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Food Safety in Europe (FOSIE): risk assessment of chemicals in food and diet: overall introduction

1. Introduction

Food safety policy in the European Union (EU) is based on a comprehensive, integrated approach of risk analysis throughout the food chain [from farm to table (EC, 2000a)]. Risk analysis has three main components: risk assessment (scientific advice and information analysis), risk management (regulation and control) and risk communication.

Risk assessment provides the scientific foundation upon which the risk analysis process is built. Risk assessment is defined as "A process of evaluation including the identification of the attendant uncertainties, of the likelihood and severity of an adverse effect(s) occurring to man or the environment following exposure under defined conditions to a risk source(s)" (EC, 2000b).

A risk assessment is comprised of hazard identification, hazard characterisation, exposure assessment and risk characterisation steps. For consistency in terminology in this project the terms developed in glossary (EC, 2000b) are used throughout (see Appendix 1 for further definition of terms).

The European Commission (EC) Scientific Steering Committee recognised the potential benefits of progressive harmonisation of human and environmental risk assessment procedures based on current scientific understanding in terms of:

- enhancing the quality of the risk assessment procedures
- achieving greater consistency when the same or very similar risk sources are assessed by different scientific committees
- improving transparency and risk communication
- enabling the EU to demonstrate externally a consistent high quality scientific approach for all risk assessments conducted on its behalf pertaining to the protection of human health and the environment.

The importance of harmonised science-based risk assessments is also recognised under the World Trade Organisation (WTO) where the "Agreement on the Application of Sanitary and Phytosanitary Measures" (SPS Agreement), specifically cites Codex standards, guidelines and recommendations as reflecting international consensus regarding the requirements to protect human health from foodborne hazards.

Therefore a project reviewing and updating the risk assessment of chemicals in food is a timely activity in the light of:

- the ongoing international harmonisation of WTO
- the setting up of the European Food Authority
- the need to identify key topics for consideration in the EU Sixth Framework allocation of funds for research.

In response to these developments, The International Life Science Institute—European branch (ILSI Europe) elaborated a project proposal for a European Concerted Action to critically examine and further develop the methodology of risk assessment.

2. Challenges to the current approaches of risk assessment

The current procedures employed for risk assessment have served well to protect human health; however, as in any scientific field there is always the need for reappraisal and improvement. The two main reasons driving the need/opportunity for improvement are as follows:

i. development of new scientific approaches and knowledge
ii. the need to assess the safety of new foods and food ingredients such as macronutrients and whole foods

These issues are briefly discussed below, following an outline of the current risk assessment approach.

Current approaches of risk assessment were developed principally for low molecular weight chemicals (such as food additives) added to or found in food. Most toxicological data for risk assessment are derived from animal studies, supplemented with in vitro studies to aid with mechanistic interpretation of results. It is essential for such studies to be conducted according to internationally accepted test protocols and methodologies that are appropriately validated. Validation in this context has multiple dimensions, one dimension is that

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the test system should be valid for its intended purpose, for example its ability to predict specific effects that may occur in humans. A further dimension is the validation of the test itself (i.e. accuracy and precision of the test when applied in different laboratories).

The in vivo studies should identify both the major toxic effects of the test compound and the intake level that does not result in adverse effects, that is the no-observed-adverse-effect level (NOAEL). The acceptable daily intake (ADI) may then be derived from the NOAEL by using uncertainty factors (sometimes referred to as safety factors) that take into account both the uncertainty of extrapolating results from animals to man and interindividual variation among humans. The ADI is an estimate of the amount of a compound that can be ingested daily over a lifetime without appreciable health risk (notional zero risk). Typically, no quantitative assessment of risk is made for the setting of the ADI, the risk is considered to be so small as to be negligible from the public health perspective.

Such a strategy requires that the dose or intake levels used in vivo are substantially greater than the expected level of exposure in man. This is feasible for the discretionary addition of low-level components (such as food additives) to food. However, it is technically not possible to use such high dose levels for in vivo studies on macro-constituents of the diet, as this would result in toxic effects related to nutritional disturbance from the test animals' diet. Therefore, new approaches are required under these circumstances.

In vitro studies are considered to help with hazard identification and mechanistic interpretation of the results from the in vivo studies. However, careful consideration should be given to an integrated approach for carrying out in vivo and in vitro studies to optimise the information required for an effective risk assessment (Hugget et al., 1996). Risk assessment is faced by many challenges, for example, the greatly increased sensitivity of analytical techniques that allow detection and measurement of chemicals in food at levels where little or nothing is known about the toxicological relevance.

The use of human (epidemiological) data has been very limited in this area until now and the challenge will be to integrate such data into the risk assessment process.

The use of biomarkers (i.e. any measurement reflecting an interaction between a biological system and an environmental agent) as surrogate measures of exposure, effect or susceptibility, constitute important tools for risk assessment. Bottrill (1998) extended the definitions where biomarkers of exposure include those for external dose, internal dose and biologically effective dose, while biomarkers of effect include those of early effects and of subclinical disease. Alternative approaches to definition and classifications of biomarkers have been undertaken (COST Action B15 report 2000); however, the definitions in Bottrill (1998) have been used in this project. The use of biomarkers in toxicological assessment is not new but extension of their use in, for example, carcinogenesis, poses difficult challenges for validation and acceptance.

Furthermore, the scientific advances in genomic understanding and the application of genomic and proteomic techniques offer exciting opportunities to improve the quality of risk assessment. However, as with any scientific advance, further work must be done to enable a meaningful interpretation of results to help with risk assessment. For example, it is necessary to understand whether the signals detected reflect an adverse change or merely an adaptive response to maintain homeostasis without toxicological consequence.

The increasing demand for risk assessment of food chemicals must be balanced against the need to apply the three R's (refinement, reduction and replacement) of animal studies. This poses in particular an ethical constraint, but there is also a practical consideration taking into account the limitation of the resources available for risk assessment. Therefore, it is essential to develop consistent and objective schemes to assess food chemicals. This will allow the setting of priorities for action that make optimal use of the limited resources available while retaining the highest standards of science and consumer protection. Allied to these approaches is the need to make better use of existing knowledge (for example through the use of bioinformatics) to avoid unnecessary repetition of toxicological studies.

3. The objectives of the project

The project "Food Safety in Europe: Risk Assessment of Chemicals in the Food and Diet" (acronym: FOSIE) is an EU Concerted Action funded via the EU Fifth Framework Programme. The aim of this project is to establish a multidisciplinary European network to critically examine and further develop qualitative and quantitative methodologies to assess risks from foodborne hazards.

The specific objectives can be summarised as:

1. To explore means of improving the principles applied to, and scientific basis of, risk assessment with respect to natural toxicants, food additives and contaminants in the food chain. To consider possible interactions between individual chemicals and effects of the food matrix.
2. To identify gaps in knowledge that might lead to differences in interpretation of toxicological and exposure data, and the research needs to reduce these.
3. To determine the nature and level of testing needed for safety evaluation relevant to the

nature of the chemical, level of use/occurrence in the diet and human exposure (including novel foods, nutritional supplements).
4. To add a European contribution to international initiatives to harmonise principles, terminology and methodology for risk assessment.
5. To contribute towards a consensus on risk assessment issues that is scientifically transparent and justifiable.
6. To assist risk managers in developing appropriate, defensible food standards that adequately protect the safety of the consumer while allowing for innovation in food production and processing.

There is general agreement on the stages involved in risk assessment however, it is not laid down how the risk assessment should be performed in practice and there is less agreement on requirements of each stage of the process or how some components of the overall data should be applied.

Individual Theme Groups (ITGs) were established to assess the current state of the art, to establish the science base for new risk assessment methodologies and to identify gaps in current knowledge and the research needs to fill these gaps. The ITGs were designed to address all the steps involved in risk assessment using a pragmatic approach. However, it was recognised that such an arbitrary separation based on the steps of risk assessment should not limit the coverage of the overlapping scientific issues, therefore the content of the ITGs is in some cases much broader than that inferred by their titles. The ITGs were organised as follows:

Hazard Identification:

ITG–Hazard identification by methods of animal-based toxicology

ITG–Methods of in vitro toxicology

Hazard Characterisation:

ITG–Dose–response, mechanisms and extrapolation issues

ITG–Mathematical modelling and quantitative methods

Exposure Assessment:

ITG–Assessment of intake from the diet

ITG–The contribution of epidemiology

Subsequently, the output of ITG will be integrated in a comprehensive appraisal of characterisation and quantification of risk in:

Risk Characterisation:

ITG G—Characterisation and quantification of risk

The project focuses on developing integrated approaches to improve the quality of risk assessments. The approach taken was not only to characterise the issues in need of resolution but also to identify methods and research needs for helping with their resolution.

4. Scope of the project

The word chemical in the project title is broadly applied to include compounds that occur naturally in food (phytotoxins, phycotoxins and mycotoxins); those introduced deliberately into the food chain (food additives, pesticides, and other agrochemicals, feed additives and veterinary drugs) and those present adventitiously in food (contaminants).

The food categories addressed by all ITGs in the project were as follows:

a. low molecular weight chemicals (such as food additives)
b. micronutrients and nutritional supplements
c. macronutrients
d. whole foods
e. novel foods
f. food processing.

Two topical and important food safety issues were not addressed in the project:

i. Risk assessment of genetically modified organisms (GMO) and derived ingredients in food. A separate EU funded thematic network called ENTRANSFOOD specifically covers this topic.
ii. Risk assessment of Transmissible Spongiform Encephalopathies (TSEs or prion diseases) the fatal brain diseases that occur in a number of mammalian species including humans, for example bovine spongiform encephalopathy (BSE) in cattle and in humans as a variant of Creutzfeldt–Jakob disease (vCJD). While this is recognised to be a very important issue for risk assessment, too little is known about the underlying mechanisms of disease transmission. The FOSIE project team did not have the appropriate expertise to cover this issue effectively. The Scientific Steering Committee of the EU is actively concerned with developing approaches to risk assessment of BSE (http://europa.eu.int/comm/food/fs/bse/index_en.html)

A decision was also taken not to consider risk evaluation (risk vs benefit) in the project. The analysis of benefit requires a separate paradigm to risk assessment and therefore considered to be outside the scope of the project. Certain risk vs benefit considerations are inherent in the risk assessment of specific food components for example, ensuring that there is a technical need for a new food additive. Furthermore, use of the 'as low as reasonably achievable' approach for certain contaminants (that is the concentration of a substance that cannot be eliminated from a food without discarding that food altogether or severely compromising the availability of the food

supply) weighs the risk of the contaminant against the benefit of the availability of a diversified food supply.

However, the weighing of risk vs benefit is not solely a scientific issue but also a societal decision to be undertaken by the risk (benefit) managers with guidance from risk assessors.

5. FOSIE — ways of working

Following acceptance of the project proposal a first plenary meeting was organised with invitations to recognised experts in the various stages of the risk assessment process. Brainstorming sessions took place for each theme group under an appointed ITG chairman. Agreement was reached on the composition (full and corresponding members) and work programme for each ITG. The work programmes were discussed in plenary session to ensure that neither gaps nor unnecessary overlaps were evident between ITGs.

Each ITG then held two to three meetings to ensure that the work programme was completed and a report prepared.

The ITG reports were reviewed in cross-ITG discussion groups to ensure a consistent approach and comprehensive coverage of the relevant issues. The ITG reports were then discussed at a second plenary meeting (with additional invitations made to risk assessment experts that had not participated in the project). This peer review process resulted in the publications that follow this introduction.

6. Risk characterisation

The seventh ITG (risk characterisation) began its work when ITGs were in the final stages of completion of their work on hazard identification, hazard characterisation and exposure assessment. ITG will evaluate and combine the output of the six ITGs into an integrated recommendation for risk characterisation. The output will include recommendations on dealing with variability and uncertainty and how the uncertainty can best be characterised to aid the risk managers' decision making. The report and recommendations on risk characterisation will be discussed in a final plenary meeting of the FOSIE project and the results will be published in a scientific journal. The final publication on risk characterisation will follow within approximately 1 year of the publications herein.

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