, it is important to keep in mind that it is difficult to know just how conservative the result will be.

When high-percentile values for either food consumption or food concentration levels are not known, there are default procedures that can be used to develop proxies for these points.

(a) Modelling high consumers

Model diets for high consumers can be developed on the basis of published data from food consumption surveys as an alternative to the budget method or as an additional step in the screening process. For example, a model diet has been used in Europe to estimate chronic dietary exposure based on the assumption that a person might consume average amounts of several different foods but only one or two at high levels (EC, 1998). The behaviour of such a consumer in the European model is determined by adding up potential dietary exposure to a food chemical at the 97.5th percentile of consumers of the two food categories that lead to the highest dietary exposure with the mean potential exposure for all other food categories (EFSA, 2008). The choice of the upper percentile of dietary exposure that represents a high consumer is, however, dependent on the purpose of the dietary exposure and the data available to the risk assessor and risk manager. The European high-consumer model has the advantage of being applicable to surveys for which only data on mean and high consumption of large food groups are available, without the need to have access to the raw data of individual dietary records. It can therefore be used on the basis of published data. This approach has usually been used by EFSA and more recently by JECFA for chronic dietary exposure assessments for additives where the food consumption data have been aggregated into fewer than 20 large food categories. The basic assumption of this model diet is considered valid if the number of food groups is limited.

Food consumption amounts and dietary exposures for high consumers can also be derived from distributional data. The percentile of distribution selected to represent a high consumer depends on the purpose of the dietary exposure assessment and the type of food consumption data available. For example, for chronic dietary exposure estimates based on 1 or 2 days of food consumption data per individual, the 90th percentile of dietary exposure for consumers (eaters) only is often used to represent a high consumer. Where more survey days of food consumption data are available such that average (mean) daily food consumption amounts over a period of time can be derived for each individual, the use of a higher percentile may be appropriate. For acute dietary exposure estimates for consumers of foods containing the food chemical, the 97.5th percentile is derived from multiple consumer days with no averaging across survey days for individuals (see section 6.2.2.3).

The derivation of high-percentile values needs to be undertaken with caution, first checking that there are a sufficient number of consumers of the foods containing the chemical to make the derivation valid. This can be a problem for infrequently consumed foods or where dietary exposure estimates for subpopulation groups are undertaken. In cases where the high-percentile value cannot be derived, food consumption data for the parent food group can be used instead of that for a single food, providing they are generally consumed in a similar way. For example, a 97.5th-percentile consumption of all root vegetables could be used for carrots in an acute dietary exposure assessment, if there were not enough carrot consumers. Alternatively, statistical methods can be used to construct a distribution curve from summary food consumption data (e.g. mean, standard deviation), from which a high percentile of food consumption can then be derived (Cullen & Frey, 1999).

Modelling dietary exposures for high consumers of a food chemical can be accomplished by conducting a full distributional analysis using Monte Carlo techniques (see section 6.3.5). Where adequate data are not available to conduct a distributional analysis, arbitrary factors may be incorporated in a point estimate to simulate the upper end of the distribution of food chemical exposure (e.g. by assuming that the distribution is lognormal, a factor of 2 or 3 might be applied to the mean to roughly estimate the dietary exposure of high consumers). Different assumptions may be appropriate when modelling acute and chronic dietary exposures, as the concentrations of the substances will not always be high.

(b) Regular consumers

The tendency of consumers to repeatedly purchase and consume the same food products, sometimes termed consumer loyalty, may need to be considered and a range of concentrations may need to be used to generate dietary exposure estimates to cover various scenarios of consumer behaviour. Thus, if a specific brand of processed food contains a high concentration of a substance, regular consumers of that brand would have higher dietary exposure to the substance than those consuming brands without, or with lower amounts of, the substance. Consideration of regular consumers may be relevant when assessing high chronic dietary exposure to food chemicals present in processed

foods, such as additives, including flavouring agents, processing aids or chemicals migrating from packaging (Arcella et al., 2003). The impact of regular consumption of a certain food is likely to be less important in the case of residues of pesticides or veterinary drugs, as there is frequent mixing of raw agricultural commodities before purchase by consumers. However, consumer behaviour in relation to food purchases may need to be taken into account in relation to the selection of organic versus non-organic foods or regional foods if pesticide and veterinary drug use varies. Consumer behaviour towards fortified and non-fortified foods may also need to be considered when assessing nutrient intakes.

6.3.4.3 *Further examples of point estimates using model diets*

Some examples of more refined point estimate models are summarized below.

(a) GEMS/Food consumption cluster diets

Data submitted on the priority contaminants/commodities in GEMS/Food (section 6.2.1.8) have been used to assess the potential risk to human health from such exposures (UNEP/FAO/WHO, 1988; WHO, 1989b; UNEP, 1992; Bhat & Moy, 1997; Schutz et al., 1998). In these assessments, the estimated dietary exposures determined for each country were compared, when possible, with relevant ADIs or provisional tolerable weekly intakes (PTWIs) established by JMPR and JECFA. GEMS/Food provides relevant information to JMPR, JECFA and CAC and its subsidiary bodies as appropriate.

The GEMS/Food consumption cluster diets are used as model diets by both JMPR and JECFA in chronic dietary exposure assessments (see section 6.2.2.5 for more detailed information on the diets; WHO, 1989a). Since 1996, following the recommendations of a Joint FAO/WHO Consultation held in York, England (FAO/WHO, 1995b), the dietary exposure estimates of pesticide residues undertaken by JMPR use STMR levels in the calculation of international estimated daily intakes (IEDIs). JMPR uses this procedure in a single-step approach, using the best available information, rather than the stepwise approach adopted for some other food chemicals. Whenever possible, residues are estimated for the edible portion. This may require the use of processing

factors and data on consumption of processed food. Although it is appropriate to correct for the edible portion if the commodity is always prepared in the same way, care should be taken with processes such as peeling, where it is often assumed that the commodity is always peeled before consumption, whereas in reality this is not true.

One of the principles for international exposure assessment is that the underlying data should be conservative. The GEMS/Food diets fulfil these requirements as long as a significant proportion of the commodities containing the food chemical is included in the diets. The FAO food balance sheet data, which form the basis of the consumption cluster diets, tend to overestimate mean food consumption for the population, as they report food available for consumption. However, because the calculation of per capita mean food consumption divides the amount of food available for consumption in a country or region by the whole population (consumers of foods and non-consumers), the consumption cluster diets tend to underestimate food consumption for consumers of specific foods. The consumption cluster diets were not intended to represent high consumers, although a correction factor can be applied to mean consumption amounts to approximate the high percentiles of dietary exposure (WHO, 1985).

(b) Total diet studies (TDSs)

TDSs are designed to assess chronic dietary exposure to food chemicals using the amounts of chemicals in food actually ingested by the population living in a country and, if possible, population subgroups (WHO, 1992). This is accomplished by measuring chemical concentrations in food "as consumed", including drinking-water. Although the traditional focus of TDSs has been on assessing dietary exposure to pesticide residues and contaminants, the advent of multielement analyses has seen TDSs increasingly include selected nutrients. TDSs have also been used for estimating dietary exposure to food additives. TDSs differ from other chemical surveillance or monitoring programmes because they aim to assess dietary exposure to food chemicals across the total diet in one study. If conducted on a regular basis, TDS results can provide a continuous means of checking the effectiveness of regulatory measures that have been established to control the levels of chemicals in the food supply, as well as monitor trends in dietary exposures.

The majority of TDSs worldwide use the point estimate (deterministic) approach to assess mean dietary exposure for a whole population. In some studies, high-consumer dietary exposures are estimated by applying specified factors to mean consumption data (WHO, 1985). Estimates for specific population subgroups (e.g. infants or young children) can also be determined if food consumption data are available. Some countries combine distribution of food consumption data at an individual level with one fixed value for the concentration of the chemical in the TDS foods or food groups (FSANZ, 2003; FSA, 2004; Leblanc et al., 2005). TDSs are not suitable for the assessment of acute dietary exposures because of the high degree of compositing of samples.

6.3.4.4 Specialized studies designed to answer specific questions

If necessary, studies may be designed to answer specific questions about consumer dietary exposure. The study may measure exposure directly or may provide additional information about one or more parameters of the exposure assessment algorithm. Examples of specialized studies are given below.

(a) Selective studies of individual foods

In some cases, surveys that encompass the whole diet, such as a TDS, may not be necessary. Surveys of specific foods are particularly useful if the dietary exposure to a chemical is predominantly influenced by one, two or a limited range of foods or when food surveillance or monitoring has already established average chemical concentrations in the foods (WHO, 1985). For example, mercury in fish and seafood, persistent organic pollutants (POPs) in fat-containing foods (van Zoonen in WHO, 2002a; Baars et al., 2004), mycotoxins (Leblanc et al., 2005), additives (Chen in WHO, 2002a; Yoon in WHO, 2005a) and veterinary drugs would all generally be best approached via a selected individual foods approach.

(b) Duplicate portion studies

Duplicate portion studies may also be used to assess dietary exposures for population subgroups, as they provide dietary exposure information at the individual level, based on the diet "as consumed". This can be especially useful for well-defined population subgroups, such

as vegetarians (MAFF, 2000; Clarke et al., 2003), children (Wilhelm et al., 2002; Murakami et al., 2003), breastfeeding mothers (Gulson et al., 2001), adult women (Tsuda et al., 1995) or people who consume catering establishment meals (Leblanc et al., 2000). However, such studies are very costly in terms of participant involvement and management and are used for small groups of people only (IPCS, 2000). Nonetheless, such a study can be very useful, in that it can provide an estimate of total dietary exposure that can be used as a benchmark for estimating the degree of overestimation or underestimation of exposure when assessments are conducted with more limited data. For example, in the early evaluations of dietary exposure to acrylamide, a TDS conducted by the Swiss government (Swiss Federal Office of Public Health, 2002) provided an estimate of total exposure that was used to assess whether the foods that had already been analysed were those that represented the most important sources of acrylamide or whether other significant sources remained to be identified.

6.3.5 Refined dietary exposure assessments (probabilistic distributional analyses)

If the existence of a safety concern cannot be ruled out on the basis of dietary exposure assessed at the initial steps, more accurate assessments of dietary exposure may be needed. It should be emphasized that the consumer exposures are not altered; rather, the accuracy with which those exposures are estimated is improved by using more refined methods. Probabilistic analysis gives more information on the variability in dietary exposure estimates across the population of interest for use by risk assessors and risk managers. It is noted that a probabilistic approach would not necessarily give a lower dietary exposure estimate than the deterministic approach.

Refinements could include more defined information about the foods that are consumed (less conservative assumptions about the amounts consumed, the concentrations of the chemical in the foods, impact of processing and food preparation, etc.), or more complex exposure assessment models can be employed that allow more realistic simulation of consumer practices.

Nonetheless, further steps to allow the refinement of the dietary exposure assessment should be designed in such a way that potential

high dietary exposures to a specific chemical are not underestimated. The methods should take into consideration non-average individuals, in particular those who consume large portions of specific food items or are loyal to those foods containing the highest concentration of the chemical of interest and those who have low or infrequent consumption of foods with very high concentrations of the chemical of concern.

For the models to be accurate, the food consumption data and food chemical concentration data should be for the same food products (see section 6.2.2.3). Good estimates are derived from good data, and a complex or complete model will not transform insufficient or deficient data into good data. Additional data may need to be collected to adequately represent the actual exposure situations.

6.3.5.1 *Overview of probabilistic estimates of exposure*

For substances requiring further refinement beyond screening methods or point estimates of exposure (as described above), a probabilistic analysis of exposure variability can be conducted. Conceptually, population exposure must be thought of as a range of values, rather than a single value, because individual members of the population experience different levels of exposure. Factors that contribute to this variability include age (due to differences in body weight and the type and amount of food consumed), sex, ethnicity, nationality and region, and personal preferences, among others. Variability in dietary exposure is often described using a frequency plot (see Figure 6.2). Sometimes, the frequency distribution is approximated as a continuous probability distribution (see Figure 6.3). In both cases, the horizontal axis corresponds to the level of exposure, and the vertical axis corresponds to the relative proportion of the population.

The variability distribution can be characterized by referring to representative members of the population. For example, the median individual has an exposure at the middle of the distribution (i.e. half of the population has exposures that are less than that of the median individual, whereas the other half has exposure levels exceeding that of the median individual). The 95th-percentile individual has an exposure that exceeds the levels experienced by 95% of the population. The average or mean exposure does not necessarily represent any particular individual. Instead, it is computed by summing the exposures of all individuals and dividing by the size of the population.

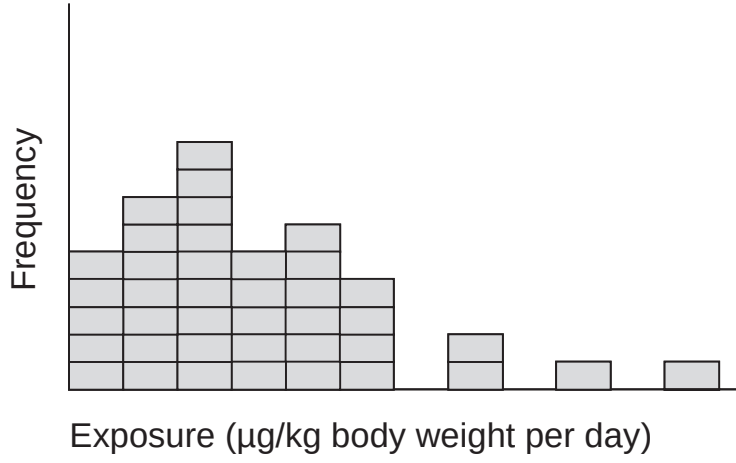

Fig. 6.2. Frequency distribution

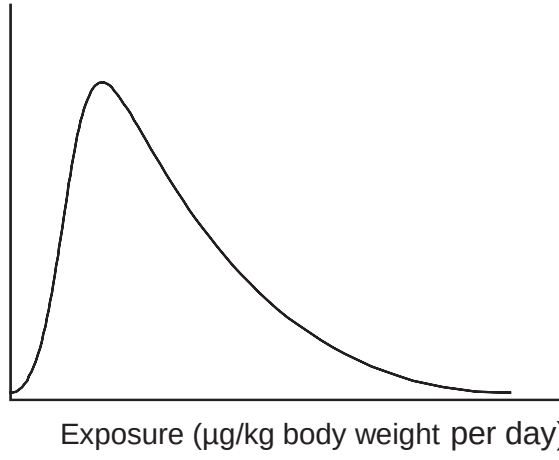

Fig. 6.3. Continuous probability distribution

Section 6.3.5.3 discusses some of the models that are available for conducting probabilistic assessments. Finally, in those cases warranting the greatest level of scrutiny, so-called two-stage simulation techniques can be used to characterize both uncertainty and variability (see chapter 7, section 7.2.2). In all instances, adequate data must be available to allow meaningful assessment.

6.3.5.2 *Probabilistic models*

The structure of a probabilistic model is similar to that of the deterministic models described previously in section 6.3.4, in that it is based on the same basic equations whereby food consumption data are combined with concentration data to estimate dietary exposure. The fundamental difference is that at least one variable is represented by a distribution function instead of a single value and the model sample from each distribution is a distribution of potential dietary exposures generated using several thousand iterations. As for point estimate models, it may be possible to further refine probabilistic models by taking account of factors such as edible portion, percentage crop treated or consumer behaviour, where appropriate to do so (see section 6.3.4.2). Simple probabilistic models may account for the food chemical in only a single food, but more complex models can include the possibility that a person may consume several foods containing the food chemical in a single meal or day. The following text is a discussion of approaches to developing probabilistic models for dietary exposure assessments.

(a) Simple empirical distribution estimate

Dietary exposure assessments can be based on a food consumption distribution determined empirically from a food consumption survey and a single point estimate to represent the chemical concentration in the relevant food product. Each point of the distribution curve of food consumption can be multiplied by the concentration in the relevant food commodity. Conversely, it is possible to have a single point estimate for consumption and an empirical distribution of chemical concentrations in that food.

(b) Developing probabilistic models from data sets

This approach requires data sets representing the distribution of concentrations in each relevant food category and also distributions of consumption for the same food categories for the population of interest. It explicitly takes into account the variability of input data, providing a more realistic result than that produced by simple deterministic or simple empirical distribution scenarios, which generally are constrained by conservative default assumptions when a single value is selected to represent the entire distribution.

There are two general approaches to developing distributions for use in a probabilistic assessment. Non-parametric techniques can be used when actual data sets are available for a parameter. In these cases, the data sets can be assumed to represent the distribution of interest. The probabilistic assessment is implemented by randomly selecting one of the values from the data set for each iteration of the simulation. For example, if a data set with 100 concentration measurements contains two observations of 5 mg/kg, then the probabilistic assessment will effectively assume that there is a 2% frequency of the concentration being equal to this value.

Parametric techniques interpolate among the data points and extrapolate beyond them by assuming a particular distributional form. For example, standard techniques can be used to fit a normal, lognormal or any other type of distribution to a data set. Although the extrapolation "fills in" gaps that may be particular to a specific data set, the elimination of these gaps comes at the cost of requiring an assumption to be made as to the functional form of the distribution. The assessor can evaluate the impact of the assumption by repeating the analysis assuming alternative (but plausible) functional forms.

Other methods, including iterative simulation methods, have been used in exposure assessment modelling but are beyond the scope of this chapter. In general, the primary differences in the techniques are the methods that are employed to draw values from the data and in the evaluation of uncertainty and variability. Simple risk assessment models of the multiplicative form may be appropriate for a variety of exposure assessments (Slob, 1994).

(c) Stratified sampling

A stratified sampling method is a way of selecting data to ensure that the probabilistic model selects values at regular intervals throughout each distribution of the food consumption and concentration data. For example, the mean or median of each quartile of each distribution may be determined. The primary disadvantage of the single-stratum calculation is that it produces no estimates for extreme values. This problem may be ameliorated, but never entirely overcome, by using more strata (e.g. estimating the mean of each decile instead of estimating a value for each quartile). Detailed, accurate and reproducible characterizations of the output distributions may be obtained by using many strata. The difficulty with stratified sampling is that the number

of iterations required may become very large and may require additional computer software or computer expertise.

(d) Random sampling (Monte Carlo simulation)

Monte Carlo simulation involves the use of random numbers to select values from the input distributions. The technique has been applied to a wide variety of modelling scenarios. As a result, it can be concluded that when conducted appropriately (e.g. with appropriate data and when the simulation is conducted with a sufficiently large number of "iterations"), the results will simulate the actual situation, because the technique utilizes values throughout the range of each input distribution. Because the sampling is random, there is the possibility that the Monte Carlo simulation will be inaccurate at the extreme (upper, lower) ends of a distribution, which is particularly true if using parametric distribution rather than non-parametric (empirical) distribution data. In such a case, when using a parametric approach for contamination data, a cut-off limit in the distribution tail in regard to a "realistic" maximum observed value in selected foods may be introduced to avoid taking "unrealistic" contamination events that would never occur in real life into account in the model.

(e) Latin hypercube

Latin hypercube is a statistical method that is essentially a hybrid of the stratified and random sampling methods. Distributions are divided into strata, and then random samples are drawn from each stratum in order to ensure that the iterations are balanced throughout the range of each concentration and food consumption data distribution. This method also allows for some samples to be drawn at the extremes of the distributions.

6.3.5.3 Applicability of a probabilistic approach at the international level

Probabilistic models are increasingly being considered at national and international levels. For example, the United States Environmental Protection Agency uses this approach for acute dietary exposure estimates for pesticide residues (USEPA, 1998, 2000a). In Europe, there have been projects that outline potential models (EU Monte Carlo project, http://montecarlo.tchpc.tcd.ie/, and the data sets available for use in the models; SAFE FOODS, http://www.safefoods.nl/default.aspx).

At an international level, time and resources should be dedicated to the application of probabilistic methodology only when there is a dietary exposure concern that cannot be refined using simpler and less resource-intensive methods. Where this is the situation, it may be useful to evaluate probabilistic exposure estimates derived for a representative selection of national populations to arrive at an understanding of the international situation.

It may be more feasible in many cases to refine the point estimate of dietary exposure than to use a probabilistic method as described in section 6.3.4.2. For example, for contaminants and pesticide and veterinary drug residues, the dietary exposure assessment may be refined by incorporating processing factors that adjust the initial concentration data to reflect the impact of processing (rice → polished rice; fruit → peeled fruit; potato → cooked potato). Likewise, the consumption data can be refined to provide estimates of dietary exposure of different forms of the food (raw, processed).

6.3.6 Specific considerations for modelling approaches for acute and chronic dietary exposure assessments

Different methods for conducting dietary exposure assessments may need to be selected based on the length of exposure times required to elicit the toxic or beneficial effects. Two time frames—chronic (long-term) and acute (a single meal or over a whole day)—have been considered for some assessments at the international level and by some national governments. These time frames are discussed below; however, it should be noted that these are arbitrary, and other lengths of time may be more appropriate for some chemical substances. Different assumptions will be appropriate when modelling acute and chronic exposures.

6.3.6.1 *Chronic dietary exposure assessments*

Typically, toxicological studies carried out to examine the adverse health effects resulting from consumption of a chemical substance in the diet are completed over a long period of time (e.g. several months or a substantial portion of the lifespan of test animals). Adverse effects generally arise at lower dose levels following long-term exposure to the substance being studied. Exposure assessments conducted to be comparable have been termed chronic dietary exposure assessments.

Typically, a mean dietary exposure will be compared with a chronic (long-term) health-based guidance value (e.g. ADI, PTWI). The mean dietary exposure may be calculated by applying a deterministic model using average food consumption levels and the average concentrations in the relevant food products. Where desired, it is possible to also conduct this assessment using parameters that will compute the dietary exposure of consumers with high exposure. Where data are not available, as a rough approximation, exposures of individuals with high consumption can be estimated by using a fixed factor of multiplication to simulate an upper percentile.

For a chemical with long-term effects, the mean chemical concentration is typically used, assuming that this value represents the long-term average of truly encountered concentrations. In some cases, the median concentration may be selected (see section 6.2.1.4). This value (mean or median) is combined with high percentiles or with the full distribution of food consumption. In the case of a non-staple food (i.e. a food not typically consumed every day by most consumers), high-percentile estimates assessed for the whole population may be low owing to the fact that a large number of non-consumers are included. In this case, high-percentile estimates should be assessed in consumers only rather than in the whole population, in order to avoid underestimation of high levels of exposure. However, one must bear in mind that high levels of exposure assessed on the basis of a short-duration survey in consumers provide an overestimate of high levels of exposure over the long term (IEFS, 1998; Tran et al., 2004; see section 6.2.2.4 for details on how statistical adjustments can be made to correct the food consumption data for "usual" consumption patterns).

If this first point estimate for dietary exposure is below the health-based guidance value, further refinement steps are not necessary, and the chemical is unlikely to be of safety concern. However, when the initial screening results in an estimate of dietary exposure close to or above the health-based guidance value, a more accurate assessment will usually be necessary.

6.3.6.2 *Acute dietary exposure assessments*

In the early 1990s, it became apparent that, in some cases, residues of a chemical substance could pose risks due to a single or at most a few days of exposure.

Two developments focused attention on acute dietary exposure assessments. First, as chronic dietary exposure methodology has improved, there has been a move away from "worst-case" estimates of chronic dietary exposures. Whereas in the past there were always large conservative assumptions to account for lack of data, now, with more data available, the chronic dietary exposure assessments are more realistic. This has directed more attention to a greater need for an explicit consideration of acute dietary exposure. Secondly, research on residues of acutely toxic pesticides (organophosphates and carbamates) in individual fruits and vegetables revealed random occurrences of comparatively high residue levels. Some individuals who consume significant amounts of such foods will occasionally eat the "hot" commodity unit. Acute dietary exposure assessments may be deterministic (point values) or distributional (probabilistic or stochastic). At an international level, a deterministic methodology was developed to address the calculation of the acute dietary exposure (Hamilton & Crossley, 2004).

(a) Pesticide residues

The FAO/WHO Consultation held in Geneva in 1997 (FAO/WHO, 1997) recommended a procedure for performing acute dietary exposure assessment for compounds for which an acute reference dose (ARfD) was established (see chapter 4, section 4.4). This was followed by the International York Consultation (MAFF, 1999) and the ad hoc Expert Meeting held before the 1999 CCPR session (see Annex V of FAO/WHO, 1999b) that further developed the method. Although it was recognized that probabilistic modelling would provide the most refined estimate, it was also recognized that this would be difficult at the international level, and a simpler method was developed. At its 1999 meeting (FAO/WHO, 1999b), JMPR performed acute dietary exposure assessments for the first time, by calculating IESTI. For compounds with low acute toxicity, JMPR concluded that "an ARfD is unnecessary" and that assessing the acute exposure is irrelevant. In the IESTI method, the estimates are performed for each crop separately, as it is considered that it would be unlikely that an individual will consume, within a meal or 24 h, two different commodities of LP weights that contain the same pesticide at the highest residue level. This methodology has been further refined by subsequent JMPR meetings, and the equations used by JMPR are shown in appendix 6.1. Figure 6.4 shows the decision tree for acute dietary exposure assessment, which could be applied to any food chemical with an ARfD.

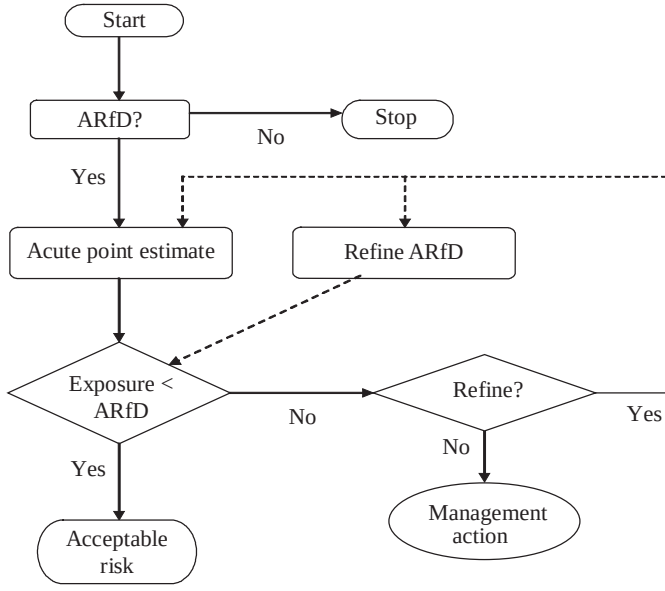

Fig. 6.4. Decision tree for acute dietary exposure assessment

(b) Veterinary drug residues

For veterinary drug residues, some of which may also represent an acute hazard, the manner in which MRLs are established ensures that the ADI (which may be based on an acute effect if it is produced at lower doses than are chronic effects) in general is not exceeded. Substances with acute pharmacological or toxicological properties are of concern and include classes such as beta-blockers, beta-agonists, anaesthetics, tranquillizers, vasodilators and compounds that may trigger acute hypersensitivity reactions (e.g. penicillins).

There is also a potential concern that even though the model diet used by JECFA (see section 6.3.4.1) is considered to be rather conservative and would therefore be sufficient to use for an acute dietary exposure, in some cases it may not be adequate. For example, when these daily food consumption amounts were compared with the values that JMPR uses in its acute dietary exposure assessments, based on the highest available 97.5th percentile of consumption from six countries (WHO, 2004), it was found that in some cases the food consump-

tion amounts in the model diet were lower than the 97.5th percentile amount, and hence use of the diet may in fact underestimate the acute dietary exposure for that food. In cases where an ARfD for a veterinary drug residue has been set, specific exposure scenarios are used instead of the model diet (e.g. for assessment of injection site residues).

Although the procedures for establishing MRLs appear to deal adequately with drug residues of the acutely toxic compounds in the principal edible tissues noted previously (see section 6.3.4.1), JECFA and CCRVDF are developing guidelines for injection site residues. These residues pose the potential problem of exceeding the health-based guidance value even when residues in other tissues are at or below their MRLs.

(c) Contaminants and food additives, including flavourings

For contaminants, when the toxicological evaluation indicates a need for an acute dietary exposure assessment, the case 1 IESTI calculation can be used (see appendix 6.1 for details of the calculation), with the GEMS/Food value for the highest reported 97.5th percentile of consumption (WHO, 2004).

For most food additives and flavourings, no acute toxicity occurs at the doses used as the basis for deriving health-based guidance values for the potential levels of human exposure, and therefore no acute dietary exposure assessments are needed. Occasionally, acute intolerance reactions may be relevant, such as laxation from polyol sweeteners. For some chemicals, allergic reactions may sometimes be of concern, but there are currently no clear health-based guidance values for allergic reactions to use in evaluating the significance of acute exposures. Research is under way to allow the identification of thresholds for allergenicity of a variety of food allergens.

6.3.7 Aggregate/cumulative exposures

Historically, the safety of food additives and residues of pesticides and veterinary drugs and the risk of chemical contaminants have been evaluated on the basis of single-chemical and single-exposure pathway scenarios. That is, risk assessors generally performed risk assessments and risk managers developed management options by examining each chemical exposure scenario separately. In general,

exposures to a chemical through the food, drinking-water and residential/occupational pathways were each assessed independently, and no concerted effort was made to evaluate potential exposures through multiple pathways simultaneously. This problem is often exacerbated because the responsibility for these different routes of exposure resides in different parts of national governments and international organizations.

Although different chemicals may act by the same mechanism and produce the same effect (e.g. organophosphate pesticides and acetylcholinesterase [AChE] inhibition), in the past, consideration was seldom given to the fact that exposure to multiple chemicals could occur and that the toxicological effects might be additive or synergistic (see sections 4.13 and 7.3 in chapters 4 and 7, respectively). For example, although two pesticides might act by a common mechanism of toxicity (e.g. AChE inhibition) and exposure on any given day might result in additive effects, standard or traditional exposure assessment methodologies did not consider this potential.

This concern was recognized in 1993 in a report issued by the United States National Research Council entitled *Pesticides in the Diets of Infants and Children* (USNRC, 1993). Subsequently, similar reports were issued by the United Kingdom Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (FSA, 2002), the Health Council of the Netherlands (2004), Boon et al. (2004) and EFSA (2007). These reports made several recommendations on how to improve the assessment of health risks posed by pesticides in the diets of infants and children. One recommendation was that consideration be given to all sources of dietary and non-dietary exposures to pesticides. Consideration of combined exposures to a single chemical across multiple routes (oral, dermal, inhalation) and across multiple pathways (food, drinking-water, residential) is known as *aggregate exposure*. The reports also recommended that consideration be given to the assessment of risks from exposure to multiple pesticide residues that have a common mechanism of toxicity. This consideration of combined exposures associated with multiple chemicals that act by a common mechanism is termed *cumulative exposure*.

This issue of aggregate and cumulative risk assessments was also recognized and discussed during an FAO/WHO Consultation held in

Table 6.5. Scenarios and the range of exposure assessments[a]

Toxic concern	Exposure route	Assessment type
Single chemical	Single food	Dietary assessment
	Multiple foods	Aggregate dietary assessment
	Multiple media	Aggregate assessment
Multiple chemicals with the same mechanism of action	Single food	Dietary assessment
	Multiple foods	Cumulative dietary assessment
	Multiple media	Cumulative assessment

[a] Table modified from that appearing in the original report (FAO/WHO, 1997) to clarify naming conventions.

Geneva during 1997 (FAO/WHO, 1997). Specifically, the Consultation noted that exposures to food chemicals through other routes may occur and that exposures to chemicals or drugs sharing the same mechanism of action (toxicity) may also be encountered. These scenarios and the range of exposure assessments that can be developed, as summarized at the meeting, are shown in Table 6.5.

The method for estimating cumulative dietary exposure to chemical substances with a common mechanism of toxicity could be considered at the international level regardless of the development of probabilistic methods. One of the approaches in cumulative risk assessment for specific chemicals is to use a toxic equivalency factor (TEF). These factors, representing the toxicities of individual substances relative to an "index compound", are applied to the concentration data of each substance within a group with a common mechanism and a total exposure is calculated, expressed in terms of the index compound. This approach was used by JMPR for dithiocarbamates (FAO/WHO, 1999a) and by JECFA (WHO, 2002d) for chlorinated dibenzo-*p*-dioxin congeners. Different compounds have been used as the index compound for the AChE insecticides, including chlorpyriphos, methamidophos and acephate. The choice of the index compound, however, is not trivial and will greatly depend on the toxicity database available and the toxicological end-point used. Ideally, data on the concentrations of substances in food should be collected in a manner that determines the co-occurrence of residues, but such data may not always be available at the international level.

Guidance for estimating aggregate exposure and for performing cumulative risk assessments has been issued by IPCS (2009), EFSA (2007) and USEPA (2001, 2002).

6.3.8 Biomarkers of exposure

Biomarkers include a broad class of biological changes to the body that are measurable, subclinical and reversible (Grandjean, 1995). These terms are further described by USNRC (1987) and include biomarkers of exposure—i.e. "agents or their metabolites either in tissues, secreta, excreta, expired air or any combination of these" (Berlin et al., 1984) that can be independently used to quantify overall exposure to a substance. Examples of biomarkers of exposure include the concentration of lead in blood (µg/dl blood), the concentration of mercury in either blood (µg/l blood) or hair (µg/g hair) and the concentrations of pesticides or their metabolites in serum, fat, urine, blood or breast milk (Anwar, 1997; USCDC, 2003, 2004).

Biomarkers of exposure do not depend on food consumption and substance concentration data; because they are "downstream" from consumption and hence causally closer to the health effects of interest, they represent a measure of exposure that is potentially more appealing than conventional measures of exposure expressed as estimated dietary exposures or intakes. Perhaps the greatest challenge associated with the use of biomarkers of exposure is interpreting their public health significance and particularly their quantitative relationship to adverse health effects, because data on the same biomarker are rarely available for both toxicity studies and exposure estimations. Biomarkers can be used effectively to evaluate whether a control measure has successfully altered the level of exposure in a population (Schulte & Waters, 1999) or to compare one consumer group with another non-exposed subpopulation. On the other hand, it is often difficult to characterize the relationship between biomarker levels and health risk.

A second challenge associated with the use of biomarkers relates to source attribution. Because biomarkers are integrative measures of exposure, they do not distinguish between alternative sources of exposure (Aitio & Kallio, 1999). For example, exposure to polycyclic aromatic hydrocarbons (PAHs) not only is via the diet but also can result from smoking (or being in the vicinity of smokers), coal tar

treatments and occupational activities (e.g. road paving and work near coke ovens) (Strickland et al., 1996). Even among individuals with no apparent notable exposure to PAHs, PAH metabolites have been detected in urine, albeit at low levels (Strickland et al., 1996).

Relating changes in biomarker levels to changes in exposure is further complicated by analytical considerations (Aitio & Kallio, 1999). With measurement of the parent compound (e.g. benzene or lead in blood, mercury in hair or blood), specificity is precise. However, whereas some metabolic products are relatively specific (e.g. methylhippuric acids in the case of exposure to xylene, or mandelic acid in the case of exposure to styrene or ethylbenzene) (Aitio & Kallio, 1999), in other cases specificity is limited. For example, phenol or hippuric acid concentrations in urine can be used as indicators of exposure to benzene or toluene, respectively, but these metabolites may also be generated by exposure to other parent compounds (Aitio & Kallio, 1999).

Differences in biomarker persistence pose an additional challenge to their use. Although some biomarkers (e.g. bone lead concentrations) have a half-life of many years, others, such as the concentration of contaminants in blood, typically have much shorter half-lives. For example, the half-life of mercury in blood is approximately 60 days (Aitio & Kallio, 1999). In these cases, representative measurements of exposure depend on more frequent monitoring. In some extreme examples, such as urinary iodine, the half-life is in the order of hours (Wild et al., 2001). In these cases, characterizing exposure for an individual would require multiple measurements in a single day. Measurement results for a group of individuals (taken at different times of the day) might be interpreted as representing the distribution of biomarker levels for the population, even though such measurements are not adequate for the purpose of characterizing individual levels of exposure.

Finally, even if a biomarker with a long half-life is available, it is not always the case that it is the most relevant measure of exposure for the purpose of risk assessment. Exposure measured as the product of the average rate of exposure and time is thought to be the most relevant measure of exposure in some cases. The assumption that toxicity depends on this exposure measure is known as Haber's Law

(Weller et al., 1999). On the other hand, some acutely toxic effects may instead depend on the magnitude and frequency of peak exposure levels (Lauwerys et al., 1995). In this case, levels of biomarkers with long half-lives may offer a misleading characterization of risk.

Human milk is a unique biological matrix for monitoring certain environmental contaminants, because it can provide exposure information about both the mother and the breastfed infant through a non-invasive method of collection. For some chemicals, levels in milk can provide an integrated assessment of exposure from multiple foods and multiple media. Although human milk is the natural food for infants, with the optimal composition to meet their nutritional needs in early life and providing associated immunological, psychological and economic advantages (WHO, 2002c), it has been unintentionally compromised by chemicals from our environment. Nevertheless, the mere presence of an environmental chemical in human milk does not necessarily indicate a health risk for breastfed infants.

POPs in human milk are good examples of exposure biomarkers, as POPs are known to accumulate in the food-chain. Consequently, human milk monitoring can yield information about the kinds and quantities of POPs in the environment as well as in our bodies. Better understanding of our exposure to harmful environmental chemicals will help us to better manage them by eliminating or reducing their emissions or by limiting their presence in the food supply.

Over the past several decades, GEMS/Food, whose interest is in international studies on levels of contaminants in food, has collected information on the levels and time trends of many POPs in food, including human milk (e.g. WHO, 1989b, 1996; Van Leeuwen & Malisch, 2002). Results have shown a variety of contamination profiles, indicating different sources of exposure. Consistent with dietary exposure assessments submitted to GEMS/Food prior to 1992 and risk assessments of certain organochlorine compounds in human milk performed in 1998, basic monitoring and assessment programmes in all countries for organochlorine compounds in food and human tissues are essential in order to appropriately protect public health from these risks.

In summary, the use of biomarkers of exposure offers some advantages over conventional estimates of exposure measured in terms of

food consumption and food concentration. Biomarkers integrate exposure over time from multiple sources. Moreover, they can be measured directly and hence do not rely on mathematical models developed using multiple assumptions, with their attendant uncertainties, to estimate exposure. In a causal sense, they are also "closer" to adverse health effects of interest than are other types of exposure estimates. On the other hand, their interpretation is complicated by the fact that data on toxicity end-points related to different levels of the biomarker are generally unavailable. In addition, because of their integrative nature, it can be difficult to attribute changes in biomarker levels to a particular exposure source, or in some cases even to a particular substance. Finally, the use of biomarkers can be complicated if their half-life is short.

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Appendix 6.1: Acute dietary exposure estimates currently used by JMPR

Since its introduction in 1997, the methodology for estimating the acute dietary exposure to pesticide residues has been refined by JMPR (FAO/WHO, 2002, 2004a,b). The calculated exposure is called the international estimated short-term intake (IESTI) or national estimated short-term intake (NESTI).

Calculations of the acute dietary exposure 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 (LP) size, respectively. Case 3 allows for the likely bulking and blending of processed commodities such as flour, vegetable oils and fruit juices.

The concept of a variability factor (v) was introduced by JMPR to take into account the different concentrations of residues in individual units of a composite sample. JMPR concluded in 2004 that owing to the inevitable random nature of the variability factor derived from the combined uncertainty associated with sampling and analysis, the best estimate of the default variability factor is the mean of the variability factors derived from samples of various crops. The mean variability factor was found to be 3 (FAO/WHO, 2004b) and has been used as a default value by JMPR since 2003. It is important to note that the variability factor as described here can be applied only for samples coming from single lots. Analysts conducting acute exposure assessments for pesticides may want to select an appropriate variability factor for the specific evaluation.

The following definitions apply to all equations:

- LP — Highest large portion reported (97.5th percentile of eaters), kg of food per 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 that 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.

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). Case 1 also applies to meat, liver, kidney, edible offal and eggs, and for grains, oilseed and pulse commodities when the estimates were based on post-harvest use of the pesticide.

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

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 × *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 × *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. Case 3 also applies to milk and to grains, oilseeds and pulses for which the estimates were based on preharvest use of the pesticide.

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

The concept of variability factor was introduced to take into account the different concentrations of residues in individual portions of a composite sample and average residue concentration in the sample lot represented by the composite sample. The variability factor (*v*) was defined as the 97.5th percentile of the residue concentrations

presented in crop units divided by the mean residue concentration of the sample population. The default variability factors of 5 and 10 were replaced by a common default of 3 (FAO/WHO, 2004b).

In this methodology, the estimates are performed for each crop individually, as it is unlikely that an individual will consume, within a meal or 24 h, a large portion of more than one food containing the highest residue level (the one that incorporates the variability factor).

The LP (highest large portion reported [97.5th percentile of eaters], kg of food per day) should be matched to the Codex commodity to which the HR or STMR relates. In the case of commodities that are predominantly eaten as the fresh fruit or vegetable, the LP should relate to the raw agricultural commodity. However, when major portions of the commodity are eaten in a processed way (e.g. grains) and when information on the residue in the processed commodity is available, the LP should relate to the processed commodity (e.g. flour or bread).