EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate C - Scientific Opinions
C1 - Follow-up and dissemination of scientific opinions

FIRST REPORT ON THE HARMONISATION OF RISK ASSESSMENT PROCEDURES

PART 1 :

The Report of the Scientific Steering Committee's Working Group on Harmonisation of Risk Assessment Procedures in the Scientific Committees advising the European Commission in the area of human and environmental health 26-27 October 2000

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1 EXECUTIVE SUMMARY

1.1 The principal purpose of this Report is to promote an active debate on current practices for risk assessment used by the Scientific Committees of DG SANCO and to make proposals for developing convergent approaches which will aid harmonisation.

Progressive harmonisation of human health and environmental protection risk assessment procedures within the EU is both of practical importance and scientifically sound. However, it is recognised that total harmonisation of risk assessment procedures in the EU is not achievable in the short to medium term.

1.2 DG SANCO Scientific Advisory Committees cover a very wide range of risk sources including:

- Agents (new and existing chemical, biological and physical agents);
- Complex media (e.g. food, air, water);
- Commercial and industrial processes from manufacture to disposal;
- Procedures (e.g. transport of animals, storage of materials);
- Specific localities.

Assessments may cover the risk to individuals, human population groups, workers, target species, fauna and flora or physical aspects of the environment. As far as the Committee is aware, this Report represents the first attempt by any body, national or international, to assess the extent to which such a broad spectrum of risk assessment activities could be harmonised.

1.3 The investigation has embraced both the scientific basis of risk assessment and the administrative / organisational framework in which it is conducted. The approach used has been to:

a) identify the current activities of each DG SANCO Scientific Advisory Committee in risk assessment. [NB: It is acknowledged that each committee also performs other tasks for DG SANCO and other DGs].

b) characterise any differences in risk assessment procedures between Committees and identify, where possible, the extent to which these differences reflect:
   - the needs inherent in the category of the risk sources involved;
   - variations in legislative / regulatory requirements;
   - historic, administrative or other influences.

c) evaluate how possible changes in technology, organisational support, and societal attitudes may influence risk assessment procedures.

d) determine those activities in which harmonisation of risk assessment procedure is both desirable and achievable.

1.4 The Report does not deal with technical details, nor with issues such as the harmonisation of test protocols. However, references are provided for these topics. In view of the scale of the task many issues have not been dealt with in depth. In this

sense the task set has not been completed. The has been produced by a Working Party of the SSC, comprising representatives of each Scientific Advisory Committee, plus a number of additional experts. It consists in two parts: Part 1 comprises a main section of 14 chapters (including this summary), a list of references, and membership of the Working Party and its working groups. Part 2 comprises 8 appendices which address specific issues.

1.5 The main recommendations drawn from the Report are as follows:

i) Standardise, as far as is practicable, the use of terminology (see Chapter 11 and Appendix 1). Currently there are no agreed definitions of terms. Moreover, a variety of terms are in use to describe apparently the same phenomenon, e.g. 18 different terms have been identified in the EU to describe *de minimis* risk. This is unnecessary and a potential source of confusion in risk communication. Proposals for definitions of terms are given in Appendix 1 of the Report.

ii) Standardise the format for the presentation of risk assessment findings (see Chapter 11 and Appendix 6). The Report identifies not only variations in the form of presentation of findings between committees, but also within committees. A format is recommended for future application by all the scientific committees.

iii) Enhance commonality in the working procedures of the committees (see Chapter 12). Among the key issues which have been identified are the need to improve the interface with and level of support from Commission officials, while preserving the independence of committee members. Agreed procedures for interaction with other stakeholders is also important.

iv) Establish a well resourced common facility for the ready provision of key information required by the committees for their risk assessment activities (see Chapters 5 and 6). This should include all the scientific data utilised by committees of the Commission on a particular risk source.

v) Ensure that all opinions include an expression of the degree of uncertainty in the risk assessment (see for example Chapter 9 and 11). This should be in a common style between committees where practicable. It is also recommended that work is conducted to identify possible bench marks against which a particular risk can be compared (risk comparison).

vi) Increase the post-marketing monitoring and surveillance of important new products (see Chapters 5 and 12). Consideration should be given to establishing a common “clearing house” in the commission to co-ordinate this very important activity.

vii) Develop formal means by which issues such as animal welfare, quality of life, socio-economic considerations, and sustainability can be incorporated into the risk assessment process (see Chapter 10).

viii) Give more attention to the environmental effects of products approved for marketing. While the environmental impacts of pesticides are subject to detailed study for other commercial products there is often cursory or no examination of their possible environmental effects (e.g. human medicines). A common framework for dealing with such environmental issues is highly desirable. This development would be assisted by the adoption of an integrated approach to risk assessment (i.e. examination of human and environmental risk assessments alongside one another) thereby facilitating each other assessment (this includes harmonisation of methodologies and models) (see Chapters 5 and 9).

ix) Develop, or contribute to the development of, data bases which enable structure activity relationships and vulnerable population groups to be identified (see Chapters 5 and 9). It is recognised that currently much of the data received by the Commission is classified as "in confidence" and is therefore not available for access by other committees. However, the achievement of more reliable risk assessments depends on better data bases (see also recommendation IV). It is unacceptable for new animal studies to be required if suitable data already exists. Means have to be found of accessing this confidential information while ensuring the commercial advantage of those producing it.

x) Characterise risk in a more quantitative form where appropriate. Techniques in quantitative risk assessment are developing quite rapidly. (See Chapter 8 and Appendices 3 and 4). Consideration should be given to the adoption of these techniques, where useful, by the scientific committees.

xi) Develop more standard scenarios for use in exposure assessment (see Chapter 7). At present, for example, there is no agreed "standard European diet" to be used for assessing exposure from contaminants, nor are there any commonly adopted mathematical models for calculating the distribution of substances released into the environment. Co-operation is required with other organisations to achieve this.

xii) Ensure that a regular review is carried out of technical developments relevant to risk assessments (see for example Chapter 6). For example, new more sensitive methods are likely to identify biological changes occurring below currently recognised threshold levels. It is important that committees have a common approach on which biological changes are deemed "adverse" and which are not.

xiii) Establish an induction programme for new committee members and regular workshop programme for all members on key items such as risk communication (see Chapters 11 and 12). Facilitation of advanced training programmes across Member States is also required to ensure the availability of the necessary risk assessment expertise in the future.

xiv) Develop a formal link between the Scientific Advisory Committees related to DG SANCO and those other scientific advisory committees concerned with

risk assessment and human and environmental health in order that consistency is improved in advice throughout the Commission services.

xv) Ensure that there is a clear interface between completion of a risk assessment and the application of the Precautionary Principle.

1.6 Each scientific committee should be charged, by the SSC, with responding to the proposals for harmonisation set out in this Report.

1.7 The SSC should establish a task force to receive the responses of the scientific committees and to facilitate the implementation of those proposals deemed appropriate. The task force should also have the key role in identifying for the Commission new developments in risk assessment and areas in which there is scope for improving compatibility of approaches with other international and national bodies.

2 INTRODUCTION

"Out of this nettle, danger, we pluck this flower, safety"
William Shakespeare (1597)

Background and objectives

2.1 A “risk assessment” is required in an increasing number of human activities, ranging from prognoses for mental health patients, through industrial plant safety to sensitive ecological sites and consumer protection. High quality scientific advice for the drafting and amendment of Community rules, regarding Consumer Protection in general and Consumer Health in particular, is of the utmost importance. This is underlined in the Commission Communication on Consumer Health and Food Safety [COM (97)183, 30 April 1997]. Here, consumer health is regarded as including matters on public health, as well as animal health and welfare, plant health and environmental health. Other recent Commission Communications stress the importance attached to securing the health of workers.

2.2 Many issues relating to consumer health are of a multidisciplinary nature and require input from various scientific disciplines. Presently, the advice to the European Commission is provided via DG SANCO by a Scientific Steering Committee (SSC) and by eight additional Scientific Expert Committees (SEC): Food, Animal Nutrition, Animal Health and Animal Welfare, Veterinary Measures relating to Public Health, Plants, Cosmetic Products and non-food products, Medicinal Products and Medical Devices, Toxicity, Ecotoxicity and Environment. In addition, there are some scientific committees concerned with occupational, public and environmental health associated with other DGs.

2.3 The mandate of the DG SANCO Committees includes providing scientific advice or opinions on scientific and technical questions in their respective field of competence, following a request by the Commission relating to Community legislation or when any new development may cause concern for consumer or environmental health. In addition, Committees may have a proactive role. This is without prejudice to the specific competence given to other Committees (e.g. the Committees established in the European agency for the Evaluation of Medicinal Products, or the Scientific Committee for Occupational Exposure Limits to Chemical Agents). The advice and opinions of the Scientific Advisory Committees, in the interest of stakeholders, including consumers and industry, are based on the principles of excellence, independence and transparency.

2.4 The Commission Communication on Consumer Health and Food Safety (1997) established the tenet that "risk assessment forms the foundation of scientific advice with regard to consumer health. Scientific risk assessment offers the Commission a sound basis for proposals and measures in the field of consumer health and food safety". It is important that in providing this advice there is consistency on scientific matters within and between Committees.

2.5 The process of risk assessment may be summarised as the evaluation of the likelihood of an adverse effect(s) event(s) occurring under a defined set of conditions, together with a value judgement on the results. Risk assessment may be initiated for a variety of purposes, such as:

i) legal / regulating requirements
ii) political / public concern

iii) change in scientific knowledge leading to increased human and/or environmental health concerns
iv) new or rapidly emerging issue requiring policy advice
v) for harmonisation purposes between Member States
vi) a major increase in the use of a risk source or a change in the type of use.

2.6 Most commonly a risk assessment is triggered by a legal requirement. For many risk sources, a risk assessment is a prerequisite to obtain permission to market a product, build a facility, etc. Nevertheless, many products are marketed without a requirement for a risk assessment. A preliminary risk assessment may be required which will include requirements for further work before a product can be marketed. For example, a pre-clinical assessment of a drug may be required to enable full clinical trials to be initiated. A phased approach may also be adopted to identify the requirement for detailed environmental assessments. Risk assessments may also be conducted to establish whether corrective measures are needed for existing practices.

2.7 There is at present a general agreement that risk assessment is best addressed in four stages, i.e. hazard identification, hazard characterisation, exposure assessment and risk characterisation (see Appendix 1 for working definitions). These four stages are key common elements between all the Commission's Scientific Committees.

2.8 Currently, however, differences have been identified in the way risk assessments are conducted by the different Scientific Committees. The observed differences may, to a certain extent, be explained by a series of factors such as the specific characteristics of the technological sector, the availability of information and data, or by historical, administrative, legislative or regulatory requirements which, in a number of cases, impose constraints on how the risk from a particular factor should be assessed. These factors bear on the specific methodologies applied which may range in sophistication from crude algorithms to use of mathematical modelling and detailed prescribed procedures.

2.9 In view of the above, the adoption of identical approaches may not be an attainable goal. However, the Scientific Steering Committee expressed concern that unjustified differences may result in discrepancies, lack of transparency and difficulties in subsequent risk communication.

2.10 Therefore, the Scientific Steering Committee advised the Commission to establish a Working Party on "Harmonisation of Risk Assessment Procedures" (WP) to address specifically the general principles of risk assessment and its application to broad consumer health issues, with a particular reference to measures that would enhance compatibility of approaches between the Scientific Advisory Committees.

2.11 The key objectives of the Working Party, as delineated by the Scientific Steering Committee, were to:

- situate risk assessment in the consumer health context;
- explore underlying principles and key steps applicable to risk assessment;
- identify the range of important issues of common interest, involved in advancing, and where appropriate, ensuring compatibility of risk assessments within the Scientific Committees;

- produce a report which makes recommendations for progress towards harmonisation.

2.12 There is a number of reasons for giving further priority to the harmonisation of assessment within the Commission at the present time:

i) To aid transparency in risk communication

ii) To improve consistency. At present, the same chemical, biological or physical agent(s)/ risk factors may be dealt with quite independently by different Scientific and Expert Committees in different contexts resulting in potential inconsistency in the assessment and confusion in its application, at least as far as the grand public are concerned. For legal purposes, the decisions of these Committees are widely available and, since they may influence trade, may be challenged by national and international authorities.

iii) The procedures used have not been formally reviewed previously across a wide range of risk sources. To ensure the most appropriate development of risk assessment, it is crucial that in the European Community the risk assessment methodology is regularly reviewed and updated, and as far as reasonable, all assessments are based on the best scientific understanding rather than historic precedence.

2.13 While recognising that a completely common methodology for the activities of the Scientific Advisory Committees of the Commission services may not be achievable, there is very considerable potential value to be gained from developing more compatible approaches for risk assessment. Compatible approaches would, in particular:

- help to focus discussions by the scientific community on the generic issues of risk assessment, outside the sometimes charged context of particular sectors or regulatory frameworks;

- facilitate, where appropriate and feasible, the transfer of scientific advances from one sector to other sectors where risk assessment is less advanced;

- encourage the most appropriate development of the science base for risk assessment, and, where appropriate, ensure that assessments are based on the best scientific understanding rather than historic development or precedence;

- stimulate research interest and lead to evolutionary improvement in the methodologies utilised and thus in the quality of risk assessments;

- improve consistency in application of risk assessment techniques and aid the comparison of risks from different sources;

- facilitate the involvement of several Scientific Committees in dealing with complex issues where it is necessary to develop an integrated approach to include features not covered by one specific Committee while avoiding potential discrepancies;

- and, as a whole, ensure transparency and clarity both in the process and its presentation.

2.14 Furthermore, there is currently a strong trend, internationally, to formalise procedures for dealing with risk issues and to promote commonalties of approaches throughout the different sectors where risk assessment may be developed. In this regard, the identification of issues of common strategies and needs within the European Union would also contribute to bringing its risk assessment approaches in line with other international developments.

The Working Party's approach to its task

2.15 The Working Party developed its activities over one full year. Membership included experts appointed by the different Scientific Committees. In addition, several experts in aspects of risk assessment methodology, who were not members of the EU Scientific Committees, contributed to the discussions and activities of the Working Party and its working sub-groups. The remit of the Working Party was taken forward by a combination of structured discussions in plenary sessions, and activities in working groups and sub-groups. These were established on a temporary basis to tackle issues identified by the Working Party. They were charged with the development of working papers and reports to the Working Party for each of the issues considered. The findings from the working papers produced by the working groups and their sub-groups have been collated by the Working Party and merged in the core of this document. Some of their reports, dealing in depth with key areas, are reproduced in their entirety as appendices.

2.16 The Working Party agreed that its principal role was to address approaches to risk assessment and to make recommendations, while considering the potential for enhancing compatibility of approaches between the different Scientific Committees and where possible with advances of international bodies. This was facilitated by the fact that several members of the Working Party also serve on other International Committees such as JECFA and IPCS Committees, and/or on national committees of Member States. The Working Party determined that several tasks should be undertaken, with in depth consideration of specific areas of the risk assessment process being carried out:

a) To agree definitions as far as possible. The aim was to have a common glossary of terms compiled for all Scientific Committees which, as far as practicable, are common also to other international bodies.
b) To identify those papers/reports which are accepted as primary reference material(s) to serve as the initial working documents for the Working Party's task.
c) To explore underlying principles and key steps applicable to risk assessment, with a view of identifying the range of important issues involved in advancing, and where appropriate, enhancing compatibility of risk assessments.
d) To specifically discuss the issues involved in developing quantitative approaches to risk assessment in two horizontal domains : microbiological risk assessment (separate consideration being given to foods and other contaminated products, and to animal transmissible diseases) and risk assessment of toxic chemicals.
e) To aid the efficiency and utility of the Risk Assessments and suggest procedures intended to facilitate the dialogue between the risk managers defining the

questions and the risk assessors attempting to answer them, one important aspect of this dialogue being agreement on the degree of sophistication of the risk assessment required for risk management purpose.

Scope and use of this report

2.17 The primary intention of this Report is to outline approaches to risk assessment used by the different Scientific Advisory Committees and to identify general issues of common interest where further development work is required. It has not been the intention to provide a critical review of all current practices of these Committees, nor to address any issue in full detail. It is hoped that the SSC will agree to mandate a task force on the harmonisation of risk assessment to develop specific aspects of this Report.

2.18 This report considers *approaches* to risk assessment, issues of common interest or concern with regard to current procedures, areas on which the risk assessment process would benefit from increased compatibility, and areas where risk assessment procedures might be improved by targeted research and other means. It does not provide detailed guidance on *how* to carry out a risk assessment, neither does it delineate the specific processes, procedures or methods to be used to conduct a risk assessment in specific situations. It goes without saying that when risk assessments are performed, the accuracy of such assessments is directly related to the reliability of the data utilised and the expertise of those conducting the assessment. In discussing the risk assessment process, quality control procedures, although important, have not been considered in this report due to lack of time.

2.19 This report focuses on key aspects or issues in risk assessment and is intended as the first Report of several. It concentrates particularly on human health issues from chemical hazards. To a lesser extent it addresses microbiological and environmental stressors and does not cover risk assessment of physical factors. It does not address risk management nor risk communication in any detail (although these are important areas which would benefit from a more harmonised approach), except insofar as proposing a common format for expressing risks and suggestions as to how some interactions between risk assessors and risk managers might be improved to maximise the utility of risk assessment.

2.20 In sponsoring this report, it is the aim of the Scientific Steering Committee to make a contribution to the scientific debate on risk assessment, providing information on the application of current concepts, raising issues for improvement, and, where appropriate and feasible, enhancing compatibility of approaches. It covers many key areas, but is not intended to be exhaustive. The report's recommendations address these issues and suggest particular areas in which work should be progressed in order for the considerable and growing activity in the EU in the field of risk assessment is to realise its considerable potential value to the Commission. Since the Report covers a very wide field, it cannot be assumed that every member agrees fully with every point made in the Report.

2.21 Finally, it must be recognised that the contribution that this Report makes to the debate is at a specific point in time, whereas the process of risk assessment is still evolving. In this regard, it is hoped that this report will constitute the basis for a new

phase of activities. This might encompass for instance a detailed and critical examination of current practices in the different Scientific Committees, with a view to progressive harmonisation of procedures. Where this is appropriate Scientific Committees should be encouraged to develop detailed guidelines with a view to delineating the specificity of the risk assessment in their respective sectors, together with the rationale. This report will have served its purpose if it stimulates an active debate and actions which will lead to convergence of approaches to risk assessment, as well as encouraging effective use of resources.

3 RISK ASSESSMENT IN THE CONTEXT OF THE RISK CYCLE

"Science must begin with myths,
and with the criticism of myths"
Karl Popper (1957)

DEFINITION OF MAIN TERMS USED (See also Appendix 1)

3.1 The terms hazard and risk are often used synonymously in everyday life. However, from a scientific stand point they have different meanings (Ahl *et al*., 1993; Kaplan, 1997).

The term **hazard** is associated with the potential of an agent or situation to cause an adverse effect(s)/event(s). It refers to an inherent property of that agent or situation. Hence, the term is often applied to the agent or situation having that property.

Risk is widely recognised as a function of the probability and severity of an adverse effect/event occurring to man or the environment following exposure, under defined conditions, to a hazard.

The term "safety" is often used to describe situations in which there is no appreciable risk. In this Report, the emphasis is on defining the risk.

3.2 For the purpose of this report, the term "**risk source**" has been introduced. Risk sources are commonplaces in our everyday life. They may encompass agents (also termed “stressors”), media, commercial/industrial processes, procedures or sites with the potential to cause an adverse effect(s)/event(s).

3.3 Characterising risks to human health and safety and to environmental quality is an evolving field. Various aspects of the theory and practice continue to be debated among scientists, risk professionals, policy makers, and the risk interested public. Nonetheless, in relatively recent years, there has been a wide recognition that dealing with risk should follow a structured approach, described as **risk analysis**. [NB: EURATOM has proposed the alternative term “**risk governance**”]. Although this term does not immediately identify its scope, there is agreement that *risk assessment, risk management* and *risk communication* are its essential elements. These terms have been given specific meanings.

Risk assessment is a process of evaluation, including the identification of the attendant uncertainties, of the likelihood and severity of an adverse effect(s) / event(s) occurring to man or the environment following exposure under defined conditions to a risk source(s). A risk assessment comprises four steps: *hazard identification, hazard characterisation, exposure assessment,* and *risk characterisation*.

Risk management is the process of weighing policy alternatives in the light of the result of a risk assessment(s) and of other relevant evaluations, and, if required, of selecting and implementing appropriate control options (including, where appropriate, monitoring/surveillance activities).

Risk communication is the interactive exchange of information and opinions throughout the risk analysis process concerning risk. It should involve not only risk assessors and risk managers, but also consumers and a wide range of other actual or potential stakeholders.

3.4 Risk analysis is intended to make a critical contribution to recognising potentially situations which might affect the health of humans and/or the environment as early as possible, to confronting them and making best use of available information to plan efficient and cost-effective preventive or ameliorating measures. The main requirements are that each case is considered on the basis of all the available, pertinent scientific information. In a number of sectors, the protection of human health is typically the primary consideration in risk related decisions. In recent years, there has been an increasing recognition of assessing potential environmental impacts too. These two concerns can be considered together in a process of integrated risk assessment. The decision making process must be transparent with all interested parties having the opportunity to participate The analysis should be reviewed as a matter of course as the situation (including new important data and/or feedback information gained from monitoring/surveillance) develops., At present, there is no reliable triggering procedure to ensure that this occurs. It follows that it is important to achieve wide spread acknowledgement that the three components of risk analysis are interdependent, and none can function well in isolation. A functional separation of risk assessment is necessary to ensure the scientific integrity of the risk assessment process and reduce any conflict of interest between science and policy considerations. Nevertheless, interactions between risk managers and risk assessors are essential for full understanding of the issues and to maximise the utility of the risk assessments.

3.5 An on-going reciprocal communication among all interested parties is an integral part of all aspects of the risk analysis process. Risk communication is more than the dissemination of information on risk assessment findings to the public at large. Risk communication is the process by which information and opinion concerning risk, risk-related factors and risk perceptions are considered and integrated into the risk management decision. Thus the process of risk analysis is not linear, but fluid, dynamic and iterative. It requires both thought and action. At any stage of the process, other phases might be revisited or refined. Also, it is vital that subsequent to the application of any risk related decision, periodic evaluation should be made to determine its effectiveness and that monitoring and other activities are identified and implemented to carry out the review effectively.

3.6 In view of the nature of the overall process the concept of the "**risk cycle**" has been considered more appropriate (see Figure 3.1). This concept is utilised to briefly comment on the relationship between its different components, while situating risk assessment in perspective.

THE "RISK CYCLE"

The risk cycle involves the interplay of activities belonging to the three basic components of risk assessment, risk management and risk communication. Several schemes have been proposed to define and structure the activities involved. Common denominators in all of these schemes are the role of science in risk assessment, the functional separation of risk assessment from risk management, and the importance of risk communication throughout the process. The principal differences are in :

- The roles of individual stakeholders (e.g. the regulatory authorities, the industry, the consumers, other social partners, non-governmental organisations)
- their degree of involvement in each stage of the process
- the relative emphasis on risk management as opposed to risk assessment

- the definition and complexity of the stages and activities involved in risk assessment and risk management.

Two examples are provided for illustration in tables 3.1 and 3.2.

It is recommended that further consideration is given by the Scientific Committees to adopting a common terminology, possibly along the lines of FAO/WHO, 1997.

Table 3.1 : Risk management elements (source: *Risk Management and Food safety*, report of a Joint FAO/WHO Consultation, Rome, Italy, 27-31 January 1997, FAO Food and Nutrition Paper n°65)

A. Risk evaluation
Identification of a food safety problem
Establishment of a risk profile
Ranking of the hazard for risk assessment and risk management priority
Establishment of risk assessment policy for conduct of risk assessment
Commissioning of risk assessment
Consideration of risk assessment results

B. Risk management option assessment
Identification of available management options
Selection of preferred management option, including consideration of an appropriate safety standard
Final management decision

C. Implementation of management decision

D. Monitoring and review
Assessment of effectiveness of measures taken
Review risk management and/or assessment as necessary

Table 3.2 : Framework for risk management (source: The US Presidential/Congressional Commission on Risk Assessment and Risk Management. *Framework for Environmental Health Risk Management*. Final report, volume 1, 1997)

1. Defining problems and putting them in context
Identify and characterise the problem
Carefully consider the context
Identify risk management goals
Identify risk managers
Establish a process for engaging stakeholders

2. Assessing risks

3. Examining options
Identify options
Analyse options (expected benefits/effectiveness; expected costs; distribution of benefits and costs; feasibility; potential adverse consequences; linking risk and economics)

4. Making a decision

5. Taking action

6. Evaluating results

3.7 For the purpose of this report, it is suggested that the risk cycle would encompass, as a minimum, the main stages as laid out in figure 3.1. These stages are interdependent and are relevant whatever the nature of the risk. Furthermore, the concept of "risk cycle" suggests that the process is phased, iterative and dynamic and that any outcomes may need to be revised as new information becomes available or new perceptions are developed (see also section 3.34).

i) Identification of concern(s)

3.8 This is the very first stage of the cycle, which identifies a problem, and/or determines the cause(s) of concern. A human health or environmental problem may already be well recognised or may be a potential problem. Problems may be identified in different ways. For example, problems or concerns may be identified through a range of indicators, using scientific investigation, methods and information (e.g. disease surveillance, epidemiological studies, biological monitoring, laboratory testing of biological or chemical agents, environmental monitoring, testing using sentinel species in the environment, emission inventories). Problems or concerns may also be associated with events such as development of new technologies, or lack of compliance with standards to control contaminant concentration. Identification of the cause of concern may be performed by the public authorities, and/or by public or private scientific sources, or based on expert opinion. Alternatively, concerns or problems may be raised by consumer groups or mass-media reaction. Problem or concern identification translates into a statement by the public authority of why risk analysis may be needed, and a sequence of information gathering and investigations then needs to be set in train with the aim of formulating pertinent risk management questions.

ii) Formulation of risk management questions - Problem definition

3.9 Formulation of risk management questions requires an excellent understanding of the practical issues the problem involves. This entails a situation analysis which characterises the problem in summary and as accurately as possible and its context and actions that may be necessary, with particular regard to determining what is known, what is not known, and uncertainties that need resolution. In some risk analysis schemes, this activity is described as "*problem characterisation*" or "*risk profiling*". In this Report the term « *problem definition » will be used*

Specification of the problem(s) in an unambiguous and transparent form is essential for appropriate use of resources and for effective risk management. It involves identifying scientific information on the problem in its broad outlines and clearly articulating the problem in its public health and societal context. The scientific information necessary relates to:

- the nature of the hazard,
- the possible adverse effects to human health or the environment,
- the relevant sources of exposure,
- the population exposed,
- the ecological receptors exposed and the exposure route(s) for each receptor.

It should also include characterisation of the scientific evidence, of the range of informed views on the problem at stake, on data gaps and uncertainties.

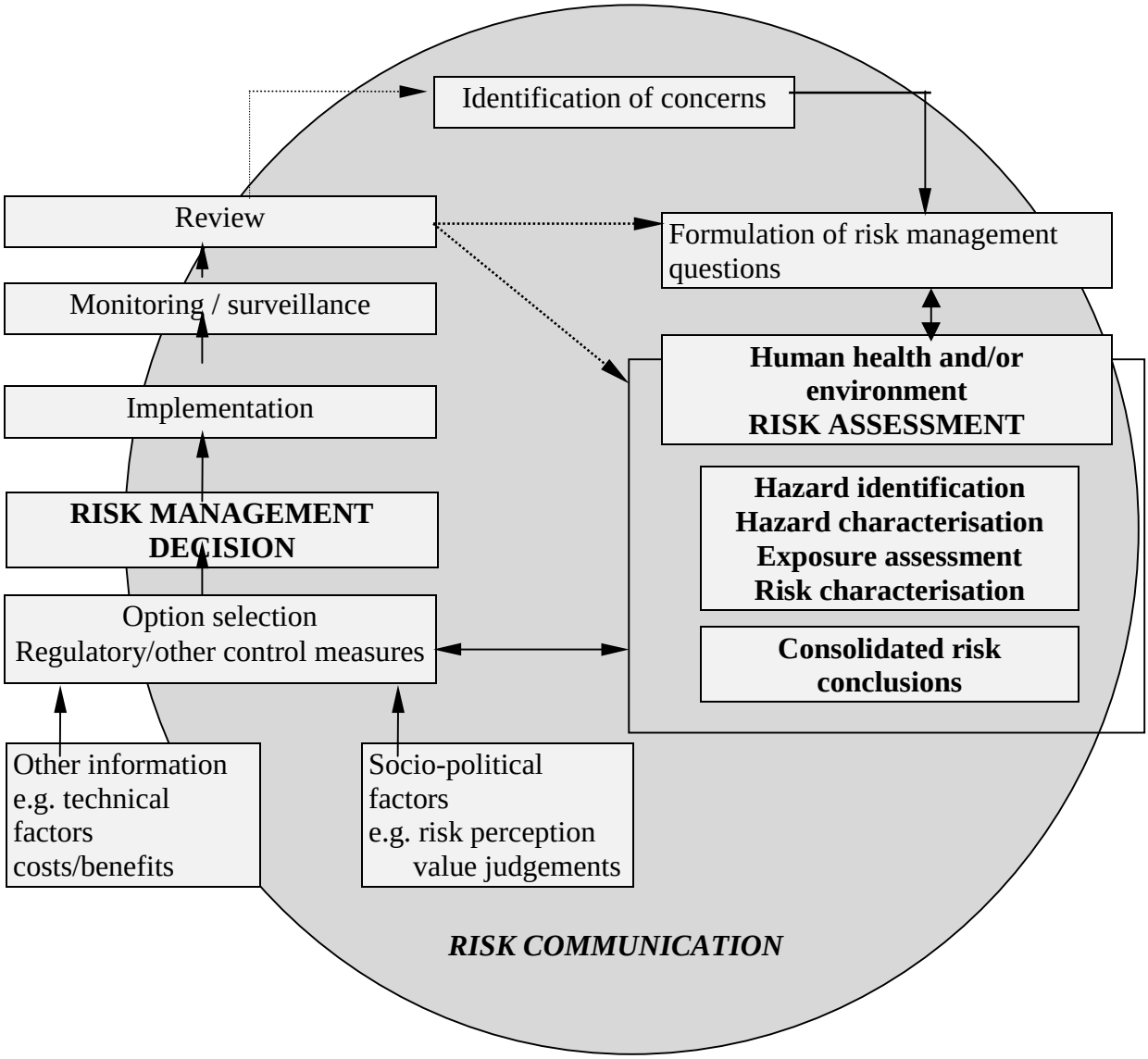
3.10 The framing of the question (problem) involves consideration of the legislative and regulatory framework, of the values expected to be affected besides public health or environment quality, distribution of risks and benefits, consumer and other stakeholders perception of the problem.

3.11 Formulating risk management questions, and answering them, may be iterative, requiring several attempts and refinements as the relevant information is gathered progressively.

3.12 A framework of questions which may help to identify the information required for a risk analysis might be along the following lines:

- What is the problem ?
- Why is it a problem ?
- How was it recognised ?
- What is its scale ?
- Is it a familiar problem or is it a "novel" one?
- What types of adverse effects to human health or the environment might the problem cause ?
- What is their severity ?
- How imminently might the effects be experienced (e.g. in the near future, later on in life, or in future generations) ? How urgent is the need for action ?
- Who and how many may be exposed ? Does the exposure pose different risk to different groups ?
- Which ecological receptors may be exposed ? Is there any taxonomic group or ecological endpoint expected to be the key element in the risk assessment ?
- What are all the relevant sources of exposure ? How much does each source contributes to the problem ?
- Are the exposures likely to be short term or long term ? What is their frequency ?
- How do stakeholders perceive the problem ? Do different groups of stakeholders have different perceptions and concerns ?
- What legislation / regulations are relevant to the area of concern?
- What are the available managerial options ? What are the potential consequences of action taken or which might be taken (comparative risk assessment) ?
- What is expected to be at risk, besides public health or environment quality ?
- What is the distribution of risks and benefits ?

Figure 3.1: the "risk cycle" (components of risk analysis)



3.13 It may be appropriate for some risk assessments to adopt a phased process. A preliminary or exploratory assessment, whether qualitative or quantitative, may be required which can be used to evaluate the situation ("screening", sometimes termed "preclinical, scoping, profiling or preliminary", risk assessment), to determine whether further in depth analysis is necessary, and if so, to identify data needs, and/or to prioritise resources. For some types of products, e.g. drugs, it may be mandatory as a prelude to embarking on clinical trials.

3.14 Formulating risk management questions is extremely important and requires considerable expertise. It constitutes the basis for ranking of the hazard (problem or concern) for risk assessment and risk management priority and, more importantly, for **commissioning the risk assessment**, thus ensuring that the assessment will be relevant to human and environmental health and to regulatory concerns. It is essential to ensure that risk management questions asked to the Scientific Advisory Committees are not ambiguous, nor unresolvable because the information is lacking or insufficiently related to the risk management options available (see Chapter 12 for further details).

Formulating risk management questions should culminate in a planning activity that identifies the goals, approach, scope and scale of the risk assessment to be developed, the regulatory and policy context of the assessment, and the major factors that will need to be addressed.

3.15 Risk assessments may be initiated for a variety of reasons (e.g. to determine the safety of a new chemical, to assess the potential for human risk associated with exposure to a biological or chemical contaminant in a product, to determine critical points for control, to gauge the environmental impact, to establish standards etc.).

3.16 Based on the identification of concern and appropriate formulation of risk management questions, the strategy for conducting the risk assessment must be identified e.g. the overall approach to be taken (qualitative or quantitative), having regard to the estimated quality, quantity and availability of data to be analysed and the potential sources and types of variability and uncertainty. Subsequently, the scope (e.g. exposure pathways; adverse consequences of concern; endpoints to be considered) and the scale (e.g. target populations; geographic region) of the assessment, and the specific questions to be addressed should be determined.

3.17 In addition, to ensure the scientific integrity and independence of the assessment, and to address the issues of transparency and consistency, a *risk assessment policy* (guidelines) may complement the definition of purpose, providing guidelines for value judgements and policy choices which may need to be applied at specific points in the assessment process. This policy guidelines should be used for guidance purposes only, not as a mandatory procedure.

3.18 Formulating risk management questions, and commissioning the risk assessment (including statement of purpose and risk assessment policy) are viewed typically as managerial responsibilities. Very often in the past this has resulted in scientists being totally excluded from the process. However, to ensure that scientific and societal goals are met and to maximise the utility of the risk assessment, especially when

significant commitment of resources is likely, it is crucial that these activities are carried out in full collaboration between risk managers, risk assessors and other appropriate parties (stakeholders). In particular, the risk managers can ensure that the assessment considers and provides information necessary for making policy decisions, the assessors can ensure that the appropriate scientific concerns are addressed, and other stakeholders can provide insight into the scale of the problem, practical issues, and the resources necessary to generate data for the assessment. All these perspectives are important to ensure the appropriate use of resources and to produce scientifically sound risk assessments that are relevant to risk management decisions and public concerns. Mechanisms need to be put in place to achieve this.

iii) Risk assessment

3.19 Risk assessment is intended to be of practical use. The requirement of a risk assessment is to identify and characterise a risk from a "risk source" (based on the assessment of the available data in the light of current understanding of science) in order to provide a sound basis for a decision on whether this risk needs to be contained/avoided/eliminated or whether the risk is sufficiently small as to be deemed acceptable / insignificant (see also Appendix 2). Risk assessments can also be used to compare or rank different risks (see Chapter 11). In practice, risk comparison and risk ranking is not a simple process.

3.20 There is an extremely wide variability in both the quantity and the quality of data available on different risk sources. For chemicals, in some cases there are sufficient data to establish species differences in toxicokinetics between test animals and humans, and also information related to the biological mechanism causing the toxicity. In such cases it is possible to develop a biologically-based, dose-response model such that the extrapolation across the species and from high to low doses is securely based on scientific principles and data. However, in the vast majority of cases risk assessments may be necessary for compounds for which only limited data are available (Figure 3.2a). Such data may be extremely restricted and not allow a full characterisation of the dose-response relationship or an understanding of metabolic or mechanistic differences between the test species and humans. In consequence, a risk assessment process has to encompass a range of possible options from relatively unsophisticated default approaches for sparse data sets, to sophisticated dose-response modelling for data-rich compounds.

A similar situation can be observed for the environment. In some cases, the toxicological information is restricted to a few single-species toxicity tests, while in others, effects on population dynamics and inter-population relationships (including indirect effects) have been produced using higher-tier field studies and/or multi-species studies assessing ecological endpoints (Figure 3.2.b). However, the lack of information is the most common practice, and even in some cases, the risk assessments must extrapolate even between organisms representing different compartments and possessing large taxonomic, physiological and behavioural differences (for example from aquatic organisms to soil and/or sediment dwelling organisms).

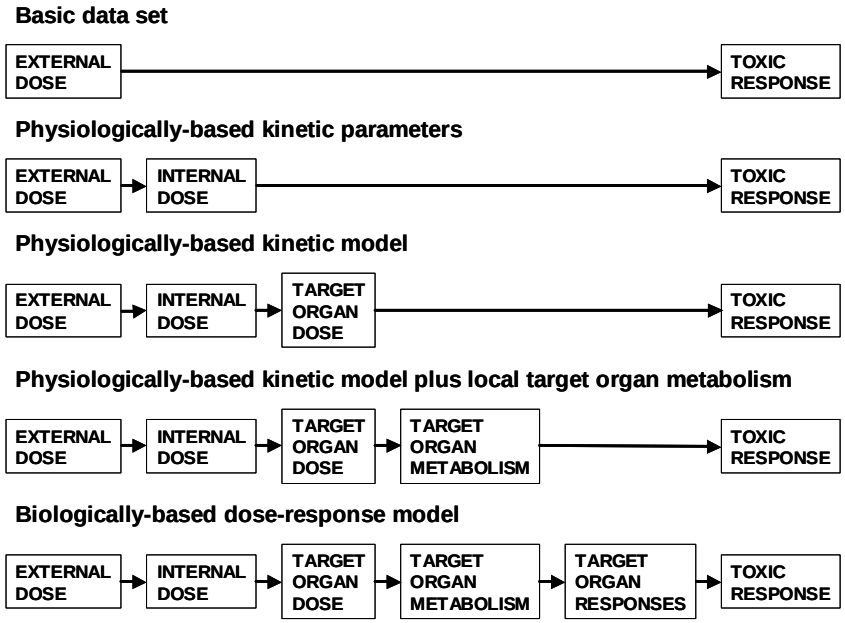


Figure 3.2a: The different databases on which human health quantitative risk assessment may be required.

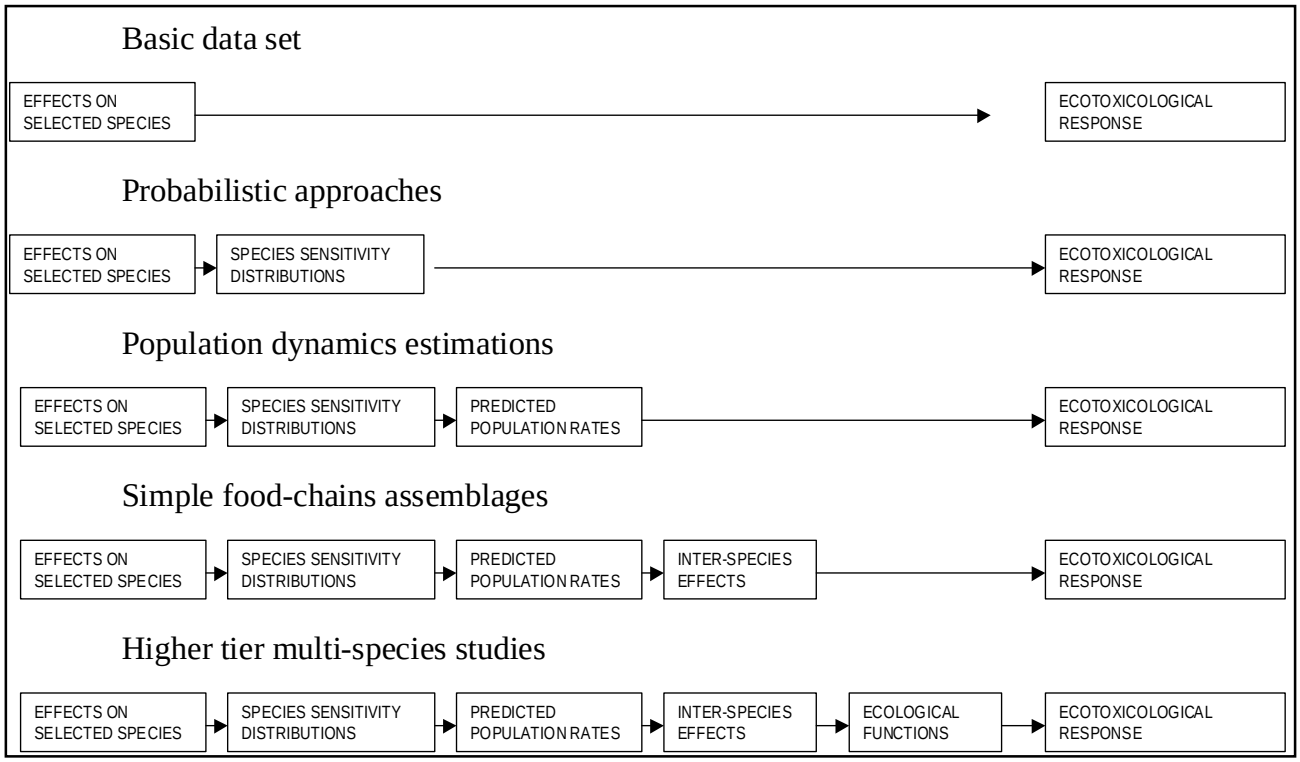


Figure 3.2b. The different databases on which ecological quantitative risk assessment may be required (J.V. Tarazona, personal communication)

3.21 Risk has a two dimensional scale :

- Numbers affected
- Severity of effect

In the case of engineering safety and related risks, these risks are normally presented as “F” (frequency of effect) “N” (numbers affected) curves. For risks from chemicals and micro-organisms usually an uni-dimensional presentation is used. This is based on the assumption that for all effects (with the assumed exception of cancer initiation) there is a threshold level of exposure below which no adverse effects will occur. In practice, a threshold is very likely for an individual human or other organism. However, it is more difficult to estimate precisely for a population because of biological variability in response to identical exposures (individual sensitivity). A problem for the presentation of risks from chemicals and micro-organisms is that the public do not view risks as uni-dimensional.

3.22 The risk assessment approaches shown in Figure 3.3 have historically resulted in different risk characterisations. Quantitative risk assessment by low-dose extrapolation provides an estimate of the risk, or incidence, associated with a particular level of exposure, or can be used to estimate the exposure associated with a particular pre-defined level of risk. It is currently generally used for non-threshold substances.

3.23 Standards can be set based on low-dose risk estimation to ensure an appropriately low level of risk. "Safety assurance", based on an assumption that there is a threshold, is used to characterise an exposure considered to be of negligible risk, and is used for standard setting such as an acceptable daily intake or an occupational exposure standard.

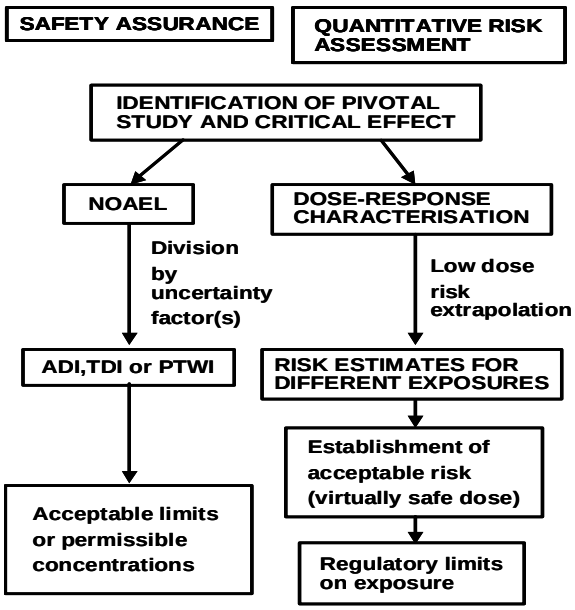


Figure 3.3. Alternative approaches adopted for establishing acceptable levels of human exposure (see Appendix 3).

3.24 The risk assessment approach that is adopted depends on the nature of the toxic effect or hazard, which is the basis for risk assessment (Figure 3.2a and b). For some hazards, such as genotoxic chemicals, it is considered that there may be no threshold for the effect and therefore estimates are made of the possible magnitude of the risk (usually incidence) at human exposures (dose-response extrapolation). In contrast, for other hazards, such as non-genotoxic effects, it is considered that there is a threshold of exposure below which no biologically significant effect will be produced. Each of these approaches usually involves the uncertainties of extrapolating from high-dose animal studies to low-dose human exposure, and from small groups of genetically homogeneous animals to the larger and more diverse human population.

[NB : The four stages in risk assessment, i.e. hazard identification, hazard characterisation (also termed dose concentration – response (effects) assessment), exposure assessment and risk characterisation (See Appendix 1 for working definitions) are discussed in details in subsequent sections.]

When situating risk assessment in perspective, it is important to remember that one consequence of its practical use is that risk assessment is very often constrained by factors such as time, availability of relevant information and other resources (see figure 5.1). Every risk assessment inevitably has deficiencies which may be exacerbated by time pressures, etc. It should be a requirement of every risk assessment that the constraints in the assessment are identified.

General constraints in risk assessments

3.25 There are a number of clear restrictions on the conduct of many risk assessments. These include :

a) Legislation often imposes specific requirements for testing (testing protocols). This has the advantage that risk sources can be compared on the basis of the results obtained in these common tests. Such requirements, in a number of cases, also serve to reduce unnecessary testing which has important benefits in terms of both animal welfare and economics of testing. Common test methodology is also the basis for a wide acceptance of test data between countries, both within the EU and wider, through bodies such as the OECD. However, emphasis on internationally acceptable tests may also serve as a barrier to the development of new tests and to the withdrawal of unnecessary tests. It may also make direct comparisons of risk assessment for different types of risk source difficult where different testing regimes are required for different sources.

b) Economic and ethical factors. The high costs of conducting long term tests in particular serves as a major constraint on obtaining information on the adverse effects of risk sources already on the market. In addition there is increasing pressure on toxicologists to avoid the use of whole animal testing. There is also a major constraint on experimental studies in humans (see Chapter 10).

c) Inability to access existing information. For proposed new products normally all the information, or nearly all of it, is provided by the manufacturer / marketing company. It has to be assumed that the company has provided **all** the relevant information, even that unfavourable to its case. This may be very difficult to confirm.

At present, there is no reliable data bank incorporating most chemicals which have been tested. Development of such a data bank would also facilitate reduced animal testing (see for example Chapter 6). A very important potential source of information is structure activity relationships (SARs) drawn from studies on existing risk sources. Although SARs are already used in some sectors, the use is rather limited.

d) Historic rationale for conducting risk assessments in a particular way. A particular concern here is to identify where conservatism is or is not built into each stage of the risk assessment process and its magnitude and appropriateness.

Risk assessment and risk management are distinct processes, and the risk assessors clearly should not have an exclusive role in identifying what is an acceptable risk, this being considered to be part of risk management. Nonetheless, the risk assessors should probably contextualise each risk assessment as far as is appropriate in order to ensure that their conclusions are clearly understood ("consolidated risk conclusions"), and the risk assessors may need to provide advice on the magnitude of the risk reduction which could be achieved through various risk management options. This may include consideration of the impacts of substitute risk sources. More effective dialogue between risk managers and risk assessors is essential to optimise the value and efficiency of the risk assessment processes. Traditionally, the risk assessment process has been the exclusive province of scientific experts with no apparent involvement of either risk managers or other stakeholders. Discussions are needed on whether this is either appropriate or acceptable to society in the future. On the one hand, risk assessment must remain a science centred activity, on the other, lack of additional inputs may lead to some significant factors being overlooked and a failure to challenge out-dated preconceptions.

iv) Risk management option selection

3.26 This stage involves determining the appropriate level of public health (or environment) protection that should be guaranteed and maintained, and identifying and selecting the regulatory and other control measures necessary to achieve the chosen level of protection. Discussion of this key issue goes far beyond the scope of this Report. The intention here is only to comment on how this activity may relate with assessment activities. It is noted, however, that as far as the European Union is concerned, it remains an area where there is substantial ambiguity and uncertainty in defining the ‘acceptable ‘ risk from many risk sources (Van Leeuwen *et al*., 1996).

3.27 The process of identifying risk management options may begin appropriately during the formulation of risk management questions, thus contributing to focusing the risk assessment and to formulating the specific questions that the assessment would need to answer (e.g. determining the effectiveness of a specific measure(s) with regard to risk reduction). Nevertheless, a full risk assessment is expected to provide important information for identifying and analysing risk management options.

3.28 There are usually many different regulatory and non regulatory approaches to controlling or reducing risk. Questions then arise regarding the elements that should be taken into account to provide input into selecting an option (or a combination thereof).

Risk assessment results are necessarily the primary element in taking risk management decisions. However, a crude expression of the probability and severity of an adverse health effect may not provide a complete picture of all the relevant information on the risk, as it does not account for how individuals and societies value certain adverse consequences. These might be expressed in terms of relative perception of the risk, relative preferences, ethical choices or constraints. A variety of techniques and indicators have been proposed to incorporate the values held by different stakeholders to the evaluation of risks, such as social-welfare economics, disease-burden evaluations, elicitation of individual or societal preferences, ethics. It needs to be considered whether these evaluations should constitute an additional dimension to the risk assessment *sensu-stricto*, or be conducted in a separate but interactive process. This is recognised of increasing importance in establishing the significance of the risk for the purpose of selecting appropriate and acceptable risk management options.

3.29 A framework needs to be developed to allow risks costs and benefits to be compared in an understandable and transparent way. Progress in this area is essential. In its absence it is very likely that even very small risks may be deemed by the public / politicians to be unacceptable. This must include approaches to the age old question of how to deal with situations where the risks and benefits are not equally shared (see Chapter 11). Other information should thus be considered, where appropriate. However, this must be of good quality. This includes :

- the technical practicability of options (e.g. availability of technology, practical feasibility of relevant production or processing methods, legal or regulatory constraints, potential difficulties involved in control, inspection and/or compliance determinations),
- the economic and social costs and benefits (e.g. cost of available or alternative technology, expected benefits/effectiveness, distribution of benefits and costs), while taking into account preferences expressed by stakeholders. A number of tools may be used for considering these factors and specific emphasis has been placed on economic analyses (e.g. cost-benefit analysis; cost-effectiveness analysis).

Economic and social analyses have strengths and limitations, and discussing their value goes far beyond the scope of this document. Suffice it to say that the risk assessment results should provide an essential input into economic analyses, (and these analyses should be conducted with the same rigour as risk assessments) to foster consistency between public health and socio-economic approaches.

v) Risk management decision

3.30 Making a decision on the extent to which, and how, a particular risk source should be controlled is thus as much a question of values as of science, and has strong political dimension. With regard to public health or the environment, public authorities play a pivotal role in risk management and would usually make the decision and implement it. However, it has to be acknowledged that responsibilities for the decision should involve in many cases consumers, manufacturers, and/or other stakeholders. It is important to ensure clarity and effective communication and to improve the level of consensus on the decision taken. Involving stakeholders and incorporating their recommendations where practicable and broadly held is essential in order to integrate and reconcile science and values, to promote confidence in the decision-making

process, to gain greater acceptance of the decision and contribute where possible to its implementation and to the monitoring process.

3.31 What constitutes an optimal decision depends on each particular situation. From a general point of view, and in order to be meaningful and practicable, the risk management decision would, in particular:

- be based on the best available scientific and technical information;
- be determined primarily by human health and environment quality considerations, while being sensitive to social, cultural, legal and political considerations;
- give priority to preventing avoidable risks, not just controlling them;
- select options that are feasible, with benefits reasonably related to their costs;
- if appropriate (see Chapter 11), apply the Precautionary Principle;
- incorporate a built-in monitoring, surveillance and review mechanism.

vi) Implementation

3.32 The implementation of risk management decisions will take different forms depending upon the options that have been selected, and may include regulatory and non-regulatory actions. As for decision making, traditionally, for public health and environmental matters, implementation has been driven by regulatory agencies requirements. However, it is increasingly recognised that the chances of success are significantly improved when other stakeholders are involved. Depending on the situation, stakeholders who should be involved in implementation of risk management decision may include for example, besides the regulatory authorities, businesses and industries, consumers and citizens, scientists and technical experts. In particular, in enhancing the reliability of the risk assessment, scientific and technical experts may help in providing additional scientific and technical information necessary for appropriate implementation of options, develop improved technical procedures, provide appropriate support for technological transfer, education and training. Other involved stakeholders may contribute developing the relationship, knowledge, communication channels, and other mechanisms to work together in implementing the decision.

vii) Monitoring/surveillance

3.33 For many risk sources this has been a much neglected aspect of the risk cycle. However, monitoring / surveillance are vital activities aimed at determining what risk management measures have been implemented and, more importantly, at evaluating the effectiveness of measures taken. Monitoring and surveillance provide important information and feedback about :

- what actions have been taken and their progress;
- whether they have been successful;
- whether any modification is needed to improve success;
- what information is missing;
- whether any new information has emerged that indicates a stage of the risk cycle may be revisited;
- what lessons can be learned to guide future decisions or to improve the risk management process;

- if the case may be, whether decisions based on the Precautionary Principle were valid.

This involves scientific information, expertise and advice. Health and environmental monitoring, disease surveillance, epidemiological studies, scientific research are essential tools. Among specialists in public health and environment, there is a growing recognition of the need to improve and strengthen these activities and to apportion adequate resources. Until now, evaluations based on monitoring and surveillance, when conducted, have been performed by the regulatory authorities themselves. As with other stages of the risk cycle, stakeholder input should be encouraged. Indeed, stakeholders may make an important contribution to the monitoring and surveillance process.

viii) Review

3.34 Results of monitoring/surveillance and/or new information may indicate that some stages of the risk cycle should be repeated. For instance, information gathering, research, analysis of risks or options may change focus to a different concern (e.g. a use change), identify other risks, indicate that the risk should be considered in a broader context, clarify or redefine the problem, provide evidence that risk management options should be revisited. The concept of the "risk cycle" suggests that the process should not be linear, but rather flexible, phased and iterative as important ideas, new information, or evolution of perceptions come to light.

4 A BRIEF HISTORY OF RISK ASSESSMENT IN AN INTERNATIONAL CONTEXT

"History is philosophy from examples"
Dionysius of Halicarnassus (30-7 BC)

4.1 Natural risks and those involved in personal and business life have long been recognised and some process of risk assessment has been part of human activities since long. There have also been straightforward responses to these risks, e.g. from the Kosher laws of Moses to more recent food control activities aimed at managing the wholesomeness of foods. When considered from a modern point of view, the traditional responses appear to be mainly intuitive and measures against perceived threats decided on a hit-and-miss basis, involving essentially consideration of past experiences, technical know-how and qualitative estimates of the risk.

4.2 Today, decisions in the modern society have become more complex. The outcome of decisions carry ever larger actual and perceived consequences and may give rise to debate and controversies as many societal, economic, ethic or political values or impact may be involved. This has resulted in the search of ways to improve decision making. In this regard, a **formal risk assessment** has emerged as a useful tool, as it provides the necessary structure for informing the debate on the risks that a society is prepared to accept (Covello and Merkhofer, 1993). Risk assessors need to recognise however that other factors inform the course(s) of action adopted, such as the public perception of the risk, values established by political debate and public willingness to tolerate risks in return for benefits.

4.3 The major characteristics of a formal risk assessment are that it employs science, utilises information and methods of various scientific disciplines and focuses on a probabilistic approach to risk understanding based to the larger possible extent on quantitative estimates. Nonetheless, it may not be entirely objective and definitive since the process is assumption and value laden and subject to uncertainties that need to be exposed. However, a formal risk assessment has now become the driving force in many fields of operations.

History of the ADI and safety factors

4.4 The concept of “acceptable daily intakes” (ADI) was developed during the period from the mid fifties. Although no one person can be seen as the inventor of the concept, there is a wide recognition that the late professor René Truhaut of the University of Paris, France, is the “nestor” or the “obstetrician of the concept” (Truhaut, 1991; Poulsen, 1995).
Although discussed in various fora (e.g. Council of Europe Partial Agreement on Pesticides), the ADI concept is closely linked at that time to the work of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Professor Truhaut participated in these meetings up to the 33rd meeting in 1988. Already at its first meeting in 1956 (JECFA, 1957) the Committee noted when discussing the general principles governing the use of food additives, that when setting upper levels the “minimal levels which in animal studies produce significant deviations from normal physiological behaviour" should be taken into account. In addition, the Committee recommended “an adequate margin of safety to reduce to a minimum any hazard to health in all groups of consumers.”

4.5 In its second meeting in 1957 (JECFA, 1958) the Committee set out guidelines for testing and evaluating food additives and noted that from various investigations in animals “a dosage level can be established that causes no demonstrable effect in the

animals used. In the extrapolation of this figure to man, some margin of safety is desirable to allow for any species difference in susceptibility, the numerical differences between the test animals and the human population exposed to the hazard, the greater variety of complicating disease processes in the human population, the difficulty of estimating the human intake and the possibility of synergistic action among food additives." Later in the text it is noted that it is "inescapable that some arbitrary factor must be applied in order to provide an adequate margin of safety. Where the maximum ineffective dose in animals is calculated in g/kg body-weight, a margin of safety of the order of 100 has been widely used. In the absence of any evidence to the contrary, the Committee believes that this margin of safety is adequate." It is thus clearly stated that any safety factor must be arbitrary and that the later conventional factor of 100 already seems to be in use at that time although no references are given.

4.6 It is not until the 17th meeting in 1973 (JECFA, 1974) that the Committee comments on the choice of expressing an acceptable dose in mg/kg body-weight. It notes that it recognises "that the expression of the ADI in terms of body weight (BW) does not reflect the relative exposure of animals of different size as accurately as would the metabolic mass, which is equal to $W_b^{0.75}$. However, in practice the method of expressing the dose in terms of mg/kg body weight has proved satisfactory." As for the size of the safety factor (as it is now called) the Committee in the same report argues that although they in the past recommended a factor of 100 this figure can in some cases be too rigid and in other cases not rigid enough. This, however, was not new to the Committee at that time as already at its sixth meeting in 1961 (JECFA, 1962), (which was the first meeting where it set ADI's at all), margins of safety from 10 to 500 were used. In fact, the factor of 100 was only used in setting about 10% of the unconditional ADIs and in 25% of the conditional ADIs.

4.7 In 1967 JECFA introduced the term "temporary" ADI and one of the conditions for setting such ADIs were that the safety factor to be applied should be notably higher (at least double) that for the calculation of a normal ADI (in practice, in the large majority of cases, a factor 2 has been used).

Quantitative risk assessment

4.8 The development of a quantitative approach based on the probabilistic concept of risk owes much to scientists, statisticians and philosophers from Europe. In 1814, Laplace set out the basis of the theory of probabilities. Around 1930, researchers like Ramsey (1931) or Di Finetti (1937) elaborated a framework for analysis of decisions in the face of uncertainties.

4.9 The technical and practical experience in dealing with probabilities and uncertainties evolved largely over the three last decades. A number of researchers established the principles and developed application of decision analysis and ways to encoding probability and uncertainties in such decisions.

4.10 As an example, in the US, the National Academy of Engineering and the National Academy of Sciences organised the first conference on risk analysis in 1972, and their common body, the National Research Council, edited a series of reports in this field.

4.11 This culminated in 1983 with the publication of the report "Risk Assessment in the Federal Government: Managing the Process", also called "the red book", by the US National Academy of Science-National Research Council (NRC, 1983). The main feature of this report is that it established the four steps paradigm for risk assessment (hazard identification, hazard characterisation, exposure assessment, and risk characterisation).

4.12 This framework was originally designed for human health assessment only, but was later adopted for environmental risk assessment.

4.13 Today, most, if not all of the frameworks for risk assessment are based on this report. Differences, where they exist, are mainly with regard to terminology. The main difference refers to the use of "hazard identification" which is at times used to indicate the stage at which hazards of concern are selected, whereas, in other schemes, hazard identification refers to the identification of adverse effects a hazard has an inherent capacity to cause. Other differences are minor and generally do not lead to confusion.

4.14 However, if the division of the risk assessment process in four stages is now universally accepted, within each stage there may be similarities and differences in approaches, possibly leading to difficulties in comparing and contrasting results. This fostered strong international trends to internationally harmonise risk assessment methodologies.

Role of international bodies

4.15 The World Health Organisation (WHO) has for several decades played a pivotal role in regard of the assessment of risks to human health and the environment from exposure to chemicals, via the Environmental Health Criteria Programme (EHC). The original impetus for the programme came from World Health Assembly resolutions and the recommendations of the 1972 UN Conference on the Human Environment. In 1973 the WHO Environmental Health Criteria Programme was initiated with the following objectives:

- to assess information on the relationship between exposure to environmental pollutants and human health, and to provide guidelines for setting exposure limits,
- to identify new or potential pollutants,
- to identify gaps in knowledge concerning the health effects of pollutants,
- to promote the harmonisation of toxicological and epidemiological methods in order to have internationally comparable results.

Subsequently, the work became an integral part of the International Programme on Chemical Safety (IPCS), a co-operative programme of UNEP, ILO, and WHO. More recently, the recommendations of the 1992 UN Conference on Environment and Development and the subsequent establishment of the Intergovernmental Forum on Chemical Safety lend further weight to the need for assessments of the risk of chemical and harmonisation of risk assessment methods in this field.

4.16 One specific outcome of the EHC programme is the publication of several monographs related for instance to the safety assessment of food additives and contaminants in foods (1987), to assessing human health risks for chemicals with specific consideration of derivation of guidance values for health-based exposure limits (1994), and to the principles for the assessment of risks to human health from

exposure to chemicals (1999). These monographs furnish a practical overview of different aspects of chemical safety, and address methodologies for the assessment of risks from exposure to chemicals. They are not prescriptive in nature. Nevertheless, they have become widely established, recognised and used throughout the world.

4.17 With specific regard to human, animal and plant heath, a salient fact is that the Uruguay Round of the General Agreement on Tariffs and Trade (GATT) and the subsequent Sanitary and PhytoSanitary (SPS) Agreement established the tenet for all member countries that "members shall assure that their sanitary and phytosanitary measures are based on an assessment, as appropriate to the circumstances, of the risk to human, animal or plant life or health, taking into account risk assessment techniques developed by relevant international organisations" (Art.5.1). It is not the purpose of this report to cover the requirements and impact of the SPS agreement in detail. Suffice it to say that, in an effort to reduce arbitrary trade restrictions, the SPS agreement places emphasis on the scientific assessment of the risk to health (Risk Assessment) as a means of justification of sanitary measures which do not conform to standards, codes or recommendations elaborated under the aegis of international organisations such as Codex Alimentarius, when such measures may constitute obstacles to free trade. The SPS agreement has also identified the relevant international organisations responsible for the development and promotion of international standards, guidelines and recommendations in relation to human, animal, and plant health. Arbitration on such issues is carried out by the World Trade Organisation (WTO) in Geneva. They have identified that consistency in Risk Assessments is an important consideration in making their judgements.

4.18 In line with SPS direction, the Codex Alimentarius Commission (CAC) initiated in 1993 a survey of risk assessment procedures used by the CAC and its subsidiary and advisory bodies. In 1994, the CAC Executive Committee issued recommendations to FAO, WHO and CAC on the most appropriate approach to the application of risk analysis to food standards and safety issues. As a follow-up to these recommendations, FAO and WHO convened three experts consultations, one in 1995 on the application of risk analysis to food standards and safety issues which dealt principally with risk assessment (FAO/WHO, 1995) , one in 1997 on risk management and food safety (FAO/WHO, 1997), and one in 1998 on risk communication (FAO/WHO, 1998).

4.19 The principles and recommendations contained in the reports are expected to serve as guidelines for the Codex Committees to review the standards and advisory texts in their respective areas of responsibility. In the same way, they provide a common framework to governments, industry and other parties wishing to develop risk analysis activities, and risk assessment in particular, in the field of food safety.

4.20 Having assured itself that the assessment of risks to human health from exposure to chemicals had been already well advanced under the EHC programme, the Food and Agriculture Organisation (FAO) and the World Health Organisation (WHO) have recently given emphasis to the development of appropriate methodology for the conduct of microbiological risk assessment. An essential step has been the publication in 1999, by the Codex Alimentarius Commission, of a document on "Principles and Guidelines for the Conduct of Microbiological Risk assessment"- ALINORM 99/13A (CAC, 1999. See also Appendix 4). This document describes a

structured approach to microbiological risk assessment, providing an outline of the elements that need to be considered at each stage of the assessment. It is now widely recognised and constitutes a reference for microbiological risk assessment world-wide.

4.21 In line also with the SPS agreement, and in relationship to its role with respect to the World Trade Organisation, the International Office of Epizootics (Office International des Epizooties, OIE) addressed the issue of risk assessment pertaining to animal infectious diseases and collated a compendium of methods and examples of application in two special issues of its Revue Scientifique et Technique de l'Office International des Epizooties (vol. 12, 1993 and vol. 16, 1997). More recently, the OIE took the opportunity of the meeting of the OIE International Health Code Commission (Paris, January 1999) to propose a revision of its International Animal Health Code to include, in particular guidelines for risk analysis (revised section 1.4 of the Code, OIE, 1999). This revised section intends "to provide importing countries with an objective and defensible method of assessing the disease risks associated with the importation of animals, animal products, animal genetic material, feedstuffs, biological products and pathological material". It includes the development of principles and detailed guidelines for risk assessment as well as principles for risk management and risk communication in this field.

4.22 Apart from the above mentioned International Organisations, the Organisation for Economic Co-operation and Development (OECD) is actively involved in Hazard/Risk Assessment. The OECD was founded in 1961. It succeeded the Organisation for European Economic Co-operation (OEEC), which was established in 1948 to help implement the Marshall Plan. Today, the OECD has 29 Member Countries. Its principle aim is to promote policies for sustainable economic growth and employment, a rising standard of living, and trade liberalisation. With specific regard to hazard/risk assessment many activities are currently going-on within the OECD. These activities are being carried out under various programmes (e.g. Existing Chemicals Programme, Pesticides Programme, Environmental Health and Safety Programme). These include: 1. Activities on Registration/Notification/Co-operative Assessment (Harmonising formats for industry data submission; Harmonising formats for governmental/international assessment reports; Electronic data submission; Database on review reports available/who has reviewed what; Increasing consistency of data requirements) - 2. Support and guidance (Good assessment practice; Databases that support assessments; Developing guidance on assessment approaches) - 3. Others (Harmonised classification systems; Performing hazard assessment; Performing risk assessment; Release of risk assessment results; Promotion of risk communication).
Of particular interest in regard to the scope of this report is the Risk Assessment Programme developed in the framework of the Environmental Health and Safety (EHS) Programme. This programme focuses on the development and harmonisation of risk assessment methods, particularly in support of the EHS programmes on new and existing industrial chemicals and pesticides. For example, harmonised guidance has been developed for: evaluating the effects of industrial chemicals on human health and aquatic organisms; estimating the exposure of workers, consumers and the aquatic environment to industrial chemicals; measuring the exposure of workers who apply pesticides. Two more general Risk Assessment Programme activities are being carried out jointly with the International Programme on Chemical Safety (IPCS). One is the creation of an inventory and on-line database of risk assessment methods used by

governments and others. The other is the harmonisation of basic terminology used in risk assessment. Both activities aim to increase opportunities for countries to use each other's assessments of chemicals by improving their understanding of how these assessments are carried out. This will help OECD countries share the work of chemical evaluation and reduce their individual workloads.

4.23 A major contribution on ecological risk assessment development by international scientific societies has been done by the Society of Environmental Toxicology and Chemistry (SETAC), which include advisory groups on ecological risk assessment and on environmental risk assessment of pesticides among others. At a global level, SETAC has been responsible for the (co-)organisation of several workshops and the publication of key guidelines. In addition, the continental units (SETAC Europe, SETAC North America, SETAC Asia-pacific) have being directly involved in the development of the risk assessment guidelines and protocols for decision making currently used by the European Union, US Environmental Protection Agency, Environment Canada, etc.

4.24 Several other organisations, societies or groups have been actively involved in the development of frameworks and guidelines for risk assessment and other risk related activities, whether internationally or at a national level. In this regard, the activities of the Society for Risk Analysis (SRA) deserve specific consideration. The SRA was founded in the United States in 1981. The SRA is now an international, multidisciplinary and interdisciplinary, society that provides an open forum for all who are interested in risk analysis. It brings together individuals from diverse disciplines and from different countries and provides them opportunities to exchange information, ideas, and methodologies for risk analysis and risk problem-solving. It fosters understanding and professional collaboration among individuals and organisations for the purpose of contributing to risk analysis and risk problem-solving. It facilitates the dissemination of knowledge about risk analysis methods and their applications. It promotes advancement of the state-of-the-art in research and education on risk analysis. The SRA has different speciality groups, each of which represents a substantive or disciplinary area of interest (e.g. speciality group on dose-response; exposure assessment; food/water safety risk). The SRA publishes a journal, *Risk Analysis*, a letter of information, *Risk Newsletter*, and the proceedings of its annual congress. The SRA has established sections that represent the members from a group of countries and operate relatively independently of the original society. The current sections of the society are the Japan Section and the European Section. They jointly publish the *Journal of Risk Research* and the proceedings of their annual meetings.

Other groups active in this field are, for example, the International Life Science Institute (ILSI) which has a European section (ILSI-Europe), the Presidential/Congressional Commission on Risk Assessment and Risk management in the USA, the Interdepartmental Liaison Group on Risk Assessment (ILGRA) in the United Kingdom, and the Netherlands Health Council.

CONCLUSIONS

i) Risk assessment is becoming a formal tool in an increasing number of areas of human activity. It involves a growing range of national and international bodies, and requires an increasing level and range of expertise.

ii) Historically, risk assessment procedures for different types of risk source have developed largely independently. Different countries have often adopted different approaches to the assessment of the risk from the same type of risk source.

iii) With the increasing globalisation of markets and the consequent need to remove barriers to trade, it is important that convergence is achieved progressively in risk assessment procedures. This must be based on current high quality science.

iv) This requires co-ordination between the extensive activities in risk assessment within the EU and those of bodies such as WHO, OECD and professionals societies / organisations such as ILSI, ECETOC, SETAC, etc.

5 RISK ASSESSMENT IN THE DG SANCO COMMITTEES

"Life is short,
science is long to learn,
opportunity is elusive,
experience is dangerous,
judgement is difficult"
Hippocrates (460-377 BC)

5.1 The Scientific Advisory Committees of DG SANCO are involved in Risk Assessment procedures in many aspects of their work, although many of them have a much broader remit than simply risk assessment. Their advice in relation to risk assessment may be required in a number of different situations. Firstly, they may be required to conduct a *de novo* risk assessment. Secondly, they may be asked to review risk assessments carried out by others. Thirdly, they may be asked to comment on the development of specific risk assessment procedures or methods that are being incorporated into Community legislation.

5.2 The assessment of risk is conducted in the EC for a wide variety of purposes. It includes examination of :

- Agents also often termed "stressors" (new and existing chemical, biological, and physical agents)
- complex media (e.g. food, air, water)
- commercial and industrial processes (both during normal and abnormal operations, e.g. explosions)
- procedures (e.g. transport of animals, storage of materials)
- specific sites

There is no widely used terminology embracing all these aspects. For the purpose of this paper the term *"risk sources"* will be used generically.
It should be noted that, besides DG SANCO, some other DGs have scientific advisory committees on aspects of human and environmental health. It has unfortunately proved not possible to include consideration of their work in the present Report.

5.3 Risk assessment may include impacts on one or more of the following: individuals, consumers, human population groups, workers, "target species", fauna and flora or physical aspects of the environment. Table 5.1 summarises the risk assessment activities of the various DG SANCO Scientific Committees. It demonstrates that the work of the Committees in risk assessment involves a very wide range of consumer, occupational, public and environmental exposure situations.

5.4 In a number of areas, Community legislation has already been adopted which includes specific guidelines for carrying out risk assessments. This legislation itself represents a degree of harmonisation between Member States, some examples from these procedures are quoted in the following sections. However, the legislation pertaining to chemicals intended for different uses in a number of instances sets out defined practices which are not always compatible with one another and therefore, in practice, run counter to the aims of harmonisation of risk assessment in the work of the Scientific Committees.

5.5 The Scientific Advisory Committees vary considerably in the source(s), nature and detail of the data available to them. The information required for a risk assessment for new human medicinal products and devices, animal growth promoters, pesticides, food additives and cosmetics is defined largely by Directives and Guidelines and is provided chiefly by the companies wishing to have a permit to market them. In the absence of suitable data, marketing permission can be withheld.

5.6 For many existing substances the situation is rather different. There may be many manufacturers and a great reluctance by them to provide information and where it is lacking to initiate any work to rectify the key deficiencies. For example, of the ~100,000 existing chemicals in the EINECS listing, it is estimated that for less than 1000 is there a reasonable data base.

5.7 The same risk source may be reviewed by different scientific advisory committees in different contexts. For example, phthalates have been reviewed for different uses by the SCF, SCTEE and SCCNFP. This may lead to inconsistencies in the risk assessment because:

- The data available to the Committees may differ, depending on the organisations that provide the information and the date of the opinion.
- A lack of knowledge of the work done by the other Committees on specific risk sources.
- Variations in legislative requirements and guidelines for conducting the risk assessment.

This is not a desirable situation, either scientifically or from a risk communication and risk management viewpoint.

5.8 Many factors influence the scope and quality of risk assessments. These include:

- Appropriateness of the questions asked.
- Available direct and indirect information and its quality.
- State of understanding of the pertinent science.
- Expertise of the risk assessors.
- Resource issues such as time available for the assessment.

The overall process is set out in Figure 5.1. The Commission is very fortunate in the breadth and depth of expertise it has been able to draw on for its Scientific Advisory Committees. However, this resource is reducing rather than expanding. In contrast, the number of issues where a risk assessment is required is likely to continue to grow. (See Chapter 12).

5.9 A key requirement for progress is much more effective dissemination of **all** the relevant available information to each scientific committee. This would require the Commission to establish or become a contributor to a high quality validated data base (see Chapter 6) covering the various available and necessary components for the risk assessment of risk sources.

5.10 Currently, the Commission is unable to identify readily each of the risk assessment opinions which it has itself authorised. It is also unable to access readily the support documents which have informed many of these risk assessments. As a consequence there is often duplication of effort and misuse of the time of members of the scientific committees in searching for important documents.

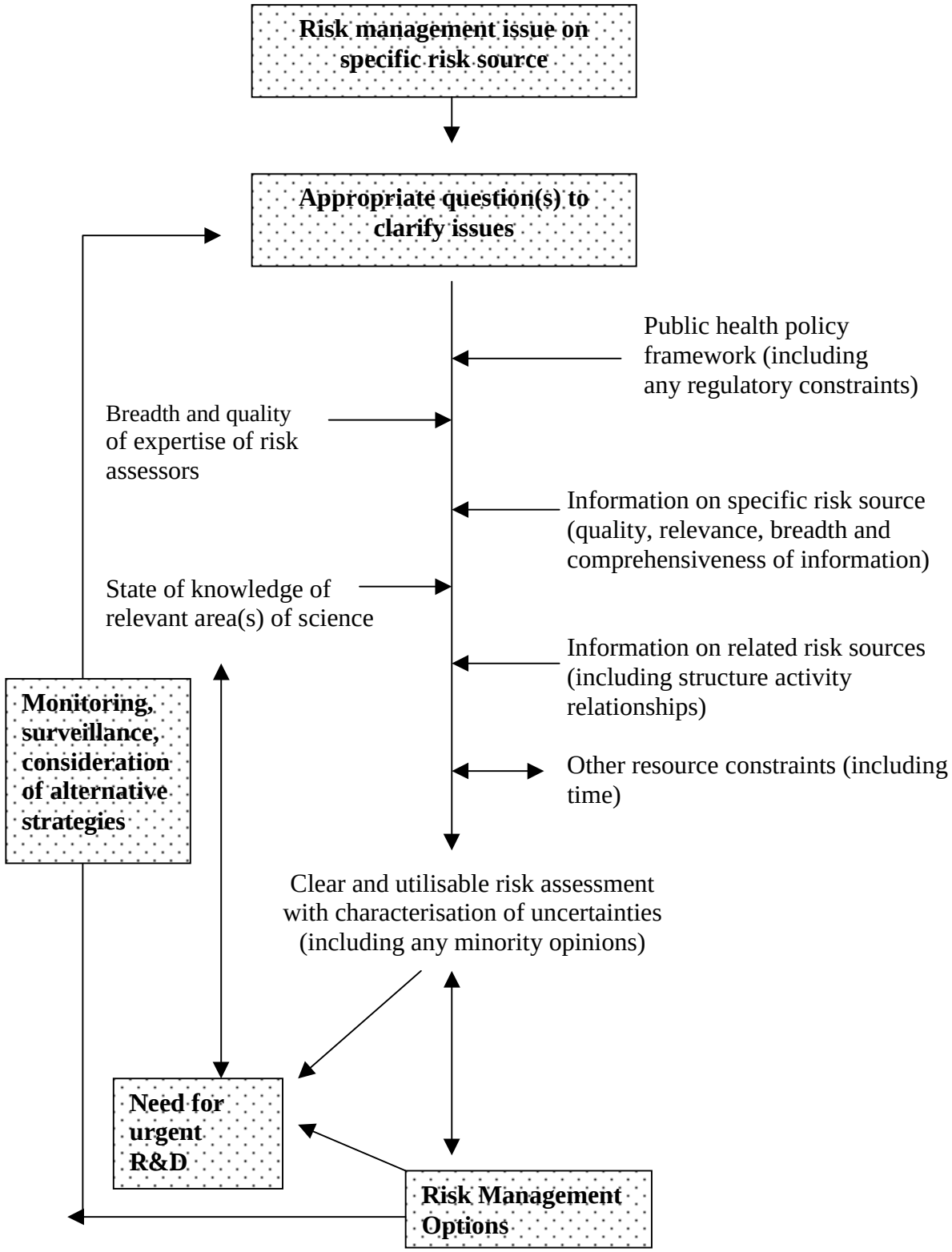
TABLE 5.1

COMPARISON OF RISK ASSESSMENT ACTIVITIES OF DGXXIV SCIENTIFIC COMMITTEES

COMMITTEE	MAIN DATA SOURCES	HAZARD IDENTIFI-CATION	HAZARD CHARACTER-ISATION	EXPOSURE ASSESSMENT	USE OF SAFETY FACTORS IN RISK CHARACTERISATION
1) SCAN	PG, M, PMS	Ch, Biol	TS, C, W, E	Cons Ind, Env Dir	Yes, ADI / MRLs (in future)
2) SCMPMD	PG, M, PMS	Ch, Biol, Mat	C	Cons Dir	Some use of therapeutic index, etc.
3) SCP	PG, M	Ch, Biol	TS, C, W, E	Cons Dir, Env Dir	Yes, MRLs
4) SCF	PG, M	Ch, Biol, Pro, Mat, Ph	C	Cons Ind, Cons Dir	Yes, MRLs, etc
5) SCTEE	-	Ch, Biol, Mat, Ph, Pro	C, W, E	Cons Dir, Cons Ind, Env Ind, Env Dir	Yes
6) SCCNFP	PG, M	Ch, Biol, Mat	C	Cons Dir	Yes
7) SCAHAW	-	Ch, Biol, Pro	TS, C, W, E	Cons Ind	No
8) SCVPH	-	Ch, Biol, Pro	TS, C, W	Cons Ind, Cons Dir	No

Key: TS = target animal species; C = Consumers; W = Workers; M = Manufacturer main information source;
E = environment; PMS = post-marketing surveillance data; PG = published guidelines; Ch = chemical agents ;
Biol = biological agent; Ph = physical agents; Pro = Processes and procedures; Mat = materials;
Cons Ind = consumer indirect; Cons Dir = consumer direct; Env Ind = environment indirect
Env Dir = environment direct

FIGURE 5.1: KEY INPUTS INTO THE RISK ASSESSMENT PROCESS



5.11 It is recognised that a further major barrier to the use of available information is that much of it is provided to the Commission "in confidence". It is important to respect the need to protect the commercial advantage of companies who have invested their resources in building the requisite data. A means has to be found of maintaining this commercial advantage that nonetheless enables the information to be used more widely for risk assessment purposes.

5.12 Each scientific committee has a distinctive brief of responsibilities and duties. Members of individual Committees may perceive that their problems and procedures are unique. Some Committees are only involved with one DG, others with several. Inevitably, clear differences exist too in the legal frameworks under which they are requested to provide an opinion. For some committees benefit as well as risk may be taken into consideration, for others not.

5.13 In the case of human medicines, there may be a very small margin of safety between the beneficial (therapeutic) dose and the toxic dose. Identification of this safety margin requires extensive studies in suitable patients. In the case of industrial workers it is quite common also for there to be a small safety margin between exposure levels and those at which an adverse effect may occur. This is only likely to be acceptable if there is good human data. If human data is inaccessible or unreliable and / or when the concern is exposure of the general public larger safety margins are normally required. For most risk sources there is little, if any, human data available. Means must be found to obtain more information in man once a product is marketed or a new industrial process is in operation.

5.14 Harmonisation of risk assessment clearly cannot mean that the same safety factors are employed for all risk sources regardless of the data base and the intended use of the risk source. However, it should mean that the drugs / drug residues released into the environment (e.g. through excretion) are treated from a risk assessment viewpoint in a similar manner to other residues which may enter a sewage works with possible passage into the water supply, etc. Similarly, worker risk from manufacturing or administering drugs (e.g. anticancer drugs) should be considered for risk assessment purposes in the same way as other risk to workers from other risk sources.

5.15 Harmonisation ought also to be achievable in:

- Risk terminology
- Style of presenting risk assessment opinions.

The process of editing the language of opinions by Committees is a highly inefficient one.

5.16 The Working Group is aware that in some Member States, scientific advisory committees in the course of their activities are in dialogue with non-scientists. This takes a number of forms:

- One or more stakeholders being observers or even full members of the committee
- Annual (or even more frequent) meetings with stakeholders, including politicians
- Publication of a non-technical annual report.

This is not normally the case for the DGSANCO scientific advisory committees.

5.17 A further important issue, where an agreed view would be helpful, is whether, for chemical agents at least, a generic exposure value (sometimes termed threshold of toxicological concern or TTC) can be set below which, regardless of its chemical nature, an agent can be considered to be without adverse effects to man and / or the environment.

Question (Problem) Formulation

5.18 Risk assessment must be of practical use. As identified in Chapter 3, risk assessment may be conducted for a variety of purposes. The first crucial element in the risk assessment process is to ensure that those carrying out the risk assessment are very clear about its purpose(s). In most cases Scientific Advisory Committees conduct risk assessments in response to questions formulated by the Commission.

5.19 Formulation of appropriate questions requires a high level of understanding of the possible human and environmental health issues. For approval of new products (drugs, feed additives, cosmetics, pesticides) the questions have become standardised and the committee involved typically works to guidelines which they have developed to carry out the risk assessments. Committees have developed their guidelines independently and it is appropriate to review whether their compatibility could be improved.

5.20 In the case of other risk assessments, the provision of questions alone is often insufficient to ensure that the members of the Scientific Advisory Committee understand fully the purpose for which the risk assessment is required. In such cases a dialogue is essential with the appropriate risk managers. (This issue is discussed in more detail in Chapter 12). Poorly formulated questions can result in a number of unfortunate consequences including: an un-utilisable risk assessment, identification of risks not relevant to the actual problem, waste of precious time of committee members and delay in establishing a sound basis for a risk management strategy. The question formulation should indicate the level of sophistication of the response required. Is a sophisticated numerical answer needed, or is a more qualitative conclusion sufficient for the purpose?

Data provision and data acquisition

5.21 Ready access to all the relevant data is the second essential prerequisite for a sound risk assessment. This is an important deficiency in the work of many of the Scientific Advisory Committees.

5.22 Where new products are required to be assessed, with few exceptions, all the data is provided by the company wishing to market the product. Data on closely related products, etc. is not available although this would often assist in validating the information presented. Moreover, because the data provided by the company is “in confidence” the work of the Committee cannot be considered as fully transparent. Procedures need to be developed to overcome these deficiencies.

5.23 For other risk sources the data provided by the Commission can be very variable. One approach is to use external consultants to provide the literature review, or even a

risk assessment, which the Committee is then asked to comment on. This raises the dilemma for the Committee of either relying on the data cited in the consultants' report or drawing on the resources available to individual members of the Committee. In other cases, the DG responsible for the questions may provide a very limited number of publications / reports to assist the Committee in answering the questions.

5.24 It is a legitimate question as to whether it is reasonable to expect individual committee members to take responsibility for making up any deficiencies in the data base provided (often a very time consuming process without any form of reimbursement to either the individual or to their parent organisation). This situation is quite unlike that in many Member States who employ experienced scientists to ensure that their Scientific Advisory Committees are provided with all the relevant information. It is recommended that the Commission considers the appointment with the skills and time to perform this increasingly essential role.

5.25 Risk assessments of new products have the opportunity for requesting further studies by the proposing company prior to making a decision. This is not usually the case of existing risk sources. Effective mechanisms need to be identified and fully understood by which studies are considered by a Scientific Committee as crucial to a risk assessment which can be initiated promptly.

Integrated risk assessment

5.26 Human health risk assessment and environmental risk assessment have, for historic reasons, developed separately. However, the processes have much in common (The IPCS has recently produced a draft report on this item). Since the objective of all the Scientific Advisory Committees should be to protect effectively both human health and the environment, it is important to develop a more holistic approach to risk assessment (termed "integrated risk assessment") which embraces both. There are good practical and scientific reasons for developing this strategy within the EU, namely:

- Potential for improved efficiency. With the exception of agents which are deliberately administered to man, the processes of release, transport and transformation are largely common to both human and environmental receptors. Consequently, exposure methodology should be common. Moreover, knowledge of both toxicokinetics and adverse effects (toxicodynamics) in laboratory animals can be applied in the assessment of potential impacts on wild life. In fact, the risk for terrestrial vertebrates is commonly estimated using the information on mammalian toxicity generated for the human health risk, after the re-evaluation of the toxicological results selecting ecologically relevant end-points. In addition, specific hazards, such as potential for endocrine disruption, can be detected in any part of the assessment.
- Identification of relevant scenarios. Risks to humans and environmental receptors (ecological risks) often have some element of interdependence. This may be easily neglected if these risks are considered separately.
- Early warning indicators. Concerns about potential or real adverse effects may be picked up in either humans or particular environmental receptors as a result of monitoring and surveillance programmes, change observations or specific

research studies. An integrated approach would ensure that these concerns were examined holistically rather than on a piece meal basis.

- Coherence of advice to risk managers. Individual risk sources may affect both human health and that of the environment. It is important that these risks are described in a common and clear way.

5.27 In some cases, comparisons may be required between the impacts of different risk sources (eg: pesticides). If one affects human health but has less effect on the environment, while the second risk source affects the environment more than human health, it is necessary to have a coherent format to aid risk management decisions.

5.28 It is recommended that the Scientific Advisory Committees consider a common approach to the development of a more integrated risk assessment. This might follow the lines proposed by WHO 2000.

CONCLUSIONS

i) The Scientific Advisory Committees of DG SANCO are involved in the risk assessment for public health and the environment of a very wide variety of risk sources, including: the impacts of chemical, biological and physical agents, often in complex media, and procedures and processes.

ii) In many cases, the requirement for a risk assessment is laid down in community legislation. Typically this legislation also constrains the nature of the risk assessment process.

iii) Despite this, the general approach used by the Scientific Advisory Committees has much in common following the sequence: hazard identification, exposure assessment, hazard characterisation and risk characterisation.

iv) The quality and appropriateness of the risk assessments conducted is influenced by many factors, but in particular: the appropriateness of the questions asked of the Committees and the availability of suitable data for the assessment. In the latter case, major improvements are necessary in current practices.

v) Better co-ordination is needed between committees to ensure that where appropriate common approaches are employed for comparable problems. In the short term, progress should be readily achievable in agreeing use of risk terminology and style of presentation of opinion.

vi) Other issues include: involvement of stakeholders in the work of the Scientific Advisory Committees, development of common approaches for environmental risk assessment and adoption of an integrated risk assessment approach.

vii) It has not proved possible to consider in this Report the work of Scientific Committees of other DGs concerned with risk assessment. On the grounds of harmonisation it is hoped that this work can be conducted in the near future.

6 HAZARD IDENTIFICATION

"Our lungs admit hindrance an elixir of life
and a deadly poison"
Gladkov (1975)

GENERAL

6.1 Hazard identification is defined as the identification of a risk source(s) capable of causing adverse effect(s) / event(s) to humans and/or the environment, together with a qualitative description of these effect(s) / event(s). Hazard identification may be carried out for a variety of purposes:

i) As the first step in the risk assessment process of a product or other risk source;
ii) To clarify a human health or environmental issue, e.g. local pollution by a chemical (see also Chapter 7);
iii) To aid policy, e.g. to rank risk sources:
iv) To determine hazard labelling of products;
v) To select appropriate species or taxonomic groups for further testing. This is particularly relevant for ecotoxicity.

In some cases, only hazard identification may be conducted.
Hazard identification is conventionally regarded as the first step in risk assessment. There are a number of reasons for this, the most obvious being that in hazard identification the issues of concern for a subsequent analysis are defined. However, often in practice there is overlap between hazard identification and exposure assessment.

Hazard identification considerations (see also Figure 6.1)

6.2 i) Identify and characterise properly the risk source viz. one or more chemicals, micro-organisms.
ii) Determine what effects are the potential target(s) (humans, other species, environmental compartments).
iii) Examine whether the experimental procedure(s) and/or field studies reflect the exposure conditions of concern and are they of appropriate quality, etc., i.e. are they appropriate? It is also essential to establish that the risk source that has been used for testing purposes or human or field observations is for all practical purposes relevant for the risk source being assessed.
iv) Establish what is a significant adverse effect. It is important to thoroughly evaluate, for example, the arguments for a particular effect(s) being discounted.

Hazard identification may be regarded as an initial qualitative effect description for the quantitative hazard characterisation in that, for various reasons, there can be no further investigations of a number of possible effects. It follows that a key element of hazard identification is to ensure that all significant adverse effects are recognised and considered.

Identification and characterisation of the risk source

6.3 It is essential, from the outset, to have a clear identification of the risk source. In regard to chemicals, this requires precise information about the identity of the chemical. This includes identification of possible stereoisomers, characterisation of the components of complex substances, consistency of composition and nature and

levels of impurities. Information on chemical stability and physical form of the chemical is also necessary.

6.4 It must be shown that the chemical composition of the risk source of interest is the same for all practical purposes as that used for assessing the adverse effects. This is in principle straightforward where a risk assessment is being conducted on a new product for proposed commercial use. For existing substances, there may be interbatch variations in composition which was not taken full account of in the original toxicity tests. It may be much more problematic in situations where an adverse effect due to environmental exposure is under investigation, where the physical and/or chemical form may change due to chemical or biotic influences. There is a danger that in such situations what is readily measurable is assumed to be the causative agent, whereas the effect may be due to another risk source or to a combination of risk sources.

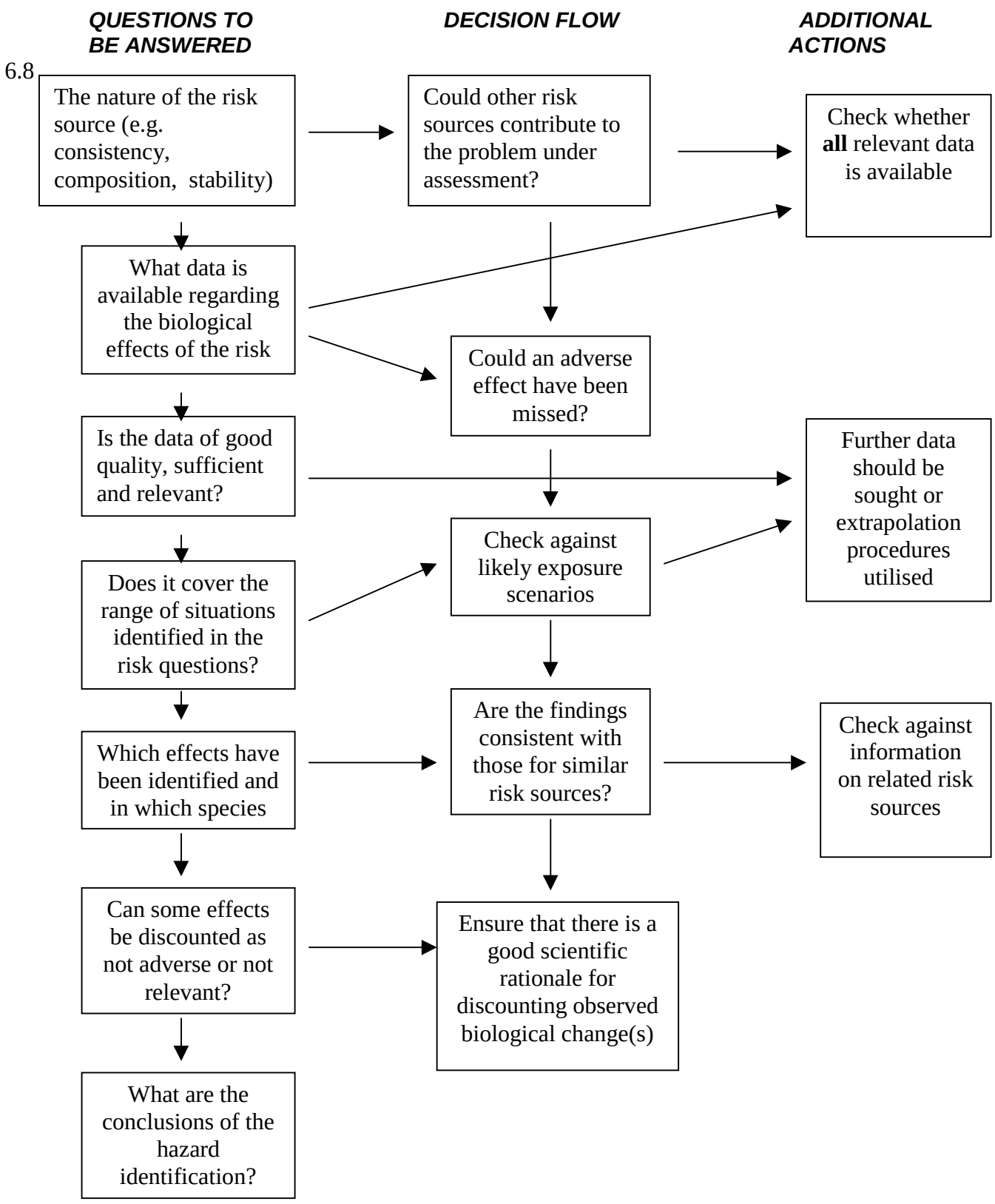
6.5 Some of the scientific committees require completion of a standardised format which covers physicochemical properties, including impurities. Others do not. It may be helpful for committees to compare these formats to assess their coverage and general utility.

Determination of potential targets (hosts)

6.6 In the great majority of risk assessments conducted by DGSANCO Scientific Committees effects on humans (either the public at large, consumers, patients or workers) is a principal objective. Nonetheless, assessment of the impacts on the environment is being of increasing importance. Human and environmental risk assessments have much in common, indeed information from one assessment may often inform the other. Progressive integration between these processes is therefore highly desirable.

6.7 For human drugs, cosmetics, foods and personal care products there is, as yet, no legal requirement for an environmental risk assessment. However, it is likely in the future that some form of evaluation of possible environmental effects will be required. This might take the form of a simple algorithm(s) utilising information on release routes, and levels rates, together with physicochemical data. Such an approach has been adopted in the last few years for veterinary drugs and is under development for animal growth promoters. The use of tiered approaches starting from simple estimations is of obvious cost-effective value, however, the scientific basis of the protocol must be guaranteed. The environmental risk assessment for veterinary drugs includes a first tier based exclusively on an exposure assessment, without considering or requesting (eco-)toxicological information. From a scientific point of view a “risk assessment” which does not consider the effect assessment is not valid. For biologically active substances, the assumption of “low exposure equal to low risk” is not acceptable because of the potential for significant effects at very low doses. Therefore, the procedure for the environmental assessment of veterinary drugs requires a re-evaluation. The harmonisation of the protocols, including the definition of conceptual models and analysis plants for each risk assessment procedure will allow the detection of inconsistencies in the technical development of the EU legislation.

FIGURE 6.1: DIAGRAMMATIC REPRESENTATION OF THE PROCESS OF HAZARD IDENTIFICATION



6.8 It is anticipated that under the theme of sustainability there will be an increasing requirement of scientific committees to consider the risk involved in all aspects of the life cycle of a product. Of particular importance is likely to be waste disposal (see also Chapter 10).

6.9 It may be valuable to establish a working party drawn from different scientific committees to consider a more unified strategy for the initial environmental impact assessment of commercial products.

Experimental protocols and/or field studies

6.10 Hazard identification has been reviewed both regionally and internationally. The IPCS has dealt with this issue in the context of identification of hazards for human health in a number of Monographs (WHO, 1987, 1994, 1999). These reviews have mainly considered issues directly related to chemicals and their effects on human health.

In Europe, environmental risk assessment has been considered by the European Environment Agency (EEA, 1998). Environmental risk assessment has also been considered in the US (US Presidential / Congressional Committee on Risk Assessment and Risk Management, 1997; USEPA, 1998). Examples of the application of this approach are given in National Science and Technology Council (1999). In this Chapter, attention will be focused on how information for hazard identification is derived and applied in general terms and areas where a more harmonised approach would be beneficial and the constraints in achieving this.

CHEMICALS

[*Note*: see also Appendix 3, Report on risk assessment for toxic chemicals]

Current testing requirements

6.11 It is not appropriate for the purposes of this Report to review in any detail the large range of current toxicity and eco-toxicity tests as well as tests for chemical, physical and microbiological characteristics of the test material. For useful reference on test, the reader is referred to Appendix 3. It should be noted here however that the OECD, over the last 30 years, has made an important contribution to the harmonisation of risk assessment through its work in validating and standardising toxicity and eco-toxicity tests *in vivo* and *in vitro* as well as tests for chemical and physical characteristics. Each test guideline identifies the agreed number of samples, dosages, number of test units (animals, tubes) for each dosage, duration of exposure, route of administration etc. and the number of parameters to be measured. OECD also prescribes the conditions for performing test and reporting the test results, through GLP (Good Laboratory Practice). The standardised tests have gained world-wide acceptance for all types of chemicals. So far, animal tests still are considered to give the most appropriate answer to the question about possible human health concerns, but it is generally agreed to limit the use of animals to a minimum by a stepwise approach where the new chemical only goes into animal testing when chemical and physical properties are elucidated as well as targeted *in vitro* tests covering dynamic

interactions at the cellular level. The animal studies then cover the toxicokinetic features as well as identification of potential target organs. For "old" chemicals, human and experimental toxicity data is identified before the necessary supplementary data set will be requested.

6.12 In the context of harmonisation it is appropriate, however, to consider briefly future trends in the methodology for hazard identification and legal and other factors which may affect substantially the choice of methodology employed to identify and characterise hazards. The availability of appropriate test methodology is essential to the proper identification of the potential hazards. Frequently, there are a variety of available test methods, of differing complexity. This leads to the need for developing a test strategy in order to ensure that testing is carried out optimally. This can help to ensure that on the one hand, the hazards of concern are adequately identified, and on the other that unnecessary additional testing is avoided. Additional testing not only involves extra costs, but where biological effects are concerned, this will often involve animal studies, which should be avoided whenever possible. The recognition that hazard identification and development of appropriate testing are intimately linked is reflected in a somewhat different terminology in some risk assessment frameworks (e.g. USEPA, 1998; ILSI, 1996, 2000) which refer to “Problem Formulation”. This term is used to describe the phase of a risk assessment that covers the identification of issues of concern for the analysis (hazard identification), as well as the selection of appropriate *in vivo* and *in vitro* test methodology and, where appropriate, test strategy.

6.13 The differences in the needs of different risk assessments can justify differences both in the hazards identified as well as in the levels of adversity that are considered to be hazardous. However, the reasoning for the choices needs to be clearly identified in all cases. The choices made for hazard identification and associated test methodology should be clear and justified in all cases, both where there is sufficient agreement that these choices can be included in binding legislation and in cases where a more ad hoc approach is necessary. For cosmetics in particular there are legal constraints on the use of in vivo tests.

6.14 There are also examples of more or less mandatory reduction. The first is in the Preparations Directive. This gives rules for how to evaluate mixtures of chemicals. European Parliament and Council Directive1999/45/EC of 31 May 1999, JO L200, 31.7.1999 p.1. This replaces 88/378/EEC of 3. May 1988, JO L187, 16.7.88. There are no major differences in the two texts as regards animal welfare. Here there is a specific reference to 86/609/EEC (considerant no. 8):
"whereas, therefore, this Directive makes use of the results of assessments of toxicological and ecotoxicological properties only when these are already known and entails no obligation to conduct further experiments on animals.".

6.15 In addition it provides a calculation method to determine the toxicological (Article 6, Annex II) and ecotoxicological (Article 7, Annex III) properties of a mixture of substances, based on the properties of the individual components. This is intentionally made as "accurate" as possible, in order to discourage animal tests of mixtures. Whilst for most toxicological or ecotoxicological endpoints, the calculation method is an alternative to results of tests on specific mixtures (cf. argument above), for certain end-points, cancer, mutagenicity and reproductive toxicity, the use of the calculation method is

mandatory. (Article 6 (2)). As a result, long-term studies to evaluate the carcinogenicity (or reproductive toxicity) of mixtures are in reality banned, since the results cannot be used as a substitute for the calculation method.

6.16 The other example is that of notification of new substances. In earlier versions of the testing requirements for new (notified) substances under Directive 67/548/EEC, there was a requirement to test. This ignored the fact that there might be several companies/importers wanting to notify the same substance. This could then lead to each company carrying tests on the same substance. Again, there is a specific reference to 86/609/EEC in the seventh amendment (Council Directive 92/32/EEC of 30 April 1992, JO 154, 5.6.1992, p.1). Whereas no. 9 (unnumbered in text) includes: "whereas all appropriate measures should be taken to avoid the duplication of tests on animals".

6.17 The new rules are found in Article 15, which introduces a mechanism to prevent duplication of testing, if there is more than one notifier.

6.18 Article 10 (5) deals with further testing.

"When manufacturers or importers are asked for further information and/or testing, they must also check, in view of the need to limit practical experiments on vertebrates, whether the information needed to evaluate the substance is not available from former manufacturers or importers of the declared substance and cannot be obtained, possibly against payment of costs. Where experiments are essential, it must be checked whether tests on animals cannot be replaced or limited by other methods. Necessary laboratory tests must be performed with due respect for the provisions of 'good laboratory practice' as laid down in Directive 81/18/EEC and for provisions of 86/609/EEC."

6.19 Legislative requirements for testing are not purely scientific, cost of testing considerations may also be considered. This can be seen in the choice of testing strategies for new notified industrial chemicals (EEC, 1992). Here the test requirements vary with the amounts of the substance to be put on the market. This differentiation reflects both scientific and risk management concerns. The amounts put on the market are viewed pragmatically as a surrogate measure of the extent of exposure, and hence smaller market volumes represent a potentially smaller exposure, and hence a potentially lesser risk. At the same time, increasing test requirements matching an increasing market potential also reflects the economic burdens imposed on the producers or manufacturers. It is important, however, to understand the likely use and distribution of the chemical for this pragmatic approach to be acceptable for individual products.

6.20 In contrast for the investigation of the effects of a particular emission source on the environment, it is difficult to specify in advance a unique set of issues that need to be considered. The geographical scope of the risk assessment can be set at different levels, each of which would require different types of hazard identification. Depending on the circumstances, studies could be limited to an evaluation of the acute toxicity to the aquatic species present at the site. Under other circumstances, a range of additional issues involving testing from chronic as well as acute effects and testing of the effect on whole biotopes rather than individual species might be relevant. In

particular, it is important to recognise that whilst only a small number of surrogate species may be studied, a full risk assessment should ideally cover the whole range of potential impacts on the environment (receptors).

6.21 Two types of test for identifying hazard may be identified:

a) specific endpoint tests, which are designed to identify a single biological effect only, e.g. mutagenicity tests

b) non-targeted endpoint tests, e.g. sub-acute and chronic tests.

For most purposes both types of test are necessary. However, the more background information that is available on the risk source or closely related risk sources, the greater the usefulness of endpoint specific tests.

6.22 Future developments in hazard identification and hazard characterisation tests are likely to be influenced strongly both by advances in the science of molecular biology and by socio-economic factors. These external forces are unlikely to pull in the same direction. There will be undoubted pressures for increased testing, both by regulatory authorities (to meeting continuing public concerns about product safety and to comply with international harmonisation agreements) and by companies (in order to protect themselves from product liability litigation). Demands will also continue to reduce in vivo testing because of issues of mounting costs and societal worries about animal welfare and ethical issues regarding biological experimentation (see also Chapter 10).

6.23 It is considered that the outcome of this continually evolving environment for hazard identification and hazard characterisation investigations will be:

a) development of a comprehensive data bank which will allow much more reliable prediction of adverse effects likely to be produced by new / existing sources;

b) an increasing emphasis on non-invasive methods of assessing the health status of test animals and the use of dosage regimens which do not cause frank toxicity;

c) more specific and shorter term in vivo studies;

d) further development of endpoint specific in vitro tests;

e) progressive availability of sensitive molecular biological methods (and other analytical methods) for a far wider range of parameters. Progress in the human genome project (e.g. the National Institute of Environmental Health Sciences-NIEHS Environmental Genome Project in the USA) is likely to be one very important stimulus to this process;

f) Better observation of the risk source in use, i.e. in field studies, epidemiological investigations;

g) Application of a threshold of toxicological concern in hazard characterisation.

Improved data bases

6.24 An important barrier to hazard identification is the lack of a comprehensive data base which can readily provide:

- Information on structure activity relationships and structural alerts;
- Evaluated summaries of previous studies for each risk source;
- Indications from new areas of biological research which are prompts for an alert for certain classes of chemicals.

Although a number of data bases are available for particular purposes (e.g. IUCLID, European Chemical Bureau of DG Environment), none at present are available which come close to meeting this need. A database of this nature would enable the existing substances testing regimes to concentrate on those substances of variable or uncertain composition. For an effective database to be established, it will also be necessary to conduct in addition specific research along the following lines:
- testing of "key" substances that enable important gaps to be filled (a number of those key substances may have no commercial use);
- testing of selected chemicals to validate existing databases.

Non-invasive methods

6.25 Non-invasive methods are of particular utility because they tend to be ethically (sociologically) more acceptable, minimise the effects of stress on the parameters being measured and may be less demanding on the toxicologists' time. (This might result in cost saving). Techniques which are already being applied in a rather limited way in human patients which should in principle be readily utilisation in the field of animal studies to identify and characterise hazards include:

- Nuclear magnetic resonance spectroscopy
- Electron spin resonance spectroscopy
- Breath analysis / measurement of other volatile substances exhaled by the body.

More purpose specific tests

6.26 The principal emphasis in vivo toxicity test development for the past two decades has been the introduction of a growing array of guidelines for test procedures. There are several benefits of standardisation of approaches. However, one can also envisage a number of disadvantages. Of one concern being the inappropriate use of scarce resources on tests. The development of an increasing range of genetically modified strains of laboratory animals opens up possibilities for selection of test species which may be more relevant for testing particular classes of xenobiotics. Establishment of reliable data bases (see above) will also inform a more selective and scientifically justified testing approach. The emphasis is likely to be on the more effective use of smaller number of animals and the termination of experiments before long-term outcomes have developed (e.g. transgenic systems for carcinogenicity testing). The following are among expected technological developments which may facilitate this change in the emphasis of testing :

- New strains of genetically modified animals;
- Implanted biosensors to analyse changes in levels of endogenous or exogenous substances in the body;
- Implanted or external strain gauges to detect body movement.

Clearly, employment of the latter techniques is dependant on the micronisation of currently available devices.

Better integration of in vivo and in vitro studies

6.27 In vitro studies provide the opportunity for obtaining human information that otherwise, for ethical and / or practical reasons, would not be achievable. Significant progress in developing suitable methodology is being made in many areas, e.g. cell

culture on permeable membranes for electro-physiology studies, multi-cell type systems. At its 13th meeting, the Scientific Group on Methodologies for the Safety Evaluation of Chemicals (SGOMSEC) has comprehensively and critically discussed the issue of alternative testing methodologies both for toxicology and ecotoxicity testing. All major areas in toxicology have been addressed. The results and critical evaluations have been published as a special issue of Environmental Health Perspectives (*Environmental Health Perspectives*, Supplements, Vol. **106**, Supplement 2, April 1998). However, as such methodology becomes utilised for toxicology studies, it will be increasingly important that scientific committees have a consistent view of how to validate and interpret the results obtained.

More sensitive analytical techniques

6.28 Developments in analytical methodology have been very rapid over the past 20 years. It is inevitable that both the scope of substances which can be measured and the sensitivity which can be achieved will continue to improve. This will aid, in particular, the early detection of changes following the administration of test substances. However, there is a possibility that the availability of such techniques will lead to the identification of changes which will be difficult to interpret in toxicology terms. The availability of more sensitive analytical methods is also likely to result in the detection of trace levels of more and more foreign substances in the human body (see Chapter 7). Advances in DNA / RNA analysis and protein identification are likely to have a growing influence on the scope of hazard identification.

Better field observations

6.29 For certain risk sources, prior to approval for marketing, if no field data already exists, some form of monitoring and surveillance should be a prerequisite. For existing risk sources the not uncommon view that the absence of data about any adverse effects equates with the absence of adverse effects is likely to be increasingly challenged. Field studies are needed to fill the serious data gaps. This is likely to be the case both for human and environmental impacts. New monitoring protocols will need to be developed to meet this need. An integrated human and ecosystem approach to risk assessment would be valuable in this area.

Application of the principle of threshold of toxicological concern

6.30 The demand for the demonstration of the safety of an ever widening group of both natural and synthetic chemicals (e.g. all existing substances, natural flavourings) will require, if it is to be addressed successfully, a reliable means of assessing priorities. It is inconceivable for both practical and ethical reason to achieve this by using a basic data set of *in vivo* and *in vitro* toxicity testing for all agents. Rather, priorities will need to be determined on the basis of:

- Reliable assessment of actual exposure levels
- Consideration of physico-chemical properties including structural alerts.

6.31 The underlying premise to support such a strategy is that a common exposure level can be defined that will not cause any significant adverse effect (see Chapter 8 – Thresholds) for any chemical regardless of its chemical class. This exposure level is

termed the "threshold of toxicology concern" (TTC). On this basis, provided the exposure level to a chemical is below the TTC value, it can be regarded as having no appreciable risk even in the absence of any toxicological data. In practice, it is important to have some additional reassurance by checking that the chemical structure does not indicate the potential for a potent irreversible or serious toxic effect (i.e. there are no structural alerts).

6.32 The concept is widely accepted by toxicologists. However, there is an ongoing debate about the actual level at which the TTC value should be set. In view of the great importance of the concept to addressing the risk resulting from exposure to an ever increasing number of chemicals in a transparent manner, the Scientific Committees should address the concept of the TTC and identify guidelines as to how it should be applied. It must be noted that the application of TTC depends greatly on the development of agreed methods (including models) for the adequate assessment of total exposure to each chemical. This should therefore be a priority for further research.

MICROORGANISMS

[*Note*: see also Appendix 4, Report on microbiological risk assessment, and Appendix 5, Report on risk assessment for transmissible diseases]

6.33 As for chemicals, microbiological risk assessment usually begins with hazard identification. The context and use of the risk assessment determine the focus and extent of microbiological hazard identification. Applications of microbiological risk assessment may be employed to understand a public health problem, assess the risk from exposure to a defined product, or for policy determination (ACDP, 1996). The hazard identification process may be quite different in each category.

6.34 Firstly, the case of microbiological risk assessment as applied to understanding a public health problem, i.e. to situations where the focus is primarily on a disease and its potential outcomes. For example, assessments may be applied to circumstances such as recent recognition (or suspicion) of the aetiology of a disease (e.g. *Campylobacter jejuni* and gastro-enteritis), situations involving a recognised pathogen (e.g. long term consequences of infection by *Salmonella*), instances where the etiological agent is rapidly changing in character (e.g. influenza), or where a recognised organism is found in new situations (e.g. *Staphylococcus aureus* and toxic shock syndrome).

In such situations, microbial hazard identification is quite similar to hazard identification for toxic chemicals. It consists in identifying (or confirming) the inherent capability of a microbial agent to cause adverse effects, the potential harm, and the circumstances in which adverse human health effects may be expected. Hazard identification is based on analyses of a variety of data that may range from laboratory analyses to clinical observations and epidemiological information. In this regard, traditional pathogens are relatively well documented and the formal requirements for hazard identification are minimal. However, for new, emerging pathogens, or when facing new situations, an essential aspect of hazard identification is to evaluate the weight of the scientific evidence for adverse effects in human (or

animals), the ways in which they can be expressed, and the major sources of exposure.

6.35 Hazard identification, when developed in the framework of the assessment of the risk from exposure to a defined product, requires a different approach. Here, the question of interest is which pathogens may be transmitted by the product (e.g. which pathogens may be transmitted by a given food commodity, or which pathogens may be introduced in an importing country via import of live animals or their products). In this context, hazard identification is a categorisation activity, identifying which microbiological agents may be potential hazards. In such circumstances, the focus of hazard identification will be to use available microbiological and epidemiological data to determine which pathogens have been, or potentially could be, associated with the product.

Reliable hazard identification is dependant on the availability of public (or animal) health data and information on the occurrence and levels of pathogenic micro-organisms in the product of concern. In this context, an essential aspect of hazard identification is to differentiate between trivial and non-trivial concerns. More than one hazard may be identified, arising from the same product, but possibly in different circumstances. Usually, the subsequent stages of the risk assessment would be applied to each hazard identified.

6.36 Microbiological risk assessment may also be utilised as a basis for policy determination. For instance, the assessment may be an aid to identify whether and which action has to be taken, to identify the best points at which to implement control, to compare the merits of different preventative/control approaches, to establish product standards. In such circumstances, the situation of concern is already identified by the risk managers. It usually involves the definition of a pathogen/product or process combination (e.g. assessment of the health risk from *Listeria monocytogenes* in ready to eat foods). There, hazard identification is straightforward and consists mainly in collecting information on the characteristics of the pathogen that affect its ability to be transmitted by the product and to cause disease in the host. For example, in the food sector, most of the formal risk assessments that have been recently published fall in this category, where the hazard identification stage focuses on gathering information on a specified microbial pathogenic contaminant with regard to a given food or groups of foods, to serve as input to the elaboration of a (process) risk model utilised for further analysis.

6.37 In all these situations, the key to hazard identification is the availability of public (or animal) health data. For this purpose, there is a general need to develop and improve etiological studies, (identification of causal relationships; determination of the fraction of illness attributable to specific (groups of) products), surveillance systems, and investigation of disease outbreaks. Even for well known pathogens, research is needed to better characterise the pathogenicity of micro-organisms, the elements/factors influencing pathogenicity/virulence, including, because micro-organisms may change in character, the acquisition and loss of virulence factors and the mechanisms involved.

6.38 Finally, an important element for hazard identification is the development of better analytical methods, to facilitate detection and characterisation of pathogens

responsible for illness (e.g. at present, in many food-borne outbreaks, the pathogen responsible is not detected), to detect and characterise pathogenic types or strains, and to enumerate them. Appropriate strategies should be developed to that aim.

CONCLUSIONS

i) Hazard identification is conducted to identify characteristics and ranges of adverse human and environmental health effects due to exposure to the risk source. Although it is typically part of a full risk assessment, it may also be used without any consideration of dose response, species variation or exposure assessment. Under such circumstances, it is essential that hazard identification is not confused either by risk managers or other with a risk assessment.

ii) Essential requisites for a high quality scientific hazard identification are considered. The process must start with a reliable characterisation of the hazard.

iii) The availability of comprehensive data bases to allow the most cost effective and reliable prediction of adverse effects is considered a high priority for improving the quality of chemical hazard identification.

iv) Some predictions are made regarding the development of methods for identifying the effects caused by risk sources e.g. *in vitro* methods and structure activity considerations to supplement and/or replace animal *in vivo* studies.

v) It is important that the formalisation of hazard identification does not result in the discarding of important information. This is particularly likely if data is of a qualitative value only.

vi) A critical element of hazard identification is the decision on what constitutes an adverse effect. For gross toxic effects there is unlikely to be any doubt that they are adverse as far as the test species is concerned. However, as indicated above, the technical ability to detect increasingly subtle changes has increased very considerably over the past 2-3 decades and there is no doubt that these developments will continue. The application of methodology for analysing endogenous substances in tissues and tissue fluids is likely to remain ahead of the understanding of the significance of short or longer term biological changes due to these components. Also, the recent developments in genomics and proteonomics technology will create interpretation challenges in the future in relation to hazard identification and hazard characterisation. The question as to which changes are really adverse and which are normal physiological adaptations will become any increasingly challenging one to answer. A means of ensuring a common approach to such evaluations is required.

7 EXPOSURE ASSESSMENT

"The best way to suppose what may come,
is to remember what is past"
Lord Halifax (1750)

GENERAL

[*Note*: see also Appendix 2: Report on exposure assessment]

7.1 Exposure assessment is concerned with the likely actual levels and duration of exposure to the risk source of human and environmental species. An exposure assessment characterises the nature and size of the human populations and/or ecological communities exposed to an emission source and the magnitude, frequency and duration of that exposure. For agents such as medicines given to patients, the oral exposure can usually be defined quite readily. However, for other agents, for example environmental contaminants, assessing the extent of human exposure can be very difficult, particularly where multiple routes of exposure are involved. For assessing the total risk, it may be necessary that every significant source of exposure to a risk source is properly identified.

7.2 In the case of microbiological agents, there is an added dimension of micro-organism replication under particular storage/processing/*in vivo* conditions. For chemical agents too there are additional considerations, for example it is necessary to give proper consideration to the role of degradation products and / or metabolites in either increasing or decreasing specific adverse effects. For many of the Scientific Committees the reliable estimate or exposure represents the most challenging step in a risk assessment. Also, there is usually greater uncertainty in exposure assessment, compared with hazard characterisation.

7.3 Exposure assessment may be carried out to estimate past, present and/or future exposures. Exposure assessment may be carried out:

i) to relate effect to exposure. Many retrospective epidemiological studies have floundered on the failure to identify the levels and temporal aspects of exposure of the population groups being investigated. In the case of current exposures in principle relevant analytical studies can be performed while for prospective assessment some form of extrapolation / modelling needs to be applied.

ii) to establish temporal changes and regional differences in exposure. This is particularly the case for exposure of environmental species. Concern may be directed to a substance which has not been measured previously. The solution is the development of banks of stored biological and other samples collected over many years which can be analysed should such a situation arise. Some sample banks of this nature are in existence (e.g. the German Federal human and environmental specimen banks) but others are needed to represent the conditions of environmental exposure across the existing and new Member States.

iii) to provide assurance that exposure will remain below a defined level. This is the most common use of exposure assessment among the DG SANCO Scientific Committees. An issue which needs to be clarified is the extent to which such assessments are only performed during “normal / recommended”

use of a risk source. Should extreme release/exposure scenarios also be assessed and, if so, how should they be selected?

7.4 Exposure assessment considerations. The first step is to characterise as fully as possible the nature of the risk source (see Hazard Identification). Following this "exposure" may be defined in a number of ways:

i) Identification of the levels of each component of the risk source in contact with the "receptors" (human and/or environmental species) (usually termed "exposure dose" or "external dose");

ii) Estimation or measurement of the uptake of the risk source into the human body / organisms and levels being modified by distribution metabolism (inactivation) and excretion (usually termed "the absorbed dose" or "internal dose" or "bioavailability");

iii) Determination of the time-integrated concentration of the risk source at the target (critical) organ/tissue (often termed "the critical organ dose" or "target dose"- see Figure 7.1).

An important issue is how the external dose should be expressed. Traditionally the term "per unit body weight" has been favoured. A review should be conducted across the Committees to assess whether from a scientific point of view this remains the most appropriate means of expressing external dose. Other options (see 8.36) are "per unit metabolic activity body surface area" or "rate of apoptosis". Consideration should also be given for each chemical in considering the expression of dose as to whether peak levels are the most important factor or the integration of levels over time (i.e. Haber's Rule).

CHEMICALS

[*Note*: see also Appendix 3: Report on risk assessment for toxic chemicals]

7.5 For a number of purposes, some assessment of the extent and rate of absorption, distribution, metabolism and excretion is needed – in most cases it is desirable. In the absence of actual measurements, modelling may be employed. The assumptions in such modelling/calculating absorption by the oral, dermal and inhalation routes in man and environmental organisms including assessing the bioavailable portion need to be identified and justified. Monitoring / surveillance is very important in order to check the validity of such models and, where appropriate, to improve them. Exposure assessment in chemicals often relies on data on usage and/or mathematical modelling which may be difficult to verify. This is an area where a number of committees may need additional expertise.

7.6 Risk assessment and specifically exposure assessment(s) are conducted in different legislative/regulatory frameworks. There is a range of ultimate goals of exposure assessments for consumers and the environment which also result from different technological sectors of the use of chemical substances as well as from the consideration of basic differences in hazard potentials for groups of substances. While the ultimate goal of consumer protection is to protect each individual, for the environment protection of populations and systems are the priority. In the framework of exposure assessment this implicates principally differing sets of information as well as precision required. These principal differences of groups of products for

which exposure assessment has to be done, clearly show that a full harmonisation of exposure assessment aiming at using identical approaches is impossible.

7.7 This constraint can easily be understood when comparing different sectors:

Establishing food safety e.g., with regard to contaminants needs an quite different approach as compared to cosmetics safety e.g., to which humans are intentionally exposed. Plant protection agents being intentionally biologically active need a more precise exposure assessment than low hazard chemicals. An important source of differences in exposure assessment, from a practical point of view, relates to the way in which exposure of the final consumer is determined (e.g. use of mean exposure; use of standardised consumption patterns such as the FAO food balance sheet; treatment of specific sub-groups of consumers/specific at-risk groups). For the assessment of the environmental exposure there are similar practical differences, e.g. using monitoring information or estimates from model calculations. The sectorial legislation and the resulting specific requirements for exposure assessment are presented in some details in Appendix 2 (Report on Exposure Assessment).

7.8 The major objective of harmonisation therefore should be to have for all areas a compatible assessment leading to results most appropriate for the required level of risk assessment. Where different approaches to exposure assessment have to be taken, the primary question is whether exposure assessment is carried out at similar levels with regard to safety considerations. Refined national exposure assessments for consumers and the environment should be increasingly used to be combined to the EU-level.

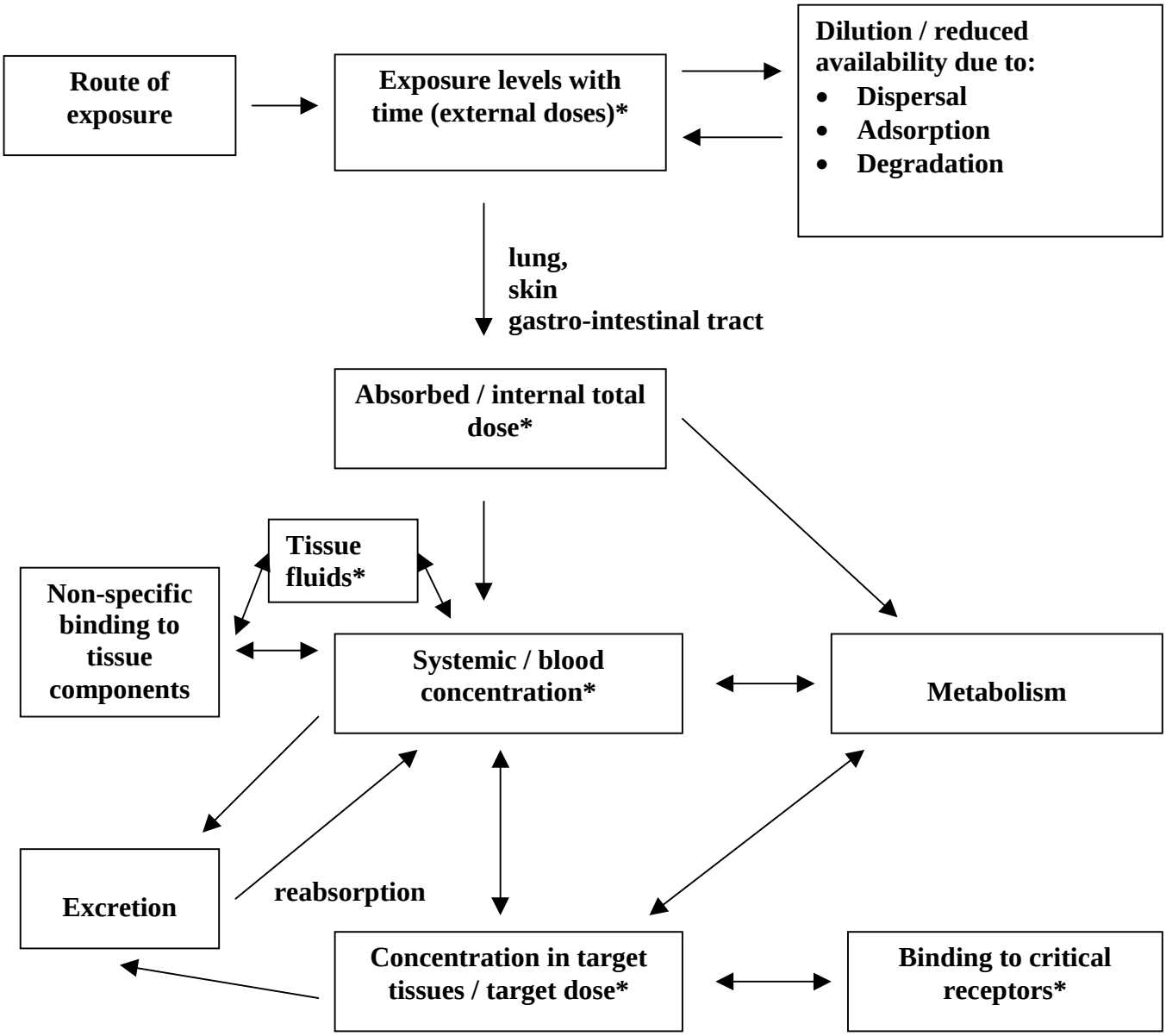
7.9 There is a need for a common and precise "language" in exposure assessment ("semantic homogeneity" both in the data utilised and in the approach taken for the assessment). While obvious to the experts commissioned for doing the assessment, there is a need to communicate to the users the nature and meaning of the assumptions made and of the approach taken and how these would influence the interpretation of the results provided across all the Scientific Committees and internationally. Of all the areas where the terminology is confused, exposure assessment terminology is probably the least standardised.

Use of Scenarios

7.10 Essentially in all approaches to exposure assessments as a case-by-case exercise evaluative or interpretative scenarios are used. Depending on information availability and final assessment (deterministic or probabilistic), they are undergoing improvements with the advancement of scientific understanding and data availability. Details on scenario building in the different Scientific Committees are given in Appendix 2.

7.11 An important issue is the identification of the database utilised and the availability of this database to other potential users.

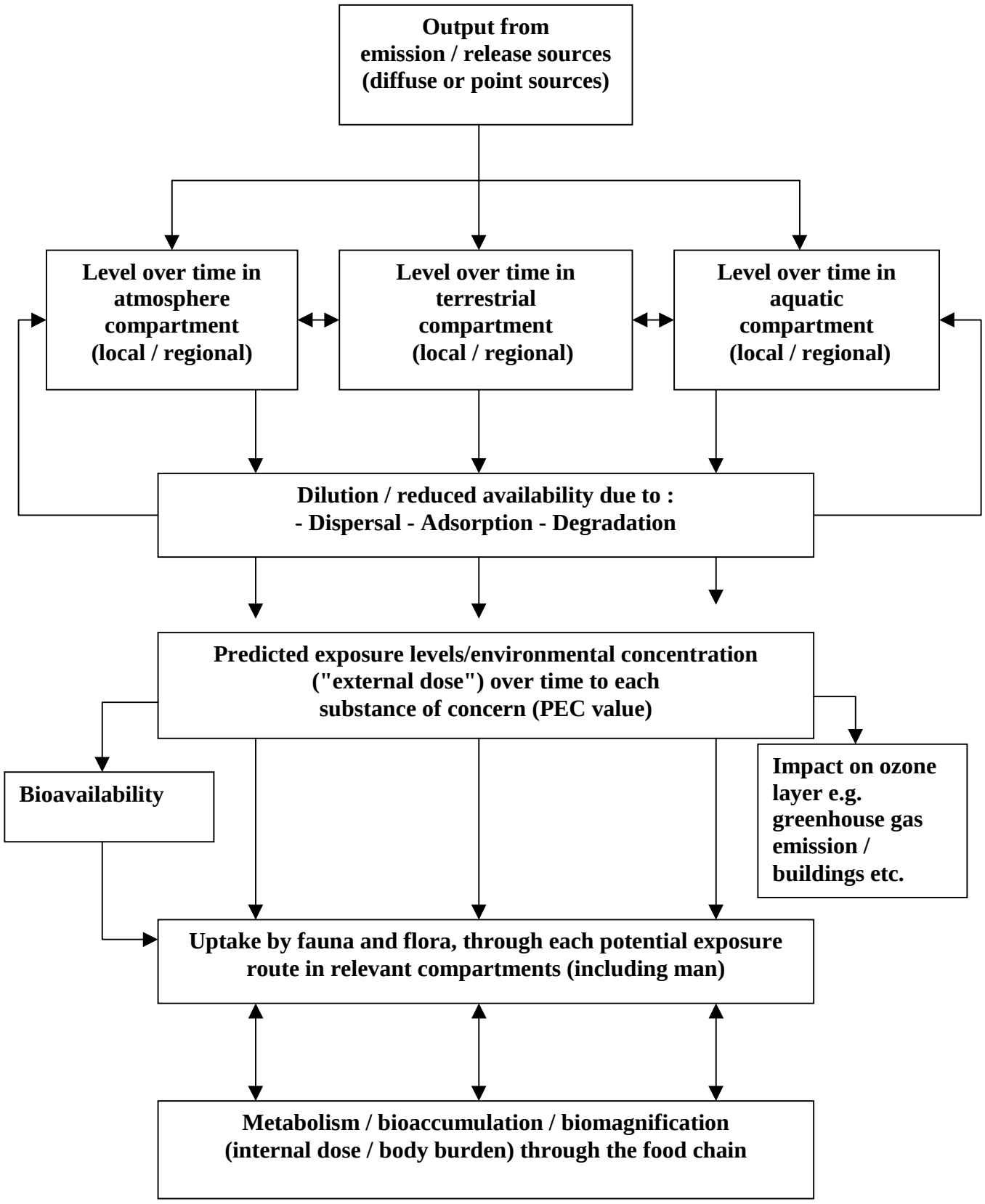
Figure 7.1: Considerations in integrated human exposure assessment



*** Situations for which exposure may be assessed (expression of "dose")**

[NB: It may or may not include selected or all metabolites / degradation products]

Figure 7.2 : Considerations in environmental exposure assessment



7.11 All scenarios are not intended to reflect one specific local situation, but have the objective to be representative of mean, typical or most sensitive situations in a region or throughout the European Community. Nevertheless, when a standard scenario is used, it is currently still difficult to determine its representativeness. Such scenarios are either built on available data or are the basis for collection of data. Therefore, attention should be given to the comparability of data collected in different contexts.

"Total" Exposure Assessment

7.12 A comprehensive exposure assessment is important in addition to the specific ones, e.g. via food, since the total exposure of humans and the environment have to be considered in risk assessments. The exposure assessments by the scientific committees follow the respective legislation and it is only the chemical substances legislation/Directives which follow this integrated approach. The others only consider a certain use of chemicals, e.g. in plant protection or a pathway, e.g. in food safety. The same chemicals, however, may be used for other purposes or exposure may be by other media than those in the focus of legislation.

7.13 A realistic description of the exposures of consumers and environment requires a stratification of input-data in relation to ways and means of primary production and primary products and the full life-cycle of the product. This means that this rigid sectorial scheme is not only unrealistic, but also limited in its ability to cope with exposures in a timely and efficacious way. Where a given chemical is used in different sectors, or exposure is via different media, important pathways may be overlooked resulting in a problem from the consumer point of view.

7.14 A "total" exposure assessment may be difficult to be carried out in practice. Sources of difficulties may include for instance: the provision of an appropriate figure of all relevant pathways (difficulties for the assessors specialised in one sector to identify all relevant pathways in other sectors); the potential variability of such pathways; the treatment of specific groups of consumers/at-risk groups (difficulties in determining specific exposure rate for particular groups; percentage of the particular groups in the population); the differences in metabolic pathways vs. different exposure routes.

7.15 Nevertheless, when different pathways (routes of transmission) can be envisioned, there is a need to take all of these into consideration. Interaction between the different scientific committees and regulatory agencies in this regard is an important issue (e.g. sequentiation of pathways; where the competence of a committee stops, another committee should take over the assessment in a concerted approach).

General Issues Related to Data Availability

7.16 For economical reasons exposure related data are usually estimated or measured following the requirements of the usually formalised steps in the sequence of assessment. At the higher levels of assessment monitoring data provide a crucial tool.

7.17 There is a need to improve the comparability of data critical for the conduct of exposure assessments (data sets should be homogenous in the sense, that their comparability has been established. Harmonisation should be at least to the extent,

that data provided should follow a similar format and giving minimum information for the requested purpose.)

7.18 To that aim, there is also a need to study and experimentally implement EU-wide surveillance systems to generate "minimal homogeneous data sets". It is unrealistic to consider average exposures to an agent to be assessed for the whole European Community. Even the extrapolation of data in a given geographical area to the entire Union is as inappropriate.

7.19 A "probabilistic" approach is essential to represent the complexity of real situations and taking into account variability and uncertainty. Although complicated, a probabilistic treatment of exposure information improves the comprehension of the consumer in risk communication. It is recognised that the development of this approach will rely on the collection of more, accurate, quantitative data. While such data collection will in many cases be dealt with at member state level, common guidance for the data collection should be established at EU-level in order to facilitate data exchange and comparability. It can identify variables with the greatest impact on the estimates (sensitivity analysis).

7.20 Apart from these issues, following experience of exposure assessments, there are exposure related problems, which are not systematically dealt with and consequently no reliable data are available. One of these issues is the accumulation of contamination by recycling of technical and biological materials, which may lead in the long-term to an increased exposure without being attributable directly to use in a technological sector. An increasing variety of models are becoming available for modelling exposure in different situations. It is important to have a common policy between Scientific Committees on the validity and areas of utility of these models.

7.21 On the other hand, as indicated above, for the temporal trend assessment of exposure, banked environmental and human specimen provide an important tool which has not been utilised so far according to its potential.

7.22 Technical developments which are likely to impinge increasingly are:

a) progressive improvement in the sensitivity and specificity of analytical methods. These will affect the assessment of “external” dose / exposure but will have a much greater impact on the assessment of “internal dose” / “critical organ dose”.
b) Simplification and improved robustness of personal samplers. This will enable estimates to be made of 24 hr exposure or longer to air borne substances, both external and in the home.
c) Development of readily accessible data bases and banks of exposure information across Member States.

MICROORGANISMS

[*Note*: see also Appendix 4: Report on microbiological risk assessment, and Appendix 5, Report on risk assessment for transmissible diseases]

7.23 For microbial pathogens, it has to be realised that the exposure assessment cannot simply be the probability of presence or absence of the pathogen. Because the probabilities of infection, morbidity and mortality increase substantially when the levels of pathogens are increased, microbiological exposure assessment must also estimate the numbers of micro-organisms that are likely to come into contact with the host (having regard to the transport medium and the route of transmission, e.g. the number of micro-organisms likely to be ingested for foodborne pathogens). In regard to the latter, microbiological exposure assessment is basically faced with the need to develop a more dynamic approach compared to traditional chemical exposure assessment to account of numerical changes in the microbial population (ICMSF, 1998). In particular, micro-organisms have the potential to multiply and/or die in a product or transport vehicle. Microbiological exposure assessment must account of these changes in response to intrinsic and extrinsic factors while taking into consideration the influence of the conditions of production, processing, storage and use of the product vehicle.

7.24 Microbiological exposure assessment is therefore a process which involves the interactive characterisation of the source(s) and route(s) of exposure, and the determination of pathogen occurrence, to culminate in the evaluation of the magnitude, frequency, and pattern of exposure to a pathogen. Where the risk from exposure to a defined product or for policy determination is involved, the specifics of the exposure assessment will depend on the situation of concern and the scenario(s) selected when commissioning the assessment.

Characterisation of the source(s) and the route(s) of exposure

7.25 Many elements may be considered, such as identification of the media, units of exposure, routes of exposure, size of the exposed population, demographic of the exposed population, spatial and temporal nature of exposure(whether single or multiple exposures), behaviour of exposed population. The vehicle(s), such as a cosmetic product, drinking water or food, should be identified. From a general point of view, a variety of media may be potentially involved in the transmission of microbial pathogens, such as food and drinking water, medicines and medical devices, cosmetics, household products, and the general environment (e.g. air or recreational water).

7.26 When the risk assessment is utilised with reference to a specified product or group of products, this activity is straightforward (e.g. ingestion of identified pathogen(s) with a given food product potentially contaminated). The associated unit and route(s) of exposure (for instance, number and size of food servings) should also be determined, together with their possible variability. The size and demographics of the population exposed should be determined. Consideration of the temporal nature or duration of exposure, and potential for secondary transmission may also be important. Routes of exposure and transmission potential are in turn influenced by the behavioural characteristics of the potentially exposed population.

Pathogen occurrence

7.27 The basis for pathogen occurrence determination is information on the characteristics of the pathogen that affect its ability to be present, survive, multiply or die in a given vehicle. This basically encompasses gathering information on the ecology of the pathogen and its behaviour in response to environmental conditions such as nutrient availability, temperature or pH. When not already done in the hazard identification stage, collating this information is relevant at this stage of the risk assessment.

7.28 Based on the above information, pathogen occurrence involves describing the occurrence of a pathogen in a medium, including identification of average levels, frequency distribution, peaks, seasonal variation, and association with other temporal or spatial changes. As previously indicated, essential to pathogen occurrence is the determination of frequency and level or concentration of the pathogen in the environmental media of interest and/or the potential source of the pathogen (e.g. number or percentage of samples of a food product potentially contaminated, and number of micro-organisms likely to be ingested, with their inherent variability). Such estimates may be influenced by a number of factors.

7.29 The physical state of the pathogen in the environment or in a given product is an important factor. For instance, aggregation or particles association can provide protection to stressing factors and can also result in a higher exposure than suggested by analytical results. A thorough understanding of the niche of a pathogenic micro-organism may also be important for some assessments. For instance, some assessments may be concerned with the impact of a plant or equipment lay-out or material, or of product design (structure, composition) that may greatly affect the ability of a pathogen to survive or multiply. Other variables affecting occurrence may be seasonal, geographic, or climate related.

7.30 Where the primary goal of the risk assessment is to evaluate, as accurately as possible, the risk to a population from a given pathogen/product combination, the exposure assessment should utilise data and information as close to the final exposure point as possible. When the risk assessment may be utilised for policy making, this approach may not be sufficient, and the exposure assessment should be structured so as to provide insight into the factors responsible for magnifying the risk, or ways to reduce the risk. In such a situation, determination of the pathogen occurrence should take into account the various factors that may influence the level(s) or concentration of the pathogen before the product reaches the consumer, and of their relative influence on the occurrence and distribution of the pathogen.

7.31 Pathogen occurrence determination then requires integration of three different types of information. The first is related to the presence of the pathogen in the raw materials. The second should incorporate the effects that processing, distribution, handling, preparation or use may have on the level and distribution of the pathogen. In this regard, control processes, such as water treatment or thermal inactivation in a food process, may have significant effects on pathogen occurrence and should be considered. Variability and reliability of control processes and the interdependence of multiple control processes should be analysed, as well as the potential for recontamination after treatment. The third focuses on consumption/use patterns and

on consumer practices that may affect microbial levels. When information on a particular pathogen is lacking, it may be necessary to use occurrence data for surrogate or indicator species. The limitations and uncertainty associated with those data and their use should be considered.

7.32 "Exposure assessment" is intended to provide a qualitative and/or quantitative evaluation of the magnitude, frequency, and patterns of exposure to a pathogen. When the emphasis is on a pathogen/product combination, and because microbial pathogen levels can be dynamic, an important feature of exposure analysis is the description of the pathways from production to consumption. Scenarios can be constructed to predict the range of possible exposures. They should reflect the effects of the variety of factors that impact on pathogen levels and distribution, and account for variability and uncertainty in the parameters involved.

7.33 The present tendency is to construct exposure assessment models, to describe and analyse the interaction of the above mentioned factors. The structure, comprehensiveness and level of details of the model depends on the purpose of the risk assessment. For example, if the assessment is a nation-wide evaluation of an industrial sector for broad policy considerations, the model would reflect the diversity in product formulation, production facilities, sources of raw material, distribution systems, marketing options. If the purpose of the risk assessment is more focused, then a modular unit operation approach has been suggested, where the model describing the pathways and processes leading to exposure are divided into discrete units or sub-modules, eventually linked together.

7.34 For qualitative (or semi-quantitative) assessments, simple models that describe the pathways of exposure can be developed. More complex representations may be incorporated involving for example Event Tree or Fault Tree analyses, which identify risk variables, or events that could occur, and may incorporate a semi-quantitative expression of certain parameters and probabilities.

7.35 In quantitative exposure assessments, the relationships between the components of the assessment are modelled mathematically. A significant figure of quantitative exposure assessment for microbial pathogens is the use of predictive microbial models, as sub-sets of the larger exposure model. Predictive microbial models use mathematical expressions to describe how bacterial numbers change with time and how the rate of change is influenced by environmental conditions. Significant advances have been made in this field in recent years and models for growth or inactivation of pathogens are now available (see Appendix 4).

7.36 The same mathematical model may be the basis for a deterministic or a probabilistic approach, depending on how the model variables are represented. In a deterministic approach, a quantitative assessment of the exposure is conducted based on single point estimates of the model parameters. The sensitivity of the deterministic model can be evaluated by selecting different combinations of each input parameter, to see how much the outcomes vary. Deterministic models have several limitations, in particular, by using a single value to represent a data set, they tend to ignore variability and uncertainty. Probabilistic approaches have been recently developed to overcome these limitations. In probabilistic modelling, variability and uncertainty are taken into account by substituting probability distributions to point estimate values.

Probability distributions are assigned based on experimental data, knowledge of the underlying phenomena, or may even be derived from expert elicitation if no other information is available. A range of values is used and the frequency with which different values occur is also characterised. Probabilistic assessments can de developed using analytical (algebraic) techniques. This, however, is not always possible and may be tedious even for a simple model. An alternative to the analytical solution is to use stochastic simulation techniques, such as Monte Carlo simulation. This technique employs a value-generating protocol that randomly selects a value for each parameter in the distribution assigned. The single values for the different parameters are used to calculate a mathematical solution defined by the model and the result is stored. This sequence is repeated several thousand times (trials or iterations) with a different set of values until a profile emerge and the system stabilise. The result is a frequency distribution for the output of interest, which represents the combined ranges and frequency of the input parameters. Several commercial software that facilitate this approach are presently available. Despite its increased complexity over the deterministic approach the probabilistic approach is now becoming the preferred approach to quantitative microbiological exposure and risk assessment (an extensive discussion of exposure assessment modelling may be found in Appendix 4).

7.37 Key to exposure assessment is the availability of data needed to estimate the exposure. This relates first to data describing the occurrence and levels of micro-organisms in the environment or in specific products. Since microbiological analyses are to a high degree method sensitive, and the result determined by the sensitivity and specificity of the method used, the sampling plan utilised etc. it is often difficult to use and compare data from different sources. An important element for improvement of the assessments is therefore the use of equivalent analytical methods and sampling plans. Second, since in most cases microbial contamination and microbial evolution need to be investigated throughout long or multiple pathways, there is a need to obtain more precise data on the nature and effect of intrinsic and extrinsic factors and process parameters. Third, additional information is needed on use/consumption patterns. This relates to what different groups of people use, drink or eat, how much, handling and consumption practices, including abnormal, or extreme exposures. In many sectors where microbial risk assessment may be applied available data are qualitatively and quantitatively insufficient. Appropriate strategies for data collection, management and retrieval need to be developed.

CONCLUSIONS

i) Harmonisation efforts in exposure assessments for human and the environment should be focussed in order to achieve consistency on improvements in data acquisition and quality.

ii) In order not to overlook important pathways of exposure, it is proposed that in exposure assessment a comprehensive, integrated approach is adopted where appropriate

iii) It is important that in the exposure assessment area a common language and strategy is adopted in respect to expression of "dose", data, assessment concepts (tiered approaches, etc.) and interpretation.

iv) With advances in the use of stochastic procedures, a consistent development of modelling scenarios representing specific groups of population, endangered ecosystems, regional and national differences is required.

v) In order to validate models of exposure scenarios, it is necessary in many cases to implement research programmes for EU-wide surveillance systems which will generate minimal data sets.

vi) A common approach is needed for defining the uncertainties in exposure assessments.

vii) In many cases, the most appropriate approach is to adopt a phased/stepwise approach starting with a rough estimate. If a sufficient margin of safety is evident, further sophistication of the exposure assessment may not be required.

8 HAZARD CHARACTERISATION

"What was vital was overlaid and hidden by what was irrelevant. Of all the facts which were present to us we had to pick just those which we deemed to be essential, and then piece them together in their order"
Conan Doyle (1894)

GENERAL

8.1 The first stage of a risk assessment, hazard identification is primarily a question of identifying the effects that are considered as adverse. Hazard characterisation is centred on the quantification of these effects, so that the dose-response relationship identified at this stage of the risk assessment can be compared subsequently with the potential for exposure (risk characterisation).

8.2 **Stages in hazard characterisation**

- Establishment of the dose response relationship for each critical effect.
- Identification of the most sensitive species and strain etc., species comparison of differences and similarities. For environmental species, sensitivity distribution needs to be identified.
- Characterisation of the mode of action / the mechanisms for the critical effects (including the role of possible active metabolites).
- High to low dose (exposure) extrapolation, interspecies extrapolation.

Dose response relationships

8.3 For an individual risk source it is generally, but not always, appropriate to consider each of the above stages in depth. Implicit behind hazard characterisation is the assumption that the relationship between the exposure and the effects considered can be determined. In some cases, a hazard may have a dose-response relationship, but the nature of the available data in general rules out the possibility of establishing this. An example of this kind of situation is irritation and corrosivity. The Technical Guidance document on risk assessment for new notified substances (Directive 67/548/EEC) and existing substances (Regulation EC 793/93) gives guidance for the hazard characterisation of these effects. The advice given on the assessment of the dose-response relationship (Section 3.7.4) recognises that whilst it may be possible to derive reliable non-irritating concentrations from human studies, “sometimes there is only simply the information that a substance is irritant or, often by inference only, that it is not”. Standard OECD tests used for identifying the hazard are not usually designed to give results with dose-response curves. However, some information of potency can be gleaned from these tests.

8.4 It must be recognised that no risk assessment can be final, as awareness of the range of potential hazards may develop along with greater scientific insight. An obvious example is the increasing awareness of concerns for the effects of endocrine disrupters on several species in the environment. The Scientific Committees have an obvious role in both an early identification of such developments (“emerging issues”) and in providing scientifically based advice regarding the risks involved.

8.5 Critical considerations in relation to dose response information are:

- How should dose-response data be handled? Current approaches often put emphasis on the data only for the highest dose which produces no detectable adverse effect (No-Observed-Adverse-Effect-Level, NOAEL). Is this always appropriate? Should trigger levels for each biological effect also be identified? For each effect deemed of concern, the question needs to be asked – can a threshold for this effect be assumed even in the absence of direct data to support it?

- Is there an appropriate means, where a threshold cannot be demonstrated, e.g. a mathematical model for extrapolation to low doses for genotoxicity mediated carcinogens ? There are major differences between the USA and most DG SANCO Scientific Committees on the treatment of non-threshold risk factors. The USA favours mathematical modelling while the DG SANCO Scientific Committees have normally used enhanced safety factors. Is there stronger scientific justification for the approach used by the EU Scientific Committees? Should Committees be encouraged to request mathematical modelling data if it is not provided? It is understood that alternatives using tumorigenic potency and a margin of exposure approach are being addressed within the EU.

- To what extent should structure activity relationships and physico-chemical properties be used to predict adverse effects? Should they be considered normally as part of the risk assessment of a particular risk source where relevant? If no, why not? Currently this approach is used widely to assess environmental impacts but uncommon for characterisation of hazard to man.

CHEMICALS

[*Note*: see also Appendix 3: Report on risk assessment for toxic chemicals]

In the case of chemicals the term dose (concentration) – response (effects) assessment is commonly used instead of hazard characterisation. However, for consistency in approach in this report, hazard characterisation will be used.

Threshold for toxicity

8.6 A threshold level of exposure, on a case by case basis, has been a generally accepted paradigm used for the past 40 years (Lu, 1988; Truhaut, 1991) in order to determine intakes of non-genotoxic chemicals that are likely to be associated with unquantified, but "negligible" risks when consumed by humans daily throughout life. Often, the existence of a threshold is assumed, even without strong scientific evidence. Is this acceptable?

8.7 This assumes a threshold of daily intake for the great majority of chemicals below which measurable toxicity will not be produced; therefore it is possible to calculate exposures for humans, which would be without significant adverse health effects (safety assurance). Safety assurance is an example of quantitative risk assessment where the level of risk is considered to be "insignificant" rather than a specific quantitative estimate. The term "safety assurance" gives the implication of complete absence of risk, but all outputs are defined as "without significant" or "without appreciable" adverse health effects.

Non-threshold effects

8.8 In the case of effects which are often considered to be non-threshold, e.g. genotoxicity, extrapolation of dose response data to very low exposure levels may be necessary. Inevitably, the extrapolation of the dose-response curve outside the range of the observations is the subject of both assumptions and errors. These relate to the choice of the starting point and data used for extrapolation, the slope of the curve used for the extrapolation and the mechanisms by which interspecies differences and inter-individual variability are taken into account in the extrapolation process. Potential errors arise from the extent to which unquantified assumptions have to be made in relation to these criteria.

Dose-response data in humans

8.9 Dose-response data in humans may be available from either epidemiological studies or very rarely by direct experimentation (for example, the effect of compounds on enzyme activity, such as acetylcholinesterase; inhalation chamber exposures to ambient concentration of air pollutants). Such data require information on, and measurements of, effects in humans and, therefore are not obtainable for the great majority of risk assessment purposes. There are ethical issues relating to the intentional production of adverse health effects in humans by direct experimentation, although response measurements using biomarkers of minor and reversible changes can provide valuable human data for risk assessment. Therefore, the majority of risk assessments involve the interpretation of studies in experimental animals, and the extrapolation of data across species (see below).

8.10 The dose-response relationships available from epidemiology studies typically involve estimates of current levels of exposure of humans and the current incidence or risk of the adverse effect of concern. Such a temporal relationship would be suitable for acute effects or effects produced soon after exposure, but it may not provide a reliable risk estimate if there was an interval between exposure and development of the adverse effect, for example, carcinogenicity. Cumulative exposure estimates may be available in some rare cases, for example following workplace exposures and data may be limited to recent years when reliable monitoring procedures were established. Nonetheless, quantitation of exposure is frequently imprecise. In contrast, a distinct advantage of the use of human data is that quantitation of the risk for either higher or lower exposures would not normally require extrapolation of the dose-response relationship far beyond the available data (see below). There is a great need for a reliable data back of human data.

Dose-response data in animals and model systems

8.11 An advantage of the use of experimental models (both *in vivo* and *in vitro*) is that the exposure levels can be carefully controlled and there is the opportunity to increase the incidence, and hence the ability to confirm a potential hazard, by increasing the dosage. Because of the high doses used to generate a reproducible incidence of adverse effects in experimental studies (allowing hazard identification), when compared with the potentially acceptable exposure in the human population, the dose-response relationship from experimental studies in animals may need to be

extrapolated over three or more orders of magnitude outside the range of the experimental data. Such extrapolation has to make assumptions about the slope of the dose-response relationship beyond the range of the experimental observations.

8.11 For adverse effects associated with a threshold, such low-dose extrapolation is not required, and quantitative risk assessment would involve determination of the possible incidence of individuals for whom their threshold for response was less than the level of exposure, in other words the incidence of "at risk" subjects (see Chapter 10).

Types of response data

8.12 The effect or response data may be determined either as quantal data or as a continuous variable. An example of quantal data would be the incidence of a specific lesion, such as a tumour, whilst examples of a continuous variable would be a change in organ weight or body weight. Quantitative risk assessment could, therefore, define either an exposure-related incidence of a specific lesion or an exposure-related change in a particular body function, rather than increasing the confidence that the NOAEL would not pose a hazard. Continuous variables can be converted to quantal data provided that a range of normality can be defined. In other words, upper and lower level limits can be set, below and above which any observation would be considered abnormal (outside the usual range), and hence the response in an individual converted to quantal effect.

Hormesis – a problem for quantitative risk assessment or a stimulus for change?

8.13 An interesting challenge to the conventional risk assessment procedures outlined above is the recognition for some risk sources at least that low doses in experimental animals sometimes produce a response which is statistically significantly less than the background incidence in untreated animals, a phenomenon known as 'hormesis' (Calabrese and Baldwin, 1998). The converse situation may also be possible. Although the importance of hormesis remains controversial, it is not without biological plausibility (Sielken *et al*, 1995) because a low exposure may serve to stimulate cytoprotective and homeostatic processes in excess of the amount of added insult to the system. Assuming this to be the case, it would be expected that at higher exposures the magnitude of the added adverse stimuli would exceed the induced cytoprotective or homeostatic mechanisms so that an adverse response would become measurable. The presence of hormesis would not significantly affect risk estimations based on assumptions that there is a threshold to the biological response. However, hormesis would profoundly affect, and largely invalidate low-dose risk extrapolation and risk management strategies based on minimising exposure. Indeed, it might be argued that low dose exposure was in some sense beneficial. Until the importance of hormesis as a general biological principle is establish, such interpretations are simply speculative. For the stability of the environmental communities, hormesis cannot be beneficial since it upsets the balance between species.

Scientific evidence to support a threshold

8.14 Although the proof of the presence or absence of a threshold remains a matter for debate in risk assessment, subdivision of toxic effects into threshold and non-threshold has been the basis for risk assessment for the past 30-40 years (WHO 1999).

In most cases, the presence of a threshold cannot be demonstrated readily from experimental data, because even a non-threshold, linear dose-response relationship could give no measurable response in small groups of experimental animals given low doses.

8.15 However, any experimental dose-response study aims to include doses without a measurable (or statistically significant) biological effect in the test system. While the existence of biological thresholds cannot be proven or disproven, the possibility of a level of exposure that does not produce any effect (rather than any measurable effect) has to be based on experience and expert judgement of the underlying biology of the test system (which requires some understanding of the mode of action (see below). Although it can be argued that thresholds cannot exist in absolute terms, i.e. a very low concentration will still interact with biological systems, in reality the presence of homeostatic and cytoprotective processes means that the interaction between the chemical and the biological system has to exceed the homeostatic or other protective processes in order to elicit a response. Therefore, the concept of thresholds can be converted into quantitative terms by defining the magnitude of any measurable response that would not be considered to be adverse (Slob, 1999). Because different risk assessment procedures have been adopted depending on whether there is or is not a biological threshold, this issue is critical for the risk assessment procedure.

8.16 Recent meetings, for example those organised by the Society of Toxicology in the USA and the EUROTOX in Europe, discussed the important issue of the compatibility of cancer and non-cancer risk assessments. Both concluded that biological thresholds are probably present in the mechanisms of action for both genotoxic and non-genotoxic compounds. This is an issue where international harmonisation of approaches to risk assessment is needed.

8.17 It is usually assumed that any risks related to other hazards detected only at higher doses, will be lower than those relating to the critical effect. This is only valid if true thresholds have been established for each effect, however.

8.18 Safety assurance is based on using the dose-response relationship to define an approximation of the threshold for toxicity in the animal study. The endpoint normally used as a surrogate for the threshold is the no-observed-adverse-effect-level (NOAEL) (WHO, 1999), which is a sub-threshold dose. The term no-observed-effect-level (NOEL) is also used, but not all observed effects are adverse and would be the basis for quantitative risk assessment. In consequence, NOAEL has tended to be used more in recent years.

8.19 Usually, adverse effects are detected at lower doses in chronic studies, than in sub-chronic tests, and in consequence the NOAEL used when there is chronic low level human exposure is usually based on data from chronic bioassays. Where only data from sub-chronic tests exists extrapolation to the chronic exposure situation may be necessary (see Chapter 9). However, sometimes 90-day studies show greater sensitivity, because the adverse effect due to the compound is not masked by the effects of ageing.

8.20 The approach adopted for non-genotoxic carcinogens, in food and drinking water, varies between different national and international bodies in respect of the use of

standard uncertainty factors (see Chapter 9), additional uncertainty factor(s), and low-dose risk-extrapolation. Linear low-dose extrapolation is difficult to justify because non-genotoxic mechanisms arising from altered physiological or metabolic processes would be expected to exhibit a threshold. Non-genotoxic mechanisms include excessive secretion of trophic hormones that control endocrine function, the activation of cytosolic receptors regulating DNA transcription, and chronic cell proliferation and hyperplasia. The outcome of either the use of uncertainty factors or low-dose extrapolation is the definition of a daily or weekly exposure to a non-genotoxic carcinogen that is considered to be "acceptable", "tolerable" or "virtually safe". Alternatively, the human exposure can be compared with the dose-response data in animals to calculate a margin of exposure or "safety margin" (Doull *et al*, 1999; Wilkinson and Lamb, 1999).

8.21 The NOAEL expressed on a body weight basis (eg mg/kg body weight/day) is divided by an **uncertainty factor** or **safety factor** to derive the level of human exposure that will be without significant adverse effects. Although the terminology differs between regulatory bodies (NOEL *vs.* NOAEL; acceptable daily intake (ADI) *vs.* tolerable daily intake (TDI) *vs.* reference dose (RfD – used in the USA, Swartout *et al*. 1998); safety factor *vs.* uncertainty factor), in this regard there is a common underlying approach. The "safe" human exposure is often termed "acceptable" (for an additive) or "tolerable" (for a contaminant) together with a time base, which is related to the potential for accumulation, eg acceptable daily intake (ADI) or provisional tolerable weekly intake (PTWI) for chemicals that accumulate. These assessments should be dated to indicate the time at which the database was assessed (Rubery *et al*, 1990). Despite the commonality of approach, there are frequently wide differences in the values derived by different bodies assessing the same compound (Dourson and Lu, 1995). The rationale for such discrepancies needs to be determined and resolution of any scientific issues embarked on. For environmental species, NOEL are also used. Uncertainties lie in the extrapolation between species.

8.22 The simplistic nature of the common current methods applied to threshold toxicity, means that they can be applied readily to a wide range of different databases. The equally simplistic linear low-dose extrapolation appears at first sight more sophisticated, because of the data fitting undertaken and the fact that it generates numerical data, but in reality is supported by less biological plausibility, and largely ignores certain aspects, such as human variability. However, it is generally based on worst case assumptions, so that it is assumed that the most sensitive human individual is considered.

Extrapolation procedures in risk assessment

8.23 The available dose-response data for the adverse effect may be analysed in various ways, each of which involves a number of assumptions and uncertainties. Information which can be taken from the dose-response relationship and used for quantitative risk assessment include:

a) the slope of the dose-response curve,
b) a fixed point on the dose-response curve, and
c) the threshold, or an approximate threshold, such as the NOAEL or NOEL.

8.24 Assuming there is no biological threshold, the slope of the incidence data in the experimental range can be extrapolated by a mathematical model to low dose levels in order to provide a quantitative risk estimate directly. In contrast, dose-response extrapolation below a threshold would not give a meaningful estimate of the risk: therefore, analysis of low dose risks in relation to thresholds has to be on the basis of the number of individuals in a population whose individual thresholds for a response are less than the exposure level of concern (See Chapter 10).

8.25 Human variability is rarely taken into account in these non-threshold dose-response extrapolation procedures. An approach that has been adopted is the use of the upper 95^{th} percentile of the dose-response relationship since the variability in response will be reflected in the variability in the experimental data. However, much of this will relate to variability arising from the small number of animals in each experimental group, and will relate to variability within the test species not within the humans. The use of the 95^{th} percentile to produce a dose-response relationship which allows for variability in the test animals may not be appropriate to represent human variability and the slope arising from human variability. Therefore, simple extrapolation of the slope of the animal dose-response curve or its upper 95^{th} percentile confidence intervals will not necessarily represent the dose-response relationship present in the human population. Different age groups of the human population probably have different dose-response relationship.

8.26 The slope of the dose-response and the mathematical model used will be the major variable in the estimate derived by quantitative risk assessment when extrapolation has to be made over 3 or 4 orders of magnitude (ECETOC, 1996). If the actual slope of the animal dose-response curve is not extrapolated, then an arbitrary choice about the appropriate model and slope has to be made. The dose-response relationship selected will have a profound influence on the final risk characterisation and, therefore, it is a particular requirement to justify the selection of the mathematical model both for genotoxic and non genotoxic compounds.

8.27 A number of different models have been proposed for genotoxic carcinogens (Figure 8.1), although only a restricted number have been used widely for risk assessment purposes (ECETOC, 1996).

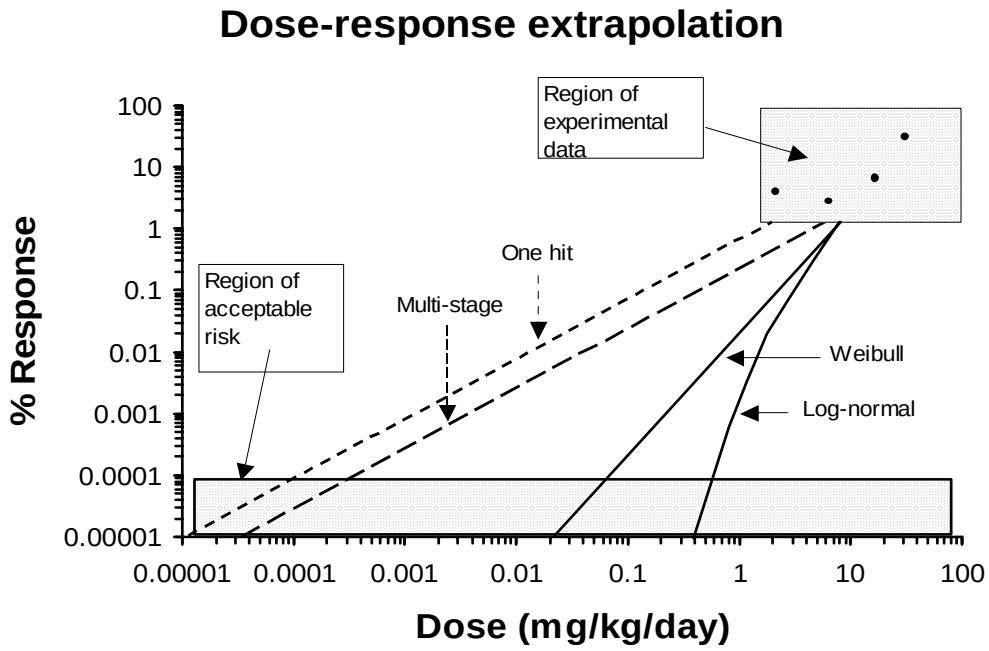


Figure 8.1 Mathematical models for low-dose risk estimation for non-threshold chemicals (based on ECETOC, 1996)

8.28 The different models are:

Stochastic models (e.g. one hit, and linearised multi-stage). The linearised multi-stage model assumes that cancer arises from a sequence of events, that at least one event is linearly related to dose, and that a background incidence is always present. In consequence this gives a linear extrapolation at low exposures (Figure 8.1) and the slope is determined largely by the top dose used in the study (Lovell and Thomas, 1996).

Tolerance distribution models (e.g. Weibull, log-probit and logit). The log-probit and logit give a sigmoid curve in the experimental range but differ in low-dose extrapolation. The Weibull model is capable of representing thresholds, and is sensitive to the slope of the dose-response curve.

Time to tumour models (eg Weibull distribution). These models are considered to be better because they do not use quantal data. These models have not been adequately validated and generally offer no advantage over incidence data that have been corrected for differences in life span between different experimental groups.

Biologically-based models (eg Moolgavkar-Venzon-Knudson (MVK) model). Although stochastic models were introduced because low-dose linearity was considered to be a conservative interpretation of the underlying biology, they do not

adequately represent the processes involved. The MVK is a biologically credible model, but requires data on rates of cell division and cell death at different stages of tumour growth, from the stem cell to the initiated cell to the transformed cell, and such data are not currently available.

8.28 Thus a major problem with low-dose risk extrapolation is that the mathematical model or equation selected for the extrapolation process becomes the major variable in the final risk estimate when extrapolating to very low exposures (Figure 8.1). Fitting the different models to the same dataset can give risk-specific doses (e.g. the dose giving a 1 in 10^6 risk) that differ by several orders of magnitude! Despite the precision frequently reported for extrapolated risk estimates, there remain a number of uncertainties relating to inter-species differences and inter-individual variability in toxicokinetics and sensitivity within the heterogeneous human population compared with the test species. At low doses, the confidence intervals may span a risk from zero up to the upper-bound risk estimate. It is appropriate for the Scientific Committees to discuss when and how such mathematical models should be used for risk assessment purposes in order to determine a common EU position.

8.28 The USEPA has recently proposed to use the dose descriptor LED_{10} (the 95% lower confidence limit on a dose associated with 10% extra tumour incidence adjusted for background) as a point of departure for linear extrapolation to lower exposures as a default procedure (U.S. Environmental Protection Agency -1996- Proposed guidelines for carcinogen risk assessment. *Fed. Reg*. 61, 17960-18011). The LED_{10} is determined from the benchmark dose for 10% incidence with the use of the multistage model for curve fitting. In the EU, linear extrapolation using the tumorigenic dose-descriptor T25 as starting point has been applied (Dybing *et al*., 1997).

Threshold approaches to animal doses-response data

No-observed-adverse-effect-level (NOAEL)

8.29 The NOAEL is a level of exposure in which the treated animals do not differ significantly from untreated control animals in measurements related to the critical effect recognised at higher doses. The NOAEL is a dose without measurable activity (Figure 8.2), and therefore can be considered to be below the threshold in animals.

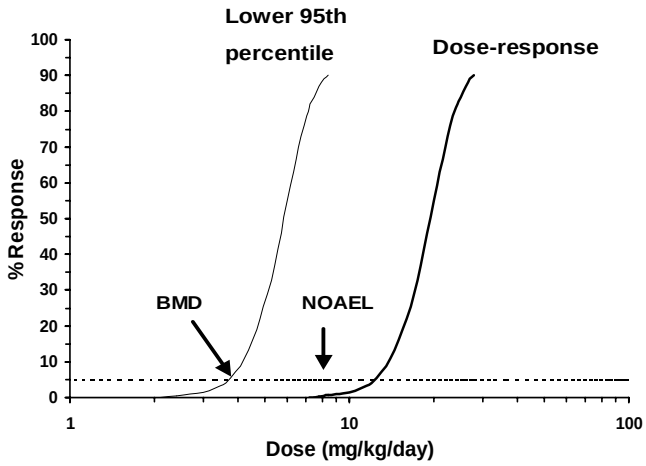


Figure 8.2. Comparison of no-observed-adverse-effect-level (NOAEL) and the benchmark dose (BMD)

8.30 The value of the NOAEL is dependent on three main factors of the study design:-

- *Group size* - the larger the group size, the greater will be the sensitivity. The group sizes currently recommended in testing guidelines represent the best compromise between sensitivity and practicability: group sizes would have to be increased considerably in order to provide a measurable increase in sensitivity over the current recommendations.
- *Test sensitivity* - the more sensitive the method of detection, the lower the NOAEL. The consequence of poor or inadequate methods of assessment of adverse effects is that the NOAEL is higher - thereby inappropriately rewarding poor techniques. It is this problem which stimulated the regulatory requirement that studies which are submitted for regulatory purposes should comply with GLP or be reported in sufficient detail to provide quality assurance to those undertaking the risk assessment.
- *Dose spacing* – a major determinant of the NOAEL in real databases is the choice of the spacing between doses given to the animal. The NOAEL is the next dose down from the minimally effective dose: hidden in this simple statement is the fact that the experimental NOAEL may be a gross underestimate of the true threshold, especially if the doses are separated by factors of 10-fold. For example, if the doses in a study were 10, 100 and 1000mg/kg body weight per day and the biological threshold was 80mg/kg/day, the NOAEL (10mg/kg/day) would be a factor of 8-fold below the true threshold. The NOAEL from modern databases, in which the doses differ by a factor of 3-fold or 5-fold, are closer to the true threshold.

8.31 These different aspects affect the relationship between the NOAEL and the biological threshold for toxicity in different directions. They may cancel each other out, because group size and test sensitivity would result in the true threshold being below the NOAEL, but due to dose-spacing (selection) the threshold could be substantially above the NOAEL (this is an important consideration discussed later).

Benchmark dose (BMD)

8.32 The BMD (Figure 8.2) is an alternative method of defining an intake close to the threshold (Crump, 1984). Unlike the determination of a NOAEL, this method uses the full dose-response data to determine the incidence associated with a defined low level of response (WHO, 1999a). The value is derived by modelling the experimental data in the observed range and selecting the 95^{th} percentile lower confidence limit on the dose causing a particular incidence of the effect, for example 5% of the maximum response (Auton, 1994; Barnes *et al*, 1995). A 5% difference in a continuous variable, such as an organ weight, may be within the background variability in control animals and therefore not represent a clear "adverse" effect. In consequence, the BMD is most suitable for application to quantal variables, such as the incidence of a histological lesion, or the incidence of abnormal liver weight (where the normal range has been defined based on the variability in control animals). Because the dose-response relationship is not extrapolated far beyond the experimental observations, the BMD is not subject to the errors, or the dependency on the model, which are inherent parts of low-dose risk-extrapolation. Advantages of BMD are that it rewards good dose-response data because this will be associated with narrower confidence intervals, and also it is not subject to the limitations discussed above for the NOAEL. The BMD is by definition greater than the threshold and the way that this can be used in risk assessment and the choice of uncertainty factor are still the subject of debate. (See Chapter 9). Unlike the NOAEL, a BMD cannot be calculated when none of the experimental observations produce an adverse effect, and is very approximate when the adverse effect is detected at the top dose only. Use of benchmark doses would appear to have a number of advantages over the much more widely determined NOAEL value. It is an issue that should be discussed by the Scientific Advisory Committees with a view to adopting a common position.

Lowest-observed-adverse-effect-level (LOAEL)

8.33 The LOAEL is used instead of the NOAEL when all test groups produce a significant effect compared to controls. In consequence, this estimate is above the threshold and in risk assessment this is usually taken into account by the use of additional uncertainty factors (see below). The LOAEL, like the NOAEL, is an experimental observation and dependent on the design of the study as discussed above for the NOAEL. Consequently, the BMD would represent a more scientifically credible way of dealing with risk assessment for databases which do not allow determination of a NOAEL.

Extrapolation of data between species for human hazard characterisation

8.34 Typically data on adverse effects is derived from animal studies. Often the species employed for this purpose is not that for which an assessment of the risk is required. In this case, some form of species extrapolation is required.

8.35 A number of approaches have been used to extrapolate between species. Ideally, adverse effects data in one species would be used to predict risks to another based on:

- Comparison of the levels and persistence of the agent (and/or its biologically active products) at the critical organ(s);
- Demonstration that the toxico-dynamic process is likely to be comparable (see below).

With the exception of some human medicines such information is rarely available and is most unlikely to be obtained.

8.36 Consequently, procedures have to be adopted for species extrapolation purposes. The general approach has been to use surrogates (scaling factors) for comparison of the concentration of the risk source at the critical organ(s). Scaling factors may be based, for instance, on a comparison of:

- Pharmacokinetic profiles
- Blood levels
- General drug metabolism activity
- Calorific demands / metabolic activity
- Rate of apoptosis
- Body surface area
- Body weight.

Body weight is by far the most commonly used for historical and pragmatic purposes. Although from a scientific viewpoint it is not a reliable scaling factor, there has been little progress in agreeing a convenient substitute during the past 30 or more years. Instead, the favoured approach has been to apply uncertainty (safety or default) factors to allow for the unreliability of using body weight as a basis for extrapolation (see Chapter 9). From a scientific viewpoint this is a very unsatisfactory element of risk assessment. Extrapolation from species to species of course involves other uncertainties in addition.

8.37 In the case of chemicals, it is often possible to obtain some basic metabolism and toxico-dynamic data (probably in vitro) to reduce the uncertainty of the extrapolation process. This is an issue which is relevant to most of the Scientific Advisory Committees. The alternative is to narrow the uncertainty is to conduct tests in a much wider range of species. This may not be acceptable, however, from an ethical and animal welfare perspective (see Chapter 10). Application of physiologically-based kinetic models and dose-response models will greatly reduce the uncertainties in intraspecies extrapolations (see figure 3.2).
In order to reduce uncertainty regarding toxicity to environmental communities, multispecies (microcosm) experiments are helpful but rather expensive.

Mode of action / mechanisms studies

8.38 Risk assessments are likely to be most reliable when the means by which the risk source causes its adverse effects is understood. For drugs and , information of this kind is often available. However, for many other risk sources it is very limited and not provided.

8.39 For chemicals, mutagenicity testing is used routinely to confirm or refute a genotoxicity mechanism for cancer initiation. This reflects the seriousness with which the “public” view cancer as a consequence of exposure to a chemical. Mechanisms research is often stimulated by concerns that toxicity data in a particular species is giving a disproportionate concern about the actual risk.

8.40 There appears to be no coherent national or international strategy for prioritising mechanisms research despite its undoubted importance. Instead, such research tends to follow scientific “fashions”. Some means of identifying priorities for such research needs to be found if major advances are to be made in the science of risk assessment.

8.41 A reliable data base on a range of related risk sources would assist greatly in establishing such priorities. As discussed in Chapter 6, no reliable data base of this nature is yet available.

MICROORGANISMS

[*Note*: see also Appendix 4: Report on microbiological risk assessment, and Appendix 5: Report on risk assessment for transmissible diseases]

8.42 Hazard characterisation usually receives a broad definition: "the qualitative or semi-quantitative evaluation of the nature of the adverse health effects to humans and/or the environment following exposure to a risk source. This must, where possible, include a dose-response assessment" (Appendix 1). Such a definition equally applies to chemical and microbiological risk assessment. However, it has to be realised that the response of a human (or animal) population to a pathogen is highly variable. This reflect the fact that the frequency, extent or severity of a microbial disease is dependant on a variety of factors such as: the characteristics of the pathogen that affect its pathogenicity/virulence; the number of microbial bodies that come into contact with a host, overcome the natural barriers and determine infection; the general health or immune status of the host which may determine translation of infection into illness and its severity; the attributes of the vector (in particular in the case of a food product). The likelihood that any specific individual may become ill due to an exposure to a microbial pathogen is dependant on the integration of the pathogen, the host and the matrix (e.g. food) effects. These interactions are often referred to as the "infectious disease triangle". In addition to characterising the nature of the adverse health effects, analysing and evaluating these interactions based on collating information on the pathogen, the host and the matrix, are keys to microbiological hazard characterisation. In this regard, it has to be realised that there may be some overlap between hazard identification and hazard characterisation with regard to determination of the characteristics of microbial pathogens, and their ability to cause disease in a host. This is not important, provided the approach taken is comprehensive, is internally consistent and constitute a logical and practicable procedure (e.g. in the development of risk models). The term of "characterisation of (human) health effects" has been proposed in some documents (e.g. ILSI, 1996, 2000) to take into account the particularity of this stage in the assessment of microbiological risk. This suggestion needs to be carefully considered, as it offers the advantage of a clear scope for, and demarcation between, microbial hazard identification and the subsequent stages of the analysis.

8.43 Having regard to the above, microbiological hazard characterisation involves the interactive analysis of three critical components: the review of the factors related to the pathogen, the host and the matrix; the evaluation of the (human) health effects; analysis of the dose-response relationship.

Review of factors related to the pathogen, the host and the matrix

8.44 When not already done in the hazard identification stage, specific consideration should be given to the intrinsic properties of the pathogen that influence infectivity, virulence and pathogenicity; their variability; and the factors that may affect or alter the infectivity, virulence or pathogenicity of the micro-organism under consideration.

8.45 The factors related to the host refer to the characteristics of the potentially exposed human population that may influence susceptibility to the particular pathogen, taking into account a host's intrinsic and/or acquired traits that modify the likelihood of infection or, most importantly, the probability and/or severity of illness. Many factors may influence susceptibility and severity such as age, immune status, genetic factors, concurrent or recent infections, use of medications, pregnancy, breakdown of physiological barriers, nutritional status, demographic, social and/or behavioural traits. Not all of these factors would be relevant, or important for all pathogens. In all cases however, an important issue in hazard characterisation is to provide information on who is at risk (identification of susceptible sub-populations) and on the stratification of the exposed population with regard to the relevant factors that influence susceptibility and severity.

8.46 The factors related to the matrix depend on the product/vector considered and the transmission route. For instance, for foodborne pathogens, the factors related to the food matrix are principally those that may influence the survival of the pathogen through the hostile environment of the stomach. They may include the composition and structure of the food matrix (e.g. highly buffered foods; entrapment of bacteria in lipid droplets), the processing conditions (e.g. increased acid tolerance of bacteria following pre-exposure to moderately acid conditions), as well as the conditions of ingestion (e.g. initial rapid transit of liquids in an empty stomach).

Evaluation of the adverse health effects (human, livestock and wildlife)

8.47 Evaluation of the adverse health effects should consider the whole spectrum of possible effects in response to the microbial stressor, including asymptomatic infections and clinical manifestations, whether acute, sub-acute and/or chronic (e.g. long term sequellae). Where clinical manifestations are concerned, the description would include consideration of the diverse possible clinical forms, together with their severity. Severity may be defined as the degree or extent of clinical disease produced by a micro-organism, and may be expressed in a variety of ways, most of which include consideration of possible outcomes. For example, for mild gastrointestinal symptoms, severity may be expressed as duration of the illness, or as the proportion of the population affected (morbidity). Where the gravity of the distress requires medical cares and/or include long-term illness, severity may be expressed in terms of the costs to society, such as the proportion of workdays lost or cost of treatment. Some pathogens and the related clinical forms may be associated with a certain degree of mortality and therefore severity may be expressed as mortality rate. For pathogens that cause chronic illness (i.e. the disease leaves long-term sequellae) it may be desirable to include in the characterisation of the human health effects considerations related to the quality of life as it may be affected by the disease. Quality of life may be expressed in a variety of ways, depending on the nature of the illness. For instance, human life expectancy may decrease, chronic debilitation may occur, or quality of life may be affected by episodic bouts of disease.

8.48 In addition to a description of the human adverse health effects, information on the disease should include consideration of the epidemiological pattern and indicate whether the disease may be sporadic, anademic or epidemic. The frequency, incidence and prevalence of the disease and/or its clinical forms should be addressed, together with their evolution with time and possible seasonal variations. The description should include consideration of the repartition of clinical forms according to specific at-risk groups. Finally, the potential for, extent or amount of, asymptomatic carriers and of secondary transmission should also be characterised.

8.49 In all cases, it is important that the characterisation include a definition of what should be considered as the "infection" of the host by the pathogenic agent and of what constitutes a clinical "case". In addition, a definition of the severity scale should be provided, specifying what is the indicator chosen (e.g. disease end-point, consequences) and how it can be measured. The description should also include information on uncertainties and their sources. To the extent possible, the characterisation should incorporate information on the physiopathology of the disease, i.e. on the biological mechanisms involved.

Analysis of the dose-response relationship

8.50 The third, and essential, element in microbiological hazard characterisation is the analysis of the relationship between dose, infectivity, and the manifestation and magnitude of health effects in an exposed population.

8.51 Description of the dose-response relationship involves consideration of the elements or factors related to the pathogen, the host and the matrix, insofar as they may modulate the response to exposure. Where appropriate information is available, it also involves a discussion about the biological mechanisms involved, in particular whether a threshold, or a collaborative action of the pathogens, may be a plausible mechanism for any harmful effect or whether a single micro-organism may cause adverse effects under certain circumstances. Elements to be considered may include considerations related to the organism type or strain, the route of exposure, the level of exposure (the dose), the adverse effect(s) considered (the response), the characteristics of the affected population, the duration and, where relevant, the multiplicity of exposures.

8.52 Where clinical or epidemiological data are available, discussion of the dose-response relationship will generally be based on such data. However, the evaluation is affected by the quality and quantity of data available. (See Appendix 4 for a discussion of the strengths and limitations of the different types of data). What is important is to realise that there is a need to consider what actually constitutes the dose (e.g. amount of pathogens as enumerated per food unit, amount of pathogens actually ingested, amount of pathogens that survive through the stomach and interact with a host) and what is the response (e.g. infection, illness, specific outcome). A specific difficulty refers to the lack of data to characterise infection, or to characterise the translation of infection into illness and of illness into different outcomes. In many cases, the analysis may only be able to describe a relationship between a dose and clinical illness. Other difficulties arise from several sources of variability e.g. variability in virulence and pathogenicity of the micro-organisms, variation in attack rates, variation in host susceptibility, type of vehicle which modulates the ability of pathogens to infect and otherwise affect the host. Therefore, it is essential that the dose-response

analysis would clearly identify which information has been utilised and how the information has been obtained. In addition, the variability should be clearly acknowledged and the uncertainties and their sources (insufficient experimental data or lack of knowledge of the pathogen/host/food being studied) should be thoroughly described.

8.53 Concurrently to the analysis of raw clinical or epidemiological information or data, mathematical modelling have been advocated to provide assistance in developing dose-response relationship, in particular when extrapolation to low doses is necessary. Mathematical models have been used since long in the field of toxicology. In the field of microbiology, it is currently recognised that they may facilitate the approach, and provide useful information while accounting for variability and uncertainty. However, the assumptions on which the current models are based, their use and possible limitations should be carefully considered. An extensive discussion on dose-response modelling for microbial pathogens is found in Appendix 4.

8.54 Strengthening the available data base and improvement of modelling techniques would presently deserve greater attention. For most micro-organisms of concern, there is a large body of literature describing the range of associated health effects. However, to facilitate the development of formal (and to the extent possible of quantitative) risk assessments, there is a need for better standardisation of infection- and case-definitions. More information (possibly quantified) is also needed on the probability of translation of infection into illness and specific outcomes. Population based epidemiological studies need to be developed to fill this gap. At present, most models are empirical and incorporate only a small number of parameters. However, realistic dose-response models need to quantify the probability of infection, disease, and its possible outcomes in relation to a large number of variables. The relative importance of these should be determined and quantified. This requires a major, long term effort to incorporate available information in a new generation of dynamic (mechanical, or physiopathology based) models. Finally, current dose-response models do not consider simultaneous exposure to different micro-organisms. Yet interactions between microbes can alter the susceptibility of the host. For instance, infection with respiratory viruses may increase the susceptibility to bacterial pathogens such as bacterial agents of pneumonia. Alternatively, the susceptibility of a host to a certain infection may decrease because existing immune memory to an unrelated infection. Also, the interaction between microbial infection and allergic reactions should be further explored. The experimental data-base for such evaluations is presently poor, and needs to be expanded.

CONCLUSIONS

i) Current approaches for hazard characterisation tend to favour a situation in which:

- Poorer quality data can result in the identification of a less strict threshold value. This is clearly unacceptable. Means of circumventing this real possibility need to be discussed. They could include:
  - Use of higher uncertainty (default values) (see Chapter 10)
  - Calculation of the degree of uncertainty in the hazard characterisation.

- Undue emphasis is placed on a single data point in the dose response studies, namely that at which there is no observed adverse effect. Adoption of approaches which involve the utilisation of all the data points, e.g. benchmark doses need to be considered.

ii) A consistent approach to the use of mathematical models for dose response data extrapolation for both chemical and microbiological risks is very desirable. This includes reconsideration of whether thresholds are applicable to genotoxic chemicals and how quantitative risk assessment can be applied to non-genotoxic chemicals.

iii) Particular attention needs to be given to the phenomenon of hormesis because it could have a major influence on the conduct of risk assessments in the future.

iv) A review by the Scientific Committees is required of the use of particular interspecies scaling factors and their scientific justification.

v) Where microbiological hazard characterisation is concerned, there is a need to expand and strengthen the available data-base with particular regard to: gaining more (quantified) information on the probability of translation of infection into illness and specific outcomes, determination and quantification of related variables, effects of simultaneous exposure to different micro-organisms. This would facilitate the development of dynamic (mechanical or physiopathology based) models.

9 RISK CHARACTERISATION

"If man will begin with certainties, he shall end in doubts; but if he will be content to begin with doubts, he shall end in uncertainties"
Francis Bacon (1605)

GENERAL

9.1 Risk characterisation relates to the estimation (which should include the attendant uncertainties) of the probability of the occurrence and the severity of adverse effects in a given human and/or environmental population (based on the previous three stages) by comparing the estimated exposure and the hazard characterisation. This is based on the general applicability of the equations : $E = f\,D$ and $E = f\,(D - D_0)$ where E = effect, f = a function, D = dose, and D_0 = threshold dose.

9.2 In principle, if the exposure estimate is reliable and appropriate and the dose response data of good quality and covers this exposure range and has been obtained in the relevant species, risk characterisation is a quite straightforward process. However, this is often not the case.

9.3 There may be as a consequence a number of questions to be addressed in risk characterisation. These include:

- What allowance should be made for the absence of specific data or for poor quality data?
- What allowances should be made for possible unidentified inter and intra species variations?
- What uncertainties are involved in other extrapolations including route of exposure time (e.g. short-term to long-term), location (one site to different sites) space (e.g. local to regional and national and vice versa)?
- To what extent should exposure to the same agent from other sources or very closely related structures be considered?
- Can particular 'at risk' groups be identified and how should they be included in the final risk assessment opinion?
- What weighting should be given to simultaneous or co-exposure to other related agents/media and if so on what scientific basis?
- In what form should the characterisation and expression of the above and other uncertainties be presented? (This will be addressed in Chapter 10).

CHEMICALS

[*Note*: see also Appendix 3: Report on risk assessment for toxic chemicals]

Use of uncertainty factors

9.4 The terminology for the use of numerical values to correct for variabilities and uncertainties in the risk estimate differs. Terms employed included "safety factors", "default values", "uncertainty factors" , "assessment factors", and "correction factors". In this report "uncertainty factors" is the preferred term.

9.5 Uncertainty factors may need to be applied for one or more reasons:

i) deficiencies in the appropriateness or quality of the actual data available, inappropriate route of exposure used, lack of chronic data, etc. (data base factors);
ii) inadequacies of the scientific basis for extrapolating effects and dose response data between species, to allow for intraspecies variability (intraspecies extrapolation factors); extrapolation from acute to chronic data or from laboratory to field effects;
iii) exposure estimation uncertainties, e.g. degree of confidence in modelling systems and scenarios employed, reliability of analytical measurements, etc. (exposure estimation factors);
iv) risk management purposes, e.g. to address public concern (risk management factors). This is not strictly within the remit of the Scientific Advisory Committees.

Uncertainty factors may be used differently in human and environmental risk characterisation. It has to be acknowledged that it may not be possible to identify specifically every uncertainty, particularly in a complex risk assessment.

Human risk characterisation

9.6 In principle, the lower the degree of confidence in the scientific basis of the data, the extrapolation process or the modelling system and scenarios, the greater the uncertainty factors should be. Although this is in principle within the remit of the Scientific Committees, often an overarching default uncertainty factor of 100 is employed regardless of the degree of uncertainty. Although this default factor in general has been shown to be protective, this approach is not appropriate from a scientific point of view. It should be the case that if the understanding in one or more of the above areas is improved substantially, the uncertainty factor should be replaced by chemical specific assessment factors (e.g. "Chemical-Specific Adjustment Factors-CSAF", as in the, in preparation, IPCS guidance document for the use of data in development of Chemical-Specific Adjustment Factors for interspecies differences and human variability in dose/concentration response assessment). In Figure 9.1 the conventional uncertainty factors which are applied in risk assessments to protect public health are set out (for further details of their rationale see Appendix 3). Note that there is no allowance in the scheme for uncertainties in the exposure assessment apart from route of exposure aspects. This is clearly an area on which further work is required since estimation of exposure assessment can be particularly problematic. It should also be noted that such uncertainty factors are not applied in areas such as protection of worker health or for human medicines.

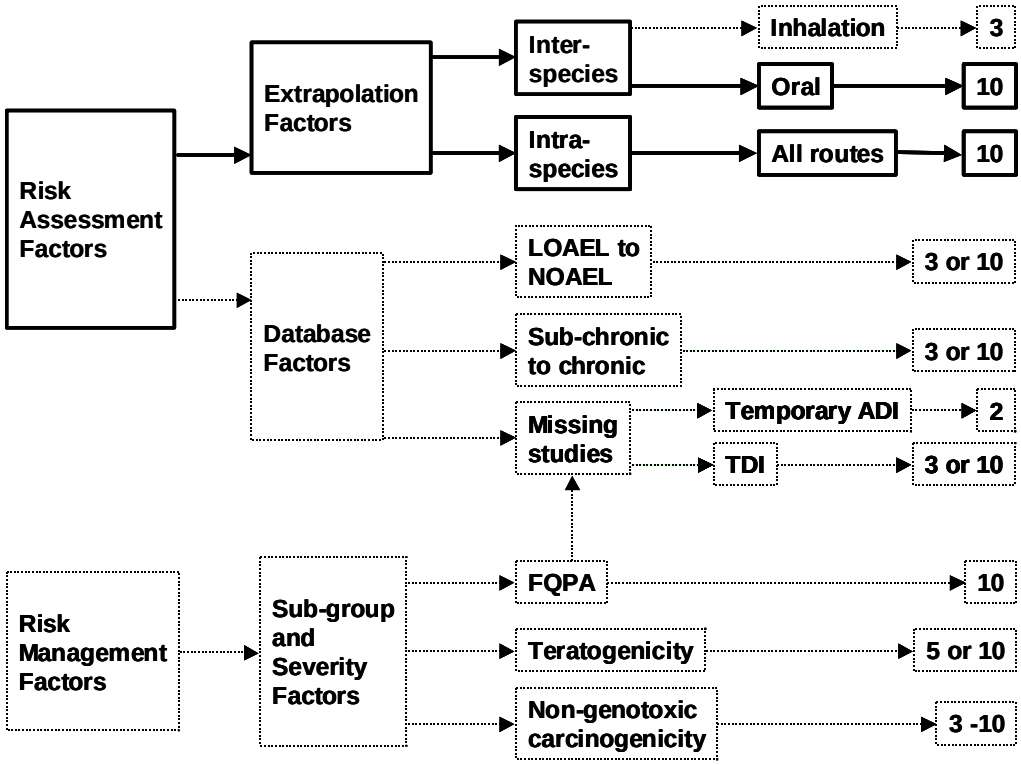


Figure 9.1 **Uncertainty factors used to establish acceptable levels of human exposure based on animal databases. The factors shown with continuous lines are those usually used in the EU for the assessment of food additives and pesticides. Other factors may be applied for other types of chemicals (e.g. contaminants) and by authorities and bodies outside the EU. The numerical values represent usual practice.**

9.7 For animal data, a 100-fold uncertainty factor is usually applied to the NOAEL. This is made up of a 10-fold factor to allow for differences between animals and an average human, and 10-fold to allow for differences between average humans and sensitive sub-groups (WHO, 1987). Thus, one 10-fold factor is considered to move the intakes (expressed per kg body weight) from a population sub-threshold value for a group of test animals down to a population sub-threshold value in a similarly sized, and relatively homogeneous, group of humans. The second 10-fold factor is to allow for sensitive humans and is equivalent to moving the intake from a population sub-threshold value for humans down to the value for sensitive individuals (Paragraph 9.11 and Figure 9.2). The basis for the common practice of applying a 100-fold factor to the NOAEL from studies in animals and a 10-fold factor to the NOAEL from studies in humans has been the subject of numerous reviews (see Appendix 5 for references)

These reviews have been post-hoc analyses of the validity of the "uncertainty factors" which were selected in the 1950's, before recent advances in the fields of toxicology and risk assessment.

9.8 The processes giving rise to an adverse effect can be divided into two main aspects, delivery of the compound to the target organ (toxicokinetics) and the response of the target organ to the compound (toxicodynamics). This sub-division has been used as the basis for an analysis of the adequacy of the usual uncertainty factors (Renwick, 1991), which concluded that while the value of 100-fold was a reasonable value, different situations could occur for which the value was either excessive or inadequate.

9.9 The inter-species differences comprise both kinetic and dynamic aspects. Ideally, compound-specific data should be used instead of defaults (see later). Alternatively, default values are possible for the kinetic aspects, such as the ratio between the test animals and human body weight ratio, or a generic kinetic default may be used (see Appendix 3 and figure 9.1).

9.10 The 10-fold factor for human variability is to allow for inter-individual differences in response to the external dose. In classic dose-response terms it is to allow for differences in the position of the dose-response curve for the individual, compared with the population mean. In relation to risk assessment and the ADI/TDI/RfD/MOS, the 10-fold factor allows for inter-individual differences in the position of the NOAEL. Differences between dose-response curves are usually defined by estimates such as the ED_{50} (the dose that results in an effect in 50% of individuals); for parallel dose-response curves, the difference between individuals will be the same at any particular effect level, including the NOAEL. The 10-fold factor has to allow for variability in both kinetic and dynamic processes and default factors have been proposed for each (WHO, 1994). Ideally, compound-specific data should be used instead of defaults (see below). The analysis of human variability by Renwick and Lazarus (1998) demonstrated that the 10-fold factor was an adequate default, but that situations could be envisaged in which the compound might show metabolic characteristics that would greatly increase human variability (for example polymorphisms in xenobiotic metabolism.

9.11 It has been proposed (WHO, 1994) that the 100-fold factor can be regarded as comprising 4 sub-factors which when multiplied together give the usual default of 100. Each of the 10-fold factors is considered to allow for differences in 2 aspects; *toxicokinetics* (which determines the delivery of the chemical to the target site) and *toxicodynamics* (which determines the reaction of the target site to the presence of the chemical).

Thus:

	Interspecies differences				Inter-individual differences		
100 =	10			times	10		
	kinetics		dynamics		kinetics		dynamics
100 =	4.0	x	2.5	times	3.16	x	3.16

The overall scheme developed by the IPCS (WHO, 1994) is shown in Figure 9.2.

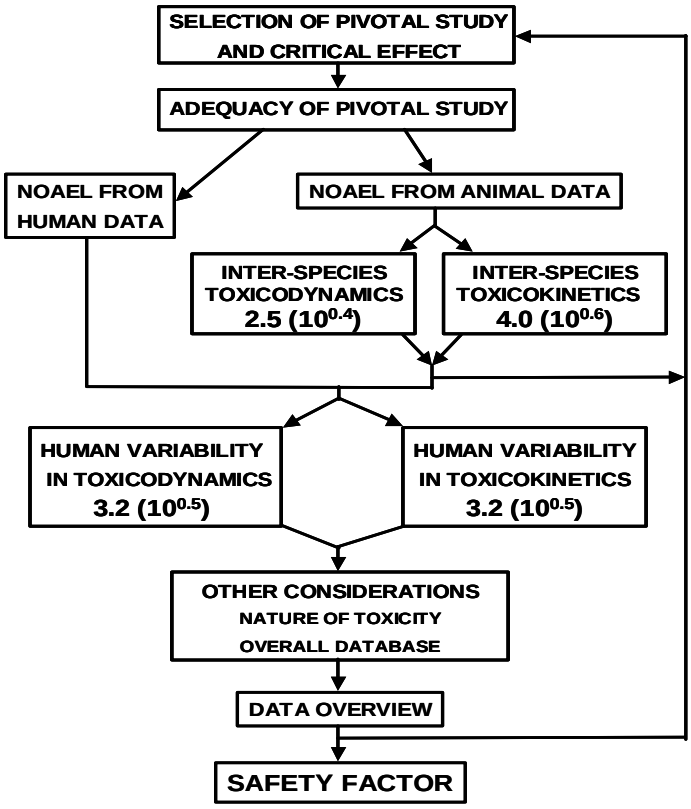


Figure 9.2. Scheme for risk assessment of threshold toxicants (based on WHO, 1994). At a recent IPCS meeting on the harmonisation of risk assessment procedures (August 2000) it was recommended that when a default value is replaced by a value based on quantitative chemical-specific data the value should be termed an adjustment factor, and the term uncertainty factor retained for the default values shown in the risk assessment scheme above. Thus the "safety factor" in the above scheme would be the product of chemical-specific adjustment factors (for aspects where data are available) and default uncertainty factors (for the remaining aspects where data are not available).

9.12 The replacement of a default value for either interspecies differences or human variability by a quantitative chemical-specific adjustment factor requires experimental data generated from *in vivo* or *in vitro* studies in humans. Such data is rarely

available for chemicals other than drugs and pesticides. This description may be a classic multi-compartmental model, or the more relevant non-compartmental parameters such as clearance and bioavailability, or a PBPK model. Partitioning of xenobiotic chemicals between blood and tissues is usually by simple diffusion, and is not a major cause of inter-species differences or human variability. In consequence valid comparisons can be made based on concentrations in blood or plasma. Interactions occurring within the target tissue (including any local bioactivation/inactivation processes) are not readily amenable to toxicokinetic analysis in humans, and in the context of sub-dividing uncertainty factors should be considered to be a part of toxicodynamics.

9.13 The principal aim of the sub-division of the 10-fold factors is to allow compound-specific data to be used quantitatively in risk assessment and the determination of chemical-specific, data-derived uncertainty factors (Renwick, 1993). In reality, there are few databases currently available which contain the appropriate information to allow replacement of one of the sub-factors (Kroes *et al*, 1993). However, the sub-division into kinetics and dynamics has proved to be a particularly useful approach for the analysis of special situations.

9.14 A balance needs to be struck between the benefits of formalising the value for each uncertainty factor in terms of greater transparency of the process and the disbenefits in terms of both the input from scientific judgement and the apparent disincentive it implies to companies or organisations who conduct very thorough research to try to identify the probable risk. A compromise should be that the scientific judgement is used to modify the uncertainty factors in specific cases where there is sound scientific data to justify this.

9.15 It is important that research is continued to improve the scientific basis for the use of the currently used uncertainty factors (see for example Vermeire *et al*., 1997, 1998; Renwick and Lazarus, 1998). Research is also necessary to identify uncertainty factors that might be applied to allow for deficiencies in the estimation of exposure.

Additional uncertainty factors to allow for sensitive groups of the human population

9.16 The question needs to be asked as to whether there is a particular population group(s) who are especially vulnerable to chemicals generally. There are an increasing number of publications on this topic of chemical sensitisation (see for example Rea, 1992, 1995). It is important to develop a proper understanding of this issue and the nature of the sensitivity and numbers of those affected. It has been proposed that infants may also fall into this category of generally more sensitive as may individuals with various chronic diseases. However, the scientific basis to confirm or deny this remains poor. Certainly for specific chemicals there may be a particularly vulnerable population group. The application of probabilistic methods can be used to analyse the likelihood that the use of the uncertainty factors of 10 for human variability is sufficient (see Appendix 3) to cover sensitive sub-groups of the population. These sub-groups can then be analysed either separately (Renwick and Lazarus, 1998), or by modification of the population distribution of the appropriate parameter estimate. In some cases, the sub-group will be clearly identifiable, more commonly there is insufficient information to identify them.

Infants and Children

9.17 The immaturity of hepatic metabolism and low clearance in pre-term infants means that they represent a potentially vulnerable subgroup. Such vulnerability could be taken into account quantitatively by modification of the population distribution using the appropriate coefficient of variation and the magnitude of the difference between neonates and adults in order to estimate the risk for threshold effects. A recent review on the differences in kinetics between adults and children concluded that young children frequently eliminate drugs and foreign compounds more rapidly by metabolism and excretion compared with adults (Renwick, 1998). In consequence, a smaller proportion of a population of children would be at risk compared with adults.

9.18 Quantitation of differences in sensitivity between neonates, or children, and adults in target organ response using *in vitro* studies, could be used to alter the default factor for human variability in toxicodynamics. There appears to be no general case for treating children as a particularly sensitive sub-group. In specific cases, the nature of the toxic effect and/or the particular exposure situation may nonetheless require children to be considered specifically.

Ethnic differences

9.19 Ethnic differences can arise from genetic and environmental factors and result in differences in both kinetics and response (Renwick, 1996). In many cases, differences in mean kinetic parameter estimates between different ethnic groups are small (Renwick and Lazarus, 1998) and ethnicity would not influence the validity of the default factor of 3.16. However, a 3.16-fold factor would be less adequate in cases where a different ethnic group showed a decrease in clearance, combined with an increase in variability, e.g. desipramine, diazepam, methylprednisolone and nifedipine. It is clear that ethnicity should be considered for some P450 mediated oxidation reactions, although this would need to be on a case-by-case basis.

Polymorphic metabolism

9.20 Calabrese (1985) illustrated that genetically determined biochemical differences could exceed greatly the 10-fold factor for human variability. That analysis interpreted variability in enzyme activities in relation to the full 10-fold factor and included *in vitro* estimations of activity as well as diagnosed clinical conditions. In cases of diagnosed clinical conditions, specific advice can be given; for example phenylketonurics are advised that the sweetener aspartame is a source of phenylalanine. Of greater potential concern are undiagnosed and unrecognised sources of variability, such as genetically determined differences in enzymes affecting kinetics, which have to be covered by the default uncertainty factor.

9.21 Genetically determined differences are of greatest relevance to risk assessment when the polymorphic pathway represents the major route of elimination. Poor metaboliser subjects would be at greater risk if the polymorphic pathway resulted in detoxication, but at less risk than the extensive metaboliser group in cases where the pathway is involved in a bioactivation process leading to toxicity. Therefore, knowledge that a chemical is a substrate for a metabolic pathway which shows polymorphic expression raises questions about the validity of the 3.16-fold default uncertainty factor for kinetics, (and therefore the combined 10-fold factor for human variability), but does not automatically invalidate the default values. Again known differences could be

incorporated into an analysis based on thresholds and the population distribution, but could not be incorporated readily into low-dose extrapolation methods unless a PBPK model was part of the extrapolation model.

Environmental risk characterisation

9.22 Environmental risk characterisation has much in common with human risk characterisation. In contrast to human risk characterisation however, the emphasis is on the protection of communities/ecosystems rather than individuals. As discussed in Chapter 5 there is a strong case for integrating human and environmental risk assessment activities.

Figure 9.3: Uncertainty factors used to establish acceptable levels of environmental exposure

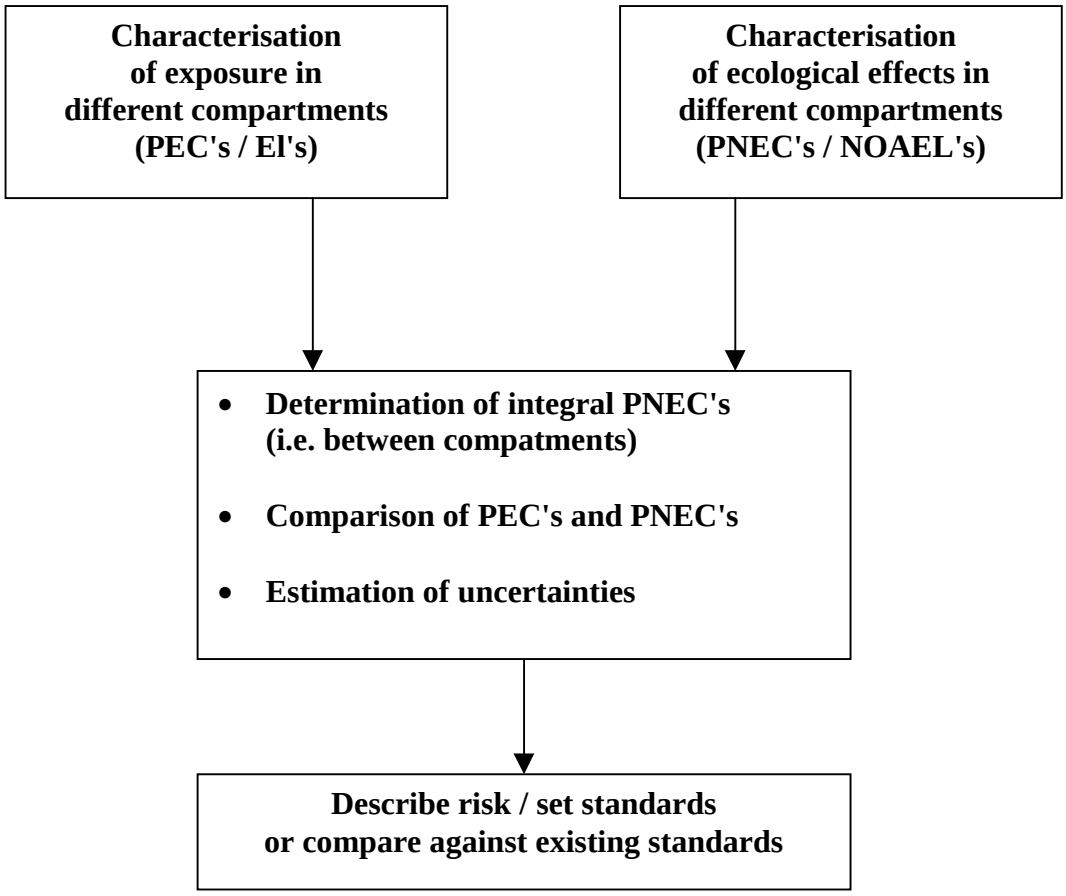
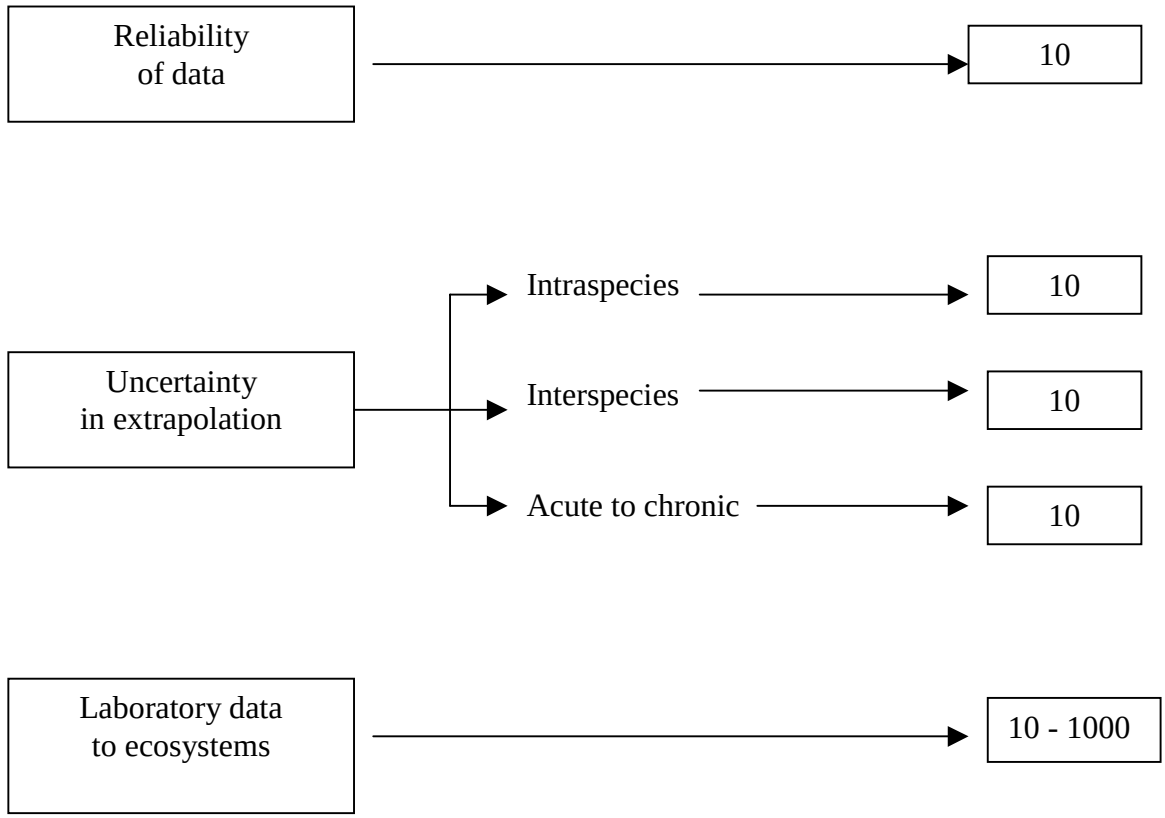


Figure 9.4: Typical uncertainty factors for environmental risk assessment



9.23 A particular challenge for environmental risk assessment is the extrapolation of data from a few surrogate test species to relevant effects on the structure and functioning of the ecosystem. For this reason, higher tier multi-species tests and field study findings where available are of major importance. The exposure assessment is a key element when identifying the ecological receptors which must be considered in the analysis plan. Information derived from structure activity considerations can be an important aspect of the exposure assessment, particularly in relation to persistence of exposure. Thus, a crucial element of the risk assessment report needs to be a clear expression of the uncertainties in the exposure assessment and intra and interphylla extrapolation (see Figure 9.3).

9.24 The assessment should identify:

- The nature and intensity of the effects
- The spatial and temporal scale
- The potential for recovery.

In ecosystems, effects on one species often impinge on another. It is important as a component of identifying the nature and intensity of the effects to distinguish adverse ecological changes from normal ecosystem variability.

Simultaneous exposure to several risk sources

9.25 Although simultaneous exposure to several risk sources is the situation in practice, this is rarely taken into account in the risk assessment process. A strategy needs to be developed by the Scientific Committees for addressing this issue.

MICROORGANISMS

[*Note*: see also Appendix 4 : Report on microbiological risk assessment, and Appendix 5: Report on risk assessment for transmissible diseases]

9.26 Risk characterisation is the integration of hazard identification, hazard characterisation including a dose-response assessment and exposure assessment to provide an overall probability of a given population being subjected to infection, morbidity, mortality, or to whatever biological response is being considered. Microbiological risk characterisation consists in two major elements: risk description and risk estimation. Risk description involves describing the event according to its nature, severity and consequences. Risk estimation describes the types and magnitude of effects anticipated from exposure to the pathogen, medium or product and can be qualitative or quantitative depending on the data and methods used. The final result can be expressed as an individual risk estimate (e.g. one in a million probability of illness) or as a population risk estimate (e.g. 10 illnesses per year in a certain region). Alternatively, risk can be modelled dynamically to consider the individual within a community rather than as an isolated individual, including elements such as host immunity or secondary transmission.

9.27 A particular aspect of risk characterisation for microbiological pathogens refers to expressing the severity of the related disease. Microbial pathogens may cause a great diversity of illnesses, with widely different impact on public health. Even one agent is usually related to different illnesses, possibly in different populations. A public health based standard for acceptable risk from pathogenic micro-organisms should therefore not only be based on the probability of disease but also on its severity. Notwithstanding the unit utilised to express the risk (e.g. probability of infection, or of illness), this calls for a non-specific approach to measuring the health burden of foodborne illness. Health-related quality of life scales (quality or disability adjusted life years, QALYs or DALYs) are commonly used for this purpose in health economics and medical decision making. They are increasingly being used in the domain of public health. The use of these human health parameters should be considered when progressing microbiological risk characterisation (see section 10 for discussion).

9.28 The two components, variability and uncertainty, describing the degree of reliability of the risk estimate, should be clearly and distinctly described. The variability is the effect of chance and is a function of the system, whereas uncertainty is the assessors lack of knowledge about a given parameter and may include parameter uncertainty, model uncertainty and scenario uncertainty. The separate effect of variability and

uncertainty on the risk estimate should be made clear. Estimating separately variability and uncertainty will provide useful information, in particular for some decisions that could follow from the risk assessment. If uncertainty is large, collecting further samples, and/or additional research, will contribute improving the knowledge about a given factor, thereby increasing the reliability of future, revised, risk assessments. If on the other hand, if variability predominates, collecting more samples is often a waste of time, as more samples will only contribute to describe the heterogeneity of the factor considered, but not to reduce the variability component. There, with specific regard to improving the reliability of the risk assessments, assessors and managers may consider reducing variability by changing the system, i.e. by controlling a manufacturing process, which may narrow down the number of possible scenarios. In any case, because in quantitative microbiological risk assessment the output of risk characterisation is a probability distribution of the risk, it should be clearly stated if this distribution represents variability, uncertainty, or both.

9.29 Variables used for data input should be evaluated for their effect on the final risk estimates. Sensitivity analyses of the result of probabilistic modelling should be performed, to provide knowledge on how the effect of changes in the mathematical approach impacts on the result of the risk estimate (Vose, 1997, 2000). A sensitivity analysis has two objectives. The first is to identify the elements or factors that most impact on the magnitude of the risk. The second is to "move around" with the uncertainties/assumptions to see how much they affect the results, i.e. to determine the robustness of the model toward these uncertainties/assumptions. In the context of microbiological risk characterisation, it is advisable to examine two aspects:
- the effect of changes in the estimated parameters (such as the mean and the variance for an input distribution) and the comparing of which parameters have the largest effect on the output.
- the effect of the choice of input distributions (triangle, normal, poisson, etc..) or other assumptions/specifications

9.30 The sensitivity analysis for the parameters could be carried out in different ways. One very simple way of carrying out a sensitivity analysis is to carry out a relative sensitivity analysis, where a small change in a given parameter is compared with the percentage change in the output parameters. Rank Order Correlation may be a better solution. Ranks can cope with non-linear relationships between the input – output distributions, allowing the use of linear regression techniques. Rank-transformed statistics are more robust, and provide a useful solution in the present of long-tailed input and output distributions. A scenario analysis determines which input parameters contribute significantly towards reaching a goal. For example, which parameters contribute to exceptionally high risk or which parameters contribute to exposure below a certain value? The scenario analysis is related to sensitivity analysis, and is also referred to as 'two sample tests' in context with sensitivity analysis or 'reliability analysis'.

9.31 The sensitivity analysis for the input distributions is not so well defined. A suggestion could be to replace each input distribution at a time with a quite different but still realistic input distribution. The mean and/or the shape of the output distribution may be affected by the replacement.

9.32 A critical component of microbiological risk characterisation, not unlike risk characterisation for toxic chemicals, is an assessment of the assumptions that are made during the analysis, and of the sources of uncertainty and their impact (Morgan and Henrion, 1990). In many microbiological risk assessments, relevant data may not be available for all aspects of the analysis and/or data may not be of adequate quality. Consequently, a number of assumptions may be made, each with varying degree of uncertainty. Uncertainty refers to the lack of knowledge about specific elements and may have several sources, such as scenario uncertainty (e.g. descriptive errors, errors in professional judgement, incomplete analysis), model uncertainty (e.g. simplification of real world processes, inappropriateness of model structure, model misuse, inappropriate surrogate variables) or parameter uncertainty (e.g. errors in study design, measurement or sampling). Uncertainty and their sources should be carefully identified and analysed (and where possible quantified), together with an evaluation of their impact on the risk estimate and how it should be utilised.

9.33 Associated is the expression of the confidence in the risk estimate. This includes verification and validation. Verification is basically a technical exercise, aimed at assuring the precision of parameter estimates and implementation of computer software. It is mainly the responsibility of the analyst, but could involve specialist review. Validation is concerned with the scientific acceptability of model assumptions, model formulations and criteria for data selection and treatment. This involves communication with the scientific community at large. If different assumptions or approaches are deemed feasible, the effects of alternative assumptions or scenario's should be carefully evaluated and the results should be communicated to the risk manager. Another aspect is comparison with empirical data. Microbiological risk assessment is unique because often the diseases of concern do actually occur in the population, and model estimates could be compared with observational data from epidemiological studies, which include cross sectional surveys, cohort studies, case control studies, intervention studies. It is critical to recognise the strengths and weaknesses of each of these study types when comparing quantitative microbiological risk assessment information. At present, there is a crucial need to conduct high quality, targeted, more searching epidemiological studies to validate the models currently used and improve the estimates.

9.34 Finally, the risk characterisation should include a discussion of the constraints faced and of whether the assessment adequately addresses the questions delineated by the managers that commissioned the risk assessment.

CONCLUSIONS

i) The principal concerns in risk characterisation are:
- To identify the risk based on the exposure assessment and the dose response analysis which is part of the hazard characterisation.
- To define the uncertainties in this identification in a clear and transparent manner and propose means for addressing them.

- It is recommended that such factors are applied, bearing in mind the scope, quality and relevance of the data provided. Unless this is done, there is a danger that

hazards for which there is a poor data base are viewed as of a lower risk than hazards for which there is a comprehensive data base.

- Risks may be expressed in terms of probabilities using descriptive terms. Currently, the DG SANCO Scientific Committees probabilistic analysis is rarely used. However, it is recommended as the preferred approach where the data permits. It would be appropriate to review the potential benefits and disadvantages of moving towards a more probabilistic approach.

- The scientific basis for widely used uncertainty factors has been assessed and harmonisation is recommended.

- There is pressure from various sources to re-examine the way in which groups that are considered to be particularly sensitive (e.g. infants) are incorporated into risk assessments. The preliminary conclusion has been that there may be specially sensitive groups for particular hazards (e.g. individuals with particular metabolism deficiencies) but no generally ultra-sensitive population group has so far been identified. However, further evaluation of this issue is important, based on sound science.

ii) Many of the risk assessment activities of the Scientific Advisory Committees culminate in a decision on an exposure level which is deemed to be "without significant adverse effects to human health or to the environment". It is proposed that:

- Where appropriate, Scientific Committees should also be requested to recommend appropriate work which could be conducted to reduce the main uncertainties. These proposals for further work should be reviewed by a task force of the Scientific Committees from time-to-time to identify common themes which might justify more generic research and which could be fed into the DG RESEARCH Framework Programme.

- A clear distinction be made between exposure levels which are considered, on the best available scientific evidence, to be without significant adverse effects to human health or to the environment and "acceptable" exposure levels. The latter is influenced by public and political perception, cost benefit assessment and a number of other factors in addition to science. Nonetheless, the EU should be encouraged to develop the debate with appropriate stakeholders on what constitutes an acceptable level. Risk assessors have an important contribution to make to such a debate.

- Scientific Committees be encouraged to identify both the exposure level, which is "without significant adverse effects to human health or to the environment" **and** levels which if exceeded constitute "concern" and "serious concern" (i.e. different action levels). In the absence of such action levels it is often assumed by non-scientists that there is an important public health risk from even a small exceedence of the "without significant adverse effects" exposure level.

10 OTHER RELATED ISSUES

"All animals are equal but some animals are more equal than others"
George Orwell (1945)

There are a number of important issues which are currently not incorporated in the formal risk assessment process, but nonetheless should be taken into account in making a judgement. These include in particular animal welfare, sustainability, and human quality of life parameters.

- **ANIMAL WELFARE**

Introduction

10.1 Animal welfare under human control has been identified in Europe as an important social issue. Animals are considered as sentient creatures; they can experience suffering as well as pleasure. Regardless their utility to humans (e.g. as food, clothes, sport, companions, laboratory) they have an intrinsic value in their own right.

10.2 Under a protocol agreed in the Amsterdam Treaty (1997) the member states agreed that they desire "*to ensure protection and respect for the animals as sentient beings*…". Several regulations on that topic have already been published during the recent years (see http://europa.eu.int/eur-lex/fr/lif/reg/fr_register_1540.html). Such decisions on regulations should be based as much as possible on a scientific assessment of human actions on the welfare of the animals.

Definitions

10.3 It is assumed that a good welfare or a good quality of life is reached when the "animal is in harmony with its environment and with himself, both physically and mentally" (Hughes, 1976).

10.4 In order to safeguard welfare and to avoid suffering, animals must be kept under conditions that respect both their physiological and behavioural needs. The welfare of an animal is therefore at the intersection between its biological features and the housing and management conditions to which it is subjected. The biology and behaviour of present day animals are the outcome of the process of evolution. Evolution has resulted in animals that are adapted to their natural environment or "niche". A niche defines the pattern of adaptive behaviour essential to an animal's survival and reproduction. Some elements of this adaptation process are common to all animal species, such as orientation, foraging and feeding, whereas others are specific to a particular niche, such as life in extreme cold or in semi-aquatic conditions. Because niches have many features in common, specially in terms of temporal and spatial constraints, adaptive behaviour is usually sufficiently flexible to allow an animal to adapt to environmental conditions different from those in which it has evolved, providing they bear sufficient similarities to the original niche. Domestication makes use of this flexibility. Welfare assessments occur at two levels that of the general ability of the species, and that of the individual and there may be important differences e.g. a wild animal captured and kept in a cage compared to individuals from the same species being bred in captivity.

10.5 The welfare of an animal is at risk if it cannot successfully adapt to the conditions in which it is kept. This can occur in several ways. At the behavioural level, an animal can be prevented to develop the full repertoire of its species specific behavioural activities because of restricted space or the lack of appropriate substrate for these activities. The thwarting of behavioural needs is claimed to induce suffering, the extent of which depends on the importance of the behavioural activity in the repertoire of the species to which the animal belongs. At the physiological level, excessive constraints upon the animal's adaptive abilities trigger a non-specific neuroendocrine response that is usually referred to as the "stress response". This is particularly the case in unpredictable and uncontrollable situations in which temporal and instrumental contingencies are difficult to establish. In all these cases, adaptation failure usually results in a number of altered body functions of which the visible manifestations can be used to assess welfare. Whether this is associated with altered emotional states and feelings depends on the emotional and cognitive abilities of the organism under consideration.

10.6 In line with these general principles, welfare has been defined as the state of an animal as regards its attempt to cope with its environment (Broom, 1996). Welfare therefore varies from good to bad, or more precisely from ease of coping to difficulty of coping. Pleasurable mental states are believed to accompany good welfare whereas unpleasant states are associated with coping failure.

10.7 It is also proposed that the welfare of an animal is reached when five freedoms are fulfilled (-freedom from hunger, thirst and malnutrition, - freedom from discomfort, - freedom from pain, injury or disease, - freedom from fear and anxiety, - freedom to express normal behaviour) (UFAW, 1992)

10.8 The welfare is depending on the cognitive and emotional abilities of the animals. Some scientists assume that those abilities can be higher for some animals than for others. Usually vertebrates are the only animals to be considered. Within those vertebrates, primates are supposed to have the highest abilities.

The assessment of welfare

10.9 Animal welfare can be assessed in an objective and quantitative manner, and indicators of welfare include health, bodily functions, and behaviour. For an adequate assessment of welfare, a wide range of indicators must be used, although single indicators can show that welfare is at risk.

10.10 Environmental conditions that significantly depart from an animal's niche can be at the source of welfare problems, the extent depending on the duration and intensity of the condition under scrutiny. The reality of such welfare problems can be assessed in the subjected animals by a combination of measures taking into account their physical health, biological functions and behaviour. In general, minimum mortality, low morbidity, little or nor risk of body injury, the ability to express species specific activities including social interactions, grooming, exploration and play, as well as the lack of abnormal behaviour and of physiological signs of stress, including alterations in immunity, indicate that there are no major animal welfare problems.

10.11 Despite the fact that several protocols are in used for evaluating the quality of life of human, not all those methods can be used adequately for animals because they are assessed through the language (Smith *et al*.,1999). However animal welfare analysis is possible using a multidimensional approach including health, physiology and behaviour items. This has been described extensively in previous reports on animal welfare of the Commission and elsewhere in books (Broom and Johnson, 1993 ; Appleby and Hughes, 1997). A short review of those methods will be presented below.

Mortality and morbidity

10.12 Different from important infectious diseases, welfare problems are mainly represented by the impairment of health due to the environment or due to genetic defects. Death on farms can be spontaneous, caused for example by disease, injury or physiological failure, indicating that the welfare has been poor. Animals can also be culled for the same reasons, and in such cases, culling can be treated similarly as a sign of poor welfare. In addition, welfare is poorer if the incidence of production related diseases is higher than in similarly aged animals which have not been exposed to the same management, housing or selection. If inherent weakness or abnormality means that the individual will be more likely to succumb to disease or injury, then the welfare is poorer than that of an animal which does not show this weakness or abnormality. In a group of animals, the impairment of welfare caused by a pathological condition is a function of its incidence, severity and duration. Health indicators of animal welfare must be studied with a broad population perspective; an increased use of preventive and therapeutic veterinary medicines in a certain population may indicate that welfare is more at risk in those animals than in animals belonging to populations where such mediation is not necessary.

Body condition and reproduction

10.13 Welfare is impaired if the physical condition is affected and if there is an imbalance in organ function. Reproduction is an indicator of well-balanced body functions. Given adequate conditions for reproduction, a delayed reproductive activity or capacity is indicative of a poor animal welfare.

Behaviour

10.14 Animals use behaviour as one of the most important means of adapting to their social and physical environment. Behavioural activities are normally triggered by a set of endogenous and exogenous causal factors, and their performance is the source of regulatory feedback. If there is a mismatch between different causal factors, deviations from normal behaviour can occur, e.g. when endogenous factors set up the conditions for appearance of a behavioural activity for which there is no adequate substrate. These alterations in behavioural expression may be important signs of welfare risks. Varying behaviour including abnormalities is an indicator of poor welfare.

10.15 Preference methods are another way to estimate the importance for the animals of specific items of their environment (food, social contact, bedding,…). Preferences are analysed by giving animals a choice between various items. The price the animal is

willing to pay to obtain some resource can also be measured. These methods have also some limits for example if the animals have to choose between short and long term benefits (Fraser *et al*., 1997).

10.16 It is important to point out that the ability of animals to engage in at least some behavioural activity is important for their welfare. Not allowing sufficient locomotion for instance can lead to muscular-skeletal problems. In addition, the inability of animals to engage in appropriate behavioural patterns during development may impair their ability to regulate the corresponding behavioural in the future.

Physiology

10.17 Physiological indicators of stress, which include alterations in the regulation of adrenal hormones' synthesis and release, changes in autonomic balance and changes in the distribution and functions of immune cells, are also indicators of poor welfare, especially when associated with specific behavioural abnormalities.
Tissue damaging related to human activity either directly (mutilation, mistreatment) or indirectly when associated with disease is often a cause of pain. Human pain is defined "as an unpleasant emotional experience associated with actual or potential damage or described in terms of such damage" (International Association for the study of pain, 1979). That definition can likewise be used for animals except that they cannot describe the experience they are making. Several authors have proposed protocols to measure pain in animals (Morton and Griffith, 1985; Brugère et al., 1992; Lawrence Podolsky and Lukas, 1999).

Consequences of animal welfare concerns

10.18 Considerations of animal welfare have important consequences on several areas related to risk analysis. The main ones refer to laboratory animals and farm animals.

Laboratory animals

10.19 There is a major public concern about the suffering of laboratory animals used in medical research (Pifer et al, 1994) and that concern has consequences on the scientific process itself (Veissier, 1999):

- A first idea is that it is necessary to maintain the animal welfare status during an experiment to obtain meaningful results.
- Another idea is that animal's sufferings should be avoided from an ethical viewpoint. Even if some people consider any provoked suffering as not acceptable, Singer (1990) justifies such suffering if future benefit for humans or animals exceeds the suffering of animals during an experiment.

10.20 Russel and Burch published in 1959 a text entitled "Principles of humane experimental technique" (cited by Monamy, 1996). They proposed a 3R rules: "Replacement, Reduction, Refinement". That 3R rule has been adopted by Canadian, American, Australian, New Zealand, British and European (European Centre for the Validation of Alternative methods) institutions:

- ***Replacement***: it is important to use alternative methods avoiding the involvement of animals. In vitro techniques and modelling have to be promoted (Orlans, 1987).

When it is not possible to avoid using animals it should be preferred to choose animals with the lowest cognitive abilities. It is also necessary to avoid using rare animals that could impair the biodiversity.

- ***Reduction***: it is necessary to limit the number of experiments and to avoid duplications. It is also important to limit the number of animals involved in an experiment for instance by using very homogeneous animals, twins or clones (Mann et al., 1991).
- ***Refinement***: it is necessary to limit suffering of animals involved in experiments - by using appropriate "pain killers", - by sacrificing the animals before they suffer too much or too long, - and by handling them correctly (attitudes of scientists, technical assistants and keepers are crucial in that respect).

10.21 Ethics committees have been set up for analysing experimental protocols in particular in order to limit animal suffering. Some authors have proposed methods how to analyse an experiment on animal welfare grounds (for examples Porter, 1992 and Bateson, 1986). Bateson tried to make a cost benefit analysis by weighing the quality of the research, the expected scientific output and the degree of animal suffering. Various national regulations have been published in different countries for the control of experiments. In some of these countries it is compulsory that the protocol of each experiment is accepted by an ethical committee, whereas in other countries licences are given to researchers and experimental houses (Veissier, 1999).

10.22 A lot of regulations have been published in order to limit the use of animals for research or for control purposes. One example is the Resolution from the Council of Europe (ETS123, 24 November 1986) on the European Convention for the protection of vertebrate animals used for experimental and other scientific purposes.

10.23 Some regulations are banning or limiting drastically the use of animals for control analysis. This trend is particularly true in cosmetic control for example Directive 76/768/EC. In its article 4 it states: "… member states shall prohibit the marketing of cosmetic products containing:… (i) ingredients or combinations of ingredients tested on animals after 30 June 2000…". In its Article 10 it states: "Before submitting such measures, the Commission will consult the Scientific Committee on Cosmetology. The Commission shall present an annual report to the European Parliament and the Council on progress in the development, validation and legal acceptance of alternative methods to those involving experiments on animals. That report shall contain precise data on the number and type of experiments relating to cosmetic products carried out on animals. The Member States shall be obliged to collect that information in addition to collecting statistics as laid down by Directive 86/609/EEC on the protection of animals used for experimental and other scientific purposes. The Commission shall in particular ensure the development, validation and legal acceptance of experimental methods that do not use live animals".

10.24 The Existing Chemicals Regulation (EC) 793/93 of 23 March 1993 (JO L84 of 5.4.93) is also of interest. It too makes a specific reference to 86/609/EEC. Whereas a clause not numbered in text states: "whereas wherever possible and in consultation, in particular, with the European Centre for Alternative Testing methods, the use of animals must be avoided by recourse to validated alternative procedures". Article 10 (5) deals with further testing: "When manufacturers or importers are asked for further information and/or testing, they must also check, in view of the need to limit practical

experiments on vertebrates, whether the information needed to evaluate the substance is not available from former manufacturers or importers of the declared substance and cannot be obtained, possibly against payment of costs. Where experiments are essential, it must be checked whether tests on animals cannot be replaced or limited by other methods. Necessary laboratory tests must be performed with due respect for the provisions of 'good laboratory practice' as laid down in Directive 81/18/EEC and for provisions of 86/609/EEC."

Other regulatory texts include considerations of animal welfare (88/378/EEC, 86/609/EEC, 86/698/EEC).

10.25 Hence the possibility to use a large number of animals and to induce animal suffering is limited by regulations based on ethical grounds. That can have consequences for example on the statistical power of the experiments.

Farm animals

10.26 Hazards to farm animals are illustrated in table 10.1. Regulations on the welfare of farm animals can have consequences on several areas related to public health by promoting specific management practices while prohibiting others. The general trend of those regulations is to allows the animals to express their normal physiology and behaviour (more space, enriched environment,…).

10.27 Several authors have shown that stress has a negative impact on the resistance to disease. Management that limits stress to animals should result using less drugs, in particular antibiotics. However even if this idea is generally important it may lead to increased product contamination. For example, it seems more difficult to control the microbial contamination of eggs when hens are kept in aviaries as compared with standard cages (Report on the Welfare of Laying Hens VI/BII.2 VI/8660/96).

10.28 The modification of management systems can also be detrimental to worker’s health. For example, in egg production units, it seems that the risk of allergic reactions of the workers is higher if the hens are in aviaries rather than if hens are kept in battery cages. Likewise it seems more dangerous for workers to take care of lactating sows when these are free as when they are kept in crates (The Welfare of Intensively Kept Pigs. XXIV/B3/ScVC/0005/1997). However the job satisfaction of caretakers working in farms where the animal welfare conditions are good may be much higher than if they are not.

Table 10.1: Some examples of hazards to take in account when analysing animal welfare (the items with a star can be analysed following a "dose" response procedure)

Substances*	***BST***
	Growth promoters
Feeding	***Pathogenic substances****
	Starvation*
	High concentrate diet*
	Only milk diet (veal calves)*
	Force-feeding
Mutilation	***Castration***
	Dehorning
	Tail docking
Genetics	***Genetic engineering***
	Quantitative selection (growth, milk)*
Microclimatic environment*	***Temperature***
	Humidity
	Toxic substances
Housing	***Space****
	Floor
Handling	***Handling devices***
	Human attitudes and behaviours*
Manipulations	***Milking***
	Transport
	Stunning
Social constraints	***Isolation***
	Density*
	Mixing
	Weaning

Animal welfare and risk assessment

10.29 The animal welfare analysis is very close to the one of the quality of life in humans.

- Data have been collected, in order to estimate the animal welfare, that are related to the physiology and behaviour of those animals.
- Variable features of the environment and genetic background can influence those data.. The physical environment (temperature, humidity,…), the biological environment (food, water, parasites,…), specific treatment (BST for dairy cows is an example) but also the social environment (maternal, peers, human,…) can be important.
- It is then possible to make a risk assessment of the welfare of animals using the general methodology.
- Welfare analyses have to deal with several types of hazards. Some examples are given in Table 10.1.
- Most of those hazards are quantity dependent and can be analysed following a "dose" response assessment.
- Exposure assessment can be achieved through the analysis of the current practises of the industry.
- Risk characterisation is the integrated analysis taking in account the interaction between the different hazards and exposures.

10.30 However, animal welfare analysis differs from risk analyses in other fields by several points:

- An analysis can be done on animals of the target species. It is then not necessary to make assumptions about the risk by extrapolating the results from one species to another.
- Some parameters can be much higher in farm animals than in human. For example, mortality of piglets before weaning can reach 10%. Mortality of broilers is higher than 4% (see the report on the welfare of chicken kept for meat production (broilers) Sanco.B.3/AH/R15/2000. 150 pages). The observed increase of losses is usually over 1% which is much higher than what is considered as acceptable in human risk analyses (a few per million). It is then difficult to define negligible risks and threshold values. As a consequence, most of the models used in risk analyses for humans where adverse effects to substances are assessed are not really useful in a risk analysis of animal welfare. The limit between acceptable and unacceptable is not straightforward.

Competitiveness of the industry

10.31 This is a major point of concern of the industry. It is clear that constraints put on an industry can impair the return or increase the cost of the products. Such an increase can introduce a distortion of competition for other products. For example a higher veal price can have the consequence that consumers prefer to buy turkey meat. However a major point is that as ethical concerns are not part of the WTO agreement, distortion of competition can occur to the European industries due to European regulation on animal welfare.

- **SUSTAINABILITY**

10.32 Sustainability is widely recognised as an important environmental objective. The Earth Summit in Rio in 1992 was the watershed as far as national and international support for the concept of sustainable development is concerned. Sustainability has been defined as "developments (eg: products, processes, facilities, locations) which meet the needs of the present generation without compromising the ability of further generations to meet their own needs". This definition is very broad and therefore subject to various interpretations. Two main issues underlying sustainable development can, however, be recognised, namely:

- The environment is to be recognised as an integral part of mankind's development. This implies minimal use of non-renewable resources and minimal emission of pollutants. A priority for the latter is a reduction in persistent organic pollutants (POPs).
- A multi-generation time scale over which impacts should be considered. Various models have been developed of life cycle analysis (life cycle assessment) which consider sustainability from the manufacture of product to its disposal (cradle to grave) or reuse (cradle to cradle). For the great majority of products, it is unlikely that enough data will be available to conduct a meaningful life cycle analysis.

Whether social considerations, such as enabling the autonomy of future generations and the promotion of equity in world development are embraced within the term "sustainability" remains controversial. These are certainly areas outside the scope of the Scientific Advisory Committees as currently constructed.

10.33 At present, where sustainability is considered at all as part of the risk cycle, it is likely to be dealt with by applying the precautionary principle. This is appropriate if there is a high degree of uncertainty, but not where the impacts of a hazard on sustainability can be quite well defined. The adoption of an integrated approach to risk assessment should ensure that issues of sustainability relating to health will, in the future, become incorporated progressively into risk assessments. In order to achieve this, relevant indicators of sustainability or unsustainability need to be determined. For risk assessment purposes it may be most appropriate to define science based indicators of unsustainability in long-term health / quality of life terms.

10.34 It is likely that progressively sustainability will become a parameter in comparing industrial processes, facilities and products. Assuming the current composition and expertise of the Scientific Advisory Committees, it would be inappropriate for them to evaluate those issues of sustainability which are principally economic or psychosocial. Nonetheless, it may be appropriate for these Committees to assess those aspects of sustainability which are related to health and which draw principally on scientific data.

10.35 It would be appropriate for the EU to begin to develop a framework in which issues of sustainability can be incorporated into the risk cycle (see Figure 3.1). The framework might focus initially on specific issues of sustainability where clear answers can be given, e.g. likely difficulties in recycling/disposal, environmental persistence, contribution to global warming and other environmental categories. As sustainability becomes an increasing priority, it is likely that more emphasis will be given to multigeneration studies.

- **HUMAN QUALITY OF LIFE PARAMETERS**

10.36 Pathogenic agents may cause a great diversity of illnesses, with widely different impact on public health. Even one agent is usually related to different illnesses, possibly in different populations. As an example, for foodborne microbial pathogens, the health impact may vary from mild gastrointestinal disturbances to life-long sequelae and even death. In this context, current risk assessment analyses or models estimate the probability of an adverse effect, of a disease, and/or mortality. The severity of the adverse effect, of the disease, and the possibility of different health outcomes are not usually taken into account explicitly. This makes it difficult to determine a common set of standards for different stressors which may lead to health effects of widely different severity, and to compare the costs and benefits of possible interventions. Also, it is not possible to make transparent decisions when a particular intervention reduces the probability of one type of adverse effect or disease, but increases the probability of another. A typical example is provided by the debate about disinfection of drinking water. Disinfection of drinking water reduces the risk of infectious disease, but oxidants like chlorine or ozone react with water constituents to produce a variety of by-products, some with toxic and carcinogenic properties. The dilemma on how to balance these positive and negative health effects has long hampered decision making about implementing or modifying drinking-water disinfection processes.

10.37 Hence, a non-specific approach to measuring the health burden of illness is increasingly advocated in the domain of public health. This approach implies health-related quality of life scales that enable integrating different disease end-points. The concept of Disability Adjusted Life Years (DALYs) is particularly suited for that purpose. Similar concepts, such as Quality Adjusted Life Years (QALYs), have been used extensively in medical technology assessment and in health economics to optimise decision making, both from the perspective of individual patients and from the societal perspective (Havelaar, *et al.*, 2000b). The concept is increasingly being used in public health research, as demonstrated by the publication of the Global Burden of Disease study (Murray and Lopez, 1996), and has been adopted as a basis for public health policy in a few countries, such as the Netherlands (Havelaar *et al.* 2000a, b).

Life years lost

10.38 The basis of quality of life scales is the concept of loss of (healthy) life years. The number of life years lost (LYL) is defined as the difference between the actual age at death, and the life expectancy at that age. If mortality affects the population in a random fashion, the life expectancy can be derived from standard life tables. If mortality affects a susceptible sub-population, disease specific information is necessary to estimate the additional loss of life years by the disease under consideration.

Years lived with disability

10.39 Morbidity is considered to reduce the value of life during the period of disease and because of the impact of possible chronic sequelae. This is expressed by the concept

of years lived with disability (YLD). To estimate the YLD on a population basis, the number of cases is multiplied by the average duration of the disease and a severity weight factor that accounts for the severity of impact that specific diseases may have on individual or population health. The severity weight factor is determined on a scale from 0 (perfect health) to 1 (death). If necessary, the disease process can be subdivised into several stages with different duration or severity. This can be obtained by dividing the total group of patients into sub-groups, who develop different disease patterns, or by dividing the time course of the disease in different stages, or by a combination of both.

Evaluating the health burden: Disability Adjusted Life Years

10.40 The global burden of disease is evaluated via a single indicator, the Disability Adjusted Life Years (DALY). The DALY in a population is computed by the summation of life years lost (LYL) and the years lived with disability (YLD). Thus the DALY provides an integrated measure of public health, combining years of life lost by premature mortality with years lived with a disability that are standardised by means of severity weight.

Measuring health

10.41 Health has been defined as "a state of complete physical, mental and social well being, and not merely the absence of disease or infirmity" (WHO, 1992). This classical definition implies that health needs to be assessed in three different domains: the physical, psychological, and social domains. Each of these domains is an aggregate of a number of dimensions that are usually measured by means of questionnaires. There are three main types of questionnaires for health status measurement: generic, disease-specific, and domain-specific (Essink-Bot, 1995), whereas the choice between these types of instruments depends on the purpose and the perspective of the study.

10.42 Information from questionnaires gives a descriptive evaluation of health status, which needs to be valuated for further analysis. Different valuation methods are available. These include Standard Gamble (SG), Time Trade Off (TTO), Person Trade Off (PTO), and Visual Analog Scale (VAS) (Torrance, 1986; Murray, 1996; Brooks, 1996). It is considered that the PTO and the TTO approaches are the most natural approaches, whereas the PTO protocol is by nature the most suitable for evaluation of health care programmes from a societal perspective (Nord, 1995). As an example of application, in their Global Burden of Disease study, Murray and Lopez (1996) utilised a set of 22 indicator conditions, representing different grades of disability in the dimensions of physical functioning, neuro-psychological conditions, social functioning, pain, and sexual/reproductive functions. In a formal procedure, using the Person Trade Off protocol (PTO) these indicator conditions were assigned disability weights and classified into seven disability classes. In a next step, several hundred outcomes were evaluated with respect to the distribution of each condition across the seven disability classes. From these data, a composite disability weight for each condition was calculated.

Quality of life parameters and risk assessment

10.43 The use of human quality of life parameters can be valuable adds-in to the traditional risk assessment process, which implies hazard identification, hazard characterisation, exposure assessment and risk characterisation. In the risk characterisation stage, following an evaluation of the probability of adverse event(s) occurring, the severity of the disease and its public health dimension can be characterised by use of quality of life indicators such as the DALY. The number of life years lost (LYL) is calculated by accumulation over all relevant diseases of the product of the number of deaths due to a particular disease and the standard life expectancy at the age of death due to that disease. The years lived with disability (YLD) is calculated as the accumulated product of the number of persons affected by a non-lethal disease, the duration of this disease, and a weight factor for its severity. The DALY is the summation of LYL and YLD. As with other risk estimates, uncertainty in the estimated health effects is characterised and a sensitivity analysis is performed to evaluate the robustness of the overall conclusions, to determine the most important variables in the study for the final result, and to determine the factors that most impact on health loss (Havelaar *et al*., 2000a).

10.44 A major advantage of the use of human quality of life parameters (e.g. the DALY) is that it leads to a logical, transparent and comprehensive evaluation of health losses or gains in terms of established public health concepts, using time as a unit of measurement. Potential difficulties are not unique for this method but bear upon health impact assessments in general. Almost inevitable shortcomings are at present the imprecision of population exposure assessment, the unknown shape of the dose-response curves at low environmental levels of exposure, and the translation of information from animal studies to humans. Another important issue is the internal and external validity of epidemiological results. Also, because the limited availability of data leads to extensive use of models to arrive at final estimates, several assumptions are made that add to the overall uncertainty (Havelaar *et al*., 2000a).

10.45 Following the landmark publication of Murray and Lopez (1996), made on behalf of the World Health Organisation and the World Bank, several studies have documented very recently the applicability and utility of the method for drinking water and food safety determinations, e.g. Balancing the risks and benefits of drinking water disinfection (Havelaar *et al*. 2000a) or Determination of the health burden in the Netherlands due to infections with thermophilic *Campylobacter* species (Havelaar et al, 2000b). In particular, quality of life indicators such as DALY provide a flexible approach that can be used for comparisons of risks by different agents or in more advanced studies that emphasise the interaction of public health and consumer safety determinants. Until now, most of risk assessments focused on estimating the risk associated with a single stressor. At present, there is an increasingly perceived need to combine, to the largest extent possible, the dominant hazard oriented approach with a public health perspective to develop a holistic appreciation of food (other products, other sources) safety problems in their public health context. Quality of life parameters may aid in determining the desirable level of protection that should be guaranteed (Havelaar *et al.* 1999) and can contribute enhancing consistency among risk management strategies.

10.46 Quality of life indicators specifically address the health dimension of a safety problem to inform the risk management decision. However, they do not capture the public perception of the risk at stake, nor do they address the economical, social or cultural values potentially involved, all perspective that would contribute to the final decision making process.

CONCLUSIONS

i) A number of issues have been identified which are viewed by many as of increasing importance and yet are not currently incorporated in the risk assessment process. Three such issues that in several ways are inter-related have been addressed in this Chapter: animal welfare, sustainability, and human quality of life parameters.

ii) In each case, means of assessing the degree to which each deviates from an acceptable norm are outlined. It would be appropriate to develop guidelines for the Scientific Advisory Committees on when and how such considerations should be incorporated into the risk assessment process.

iii) In regard to animal welfare, some key elements should be considered:

- The welfare of some animals may be lowered if it results in an increase of the welfare of humans or of other animals. For experimental purpose, it is commonly accepted that some animals may suffer if it helps humans to live better. Some animals can be sacrificed for the sake of other animals and whole herds can be killed in order to protect other herds (for example during the recent classical swine fever epidemic).
- It is possible to select animals for their ability to adapt to specific environmental conditions and further to improve their welfare (continuing the process on domestication which has been working for thousands of years).
- It is important to have a cost benefit analysis of the recommended actions in order to help the risk manager to make decisions. The benefit is the increase of animal welfare. Costs could be the consequences of regulations for the well being of humans, the biodiversity, the environment and possibly the competitiveness of the industry.

iv) Quality of life parameters, such as the Disability Adjusted Life Years (DALY) parameter are additional evaluations that may appropriately complement the traditional risk assessment approach to effectively picture a consumer safety problem in its public health perspective. The application of quality of life parameters allows in particular a more explicit comparison of the public health risks and benefits of different managerial options, and thus to foster consistency among different risk management strategies. As is typical with other aspects of risk assessment, the application of quality of life parameters requires appropriate information and data.

v) It has to be considered whether quality of life evaluations should constitute an additional dimension to the risk assessment *sensu-stricto*, or be conducted in a

separate, but interactive process, to provide an essential input in establishing the public health significance of a consumer safety risk.

11 RISK COMMUNICATION

"The technology of the global communication network provides us with a remarkable tool. But how do we use its real potential?"
Sergei Kapitza (1988)

11 RISK COMMUNICATION

Risk communication to stakeholders is a key area where close collaboration between risk assessors and risk managers is required to ensure that the expression of each risk assessment is unambiguous, transparent and relevant. To be effective requires an understanding of risk perception issues. It is likely to be particularly challenging where it is difficult to specify the precise benefits, or the benefits are unevenly distributed, or some sections of society will be disadvantaged, or there are differences of scientific opinion on the actual risk, or there is a possibility for a large catastrophic effect.

RISK COMMUNICATION AND THE ACTIVITY OF THE SCIENTIFIC COMMITTEES

11.1 It is important to improve the consistency as far as is appropriate in risk expression. The present situation is a potential source of confusion. There is no common approach across the EU Scientific Committees for presenting the findings for risk assessments. In a number of cases the means used owes more to history than to the actual practical application for risk management or risk communication purposes. Common forms of risk assessment conclusions are:

- Whether or not a defined standard or action level will be achieved.
- Percentage or fold difference below or above a defined threshold value.
- Use of formalised risk phrases or classification categories.
- Number of population at risk per unit of population per annum.
- Likelihood of an individual experiencing an effect over a lifetime exposure.
- Potency in terms of a particular endpoint compared with a particular (standard) agent.
- In a risk benefit or cost context.
- Non numerical expressions of risk of which there are many, such as ‘acceptable’ or ‘minimal’ risk (see Appendix 2).

11.2 The appropriateness of each these forms to express the conclusions both from a risk management and a “public” communications perspective needs to be addressed.

In the risk conclusions it may be necessary to set the human and environmental risks alongside one another. This is likely to be of particular importance where the risk assessment involves a comparison between tworisk sources with different human and environmental impacts. How should this (termed ‘integrated risk assessment’: see Chapter 5) be formalised?

11.3 Among the main concerns of the European Commission when the new Scientific Committees were created three years ago, was to ensure easy access to information by the public and transparency in the risk communication. To this end it was decided to post at the Internet web site of the Commission the text of the opinions delivered by the Scientific Committees. This decision was considered of utmost importance to gain confidence by the public and to demonstrate openness and transparency in the discussion of the delicate matters about which the Committees are consulted. On the

other hand, given the complexity of the technical issues handled by the Committees, the fact that the opinions are of public domain has generated the need for the Committees to make themselves understood and to write the opinions in a way that they are comprehensible documents, but scientifically sound and referenced.

11.4 Although all the Committees in general deal with questions related to risk assessment, the various Committees operate in rather different fields of science, have to deal with questions of different complexity, and have been left free to adopt a non-standardised style of work and reporting, which may have caused the adoption of different criteria and methods of assessment, a different terminology, and a different format of reporting. This situation does not favour an effective risk communication as it may confuse the readers, be a cause of criticism, and, in the end, generate difficulty in proper understanding the work involved in the risk assessment. This could result in distrust in the scientific approach itself and in the Commission activities.

11.5 In order to avoid such problems and improve the transparency and efficacy in risk communication by the Committees, a review was made of a sample of opinions presented by the Scientific Committees, their framework and formulation, and suggesting recommendations for an harmonised opinion presentation by the various Committees. These were evaluated according to a grid (see Appendix 6) including the following elements:

- terms of reference – originator of the questions
- sources, type of information used and other constraints in the risk assessment, eg: time
- references to the assessment process used (regulations, guidelines)
- mode of uncertainty expression
- wording and expressions used
- editorial format
- coherence and transparency
- mode of expression of the final risk evaluation
- refusal - impossibility to answer

and expressed some recommendations for the future activities of the Committees. The full report of this survey is in the Appendix 6 to this document.
The conclusions of this work can be summarised as follows.

11.6 There were major differences in size, degree of detail, format and scope among the reviewed opinions. They ranged for one page short comments to full detailed reports consisting of more than 100 pages. Thus it seems to be unavoidable that some differences in format may remain even after a process of format harmonisation.

The Commission requested nearly all of the opinions; very few of them were prompted at the Committee's initiative.

The source of information was stated in most opinions, often in a reference list. However the quoted documents or literature were not always fully referenced.

Existing guidelines were often used as a reference, depending on the scope of the opinion and the existence of specific guidelines; however, the reader was not always systematically informed about this point.

Numerical calculations done by the Committee were accessible only in a limited number of cases, but values and calculations from references were often presented. In general, the transparency of the calculation process adopted was considered not to be adequate.

11.7 The uncertainty in the assessment of risk was generally not expressed in a single concluding sentence, but given more generally during the discussion or including adverbs or modal verbs in the conclusions. It was not always complete. The variety of solutions on this matter adopted in the examined opinions probably reflects the difficulty in standardising the uncertainty concept in a single way of expression.

11.8 The editorial format among the opinions of different Committees was far from homogenous. In particular, in several cases it was difficult to identify the main messages and the conclusions without an extensive reading of all the text. Most of the opinions did have a chapter with final conclusions, but named in different ways. Some Committees had already standardised the editorial format.

11.9 The wording used for the expression of risk varied depending in part on the scope of the opinions and the context in which the opinions were given. Many different synonyms were used to express similar risk concepts, but it was not clear whether different words or expressions actually meant the same risk judgement or they were used to rank or graduate a different intensity of risk. Quantitative risk expressions were seldom used and only occasionally specific numerical values were recommended (see Chapter 9).

11.10 Request for further information/data was done in a few cases, and in some cases the opinion included a statement of the actual impossibility to answer specific questions. Based on this analysis, the following recommendations are made regarding the presentation of opinions. Further consideration needs to be given to how to express any minority opinion. It is recommended that such minority opinions are only included where there is some scientific rationale.

Harmonisation and preparation of a Guideline Document

11.11 It is recommended that a Guideline Document be developed by the Steering Committee to harmonise some aspects related to the presentation of opinions by the Scientific Committees.
The pronounced diversity in the questions asked to the different Committees naturally limits the extent to which harmonisation can be achieved. These limits will have to be considered in the preparation of a Guideline Document on presenting opinions.

Editorial format

11.12 More consistency in the format of the opinions would facilitate the understanding and use of opinions, at least for non-professional readers who wish to quickly get the answers and are sometimes less interested in (or less able to understand) the technical reasons underpinning the answers.

11.13 To this aim, it would be beneficial to use the same format and titles across the Committees for 'identical' chapters. At least for the opinions released to answer a question posed by the Commission, a recommended structure is:

i) Title

ii) Terms of reference (where the questions are reported)

iii) Opinion (where the essence of the opinion is summarised)

iv) Background (where the context of the question is detailed and reference is made to the source of documents and to the normative framework and other constraints on the risk assessment process are identified)

v) Main text. Scientific arguments supporting the opinion (where the topic is discussed in details, with subdivision in chapters, each one with a title, when appropriate. Expression of any uncertainties in the risk characterisation (see Chapter 9).

vi) Conclusions. These may be an expanded text from which the essence of the opinion is extracted.

vii) Recommendations.

viii) References (where the quoted literature should be reported; as to the documents specifically made available by the Commission to answer the question, they should be mentioned in the Background section and not here).

Wording of the risk assessment evaluations

11.14 The Scientific Committees should agree among themselves on a glossary for the words and expressions to be used regarding risk assessment (see Chapter 5 and Appendix 1). Such an agreed glossary would also serve as a ‘reference glossary’ for both the instigator of the opinion and other readers.

11.15 In developing such a glossary, the Scientific Committee should be aware that adjectives such as minimal, negligible, etc. and expressions as ‘no risk’, ‘acceptable risk’, etc. may have a different meaning for scientists, experts and the layman. The glossary should explain the exact meaning attributed to these expressions or, alternatively, each opinion should explain the exact context in which such expressions are used. In general, judgements about ‘acceptability’ ought to be used only when clear legislative terms of reference are available (cf. the limit of 0.1 μg/L for ground water for pesticides); otherwise the criterion of acceptability should be explained in detail. In every case, it is important that the reader is informed about existence or non-existence of official EU legislation of reference within the frame of which the risk assessment judgement is formulated.

11.16 When the opinion of a Committee contains specific reference to risk management decisions or consists of advise on risk management, the Committees should be aware

that this may be beyond the mandate of a "scientific" group and carefully consider the appropriateness of releasing such views. The contents of an opinion must be defendable in scientific terms with the arguments detailed in the opinion, such a documented scientific justification may not be possible with regards to managerial aspects.

Summarised presentation of opinions

11.17 Taking into consideration the likely large number of opinions required in the future, it may be useful if a tabular list could be developed for past and future opinions. This summary would particularly help in scanning the web site.

Expression of uncertainty in the opinions

11.18 Particular attention is needed to this subject. Although a simple and totally common way of expressing uncertainty may not be easily achievable, it is necessary that uncertainty is clearly addressed in each opinion, thereby informing the reader about the solidity of the statements made and the nature of uncertainty in the judgement. To avoid possible misunderstanding by the reader, the Committees should also make clear whether this issue is of relevance to the final use of the opinions or not.

Adequacy of the opinions to the final purposes of the requesters.

11.19 It is also important to ascertain whether the main client (The Commission) is satisfied with the opinions and whether problems have been encountered regarding the interpretation and appropriateness of the opinions (see Chapter 12).

11.19 **Minutes of meetings**

The above discussion relates to the expression of opinions on specific risk assessments. A common format is also required for the minutes of meetings of the Scientific Committees and their working parties. Particular issues include: the detail in which individual discussions are described, whether attribution of statements to named members are made and the degree to which minutes should be understandable by non-technical experts. It is proposed that common guidelines are established for the presentation of minutes.

RISK PERCEPTION IN THE CONTEXT OF RISK COMMUNICATION

11.20 An awareness of risk perception issues is very important in risk communication. While the role of Scientific Committees is to concentrate on scientific issues in communicating their findings, it would be naïve not to consider risk perception aspects. Risk perception denotes the appreciation and assessment of risk often without making use of a rationale, technically-informed process, but rather basing the judgement on a global impression, generally deriving from a limited, apparently unstructured set of information. There is therefore a dichotomy with the process of risk assessment which and more tends to be formally structured and audited and subjected to standardised and scientifically-accepted rules and procedures.

11.21 In general terms, while the formal risk assessment is the process adopted by the scientists and the experts when facing a public health or an environmental problem,

risk perception is the process dominating the judgement about such risks for the laymen and the general population.

11.22 The existence of a different approach in health risk evaluation between experts and laymen is almost inevitable, since many of the health risk to be assessed in public health are so complex in their causes, mechanisms and consequences that realistically a non-specialist in the field very seldom has the possibility to have a personal full-informed opinion on the issue. Rather his/her "personal" opinion is formed by the kind of information he/she receives from a number of sources (media, authorities, colleagues, etc.) and the way this information integrates with, and impacts on, his/her life and personal experience. It is of course the case that scientific experts themselves cannot be entirely objective in the judgements (see Chapter 12). A number of factors have been identified which influence public perception of risk: many are not formally addressed in the risk assessment process, eg:

- Whether the risk is controllable
- The possibility of catastrophic or irreversible outcomes
- The novelty of the risk form (dread factor)
- The extent to which the risk is voluntary
- Whether future generations could be affected.

11.23 The consumer in the modern societies wants (and has the right) to be thoroughly informed about health and environmental risks and to be involved as a stakeholder about critical risk management issues. However, the extent to which this goal can be reached strictly depends on the risk communication and information policy adopted by the authorities and the effectiveness of its implementation.

11.24 The key rules governing an effective risk communication can be summarised in the following aspects:

- completeness of information
- public access to documentation
- transparency of discussions and motivations
- frank acknowledgement of the various positions and contrasting views, including speculations
- clarity in wording and accuracy in use of specific expressions
- recognition of different interests and stakeholders
- recognition of social, cultural and ethical issues.

11.25 In addition to these general rules, risk communication must be professionally planned and carried out with continuity, recognising that such activity requires time, professionalism, financial investments and regular auditing for their clarity and effectiveness. In analogy with the chronic diseases, misperception of risk has to be effectively prevented because its eradication once established is extremely difficult, time-consuming and sometimes impossible.

11.26 With regard to the activity of the Scientific Committees of the European Commission, the publication of their outputs can contribute to an informed perception of risk by the community but alone is insufficient to achieve the goal. Other requirements include elimination of the restricted access to relevant documentation.

11.27 The demand for greater transparency inevitably means that the experts serving in the Committees will become more and more involved in risk communication with stakeholders (see also Chapter 12). It may be appropriate to enhance the effectiveness of this process to:

- Set up a task force to address issues of risk communication
- Establish regular programmes in risk communication for scientists and officials.

RISK COMPARISONS AND RISK RANKING

11.28 As discussed previously, risks can be expressed in various forms ranging from numerical values to use of selective descriptive terms. Use of either form of expression may not be understood by the public and politicians or even by many risk managers, unless it can be put in some form of context. There are a number of ways in which this may be achieved:

i) by defining an acceptable risk level or exposure level against which the outcome of a particular risk assessment can be described, e.g. acceptable, tolerable, intolerable, unacceptable. At present the EU has no agreed general criteria of "acceptable". Although in the case of food additives and contaminants, use of an ADI which is normal one hundredth of the NOAEL is formally recognised by the EU. A number of national and international bodies have identified a numerical risk value for cancer risk: it would be appropriate for the Commission to review its position on this issue.

ii) By comparison with risk assessments from related risk sources to enable some form of risk ranking. This is a complex issue but one in which further debate with stakeholders would be timely.

iii) In relation to likely alternatives, if the particular risk source is being considered for replacement.

iv) By setting the risks against the benefits (i.e. risk benefit analysis).

For risk management purposes, consideration needs to be given to whether the current practice of identification of a simple standard is the most appropriate. An alternative would be to identify a standard for *de minimis* risk, a standard at which active monitoring is needed and an action level standard. This might help to allay concerns regarding the significance of exceedence of the *de minimis* standard. Such an approach is already in operation for ambient air pollutants.

Risk ranking

11.29 There is common-sense appeal in risk comparisons and risk ranking and in linking comparative risk analyses with priority setting and programme planning. Nonetheless, the methodological challenges in conducting comparative risk analyses should not be underestimated, and opinions vary widely on the value that such analyses can add to policy making.

11.30 Currently, comparative risk analyses may consist in one of two analytical activities: *specific risk comparisons*, which involve side-by-side evaluations of distinct risks on the basis of likelihood and severity of effects, and *programmatic risk comparisons*,

which seeks to make comparisons among many and widely differing hazards (American Chemical Society, 1998).

11.31 Specific risk comparisons can be useful when one is considering the relative importance of risks within the context of similar products, activities, or risk management actions. Such comparisons are also helpful in facilitating non-technical audiences' understanding of the significance of varying risk levels.

11.32 Paired comparisons of reasonably similar risks are rather straightforward and might be conducted simply, based on estimated risk levels and the extent of anticipated harm. However, even so, difficulties may arise, because the health effects relevant for consideration may be multiple, or may differ significantly by hazard. Comparisons become more difficult as the dissimilarity of the compared risks increases. Risks can significantly differ in several dimensions, with respect to the source of the hazard, the type of adverse effects, the distribution of effects over space or time, and the non-damage attributes that may be relevant (e.g. whether the risk is voluntarily taken or involuntarily borne, the extent to which the risk is controllable, the degree of dread associated with the risk). Furthermore, significant differences may exist with respect to the state of knowledge about causes and effects. In this regard, risk comparisons depend on integrating these various characteristics into a common measure. This however, may involve attributes that are difficult to scale, and/or developing judgements about how dissimilar attributes trade-off against each other. Additionally, the uncertainties that pervade the process may often blunt the precision of the comparison process. Furthermore, risk comparisons become considerably complex when the views or perceptions of differing individuals are brought into focus.

11.33 Programmatic risk comparisons are relevant for priority setting within and across the various statutes of a regulatory authority. Developing programmatic risk comparisons require consideration of a number of issues that have to be clarified at the outset of the analysis. These include in particular defining the scope and direction of the study, determining the approach to risk estimation, determining the approach to risk comparison, identifying the procedures for follow-up applications of study findings (Davies, 1996). Many of these issues come with various options and involve consideration about the scope and depth of the desired findings, study process, analytical methods and limitations. Furthermore, all of the methodological complexities of specific risk comparisons (see 11.32) carry forward into programmatic risk comparisons, and, in fact, arise at a much larger scale because, by its nature programmatic risk comparison spans many, dissimilar risks.

11.34 Risk comparison and risk ranking is therefore a complex issue, and may be controversial (Wilson and Crouch, 1987). Arguably, however, the strength of the approach is the opportunity it provides for discussion and debate among various important point of views: the scientific and technical experts, the policy makers, and the public. Additionally, the process facilitates addressing in a systematic fashion important policy questions, which would otherwise be resolved through untransparent trade-offs if not answered through risk comparison analyses. Whereas risk assessment and risk management should remain functionally separated, it is foreseeable that that risk assessors would increasingly been asked to contextualise their conclusions and to make recommendations upon request of those responsible for risk management.

Further discussion on this complex but essential issue between risk managers, risk assessors and other stakeholders where appropriate is timely.

RISK BENEFIT ASSESSMENT

11.35 An additional / alternative means of establishing a perspective on risks is to set them in the context of the benefits. This is rarely simple because the risk and benefits (except for human drugs) may not be distributed equally. Nonetheless, for many hazards, particularly novel sources, a transparent risk benefit analysis is much needed. On occasion, Scientific Advisory Committees have been asked to comment on such analyses. However, as they are currently structured, this is outside their area of expertise. Assessment of the benefits needs to be carried out with the same rigour and expression of uncertainties as risk assessment. There are potential advantages from structuring benefit assessment in the same framework as risk assessment, viz.

- Value identification
- Value characterisation
- Use assessment
- Benefit characterisation.

11.36 A subset of risk benefit assessment is "cost benefit analysis" in which the benefits and the risks are compared using a common denominator of money. This outcome of such a uni-dimensional approach is at face value very convenient from the point of view of the risk manager and for risk communication purposes. However, in practice, it requires assumptions about costs of human life loss or changes in quality of life which are highly controversial. Furthermore, the financial implications of a change in biodiversity or the existence of a particular invertebrate species may not be translatable into financial terms. An alternative approach has been to ignore those factors for which it is difficult to agree a financial figure. This is also problematic.

11.37 The EU should consider the establishment of an Advisory Committee of experts to develop a rational scientific framework for benefit assessment of those products, processes installation for which there is a significant potential or perceived risk to the health of humans or the environment. In terms of its application, the priority should be "emerging issues". The relationship of the Advisory Committee to those of the existing Scientific Advisory Committees would need to be considered. It is recommended that there should be some common members.

PRECAUTIONARY PRINCIPLE

11.38 The precautionary principle has become enshrined in numerous international treatise and declarations. It is important that it is applied consistently. The recent communication from the Commission (Communication from the Commission on the precautionary principle, COM (2000) 1) emphasises that the precautionary principle should be "considered within a structured approach to the analysis of risk which comprises three elements: risk assessment, risk management, risk communication. Scientific information is a pre-requisite for the application of the precautionary principle". The precautionary principle is part of the management of risk, not of risk assessment. It is distinct from the uncertainty in the scientific risk assessment, though related to it. Thus, the precautionary principle should only be involved in cases where the relevant scientific evidence is insufficient. This inadequacy "may include non-

quantifiable data of a factual or qualitative nature and is not uniquely confined to purely quantitative scientific data". "The precautionary principle is relevant only in the event of a potential risk, even if this risk cannot be fully demonstrated or quantified or its effects determined because of the insufficiency or inclusive nature of the scientific data. Clarification is needed as to whether the precautionary principle is only be applied on the basis of the scientific risk assessment or also takes into consideration political and public concern.

11.39 It is necessary to reconcile the precautionary principle with the weight of evidence approach used by the Scientific Advisory Committees. For the sake of transparency it is important to establish guidelines indicating the degree of uncertainty needed to trigger the uncertainty principle. No risk assessment is entirely free of uncertainties. It is therefore important to establish a continuing dialogue with risk assessors so that they can understand how to present their evaluations , the extent of their uncertainties and their relative importance.

11.40 Application of the precautionary principle ought, in many cases, to lead to the initiation of research to fill the key information gaps. Those involved in the risk assessment should have an important role to play in identifying the priority research requirement.

CONCLUSIONS

i) Risk communication has become a major consideration in the expression of the findings of risk assessments. Currently, there is no common approach by the Scientific Advisory Committees for presentation of the findings of risk assessments. Indeed, major differences have been identified in the opinions of different Scientific Committees in regard to scope, format, degree of detail, size and use of terminology.

ii) Uncertainty in the assessment of risk was often not expressed clearly and committees varied in the way in which they addressed these uncertainties. A format has been proposed which is viewed as relevant to the expression of opinions of all the Scientific Advisory Committees.

iii) Ways in which conclusions of risk assessments may be expressed in a more user-acceptable manner have been addressed briefly, namely:

- By comparison with possible replacements
- Risk ranking
- Risk benefit assessment.

The strength and weaknesses of these approaches is outlined. Further work is required involving a range of stakeholders in order to progress this aspect of risk communication.

iv) Application of the precautionary principle is the province of risk management. However, it is pertinent to consider whether Scientific Advisory Committees have any role in decision to implement the "precautionary principle". Areas where further discussion is appropriate are identified.

12 MANAGING THE PROCESS

"We took risks, we knew we took them;
things have come out against us,
and therefore we have no cause for complaints"
Robert Falcon Scott (1913)

The final aspect of risk assessment which needs to be addressed both from a harmonisation viewpoint and in terms of future development is the "management" of the process. Inevitably, the organisational framework in which the risk assessment is conducted influences the process itself. Issues include: interactions with risk managers and other stakeholders, availability of necessary expertise, ease and comprehensiveness of data available for the purpose, adequacy of scientific and administrative support, means of validating opinions and feedback on the use of risk assessments.

THE INTERFACE BETWEEN RISK ASSESSMENT SCIENTISTS, MANAGERS AND OTHER STAKEHOLDERS

12.1 Historically, the work of the Scientific Committees has been largely separately from the work of officials responsible for risk management, presumably on the grounds that the scientists' advice might be unduly influenced by the demands of the risk managers?

12.2 Risk assessments/peer review are normally only conducted by each Scientific Committee in response to questions formulated by officials from the relevant DG/DGs. The questions may or may not have been fully agreed with the Secretary to the Committee prior to their receipt by the Committee. Furthermore, the Chairman, or other nominated member(s) of the Committee may or may not have had the opportunity to discuss the intent of the questions with officials from the relevant DG prior to the start of the risk assessment by the Committee / its Working Party. In a number of cases the availability of information to enable the questions to be addressed is also unclear at the start of the process. Typically, officials are not involved in the risk assessment/peer review process per se, though they often attend meetings of the Committee / Working Party. Finally, at the end of the process, each Committee tends to have its own format for presentation of its findings (see Chapter 11). This is usually written in scientific language, with a number of qualifying statements and may not readily be understood by non-scientists, including officials. This has, in the past, resulted in misinterpretation of committee opinions and in committees generating opinions which are not utilisable by risk managers.

12.3 A rather more structured, open procedure is needed, but one which aims to avoid unnecessary bureaucracy. It is proposed to comprise three main stages and two subsidiary stages.

Stage 1: Initiation of the Process

12.4 The aim of this stage is to ensure that both the Scientific Committee members and the appropriate Commission officials understand and agree the task and any substantive constraints in achieving it (e.g. time, availability of required information).

Thus, the main elements of the initiation stage are:

i) Formulating the questions

12.5 This is clearly a role of a Commission official (termed the "lead official" hereafter in this paper). The lead official is defined here as someone who is expected to have a subsequent involvement in the risk management process and therefore is clear on the purpose of the questions. In some cases, officials from several DGs are, or should be, involved through the process of inter-service consultation. This may produce some complications which must be dealt with by the relevant officials.

12.6 It is evident that in some DGs there is, as yet, rather limited expertise in drafting questions for Scientific Committees. [It would be appropriate if a paper could be produced which identifies the services the Scientific Committees and the officials are able to offer other DGs. One element of this could be an "Advisory Group of Secretaries to Scientific Committees" providing an assistance service for such DGs.] To ensure that the questions are likely to be answerable by a Scientific Committee, it is proposed that following initial formulation the questions are discussed with either the Chairman of the relevant Scientific Committee or with their deputy for the purpose (often the Chairperson of the Working Party which will address the details relating to the question(s)). In principle, a Scientific Committee has the right to refuse to answer a question they consider to be inappropriate, but this should be seen as a last resort and a serious communications failure. For the future, the Commission may see the need for additional stakeholders to contribute to the problem / question formulation.

ii) Identifying potential overlap with the work other Committees (ongoing or previous)

12.7 Ideally, this would be discussed at an early stage at the Scientific Steering Committee. In practice, this is unrealistic. It might be more practical for the "Advisory Group of Secretaries to the Scientific Committee" to identify such overlaps (or gaps) and to make proposals on how to deal with them.

iii) Provision of requisite information to address the question(s) and its timing

12.8 Practice varies greatly between committees because of the differences in their mandates. For those Scientific Committees which deal principally with applications from commercial companies for approval of a product, the position regarding information provision is normally straight forward, that is the Committee will not start, or will put a hold on its task until the company involved has provided the relevant data. For other Committees, it is unclear in some cases what information is available and who should provide it. It is obvious that if the information base is inadequate a risk assessment will be compromised from the start. A particular issue in this context is to establish an effective process at an early stage to ensure Committee awareness of relevant documentation held within Commission services, on previous opinions by EU Scientific and Expert Committees. This again might be a role for the "Advisory Group of Secretaries to Scientific Committees". It is noted that in many Member States Scientific Committees are provided with reviews of the pertinent literature before they commence their task. The Commission should consider how they can provide a similar service to the Committees. Some Committees are asked to review a report produced by an external consultant. In some case, it has been evident that the brief given to the consultant was wrong, or lacked clarity. It is recommended that where

possible the appropriate Scientific Committee has some input into the briefing of such consultants before they begin their task. A further element is whether all stakeholders should be invited to submit any scientific information pertaining to the question and, if so, how this process could be managed.

iv) The form in which the answers are required and any time limits involved

12.9 As well as understanding the questions, the Scientific Committees need to have a picture of the form in which the response is required and any time constraints. It is suggested that at the end of this "initiation" process, a note of agreement is generated and signed, confirming the Committee's brief.

Stage 2: Communication during the process

12.10 It is important that dialogue between the relevant Commission officials and the appropriate Scientific Committee members continues during the risk assessment/peer review process. As a Committee / Working Group examines the usefulness of the information provided to answer the questions, not uncommonly it will identify significant gaps in the information that limit its ability to answer the question(s). Collaboration with the lead official(s) in filling these information gaps, or if this is not possible, in reconsidering the questions or updating the mandate, is important.

12.11 Other procedural matters where a policy is required include:

- how to deal with unsolicited information provided to individual Committee members by special interest groups, attempts at lobbying etc.
- what to do about information that arrives after the deadlines set by the Committee.
- Can questions be addressed to Scientific Committees by bodies other than the DGs, eg: European Parliament?
- What mandate should Scientific Committees have for a pro-active role in developing reports on emerging issues/risk profiles, etc.

Commission officials should also have a role in ensuring that the Committee is not distracted by issues which though perhaps of scientific interest are not important to answering the question(s) in hand.

Stage 3: Completion of the Risk Assessment/Peer Review

12.12 It is evident that for the purposes of subsequent risk management the answers to the questions are clear and unambiguous. It is recommended (see Chapter 11) that a common format for expressing the risk is adopted as far as practicable by all the Scientific Committees. To deal with possible issues of ambiguity or lack of clarity, it may be appropriate for a discussion between the Committee Chairman / Chairman of the Working Group and the lead officials to take place on completion of the assessment work and before the final wording is put to the Committee. It may be helpful where a Scientific Committee is asked to peer review a risk assessment by an external consultant of an export body to have common framework questions, such as:

- The conclusions are fully supported by the scientific evidence;
- The conclusions are not fully supported by the scientific evidence;
- The conclusions are open for debate.

In those situations where a press release is likely to be prepared following a risk assessment, it is proposed that an appropriate representative of the Committee is involved in the preparation / or checking it before it is released. It may be appropriate for each Committee to have a small editorial sub-group to take responsibility for details of formatting, including the web page presentations. Meetings of large Committees are not an efficient environment for editorial tasks.

Stage 4: Follow up

12.13 To improve the effectiveness of the Scientific Committees and strengthen the motivation of members, two further steps are proposed:

(i) Committees should always be kept informed of the follow-up taken in the areas in which they have conducted a risk assessment/peer review and the usefulness or otherwise of their assessment in the risk management process;

(ii) Where it is practicable to obtain subsequent data through monitoring auditing or other processes (see below) on the soundness of substantive risk assessments this should be done and the findings fed back to the Committee. Such a process would serve to refine future risk assessments. This might aid in the identification of research needs. An effective process for communicating these needs with officials of DG Research is required.

Related issues

12.14 Particular consideration needs to be given on the most appropriate means of demonstrating transparency throughout the process. This transparency must include the work of both the main committees and their working parties and communications between officials and committee/working party members. A second crucial element is to ensure that the independence of the Scientific Committee members is not compromised. A continuing major role for the secretariat to the Committees is envisaged to facilitate these objectives.

12.15 To assist the harmonisation process between Committees, enhance transparency and facilitate the introduction of new committee members it is proposed that clear guidelines are provided for all members of Scientific Committees. These should include: a standard form for the identification and recording of possible conflicts of interest, provision of information on realistic expectations of time commitment, explanation of the key directives influencing the Committee work, etc. It is further proposed that:

a) a formal induction programme is provided for all new members;
b) the Commission sponsors a regular expert seminar programme, which brings together key officials, external scientific experts and committee members to discuss emerging issues, the implications of new/impending legislation, etc.

Monitoring and surveillance

12.16 Monitoring and surveillance is necessary to evaluate the effectiveness of particular risk assessments and the subsequent risk management response. Although patient monitoring and surveillance is common following the approval for marketing of a new

drug and selective environmental monitoring may also be a requisite for the approval of a new pesticide, this is rarely the case following the risk assessment of other risk sources. Assurance that effective monitoring and surveillance is take place is also very likely to become an increasingly important element in enhancing the confidence of the general public in the work of both risk managers and risk assessors.

12.17 As discussed in paragraph 3.33, monitoring and surveillance findings are crucial to achieving a continual improvement in the practice of risk assessment in that they enable a direct comparison between the estimated risk and the risk in practice. Monitoring and surveillance findings are of particularly importance where use of modelled exposure scenarios is a major component of the risk assessment. Since it is very important to establish the validity and scope of such models and their limitation. Monitoring and surveillance is also needed in situations where there is no human data to support a public health risk assessment for a particular hazard. Under such circumstances monitoring and surveillance represents the only ethical means of assessing the actual impacts on humans of such hazards.

12.18 Some form of follow-up should be a common practice where a risk assessment results in a risk management decision to continue with or allow the increased use of a risk source. Recommendations as to the nature and extent of this follow-up should be required of each Scientific Advisory Committee wherever appropriate.

12.19 Key factors which should influence the form of follow-up should be :

- The degree of uncertainty of the risk assessment. This should concentrate on aspects where there are serious gaps in the data available ;
- Potential seriousness of the adverse effect ;
- Likely scale of initial use. This to include range of species / number of the public exposed ;
- Potential to identify adverse effects and / or use excedencies if they occur ;
- Novelty of the risk source. Priority should be given to those sources where there is little if any relevant experience from comparable sources and / or where the source under consideration is likely to be the first of a series of similar risk sources.

12.20 It is recommended that the Commission develops a policy for monitoring and surveillance in conjunction with Member States. DG SANCO should consider the establishment of a small unit to coordinate and audit monitoring and surveillance programmes for public health and the environment. Close cooperation with DG RESEARCH will be required to ensure that this crucial activity is optimised. It will also require, in many cases, stakeholder involvement both in the design of the programmes and in the actual collection of pertinent data.

AVAILABILITY OF EXPERTISE

12.21 The role of the Scientific Committees is to provide expert judgement. Expert judgement is required throughout the risk assessment process, including:

- Evaluating the quality and relevance of individual studies;
- Identifying critical gaps in the data base;
- Deciding on which effects are adverse and which are not;
- Selecting exposure scenarios which reflect the actual (likely) use and abuse of the risk source;
- Choice of extrapolation methods (between species, routes of administration, etc);
- Determining the degree of uncertainty in the estimate of risk;
- Consideration of animal welfare and other ethical issues associated with experimentation;
- Examining the consistency of the risk assessment with that for other comparable risk sources.

12.22 It is also essential that judgements are made on the basis of current scientific understanding and that experts draw to the attention of the Commission emerging trends relevant to specific risk assessment or to the risk assessment process in general.

12.23 It is assumed that both at the EU and at the national level, individuals with the appropriate expert judgement will be readily available. However, there is no concerted action to ensure that this will continue to be the case (see below).

Expert judgement: development of an optimal opinion

12.24 Complete scientific information for an unequivocal quantitative error-free risk assessment is probably unattainable. The objective therefore can only be to make best use of available information, or, in some cases conclude that the available information is insufficient for any assessment. It is necessary to update regularly risk assessments where there is relevant new information. Most questions are of an interdisciplinary character or are even intersectorial. This means that different specific risks with different degrees of confidence, with different significance and magnitude of harm and with many orthogonal elements or factors (partly with different physical dimensions) need to be integrated into one assessment. In order to achieve an equal and comparable judgement for different issues, harmonisation of the procedures is needed.

12.25 There are several pitfalls, which can preclude a scientifically balanced point of view. Scientific data in the health and environmental area often give room for a range of different, but nevertheless valid interpretations. Particular attention has to be given to the problem of contradictory published scientific data or contradictory scientific conclusions arising from these and transparent arguments for the selection of one rather than another.

12.26 Personal biases exist despite the independence, integrity and an excellence in science of the experts who provide scientific advice. They arise from personal experience (intuition), personal specific scientific interests (scientific expertise), personal approach to uncertainties (caution) and personal values (preferences). At least subconsciously, risk management implications, benefits and societal reactions may be also considered. These factors may result in somewhat subjective weighting of selected facts.

12.27 Inevitably, because the work is of a multidisciplinary nature, there is commonly a difference in the depth of involvement of an individual expert on a committee on a particular issue. The well established approach for dealing with these individual biases in the development of an opinion is intensive discussions in an appropriate expert group to find a consensus. It might be argued, that a compromise has biases in itself, but finding consensus is considered the appropriate tool to achieving a scientifically balanced point of view. A growing issue is how to demonstrate the quality and transparency of this process.

12.28 It may be considered appropriate to conduct auditing of selected opinions. This might evaluate clarity, consistency with previous assessments, scientific data used and the weighting given to it. A retrospective assessment might allow a comparison with subsequent information on the actual risk. Comparison of opinions and the basis for these, with those carried out by international bodies such as WHO or in different countries might also be informative.

Ensuring the development and maintenance of scientific expertise

12.29 There is an ever growing demand for independent, high level scientific experts in a variety of scientific fields which involve the range of risk assessment issues considered by the SSC. This demand is coming from Member States, other European Countries, the European Union and international bodies such as WHO, OECD, etc. This reflects both the increasing breadth of areas (and their technical complexity) where a reliable risk assessment is needed for risk management purposes.

12.30 The criteria for such experts are widely agreed to, they include:

- High level of expertise in a specific relevant area and a good knowledge of other interdisciplinary areas;
- Objectivity;
- Ability to understand the contributions of other disciplines to human and ecosystem health issues. (This requires a broad background experience);
- Demonstrable independence (which increasingly is ruling out those with direct or even indirect industrial links and may eliminate those with other allegiances too);
- Ready access to information search systems, etc. in order to be up-to-date with the latest development of their subject and make up for the deficiencies in the information provision by the Commission.
- Time and (for some bodies, including the EU) willingness to dedicate their private time to the governmental / international committee with no real financial benefit;
- Team working and presentational skills, plus the ability to withstand public criticism from lobby groups, etc.

12.31 Unfortunately, the availability of scientists in Europe who meet these criteria is unfortunately diminishing progressively. There are a number of reasons for this decrease in the availability of high level experts.

Firstly, progression in an academic career depends increasingly on a ever-narrowing area of specialism. Thus, opportunities and incentives to develop a broad experience are the exception rather than the rule.

Secondly, the above mentioned areas are applied multi-disciplinary subjects. In comparison for uni-disciplinary subjects, such as molecular biology, applied disciplines have a low status in the academic hierarchy. This has led to a number of departments / institutes being reduced or closed and the resources redirected to more fashionable disciplines. Furthermore, funding for research is difficult to attract from research councils, etc. Funding from industry is available (usually with conditions attached), but such funding is perceived by many to compromise the objectivity of the recipients, both immediately and in the long term. Funding problems also mean difficulty in attracting the most able students into these areas.

Thirdly, universities and non-governmental research institutions are increasingly reluctant to allow their staff to spend more than a small percentage of time working for national government or international bodies without some form of reimbursements of the Institution. For Scientific Committee members themselves, the Commission needs to reconsider the incentives it is able to offer to those giving more than say 10% of their working week to Commission activities. Committee members frequently note the enormous discrepancy between the way the Commission remunerates its own staff and the reimbursement of its external experts. For most of the individuals concerned, such work is unlikely to help career advancement in their institution and may preclude them from increasing their income through consultancy work. The very considerable amount of time required for preparation of meetings of Committees by members is not acknowledged either by financial reimbursement, or in any other way. A further disincentive for many is that health experts are increasingly exposed to pressure from the media, lobby groups, etc. The situation is particularly difficult for toxicologists in some countries because working with animals is vilified by the public as inhumane and unnecessary.

12.32 As an example of the general problem, an analysis has been made of the present situation for human toxicology, ecotoxicology and environmental (public) health and the results appear to apply in Higher Education Institutions of all Member States. The position for candidate Member States is even more bleak in terms of availability of high level expertise.

The seriousness of the situation is well illustrated by the position of toxicologists in Germany. Within the last decade, 10 of the 20 academic Institutes of Toxicology have been closed or have been drastically reduced in size. During the coming 5 years, 8 of the remaining 10 chairmen will retire, so that a further reduction in the number of practising toxicologists is expected. Over the years this has led to a drastic reduction of toxicological competence within Germany, the communication of new developments and toxicological concerns to the public has diminished and a

decreasing availability of experts for national and international advisory bodies became apparent. Many academic institutions appear to believe mistakenly that expertise in the very narrow field of "molecular toxicology" is the central theme of toxicology. To overcome this trend, the Deutsche Forschungsgemeinschaft has published a memorandum on toxicology, asking the universities, regulatory agencies and ministries for support. The safety evaluation and risk assessment of the rapid development and use of new chemicals and technologies is an area of ever-increasing importance. Academic toxicology is essential to provide the experimental basis to meet this challenge which is indispensable for a sustained economic development of the country.

12.33 A further major problem will arise as the EU expands because there is little evidence that the states expected to joint the EU have any greater experience than that within the EU. Often it is much more limited. This is a particular problem because the expanded EU will have new Member States with much greater problems involving food, public health and the environment than those currently in the EU. The EU's capacity to cope with risk assessment will therefore be put under even greater strain. Action by the EU to improve the expertise within candidate Member States also needs to be given some priority because, by its nature, developing such expertise will take time. One action, which might facilitate the development of expertise in candidate Member States, would be to invite each of them to nominate an expert to set as an observer on each Scientific Advisory Committee. Whether these individuals should be invited to attend all meetings, or just selected meetings initially, needs to be discussed.

CONCLUSIONS

i) It is recommended that the EU considers as a matter of increasing importance how it can remedy the current progressive loss of high level expertise in risk assessment science. Options which should be considered include supporting high level academic courses, expert workshops, etc

ii) The organisational framework in which risk assessments are conducted inevitably has an influence on the risk assessment process itself. Issues which are considered in this Report include: interactions with risk managers and other stakeholders, availability of necessary information, time and other resource constraints, effectiveness of feedback processes and the future availability of the necessary scientific expertise.

iii) Traditionally there has been a clear separation between the activities of the risk assessors and those responsible for risk management. While this has helped to demonstrate the independence of the scientists who make up the membership of the Scientific Advisory Committees, it has been found to have a number of disadvantages, notably:

- Failure on occasion of committees to understand fully the questions being asked and their purpose.
- Misunderstanding of the conclusions of some risk assessments and their meaning.

iv) A proposal is made as to how to improve the interface between risk assessment scientists, managers and other stakeholders in a transparent manner.

v) It is recommended that in future a much greater emphasis in risk analysis (the risk cycle) should be given to the development of much more far reaching monitoring and surveillance programmes. It is suggested that the Commission establishes a small unit to co-ordinate and audit these programmes.

vi) Progress in scientific risk assessment requires a developing research base. Means need to be found for identifying and consolidating the research priorities within the Scientific Committees and for ensuring that the analysis is disseminated to DG RESEARCH and other bodies whose role is to promote relevant research.

13 MAIN CONCLUSIONS

"Success is relative: it is what we can make of the mess we have made of things"
T S Elliot (1939)

13.1 Risk assessment is increasingly used as a formal tool prior to risk management. With increasing globalisation of markets and the consequent need to remove barriers to trade, there is a major need for establishing as far as possible common approaches to risk assessment for different risk sources and between countries.

13.2 DG SANCO has nine Scientific Advisory Committees which, as an important part of their function, are required to conduct risk assessment. These DG SANCO Scientific Advisory Committees all utilise the following structure for their risk assessment activities:

- Hazard identification
- Hazard characterisation
- Exposure assessment
- Risk characterisation

Nonetheless, there are variations in the details of the process. In part, this is due to variation in Community legislation relating to different risk sources. Some of these are historic, others relate to the nature of the risk source being assessed.

13.3 It is not appropriate to attempt to achieve a position where each committee carries out an identical procedure for all risk assessments. Nonetheless, a substantial measure of convergence is achievable which would not detract from their current activities and would have considerable other benefits. In particular it would:

- Improve transparency and risk communication
- Enhance consistency where the same risk source has been considered by different committees

It is considered that the work of other EU committees concerned with human and environmental risk assessment could probably be harmonised in a common operating framework. However, the Working Party was unable to investigate this prospect in detail because of time constraints.

13.4 It is important, to ensure progress to harmonisation of risk assessment, that there is an overarching body in the EU with responsibility for facilitating and supporting the process. The Scientific Steering Committee (SSC) appropriately has this role at present. Means need to be found of involving those EU Scientific Committees not currently associated with the SSC to be involved in this co-ordination process. This is in line with the wider issue that there is a very important need to establish a robust procedure for co-ordinating **all** public and environmental issues within the EU. The Working Party notes that the establishment of the European Food Agency could result in the complete segregation of food issues from other public and environmental health issues. From an harmonisation of risk assessment point of view, this would be extremely unfortunate.

13.5 A particular need is to ensure that each Committee is able to access readily all relevant data relating to each risk source (and related risk sources). This is not the situation at present.

13.6 The Working Party has identified that the strategies adopted for various uses of chemicals are also applicable to micro-organisms and probably other risk sources such as physical factors. Similarly, it is identified that there is much in common between human and environmental risk assessment processes.

13.7 A number of scientific developments have occurred which should be considered in the risk assessment process. Such developments are likely to continue. Means are needed to ensure that the risk assessment procedure is fully informed by current relevant science and does not remain static. An important aspect of this developing science base is for harmonisation over which biological changes are considered adverse and which are not. The phenomenon of hormesis, if widely applicable, represents a major challenge for risk assessments.

13.8 Risk assessment will be required for an increasing range of purposes. This has profound resource and other implications. However, on animal welfare and ethical grounds there is a continuing pressure to reduce the use of animals for testing to establish the hazards and characterise them. New approaches are needed to meet this challenge.

13.9 Of all the areas where major improvements in approach are needed, the most important is that of exposure assessment. This includes:

- harmonisation of exposure assessments for human and the environment;
- consistent modelling scenarios representing specific groups of the population, endangered ecosystems, regional and national differences;
- validation of exposure assessment models against actual surveillance and monitoring data;
- standardisation of means of expressing uncertainties.

13.10 Traditionally, genotoxic chemicals are considered not to have a threshold for their effects while for nearly all other biological endpoints a threshold is assumed. There is a need to reconsider the validity of this fundamental assumption.

13.11 Common approaches to hazard characterisation and risk characterisation is needed to ensure:

- a consistency in the use of uncertainty (default) factors;
- a rational framework in development and use of mathematical models for dose-response extrapolation purposes;
- a coherent strategy for dealing with sensitive sub-groups of human and environmental populations.

13.12 It is timely to consider how progress towards harmonisation can be achieved in practice. This requires discussions with stakeholders and, in some cases, more detailed investigations. In this respect a number of recommendations have been identified (see Chapter 14).

13.13 In addition to the aspects mentioned above, progress in risk assessment will require a combination of elements including:

- new "early warning" *in vivo* tests;
- more predictive in vitro tests and mathematical models;
- introduction of concepts such as thresholds for toxicological concern (i.e. recognition of a generic exposure level(s) below which a risk source will not produce adverse effects);

- a move away from deterministic risk assessment to quantitative, probabilistic risk assessment;
- a more integrated approach to risk assessment between evaluating the effects in man and impacts on the environment.

13.14 Agreement on the criteria for what constitutes an acceptable risk is required. Currently, it has been identified that acceptability is built in some risk assessments, e.g. assessment of food additives, but not other risk sources.

13.15 A number of important issues of increasing importance, such as sustainability, animal welfare, quality of life are currently not considered to be part of the risk assessment process. Some formalised procedure for their consideration are suggested.

13.16 In addition, attention needs to be given to various approaches for the formal contextualisation of risk, e.g. by
- comparison with possible replacements,
- risk ranking,
- risk / benefit assessment.
The strengths and weaknesses of these approaches are outlined.

13.17 The Working Party has identified many unnecessary inconsistencies in the mode and language of reporting of risk assessments within and between Scientific Committees. This is considered to be an obstacle to transparency. Recommendations are provided on a common format for expressing opinions.

13.18 The process of risk assessment is and must remain science based. However, at various points in the process for a number of risk assessments dialogue with stakeholders, including risk managers, may be desirable. It is important that a mechanism is established for an effective and open dialogue with risk managers in formulating the questions which form the basis for initiating the great majority of risk assessments. It is also crucial that the conclusions of risk assessments are concise, unambiguous and utilisable. This again requires effective dialogue. In addition, committees require a greater input from Commission officials with the appropriate scientific training. In many Member States, suitably qualified and experienced officials provide background papers to facilitate the risk assessment process. Many of the DG SANCO Committees are severely under-resourced and do not receive this kind of support. As a consequence, an unreasonable burden is often placed on committee members.

13.19 Concern is expressed regarding the future availability of individuals with sufficient expertise to deal with the increasingly complex issues involved in risk assessments. Proposals are made on how this worrying deficiency can be addressed.

13.20 Other areas where progress is needed include:
a much enhanced monitoring and surveillance activity with the findings being used to challenge or verify important risk assessments;
enhanced interactions between the Committees and DG RESEARCH in order that important research needs in risk assessment may be incorporated into the European Community research programmes.

14 OVERALL RECOMMENDATIONS

"Success is a science;
if you have the conditions you get the result"
Oscar Wilde (1883)

14.1 The recommendations are addressed to the Commission. They require an early and on-going dialogue between members of the Scientific Committees and Commission Officials to ensure their effective implementation. The recommendations cover both human health and the environment, and fall into three categories, namely those where:

i) early adoption is appropriate
ii) progressive implementation is considered to be achievable
iii) further developments are needed

The Working Party is concerned that the proposed formation of the European Food Authority would result in the separation of three of the Scientific Committees from the other Scientific Committees and that this may detract from the harmonisation process, particularly in regard to the integration of public health and environmental risk assessment. Means must be found to ensure continuity of collaboration.

Recommendations for early adoption

14.2 Agreement that all the Scientific Committees adopt a common glossary of risk terms. It is also important that committees adopt a common language to describe different levels of risk. This should consider how these terms will be translated into the different languages of the Member States.

14.3 Identify a common format for expressing the uncertainties in risk characterisation.

14.4 Standardise the format for the presentation of risk assessment findings. It is proposed that in future, unless there are specific reasons why it is not appropriate, the following structure is used by all Scientific Committees:

a) Title
b) Table of contents
c) Terms of Reference (e.g. questions asked of the Committee)
d) Opinion
e) Executive summary
f) Background (where the context of the question formulation is set out and reference is made to the source documents and the data which are provided)
g) Main text providing the scientific arguments which have to lead to the opinion. This should also identify in a transparent way the uncertainties in the risk characterisation
h) Conclusions (from which the essence of the opinion is extracted)
i) Recommendations
(If so requested by risk managers, these may include priorities for obtaining missing data. Recommendations of risk management nature should be presented by indicating recommended risk management options for the expected level of risk.)
j) References (separately from those listed in section f).

It is noted that where committee are dealing with information provided to it in confidence, access to the full report may be restricted. In such cases, sections a), c), d), and e) may be presented separately.

14.5 Introduce a procedure for regular scientific review of the strategies, methods, and other aspects of the general risk assessment process. Consideration should be given to extending the risk assessment elements of the 5th Framework Programme and of future Commission Research Programmes to develop and evaluate new methodologies.
It is proposed that an inter-committee Task Force is established which should report regularly to the SSC to promote these aims.

14.6 Establish an agreed transparent framework for interactions between members of Scientific Committees and risk managers. A principal requirement is to establish an effective dialogue to ensure that questions put to the committees by the Commission are clear, unambiguous and relevant to the needs of risk management, that all relevant data sources are defined and provided efficiently, and that time scales and other constraints in providing the risk assessment are identified and agreed. Ground rules for discussions with risk managers need to be defined, while taking account of the necessary independence of Scientific Committee members.

14.7 Establish effective induction programme(s) for new members of Scientific Committees and regular workshops at which key issues can be discussed. Facilitate a high level training programme(s) to meet the increasing requirement for expertise in risk assessment. This would require the support of Commission' services.

14.8 Develop guidelines for carrying out quantitative risk assessments and for assessing their validity.

Areas where progressive implementation is achievable

14.9 Develop a resource within the Commission for the ready provision of data required for risk assessment purposes. It is also recommended that the Commission services play a key role in the development of databases which will enable better predictions to be made of potential adverse effects and to aid consistency in developing risk assessments. It is recognised that issues of confidentiality of data will need to be overcome to achieve this. The access to all relevant data will also aid the reduction of animal use for risk assessment purposes.

14.10 A priority should be to agree a stepwise procedure for assessing exposures. This procedure should provide the tool for integrated exposure assessment including all relevant exposure sources and pathways and keep the specific needs of the different Scientific Committees as separate elements. Develop common exposure model scenarios and ensure procedures for their validation. Consideration should be given to drawing on data from existing banks of appropriate samples of aquatic, terrestrial, atmospheric, and human origin to enable validation of such models. The models should also be validated where practicable by direct experimentation.

14.11 Assessment of environmental effects is demanded for an increasing range of risk sources. Common guidelines for the assessment of these environmental impacts need

to be developed. This should include as far as appropriate an integrated risk assessment strategy (i.e. examination of human and environmental risk assessments together).

14.12 Introduce requirements for monitoring and surveillance for an increasing range ofrisk sources for which:
- there is significant uncertainty in the risk assessment, in particular where there is an absence of data in humans and / or environmental species of concern, **and/or**
- a wide exposure of the public and / or of the environment is anticipated, **and/or**
- there is considerable uncertainty regarding actual levels of exposure, **and/or**
- the risk source is novel, i.e. there is no previous experience of risk sources of this nature.
It is recommended that DG SANCO should co-ordinate this activity. This is important not only from a scientific point of view but also to provide public reassurance.

14.13 A review should be conducted by the Scientific Steering Committee within an agreed time scale to ensure that implementation of the above (14.1 to 14.12) has been effective.

Areas for further development

14.14 There are several areas where further work is needed, for example:

a) the introduction of a "thresholds of toxicological concern" approach as a means of reducing unnecessary testing and determining priorities for risk assessment;

b) means by which issues such as animal welfare, quality of life and sustainability can be taken into account in the risk assessment process;

c) involvement of stakeholders on the issue of suitable means to setting the risk assessment findings in the context of other risks and/or of benefits. These discussions should also consider criteria for "acceptable" risk and whether "action" levels for various risk sources should be identified as part of the overall risk analysis process.

Implementation

The Working Party recommends that its findings are published and disseminated widely, both in print and electronic forms.
There is a need for the Scientific Committees to be made aware promptly of new scientific data in the field of risk assessment and related areas in order to incorporate these into their work. It should be realised that conflicting interests may exist for scientists and policy makers to share scientific data, as they emerge, with the Scientific Committees, and a mechanism should be implemented to secure the flow of scientific information wherever appropriate. The Working Party recommends that the Task Force (see recommendation 2.5) should include this within its remit, along with the investigation of opportunities for harmonisation of risk assessment procedures both across the EC Scientific Committees and with scientific committees of other national and international bodies. Funding should be made available to facilitate this. Discussions should be initiated with Member States to identify areas where specific progress can be made.

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[*Note*: the following list references the authors cited in Part 1 of the report. Extensive lists of additional references related to risk assessment of chemicals, microbiological risk assessment for foods, risk assessment for animal infectious diseases are found in Part 2, appendices 3, 4 and 5 respectively]

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