# IPCS

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

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Environmental Health Criteria 240

# Principles and Methods for the Risk Assessment of Chemicals in Food

## Chapter 1
## INTRODUCTION

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

Food and Agriculture Organization of the United Nations

World Health Organization

## Environmental Health Criteria 240

# PRINCIPLES AND METHODS FOR THE RISK ASSESSMENT OF CHEMICALS IN FOOD

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Published under the joint sponsorship of the United Nations Environment Programme, the International Labour Organization and the World Health Organization, and produced within the framework of the Inter-Organization Programme for the Sound Management of Chemicals.


Food and Agriculture Organization of the United Nations

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

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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# 1. INTRODUCTION



## 1.1 The need for updated guidance on risk assessment

The Food and Agriculture Organization of the United Nations (FAO) and World Health Organization (WHO) have a long history of collaboration in the safety evaluation of chemicals in food. This activity began in 1956, when the first meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) was convened by the two organizations, and was strengthened in the early 1960s, when the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) first met.

JECFA and JMPR follow the same general principles and methods for chemical risk assessments, which have been published in the reports of both committees. In response to recommendations made by JECFA and JMPR in the early to mid 1980s to review the validity of the evaluation procedures then in place, the International

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

Programme on Chemical Safety (IPCS) sponsored the preparation of Environmental Health Criteria monographs (EHCs) on Principles for the Safety Assessment of Food Additives and Contaminants in Food, EHC 70 (IPCS, 1987), and Principles for the Toxicological Assessment of Pesticide Residues in Food, EHC 104 (IPCS, 1990). These monographs and the principles laid out in subsequent reports have served as the basis for the assessments that have been performed by JECFA and JMPR, respectively, since they were published.

Although much of the guidance set out in EHC 70 and EHC 104 remains valid today, considerable development has taken place in the procedures for and complexity of assessments of chemicals in food since these monographs were prepared. There have been significant advances in chemical analysis, toxicological assessment and risk assessment procedures. JECFA and JMPR have developed many new general principles, and other international organizations and national governments have developed or are developing food safety risk assessment approaches and criteria. In addition, since the publication of these monographs, JECFA has also been charged with the evaluation of the safety of veterinary drug residues.

A conference on international food trade that was held in Melbourne in 1999 (FAO, 2000) recognized these developments and the fact that the evaluations performed by JECFA and JMPR serve as the scientific foundation for international food standards, which are of increasing importance within the Codex Alimentarius Commission (CAC) and the World Trade Organization. The conference recommended that WHO should consider updating and harmonizing all the common principles used by JECFA and JMPR in the toxicological evaluation of food chemicals and publish the information in a single consolidated document.

Following this recommendation, FAO and WHO initiated a project to update, harmonize and consolidate principles and methods for the risk assessment of food additives, food contaminants, natural toxicants and residues of pesticides and veterinary drugs. This monograph is the outcome of that project.

## 1.2 Development of the monograph

To develop this monograph, the principles and procedures used by JECFA and JMPR, including those in EHC 70 (IPCS, 1987) and

EHC 104 (IPCS, 1990) and those subsequently adopted by meetings of JECFA and JMPR, were reviewed. Those principles and methods that remain valid in view of current scientific knowledge have been reaffirmed. In addition, where possible, risk assessment procedures for different classes of chemicals in food (e.g. additives, contaminants, pesticide residues, veterinary drug residues and natural toxicants) have been harmonized. For those aspects that could not be harmonized, the reasons for the differences are elaborated.

FAO, WHO and other organizations have recognized the importance of the harmonization of risk assessment procedures to enhance the quality of risk assessments, achieve greater consistency when evaluating the risks from different sources of exposure, improve the transparency of the risk assessment process and facilitate risk communication. Therefore, approaches to risk assessment by other scientific groups (including national, regional, other public health and environmental organizations) were reviewed for these harmonization efforts. In particular, the outcomes of the IPCS Harmonization Project (http://www.who.int/ipcs/methods/harmonization/en/) and the Food Safety in Europe project of the European Commission (Barlow et al., 2002; Renwick et al., 2003) have been used in the development of this monograph.

## 1.3 Purpose, scope and outline of the monograph

### *1.3.1 Purpose*

The primary purpose of this monograph is to provide descriptive guidance for JECFA and JMPR to ensure the continuation of transparent and sound expert evaluations of scientific data for risk assessments of chemicals in food. The principles and methods described are focused on meeting the needs of JECFA and JMPR for their provision of scientific advice to FAO and WHO, particularly in the context of CAC. This monograph is also intended to be informative for users of the outputs from JECFA and JMPR, such as risk managers and other risk assessment bodies in Member countries and regional authorities.

Another purpose of this document is to facilitate the incorporation of new scientific tools, approaches and knowledge in the implementation of risk assessment of food chemicals, as discussed in section 1.5

below. In order to allow rapid incorporation of useful new information and guidance, this monograph will be available via the Internet, with each chapter published as a "stand-alone module".

The principles and methods in this document are presented as descriptive guidance. In the final analysis, expert risk assessment bodies, including JECFA and JMPR, must decide on the most appropriate approaches for the available scientific data in order to address the risk assessment and risk management questions that have been formulated for each food chemical considered.

### 1.3.2 Scope

This document describes general principles and methods for the risk assessment of additives, contaminants, pesticide residues, veterinary drug residues and natural constituents in foods. It also includes general guidance on the risk assessment of novel and non-traditional whole foods.

For some food and food ingredient terms, such as "novel", "foods for special dietary uses" and "nutrient", there are differences in the definitions used by national and regional authorities. In this document, the definitions given are those developed by JECFA and JMPR or CAC.

Some general guidance is also given on risk assessment related to upper levels for nutrients and other potentially beneficial food components (see also FAO/WHO, 2006a). Nutrient requirements and the determination of the efficacy of potentially beneficial dietary components are not addressed.

### 1.3.3 Outline

This document is organized to support risk assessment in the framework of the risk analysis paradigm, with considerations of risk profiling and problem formulation and the necessary interactions between the risk assessors and risk managers. The risk analysis paradigm is only briefly reviewed, as other publications have covered that topic in more detail (see, for example, FAO/WHO, 2006b).

Chapter 2 describes the role of risk assessment in risk analysis.

Chapter 3 describes the importance of and varying requirements for chemical characterization and analytical methods in risk assessment and risk management.

Chapter 4 covers the general principles of toxicological testing methods and studies required for hazard identification and characterization. These areas were covered extensively in EHC 70 and EHC 104.

Chapter 5 on dose–response assessment continues the theme of hazard characterization. It discusses the derivation of health-based guidance values and dose–response modelling.

Chapter 6 provides a summary of approaches to estimating dietary exposure (intake), with consideration of the concentration and food consumption data sets that may be used to derive these estimates. Dietary exposure assessments were not covered extensively in either EHC 70 or EHC 104. Subsequently, guidance was developed at several consultations, and EHC 214 (IPCS, 2000) was devoted to the topic of human exposure assessment.

Chapter 7 describes the considerations for risk characterization, including the provision of advice to risk managers and for risk communication.

Chapter 8 reviews the JMPR and JECFA approaches to maximum residue limit (MRL) recommendations for pesticides and veterinary drug residues. Historically, the approaches for the determination of MRLs for pesticides and veterinary drug residues have differed in a number of respects, and this chapter presents those for which harmonization has been agreed and explains those for which harmonization is not currently possible.

Chapter 9 describes some principles of risk assessment related to specific groups of substances consumed in small amounts, such as flavouring agents, substances used in food contact materials and residues of products used in the processing of foods; and substances consumed in large amounts, such as nutrients and novel foods. It is recognized that different national and regional regulatory authorities may have differing regulatory definitions of and requirements related to some of these substance groups. The terms used in this document are those used by JECFA and JMPR.

Finally, the glossary includes definitions of terms used in this report.

## 1.4 Historical background to the work of JECFA and JMPR

### 1.4.1 JECFA

JECFA was established following recommendations made to the Directors-General of FAO and WHO by the Joint FAO/WHO Expert Committee on Nutrition at its fourth session (FAO/WHO, 1955), and the subsequent first Joint FAO/WHO Conference on Food Additives was held in September 1955 (FAO/WHO, 1956). The first meeting of JECFA (FAO/WHO, 1957) was held in 1956, and acceptable daily intakes (ADIs) for some food additives were first established at the sixth meeting in 1961 (FAO/WHO, 1962a). The terms of reference of the earlier meetings of JECFA related to the formulation of general principles governing the use of food additives and consideration of suitable uniform methods for evaluating their safety. For these purposes, food additives were defined by the Conference as "non-nutritive substances added intentionally to food, generally in small quantities, to improve its appearance, flavour, texture, or storage properties" (FAO/WHO, 1955). From a practical standpoint, the "food additive" definition has been expanded since then, because a variety of compounds, including nutritive substances, have applications as food additives.

Following recommendations of the third Joint FAO/WHO Conference on Food Additives and Contaminants (FAO/WHO, 1974) and requests from Codex committees, these terms of reference were broadened to include substances unintentionally introduced into human food, such as veterinary drug residues, components of packaging materials, solvents used in food processing, aerosol propellants, enzymes used in food processing, contaminants, including metals in foods, and naturally occurring toxicants. Compounds that may be incorporated into foods as ingredients, at levels higher than those previously envisaged for food additives, have also been evaluated.

The first (FAO/WHO, 1957), second (FAO/WHO, 1958) and fifth (FAO/WHO, 1961) meetings of JECFA established principles for the use of food additives and made recommendations on methods for establishing their safety in use and for the evaluation of carcinogenic

hazards. From the outset, the Committee recognized that "no single pattern of tests could cover adequately, but not wastefully, the testing of substances so diverse in structure and function as food additives" and that "the establishment of a uniform set of experimental procedures that would be standardized and obligatory is therefore undesirable" (FAO/WHO, 1958).

The Committee at its second meeting (FAO/WHO, 1958) concluded that "it was only possible to formulate general recommendations with regard to testing procedures". Subsequent meetings of JECFA have consistently avoided the adoption of rigid protocols for the testing and evaluation of food additives. This allows the Committee to respond to new problems as they arise and to encompass non-routine and ad hoc studies in the safety evaluation.

In recognition of the fact that many features of toxicity testing and evaluation are relevant to both JECFA and JMPR, the twenty-fifth meeting of JECFA (FAO/WHO, 1981) recommended that a group of experts should be convened to study the application of advances in methodology to evaluation of food additives and contaminants, and also of pesticide residues. The urgency of the need to implement this recommendation was stressed by the twenty-sixth (FAO/WHO, 1982) and twenty-seventh (FAO/WHO, 1983) meetings of JECFA.

In response to the Committee's repeated recommendations, IPCS sponsored a project to formulate specific recommendations in order to bring up to date:

- the principles set out in earlier reports of JECFA concerning safety evaluation in relation to specific toxicological problems or specific chemical entities or groups;
- the test methods used in the toxicological evaluation of chemicals in food; and
- the assessment procedures adopted by JECFA in determining quantitative end-points, including the use of "safety factors" for extrapolating animal data to humans and to allow for variability within the human population.

A unified document on these issues was drafted and reviewed at the twenty-eighth (FAO/WHO, 1984), twenty-ninth (FAO/WHO, 1986a)

and thirtieth (FAO/WHO, 1987a) meetings of the Committee. The final monograph was published as EHC 70 (IPCS, 1987).

JECFA meetings on food additives and contaminants provide an evaluation of food additives, novel foods and nutrients used as food additives to the Codex Committee on Food Additives (CCFA) and an evaluation of contaminants and natural toxicants to the Codex Committee on Contaminants in Food (CCCF) for risk management decisions by these committees. Prior to 2007, these two committees were joined as the Codex Committee on Food Additives and Contaminants (CCFAC). JECFA does not recommend maximum levels (MLs) for food additives and contaminants to these Codex committees. In contrast, MRLs for veterinary drugs are recommended by JECFA meetings on veterinary drugs, but their final recommendation and adoption as Codex MRLs are risk management decisions taken by the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) and CAC.

### 1.4.2 JMPR

The concept of JMPR was first proposed in 1959, when an FAO Panel of Experts on the Use of Pesticides in Agriculture (FAO, 1959) recommended that FAO and WHO should jointly study:

- the hazard to consumers arising from pesticide residues in and on food and feedstuffs;
- the establishment of principles governing the setting up of pesticide tolerances; and
- the feasibility of preparing an international code for toxicological and residue data required in achieving the safe use of a pesticide.

Consequently, in 1961, a Joint Meeting of the FAO Panel of Experts on the Use of Pesticides in Agriculture and the WHO Expert Committee on Pesticide Residues was convened. The report of the 1961 meeting (FAO/WHO, 1962b) recommended that "toxicological and other pertinent data … on those pesticides known to leave residues in food when used according to good agricultural practice" should be evaluated. The evaluations would include the estimate of an ADI and an explanation of its derivation.

To implement this recommendation, the first Joint Meeting of the FAO Committee on Pesticide Residues in Agriculture and the WHO Expert Committee on Pesticide Residues was convened in 1963 (FAO/WHO, 1964). This meeting adopted the concept of the ADI, which was based on:

- the chemical nature of the residue;
- the toxicity of the chemical based on data from acute, short-term and long-term toxicity studies and knowledge of metabolism, mechanism of action and possible carcinogenicity of residue chemicals (usually determined in animals);
- knowledge of the effects of these chemicals on humans; and
- the use of "safety factors" for extrapolating animal data to humans and to allow for variability within the human population.

The 1963 and 1965 meetings (FAO/WHO, 1964, 1965) were concerned solely with ADIs and did not consider tolerances (a term later replaced by MRLs). Separate meetings of an FAO Working Party on Pesticide Residues examined the issue of tolerances approximately 2 months after the 1963 and 1965 meetings and issued separate reports. The first report considered principles (FAO, 1964), and the second proposed tolerances for pesticides on raw cereals (FAO, 1966).

The 1966 JMPR (FAO/WHO, 1967) was the first to consider both ADIs and tolerances. Since then, JMPR has met yearly, with reports and evaluations published subsequently. The products of the meetings, which include ADIs, temporary ADIs, MRLs, temporary MRLs and extraneous residue limits, have remained essentially unchanged.

Principles and methods of toxicological and residue assessments have evolved continuously as new data have been evaluated by JMPR. In view of this, the 1985 JMPR (FAO/WHO, 1986b) recognized the need to consider the quality of data and provide general guidance on the methods used for toxicological evaluations. The Meeting recommended that an international meeting consider the toxicological basis and data requirements for the estimation of an ADI or temporary ADI and to provide general guidance on relevant toxicological methodology. The 1987 JMPR (FAO/WHO, 1987b) and 1988 JMPR (FAO/WHO, 1988b) noted the progress that had been made in preparation of

a monograph covering these issues, and the 1989 JMPR (FAO/WHO, 1989b) reviewed the draft monograph, which was published in 1990 as EHC 104 (IPCS, 1990).

Maximum residue levels for pesticide residues can be estimated and recommended by JMPR for use as MRLs by the Codex Committee on Pesticide Residues (CCPR), but their final recommendation and adoption as Codex MRLs are risk management decisions taken by CCPR and CAC.[1]

### 1.4.3 Relevant activities since the publication of EHC 70 and EHC 104

New activities not considered in the preparation of the earlier monographs include:

- the evaluation of residues of veterinary drugs in food;
- the development and refinement of methods for estimating the dietary exposure to chemicals in food;
- safety evaluation related to acute exposure; and
- the development of the Procedure for the Safety Evaluation of Flavouring Agents.

These activities are described in more detail below (see sections 1.4.3.1–1.4.3.4). Another new activity not considered previously is the formalization of the risk analysis framework by FAO, WHO and CAC.

An FAO/WHO Conference on Food Standards, Chemicals in Food and Food Trade (in cooperation with the General Agreement on Tariffs and Trade) was held in Rome in March 1991 (FAO/WHO, 1991). This Conference recognized the importance of JECFA and JMPR in providing evaluations based on sound science and risk assessment principles. The Conference recommended that FAO and WHO review the terms of reference of JECFA to ensure that it has the authority and responsibility to review food products derived from contemporary biotechnology. It also recommended that WHO should seek to develop

[1] JMPR distinguishes between a "maximum residue level", which is a scientific estimate with its attendant uncertainty, and a "maximum residue limit" (MRL), which is equivalent to a legal limit.

internationally agreed principles for risk assessment of substances that had been shown to be carcinogenic in animal studies.

#### 1.4.3.1 *Evaluation of veterinary drug residues*

Several antibiotics used as veterinary drugs were evaluated at the twelfth meeting of JECFA (FAO/WHO, 1969), and the two agents proposed for use as growth promoters were considered at the twenty-sixth (FAO/WHO, 1982) and twenty-seventh (FAO/WHO, 1983) meetings. However, the extensive efforts that FAO and WHO have put into the evaluation of residues of veterinary drugs in food did not really begin until 1987 with the thirty-second meeting of JECFA (FAO/WHO, 1988a), which was the first meeting dedicated exclusively to veterinary drugs.

A Joint FAO/WHO Expert Consultation was held in Rome in 1984 (FAO/WHO, 1985) to consider various issues relating to the presence in food of chemicals used in animal husbandry and veterinary medicine. The Consultation recommended inter alia that immediate consideration should be given by CAC to the establishment of CCRVDF. It also recommended that the Directors-General of FAO and WHO convene an appropriate scientific body to advise Member governments and CCRVDF on questions pertaining to residues of veterinary drugs in foods of animal origin, in terms of both potential public health hazards and barriers to international trade. FAO and WHO gave this task to JECFA and set up separate meetings for this purpose.

The development of principles governing the safety evaluation of residues of veterinary drugs in food was begun at the thirty-second meeting (FAO/WHO, 1988a) and has continued since. At its thirty-second meeting, the Committee considered it appropriate and helpful to outline these general principles, but believed that it was desirable to encourage innovation and further developments in such areas as toxicology and residue analysis and did not wish to be unduly rigid in its requirements for data and their interpretation.

Although similar procedures for toxicological assessments are used by JECFA and JMPR, differences in assessment methods exist between JECFA in its assessment of residues of veterinary drugs and JMPR in its assessment of pesticide residues. This became apparent when JECFA and JMPR began evaluating residues of the same chemicals but from different sources. A meeting to harmonize

the work of JECFA and JMPR was therefore held in 1999 (FAO/WHO, 1999a), at which issues relating to the evaluation of chemicals used as both pesticides and veterinary drugs were discussed. It was noted that differences in the evaluation procedures used by the two scientific committees had led to different approaches to the definition of residues, estimation of dietary exposure, description of commodities for analysis and recommendations for MRLs. Other topics discussed at the meeting included risk assessment and tissue matrices used for the analysis of residues in meat/muscle, fat, milk and eggs.

The recommendations of this meeting were reviewed by the 1999 JMPR (FAO/WHO, 1999c) and the fifty-fourth meeting of JECFA (FAO/WHO, 2001a), the responses of which are included in the respective reports. Both scientific committees agreed to implement the recommendations to the extent feasible. Two issues were the different ways in which dietary exposure was estimated (see section 1.4.3.2) and differences in the way in which MRLs are derived by JECFA and JMPR. The MRLs for veterinary drug residues recommended by JECFA are based on the approved conditions of use in accordance with Good Practice in the Use of Veterinary Drugs (GPVD) and in compliance with the ADI, whereas the MRLs for pesticide residues established by JMPR are based on Good Agricultural Practice (GAP). This aspect is explained further in chapter 8. In order to bring its definitions more closely in line with those of JMPR, the fifty-fourth meeting of JECFA (FAO/WHO, 2001a) proposed revised definitions for egg and meat and a new definition for fat, foods included in the "food basket" used to estimate dietary exposure to veterinary drug residues (see chapter 8, section 8.2.2).

The Committees agreed that when JECFA and JMPR have recommended MRLs for the same chemical with the same residue/marker definition for the same commodity, the higher MRL will prevail.

#### *1.4.3.2 Dietary exposure assessments*

The procedures used for estimating dietary exposure to various types of chemicals in food have to some extent been developed separately by JECFA and JMPR. An FAO/WHO Consultation on Food Consumption and Exposure Assessment of Chemicals was held in 1997 (FAO/WHO,

1997b) to collate information on different approaches used for different food chemicals, followed by a joint workshop of risk assessors and risk managers (JECFA/CCFAC) on approaches to dietary exposure for contaminants and natural toxicants (FAO/WHO, 2000a). A more recent expert consultation on dietary exposure assessment was held in 2005 to harmonize approaches for the different types of chemicals considered by JECFA and JMPR, where possible. The outcome of that workshop (FAO/WHO, 2008) forms the basis of chapter 6 on dietary exposure assessment, with the history of consideration of dietary exposure estimates for different food chemicals outlined below.

(a) Pesticide residues

JMPR has been publishing chronic dietary exposure assessments as an integral component of its dietary risk assessments since 1998. The CCPR, at its eighteenth and nineteenth sessions in 1986 and 1987 (FAO/WHO, 1986c, 1987c), recommended that guidelines be developed for estimating the intake of pesticide residues, which would provide a procedure to ensure that MRLs adopted by Codex would be such that total dietary exposure to the residue did not exceed the ADI. Guidelines for predicting dietary intake of pesticide residues were published in 1989 (WHO, 1989) and revised in 1995 (WHO, 1997).

The original approach outlined in the 1989 guidelines (WHO, 1989) was a stepwise one, which first calculated a theoretical maximum daily intake (TMDI) as a screening step, assuming residue concentrations at the MRL for the pesticide and a hypothetical global diet. If the estimated dietary exposure exceeded the ADI on the basis of this worst-case calculation, a refined estimate was undertaken, the estimated maximum daily intake (EMDI), which included corrections for edible portion and losses on storage, processing and cooking. If dietary exposure exceeded the ADI on the basis of this calculation, an estimated daily intake (EDI) could be undertaken at a national level based on national diets and including information on the known residue level, corrections for edible portion and losses on storage, processing and cooking, national diets and known uses of the pesticide.

The revised guidelines of 1995 (WHO, 1997) moved away from a screening approach and recommended use of the best available data to calculate an international estimated daily intake (IEDI), based on the

WHO Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme (GEMS/Food) diets for different regions in the world (discussed in chapter 6, section 6.2.2.5) and the supervised trials median residue (STMR) level with plausible correction factors for edible portion and processing (see chapter 8). These guidelines also considered the calculation of acute or short-term dietary exposure for comparison with reference values for acute toxicity (see section 1.4.3.3 below; also chapter 6, section 6.3.6.2, appendix 6.1).

(b) Veterinary drug residues

From the beginning of its work on veterinary drug residues, JECFA used a "food basket" or model diet combined with residue levels at the MRL to estimate the maximum dietary exposure to veterinary drug residues (TMDI), ensuring that MRLs consistent with good veterinary practice would not result in chronic dietary exposures higher than the ADI (FAO/WHO, 1989a, 2001a). Since 2006, the median veterinary drug residue level for foods in the model diet has been used to estimate potential dietary exposure as an EDI to better align with the JMPR approach (FAO/WHO, 2006c) (see also chapter 6, section 6.3.4.1; chapter 8).

(c) Food additives and contaminants

CCFAC developed guidelines for the simple evaluation of contaminant intake (WHO, 2000) and food additive intake (FAO/WHO, 1989c, Annex IV). With the development of the General Standard for Food Additives and the General Standard for Contaminants and Toxins in Foods, CCFAC recognized the need to ensure that the acceptance of a standard would not result in dietary exposures exceeding the ADI for food additives or the tolerable intake for contaminants. In recognition of this need, JECFA further developed principles for dietary exposure assessments, which have been used on a routine basis since the fifty-first meeting of JECFA in 1998 (FAO/WHO, 2000b). In general, the GEMS/Food diets are used by JECFA in the estimation of dietary exposure to contaminants and natural toxicants, but these diets are not suitable for an assessment of food chemicals added to processed foods, such as food additives. JECFA evaluates dietary exposure estimates for food additives, novel foods and nutrients used as additives submitted by individual countries, which are usually based on national

food consumption data. Since 2008, JECFA has also had access to summary food consumption data for processed food categories for various European countries (EFSA, 2008) for use in its evaluations.

#### 1.4.3.3 *Assessment of acute toxicity*

Most work in this area was instigated by JMPR when it was recognized that some pesticide residue–crop combinations could give rise to wide unit-to-unit (e.g. carrot-to-carrot) variation in residue levels, which could result in sporadic high dietary exposures to the pesticide residue. In response to observations by CCPR that the traditional ADI was probably not an appropriate toxicological benchmark to be used in assessing risks due to short-term exposure to acutely toxic pesticides, the assessment of acute toxicity has been a regular item on the agenda of JMPR since 1994. The 1995 JMPR (FAO/WHO, 1996) developed and defined the acute reference dose (ARfD) and established ARfDs for several pesticides. The 1998 JMPR (FAO/WHO, 1999b) published procedures for estimating an ARfD and concluded that, in future, the possibility of establishing an ARfD would be considered for all pesticides, unless, on the basis of its toxicological profile, a pesticide was considered unlikely to present an acute hazard.

The 2000 JMPR (FAO/WHO, 2001b) provided further guidance on the establishment of the ARfD, and additional guidance on the derivation of the ARfD was published in the 2002 and 2004 JMPR reports (FAO/WHO, 2002, 2004b). All the guidance to date on ARfDs has been collated into one publication (Solecki et al., 2005). JECFA has also adopted the principles of establishing ARfDs when needed. Further details on ARfD setting are given in chapter 5 (section 5.2.9).

It has been clear from the beginning of JMPR's consideration of acute toxicity that it was not appropriate to use chronic dietary exposure estimates to compare with the ARfD as part of the risk characterization of acutely toxic pesticide residues. The FAO/WHO Consultation on Food Consumption and Exposure Assessment of Chemicals that was held in 1997 (FAO/WHO, 1997b) developed procedures for estimating short-term or acute dietary exposure, termed the international estimated short-term intake (IESTI), which have been used by JMPR since 1999. A number of different cases were developed for different

commodities that were blended (e.g. grains, milk) or consumed as a single entity (e.g. fruit, vegetables), which have been refined by JMPR at subsequent meetings (FAO/WHO, 2002, 2004a,b); these are discussed in more detail in chapter 6, appendix 6.1.

#### 1.4.3.4 *Evaluation of flavouring agents*

EHC 70 (IPCS, 1987) recognized that there were special issues associated with the safety evaluation of flavouring agents related to the very large number of substances used as food flavouring agents, many of which occur in natural products, and to the generally low and self-limiting levels of use. Most flavouring agents have not been subjected to detailed and comprehensive toxicity tests.

A paper outlining a procedure for the safety evaluation of flavouring agents in a consistent and timely manner was considered at the forty-fourth meeting of JECFA (FAO/WHO, 1995). It incorporated a series of criteria that took account of available information on annual production data for flavouring agents, structure–activity relationships, metabolism and toxicity data and is a form of risk characterization that relates dietary exposure estimates to the potential for toxicity. The production data for the flavouring agents were used to derive a population-based estimate of chronic dietary exposure to each flavouring agent for use in the procedure.

The procedure was developed further at the forty-sixth meeting of the Committee (FAO/WHO, 1997a), at which time 46 flavouring agents in three chemical groups were evaluated. The procedure was refined at the forty-ninth meeting (FAO/WHO, 1999d) and formally adopted as the Procedure for the Safety Evaluation of Flavouring Agents; 224 flavouring agents in seven chemical groups were evaluated. Between 100 and more than 200 flavouring agents have been evaluated at each of several subsequent meetings of JECFA. At the sixty-ninth meeting of JECFA (FAO/WHO, 2009), the Procedure was again revised to include an additional dietary exposure estimate based on added use levels for flavouring agents in foods and typical food portions, to account for consumers who regularly consume a certain food containing a flavouring agent and the potential for an uneven distribution of dietary exposures to that agent. The procedure for flavouring agents is discussed in detail in chapter 9.

## 1.5 Framework for identification, evaluation, development and incorporation of new principles and methods

The development of new principles and methods and the re-evaluation of existing principles and methods are conducted at regular meetings of JECFA. Special meetings or working groups are convened as appropriate.

Historically, new general principles have been developed for issues relative to the deliberations of the meeting at hand. The conclusions of the meeting with regard to general principles and methods will continue to be published as part of the report of the meeting.

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