CHAPTER 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. Throughout their histories, general principles and methods of assessment 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 Programme on Chemical Safety (IPCS) sponsored the preparation of Environmental Health Criteria (EHC) No. 70 (IPCS, 1987) and EHC No. 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.

While much of the guidance set out in EHC Nos. 70 and 104 remains valid today, considerable changes have 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.
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 (WTO). The Conference recommended that WHO should consider updating and harmonizing between JECFA and JMPR all the common principles of 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 and consolidate principles and methods for the risk assessment of food additives, food contaminants, and residues of pesticides and veterinary drugs. This EHC 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 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) 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 (FOSIE) 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 use 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 the 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 1.4 below. In order to allow rapid incorporation of useful new information and guidance, this monograph will be available via the Internet. Each chapter will form a “stand-alone module” that can be updated independently from the other chapters.

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 address the risk assessment and risk management questions that have been formulated.
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 among national and regional authorities. In this document, the definitions given are those developed by JECFA and JMPR or the CAC.

Some general guidance is also given on risk assessment related to upper levels for nutrients and other beneficial food components (see also the IPCS Project on Nutrient Risk Assessment, available at http://www.who.int/ipcs/methods/nra/en/index.html). Nutrient requirements or the determination of the efficacy of beneficial dietary components are not addressed.

1.3.3 How to use the monograph
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. While the risk analysis paradigm is briefly reviewed, other publications have covered that topic in more detail (see, for example, FAO/WHO, 2006).

Chapter 2 describes the process of risk assessment analysis.

Chapter 3 describes the importance 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 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.

Exposure and intake assessment 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 6 provides a harmonized summary of the guidance relevant for chemicals in food and additional considerations for the use of exposure and intake data.

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

In the risk analysis paradigm, maximum residue limits (MRLs) for residues of pesticides and veterinary drugs can be recommended by the risk assessors (JMPR and JECFA, respectively), but their adoption is a risk management decision taken, respectively, by the Codex Committee on Pesticide Residues (CCPR) and the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF). Historically, the approaches for the determination of the MRLs for pesticides and for veterinary drugs have differed in a number of respects. Chapter 8 reviews these approaches, presents those for which harmonization has been agreed and explains those for which harmonization is not currently possible.

Chapter 9 describes some special considerations for specific substances, especially where there may be risk management decisions involved, such as the use of the threshold of toxicological concern (TTC) approach. The chapter also covers 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 terms. The terms in this document are those used by JECFA and JMPR.

1.4 Framework for identification, evaluation, development and incorporation of new principles and methods into the monograph

The FAO and WHO Secretariats will assign the development of new principles and methods and the re-evaluation of existing principles and methods to regular meetings of JECFA and JMPR or to special meetings or working groups as appropriate.

In most cases, this will be accomplished by the review by JECFA and JMPR, as appropriate, of working papers prepared in advance of the meetings. 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. In addition, future general principles and methods will be available for review and comment on the FAO and WHO websites. If there are no substantive comments received, these new or revised general principles and methods will be incorporated into the General Principles and Methods for the Risk Assessment of Chemicals in Food. If substantive comments are received, these comments will be given to the appropriate subsequent meetings of JECFA and JMPR to consider. The decision of the meetings at this time will be final.

1.5 Historical background to the work of JECFA and JMPR

1.5.1 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 Joint Conference as “non-nutritive substances added intentionally to food, generally in small quantities, to improve its appearance, flavour, texture, or storage properties”. 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 (FAO/WHO, 1974), 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. Novel foods and ingredients that may be incorporated into foods 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 meetings (FAO/WHO, 1961) 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 the 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).

1.5.2 JMPR

The concept of a 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 Joint 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 two months after the Joint 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, Joint Meetings have been held yearly, and reports and evaluations published subsequently. The products of the Joint Meetings, which include ADIs, temporary ADIs, MRLs (replacing the term “tolerance”), temporary MRLs and extraneous residue limits, have remained essentially unchanged.

Principles and methods of toxicological and residues 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 (FAO/WHO, 1987b) and 1988 (FAO/WHO, 1988b) Joint Meetings 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).

1.5.3 Relevant activities since the publication of EHC 70 and EHC 104

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

- evaluation of residues of veterinary drugs in food;
- development and refinement of methods for estimating the intake of chemicals in food;
- safety evaluation related to acute exposure;
- development of the Procedure for the Safety Evaluation of Flavouring Agents; and
- formalization of the risk analysis framework by FAO, WHO and the CAC.

These activities are described in more detail below (see sections 1.5.3.1–1.5.3.5).

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

Although similar procedures for toxicological assessments are used by JECFA and JMPR, many 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, 1999), 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 intake, 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 and the fifty-fourth meeting of JECFA, the responses of which are included in the respective reports (FAO/WHO, 1999b, 2001a). Both scientific committees agreed to implement the recommendations to the extent feasible; one issue is the different ways in which intake is estimated and differences in the way that 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 (GVP) and in compliance with the ADI, whereas the MRLs for pesticide residues established by the 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. The Committee 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 shall prevail.

1.5.3.1 Evaluation of veterinary drug residues
Several antibiotics used as veterinary drugs were evaluated at the twelfth meeting of JECFA (FAO/WHO, 1969), and the xenobiotic anabolic agents trenbolone acetate and zeranol were considered for use as growth promoters 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 the CAC to the establishment of a CCRVDF. It also recommended that the Directors-General of FAO and WHO convene an appropriate scientific body to advise Member governments and the Codex Committee 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 the JECFA.

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.

From the beginning of its work, it was apparent that the data on safety and residues on the majority of veterinary drugs were incomplete and did not meet modern standards. Using standard evaluation procedures, in many cases, the Committee was unable to establish ADIs or
recommend MRLs. This issue was addressed at the fortieth meeting (FAO/WHO, 1993), when the Committee concluded that for certain products with a long history of use (often referred to as older veterinary drugs), data that do not meet modern criteria may nevertheless be useful in the safety assessment of residues in human food. The scientific literature and experience with human use of such drugs could provide additional information. The basic approach taken by the Committee was that, when all areas of concern are not addressed by animal studies, the manufacturer should provide an evaluation report that includes a comprehensive review and analysis of the scientific literature, relevant human data and/or relevant data for the target species. An ADI and MRL are normally established for veterinary drugs when human food safety can be assessed adequately from the available data.

Evaluation reports submitted since the fortieth meeting have enabled the Committee to establish ADIs and recommend MRLs on a large number of veterinary drugs with a long history of use.

1.5.3.2 Intake assessments
Committees of the CAC began requesting intake assessments of chemicals in food in the mid-1980s, and the Codex Committee on Food Additives and Contaminants (CCFAC) developed guidelines for the simple evaluation of food additive intake, which were published as Annex IV of the report of its Twenty-first Session in 1989 (CAC, 1989). The CCPR, at its Eighteenth and Nineteenth Sessions in 1986 (CAC, 1986) and 1987 (CAC, 1987), 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 not be such that dietary intake exceeded the ADI. In response, FAO and WHO held a consultation in October 1987 at which Guidelines for predicting dietary intake of pesticide residues (WHO, 1989) were developed.

The procedures used for estimating the intake of various types of chemicals in food present different types of problems and have been developed independently of one another. An International Expert Workshop on Exposure Assessment was held in 2005 by FAO/WHO, which attempted to provide an agreed tiered approach that would be harmonized for the different types of chemical considered by JECFA and JMPR. The outcome of that workshop forms the basis of chapter 6 on dietary exposure assessment.

(a) Pesticide residues
JMPR has been including intake assessments as an integral component of its dietary risk assessments since 1998. The guidelines for predicting dietary intake of pesticide residues were published in 1989 (WHO, 1989) and used a series of estimations, starting with a conservative screening approach and applying more data-intensive methods if necessary. The first value that was calculated, the theoretical maximum daily intake (TMDI), was based on the MRL for the pesticide and a hypothetical global diet. When intake exceeded the ADI on the basis of this worst-case calculation, an estimated maximum daily intake (EMDI), which included corrections for edible portion and losses on storage, processing and cooking, was calculated. When intake exceeded the ADI on the basis of this calculation, an estimated daily intake (EDI), which included 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, was calculated. Since most of this information is available only at the national level, the EDI can be calculated only on a national basis.

While these guidelines aided the CCPR in deciding on the acceptability of MRLs, the Committee recognized after a few years of use that they should be modified to take into account new information and recommended to FAO and WHO that they be revised. An FAO/WHO expert consultation on risk analysis (FAO/WHO, 1995a) made a similar recommendation. In
response, FAO and WHO convened a consultation in May 1995 that developed revised
*Guidelines for predicting dietary intake of pesticide residues* (WHO, 1997). These guidelines
moved away from a screening approach, since this can generate the perception that the sole
purpose of refining intake is to bring the number below the ADI. The guidelines recommend the
calculation of an international estimated daily intake (IEDI), which includes factors for edible
portion and processing. In addition, the concept of the supervised trials median residue (STMR)
level was introduced, which serves as the basis for the residue level. These guidelines also
consider the calculation of short-term intake, which should serve as the comparison against
reference values for acute toxicity (see section 1.5.3.3 below). Because of the potential for acute
toxicity from exposure to pesticides (see below), estimates are made for both acute intakes and
average long-term intakes.

(b) Veterinary drug residues

From the beginning of its work on veterinary drugs, JECFA has used “food factors” as a
component in ensuring that MRLs consistent with good veterinary practice would not result in
daily intakes higher the ADI. The daily food consumption values (food factors) used are 300 g of
meat (as muscle tissue), 100 g of liver, 50 g of kidney, 50 g of tissue fat, 100 g of egg and
1.5 litres of milk (FAO/WHO, 1989a). The Committee describes intake calculations based on
these food factors and the MRL values as theoretical maximum daily intakes, which are
comparable to the TMDIs that were calculated based on the earlier guidelines for predicting
dietary intake of pesticide residues. Unlike the approaches used for food additives and pesticide
residues, JECFA does not attempt to refine the intake calculations.

(c) Food additives and contaminants

With development of the General Standard for Food Additives (GSFA) and the General Standard
for Contaminants and Toxins in Foods (GSCTF), CCFAC has recognized the need to ensure that
the acceptance of a standard would not result in intake exceeding the ADI for food additives or
the tolerable intake for contaminants. In recognition of this need, JECFA has been developing
principles for intake assessments and has been assessing the intake of food additives and
contaminants on a routine basis since the fifty-first meeting in 1998 (FAO/WHO, 2000). Intake
assessments are now an integral component of the safety assessments performed by JECFA.

1.5.3.3 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,
which could result in sporadic high intakes. In response to observations by CCPR that the
traditional ADI was probably not an appropriate toxicological benchmark to be used in assessing
risks reflecting short-term intake of acutely toxic pesticides, the assessment of acute toxicity has
been an item that has been on the agenda of JMPR regularly 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, 1999a) 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 is
considered unlikely to present an acute hazard.

The 2000 JMPR (FAO/WHO, 2001b) provided further guidance on the establishment of
the ARfD and prepared a proposed test guideline for studies with single oral doses (for use in
establishing ARfDs for chemical residues in food and drinking-water) for submission to the
Organisation for Economic Co-operation and Development (OECD). The 2002 JMPR reviewed
the report of a working group that had been constituted by WHO to consider issues surrounding
ARfDs. Further guidance on derivation of the ARfD, based on the report of the working group, was published in the JMPR report (FAO/WHO, 2002), and all the guidance to date on ARfDs has been collated into one publication (Solecki et al., 2005).

It has been clear from the beginning of JMPR’s consideration of acute toxicity that it was not appropriate to compare intake based on long-term food consumption with the ARfD. An FAO/WHO Consultation on food consumption and exposure assessment of chemicals that was held in 1997 (FAO/WHO, 1997b) developed procedures for estimating intake that would be appropriate for comparison with an ARfD, which at the international level was termed international estimate of short-term intake (IESTI). Short-term intakes of pesticides for which ARfDs have been allocated have been estimated by JMPR since 1999. These are used in dietary risk assessments by comparing the estimates with the ARfD. Further details on ARfD setting are given in chapter 4 (section 4.4.2).

1.5.3.4 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, 1995b). It incorporated a series of criteria that take into account available information on intake from current uses, structure–activity relationships, and metabolism and toxicity data.

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 further at the forty-ninth meeting (FAO/WHO, 1999c) and was named 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 several subsequent meetings of JECFA at which food additives have also been evaluated. The procedure is a form of risk characterization that relates intake to the potential for toxicity. Recent meetings of JECFA have considered pragmatic methods of intake estimation that would be relevant to consumers loyal to foods flavoured with particular flavouring substances and therefore could be exposed to higher amounts of such substances. The estimation of intake of flavouring agents is discussed in detail in chapter 6.

1.6 References
Update Project  Chapter 1: Introduction  Draft May 2008


