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# APPLICATION OF RISK ANALYSIS TO FOOD STANDARDS ISSUES

Report of the Joint FAO/WHO Expert Consultation

Geneva, Switzerland

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the 1990s, the number of people in the world who are under 15 years of age is expected to increase from 1.1 billion to 1.4 billion.

The number of people in the world who are aged 65 and over is expected to increase from 300 million in 1990 to 600 million in 2020.

The number of people in the world who are aged 75 and over is expected to increase from 100 million in 1990 to 200 million in 2020.

The number of people in the world who are aged 85 and over is expected to increase from 20 million in 1990 to 50 million in 2020.

The number of people in the world who are aged 90 and over is expected to increase from 5 million in 1990 to 15 million in 2020.

The number of people in the world who are aged 100 and over is expected to increase from 1 million in 1990 to 3 million in 2020.

The number of people in the world who are aged 105 and over is expected to increase from 100,000 in 1990 to 300,000 in 2020.

The number of people in the world who are aged 110 and over is expected to increase from 10,000 in 1990 to 30,000 in 2020.

The number of people in the world who are aged 115 and over is expected to increase from 1,000 in 1990 to 3,000 in 2020.

The number of people in the world who are aged 120 and over is expected to increase from 100 in 1990 to 300 in 2020.

The number of people in the world who are aged 125 and over is expected to increase from 10 in 1990 to 30 in 2020.

The number of people in the world who are aged 130 and over is expected to increase from 1 in 1990 to 3 in 2020.

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The number of people in the world who are aged 215 and over is expected to increase from 0 in 1990 to 0 in 2020.

The number of people in the world who are aged 220 and over is expected to increase from 0 in 1990 to 0 in 2020.

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## LIST OF ABBREVIATIONS

ADI	Acceptable Daily Intake
ALARA	as low as reasonably achievable
BHA	butylated hydroxyanisole
CAC	Codex Alimentarius Commission
CCFAC	Codex Committee on Food Additives and Contaminants
CCFH	Codex Committee on Food Hygiene
CCFICS	Codex Committee on Import and Export Food Inspection and Certification Systems
CCMH	Codex Committee on Meat Hygiene
CCPR	Codex Committee on Pesticide Residues
CCRVDF	Codex Committee on Residues of Veterinary Drugs in Foods
EMDI	Estimated Maximum Daily Intake
EPA	U.S. Environmental Protection Agency
FAO	Food and Agriculture Organization of the United Nations
FDA	U.S. Food and Drug Administration
GAP	Good Agricultural Practice
GEMS/Food	Joint UNEP/FAO/WHO Food Contamination and Monitoring Programme
GLP	Good Laboratory Practices
GPVD	Good Practice in the Use of Veterinary Drugs
GSC	General Standard for Contaminants
GSFA	General Standard for Food Additives
HACCP	Hazard Analysis Critical Control Point
ICMSF	International Commission on Microbiological Specifications for Food
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
MRL	Maximum Residue Limit
MTD	Maximum Tolerated Dose
NGOs	nongovernmental organizations
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NRC	U.S. National Research Council
OECD	Organization for Economic Co-operation and Development
PMTDI	Provisional Maximum Tolerable Daily Intake
PTWI	Provisional Tolerable Weekly Intake
QA	Quality Assurance
QC	Quality Control
SPS Agreement	Agreement on the Application of Sanitary and Phytosanitary Measures
TBT Agreement	Agreement on Technical Barriers to Trade
TMDI	Theoretical Maximum Daily Intake
WHO	World Health Organization
WTO	World Trade Organization

The first part of the document discusses the importance of maintaining accurate records of all transactions. It emphasizes that every entry, no matter how small, should be recorded to ensure the integrity of the financial statements. This includes not only sales and purchases but also expenses and income. The document also highlights the need for regular reconciliation of bank statements and the company's records to identify any discrepancies early on.

In addition, the document provides a detailed overview of the accounting cycle, which consists of eight steps: identifying the accounting cycle, journalizing, posting, determining trial balances, adjusting entries, preparing financial statements, and closing the books. Each step is explained in detail, with examples provided to illustrate the process. The document also discusses the importance of maintaining proper documentation for all transactions, including invoices, receipts, and contracts.

The second part of the document focuses on the preparation of financial statements. It explains how to calculate net income, gross profit, and operating profit. It also discusses the importance of understanding the relationship between the income statement and the balance sheet, and how changes in assets and liabilities affect the company's financial position. The document provides a step-by-step guide to preparing the income statement, balance sheet, and statement of cash flows.

Finally, the document discusses the importance of budgeting and forecasting. It explains how to develop a budget for the company and how to use it to monitor performance and make adjustments as needed. It also discusses the importance of forecasting future sales and expenses, and how to use this information to make strategic decisions about the company's future.

## EXECUTIVE SUMMARY

A Joint FAO/WHO Expert Consultation on the Application of Risk Analysis to Food Standards Issues was held at WHO Headquarters, Geneva, Switzerland from 13 to 17 March 1995. Participants included experts in food safety and risk analysis, representatives of international organizations and observers from relevant Codex Committees. The Consultation was convened at the request of the 41st Session of the Codex Alimentarius Commission (CAC) Executive Committee which wished to promote consistency and transparency in the establishment of Codex standards, guidelines and recommendations. The main objective was to provide FAO, WHO and CAC as well as member countries with advice on practical approaches for the application of risk analysis to food standards issues

To accomplish this task, the Consultation first agreed on a number of definitions for food safety risk analysis. In doing so, the Consultation agreed upon a model for risk assessment which consists of four components: (1) hazard identification, (2) hazard characterization, (3) exposure assessment, and (4) risk characterization. In elaborating on this model, the Consultation limited its considerations to biological and chemical agents in or on food.

The Consultation did not discuss risk management and risk communication *per se* but did recognize that risk assessment and risk management had a number of significant interfaces. For example, establishing priorities and policies for risk assessment often includes input from risk management considerations.

In considering current Codex practices in the context of the risk assessment model, the Consultation recommended several changes in Codex practices to foster a harmonized approach within Codex, consistent with science-based risk assessment. In general, the Consultation recommended the separation of risk assessment and risk management activities particularly in the light of the World Trade Organization's Agreement on the Application of Sanitary and Phytosanitary Measures. In addition, the Consultation recommended that exposure assessment generally be strengthened. The Consultation also recognized that risk managers in the Codex system needed to be informed of the degree of uncertainty associated with the output of risk assessment.

In considering the risk assessment of chemical hazards, the Consultation emphasized the need for better information to enhance the risk assessment process. In particular, obtaining better information on the mode of action of a chemical was considered to be an integral part of the approach. At the same time, the Consultation recognized that only in rare instances would all of the necessary information be available. Nevertheless, the Consultation considered that Codex had the responsibility to be "technology forcing" and strongly recommended the development of such data.

The estimation of risk from biological agents was also considered by the Consultation. Although less is known about the process of evaluating microbiological risks, such risks are in

many ways a much larger and more immediate problems to human health than risks associated with chemicals in food. For these reasons, the Consultation considered how microbiological risks could be quantified and evaluated. While it is possible to develop useful techniques for risk assessment at this time, the Consultation recognized that more information and knowledge is required to adequately address risk assessment of microbiological agents.

The Consultation also considered ways in which uncertainty was associated with risk assessment. The process of risk assessment inevitably leads to an estimate of human risk. When that estimate is expressed quantitatively, the numerical result is often viewed as possessing a high level of precision. In reality, this number usually has large boundaries of uncertainty around it and risk managers must understand the nature of that uncertainty when weighing risk management options.

Finally, the Consultation recognized that additional consultations would need to be convened regarding specific issues in risk assessment as well as general consultations on risk management and communication. Nevertheless, the Consultation concluded that implementation of its recommendations would contribute significantly to the ability of Codex to meet its responsibilities of protecting consumers and facilitating international trade in food in a more consistent and open manner.



## 1. INTRODUCTION

The Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) convened a Joint FAO/WHO Expert Consultation on the Application of Risk Analysis to Food Standards Issues which was held at WHO Headquarters, Geneva, Switzerland from 13 to 17 March 1995; the list of participants is presented in Annex 1.

The Consultation was opened by Dr G. Quincke, Director, Division of Food and Nutrition, WHO. He noted that while the need for greater consistency and transparency in the work of Codex was recognized by the 1991 Joint FAO/WHO Conference on Food Standards, Chemicals in Food, and Food Trade, the Consultation was convened at the urgent request of the 41st Session of the Codex Alimentarius Commission (CAC) Executive Committee, which met in June 1994 in Rome. The main objective of the Consultation was to provide recommendations to FAO, WHO, CAC and the member countries concerning the most appropriate approach to the application of risk analysis to food standards and safety issues. To the greatest extent possible, the recommendations should provide a practical approach, which is suitable for rapid adoption by FAO, WHO and the CAC and its advisory and subsidiary bodies, and should include: (i) definitions of risk analysis terms; (ii) principles for risk assessment methodology; and (iii) recommendations to promote the implementation of harmonized and transparent risk assessment methodologies.

Dr Quincke referred to the mandate of the Joint FAO/WHO Food Standards Programme and its CAC to protect the health of consumers and ensure fair practices in the food trade. In addition, it was important to point out that protection of food was considered as one of the essential actions to be taken by governments to improve nutrition and was explicitly incorporated into the World Declaration and Plan of Action for Nutrition adopted by the International Conference on Nutrition in Rome in 1992. In this regard, FAO and WHO were specifically requested to encourage involvement of all countries, in particular developing countries, in Codex activities.

The health component of the Codex Alimentarius has become even more important since the World Trade Organization's (WTO) Final Act included the "Agreement on the Application of Sanitary and Phytosanitary Measures" (SPS Agreement), which specifically cites Codex standards, guidelines and recommendations as reflecting international consensus regarding the requirements to protect human health from foodborne hazards. In addition, WTO's "Agreement on Technical Barriers to Trade" (TBT Agreement) has implications for the international food trade and Codex as well.

Dr Quincke noted that the work of this Consultation will lay the foundation for assuring that scientifically sound and consistent methodologies for risk assessment will be employed by CAC and its subsidiary and advisory bodies. The recommendations of the Consultation may be instrumental in assuring that the health-related aspects of Codex standards, guidelines and recommendations have the widest possible acceptance by governments, industry and trade, and, most importantly, consumers.

Welcoming those attending on behalf of the Director-General of FAO, Mr A.J. Whitehead, Senior Officer in the Food Quality and Standards Service of FAO's Food and Nutrition Division, expressed appreciation to all for their attendance and emphasized the importance of the task that lay ahead of the Consultation. He pointed out that the involvement of FAO in food quality and safety standards issues was wider than its work in the CAC alone, and included working with developing countries in the development and strengthening of food control programmes covering all aspects of food quality, including safety. Noting that there was as yet no generally accepted model that might be applied to food standards work, Mr Whitehead challenged those participating in the Consultation to work together during the week ahead to achieve this important goal.

The Consultation agreed that Dr Sanford Miller should be Chairman, Dr Steven Hathaway should be Vice-Chairman and Dr Stuart Slorach should be Rapporteur.

The deliberations of the Consultation were based on a number of working papers (Annex 2). Unfortunately, Dr Joseph Rodericks was unable to attend the Consultation, but his paper was considered during the Consultation.

## 2. BACKGROUND

Modern science has provided detailed information into the mechanisms of life itself, and modern chemistry has allowed the identification and quantification of chemicals, even down to a few molecules. Yet knowledge of facts does not automatically give insight, nor does it provide direction as to what to do with that knowledge. The capability of modern science to detect an increasingly smaller number of molecules, for example, does not itself provide any better understanding of the biological meaning of those small numbers of molecules or in turn their significance to human health. This lack of insight in turn often leads to confused or inappropriate public policy. Increasingly, policy makers have come to realize that the only rational future for the development of public policy concerned with the safety of the food supply must depend on sound adequate science and on the development of processes and procedures that utilize the available science in a rational way to arrive at public policy decisions.

From a historical point of view, the development of food safety evaluations has reached an important crossroads. For the first time, modern biology is being applied to the issues of food safety. Distinctions among chemistry, toxicology, nutrition and microbiology are being removed. Evaluation of food safety through this integrated mechanism will permit generic and, ultimately, predictive outcomes. To a significant extent, all of these processes have come to focus on this evaluative framework, namely risk assessment.

The importance of risk assessment lies not only in its ability to estimate human risk, but also in its use as a framework for organizing data as well as for allocating responsibility for analysis. Within common boundaries, it is important to understand that risk assessment is a process that can include a variety of models to reach conclusions. The concept of the Acceptable Daily Intake (ADI), for example, may be considered as a component of risk assessment, although a notionally zero risk, when combined with exposure assessments. Common structure permits a transparent and relatively uniform approach to the problem of

providing useful information to risk managers. Moreover, for the evaluators, it provides a way to identify areas in which the available data are insufficient to reach reasonable decisions. The use of a common framework also facilitates harmonization of food safety evaluation processes among nations.

The convening of this Joint FAO/WHO Expert Consultation on the Application of Risk Analysis to Food Standards Issues is a landmark in the development of international food safety evaluation. For the first time, an international trade agreement, the SPS Agreement, explicitly recognizes that for establishment of rational harmonized regulations and standards for food in international trade a rigorous scientific process is required. Consequently, for food, CAC is required to provide the scientific framework on which adherence to the SPS Agreement will be based. While Codex standards will technically remain voluntary until they are accepted or used by countries, the SPS Agreement provides a mechanism for the collective adoption of Codex standards, guidelines and recommendations by WTO Member countries. Countries maintaining national standards more stringent than those of Codex may be required to defend their standards before WTO panels.

The outcome of the Consultation's deliberations can form the basis for the full integration of risk assessment into Codex decision making. Equally important, the outcome can also be used by many countries to establish food safety standards for their internal use.

### **3. RISK ANALYSIS DEFINITIONS**

#### **3.1 Context of definitions**

The 41st Session of CAC Executive Committee clearly identified the need for uniform definitions for various risk analysis terms. The Consultation considered definitions adopted or proposed by various bodies, including Codex, other international organisations and national bodies. The Consultation considered the definition of "risk assessment" given in the SPS Agreement and noted that the definition was broader in scope than, but not inconsistent with, the definition developed by the Consultation.

These definitions relate to food safety as influenced by foodborne agents. For the purposes of the Consultation, foodborne agents were considered to be chemical, biological and physical agents in or on food whether added intentionally or through natural processes. However, these definitions do not take into account live animals, food itself or the natural components of food when present within normal limits.

#### **3.2 Definitions of risk analysis terms related to food safety**

**FOOD:** Any substance, whether processed, semi-processed or raw which is intended for human consumption, including drinks, chewing gum and any substance which has been used in the manufacture, preparation or treatment of "food" but excluding cosmetics, tobacco and substances used only as drugs.

- HAZARD:** A biological, chemical, or physical agent in or property of food that may have an adverse health effect.
- RISK:** A function of the probability of an adverse effect and the magnitude of that effect, consequential to a hazard(s) in food.
- RISK ANALYSIS:** A process consisting of three components: risk assessment, risk management and risk communication.
- RISK ASSESSMENT:** The scientific evaluation of known or potential adverse health effects resulting from human exposure to foodborne hazards. The process consists of the following steps: (i) hazard identification, (ii) hazard characterization, (iii) exposure assessment, and (iv) risk characterization. The definition includes quantitative risk assessment, which emphasizes reliance on numerical expressions of risk, and also qualitative expressions of risk, as well as an indication of the attendant uncertainties.
- HAZARD IDENTIFICATION:** The identification of known or potential health effects associated with a particular agent.
- HAZARD CHARACTERIZATION:** The qualitative and/or quantitative evaluation of the nature of the adverse 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 is obtainable.
- EXPOSURE ASSESSMENT:** The qualitative and/or quantitative evaluation of the degree of intake likely to occur.
- RISK CHARACTERIZATION:** Integration of hazard identification, hazard characterization and exposure assessment into an estimation of the adverse effects likely to occur in a given population, including attendant uncertainties.
- RISK MANAGEMENT:** The process of weighing policy alternatives to accept, minimize or reduce assessed risks and to select and implement appropriate options.
- RISK COMMUNICATION:** An interactive process of exchange of information and opinion on risk among risk assessors, risk managers, and other interested parties.
- DOSE-RESPONSE ASSESSMENT:** The determination of the relationship between the magnitude of exposure and the magnitude and/or frequency of adverse effects.

**SCENARIO SET:** A construct characterizing the range of likely pathways affecting the safety of the food product. This may include consideration of processing, inspection, storage, distribution and consumer practices. Probability and severity values are applied to each scenario.

#### **4. CURRENT PRACTICES IN THE CODEX ALIMENTARIUS COMMISSION AND RELATED EXPERT COMMITTEES**

Risk analysis within the Codex system is carried out by a number of different bodies. Some of these are subsidiary to the CAC and include the Codex Committees on Food Additives and Contaminants; Pesticide Residues; Residues of Veterinary Drugs in Foods; Food Hygiene; Meat Hygiene; Food Import and Export Inspection and Certification Systems; and Nutrition and Foods for Special Dietary Use. These are intergovernmental bodies, whose tasks are to prepare draft standards, guidelines and recommendations for consideration by CAC.

Scientific input into the Codex decision-making process is routinely provided by independent expert bodies, including the Joint FAO/WHO Expert Committee on Food Additives (JECFA) for additives, chemical contaminants and veterinary drug residues and the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) for pesticide residues. Codex committees from time to time also draw on advice from other bodies outside the Codex system, for example, the International Commission on Microbiological Specifications for Food (ICMSF).

Risk management issues are normally discussed within Codex committees but on rare occasions JECFA has issued recommendations in this area. Risk communication is usually dealt with by Codex committees, Member States and nongovernmental organizations (NGOs). A discussion of the risk analysis process within Codex can conveniently be divided into the following areas:

- food additives
- chemical contaminants
- pesticide residues
- veterinary drug residues
- biological agents

In describing practices in the existing Codex system, risk assessment terminology as defined by the Consultation has been used, with the recognition that in some cases, Codex risk assessment activities are deficient and/or inconsistent with these definitions.

##### **4.1 Food additives**

The risk analysis procedure for food additives is usually initiated by the Codex Committee on Food Additives and Contaminants (CCFAC) when it proposes additives for evaluation by JECFA. This process may also be triggered by direct requests to FAO/WHO from member countries. The initiation of the evaluation procedure serves as the hazard identification step.

JECFA carries out toxicological evaluations of food additives, normally resulting in an estimate of the amount of the additive, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk (notionally "zero" risk). This is referred to as the ADI. In setting an ADI, a safety factor is applied to the no-observed-effect level (NOEL) determined in the most appropriate (usually the most sensitive) animal species (WHO, 1987). JECFA does not make a quantitative estimate of risk at an intake corresponding to the ADI, but concludes that the risk is so small as to be negligible from a public health point of view. The toxicological evaluation can be considered to be mainly the hazard characterization step.

There are occasions when JECFA considers the use 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". JECFA 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 JECFA, 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.

When JECFA has recommended an ADI for an additive, CCFAC is then able to endorse the use of the additive in specific foods at defined use levels. Proposals for such use and use levels often come from Codex commodity committees. The use level is based on the amount needed to achieve a desired technological effect in the food. Until recently, the CCFAC has worked on an ad hoc commodity-by-commodity basis, without consideration of the overall use of the additive. However, CCFAC is currently developing a General Standard for Food Additives (GSFA) covering the use of additives in all foodstuffs. CCFAC has also had an ad hoc working group on food additive intake.

In the current process, the establishment of levels of use for additives takes little account of the potential total exposure to the additive concerned. However, the approach recommended to be used in the GSFA provides the framework in which exposure assessments will be considered.

#### 4.2 Chemical contaminants

For the purposes of this discussion chemical contaminants comprise industrial and environmental contaminants (e.g. heavy metals, persistent organo-halogen compounds) and naturally occurring toxicants (e.g. mycotoxins).

Within the Codex system, risk analysis of chemical contaminants is normally initiated by CCFAC but occasionally it may be initiated by member countries as in the case of additives. This serves as the hazard identification step.

The toxicological evaluation is carried out by JECFA and normally results in the estimation of a Provisional Tolerable Weekly Intake (PTWI) or Provisional Maximum Tolerable

Daily Intake (PMTDI). This corresponds to the hazard characterization step. As in the case of ADIs (see 4.1 Food additives), these are health-based estimates of the intakes associated with negligible risk. While ADIs are intended to be used in allocating the acceptable amounts of an additive for necessary technological purposes, trace contaminants have no intended function, so the term "tolerable" was seen as a more appropriate term than "acceptable". This is intended to signify permissibility rather than acceptability for the intake of contaminants unavoidably associated with the consumption of otherwise wholesome and nutritious foods. In this convention, tolerable intakes are expressed on a weekly basis, because the contaminants given this designation may accumulate within the body over a period of time. The PMTDI has been established for food contaminants that are not known to accumulate in the body, such as tin, arsenic and styrene. 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. As in the case of additives, they are based on the determination of a NOEL and the application of safety factors. This approach assumes that there is a threshold, i.e., a dose level below which no significant adverse effects will occur. In cases where no threshold is thought to exist (e.g. contaminants, such as aflatoxins which are genotoxic carcinogens), JECFA does not allocate a PTWI or PMTDI. Instead it recommends that the level of the contaminant in food should be reduced to as low as reasonably achievable (ALARA). The ALARA level, which may be viewed as the irreducible level for a contaminant, is defined as that concentration of a substance that cannot be eliminated from a food without involving the discarding of that food altogether or severely compromising the ultimate availability of major food supplies.

The question of establishing maximum levels for chemical contaminants in food is considered by CCFAC in consultation with Codex commodity committees. Exposure assessments for contaminants have been carried out by JECFA, CCFAC and GEMS/Food as well as by national bodies, and these assessments have been used in the development of Codex maximum levels or, in some cases, guideline levels. CCFAC is currently developing a General Standard for Contaminants (GSC) based on risk assessment and risk management principles, which will provide the framework for the routine incorporation of exposure assessment into the standard setting process.

#### 4.3 Pesticide residues

The risk analysis procedure for pesticide residues is usually initiated by the Codex Committee on Pesticide Residues (CCPR) when it proposes specific pesticides for evaluation by the JMPR. The process may occasionally be triggered by direct requests from member countries or industry to FAO/WHO. The CCPR has also established procedures for the re-evaluation of selected pesticides.

The JMPR carries out toxicological evaluations of pesticide residues, normally resulting in an estimate of the ADI (WHO, 1990). In addition, JMPR proposes Maximum Residue Limits (MRLs) for individual pesticides in or on specific commodities. These MRLs are primarily based on the residue levels estimated in supervised field trials when the pesticide is used according to Good Agricultural Practice (GAP).

Using the MRLs, preliminary exposure estimates are made and compared with the ADIs (GEMS/Food, 1990). GEMS/Food currently performs the calculations of the Theoretical Maximum Daily Intake (TMDI) based on the MRLs and estimates of commodity intake based on a global diet. This calculation is known to greatly overestimate the exposure and is conducted for screening purposes. If the TMDI exceeds the ADI, the Estimated Maximum Daily Intake (EMDI) is calculated based on global and regional diets and may include correction factors to improve the accuracy of exposure estimates. For example, data on the edible portion of the food and the fate of residues during processing may be used to make a more accurate calculation of exposure. GEMS/Food also collects data on the actual exposure to pesticides, but such data are mainly limited to developed countries and are often not comparable (GEMS/Food, 1988, 1992).

The ADIs and MRLs recommended by JMPR are then considered by the CCPR and on occasion the MRLs are modified before they are forwarded to the CAC for adoption. The CCPR also estimates exposure by a variety of methods. In cases where initial estimates indicate that the ADI may be exceeded, more refined intake calculations are performed using national food consumption data and information from pesticide residue monitoring programmes.

#### **4.4 Veterinary drug residues**

The risk analysis of veterinary drug residues is normally initiated by the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF). The process may also be triggered by direct requests to FAO/WHO from member countries. This represents the hazard identification step.

JECFA carries out toxicological evaluations of veterinary drugs and normally derives an ADI in the same way as for food additives. The NOEL from the most sensitive animal model is usually used. However, antimicrobial activity may become the end-point for setting the ADI when residues of an antimicrobial veterinary drug ingested in food may disrupt intestinal flora and impact on human health. This corresponds to the hazard characterization step.

JECFA also estimates potential intake of residues of veterinary drugs using standard assumptions about the consumption of edible animal products, such as meat and milk, and proposes MRLs that are consistent with Good Practice in the Use of Veterinary Drugs (GPVD). These estimates of potential intakes are compared with the ADIs. This is the risk characterization step.

The MRLs proposed by JECFA are circulated to Governments by the CCRVDF, whose primary role is to formally recommend MRLs. Scientific issues are not discussed in detail at CCRVDF but risk management options may be considered in the light of government comments.

#### **4.5 Biological agents**

Biological agents (bacteria, viruses, helminths, etc.) have not been the subject of systematic risk analysis by the CAC. Foods have, however, been studied on a case-by-case



basis when potential pathogens have been identified as being of concern to public health and international trade. Since the mid-1970's the Codex Committee on Food Hygiene (CCFH) has used a qualitative approach in identifying foodborne hazards, using principally the qualitative risk descriptions proposed by the ICMSF and matching these to foods associated with specific outbreaks of foodborne illness or to foods which were known historically to be associated with such outbreaks. The recommendations of the CCFH have been in the form of Codes of Hygienic Practice, often supplemented by advisory microbiological specifications which are used to verify that the control processes described in the code have been carried out properly. End-product specifications were assumed to be particularly useful for examining products of unknown origin. Codes of Hygienic Practice were frequently developed in consultation with specific Codex commodity committees.

Meat hygiene has also been the subject of a commodity-specific approach by the Codex Committee on Meat Hygiene (CCMH). However, a very different risk-based approach has been used in developing Codes of Hygienic Practice and, in particular, the Code for the Ante-Mortem and Post-Mortem Judgment and Post-Mortem Inspection of Meat.

More recently, the CCFH has examined certain pathogens, such as *Listeria monocytogenes*, from the point of view of their occurrence in the diet. Although this has not, as yet, resulted in the development of recommendations for the control of these organisms, the first steps have been taken in establishing a risk-based approach for developing international recommendations.

The Codex text on the Hazard Analysis Critical Control Point (HACCP) system developed by the CCFH requires the use of risk-based decision making in identifying significant hazards at different points in the food processing chain and establishing critical limits at specified critical control points. This system is being integrated into the Revised General Principles of Food Hygiene and will be applied to other existing Codes of Hygienic Practice.

#### 4.6 Other Codex Committees

The Codex Committee on Import and Export Food Inspection and Certification Systems (CCFICS) has confirmed that risk-based approaches should be used in the development of national food import inspection systems. Such approaches will target problem areas more effectively and provide greater consumer protection than systems based purely on random inspection procedures. Detailed protocols have yet to be developed.

### 5. RISK ASSESSMENT OF CHEMICAL AGENTS IN FOOD

#### 5.1 Introduction

For the purpose of this chapter, only intentionally introduced chemical agents, inadvertent contaminants and naturally occurring toxicants have been considered. This includes food additives, residues of pesticides and other agricultural chemicals, residues from veterinary drugs, chemical contaminants from any source, and natural toxins, such as mycotoxins and ciguatoxin.

Microbial toxins, such as *Clostridium botulinum* toxin, are not included.

Risk assessment is seen primarily as a method of systematically organizing scientific and technical information, and its associated uncertainties, to answer specific questions about health risks. It requires evaluation of relevant information, and selection of the models to be used in drawing inferences from that information. Further, it requires explicit recognition of uncertainties and, when appropriate, acknowledgement that alternative interpretations of the available data may be scientifically plausible.

The steps involved in risk assessment of chemical hazards have been discussed at greater length elsewhere (NRC, 1983, 1994). Risk assessment is subject to uncertainties related to data and to the selection of the appropriate model. Uncertainties are discussed in further detail later in this report. However, it should be pointed out at this juncture that data uncertainties arise both from limitation on the amount of data available and from evaluation and interpretation of actual data obtained from epidemiological and toxicological studies. Model uncertainties arise whenever attempts are made to use data concerning the occurrence of certain phenomena obtained under one set of conditions, to make estimations or predictions about phenomena likely to occur under other sets of conditions for which data are not available.

The process of risk assessment requires adequate toxicological information preferably based on standardized testing protocols which have been accepted by the international community. In addition, a credible risk assessment requires at least a minimum data set which has been already defined by others, e.g. JECFA, JMPR, EPA, FDA, OECD.

Depending upon the chemical, empirically-based answers to toxicological questions may be available for the purpose of risk assessment. However, in no case will the scientific information be comprehensive enough to provide a high degree of certainty. When several sets of animal toxicology data are available, there are usually insufficient data to identify the set (i.e. species, strain, toxicity end-point) that best predicts human response. As a result, it has become traditional to rely on toxic responses which occur at the lowest dose in a study of acceptable quality.

Minimum data requirements for risk assessment are difficult to specify in advance. Hazard, dose-response, and exposure data bases for substances that may become subjects for risk assessment vary enormously in size, scope, and quality. In some instances, the data may be very limited and practically impossible to obtain. The latter is especially the case for contaminants and naturally occurring substances. When a risk assessment is necessary, risk assessors are required to make the best use of whatever information is available, and to deal explicitly with data uncertainties. In cases where this is not possible, risk assessors should provide the reasons for such judgements. Perhaps the appropriate option is to leave the question of minimum data requirements open to such case-by-case judgements.

Other issues related to the process of risk assessment include the use of default assumptions to fill knowledge and data gaps. This provides the advantage of ensuring consistency in approach and minimizing or eliminating case-by-case manipulations of the conduct of risk assessment to meet predetermined risk management objectives. One major disadvantage, however, is the potential for displacement of scientific judgement by rigid guidelines. One

intermediate approach is to allow risk assessors to replace defaults in specific cases of chemicals for which relevant scientific data are available to support alternatives. Specific and explicit justification for any such departures should be provided.

## 5.2 Hazard identification

The goal of hazard identification is to identify potential adverse health effects in humans associated with exposure to a chemical, the likelihood of such effects occurring and the certainty or uncertainty associated with such effects. In this context, the hazard identification does not imply the quantitative extrapolation of risk for exposed human populations as in the dose-response and risk characterization step, but rather an evaluation of the qualitative likelihood of the effect occurring in exposed human populations.

Because data are often insufficient, hazard identification is best conducted using the weight-of-evidence approach. The approach requires an adequate and documented review of relevant scientific information obtained from appropriate databases, peer-reviewed literature and, if available, unpublished studies from other sources, such as industry. This approach places emphasis on studies in the following order: epidemiological studies, animal toxicological studies, *in vitro* assays and, lastly, quantitative structure-activity relationships.

### 5.2.1 Epidemiological studies

Where data from positive epidemiological studies are available, their use in the risk assessment process is encouraged. Data derived from human clinical studies, where they are available, should also be utilized in the hazard identification step, as well as perhaps other steps. However, clinical and epidemiological data are unlikely to be available for most chemicals. In addition, negative epidemiological data may be difficult to interpret for risk assessment purposes because the statistical power of most epidemiological studies is inadequate to detect effects at relatively low levels in human populations. Finally, although the value of epidemiological data is recognized, positive data indicate that an adverse effect has already occurred; thus, risk management decisions should not be delayed pending the development of epidemiological studies. Epidemiological studies from which data for risk assessment are derived should be based on recognized standardized protocols.

During the design of epidemiological studies, or where positive epidemiological data are available, consideration must be given to the variability in human susceptibility; genetic predisposition, age-related and gender-related susceptibility, and the impacts of factors such as socio-economic status, nutritional status, and other possibly confounding factors.

Due to the cost of epidemiological studies and due to the paucity of data such studies provide, hazard identification will ordinarily need to rely on data derived from animal and *in vitro* studies.

### 5.2.2 Animal studies

Most toxicological data for risk assessment are derived from animal studies and it is, therefore, essential that these studies be conducted following widely accepted, standardized testing protocols. While many such protocols exist, e.g. OECD, EPA, guidance is not available concerning the selection and use of specific protocols for food safety risk assessment. Regardless of which protocols are used, all studies should follow Good Laboratory Practices (GLP) and standardized quality assurance/quality control (QA/QC) procedures.

Adequate minimum data sets are generally available for food safety risk assessment and should be used. These include specification of the number of species/strains/stocks, use of more than one sex, appropriate selection of doses (see below), route of exposure, and adequate sample size. In general, the source of data (published studies, unpublished studies, corporate data, etc.) is not a point of great concern as long as studies are transparent and can be demonstrated to conform to GLP and QA/QC procedures.

Animal data from long-term (chronic) studies are critical, and should address significant toxicological effects/end-points, including cancer, reproductive/developmental effects, neurotoxic effects, immunotoxic effects, and others. Animal data from short-term (acute) toxicity studies will also be useful and should be generated. Animal studies should facilitate identification of the range of toxicological effects/end-points (including those listed). Data on the relationship between toxicity and essentiality should be gathered for those substances which are required to meet nutritional requirements, e.g. copper, zinc, and iron. Animal toxicological studies should be designed to identify a NOEL, a no-observed-adverse-effect level (NOAEL) or a benchmark dose; that is, doses should be selected to identify these end-points. Doses should also be selected at levels high enough to reduce the likelihood of false-negatives as much as possible, while considering issues such as metabolic saturation, cytogenic and mitogenic induced cell proliferation, etc. Presently, the selection of the highest dose for chronic rodent bioassays is being debated. Discussion is focused on the selection, use, and interpretation of data from studies which employ the Maximum Tolerated Dose (MTD). Mid-range doses should be selected to provide relevant information on the shape of the dose-response curve.

Animal studies should, where possible, identify not only potential adverse effects for human health but also provide information on the relevance of these effects for human risk. Information on relevance may be provided by studies that characterize the mechanism of action, the relationship between administered and delivered dose, and by pharmacokinetic and pharmacodynamic studies.

Mechanistic data may be supplemented by data from *in vitro* studies, such as information on genotoxicity derived from reversion assays or other similar assays. These studies should be conducted following GLP, and other widely accepted protocols. However, data from *in vitro* studies should not be used as the sole source of information to predict human risk.

The results of *in vivo* and *in vitro* studies can enhance the understanding of mechanisms and pharmacokinetics/dynamics. However, such information may not be available in many cases and the risk assessment process should not be delayed pending development of mechanistic and pharmacokinetic/dynamic data.

Information on administered versus delivered dose will be useful as part of the evaluation of mechanism and pharmacokinetic data. The assessment should also consider information on chemical speciation (administered dose) and metabolite toxicity (delivered dose). As part of this consideration, the issue of chemical bioavailability should be addressed (bioavailability of parent compound, metabolites, etc.) with specific consideration given to absorption across the appropriate membrane (i.e., the gut), transport to systemic circulation, and, ultimately, to the target organ.

Finally, structure-activity relationships may be useful to increase the weight-of-evidence for human health hazards identification. Where classes of compounds are of interest (e.g. polycyclic aromatic hydrocarbons, polychlorinated biphenyls and dioxins), and where adequate toxicological data are available on one or more members of the class, a toxic equivalence approach may be useful to predict the human health hazard associated with exposure to other members of the class.

### 5.3 Hazard characterization

The chemicals in food being considered include food additives, pesticides, veterinary drugs and contaminants. They are often present in food at low levels - typically at a part per million or less. However, to obtain adequate sensitivity, animal toxicological studies must be conducted at high levels which may exceed, depending on the intrinsic toxicity of the chemical, several thousand parts per million. The significance that the adverse effects detected in high-dose animal studies have for low-dose human exposures is the major question posed in the hazard characterization of chemicals.

#### 5.3.1 Dose-response extrapolation

In order to be compared to human exposure levels, animal data need to be extrapolated to doses much lower than those studied. This extrapolation procedure is uncertain both qualitatively and quantitatively. The nature of the hazard may change with dose or may disappear entirely. The selected dose-response model may be incorrect if the nature of the response in animals and humans is qualitatively the same. Not only is the equivalent dose estimate in animals and humans a problem in comparative pharmacokinetics, but also is the change in metabolism with dose. The metabolism of chemicals at high and low doses may differ. For example, high doses often overwhelm normal detoxification/metabolism pathways and produce adverse effects that would not occur at lower levels. High doses can induce higher rates of enzyme production, physiological changes and dose related pathological changes. The toxicologist must consider the potential impact of these and other possible dose-related changes on the extrapolation of the adverse effect to lower doses.

#### 5.3.2 Dose-scaling

Toxicologically equivalent doses in animals and humans is a debatable issue. JECFA and JMPR have typically used mg per kg of body weight for interspecies scaling. Recently

regulatory authorities in the USA have proposed a scaling equivalent to mg per 3/4 kg of body weight, which is based on more recent pharmacokinetic information. The ideal scaling factor would be obtained by measuring tissue concentrations and clearance rates in the target organ of the animal and human; blood levels would approximate this ideal. Generic interspecies scaling factors should be recognized as default values that are used in the absence of better information, which is seldom available.

### 5.3.3 Genotoxic and non-genotoxic carcinogens

Traditionally, toxicologists have accepted the existence of thresholds for adverse effects with the exception of carcinogenicity. The tradition extends from the early 1940s when it became evident that the initiating event in carcinogenesis could be a somatic mutation. In theory, a few molecules, even a single molecule, could cause a mutation that could persist in the animal or human and ultimately be expressed as a tumour. Theoretically, there may be no safe dose for a carcinogen that acts through this mechanism.

In recent years it has been possible to discriminate between carcinogens and to identify a category of non-genotoxic carcinogens that are themselves not capable of producing mutations but act at later stages of the cancer process on cells already "initiated" by other carcinogens or other processes e.g. radiation. In contrast, other carcinogens induce genetic alterations in somatic cells with activation of oncogenes and/or inactivation of cancer suppressor genes. Thus, genotoxic carcinogens are defined as chemicals which can cause genetic alterations in target cells, either directly or indirectly. While the major target of genotoxic carcinogens is genetic material, non-genotoxic carcinogens act at extra-genetic sites, leading presumably to enhanced cell proliferation and/or sustained hyperfunction/dysfunction at the target sites. Regarding species differences in carcinogenic effects, a large body of data has been reported indicating that quantitative differences exist in both genotoxic carcinogens and non-genotoxic carcinogens. In addition, certain non-genotoxic carcinogens, called rodent-specific carcinogens can be raised as examples of substances for which there are qualitative differences in the ultimate carcinogenic effects. In contrast, no such clear-cut examples have been reported for genotoxic carcinogens.

Toxicologists and geneticists have devised tests to detect chemicals capable of causing mutations in DNA; the Ames test is a well known example. Several such tests, both *in vitro* and *in vivo* tests are used, typically in the form of a battery, to determine the mutagenic potential of chemicals. While the exact tests to include in such a battery may be debatable, in general these tests have been useful in distinguishing between genotoxic and non-genotoxic carcinogens.

Food safety authorities in many countries now make a distinction between genotoxic and non-genotoxic carcinogens. While this distinction cannot be applied in all instances due to insufficient information or knowledge on carcinogenesis, the concept can still contribute to the establishment of evaluation strategies for cancer risks posed by exposure to chemicals. In principle, non-genotoxic carcinogens may be regulated using a threshold approach, such as the "NOEL-safety factor" approach. In addition to the demonstration that the substance is not likely to be a genotoxic agent, scientific information is often required on the mechanism of carcinogenicity.

### 5.3.4 Threshold approaches

A safe level or Acceptable Daily Intake (ADI) is derived from an experimental NOEL or NOAEL by applying appropriate safety factors. The conceptual basis for their use is that thresholds will exist at reasonably comparable doses in both humans and experimental animals. For humans, however, sensitivity may be greater, genetic outbreeding may be larger and dietary habits may be more variable. As a consequence, a safety factor is applied by JECFA and JMPR to take into account these uncertainties. A safety factor of 100 is typically applied when data from long-term animal studies are available but other safety factors are used by different health agencies. JECFA also uses a larger safety factor when the data are minimal or when the ADI is assigned on a temporary basis. Other health agencies adjust the ADI for the severity or irreversibility of the effect. These differences in ADI values constitute an important risk management issue which deserves some attention by appropriate international bodies.

The message communicated with an ADI is that there is no significant risk if the chemical is ingested at or below the ADI. The safety factor, as indicated, is selected to subsume anticipated variations in human responses. It is, of course, theoretically possible that some individuals are even more sensitive than provided for by the safety factor. The safety factor approach, like the quantitative risk approach discussed below, cannot guarantee absolute safety for everyone.

Another approach to ADI development has been to move away from reliance on the NOEL/NOAEL and toward the use of a lower effective dose, such as ED10 or ED05. This approach, called the benchmark dose, draws more heavily on data near the observed dose-response range, but is still subject to the application of safety factors. Thus, while it may allow a more accurate prediction of low dose risk, the benchmark dose-based ADI may not differ significantly from a NOEL/NOAEL-based ADI. Special population groups, like children, are protected by an appropriate choice of the intraspecies conversion factor and by special consideration of their exposures, if necessary (see 5.4 Exposure assessment).

### 5.3.5 Non-threshold approaches

For genotoxic carcinogens, the "NOEL-safety factor" approach is generally not considered a suitable method for setting acceptable intake levels. The consensus is predicated on the anticipated presence of risk at all doses, even the lowest. At this point, two management approaches are available: (1) to ban the chemical from commercial use, or (2) to establish a level of risk that is sufficiently small to be deemed negligible, insignificant or societally acceptable. The implementation of this latter approach has given rise to quantitative risk assessment for carcinogens.

Various extrapolation models have been utilized for this purpose. Currently models use experimental measurements of tumour incidence and dose and virtually no other biological information. None of these models have been validated beyond the experimental range. No correction for high dose toxicity, enhanced cellular proliferation, or DNA repair is made. For these reasons, the current linear models are considered to be conservative estimates of risk. This is usually expressed by characterizing the risks generated by such models as "plausible upper

bounds" or "worst-case estimates". It is acknowledged by many regulatory agencies that actual or probable human risks are not being predicted. Some countries attempt to reduce the conservatism inherent in linear extrapolation by using non-linear models. An essential component of this approach is the determination of an acceptable risk level. In the USA, FDA and EPA have chosen a risk level of one in a million ( $10^{-6}$ ). This acceptable level was chosen because it was considered to represent an insignificant risk. But the choice of a risk level is ultimately a risk management decision for each country to decide.

For food additives and residues of pesticides and veterinary drugs, a fixed level of risk is practical as the substances can be disallowed if the estimated risk exceeds the regulatory acceptable level. But for contaminants, including discontinued pesticides which have become environmental contaminants, an established acceptable level can easily be exceeded. For example, in the USA, dioxins are estimated to present a worst case risk of around  $10^{-4}$ . For ubiquitous carcinogenic contaminants like polycyclic aromatic hydrocarbons and nitrosamines, the  $10^{-6}$  risk level is also exceeded.

#### 5.4 Exposure assessment

Estimates of dietary intakes of food additives, residues of pesticides and veterinary drugs and contaminants require information on the consumption of relevant foods and the concentrations of the chemical of interest in those foods. In general, three approaches are available in exposure assessment: (1) total diet studies; (2) selective studies of individual foods, and; (3) duplicate portion studies. Guidelines for the study of dietary intakes of chemical contaminants are available from WHO (GEMS/Food, 1985). In recent years, direct monitoring of human tissues and body fluids has been increasingly used to assess exposure. For example, the determination of levels of organochlorine compounds in breast milk, which are mainly derived from the diet, has provided an integrated assessment of human exposure to these substances (GEMS/Food, in press).

Dietary intake determinations can be relatively straight-forward for additives, pesticides and veterinary drugs as the relevant foods and their use levels are specified by their approved conditions of use. However, the actual levels of additives and residues of pesticides and veterinary drugs present in foods are often well below the maximum levels permitted. In regard to residues of pesticides and veterinary drugs, levels on or in food are often totally absent because only a portion of the crop/animal population is usually treated. Data on the levels of food additives in foodstuffs can be obtained from the manufacturers. The dietary intake of contaminants requires information on their distribution in foods that can only be obtained by analyzing representative samples of foods with sufficiently sensitive and reliable analytical methods. Guidelines for establishing or strengthening national food contamination monitoring programmes have been elaborated (GEMS/Food, 1979).

Maximum Residue Limits (MRLs) for pesticides and veterinary drugs and Maximum Levels for additives can be established from their conditions of use. In the simplest case, a food additive used at a specific level would be stable in the food until consumption. The Maximum Level would then equal the intake level. However, in many cases, the amount of the chemical of interest may change prior to consumption. For example, food additives may degrade during



storage or react with the food. Pesticide residues in raw agricultural products may degrade/accumulate during further processing. The fate of veterinary drug residues in food products is influenced by metabolism, kinetics, distribution and withdrawal periods required for treated animals.

The establishment of MRLs must take into account any changes in the nature or level of the residue that may occur prior to a commodity entering commerce or that may occur under any anticipated conditions of subsequent use. Contaminants have no intended technicological effect in the food and guideline levels are usually set as low as reasonably achievable.

The theoretical total dietary intake of additives, pesticides and veterinary drugs must be below their corresponding ADIs. Frequently, the actual intake is well below the ADI. Setting guideline levels for contaminants present special problems. There is usually a paucity of data to establish a provisional tolerable intake. On occasion, the levels of the contaminants are higher than what an established provisional tolerable intake would permit. In these cases, the guideline levels are set on economic and/or technical considerations.

Reliable food intake data are essential for exposure assessments based on measuring levels of chemical agents in food. Detailed food consumption data for the average and median consumer as well as for different population groups are important for assessing exposure, particularly by sensitive groups. In addition, comparable food consumption data, particularly with respect to staple foods from different regions of the world are essential for developing an international risk assessment approach to food safety.

GEMS/Food currently maintains a database of five regional diets as well as a composite "global" diet. Daily dietary intakes of nearly 250 individual primary and semi-processed food commodities are available. The African, Asian, East Mediterranean, European and Latin American regional diets are based on selected national data from FAO Food Balance Sheets. Consumption data derived using this approach provide no information on extreme consumers. No information is available in GEMS/Food on the intake of food additives although intakes in developed countries are anticipated to be greater than in developing countries because of the higher portion of processed foods in the diet.

## 5.5 Risk characterization

The outcome of the risk characterization is an estimate of the likelihood of adverse health effects in human populations as a consequence of the exposure. The risk characterization is performed by taking into consideration the results of the hazard identification, hazard characterization, and exposure assessment. For threshold acting agents, population risk is characterized by comparison of the ADI (or other measures) with exposure. In this case, the likelihood of adverse health effects is notionally zero when exposure is less than the ADI. For non-threshold acting agents, population risk is the product of exposure and potency.

At the risk characterization step, the uncertainties involved in each step of the risk assessment process should be described. Uncertainty in risk characterization will reflect the uncertainties in the preceding steps. The extrapolation of results of animal studies to the human

situation may produce two types of uncertainties: (i) uncertainties with respect to the relevance of the experimental findings to the humans. For example, forestomach tumours in rats fed butylated hydroxyanisole (BHA) and neurotoxic effects in mice produced by aspartame may not have human parallels; and, (ii) uncertainties with respect to specific human sensitivity for effects of a chemical that cannot be studied in experimental animals. In this case, hypersensitivity to glutamate is an example. In practice, these uncertainties are dealt with by expert judgement and by additional studies, preferably in humans. These studies may be performed during the pre-marketing phase as well as during the post-marketing phase.

## **6. RISK ASSESSMENT OF BIOLOGICAL AGENTS IN FOOD**

### **6.1 Introduction**

Food will always present some minimal biological risk and it is the task of the food industry to maintain the level of risk at the minimum which is practical and technologically feasible. It should be the role of official bodies to use risk analysis to determine realistic and achievable risk levels for foodborne hazards and to base food safety policies on the practical application of the results of these analyses.

Biological agents (hazards) of concern to public health include pathogenic strains of bacteria, viruses, helminths, protozoa, algae, and certain toxic products they may produce. Of these hazards, the presence of pathogenic bacteria in foods currently presents the most significant problems internationally. The analysis of risk associated with bacterial pathogens presents unique features for risk assessment. There is a need to ensure these hazards are eliminated or reduced to an acceptable level and the CAC and its subsidiary bodies have elaborated a multitude of standards and Codes of Practice which contain procedures designed to address this issue. However, the need for a more formal approach to the process of controlling biological hazards has been recognized by Codex. In adopting the Codex text on the Hazard Analysis Critical Control Point (HACCP) system, the CAC acknowledged that the HACCP system was the most cost-effective method devised to date for controlling foodborne hazards.

HACCP is a system which identifies specific hazards and preventative measures for their control. The seven principles of HACCP, as adopted by Codex, establish the framework for developing specific HACCP plans for each food product/production line combination. When developing a specific HACCP plan, the identification of all potential hazards which are "of such a nature that their elimination or reduction to acceptable levels is essential to the production of a safe food" is required. However, the determination of which potential hazards are "essential" to control, will involve a risk-based hazard assessment. This hazard assessment will result in a list of the significant hazards which should be addressed within the HACCP plan.

### **6.2 Risk assessment of biological hazards**

Risk assessment is the scientific evaluation of the known or potential adverse health effects resulting from human exposure to foodborne hazards. It provides an estimate of the severity and likelihood of harm resulting from exposure to a hazard. When one is considering

public health risks posed by chemical or biological hazards in food, the objective of a quantitative risk assessment is to derive a mathematical statement, based on the probability of certain events, of the chance of adverse health consequences resulting from exposure to an agent capable of causing harm. Possible approaches for conducting a risk assessment for foodborne pathogens include probabilistic scenario analysis, fault tree analysis, event tree analysis and following the quantitative risk assessment paradigm proposed for chemicals.

Biological hazards may act through two general mechanisms in causing human illness. One mode of action is to produce toxins which may cause effects that range from mild symptoms of short duration to severe intoxications that can have long-term or life-threatening consequences. The second mode of action is to produce pathological responses that result from ingestion of viable organisms capable of infecting the host. Threshold levels for concern are easier to quantify in the former case. In these cases, as with certain other biological agents, a quantitative risk assessment may be possible. When considering hazards from pathogenic bacteria, however, a qualitative risk assessment may be the only feasible method currently available to derive an assessment of the severity and the likelihood of harm associated with exposure through ingestion of a food. However, both the quantitative and qualitative methods will depend on the type and quality of information developed during the risk assessment process.

While the basic steps are the same, their application will be different when conducting a qualitative assessment, as the analyst will not have the information necessary to develop a mathematical estimate of the probability and/or severity of an adverse consequence. When assessing risk for some biological agents, sufficient data may be available to conduct a quantitative analysis. However, the analyst will find that in most cases the many uncertainties associated with how and when an organism may express pathogenic potential will make a quantitative assessment impractical. Further research is required to permit more accurate and quantitative assessments in the future.

In the absence of quantitative data to develop an exposure assessment, measurement of hazard levels at particular process steps, or segments of the production chain, may provide a qualitative indication of likely risks to consumers. In this respect comparative studies on biological hazard levels and qualitative estimates of the likely effects of differences to human health can be used.

### 6.3 Risk assessment of bacterial hazards

The analysis of risk associated with bacterial pathogens presents unique challenges. Any method used to assess the risk of hazards from foodborne bacteria will be complicated by factors resulting from methods used to grow, process, store and prepare food for consumption. These can vary greatly depending on cultural and geographical differences. Such factors describe the scenario set for a given food and are an essential element in a risk assessment for bacterial hazards.

As already noted, in many cases sufficient data will not be available to support a quantitative assessment of risk associated with pathogenic bacteria. The following present an indication of the type of challenges that make quantitative risk assessment difficult for pathogenic bacteria associated with foods.

### **6.3.1 Hazard identification**

Bacterial agents known to cause foodborne disease have been identified by using epidemiological and other data to link the organism and its source to illness. However, as only a limited number of outbreaks are adequately investigated, it is likely that a number of bacterial pathogens in food remain to be identified.

Limitations on hazard identification include (i) the expense and difficulty involved in outbreak investigations; (ii) the lack of reliable or complete epidemiological data; and, (iii) the inability to isolate and characterize new pathogens.

### **6.3.2 Hazard characterization**

The purpose of this step is to provide a qualitative or quantitative estimate of the severity and duration of adverse effects due to the presence of a pathogen in food. Dose response data are useful when addressing toxigenic bacteria. However, when characterizing hazards from invasive strains of pathogenic bacteria, such information may be of little utility. For many foodborne pathogenic bacteria, dose-response data are limited or non-existent. Information on which to base dose-response estimates is difficult to obtain and may also be inaccurate for a variety of reasons, such as:

- (i) host susceptibility to pathogenic bacteria is highly variable;
- (ii) attack rates from a specific pathogen vary widely;
- (iii) virulence of a pathogenic species is highly variable;
- (iv) pathogenicity is subject to genetic variation resultant from frequent mutation;
- (v) antagonism from other bacteria in foods or the digestive system may influence pathogenicity; and,
- (vi) foods will modulate the ability of bacteria to infect and/or otherwise affect the host.

### **6.3.3 Exposure assessment**

An exposure assessment will give an estimate of either the number of pathogenic bacteria or the level of bacterial toxin consumed in food. While levels of chemical agents in food may change slightly due to processing, populations of bacterial pathogens are dynamic and may increase or decrease dramatically in food matrices. Changes in populations of bacteria are affected by complex interactions of factors such as those listed below:

- (i) ecology of the bacterial pathogen of concern;
- (ii) processing, packaging and storing of food;

- (iii) preparation steps, such as cooking, which may inactivate bacterial agents; and,
- (iv) cultural factors relating to consumers.

#### **6.3.4 Risk characterization**

Characterizing the risk associated with biological pathogens will depend on the considerations and information described in the hazard identification, hazard characterization and exposure assessment steps. A risk characterization will result in a qualitative or quantitative estimate of the potential for adverse effects from a particular bacterial agent on a specific population.

It has not yet been determined whether a quantitative risk assessment approach is possible and appropriate for characterization of risk associated with foodborne bacterial pathogens. Thus, by default, the qualitative approach to characterizing risk may be the only current alternative.

The qualitative risk assessment process depends on experience with a specific food, a knowledge of ecology of bacterial pathogens, epidemiological data, and expert judgement regarding hazards associated with the manner in which the food is produced, processed, stored, and prepared for consumption.

#### **6.4 Risk assessment of other biological hazards**

The steps in risk assessment for biological hazards other than bacteria that must be followed, for example, to provide input into HACCP plans, are identical to those described above. The variations come within the steps where the particular properties of the biological agents sometimes make the assessment more simple or more difficult in terms of developing quantitative data. The factors that complicate risk assessment for foodborne biological hazards (other than bacterial hazards) vary, but are not as great as those for bacterial hazards, as the agents typically do not increase in number when in food.

#### **6.5 Role of the CAC in risk assessment of biological hazards**

Through the CAC and its subsidiary bodies, standards, guidelines and recommendations are elaborated which are designed to address food safety issues related to biological, chemical, and physical hazards. Risk assessment is a key to developing meaningful food safety standards.

For the chemical hazards, standards are generally expressed in numerical values based on scientifically derived Acceptable Daily Intake levels. In the case of biological hazards, Codex has elaborated standards, guidelines and recommendations which describe processes and procedures, the application of which supposedly eliminates hazards or reduces them to acceptable levels. For many of the procedures, there is little quantitative data or other scientific evidence to link specific procedures with potential biological hazards, or with a specific health outcome. These linkages are necessary to enable validation of procedures and processes in standards and

Codes that might come before the WTO in adjudicating disputes on food safety measures. In addition, these linkages are needed to assess or validate equivalence of alternate processes and procedures. The absence of criteria to judge equivalence is detrimental to international trade because it reduces flexibility in achieving a specified outcome.

The current procedures and processes contained in Codex standards, guidelines and recommendations do not permit a comparison of relative risk or comparative risk between food safety hazards. There is no established means of comparing chemical hazards with biological hazards, or for comparing biological hazards. This may result in the choice of alternatives which increase overall health risk associated with the food. For example, the use of super-chlorinated wash water to reduce pathogenic bacterial hazards creates a chemical hazard from chloramines. As HACCP relies on a determination of the significance of hazards, methodology needs to be available to compare risks.

## **7. UNCERTAINTY AND VARIABILITY IN THE RISK ASSESSMENT PROCESS**

### **7.1 Introduction**

As applied to hazardous agents in food, health-risk assessment is a quantitative evaluation of information on potential health hazards from exposure to various agents and involves four inter-related steps discussed earlier, namely, (i) hazard identification; (ii) hazard characterization; (iii) exposure assessment, and; (iv) risk characterization. There are many sources of both uncertainty and variability in the process of human health-risk assessment (Covello and Merkhofer, 1993; Finkel, 1990; IAEA, 1989; Morgan and Henrion, 1990; NRC, 1983, 1993, 1994). While effective risk management policies are possible under conditions of both uncertainty and variability, such policies must take both into account.

An uncertainty analysis is an important component of risk characterization. It provides a quantitative estimate of value ranges for an outcome, such as estimated numbers of health effects. The ranges in the outcome are attributable to the variance and uncertainties in data and the uncertainties in the structure of any models used to define the relationship between exposure and adverse health effects. This section addresses the problems of defining, characterizing, and propagating uncertainty and variability in risk characterization. The nature of variance and uncertainties in data and models are considered, and variability (heterogeneity) and true uncertainty (lack of precise knowledge) in data and models are distinguished. Methods for addressing uncertainties in data, the relationship between the true uncertainty and variability inherent in models and data, and the nature of the uncertainties likely to be confronted at each stage of the risk assessment process are identified.

## 7.2 Uncertainty versus variability

One of the issues in uncertainty analysis that must be confronted is how to distinguish between the relative contribution of variability (i.e., heterogeneity) and true uncertainty to the characterization of predicted population risk. Variability refers to quantities that are distributed within a defined population, such as: food consumption rates, exposure duration, and expected lifetime. These are inherently variable and cannot be represented by a single value, so that we can only determine their moments (e.g., mean, variance, skewness, etc.) with precision. In contrast, true uncertainty or model-specification error (e.g., statistical estimation error) refers to a parameter that has a single value, which cannot be known with precision due to measurement or estimation error. Variability and true uncertainty may be formally classified as follows: (i) Type A uncertainty that is due to stochastic variability with respect to the reference unit of the assessment question, and; (ii) Type B uncertainty that is due to lack of knowledge about items that are invariant with respect to the reference unit of the assessment question. There are situations in which true (Type B) uncertainty is negligible relative to variability (Type A uncertainty). In these situations, the outcome of a variance propagation analysis represents the expected statistical variation in dose or risk among the exposed population. When neither variability nor uncertainty are negligible, the shape of the distributional curve representation of variability is unknown because of uncertainties.

## 7.3 Model uncertainty versus input (parameter) uncertainty

Uncertainty in model predictions arises from a number of sources, including specification of the problem, formulation of conceptual and computational models, estimation of input values, and calculation, interpretation, and documentation of the results. Of these, only uncertainties due to estimation of input values can be quantified with variance propagation techniques. Uncertainties that arise from mis-specification of the model can be assessed using decision trees and event trees based on elicitation of expert opinions. In some cases, using methods such as meta-analysis, model specification errors can be handled using simple variance propagation methods.

### 7.3.1 Nature of models

Because the magnitude of chemical or microbial risks attributable to food can rarely be measured, such outcomes are estimated using models or projections from historical data. Exposure-effect models range from simple "rule-of-thumb" models to complex stochastic models. The reliability of these models is determined by the precision of the inputs and the accuracy with which the model captures the relevant biological, chemical, and physical processes. Uncertainty analysis can be used to assess how model predictions are impacted by model reliability and data precision.

### **7.3.2 Methods for addressing model uncertainty**

When there is uncertainty about the appropriate scenario or model, techniques can be used to assess the implication of alternate models on the predicted outcome. Methods such as probability trees, event trees, and fault trees can be used to portray the multiple events leading to the outcome of interest. An event tree starts with some initiating event and contains all the possible outcomes. The probability associated with each event may be represented by a probability distribution. The strengths of this approach include the visual portrayal of all the potential scenarios and the use of probability distributions as interpretations of relevant evidence.

### **7.3.3 Methods for representing and propagating input variance**

Describing uncertainty in the risk involves quantification of the arithmetic mean value, the arithmetic or geometric standard deviation, and upper and lower quantile values of risk. Convenient tools for presenting such information are the probability density function or the cumulative distribution function for risk. However, the probability density function or cumulative density function of risk can often only be obtained when there are meaningful estimates of the probability distributions of the input variables used to estimate risk. There are five steps in an uncertainty analysis:

- (i) identify inputs that could contribute to uncertainty in the predictions of a model;
- (ii) construct a probability density function to define the values that an input parameter can take;
- (iii) account for dependencies (correlations) among input parameters;
- (iv) propagate the uncertainties through the model to generate a probability density function of the outcome values; and,
- (v) derive confidence limits and intervals from the probability density function of predicted values of the outcome variable.

The relationship between variance in model parameter inputs and the variance in the model predictions are estimated using variance propagation methods. Exact analytical, approximate analytical, and statistical simulation methods are available that can be used to propagate variance.

## **7.4 Uncertainty and variability in hazard identification**

The hazard identification step involves the determination that a health hazard is or may be associated with a biological, chemical, or physical agent present in foods. The step is generally based on screening methods and short and long-term cell or animal assays. Some examples and assay systems include quantitative structure-activity relationships, short-term bioassays, and animal bioassays. This step provides a dichotomous answer - that is, the factor



is or is not thought to be a human health hazard. The uncertainty involves the correct classification of the agent (i.e., it is or is not a human health hazard) and performance of the assay in classification of the agent. If the agent is evaluated in the assay multiple times, it is predicted to be either positive or negative with a certain degree of precision that is related to the performance of the assay. For example, one assay used to determine if a chemical is a mutagen is the Ames bacterial revertant assay. Uncertainty associated with the analysis of a chemical in this assay derives from knowing whether the assay is actually capable of predicting whether a positive response (or negative response) means that the chemical is capable (or incapable) of producing cancer in humans. The performance of the assay involves determining how the same chemical is characterized if analyzed in this assay system at several different times and in different assay systems.

Three issues are considered potentially significant contributions to uncertainty and variability in hazard identification. First, is the misclassification of an agent - either identification of an agent as a hazard when it is not or the reverse. Second, is the issue of the reliability of the screening method both for appropriately identifying a hazard and the reliability of the assays to give the same result each time the assay is performed. Third, is the issue of extrapolation because all screening methods are used to extrapolate the information provided by the test to predict human hazards. Epidemiological studies are used to predict the impact of exposures on human populations in the future. As an example, in epidemiological studies, the extent of the extrapolation needed to predict health hazards for future human populations is generally minimal; whereas, other assays have substantially greater need for extrapolation to produce predictions of potential adverse health effects for human populations.

## **7.5 Uncertainty and variability in hazard characterization**

Hazard characterization is the process of defining the site, mechanism of action and at minimum the dose-response (proportion responding or severity of response) relationship. In this step, it is likely that a series of models may be developed. The models vary from purely mathematical representations to biologically-based representations. As a result, each has varying degrees of representation of the actual human disease process and as a result varying degrees of uncertainty.

Model uncertainty is likely to be an important issue in the hazard characterization step. Mathematical dose-response relationships have the greatest uncertainty in actual representation of the biological processes. Despite the admitted large uncertainty, dose-response models are currently the most commonly used methods for predicting human health effects and have often proved useful in establishing policy. As interest in risk assessment has grown, the sophistication of the models, including the accuracy and completeness of their representation of the biological processes, has also grown.

An important issue of both variability and uncertainty that arises in hazard characterization is in the variance in the dose-response at the dosage levels for the species studied. To increase power and the value of a negative study, typically large exposures are used in bioassays. These exposures are generally substantially greater than usual human exposures. That means that models including exposure response information gathered at high exposures may not be accurate at the low exposure levels of concern for human risk assessment. In addition, there is variance by animals in response at a given dose, despite the fact that most experimental animals are generally inbred and expected to be genetically identical. If outbred animals are used, the variability in the dose response relationship is expected to be larger, and if humans are exposed, the variance is also expected to be large.

Another issue of both uncertainty and variability that arises in hazard characterization is the need to extrapolate between species. Approaches used for extrapolation between species include both uncertainty about the appropriate model for performing the extrapolation as well as variability in the parameters used for extrapolation.

## **7.6 Uncertainty and variability in exposure assessment**

Any model used to represent exposure should include several pieces of information:

- (i) the level of an agent measured in a commodity or the levels measured in soil, plants, or animals that supply this commodity;
- (ii) the depletion/concentration ratio which defines changes in the level of an agent as a result of processing, preparation, and dilution;
- (iii) the frequency and magnitude of human intake of a commodity;
- (iv) the duration of contact or the fraction of a lifetime during which an individual is exposed to a commodity; and,
- (v) the averaging time for the type of health effects under consideration to be clinically detectable.

These factors typically converge in the process of defining the distribution of population exposure.

The population at risk for exposure refers to the population that consumes food containing the hazard. An exposure assessment is the key input to the assessment of dose, which reflects the amount of the agent delivered to the target organ or tissue, where the adverse effect can be induced.

Defining exposure pathways is an important component of the exposure assessment. An exposure pathway is the course a biological, chemical, or physical agent takes from a known source to an exposed individual. In the case of agents in food, concentrations of chemicals and/or organisms (microbes, parasites, etc.) can change between what is measured in soil,

plants, animals and raw food and what is ingested by an individual. In the case of chemicals, there can be some increases of contaminant concentration due to process (i.e. distillation), but more likely the storage, processing and preparation of the food product will result in a reduction of contaminant concentration. For organisms, there might be significant increases of microbe or contaminant concentration due to replication under favorable environmental conditions. Thus, significant uncertainties might be expected in the ratio of the concentration of a bacterial agent in food at the time of consumption to the concentration measured in raw foods or measured in animals, plants, or soil.

## 7.7 Uncertainty and variability in risk characterization

Once hazard characterization and exposure information have been collected, risk characterization is carried out by constructing a model for the distribution of individual or population risk. This is done by summing the effect over all exposure routes. Because of the uncertainties and variabilities involved in its constituent steps, the overall process of risk characterization might involve potentially large uncertainties.

An important final step in the risk characterization process is the characterization of uncertainties. In order to directly characterize uncertainties in risk assessments, it is necessary to take a tiered approach to uncertainty analysis. Three tiers can be used. First, the variance of all input values should be clearly stated and the impact of these variances on the final estimates of risk assessed. Second, a sensitivity analysis should be used to assess how model predictions are impacted by model reliability and data precision. The goal of a sensitivity analysis is to rank the input parameters on the basis of their contribution to variance in the output. Finally, variance propagation methods should be used to carefully map how the overall precision of risk estimates is tied to the variability and uncertainty associated with the models, inputs, and scenarios.

## 8. CONCLUSIONS AND RECOMMENDATIONS

### 8.1 General

The Consultation recognized that increased scientific, legal and political demands are being made on the standards, guidelines and other recommendations elaborated by Codex. This is, in part, due to:

- increased consumer interest in food safety
- the WTO's SPS and TBT Agreements
- harmonization initiatives
- calls for increased scientific rigour
- the need for transparency
- shrinking national regulatory resources.

To respond to these increasing demands, the greater application of risk assessment in the Codex decision-making process is essential. However, the generic framework for risk

assessment described here represents a structural goal and may not be able to be fully utilized when adopting a risk assessment approach for some classes of hazards in food, such as biological hazards. In this respect, the Consultation recognized that Codex must be "technology forcing" if necessary data are to be developed.

An important principle is the functional separation of risk assessment from risk management. However, certain interactive elements are essential for a systematic risk assessment process. These elements may include ranking of hazards in the hazard identification step and risk assessment policy issues. Where risk management issues may intrude in risk assessment, the decision-making process should be transparent.

The broad mandate of a risk assessment approach to food safety encompasses a range of activities in addition to elaboration of standards, guidelines and other recommendations. Examples are the design of import and export inspection systems, acceptance/rejection criteria for foods, monitoring and surveillance programmes, development of information needed to formulate efficacious management strategies, and the overall allocation of food safety regulatory resources proportional to all classes of hazards in food. In the future strategic plan for utilization of risk assessment, this broad mandate should be addressed whenever appropriate in the Codex system.

Finally, the Consultation recognized that additional consultations would need to be convened regarding specific issues in risk assessment, as well as generally addressing the topics of risk management and risk communication. Nevertheless, the Consultation concluded that implementation of its recommendations would contribute significantly to the ability of Codex to meet its responsibilities of protecting consumers and facilitating international trade in food in a more consistent and open manner.

## **Recommendations**

- 8.1.1 Scientific risk assessment should be the basis for Codex risk management decisions involving health and safety aspects of food standards. An important principle in this regard is the functional separation of risk assessment from risk management, while recognizing the interactive elements that are essential for a pragmatic risk analysis approach.
- 8.1.2 In regard to chemical hazards, the Codex should assure harmonized approaches to the risk assessment of food additives, contaminants, and residues of pesticides and veterinary drugs, particularly in the assessment of exposure.
- 8.1.3 Codex should encourage the development of risk assessment for biological hazards with the recognition that scientific understanding and knowledge are not currently adequate to quantitatively assess risk in most instances.
- 8.1.4 To meet its obligations under the SPS Agreement, Codex must be "technology forcing" to develop the necessary scientific information for the risk assessment of chemical and biological hazards.

## 8.2 Chemical hazards

Risk assessment of chemical hazards in foods usually results in the selection of risk management options to ensure that foodborne risks to consumers are not appreciable (notionally "zero"). This approach to food safety needs to be carefully examined with respect to the intent of the SPS Agreement and the concepts of "acceptable risk" and equivalence. For chemical hazards not evaluated by means of an authentic quantitative risk assessment model, issues of equivalence may take the form of a comparison of equivalent margins of safety above this notionally "zero" risk baseline.

### Recommendations

- 8.2.1 Exposure assessments for food additives, contaminants, and pesticide and veterinary drug residues should be considered an integral part of the Codex risk assessment procedure for these substances. Because this is primarily a scientific task, exposure assessments should continue to be carried out by the JECFA/JMPR. Where necessary, exposure assessment should be expanded to take into account differences in dietary patterns, both within and between countries, and include estimates of intake by especially vulnerable groups.
- 8.2.2 CAC should request all Member States to make available dietary exposure data, including information on levels of chemicals in various foods and intakes of those foods by their population. Where such information is not available, CAC should encourage countries to develop appropriate food contamination monitoring programmes consistent with national priorities and to obtain dietary intake information for the general population and, if feasible, sub-groups of interest.
- 8.2.3 The methodology and guidelines currently used for predicting the dietary intake of pesticide residues should be reviewed with a view to obtaining more accurate estimates of human exposure.
- 8.2.4 Consideration of exposure scenarios for acute and chronic adverse health effects should be applied wherever appropriate in risk assessment of residues of veterinary drugs.
- 8.2.5 For contaminants for which adequate data exist and no threshold for adverse health effects can be established, JECFA should be requested to provide a quantitative estimate of the health risks associated with specified levels of intake, including attendant uncertainty.
- 8.2.6 The process by which the JMPR derives MRLs should be made more transparent.
- 8.2.7 To promote the transparency and credibility of the risk assessment process and to facilitate review of the proceedings when necessary, it is recommended that decisions be thoroughly documented and that all significant supporting data and other information be archived. This information should be available to Member States and to appropriate oversight international organizations.

- 8.2.8 To promote the quality and consistency of toxicological and other data, FAO and WHO should encourage the use of standardized test protocols and minimum data requirements that have been or will be recommended by recognized international expert groups.
- 8.2.9 WHO should review criteria for establishing safety factors, benchmark doses and generic cross-species scaling factors, taking into account the efforts that are being made by other international groups.
- 8.2.10 Scientific data are often necessary to depart from default assumptions, particularly in the evaluation of carcinogenic risk. Codex should encourage efforts to develop scientific criteria to help resolve differences in the requirements for and interpretations of such data.

### **8.3 Biological hazards**

Biological hazards in foods continue to pose significant risk and have a high profile internationally. There is a need to reduce the risk to the minimum which is technically feasible and practical. International standards and guidelines developed to address risk reduction must be transparent and outcome oriented. To facilitate this, risk assessment techniques must be applied to determine the significance of hazards and be used as a tool to evaluate risk management strategies such as HACCP. The utilization of risk assessment techniques to provide an estimate of potential adverse health effects will be an essential component of the process for establishing international trade policies. Additional information must be developed in order to facilitate quantitative approaches to risk assessment for biological agents. At present however, a qualitative approach is the only one available for accomplishing such a risk assessment. Therefore, the CAC should produce an overall strategy and implementation plan to address the following recommendations.

#### **Recommendations**

- 8.3.1 The standards, processes and procedures relating to biological hazards and contained within Codex standards and codes of practice should be based on sound science and quantitative risk assessment to the maximum extent possible. This would imply an analysis of individual biological hazards in a broad range of foods, rather than the study of multiple risks associated with single foods.
- 8.3.2 Where Codex produces standards or codes of practice that contain processes and procedures, the intended outcome of the processes or procedures in terms of food safety should be clearly stated.
- 8.3.3 Guidance should be provided to enable assessment of equivalence of alternate processes or procedures that meet the intended outcome.
- 8.3.4 Consideration should be given to a means of comparing relative risk of different options being considered to control a hazard. Overall minimization of risk of adverse effects should be the goal and CAC should consider not only relative risks of biological origin but all potential risks.

- 8.3.5 A review should be undertaken of the risk analyses implied by the use of 2- and 3- class sampling plans for microbiological end-product specifications, especially in the light of the wider use of HACCP based systems and the improved process controls which result.
- 8.3.6 Specific research directed towards identifying and characterizing biological hazards of concern should be encouraged by the CAC to enable more quantitative risk assessment.
- 8.3.7 Quantitative methods of risk assessment should be developed for biological hazards to facilitate and improve the application of HACCP.

#### **8.4 Uncertainty and variability**

Many sources of both uncertainty and variability exist in the process of risk assessment of foodborne hazards to human health. Explicit consideration should be given to uncertainty and variability in the risk assessment process so that these may be taken into account in the formulation of risk management policies.

#### **Recommendations**

- 8.4.1 The limitations of the risk characterization methods presented here make clear that risk managers should be aware of the uncertainty in risk estimates and include this awareness in their decisions and their communications of risk to the public.
- 8.4.2 This situation suggests the need to consider carefully the uncertainties of model assumptions and inputs so that effort is directed at those components having the largest contribution to overall variance in model predictions.

ANNEX 1

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## ANNEX 2

## LIST OF WORKING PAPERS

A number of working papers were presented over the course of the Consultation and served as the basis for the discussions which led to the development of the report recommendations. The titles of the working papers and author information is listed in this Annex. Some of the working papers may be published in the scientific literature: all enquiries should be directed to the contacts listed below.

TITLE	AUTHOR(S)	CONTACT
Overview of the Risk Analysis Approach and Terminology: The Merging of Science, Judgement, and Values (CONRIS 95/2A)	Dr T.E. McKone	Chief, Food Quality and Standards Service, FAO, Rome, Italy
Risk Assessment and Foodborne Microorganisms: The Difficulties of Biological Diversity (CONRIS 95/2B)	Dr D.T. Bernard and Dr V. N. Scott	Chief, Food Quality and Standards Service, FAO, Rome, Italy
Risk Assessment Activities of the International Programme on Chemical Safety (IPCS) - an Overview (CONRIS 95/3A)	Dr J. L. Herrman and Dr C. Sonich-Mullin	Programme on Chemical Safety, WHO, CH1211, Geneva, Switzerland
The Experience of the OIE in Applying Risk Analysis in Zoonosanitary Issues (CONRIS 95/3B)	Dr R. S. Morley	International Organization for Epizootics, 12 rue de Prony 75017, Paris, France
Considerations in the Practical Application of the Risk Assessment Approach - Theory -vs- Practice (CONRIS 95/4A)	Dr J. V. Rodericks	Environ International Corp., 2350 North Fairfax Drive, Arlington, Virginia 22203, USA
A Framework for Environmental Risks.(CONRIS 95/4B)	Dr D. Mattison	Graduate School of Public Health, University of Pittsburg, 130 Desoto Street, Pittsburg, PA 15261, USA
Addendum to: Risk Assessment Procedures used by the Codex Alimentarius Commission, its Subsidiary and Advisory Bodies ALINORM 93/97 (CONRIS 95/5)	Dr S.C. Hathaway	Chief, Food Quality and Standards Service, FAO, Rome, Italy

ANNEX 3

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