

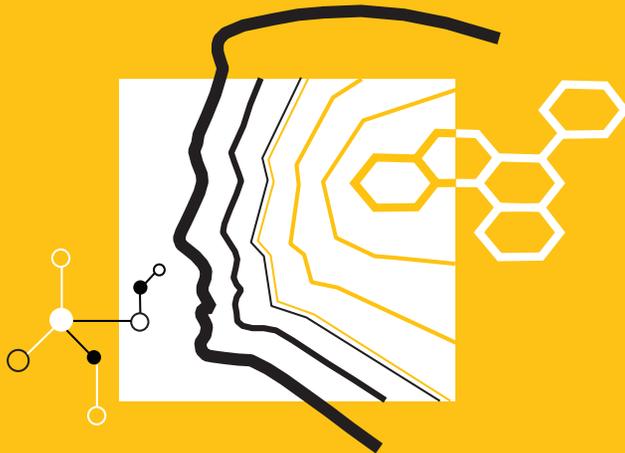
IPCS

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY



Environmental Health Criteria 240 Principles and Methods for the Risk Assessment of Chemicals in Food

Chapter 2 RISK ASSESSMENT AND ITS ROLE IN RISK ANALYSIS



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



Food and Agriculture
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the United Nations



World Health
Organization

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Environmental Health Criteria 240

PRINCIPLES AND METHODS FOR THE RISK ASSESSMENT OF CHEMICALS IN FOOD

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

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



**Food and Agriculture
Organization of the
United Nations**



**World Health
Organization**

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

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

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2. RISK ASSESSMENT AND ITS ROLE IN RISK ANALYSIS

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2.1 Introduction

The Joint Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO) Expert Committee on Food Additives (JECFA) and the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) have provided scientific advice to Member States of FAO and WHO since 1956 and 1961, respectively, and to several general subject committees of the Codex Alimentarius Commission (CAC) since its formation in 1963. However, the structural framework for the interaction between both scientific bodies and the Codex committees was not formalized until the development and the adoption of the risk analysis paradigm.

Risk analysis has been defined by CAC as “a process consisting of three components: risk assessment, risk management and risk communication”, which are themselves defined as follows (FAO/WHO, 2008):

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

- *Risk assessment*: A scientifically based process consisting of the following steps: 1) hazard identification, 2) hazard characterization, 3) exposure assessment and 4) risk characterization.
- *Risk management*: The process, distinct from risk assessment, of weighing policy alternatives, in consultation with all interested parties, considering risk assessment and other factors relevant for the health protection of consumers and for the promotion of fair trade practices and, if needed, selecting appropriate prevention and control options.
- *Risk communication*: The interactive exchange of information and opinions throughout the risk analysis process concerning risk, risk-related factors and risk perceptions, among risk assessors, risk managers, consumers, industry, the academic community and other interested parties, including the explanation of risk assessment findings and the basis of risk management decisions.

The risk analysis paradigm (see [Figure 2.1](#)) is a formal description of the risk analysis process that emphasizes the functional separation of its three components while at the same time demanding the need for communication and interaction between those with responsibility for each of the three components. Within risk analysis, the functional separation between risk assessors and risk managers is essential to ensure scientific objectivity of the risk assessment process. Further background information can be found in an FAO/WHO publication on food safety risk analysis (FAO/WHO, 2006).

The use of a structured risk analysis process facilitates consistent, science-based and orderly decision-making in the area of food safety. The scientific part of this process, the risk assessment for food safety matters, is undertaken at an international level by joint FAO/WHO expert bodies. JECFA and JMPR, the expert committees that deal mainly with chemical risks in food, base their evaluations on scientific principles and ensure necessary consistency in their risk assessment determinations. CAC and its respective committees that deal with chemicals in food are responsible, as risk managers, for the final decisions on establishing maximum limits for pesticide residues, veterinary drug residues, contaminants and additives in food and adopting other related measures.

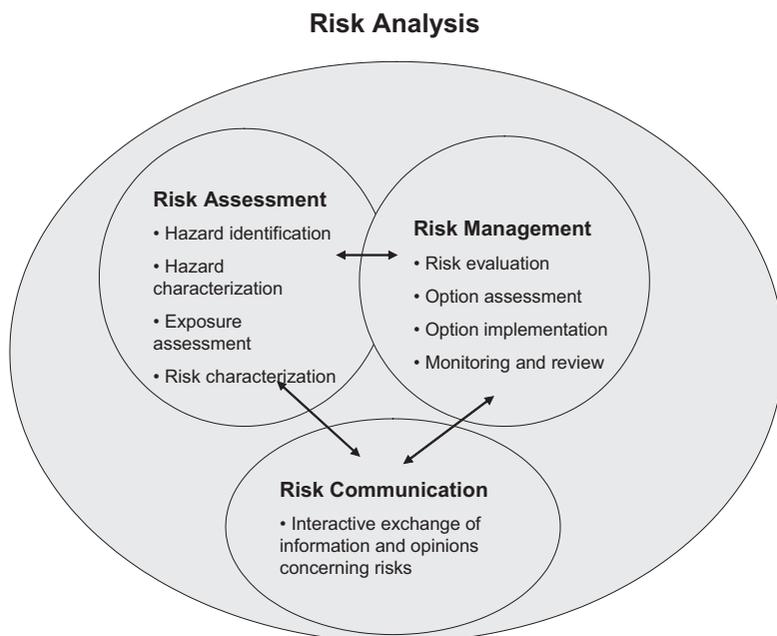


Fig. 2.1. Risk analysis (adapted from FAO/WHO, 1997)

As part of the discussion that led to the adoption of the risk analysis paradigm, CAC recognized the need to revisit existing risk analysis approaches as applied by Codex committees and JECFA/JMPR. At its request, three consecutive expert consultations were held by FAO and WHO, which focused on risk assessment (1995), risk management (1997) and risk communication (1998) as related to food safety (FAO/WHO, 1995, 1997, 1999).

2.2 Definitions of hazard and risk

The first consultation (FAO/WHO, 1995) explored the risk analysis domain and focused on risk assessment. The consultation was also aware of the need for uniform terminology on risk analysis in the work of Codex and considered risk analysis definitions from different sources. The consultation drafted definitions of risk analysis terms related to food safety and recommended them to CAC. CAC subsequently amended these definitions and published them in the Procedural Manual (FAO/WHO, 2004). The definitions of two terms,

hazard and risk, should be mentioned in particular, as they are fundamental in the risk analysis process, but differentiating words for these two terms do not exist in many languages. Codex has adopted the following definitions for hazard and risk in relation to food that cover not only chemical agents, but also biological and physical agents:

- *Hazard*: A biological, chemical or physical agent in, or condition of, food with the potential to cause an adverse health effect.
- *Risk*: A function of the probability of an adverse health effect and the severity of that effect, consequential to a hazard(s) in food.

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

- *Hazard*: Inherent property of an agent or situation having the potential to cause adverse effects when an organism, system or (sub)population is exposed to that agent.
- *Risk*: The probability of an adverse effect in an organism, system or (sub)population caused under specified circumstances by exposure to an agent.

These IPCS definitions apply to all areas of chemical risk assessment that most clearly describe the approaches of JECFA and JMPR, and therefore they are used in this monograph.

2.3 Role of risk assessment in risk analysis for food chemicals

Risk assessment is the central scientific component of risk analysis and was developed primarily because of the need to make decisions to protect health in the face of scientific uncertainty. Risk assessment

of food chemicals can be generally described as characterizing the potential hazards and the associated risks to life and health resulting from exposure of humans to chemicals present in food over a specified period.

Risk managers decide eventually whether a risk assessment is possible and necessary and commission the risk assessment, carrying out tasks such as describing the purpose of the risk assessment and the food safety questions to be answered, establishing a risk assessment policy, setting time schedules and providing the resources necessary to carry out the work.

Risk assessment of chemical substances used on or present in food is one of the key components of the work of JECFA and JMPR. Risk assessment provides the scientific basis for the risk management executed by CAC and its member governments. Accordingly, aspects of this component are examined in more detail in this monograph, whereas the other two components of risk analysis, risk management and risk communication, are not further discussed.¹

2.4 The four steps of risk assessment for food chemicals

Risk assessment (in particular in the food context, also often called “safety assessment”), comprising the four steps of hazard identification, hazard characterization (including dose–response assessment), exposure assessment and risk characterization, is a conceptual framework that, in the context of food chemical safety, provides a mechanism for the structured review of information relevant to estimating health outcomes in relation to exposure to chemicals present in food. In this monograph, the terms “risk assessment” and “safety assessment” are used interchangeably.

Risk assessment can include a key component in which the probability of harm is estimated. As a probability calculation, a risk assessment will include both a statement of the nature of the harm and the basis for the assertion that the harm may occur (i.e. the probability).

¹ The interested reader is referred to other publications for further background reading, such as those recommended in FAO/WHO (2006).

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

As discussed previously, the work of JECFA and JMPR is best described making reference to the definitions that have been developed and confirmed by IPCS in the ongoing project on Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals (IPCS, 2004). These definitions are the ones discussed in the following sections and used, where applicable, in this monograph. The differences between these definitions as applied by JECFA/JMPR and those used by Codex are important but do not affect communication and the joint work of risk assessors and risk managers, if taken into account consciously.

2.4.1 Hazard identification

Hazard identification is defined as follows (IPCS, 2004):

The identification of the type and nature of adverse effects that an agent has an inherent capacity to cause in an organism, system, or (sub)population. Hazard identification is the first stage in hazard assessment and the first of four steps in risk assessment.

The purpose of food chemical hazard identification is to evaluate the weight of evidence for adverse health effects, based on assessment of all available data on toxicity and mode of action. It is designed to primarily address two questions: 1) the nature of any health hazard to humans that an agent may pose and 2) the circumstances under which an identified hazard may be expressed. Hazard identification is based on analyses of a variety of data, ranging from observations in humans or domestic animals and studies in laboratory animals and *in vitro* laboratory studies through to analysis of structure–activity relationships. From the range of studies and observations available, the nature of any toxicity or adverse health effects occurring and the affected target organs or target tissues are identified.

2.4.2 Hazard characterization

Hazard characterization is defined as follows (IPCS, 2004):

The qualitative and, wherever possible, quantitative description of the inherent properties of an agent or situation having the potential to cause adverse effects. This should, where possible, include a dose–response assessment and its attendant uncertainties. Hazard characterization is the second stage in the process of hazard assessment and the second of four steps in risk assessment.

Hazard characterization describes the relationship between the administered dose of, or exposure to, a chemical and the incidence of an adverse health effect. The critical effect—that is, the first adverse effect observed as the dose or exposure is increased—is determined.

In cases where the toxic effect is assumed to have a threshold, hazard characterization usually results in the establishment of health-based guidance values—for example, an acceptable daily intake (ADI) for additives or residues or a tolerable intake (TI) for contaminants.

For some substances used as food additives, the ADI may not need to be specified; in other words, no numerical ADI is considered necessary. This may be the case when a substance is assessed to be of very low toxicity, based on the biological and toxicological data, and the total dietary intake of the substance, arising from the levels used in foods to achieve the desired function, does not represent a hazard.

2.4.3 Exposure assessment

Exposure assessment is defined by IPCS (2004) as follows: “Evaluation of the exposure of an organism, system, or (sub)population to an agent (and its derivatives). Exposure assessment is the third step in the process of risk assessment.”

According to CAC, the exposure assessment of food chemicals may be described more narrowly as “The qualitative and/or quantitative evaluation of the likely intake of chemical agents via food as well as exposure from other sources if relevant” (FAO/WHO, 2008).

In the case of food chemicals, dietary exposure assessment takes into consideration the occurrence and concentrations of the chemical

in the diet, the consumption patterns of the foods containing the chemical and the likelihood of consumers eating large amounts of the foods in question (high consumers) and of the chemical being present in these foods at high levels. Usually a range of intake or exposure estimates will be provided (e.g. for average consumers and for high consumers), and estimates may be broken down by subgroup of the population (e.g. infants, children, adults).

2.4.4 Risk characterization

Risk characterization is defined by IPCS (2004) as follows:

The qualitative and, wherever possible, quantitative determination, including attendant uncertainties, of the probability of occurrence of known and potential adverse effects of an agent in a given organism, system, or (sub)-population, under defined exposure conditions. Risk characterization is the fourth step in the risk assessment process.

This definition of the final step of risk assessment is, if restricted to the population of consumers only, practically identical to the one agreed to and used by Codex (FAO/WHO, 2008).

In risk characterization, the information from the intake or exposure assessment and the hazard characterization is integrated into advice suitable for decision-making in risk management. Risk characterization provides estimates of the potential risk to human health under different exposure scenarios. It should include all key assumptions and describe the nature, relevance and magnitude of any risks to human health.

The information and advice provided to risk managers may be qualitative or quantitative. Qualitative information may include:

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

Quantitative information may include:

- a comparison of dietary exposures with health-based guidance values;

- estimates of risks at different levels of dietary exposure;
- risks at minimum and maximum dietary intakes (e.g. nutrients); and
- margins of exposure.

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

2.5 Interactions between risk assessment and risk management

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

Within the framework of CAC, the responsibilities of the Codex committees as risk managers and the expert committees as risk assessors are defined in more detail in Section III of the Codex Procedural Manual (FAO/WHO, 2008). This section of the Procedural Manual also addresses specific risk analysis principles and risk assessment policies employed by JMPR and the Codex Committee on Pesticide Residues (CCPR) and by JECFA and the Codex Committee on Food Additives (CCFA), the Codex Committee on Contaminants in Food (CCCF) and the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) (FAO/WHO, 2008).

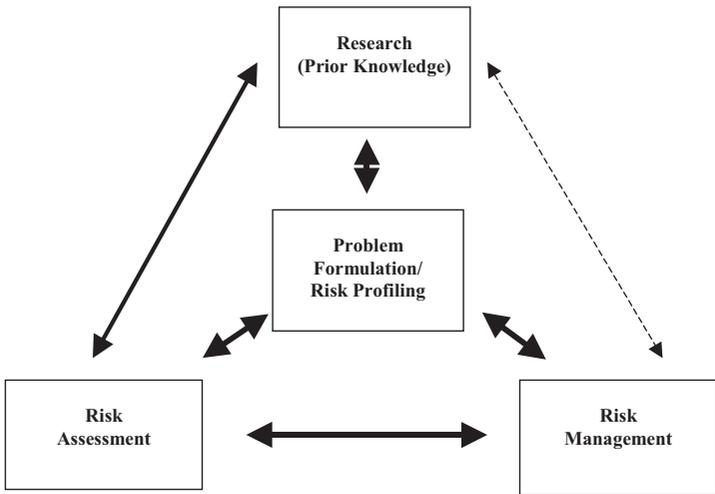


Fig. 2.2. Interactions of risk assessment with risk management

2.5.1 Problem formulation

As a general rule, formal risk assessments are preceded by a preliminary consideration of the necessity for a risk assessment and its objective. These may be subjective and informal and may be initiated either from inside or outside the risk management, risk assessment and scientific communities. The transition process from preliminary considerations to formal risk assessments has been described as problem formulation or risk profiling (Renwick et al., 2003). It is an iterative process involving risk assessors and risk managers that determines the need for—and, if needed, the extent of—a risk assessment. Communication with other interested parties (stakeholders) is particularly important during problem formulation.

Within the risk analysis process that addresses chemicals in foods, problem formulation describes the food safety problem and its context, in order to identify those elements of hazard or risk associated with a chemical that are relevant to potential risk management decisions. Problem formulation would include identifying those aspects relevant to prioritization in relation to other food safety problems, the establishment of risk assessment policy, including the choice of acceptable levels of risk, and identification of management options. A

typical problem formulation in case of chemical risk analysis might include the following:

- a brief description of the intended application of the product (e.g. food additive) and the commodities involved;
- the issues expected to be affected (e.g. human health, economic concerns) and the potential consequences;
- consumer perception of the hazards or risks;
- the distribution of possible risks among different segments of the population; and
- possible benefits associated with the use of the chemical in food.

The output is a plan for the risk assessment process for an identified chemical substance and potential hazard, which can be changed as the risk assessment progresses. The desired outcomes of problem formulation are 1) the questions that need to be answered under risk characterization to meet the needs of the risk manager, 2) determination of the resources that are needed and available and 3) the time frame for completing the assessment. For defined categories such as food additives or residues of pesticides, formal plans or procedures are in place that define the questions to be posed and the data necessary for initiating a risk assessment.

2.5.2 *Priority setting for JECFA and JMPR*

The selection of new or existing chemicals for consideration by JECFA or JMPR and recommending priorities for review are the responsibility of FAO and WHO, their Member countries and CAC, through its committees. For JECFA, these committees include CCFA, CCCF and CCRVDF. For JMPR, the primary source of input is CCPR. The protection of human health should be the main criterion for prioritization for risk assessment. The exposure levels and toxicity of the substance and the existence of particularly susceptible populations are key determinants that impact human health. However, the lack of available data may also be a factor in prioritization for risk assessment.

Re-evaluation may be particularly of high priority for substances for which new data raise suspicion of significant hazard, where there is

evidence to question the validity of the data submitted for the previous evaluation or with a previously allocated temporary ADI.

The FAO and WHO Joint Secretaries for JECFA and JMPR, as representatives of their respective organizations, have the final responsibility and authority for the determination of the priorities of substances to be evaluated in their respective areas. This can be dependent in part on available resources.

2.5.3 *Periodic reviews and specific re-evaluations*

JECFA and JMPR have indicated already during their initial deliberations on the principles they would apply in their work that it will be necessary to review assessed substances as new data become available. It was also recognized that safety assessments and resulting guidance such as an ADI for a specific substance would be subject to future modifications as a result of the accumulation of experience and improvements in toxicological methodology in general.

Reviews of past decisions on safety regarding food additives, contaminants and residues of pesticides and veterinary drugs may be necessary as a result of one or more of the following developments (adapted from FAO/WHO, 1970):

- a new manufacturing process;
- a new specification;
- new data on the biological properties of the compound;
- new data concerning the nature and/or the biological properties of the impurities present;
- advances in scientific knowledge relevant to the nature or mode of action;
- changes in consumption patterns, levels of use or dietary exposure estimates; and
- improved requirements for safety evaluation. These are made possible by new scientific knowledge and the quality and quantity of safety data considered necessary in the case of food additives and residues of pesticides and veterinary drugs.

For pesticide residues, at the request of CCPR or national governments, JMPR has always re-examined data supporting ADI estimates

and data on residue trials and registered use information supporting maximum residue limits (MRLs). Because MRLs are related to registered uses, when a registered use changes or is withdrawn, the remaining MRL may have to be revised. However, it is very difficult to know the registration status throughout the world, whether adequate data are available to support the current or revised MRL or if the MRL should be withdrawn. CCPR has a Periodic Review Programme in place that provides an opportunity for data submission for required compounds and MRLs, while introducing a timetable for ADIs and MRLs to be deleted if no data or inadequate data were provided. The first periodic reviews were carried out by JMPR in 1992 following wide discussion of the principles at CCPR sessions in 1991 and 1992 (FAO/WHO, 1991, 1992). CCPR applies criteria for periodic re-evaluation, such as the level of public health concern, available data, the elapsed time since the last toxicological review (>15 years) or issues in trade. JMPR will evaluate available studies according to modern scientific standards and will not rely on data submissions to FAO and WHO from previous years.

JECFA meetings on food additives, contaminants and residues of veterinary drugs and the relevant Codex committees have not established formal re-evaluation approaches as implemented for JMPR. On a case-by-case basis, either the risk assessor or the risk manager (or both together) will discuss and decide whether an existing risk assessment remains valid or requires an update in view of available data.

That a considerable amount of re-evaluation of substances is already carried out within the system is evident when the year-to-year agendas of JECFA and JMPR are examined. Temporary ADIs have been allocated by JECFA and JMPR to permit the acceptance of substances where there are sufficient data to conclude that the use of the substance is safe over the relatively short period of time required to produce further safety data, but are insufficient to conclude that the use of the substance is safe over a lifetime. An expiry date is generally established by which time appropriate data to resolve the safety issue should be submitted. JECFA, as part of its recommendations in the evaluation of specific contaminants, often makes requests for additional data and recommendations for subsequent re-evaluation.

Establishing a priority order for the re-evaluation of compounds requires input from a number of sources. Within the risk analysis

paradigm, the system for periodic review, including the determination of priorities for re-evaluation, is part of risk management and, for JECFA and JMPR, the responsibility of FAO, WHO and CAC, through its committees.

The following situations are triggers for prioritizing substances for re-evaluation:

- substances for which new data raise suspicion of significant hazard;
- substances for which there is evidence to question the validity of the data submitted for the previous evaluation;
- substances previously allocated a temporary ADI, where the requested additional data are available;
- substances whose re-evaluation has been requested by FAO or WHO; and
- substances whose re-evaluation has been requested by CAC.

The use of an international forum to devise and implement a system for the periodic review of chemicals used in or on food and contaminants of food could also be of great economic and practical value to Member States. It would ensure a uniform approach, duplication of effort would be minimized, and emphasis on such a programme would give added reassurance to consumers throughout the world that the food supply continues to be safe. Such a programme could be developed in cooperation with CAC.

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