Chapter 6

Dietary exposure assessment for chemicals in food

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6. DIETARY EXPOSURE ASSESSMENT FOR CHEMICALS IN FOOD

This chapter updates Chapter 6 of Environmental Health Criteria 240 (EHC 240), which was originally published in 2009, and includes advances in dietary exposure assessment methods, new information on publicly available data sources and links to web-based tools for use in dietary exposure assessments. It was developed through a consultation process culminating in a Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO) expert workshop held in September 2019 and a process of public consultation on the final draft from that workshop.

For abbreviations used in the text, the reader may refer to the list of abbreviations at the front of this chapter. Definitions of select terms may be found in the glossary in Annex 1 of EHC 240 (http://www.inchem.org/documents/ehc/ehc/ehc240_annex1.pdf).

List of abbreviations

ADI	acceptable daily intake
AI	adequate intake
ALARA	as low as reasonably achievable
APET	added portion exposure technique
ARfD	acute reference dose
BMD	benchmark dose
BMDL	lower confidence limit of the benchmark dose
CARES NG	Cumulative and Aggregate Risk Evaluation System Next Generation
CIFOCOss	Chronic Individual Food Consumption database – summary statistics (FAO/WHO)
DIFe	German Institute of Human Nutrition
doi	digital object identifier
EAR	estimated average requirement
EDI	estimated daily intake
EFSA	European Food Safety Authority
EHC 240	Environmental Health Criteria 240
EU	European Union
EU Menu	What's on the Menu in Europe? (EFSA)
EuroMix	European Test and Risk Assessment Strategies for Mixtures
FACE	Feed Additive Consumer Exposure
FAIM	Food Additive Intake Model
FAO	Food and Agriculture Organization of the United Nations
FEIM	Food Enzyme Intake Model
FEMA	Flavor and Extract Manufacturers Association of the United States
FFQ	food frequency questionnaire
FSANZ	Food Standards Australia New Zealand
GEADE	global estimate of acute dietary exposure
GECDE	global estimate of chronic dietary exposure
GEMS/Food	Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme
GIFT	Global Individual Food consumption data Tool (FAO/WHO)
GMO	genetically modified organism
GRAS	generally recognized as safe
HBGV	health-based guidance value

IEDI	international estimated dietary intake
IESTI	international estimated short-term intake
INFOODS	FAO International Network of Food Data Systems
IPCS	International Programme on Chemical Safety (WHO)
ISU	Iowa State University (USA)
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LNN	logistic-normal-normal
LOAEL	lowest-observed-adverse-effect level
LOD	limit of detection
LOQ	limit of quantification
LOR	limit of reporting
MCRA	Monte Carlo Risk Assessment
ML	maximum level
MOE	margin of exposure
MRL	maximum residue limit
MSDI	maximum survey-derived intake
MSM	multiple source method
NCI	National Cancer Institute (USA)
NEDI	national estimated dietary intake
NESTI	national estimated short-term intake
NOAEL	no-observed-adverse-effect level
OECD	Organisation for Economic Co-operation and Development
PAH	polycyclic aromatic hydrocarbon
PCB	polychlorinated biphenyl
PCDD	polychlorinated dibenzodioxin
PCDF	polychlorinated dibenzofuran
PTMI	provisional tolerable monthly intake
PTWI	provisional tolerable weekly intake
RACE	Rapid Assessment of Contaminant Exposure
RIVM	National Institute for Public Health and the Environment (the Netherlands)
RPF	relative potency factor
SPADE	Statistical Program to Assess Dietary Exposure
SPET	single-portion exposure technique
STMR	supervised trials median residue
TDI	tolerable daily intake
TEF	toxic equivalency factor
TMDI	theoretical maximum daily intake

TTC   threshold of toxicological concern
UL   upper level of intake
USA   United States of America
USDA   United States Department of Agriculture
USEPA   United States Environmental Protection Agency
USFDA   United States Food and Drug Administration
WHO   World Health Organization

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6.1 Introduction

The Codex Alimentarius Commission's Procedural Manual (FAO/WHO, 2019a) 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."[1] This chapter deals with the assessment of dietary exposure of humans to chemicals present in food (i.e. food additives, contaminants, nutrients, pesticide residues and residues of veterinary drugs). The general principles and approaches described here are applicable to dietary exposure estimates for use in risk assessments for all types of food chemicals and novel foods, which may include genetically modified organisms (GMOs), and biological agents in food, although the latter use is not explicitly addressed in this chapter.[2]

6.1.1 Role of dietary exposure assessment in risk assessment

Dietary exposure assessments are an essential element of the four-step risk assessment process for chemicals in food followed by the Codex Alimentarius Commission, joint FAO/WHO committees such as the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the Joint FAO/WHO Meeting on Pesticide Residues (JMPR), and other food regulatory or food safety agencies. The outcomes from the hazard identification and hazard characterization

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[1] The definition of food varies from country to country and for dietary exposure purposes includes beverages and drinking-water. Codex defines food as "any substance, whether processed, semi-processed or raw, which is intended for human consumption, and includes drink, chewing gum and any substance which has been used in the manufacture, preparation or treatment of 'food' but does not include cosmetics or tobacco or substances used only as drug" (FAO/WHO, 2019a). Food chemicals present in dietary supplements may be included in dietary exposure estimates, but they may not be included in the definition of food, as jurisdictions regulate dietary supplements differently.

[2] "Food additives" includes flavouring agents and processing aids, including enzyme preparations. "Contaminants" includes natural toxins. Chemicals migrating from packaging may be regulated as contaminants or indirect food additives. "Novel foods" includes novel foods – for example, single modified sugars or fats that may be foods in their own right – and novel food ingredients.

steps of the risk assessment (steps 1 and 2) drive the dietary exposure assessment (step 3), including the selection of appropriate sources of data on food consumption and on concentrations of the chemical of interest in food and the method of combining the two data sets.[3]

The general equation to calculate dietary exposure to a food chemical for a population of interest combines summary or individual food consumption data for that population with data on the concentration of the chemical in food:

Dietary exposure = Σ (Concentration of chemical in food × Food consumption)

The resulting dietary exposure estimate for a population may be compared with the relevant health-based guidance value or a cancer potency factor for the food chemical of concern, as part of step 4 of the risk assessment process, risk characterization (see Chapters 4, 5 and 7 for details of the hazard identification, hazard characterization and risk characterization steps).

The health-based guidance value may relate to an acute or chronic toxicological end-point. For acute dietary exposure calculations, the above equation may apply to a single food; for chronic dietary exposure calculations, the above equation may apply to a single food, but is more commonly applied over all foods.

Where the comparison is with a health-based guidance value, which is expressed per kilogram of body weight, the estimated dietary exposure is adjusted for body weight for ease of comparison:

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

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[3] The use of standard terminology is recommended to ensure consistent application and understanding. The term "consumption" should 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" may be used synonymously with the term "dietary intake" in some circumstances, depending upon existing regulatory frameworks; for example, "dietary intake" is commonly used for nutrients.

If a health-based guidance value has not been established (e.g. where no threshold for the critical effect can be established), and where a dose–response modelling approach has been employed, the chronic dietary exposure estimate may be compared with a benchmark dose (BMD[4]) to determine the margin of exposure for a given population (refer to Chapter 5 for toxicological aspects of health-based guidance values and BMD modelling and Chapter 7 for comparison of health-based guidance values with estimates of dietary exposure in risk characterization).

The threshold of toxicological concern (TTC) approach also uses a chronic dietary exposure estimate to determine whether the threshold exposure for the relevant Cramer class for the chemical of interest is likely to be exceeded (see Chapter 9 for information on the TTC approach; Cramer, Ford & Hall, 1978; EFSA, 2012a,b; Dewhurst & Renwick, 2013; EFSA & WHO, 2016).

The role of dietary exposure assessment in the risk assessment of chemicals in food and novel foods is summarized in Table 6.1. If a hazard is not characterized in step 2, then it is not necessary to complete the risk assessment process, although a dietary exposure estimate may be made for other reasons.

6.1.2 General considerations when undertaking dietary exposure assessments

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

- A harmonized approach to risk assessment means that procedures undertaken for all food chemicals and novel foods should be based on the same principles and use methodologies consistent with identified toxicological concerns. For example, acute or chronic hazards would necessitate an acute or chronic dietary exposure assessment, respectively.

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[4] Typically, the lower 95% confidence limit of a derived BMD, termed the BMDL, is compared with the estimated chronic dietary exposure to determine the margin of exposure.

Table 6.1. Role of dietary exposure assessment in risk assessment

Step	Options for each step			
1: Hazard identification	Hazard identified			
2: Hazard characterization (refer to Chapters 4, 5 and 9)	*Acute effect* ARfD set	*Chronic effect* HBGV set on basis of LOAEL/ NOAEL or BMD/BMDL (e.g. ADI, TDI, PTWI)	*Chronic effect* HBGV not set BMD established (e.g. BMDL)	*Chronic effect* TTC approach applied
3: Dietary exposure assessment (for general population and subgroups of toxicological interest)	Acute dietary exposure estimate	Chronic dietary exposure estimate		
4: Risk characterization (refer to Chapters 7 and 9)	Compare acute dietary exposure estimate with ARfD	Compare chronic dietary exposure estimate with HBGV	Calculate MOE by dividing BMDL by chronic dietary exposure estimate	Compare chronic dietary exposure estimate with Cramer threshold for structural class 1, 2 or 3 chemicals

ADI: acceptable daily intake; ARfD: acute reference dose; BMD: benchmark dose; BMDL: lower 95% confidence limit of the benchmark dose; HBGV: health-based guidance value; LOAEL: lowest-observed-adverse-effect level; MOE: margin of exposure; NOAEL: no-observed-adverse-effect level; PTWI: provisional tolerable weekly intake; TDI: tolerable daily intake; TTC: threshold of toxicological concern

- Dietary exposure assessments for food additives, pesticide residues, veterinary drug residues, contaminants, other chemicals in food and novel foods may use specific models and statistical approaches to combine food consumption and concentration data that differ depending on the chemical, the purpose of the assessment and the information available, including information on how the chemical ends up in food for consumption (e.g. added to food, naturally occurring, present due to contamination, present as a metabolite or active substance).

- The methods used may also be applied to estimating nutrient intakes as part of a risk assessment – for example, when determining whether an upper level of intake (UL) is exceeded or an average requirement is not achieved.

- The objective of the dietary exposure assessment must be clearly identified before the method, appropriate data on food consumption and appropriate data on concentrations of the chemical in food may be selected. The level of consumer protection to be achieved is determined by risk managers, and, in some circumstances, different goals for consumer protection may be selected for different chemicals.

- Dietary exposure assessments should provide dietary exposure estimates that are conservative (i.e. highly protective of health) and be conducted using methods that are fit for purpose. International assessments should take into consideration all available individual national dietary exposure estimates. Preferably, data sets from different countries should not be merged for a combined estimate, but should be presented separately in the assessment.

- Dietary exposure assessments should cover the general population as well as specific population subgroups that have been identified as relevant from toxicological profiling (e.g. infants, children, pregnant women, older adults).

- Dietary exposure assessments may be required to address specific questions from risk managers – for example, about the population likely to have exposures at the top end of the distribution of exposures. Information on high-percentile dietary exposures may be expected to cover all groups that may not have typical food consumption patterns (e.g. people with diabetes or people with specific diets, such as vegans or vegetarians). If necessary, separate assessments may be required for specific population subgroups.

- If an international dietary exposure estimate determined by JECFA or JMPR does not exceed a relevant health-based guidance value, the dietary exposure at the national level should be acceptable, providing the same consumer level of protection is required, as dietary exposure assessments undertaken by

international committees tend to use the most conservative values from available information from different countries or regions of the world.

- Information about the dietary model selected, food definitions, food consumption and associated concentrations of the chemical in food (including data sources used), model choices, data limitations and uncertainties should be clearly documented for purposes of transparency.

6.1.3 Documentation and definitions

Information (metadata) is required to be documented on all aspects of a dietary exposure assessment for use by risk assessors and risk managers, as outlined below:

- *Dietary exposure assessment*: Purpose of the assessment (see sections 6.2.1–6.2.5).

- *Dietary model*: Type of model and statistical approach selected (see sections 6.6.2–6.6.8).

- *Food definitions*: Food classification system used, food grouping, level of disaggregation of data (see section 6.5.1).

- *Data on concentrations of chemical in food*: Date and location of each analytical survey, including geographical location where samples were sourced and place of purchase, agency/person submitting data, sampling and analytical procedures, including details of chemicals analysed (e.g. parent compound, isomers, metabolites), foods sampled and form of food (e.g. raw, as sold, prepared as consumed), derivation of the food chemical concentrations for the dietary model (e.g. mean, median, percentile selected or full distribution, exclusion criteria used) (for further information, see section 6.3 and Appendix 6.1).

- *Data on food consumption*: For each survey, date and place of the dietary survey, agency/person submitting data, data collection methods, number of days of individual dietary records, population subgroups covered in the survey (sex, age), body weight data, sample weighting and derivation of the food consumption amounts for the dietary model (e.g. all respondents,

consumers only, percentile of consumption used to represent high consumers) (for further information, see section 6.4).

- *Model choices*: Choices made in setting up the model – for example, mapping of concentration data to foods in the consumption data set and use of recipes/disaggregation, use of concentration data from limited brands of a food to characterize concentrations in all similar foods and foods excluded from the model (see section 6.5.2); use of factors to adjust concentration data from food as analysed to food as consumed (see section 6.5.3); treatment of non-detected and non-quantified results and quality assurance data (see section 6.5.4); market share adjustments (see section 6.5.5); and use of usual intake models if relevant (see section 6.5.6).

- *Limitations and uncertainties*: These should be documented for food concentration data sets, food consumption data and the dietary exposure assessment (for details, see section 6.6.1.2).

The term "consumer" can be confusing and needs to be clearly defined when reporting each dietary exposure assessment, as it is often used in conversation to mean the general public. In relation to dietary exposure estimates, "consumer" and "general population" have specific meanings when used in a dietary exposure assessment report, as defined below:

- *General population*: All respondents sampled in a survey – i.e. consumers and non-consumers of foods containing the chemical of interest.

- *Consumers*: Subset of the population that reported consuming the foods containing the chemical of interest or foods proposed to contain the chemical of interest (sometimes termed "consumers only" or "eaters only") and could therefore be exposed to that chemical.

- *High consumers*: Subset of consumers in the population who report consuming large amounts of food(s) that contain the chemical of interest or have a dietary exposure at the top end of the exposure distribution, which may be due to being a high food consumer, consuming foods with high concentrations of the chemical of interest or consuming a number of different types of foods in average amounts that all contain the chemical of interest.

If high consumer values are included in a dietary exposure assessment, a definition of a high consumer and how the high percentile value was derived from the food consumption or dietary exposure data set should be provided.

Depending on the purpose of the assessment or data available, a high consumer may be represented by a 90th, 95th, 97.5th or 99th percentile value derived from the distribution of food or exposures for consumers only. A high consumer percentile value may also be derived for the general population. A minimum number of data points are required to derive a reliable (statistically valid) high percentile of food consumption or dietary exposure from a distribution of values; in general, the derived value should represent a real data point. This requirement may not be met for some data sets, especially for population subgroups. In these cases, a lower percentile should be used, such as a 90th percentile or 50th percentile (median). Different rules for minimum numbers have been set by different regulatory agencies. 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 (e.g. 2 times the mean estimate for a 90th percentile, 2.5 times the mean estimate for a 95th percentile, 3 times the mean estimate for a 97.5th percentile; WHO, 1985).

- *Regular consumers*: Subset of consumers in the population who routinely consume the same food product(s) from the same brand or source, which, if the food product always contains the chemical of interest in high concentrations, may lead to high dietary exposures for those individuals. Regular consumers who routinely consume the same brand of processed foods are sometimes termed "brand-loyal" consumers. Depending on the purpose of the assessment and data available, a regular consumer may be represented by a 50th percentile (median) or mean value, derived from the distribution of food or exposures for consumers only.

6.1.4 Framework for selecting appropriate methods for dietary exposure assessments

A framework can be used to help select the most appropriate method(s) for conducting a dietary exposure assessment, based on the following general principles and considerations:

- The specific method that is most appropriate for estimating dietary exposure depends on several considerations, including:

  1) the purpose of the assessment, which determines the type of estimate needed;
  2) the type of substance being evaluated (i.e. food additive, pesticide residue, veterinary drug residue, contaminant, nutrient, other food chemical or novel food);
  3) the duration of exposure required to produce the toxic or beneficial effect and whether the concern is the potential for too much exposure or, for nutrients, too little intake;
  4) the need to evaluate exposure for different subgroups or individuals within the population; and
  5) the resources available.

- To prioritize resource allocation for a number of chemicals, a stepwise or tiered approach can be employed. Screening methods can be applied first to identify the likely level of safety concern (low, medium, high). This may then be followed by more refined estimates of dietary exposure, where required. The screening stage of the tiered approach uses minimal resources in the shortest possible time to identify those chemicals that require more detailed assessments.

- Screening methods, if used, should aim to overestimate the potential dietary exposure for high consumers by using conservative assumptions in terms of food consumption and concentrations of the chemical in food (see section 6.6.5.1). The intention is to avoid situations where dietary exposure is underestimated and the screening erroneously indicates that no safety concern exists.

- To effectively screen chemical substances and establish risk assessment priorities, unsustainable diets with unrealistically high levels of food consumption should not be used in the screening procedure; rather, physiological limits of consumption should be taken into account.

- When more refined assessments are required for individual chemicals, the best (most detailed) data available should be used.

- If refinement of the dietary exposure assessment is required, the analysis should be designed such that any potential high dietary

exposure is not underestimated. The method(s) selected should take into consideration non-average individuals, such as those who are disproportionately at risk to the adverse effects of the chemical and those who are high consumers because they habitually or occasionally consume large portions of foods containing the chemical of interest, consume many foods that contain low levels of the chemical, or habitually or occasionally consume foods with very high concentrations of the chemical. For example, some consumers may be loyal to particular foods or brands of food. This may be a consideration in selecting an appropriate dietary model for chemicals that have been deliberately added to food products (e.g. food additives, nutrients) or where a food is sourced from a particular area known to have high contamination levels, such that the model includes a scenario where the food always contains the highest concentrations of the chemical of interest.

These general considerations may be represented as a framework that can be used by the analyst to select the most appropriate method(s) for the intended purpose of the assessment, as illustrated in Fig. 6.1. In the framework, screening methods that use minimal resources may be selected to give a first estimate of dietary exposure. However, as more accurate and precise dietary exposure assessment methods are used, more resources are required to improve the quality of the data on food consumption and on concentrations of the chemical in food, to better reflect actual concentrations of the chemical in food and patterns of food consumption. In general, when working within a tiered approach where refinements are required, the most realistic dietary exposure estimate for chemicals in food or novel foods should be made based on the purpose of the assessment, ensuring that the dietary exposure to chemicals in food is not underestimated for food additives and contaminants, for example, or overestimated when assessing nutrient adequacy.

Some data sources may be suitable only for specific methods used for dietary exposure assessment. For example, data from total diet studies are not suitable for acute dietary exposure assessments because of the way in which the data are collected. These considerations are further elaborated below in sections 6.2–6.6.

Fig. 6.1. Dietary exposure assessment framework
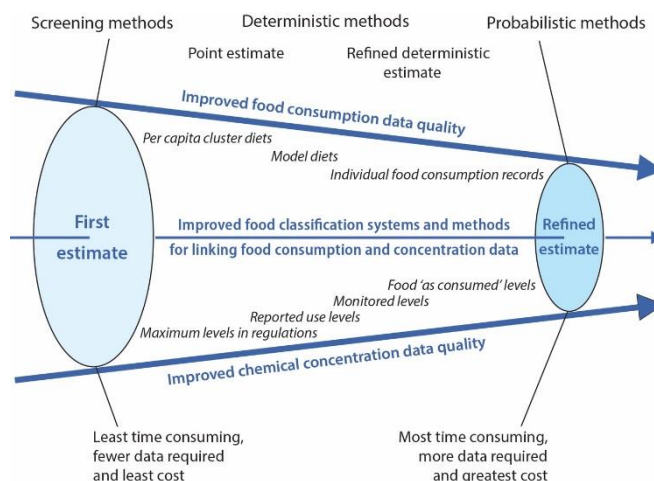
6.1.5 Chapter overview

This chapter aims to provide guidance to WHO and FAO and their expert advisory bodies, the Codex Alimentarius Commission, national governments and the risk analysis community at large on how to perform and interpret dietary exposure assessments. The chapter provides updated information on current approaches to dietary exposure assessments at international and national levels, highlighting available data sources and web-based tools. The aim is to provide practical advice to a risk assessor on how to select appropriate methods for conducting dietary exposure assessments from the options available that are suitable for the purpose of the assessment.

The general principles and methods described in this chapter can be applied at international, regional, national and local levels.

An overview of data requirements for each type of dietary exposure assessment is given below in section 6.2. Details on possible sources of data on concentrations of chemicals in food and on food consumption are given in sections 6.3 and 6.4, data collection and data management techniques are discussed in section 6.5, dietary exposure assessment methods are described in section 6.6 and biomarkers of exposure are explained in section 6.7, with references provided in section 6.8.

6.2 Types of dietary exposure assessment

Dietary exposure can be assessed for a chemical 1) before it has been approved for use in food (pre-regulation), 2) after it has been approved and 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 general, pre-regulation assessments are made for new food additives, pesticide residues, veterinary drug residues or novel foods, new uses of food chemicals already approved and, in some cases, nutrients proposed to be added to foods for specific purposes (e.g. fortification or nutrient replacement).

Three different types of dietary exposure assessment can be undertaken for each of the three situations described above, the selection being driven by the outcome of the toxicological hazard characterization: 1) acute, 2) chronic over a lifetime and 3) chronic shorter-than-lifetime. These types of assessment may be undertaken for assessment of 1) a single chemical in the diet, 2) aggregate exposure that combines a dietary exposure estimate with an estimate of exposure to the chemical from other non-dietary sources or 3) cumulative exposure to multiple chemicals with the same mode of action, end-point, congeners or target organ either from the diet alone or combined with exposure from other sources.

For all of these types of dietary exposure assessment, several approaches are available: 1) a deterministic or point estimate (using single values for the concentration of a chemical in food and food consumption); 2) a refined deterministic estimate (e.g. empirical distribution of food consumption combined with a single concentration of the chemical in food for each food, or vice versa); and 3) a probabilistic/stochastic estimate that uses parametric or non-parametric techniques to generate a distribution of exposures (see sections 6.6.2 and 6.6.3). A tiered approach to a dietary exposure assessment may use these three approaches in sequence, if triggered by the initial screening step; alternatively, a more realistic estimate may be used in the first instance, providing resources are available to do so. A summary of options is given in Table 6.2.

Table 6.2. Toxicological concern, type of assessment and approach to dietary exposure assessment

Toxicological concern	Number of chemicals of concern	Exposure route	Assessment type	Approach to dietary exposure assessment
One or more of the following: Acute Chronic (lifetime) Chronic (shorter-than-lifetime)	Single chemical	Single food	Dietary exposure assessment	*One or more of the following*: Screening Deterministic Refined deterministic Probabilistic/stochastic
		Multiple foods	Dietary exposure assessment	
		Multiple sources[a]	Aggregate exposure assessment	
One or more of the following: Acute Chronic (lifetime) Chronic (shorter-than-lifetime)	Multiple chemicals with the same mode of action, end-point, congeners or target organ	Single food	Cumulative dietary exposure assessment	*One or more of the following*: Refined deterministic Probabilistic/stochastic
		Multiple foods	Cumulative dietary exposure assessment	
		Multiple sources[a]	Cumulative exposure assessment	

[a] Multiple sources or routes of exposure; dietary exposure estimates are the focus of this chapter, but may also form part of a combined assessment of exposure from all sources.

International committees such as JMPR and JECFA undertake different types of dietary exposure assessment, as determined by the purpose of the assessment and information available, as do national and regional food safety and regulatory agencies. The outcomes are considered by risk managers as part of the overall risk analysis of the food chemical or novel food of interest.

6.2.1 Acute (<24 hours) dietary exposure assessment

In some cases, the presence of a chemical substance in food can pose acute toxicity risks from consumption of a single meal or through a single day (24 hours) of dietary exposure. In these cases, a health-based guidance value called an acute reference dose (ARfD) may be established, and an acute dietary exposure assessment is required to complete the risk assessment process. It may be a deterministic or a probabilistic estimate of acute dietary exposure. In either case, dietary surveys are used as the source of food consumption data, with summary data derived from individual records used where distributional data are not required.

Data on concentrations of a chemical in food and on food consumption are selected to represent the high end of data distributions for a deterministic estimate of potential acute dietary exposure. That is, the assessment uses inputs for a high consumer of the food (e.g. 97.5th percentile of consumption for those reported in the dietary survey as eating the food) containing a high amount of the chemical of interest during a meal or over 24 hours (single day). If the food consumption data do not support the derivation of a valid high-percentile consumption amount for a single food owing to a small data set, lower percentiles can be used (e.g. 90th or 95th percentile instead of a 97.5th percentile), or the high-percentile food consumption amount can be taken for a broader food group (e.g. berries rather than strawberries).

In refined deterministic models, the whole range of individual data for food consumption is used, combined with a high concentration of the chemical in food and a 97.5th percentile of exposure derived from these data. A distribution of concentration data could also be combined with a 97.5th percentile food consumption amount. In a probabilistic model for estimating acute dietary exposure, the whole range of individual data is required for both concentration of the chemical in food and food consumption (see section 6.6.4.2). When using food consumption data taken from

multiple-day dietary surveys in a refined deterministic or probabilistic assessment, individual single-day records rather than averaged food consumption over all the days are used in an acute dietary exposure assessment (see section 6.6.4).

6.2.2 Chronic (lifetime) dietary exposure assessment

For substances with toxicity that manifests over long-term repeated exposures, a chronic dietary exposure assessment is required as part of the risk assessment process. Typically, toxicological studies carried out to examine the adverse health effects resulting from ingestion 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). At lower doses, adverse effects generally arise only following long-term exposure to the substance. In these cases, a chronic health-based guidance value may be established (e.g. acceptable daily intake [ADI] for food additives, pesticide residues or veterinary drug residues, tolerable daily intake [TDI]/provisional tolerable weekly intake [PTWI]/provisional tolerable monthly intake [PTMI] for contaminants, UL for nutrients; refer to Chapters 4, 5 and 9). The estimated chronic dietary exposure is then compared with the relevant health-based guidance value. The BMDL derived from BMD modelling, other reference point or point of departure may be used in a margin of exposure approach where a health-based guidance value has not been set (IPCS, 2009a; USEPA, 2012a). Chronic dietary exposure estimates are also used in the TTC approach to risk assessment (Sand, Victorin & Filipsson, 2008; EFSA, 2017a; refer to Chapter 9).

Chronic dietary exposure assessments may be made using deterministic, refined deterministic or probabilistic models (see sections 6.6.2, 6.6.3 and 6.6.5). In all cases, multiple-day dietary surveys are used as the source of the food consumption data, which are averaged over the number of days of the survey for each individual prior to use in the dietary exposure assessment or adjusted to represent usual patterns of consumption. A usual intake estimate for chronic dietary exposure or nutrient intake statistically adjusts for within-person variation, but it is not appropriate for use in acute dietary exposure assessments (see section 6.5.6).

Summary data derived from individual records are used where distributional data are not required or available for public use. Data on concentrations of the chemical in food and on food consumption

are selected to represent patterns of occurrence and consumption over a lifetime to estimate chronic dietary exposure.

For a deterministic estimate of mean dietary exposure to a chemical with long-term effects, mean food consumption amounts for the general population are combined with mean concentrations of the chemical in each food containing the chemical of interest. This assumes that this value represents the long-term average of truly encountered concentrations. The contributions from each food to total dietary exposure are summed over the total diet (see section 6.6.5).

Chronic dietary exposures may also be estimated for those who report consuming the foods containing the chemical of interest only, presented as a mean dietary exposure for consumers or a dietary exposure for high consumers (e.g. 90th or 95th percentile of exposure). Decisions on the relevant information to present in a dietary exposure assessment are determined by the overall purpose of the risk assessment (see section 6.6.5).

In cases where concentration data are not available – for example, in pre-regulation assessments – the proposed maximum levels may be used (see section 6.3.1 for sources of concentration data). In some cases, the distribution of data on concentrations of the chemical in food is highly skewed to the right-hand side by a small proportion of high values or outliers, where the mean is considerably higher than the median value. Options available as alternatives to using the mean are discussed further in section 6.3.1 and may include use of a median, use of a geometric mean or trimming the distribution of concentration values.

6.2.3   *Chronic (shorter-than-lifetime) dietary exposure assessment*

In some cases, there may be toxicological concerns about regular shorter-than-lifetime exposures (also known as less-than-lifetime exposures) to a food chemical for specified population subgroups – that is, a level of exposure that is not expected to be experienced over the whole lifetime but is longer than the 24-hour period usually considered in acute dietary exposure assessments. Chronic dietary exposures can be routinely estimated for standard age/sex groups (mean population and high consumers) and reported as part of the dietary exposure estimate for a total population, as described in sections 6.6.5 and 6.6.6. The high-consumer scenarios are considered to be sufficiently protective for shorter-than-lifetime dietary exposure

(i.e. a regular high consumption during more than 1 day and less than a few years).

If a specific life stage (e.g. infants, young children, pregnant women, older adults) is identified as being a potentially "vulnerable group" in the toxicological profiling process, the dietary exposure estimates for the population group of interest may then be discussed separately in the risk characterization step (see Chapter 7). For example, lead exposure may adversely affect the development of infants and children, so chronic dietary exposure for this group could be assessed separately. Population subgroups may also be vulnerable due to their dietary patterns at a particular life stage and require special consideration – for example, exclusively breastfed or bottle-fed infants consume a single food only, and young children often consume less variety in foods compared with adults. There may also be a need to consider instances of intermittent exposures, where a batch of food is consumed by an individual or subpopulation over a period of weeks rather than days, potentially exposing consumers of the food to a higher concentration of a chemical in the food than the mean concentration for that time period (Zarn & O'Brien, 2018).

6.2.4 *Aggregate exposure assessment*

Aggregate exposure is the combined exposure to a single chemical across multiple routes (oral, dermal, inhalation) and across multiple pathways (food, drinking-water, residential/occupational). Aggregate exposure assessments may require an estimation of acute or chronic dietary exposure (see sections 6.6.4 and 6.6.5). Total exposure from all sources (dietary and non-dietary sources of exposure) is then assessed in the final risk characterization step, if suitable data are available.

Historically, the safety of residues of pesticides and veterinary drugs and the risk associated with exposure to chemical contaminants have been evaluated based on 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. The problem of assessing total exposure to a chemical from different routes was often exacerbated because the responsibility for assessing different routes of exposure resided in different parts of national governments and international organizations.

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 Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment of the United Kingdom Food Standards Agency (FSA, 2002), the Health Council of the Netherlands (2004), Boon et al. (2004) and the European Food Safety Authority (EFSA, 2007). These reports made 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 potential sources of exposure (dietary and non-dietary) to pesticides.

Guidance for performing aggregate risk assessments was first issued by the United States Environmental Protection Agency (USEPA) in 2001 (USEPA, 2001). A more recent review of methods for assessing the risk of non-dietary exposure to chemicals was undertaken by EFSA in 2016, covering potential exposure from use of consumer products and via the environment (EFSA, 2016a).

6.2.5   Cumulative exposure assessment

Cumulative exposure is the combined exposure to multiple chemicals that have a common mode of action, end-point, congeners or target organ from the diet alone or from multiple sources. In some cases, health-based guidance values for groups of chemicals, including metabolites and active substances, may apply (e.g. group ADI/TDI). For example, two pesticides might produce the same effect (e.g. organophosphate pesticides act via acetylcholinesterase inhibition), and exposure over a given time period to both chemicals might result in additive or synergistic effects. Standard dietary exposure assessment methodologies do not consider this potential.

Cumulative risk assessments for pesticide residues in food were pioneered by the USEPA (2002, 2003) and have been developed more recently by others, with WHO's International Programme on Chemical Safety (IPCS) and the Organisation for Economic Co-operation and Development (OECD) now using the term "risk assessment of combined exposure to multiple chemicals" rather than "cumulative risk assessment" (IPCS, 2009b; Meek et al., 2011; OECD, 2018; EFSA, 2019d). Cumulative exposure assessments may require an estimation of acute or chronic dietary exposure and are discussed in more detail below (see section 6.6.8). Some chemicals

have long half-lives and are only slowly eliminated from the body. Consequently, recurrent exposure results in bioaccumulation – that is, an increasing body burden over time. For this reason, the accumulated amount in the body (body burden), rather than the daily exposure, is typically considered a more relevant exposure end-point to be used in risk assessments for these chemicals. In such cases, there are two options for estimating exposure for a risk assessment: 1) estimate a chronic dietary exposure at a given point in time (see section 6.6.5) and/or 2) estimate the body burden corresponding to the dietary exposure accumulated over time (see section 6.6.8.4). Body burden estimates are particularly important in cases where a health-based guidance value for the chemical or chemical group is set, but not if a margin of exposure approach is taken (FAO/WHO, 2016).

6.3   Data on concentrations of chemicals in food

Different types and sources of concentration data may be selected according to the purpose of the dietary exposure assessment (see sections 6.3.1 and 6.3.2). The selection of concentration data for use in an estimate of dietary exposure should be based on consistent procedures; this is particularly important at the international level, where data on concentrations of a chemical in food from several countries may be available. For each risk assessment, it is crucial to consider sampling, analysis and reporting procedures when assessing whether data on concentrations of a chemical in food are consistent and comparable (WHO, 1985; Petersen, Chaisson & Douglass, 1994). In a database collating information from different countries, such as the WHO Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme (GEMS/ Food) contaminants database (see section 6.3.2.3(d)), a standardized format is employed for data submissions. For example, it should be questioned whether a country reports the concentration of a chemical in infant formula either as a dry powder or "made up" ready to drink, in grains in either a raw or cooked form or in fish as either a whole fish or a fish fillet (see section 6.5.3 on use of conversion factors).

Issues to be considered include the following:

- study design (e.g. foods to be included, number of samples, individual versus composite samples);

- sampling design (e.g. representativeness of the sample across different geographical areas in a country, over seasons and across years, targeted versus random sampling);
- sample preparation and processing (including whether foods are cleaned, sorted, raw, prepared and/or cooked before analysis);
- method of sample analysis (including limit of detection [LOD], limit of quantification [LOQ] and limit of reporting [LOR]);
- quality assurance procedures; and
- reporting of data (e.g. handling of non-detected results, basis of results reported [e.g. fresh weight versus lipid weight]).

Detailed information on sampling (e.g. sample plans and sample preparation), methods of analysis and quality assurance for surveys of concentrations of chemicals in food is given in Appendix 6.1. Reporting of data on concentrations of chemicals in food used in dietary exposure assessments is covered in sections 6.5.3 and 6.5.4.

6.3.1 Selecting concentration data for use in estimating dietary exposures

Different approaches for selecting data on concentrations of chemicals in food are required for pre-regulation and post-regulation dietary exposure assessments. Potential sources of data on concentrations of chemicals in food are summarized in Table 6.3.

Where chemicals are deliberately added to food (food additives, nutrients, novel foods), data on concentrations of the chemicals in food are generally available from or estimated by the manufacturer or food processor, either pre-regulation or post-regulation. For agricultural and veterinary chemicals that are applied to food crops or animals, trial data/residue depletion studies on residues in food should be available from sponsors or manufacturers during the pre-regulation process. For pesticide residues or veterinary drug residues, the residue definition for enforcement purposes (referencing a marker compound) may differ from that required for consideration in a risk assessment, both for establishing relevant health-based guidance values and in the dietary exposure assessment (active compound plus metabolites of toxicological significance). In these cases,

concentration data are required for both the active compound and metabolites (see section A6.1.2 in Appendix 6.1).

Table 6.3. Sources of data on concentrations of chemicals in food

Chemicals in food	Pre-regulation dietary exposure assessments	Post-regulation dietary exposure assessments[a]
Food additives, novel foods	Proposed MLs Proposed manufacturers' use levels	Reported manufacturers' use levels, food label data (use only) Food industry surveys Monitoring and surveillance data Total diet studies
Contaminants	Monitoring and surveillance data, or proposed MLs if other data not available Total diet studies Migration data from model diets (for packaging materials)	MLs Monitoring and surveillance data Total diet studies
Pesticide residues	Proposed MRLs Highest residue level found in trials STMR level	Monitoring and surveillance data Total diet studies
Veterinary drug residues	Proposed MRLs Residue depletion studies	Monitoring and surveillance data Total diet studies
Nutrients	Proposed MLs for fortification Maximum claimable levels Food composition data	Monitoring and surveillance data Food composition data (see section 6.3.2.3(c)) Food industry surveys Food label data (use or amount if given on label) Total diet studies

ML: maximum level; MRL: maximum residue limit; STMR: supervised trials median residue

[a] In addition to all pre-regulation data sources.

Data for all chemicals in food can also be obtained from analysis of food in the production chain, either at the farm gate for raw commodities or in stores for raw and processed foods. There may be national or international databases on concentrations of chemicals in food available for use (see section 6.3.2.3).

For ingredients such as food additives and added nutrients, the ingredient list on a food label indicates their presence but not their amount, unless this information is given elsewhere on the label (e.g. caffeine content or vitamin D fortification levels). For some nutrients, data on concentrations in food may be available from the nutrition facts section of the food label, but these will be for total nutrient content (naturally occurring plus added nutrients). In some countries, a database of labels for foods available for consumption may be maintained or commercially available for a fee; however, these databases require ongoing resources to keep up to date with the current food supply.

Selection of data on concentrations of chemicals in food is also determined by whether an acute or chronic dietary exposure assessment is required. A deterministic, refined deterministic or probabilistic approach can be taken for both acute and chronic dietary exposure assessments. In a probabilistic approach, a parametric or non-parametric distribution of available concentration data is used (see section 6.6.3). Generally, a concentration data distribution is not used in chronic dietary exposure assessments, as consumers would be exposed to the range of the concentration distribution over time, resulting in their chronic exposure being that related to the mean concentration value per food. In certain cases – for example, where consumers are loyal to a food brand that may always contain a high level of a food additive or fortificant or where there is local contamination that is known to increase chemical concentrations in food – a higher concentration than the mean may be selected in a consumer model to reflect this.

International committees and food safety or regulatory agencies may have access to data on concentrations of chemicals in food provided by national governments for use in dietary exposure assessments as well as from other sources, such as international databases (e.g. WHO GEMS/Food) and the scientific literature. It is important, wherever possible, to have detailed information on the data source, survey type or design, sampling procedures, sample

preparation, analytical method, LOD or LOQ, and quality assurance procedures. This background information ensures that data from different sources are used appropriately in the dietary exposure assessment.

The approach taken and underlying reasoning for the selection of data on concentrations of chemicals in food and derivation of the values used in a dietary exposure assessment should be clearly stated in the assessment. Data sources should always be carefully described and evaluated.

6.3.1.1   Concentration data for estimating acute dietary exposure

An estimate of the top end of the range of the concentration data distribution is required for a deterministic estimate of acute dietary exposure; for example, the highest residue level from a pre-application supervised pesticide residue trial is used. If a distribution of concentration data is available, the highest reliable percentile concentration is used. A minimum number of data points are required to derive a robust (statistically valid) 97.5th percentile of food chemical concentration from a distribution of values, which may not be met for some data sets. In this case, a lower-percentile concentration value may be selected (e.g. 90th, 95th percentile).

Summary monitoring data will not be suitable for acute dietary exposure assessments if estimates of central tendency only (mean, median) are provided. Monitoring data, where samples have been pooled before analysis or for reporting purposes (composite samples), do not provide reliable estimates of the highest residue levels in single food units and may require a correction factor, such as the variability factor used in model diets for acute dietary exposure assessments for pesticide residues (see section 6.6.4). Variability factors do not need to be applied when distributions of individual concentration data are available (e.g. EFSA, 2019d).

6.3.1.2   Concentration data for estimating chronic dietary exposure

Summary statistics, such as the mean, may be derived from the concentration data set for each food or food group for use in a deterministic estimate of chronic dietary exposure. In this case, pooled or summary monitoring data may be considered for use in the estimate. In pre-regulation assessments, proposed maximum levels (MLs) or maximum residue limits (MRLs) may be used.

In some cases, the distribution of concentration data may be highly skewed to the right-hand side by a small proportion of high values or outliers, where the mean is considerably higher than the median value. Options available as alternatives to using the arithmetic mean include 1) using the median concentration, particularly for chemicals where there are few data points, 2) trimming the distribution to remove outlier values when they are considered to not represent the levels to which people are likely to be exposed, then calculating the arithmetic mean value, or 3) using an alternative method to define the central tendency measure (e.g. mode, geometric mean), which reduces the impact of a small number of very high concentration values. The geometric mean is not commonly used in dietary exposure assessments, but may be of use in cases where the data distribution is skewed and/or the median is below the LOD or LOQ.

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 and will depend on assumptions made concerning the treatment of non-quantified (i.e. <LOQ) or non-detected (i.e. <LOD) values, whereas the mean can be heavily influenced by a cluster of very high results. Although this may not influence the calculated average value when the LODs/LOQs from different data sets for the same food are similar, it can have a substantial effect when some LODs/LOQs are much higher than the rest. Inclusion of data from difference sources should be considered on a case-by-case basis for each data set prepared for use in the dietary exposure assessment, and all assumptions made need to be recorded (see section 6.5.4). There are, however, different opinions on the legitimacy of using a median value from a statistical point of view, as some argue that because consumers are randomly sampling from the food supply, the long-term concentration to which they will be exposed will be the mean (arithmetic or geometric), not the median.

Generally, the mean concentration is used where there is a data set of sufficient size to derive a mean that is statistically valid (minimum number of data points or a single well-composited sample). Different agencies may apply different rules; for example, the mean or median may be selected, whichever is higher. Examples illustrating the use of mean or median concentrations for different types of food chemicals are given below:

- For chemicals that are intentionally added to foods, such as food additives, nutrients and novel foods, the mean concentration is often used to reflect the expected concentration in food over time and may be derived from food producers' use data or monitoring and surveillance data. Where there is a possibility that consumers may be loyal to specific brands/products and the concentration of the chemical may be higher than the mean in some products, then this higher value may be selected for use in a high-consumer model (for examples, see FSANZ, 2011a; EFSA, 2017b). For pre-regulation assessments, the proposed ML may be used to estimate potential dietary exposure.

- Nutrients may occur naturally in foods or be added as fortificants or to nutrient supplements. The mean concentration of the nutrient in food has traditionally been reported in food composition tables, even when sample sizes are small. If the nutrient is intentionally added to foods, then manufacturers may be able to provide additional information on intended total concentrations of the nutrient in the food. In some cases, the total nutrient concentration may be declared on the nutrition facts section of the food label.

- For pesticide and veterinary drug residues that may be found in food after application of the pesticide or veterinary drug to food crops or animals, it has been the convention to use median residue levels. The median levels are derived from supervised pesticide trials (supervised trials median residue, or STMR) or veterinary drug residue depletion studies submitted for consideration in pre-regulation dietary exposure assessments. These approaches are currently used by JMPR and JECFA. For many trial studies, the small number of data points in each data set means that derivation of a median is preferred, as it may not be statistically valid to derive a mean concentration. In some cases, monitoring and surveillance data may be available, which provide more accurate information on concentrations of chemicals in food as sold or consumed; in this case, mean concentrations can be derived.

- For contaminants, the mean concentration of the chemical in food, derived from monitoring and surveillance data, is often used in estimating dietary exposure. Where there is a highly skewed distribution of concentration data, the median may be

selected, or, where a significant proportion of results are below the LOD or LOQ, the geometric mean may be used (refer to section 6.5.4 on handling results below the LOD/LOQ). Where the set of analyses is from composite samples, which are in effect an average of the components of each unit in the composite sample, a mean of the samples may be considered more appropriate than the median.

Certain foods are widely blended across many individual units or sources (e.g. grains, milk, orange juice, oils); in these cases, it may be appropriate for both acute and chronic dietary exposure assessments to estimate the concentrations of a chemical in blended commodities by using the mean of the concentrations from individual or composite samples.

6.3.2 Sources of concentration data for use in estimating dietary exposure

The possible sources of data on concentrations of chemicals in food for use in dietary exposure assessments are discussed below; the selection depends on the purpose of the assessment and the data available. In some cases, conversion or dilution factors may be applied to the concentration data in a refined dietary exposure estimate (see section 6.5.3).

6.3.2.1 Maximum levels (MLs) and maximum residue limits (MRLs)

Maximum concentrations (MLs or MRLs) should be used in pre-regulation dietary exposure assessments for chemicals proposed to be deliberately added to foods. They may also be used in a first step of assessments in a tiered approach in post-regulation assessments. If no safety concerns are raised in this conservative assessment, there may be no need to obtain measured concentration data for the second step. For contaminants, it is preferable to use monitoring or surveillance data, although MLs may occasionally be used where no other information is available. It is important to understand the method of derivation of MLs or MRLs for various food chemicals when considering the potential uncertainties in the data; these methods may be different at Codex Alimentarius Commission and national levels.

The FAO/WHO's Codex Alimentarius, or "Food Code", is a collection of standards, guidelines and codes of practice adopted by the Codex Alimentarius Commission that aim to protect consumer

health and promote fair practices in food trade. The food standards provide information on MLs and MRLs for different types of chemicals in food, including food additives, contaminants and natural toxins, pesticide residues, veterinary drug residues and novel foods (http://www.fao.org/fao-who-codexalimentarius/en/).

For food additives, novel foods and added nutrients, proposed MLs are based on information from manufacturers or food producers, usually submitted in an application to a food safety organization or regulatory agency for a new food chemical or ingredient or extended use. An evaluation would determine whether the proposed levels are sufficient to achieve the required technological function in the food while maintaining consumer safety:

- For food additives, MLs proposed by the food industry are assessed by the relevant food safety organization or regulatory agency undertaking the evaluation. For a JECFA evaluation, proposed MLs are considered from submissions to JECFA, and recommendations are made to the Codex Committee on Food Additives, with a final decision by the Codex Alimentarius Commission.

- For nutrients and some novel foods, evaluations are complex, as both added and naturally occurring sources of the substance of interest need to be taken into account in the dietary exposure assessment, although data on natural sources may not be part of the industry submission. For a JECFA evaluation, recommendations on MLs may be made to the Codex Committee on Food Additives or the Codex Committee on Nutrition and Foods for Special Dietary Uses, with a final decision by the Codex Alimentarius Commission.

In the cases of pesticide and veterinary drug residues, proposed MRLs are usually based on good practice considerations, taking consumer safety into account:

- For pesticide residues, MRLs are based on field trial studies performed under Good Agricultural Practice that determine the required amount of pesticide to be applied to achieve a technological function, such as pest control. MRLs are derived by the relevant food safety organization or regulatory agency undertaking the evaluation. For a JMPR evaluation, MRLs are proposed based on trial data, from submissions to JMPR, and

recommendations are made to the Codex Committee on Pesticide Residues, with a final decision by the Codex Alimentarius Commission.

• For veterinary drug residues, MRLs are derived by the relevant food safety organization or regulatory agency undertaking the evaluation from controlled residue depletion studies carried out in compliance with Good Practice in the Use of Veterinary Drugs that determine the required amount of drug to be given to animals to achieve the required technological function. For a JECFA evaluation, MRLs are proposed based on residue depletion studies from submissions to JECFA, and recommendations are made to the Codex Committee on Residues of Veterinary Drugs in Foods, with a final decision by the Codex Alimentarius Commission.

For contaminants, proposed MLs are generally based on the "as low as reasonably achievable" (ALARA) principle – i.e. the lowest level of contamination that can be reasonably achieved without removing the food from the food supply. In some cases, additional risk management measures are required as well as setting food standards, such as food labelling, provision of consumer advice on consumption of contaminated foods, changes in agricultural or manufacturing practices or limiting non-food sources of the contaminant to improve public safety. Results from JECFA evaluations are provided to the Codex Committee on Contaminants in Food, which proposes MLs, subject to review and adoption by the Codex Alimentarius Commission. MLs for contaminants are usually established in Codex standards only for those contaminants that present both a significant risk to public health and a known or expected problem in international trade and for commodities that contribute significantly to dietary exposure (for a full list of principles by which MLs are set, refer to the Codex General Standard for Contaminants and Toxins in Food and Feed; FAO/WHO, 2010).

For chronic dietary exposure assessments for contaminants, pre-regulation estimates of dietary exposure are generally based on monitoring and surveillance data, although existing MLs for individual foods may be used if no other information is available. Concentrations in all relevant foods should be included in the dietary exposure assessment, to provide a more accurate estimate – that is, potential background exposure should be considered. If monitoring

or surveillance data are available, it is preferable to use these data in dietary exposure assessments, as MLs for contaminants do not generally reflect actual levels occurring in foods as consumed.

For contaminants, the setting of an ML for a chemical in the food in which it occurs will have an impact on the future exposure of the population to the chemical over time; mean food chemical concentrations would be expected to decrease when a product containing the contaminant at levels exceeding the ML is withdrawn from the market.

6.3.2.2   *Measured or reported concentrations*

Proposed MLs and MRLs are convenient values with which to estimate dietary exposure for new chemicals for pre-regulation purposes, but it is recognized that a person would not always consume foods containing chemicals at these levels or limits. In a tiered approach, MLs and MRLs could be used in the first step of a post-regulation assessment. For example, for pesticide residues, MRLs may be used in the first step and trial data in a second step, with monitoring data required only if the outcomes of steps 1 and 2 indicated a need for a more refined dietary exposure estimate. If the tiered approach is not taken in a post-regulation dietary exposure assessment, measured concentrations or reported use levels from food producers should be used, when available.

(a)   Supervised trials (pesticide residues only)

Traditionally, the primary source of pre-regulation residue data for pesticides in foods has been supervised trial data that must be submitted to regulators in support of the registration of a pesticide.

The trials are usually performed on plant crops by a manufacturer or other parties, where a maximum registered pesticide use scenario (with respect to pesticide application rates, number of applications, pre-harvest or withdrawal intervals, etc.) is simulated. The trials are designed to determine the maximum residue concentrations that may be present in the harvested product at the earliest point at which these commodities could enter commerce as food or feed for animals (shortest permitted post-harvest interval). Models may be used to determine potential residue levels in the final food or feed products.

These maximum observed residue concentrations often overestimate the residue concentrations that are likely to occur in food as actually consumed. Therefore, these data are not the first choice when assessing chronic dietary exposure; instead, the STMR level is used. For an acute dietary exposure assessment, the maximum residue concentration, termed the highest residue, reported for a given chemical/food combination is used, although the STMR level may be used in certain cases for blended commodities (see section 6.6.4). Information on STMRs for different pesticide residue/food matrices is available in published evaluations undertaken by JMPR and by national food safety or regulatory agencies.

(b)   Residue depletion studies (veterinary drug residues only)

For veterinary drugs, residue depletion study data must be submitted to regulators in support of the registration of the drug. 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 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 dietary exposure. A software-based workbook for statistical evaluation of residue depletion data for veterinary drugs is available on the FAO website ([http://www.fao. org/food/food-safety-quality/scientific-advice/jecfa/guidelines0/ residue-depletion/en/](http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/guidelines0/residue-depletion/en/)). The approach is primarily based on linear regression analysis and statistical estimation of one-sided upper tolerance limits for the marker residue depletion in the individual target tissues. MRLs are derived to represent the upper 95% confidence limit of the 95th percentile of the residue concentrations at the chosen time point on the residue depletion curve.

The median residue concentration at the appropriate withdrawal time is usually used as a basis for chronic dietary exposure assessment for veterinary drugs. JECFA evaluations of veterinary drug residues are published as useful references for available concentration data, as are those published by national food safety or regulatory agencies. Using the MRLs in dietary exposure assessments would overestimate the veterinary drug residue concentrations that are likely to occur in food products of animal origin at the point of sale or consumption, as it would assume that all animals of a target

species would be treated and that residue concentrations equivalent to the MRL remained in the food product. In general, the MRL values should not be considered when assessing chronic dietary exposure post-regulation. However, MRLs may be used in the first step of a tiered approach or for a conservative (high) assessment of dietary exposure in the case where low or non-detectable residue levels are reported in the depletion studies or when the MRLs are based on other considerations, such as the LOQ of the analytical method.

(c)   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 than the earliest point at which these food commodities could enter commerce.

There are two types of monitoring and surveillance data, based on analysis of targeted or random food samples.

*Targeted sample*s are collected in analytical surveys for enforcement purposes in response to specific problems (e.g. heavy metal contamination from a known source). Concentration data from such samples would not normally be used in dietary exposure assessments, as they are not likely to be representative of all the food available for sale or may not represent the concentration in foods consumed over a lifetime in the context of a chronic risk assessment.

Random samples, with a sampling plan for the analytical survey used to generate representative residue data for all food chemicals of interest, may be available at a national or local level or collated at a regional level. Surveys that collect random samples may still target foods likely to contain specific food chemicals, such as a group of food additives (e.g. preservatives), colours or packaging chemicals, or include a wider chemical screen, such as those used for heavy metals, pesticide residues and veterinary drug residues. These data generally provide a better characterization of chemicals in foods as purchased or as consumed (e.g. USFDA, 2019a; EFSA, 2020a,b; USDA, 2020).

For post-regulation acute and chronic dietary exposure assessments for pesticide and veterinary drug residues, suitable monitoring and surveillance data are preferred over data from supervised trials and depletion studies if a refined dietary exposure

assessment is required, as these are more likely to represent levels present in food as consumed. Supervised trial data and the results of residue depletion studies do not account for residue degradation that may occur between the farm and the market and between the market and the home or subsequent residue losses when food is processed and prepared for consumption.

The samples are usually collected on a random basis close to the point of consumption – for example, at terminal markets and distribution centres immediately prior to distribution to retail outlets or closer to the point of sale, at fresh food markets, 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.

Monitoring programmes are mainly designed to measure compliance with a given standard only and may not use the most sensitive methods of analysis. The resulting concentration data may not be appropriate for use in dietary exposure assessments, as the LOQ/LOD may be higher than for other data sets, leading to a higher level of uncertainty in the dietary exposure estimates. However, in some cases, this type of data may be the only data available for use. It may be difficult to combine data sets obtained for different purposes, usually due to differences in method sensitivity; however, it is possible (see section 6.5.4 and Appendix 6.1). In these cases, the limitations of using the data sets should be discussed in the dietary exposure assessment report (see section 6.6.1).

Veterinary drug residue concentrations may be monitored in marker organs of an animal (e.g. levels of heavy metal contamination in the liver), rather than the more usually consumed muscle meat. Conversion factors may be available from other animal studies to estimate levels in other tissues, but their use also increases the level of uncertainty in the dietary exposure estimate.

Although monitoring and surveillance data are preferred for use in dietary exposure assessments, there are some limitations due to the fact that only a small proportion of any commodity entering the food-chain is monitored. In particular, the range of possible concentration values may not be captured in the samples taken, which could affect the derivation of accurate high residue values for use in acute dietary

exposure assessments. Another limitation is that analytical methods may not capture all the relevant metabolites or active substances of interest in a risk assessment. For example, the legal residue definition for a pesticide MRL may include metabolites of the parent chemical that are of toxicological concern and hence need to be included in the dietary exposure estimate, but the relevant concentration data may not be available.

(d)   Concentration data from total diet studies

Total diet studies are a subset of monitoring and surveillance data and in principle provide the most accurate measure of the average concentrations of pesticide residues, contaminants, nutrients and other chemicals in foods. This is because concentrations of chemicals are measured in foods "as consumed" – that is, after they have been prepared for normal consumption by the population (and, if possible, population subgroups) living in a country. For example, bananas are peeled, and the skin is discarded along with any associated chemical residues. A total diet study also incorporates the impact of cooking on less stable chemicals and on the formation of new ones. Concentration data from total diet studies are suitable only for chronic dietary exposure assessments, because they provide average concentrations of chemicals in foods (EFSA, FAO & WHO, 2011).

The reliability of a total diet study is dependent on sample size, coverage of different geographical locations within a country and seasonal variations, compositing of samples and survey duration (see Appendix 6.1). Therefore, when using concentration data obtained from a total diet study in a chronic dietary exposure assessment, it should be considered whether the total diet study concentration data are fit for the purpose of mapping with the food consumption data used.

Analytical methods used in a total diet study should be sensitive enough to measure 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 total diet studies.

The broad scope of a total diet study may necessitate significant compositing of samples if resources are limited (see also section A6.1.1 in Appendix 6.1). Compositing may be on either an individual food basis or a food group basis. Such compositing will not prevent

the estimation of total chronic dietary exposure but may limit the ability to identify the specific sources of the food chemical. Owing to resource considerations, total diet studies usually generate a small number of concentration data (usually $n = 1$–15) for each individual food or food group included in the study, in contrast to data generated through surveillance or monitoring of individual food commodities (where $n = 30$–50 or more). However, if the samples analysed are derived from a suitably designed sampling plan, then the mean (or median) concentration derived from the resulting samples can be suitably robust. Guidance on designing and implementing total diet studies in a harmonized way is given in a joint EFSA, FAO and WHO document (EFSA, FAO & WHO, 2011).

6.3.2.3   *Publicly available databases for concentrations of chemicals in food*

(a)   Codex online databases

Codex provides a searchable database for MLs in the General Standard for Food Additives (GSFA online database: http://www.fao.org/fao-who-codexalimentarius/codex-texts/dbs/gsfa/en/). There are similar databases for Codex MRLs for pesticide residues (Codex pesticide residues in food online database: http://www.fao.org/fao-who-codexalimentarius/codex-texts/dbs/pestres/en/) and veterinary drug residues (Codex veterinary drug residues in food online database: http://www.fao.org/fao-who-codexalimentarius/codex-texts/dbs/vetdrugs/en/).

(b)   National and regional databases

There is some information publicly available for measured concentrations of food additives in processed foods. Regulatory agencies may develop databases for internal use for food additives under evaluation and publish information on concentrations used in specific dietary exposure assessments.

Some countries publish databases for some pesticide residues (e.g. USEPA, 2002; USDA, 2020). The underlying concentration data sets for contaminants, pesticide or veterinary drug residues and other chemicals included in a total diet study may also be available separately for some countries, published with the summary report by the relevant national or regional agency (see section 6.6.5.2(b)).

The European Information Platform for Chemical Monitoring (https://ipchem.jrc.ec.europa.eu/) is the European Commission's

reference access point for searching, accessing and retrieving chemical occurrence data collected and managed in Europe (Comero et al., 2020). The platform is divided into four modules: environmental monitoring, human biomonitoring, food and feed, and products and indoor air. The Zenodo database (http://zenodo.org) can also be used to access chemical monitoring data for European countries. Zenodo is a general-purpose open-access repository developed under the European OpenAIRE programme and operated by the European Organization for Nuclear Research. It allows researchers to deposit data sets, research software, reports and any other research-related digital artefacts. For each submission, a persistent digital object identifier (doi) is minted, which makes the stored items easily citable.

For dietary exposure assessments on pesticide or veterinary drug residues or contaminants undertaken by JMPR or JECFA, the WHO GEMS/Food contaminants database could be used as a source of concentration data (see section 6.3.2.3(d)), as well as the scientific literature, in addition to data provided in submissions for a substance under consideration.

For nutrients, national and regional food composition databases are regularly compiled and published, with links given in the FAO International Network of Food Data Systems (INFOODS), an FAO programme that collates these databases (see section 6.3.2.3(c)).

For countries with no national food concentration data, it may be useful to determine whether data on concentrations of chemicals in food from other countries with a similar climate, range of foods available and patterns of food use could be used in their national dietary exposure assessments.

(c)   Nutrient databases

Food composition databases contain information on the nutrient content of various foods and beverages available in the country or region covered. They are based on chemical analysis of nutrients in foods, complemented with calculated and imputed values, particularly for mixed foods, where concentrations are not available from direct analysis for the wide range of foods available for consumption.

FAO's INFOODS was established in 1984 and collects details of food composition databases from around the world. The network is organized into several regional data centres, with a global coordinator; links to national and regional databases are available on its website (http://www.fao.org/infoods/infoods/en/).

Examples of regional nutrient databases available via INFOODS are the recently published FAO/INFOODS Food Composition Table for Western Africa (Vincent et al., 2020) and "FoodEXplorer", a database of the international non-profit organization EuroFIR AISBL (http://www.eurofir.org). This latter database also includes some food composition data from non-European countries, such as New Zealand, Canada, the USA and the United Kingdom. Many countries publish their own nutrient databases, one of the most extensive being the United States Department of Agriculture's (USDA) National Nutrient Database for Standard Reference, which is integrated into the USDA's FoodData Central database (https://fdc.nal.usda.gov/).

INFOODS also stands as a forum through which international harmonization and support for food composition activities can be achieved and advocated. In this context, INFOODS and FAO provide guidelines, standards, compilation tools, databases, capacity development tools, policy advice, advocacy tools and technical assistance at the country level to facilitate the collection of high-quality data. Despite this, nutrient values may not be readily comparable at an international level owing to unavoidable differences in foods from different countries (e.g. biodiversity, variety, soil, processing and level of fortification). Artificial differences as a result of component identification, food description and nomenclature, analytical methods, mode of expression and units used should be decreasing over time with increasing harmonization of approaches to data compilations, but still need to be evaluated.

The ongoing development of new food products plus mandatory and voluntary fortification of a wide array of foods create 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 so that sufficient nutrient information for processed foods is available to ensure that food composition data match the foods consumed for accurate nutrient intake estimates. For fortified foods, analysis should be specific enough to accommodate different brands and formulations of

the same foods. However, this is an expensive exercise, and often sufficient resources are not available.

(d)   GEMS/Food contaminants database

GEMS/Food was established in 1976 to inform governments, the Codex Alimentarius Commission and associated committees, such as JECFA and JMPR, as well as the public, on current levels and trends in levels of contaminants in food and provide data for use in risk assessments. WHO implemented the programme in cooperation with a network of Collaborating Centres and recognized national institutions located all around the world (http://www.who.int/ foodsafety/areas_work/chemical-risks/gems-food/en/).

Since the implementation in 2011 of a new web-based interface (OPAL-web), GEMS/Food has collated more than 6 million analytical results on the occurrence of about 300 chemicals in food. The GEMS/Food contaminants database includes individual and aggregated analytical data on contaminants in foods (raw commodities and some processed foods). Total diet study data from individual countries may be submitted to the WHO GEMS/Food programme. Originally, the GEMS/Food contaminants database collated data only on concentrations of contaminants in food, but as total diet studies have expanded their scope, data for other food chemicals, such as pesticide residues and veterinary drug residues, from these studies may also be submitted.

In 2016, GEMS/Food started collating data from the private sector and developed specific agreements to define the use of these data. WHO, in collaboration with Chulabhorn Research Institute in Thailand, developed an online learning tool to facilitate the use of GEMS/Food data. GEMS/Food provides information to assist in understanding the terminology used and how to submit data (WHO, 2011a). Data may be submitted by countries on a routine basis following national surveys or in response to WHO data calls for specific purposes, such as a planned JECFA evaluation.

6.4   Data on food consumption

Food consumption data reflect what individuals or groups consume in terms of foods, beverages, including drinking-water, and dietary supplements. Food consumption can be estimated through food consumption surveys at an individual, household or population

level or approximated through food production statistics at the population level only.

6.4.1 Food consumption data requirements

To the extent possible, food consumption data from national dietary surveys used in dietary exposure assessments should include information on factors that may influence access to food and food consumption patterns and hence potential dietary exposure. Such factors include demographic characteristics of the population sampled (age, sex, ethnicity, socioeconomic group), body weight, geographic region, season in which the data are collected and day of the week on which the data are collected.

Consideration of food consumption patterns for potentially sensitive population subgroups (e.g. young children, pregnant women, older adults) and for individuals at the extreme ends of the food consumption distributions (low/high consumers of relevant foods) is also important. Often women of childbearing age are used as a proxy for pregnant women, as information may not be available on pregnancy status. Given that the design of food consumption studies can have a critical impact on the results of any dietary exposure assessment, harmonization of study design should be advocated 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 collecting individual dietary records on at least 2 different non-consecutive days per person in the survey.

Food consumption data used at the international level should consider the differences in food consumption patterns between different countries or regions. For risk assessments undertaken by international committees, it is important that each national survey included in the assessment be based on a statistically representative sample of the population surveyed and covers the whole population, with data for key population subgroups.

6.4.2 Collection of food consumption data

Methods for collecting food consumption data include population-, household- and individual-based methods.

It is essential to recognize that population-, household- and individual-based data sets are not directly comparable and give different levels of information on food consumption patterns. Hence, the assumptions and limitations of each data set need to be understood and taken into account in the risk assessment. The quality of data for use in a dietary exposure assessment depends on the survey design, the method and tools used, the motivation and memory of the respondents, the statistical treatment and the presentation (e.g. foods as purchased versus foods as consumed) of the data.

Individual record data will generally provide the most precise estimates of food consumption. Broad surveys, covering the food consumption patterns of the whole population, should seek to cover specific subgroups of the population where it is known that the food in which the chemical of interest is found is consumed only by these groups. If resources are limited, small-scale studies may be appropriate and may cover specific foods or target population subgroups (e.g. children, breastfeeding women, ethnic minorities or vegetarians). This approach can improve the precision of estimates of dietary exposure for specific population subgroups or specific food chemicals.

All types of food consumption data can play a valid role in dietary exposure assessments, providing different information or pieces of a "jigsaw puzzle" of the whole picture.

6.4.2.1 *Population-based methods*

Population-based methods provide data on the annual amount of food (including some beverages, but excluding drinking-water) available to the whole population for consumption as raw commodities and for some food groups as semi-processed or fully processed foods. Data collected using population-based methods 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.

Food supply data at the national level, such as multi-annual supply utilization account data, also referred to as food balance sheets or food disappearance data, provide gross annual estimates of the

national availability of food commodities (e.g. FAO food balance sheet data: http://www.fao.org/economic/ess/fbs/en/).

These data may also be used to calculate the average per capita availability of energy and macronutrients and dietary exposure to chemicals in food where concentration data are available for the raw and semi-processed commodities (e.g. nutrients, pesticide and veterinary drug residues and contaminants). These data are not generally useful for calculating average per capita dietary exposure to food additives because they are usually expressed in terms of raw and semi-processed commodities, not foods as purchased. However, by mapping processed foods to their raw commodity components using recipes, it is possible to calculate average per capita food consumption for use in estimating dietary exposures (see section 6.5.2).

The major limitation of national supply utilization account 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), supply utilization account 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 the consumption of drinking-water. Where drinking-water consumption data are not available, a default consumption value of 2 litres of drinking-water per adult per day may be used, as per the WHO drinking-water guidelines (WHO, 2017).

Despite these limitations, supply utilization account data may be 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. The data also offer a huge advantage in providing a consistently formulated representation of food consumption across a large number of countries.

The supply utilization account data do not differentiate different consumption patterns for different subgroups in the population or frequency of consumption and therefore cannot be used to evaluate nutrient intake or dietary exposure to chemicals in food at an individual level or by subgroups of the population at risk. Use of these

data sets at the broad population level introduces uncertainty into dietary exposure assessments (see section 6.6.5.1).

6.4.2.2 Household-based methods

Household consumption and expenditures surveys, mainly conducted to assess food security, provide data on food stocks available to each household in a survey of the general population or population subgroups over a period, with data more often used at the national level (Fiedler et al., 2012; Russell et al., 2018).

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.

6.4.2.3 Individual-based methods

Individual-based methods provide data on foods consumed by individual respondents in a survey. These data are collected face to face, by phone or electronically using various approaches (e.g. diary record, diet history, food frequency questionnaire, 24-hour dietary recall over 1 or more days). In some studies, a combination of these methods is used to give a fuller picture of overall food consumption patterns.

In general, it is important that foods consumed are described in detail according to a nominated food classification system and that industrially produced composite foods or home-made dishes, such as a ready-made frozen pizza or a home-cooked beef stew, are disaggregated as much as possible into their main ingredients at a level that can be reported by the subjects (see sections 6.5.1 and 6.5.2; Verger et al., 2002; EFSA, 2009).

A summary of available methods for population studies that are used to collect records at an individual level and their capabilities is given in Table 6.4 (adapted from a United States National Cancer Institute [NCI] primer on dietary assessment methods for use in

Table 6.4. Dietary survey instruments used in studies with different research objectives

Characteristics of research study		24 h recall	Food record	FFQ	Food habit questionnaire
Study design	Cross-sectional	√	√	√	√
	Retrospective			√	√
	Prospective	√	√	√	√
	Intervention	√		√	√
Scope of interest	Total diet	√	√	√	
	One or a few components			√	√
Captures contextual details[a]	Yes	√	√		
	No			√	√
Time frame	Short term	√	√		
	Long term			√	√
Can query diet in distant past	Yes			√	√
	No	√	√		
Allows cross-cultural comparisons	Yes	√	√		
	No			√	√
Major type of measurement error	Random	√	√		
	Systematic			√	√
Potential for reactivity	High		√		
	Low	√		√	√
Time to complete	<15 minutes				√
	>20 minutes	√	√	√	
Memory requirements	Specific	√			
	Generic			√	√
	Does not rely on memory		√		
Cognitive difficulty	High			√	√
	Low	√	√		

FFQ: food frequency questionnaire

[a] Context may include details of food preparation/cooking method, timing of meals, location of meals, etc.

studies with different research objectives: https://dietassessment primer.cancer.gov/profiles/table.html).

(a)   Twenty-four-hour dietary recall method

The 24-hour dietary recall method consists of listing foods and beverages (including drinking-water and dietary supplements) consumed during the day (24 hours) immediately 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 the foods were 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 may result in less reliable data. Researchers have developed multipass methods that guide the respondent through the 24-hour reference period several times, providing opportunities for the respondent to remember food details and additional foods (Slimani et al., 2000; Raper et al., 2004; Subar et al., 2012; Castell, Serra-Majem & Ribas-Barba, 2015; Timon et al., 2016). Food model booklets are often provided to assist respondents in more accurately determining the size of portions by way of pictures of plates and glasses, servings of foods, packet sizes, rulers or size of wedges of foods such as cakes or pizza.

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 6.5.6).

(b)   Food record

The food record, or food diary, requires the subject (or observer) to report all foods consumed during a specified period (usually 7 days or less). Food records 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 the foods are consumed. The amounts consumed should be measured as accurately as possible. Amounts may be determined by weighing or measuring volume.

(c)   Food frequency questionnaire

The food frequency questionnaire, 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. This information can be used to determine whether a food is regularly, infrequently or never consumed by a population of interest over a given period of time, noting that different definitions of these categories may be used in different studies. Food frequency questionnaires may be unquantified, semi-quantified or completely quantified. The unquantified questionnaire does not specify serving sizes, whereas the semi-quantified tool provides a typical serving size. A completely quantified food frequency questionnaire allows the respondent to indicate any amount of food typically consumed. Some food frequency questionnaires 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 food frequency questionnaires depends on the representativeness of the foods listed in the questionnaire for the population being studied. Food frequency questionnaires may not produce reliable intake estimates for some macronutrients and population subgroups (Schaefer et al., 2000; Thompson et al., 2000; Brunner et al., 2001; Wakai, 2009; Moghames et al., 2016). Food frequency questionnaires can be subject to certain personal biases, such as overestimation of the frequency of consumption of infrequently consumed foods and underestimation of the frequency of consumption of foods that the respondent perceives as "unhealthy" or "bad" (Haftenberger et al., 2010).

Food frequency questionnaires are commonly used to rank individuals by consumption of selected foods or nutrients. Although food frequency questionnaires 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 in dietary exposure and for which there are relatively few significant food sources. Brief food frequency questionnaires may focus on one or several specific nutrients or food chemicals and include a limited number of food

items. In addition, food frequency questionnaires can be used in the identification of absolute non-consumers of certain foods – those who report never consuming the food.

(d)   Food habit questionnaire

The food habit questionnaire (or screener) 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 with the other 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.

(e)   Diet history survey

The meal-based diet history survey is designed to assess usual individual food consumption and is not suitable for population surveys. 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, Hatenberger & Thamm, 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.

(f)   Combined data collection methods

All methods for collecting food consumption data may be prone to bias. For instance, several studies have found that nutrient intakes derived from 24-hour recalls tend to underestimate true intakes of some macronutrients for some subjects (Willett, 2001; Banna et al., 2017). Regression analyses between recalled 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". Participants in a food record study may alter or simplify what they normally eat for ease of recording.

Consumption data obtained by different collection methods may be combined to improve accuracy and facilitate the validity of the dietary data for population studies. Examples of the use of two or more methods of collecting food consumption data include the United States National Health and Nutrition Examination Survey, where two non-consecutive 24-hour recalls and targeted food frequency questionnaires, including use of dietary supplements, were used (Ahluwalia et al., 2016); the Australian Health Survey, where two non-consecutive 24-hour recalls of food and dietary supplement consumption and a short questionnaire on food habits were used (ABS, 2013); and EFSA's What's on the Menu in Europe? (EU Menu) food consumption survey, where the most cost-effective method for harmonizing food consumption data for people aged 3 months to 74 years between European Union member countries was determined to be the use of two non-consecutive 24-hour recalls plus a short food propensity questionnaire to collect information on the consumption of some less frequently eaten foods and the consumption frequencies of food supplements (EFSA, 2014a). Various research groups have also recommended that the 24-hour recalls be undertaken in combination with a questionnaire on habitual consumption of infrequently consumed foods to get insights into the proportion of non-consumers (e.g. Brussaard et al., 2002; Tran et al., 2004). Other combinations of consumption data from different sources may be appropriate, depending on the purpose of the dietary exposure assessment.

(g)   Using summary data

Data from individual food consumption surveys are often not publicly available in raw format (i.e. at the individual respondent level), and risk assessors must rely on published summary statistics. When comparing food consumption data between countries or surveys, caution should be exercised even if similar data collection methods have been used (e.g. 24-hour recall), because the results may not be readily comparable owing to differences in study design, tools, food classification and coding conventions, statistical analysis and reporting of results (Slimani et al., 1999, 2000; Brussaard et al., 2002).

When only summary food consumption data are available, it is important to know and document the basic data requirements listed in section 6.4.1 as well as how the data were handled to derive the summary statistics. The following should be noted: how the data were aggregated, the commodity, the type of commodity (e.g. raw juice, juice concentrate), what individual foods were included in the final food consumption data for each food code used for the dietary exposure estimate, whether the calculation included ingredients from mixed dishes by use of recipes, whether the dietary exposure estimates refer to consumers of the food only or to the total population (all survey respondents, per capita estimates), whether they refer to regular or high-end consumers, how a regular consumer was defined (e.g. median or mean food consumption or dietary exposure level) and whether the dietary exposure estimates represent daily consumption, consumption per eating occasion or per meal or averages across survey days (in the case of multiday surveys).

6.4.2.4   Typical food portions

In dietary exposure assessments, information may be needed on unit weights, standard portion sizes and large portion sizes. Unit weights and large portion sizes are used in acute dietary exposure assessments for pesticide residues (see section 6.6.4), and large portion sizes in some model diets are used to estimate chronic dietary exposure (see section 6.6.5.2).

(a)   Unit weights

Unit weights represent weights of typical raw commodity units (e.g. a single apple or a single banana), usually reported as the edible portion or with a note of the proportion of edible portion of a commodity. Unit weights may be collected as part of a dietary survey or as a separate survey exercise. Unit weights are used in the calculation of acute dietary exposure estimates, such as the international estimated short-term intake (IESTI) (see section 6.6.4). Unit weights may also be used to convert reports of food consumption by single units in a food frequency questionnaire or 24-hour recall survey to gram weights. GEMS/Food compiles a unit weight database, based on surveys in which individual foods have been measured and submitted by FAO/WHO Member Nations/States, available at https://www.who.int/foodsafety/areas_work/chemical-risks/IESTI_calculation20_data_overview.xlsx.

(b)   Standard portion sizes

Standard portion sizes are used to assess the consumption of a wider range of foods and beverages in dietary surveys using the recall method. That is, a standard weight will be assigned to the food reported "as consumed" – for example, a banana, a cookie or a glass of soft drink. These portions can be specified with different levels of detail (e.g. differing weights for different glass sizes or small/medium/large-sized fruit or vegetables) and are often survey and country specific. Countries may publish standard portion sizes used in national dietary surveys as part of the survey background data. In some countries, standard portions/serving sizes are mandated for reference in food regulations – for example, in the USA's nutrition labelling standards (e.g. USFDA, 2019b).

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 to an underestimate of high portions and thus to an overestimate or underestimate of the corresponding dietary exposures. 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 on the estimate of low levels of intake for nutrients.

(c)   Large portion sizes

Large portion sizes have been used in dietary exposure assessments for a variety of risk assessments by regulatory agencies. For these purposes, the large portion values have been based on a high percentile of food consumption (e.g. 97.5th percentile is a commonly used statistic) derived from records of individual consumer days (i.e. survey day is a 24-hour period during which the food or foods of interest were consumed). Large portion sizes could also be derived from individual eating occasion data, where these have been recorded separately in a dietary survey if specifically required in a risk assessment. The large portion may contain more than the equivalent of one unit weight of a food (e.g. large portion for apples is more than one apple) or less than the unit weight of a large fruit or vegetable (e.g. large portion is a piece of a watermelon or pumpkin). GEMS/Food compiles a large portions database from submitted national dietary surveys (see section 6.4.4.2(d)).

For use in an acute dietary exposure assessment for pesticide residues (see section 6.6.4), the large portion value should be matched to the commodity in the Codex Alimentarius Commission or other classification system to which the residue data relate. In the case of commodities that are eaten predominantly fresh, such as fruits and vegetables, the large portion value should be derived for the raw commodity (edible portion). When a high proportion of the commodity, such as cereal grains, is consumed in a processed form, the large portion value should relate to the processed commodity (e.g. bread, flour), provided matching data on residue concentration are also available for the processed food.

Upper-percentile and lower-percentile food consumption amounts should be defined based on individual consumer days for acute dietary exposure estimates 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 should not be 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.

- The number of consumers of a given food is critical, and care should always be taken when deriving the 97.5th percentile food consumption amount for consumers only, ensuring that the derived number is statistically valid (see section 6.1.3).

Caution should be used where recipes have been applied to mixed foods, and rules may need to be applied to exclude consumption of some mixed foods when deriving the large portion value for a specific food or raw commodity, particularly mixed foods containing a very low proportion of the ingredient of interest. Counterintuitively, the 97.5th percentile of consumption for consumers of a single food is likely to be higher than that for a food group due to higher numbers of consumers and the range of consumption patterns of foods within the broader food group. For example, in determining the large portion value for oysters, the

exclusion of consumers of fish sauce or oyster sauce may be considered. Oysters are often reported as consumed by a relatively low proportion of the population in a survey; however, the number of consumers of oyster sauce and fish sauce may be higher. As these sauces contain very small proportions of oyster, the inclusion of these consumers in the derivation of the large portion value would increase the number of consumers of oysters, distort the distribution of amounts of oysters consumed and reduce the value of the 97.5th percentile consumption amount used to derive the large portion, which may not be desirable in an acute dietary exposure assessment. To avoid this situation, a minimum proportion of a food ingredient in a mixed food could be established, above which that ingredient can be included in a recipe used in a dietary exposure estimate.

If the approximate shape of the distribution for a food consumption parameter is known, more accurate high-percentile estimates can be predicted; otherwise, a default uncertainty factor should be applied to the food consumption estimate.

6.4.3   Adjusting food consumption using body weight data

Body weight data are one of the important demographic parameters collected during a national dietary survey reporting on food consumption patterns. For the purposes of dietary exposure assessments, where the health-based guidance value is expressed per kilogram of body weight, national food consumption data based on individual records should be presented such that individual consumer body weights are applied to the consumption figures for each survey respondent or to the dietary exposure estimate for that individual, prior to the derivation of population statistics. Measured body weights are much preferred to self-reported body weights, as use of the latter may result in systematic bias in the data set, often due to under-reporting of actual body weights, hence increasing the uncertainty in the dietary exposure estimate (Merrill & Richardson, 2009).

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. For risk assessments undertaken by international committees, such as JECFA and JMPR, which include data from individual countries, it is preferable to use the mean body weight from

the relevant national survey in dietary exposure estimates for each country.

In the absence of body weight data, default body weights can be assigned according to the following steps, taken in order:

1) For missing body weight values within a national dietary survey that collected body weight data, impute values by calculating mean body weights for specific age/sex groups from respondents who have provided body weight data and assign those imputed values to individuals from the same age/sex groups who have missing body weight values.

2) For dietary surveys with no body weight data, check data holdings for body weight data from a country in the same region, calculate mean body weights for specific age/sex groups and assign to individual records or population subgroups as required; potential data sources are the FAO/WHO Chronic Individual Food Consumption database – summary statistics (CIFOCOss), the FAO/WHO Global Individual Food consumption data Tool (GIFT) initiative (see section 6.4.4.2) or, for European countries, the EFSA standard values (EFSA, 2012c).

3) For surveys with no body weight data for children aged 0–5 years, determine median body weights from the WHO international child growth standards for the age/sex groups required (https://www.who.int/childgrowth/standards/en/).

4) On the rare occasions that sufficient individual body weights are not available on an age/sex basis for a specific country, assign an appropriate default body weight for the whole population (e.g. 70 kg body weight for adults has been used by the USEPA and EFSA in some circumstances: USEPA, 2011; EFSA, 2012c).

5) For general populations with no other data sources available to derive a body weight as described above, assign the WHO standard default average body weight of 60 kg for the whole population; or, for Asian populations, a default average body weight of 55 kg.

Use of default population body weights adds some uncertainty to the dietary exposure assessment. If the default body weight underestimates the actual individual body weights, the dietary

exposure estimate on a per kilogram of body weight basis will be overestimated. Likewise, if the default body weight overestimates the actual individual body weights, the dietary exposure estimate on a per kilogram of body weight basis will be underestimated. The principle of conservatism in risk assessment means the former case (overestimation) is preferable to the latter (underestimation), except where nutrient adequacy is being assessed, where the reverse is true.

6.4.4   Food consumption databases

6.4.4.1   Data collected using population-based methods

(a)   FAO supply utilization account data

FAO has compiled food and agricultural supply data from Member Nations since 1961 in the statistical database FAOSTAT (http://www.fao.org/faostat/en/#home).   National   statistics   are currently available for 245 Member Nations in 35 regional areas. Food supply (apparent food consumption) statistics may also be published separately by individual countries – for example, the food supply and demand statistics compiled by the USDA's Economic Research   Service   (https://www.ers.usda.gov/topics/food-choices-health/food-consumption-demand.aspx). Although FAOSTAT data may be submitted at any time, annual supply utilization account data are compiled and published from FAOSTAT data and represent the amounts of foods available for human consumption derived from food production, disappearance and utilization data in a given year.

(b)   GEMS/Food cluster diets

In cases where national food consumption data sets are not available, one alternative is to use estimates of mean food consumption for the relevant region in the world, such as the cluster diets published by WHO's GEMS/Food. These diets are intended to represent mean food consumption amounts for the general population for groups of countries with similar food supplies.

The GEMS/Food cluster diets are based on FAO supply utilization account data and represent average per capita food consumption for 17 groups of countries in the world, where the amount of food available for consumption in each group of countries is divided by total population numbers (weighted to take account of individual country populations in each region). A cluster analysis approach is used, where countries with similar patterns of food

consumption are grouped together, resulting in 17 cluster diets (Sy et al., 2013). Summary statistics are published for three levels of food categorization, with a total of about 500 food items at the most detailed level 3 in the GEMS/Food consumption database (https://www.who.int/foodsafety/databases/en/).

The cluster diets are reviewed and updated by WHO from time to time, so they may not reflect the most recent supply utilization account data published by FAO. The GEMS/Food cluster diets were last updated in 2012 and are expected to be updated every 10 years. For some countries, information on foods available in a country may be the only data available to use in a dietary exposure assessment in the absence of food consumption data from a national dietary survey.

The GEMS/Food cluster diets are used as a tool for assessments of chronic dietary exposure to chemicals in food, but are suitable only for estimating mean dietary exposure for the general population. They should not be used to generate high-percentile food consumption amounts for use in dietary exposure estimates for high consumers. The cluster diets are used in conjunction with national survey data by JECFA, most commonly for contaminants, and by JMPR, for pesticide residue evaluations (cluster diets with additional disaggregated information on some food groups). In general, the cluster diets are not suitable for food additive risk assessments, as most of the data are reported as raw commodities, not processed foods. However, the cluster diets may provide useful apparent consumption data for specific processed product commodities such as flour or wine.

6.4.4.2 Data collected using individual-based methods

(a) National dietary surveys

Many countries collect food consumption data at an individual level via national dietary surveys, either as continuous surveys – for example, the USA's National Health and Nutrition Examination Survey/What We Eat in America (https://www.cdc.gov/nchs/nhanes/wweia.htm) and associated USEPA Food Commodity Intake Database 2005–2010 (https://fcid.foodrisk.org/); the Republic of Korea's National Health and Nutrition Examination Survey (Kweon et al., 2014); and the United Kingdom's National Diet and Nutrition Survey (https://www.gov.uk/government/collections/national-diet-and-nutrition-survey) – or as periodic surveys – for example, the

China Health and Nutrition Survey (https://www.cpc.unc.edu/projects/china) and the Australian Health Survey (e.g. https://www.abs.gov.au/statistics/health/health-conditions-and-risks/australian-health-survey-nutrition-first-results-foods-and-nutrients/latest-release). Such surveys are usually published by national statistical agencies or health departments in a summary form and in some cases with access to individual records, provided that privacy requirements are met. For example, the USEPA publishes summary statistics on water and liquid consumption patterns for the whole population of the USA (USEPA, 2019a). National dietary survey data may be used by regulatory agencies or food safety organizations to underpin risk assessments for food chemicals as part of developing national food regulations.

The European Union has one set of food standards for all member countries; hence, risk assessments that underpin European Commission food standards are generally undertaken for the region by EFSA, with reports summarizing the dietary exposure estimates for each member country. As part of this work, EFSA collates individual records from national dietary surveys submitted by each member country. EFSA publishes summary statistics on food consumption from these national dietary surveys for different age groups, the general population and consumers only in the Comprehensive European Food Consumption Database (http://www.efsa.europa.eu/en/food-consumption/comprehensive-database). Food consumption data are available for external use, including by international committees, and guidance is provided on database use (EFSA, 2011b). This is in line with EFSA's policy of making much of its scientific data and evidence accessible (EFSA Knowledge Junction: https://zenodo.org/communities/efsa-kj/?page=1&size=20). In the past, European Union member countries used different methods to collect food consumption data, which sometimes made it difficult for data users; now, the What's on the Menu in Europe? (EU Menu) project provides a dietary survey tool for the collection of standardized food consumption information across the European Union (see section 6.4.2; EFSA, 2014a).

National survey results may be submitted to WHO as summary food consumption statistics or to FAO as individual data records for wider use, particularly in risk assessments undertaken by international committees (see sections 6.4.4.2(b) and 6.4.4.2(c)). In cases where national data sets are not available, the WHO

GEMS/Food cluster diets could be used (see section 6.4.4.1(b)). For estimates of dietary exposure to food additives, a national data set from the region could be used, provided that consumption patterns of processed foods were known to be like those in the country of interest. However, for assessments of nutrients, pesticide residues, veterinary drug residues or contaminants, differences in agricultural practices, climate and soils that may lead to different levels of chemicals in the same food mean that this approach is less likely to be feasible.

(b)   FAO/WHO Chronic Individual Food Consumption database –
       summary statistics (CIFOCOss)

CIFOCOss is a database hosted by WHO that contains summary statistics data on individual food consumption from national dietary surveys. By February 2020, CIFOCOss had incorporated information from 34 countries (only surveys with a data collection duration of 2 days or more). It was developed to collate available data from different countries in the same format for use by the FAO/WHO scientific committees of the Codex Alimentarius Commission for the purposes of chronic dietary exposure assessments, using an internationally agreed food classification system (WHO, 2012). In 2018, CIFOCOss was updated to incorporate the EFSA FoodEx2 food classification system (see section 6.5.1) with a new facility to access and describe food consumption data by sex or age group for each country. The database provides summary statistics available for adults, children, infants, toddlers and the general population, depending on the survey content.

In the future, CIFOCOss will be continuously updated with data from additional surveys and from the FAO/WHO GIFT initiative (see section 6.4.4.2(c); http://apps.who.int/foscollab).

(c)   FAO/WHO Global Individual Food consumption data Tool (GIFT)

FAO/WHO GIFT is a free online platform hosted by FAO that provides access to quantitative food consumption data for individuals that have been collected in national dietary surveys and submitted by FAO/WHO Member Nations/States (http://www.fao.org/gift-individual-food-consumption/en/).

Simple indicators of food consumption, food safety and nutrition in the form of infographics are available on the FAO/WHO GIFT

website for each data set that is available in the platform, following statistical processing. Moreover, microdata shared through the FAO/WHO GIFT platform can be downloaded by individual users and used for more refined analyses. GIFT food consumption data are recorded using the FoodEx2 classification system (see section 6.5.1) and can be used in acute or chronic dietary exposure assessments. Microdata could also be statistically adjusted by the user to better represent long-term or usual consumption for chronic dietary exposure assessments (see section 6.5.6).

Summary statistics on food consumption derived from the FAO/WHO GIFT database (mean, median and other percentiles for data sets with 2 or more days of records per person) are also available in the FAO/WHO CIFOCOss database at a national level (see section 6.4.4.2(b)).

(d)   WHO GEMS/Food portion size database

Large portion (97.5th percentile) consumption values are compiled by WHO in the GEMS/Food database (available at https://www.who.int/foodsafety/areas_work/chemical-risks/IESTI_calculation20_data_overview.xlsx), derived from individual records from national dietary surveys submitted by FAO/WHO Member Nations/States to WHO or to the FAO GIFT programme. Large portion sizes may be used in model diets used for acute dietary exposure estimates (see section 6.6.4) or in some model diets for chronic dietary exposure estimates (see global estimate of chronic dietary exposure [GECDE] model diet in section 6.6.5.2(a)).

This database continues to expand to include data from additional countries to better represent all FAO/WHO Member Nations/States. 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 large portion values.

6.5   Data collection, standardization, handling and reporting techniques

6.5.1   *Food classification systems*

National dietary surveys utilize food classification systems that are specific to each country. Use of data from several countries in a

single risk assessment, as undertaken by JECFA, JMPR or EFSA, requires a harmonized classification system.

The Codex food standards provide generic food classification systems for different food chemicals, the classification system being determined by the different food groups and subgroups assigned an ML or MRL for food chemicals in the relevant standard, with Codex online databases available for pesticide residues, veterinary drug residues and food additives (http://www.fao.org/fao-who-codex-alimentarius/codex-texts/dbs). The Codex General Standard for Contaminants and Toxins in Food and Feed (FAO/WHO, 2010) is also available to view the food categories used. However, the way in which foods are described in Codex and national food standards does not necessarily match the food classification systems used in national dietary surveys to describe foods reported as consumed.

Since 2005, WHO and FAO have worked on developing generic food classification systems for use by countries when submitting food consumption data from national dietary surveys (individual records or summary statistics) that can be used to match survey food codes with permissions for use of chemicals in Codex food standards through use of a mapping process (see section 6.5.2). This work has advanced, enabled by more sophisticated computer programs for submitting data to central collections as well as through the development of better data handling techniques. Such generic systems can also be used to standardize submissions of data on concentrations of chemicals in food. Data sets that are consistent and comparable across countries are particularly useful for dietary exposure assessments that are part of risk assessments undertaken by international committees. However, comparability should not be assumed even when using a generic food classification system, because the method of collection of data may differ from country to country, and naming conventions for the same food may vary.

FoodEx2 serves as a harmonization tool for information included in the FAO/WHO GIFT and CIFOCOss platforms and assists in improving the quality of data available for dietary exposure assessments (Fabiansson & Vernazza, 2012). FoodEx2, a standardized food classification and description system initially developed by EFSA, provides specifications aimed at harmonizing the collection of analytical data on chemical substances and microbiological agents in different matrices of a non-human nature

(i.e. food, feed, animals, water). Food codes for raw and processed foods are included (EFSA, 2014a, 2015). FAO, WHO and EFSA are collaborating on further expanding FoodEx2 to cover foods consumed globally. This will enable non-European national surveys to be more easily mapped to the FoodEx2 classification system prior to being entered into the FAO/WHO GIFT and CIFOCOss databases.

6.5.2   Mapping and food recipes

6.5.2.1   Mapping

Mapping is a process of matching the food classification systems used in dietary surveys to describe foods reported as consumed in a population of interest to food classification systems used for food chemical concentration data, such as MLs or MRLs in food regulatory systems (e.g. Codex standards or national food standards), or matching food consumption to measured or reported food chemical concentrations. In a total diet study, food mapping can also be used to assign a limited number of analytical concentrations to a wider number of foods in the diet to enable an estimate of total dietary exposure to chemicals (Boorman et al., 2013).

Food consumption data may be required at different levels of aggregation, depending on the purpose of the risk assessment. For example, for a dietary exposure assessment for a food additive, data on foods reported as consumed may be sufficient, as approved use levels in food regulations for food additives in processed foods are generally given at the food group or subgroup level (e.g. GSFA online database: http://www.fao.org/fao-who-codexalimentarius/codex-texts/dbs/gsfa/en/). However, if the food additive is present in a mixed food that does not have a food additive permission in its own right, a recipe may be required if an ingredient in the food contains the food additive (termed "carry-over"). Application of a recipe determines the amount of the ingredient consumed, as described in section 6.5.2.2, and then the exposure to the food additive from that food ingredient can be estimated as part of the total dietary exposure estimate for the food additive. Novel foods (including novel food ingredients) in mixed foods, including those with GMOs, would be treated in a similar way to food additives.

For a contaminant, pesticide residue or veterinary drug residue, raw foods are usually analysed, because approved use levels are generally given in food regulations at the raw commodity level

(Boorman et al., 2013; EFSA, 2018a,b). For example, raw agricultural commodities and some semi-processed commodities (e.g. polished rice and flour) may be analysed as described in the food classification systems given in the Codex MRL standard for pesticide residues or in national standards (see section 6.5.1). For a dietary exposure estimate for a contaminant, pesticide residue or veterinary drug residue, recipes are required for mixed foods to disaggregate foods consumed into raw ingredients, including conversion factors to convert ingredients to their raw counterparts – for example, flour to wheat (see section 6.5.3). Consumption data for the raw ingredients can then be mapped to concentration data for chemicals in these foods.

6.5.2.2   *Food recipes*

In all food classification systems, there will be some foods – often mixed foods and composite dishes – that cannot be directly classified. Foods may be consumed as such or as an ingredient in a mixed food. 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.

Standard recipes may be used to account for consumption of mixed foods, such that the proportion of ingredient foods in the mixed food is used to estimate consumption amounts for each of the ingredient foods, which can then be linked back to their respective survey food codes (e.g. USEPA Food Commodity Intake Database recipes: https://fcid.foodrisk.org/recipes/). The proportion of each ingredient in the recipe is applied to the total amount of the mixed food consumed by each individual in the survey to estimate the amount of the ingredient consumed, which is then added to the total consumption of that food from all sources for each person in the survey (e.g. "apples" may include fresh apples, the apples in a baked apple pie and apple juice; and "potatoes" may include french fries and potato chips/crisps; or potatoes and french fries may be considered separate foods). The mapping approach and whether and how recipes were used need to be documented.

The use of recipes in national surveys may vary, and it is one of the many challenges for international committees to determine how and when recipes have been applied to mixed foods to generate the data submitted by each country to the committee or to a collating

agency (e.g. WHO, FAO, EFSA) for use in the FAO/WHO CIFOCOss, FAO/WHO GIFT or Comprehensive European Food Consumption Database and whether data sets and recipes are comparable as a result.

The use of recipes to disaggregate mixed foods into ingredients will have an impact on the proportion of the survey respondents who are considered consumers of these ingredients (i.e. increasing the number of consumers) and on the distribution of consumption amounts. The potential impact of using recipes on the derivation of large portion sizes is discussed above (see section 6.4.2.4(c)). Some ingredients may never be consumed in their own right (e.g. flour). EFSA has developed a probability approach, where each person is assigned a single food from a possible list of ingredients of a mixed food, related to a recipe – for example, instead of assigning both lemon juice and orange juice to all those who reported drinking a mixed fruit juice, each person is assigned only one of the fruit ingredients in their food consumption records, the proportion of people allocated to each fruit being directly related to the percentage of that fruit in the drink (e.g. 5% lemon juice, 95% orange juice). In some other cases, the record of consumption may not be specific enough – for example, a person may report consuming a spread on bread; in this case, each person is assigned a specific spread (butter, olive oil, sunflower oil spread, etc.), depending on the probability of consuming that type of spread. This approach makes no difference to mean dietary exposure estimates for the whole population, but it does affect consumer results, in that it better predicts the proportion of consumers and their likely consumption amounts (EFSA, Dujardin & Kirwan, 2019).

The use of standard recipes and the attribution of the ingredients to individual foods (e.g. assuming that, on average, 70% of bread is flour) introduce some uncertainty into consumption data. However, 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 consumption surveys to foods with chemical concentration data, because, in many cases, the food and the food description do not correspond exactly (Slimani et al., 2000).

6.5.3   Adjustment factors

It is very common that the form of food analysed for the chemical of interest or assigned an approved ML or MRL in food standards differs from the form of the food consumed. It is very important that the dietary exposure assessment accounts for this by applying factors to the concentration data so that the amount of chemical assumed to be consumed in the dietary exposure estimate better reflects the actual exposure amount. The adjustment factors can take a variety of forms, such as generic, processing or conversion factors.

Adjustment factors can be used generically in dietary exposure assessments for all food chemicals or may be specific to a food/food chemical matrix. When matching food consumption records to concentration data for food chemicals, the adjustment factors need to be selected carefully. Failure to apply adjustment factors to concentration data can cause inaccuracies in the dietary exposure assessment, as there can be a large difference in the amount consumed between the two forms of the food. For example, tea leaves may be analysed in a survey, but the food record is for tea ready to drink made up with hot water (weight of tea leaves is approximately 1 g compared with approximately 250 g for a cup of tea); or dry pasta may be analysed, but the food consumption record is for cooked pasta. Care should be taken when using several adjustment factors in a dietary exposure assessment to check the definition of each factor to avoid double counting the effects of generic, processing and food conversion factors.

Adjustment factors have not traditionally been standardized by either numerical value or term used and tend to be developed at a national level, with the values rarely published as part of additional information (metadata) given when reporting the dietary exposure estimate. Hence, different terms may be applied to these factors by different regulatory and food safety agencies or other groups. It is often difficult to determine whether submitted national dietary survey data sets for consideration by international committees are comparable in this regard.

6.5.3.1   Generic factors (concentration/dilution factors)

Standard mass balance assumptions, based on general information on the effects of some processing operations that may concentrate or dilute the chemical in the food, such as drying of

grapes to make raisins or pressing to make wine, may be used to match the food as analysed with the foods consumed. For some foods, these conversion factors may be derived from food composition tables using moisture content data (see section 6.4.4) or from processing studies. Most of the published factors are from studies on pesticide residues (USEPA, 1996; OECD, 2008; EFSA, 2018a,b).

Conversion factors are also used to determine concentrations in processed foods where the concentration data are available only for the raw ingredients – for example, data for milk can be used to derive a concentration value for cheese or yoghurt, based on one characteristic, such as fat content relative to milk (see EFSA, 2018a, for examples of factors).

6.5.3.2   Processing factors

Processing of raw agricultural commodities can increase or decrease concentrations of chemicals or alter the nature of chemicals in foods. A processing factor is the ratio of the concentration of a specific chemical in a processed food to the concentration in the starting commodity, usually the raw primary commodity, and is most commonly derived for pesticide residues. Alternative terms are sometimes used for a processing factor for pesticide residues in a food, such as a "concentration factor" when residue levels increase or a "reduction factor" when residue levels decrease on processing.

Processing studies are usually regarded as specific for the food, the active substance and the process, with the derived processing factors then available for use in pesticide residue dietary exposure assessments. These processing studies are often required for registration of an active ingredient if used on specified crops/foods (e.g. use of a pesticide on wine grapes will require a specific study on grapes processed into juice and wine; OECD, 2008).

6.5.3.3   Food conversion factors

Conversion factors may account for differences in concentrations of an active substance due to food handling following processing – for example, during storage, transport, food preparation and cooking processes – which may lead to degradation in activity or formation of metabolites. Other conversion factors specific to each food chemical may account for changes in concentration of the food chemical due to washing the surface of the food, peeling of an outer

skin (e.g. banana) or discarding other inedible portions of the food (e.g. outer cabbage leaves). If data on the concentration of the chemical in food are available for the edible portion of the raw agricultural commodity, these data are used in the dietary exposure assessment. In some cases, conversion factors may also be available to account for the effect of cooking the food prior to eating on food chemical concentrations.

Some of these conversion factors are country or region specific and may be appropriate only when undertaking national dietary exposure assessments. Conversion factors derived from data for a single country or region should not be used in dietary exposure assessments undertaken by international committees unless there is evidence from known food uses that they apply to that food in all countries included in the assessment.

6.5.4   Handling results below the LOD or LOQ

The appropriate handling of non-quantified (<LOQ) and non-detected (<LOD) results from an analytical survey is critical in dietary exposure assessments. The decision on what numerical value to assign to such values can make an appreciable difference to the estimate of dietary exposure, depending on the proportion of non-quantified and non-detected results in the data set on concentrations of the chemical in food.

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, foods that undergo extensive processing during which a chemical is likely to be completely removed or a food additive not permitted in regulations), it should be assumed that samples without detectable or quantifiable concentrations may contain the chemical at a level below the LOD or LOQ. The risk assessor must decide what concentration value to assign to such samples. Concentrations should be assigned to results below the LOD or LOQ so that the exposure assessment errs on the side of nutritional or toxicological caution (i.e. conservative approach taken), while remaining scientifically defensible.

Common options for handling non-quantified or non-detected food chemical concentration results are to 1) assign a value of zero (lower-bound estimate), 2) assign the LOD or LOQ (upper-bound estimate) or 3) assign one half the LOD or LOQ (mid-bound estimate)

to these results. This last option assumes that the true concentration values are uniformly distributed between zero and the LOD/LOQ. Results from all the options may be presented in a dietary exposure assessment and can be used in a sensitivity analysis to determine the impact of decisions about data handling on the final dietary exposure estimate (see section 6.6.1.2(c)). The presentation of results from different options is also useful where the presence, form of the chemical (e.g. congener, isomer) or distribution of the chemical differs between food types. An alternative hybrid approach has been used by the USEPA (e.g. Xue et al., 2010) and the United States Food and Drug Administration (USFDA) (Spungen, 2019; Gavelek et al., 2020), where values below the LOD are set to zero if there were no detected levels in data for a specific food over a long period of time; and values below the LOD are set to half the LOD (or the LOD) if there has been at least one detected level in that food.

If the number of samples with non-detected or non-quantified food chemical concentrations is large (highly left-censored), such replacement would have a major impact on the calculated mean and standard deviation concentration values. Assigning half the LOD to non-detects has historically been considered to be appropriate for nutrient assessments, so that nutrient intake is not deliberately underestimated or overestimated, particularly where both essentiality and toxicity are assessed. When submitting survey data on concentrations of chemicals in food to a database, such as the GEMS/Food contaminants database, information on an "indicative value" for results between the LOD and LOQ is useful as part of the metadata submitted to the database (i.e. value assigned to non-detected results by country submitting results).

In general, for chemicals likely to be present in the food (e.g. naturally occurring contaminants and nutrients), both lower and upper bounds should be calculated for the mean concentration of the chemical in food. The difference between the lower-bound and upper-bound estimates of the mean concentration of the chemical in food is an expression of the uncertainty in this summary statistic. It is problematic where the lower-bound scenario results in an estimated dietary exposure less than the relevant health-based guidance value but the upper-bound scenario results in an estimate greater than the health-based guidance value. In this case, it would be preferable to obtain data on concentrations of the chemical in food that have been

collected using a more sensitive method of analysis, but otherwise it would be left to expert opinion to make a comment on the results.

Alternatively, more sophisticated statistical methods, such as maximum likelihood estimation or regression on order statistics, can be used to estimate the mean and standard deviation of the censored data on concentrations of the chemical in food. However, most of these methods require an assumption that the data on concentrations of the chemical in food conform to a particular statistical distribution.

The handling of non-quantified and non-detected results has been extensively considered over time (USEPA, 2000; Vannoort, Cressey & Silvers, 2000; Egan et al., 2002; Kroes et al., 2002; Renwick et al., 2003; Tressou et al., 2004; Counil, Verger & Volatier, 2005; Sinha, Lambert & Trumbull, 2006; Jain et al., 2008). Further research was undertaken by EFSA on treating left-censored data to make the best use of available data. Results showed that the number of samples had a relatively limited impact on the accuracy and precision of the estimates, but the degree of censoring had a large effect. EFSA outlined recommendations, including the use of appropriate statistical tests, on how to handle left-censored distributions of data on concentrations of chemicals in food in the context of dietary exposure assessment (EFSA, 2010a). A later technical report described a stepwise approach to selecting the most appropriate cut-off values for censoring limits based on 1) legal requirements, 2) typical expanded uncertainty levels or 3) distributions of the quantified values and reported LOQs and LODs. This approach is intended to minimize the influence of left-censored data on the uncertainty associated with the dietary exposure estimates (EFSA, Arcella & Gómez Ruiz, 2018).

6.5.5 Market share adjustments

In some cases, the risk assessor may refine estimates of chronic dietary exposure by taking account of the proportion of the food supply likely to contain the chemical of interest. This approach, termed market share adjustment, is used mainly when the substance being evaluated has been deliberately added to the food – for example, additives in processed foods (Arcella, Soggiu & Leclercq, 2003), fortification of food with nutrients or percentage of crop treated with a pesticide – because the proportion of the food available likely to be treated with the chemical is known or can be estimated. For example, intense (low calorie or no calorie) sweeteners are added

only to the low-energy version of foods, and pesticide residues may be present only in food produced domestically or only in imported food.

When using a refined deterministic approach for a chronic dietary exposure assessment (see section 6.6.2.2), data on concentrations of the chemical in food are corrected to reflect the proportion of the food category expected to contain the food chemical (e.g. the proportion of low-joule soft drinks expected to contain a specific intense sweetener or the proportion of crop treated with a pesticide). A refined deterministic approach using market share correction factors is more reflective of typical consumer food consumption patterns and may better estimate mean dietary exposure for the general population, but it does not reflect the dietary exposure for the most exposed proportion of the population (i.e. consumers who are loyal to the food products containing the chemical of interest), as it may underestimate their actual dietary exposure. A probabilistic approach should be used if consumer only estimates are required (see section 6.6.3). In a probabilistic approach, the proportion of the food in which a chemical is used can be reflected in the proportion of the censored data assigned a value of zero (e.g. Boon et al., 2009, 2015; EFSA, 2010a).

When assessing dietary exposure to food additives, market share data should consider product or brand loyalty, where feasible. In this case, a consumer/brand-loyal model may be used for estimates of dietary exposure to the food additive, in addition to a general population estimate, where it is assumed that a person may consume all the foods that contain the chemical of interest at the mean or highest concentration. For pesticides, although a correction for the percentage of crop treated can be considered when setting MRLs pre-regulation, in post-regulation evaluations, consideration should be given to the possibility that a section of the population may systematically consume foods derived from treated crops only.

6.5.6   *Usual food consumption patterns*

In a typical dietary survey, food consumption data are collected from respondents across a range of age groups over a period of a few days. These data are then used to represent or model food consumption during a lifetime, recognizing that the data are not strictly representative of true long-term consumption patterns. It is difficult from a methodological point of view to obtain representative

data from single subjects to represent the exposure of consumers over a lifetime or over a specific life stage.

Lambe & Kearney (1999) warned that care should be taken when using short-term food consumption data unadjusted for within-person variation for estimating long-term or usual food consumption and nutrient intakes, as survey duration affects estimates of the proportion of consumers, high consumption amounts and the classification of individuals as high or low consumers of foods or nutrients. However, for the general population, mean estimates of dietary exposure based on short-term food consumption data are reliable.

Approaches that have been used to estimate long-term or habitual consumption include methods that:

- calculate the average daily food consumption amount for each individual over the duration of the survey;
- combine food frequency questionnaire data for a long time period (e.g. 1 year) with consumption amount information from a dietary survey conducted over a few days (e.g. Lambe & Kearney, 2000; Tran et al., 2004); and
- use a statistical approach to estimate the "usual" intake of food or nutrients or exposure to other food chemicals based on short-term consumption data.

The usual intake models are most appropriate when the chemical of interest occurs in a number of staple foods, resulting in a nutrient intake or chemical dietary exposure different from zero for virtually every individual each day. Parametric and non-parametric methods may be needed in order to better simulate the frequency of consumption for occasionally eaten food on a long-term basis. Several publicly available models are discussed further below (see section 6.5.6.1).

Usual intake methods remove within-person variation but not between-day variation, thereby decreasing the standard deviation of the distribution of nutrient intakes or estimated dietary exposures, as demonstrated in Fig. 6.2. For some usual intake models, at least 2 days of records are needed; for others, only a proportion of respondents need to have second-day records. Many of the usual intake models were developed to assess nutrient intakes but can also be used to estimate chronic dietary exposures to food chemicals (Hambridge & Baines, 2014). In a probabilistic assessment, care

needs to be taken to ensure that the desirable component of within-person variability of food consumption generated by the probabilistic simulation is not inadvertently removed during the calculation of usual exposure; the variance between survey days should be removed, not the variance between randomly assigned concentrations (Kuiper-Goodman et al., 2010).

Fig. 6.2. Comparison of 1-day and usual nutrient intake distributions
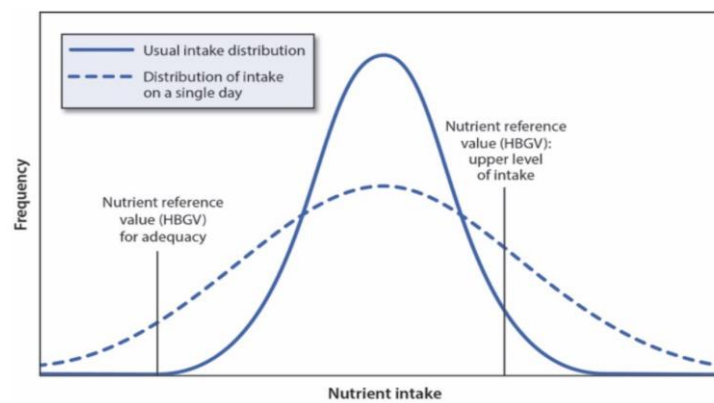
HBGV: health-based guidance value

Application of methods that adjust short-term food consumption records to better estimate long-term patterns of consumption will result in a distribution of long-term intakes of food or nutrients or dietary exposures to food chemicals that is narrower and shows less variability than the distribution of dietary intakes or exposures directly derived from the food consumption data for a single day prior to adjustment (Carriquiry, 2003; Herrick et al., 2018). For chronic mean dietary exposure estimates for the general population, the distribution range will not make a difference, but it will influence estimates for consumers only (mean and high consumers) of the food or chemical.

Usual intake models can be very time and resource intensive, which may not be justified for routine dietary exposure assessments (Vilone et al., 2014).

6.5.6.1   Statistical models for estimating usual intakes

Statistical models available for estimating usual intakes include the Iowa State University, NCI, Multiple Source Method, Statistical Program to Assess Dietary Exposure (SPADE) and logistic-normal-normal models.

PC Software for Intake Distribution Estimation was produced by researchers in the Department of Statistics at Iowa State University in the USA in 2001 (http://www.side.stat.iastate.edu/). The program can be used to implement the *Iowa State University method* (Nusser et al., 1996) to estimate the distributions of usual intake of nutrients, foods consumed almost daily and other dietary components. It can also be used to adjust biomarker data for within-person variability (Taylor et al., 2013).

The United States *NCI method* (https://epi.grants.cancer.gov/diet/usualintakes/method.html) can be used to model particular aspects of usual dietary intakes of foods and nutrients using 24-hour recalls. This method can be used to estimate the distribution of usual intake for a population or population subgroup, assess the effects of non-dietary covariates[5] on usual consumption and correct (at least partially) bias caused by measurement error in estimated associations between usual dietary intakes and health outcomes using the statistical technique of regression calibration. The NCI model can be used where only a proportion of survey respondents have a second-day record ($\geq 25\%$ and at least 50 people in each population subgroup studied) (ABS, 2013). This modelling technique does not accurately estimate usual intake for individuals.

The *Multiple Source Method* (https://msm.dife.de/), developed by the former Department of Epidemiology of the German Institute of Human Nutrition Potsdam-Rehbrücke, is freely available for use to calculate the usual dietary intake from 24-hour recall information and supporting data, such as food frequency questionnaire data. The Multiple Source Method is characterized by a two-part shrinkage technique (to reduce the effect of sample variation) that is applied to residuals of two regression models, one for the positive daily intake data and one for the event of consumption. The additional use of a

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[5] Non-dietary covariates may include demographics, health status, medication, physical activity, anthropometric measures and other non-diet-related factors that may influence food consumption patterns.

food frequency questionnaire is possible. The statistical method is applicable to nutrient and food intake, including episodically consumed foods. Variation in intake that is explained by sociodemographic variables selected in advance is not affected by the method.

The *Statistical Program to Assess Dietary Exposure (SPADE) model* (https://www.rivm.nl/en/spade), developed by the National Institute for Public Health and the Environment of the Netherlands (RIVM), estimates usual intake distribution for staples and episodically consumed foods or dietary components based on food consumption measured on a limited number of days. It also provides models to estimate usual intake distributions from different sources separately and adds these usual intakes in order to get the overall usual intake distribution.

To be in line with the other statistical models, a usual intake/exposure model – namely, the *logistic-normal-normal model* (comparable to the NCI usual intake model; see above) – is available on the Monte Carlo Risk Assessment (MCRA) platform developed by RIVM (https://www.rivm.nl/en/food-safety/chemicals-in-food/monte-carlo-risk-assessment-mcra), which is discussed in section 6.6.3.3.

In previous reviews of available usual intake methods for a European Trade Union Institute–funded project, a computational tool was delivered with several models to estimate usual intake distributions. Connected to this, guidelines to choose the optimal model for a given situation were recommended, with the logistic-normal-normal model the recommended tool for use in Europe (Van der Voet & Van Klaveren, 2010; Van Klaveren et al., 2012). Laureano et al. (2016) also reviewed the methods described above for estimating nutrient intakes using 1000 simulated samples for 12 different scenarios to compare the accuracy of estimates.

6.5.7 Specific data handling issues for chronic dietary exposure assessments

In some chronic dietary exposure assessments, the food chemical concentration or food consumption data required may not be readily

available, or the data that are available need to be manipulated prior to use, to better reflect the known situation.

For food chemical concentration data, for example, when considering additional uses of already regulated substances, proposed MLs may be used in a chronic dietary exposure assessment instead of use levels, as these will not yet be known. For food additives, it is likely that proposed use levels are those known from efficacy studies to achieve the desired technological function for the additive, so levels proposed by manufacturers pre-regulation and levels of use post-regulation may be similar. The dietary exposure from these new uses would be combined with that from foods where use is already permitted in the marketplace. The combination of MLs and measured concentrations more accurately estimates the overall probable total dietary exposure (see Table 6.3 for sources of data on concentrations of chemicals in food).

Some chemicals, particularly contaminants for which there are many congeners, may require the sum of concentrations from a number of congeners before the dietary exposure assessment (i.e. a cumulative dietary exposure assessment; see section 6.6.8) can be undertaken. For example, for non-dioxin-like polychlorinated biphenyls (PCBs), six congeners were noted to be of relevance at the eightieth meeting of JECFA, and the concentrations from these six congeners were summed for the dietary exposure assessment (FAO/WHO, 2016).

In some cases, the concentration data available for the dietary exposure assessment may not be for the specific food chemical of toxicological interest, and concentration data for an active ingredient may be used. For example, at the eighty-second meeting of JECFA, rosemary extract was evaluated as a food additive (antioxidant), but for the safety assessment, the sum of carnosic acid plus carnosol was used in the dietary exposure assessment, as these were the active ingredients (FAO/WHO, 2017a).

Dietary exposure assessments, and hence food chemical concentration data, may be required for breakdown products or metabolites of the substance of interest. For example, at the eighty-sixth meeting of JECFA, methacrylate copolymers used as coatings on food supplements were evaluated. As necessitated by the hazard assessment, dietary exposure assessments were done for the

copolymer itself, as well as the monomers and additional metabolites (FAO/WHO, 2019c).

The potential for interconversion between different forms of a chemical that can occur naturally or form during storage and processing, such as that which occurs between nitrates and nitrites, may also need to be taken into account. This potential interconversion may need to be considered when analysing foods or interpreting analytical concentration data. Another example is potassium polyaspartate, which is added to wine to prevent crystallization of tartrates and which was evaluated at the eighty-seventh meeting of JECFA. The relevant breakdown product is aspartic acid; however, this exists in D- and L- configurations, and separate dietary exposure assessments for these forms were needed, again based on the hazard assessment (FAO/WHO, 2019b).

For food consumption, in cases where only summary food consumption data are available, it is possible to sum potential dietary exposures to a chemical from multiple foods in a chronic dietary exposure assessment, but only where the same population group is used (i.e. for all respondents in the survey). The population of consumers of individual foods will be different in each case, so it is not valid to sum across consumers of foods only or to sum dietary exposure contributions based on high-percentile consumption estimates for different foods.

6.6 Estimating dietary exposure by combining data on food chemical concentration and food consumption

6.6.1 Introduction

Dietary exposure assessments are an important part of risk assessments that aim to identify substances that may be of safety concern using a minimum expenditure of resources and the best available data. For risk prioritization purposes, a tiered approach, in which the initial steps rely on highly conservative screening methods, may be the most appropriate. If no safety concerns are identified by these conservative screening methods, no additional dietary exposure assessment is required. The subsequent steps of the framework provide methods that incorporate increasingly specific or refined data and exposure models (and require more resources), as illustrated in section 6.1.4 and Fig. 6.2 above (see FAO/WHO, 1997, 2006a, 2008a; EFSA, 2011a). A summary of approaches commonly used for

each type of food chemical is given in Appendix 6.2 for easy reference, with details of these approaches and specific methods discussed below.

A tiered approach has been used by JECFA for determining chronic dietary exposures to food additives and contaminants, although it is now recognized that this approach may not always be the most efficient (FAO/WHO, 2019b). For example, agencies with adequate resources may decide that an estimate based on all available data should be undertaken straight away to make the best use of their resources (time, data, expertise), or a decision may be made to report the end result only, not the results of each step. In all cases, it is important to select an approach that errs on the conservative side and does not underestimate dietary exposure (or overestimate nutrient intakes, if assessing nutrient inadequacy). Other examples of a tiered approach for specific food chemicals are also available in the literature (e.g. Martyn et al., 2017 for benzoates; Tran et al., 2020 for food colours); a web-based tool (the Health and Environmental Sciences Institute's Risk Assessment in the 21st Century (RISK21) project: https://risk21.org/) is also available for use in tiered exposure assessments.

Refinements of dietary exposure estimates can include more defined information about the population subgroups of interest, foods that are consumed (less conservative assumptions about the amounts consumed, the concentrations of the chemical in individual foods within a food group or subgroup, impact of processing and food preparation, etc.), or more complex exposure assessment models can be employed that allow more realistic simulation of consumer practices. For example, the dietary exposure assessment may be refined by incorporating adjustment factors that reflect the impact of processing and food preparation on the concentration of a chemical in a food (raw rice → polished rice; fruit → peeled fruit; potato → cooked potato). Likewise, the consumption data can be refined to provide estimates of consumption of different forms of the food (raw, processed, food subgroups) (see sections 6.3.1, 6.4.1 and 6.5.3 for further details), or weighted mean concentration values can be applied to adjust for market share of different foods within a food group (see section 6.5.5).

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, particularly for population subgroups of interest. The methods should take into consideration specific life stage population subgroups or other susceptible populations. When a refined risk assessment is indicated, toxicological information generated in previous steps may also be reviewed and other information considered for inclusion in the assessment, such as internal rather than external dose and toxicokinetic models (for further details on hazard characterization and derivation of health-based guidance values, see Chapters 4 and 5). Non-average individuals, those who consume large portions of specific food items, those who consume many foods containing the chemical, those who are loyal to brands or types of foods containing higher concentrations of the chemical and those who have low or infrequent consumption of foods with very high concentrations of the chemical of concern may also be of interest to a risk assessor.

At an international committee level, resources should be dedicated to the application of refined deterministic or probabilistic methods only when there is a toxicological or dietary exposure concern that cannot be addressed using simpler and less resource-intensive methods or where probabilistic modelling is the only option – for example, in cumulative risk assessments. Where this is the situation, probabilistic dietary exposure estimates may be evaluated for a representative selection of national populations to arrive at an understanding of the overall situation. At a national agency level, refined deterministic or probabilistic assessments can be undertaken if the risk assessment indicates that there is a need for further information on exposure to inform a risk management decision and resources are available.

For the models to be as accurate as possible, the data on food consumption and the data on concentrations of the chemical in food should be for the same food products (see section 6.5.2). Reliable (statistically valid) dietary exposure estimates are derived from good data on food consumption and on concentrations of the chemical in food, 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 assess the potential dietary exposure situations.

In the subsections that follow, the statistical options for combining food chemical concentration and food consumption data

sets are discussed in more detail. The available methods may be deterministic (single point), refined deterministic (single point concentration estimate combined with distribution of individual food consumption values, or vice versa) or probabilistic estimates (characterizing the distribution of consumer exposures). The most appropriate approach will depend on the purpose of the risk assessment and data inputs available. It is not always necessary to undertake a probabilistic approach to obtain the best estimate of dietary exposure. In many cases, a deterministic approach based on comprehensive data sets is appropriate to ascertain risk. In addition, examples of specific methods for combining concentration and food consumption data sets are discussed, organized by type of assessment (acute, chronic, shorter-than-lifetime and aggregate and cumulative assessments), to assist the reader in selecting the most appropriate methods for each step of the framework, depending on the purpose of the assessment and data available (see Fig. 6.1 above).

6.6.1.1 *Documenting dietary exposure assessment methods*

As noted in section 6.1.2, when undertaking dietary exposure assessments, information about the dietary model selected, food definitions, sources of data on food consumption and concentrations of the chemical in food, and model assumptions should be clearly documented for purposes of transparency. The definitions of terms used and information (metadata) required to be documented on all aspects of a dietary exposure assessment are outlined in section 6.1.3. Details of documenting data limitations and uncertainties in dietary exposure assessments are given below in section 6.6.1.2.

Dietary exposure may be estimated using single-point deterministic, refined deterministic or probabilistic approaches (see sections 6.6.2 and 6.6.3). Specific methods available for estimating dietary exposure for acute or chronic toxicological concerns are covered in sections 6.6.4 (acute effects), 6.6.5 (chronic effects over a lifetime) and 6.6.6 (chronic effects over a shorter-than-lifetime period). An aggregate exposure assessment (see section 6.6.7) or a cumulative exposure assessment (see section 6.6.8) may also be undertaken for acute or chronic exposures.

For all approaches, it may be of interest to evaluate the general population, specific age/sex groups or the subgroup of the population that consumes the foods containing the chemical of interest, including high consumers. The terms used and assumptions made about

population subgroups in the dietary exposure assessment should be documented, together with other details of the approach used (as outlined in section 6.1.3).

6.6.1.2 *Documenting data limitations and uncertainties in dietary exposure assessments*

Data limitations and uncertainties in each dietary exposure assessment should be documented as far as is possible, to enable correct use of the dietary exposure estimates by the risk assessor in the risk characterization stage of the risk assessment (step 4) and by risk managers. A distinction should be made between variability in data (diversity of values) and uncertainty (lack of data or lack of understanding in the context of a risk assessment). Variability in data can be better described or characterized, but not reduced; uncertainty can be reduced or eliminated with more or better data (USEPA, 2019b).

All data sets have limitations as a result of the methods used to collect, record, code and analyse the data. These limitations may be due to the methods themselves or to errors in the process. Additional uncertainties are created by combining several data sets to derive an estimate of dietary exposure. These may be due to model choices, the representativeness of the food surveys available, foods consumed and the population of interest, and the adequacy of the dietary model selected to provide answers to the risk assessment questions. For the risk characterization step, there may also be uncertainties in the derivation of the health-based guidance value or the BMDL used in a margin of exposure approach that should be considered.

(a)   Uncertainty in data on concentrations of chemicals in food

The use of maximum concentrations of chemicals in food (MLs and MRLs) in dietary exposure assessments will overestimate the concentrations of chemicals present in foods, and these data introduce uncertainty into the dietary exposure assessments if used for any purpose other than a worst-case analysis. However, in the first step of a tiered approach, MLs or MRLs may be used (refer to Fig. 6.2), because it is desirable to estimate the maximum possible dietary exposure (worst case).

Concentration data for foods from supervised trials that measure chemical concentrations after treatment of crops with pesticides or

from animal tissues after treatment with veterinary drugs or reported manufacturer use levels for food additives may also overestimate actual levels in foods as sold or consumed, but are more representative of levels found in the food supply than maximum concentrations and introduce less uncertainty into the dietary exposure assessment. Still more accurate information on concentrations of chemicals in food may be available from national monitoring and surveillance surveys, especially when undertaken on food at the point of sale. Although measured data contribute to a more accurate estimate of dietary exposure, they do not necessarily reflect the impact of storage, transportation or preparation on the concentration of the chemical in the food. The most relevant concentration data are obtained from the measurement of concentrations of the chemical in foods as consumed, as in a total diet study. Although the total diet study approach would provide the least uncertainty, it is typically the most resource intensive, and use of concentration data from a total diet study is limited by its applicability to chronic dietary exposure assessments only (see section 6.6.5.2(b)).

Uncertainty in measured data is introduced by sampling that does not represent the food supply from different regions or different species of food types commonly consumed, lack of information on metabolites of the parent chemicals in the food, analytical errors (see Appendix 6.1) as well as choices on how to derive the concentration data for use in a dietary exposure assessment. The handling of censored values (non-detected or non-quantified results) in the data set of concentrations of a chemical in food is of importance when calculating summary statistics, such as the mean, as assumptions about assigning a value to non-detected or non-quantified results may influence the result of the assessment (see section 6.5.4). Based on the implied uncertainty in the range of values obtained from the lower- and upper-bound approaches, the risk manager can then determine whether the expenditure of time and resources necessary to gather additional information about the range of concentrations of the chemical in foods to further refine the dietary exposure estimate is warranted.

Uncertainties in data on concentrations of a chemical in food can be reduced by collecting higher-quality data (see Appendix 6.1). For example, a more sensitive method of analysis or method of quantification could be used to reduce the proportion of non-detected and non-quantified results, which would reduce the level of

uncertainty in the summary statistics. Indicators of data quality need to be clearly defined and provided to users of the data. This information should be sufficiently complete for users to be able to make critical decisions about the appropriateness of the available data for the specific use.

It is common for data on concentrations of a chemical in food to have a skewed distribution and for different data sets to be collected using different LORs (i.e. LOQ or LOD), making it difficult to combine data sets. For example, it is not best practice to combine individual and composite data into one data set; however, this is possible if no other information is available, provided that limitations and potential uncertainties are noted in the assessment (for further details, see section 6.5.4). Changes in concentrations of certain chemicals in food over time should also be considered prior to combining data sets collected over different years, as there may be real changes due to changes in agricultural or manufacturing practices or in the environment that should be considered separately.

(b)   Uncertainty in data on food consumption

National dietary surveys are generally intended to be representative of the populations surveyed; however, this is not necessarily true for smaller population subgroups of interest in a risk assessment. Use of a non-representative survey sample may introduce uncertainty in the food consumption data. The use of a point estimate for food consumption for the mean or a high-consumer amount in a dietary exposure assessment introduces more uncertainties than the use of a distribution of reported food consumption values. There may also be errors of recall by survey respondents, as well as food classification, coding and measurement errors. These have been well-documented elsewhere (EFSA, 2009). Application of recipes to disaggregate combined foods into ingredients or raw commodities can also introduce uncertainties where standard recipes are used; however, it does mean that combined foods can be included in the assessment, reducing uncertainties in the dietary exposure assessment (EFSA, 2014a).

(c)   Uncertainty in dietary exposure estimates

It may not be possible to quantify the level of uncertainty in the dietary exposure estimate; however, descriptions of where uncertainties are likely to occur and the potential impact of these

uncertainties on the final results are helpful for end users of the information (Hart et al., 2003). For example, uncertainties about concentrations used in the assessment of dietary exposure are often handled by performing a sensitivity analysis with different scenarios, such as use of lower-bound, middle-bound and upper-bound concentration values for non-detected results to estimate dietary exposures (see section 6.5.4).

Differences in the quantity and quality of concentration data available for different foods may lead to a lack of balance in a dietary exposure estimate, particularly for models that include both MLs/MRLs and measured/reported levels available for different foods. This has the potential for foods assigned an ML or MRL to drive the estimate of dietary exposure and increases the level of uncertainty in the assessment. Use of default body weights or self-reported body weights rather than application of measured body weights to food consumption amounts for an individual prior to including the data in a dietary exposure assessment also introduces uncertainty (see section 6.4.3).

A sensitivity analysis can be undertaken to determine the impact of the risk assessor's decisions about data handling and model assumptions on the final dietary exposure estimate. Apart from sensitivity analyses, in probabilistic modelling, more tools are available to include uncertainties, such as bootstrapping and parametric modelling (see section 6.6.3). The uncertainty can then be described as a 95% confidence interval around percentiles of dietary exposure. Agencies undertaking food chemical risk assessments may develop their own ways of documenting and describing the uncertainties in their assessments.

(d)   Use of expert knowledge elicitation techniques to document uncertainties

Expert elicitation refers to a systematic approach to obtaining and synthesizing subjective judgements from experts on a subject where there is uncertainty due to insufficient data or when such data are unattainable because of physical constraints or lack of resources. It seeks to make explicit and usable the unpublished knowledge and wisdom held by the experts, based on their accumulated experience and expertise. This may include insights into the limitations, strengths and weaknesses of the published knowledge and available data. Usually the subjective judgement is represented as a subjective

probability density function, reflecting the experts' belief regarding the quantity at hand and their level of confidence in that belief. An expert elicitation procedure should be developed in such a way that minimizes inherent biases in subjective judgement and errors related to that in the elicited outcomes.

Expert elicitation could potentially be used to fill gaps in information on food consumption and concentrations of chemicals in food as well as on dietary exposure estimates. However, it is a laborious and time-consuming process and should be used only when required.

In the food safety domain, expert elicitation has most frequently been used in relation to microbiological food safety issues. For example, expert elicitation has been used to estimate the proportion of the incidence of specific microbial diseases that is due to transmission through food (Vally et al., 2014; Butler, Thomas & Pintar, 2015; Hald et al., 2016; Cressey et al., 2019). In relation to chemical food safety, expert elicitation has been used to identify and prioritize indicators for emerging mycotoxins (Van der Fels-Klerx et al., 2009) and in cumulative dietary exposure assessments for pesticide residues (EFSA, 2020c,d).

(e)   Guidance documents on documenting uncertainties

The steps required to assess and document uncertainties at each stage of a dietary exposure assessment for different dietary exposure models are described by IPCS (2008), Kettler et al. (2015) and Tennant et al. (2017). Comprehensive guidance is provided by the USEPA (EPA EXPOsure toolBox [EPA ExpoBox]: https://www.epa.gov/expobox; USEPA, 2019b) and EFSA (2018c,d, 2019a) to assist with analysis of and communication of the level of uncertainty associated with a scientific risk assessment. Specific guidance for assessors is given on how best to report the various expressions of uncertainty, including templates for identifying expressions of uncertainty in scientific assessments.

6.6.2   *Deterministic estimates*

A deterministic estimate of dietary exposure in its most simple form uses a single value for both food chemical concentration and food consumption to estimate dietary exposure for a population or population subgroup. In a refined deterministic approach, either a

distribution of food consumption data is combined with a single value for concentration of the chemical in each food known to contain the chemical of interest or a distribution of food chemical concentration data is combined with a single value for food consumption.

6.6.2.1   *Single-point deterministic estimates*

Deterministic models may use a single point estimate for each model parameter:

- *Concentration data*: The point estimate may be the mean, the median, a high percentile of all observed values or the maximum concentration proposed by national or international food regulatory authorities. Concentrations can be further modified using additional conversion factors as appropriate (see section 6.5.3).

- *Food consumption data*: The point estimate may be the mean, median or a high percentile of all the consumption values of a considered food in the population of interest for the whole population (consumers and non-consumers of foods containing the chemical of interest), a population subgroup or consumers of the food containing the chemical of interest (see section 6.4). A point estimate can be derived from distributional data – for example, a mean value for the general population could be derived; or, for consumers only, a 50th percentile (median) to represent regular consumers or high percentiles (e.g. 90th or 95th) to represent high consumers could be derived. For chronic dietary exposure estimates where there are 2 or more days of data, food consumption data are first averaged across the days of the survey for each individual to better represent long-term food consumption patterns before deriving summary data.

   Although it is preferable to record more than 1 day of dietary records, surveys with 1 day of food consumption data per individual can be used to determine mean chronic dietary exposures for the population, but should not be used to derive summary statistics for consumers only of the foods of interest because high-percentile values increase levels of uncertainty about whether the top end of the distribution range represents typical food patterns for the population studied.

A 1-day survey results in a wider range of food consumption amounts compared with a multiple-day survey, where amounts of food consumed have been averaged over the number of days for each person, with the range of averaged food consumption values decreasing and the proportion of consumers of the foods increasing as the number of survey days increases (Lambe & Kearney, 2000; Doell et al., 2016). For 2-day or 3-day survey data, a lower-percentile value can be used for chronic dietary exposure estimates to represent consumers only; for example, the USFDA and Food Standards Australia New Zealand (FSANZ) routinely use a 90th percentile for consumers only to represent a high consumer, based on 2-day surveys.

6.6.2.2   Refined deterministic estimates

Refined deterministic estimates use a distribution of values for one variable. Most commonly, a point estimate of concentration for a given chemical for each food is combined with individual dietary records from a national dietary survey. These models may be used for chronic and acute dietary exposure assessments. In a chronic dietary exposure model, the mean is used as the point estimate of the concentration of the food chemical of interest.

Each point on the distribution curve of food consumption can be multiplied by the concentration in the relevant food commodity. A distribution of total individual dietary exposures is generated, from which population summary statistics are derived. With the use of additional models, the usual dietary exposure or usual nutrient intake based on this distribution can also be assessed by removal of the within-person variation (see section 6.5.6).

It is possible to have a single point estimate for consumption and an empirical distribution of chemical concentrations in that food. This approach is not commonly used, but would be more relevant to an acute dietary exposure assessment.

6.6.2.3   Use of deterministic dietary exposure estimates

Deterministic estimates may be used for 1) screening methods, 2) model diets and 3) more refined methods using distributional data as a starting point. The initial screening methods may use very few data and generally include very conservative assumptions, whereas refined exposure assessments may include extensive underlying data

in order to more realistically estimate the desired dietary exposure. In some screening methods, actual food consumption data are not utilized at all – for example, in the poundage and budget methods (see section 6.6.5.1).

Factors such as edible portion, effect of processing, percentage of crops treated for pesticide residues and consumer behaviour, such as being loyal to certain brands or products, can also be applied where relevant to all deterministic estimates (see section 6.5.5), if the information is available.

6.6.2.4   *Advantages and limitations of deterministic estimates*

A deterministic dietary exposure estimate is not inherently "conservative" or "realistic". The conservatism incorporated into the estimate is determined by the data and assumptions that are used in its calculation. The results are dependent on the input data and their appropriate treatment, but the impact may not be readily apparent. For example, 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 or high consumption values) are used in the estimation, the resulting exposure estimates will overstate typical dietary exposures. This may be useful in the first steps of a tiered approach or when determining a worst-case scenario to decide whether further refinements in the dietary exposure assessment approach are necessary (Tran et al., 2020). Nonetheless, it is important to keep in mind that it is difficult to know just how conservative the result will be.

Deterministic methods have the advantage of being relatively simple to implement, with less resources required than for probabilistic modelling. Models can often be "developed" by using tools such as spreadsheet or database programs. However, where such models contain limited additional information about the source of the data used, interpretation of the results can be problematic.

Consumption data need to be on an "all respondent" basis when deriving a point estimate for the general population where there are numerous foods containing the chemical and the exposures from each food need to be summed to obtain an estimate of dietary exposure for the population. This may lead to underestimates of dietary exposure if the foods are not consumed by a large proportion of the population and many zero consumption amounts skew the mean consumption

amount down. Estimates of dietary exposure may therefore not reflect actual dietary exposures for consumers of the foods containing the chemical of interest. If this is of interest to risk managers, summary results for consumers only (not the total population) of foods containing the chemical of interest are derived. This is particularly important for non-staple foods (i.e. foods not typically consumed every day by most people). Where a full distribution of food consumption data is available, then individual dietary exposures are calculated, and a high-percentile dietary exposure is selected from the distribution of dietary exposures to represent a high consumer (refined deterministic or probabilistic approach).

The contributions to total dietary exposure from each food containing the chemical, calculated as a percentage of the total mean dietary exposure, may be presented in a dietary exposure assessment report. Care should be taken in interpreting these results if a single food significantly impacts the total dietary exposure for consumers, in which case the distribution of exposures may be multimodal.

6.6.3 *Probabilistic/stochastic estimates*

The structure of a probabilistic/stochastic model is like that of the deterministic models described above in section 6.6.2, in that it is based on the same basic equations whereby food consumption data are combined with food chemical concentration data to estimate dietary exposure. The fundamental difference is that variables are represented by a distribution instead of a single value and the models sample from each distribution (food consumption and food chemical concentration) to produce a distribution of potential dietary exposures.

A range of dietary exposures for a population is estimated by generating multiple iterations of combinations of the two data sets. Each iteration is a deterministic calculation using food consumption and food chemical concentration values randomly selected from the input distributions. These models could be used for acute, chronic, aggregate or cumulative exposure assessments. Probabilistic assessments are becoming easier to undertake with improved availability of individual data sets and computing techniques.

As for deterministic estimates, where appropriate to do so, it may be possible to further refine probabilistic models by taking account of factors such as edible portion, effect of processing, percentage of

crops treated for pesticide residues and consumer behaviour, such as being loyal to certain brands or products (see section 6.5.5). Simple probabilistic acute dietary exposure 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. An example of the use of complex probabilistic acute dietary exposure assessments in the European SafeFood project has been reported (Boon et al., 2009).

Characterizing the full distribution of consumer exposures is resource intensive, as data are required that characterize the range of food consumption habits as well as the range of chemical concentrations in the foods that are eaten. When a probabilistic approach is employed, random samples are selected from both food chemical concentration and food consumption data sets to generate a range of possible consumer exposures from the food chemical concentration/food consumption combinations possible, with associated probabilities of consumers having each level of exposure described. Some of the web-based models that are available for conducting probabilistic assessments are further discussed below (see section 6.6.3.3).

Probabilistic approaches may also be applied to assess uncertainties and homogeneity of data used in the dietary exposure assessments (both refined deterministic and probabilistic) – for example, bootstrapping statistical techniques.[6]

6.6.3.1 *Developing distributions for use in probabilistic dietary exposure estimates*

There are two general approaches to developing distributions for use in a probabilistic dietary exposure estimate: 1) non-parametric and 2) parametric techniques.

Non-parametric techniques can be used when actual data sets are available for a parameter. In these cases, the data sets are assumed to represent the distribution of interest. The probabilistic assessment is implemented by randomly selecting one of the values from the data

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[6] Bootstrapping first obtains a simple random sample from the population, then generates hundreds or thousands of simulated samples by taking repeated samples with replacement from this original sample. From these, a confidence interval for the sample statistic of interest is constructed using the sampling distribution formed by the simulated samples.

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. Food consumption data sets are usually treated as empirical (i.e. non-parametric) data.

Parametric techniques interpolate among the data points and extrapolate beyond them by assuming a 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. Some evaluations may use several models and take the average of the outcomes, rather than assume that one form is the best fit. Parametric distributions are often used for data on concentrations of chemicals in food. For food consumption data, parametric distributions are not generally used for more than one food, as correlations between consumption of foods traditionally eaten together (e.g. dahl and rice, salad ingredients) cannot be taken into account, and additional uncertainties are introduced.

In general, the primary differences between the parametric and non-parametric techniques are the availability, or not, of the data, the methods that are employed to draw values from the data and the evaluation of uncertainty and variability.

Another important difference is that the non-parametric distributions have an upper-bound value, whereas the parametric distributions extend to infinity in many cases. Techniques for truncating parametric distributions to avoid unrealistic dietary exposure scenarios are available – for example, using distributions that simulate concentrations in single units using a beta distribution (for guidance on probabilistic modelling, see EFSA, 2012e; USEPA, 2014; Boon et al., 2015).

Different techniques are available in most statistical software packages for sampling from the data distributions (e.g. single stratum sampling, stratified sampling, Latin hypercube model) (Cummins et al., 2009).

For acute dietary exposure assessments, both food consumption and food chemical concentration distributions are used in the calculation. For chronic dietary exposure assessments to determine mean dietary exposure, use of the mean concentration for each food included in a refined deterministic dietary exposure assessment results in the same outcome as using the whole concentration distribution in a probabilistic approach. It is reasonable to assume a mean concentration value, as this "average" value is what is likely to be experienced over a lifetime. However, the individual concentrations per food available in the probabilistic approach are useful in that they can be used to capture uncertainty using the bootstrap approach.

6.6.3.2 *Advantages and limitations of probabilistic estimates*

Probabilistic and deterministic approaches would not necessarily give different mean dietary exposure estimates for a population if sufficient iterations are undertaken to provide a converged (stable) population distribution. Probabilistic distributional analyses give the most information on the variability in dietary exposure estimates across the population of interest for use by risk assessors and risk managers. For refined deterministic estimates, less information is available on the range of possible exposures because single input values are selected for one of the variables (e.g. mean concentration of a chemical in food); however, a range of dietary exposures is produced. Both refined deterministic and probabilistic models provide more information on the dietary exposure distribution than do deterministic estimates based on single point values. Models using distributions of food consumption data take consumer habits in relation to food consumption patterns into account in the risk assessment.

Probabilistic modelling is undertaken for more complex assessments and might be undertaken to refine dietary exposure estimates when ongoing toxicological safety concerns are expressed with results from deterministic models. It requires more resources than a deterministic model in terms of data, time and expertise.

The use of probabilistic modelling by international committees has been investigated, but it should be undertaken only on a country-by-country basis. An example of a probabilistic assessment using a Monte Carlo model was that conducted to assess consumer exposure to acrylamide by the FAO/WHO Acrylamide in Food Network

(http://www.acrylamide-food.org/). A probabilistic approach to estimating dietary exposure to acrylamide was also evident in submissions by some countries considered in the most recent JECFA evaluation of acrylamide (FAO/WHO, 2006a).

6.6.3.3 Web-based tools

There are commercially available probabilistic modelling tools (e.g. using Monte Carlo techniques), but few publicly available platforms specifically for use in the risk assessment of chemicals in food.

The MCRA platform is an example of a calculation tool containing multiple models to assess chronic and acute dietary exposures to both single and multiple compounds (https://www.rivm.nl/en/food-safety/chemicals-in-food/monte-carlo-risk-assessment-mcra). MCRA, first developed in 1999 and hosted by RIVM in the Netherlands, is being continuously updated with financial support from the Dutch government, European Union projects and EFSA and is compatible with the main features of the FoodEx2 food classification system (see section 6.5.1).

The MCRA platform can be used to undertake probabilistic modelling of dietary exposure to food chemicals using a number of models, including usual intake models and cumulative dietary exposure models (see section 6.6.8). It also contains a module for aggregate exposure (see section 6.6.7). The cumulative exposure assessment feature of MCRA has been improved over time, as part of the EuroMix project (https://www.euromixproject.eu/), with the development of a handbook and toolbox for external use (Van der Voet et al., 2020).

The Cumulative and Aggregate Risk Evaluation System Next Generation (CARES NG: https://caresng.org/about/) is another example of an online, cloud-based system that allows probabilistic estimation of aggregate and cumulative exposure for pesticide residues and estimation of risk across food, water and residential exposure routes. The dietary intake data underlying the system are from the USA's National Health and Nutrition Examination Survey/What We Eat in America (https://www.cdc.gov/nchs/nhanes/wweia.htm) 2005–2010 cycles, disaggregated using USEPA's Food Commodity Intake Database recipes (https://fcid.foodrisk.org/recipes/). Concentration data from the

USDA's Pesticide Data Program (https://www.ams.usda.gov/datasets/pdp) are also included in the system.

Modelling dietary exposures for high consumers of a food chemical can be accomplished by conducting a full distributional analysis using Monte Carlo techniques. Where adequate data are not available for both food chemical concentration and food consumption to conduct a distributional analysis, arbitrary factors may be incorporated to simulate the upper end of the distribution of exposure to the food chemical (e.g. by assuming that the food chemical concentration data distribution is lognormal). A probabilistic approach is also taken in the web-based tools available for estimating usual food or nutrient intakes (see section 6.5.6).

6.6.4   Estimating acute dietary exposure

For acute dietary exposure assessments, there is no appropriate screening method. As a first step, a model diet (deterministic approach) is used by international committees and food safety or regulatory agencies. These model diets estimate acute dietary exposure from a single food/chemical combination only and cannot account for multiple food sources of the chemical.

If a refined acute dietary exposure assessment is required and national data sets are available that include distributional data on food consumption, a refined deterministic approach can be used. If distributions of concentrations of the chemical in food are also available, a probabilistic approach can be used. A probabilistic approach can be used to estimate acute dietary exposure for several foods consumed in a single meal or day (see section 6.6.4.2). Table 6.5 indicates the different types of data that need to be derived from these data sources for estimates of acute dietary exposure to pesticide residues, veterinary drug residues or contaminants, as described in detail in section 6.6.4.1.

For most food additives (including flavouring agents), acute toxicity is not a concern at the levels to which humans are expected to be exposed through the use of the food additives. Therefore, ARfDs do not need to be established, and there is no need to undertake an acute dietary exposure assessment.

Occasionally, acute intolerance reactions may be relevant, such as laxation from polyol sweeteners. For some chemicals, allergic

Table 6.5. Data used for acute dietary exposure assessments

Dietary exposure assessment	Food chemical concentration data	Food consumption data
Deterministic Acute dietary exposure assessment for general population, population subgroups if relevant For pesticide residues: IESTI, NESTI, GEADE For veterinary drug residues: GEADE For contaminants: GEADE	*IESTI/NESTI for pesticide residues* Highest residue level derived from distribution of trial data, unit weight data, variability factor (processing factors may be applied) *GEADE for pesticide residues* Highest residue level, STMR derived from distribution of trial data *GEADE for veterinary drug residues* High and mean residue levels derived from residue depletion studies *GEADE for contaminants* High and mean percentile concentration values	*IESTI/NESTI for pesticide residues* Large portion derived from single consumer days from national survey, individual records (97.5th percentile) Expressed per kilogram body weight (may use standard body weights) *GEADE* Individual food consumption data (non-parametric) or single 97.5th percentile derived from a distribution, expressed per kilogram body weight
Probabilistic/ stochastic Acute dietary exposure assessment for general population, population subgroups if relevant MCRA web-based platform (RIVM) available for use, see section 6.6.3.3	Individual concentration data for single food units *or* use parametric techniques to generate a distribution *or* assume normal distribution and use mean and standard deviation	Individual food consumption data (non-parametric) expressed per kilogram body weight

GEADE: global estimate of acute dietary exposure; IESTI: international estimated short-term intake; MCRA: Monte Carlo Risk Assessment; NESTI: national estimated short-term intake; RIVM: Dutch National Institute for Public Health and the Environment; STMR: supervised trials median residue level

reactions may sometimes be of concern, but there are currently no 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 (USFDA, 2006; EFSA, 2014b).

6.6.4.1 Deterministic approaches

(a) Pesticide residues

Since its development in 1997 and first implementation by JMPR in 1999, the methodology for estimating acute dietary exposure to pesticide residues has been refined by JMPR (FAO/WHO, 1997, 1999a,b, 2004, 2013).

Although it was recognized that probabilistic modelling provides the most refined acute dietary exposure estimate (see section 6.6.4.2), it was also recognized that the use of probabilistic modelling was difficult at the international level, and a simpler method was developed. At the international level, a deterministic methodology was first developed in 1997 to calculate acute dietary exposure to pesticide residues at an expert consultation on dietary exposure (WHO, 1997), which was then further developed and implemented by some national food safety agencies and JMPR (Hamilton & Crossley, 2004). The international estimated short-term intake (IESTI) estimates acute dietary exposure to a pesticide residue in each food likely to contain the chemical. At a national level, this is termed the national estimated short-term intake (NESTI).[1]

IESTI or NESTI estimates are performed for each food commodity separately, as it is considered unlikely that an individual would consume, within a meal or 24 hours, two large portions of different commodities that contain the same pesticide at the highest residue level. For acute dietary exposure estimates for consumers of foods containing the food chemical, the large portion is the 97.5th percentile of consumption, derived from single consumer days, with

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[1] Since the establishment of these definitions in 1997, the use of dietary exposure terminology has changed. IESTI and NESTI equations have always been intended to estimate acute dietary exposures – i.e. from food consumption over a 24-hour period.

no averaging across survey days for individuals with multiple dietary records. For risk assessments undertaken by international committees that include large portion and food chemical concentration data from individual countries, it is preferable to use the mean body weight from each national survey in dietary exposure estimates.

For pesticide residues, three different IESTI/NESTI cases are recognized, with different acute dietary exposure equations for each one:

- Case 1 is the simple case where the residue level in a composite sample reflects the residue level in a meal-sized portion of the commodity (i.e. food has a low unit weight <0.025 kg, e.g. peas, grapes). Case 1 also applies to animal products (meat, offal, eggs) and grains, oilseed and pulses when the estimates are based on post-harvest use of the pesticide.

- Case 2 is the situation where the meal-sized portion as a single fruit or vegetable unit might have a higher residue level than the composite sample. There are two scenarios: case 2a, where the unit size is less than the large portion (e.g. apples), and case 2b, where the unit size is greater than the large portion (e.g. watermelon).

- Case 3 allows for the likely bulking and blending of processed commodities such as milk, flour, vegetable oils and fruit juices where the median residue level (i.e. STMR) represents the residue concentration in the IESTI/NESTI equation.

The concept of a variability factor was introduced by JMPR to account for the different concentrations of residues in individual units of a composite sample and is applied in the case 2a and case 2b equations. In the early 1990s, research on residues of acutely toxic pesticides (e.g. organophosphates and carbamates) in individual fruits and vegetables revealed random occurrences of comparatively high residue levels in single food units. It became apparent that some individuals who consume significant amounts of such foods (large portions) will occasionally eat the "hot" (high residue) commodity unit. 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 and has been used as a default value by JMPR since 2003 (FAO/WHO, 2004).

The equations used by JMPR are published by FAO/WHO (2013).

(b)   Veterinary drug residues

Few ARfDs have been set for veterinary drug residues by JECFA; however, a similar risk assessment can be undertaken as for pesticide residues, using a point estimate similar to the case 1 IESTI equation for animal products or the case 3 equation for dairy products.

A global estimate of acute dietary exposure (GEADE) is calculated for individual foods (Boobis et al., 2017), using either a single 97.5th percentile of food consumption and mean body weight for the population assessed or individual food consumption data per kilogram body weight to derive the 97.5th percentile of food consumption:

$$\text{GEADE} = \frac{\text{97.5th percentile food consumption (single person day)} \times \text{highest residue in each relevant tissue}}{\text{Body weight (kg)}}$$

In some cases, the impact of bioaccessibility (the amount of drug that desorbs from a food in a form that is available for absorption) and bioavailability (the extent to which residues enter the systemic circulation) may need to be considered (Boobis et al., 2017), as might the possibility of higher residues at injection sites in tissues that are consumed. JECFA and the Codex Committee on Residues of Veterinary Drugs in Foods are developing guidelines for injection site residues, where the ARfD is based on microbiological end-points. Dietary exposures to these residues pose the potential problem of exceeding the ARfD even when residues in other parts of the tissue are at or below their MRLs. 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. penicillin).

(c)   Other food chemicals (contaminants, GMOs)

There is no standardized methodology for acute dietary exposure assessments for contaminants, as ARfDs are rarely established. In the rare instances when the toxicological evaluation indicates a need for an acute dietary exposure assessment, the case 1 IESTI/NESTI or the GEADE calculation could be considered for use (see sections 6.6.4.1(a) and 6.6.4.1(b)).

For newly expressed proteins in genetically modified foods, EFSA uses an acute dietary exposure deterministic method for the average population and high consumers that takes into account acute exposure from a dominant food but also allows for background exposure from other foods. For the average population, acute dietary exposure is estimated by adding the mean dietary exposure estimate from the dominant food for the whole population (mean consumption multiplied by the 95th percentile concentration in the processed commodity) to the mean dietary exposure estimates for the whole population from all other foods using mean concentration values. Acute dietary exposure for high consumers is estimated by adding the high-percentile dietary exposure estimate for the dominant food (95th percentile on consuming days only multiplied by the 95th percentile concentration in the processed commodity) to the mean dietary exposure estimates from all other foods for the whole population using mean concentration values (EFSA, 2019c).

6.6.4.2   *Probabilistic approaches*

In cases where the chemical may be found in several foods and a combined exposure from the diet may result in an exceedance of the ARfD, a probabilistic approach is very useful, as this situation cannot be covered in the deterministic model diets described above (Boon et al., 2009; EFSA, 2012e).

Probabilistic models are increasingly being considered at national and international levels, typically for acute dietary exposure assessments for pesticide residues, but they are also applicable for other food chemicals that have an acute health-based guidance value (see section 6.6.3). They are the only option available for modelling the acute risk from cumulative dietary exposures (see section 6.6.8), which is generating increasing attention as sophisticated techniques are becoming more widely available (e.g. EFSA, 2020c).

6.6.5   *Estimating chronic (lifetime) dietary exposure*

A summary of possible methods and approaches for chronic dietary exposure assessments is given in Table 6.6. Detailed information is given below, including the data requirements for each approach.

Table 6.6. Summary of available chronic dietary exposure methods

Method	Description	Potential use
Screening		
Physiological requirements for food and drink	Budget method (risk prioritization only)	Food additives, processing aids
Poundage data	Poundage data estimates	Food additives, including flavouring agents
Supply utilization data	MSDI	Flavouring agents
	GEMS/Food cluster diet estimates	All food chemicals except food additives, unless found in the limited number of processed foods reported in cluster diets
	IEDI/NEDI	Pesticide residues
Single-point deterministic estimates		
Model diets	SPET/APET	Flavouring agents
	High-consumer models (e.g. GECDE)[a]	All food chemicals[b]
	Sweetener substitution model	Intense sweeteners
	Chemical migration model diets (e.g. model diets in EU and USA)	Packaging materials
Refined deterministic estimates		
Individual dietary survey (food consumption) data for countries with single-	Estimates undertaken by food safety organizations or regulatory agencies	All food chemicals[b]

Method	Description	Potential use
value concentration data	Total diet study estimates	All food chemicals[b]
	Web-based tools (see section 6.6.5.2(c))	
	FAIM (EFSA)	Food additives
	FACE (EFSA)	Feed additives and their metabolites
	FEIM (EFSA)	Enzymes
	RACE (EFSA)	Single contaminants
Food consumption and/or dietary exposure adjusted for long-term consumption patterns	Usual intake estimates (see section 6.5.6)	Food consumption, nutrient intakes, food chemical exposures
	Web-based tools (usual intakes)	
	ISU usual intake model	
	NCI usual intake model	
	MSM for usual dietary intakes (DIFe)	
	SPADE (RIVM)	
	LNN model (part of RIVM's MCRA platform)	
Probabilistic/stochastic estimates		
Individual dietary survey (food consumption) and individual or average food chemical concentration data	Estimates undertaken by food safety organizations or regulatory agencies	All food chemicals[b]
	Web-based tools (see section 6.6.3.3)	
	MCRA web-based platform (RIVM)	
	CARES NG web-based platform (USA)	

APET: added portion exposure technique; CARES NG: Cumulative and Aggregate Risk Evaluation System Next Generation; DIFe: German Institute of Human Nutrition; EFSA: European Food Safety Authority; EU: European Union; FACE: Feed Additive Consumer Exposure; FAIM: Food Additive Intake Model; FEIM: Food Enzyme Intake Model; GECDE: global estimate of chronic dietary exposure; GEMS/Food: Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme; IEDI: international estimated dietary intake; ISU: Iowa State University (USA); LNN: logistic-normal-normal; MCRA: Monte Carlo Risk Assessment; MSDI: maximum survey-derived

intake; MSM: Multiple Source Method; NCI: National Cancer Institute (USA); NEDI: national estimated dietary intake; RACE: Rapid Assessment of Contaminant Exposure; RIVM: Dutch National Institute for Public Health and the Environment; SPADE: Statistical Program to Assess Dietary Exposure; SPET: single-portion exposure technique; USA: United States of America

[a]   Food consumption distributions may be used to derive point estimates for high consumer models, including the GECDE, for the general population and population subgroups.
[b]   Includes nutrients.

It should be emphasized that the actual consumer exposures are not altered when going from a screening to a more refined approach; rather, the accuracy with which those dietary exposures are estimated is improved by using more refined methods. Note that for screening methods, the overestimation of potential dietary exposure is deliberate.

6.6.5.1   Screening methods

Screening methods should be designed to reflect the particulars of the dietary exposures that are to be considered and may be different for food additives, contaminants, pesticide residues and veterinary drug residues. The screening method that is selected should be easy to use and pragmatic. The dietary exposure derived using a screening method should overestimate dietary exposure of high consumers using conservative assumptions in terms of food consumption and concentrations of the chemical in food. This will avoid situations where the dietary exposure estimated by the screening process would erroneously indicate no safety concern (i.e. understate dietary exposure). However, in order to effectively screen chemical substances and establish risk assessment priorities, the first step of the procedure should not consider unsustainable diets, or the results will be too unrealistic to be useful. At a minimum, physiological limits of food consumption should be considered.

Although screening methods are sometimes criticized as being "too conservative", it must be borne in mind that their primary aim is not to assess true dietary exposure but to identify food chemicals for which a more refined and comprehensive dietary exposure assessment is necessary. This must be made clear when results are presented, as should all assumptions that have been made.

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, to provide a consistent basis for risk decision-making.

Screening methods can be created that are appropriate for a worst-case assessment of compounds that are toxic over the long term, as well as for specific population subgroups of interest. The screening methods described below are not appropriate for shorter-than-lifetime dietary exposure assessments (see sections 6.2.3 and 6.6.6), as data cannot be disaggregated into age/sex population subgroups, or for aggregate exposure assessments (see sections 6.2.4 and 6.6.7), as they do not take exposure from non-dietary sources into account.

(a)   Budget method (food additives, processing aids)

A screening method referred to as the budget method may be used to assess the theoretical maximum daily dietary exposure to food additives for the general population as the first step in using the dietary exposure assessment framework. Primarily, the budget method is a suitably conservative screen to establish risk assessment priorities (Douglass et al., 1997).

The budget method estimates a theoretical maximum dietary exposure and relies on assumptions regarding 1) the level of consumption of foods and of beverages, 2) the maximum concentration of the food additive in foods and in beverages and 3) the proportion of foods and of beverages that may contain the food additive, where information is available to determine that the food additive is likely to be used in only some food groups. 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 beverages per kilogram of body weight and the daily consumption of 100 kcal per kilogram of body weight from foods (equivalent to 0.05 kg per kilogram of body weight based on an estimated energy density of 2 kcal/g). In a 60 kg person, these levels correspond to the daily consumption of 6 litres of beverages and 3 kg of food. However, these physiological levels of consumption may be modified by assuming that only a certain proportion of solid foods or beverages contain the food additive.

For example, fresh milk and water will not contain food additives (as food regulations do not permit their addition), so a maximum of half of the total amount of the daily consumption of beverages is

generally assumed likely to contain a food additive (i.e. 50% ×
maximum physiological level of consumption of beverages,
equivalent to 0.05 litre of beverages per kilogram of body weight).
The proportion can be further reduced where it is known that the food
chemical is present in only some types of beverages (not including
milk and water).

The overall theoretical maximum daily exposure to a food
additive is calculated by summing the potential exposures from
beverages and from foods, as shown in the basic equation below:

Overall theoretical maximum daily exposure (mg/kg body weight per day)	=	[maximum level of the food additive in beverages (mg/L) × 0.1 L/kg body weight × percentage of beverages that may contain the food additive] + [maximum level of the food additive in solid foods (mg/kg) × 0.05 kg/kg body weight × percentage of solid foods that may contain the food additive]

Theoretical maximum dietary exposures are compared with the
health-based guidance value (e.g. ADI) for the food chemical
(Hansen, 1979). If the theoretical dietary exposure exceeds the
health-based guidance value, then a comprehensive and more refined
dietary exposure assessment is required.

The budget method has been used by JECFA and by other food
safety and regulatory agencies in food additive evaluations; however,
as computer systems with access to individual dietary records become
more commonly used, it is less likely to be included as a first step in
a tiered approach to dietary exposure assessment. A past example of
its use as a screening tool is in the screening of food additives in
Europe in the 1990s (EC, 1998). For 22 out of 58 food additives
assessed, the potential dietary exposure calculated with the budget
method was lower than the relevant ADI, whereas the remaining 36
of these food additives did not "pass" the budget method (i.e.
potential dietary exposure exceeded the ADI), and more refined
dietary exposure assessments were recommended. The assumptions
of the budget method with respect to energy intakes and energy
density of foods were examined in a case-study of food additives,
applying the assumptions used for European Union assessments.
Overall, the dietary exposure to food additives estimated with the
budget method was found to be higher than estimated survey-based
95th percentile dietary exposure to food additives, and assumptions

for the energy density of foods were found to be only slight overestimates (Douglass et al., 1997).

The budget method has the advantage of requiring no food consumption data and of being very simple and rapid to perform. A limitation 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" of the general food supply, such as chewing gums, which are then not used in the calculation. When such items are identified, assessment of the quantity of the specific food item that would lead to exposure in excess of the health-based guidance value should be performed as a back-calculation in parallel with the budget method and compared with known consumption patterns in order to determine whether the consumption of the specific item could potentially lead to dietary exposure in excess of the health-based guidance value (see section 6.6.5.1(b)).

In summary, the budget method is a simple, inexpensive and conservative screening method that can easily be applied to all food additives and processing aids, for comparison with their relevant health-based guidance values, provided the maximum use levels of the chemical in foods and beverages can be ascertained.

(b)   Reverse budget method (food additives, processing aids, contaminants)

A reverse budget method can be used to calculate the amount of food that it is necessary to consume for dietary exposure to reach the health-based guidance value, assuming the maximum level of use (theoretical maximum consumption amount). An assessment is made as to whether consumption of this amount of food is likely or not, by reference to available food consumption data from national dietary surveys. This model works well if the chemical is known to be present in only a few foods and can be applied to food chemicals other than food additives – for example, contaminants. If the amount of food

that may be consumed before the health-based guidance value is exceeded is lower than expected consumption, then more accurate dietary exposure assessments are required.

Alternatively, the reverse budget method can also be used to calculate a theoretical maximum allowable level of the chemical in a food that would result in dietary exposure reaching the health-based guidance value, assuming a high-percentile amount of the food is consumed (e.g. Tran et al., 2020). This model works well where the chemical is found only in a single food or beverage, but adjustments can be made to allow for background dietary exposure from other foods.

(c)   Poundage data estimates (food additives, including flavouring agents)

Poundage data provide estimates of the amount of a chemical substance available per capita for use in food manufacturing in a country over a specified period. For example, food additives (including flavouring agents) are often considered in terms of 1 year of production. These estimates take into account the original production volume and may include the amounts of the chemical from imports or exports and of foods containing it. Exposure assessments may also include non-food uses.

This is not strictly an estimated dietary exposure, as it is not based on observed consumption patterns or on data on the actual concentration of the chemical substance in foods; rather, it provides the amount of the food additive that may be available for consumption in a given population. Census data are usually used for the total population count for the country where the food additive is produced to derive per capita poundage data.

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; if data are available, the per capita dietary exposure estimate may be averaged over a number of years to obtain an annual production amount. Dietary exposure estimates based on poundage data may also be adjusted by the proportion of the population predicted to consume the food (per cent consumers) in which the chemical may be present, as well as for underreporting of the amount

of chemical produced. Nonetheless, there is a very large uncertainty in a mean dietary exposure estimate 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.

A Procedure for the Safety Evaluation of Flavouring Agents was first adopted at the forty-sixth meeting of JECFA in 1996 (FAO/WHO, 1996). The procedure used annual production volume data for different regions to determine whether estimated per capita dietary exposure exceeded the threshold exposure amount for the relevant TTC structural class of the flavouring agent. This estimate, termed the maximum survey-derived intake (MSDI), is derived from figures for the total annual production of flavouring agents, adjusting for the fact that not all the chemical produced would be reported (a factor of 0.6 was used) and assuming that the flavouring agent would be consumed by only 10% of each population considered. MSDI estimates were originally based on production and population data for the USA and Europe, but now include data from Japan, with a requirement for recent production data to be submitted by the industry to each JECFA meeting. At the sixty-eighth meeting of JECFA (FAO/WHO, 2008b), the Committee adopted a new correction factor of 0.8 for the annual production volumes reported in the surveys from Europe, Japan and the USA to account for decreased underreporting.

Poundage data can be used to provide an indication of the historical and geographic trends in the use of a substance or as a comparative measure of overall population dietary exposure relative to other substances. However, information is limited to a small number of countries. Currently, comprehensive production volume data for food additives, including flavouring agents, are available only from the USA, Europe and Japan for use by regulators in risk assessments.

Poundage data and derivative methods do not adequately describe highly exposed consumers and are therefore not sufficient to determine whether their dietary exposure is below the health-based guidance value for a particular food chemical. Additional methods based on use level data could be used in the screening step – for example, in the budget method (see section 6.6.5.1(a)).

JECFA noted that use of the MSDI might result in an underestimation of dietary exposure to a flavouring agent for regular consumers of certain foods containing that flavouring agent. An additional method of estimating dietary exposure for flavouring agents, using the single-portion exposure technique (SPET), was agreed upon in 2008 (FAO/WHO, 2009a) (see section 6.6.5.2(a)). Specific concerns were identified for low-production-volume flavouring agents that may be added at high levels to certain foods and for high-production-volume flavouring agents that could be present in many foods at different added use levels. The uneven distribution of added use levels for some flavouring agents across different food categories and within food categories and the consequent uneven distribution of dietary exposures to a flavouring agent could not be taken into account in the MSDI estimate.

(d)   GEMS/Food cluster diet estimates (contaminants, pesticide residues, veterinary drug residues)

The GEMS/Food cluster diets have been used as model diets by both JMPR and JECFA in chronic dietary exposure assessments for pesticide residues and contaminants, respectively (see section 6.4.4.1(b) for more detailed information on the diets; WHO, 2012). JECFA has not used cluster diet estimates for veterinary drug residues, although in theory the relevant cluster diet could be used for this purpose by individual countries where national dietary survey data are not available. Although the GEMS/Food cluster diets are not usually considered suitable for use in estimating dietary exposure to food additives owing to the lack of data on consumption of processed foods, in cases where the food additive is to be permitted for use only in foods included in the cluster diets (e.g. potassium polyaspartate in wine), it may be appropriate to do a cluster diet estimate (FAO/WHO, 2019b).

(e)   International estimated daily intake (IEDI) (pesticide residues)

JMPR uses STMR pesticide residue levels combined with cluster diet information in the calculation of an international estimated daily intake (IEDI). Whenever possible, potential dietary exposures from residues are estimated for the edible portion, which may require the use of processing factors and data on consumption of processed food. Hence, the GEMS/Food cluster diets as published by WHO are adjusted for use by JMPR, adding in national survey data from individual countries to fill in data gaps as required, with the resulting

cluster diet spreadsheet updated regularly at the JMPR meeting, then published (http://www.who.int/foodsafety/chem/IEDI_calculation 14_FAO1.xls). It is appropriate to correct for the edible portion only if it is known that the commodity is always prepared in the same way for all populations considered.

One of the principles for dietary exposure assessments undertaken by international committees is that the underlying data should be conservative. The GEMS/Food cluster diets fulfil this requirement if a significant proportion of the commodities containing the food chemical is included in the diets.

The FAO supply utilization account data, which form the basis of the WHO GEMS/Food cluster diets (see section 6.4.4.1), tend to overestimate mean food consumption and hence chronic dietary exposure for the population, as they report food available for consumption, not food actually consumed. However, for individual foods within a broader food group described in the GEMS/Food cluster diets, mean food consumption amount may be underestimated for specific foods. The GEMS/Food cluster diets may also underestimate food consumption and chronic dietary exposure for consumers of occasionally consumed foods, as it is assumed that everyone in the population eats the food, resulting in lower mean consumption amounts. The GEMS/Food cluster diets were not intended to represent high consumers and cannot be used to determine differences in consumption or estimated dietary exposure for different age and sex population subgroups.

One of the main advantages of the GEMS/Food cluster diets is that they provide estimates of dietary exposure across the whole world, as national estimates of dietary exposure are usually available for only a select group of countries and do not cover all geographic areas of the world or the diversity of diets within countries.

6.6.5.2   *Deterministic dietary exposure estimates*

Chronic dietary exposures for the general population, consumers, high consumers or regular consumers can be considered in model diets, refined deterministic exposure estimates or probabilistic models (see sections 6.6.2 and 6.6.3). For some of the models described below, a food consumption distribution can be used to derive point estimates of consumption for each food included in a specific model; possible options are indicated in the text below where

appropriate. Information from national surveys with individual dietary records is always preferable for deriving summary statistics to feed into model diets that include consumer behaviours. For food additives, information from countries with national surveys that have a high use of processed foods with existing permissions for use can inform an assessment of the potential impact in another country (e.g. Martyn et al., 2017; Tran et al., 2020).

The choice of the upper percentile of dietary exposure that represents a high consumer is dependent on the purpose of the dietary exposure assessment and the data available to the risk assessor and risk manager (see section 6.1.3).

Consideration of regular consumers may be relevant when assessing high chronic dietary exposure to food chemicals present in processed foods, such as food additives, including flavouring agents, processing aids and chemicals migrating from packaging (e.g. Arcella, Soggiu & Leclercq, 2003; FSANZ, 2004). 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.

Consumer behaviour in relation to food purchases may need to be considered in relation to the selection of organic versus non-organic foods or regional foods if pesticide and veterinary drug use varies geographically. Consumer behaviour towards fortified and non-fortified foods may also need to be considered when assessing nutrient intakes.

If distributional data are not available, factors can be applied to mean population food consumption amounts or dietary exposure estimates to give approximate estimates of dietary exposures for consumers only. The factors used and underlying reasons for their use should be provided with the dietary exposure results.

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 dietary exposure of consumers to different food chemicals are summarized below in section 6.6.5.2(a), including two model diets

used to assess potential exposure to chemicals migrating from packaging materials for the general population.

Chronic dietary exposure assessments that require special considerations are discussed briefly below in section 6.6.5.2(b): total diet study–based exposure estimates, nutrient intakes, novel food exposure estimates and duplicate-portion study–based exposure estimates. Web-based tools for refined deterministic chronic dietary exposure estimates for food additives and metabolites, enzymes and single contaminants are outlined in section 6.6.5.2(c).

(a)   Model diets

Model diets for high consumers. Model diets for high consumers can be developed based on published data from food consumption surveys. In a chronic dietary exposure estimate, the mean concentration value for one or two foods is combined with a high percentile of food consumption (consumers only), and this estimated dietary exposure is added to the estimated mean chronic dietary exposure from all other foods, assuming physiological limits restrict the number of foods that can be consumed at a high level. Typically, the 90th or 95th percentile of food consumption for consumers only is used to represent a high consumer in a chronic dietary exposure model, although for some models the 97.5th percentile is used (refer to the GECDE model diet below). The choice depends on the purpose of the model and the quality and quantity of data available (EFSA, 2011b).

The derivation of high-percentile food consumption 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 (see section 6.1.3). This can be a problem for infrequently consumed foods that may not be adequately captured in a dietary survey owing to a low number of survey days or where dietary exposure estimates for population subgroups are required and numbers in each subgroup are low. In cases where the high-percentile food consumption value cannot be derived, food consumption data for the parent food group can be used instead of that for a single food, provided that the single food and the parent food group are generally consumed in a similar way. For example, a 95th percentile consumption of all root vegetables could be used for carrots in an acute dietary exposure assessment if there are not enough carrot consumers in the data set. Alternatively, parametric 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). However, this approach requires an assumption that the data conform to a particular statistical distribution (e.g. lognormal).

The 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 microdata of individual dietary records. It can therefore use published data. High-consumer models have been used by JECFA for chronic dietary exposure assessments for food additives, and the GECDE model diet has been used for chronic dietary exposure assessments by both JECFA and JMPR for veterinary drug residue and pesticide residue assessments, respectively (see GECDE model below).

For high-consumer exposure estimates, high percentiles of the dietary exposure distribution estimated from dietary surveys with a small number of survey days per person are likely to be an overestimate of high percentiles of dietary exposure over the long term (Lambe & Kearney, 2000; Tran et al., 2004). Statistical adjustments can be made to correct food consumption data and dietary exposure estimates for "usual" food consumption patterns (see section 6.5.6).

Global estimate of chronic dietary exposure (GECDE). The GECDE model diet is an example of a high-consumer model diet that assumes consumption at a high level for one food category.

The GECDE model sums the highest dietary exposure for a food category based on high consumption levels (97.5th percentile food consumption) with the mean dietary exposure for all other food categories using food consumption data for individual countries for the general population and population subgroups of toxicological concern, such as infants, young children or pregnant women (Boobis et al., 2017; Arcella et al., 2019). A mean body weight is applied to the 97.5th percentile food consumption amount, or individual food consumption data can be expressed per kilogram body weight prior to deriving the 97.5th percentile food consumption amount.

The GECDE is defined as:

$$GECDE = \frac{\text{high dietary exposure for one food (97.5th percentile food consumption by consumers} \times \text{median residue level) + mean dietary exposure for all other foods (average food consumption by the general population} \times \text{median residue levels)}}{\text{body weight (kg)}}$$

Following an expert consultation in 2009, the GECDE approach was proposed by JECFA for estimating chronic dietary exposure to veterinary drug residues (FAO/WHO, 2011a, 2012, 2014) using the maximum of the mean food consumption figures across countries in a single calculation. However, this tended to overestimate dietary exposure and was considered to represent dietary patterns that would not occur in practice. This approach was further developed by a joint JECFA/JMPR expert working group. In the updated approach, the GECDE calculation is undertaken per country for each available survey by relevant population subgroup. This avoids undue overestimation of dietary exposure. Food consumption data distributions from national dietary surveys are used to derive the point estimates for use in the GECDE equation, where available. The basic assumption of this model diet is considered valid if the number of food groups is limited – for example, where the food consumption data have been aggregated into fewer than 20 food categories.

For a dietary exposure assessment by an international committee (e.g. JECFA or JMPR), CIFOCOss food consumption data for each country (see section 6.4.4.2(b)) can be used in combination with median residue levels derived from submitted residue data to determine the range of potential dietary exposures for the general population and population subgroups, as required.

The GECDE has been used by JECFA for veterinary drug residue evaluations since 2017. In the past, two different model diets were used by JECFA to estimate potential chronic dietary exposure to veterinary drug residues: 1) the theoretical maximum daily intake (TMDI) and 2) the estimated daily intake (EDI). The TMDI and EDI are no longer used by JECFA, but these calculations may be used by individual countries that have not yet adopted the GECDE as the preferred approach (WHO, 1997; FAO/WHO, 2009b). JMPR agreed in 2019 to use the GECDE approach for estimating dietary exposure to pesticide residues in addition to the existing IEDI calculation (see section 6.6.5.1(e)).

The GECDE is considered particularly useful where a chemical has dual use as a veterinary drug and a pesticide, as both uses can be included in one model (Boobis et al., 2017). It could also be applied to other food chemicals, such as contaminants.

The GECDE estimates are intended to provide a more realistic estimate of chronic dietary exposure to pesticide residues compared with the IEDI or of dietary exposure to veterinary drug residues compared with the TMDI/EDI. The GECDE estimates take account of national food consumption patterns, as summary food consumption statistics derived from individual national dietary surveys are used in the calculations. Also, results can be provided for the general population and population subgroups identified in the risk assessment as being of toxicological concern.

A potential limitation of the GECDE approach is that the robustness of the approach for use by international committees depends on the number of national dietary survey data sets that are available for inclusion in the assessment. Historically, data have been available for developed nations only. However, as the FAO/WHO CIFOCOss and GIFT databases (see sections 6.4.4.2(b) and 6.4.4.2(c)) expand to include more data from developing countries, this limited data availability will be mitigated.

Single-portion exposure technique (SPET) and added-portion exposure technique (APET) model diets for flavouring agents. A method for estimating chronic dietary exposures to flavouring agents was developed by JECFA in 2009 (FAO/WHO, 2009a) as a screening procedure, to be used in conjunction with MSDI estimates (see section 6.6.5.1(c)).

The single-portion exposure technique (SPET) estimate aims to represent the chronic dietary exposure for a regular consumer who consumes a specific food product containing the flavouring agent of interest daily, and not a high consumer of the food. It assumes daily consumption of only a single standard portion of food containing the flavouring agent, at average or usual use levels.

The SPET first identifies all food categories likely to contain the flavouring agent, then uses the following equation for each food category to determine the single food category that is likely to contribute the highest dietary exposure; it is this SPET estimate that is used in the dietary exposure assessment for the flavouring agent.

SPET estimate (µg/day) = standard portion (kg/day) × manufacturers' use level (µg/kg)

The concentration data are provided by the industry and are used in preference to Flavor and Extract Manufacturers Association of the United States (FEMA) generally recognized as safe (GRAS) levels.[1] The standard portion is taken to represent the mean food consumption amount for consumers of that food category, assuming daily consumption over a long period of time. The standard portion does not reflect high food consumption amounts reported in national dietary surveys for the food category and is therefore a more realistic prediction of long-term consumption patterns.

A summary of an analysis of MSDI (see section 6.6.5.1(c)) and SPET estimates for 225 flavouring agents for which added use level and production data for one of the three geographic regions (Europe, Japan and the USA) were available was reported at the sixty-ninth meeting of JECFA (FAO/WHO, 2009a). In nearly all cases (>90%), the SPET estimate was above the MSDI. The SPET estimate was more likely than the corresponding MSDI to be above the TTC of the relevant structural class (Cramer class I, II or III); this occurred most frequently for chemicals in class III, but also for some chemicals in classes I and II. JECFA concluded that the MSDI and SPET dietary exposure estimates provide different and complementary information (FAO/WHO, 2009a).

Inclusion of the SPET estimate in the JECFA Procedure for the Safety Evaluation of Flavouring Agents addressed previous concerns about the MSDI estimate of dietary exposure, because the SPET estimate takes account of the possibly uneven distribution of dietary exposures to a flavouring agent for consumers of foods containing that substance. The higher value of the two dietary exposure estimates (MSDI or SPET) is used within the JECFA procedure to determine whether estimated dietary exposure is above or below the TTC for the relevant structural class.

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[1] GRAS is a regulatory concept specific to the United States Federal Food, Drug, and Cosmetic Act. Any substance added to food must conform to the terms of a regulation prescribing its use, unless its intended use is GRAS. Food ingredients whose use is GRAS are not required by law to receive USFDA approval before marketing. The FEMA GRAS programme relies on safety evaluation of flavouring substances under conditions of intended use, conducted by the FEMA Expert Panel.

EFSA uses a modified SPET model diet, the added-portion exposure technique (APET), in which portions for solid foods and beverages are included in the equation and summed where the flavouring agent is used in both food categories (EFSA, 2010b).

The selection of the standard portion of food resulting in the highest dietary exposure from the SPET/APET models does not necessarily cover high consumers who are loyal to a specific brand of food with consistently high levels of a single flavouring agent, but is a reasonable proxy for long-term patterns of dietary exposure.

Sweetener substitution model. In this approach, dietary exposures are estimated for novel intense sweeteners in a pre-regulation risk assessment based on published summary information on dietary exposure estimates for other approved sweeteners for different countries (general population and population subgroups of interest, such as people with diabetes). Reported dietary exposures to approved intense sweeteners based on maximum levels or, preferably, manufacturers' use levels (expressed in milligrams per kilogram of body weight) are adjusted to predict the dietary exposure to a novel sweetener by using the relative sweetness intensities of the novel intense sweetener and the approved sweeteners (Renwick, 2008).

Model diets for chemical substances migrating from packaging materials. Currently, the European Union and the USA each have different methods for assessing chronic risks associated with substances migrating from food packaging materials into food products. The models are described below.

The *European Union model diet* for chemical substances migrating from packaging materials into food is used to establish a maximum limit of migration, the so-called specific migration limit (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 packaging material (600 cm^2 contact surface) that would always contain the substance under consideration at a concentration corresponding to the specific migration limit without exceeding the relevant health-based guidance value (e.g. 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 model was updated in 2015, in relation to assumptions about exposure to food contact materials. New food consumption values for four categories were proposed that were 9, 5, 3 and 1.2 times higher than the default model – that is, 17 g/kg body weight per day (1 kg food consumed by an adult weighing 60 kg). A fat (consumption) reduction factor for lipophilic substances was also introduced to allow for the fact that no more than 200 g fat can regularly be eaten daily. The changes were intended to provide a higher level of protection for the consumer, especially for infants and toddlers (EFSA, 2016b).

The *United States model diet* for the evaluation of 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) (USFDA, 2007). Migration levels are then assigned according to the nature of food likely to be in contact with each type of packaging material (i.e. whether the food is aqueous, acidic, alcoholic or fatty in nature).

The model used in Canada is similar to that used in the USA, with minor differences; for example, consumption of 2 kg of packaged foods and beverages is assumed, but this excludes water, and different packaging ratios (amount of food in contact with a standard area of packaging) are used (https://www.canada.ca/en/health-canada/services/food-nutrition/legislation-guidelines/guidance-documents/information-requirements-food-packaging-submissions.html).

(b)   Dietary exposure assessments with special considerations

Total diet study–based estimates. Total diet studies are designed to collect data on concentrations of chemicals in food "as consumed"

by the population living in a country and, if possible and where relevant, by population subgroup (see section 6.3.2.2(d)), for use in assessing chronic dietary exposure to food chemicals (EFSA, FAO & WHO, 2011; Moy & Vannoort, 2013). Although the traditional focus of total diet studies has been on assessing dietary exposure to pesticide residues and contaminants, the advent of multielement analyses has seen total diet studies undertaken by some countries include selected nutrients, food additives and other chemicals found in food. For example, in New Zealand, selected nutrients, such as fluoride, iodine, selenium, sodium and zinc, are regularly analysed in their total diet studies (MPI, 2018). In Australia, preservatives (sulfites, benzoates, sorbates), trace elements, nutrients and food packaging chemicals have been studied in separate total diet studies (FSANZ, 2005, 2008, 2011b, 2016). If the total diet study is targeted to certain food additives, it may include only food groups known to contain the chemicals, and not the whole diet. Total diet studies are not intended to be compliance surveys; the focus on their use for population dietary exposure assessments means that they can complement the more traditional monitoring and surveillance programmes.

A simple deterministic approach may be used to assess chronic dietary exposure for the general population based on total diet study–derived analytical data on concentrations of a chemical in food prepared as consumed. Some countries use a refined deterministic approach combining food consumption data at an individual level with the mean value for the concentration of the chemical in the foods or food groups included in the total diet study and may apply statistical methods to the data (FSA, 2004; Leblanc et al., 2005; ANSES, 2011; FERA, 2012; FSANZ, 2014, 2016; Sprong et al., 2016; Ingenbleek et al., 2017, 2020; Sirot et al., 2018; Nougadère et al., 2020). High-consumer dietary exposures may also be reported in the total diet study, but uncertainties in these results depend on the sampling design and compositing of samples. In order to ensure an appropriate risk characterization for chemical substances with a very low health-based guidance value (e.g. ADI), it is essential, in the designing phase of a total diet study, to set target analytical limits (LOD and LOQ) for the participating laboratories in order to reduce the uncertainty associated with the exposure estimation and to guarantee realistic results under an upper-bound scenario that tends to overestimate exposure levels. Use of target analytical limits for each chemical/food matrix, combined with a refinement of exposure

estimates by taking into account real or authorized agricultural uses for each crop, provides the most accurate estimates of dietary exposure to pesticide residues (Nougadère et al., 2020).

Total diet studies differ from other chemical surveillance or monitoring programmes because they aim to produce concentration data for food chemicals across the total diet as consumed for use in chronic dietary exposure assessments. If the total diet studies are conducted on a regular basis, their 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 monitoring trends in dietary exposures.

Owing to limited resources, the range of foods analysed may be restricted, and composite samples are commonly used (see Appendix 6.1). Foods analysed are "mapped" to other similar foods, applying the concentration of the analysed food to mapped foods; this can increase uncertainty in the dietary exposure estimate.

Total diet studies are not suitable for the assessment of acute dietary exposures because of the high degree of compositing of samples.

Nutrient intake estimates. Traditionally, nutrient intakes have been estimated from national dietary surveys using nutrient concentration data from national food composition tables or total diet studies. In most cases, a refined deterministic approach, in which there is a distribution of food consumption amounts from the survey across all population subgroups studied (see section 6.6.2.2), is currently used. Tools have been developed for use by food safety or regulatory agencies, research institutions and commercial companies in undertaking such assessments; these may be for in-house use or publicly available. The nutrient intake assessment may include an adjustment to estimate usual nutrient intakes for different population subgroups (see section 6.5.6).

In a risk assessment of nutrients, it is appropriate to use population-based health-based guidance values (often termed nutrient or dietary reference values or recommended dietary amounts or allowances), such as estimated average requirements (EARs), adequate intakes (AIs) and ULs, but not reference values developed specifically for the assessment of individual diets. Although Codex has established nutrient reference values for the general population

for use in food labelling (Lewis, 2019), these are not generally used in a nutrient risk assessment unless it includes an assessment of proposed changes to labelling regulations. Typically, EARs and AIs are set on a country-by-country basis. ULs can also be established at the country level; in theory, however, a UL could also be derived by an international committee, such as JECFA. To date, this has not occurred; however, other health-based guidance values have been set by JECFA for nutrients – for example, iodine (TDI) and phosphoric acid and phosphate salts as a group (maximum TDI) – with a caveat that the usual calculation for provision of a margin of safety is probably not suitable for food additives that are also nutrients. In these cases, natural sources as well as food additive and supplement use should be included in nutrient intake assessments.

There are several special considerations for intake assessment for nutrients and related substances. The intake assessment is population relevant rather than globally relevant because the nutrient content of domestically produced foods tends to be dependent on local climate and soils. Health-based guidance values are often established for specific age/sex subgroups within the population by individual countries to account for differences in nutrient requirements based on life stage and sex, so the risk characterization is usually undertaken for population subgroups. Data on the basis for the derivation of each health-based guidance value and other information from hazard identification and hazard characterization are essential for describing the risk associated with intakes that are either below the EAR or above the UL.

Microencapsulation can be used for fortification with certain nutrients, specifically for populations with nutrient deficiencies, as it enhances the stability of micronutrients in food. Estimated total nutrient intakes, including from fortified food, are then used to determine whether nutrient requirements have been met for different populations and population subgroups. Depending on the purpose of the risk assessment, the food additive used for the microencapsulation process may be evaluated separately. In these cases, the number and concentration of nutrients encapsulated in each food and the particle size and number of particles used need to be taken into account in the estimate of total dietary exposure to the food additive; this is then compared with the relevant health-based guidance value in the risk characterization step. For example, JECFA evaluated the use of basic

methacrylate copolymer in microencapsulation for up to 12 nutrients at its eighty-sixth meeting (FAO/WHO, 2019c).

Risk characterizations for nutrients can be inherently different depending on the target population and the country. The FAO/WHO Technical Workshop on Nutrient Risk Assessment reviewed in detail possible approaches to nutrient intake assessment and proposed harmonized protocols (FAO/WHO, 2006).

Novel food dietary exposure estimates. For novel foods, consumption is first estimated from proposed uses of the novel food in the food supply. The novel food itself or a chemical contained in the novel food may be of toxicological concern. Dietary exposure methods similar to those used for food additives are employed.

 Information on the intended or anticipated uses of the novel food is essential for the assessment of whether the uses will be safe or will constitute a risk. For many novel foods, accurate prediction of the likely commercial success, consumption and therefore potential dietary exposure to the novel food itself or chemicals of interest in the food is particularly difficult. Post-launch monitoring is therefore essential to verify that the pre-regulation risk characterization was appropriate.

Duplicate-portion studies. Duplicate-portion studies may be used to assess dietary exposures for population subgroups. An extra portion of the meal consumed is prepared and analysed for chemical content, which provides 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 (Clarke et al., 2003), children (Murakami et al., 2002; Wilhelm et al., 2002), 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 dietary exposure when assessments are conducted with more limited data. For example, in the early evaluations of dietary exposure to acrylamide, a duplicate-portion study conducted

by the Swiss government provided an estimate of total dietary exposure that was used to assess whether the foods that had already been analysed were those that represented the most important sources of acrylamide (Swiss Federal Office of Public Health, 2002).

(c)   Web-based tools (refined deterministic approach)

EFSA has developed four web-based tools that use a refined deterministic approach for chronic dietary exposure assessments for specific chemicals. Food consumption data from European dietary surveys, held in the EFSA Comprehensive European Food Consumption Database, are used in the calculations. For chronic dietary exposure estimates, individual food consumption data are averaged over the total survey period, for the population group of interest, excluding surveys with only 1 day of records per subject. Although the tools access individual records from the dietary surveys, an external user of the tools does not have access to these underlying individual records; only summary results are provided.

Food Additive Intake Model (FAIM). The external user of EFSA's FAIM tool (version 2.0) inserts data on food additive concentrations into the tool for specified foods or food groups (EFSA, 2012d). Exposure results are reported at mean and high levels for different general population subgroups (e.g. infants, toddlers, adults) in different European Union countries.

Feed Additive Consumer Exposure (FACE). A similar calculator to FAIM, FACE has been developed by EFSA for estimating chronic and acute dietary exposures to residues of feed additives and their metabolites present in food of animal origin (http://www.efsa.europa.eu/en/applications/feedadditives/tools).   It allows users to estimate the dietary exposure for different population groups (e.g. infants, toddlers, adults) in several European countries from food consumption data that have already been disaggregated into raw commodity amounts and provides the external user with summary statistics derived from individual records.

Food Enzyme Intake Model (FEIM). FEIM is a tool for estimating chronic dietary exposure to enzymes used in food processing. It follows the methodology recommended in the statement of the EFSA Panel on Food Contact Materials, Enzymes,

Flavourings and Processing Aids[1] on assessing exposure to food enzymes (EFSA, 2016c). FEIM comprises process-specific calculators, such as FEIM-baking or FEIM-brewing, which allow estimation of dietary exposure to enzymes used in individual food manufacturing processes. Exposure results are reported at mean and high levels for different general population subgroups (e.g. infants, toddlers, adults) in different European Union countries (https://www.efsa.europa.eu/en/applications/foodingredients/tools).

Rapid Assessment of Contaminant Exposure (RACE). The RACE tool supports risk evaluations of chemical contaminants in single foods in the context of notifications of the Rapid Alert System for Food and Feed. The analytical results detected, the food category tested and the relevant toxicological reference point are entered in the RACE tool. RACE provides estimates of acute and chronic dietary exposures to contaminants from single foods for different population subgroups, including the general population and consumers, and compares the results with the relevant toxicological reference points (EFSA, 2019b).

6.6.6 *Estimating chronic (shorter-than-lifetime) dietary exposures*

A joint JMPR/JECFA working group meeting held in October 2017 explored methods for a harmonized approach to chronic dietary exposure assessments for compounds used as both pesticides and veterinary drugs (Boobis et al., 2017). The JMPR/JECFA working group concluded that there was a need to better align the toxicological profile of the compounds with the dietary exposure model to be used as part of the risk assessment process and confirmed that the choice of an appropriate exposure model is determined by the toxicological end-point of concern. Subpopulations for whom estimated dietary exposures over a season or life-stage might result in short-term exceedances of the ADI are potentially of toxicological concern and may include the embryo/fetus (developmental toxicity), young children (offspring toxicity) and adults who were high consumers of foods containing the pesticide residue.

A chronic dietary exposure assessment may be required for different age/sex subgroups or for high consumers in the population for a shorter-than-lifetime exposure assessment, using appropriate

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[1] Now referred to as the Panel on Food Contact Materials, Enzymes and Processing Aids.

methods and approaches as outlined in section 6.6.5. For estimates of chronic dietary exposure by population subgroups, individual records from national dietary surveys are required. If the risk assessment is undertaken by an international committee, such as JECFA or JMPR, summary data by age/sex groups or for high consumers derived from individual records may be available on a country-by-country basis, preferably with a selection of data sets to represent all regions of the world.

Some dietary models using summary statistics may not be appropriate to estimate chronic dietary exposure if the food consumption data cannot be disaggregated into the age/sex population subgroups of interest. The screening methods (see section 6.6.5.1) and some of the model diet approaches (see section 6.6.5.2(a)) discussed above are not appropriate for use in estimating shorter-than-lifetime dietary exposures. For example, the IEDI calculation used by JMPR to estimate dietary exposure to pesticide residues is based on the WHO GEMS/Food cluster diets and so cannot be used for this purpose, as the data cannot be disaggregated by age/sex.

6.6.7   *Estimating aggregate dietary exposures*

For the dietary exposure estimate part of an acute or chronic aggregated exposure assessment that considers exposure from all sources (multiple pathways and routes of exposure), a dietary exposure assessment is undertaken, using appropriate methods and approaches for an acute or chronic estimate as outlined in sections 6.6.4 and 6.6.5. Methods for determining total chronic aggregate exposures (refer to USEPA, 2001; EFSA, 2016a) have been more widely used than those for acute aggregate exposures.

6.6.8   *Estimating cumulative dietary exposures*

An estimate of cumulative (combined) dietary exposure to chemical substances with a common mode of action, end-point, congeners or target organ, where there is co-exposure from different foods, can be undertaken using probabilistic methods (see section 6.6.3) for an acute dietary exposure assessment; and refined deterministic (see section 6.6.2.2) or probabilistic methods for a chronic exposure assessment. Screening methods are not appropriate. A probabilistic model requires more resources, but may in fact be the

only approach available, especially when dealing with numerous chemicals in multiple foods.

The toxicological basis for grouping the chemicals determines whether a chronic or acute cumulative dietary exposure assessment is appropriate. In some cases, there may be a health-based guidance value for a group of chemicals, including metabolites and active substances (e.g. group ADI/TDI). Relative potency factors (RPFs) (see section 6.6.8.1) (EFSA, 2020c,d) or other methods may be applied, as relevant. For mycotoxins, such as aflatoxins and fumonisins, there may be an increased potential for cancer if they co-occur. When both are present in the diet, the risk characterization should note this as an increased risk, because high exposures to both contaminants may pose a greater risk to health compared with high exposure to either separately (FAO/WHO, 2017b). Cumulative dietary exposure assessments that focus on toxicologial impacts on a target organ may include exposure from different types of food chemicals (e.g. cumulative effect of pesticide residues, contaminants and food additives on the liver; Sprong et al., 2020).

6.6.8.1 Relative potency factors (RPFs)

RPFs represent the toxicities of individual substances or congeners in a chemical group relative to an "index compound". The choice of the index compound will greatly depend on the toxicity database available and the toxicological end-point used. The ability to identify a suitable index compound may limit this approach. For dioxins, RPFs have also been termed toxic equivalency factors (TEFs).

The RPF for each chemical within a group of chemicals is applied to the concentration data for that chemical to obtain a weighted concentration value per sample, expressed in terms of the index compound. These data are then used as the concentration data set for the acute or chronic dietary exposure assessment. Ideally, data on the concentrations of substances in food should be collected in a manner that records the co-occurrence of congeners in foods analysed as well as individual chemical concentrations, but such data may not always be available for use by international committees. For example, in the case of dioxins, where 29 congeners have RPFs that weight the potency of each against an index congener, concentrations for each congener are multiplied by its RPF before summing the concentrations for use in the dietary exposure assessment

(FAO/WHO, 2002a,b; Baars et al., 2004). Aflatoxins may also be assigned RPFs in a dietary exposure assessment.

In cases where different chemicals are considered as a group for dietary exposure assessment purposes, as discussed above, the assignment of numerical values to non-detected and non-quantified concentration data results can be complex. The assignment and simple summation of concentration values equal to the LODs or LOQs may not be feasible when different LODs or LOQs were used for the analysis of each individual chemical in the group, as assigning the combined value to non-detected and non-quantified results will tend to result in an unrealistic overestimation of dietary exposure. It is unlikely that all chemicals in the group will be present in the same food at the LOD/LOQ.

6.6.8.2   *Guidance for cumulative risk assessments*

Guidance for performing cumulative risk assessments has been issued by the USEPA (2002, 2003), IPCS (IPCS, 2009b; Meek et al., 2011) and EFSA (2007, 2012e). More recently, the OECD released new guidance for assessing the risk of combined exposure to multiple chemicals (OECD, 2018), and EFSA released new guidance on harmonized methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals (EFSA, 2019d). In these guidance documents, it is noted that well-characterized shared modes of action, common end-points or common target organs are needed in order for cumulative risk assessments to be conducted. When trying to compare across different chemicals and test systems, these types of data may be lacking, and there are often data gaps; hence, application of these approaches to less well-characterized or new compounds has not been done with confidence to date and could introduce high levels of uncertainty into the dietary exposure assessment and risk characterization steps.

A deterministic model for cumulative chronic dietary exposure assessment was used by JMPR for dithiocarbamates (FAO/WHO, 1999a,b) and by JECFA for chlorinated dibenzo-*p*-dioxin congeners and non-dioxin-like PCBs (FAO/WHO, 2002a, 2016).

Examples of cumulative risk assessments using probabilistic modelling include acute and chronic cumulative exposure assessments for a select group of triazole pesticides in different

European countries (Boon et al., 2015) and two EFSA reports, a cumulative risk characterization for pesticides that have acute effects on the nervous system (EFSA, 2020c) and a cumulative risk characterization for pesticides that have chronic effects on the thyroid (EFSA, 2020d).

The USEPA has an online toolbox for both aggregate and cumulative risk assessments (EPA ExpoBox: https://www.epa.gov/ expobox/exposure-assessment-tools-tiers-and-types-aggregate-and-cumulative) as part of its suite of guidance documents. As part of the ongoing development of cumulative risk assessment models, the European Commission funded the European Test and Risk Assessment Strategies for Mixtures (EuroMix) project (https:// www.euromixproject.eu/) under the Horizon 2020 research programme, which aims to develop a tiered strategy for the risk assessment of combined exposure to multiple chemicals derived from multiple sources across different populations for use across different regulatory frameworks.

The EuroMix project was coordinated by RIVM, and the first development stage was finalized in May 2019 (Zilliacus et al., 2019) (https://www.rivm.nl/en/about-rivm/mission-and-strategy/interna-tional-affairs/international-projects/euromix). Although primarily intended for use by European Union food safety and regulatory agencies, the EuroMix handbook and toolbox (Van der Voet et al., 2020) will be made available outside the European Union in the future, although the mechanism by which this will be achieved has not yet been agreed. A joint FAO/WHO expert consultation was held in April 2019 to discuss the potential use of the EuroMix handbook and toolbox by international committees, such as JECFA and JMPR, the outcomes of which will be discussed at future meetings of these committees (FAO/WHO, 2019d).

6.6.8.3   *Synergistic effects between chemicals*

When a synergistic effect (increase in the effect of two chemicals that is more than the effect of the chemicals when found separately) is known to occur or considered a possibility, the risk assessment approach taken is carefully considered in terms of assumptions, level of conservatism warranted and intepretation of the results (see Chapters 4 and 7). For dietary exposure purposes, each chemical is assessed separately, and consideration of potential synergistic

functional effects is discussed in qualitative terms in the risk assessment report.

Co-occurrence of two food additives may result in synergistic effects, which may improve or reduce their ability to achieve the desired technical function. For example, cyclamate and saccharin are intense sweeteners. As the sweetness of each is enhanced in the presence of the other sweetener and taste profiles are improved, less of each food additive is required to achieve the desired level of sweetness in the final food. Hence, the required concentration of each food additive is decreased compared with using them separately, which results in a decrease in estimated dietary exposure for each sweetener from this use.

An example of synergistic effects between chemicals found as contaminants in food is shown by the combination of melamine and cyanuric acid, which is markedly more toxic to most animals and humans than either compound when consumed alone, with the kidney being the target organ. This effect was identified when melamine was found as a contaminant in pet food in 2007 and in milk products used for infants and young children in 2009, both due to illegal addition (WHO, 2008; Bischoff, 2011).

6.6.8.4 *Exposure estimates for chemicals with long half-lives*

Some chemicals or chemical congeners have very long half-lives in the body and accumulate over time in target organs or tissues, resulting in adverse effects over a period of time – that is, an increasing body burden over time (Ritter et al., 2011). For these chemicals – for example, dioxin-like PCBs, non-dioxin-like PCBs, polychlorinated dibenzodioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) – an estimation of the body burden is considered to be a more relevant exposure end-point to be used in risk assessment compared with a traditional dietary exposure assessment (Van Leeuwen & Younes, 2000; FAO/WHO, 2002a,b; USEPA, 2012b).

Body burdens can be modelled using kinetic exposure models (Verger, Tressou & Clémeçon, 2007; Bertail, Clémeçon & Tressou, 2010; Béchaux et al., 2014) that estimate both accumulation of chemicals in the body due to recurrent exposures and elimination that occurs over time. Model inputs include estimated dietary exposure, half-life of the substance and elimination rates. The body burden can

be estimated for the whole population or different population subgroups, noting that over a lifetime, the level of dietary exposure may change. For example, potential dietary exposure to dioxins and dioxin-like substances was known to be higher in the 1970s than it is currently, owing to changes in industrial practices as well as changes in dietary habits (WHO, 2010; Gibb et al., 2015). In 2015, JECFA evaluated chronic dietary exposure and chronic body burden for non-dioxin-like PCBs (FAO/WHO, 2016).

6.7 Biomarkers of exposure

Biomarkers include a broad class of biological and biochemical changes to the body that are measurable, subclinical and reversible (Grandjean, 1995). They may measure internal exposure or changes in effects on the body rather than directly measuring external exposure. These terms were further described by the United States National Research Council (USNRC, 1987) and include a definition of biomarkers of exposure – that is, "agents or their metabolites either in tissues, secreta, excreta, expired air, or any combination of these" (Berlin, Yodaiken & Henman, 1984) that can be independently used to quantify overall exposure to a substance. Examples of biomarkers of internal exposure include the concentration of lead or methylmercury in blood, urine or hair, the concentrations of pesticides or their metabolites in serum, fat, urine, blood or breast milk, the concentration of vitamin D in blood and the concentration of sodium or iodine in urine (Anwar, 1997; USCDC, 2003, 2004; WHO, 2007, 2011b; Taylor et al., 2013).

Use of biomarkers provides a direct measure of internal dose of chemicals or nutrients, instead of modelling the dose based on external exposure combined with toxicokinetic characteristics of the chemical. For nutrients, the use of biomarkers of exposure is particularly useful when dietary intake estimates do not capture total exposure (e.g. vitamin D is obtained from exposure to the sun as well as from the diet; Taylor et al., 2013). However, it is often difficult to characterize the relationship between biomarker levels and health risk, with challenges discussed in more detail below. It should also be noted that data validation is of particular importance in the dietary exposure assessment step.

For the most robust estimates of dietary exposure, it may be prudent to use a combination of methods (Wild et al., 2001;

Grandjean & Bodtz-Jørgensen, 2007; Penn et al., 2010). For example, for methylmercury, the exposure expected to have no appreciable adverse effects on children was first related to a maternal blood concentration of 0.056 mg/L, corresponding to hair concentrations of 14 mg/kg and to a daily intake of methylmercury of 1.5 mg/kg body weight. A dietary exposure assessment based on the mean level of fish contamination multiplied by the mean and high levels of consumption of fish for adults, including women of childbearing age, allows the potential risk of exposure to methylmercury in various countries to be calculated (Sirot et al., 2008; UNEP, 2009; Branco et al., 2018; Caetano et al., 2019).

Another challenge associated with the use of biomarkers relates to source attribution. Because biomarkers are integrative measures of exposure, they do not distinguish between different potential sources of exposure (Aitio & Kallio, 1999). For chemicals from multiple sources, the results can be difficult to interpret, unless all sources are known. For example, exposure to polycyclic aromatic hydrocarbons (PAHs) may be via the diet or 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, Kang & Sithisarankul, 1996). Even among individuals with no apparent notable exposure to PAHs, PAH metabolites have been detected in urine, albeit at low levels (Strickland, Kang & Sithisarankul, 1996).

Finally, even if a biomarker with a long half-life is available, it may not always be 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). In contrast, 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.

In summary, the use of biomarkers to estimate internal exposure offers some advantages over estimates of external exposure, such as dietary exposure, to monitor trends in populations over time and geographic regions. Biomarkers integrate exposure over time from multiple sources. In a causal sense, they are also "closer" to adverse health effects of interest than are other types of exposure estimates.

In contrast, interpretation of biomarker data is complicated by the fact that data on toxicity end-points related to different levels of the biomarker are generally unavailable. This may lead to situations where the concentration of the biomarker is converted to an equivalent dietary exposure before assessment of the toxicological implications. In addition, because of their integrative nature, it can be difficult to attribute changes in biomarker levels to an exposure source, or in some cases even to a particular substance. Finally, the use of biomarkers can be complicated if their half-lives are short.

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Appendix 6.1: Sampling, methods of analysis and quality assurance for surveys of concentrations of chemicals in food

A6.1.1 Sampling

A good study design is the most important element of any dietary exposure study (FAO/WHO, 2000). There are two main approaches to analysing foods when generating analytical data from surveys, including total diet studies, and both can have a significant, but different, impact 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).

A6.1.1.1 Sampling plans and sample collection

When programmes to generate data on concentrations of chemicals in food are undertaken, 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 – for example, a study where data are intended for use in a dietary exposure assessment or a study for enforcement purposes. Although data on concentrations of chemicals in food that are collected specifically for use in dietary exposure assessments are preferable, compliance data are often the only data available for some foods.

The following questions should be addressed when the sampling plan is designed (WHO, 1985, 2002, 2005; Kroes et al., 2002; Moy & Vannoort, 2013):

- 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 of the sources of foods available to the population?

- Should the sampling be representative of commercial food processing and/or homemade foodstuffs?

- Does sampling account for regional differences in soil composition, climate, pest vectors and good agricultural practice, as well as those foods extensively distributed on a national basis, including imported foods?

- Are seasonal differences also considered, if relevant?

- Are the main brands/cultivars covered for each food?

- Is sample size (amount of sample and number of samples) sufficient to cope with localized analytes, such as aflatoxins?

- Have standard operating procedures been established to standardize sampling?

For an acute dietary 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 section 6.6.4) to take into account the differences in chemical concentrations in sample increments or unit crops.

A6.1.1.2 Sample preparation and processing

For generating data on concentrations of chemicals in food to be used in dietary exposure assessments, information about sample preparation and processing is essential. For use in dietary exposure assessment, the concentrations of the chemical in the edible portion of the commodities are of interest; however, a different portion of the commodity, as specified in the relevant regulation, may have been prepared for analysis, if samples were collected for enforcement purposes.

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 because they are not consumed (e.g. withered leaves, stone of fruits, bones of meat).

Samples may be prepared in the form of 1) raw commodities, 2) foods as purchased or 3) foods ready for consumption (table ready). In the last case, one or more recipes or cooking methods for each food

item may be used to prepare a sample ready for consumption to account for food habits and differences in the chemical content of the end food (e.g. fat content of food may vary if fried rather than grilled). Food preparation bowls/glassware/pans and utensils should be carefully selected so as not to influence the concentration of the chemical of interest in the food sample.

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 a concentration value closer to the true average; however, the range of values will be unknown.

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 temperature control, may be required, for both processing and storage of samples. Care also needs to be taken not to introduce contaminants such as metals from the equipment used, such as blades, containers, etc. 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, 2010).

A6.1.1.2.1   Food group composite approach to sample preparation

In the food group composite approach to sample preparation, 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 information from national dietary surveys and represent the relative mean amounts of the food contributing to the composite consumed by the population of interest. The food composite approach should be selected on a case-by-case basis. It is less useful where there are known concentration differences for the chemical of interest within a food group, as it would result in an inaccurate estimate of dietary exposure to the chemical.

The food group composite approach is often used when undertaking a total diet study. As an example, a total diet study of organic environmental contaminants undertaken in the United Kingdom collected 1000 samples and prepared them as 19 food group composites (FERA, 2012). Separate groups were established for foods consumed in large amounts (e.g. staples, such as bread, milk and potatoes) and 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 dietary exposure by food group, but not by individual foods, while conserving resources. The Japanese total diet study also analyses food group composites (Kayama et al., 2013).

The advantage of the food group composite approach is that the approximate dietary exposure to chemicals can be estimated 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 dietary exposure to a chemical can be obtained by matching the concentration value for each food group composite to the amount of that food group reported as consumed in a dietary survey and summing over the whole diet. This approach may have particular value where individual analyses are complicated or expensive.

The main limitation of the food group composite approach is that it restricts the estimation of dietary exposures to a chemical 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 the diet for an adolescent, a child or an adult female, as types of foods and proportions of each consumed may differ substantially between age/sex groups.

A principal further limitation is the so-called "dilution effect" inherent in the use of composites. For example, the concentration of an analyte in one food sample in the composite may be well in excess of the LOD or LOQ, but may be diluted in the composite to below the LOD or LOQ by other foods with concentrations of the analyte below the LOD/LOQ, such that the overall composite has a not detected or not quantified 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 not detected or not quantified results (see section 6.5.4). In addition, unusual sources of elevated concentrations could be masked in the composite. These data are not suitable for acute dietary exposure assessments.

A6.1.1.2.2 Individual food approach to sample preparation

In the individual food approach, each food type is prepared and analysed separately. Often multiple samples of the same food purchased across the country are composited to get as representative a sample of the individual food type 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.

Some countries have used the individual food approach in their total diet studies – for example, Australia (FSANZ, 2014, 2016), Canada (Tittlemier, Pepper & Edwards, 2006; Tittlemier et al., 2007), France (Leblanc et al., 2005; ANSES, 2011), Ireland (FSAI, 2016), New Zealand (MAF, 2011; MPI, 2018) and the USA (USFDA, 2019; USDA, 2020).

The major advantages of the individual food approach over the food group composite approach are the ability to estimate the contribution of individual foods to total estimated dietary exposure 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). It is also possible, with the use of food recipe data, to use these data to derive a concentration for composite foods that were not measured.

The major limitation of the individual food approach is the larger number of samples that need to be analysed in order to represent all foods consumed by the population. If resources limit the sample size, this may mean that the selected foods are not representative of foods available to a population. In practice, a cut-off is often imposed, and the foods analysed will be those most commonly consumed by the population. The number of foods sampled depends on available resources but is typically 100–300 individual food composites from a larger number of individual food samples. A more limited range of food types may be sampled, with each food type assumed to be

representative of a range of foods. This approach may present problems in preparing data for use in a dietary exposure assessment because it is difficult to group or map the foods analysed to all the foods reported as consumed in a dietary survey (see section 6.5.2). Analysed foods may be matched to a food that they do not closely resemble. Depending on the assumptions made, this approach can lead to significant overestimation or underestimation of actual dietary exposure. This highlights the need for a full description of all assumptions made in performing the dietary exposure assessment.

If the individual foods are also composited, then the same limitations in relation to a dilution effect applies, as described for food group composite samples above. These composite data are not suitable for acute dietary exposure assessments.

A6.1.2 Methods of analysis and quality assurance

There may be important differences in analytical methodology depending on whether the samples are analysed to provide data for dietary exposure assessments (e.g. total diet studies) or for enforcement of MRLs or MLs. For instance, some pesticide residue metabolites that are of toxicological concern and are important for dietary exposure assessment may not be 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 estimates, the LOD or LOQ should be as low as technically possible, to minimize the number of food samples in which the analyte of interest is not detectable or quantifiable. The assumptions made about the concentration of the analyte in such samples will affect the estimated dietary exposures (see section 6.5.4). Most total diet studies utilize sensitive methods, whereas monitoring or surveillance programmes typically use less sensitive methods, if the purpose is to confirm that concentrations of a chemical are below the regulatory limits. Data on concentrations of chemicals in food that are generated for enforcement purposes can be used for dietary exposure assessments provided the appropriate assumptions for samples below the LOD or LOQ are applied and numerical data are reported, not just pass or fail results.

Obtaining the best estimates for dietary exposure is critically dependent on the quality of the data on concentrations of chemicals

in food. Concentration data should be obtained using validated methods 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);
- 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 an objective means of verifying the capability of the laboratory and comparability of the results obtained in different laboratories. The established quality control system and capability of the laboratory should be demonstrated by appropriate accreditation. The most recent guidance on good laboratory practice was published in 2017 by the International Organization for Standardization and the International Electrotechnical Commission: the ISO/IEC 17025 standard, which outlines the general requirements for the competence of testing and calibration laboratories (ISO/IEC, 2017).

Data collating centres may require certain standards to be met in terms of the method of analysis used (e.g. use of ISO/IEC 17025 standard), with data sets and metadata required to be submitted in a set format – for example, for submission of data to the WHO GEMS/Food programme (WHO, 2011) or to EFSA for use in risk assessments (de Boer et al., 2011; EFSA, 2020a,b).

A6.1.2.1 Errors in analytical measurements

Three types of error can be distinguished in most measurements:

1) *Gross errors* refer to unintentional or unpredictable errors that occur while generating the analytical result (e.g. operator error,

faulty equipment). 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.

2) *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.

3) *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 error are illustrated in Table A6.1. It should be noted that not all sources mentioned must be evaluated in the uncertainty estimation. Some sources are already incorporated in the overall uncertainty, whereas others are negligible and may be disregarded. Further information may be obtained from published documents (IPCS, 2008; FAO, 2009; Ellison & Williams, 2012).

Table A6.1. Sources of error in sampling, sample preparation and analysis

Procedure	Sources of systematic error	Sources of random error
Sampling	Selection of sampling plan Incorrect labelling Contamination of sample	Large variation in concentrations of a chemical in food or on treated crops Small number of primary samples taken Samples not statistically representative of food available
Shipping and storage	Decomposition of analytes Contamination of sample	
Sample preparation	Incorrect selection of the portion of sample to be analysed (analytical sample)	Contact of the analytical sample with and contamination by other portions of the sample Varying extents of rinsing and brushing; differential removal of stalks and stones Differences in food preparation methods (e.g. was food for analysis raw or cooked? If cooked, how was 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

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

A6.1.2.2 Procedures for estimating measurement uncertainty

Although there are several options available to laboratories for the estimation of measurement uncertainty, there are two preferred procedures, commonly described as the "bottom up" approach and the "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.

A6.1.3 References

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Appendix 6.2: Summary of options available for dietary exposure estimates for different food chemicals[a]

Food chemical	Acute *(sections 6.2.1 and 6.6.4)*	Chronic (lifetime) *(sections 6.2.2 and 6.6.5)*	Chronic (shorter-than-lifetime) *(sections 6.2.3 and 6.6.6)*	Aggregate (acute/chronic) *(sections 6.2.4 and 6.6.7)*	Cumulative (acute/chronic) *(sections 6.2.5 and 6.6.8)*
Food additives		*Screening* Budget method (section 6.6.5.1(a)) Reverse budget method (section 6.6.5.1(b)) Poundage data (section 6.6.5.1(c)) *Deterministic* High consumer model (section 6.6.5.2(a)) Sweetener substitution model (section 6.6.5.2(a)) *Refined deterministic* Total diet studies (section 6.6.5.2(b)) *Probabilistic/stochastic* Usual intakes (section 6.5.6)	*Refined deterministic by age/sex groups* *Probabilistic/ stochastic by age/sex groups*		*Probabilistic/ stochastic* (section 6.6.8)

Food chemical	Acute *(sections 6.2.1 and 6.6.4)*	Chronic (lifetime) *(sections 6.2.2 and 6.6.5)*	Chronic (shorter-than-lifetime) *(sections 6.2.3 and 6.6.6)*	Aggregate (acute/chronic) *(sections 6.2.4 and 6.6.7)*	Cumulative (acute/chronic) *(sections 6.2.5 and 6.6.8)*
Flavouring agents		*Screening* Poundage data (section 6.6.5.1(c)) MSDI (section 6.6.5.1(c)) *Deterministic* SPET/APET (section 6.6.5.2(a))	*Refined deterministic by age/sex groups* *Probabilistic/ stochastic by age/sex groups*		
Chemicals migrating from packaging materials		*Deterministic* EU model (section 6.6.5.2(a)) USA model (section 6.6.5.2(a))			
Novel foods		As for food additives (also see section 6.6.5.2(b))	As for food additives		
Genetically modified organisms	*Deterministic* (section 6.6.4.1(c))	As for food additives	As for food additives		

Food chemical	Acute *(sections 6.2.1 and 6.6.4)*	Chronic (lifetime) *(sections 6.2.2 and 6.6.5)*	Chronic (shorter-than-lifetime) *(sections 6.2.3 and 6.6.6)*	Aggregate (acute/chronic) *(sections 6.2.4 and 6.6.7)*	Cumulative (acute/chronic) *(sections 6.2.5 and 6.6.8)*
Pesticide residues	*Deterministic* IESTI/NESTI (section 6.6.4.1(a)) *Refined deterministic* *Probabilistic*	*Screening* IEDI/NEDI (section 6.6.5.1(e)) *Deterministic* GECDE (section 6.6.5.2(a)) *Refined deterministic* Total diet studies (section 6.6.5.2(b)) *Probabilistic/stochastic* Usual intakes (section 6.5.6)	*Deterministic by age/sex groups* GECDE (section 6.6.5.2(a)) *Refined deterministic by age/sex groups* *Probabilistic/ stochastic by age/sex groups*	*Refined deterministic* *Probabilistic/ stochastic*	*Refined deterministic* (chronic dietary exposure assessments only) *Probabilistic/ stochastic*

Food chemical	Acute *(sections 6.2.1 and 6.6.4)*	Chronic (lifetime) *(sections 6.2.2 and 6.6.5)*	Chronic (shorter-than-lifetime) *(sections 6.2.3 and 6.6.6)*	Aggregate (acute/chronic) *(sections 6.2.4 and 6.6.7)*	Cumulative (acute/chronic) *(sections 6.2.5 and 6.6.8)*
Veterinary drug residues	*Deterministic* GEADE (section 6.6.4.1(b)) *Refined deterministic* *Probabilistic*	*Deterministic* GECDE (section 6.6.5.2(a)) *Refined deterministic* Total diet studies (section 6.6.5.2(b)) *Probabilistic/stochastic* Usual intakes (section 6.5.6)	*Deterministic by age/sex groups* GECDE (section 6.6.5.2(a)) *Refined deterministic by age/sex groups* *Probabilistic/ stochastic by age/sex groups*	*Refined deterministic* *Probabilistic/ stochastic*	*Refined deterministic* (chronic dietary exposure assessments only) *Probabilistic/ stochastic*

Food chemical	Acute (sections 6.2.1 and 6.6.4)	Chronic (lifetime) (sections 6.2.2 and 6.6.5)	Chronic (shorter-than-lifetime) (sections 6.2.3 and 6.6.6)	Aggregate (acute/chronic) (sections 6.2.4 and 6.6.7)	Cumulative (acute/chronic) (sections 6.2.5 and 6.6.8)
Contaminants	*Deterministic* IESTI Case 1 (section 6.6.4.1(c)) GEADE (section 6.6.4.1(c)) *Refined deterministic* *Probabilistic/ stochastic*	*Screening* Reverse budget method (section 6.6.5.1(b)) *Deterministic* GEMS/Food cluster diets (sections 6.4.4.1(b) and 6.6.5.1(d)) *Refined deterministic* Total diet studies (section 6.6.5.2(b)) *Probabilistic/stochastic* Usual intakes (section 6.5.6)	*Refined deterministic by age/sex groups* *Probabilistic/ stochastic by age/sex groups*	*Refined deterministic* *Probabilistic/ stochastic*	*Refined deterministic* (chronic dietary exposure assessments only) *Probabilistic/ stochastic*

Food chemical	Acute *(sections 6.2.1 and 6.6.4)*	Chronic (lifetime) *(sections 6.2.2 and 6.6.5)*	Chronic (shorter-than-lifetime) *(sections 6.2.3 and 6.6.6)*	Aggregate (acute/chronic) *(sections 6.2.4 and 6.6.7)*	Cumulative (acute/chronic) *(sections 6.2.5 and 6.6.8)*
Nutrients		*Screening* FAO supply utilization account estimates (section 6.4.4.1(a)) GEMS/Food cluster diet estimates (sections 6.4.4.1(b) and 6.6.5.1(d)) *Refined deterministic* National dietary surveys (sections 6.4.4.2(a) and 6.6.5.2(b)) Total diet studies (section 6.6.5.2(b)) *Probabilistic/stochastic* Usual intakes (section 6.5.6)	*Refined deterministic by age/sex groups*		

APET: added portion exposure technique; EU: European Union; FAO: Food and Agriculture Organization of the United Nations; GEADE: global estimate of acute dietary exposure; GECDE: global estimate of chronic dietary exposure; GEMS/Food: Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme; IEDI: international estimated dietary intake; IESTI: international estimated short-term intake; MSDI: maximum survey-derived intake; NEDI: national estimated dietary intake; NESTI: national estimated short-term intake; SPET: single-portion exposure technique; USA: United States of America

a   For generic comments on different types of dietary exposure assessments, see section 6.2; see section 6.6.2 for deterministic and refined deterministic dietary exposure estimates and section 6.6.3 for probabilistic/stochastic estimates.