PRINCIPLES AND METHODS FOR THE RISK ASSESSMENT OF CHEMICALS IN FOOD

CHAPTER 2: RISK ANALYSIS

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2.1 Introduction

JECFA and JMPR have provided scientific advice to Member States since 1956 and 1961, respectively, and to the general subject committees of the CAC since its formation in 1963. However, the structural framework for these interactions was quite informal until the development of the risk analysis paradigm.

The first risk analysis paradigm for public health was proposed by the United States National Academy of Sciences (NAS) (NRC, 1983) and focused on assessing the risk of cancer from chemicals in food. The decision process was divided into three major steps: research, risk assessment and risk management. In the NAS paradigm, the principal steps were considered to be sequential, with the decision process commencing with research and concluding with the decision, but such an approach does not recognize the possible influence of risk analysis on data needs or of the impact of political, social and economic objectives.

2.2 The risk analysis paradigm

Risk analysis has since been defined by the CAC as “a process consisting of three components: risk assessment, risk management and risk communication” (CAC, 1997, 2006). CAC (2006) goes on to define the three components of risk analysis as follows:

Risk assessment: A scientifically based process consisting of the following steps: (i) hazard identification, (ii) hazard characterization, (iii) exposure assessment, and, (iv) risk characterization.

Risk management: The process, distinct from risk assessment, of weighing policy alternatives, in consultation with all interested parties, considering risk assessment and other factors relevant for the health protection of consumers and for the promotion of fair trade practices, and, if needed, selecting appropriate prevention and control options.

Risk communication: The interactive exchange of information and opinions throughout the risk analysis process concerning risk, risk-related factors and risk perceptions, among risk assessors, risk
managers, consumers, industry, the academic community and other interested parties, including the
explanation of risk assessment findings and the basis of risk management decisions.

The risk analysis paradigm (see Figure 2.1) is a formal representation of the risk
analysis process in which it is made clear that there is both functional separation of the three
components and at the same time a requirement for communication and interaction between
those with responsibility for each of the three components. Within risk analysis, a functional
separation between risk assessors and risk managers is necessary to ensure scientific
objectivity of the risk assessment process. Further background information on risk analysis
can be found in Kaferstein & Hueston (2000).

Figure 2.1. Risk analysis (from FAO/WHO, 1997b)

The use of risk analysis methodology facilitates consistent and orderly decision-
making. Risk assessment is undertaken by the Joint Expert Committees, like JECFA and
JMPR, rather than the Codex Committees. Joint Expert Committees base their evaluations on
scientific principles and ensure necessary consistency in their risk assessment determinations.
The respective Codex Committees take responsibility as risk managers in making the final
decisions on establishing maximum limits for pesticide residues, veterinary drugs,
contaminants and additives in food. The CAC recognized the need to revisit risk analysis
approaches applied by Codex Committees and the Joint Expert Committees. At the request of
the CAC, three consecutive Joint FAO/WHO Expert Consultations were held between 1995
and 1998 on the application of risk analysis to food standard issues (FAO/WHO, 1995,
1997b, 1999).

2.2.1 Definitions of hazard and risk

The Joint Expert Consultations were by and large devoted to the three components of risk
analysis: risk assessment, risk management and risk communication, respectively. The first
Consultation, held in 1995 in Geneva, explored the risk analysis domain and focused on risk
assessment (FAO/WHO, 1995). The Consultation was also aware of the need for uniform
terminology on risk analysis in the work of Codex and considered risk analysis definitions
from different sources. The Consultation drafted definitions of risk analysis terms related to
food safety and recommended them to the CAC. The CAC subsequently amended these
definitions, adopted them on an interim basis and published the definitions in the Procedural
and risk—should be mentioned in particular. These are fundamental in the risk analysis
process, but different words for these two terms do not exist in many languages other than
English. Codex has adopted the following definitions for hazard and risk in relation to food to
cover not only chemical agents, but also biological and physical agents (CAC, 1997, 2006):

Hazard: a biological, chemical or physical agent in, or condition of, food with the potential to cause an
adverse health effect.

Risk: a function of the probability of an adverse health effect and the severity of that effect,
consequential to a hazard(s) in food.

The Codex definition of hazard differs from that of other bodies, for which a hazard is a
property associated with the chemical or agent rather than the chemical or agent itself. Thus,
a single chemical could represent multiple hazards (e.g. it could be a reproductive toxicant
and a carcinogen). As part of the project for the Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals, the IPCS (2004) has defined hazard and risk assessment slightly differently from Codex:

**Hazard**: Inherent property of an agent or situation having the potential to cause adverse effects when an organism, system or (sub)population is exposed to that agent.

**Risk**: The probability of an adverse effect in an organism, system or (sub)population caused under specified circumstances by exposure to an agent.

It is these IPCS definitions that most clearly describe the approaches of JECFA and JMPR.

### 2.2.2 Role of exposure assessment

It should be kept in mind that in general, risk analysis principles apply irrespective of the nature of the hazard. The definition of hazard relates to chemical and microbiological contaminants as well as to changes in the condition of food as a result of genetic modification. Several components of the risk analysis process were subject of additional Joint Expert Consultations. Two Consultations focused on exposure assessment (FAO/WHO, 1997a, 2000).

With regard to chemical hazards, the Consultations pointed to the further need for harmonized approaches to the risk assessment of food additives, contaminants and residues of pesticides and veterinary drugs, particularly in the assessment of exposure. Different approaches are currently applied by JECFA and JMPR in establishing standards for the various classes of chemicals. These approaches sometimes differ for historical reasons only, while in other cases they are fully justifiable. In view of the increased importance of Codex standards under the WTO Agreement on the Application of Sanitary and Phytosanitary Measures (the SPS Agreement), harmonization of these approaches should be pursued to the extent possible. The Consultations made interesting recommendations with regard to exposure assessment. Where necessary, exposure assessment should be expanded to take into account differences in dietary patterns and should include estimates of intake by potentially vulnerable groups. It was recognized that information on food consumption by the general population and by subgroups of interest is frequently lacking. Food consumption data are a prerequisite for a consistent risk assessment of chemicals, and governments were encouraged to generate such information and to make it available to the international organizations in order to ensure that risk assessments are conducted on the basis of the current state of knowledge.

### 2.2.3 Interactions between risk assessment and risk management

More recent examinations of risk assessment/analysis methodology have paid much closer attention to the influence of risk management on the risk assessment process (NRC, 1994, 1996; Presidential Commission, 1997; WHO, 2000; Renwick et al., 2003). While it is necessary to separate the functional activities of risk assessment from those of risk management in order to ensure scientific independence, it is acknowledged that risk managers should communicate and interact with risk assessors during the process to establish the scope of the analysis, particularly during problem formulation or risk profiling. Thus, the relationship between risk assessment and risk management is an interactive, often iterative process (see Figure 2.2).

![Figure 2.2: Interactions of risk assessment with risk management](image-url)
2.2.3.1 Problem formulation
As a general rule, formal risk assessments are preceded by a preliminary consideration of the necessity for and objective of a risk assessment. These are usually subjective and informal and may be initiated from inside or outside the risk management, risk assessment and scientific communities. The transition process from preliminary considerations to formal risk assessments has been described as problem formulation (or risk profiling) (Renwick et al., 2003). It is an iterative process that facilitates the critical interface between risk assessment and risk management. Communication with other interested parties (stakeholders) is particularly important during the period of problem formulation.

Problem formulation describes a food safety problem and its context, in order to identify those elements of the hazard or risk relevant to various risk management decisions. Problem formulation would include identifying aspects of hazards relevant to prioritizing and setting the risk assessment policy and aspects of the risk relevant to the choice of acceptable levels of risk and management options. A typical problem formulation might include the following:

- a brief description of the situation, product or commodity involved;
- the issues expected to be affected (e.g. human health, economic concerns) and the potential consequences;
- consumer perception of the risk assessment; and
- the distribution of risks and benefits.

The output is a plan for the risk assessment process, which can be changed as the risk assessment progresses. The desired outcomes of problem formulation are 1) the questions that need to be answered under risk characterization to meet the needs of the risk manager, 2) determination of the resources that are needed and available, and 3) the timeframe for completing the assessment.

2.2.3.2 Priority setting for JECFA and JMPR
The selection of new or existing chemicals for consideration by JECFA or JMPR and recommending priorities for review are the responsibility of FAO and WHO, their Member countries and the CAC, through its committees. For JECFA, these committees include CCFAC, which in 2006 was divided into two separate committees, the Codex Committee on Food Additives (CCFA) and the Codex Committee on Contaminants in Food (CCCF), together with the CCRVDF. For JMPR, the primary source of input is the CCPR. The protection of human health should be the main criterion for prioritization for risk assessment. The exposure levels and toxicity of the substance and the existence of particularly susceptible populations are key determinants that impact human health. However, the lack of available data may also be a factor in prioritization for risk assessments. The FAO and WHO Joint Secretaries for JECFA and JMPR, as representatives of their respective organizations, have the final responsibility and authority for the determination of the priorities of substances to be evaluated in their respective areas. This can be dependent in part on available resources.

2.2.4 The role of risk assessment in risk analysis
The risk assessment process within risk analysis forms one of the key components of the work of JECFA and JMPR. Accordingly, it is examined here in more detail. The other two components of risk analysis—namely, risk management and risk communication—are not further discussed in this monograph, but the interested reader is referred to other publications (see, for example, FAO/WHO, 1997b, 1999).
Risk assessment, comprising the four steps of hazard identification, hazard characterization (including dose–response assessment), exposure assessment and risk characterization, is a conceptual framework that, in the context of risk analysis in the area of food safety, provides a mechanism for the structured review of information relevant to estimating health outcomes in relation to exposure to chemicals present in food. Risk assessment generally includes a key component in which the probability of harm is estimated. As a probability calculation, a risk assessment will include both a statement of the nature of the harm and the basis for the assertion that the harm may occur (i.e. the probability).

2.2.4.1 Hazard identification

Hazard identification is defined as follows: “The identification of biological chemical and physical agents capable of causing adverse health effects and which may be present in a particular food or group of foods” (CAC, 2006).

The purpose of hazard identification is to evaluate the weight of evidence for adverse health effects, based on assessment of all available data on toxicity and mode of action. It is primarily designed to address two questions: 1) the nature of any health hazard to humans that an agent may pose, and 2) the circumstances under which an identified hazard may be expressed. Hazard identification is based on analyses of a variety of data, ranging from observations in humans or domestic animals, studies in laboratory animals and in vitro laboratory studies, through to analysis of structure–activity relationships. From the range of studies and observations available, the nature of any toxicity or adverse health effect occurring and the affected (target) organ(s)/tissue(s) are identified. The outcome of hazard identification is a scientific judgement as to whether the chemical being evaluated could, under given exposure conditions, cause an adverse effect in humans.

2.2.4.2 Hazard characterization

Hazard characterization (also known as dose–response assessment) is defined as follows: “The qualitative and/or quantitative evaluation of the nature of the adverse health effects associated with biological, chemical and physical agents which may be present in food. For chemical agents, a dose–response assessment should be performed. For biological or physical agents, a dose-response–assessment should be performed if the data are available” (CAC, 2006).

The critical effect—that is, the first significant adverse effect observed as the dose/exposure is increased—is also determined. Hazard characterization describes the relationship between the administered dose of, or exposure to, a chemical and the incidence of an adverse health effect. For most types of toxic effect, it is generally considered that there is a dose below which adverse effects will not occur (i.e. a threshold). Such a dose is described as the no-observed-adverse-effect level (NOAEL) or no-observed-effect level (NOEL) and can be considered as a first approximation of the threshold for that particular chemical for that particular effect. The NOAEL or NOEL for the critical effect is usually used as a starting point or reference point for the risk characterization (see below). More recently, the option of modelling of the dose–response data for potential critical effects has been introduced to derive a benchmark dose (BMD) and its lower confidence limit (BMDL) for a particular incidence of effect (e.g. a 5% or 10% incidence). Comparisons of the BMDL values for different effects can be used to define the critical effect, with the lowest BMDL used as a starting point for risk characterization (FAO/WHO, 2006).

In contrast to threshold-type effects, for some other types of toxic effect it is assumed that there is some probability of harm at any level of exposure (i.e. that no biological threshold exists). At the present time, this assumption is primarily applied in the case of mutagenicity and genotoxic carcinogenicity. In the case of genotoxic carcinogenicity, the
BMDL derived from animal studies may be used as a point of departure for risk characterization.

### 2.2.4.3 Exposure assessment

Exposure assessment is defined as follows: “The qualitative and/or quantitative evaluation of the likely intake of biological, chemical and physical agents via food as well as exposure from other sources if relevant” (CAC, 2006).

Intake/exposure assessment is the third step in risk assessment, in which the extent of human exposure to the chemical (actual or anticipated) is determined. In the case of food chemicals, exposure assessment takes into consideration the occurrence and concentrations of the chemical in the diet, the consumption patterns of the foods containing the chemical and the likelihood of consumers eating large amounts of the food(s) in question (high consumers) and of the chemical being present in these foods at high levels. Usually a range of intake/exposure estimates will be provided (e.g. for average consumers and for high consumers) and may be broken down by subgroup of the population (e.g. infants, children, adults).

### 2.2.4.4 Risk characterization

Risk characterization is defined as follows: “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, 2006).

Risk characterization is the final step in the risk assessment process in which the information from the intake/exposure assessment and the hazard characterization are integrated into advice suitable for decision-making in risk management. It provides estimates of the potential risk to human health under different exposure scenarios. It should include all key assumptions and describe the nature, relevance and magnitude of any risks to human health. The advice to risk managers may be qualitative or quantitative.

Qualitative advice may include:

- statements/evidence that the chemical is of no toxicological concern owing to the absence of toxicity even at high exposure levels;
- statements/evidence that the chemical is safe in the context of specified use(s); and
- recommendations to avoid, minimize or reduce exposure.

Quantitative advice may include:

- health-based guidance values;
- estimates of risks at different levels of exposure; and
- risks at minimum and maximum intakes (e.g. nutrients).

The risk characterization statement should include a clear explanation of any uncertainties in the risk assessment resulting from gaps in the science base. It should also include, where relevant, information on susceptible subpopulations, including those with greater potential exposure and/or specific predisposing physiological conditions or genetic factors. The advice to risk managers can be in the form of a comparison of the relative risks among risk management options.

The risk assessment is followed by either a risk management decision or a request for further analysis, which may influence any further research that is conducted. The record
produced by a risk assessment stands as a scientific basis for any risk management decision at that time. However, the risk assessment/analysis may be reopened—for example, if additional information becomes available.

2.3 References
NRC (1994) Science and Judgement in Risk Assessment, NAS Press, Washington, DC, USA.