PRINCIPLES AND METHODS FOR THE RISK ASSESSMENT OF CHEMICALS IN FOOD

CHAPTER 7: RISK CHARACTERIZATION

7.1 General considerations

Risk characterization is the fourth step of the risk assessment process, integrating information from the hazard characterization and the exposure assessment to produce the scientific advice for risk managers (Renwick et al., 2003). The CAC (2004) has defined risk characterization as "The qualitative and/or quantitative estimation, including attendant uncertainties, of the probability of occurrence and severity of known or potential adverse health effects in a given population based on hazard identification, hazard characterization and exposure assessment" (CAC, 2004).

Historically, different approaches have been used for the risk characterization of toxic effects considered to have a threshold and for those considered to have no threshold (see section 1.5.3.2).

For threshold effects, health-based guidance values such as the ADI, tolerable intake (TI) and ARfD have been used by JECFA and JMPR. The ADI and ARfD are generally used for substances deliberately added to food and for residues of pesticides and veterinary drugs (which likewise can be controlled). For unavoidable contaminants, a TI is usually determined.

For effects such as genotoxic events, the traditional assumption is that there may not be a threshold dose and that some degree of risk may exist at any level of exposure. Thus, health-based guidance values have not been developed by JECFA for substances that are known to be both genotoxic and carcinogenic. It should be noted, however, that some chemicals increase the incidence of cancer in experimental animals by non-genotoxic mechanisms, and establishing a health-based guidance value, such as a PTWI, would be appropriate for such chemicals. The types of risk characterization advice that have been developed for substances that are genotoxic and carcinogenic include:

1) a recommendation that the exposure should be as low as reasonably achievable (ALARA);

2) quantification of the risk at different levels of exposure (e.g. aflatoxin) (FAO/WHO, 1999); and
3) ranking of the risk from different compounds producing similar hazards (e.g. substances that are genotoxic and carcinogenic) (FAO/WHO, 2006).

It is recognized that the advice in 1) is of limited value, because it does not take into account either human exposure or carcinogenic potency and does not allow risk managers to prioritize different contaminants or to target risk management actions.

While approach 2) can provide advice for risk management of a specific substance, it does not provide the information necessary to prioritize different contaminants.

Approach 3) includes the MOE approach, which is the ratio between a dose producing a small but measurable effect in animals or humans and the estimated human exposure (see sections 7.4 and 7.5). For substances that are both genotoxic and carcinogenic, this approach provides advice to inform risk managers how close human exposures are to those anticipated to produce an adverse effect. In addition, MOEs of different substances can be compared to assist risk managers in prioritizing risk management actions.

7.2 Health-based guidance values

7.2.1 Introduction

The setting of health-based guidance values provides quantitative information from risk assessment for risk managers, enabling them to make decisions concerning the protection of human health. Health-based guidance values developed by JECFA and JMPR for substances found in food and drinking-water are the quantitative expression of the range of oral exposure (either acute or chronic) that would be expected to be without appreciable health risk.

For substances intentionally added to food, such as food additives, and for residues of pesticides and veterinary drugs in food, the health-based guidance value is termed the ADI. JECFA and JMPR determine ADIs based on all the known facts at the time of the evaluation.

When appropriate JMPR and JECFA, for residues of pesticides and veterinary drugs in food, respectively, develop ARfDs (see section 4.4.2). The ARfD is defined as "an estimate of the amount of a substance in food and/or drinking-water, normally expressed on a body-weight basis, that can be ingested in a period of 24 h or less, without appreciable health risk to the consumer, on the basis of all the known facts at the time of the evaluation" (JMPR, 2002).

For food contaminants that are generally unavoidable, JECFA has used the term TI for health-based guidance values. These have included the provisional maximum tolerable daily intake (PMTDI), provisional tolerable weekly intake (PTWI) and PTMI. A TI represents the maximum acceptable exposure to a contaminant via the diet; the goal should be to limit exposure to the maximum feasible extent, consistent with the TI. The use of the term "provisional" expresses the tentative nature of the evaluation, in view of the paucity of reliable data on the consequences of human exposure at levels approaching those with which JECFA is concerned.

PMTDIs are established for food contaminants that are not known to accumulate in the body. The value assigned to a PMTDI represents permissible human exposure as a result of the natural occurrence of the substance in food and in drinking-water.

For contaminants that may accumulate within the body over a period of time, JECFA has used the PTWI and PTMI. On any particular day, consumption of food containing above-average levels of the contaminant may exceed the proportionate share of its weekly or monthly tolerable intakes. JECFA's assessment takes into account such daily variations, its real concern being prolonged exposure to the contaminant, because of its ability to accumulate within the body over a period of time.

For residues of pesticides and veterinary drugs in foods, in addition to setting ADIs and, if necessary, ARfDs, maximum levels for foods are also developed, based on the results of scientific studies, for consideration by the respective Codex committee. In essence, JMPR estimates maximum residue levels that may be used by CCPR to recommend MRLs to the CAC. JECFA recommends draft MRLVDs for consideration by the CCRVDF. The CCRVDF then recommends those MRLVDs that meet its approval to the CAC.

7.2.2 Acceptable daily intakes

7.2.2.1 Food additives

At the time of its first meeting, JECFA recognized that the amount of an additive used in food should be established with due attention to "an adequate margin of safety to reduce to a minimum any hazard to health in all groups of consumers" (FAO/WHO, 1957). The second JECFA (FAO/WHO, 1958), in outlining procedures for the testing of intentional food additives to establish their safety for use, concluded that the results of animal studies can be extrapolated to humans, and that

> some margin of safety is desirable to allow for any species difference in susceptibility, the numerical differences between the test animals and the human population exposed to the hazard, the greater variety of complicating disease processes in the human population, the difficulty of estimating the human intake, and the possibility of synergistic action among food additives.

This conclusion formed the basis for establishing the ADI, which is the end-point of JECFA risk characterization for intentional food additives. JECFA defined the ADI as "An estimate of the amount of a food additive, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk (standard man = 60 kg)" (IPCS, 1987).

The ADI is expressed in milligrams per kilogram of body weight, as a range from 0 to an upper limit, which is considered to be the zone of acceptability of the substance. JECFA expresses the ADI in this way to encourage the lowest levels of use that are technologically feasible.

Substances that have long half-lives and accumulate in the body are not suitable for use as food additives (FAO/WHO, 1962a). Data packages should include metabolism and excretion studies designed to provide information on the cumulative properties of food additives.

JECFA generally sets the ADI of a food additive on the basis of the highest NOEL in animal studies. At its sixty-eighth meeting in 2007, in order to harmonize with the practices of JMPR and other risk assessment bodies, the Committee decided to use the term NOAEL when the effect at the next higher dose is considered adverse. If such an effect is not considered adverse, then the term NOEL will be used. This includes assessments where no effects were observed at the highest dose tested. In such cases, the highest dose tested is taken as the NOEL. The same approach will be used by the Committee with respect to the terms lowest-observed-effect level (LOEL) and LOAEL (FAO/WHO, 2008).

In calculating the ADI, a safety factor is applied to the NOEL to provide a conservative margin of safety on account of the inherent uncertainties in extrapolating animal toxicity data to potential effects in the human being and for variation within the human species. When results from two or more animal studies are available, the ADI is based on the most sensitive animal species—i.e. the species that displayed the toxic effect at the lowest dose, unless metabolic or pharmacokinetic data are available establishing that the test in the other species is more appropriate for humans (see also chapter 5).

Generally, the ADI is established on the basis of toxicological information and provides a useful assessment of safety without the need for data on intended or actual use or dietary exposure. However, in setting ADIs, it may be necessary to know whether particular

subpopulations are exposed, since the ADI applies to the whole population. Therefore, general information about exposure patterns should be known at the time of the safety assessment (see chapter 6). For example, if a food additive is to be used in infant formulas, the safety assessment is not complete without looking carefully at safety studies involving exposure to very young animals.

There are occasions when JECFA considers the setting of an ADI in numerical terms not to be appropriate. This situation arises when the estimated consumption of the additive is expected to be well below any numerical value that would ordinarily be assigned to it. Under such circumstances, JECFA uses the term "ADI not specified". The Committee defines this term to mean that, on the basis of available data (chemical, biochemical, toxicological and other), the total daily intake of the substance, arising from its use at the levels necessary to achieve the desired effect and from its acceptable background in food, does not, in the opinion of the Committee, represent a hazard to health. For that reason, and for the reasons stated in the individual evaluations, the establishment of an ADI in numerical form is not deemed necessary (e.g. FAO/WHO, 1984, Annex II). An additive meeting this criterion must be used within the bounds of good manufacturing practice—i.e. it should be technologically efficacious and should be used at the lowest level necessary to achieve this effect, it should not conceal inferior food quality or adulteration, and it should not create a nutritional imbalance (FAO/WHO, 1974a, pp. 10–11). That the background occurrence of the chemical must be taken into account in the evaluation of its safety was articulated by the WHO Scientific Group on Procedures for Investigating Intentional and Unintentional Food Additives (WHO, 1967).

JECFA has encountered several situations in which either the body of available data on a new additive had some limitations or the safety of a food additive for which the Committee had previously assigned an ADI was brought into question by new data. When the Committee feels confident that the use of the substance is safe over the relatively short period of time required to generate and evaluate further safety data, but is not confident that its use is safe over a lifetime, it often establishes a "temporary" ADI, pending the submission of appropriate data to resolve the safety issue on a timetable established by JECFA. When establishing a temporary ADI, the Committee often uses a higher-than-usual safety factor, usually increasing it by a factor of 2. The additional biochemical and/or toxicological data required for the establishment of an ADI are clearly stated, and a review of these new data is conducted before expiry of the provisional period. In many cases, long-term studies are requested, but timetables are not met, which means that JECFA has had to extend temporary ADIs for further periods of time. In instances where data have not been forthcoming, JECFA has withdrawn temporary ADIs as a safety precaution.

While the availability of estimates of exposure is not a prerequisite for establishing an ADI for a new food additive, such estimates are valuable for risk managers who may need to allocate limits for the amounts that may be added to certain foods. Exposure information is also indispensable when:

- performing risk assessments for food contaminants and processing aids; and
- assessing the safety of added substances that may also be naturally present in food, to determine their relative contributions to the diet (FAO/WHO, 1974b, pp. 8–10).

In order to accurately compare exposure and acceptable intake, similar assumptions should be used for making each estimate, or, at least, the differences and similarities in the estimates should be understood. For example, if an ADI is computed from lifetime dosage, then the estimated human exposure should represent lifetime exposure to the additive. Sometimes, acceptable intakes are based on data for specific age groups or for certain

exposure conditions, such as when short-term exposure should be limited with certain food additives that cause laxative effects at high dose levels. Under such circumstances, the human exposure estimate should be for the same age group or exposure conditions.

In risk characterization, for effective comparison of exposure estimates with acceptable intakes, the assumptions used to compute exposure estimates should always be stated. Data on the functional uses of intentional food additives and information on approaches used to compute intake estimates, such as analytical studies on food constituents or migration (carry-over) models for certain contaminant situations, should be provided if possible.

7.2.2.2 Pesticides

The FAO/WHO Joint Meeting on Principles Governing Consumer Safety in Relation to Pesticide Residues indicated that the assessment of the amount of pesticide to which humans can be exposed daily for a lifetime, without injury, was the primary aim of toxicological investigations. The Meeting indicated that "when the (toxicological) investigations are completed, it is possible, by the use of scientific judgement, to name the acceptable daily intake" (FAO/WHO, 1962b, p. 9).

JMPR defined the ADI as "An estimate of the amount of a pesticide, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk (standard man = 60 kg)" (IPCS, 1990).

As for food additives, the ADI for a pesticide is expressed in milligrams per kilogram of body weight, as a range from 0 to an upper limit, which is considered to be the zone of acceptability of the substance. JMPR expresses the ADI in this way to encourage the lowest levels of use that are technologically feasible.

JMPR stated that the following information should be available in order to arrive at an ADI (FAO/WHO, 1964, p. 6):

(a) The chemical nature of the residue. Pesticides may undergo chemical changes and are frequently metabolized by the tissues of plants and animals which have been treated with them. Even when a single chemical has been applied, the residues may consist of a number of derivatives with distinct properties, the exact nature of which may differ in animals and plants and in different crops and products.
(b) The toxicities of the chemicals forming the residues from acute, short-term and long-term studies in animals. In addition, knowledge is required of the metabolism, mechanism of action and possible carcinogenicity of residue chemicals where consumed.
(c) A sufficient knowledge of the effects of these chemicals in man.

Although the ADI can be exceeded for short periods of time without significant risk, it is not possible to make a generalization on the duration of the time frame that may give rise to concern. The induction of detrimental effects will depend upon factors that vary from pesticide to pesticide. The biological half-life of the pesticide, the nature of the toxicity and the amount by which the exposure exceeds the ADI are all crucial.

The large safety factors generally involved in establishing an ADI serve to provide assurance that exposure exceeding the ADI for short time periods is unlikely to result in any deleterious effects upon health. However, consideration should be given to the potentially acute toxic effects that are not normally considered in the assessment of an ADI, and, if necessary, an ARfD should be set.

The principles discussed above were adopted by subsequent Joint Meetings but, as would be expected, have been further developed with time. Thus, the 1968 JMPR (FAO/WHO, 1969) indicated that metabolites would, under certain conditions, be considered to be included in the ADI. Generally, if the metabolites in food commodities are qualitatively and quantitatively the same as those observed in laboratory test species, the ADI would apply

to the parent compound as well as to metabolites. If the metabolites are not identical or not present at the same order of magnitude, separate studies on the metabolites may be necessary. When one or several pesticides are degradation products of another pesticide, a single ADI may be appropriate for the pesticide and its metabolites (e.g. oxydemeton-methyl, demeton-*S*-methyl sulfone and demeton-*S*-methyl) (FAO/WHO, 1989).

In 1973, when considering the accuracy with which ADIs could be estimated, JMPR recommended that ADIs should be expressed numerically using only one significant figure (FAO/WHO, 1974c). The use of more than one significant figure might be taken to imply a greater degree of accuracy than that which can be achieved when assessing the hazard from the wide range of factors that influence toxicity.

Use of the temporary ADI, first proposed by the Scientific Group on Procedures for Investigating Intentional and Unintentional Food Additives (WHO, 1967), was adopted by JMPR in 1966. Criteria were set that had to be met prior to the establishment of the temporary ADI. These included the consideration of each chemical on its own merits, the establishment of the temporary ADI for a fixed period (usually 3–5 years) and the subsequent review of original and new data prior to expiry of the provisional period.

The establishment of a temporary ADI has always been accompanied by a requirement for further work by a specified date and by the application of an increased safety factor. The 1972 JMPR considered the course of action to be taken if requested data were not forthcoming and indicated that, under these circumstances, the temporary ADI would be withdrawn. It emphasized, however, that such an action "did not necessarily indicate a potential health hazard, but only that insufficient information is available at the time of review to permit the Meeting to state with reasonable certainty that there is no likelihood of adverse effects on health resulting from ingestion over a prolonged period" (FAO/WHO, 1973, p. 7).

In 1986, JMPR (FAO/WHO, 1987) indicated that the previously utilized terms "Further work or information required" or "Further work or information desirable" were being replaced, the former by the statement "Studies without which the determination of an ADI is impracticable", and the latter by the statement "Studies which will provide information valuable to the continued evaluation of the compound." These new statements not only reflect the actual work performed by JMPR much more clearly than the previous terms "Required" and "Desirable", but they also reflect the Meeting's increasing reluctance to allocate temporary ADIs as well as the desire to continue the evaluation of a compound even after an ADI has been allocated.

In 1988, JMPR (FAO/WHO, 1988a) recommended that temporary ADIs should not be allocated for new compounds and that an ADI should not be allocated in the absence of an adequate database. The Meeting intended that monographs be published for all chemicals that are reviewed, regardless of whether an ADI is allocated, and that data requirements will be clearly specified for those chemicals with an inadequate database.

The concept of the "conditional acceptable daily intake", adopted by the 1969 JMPR (FAO/WHO, 1970), was limited to those compounds for which the use was at that time considered essential but for which the toxicological database was incomplete. This concept has been abandoned.

7.2.2.3 Veterinary drug residues

Recognizing the principles applied in evaluating a substance for the purposes of establishing an ADI in the Principles for the Safety Assessment of Food Additives and Contaminants in Food (IPCS, 1987), the thirty-second JECFA meeting elaborated many of these principles as a framework for the specific assessment of residues of veterinary drugs in food (FAO/WHO, 1988b). Most importantly, where possible and appropriate, they affirmed that an ADI based

on determination of a NOEL from animal or human toxicological data should be used as the end-point of the safety evaluation with use of an appropriate safety factor. The thirty-second Committee recognized that in some instances it might be inappropriate to establish an ADI. When it has been determined that establishing an ADI is unnecessary because of a large margin of safety, the recommendation of an MRL is also unnecessary. For example, at the fortieth meeting, an ADI "not specified" was established for the bovine somatotropins (FAO/WHO, 1993). The Committee noted the lack of oral activity of the recombinant somatotropins and the insulin-like growth factor-1 as well as the low amounts and non-toxic nature of the residues of these compounds even at exaggerated doses. The Committee concluded that these results provide an extremely large margin of safety for humans consuming dairy products from animals treated with the recombinant somatotropins and, therefore, warranted the establishment of ADI "not specified".

The Committee has noted that an ADI for a drug is usually based on the toxicity of the parent drug rather than on its metabolite(s). However, it may sometimes be necessary to calculate an ADI for individual metabolites. Although most compounds have been evaluated as individual substances, there are instances where an ADI has been established as a group ADI (e.g. streptomycin/dihydrostreptomycin, enrofloxacin/ciprofloxacin) and where an ADI has been established on a microbiological end-point rather than a toxicological end-point (e.g. spiramycin and spectinomycin). The thirty-eighth meeting of the Committee (FAO/WHO, 1991) noted that if the pharmacological effects are more relevant and sensitive than the toxicological effects, the ADI should be established on the basis of pharmacology.

As for food additives and pesticides, ADIs for veterinary drugs are usually expressed as a range extending from zero to an upper limit. This indicates that where MRLs are recommended, efforts should be made to reduce consumer exposure to residues as far as possible below the upper limit of the ADI. There have been a limited number of situations where an ADI numerical value or range was not identified. For allergenic considerations, the Committee did not establish an ADI for benzylpenicillin, as there was insufficient data to establish a NOEL (FAO/WHO, 1990). The Committee recommended that the daily intake from food should be kept as low as possible (below 0.03 mg/person per day).

The thirty-eighth meeting of the Committee also addressed the issue of establishing ADIs and MRLs for those substances that are rapidly converted to the metabolites when administered to the target animal or host (FAO/WHO, 1991). The Committee recognized that there may be occasions when drug metabolites present as residues are devoid of the specific activity of concern possessed by the parent drug. In these situations, the activity of the parent drug would be discounted in establishing the ADI on which to base the MRL; the ADI would instead be based on a toxicological property of the metabolites with an appropriate safety factor applied (e.g. febantel). An ADI was established for febantel per se, based on a study in animals administered the parent compound, but the MRL was established for metabolites, measured as oxfendazole sulfone, using an ADI established for oxfendazole.

The fortieth Committee noted that certain conditions apply regarding the identity and quality of veterinary drugs subject to Committee review (FAO/WHO, 1993). The Committee evaluations depend on studies performed with a chemical substance or product of defined identity, purity and physical form. In particular, the ADI is valid only for products that do not differ significantly in identity and quality from the material used to generate the data used for the Committee's evaluation (see chapter 3).

The thirty-eighth meeting of the Committee (FAO/WHO, 1991) affirmed that in calculating the ADI, the Committee has usually followed the procedures described in Principles for the Safety Assessment of Food Additives and Contaminants in Food (IPCS, 1987), applying a safety factor to the NOEL derived from the most relevant and appropriate toxicological, microbiological or pharmacological end-point study. The safety factor usually

chosen is 100 in the situation where a NOEL is derived from a long-term animal study on the assumption that humans are 10 times as sensitive as the test animal(s) used in such studies and that a 10-fold range of sensitivity within the human population may exist. When no adverse health effects are seen in long-term studies, a safety factor of 100 may be applied to the NOEL derived from short-term studies where higher dose levels have been used and an effect has been noted. Typically, acceptable short-term studies need to be at least 3-month studies. The Committee noted, however, that, depending on the quantity, quality and nature of the available data, a safety factor of 100 might be insufficient. This may occur when the required data are incomplete, when the study upon which the NOEL is established is inadequate (e.g. insufficient numbers of animals per test group or when no individual animal data are reported) or when irreversible effects such as teratogenicity or carcinogenicity are noted. The Committee may employ, and on limited occasions has employed, higher safety factors (e.g. 200, 500 and 1000), depending on the quality and quantity of relevant data. The Committee noted that safety factors are usually not appropriate for genotoxic carcinogens. When the only noteworthy toxicological effects are observed in human studies, a lower safety factor (e.g. 10) may be applied. The Committee stressed that the safety factor applied with each drug would be assessed on its own merits considering all the above factors.

Different factors are taken into account when considering the establishment of an ADI based on a microbiological basis (e.g. MIC or adverse effects on the human gut microflora). In these cases, the safety factor is used in an entirely different way than when applied to an ADI based on toxicological data. When establishing a microbiological based ADI, the safety factor is used to account for uncertainty about the amount and relevance of the MIC data available for review. For example, where inhibitory effects are reported on only a limited number of microorganisms, a safety factor of greater than 1 may be used. Safety factors considered appropriate for microbiological end-points are 1–10, considering the quantity and quality of the data.

Several meetings of the Committee on residues of veterinary drugs in food have had substances with limited toxicological data available upon which to establish an ADI. The thirty-sixth Committee (FAO/WHO, 1990) noted that when the Committee, in its scientific judgement, is confident that the consumption of residues of the veterinary drug is without toxicological hazard over a limited amount of time (e.g. the amount of time required to generate and evaluate further data for toxicological assessment), but not sufficiently confident that consumption of these residues over a lifetime may pose a public health concern, it may establish a temporary ADI. In applying this approach, the Committee considers whether those data might be made available to the Committee within a relatively short period of time. As is noted below, temporary MRLs may be recommended for similar or additional reasons, such as the availability of reliable residue methods or additional information on the nature of the quantification of residues.

Where the Committee has established temporary ADIs, it specifies what information is required to resolve the data needs and sets a date when the data are requested for re-evaluation by the Committee. The same approach is applied with MRLs. At the reassessment, if one is done, the Committee has the option to 1) establish a full ADI, 2) extend the temporary ADI or 3) not extend the temporary ADI (the ADI is withdrawn). The same options are available with temporary MRLs. The thirty-sixth Committee established a temporary ADI for levamisole and temporary MRLs and requested additional toxicological and residue data for re-evaluation by the Committee. Based on the additional data provided, the forty-second Committee established an ADI; however, it withdrew the temporary MRL for levamisole in milk, as no additional data were made available. Similarly, the Committee withdrew the MRL in eggs because of high amounts of residues (FAO/WHO, 1995).

7.2.3 Tolerable intakes

JECFA has considered the presence of food contaminants on many occasions since 1972, when mercury, lead and cadmium were first assessed (FAO/WHO, 1972). These food contaminants have included, in addition to heavy metals, environmental contaminants such as mycotoxins, impurities arising in food additives, solvents used in food processing, packaging material migrants and residues arising from the use of animal feed additives and/or the non-active components of veterinary drug formulations. Each of these classes of food contaminants possesses its own unique characteristics and evaluation requirements. Thus, JECFA has recognized through the years that evaluation principles should pertain to classes or groups of contaminants rather than to food contaminants in toto. JECFA has published guidelines in Annex III of Principles for the Safety Evaluation of Food Additives and Contaminants in Food (IPCS, 1987), for the evaluation of various classes of contaminants, and these guidelines are still valid.

When JECFA considered mercury, cadmium and lead in 1972, it established the concept of a PTWI, which was a departure from the traditional ADI concept (FAO/WHO, 1972). JECFA has continued to use this concept, with some modifications, ever since. The use of the term "provisional" expresses the tentative nature of the evaluation, in view of the paucity of reliable data on the consequences of human exposure at levels approaching those with which JECFA is concerned.

ADIs are intended to be used in allocating the acceptable amounts of an additive for necessary technological purposes. Obviously, trace contaminants have no intended function, so the term "tolerable" was seen as a more appropriate term than "acceptable", since it signifies permissibility for the intake of contaminants unavoidably associated with the consumption of otherwise wholesome and nutritious foods. The goal should be to limit exposure to the maximum extent feasible, consistent with the PTWI.

PTWIs are expressed on a weekly basis, because the contaminants given this designation may accumulate within the body over a period of time. On any particular day, consumption of food containing above-average levels of the contaminant may exceed the proportionate share of its weekly tolerable intake. JECFA's assessment takes into account such daily variations, its real concern being prolonged exposure to the contaminant, because of its ability to accumulate within the body over a period of time.

Another JECFA end-point, the PMTDI, has been established for food contaminants that are not known to accumulate in the body, such as tin (FAO/WHO, 1982) and styrene (FAO/WHO, 1984). The value assigned to the PMTDI represents permissible human exposure as a result of the occurrence of the substance in food and in drinking-water.

7.3 Evaluation of mixtures

7.3.1 Group ADIs/TDIs

If several substances that display similar toxic effects are to be considered for use as food additives, pesticides or veterinary drugs, it may be appropriate in establishing an ADI to consider the group of substances in order to limit their overall intake (see also section 4.13). For this procedure to be feasible, the substances should have a similar range of toxic potency. Flexibility should be used in determining which NOEL/NOAEL is to be used in calculating the ADI. In some cases, the average NOEL/NOAEL for all the substances in the group may be used for calculating the group ADI. A more conservative approach is to base the group ADI on the substance with the lowest NOEL/NOAEL. The relative quality and length of studies on the various substances should be considered when setting the group ADI. When the NOEL/NOAEL for one of the substances is out of line with the others in the group, it should be treated separately.

When considering the use of a substance that is a member of a series that are very closely related chemically (e.g. fatty acids), but for which toxicological information is limited, it may be possible to base its evaluation on the group ADI established for the series of substances. This procedure can be followed only if a great deal of toxicological information is available on at least one member of the series and if the known toxic properties of the various substances fall along a well defined continuum. Interpolation, but not extrapolation, can be performed. The use of this procedure by JECFA represents one of the few situations in which the Committee has used structure–activity relationships in its safety assessments.

In some instances, group ADIs can be established primarily on the basis of metabolic information. For example, the safety of esters used as food flavours could be assessed on the basis of toxicological information on their constituent acids and alcohols, provided that it is shown that they are quantitatively hydrolysed in the gut.

The calculation of a group ADI is also appropriate for substances that cause additive physiological or toxic effects, even if they are not closely related chemically. For example, it may be appropriate to establish a group ADI for additives such as bulk sweeteners that are poorly absorbed and cause a laxative effect (see also section 7.7).

7.4 Risks at different levels of exposure

The calculation of health-based guidance values was discussed in chapter 5 and further elaborated above. In risk characterization of substances exhibiting threshold effects, health-based guidance values are compared with estimates of dietary exposure. If exposures are below the relevant value, then no further information on risk characterization need be provided. However, in cases where exposures exceed health-based guidance values, the values themselves do not provide the risk manager with advice on the possible extent of the risk to those exposed to these higher amounts. A first consideration should take into account the fact that health-based guidance values themselves incorporate safety or uncertainty factors (see chapter 5). Thus, a small or occasional exceedance of a health-based guidance value based on a subchronic or chronic study does not necessarily imply that adverse health effects will occur in humans. If further advice is required on the possible health consequences for those exposed to amounts greater than the health-based guidance value, then the toxicity database needs to be considered with respect to the LOELs, the nature and severity of the effects observed, the shape of the dose–response relationship in the observed range (chapter 5) and whether acute toxicity is an issue.

Another type of output from dose–response modelling is the prediction of risks at specified exposure levels. This output can take the generic form of predicting “X number of health impacted individuals at exposure Y”. Examples of such estimates have been used to predict the number of excess lung cancer deaths due to smoking two packs of cigarettes per day, to predict the number of excess skin cancers from arsenic-contaminated water and the number of excess mortality cases due to air pollution. In the optimal case, such estimates are supported by parallel assessments that describe the uncertainty in such estimates by providing additional information on the range of estimates, rather than a single value. The risk manager can then make such statements such as “Up to X number of individuals may be impacted by exposure Y”. This same information can allow the risk manager to see how low the estimates of the health impact may be, and that when confidence limits are included in such estimates, many health risk estimates can be shown to include the potential for no health impact. As discussed in chapter 5, assumptions inherent in such estimates that can impact risk manager interpretation include choice of models, choice of end-points and limitations in initial data sets that were extrapolated.

One use of such information has been to evaluate the impact on risk estimates of different maximum limits for a chemical. This type of consideration was included when JECFA evaluated aflatoxin B1 (FAO/WHO, 1999, 2008). Similar assessments have also been performed for lead (Carrington et al., 1996), fumonisins B1 and B2 (Humphreys et al., 2001) and cadmium (FAO/WHO, 2006). Availability of such estimates can provide additional information for risk managers to conduct cost–benefit analyses, risk–benefit assessments and evaluations of public health interventions.

7.5 The formulation of advice on compounds that are both genotoxic and carcinogenic

JECFA has established procedures for determining health-based guidance values, such as the ADI or PTWI, for chemicals that produce adverse effects that are thought to show a threshold in their dose–response relationships. That is, there is considered to be no appreciable risk at intakes below the health-based guidance value. However, substances that are both genotoxic and carcinogenic may show non-linear dose–response relationships, and any NOEL in a study of the carcinogenicity of such substances represents the LOD in that bioassay, rather than an estimate of a possible threshold. Therefore, JECFA and JMPR do not establish health-based guidance values for compounds that are genotoxic and carcinogenic using the NOEL and safety/uncertainty factors approach. In the absence of evidence on the influence of non-linearity on the incidence of cancer at low levels of exposure, the advice given previously by the Committee on compounds that are both genotoxic and carcinogenic has been that intakes should be reduced to as low as reasonably achievable (ALARA). Such advice is of limited value, because it does not take into account either human exposure or carcinogenic potency and has not allowed risk managers to prioritize different contaminants or to target risk management actions. In addition, ever-increasing analytical sensitivity means that the numbers of chemicals with both genotoxic and carcinogenic potential detected in food will increase.

At its sixty-fourth Meeting (FAO/WHO, 2006), JECFA considered a number of substances for which genotoxicity and carcinogenicity were important issues. The Committee was aware of a number of recent developments relevant to the risk assessment of such substances. These included a 2004 IPCS Workshop that developed a strategy for dose–response assessment (IPCS, in press, b), discussions within EFSA (2005) and ILSI Europe (O'Brien et al., 2006), a subsequent joint EFSA/WHO conference (Barlow et al., 2006) and Australian recommendations for genotoxic and carcinogenic soil contaminants regarding a guideline dose that would be protective of human health (NHMRC, 1999). The Committee discussed approaches to the formulation of advice on contaminants that are both genotoxic and carcinogenic that would better inform risk managers about the possible magnitude of health concerns at different levels of intake in humans. Hazard identification would normally be based on data from studies on genotoxicity and from cancer bioassays. Some chemicals increase the incidence of cancer in experimental animals by non-genotoxic mechanisms; for these, establishing a health-based guidance value such as a PTWI would be appropriate. The present guidance relates to chemicals that are both genotoxic and carcinogenic. The guidance developed at the sixty-fourth JECFA does not address the situation where a compound shows genotoxicity or has structural alerts for genotoxicity, but where a cancer bioassay has not been performed.

As described in chapter 5, hazard characterization (dose–response assessment) would be based on the available dose–response data for cancer, which would mostly be derived from studies in rodents given daily doses many orders of magnitude greater than the estimated intakes in humans. Dose–response data from studies of epidemiology may also be used for hazard characterization and would avoid interspecies comparisons and extrapolation

over many orders of magnitude. When based on data from a bioassay for cancer in animals, the IPCS 2004 workshop recommended the use of the BMDL as a starting point for hazard characterization when the data are suitable for dose–response modelling (IPCS, in press, b).

The dose metric used for modelling could be a biomarker, providing that it was critically related to the process by which cancer arises and had been validated in relation to the external dose or intake. For carcinogenesis, selection of the dose–response data for modelling will need to consider both site-specific incidences of tumours, especially for the site showing the greatest sensitivity, as well as combined data (e.g. numbers of tumour-bearing animals) for compounds that do not show clear organ specificity. Analyses based on the numbers of tumour-bearing animals may also be appropriate under other circumstances—for example, in the assessment of complex mixtures of compounds that are both genotoxic and carcinogenic. Dose–response characterization should aim to define the BMDL for the carcinogenic response(s) of relevance to human health, at the lowest level of response (the BMR) that reliably defines the bottom end of the observed experimental dose–response relationship. A BMR of a 10% incidence is likely to be the most appropriate for modelling of data from cancer bioassays, because the values for different mathematical models show wider divergence at incidences below 10%. The consistent use of the same BMR (i.e. 10%) will facilitate comparisons of the risks associated with different compounds that are both genotoxic and carcinogenic.

Exposure (intake) assessment for a compound that is both genotoxic and carcinogenic is no different from that for other types of contaminants. Risk characterization involves comparison of the estimated exposure with the identified BMDL. In principle, this can take different forms (FAO/WHO, 2006):

- *Calculation of the MOE*. The MOE is the ratio [BMDL] / [estimated intake in humans]. The MOE can be used to prioritize different contaminants, providing that a consistent approach has been adopted. The acceptability of an MOE depends on its magnitude and is ultimately a risk management decision (IPCS, in press, b). To aid that decision, the risk assessor should provide information on the nature and magnitude of uncertainties in both the toxicological and exposure data. Although the risk assessor should not provide an assessment of the acceptability of the MOE, guidance should be given on its adequacy, taking into account the inherent uncertainties and variability.
- *Dose–response analysis outside the observed dose range.* Quantitative dose–response analysis could be used to calculate the incidence of cancer that is theoretically associated with the estimated exposure for humans, or the exposure associated with a predetermined incidence (e.g. 1 in 10^6). In order to provide estimates of the possible carcinogenic effect at the estimated exposure for humans, mathematical modelling would need to take into account the shape of the dose–response relationship between the high doses used in the cancer bioassay and much lower intakes by humans. This requires extrapolation outside the observed dose range. In the future, it may be possible to incorporate data on dose–response or concentration–response relationships for the critical biological activities involved in the generation of cancer, such as metabolic bioactivation and detoxication processes, DNA binding, DNA repair, rates of cell proliferation and apoptosis, into a biologically based dose–response model for cancer that would also incorporate data on species differences in these processes. However, such data are not currently available. At present, any estimate of the possible incidence of cancer for humans has to be based on extrapolation of cancer bioassay data by application of empirical mathematical equations that may not reflect the complexity of the underlying biology. A number of mathematical equations have been proposed for low-dose extrapolation. The resulting risk estimates are dependent on the mathematical model used; the divergence increases as the dose

decreases, and the output from different equations can differ by orders of magnitude at very low incidences (see also chapter 5).

- *Linear extrapolation from a POD.* Because the estimated risks at low doses are model dependent, linear extrapolation from the BMDL, which is conservative and simple to apply, has been used as a matter of policy by some scientific bodies/authorities in order to calculate levels of exposure associated with different theoretical incidences of cancer. The incidence used is regarded as an upper-bound estimate for lifetime risk of cancer, and the actual risk may lie anywhere between zero and the calculated upper-bound estimate. Calculation of the intake associated with an incidence of 1 in 10^6 from the BMDL for a 10% incidence using linear extrapolation is simply equivalent to dividing the BMDL by 100 000, and this approach is therefore no more informative than calculation of an MOE.

Of the three options given above, the MOE and linear extrapolation from a POD are the most pragmatic and usable at the present time. Linear extrapolation from a POD offers no advantages over an MOE, and the results are open to misinterpretation, because the numerical estimates may be regarded as quantification of the actual risk. The sixty-fourth JECFA (FAO/WHO, 2006) therefore decided that advice on compounds that are both genotoxic and carcinogenic should be based on estimated MOEs. The strengths and weaknesses inherent in the data used to calculate the MOE should be given as part of the advice to risk managers, together with advice on its interpretation.

7.6 Subpopulations at increased risk

It is preferable to set a single health-based guidance value, such as an ADI, PTWI, PMTDI or ARfD, for a substance that will cover the whole population, in particular for risk management and enforcement purposes. These values are established to protect the most sensitive subpopulation, based on the most sensitive critical health outcome. The use of safety factors has been generally assumed to take into account the differences in sensitivities in human populations, particularly from genotypic and phenotypic variations.

However, it is recognized that the most sensitive critical health outcome may not always be relevant to some population subgroups. For example, it is particularly important to ensure that any health-based guidance value is adequate to protect the embryo/fetus from possible effects in utero. While an ADI, PTWI, PMTDI or ARfD based on developmental (embryo/fetal) effects would necessarily apply to women of childbearing age, it is recognized that such a value may be unreasonably conservative and not relevant to other population subgroups. Thus, in those situations in which a developmental or other subpopulation-specific end-point determines the health-based guidance value for a substance exhibiting no other toxicity at the developmental or other subpopulation-specific NOAEL, it may be considered to set a second (higher) value based on another end-point relevant to the rest of the population.

The critical risk assessment issue that should be considered in recommending different health-based guidance values for different population subgroups is whether the most sensitive critical health outcome is irrelevant for a significant part of the whole population.

The advice for risk managers that should be considered is:

- If a higher health-based guidance value is established based on another end-point, can the exposure be controlled for the sensitive population subgroup?
- Are there potential benefits, such as beneficial food components, for less sensitive populations that would be adversely effected by health-based guidance value that is based on the most sensitive critical health outcome?

7.7 Combination risk assessment

There is an increasing awareness by those involved in risk assessment and by the general public of the need to consider any risks associated with combined exposure to mixtures of substances, both human-made and naturally occurring, each of which has undergone a separate risk assessment. Concerns over the possibility of combination toxicology were enhanced by reports of highly synergistic interactions between pesticides (Arnold et al., 1996), even though it was subsequently shown that the data were not reproducible by others or by the original study authors (McLachlan, 1997). Nevertheless, public concern over the so-called "cocktail effect" remains and has been the focus of considerable risk assessment activity around the world (WiGRAMP, 2002; IPCS, in press, a; USEPA, 2007).

In recent years, the terms "aggregate" and "cumulative" have been used to describe the risk assessments of a single chemical and a chemical mixture, respectively. *Aggregate risk* assesses the likelihood of occurrence of an adverse health effect resulting from all routes of exposure to a single substance (USEPA, 2001). *Cumulative risk* assesses the likelihood of a common toxic effect associated with concurrent exposure by all relevant pathways and routes of exposure to a group of chemicals that share a common mechanism of toxicity (USEPA, 2007).

Given the numbers of human-made and naturally occurring chemical substances to which humans are exposed, there is an almost infinite number of possible simple binary, tertiary, quarternary, etc. combinations. In consequence, direct experimentation cannot resolve this risk assessment issue, and recent research has focused on understanding the basic science of combination toxicology. As discussed in section 4.13, there are four types of combined effect or interaction:

- *Dose addition* occurs when substances produce toxicity via the same mechanism of action. For substances that have a threshold in their dose–response relationships, the total activity of the mixture is the sum of the exposures for each component multiplied by its relative potency. A consequence of this is that a biological effect may be produced if there is exposure to a mixture that contains a large number of substances that have the same mechanism of action, even though the exposures of each substance are too low to elicit a response. This mechanism is the basis for the group ADI and the use of TEFs (see section 4.13). A review of approved food additives with numerical ADI values has shown that dose addition might arise only rarely for structurally unrelated substances (Groten et al., 2000). Dose addition is the basis for recent considerations of pesticides that share the same mode of action by the Pesticide Residues Committee (2007) in the United Kingdom, in which simultaneous exposures to different AChE inhibitors are assessed on the basis of summing each exposure as a fraction of the relevant ADI (this method assumes that each ADI is based on inhibition of AChE).
- *Response addition* is possible when the substances act via different mechanisms, but the exposure to each substance has to be sufficient to produce a response in the absence of the other substance. Thus, a mixture of a neurotoxin plus a hepatotoxin, each given at an active dose, will produce neurotoxicity and hepatotoxicity to the same extent as if each were given separately. Such an interaction is not relevant to exposures to multiple substances each of which has a threshold in its dose–response relationship, providing that the exposure level for each is below its respective ADI.
- *Synergism* occurs when the effect of the combination is greater than predicted by the summed activity of each component individually at the same level of exposure that occurs in the mixture. Synergism may arise from either toxicokinetic or toxicodynamic interactions. Toxicokinetic interactions are possible when one compound alters the

metabolism of the potentially toxic component to increase the internal dose or systemic exposure of the active form of the toxic component (parent compound or metabolite). Such an interaction can increase the activity of the toxic component and is the basis for the addition to pesticide formulations of synergistic compounds, which enhance the desired pesticidal activity of the formulation in the target organism. Synergism could result in an otherwise inactive level of exposure to a potential toxicant producing an effect when it is present in combination with sufficient amounts of another component to affect its activity. Thus, synergism typically occurs when at least one of the components is present in sufficient amounts to affect the biological system in some way. In consequence, synergism is not relevant to the exposure scenario in which all components in a mixture are present at inactive levels (e.g. below their ADI values).

- *Antagonism* may arise from either toxicokinetic or toxicodynamic interactions, but usually requires that each substance is present at active doses or concentrations. Such an interaction would reduce the toxicity of the active component(s) and therefore would not result in a possible health concern. Antagonism would occur if a substance with a low efficacy, such as a partial agonist, were to compete for a site of action with a high efficacy compound, such as a full agonist. Such interaction may well occur in the application of TEFs (see section 4.13) and would make the assumption of full dose additivity a conservative approach.

7.8 References

Arnold SF, Klotz DM, Collins BM, Vonier PM, Guillette LJ Jr, McLachlan JA. (1996). Synergistic activation of estrogen receptor with combinations of environmental chemicals. Science 272:1489-192.

Barlow S, Renwick AG, Kleiner J, Bridges JW, Busk L, Dybing E, Edler L, Eisenbrand G, Fink-Gremmels J, Knaap A, Kroes R, Liem D, Müller DJG, Page S, Rolland V, Schlatter J, Tritscher A, Tueting W, Würtzen G (2006). Risk assessment of substances that are both genotoxic and carcinogenic - Report of an International Conference organized by EFSA and WHO with support of ILSI Europe Food Chem. Tox. 44: 1636-1650

CAC (2004). Codex Alimentarius Commission, Joint FAO/WHO Food Standards Programme Procedural Manual, Fourteenth Edition, World Health Organization/Food and Agriculture Organization of the United Nations, Rome.

Carrington, CD, Bolger PM, Scheuplein RJ (1996). Risk analysis of dietary lead exposure. Food Additives Contaminants 13:61-76.

EFSA (2005). Opinion of the Scientific Committee on a request from EFSA related to a harmonized approach for risk assessment of substances which are both genotoxic and carcinogenic. Adopted on 18 October 2005. European Food Safety Authority. Available at http://www.efsa.europa.eu/EFSA/Scientific_Opinion/sc_op_ej282_gentox_en3,0.pdf. Accessed on 4 December 2007.

FAO/WHO (1957). General principles governing the use of food additives. First report of the Joint FAO/WHO Expert Committee on Food Additives (FAO Nutrition Meetings Report Series No. 15; WHO Technical Report Series No. 129).

FAO/WHO (1958). Procedures for the testing of intentional food additives to establish their safety for use. Second report of the Joint FAO/WHO Expert Committee on Food Additives (FAO Nutrition Meetings Report Series No. 17; WHO Technical Report Series No. 144).

FAO/WHO (1962a). Evaluation of the toxicity of a number of antimicrobials and antioxidants. Sixth report of the Joint FAO/WHO Expert Committee on Food Additives (FAO Nutrition Meetings Report Series No. 31; WHO Technical Report Series No. 228).

FAO/WHO (1962b). Principles governing consumer safety in relation to pesticide residues, Geneva, World Health Organization (FAO Plant Production and Protection Division Report, No. PL/1961/11; WHO Technical Report Series, No. 240).

FAO/WHO (1964). Evaluation of the toxicity of pesticide residues in food. Report of a Joint FAO/WHO Meeting of the FAO Committee on Pesticides in Agriculture and the WHO Expert Committee on Pesticide Residues, Geneva, World Health Organization (FAO Meeting Report No. PL/1963/13; WHO/Food Add./23).

FAO/WHO (1969). Pesticide residues in food. Report of the 1968 Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues, (FAO Agricultural Studies No. 78; WHO Technical Report Series, No. 417). World Health Organization, Geneva.

FAO/WHO (1970). Pesticide residues in food. Report of the 1969 Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Group on Pesticide Residues, (FAO Agricultural Series, No. 84; WHO Technical Report Series, No. 458). World Health Organization, Geneva.

FAO/WHO (1972). Evaluation of certain food additives and the contaminants mercury, lead, and cadmium. Sixteenth report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series No. 505 and corrigendum. World Health Organization, Geneva.

FAO/WHO (1973). Pesticide residues in food. Report of the 1972 Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues, (FAO Agricultural Studies No. 90; WHO Technical Report Series, No. 525). World Health Organization, Geneva.

FAO/WHO (1974a). Toxicological evaluation of certain food additives with a review of general principles and of specifications. Seventeenth report of the Joint FAO/WHO Expert Committee on Food Additives (FAO Nutrition Meetings Report Series No. 53; WHO Technical Report Series No. 539 and corrigendum)

FAO/WHO (1974b). Evaluation of certain food additives. Eighteenth report of the Joint FAO/WHO Expert Committee on Food Additives (FAO Nutrition Meetings Report Series No. 54; WHO Technical Report Series No. 557 and corrigendum).

FAO/WHO (1974c). Pesticide residues in food. Report of the 1973 Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues, Geneva, World Health Organization (FAO Agricultural Studies No. 92; WHO Technical Report Series, No. 545).

FAO/WHO (1982). Evaluation of certain food additives and contaminants. Twenty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives (WHO Technical Report Series No. 683).

FAO/WHO (1984). Evaluation of certain food additives and contaminants. Twenty-eighth report of the Joint FAO/WHO Expert Committee on Food Additives (WHO Technical Report Series No. 710).

FAO/WHO (1987). Pesticide residues in food - 1986. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and a WHO Expert Group on Pesticide Residues, Rome, Food and Agriculture Organization of the United Nations (FAO Plant Production and Protection Paper 77).

FAO/WHO (1988a). Pesticide residues in food - 1988. Report of the Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues, Rome, Food and Agriculture Organization of the United Nations (FAO Plant Production and Protection Paper 92).

FAO/WHO (1988b). Evaluation of certain veterinary drug residues in food, Thirty-second report of the Joint FAO/WHO Expert Committee on Food Additives, Geneva, World Health Organization (WHO Technical Report Series No. 763).

FAO/WHO (1989). Pesticide residues in food. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and a WHO Expert Group on Pesticide Residues. FAO Plant Production and Protection Paper 99, 1989.

FAO/WHO (1990). Evaluation of certain veterinary drug residues in food, Thirty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives, Geneva, World Health Organization, 1990 (WHO Technical Report Series No. 799).

FAO/WHO (1991). Evaluation of certain veterinary drug residues in food, Thirty-eighth report of the Joint FAO/WHO Expert Committee on Food Additives, Geneva, World Health Organization (WHO Technical Report Series No. 815).

FAO/WHO (1993). Evaluation of certain veterinary drug residues in food, Fortieth report of the Joint FAO/WHO Expert Committee on Food Additives, Geneva, World Health Organization, (WHO Technical Report Series No. 832).

FAO/WHO (1995). Evaluation of certain veterinary drug residues in food, Forty-second report of the Joint FAO/WHO Expert Committee on Food Additives, Geneva, World Health Organization, (WHO Technical Report Series No. 851).

FAO/WHO (1999). Evaluation of Certain Food Additives and Contaminants, Forty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives, Geneva, World Health Organization, (WHO Technical Report Series No. 884)

FAO/WHO (2006). Evaluation of certain food contaminants, Sixty-fourth report of the Joint FAO/WHO Expert Committee on Food Additives, Geneva, World Health Organization, WHO (Technical Report Series 930).

FAO/WHO (2008) Evaluation of certain food contaminants and contaminants (Sixty-eighth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 947.

Groten, J.P., Butler, W., Feron, V.J., Kozianowski, G., Renwick, A.G. and Walker R. (2000). An analysis of the possibility for health implications of joint actions and interactions between food additives. Regulatory Toxicology and Pharmacology, 31, 77-91.

Humphreys SH, Carrington CD, Bolger PM (2001). A quantitative risk assessment for Fumonisins B1 and B2 in corn. Food Additives Contam. 18:211-220.

IPCS (1987). *Principles for the safety assessment of food additives and contaminants in food*, IPCS Environmental Health Criteria 70. International Programme on Chemical Safety, World Health Organization, Geneva.

IPCS (1990). *Principles for the toxicological assessment of pesticide residues in food.* IPCS Environmental Health Criteria, No. 104. World Health Organization, International Programme on Chemical Safety, Geneva.

IPCS (in press, a). Aggregate/cumulative risk assessment. Report of a WHO/IPCS international workshop. *Critical Reviews in Toxicology*.

IPCS (in press, b). Principles for modelling dose–response for the risk assessment of chemicals. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria).

JMPR (2002). Pesticide residues in food - 2002. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group, FAO Plant Production and Protection Paper, 172, FAO, Rome.

McLachlan JA. (1997). Synergistic effect of environmental estrogens: report withdrawn. Science 277:462-463.

NHMRC (1999). Toxicity Assessment for Carcinogenic Soil Contaminants, National Health and Medical Research Council, Commonwealth of Australia, Canberra. Available at: www.nhmrc.gov.au/publications/synopses/eh21syn.htm. Accessed on 4 December 2007.

O'Brien J, Renwick AG, Constable A, Dybing E, Müller, DJG, Schlatter J, Slob W, Tueting w, van Benthem J, Williams GM, Wolfreys A (2006). Approaches to the risk assessment of genotoxic carcinogens in food: A critical appraisal, Food Chem. Tox. 44: 1613-1635.

Pesticide Residues Committee. (2007). Pesticide Residues Monitoring Report. Second Quarter Report 2007 Quarter Ended June 2007 (pp46-47). Published: 13 December 2007. Available at http://www.pesticides.gov.uk/uploadedfiles/Web_Assets/PRC/Report_Q2_2007_13_Dec.pdf

Renwick AG, Barlow, SM, Hertz-Picciotto I, Boobis AR, Dybing E, Edler L, Eisenbrand, G. Grieg, JB, Kleiner J, Lambe J, Müller DJG, Smith MR, Tritscher A, Tuijtelaars S, van den Brandt PA, Walker R, and Kroes R (2003). Risk characterization of chemicals in food and diet. Food Chem. Tox. 41:1211-1271.

USEPA (2001). General Principles For Performing Aggregate Exposure And Risk Assessments. Environmental Protection Agency Office of Pesticide Programs. November 28, 2001 Available at: http://www.epa.gov/pesticides/trac/science/aggregate.pdf

USEPA (2007). Assessing Pesticide Cumulative Risk. Environmental Protection Agency Office of Pesticide Programs. Available at: http://www.epa.gov/pesticides/cumulative/

WHO (1967). Procedures for investigating intentional and unintentional food additives. Report of a WHO Scientific Group, (WHO Technical Report Series No. 348). World Health Organization, Geneva.

WiGRAMP (2002). Working Group on Risk Assessment of Mixtures of Pesticides. Risk Assessment of Mixtures of Pesticides and Similar Substances. Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment. Committee on Toxicity. UK. © Crown Copyright. Available at http://www.food.gov.uk/multimedia/pdfs/reportindexed.pdf.