GOVERNMENT/RESEARCH COUNCILS INITIATIVE ON RISK ASSESSMENT AND TOXICOLOGY

Risk assessment approaches used by UK Government for evaluating human health effects of chemicals

Report prepared for the Risk Assessment and Toxicology Steering Committee

The Risk Assessment and Toxicology Steering Committee aims to stimulate the development of new, improved approaches to the assessment of risks to human health from chemicals.

The Committee takes forward the work of the Government/Research Councils Initiative on Risk Assessment and Toxicology. The Initiative was established in response to a statement in the 1995 UK Government *'Forward Look of Government Funded Science, Engineering and Technology'*, which recognised the inherent limitations of current procedures and committed the Government to pursuing opportunities presented by scientific advances.

The Steering Committee comprises participants from the Department of the Environment, Transport and the Regions, the Department of Health, the Department of Trade and Industry, the Home Office, the Ministry of Agriculture, Fisheries and Food, the Environment Agency, the Health and Safety Executive, the Medicines Control Agency, the Pesticides Safety Directorate, the Veterinary Medicines Directorate, the Biotechnology and Biological Sciences Research Council, the Medical Research Council, the Natural Environment Research Council and the Institute for Environment and Health.

The secretariat is based at the Medical Research Council's Institute for Environment and Health.

The Risk Assessment and Toxicology Steering Committee operates as a subgroup of the Interdepartmental Liaison Group on Risk Assessment.

The Interdepartmental Liaison Group on Risk Assessment is an informal committee of officials responsible for policy development and practical application of risk assessment in UK Government departments. The group reports periodically to Ministers on a co-ordinated programme to promote consistency and coherence in risk assessment practices across Government.

This document presents an overview of approaches to risk assessment and is not intended to be an exhaustive review of current practice in UK Government. It has been prepared by the Risk Assessment and Toxicology Steering Committee. The opinions expressed do not necessarily represent the policies of the participating Departments, Agencies and Research Councils.

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Introduction

A number of UK Government departments and agencies have a responsibility for assessing risk to human health from chemicals in the air, soil, drinking water, food, the occupational environment, consumer products, animal feed and human and veterinary medicines. Assessments are often based on animal data[a], with the consequent need to introduce uncertainty factors when extrapolating from animals to humans, from high to low doses and from one population to another. While uncertainties inherent in such extrapolations are widely recognised, there is a marked absence of scientific knowledge to define them more precisely. A commitment was made in the 1995 UK Government '*Forward Look of Government Funded Science, Engineering and Technology*' to address this by pursuing opportunities presented by recent scientific advances. This commitment resulted in the establishment of the Risk Assessment and Toxicology Steering Committee[b], which aims to stimulate the development of new, improved approaches to the assessment of risks to human health from chemicals. As a starting point the committee carried out a detailed mapping exercise of the risk assessment procedures in use across UK Government departments and agencies. This report presents the results of that work; it identifies both the strengths and weaknesses in the current position and makes recommendations for future developments. It is an overview of approaches to risk assessment and is not an exhaustive review of current practice in UK Government.

[a] In the case of risk assessment of human medicines, human data are always available.

[b] The Risk Assessment and Toxicology Steering Committee operates as a subgroup of the Interdepartmental Liaison Group on Risk Assessment.

The risk assessment process

There is broad agreement across UK Government departments and agencies about the general approaches adopted in chemical risk assessment.

Risk assessment consists of hazard identification, hazard characterisation, exposure assessment, and risk characterisation. The basic risk assessment process can be carried out and used in a variety of different ways, depending on the purpose of the assessment; for example, an assessment may pertain to 'permissioning' activities (when a chemical must have approval from a regulatory authority before it can be marketed) or to a chemical already on the market or present in the environment.

Hazard identification and characterisation are generally based on data from animal studies, although on occasions human data may be available from volunteer studies, epidemiological studies, clinical trials or case reports, or predictions may be made from data on similar chemicals. However, not all the toxic effects seen in animal studies are relevant to human health; more information on biological mechanisms will improve the application of results from animal studies to human health assessments. For permissioning activities the regulator normally requires information on a number of toxicological end-points (e.g. carcinogenicity, respiratory irritation, skin sensitisation). Harmonisation of test protocols and data requirements to provide the necessary information promotes better use of data and resources. Such harmonisation is being pursued at the European Union (EU) level, but needs to be developed on a global scale. Regulators require data to be generated using internationally accepted protocols and standards such as GLP (Good Laboratory Practice). The need to minimise the use of experimental animals for testing purposes is well recognised, and increased harmonisation of testing and data requirements can also contribute to this.

Lack of good exposure data is frequently a problem in risk assessment. Rarely, except in the occupational setting and for human medicines, is the exposure of individuals measured directly. More often population exposures are estimated, using data on concentrations in, for example, air, water or food, coupled with estimates or assumptions about intake by humans. For risk assessments for permissioning activities, human exposures are often estimated using a variety of modelling techniques, since in these circumstances information from direct measurement will not normally be available. The exposure estimates may either be 'best estimates', usually averages based on mean concentrations or intake, or 'worst case' estimates based on extreme values of concentration or intake. There would be benefits if departments developed agreed approaches to modelling exposure data and pooled experience in exposure monitoring.

Finally, the risk characterisation presents a comparison of toxicologically-derived levels of concern with estimates of exposure.

Risk assessments are usually carried out independently for different media (e.g. water, air, food). Clear procedures are needed for carrying out integrated risk assessments for chemicals that have multiple uses or are ubiquitous in the environment.

Evaluation of risk assessment data

Most permissioning activities — notifications, approvals or authorisations for marketing and use — are subject to EU-wide schemes. A variety of approaches are in operation; in some cases one Member State may assess the relevant data on behalf of the EU, in other cases a more centralised system is in operation following an assessment by a Member State. When the UK is carrying out the risk assessment, the initial evaluation of the data is normally carried out by experts working within Government departments or agencies. Advice on risk assessments may be sought from advisory committees established for a number of chemical risk assessment schemes.

A common framework

The way the toxicological data are handled will depend on whether or not the toxic effect of the chemical under examination is considered to have a threshold, that is a level below which there is no adverse effect. There is assumed to be a threshold for the majority of toxic effects; the main exception is genotoxic carcinogenicity.

Where a threshold exists, the first step is the identification of the highest dose (usually in experimental animals) that does not give an effect. This is referred to as the No-Observed-Effect Level (NOEL). In some cases a No-Observed-Adverse-Effect level (NOAEL) is used, this is the highest dose that does not give an effect judged to be of concern to human health. The NOEL or NOAEL is then divided by an appropriate uncertainty factor to derive an acceptable level against which exposures can be assessed. Alternatively a ratio of NOEL or NOAEL to known or predicted exposures is calculated and judgements made as to whether it is sufficiently high. In the assessment of risks from human medicines, the data available generally obviate the need to use such uncertainty factors.

For the vast majority of permissioning schemes a substance with genotoxic properties would not be approved for use. For substances where humans are unavoidably exposed, such as certain contaminants in food, water and air, it is recommended that exposure is reduced as much as possible.

Diversities within a common framework

Within this common framework for evaluating risks there are considerable differences between departments and agencies in determining the degree of caution incorporated into the risk assessment. These include the sizes of uncertainty factors applied in the case of toxic effects with a threshold, the use of mathematical approaches for effects with or without a threshold, approaches to the treatment of genotoxic carcinogens, treatment of data gaps and deficiencies, the degree of protection sought in the case of the general population compared with workers, and the degree of conservatism built into 'worst case' exposure estimates.

Thus for chemicals to which the general public may be exposed an uncertainty factor of 100 has been widely used for standards derived from animal studies. This may be increased if there are significant gaps in the database or if the toxic effect on which the NOEL is based is a serious, irreversible effect (e.g. effects on reproduction). In the workplace, lower factors are used since exposures and the exposed population can be more easily monitored and exposures are limited to the hours worked. A consistent, clearly articulated approach to the application of uncertainty factors across departments would contribute to better public understanding and acceptance of chemical risk assessments.

The use of the 100–fold uncertainty factor is a convention. Nonetheless there is a need to provide further scientific data to characterise the uncertainty better and to establish whether uncertainty factors applied to the general population are sufficient to protect susceptible subgroups (e.g. the elderly and pregnant). Alternative approaches also merit consideration, such as the use of the 'benchmark dose'. This attempts to derive standards from a small increase in an effect in a proportion of the test population, rather than from use of the NOEL/NOAEL. Interest is also growing in mathematical approaches, such as Monte Carlo analysis and Bayesian methods.

The UK has always tended to avoid the use of mathematical approaches to assessing risks from genotoxic carcinogens and has instead generally favoured a weight-of-evidence approach. Mathematical approaches have been used in the USA, but recently the US Environmental Protection Agency (EPA) has moved away from them. Further development of the weight-of-evidence approach is to be encouraged.

In addition to the caution incorporated into risk assessments by the use of uncertainty factors, there is often considerable conservatism in exposure estimates, particularly when 'worst case' estimates are used. There is a need to define common default assumptions about human uptake and common procedures for deriving 'worst case' exposure estimates.

Conclusions and recommendations

There is wide agreement across UK Government departments and agencies about the philosophies and methodologies used in chemical risk assessment; there is also much commonality with approaches used elsewhere in the EU, not only in areas where risk assessment has been harmonised but also in areas where regulatory harmonisation is absent or not yet fully implemented.

Nevertheless there are some diversities in approaches to risk assessment within the UK, probably as a consequence of risk assessment schemes being developed for different purposes and for carrying out different parts of the risk assessment–risk management process. The key aspects of risk assessment which give rise to diversities in approach are the methods used to cope with the difficult areas of uncertainty, variability and lack of knowledge. Uncertainty encompasses both the uncertainties of toxicological extrapolation from animals or small groups of humans to wider populations and the uncertainties inherent in most exposure estimates. Variability encompasses both the heterogeneity of the human population and variability in the range of exposures. Lack of knowledge includes the significant gaps there may be in data relating to hazard identification and characterisation, lack of information about mechanisms of toxicity, and unanticipated toxicity or exposure.

Based on an examination of the approaches to risk assessment presented in this report the Risk Assessment and Toxicology Steering Committee recommends procedural changes and/or further research to facilitate:

- harmonisation of
  - data requirements,
  - practice in toxicological assessments, and
  - practice in intake and exposure estimates;

- development of improved methods and new approaches for risk assessment to
  - reduce uncertainty in toxicological assessment,
  - take account of chemicals with multiple uses or which are ubiquitous pollutants, and
  - provide a rationale for 'worst case' estimates of intake and exposure;

- improved transparency in the risk assessment process by
  - evaluation of the role of risk management in risk assessment, and
  - encouraging publication of risk assessments.

The following sections expand on each of these issues and suggest specific actions.

Harmonisation

Data requirements

Chemical sectors such as pesticides, biocides, food additives and animal feed additives would benefit from global harmonisation of toxicological testing requirements. The emphasis should be on harmonisation of the minimum data needed for meaningful risk assessment. Any such initiatives would need to be pursued at and beyond the EU level.

Practice in toxicological assessments

Guidance should be developed on the size and application of uncertainty factors for inter-species, and inter-individual differences and severity of effect, based on the available science and appropriate for the general and working populations, with a view to adopting common approaches across Government in the UK and assisting in ongoing international discussions.

Further consideration should be given to ways of maintaining consistency in the weight-of-evidence approach to risk assessment of carcinogens.

Practice in intake and exposure estimates

Experience with modelling intake and exposure from point and diffuse sources should be shared across Government departments and agencies, with a view to assessing the validity and utility of different exposure models. Harmonisation of approaches both nationally and internationally would be a desirable goal.

Government departments and agencies involved in monitoring and sampling programmes could benefit from pooling experience to solve problems they have in common, taking into account the requirements of existing EU statutory monitoring schemes.

Default assumptions concerning human anatomy, physiology and behaviour used for exposure estimates should be compared and discussed. Where appropriate, those that can be utilised in common across Government should be standardised and used to provide information for international harmonisation discussions. Adoption of internationally agreed default assumptions should be considered.

Development of improved methods and new approaches for risk assessment

Reducing uncertainty in toxicological assessment

The value of obtaining more toxicokinetic, toxicodynamic and mechanistic information on specific chemicals should be considered.

Further generic research should also be encouraged in the area of comparative toxicokinetics and toxicodynamics to provide better information for the selection of uncertainty factors.

The recommendations from the Risk Assessment and Toxicology Steering Committee workshop on research and development needs and regulatory application of PBPK modelling should be implemented.

Existing knowledge about human variability and the sensitivities of subgroups of the human population should be made more widely available and further research in this area should be encouraged. To this end, it would be desirable to seek ways of making available anonymised analyses of confidential data on human medicines that are relevant to human variability and comparability of responses between animals and man.

The use and application of mathematical (probabilistic) approaches should be more widely explored and evaluated in the assessment of chemicals with thresholds for toxicity, both for modelling uncertainties about effect and no-effect levels and for modelling the extent of effects at toxic dose levels.

Mathematical models should also be used, in assessment of chemicals with or without thresholds for toxicity, to evaluate the influence of varying assumptions and judgements on risk assessment outcomes.

Accounting for chemicals with multiple uses, and ubiquitous pollutants

Clear procedures should be set up within Government for conducting overall risk assessments for total human exposure to any single chemical which has multiple uses and/or is an ubiquitous environmental pollutant.

Rationale for worst case estimates of intake and exposure

Custom and practice in deriving worst case estimates for intake and exposure should be compared and discussed, both for exposure of the general public and for exposure of workers. Improvement of the statistical bases for worst case estimates and assumptions would be a desirable goal, both nationally and internationally.

Improved transparency in the risk assessment process

The role of risk management in risk assessment

The close interface between risk assessment and risk management should be more explicitly acknowledged. Those areas in the risk assessment process in which risk management policy and decisions can influence the outcome of the risk assessment process should be clearly identified

and discussed. All parties involved in risk assessment, risk management and risk communication should be clear about which elements are science-based and which are based on societal or economic considerations.

Publication of risk assessments

Government departments and agencies publishing explanations of their risk assessments should consider ways in which transparency in presentation of the thinking behind risk assessments may be enhanced. This could include releasing more of the underlying scientific information (within any essential commercial constraints), presenting discussion of any inherent uncertainties in the data and distinguishing between those elements of the risk assessment that have a clear scientific basis and those that are influenced by risk management considerations.

1 General introduction

UK Government/Research Councils Initiative on Risk Assessment and Toxicology

A number of UK Government departments have a responsibility for assessing risk to human health from potentially toxic substances that may be found in food, household products, human medicines, the environment or the workplace. Since reliable data from human populations exposed to known levels of a substance are rarely available, except in the case of human medicines, the assessment is often based on animal data. Such an approach has to accommodate the uncertainties inherent in extrapolating from animals to humans, from high to low dose and from one population to another. The uncertainties in the risk assessment process necessitate the adoption of appropriate uncertainty factors to ensure protection. It is clearly desirable to reduce the uncertainties as far as possible and to secure optimal use of resources.

The uncertainties inherent in current methodologies are widely recognised, as is the absence of scientific knowledge to define them more precisely. Recent advances in scientific techniques, such as use of novel biomarkers, *in vitro* toxicology, molecular modelling and computer simulations, may offer new possibilities. Furthermore, the use of such techniques should contribute to the reduction of animal use and the refinement and replacement of animal tests, a principle to which Government departments and agencies are committed. Government departments, together with the relevant research councils, have decided to make a co-ordinated drive to pursue these important opportunities. Their commitment was set out in the 1995 UK Government *'Forward Look of Government Funded Science, Engineering and Technology'* (HMSO, 1995) and resulted in the establishment of the Government/Research Councils Initiative on Risk Assessment and Toxicology in 1996.

The work of the Initiative is being taken forward by the Risk Assessment and Toxicology Steering Committee, which comprises participants from relevant Government departments and research councils and is co-ordinated from the Medical Research Council's Institute for Environment and Health. The Initiative aims to stimulate research so that new, improved approaches to chemicals risk assessment can be developed. It does not have its own research funds, but provides a focus, co-ordination and positive encouragement for research financed by individual Government departments or research councils (or consortia of these bodies).

The Steering Committee has organised a series of workshops on different aspects of risk assessment, with the aim of bringing together regulatory toxicologists, policy-makers from government and experts from academic institutions and industry to develop research specifications.

The Steering Committee has also undertaken a detailed mapping of toxic risk assessment procedures across Government departments, including the issue of dealing with uncertainties. This report is the result of that work.

The Interdepartmental Liaison Group on Risk Assessment

The Risk Assessment and Toxicology Steering Committee is a subgroup of the Interdepartmental Liaison Group on Risk Assessment (ILGRA). This is an informal committee of officials responsible for policy development and practical application of risk assessment in UK Government departments. In 1995 it undertook to review the principles and

practices used in Government for risk assessment with a view to identifying best practice and encouraging common approaches. ILGRA reports published in 1996 and 1998 discussed the use of risk assessment within Government, including issues relating to risk communication and perception (ILGRA, 1996, 1998). One of the areas identified for further study was the process of conducting a risk assessment. The 1998 report commented on the need to clarify the role of experts in assessing risks, with a view to opening up scientific advice to wider scrutiny, making uncertainties known and enabling stakeholders and experts to contribute appropriately to the decision-making process. The report also noted the need for departments and agencies to ensure that the use of precautionary approaches is consistent, reflects the principles of good regulation, and is compatible with sustainable development.

Scope and aims of the report

There are three important areas of Government activity in relation to chemicals and human health. These are risk assessment, risk management and risk communication.

- Risk assessment is the evaluation of the potential for adverse health effects in humans from exposure to chemicals.

- Risk management is the evaluation of alternative options and the actions taken to reduce potential risks in the light of an adverse risk assessment.

- Risk communication is the interactive exchange of information and opinions concerning risk between risk assessors, risk managers, the public and other interested parties.

These three areas can be described as separate activities and it is sometimes argued that risk assessment should be conducted without reference to risk management options, in order that assessments are unbiased. In practice, however, there is often a close interface between risk assessment and risk management. Risk managers may have to set the priorities for risk assessment and frame the questions and parameters on which they need advice. Some risk assessments also implicitly incorporate decisions of a risk management nature, such as the situation envisaged as a reasonable 'worst case' for exposure.

This report provides an overview of approaches to risk assessment currently used within UK Government departments and agencies in relation to risks to human health from chemicals; it is not intended to be an exhaustive review of all current practice. It covers effects of chemicals in air, soil, drinking water, food, the occupational environment, consumer products, human and veterinary medicines, and animal feed. It also takes into account international and European Union (EU) influences on chemical risk assessments, since a number of departments and agencies prepare risk assessments for international advisory and regulatory bodies, under the auspices of the EU, United Nations and World Health Organization (WHO). It does not address other key aspects of risk assessment, such as risks of non-chemical agents (such as radiation) and risks to the environment. Neither does it address risk management, except insofar as risk assessment and risk management are sometimes intertwined, nor does it address risk communication or risk perception. The report will be of interest to anyone involved in the assessment and management of risks from chemicals.

The principal issues addressed in the report are outlined below.

- Current risk assessment practices used in different Government departments and agencies are described.

- A common framework and diversities in the procedures used are identified, including diversity from practices in other countries.

- Major areas of uncertainty and weaknesses in current risk assessment procedures are identified.

- Recommendations are made on which areas of the risk assessment process might benefit from harmonisation across departments, which areas of uncertainty might be improved by targeted research or other means, and which areas might benefit from innovative approaches.

Data collection and presentation

The data used in this report were collected using a questionnaire developed by the Risk Assessment and Toxicology Steering Committee. The questionnaire requested information on the main purposes for which the various groups within Government utilise risk assessment and the underlying philosophy of the approaches used. It then went on to examine the ways in which

information relevant to the various stages of the risk assessment process (outlined in Section 2) is gathered, verified and evaluated. Questionnaires were received from all departments and agencies undertaking chemical risk assessments (listed in Annex 1).

The report describes the risk assessment process and purposes for which it is carried out (Section 2 and 3). It then discusses the three main elements involved in the risk assessment process; hazard identification and characterisation, exposure assessment and risk characterisation (Sections 4, 5 and 6). Then follows a discussion on how departments and agencies evaluate the risk assessment data and who does the evaluation (Section 7). Sections 8 and 9 deal with new approaches and publication of risk assessments. Throughout the report recommendations are made which could lead to improvements in and increased harmonisation of the risk assessment process; these are brought together in a final section (Section 10).

Annexes 2–4 provide additional background information on publicly available information on risk assessment, UK Government advisory committees involved in risk assessment and uncertainty factors used in risk assessment.

Terminology

Although the word ‘safe’ has been used in the context of risk assessment, its use has been avoided in this document. Similarly, although the term ‘safety factor’ is commonly used, the term ‘uncertainty factor’ has been used in this document*.

A glossary of terms is presented in Annex 5.

*These issues are discussed in more detail in the overview report by the Risk Assessment and Toxicology Steering Committee - ‘*Developing New Approaches to Assessing Risk to Human Health from Chemicals*’

2 The risk assessment process

A basic framework for the process of chemical risk assessment for human health effects has evolved through national and international consensus and is now well accepted. It generally involves hazard identification, hazard characterisation, exposure assessment and risk characterisation.

Hazard identification — the identification, from animal and human studies, *in vitro* studies and structure-activity relationships, of adverse health effects associated with exposure to a chemical.

Hazard characterisation — the quantitative (potency) evaluation of the adverse effects observed, usually by dose-response assessment, the evaluation of mechanisms of action and species differences in response.

Exposure assessment — measured, estimated or predicted intake or exposure to a chemical, in terms of its magnitude, duration and frequency, for the general population, for subgroups of the population, or for individuals.

Risk characterisation — the integration of hazard identification, hazard characterisation, and human intake/exposure assessment in order to, for example:

- predict whether or not effects in humans are likely to occur;
- predict the nature and severity of adverse effects which may occur in a given population exposed to a given concentration;
- predict the percentage of the population that may be affected;
- identify any vulnerable subpopulations; and/or
- estimate the likelihood of an event (such as accidental release of a toxic chemical) giving rise to an exposure of a particular level and duration associated with a specified level of effect upon the exposed population (Royal Society Study Group, 1983, 1992)

These four stages capture the main activities in classical risk assessment procedures for evaluating human health effects of toxic chemicals. While there is international agreement on the basic four step framework for risk assessment and there is much commonality in approach, it should be noted that there is not yet international agreement on many of the details. An initiative by the International Programme on Chemical Safety (IPCS) is underway, within the framework of the Intergovernmental Forum on Chemical Safety (IFCS), to examine the possibility of global harmonisation of assessment of risk from exposure to chemicals. The aim is to reach an understanding and acceptance of the various approaches used worldwide, to harmonise terminology and, in the longer-term, to achieve convergence of methodology. While this present report focuses on risk assessment approaches used in the UK, it is hoped that it will make a contribution to the ongoing discussions on international harmonisation, and a number of its recommendations would need to be taken forward in the EU and other international fora.

3 Purposes of risk assessment within UK Government

Risk assessments are used in different contexts within Government departments and agencies. This can influence the way in which risk assessment is approached. For example, there are clearly some constraints in the way risks can be managed when considering a chemical which is already on the market or present in the general environment compared with one that is not. Thus, the questions which a risk assessment is designed to answer may need to take account of the options available for risk management.

Risk assessment may be required for policy advice and development, for example, to enable Ministers and Government agencies to take decisions on whether individual chemicals or classes of chemicals require closer scrutiny and/or regulation (e.g. novel foods, air pollutants). It may be required to underpin guidance on how to assess and handle particular types of chemical risk (e.g. chemical accidents involving exposure of the general public, chemicals in the workplace).

In 'permissioning' activities, a policy will already have been adopted to control, by general or specific legislation, the production, marketing, use, transport, or disposal of a class of chemicals, an individual chemical, or a formulation in which it appears. Classes of chemicals subject to these kinds of regulation include new substances, pesticides, biocides, food additives, animal feed additives and human and veterinary medicines. In order to market or use such chemicals, permission must be sought from or a satisfactory notification must be lodged with the relevant competent authority. Risk assessments on such chemicals are then utilised at a variety of levels (Government, local, industry-wide, individual plant), to enable risk management decisions to be taken on whether a chemical or product can be freely used or whether restrictions on use are needed in order to protect human health.

The setting of advisory standards, such as acceptable daily intakes (ADIs) for food additives, pesticides and veterinary residues in food, is a key component in the overall risk assessment of many chemicals subject to regulatory control. Advisory standards are also used in situations where chemicals are not directly controlled by legislative means in the medium in which they give rise to human exposure (e.g. ambient air quality standards and guidelines and drinking water guideline values); although appropriate measures may be taken if those advisory standards are exceeded. In some cases, air and drinking water guideline values have been used in EU Directives to set enforceable standards. Legally enforceable standards are also set for certain chemicals in the workplace and for a few food contaminants. Both advisory and legally enforceable standards are usually set using the first two stages (hazard identification and hazard characterisation) of the basic risk assessment framework described earlier, and in the case of occupational exposure limits a consideration of the third stage (exposure) is also involved. Thus the majority of standards are health-based. A few, such as some water guideline values, may be based on additional, non-toxicological considerations, such as the aesthetic quality of water (e.g. taste or odour).

Risk assessment is also used to assess the health significance of situations which cross national boundaries (e.g. air pollution) and, at the other end of the scale, localised events or situations, such as accidental chemical releases, deliberate discharges from point sources, projected uses of contaminated land, and the siting of major industrial hazards.

4 Hazard identification and hazard characterisation

4.1 Types of toxicological information required

The information available for hazard identification and hazard characterisation of individual chemicals normally includes physicochemical data and toxicological data from laboratory studies on animals, animal and human cell lines, and lower organisms. Although experimental studies may be the major source of information for many chemicals, efforts continue to be made to minimise the use of experimental animals in testing. In addition, human data from volunteer studies, epidemiological studies, human trials or case-reports may be available. However, apart from the sector of human medicines, risk assessments frequently have to be conducted without the benefit of human data. Occasionally, information relating biological activity to chemical structure (structure-activity relationships), derived from computational or other techniques, may be available for chemicals within a related chemical group.

The toxicological information needed for risk assessment of chemicals usually requires that a number of end-points be addressed in a range of tests. For the majority of chemicals subject to licensing, approval or notification, information on absorption, distribution, metabolism and excretion, general toxicity from single and repeat dose administration, reproductive and developmental toxicity, genetic toxicity and carcinogenicity may be required. For some chemicals, information on eye irritation, skin irritation and skin sensitisation may also be required, not only for the chemical itself but also for the formulation in which it will be marketed. For a few chemicals, more detailed examination of aspects of neurotoxicity, immunotoxicity, endocrine toxicity, or other special studies may be required. In some cases, knowledge of the mechanism by which the observed toxicity is induced may be required to assess whether the mechanism of action is relevant to man. The mechanism of action may be apparent from the initial studies, or special studies may be required. However, it should be noted that many risk assessments are conducted without the benefit of mechanistic information, particularly in situations where risk assessment is used to develop a health-based standard. In such cases, the risk assessment may be unduly cautious compared with that which might be made in the light of appropriate mechanistic information.

It is recommended that consideration be given to the value of obtaining more toxicokinetic, toxicodynamic and mechanistic information on specific chemicals where this might help reduce uncertainties in risk assessment.

Risk assessments of chemicals that have been on the market for some time are needed in the areas of air and drinking water quality standards, occupational and consumer exposure, local incidents of pollution, consents for discharges, chemical accidents and the siting of major hazards. Many of these chemicals were first marketed years ago when pre-marketing notification or authorisation was not required. Risk assessments for such chemicals are generally based on whatever relevant information is available, although in some circumstances it may be possible to request additional information. Adequate physicochemical data are usually available but the extent and quality of the biological information can be very variable. Sometimes, because of experience of human exposure over time, there may be more human toxicological and epidemiological data available than is the case for newer chemicals. In contrast, a comprehensive range of *in vitro* and *in vivo* toxicological data may be absent. A number of international activities contribute to the generation and compilation of data for risk assessment of chemicals that have already been on the market for

some time. Under a global initiative co-ordinated by the Organisation for Economic Co-operation and Development (OECD), an agreed set of minimum toxicological data (Substance Information Data Sets (SIDS)) is now being generated on selected high production volume chemicals. Under the EU Existing Substances Regulation (EEC, 1993), risk assessments for occupational, consumer and environmental exposures are conducted on priority existing chemicals and there is a legal provision to enable data gaps to be filled. The IPCS also publishes internationally agreed risk assessments[a]. These initiatives will facilitate future risk assessment of widely used chemicals and some environmental pollutants on an international basis.

4.2 Guidance on requirements for particular chemical classes

For chemicals where use and/or exposure are regulated by legislation, the nature and extent of the information that should be submitted to the competent authority carrying out the risk assessment are usually laid down in guidance documents. Guidance may be produced nationally, as it has been in the past in the UK for the majority of chemical sectors or, where there is harmonised EU legislation, as is increasingly now the case, at the EU level. There are now EU guidance documents on data requirements for food additives, food packaging materials, novel foods, agricultural pesticides, biocides, industrial chemicals, veterinary medicines and additives in animal feed. To date, it is only in the area of human medicines that there has been wider international agreement on requirements for toxicological testing, under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The ICH encompasses the EU, USA, and Japan. The ICH guidelines completed to date[b] have been adopted by the EU regulatory body for human medicines, the Committee on Proprietary Medicinal Products (CPMP). A similar international harmonisation process is also now underway for veterinary medicines, under the auspices of the Veterinary ICH.

[a] International Programme on Chemical Safety, Environmental Health Criteria (EHC) Series and Concise International Chemical Assessment Documents (CICAD) Series, Geneva, World Health Organization

[b] International Conference on Harmonisation Guidelines, available in Series CPMP/ICH from Medicines Control Agency, London

It is important to note that it has been customary to set out the detail of the nature and extent of the information that should be submitted on each type of chemical in guidance documents rather than as absolute requirements in legislation. This is because the amount of information required to make a reliable risk assessment varies from one chemical to another and even within a particular class of chemicals. It will vary, for example, depending on the inherent toxicity, the nature of the exposed population, and the routes and degree of exposure to the chemical under consideration. It is therefore important to allow some flexibility in the data that need to be generated for each chemical. Scientific arguments can be given as to why a particular test has not been carried out. The regulatory authority can then accept or reject those arguments. Flexibility in requirements also allows regulatory authorities to call, on a case-by-case basis, for particular types of test beyond those set out in the basic requirements, if particular questions or concerns arise.

4.3 Benefits of harmonisation of data requirements

A key aspect of harmonisation is that standard protocols for the most widely used toxicity tests have been developed and agreed within the OECD (1987). Members of OECD, which includes all the major industrialised nations, are obliged under the Mutual Acceptance of Data agreement to accept data on chemicals for evaluation if they have been generated from studies conducted according to OECD protocols and according to the OECD principles of Good Laboratory Practice (GLP; OECD, 1982). OECD test protocols and GLP have also been adopted by the EU in Directives on chemicals (EEC, 1984, 1987a,b, 1992). OECD protocols are also widely used and accepted in the testing of food additives, food packaging materials, animal feed additives, pesticides and veterinary medicines within the EU.

Harmonisation of test protocols and data requirements within chemical sectors across the EU or more globally has been beneficial in ensuring that risk assessments on new chemicals are made from an acceptable (minimum) database. There is now less tolerance of gaps in databases than previously was the case. This helps reduce uncertainties in the overall predictive value of the data and avoids the need to use additional uncertainty factors in the setting of health-based standards to cover for missing studies (see Section 7.3.1). It has also been beneficial in reducing the

use of animals in toxicity testing by reducing differences between national requirements.

Given the global nature of trade in and use of chemicals, sectors such as pesticides, biocides, food additives and animal feed additives would benefit from global harmonisation of toxicological testing requirements. The emphasis should be on harmonisation of the minimum data needed for meaningful risk assessment. Any such initiatives would need to be pursued at and beyond the EU level.

4.4 Stage at which information is submitted

The stage at which studies of particular types are required to be submitted will vary, depending, for example, on the chemical sector, the amount manufactured, the extent of human exposure and the results of earlier studies. In some chemical sectors, progression to full approval for requested uses proceeds in stages. For example, with human medicines, clinical trial certificates or exemptions are granted after scrutiny of a limited pharmaco-toxicological database that is tailored to the needs of the risk assessment required to proceed to human clinical trials. As development of the compound proceeds, further animal and/or human studies, addressing toxicological issues, are conducted, tailored to intended clinical uses, before marketing authorisation is considered*. A similar, staged approval process applies to veterinary medicines during their development stage through clinical trials to full marketing (EEC, 1981a,b). Approval of agricultural pesticides also proceeds via initial experimental permits for crop trials, which are granted on a limited toxicological database (MAFF/HSE, 1996). At these early stages, risk assessment of agricultural pesticides focuses on occupational exposure; human exposure via food is not permitted unless residues are non-detectable or unless repeat-dose and teratogenicity studies are available and indicate limited exposure to residues is acceptable. Final approval for full commercial uses is only granted if extensive toxicity data are submitted on any residues in human food and the data are considered satisfactory.

A staged approach of a different nature applies in the case of new substance notifications. The amount of toxicity data required for production and supply of small quantities is limited to that required for an initial risk assessment, assuming there will only be low or short-term exposure. Subsequent placing of larger quantities on the market requires further notifications containing additional data, the extent of which increases as tonnages increase (HSE/DoE, 1994). This tiered supply-based approach to toxicity testing for new substances also recognises that the cost of testing has to relate to the ability of the product to stand such costs. Furthermore, the amount of testing is also linked to the careful control of the supply and the ability to monitor the situation and take remedial action if necessary. Similarly, approval of the use of substances in food contact materials follows a tiered approach, depending on the amounts shown to be migrating into food; at very low projected human exposures only genetic toxicity studies are required, at higher projected exposures additional studies are required, and at the highest exposure levels a comprehensive set of toxicity studies is required (Scientific Committee for Food, 1992). Staged approaches of this nature imply acceptance of the concept that below certain levels of production/exposure only certain toxic effects are likely to occur. Such a concept is based on both scientific considerations about thresholds for toxic effects (see Section 7.2.1) and societal (risk management) considerations about acceptance of low-level risks.

Other chemicals can be approved for marketing on the basis of a comprehensive set of toxicological and other studies submitted at the time approval is first sought. This situation applies to food additives, novel foods and processes, animal feed additives and certain cosmetic ingredients* (presently colours, UV filters and preservatives). For food additives, pesticide and veterinary residues in food, and animal feed additives, an advisory standard such as an ADI or acceptable use level in products is set, based on the comprehensive database. Uses are then approved on the basis of the advisory standard. Either a full advisory standard or a provisional or temporary one may be set. Provisional or temporary advisory standards are set when the toxicological database is sufficient to allow a conclusion that use of the chemical over the short term is acceptable, but there remain some minor questions to be answered by provision of further data. The setting of provisional or temporary standards usually entails incorporation of additional uncertainty factors to cover for deficiencies in the database (see later). The competent authority normally specifies the nature of the additional data and the deadline by which it should be submitted.

* Note for guidance on non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals, March 1998, available from, EU Committee on Proprietary Medicinal Products, DG III, Commission of the European Communities.

* Testing of cosmetics ingredients in animals was phased out in the UK in November 1998.

In the case of setting standards for chemicals present in the workplace, such as Occupational Exposure Standards (OESs) and Maximum Exposure Limits (MELs), or Air Quality Standards (AQSs) for ambient air, whether and when information is gathered are determined by the lead department. The need for occupational and ambient air standards, for example, is decided on the basis of concerns about possible human health effects. However, there may be no mandatory requirement for industry to submit data, and standards are usually set on the basis of publicly available data and voluntarily released company reports (see below).

4.5 Sources of toxicological information

When a chemical or product is subject to prior regulatory notification, approval or authorisation before it can be used or marketed, it is the responsibility of the company or consortium (the applicant) that wishes to use or market it to generate, assemble and submit the required information. This situation applies in the case of human and veterinary medicines, agricultural and non-agricultural pesticides, new substance notifications, novel foods and processes, food additives, animal feed additives, substances used in certain categories of packaging materials (plastics, cellulose film), and cosmetic ingredients in categories requiring positive approval. At this stage there is usually little or no published information available and data generated by the applicant are often submitted 'in confidence' to the competent authorities. The authority can, where necessary, request that the applicant submit additional data. If additional studies or other information are necessary, this 'request' is, in effect, a requirement since, if not submitted, approval may be denied or a temporary approval suspended. Some competent authorities can themselves commission additional studies, though this is rarely done in the case of new chemicals.

In the case of chemicals or products that are regulated or voluntarily controlled by means other than prior notification or approval, a different situation applies, since the competent authorities generally lack powers to compel chemical producers to provide information. This situation applies in the case of pollutants present in ambient air, chemicals present in drinking water (deriving from water treatment processes, waste water discharges or general pollution), chemical contaminants in food (other than certain food packaging substances and a few other regulated contaminants) and chemicals in consumer products. In these cases, unless they are subject to the EU Existing Substances Regulation, there is heavy reliance on publicly available data, such as scientific papers and reviews, and to a lesser extent, company reports released voluntarily to Government departments and agencies. The competent authorities can also commission studies to acquire information on specific issues. This is an important facility because not only do the authorities lack powers to require companies to provide data, but also in many cases such powers would be ineffectual. The chemical under consideration may not be synthesised commercially (e.g. dioxins or naturally occurring toxicants in food), or it may no longer be produced commercially (e.g. polychlorinated biphenyls), or it may be produced commercially but human exposure is not attributable to any one industry (e.g. pollutants and contaminants in air, water and food such as benzene, polycyclic aromatic hydrocarbons, and heavy metals).

Risk assessment of occupational exposure to existing chemicals and risk assessment of major hazards and land use planning are hybrid situations. Again there is heavy reliance on publicly available data and voluntarily released company reports, but companies can also be required to reveal existing data and the competent authority can itself commission further studies. In the case of certain existing substances rated as priority chemicals, the EU Existing Substances Regulation (EEC, 1993) provides a legal framework for requiring the provision of data.

5 Exposure assessment

5.1 Types of exposure information required

Lack of good exposure data is frequently a problematic area in risk assessment. The type of exposure information required depends on the purpose for which it is needed. Some risk assessments require that human exposure, via ingestion, inhalation or dermal absorption, be assessed as directly as possible, in order that it may be compared with some health-based standard for human exposure, or compared with information about exposures associated with adverse effects. Other risk assessments, used for example in assessment of major hazards and in pollution control, do not directly estimate human exposure. Instead they focus on assessing the input and dispersion of a chemical into ambient media (air, water, soil) for comparison with health-based standards for levels in the ambient media. In both cases, knowledge of the magnitude, duration and frequency of exposure may be critical to the risk assessment. For many chemicals, exposure will be variable over time; the range of intakes or concentrations to which individuals are exposed may be needed, or at least an estimated 'worst case scenario'.

In the case of risk assessments for which human exposure data are required, measurement of actual exposure of individuals is rarely carried out. It may be undertaken in special cases such as measurement of chemical concentrations in inspired air via personal samplers in occupational settings, or measurement of intake biomarkers in biological fluids. It is only in the special case of human medicines that the applied dose is known routinely with some certainty; exposure to the chemical at pre-specified doses is intentional and systemic exposure of the individual to the chemical is evaluated during clinical trials. More often, population exposures are estimated indirectly, using data on measured or predicted concentrations of the chemical in air, food or water coupled with estimates or assumptions about the human body, to predict external or internal (systemic) exposures. Lack of suitable analytical methods for different media and with appropriate limits of detection may also be a factor that limits the availability of good exposure data. In certain chemical sectors where information may initially be sparse, such as new substance notifications, human exposure may have to be modelled entirely from surrogate parameters such as physicochemical properties and knowledge of the way the chemical will be manufactured and used, coupled with default assumptions about the human body. The use of default assumptions is considered further later (see Section 7.3.4).

In the case of risk assessments requiring knowledge of inputs into ambient media, the source of pollution may be a point source or a diffuse source. Concentrations at point sources and subsequent dispersion in ambient media may be measured or modelled. This type of exposure assessment requires a considerable knowledge of factors affecting the nature of releases, the ways in which the material will disperse in air, water and soil and whether dispersions from point sources overlap and need to be aggregated. It can be used to explore management options for achieving particular discharge/emission standards. Various techniques are available for modelling each aspect of the exposure assessment and, depending on the model used, may incorporate differing degrees of conservatism.

It is recommended that experience with modelling intake and exposure from point and diffuse sources is shared across Government departments and agencies undertaking such tasks, with a view to assessing the validity and utility of different exposure models. Harmonisation of approaches both nationally and internationally would be a desirable goal.

As an alternative to modelling of dispersion, actual measurements of chemical concentrations may be taken in the relevant ambient media, but this may require extensive monitoring over time and place, which presents its own difficulties. Surveillance for sporadic contaminants in large consignments of crops or food products also presents similar difficulties concerning the selection of when and where to sample. The application of statistical techniques to the design of such monitoring programmes can aid reliability and comprehensive coverage of results.

It is recommended that Government departments and agencies involved in monitoring and sampling programmes pool experience to solve problems they have in common, taking into account the requirements of existing EU statutory monitoring schemes.

5.2 Best estimates and worst case estimates

When measurements of chemical concentrations in air, water or food, or estimates of intake are used for risk assessment, 'best estimates', 'worst case' estimates, or both may be needed for the exposure assessment. 'Best estimates' are usually averages, based on mean or median concentrations or intakes. In the case of agricultural pesticide residues in foods, for example, in the UK, median values obtained from field trials are used for risk assessment for chronic effects, rather than 'worst case' estimates.

'Worst case' estimates, in contrast, are usually based on extreme values, though not necessarily the highest values, obtained for concentrations or intakes. One such example is the 97.5th percentile intake value used for food additives and contaminants in the UK. 'Worst case' estimates can also be based on limits for maximum levels of use, where these have been set. For example, if maximum use levels have been set for a food additive in various food product categories, it is assumed that every product that could contain the chemical does so, and that the chemical is present at the maximum permitted level. When maximum residue limits in food are being set for veterinary products, they are calculated from similar 'worst case' assumptions.

In some situations, for practical reasons, 'worst case' or 'extreme consumer' estimates are the first calculations to be made. For example, in the pesticides field, provided predicted 'worst case' estimates of exposure of those applying the pesticide do not exceed the standard set (the Acceptable Operator Exposure Level – AOEL), then there is no need to refine exposure estimates any further. Similarly, for food chemicals (additives or contaminants), provided 'worst case' estimates do not exceed the relevant ADIs or tolerable daily intakes (TDIs), then no further action need be taken. In these situations the value of a 'worst case' estimation is that it is quickly and easily done and may enable reassuring conclusions to be drawn from the risk assessment process. Under these circumstances, the in-built conservatism of 'worst case' estimates is not a problem.

In other situations, emphasis is deliberately put on 'worst case' estimates rather than 'best estimates' to take account of the possibility that higher numbers may be exposed to higher levels. For example, when considering the exposure of workers manufacturing a chemical, or the exposure of professionals trained in its use, 'best estimates' under conditions of 'best practice' may be used for the risk assessment. However, when considering exposure of the general public to the same chemical, 'worst case' scenarios may be used. Similarly, in the case of chemicals present in consumer products or pesticides in products for amateur home and garden use, exposure scenarios involving reasonably foreseeable misuse are considered, though deliberate ingestion with the intent to poison is excluded from consideration. Other examples where 'worst case' estimates are critical for the risk assessment include exposure of bystanders to pesticides during or after spraying in the home or on crops, or exposure of the general public to air or water pollutants following accidental releases. In these situations, the high degree of conservatism is generally regarded as appropriate for risk assessment because of the likelihood of exposure of potentially vulnerable groups, such as infants and young children, pregnant women, the elderly or asthmatics.

5.3 Sources of exposure information

For chemicals present in food, be they deliberately added, naturally present or present as contaminants, a comprehensive knowledge of food consumption patterns, coupled with knowledge of which foods contain the chemical and at what concentrations, is the key to obtaining good exposure estimates. The UK benefits from better data on food consumption patterns and food chemical residue information than are available in many other countries. The Ministry of Agriculture, Fisheries and Food (MAFF) has developed a comprehensive food consumption database from

nutritional surveys, total diet studies, duplicate diet studies, and dietary studies of special age groups and groups with particular dietary habits.

Estimates of intakes of food additives are mostly made from information submitted by industry about the use levels they wish to employ to achieve the required technical effect. Occasionally detailed intake surveys may be carried out (e.g. on sweeteners). MAFF also undertakes extensive surveillance for chemical residues in food, including man-made contaminants (e.g. environmental pollutants, food contact materials), naturally occurring contaminants (e.g. fungal toxins), natural toxicants, and pesticide and veterinary residues. Data on pesticide and veterinary residues in food are generated from Government laboratory surveys, conducted post-marketing under statutory UK and EU monitoring programmes. Such data are mostly used to check that food is in compliance with permitted maximum residue limits. Maximum residue limits are set at the stage prior to full marketing of a pesticide or veterinary product. Residues data, including residues depletion data over time, are generated and submitted by the industry wishing to market it and these are used to set maximum residue limits and post-harvest intervals (agricultural pesticides) or withdrawal times (veterinary medicines). Monitoring data can also be used to refine 'worst case' estimates.

Information about concentrations of chemicals present in various consumer products comes largely from industry, with some from analyses commissioned by local authorities (trading standards officers/public analysts) or the Government. Estimates of 'worst case' exposure to cosmetic ingredients, for example, can be made from extreme user data provided by the relevant trade association for each type of product, in combination with maximum requested use levels or maximum permitted use levels laid down in EU Directives.

Measurements or estimates of exposure to chemicals present in the occupational environment may be submitted by industry and checked by the Health and Safety Executive (HSE), or HSE may make its own measurements or estimates, based on the application of models to data provided by the industry.

For general pollutants present in ambient air, such as ozone, oxides of nitrogen, sulphur dioxide and benzene, both published papers and data from local measurements are utilised to assess exposure. For chemicals present in drinking water, published papers, information from the water industry and, in the case of chemical contamination, local measurements are utilised. Assumptions about drinking water intake in the UK are the same as those used by the WHO. Exposure information for major accidents involving toxic chemicals is generated from mathematical dispersion modelling supported by experimentally generated data.

6 Risk characterisation

6.1 Nature of the risk characterisation

The nature of the risk characterisation step of risk assessment differs depending on the question that is being asked. Risk characterisation can be used to yield a 'yes/no' answer to the question — 'Are currently assessed human exposures or intakes below the estimated acceptable level?' — In which case the measured, estimated or predicted human exposure or intake is compared with an agreed standard, such as an OES, AQS, TDI or ADI.

A variant of this approach is used where no agreed standards and no adequate human data exist. In these situations, the ratio between the overall no-effect level (see Section 7.2.1), estimated from a range of appropriate toxicity studies, and the exposure is calculated. The ratio is variously termed the 'toxicity:exposure ratio', 'margin of exposure' or 'margin of safety'. A judgement is then made as to whether the ratio is large enough to conclude that the exposure is acceptable. This can be a difficult judgement, particularly in cases where the ratio is well below 100. It is applied in the risk assessment of exposure to non-agricultural pesticides, new and existing substances (as defined by the EU), substances in the workplace and environmental pollutants.

If the initial risk assessment shows that estimated acceptable levels are being exceeded, the risk characterisation may have to be further developed to answer questions about which groups within the population may be affected, how many within those populations may be affected and what types of adverse health effects may be expected. These are more difficult questions to answer than the initial estimation of an acceptable level of exposure, particularly when there are few human data available. Predictions of the degree of adverse effects and who may be affected require more precise answers. They require further consideration of the critical toxicological end-points for the chemical, both with respect to their nature and the rapidity with which they can be induced, toxicokinetic predictions about the behaviour of the chemical at higher intakes, and good information on the range of exposures in subgroups of the population.

In another type of risk assessment, risk characterisation is designed to assess the likelihood of a particular initiating event, such as the release of a dangerous amount of a chemical from an industrial plant into an environmental medium. This involves estimating the amount of a chemical likely to be released, its duration of release, and its dispersion in the environment, under various conditions, and comparing this with a defined level in the medium, for example, that which would be expected to cause serious health effects.

In some cases, once an initial risk assessment is completed, further steps are carried out in reverse order, to determine the extent of the actions necessary to reduce exposure below a predetermined acceptable level. This is done in the case of veterinary medicines, after the setting of an ADI. Options are then explored, using data on withdrawal times and residue depletion in edible tissues, to set maximum residue limits which will ensure the ADI is not exceeded.

Although the toxicological evaluation of human medicines has many features in common with those of other chemicals, the processes of risk assessment and characterisation are different. Adverse effects of individual products are identified in toxicity studies in animals and clinical studies. Any potential risk associated with exposure to the medicine can be set against anticipated beneficial effects.

6.2 Taking account of all sources and routes of exposure

For any type of risk assessment, ideally all known or anticipated sources and routes of exposure to the chemical under consideration should to be taken into account. Exposure may be through food, water, air, skin contact, other routes (human medicines and certain consumer products), or any combination of these. For example, workers mixing and spraying pesticides may be exposed by oral, respiratory and dermal routes. Environmental pollutants, such as heavy metals or certain ubiquitous organic chemicals, may be present in food, water and air, each contributing to a greater or lesser extent to human exposure. A risk assessment may, however, be confined to the medium under detailed consideration, for example, dietary exposure to a contaminant such as benzene; this needs to be set in the context of higher exposures of the general public via ambient air and smoking. In cases where a TDI has been set for a contaminant in food, agreement may need to be reached on the proportion of the TDI to be allocated for known exposure via another route such as water. For example, in the WHO drinking water guidelines, 10% of the ADI/TDI is allocated to drinking water for herbicides but only 1% for insecticides. Similarly, certain chemicals have multiple uses as agricultural pesticides, non-agricultural pesticides, food additives and veterinary products. Here again agreement needs to be reached on how to allocate the ADI between various uses, or how to ensure that the ADI is not exceeded when exposures via all possible uses are aggregated.

It is recommended that clear procedures be set up within Government for conducting overall risk assessments for total human exposure to any single chemical which has multiple uses and/or is an ubiquitous environmental pollutant.

6.3 Taking account of specific groups

A number of Government departments and agencies emphasise the need to consider specific groups separately in risk assessments on certain substances. Failure to consider separately risks to special groups can result in misleadingly reassuring conclusions if they are based solely on risk characterisation for average adults. Relevant specific groups include those perceived as potentially vulnerable because of, for example, genetic predisposition, age, sex, pregnancy, ill-health, particular diets or high exposure. In the case of human medicines, data from pharmacokinetic studies in special patient groups enable dose adjustments to be made prospectively. In the field of environmental air pollutants it may be the elderly and the asthmatic that are most at risk. Advice on the siting of proposed major hazard installations or on land use planning around existing installations will take into account potentially vulnerable populations such as school children or the elderly. In the case of food chemicals, infants and young children may often be at particular risk because of their smaller body weights, higher energy intakes and less varied diets. Such considerations are often a critical part of risk characterisation because they can demonstrate that only certain subgroups of the population may be at risk of adverse health effects at prevailing exposures, thus enabling more focused risk management decisions to be taken.

The differing physiological conditions or requirements and differing end-organ sensitivities of subgroups of the human population are relatively under-researched areas, but they are critical to a better understanding of risks to specific groups. This also has implications for the size of uncertainty factors selected to take account of differences within human populations (Calabrese, 1985; Hattis & Silver 1994, see Section 7.3.1). Knowledge of the range of sensitivities of subgroups of the human population and the underlying physiological or pathological mechanisms is emerging most strongly in the field of human medicine.

It is recommended that, where appropriate, risk assessors maximise the use of existing knowledge about human variability and the sensitivities of subgroups of the human population to refine risk assessments and that further research in this area be encouraged. To this end, it would be desirable to seek ways of benefiting all chemical sectors through making available anonymised analyses of confidential data on human medicines that are relevant to human variability and comparability of responses between animals and man.

7 Evaluation of risk assessment data

7.1 Who evaluates the data?

7.1.1 The role of UK advisory committees

Initial evaluation of the data available for a risk assessment is usually done by scientists working within the various Government departments and agencies. They prepare a draft risk assessment. Occasionally, outside institutions such as Research Council units, universities, independent research institutes, or consultants may be commissioned to prepare risk assessments. Apart from chemical emergencies, a draft risk assessment is then usually presented to the relevant UK advisory committee, EU forum or other international body for critical comment. The opinion of these bodies then forms the basis of the final advice to Government agencies, Ministers or the European Commission/Member States. The UK committees advising in the various chemical sectors are listed in Annex 3. Members of UK advisory committees are drawn from academia, research institutes, public laboratories, and industry. In the case of committees advising on chemicals in the workplace, the structure is tripartite, comprising members drawn from industry, trade unions and individuals independent of these groups. In other advisory committees, members are only occasionally drawn from industry. Several advisory committees also now include lay members appointed, for example, to give advice from a consumer's perspective or from the perspective of the general public. Members appointed for their expertise are expected to offer independent advice. The risk assessment process, including decisions about the quality of scientific data and how they should be used, is recognised as being the proper remit of the scientific experts involved; judgements about perceived severity of effects and how to deal with or manage them are subject to wider policy considerations. Sometimes advisory committees have two roles, both the evaluation of scientific data and making decisions about what should or should not be done to address the risk issue.

7.1.2 European Union regulatory systems

For regulatory notifications, approvals or authorisations for marketing and use made at EU level, several different systems of evaluation and decision-making operate. The system used depends on the chemical sector.

For novel foods, pesticides and animal feed additives, evaluation of an individual chemical is carried out by the relevant competent authority in one of the Member States, which acts as rapporteur on behalf of the EU. A decision on approval/authorisation is then taken within an EU standing committee in which Member State Governments are represented. Advice may sometimes also be sought from an EU scientific committee (see below).

For human medicines, there are centralised and mutual recognition procedures. The former procedure deals with requests for authorisation to market a new entity simultaneously in all EU Member States and for high technology and biotechnology products. Two members of the relevant European expert committee, the CPMP, are appointed as rapporteur and co-rapporteur. They both prepare an assessment, which the CPMP considers; after hearing any appeal, the CPMP then delivers an opinion. A European Commission decision granting or refusing to grant authorisation follows. In the case of the mutual recognition procedure applicants may also ask to market in two or more EU countries any human medicine which has already been authorised by a single Member State, according to criteria laid down in EU Directives. The assessment carried out by the Member State that granted the initial authorisation is circulated. The other Member States in which the

applicant wishes to market are asked to recognise the approval mutually. If Member States cannot agree on the matter within the allotted 90 day period, it is referred to the CPMP for arbitration. An EU decision, which Member States are required to implement, follows the CPMP's opinion.

For marketing authorisation of veterinary products, there is a centralised procedure for applications to market a new product simultaneously in all EU countries, for authorisation of an individual chemical used in a veterinary medicine, and for biotechnology products. Two members of the relevant European expert committee, the Committee on Veterinary Medicinal Products (CVMP), rather than Member States, are appointed as rapporteur and co-rapporteur. They prepare an assessment, which is then considered by the whole committee, and an opinion is sent to the Commission. The CVMP opinion is then considered by a standing committee for formal acceptance. In cases where a product is already marketed in at least one Member State, a mutual recognition procedure similar to that for human medicines applies.

A slightly different system operates in the case of the Notification of New Substances, for which there is an EU-wide notification scheme, rather than an approval or authorisation scheme. Notifications, which should contain the required information, including a risk assessment, detailed in the relevant regulations, are made by industry to an individual Member State competent authority. The competent authority then has derogated powers to accept or reject the notification, including the risk assessment, on behalf of the EU. The European Commission ensures close co-operation between competent authorities to maintain consistency of decision-making (HSE/DoE, 1994). A similar, but not identical, system operates for existing substances (as defined in EU legislation) under the Existing Substances Regulation. Here the competent authority within an EU Member State acts as a rapporteur to produce a draft risk assessment. This is then discussed within an EU-wide committee to produce a final EU- agreed risk assessment.

In the procedures outlined above, when a UK competent authority or a UK individual is rapporteur, the opinion of a national advisory committee may routinely be sought before submitting the evaluation to the relevant EU committee. Sometimes a national advisory committee opinion may only be sought if the issues are difficult or complex. Where another Member State or a non-UK individual is rapporteur, the UK will see the draft risk assessment and be able to comment but may or may not have access to the full dossier of information seen by the rapporteur. In the case of veterinary animal feed additives, veterinary medicines and new pesticides, all dossiers are seen by the UK, irrespective of which Member State is rapporteur. In the case of human medicines, novel foods and new substance notifications, access to the original dossier can be requested.

A rather different system operates in the case of food additives, food contact materials, certain food contaminants and some other consumer products. Risk assessments are prepared and carried out within the European Commission's Scientific Committees, managed since 1997 by Directorate General XXIV on Consumer Policy and Consumer Health Protection. Members of these Scientific Committees are appointed as independent experts and do not represent Member State Governments. These committees advise the European Commission, which uses the advice as the basis for legislative proposals on what substances should be permitted for use and whether any restrictions on use are required. Member States are not invited to comment on the risk assessments at draft stage and may or may not have access to the full dossier of information seen by the relevant Scientific Committee. The Commission's draft proposal for legislation is then discussed with the Member States, at which stage they may raise any concerns they may have about the risk assessment. Once Member State officials have agreed the proposals, the final decision to approve the legislation is taken by the EU Council of Ministers and the European Parliament.

Some evaluations and approvals are still carried out solely at a national level. For example, in the case of agricultural pesticides, there is currently a transition period during which the approval process for active ingredients is being transferred from a national to an EU basis (MAFF/HSE, 1996). During this period, some complete evaluations and approvals of active ingredients and formulated products are carried out nationally. Once a harmonised list of active ingredients for pesticides has been agreed at EU level, risk assessment of individual product formulations of pesticides and certain conditions of use will still remain at Member State level. Evaluations of non-agricultural pesticides are still carried out nationally, but will change to an EU-wide basis once the Biocides Directive (EEC, 1998) is implemented via regulations. Risk assessment for a chemical of any type that is normally regulated at the EU level is also carried out at the national level in cases where a manufacturer wishes to market it only in the UK. The relevant EU Directives provide for this situation, but it now occurs with

diminishing frequency. Usually, national authorisations are only permitted to run for a short period (1–3 years), beyond which authorisation must be sought at the EU level. Risk assessments are also still conducted nationally on most consumer products, as the EU at present only legislates occasionally, as problems arise.

7.2 What is the common framework for evaluation of risk assessment data?

The ways in which hazard identification and hazard characterisation data are evaluated are similar, irrespective of the purpose of the risk assessment. First, the available chemical and biological data are reviewed. The data may comprise published studies and/or studies generated by the company seeking an approval. Studies generated by companies may be conducted 'in-house' or commissioned from contract testing laboratories. Such studies should now be conducted according to the principles of GLP, which were first introduced during the 1970s, but older studies conducted prior to the introduction of GLP may still be accepted for evaluation. The year of compulsory implementation of GLP varies depending on the chemical sector, but it was not widely required until the mid-1980s.

Comprehensive examination of primary material, comprising full peer-reviewed published papers and/or original company reports, is the norm across Government for the risk assessment of most chemicals. More readily accessible data, such as reviews, key papers and computerised toxicity databases, will be consulted when rapid decisions need to be taken in the case of chemical incidents involving unusual contamination of air, water, soil or food. The evaluation of major hazards for land use planning also relies largely on reviews and readily available sources of information.

The available data are examined in detail to decide whether they are sufficient to describe the toxicological profile of the chemical. Then the critical toxic effects are identified and the relevant studies scrutinised for dose-response relationships. Subsequent treatment of the data depends on whether the critical toxic effect is considered to have a threshold or is considered to be a stochastic effect, that is an effect without a threshold.

7.2.1 Toxic effects with a threshold

For toxic effects with a threshold, it is assumed that there is a level of exposure below which no adverse health effects are likely to occur. Assumption of a threshold for the majority of toxic effects is usual. Exceptions are considered below (Section 7.2.2). The way in which data for such effects are treated is similar across all Government departments and agencies. The assumption of a threshold for the majority of toxic effects derives from theoretical considerations, from known metabolism and mechanistic information, and from empirical observations in animals and man of absence of effects below certain doses. The data are scrutinised to identify critical effects and to see if a dose without effect in the most sensitive species using the most sensitive indicator of toxicity can be defined. In doing so, the shape of any dose-response relationship is taken into consideration. The dose without effect is variously described as a No-Effect Level (NEL), a No-Observed-Effect Level (NOEL) or a No-Observed-Adverse-Effect Level (NOAEL). It should be noted that there is an important distinction between a NOEL and a NOAEL. In some cases effects may be observed that are judged not to be adverse in which case the NOAEL* will be higher than the NOEL. The NEL/NOEL/NOAEL may then be used to set an advisory or legally enforceable standard by dividing it by an uncertainty factor, to derive a daily or weekly intake or exposure level expected to be without effects in humans. Known or predicted intakes or exposures are then compared with the advisory standard to see if they exceed the standard. Alternatively, the ratio of the NEL/NOEL/NOAEL to known or estimated exposures is used to derive the margin of exposure (see Section 6.1) and a scientific judgement is then made as to whether that margin is acceptable. In the assessment of risks from human medicines, the data requirements are such that it is not necessary to use uncertainty factors.

It is important, however, to note that whilst the actual figure derived for an advisory or legal standard may be dependent on the NEL/NOEL/NOAEL from perhaps a single pivotal study that addresses the critical toxic effect, the overall health assessment for any chemical will take into account the whole of the toxicological database. Any resulting action or advice will be based not only on the value of the standard but also on the entire profile for the chemical.

* For veterinary medicines a different definition of NOAEL is used in that the NOAEL is the greatest concentration or amount of a chemical which causes no non-critical effect, (i.e. judged to be adverse but not necessarily of great toxicological significance) such as an effect which indicates exposure to a chemical without overt toxicity. In this case NOAEL is generally lower than the NOEL.

7.2.2 Toxic effects with no threshold

For stochastic effects, differing theoretical views may be held, but the practical outcome is the same. These views have traditionally applied to two related types of toxic effect, mutagenicity and genotoxic carcinogenicity. In one view, it is assumed that there is no threshold because of the mechanism of action. It is assumed that as little as one molecule of a genotoxic chemical could, theoretically, cause a mutation and eventually result in an adverse outcome such as a tumour or an inherited genetic defect. In practice, mutagenicity and carcinogenicity experiments on genotoxic chemicals may indicate an apparent threshold for activity. However, this is not used for risk assessment purposes because it is thought to derive from the inability of experiments with relatively small numbers of animals to reveal low incidence effects at low doses. In another view, it is considered that there is likely to be some threshold at some level of exposure (e.g. because of repair mechanisms) but with current knowledge and current experimental capability it is not possible to identify a threshold with any certainty. Whichever view is held, the notion of threshold is not used in the risk assessment. Instead, risk assessors in the UK follow one of three paths, the path chosen being largely dependent on the perceived options for risk management.

In the case of chemicals to which humans would be deliberately exposed, a chemical demonstrated to be an *in vivo* mutagen or genotoxic carcinogen would not normally be approved or licensed for use. This approach is applied in the regulation of pesticides, veterinary products, additives in animal feed, food additives, cosmetic ingredients, and water treatment chemicals. In the case of certain human medicines that are known or suspected genotoxic carcinogens, use may be permitted if the risk/benefit ratio to the individual patient is considered favourable (e.g. cytotoxic drugs for treatment of malignant disease).

In cases where humans are inadvertently but unavoidably exposed to chemicals, such as certain contaminants in food, water and air, probabilistic risk assessment methods may be used to derive an exposure level below which the risk is regarded as very low (see later). Alternatively, it may be recommended that exposure should be as low as technically achievable or as low as reasonably practicable.

In the case of genotoxic chemicals present in the workplace, a MEL may be set, with the intention that exposure should be kept as low as reasonably practicable below this limit and should not in any case exceed it. This level may still carry some residual risk. In the situations described above, the boundaries between risk assessment recommendations and risk management decisions become very blurred.

Recently some other exposures (i.e. not mutagens or genotoxic carcinogens) have come to be regarded as having no threshold for toxicity, for example air pollution, based on recent time–series studies, and lead.

7.2.3 Toxic effects with a very low threshold

Exposure to allergens presents a slightly different situation. Following initial sensitisation, subsequent exposure to extremely low levels of the chemical can trigger severe, life-threatening reactions. Most allergens are identified from human studies or experience because of a lack of good animal models. Many chemicals are capable of causing allergic reactions but generally do so in only a very small proportion of the population (exceptions are allergies to certain foods and sensitisation to some industrial chemicals). Because it would be impractical to ban all chemicals which ever caused an allergic reaction, it is generally recommended that such chemicals or foods be declared on labels, so that people who are sensitive may avoid exposure. In some cases, measures can be taken to prevent exposure, such as the use of coatings on jewellery containing nickel. In the case of industrial chemicals causing asthma, a MEL for the workplace may be set.

7.3 Diversities in approach within the common framework

Within the broad common framework described above there are diversities in approach between Government departments and agencies, which are instrumental in determining the degree of caution incorporated into the risk assessment. These include the sizes of uncertainty factors applied in the case of toxic effects with a threshold, the use of mathematical approaches for effects with or without a threshold, approaches to the treatment of genotoxic carcinogens, treatment of data gaps and deficiencies, the degree of protection sought in the case of the general population compared with workers, and the degree of conservatism built into ‘worst case’ exposure estimates. These are considered below.

7.3.1 Use of uncertainty factors for toxic effects with a threshold

In order to derive an acceptable intake or exposure level, which can then be used as an advisory or legally enforceable standard, an uncertainty factor is applied to the overall NEL/NOEL/NOAEL derived from animal or human studies. The selection of the size of the uncertainty factor is based on well-known conventions but is intended to be flexible to allow for scientific judgement about the degree of uncertainty involved. Thus, application of different uncertainty factors in different risk assessments does not necessarily imply diversity in approach. However, a sound scientific basis for judgement of uncertainty may be lacking and this provides an opportunity for subjective elements to be influential in the final risk assessment.

The application of a 100-fold safety factor to a NEL/NOEL/NOAEL derived from animal studies was first proposed over 45 years ago in the context of chemicals present in food (Lehman & Fitzhugh, 1954). It was assumed that humans could be susceptible to the same toxic effects as those seen in the animal studies but that, dose for dose, humans in general might be more sensitive than laboratory animals, or exhibit effects which passed unnoticed in animals, and that within the human population there might be individuals who were more sensitive than the average person. These differing sensitivities could derive from differences in the way the chemical was handled in the body (toxicokinetic factors) or differences in target-organ sensitivity (toxicodynamic factors). At the time it was proposed, the figure of 100 was an arbitrary one. Since that time, it has become widely accepted practice to divide this factor into two components (10×10); 10 to take account of inter-species differences and 10 to take account of inter-individual differences (Dourson & Stara, 1983). This too was initially an arbitrary division, but in recent years some scientific support has emerged for the biological validity of these figures and for their further subdivision into toxicokinetic and toxicodynamic components (Renwick, 1991; IPCS, 1994).

Thus, in the case of chemicals to which the general public may be exposed, an uncertainty factor of 100 has been widely used as the default figure for standards derived from animal studies, while a factor of 10 has been widely used as the default figure for standards derived from human studies. The figure of 100 may, however, be increased if risk assessors consider there are grounds for additional uncertainty. The additional uncertainties may be related to limitations in the quality or quantity of the scientific data available for risk assessment or may be related to the perceived severity of the toxic effects observed. For example, if the critical experiment determining the overall NEL/NOEL/NOAEL is deficient in some way, or shows a minimal effect level rather than a no-effect level, or a key study on a particular aspect of toxicity is missing, then an additional factor may be applied so that the overall uncertainty factor is higher than 100. Similarly, if the critical toxic effects determining the NEL/NOEL/NOAEL are serious, irreversible effects, such as birth defects or malignant tumours induced by non-genotoxic carcinogens, an additional uncertainty factor may be employed.

The range of uncertainty factors generally used by Government departments and agencies in the various chemical sectors is shown in Annex 4. The survey conducted by the Risk Assessment and Toxicology Steering Committee indicated an overall similarity in approach to extrapolation from animal studies (use of a factor of 10 for inter-species differences) and extrapolation from human studies (use of a further factor of 10 for inter-individual human differences). However, it is evident from the Risk Assessment and Toxicology Steering Committee survey on approaches in the UK and from knowledge of practices in Europe that in the occupational field the approach to uncertainty factors differs. Such factors are not usually explicitly stated but are implicit in the risk assessments made. More significantly, uncertainty factors in the occupational field may be much smaller (i.e. considerably less than 100) than the factors normally used for estimating acceptable levels of exposure of the general public to chemicals. This approach has been regarded as defensible for several reasons (Fairhurst, 1995)*. It can be expected that some of the more vulnerable members of the population (the very young, the sick, the elderly) do not form part of the exposed population, workplace exposure levels and/or patterns of exposure can be controlled, populations or individuals in a workplace can be protected and/or monitored and they are covered by legal requirements for worker protection. However, increasing knowledge of physiological and biochemical diversity among healthy populations raises the possibility that decisions to accept small margins of exposure for workers may lack a firm scientific basis. The use of low uncertainty factors involves a strong element of judgement in making the decision that the margin between exposure and NEL/NOEL/NOAEL

* See also a 1993 UK Government/Industry Working Group report on risk assessment of existing substances, available from the DETR

is sufficient to cover heterogeneity of susceptibility within a working population.

It is recommended that an agreed Government view and guidance be developed on the size and application of uncertainty factors for inter-species and inter-individual differences, based on the available science and appropriate for the general and the working populations. This would not only facilitate harmonisation of risk assessment practices in the UK but would also assist in ongoing international discussions on this topic.

A number of respondents in the Risk Assessment and Toxicology Steering Committee survey indicated that the uncertainty factors given were default figures and that if relevant data on toxicokinetic or toxicodynamic factors were available the default figures could be refined (usually reduced). The use of toxicokinetic and toxicodynamic data to refine risk assessment has been discussed in recent years (Renwick, 1991; IPCS, 1994). However, sufficient relevant data are frequently not available for specific chemicals, particularly on toxicodynamics.

It is recommended that there is a need for further research (both generic and specific) in the area of comparative toxicokinetics and toxicodynamics, to provide better information for the selection of uncertainty factors.

The use of physiologically-based pharmacokinetic (PBPK) modelling as a tool to make better predictions of comparative target tissue doses in experimental species and man has also been advocated. The application of this technique was considered at one of the workshops run by Risk Assessment and Toxicology Steering Committee (Risk Assessment and Toxicology Steering Committee, 1999). PBPK modelling is by no means a new technique in the pharmacological sciences. However, it has been rarely used in toxicological risk assessment in the UK due to lack of relevant data (requiring much more toxicokinetic information than is normally generated) and consequent lack of expertise in applying the technique. Its incorporation into the risk assessment process, particularly in the case of commercially important chemicals for which there is some concern about the adequacy of the margin of safety for humans, would reduce uncertainties and help refine uncertainty factors.

The recommendations from the PBPK workshop on research and development needs and regulatory application of PBPK modelling (Risk Assessment and Toxicology Steering Committee, 1999) should be implemented; they are also pertinent to the recommendation concerning toxicokinetics and toxicodynamics made above.

Within the UK there are some differences in dealing with poorer quality or quantity of data and with severity of the critical toxic effect; the size of additional uncertainty factors applied varies between 2 and 10. Application of further factors of 10 to the conventional 100-fold factor can result in very high overall factors of 1000 or more and derived standards that may be difficult to implement in practice. The ways in which these additional uncertainty factors are used may warrant further examination. It could be argued, for example, that using an additional 10-fold factor for severity of effect may be excessively cautious when dealing with threshold effects. Its use could be taken to imply that there is more uncertainty about a threshold for a severe effect than there is about a threshold for a less severe effect, a generalisation that is clearly not sustainable. However, the most likely explanation for its use being favoured by risk assessors is that an extra margin should be allowed in case a threshold for a severe, irreversible effect were to be incorrectly identified at too high a level, because the consequences of such an error might be serious. Here again the line between risk assessment and risk management has become blurred.

It could equally be argued that if there is confidence from the data that the mechanism of action and a threshold have been clearly established, then the application of an additional uncertainty factor for severity of effect may be unwarranted. This situation may arise, for example, when dealing with non-genotoxic carcinogens for which the mechanism of action has been established and the critical NEL/NOEL/NOAEL is based, not on the occurrence of tumours, but on preceding biochemical and pathological changes. Teratogenicity also tends to be viewed in the UK and the rest of Europe as a severe effect requiring the application of an additional uncertainty factor, but this has not been the case in USA, where the conventional 100-fold factor overall is regarded by most regulatory authorities as sufficient. It has also been pointed out, in a review of international practices, that standards have sometimes been set, inappropriately, by applying an uncertainty factor for a severe effect seen in one of the studies to a NEL/NOEL/NOAEL for an unrelated, less severe toxicity (Renwick, 1995).

It is recommended that a review of the use of additional uncertainty factors for severity of effect be undertaken with a view to adopting a common approach across Government and internationally.

The additional uncertainty factors used to take account of deficiencies in the quality and quantity of data are less amenable to harmonisation. The nature and the extent of the deficiency both influence the choice of the size of uncertainty factor, and factors up to 10 have been judged to be required. In decisions to set a temporary or provisional standard, for example, it has been customary to use an additional 2-fold uncertainty factor, as uncertainties are generally small. If the data gaps are large or pivotal studies deficient, then marketing approval or licensing may be refused. However, in situations such as risk assessments for environmental pollutants or chemical accidents, lack of data is commonplace and the use of high additional uncertainty factors to cover for possible, as yet undiscovered, effects may be necessary.

7.3.2 Use of mathematical methods for toxic effects with a threshold

There are exceptions to the general use in the UK of the NEL/NOEL/NOAEL/uncertainty factor approach for toxic effects with a threshold. One is in the estimation of risks from major hazards for land use planning. Here, the risk characterisation is expressed quantitatively as the risk of the population being exposed to a dangerous toxic load, that is a dose which will result in a defined level of a specific effect, such as percent lethality to a population. Mathematical modelling (probit analysis of the best available data set) is used, but only as one component of the risk characterisation (Fairhurst & Turner, 1993).

The more general application of mathematical methods to the toxicological aspects of risk assessment for effects with a threshold is an area of interest. Use of the mathematically derived 'benchmark dose' (Crump, 1984), for example, instead of no-effect and low-effect levels, is now being used or considered in some regulatory agencies in the USA. A benchmark dose is a measure corresponding to a small increase in a defined effect in a predetermined proportion of the test population (e.g. liver toxicity in 5% of the animals tested). Mathematically, it is a statistical lower confidence limit on a dose corresponding to a small increase in an adverse effect over the background level for that effect. It is regarded by some as offering advantages because, unlike the NEL/NOEL/NOAEL itself, it makes use of the shape of the dose-response curve and sample size and it is free from the arbitrary influence of dose selection (Crump, 1984) However, there are also limitations and drawbacks to its use. For example, from many existing studies it is not possible to define the shape of the dose-response curve because there are too few dose groups and/or small numbers of animals per group. Similarly, for some end-points such as teratogenicity, what may be regarded as a biologically significant effect level may be below 5–10%. It follows that the benchmark dose approach may require the use of more animals and an emphasis on demonstration of toxic effects in several of the dose groups. This would significantly conflict with animal welfare considerations. The calculation of benchmark doses also requires statistical expertise, which the NEL/NOEL/NOAEL/uncertainty factor approach does not. Overall, it remains to be seen whether the potentially increased precision of the benchmark dose approach offers significant advantages compared with the more user-friendly NEL/NOEL/NOAEL/uncertainty factor approach.

The application of other types of mathematical approach is also now being viewed with more interest. The application of probabilistic methods, such as Monte Carlo analysis, which is widely used in food chemical intake estimation (Douglas & Tennant, 1997), and Bayesian approaches (Baird *et al.*, 1996, see below), to toxicological aspects of risk assessment offers the possibility of predicting levels of possible harm above threshold doses.

It is recommended that the application of mathematical approaches to risk assessment of chemicals with thresholds for toxicity be further explored, both for modelling uncertainties about effect and no-effect levels and for modelling the extent of effects at toxic dose levels.

7.3.3 Treatment of genotoxic carcinogens

Mention has already been made earlier of three possible risk management approaches that may be used by Government departments and agencies when dealing with genotoxic carcinogens other than human medicines. These may be summarised as banning, reducing exposure below a level with an estimated, low but finite risk, or reducing exposure to a level as low as technically possible or reasonably practicable. These diverse approaches reflect not only the differing practical options, depending on the chemical situation under consideration, but also differences in philosophy of approach to genotoxic carcinogens, in which societal, commercial, financial and scientific considerations have become intertwined.

The differences in philosophy of approach to genotoxic carcinogens, which involve scientific considerations, are whether or not probabilistic methods are adopted for estimating risks and, if they are, what method is selected for use. Probabilistic methods, such as quantitative risk assessment (QRA) utilise animal carcinogenicity

bioassays, extrapolating from the carcinogenic effects observed at the doses tested in the bioassay to derive an estimate of the carcinogenic risk at doses below the experimental range used (Lovell & Thomas, 1997). This is then directly 'read across' as a risk prediction for man. Various mathematical models have been developed for QRA which vary in the degree of conservatism built into their assumptions (COC, 1991; Moolenar, 1994; Lovell & Thomas, 1997). One of the most conservative models used in QRA is the linearised, multistage model, using upper bound estimates, which has been favoured in the past by the US Environmental Protection Agency (EPA). The assumptions used in mathematical models for QRA are, in effect, equivalent to the uncertainty factors used in risk assessment for threshold effects. Thus, while use of a QRA method enables a precise figure to be given for the lifetime risk of developing a tumour at a given exposure level, the generation of a precise figure should not be mistaken for accuracy. QRA methods have been much criticised (Lovell & Thomas, 1996) and the estimate obtained for the lifetime risk of a tumour at low dose levels is critically dependent on the model used. Estimates based on the same experimental data set can vary over several orders of magnitude, depending on the model selected. The most conservative models are virtually insensitive to the actual experimental data and should be viewed only as a risk management solution, not a risk assessment technique.

As a result of these limitations and the failure of many of the mathematical models to take into account the complexities of the biological events leading to carcinogenesis, the Department of Health's Committee on Carcinogenicity does not support the routine use of QRA for chemical carcinogens (COC, 1991). Consequently, QRA is rarely, if ever, carried out by UK regulatory agencies. It is also notable that the US EPA has recently proposed using a different procedure, analogous to the benchmark dose approach, as its default method for carcinogens, instead of the linearised, multistage model (US EPA, 1996). Estimates of lifetime cancer risk derived by QRA in other countries may occasionally be quoted or used in the UK. This is the case, for example, for drinking water contaminants, where WHO guideline values for drinking water contaminants are followed. WHO guideline values for genotoxic carcinogens in drinking water are derived using the linearised multistage model for QRA to estimate a concentration giving rise to a less than 1 in 10^{-5} lifetime risk of cancer.

In most situations in the UK, a qualitative evaluation of carcinogenic risk is carried out, on a case-by-case basis, taking account of the weight of all the available evidence, including human evidence in the few cases where it is available (Lovell & Thomas, 1997). Such an approach has the advantage of going no further than the available science allows, but at the same time involves a considerable element of scientific judgement and is essentially an heuristic approach. It assumes that the weight of a particular piece of evidence can be judged in conjunction with other supporting evidence and against conflicting evidence, on the basis of past experience. It raises the question of whether it is possible to achieve consistent weighting of evidence among different risk assessors. An approach for weighting evidence to set priorities and standards for carcinogens has been proposed and has been used in the UK for food chemicals and air pollutants (Maynard *et al.*, 1995; McDonald *et al.*, 1996). A further consequence of the use of the weight-of-evidence approach is that once a chemical has been deemed a genotoxic carcinogen, it is not possible for the risk assessors to offer any estimate of the likelihood of cancer occurring at any defined exposure level, other than a vague, descriptive estimate such as 'small' or 'remote'.

The possibility of using other approaches could be considered. The Bayesian approach, for example, acknowledges that, in a system involving a considerable element of judgement, different experts will have different prior beliefs and that incorporating these in a formalised way into risk assessment is just as valid as conventional statistical techniques for estimating probabilities. In a Bayesian approach, simulations are run with different weightings, enabling the various elements of prior knowledge, assumptions and judgement to be formalised and made explicit in any final risk assessment (Lilford & Braunholz, 1996).

It is recommended that further consideration be given to ways of maintaining consistency in the weight-of-evidence approach to risk assessment of carcinogens.

The use of mathematical methods for evaluating the influence of judgement on risk assessment outcomes should also be explored, both for genotoxic effects (chemicals without a threshold for toxicity) and for chemicals with thresholds for toxicity.

7.3.4 Conservatism in exposure estimates

Most human exposure estimates require the use of default assumptions about the human body. They include, for example, notional figures for body weight and surface area, amounts of food and water consumed daily, respiratory rates and tidal

volumes, amounts of exposed skin, amounts deposited onto exposed skin, and systemic absorption of chemicals via different routes. Many of these assumptions need to be elaborated for various human subpopulations, such as different age groups, degrees of activity and occupation. Differing default assumptions for the same parameter may be used by Government departments and agencies and some are more conservative than others. In the occupational field, for example, various operator exposure models with differing assumptions and therefore differing degrees of conservatism can be used. Efforts are being made internationally to establish guidance values for default assumptions (IPCS, 1994).

It is recommended that Government departments and agencies consider and compare the default assumptions about humans (concerning anatomy, physiology, etc.) that are used for exposure estimates. Where appropriate, those that can be utilised in common across Government should be standardised and used to provide information for international harmonisation discussions. Adoption of internationally agreed default assumptions should be considered where they exist.

The use of 'best' and 'worst case' estimates of exposure is discussed earlier. It is probably the situation of 'worst case' estimates which gives rise to the most controversy concerning the degree of caution introduced by the assumptions made during their estimation. Just as uncertainty factors in toxicological assessments may introduce an unwarranted level of caution because of their multiplicative nature, so uncertainties in exposure assessments may be compounded to a level where the exposure scenario is very unrealistic. A hypothetical example might be exposure of a child to dioxins, in which it is assumed that the child lives downwind from a municipal incinerator, eats a spoonful of dirt a day, eats fish from a local pond, is a 95th percentile consumer of fish, and eats food grown in the garden. However, the nature and requirements for exposure estimates in different chemical sectors and different ambient media are so different that a divergence in approach to 'worst case' estimates is to be expected. There is nevertheless a case for consideration of what constitutes realistic or reasonable 'worst case' situations.

It is recommended that custom and practice in deriving worst case estimations for intake and exposure across Government should be compared and discussed. In particular, comparison of key assumptions used by different departments and agencies in worst case estimates for exposure of the general public and, similarly, comparison of key assumptions used in worst case estimates for exposure of workers should be addressed.

There is also the difficult issue of what proportion of the exposed population should be considered. For example, for food chemicals, MAFF uses the 97.5th percentile figure for intake of a chemical as a 'worst case', theoretically leaving 2.5% of the population outside of the risk assessment, whereas the US Food and Drug Administration uses the 95th percentile figure. Other European countries may use different percentiles. When exposure of large populations is being considered, choice of a relatively low percentile figure for 'worst case' estimates can potentially leave many thousands of individuals outside the risk assessment. Strictly speaking, this is a risk management decision involving issues other than scientific ones. However, in some chemical sectors such decisions have already been built into the risk assessment process. Subsequent to the risk assessment, risk managers may decide to build in further precautions, not realising that they are already dealing with extreme and, on occasions, highly unlikely scenarios.

It is recommended that Government departments and agencies review those areas in the risk assessment process in which risk management and policy decisions can influence the outcome of the risk assessment process and that these should be identified and discussed. All parties involved in risk assessment, risk management and risk communication should be clear about which elements are science-based and which are based on societal or economic considerations.

8 Application of new approaches to risk assessment

The preceding description of the various approaches used within Government for risk assessment of human health effects of chemicals reflects the methods used currently for the majority of risk assessments. However, the evaluation of other approaches and refinements that might improve risk assessment is ongoing in several Government departments and agencies. For example, the application of methodology such as PBPK modelling of dose is being tried, new exposure models are being assessed, and applied research is being commissioned on new mathematical approaches.

Another recent development is the increasing influence of time-series epidemiological analyses on assessing and quantifying the public health effects of air pollution. Such studies frequently indicate weak associations between daily variations in normal outdoor air pollution levels and hospital admissions for acute respiratory or cardiovascular conditions, and daily mortality figures. As these results present considerable problems of interpretation, and conflict with the expected toxicity of the corresponding very small doses of common air pollutants, and as there are major implications for standard-setting and risk management in this field, there is a clear need to give further consideration to how such studies should be used in risk assessment.

Exposure to mixtures of chemicals is a fact of everyday life and public concern is expressed from time to time about possible additive and synergistic effects of exposure to combinations of chemicals. While most risk assessments are currently carried out chemical by chemical, researchers and regulators are beginning to address this issue actively, as illustrated by the recent announcement of a UK review of combined exposures to organophosphate and carbamate pesticides and the soliciting of views on approaches to mixtures in a Government consultation paper (DETR, 1998). Any widespread requirement to test mixtures would inevitably lead to a considerable increase in animal testing.

9 Publication of risk assessments

Much of the information on chemicals which are subject to regulatory approval is submitted to Government 'in confidence'. This imposes a legally binding restriction on what may be published. This has resulted in a lack of transparency about how risk assessments have been conducted in some chemical sectors in the UK, EU and elsewhere. Often, brief summaries of the scientific data and the conclusions of individual risk assessments have been published or made publicly available, but the detailed scientific information underpinning the assessments has not. This has contributed to lack of understanding and trust in Government risk assessments, affected the public's perception of risks and hampered effective risk communication.

Strenuous efforts have been made in recent years in the UK and the EU to remedy this situation. Government departments and agencies and the European Commission do now publish some of the accounts of the scientific data contributing to some individual risk assessments. This is done in order to allow others not involved in the risk assessment to be aware of the range and results of the studies available and to follow the line of reasoning that has been taken by the risk assessors. The availability of published data relating to UK and EU risk assessments in the different chemical sectors is given in Annex 2. It is recognised that transparency of information on chemicals is an important and sensitive issue. This is currently being further addressed in a review of the Government's strategy on chemicals and the environment (DETR, 1998). The Government is also reviewing the requirements of the Medicines Act in relation to its Freedom of Information policy.

Further ways of enhancing transparency could be considered. For example, whilst many entire dossiers on chemicals are submitted in confidence, in practice, submitters of data may regard only certain parts of information as strictly confidential. This raises the question of whether it may be possible to publish more and fuller risk assessments than is done at present.

It is recommended that Government departments and agencies should continue to publish explanations of their risk assessments, including as much as possible of the underlying scientific information as can be released (within legal and commercial constraints) and a discussion of any inherent uncertainties in the data. Those elements of the risk assessment which have clear scientific basis should be distinguished from those which are influenced by risk management considerations.

10 Conclusions and recommendations

There is wide agreement across UK Government departments and agencies about the philosophies and methodologies used in chemical risk assessment; there is also much commonality with approaches used elsewhere in the EU, not only in areas where risk assessment has been harmonised but also in areas where regulatory harmonisation is absent or not yet fully implemented.

Nevertheless there are some diversities in approaches to risk assessment within the UK, probably as a consequence of risk assessment schemes being developed for different purposes and for carrying out different parts of the risk assessment–risk management process. The key aspects of risk assessment which give rise to diversities in approach are the methods used to cope with the difficult areas of uncertainty, variability and lack of knowledge. Uncertainty encompasses both the uncertainties of toxicological extrapolation from animals or small groups of humans to wider populations and the uncertainties inherent in most exposure estimates. Variability encompasses both the heterogeneity of the human population and variability in the range of exposures. Lack of knowledge includes the significant gaps there may be in data relating to hazard identification and characterisation, lack of information about mechanisms of toxicity, and unanticipated toxicity or exposure.

Based on an examination of the approaches to risk assessment presented in this report the Risk Assessment and Toxicology Steering Committee recommends procedural changes and/or further research to facilitate:

- harmonisation of
  - data requirements,
  - practice in toxicological assessments, and
  - practice in intake and exposure estimates;
- development of improved methods and new approaches for risk assessment to
  - reduce uncertainty in toxicological assessment,
  - take account of chemicals with multiple uses or which are ubiquitous pollutants, and
  - provide a rationale for 'worst case' estimates of intake and exposure;
- improved transparency in the risk assessment process by
  - evaluation of the role of risk management in risk assessment, and
  - encouraging publication of risk assessments.

The following sections expand on each of these issues and suggest specific actions.

Harmonisation

Data requirements

Chemical sectors such as pesticides, biocides, food additives and animal feed additives would benefit from global harmonisation of toxicological testing requirements. The emphasis should be on harmonisation of the minimum data needed for meaningful risk assessment. Any such initiatives would need to be pursued at and beyond the EU level.

Practice in toxicological assessments

Guidance should be developed on the size and application of uncertainty factors for inter-species, and inter-individual differences and severity of effect, based on the available science and appropriate for the general and working populations, with a view to adopting common approaches across Government in the UK and assisting in ongoing international discussions.

Further consideration should be given to ways of maintaining consistency in the weight-of-evidence approach to risk assessment of carcinogens.

Practice in intake and exposure estimates

Experience with modelling intake and exposure from point and diffuse sources should be shared across Government departments and agencies, with a view to assessing the validity and utility of different exposure models. Harmonisation of approaches both nationally and internationally would be a desirable goal.

Government departments and agencies involved in monitoring and sampling programmes could benefit from pooling experience to solve problems they have in common, taking into account the requirements of existing EU statutory monitoring schemes.

Default assumptions concerning human anatomy, physiology, and behaviour used for exposure estimates should be compared and discussed. Where appropriate, those that can be utilised in common across Government should be standardised and used to provide information for international harmonisation discussions. Adoption of internationally agreed default assumptions should be considered where they exist.

Development of improved methods and new approaches for risk assessment

Reducing uncertainty in toxicological assessment

The value of obtaining more toxicokinetic, toxicodynamic and mechanistic information on specific chemicals should be considered.

Further generic research should also be encouraged in the area of comparative toxicokinetics and toxicodynamics to provide better information for the selection of uncertainty factors.

The recommendations from the Risk Assessment and Toxicology Steering Committee workshop on research and development needs and regulatory application of PBPK modelling should be implemented.

Existing knowledge about human variability and the sensitivities of subgroups of the human population should be made more widely available and further research in this area should be encouraged. To this end, it would be desirable to seek ways of making available anonymised analyses of confidential data on human medicines that are relevant to human variability and comparability of responses between animals and man.

The use and application of mathematical (probabilistic) approaches should be more widely explored and evaluated in the assessment of chemicals with thresholds for toxicity, both for modelling uncertainties about effect and no-effect levels and for modelling the extent of effects at toxic dose levels.

Mathematical models should also be used, in assessment of chemicals with or without thresholds for toxicity, to evaluate the influence of varying assumptions and judgements on risk assessment outcomes.

Accounting for chemicals with multiple uses, and ubiquitous pollutants

Clear procedures should be set up within Government for conducting overall risk assessments for total human exposure to any single chemical which has multiple uses and/or is an ubiquitous environmental pollutant.

Rationale for worst case estimates of intake and exposure

Custom and practice in deriving worst case estimates for intake and exposure should be compared and discussed, both for exposure of the general public and for exposure of workers. Improvement of the statistical bases for worst case estimates and assumptions would be a desirable goal, both nationally and internationally.

Improved transparency in the risk assessment process

The role of risk management in risk assessment

The close interface between risk assessment and risk management should be more explicitly acknowledged. Those areas in the risk assessment process in which risk management policy and decisions can influence the outcome of the risk assessment process should be clearly identified and discussed. All parties involved in risk assessment, risk management and risk communication should be clear about which elements are science-based and which are based on ethical, social, technological and/or economic considerations.

Publication of risk assessments

Government departments and agencies publishing explanations of their risk assessments should consider ways in which transparency in presentation of the thinking behind risk assessments may be enhanced. This could include releasing more of the

underlying scientific information (within any essential legal and commercial constraints), presenting discussion of any inherent uncertainties in the data and distinguishing between those elements of the risk assessment that have a scientific basis and those that are influenced by wider considerations.

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ANNEX 1: List of organisational areas for which questionnaires were completed or responses provided

Department of the Environment, Transport and the Regions

Air quality

Water

Waste

Contaminated land

Environment Agency

Air Quality

Water quality including action limits for discharges

Land quality

Waste

Health and Safety Executive

New chemicals

Existing substances

Occupational exposure limits

Non-agricultural pesticides (biocides)

Major hazards (land use planning)

Department of Health

Food chemicals, novel foods and processes

Consumer products

Policy advice

Medicines Control Agency

Human medicines

Ministry of Agriculture, Fisheries and Food

Food Additives

Novel foods and processes

Food contact materials

Chemical contaminants in food

Additives in animal feeds

Technological animal feed additives

Pesticides Safety Directorate

Plant protection products

Veterinary Medicines Directorate

Veterinary medicines

Zootechnical animal feed additives

ANNEX 2: Public availability of scientific information on risk assessment and approvals of individual chemicals

Chemical sector	Publication	Source	Contents
Food additives Contaminants Novel foods & processes	Annual Reports COT, COM, COC, ACNFP	DH	Explanations of advice given on individual chemicals/foods and on generic issues
	Reports of Scientific Committee on Food	CEC	Opinions on individual chemicals/foods, including ADIs/TDIs, and advice on generic issues
	Reports of the Joint FAO/WHO Expert Committee on Food Additives (JECFA)	WHO	Summary reports of opinions on individual food additives and contaminants, including ADIs/TDIs/PTWIs
	Toxicological Monographs of JECFA	IPCS	Critical toxicological reviews and evaluations of food additives and contaminants
Pesticides	The Pesticides Register	TSO	Monthly listing of UK approvals
	MAFF/HSE Pesticides	TSO	Annually updated listing of all pesticides products approved under COPR 1986
	Evaluations	PSD	Critical evaluations including physicochemistry, toxicology, residues, consumer exposure, occupational exposure, ADIs, AOELs
	Annual Reports ACP	TSO	Explanations of approval decisions on individual pesticides and advice on generic issues
	Annual Reports WPPR	MAFF	Results of UK monitoring programme for pesticide residues in food
	Reports of Scientific Committee on Plants	CEC	Opinions on individual pesticides and advice on generic issues
	Reports of the JMPR Part I – Residues	FAO	Critical reviews of residues data on individual pesticides and MRLs
	Reports of the JMPR Part II – Toxicology	WHO	Critical toxicological reviews and evaluations on individual pesticides and ADIs
	Inventory of IPCS and other WHO Pesticides Evaluations	IPCS	Annually updated inventory of summary evaluations on pesticides by the JMPR/JMP, including ADIs
Veterinary products	Summary Reports of the CVMP	EMEA	Opinions on veterinary medicines, advice on generic issues, explanations of decisions on individual active ingredients
	Annual Report VPC	TSO	Approval decisions on individual veterinary products and advice on generic issues
	Reports of the Scientific Committee on Veterinary Measures Relating to Public Health	CEC	Opinions on individual veterinary products and advice on generic issues
	Reports of the Joint FAO/ WHO Expert Committee on Food Additives (JECFA)	WHO	Summary reports of opinions on individual veterinary residues in food, including ADIs
	Toxicological Monographs of JECFA	IPCS	Critical toxicological reviews of veterinary residues in food

Chemical sector	Publication	Source	Contents
Workplace chemicals	Toxicity Reviews/Criteria Documents/Risk Assessment Documents	HSE	Critical toxicological reviews and evaluations of individual substances
	Occupational Exposure Limits EH40	HSE	Annually updated listing of all OESs and MELs
	Summary Criteria for Occupational Exposure Limits EH64	HSE	Summary of data and reasoning used to set OESs and MELs
Existing substances/ Environmental chemicals	Environmental Health Criteria	IPCS	Critical reviews and evaluations of physico-chemistry, human effects, environmental effects and exposure data on widely used chemicals
	Concise International Chemical Assessments Documents	IPCS	Summary reviews on exposure and health effects data for individual chemicals
	Substance Information Data Sets	OECD	Summary reviews on exposure and health effects data for individual chemicals
Cosmetics	Reports of the Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers	CEC	Opinions on individual cosmetic ingredients/ products and on consumer products
Human medicines	Annual Reports CSM	MCA	Principal issues of drug safety
	Summary Reports of the CPMP	EMEA	Opinions on human medicines and scientific advice
Drinking water	Guildelines for Drinking Water Quality	IPCS	Health criteria and other supporting information for WHO guideline values
	Annual Report COT, COM, COC	DH	Explanations of advice given on individual chemicals
Air pollutants	Air Quality Guidelines	IPCS/ WHO	Health criteria and other supporting information for WHO guideline values
	Reports of UK EPAQS	TSO	Sources of exposure, exposure, and health data, supporting EPAQS recommendations for UK air quality standards
	Reports of COMEAP MAAPE	TSO	Health evaluations of air pollution episodes, specific air pollutants and current issues

Abbreviations used in Annex 2

ACNFP, Advisory Committee on Novel Foods & Processes; ACP, Advisory Committee on Pesticides; ADI, Acceptable Daily Intake; AQS, Air Quality Standard; CEC, Commission of the European Communities; COC, Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment; COM, Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment; COMEAP, Committee on Medical Aspects of Air Pollution; COPR, Control of Pesticides Regulations; COT, Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment; CPMP, Committee on Proprietary Medicinal Products; CSM, Committee on Safety of Medicines; CVMP, Committee on Veterinary Medicinal Products; DH, Department of Health; EMEA, European Medicines Evaluation Agency; EPAQS, Expert Panel on Air Quality Standards; FAO, Food and Agriculture Organisation of the United Nations; HMSO, Her Majesty's Stationery Office (now The Stationery Office); HSE, Health and Safety Executive; IPCS, International Programme on Chemical Safety; JECFA, Joint FAO/WHO Expert Committee on Food Additives; JMPR, Joint Meeting on Pesticide Residues (now JMP); MAAPE, Medical Aspects of Air Pollution Episodes; MAFF, Ministry of Agriculture, Fisheries and Food; MCA, Medicines Control Agency; MEL, Maximum Exposure Limit; MRL, Maximum Residue Limit; OECD, Organization for Economic Co-operation and Development; OES, Occupational Exposure Standard; PSD, Pesticides Safety Directorate; PTWI, Provisional Tolerable Weekly Intake; TDI, Tolerable Daily Intake; TSO, The Stationery Office; VPC, Veterinary Products Committee; WHO, World Health Organisation; WPPR, Working Party on Pesticide Residues

ANNEX 3: UK Government advisory committees involved in chemical risk assessment

Department of the Environment, Transport and the Regions

Expert Panel on Air Quality Standards (EPAQS)

Health and Safety Executive

Health and Safety Commission's Advisory Committee on Toxic Substances (ACTS) and Working Group on the Assessment of Toxic Chemicals (WATCH)

Department of Health

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT)

Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM)

Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC)

Advisory Committee on Novel Foods and Processes (ACNFP) *DH joint lead with MAFF*

Committee on Medical Effects of Air Pollutants (COMEAP)

Advisory Group on Medical Aspects of Air Pollution Episodes (MAAPE)

Medicines Control Agency

Committee on Safety of Medicines (CSM)

Medicines Commission

Ministry of Agriculture, Fisheries and Food

Food Advisory Committee (FAC)

Interdepartmental Committee on Animal Feeding stuffs (IDCAFS)

Advisory Committee on Novel Foods and Processes (ACNFP) *MAFF joint lead with DH*

Pesticides Safety Directorate

Advisory Committee on Pesticides (ACP)

Inter-Departmental Secretariat of the ACP (IDS)

Veterinary Medicines Directorate

Veterinary Products Committee (VPC)

ANNEX 4: Size of uncertainty factors used in risk assessment

Chemical sector	Animal studies to human	Human studies to human	Quality or quantity of data	Severity of effect
Food additives	100	10	2–10	10
Food contaminants	100	10	2–10	10
Agricultural pesticides	100	10	2–10	2–10
Veterinary products	100	10	2 or 5	2–10
Non-agricultural pesticides[a]	100	10	n.s.	5–10
Industrial chemicals[a]	n.s.	n.s.	n.s.	n.s.
Consumer products	100	10	2 or more	2 or more
Drinking water	100	10	10	10
Air pollutants				
Animal data only	100	10	10	10
Air quality standards[b]	n.a.	10×10	n.a.	n.a.
EAL	n.a.	100[c]	n.a.	500[c]
Human medicines	n.a.	n.a.	n.a.	n.a.
Novel foods	n.a.	n.a.	n.a.	n.a.

Abbreviations used in Annex 4

n.s., not explicitly stated; n.a., not applicable; EAL, environmental assessment levels; OES, occupational exposure standard

[a] Smaller factors accepted for workers/operators/trained professionals than for consumers or general public

[b] This example is illustrative only and was applied in the case of benzene. A factor of 10 applied to OES to extrapolate from healthy worker to sensitive individuals in general population, further factor of 10 applied to extrapolate from workplace exposure to lifetime exposure. Other air quality standards may be derived using different methods.

[c] EAL derived by applying 100-fold factor to OES or 500-fold factor to MEL

ANNEX 5: Glossary

Acceptable daily intake (ADI) Amount of a food additive or pesticide expressed on a bodyweight basis which can be ingested daily over a lifetime without appreciable risk to health.

Air quality standard (AQS) The concentration of a pollutant in the atmosphere, determined by an assessment of health effects, which can be broadly taken to achieve a certain level of environmental quality.

Carcinogenicity The ability to produce tumours, which may be benign or malignant.

Chronic toxicity The ability to produce an adverse effect which persists over a long period of time, whether or not it occurs immediately upon exposure to a chemical or is delayed, or an effect which is only induced by prolonged exposure to a chemical.

Competent authority The national body or government department with the responsibility for receiving and evaluating notifications or requests for approval to market or use a chemical or product.

Critical effect The adverse effect judged to be the most important for setting an acceptable human intake or exposure. It is usually the most sensitive adverse effect, i.e. that with the lowest effect level, or sometimes a more severe effect, not necessarily having the lowest effect level.

Developmental toxicity The ability to produce an adverse effect in embryo, fetus or immature organism, which is induced and/or manifest either prenatally or postnatally before sexual maturity.

Dose-response assessment Determination of the relationship between the magnitude of the dose or level of exposure to a chemical and the incidence or severity of the associated adverse effect.

Endocrine toxicity The ability to produce an adverse effect on the functioning of the endocrine system.

Exposure assessment The measured, estimated or predicted intake/exposure to a chemical, in terms of its magnitude, duration and frequency, for the general population, for different subgroups of the population, or for individuals.

Genotoxicity A broad term describing the ability to produce damage to the genetic material (DNA) of cells or organisms.

Genotoxic carcinogen A chemical which induces tumours via a mechanism involving direct damage to DNA.

Good laboratory practice (GLP) Principles incorporated into national legislation concerned with the organisational processes and the conditions under which laboratory studies are planned, performed, monitored, recorded and reported.

Hazard identification The identification, from animal and human studies, *in vitro* studies and structure-activity relationships, of adverse health effects associated with exposure to a chemical.

Hazard characterisation The quantitative (potency) evaluation of any adverse effects observed, usually by dose-response assessment, and the identification of mechanisms of action and of species differences in response.

Immunotoxicity The ability to produce an adverse effect on the functioning of organs and cells involved in immune competence.

Maximum exposure limit (MEL) A maximum airborne concentration for the workplace, averaged over a reference period, which may be set for chemicals that cause serious effects, and which should not be exceeded.

Maximum residue limit for pesticides (MRL) The maximum concentration of a pesticide residue permitted to be present in food commodities or in animal feeds. The value is established from data obtained by the use of pesticides according to Good Agricultural Practice. It is not based on health considerations.

Maximum residue limit for veterinary medicines (MRL) The maximum concentration of a veterinary medicinal residue permitted to be present in the tissues (muscle, liver, kidney, skin/fat) or products (milk, eggs, honey) of food-producing animals. The value is based on health considerations which ensure that summed intakes from all sources will be below the ADI.

Mutagenicity The ability to produce a permanent, heritable change in the amount or structure of the genetic material of cells or organisms.

Negligible risk The probability that any adverse effects occurring can reasonably be described as very small or the effects as trivial.

Neurotoxicity The ability to produce an adverse effect in the central or peripheral nervous system.

No-effect Level (NEL), No-observed effect level (NOEL), No-observed-adverse-effect level (NOAEL) The greatest concentration or amount of a chemical which causes no toxic effect.

Non-genotoxic carcinogen A chemical which induces tumours via a mechanism which does not involve direct damage to DNA.

Occupational exposure limit (OEL) OELs comprise occupational exposure standards and maximum exposure levels.

Occupational exposure standard (OES) An occupational exposure level which is considered to be without any risk to health, based on current knowledge.

Physiologically-based pharmacokinetics (PBPK) Modelling the dose or degree of exposure to a chemical at a target tissue, cell or receptor, by integration of pharmacokinetic data with anatomical, physiological and biochemical data.

Pharmacokinetics A description of the fate of chemicals in the body, including the time course of absorption, distribution, metabolism and excretion.

Reasonable worst case A term referring broadly to the maximum possible exposure to a chemical which could occur under reasonably foreseeable conditions of use.

Reproductive toxicity The ability to produce an adverse effect on any aspect of reproductive capacity, function or outcome. It includes effects on the embryo, fetus, neonate and prepubertal organism and on adult reproductive and neuroendocrine systems.

Risk The probability of an adverse effect arising from a specified exposure to a given hazard.

Risk assessment The evaluation of the potential for adverse health effects in humans from exposure to toxic chemicals.

Risk characterisation The integration of hazard identification, hazard characterisation, and human intake/exposure assessment in order to assess the probability of occurrence and severity of any risk to human health.

Risk communication The interactive exchange of information and opinions concerning risk between risk assessors, risk managers, the public and other interested parties.

Risk management The process of evaluating alternative options and the actions taken to reduce potential risks, in the light of an adverse risk assessment.

Safety factor (see uncertainty factor)

Stochastic An effect which is random and for which there is, in theory, no threshold of dose below which the effect will not appear. The chance of the effect happening increases with increasing dose.

Structure-activity relationship The qualitative association between the molecular structure or the physicochemical properties of a chemical and its biological properties, including toxicity.

Teratogenicity The ability to produce a structural malformation or defect in an embryo or fetus.

Threshold The lowest dose or exposure level which will produce a toxic effect and below which no toxicity is observed.

Tolerable daily intake (TDI) Amount of a chemical contaminant expressed on a bodyweight basis which can be ingested daily over a lifetime without appreciable risk.

Toxicity The ability to cause injury or an adverse effect in a living organism.

Toxicokinetics See pharmacokinetics

Uncertainty factor A numerical factor applied to the no-effect level to derive an exposure level considered to be without appreciable risk to health (the NEL is divided by the uncertainty factor). The magnitude of the uncertainty factor depends on the nature of the toxicity observed, the quality of the toxicological data available, and whether the effects were observed in humans or animals.

Worst case A term referring broadly to the maximum possible exposure to a chemical which could conceivably occur.

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Risk Assessment and Toxicology Steering Committee publications

cr 1 Developing New Approaches to Assessing Risk to Human Health from Chemicals

cr 2 Risk Assessment Approaches used by UK Government for Evaluating Human Health Effects of Chemicals

cr 3 Risk Assessment Strategies in Relation to Population Subgroups

cr 4 Physiologically-Based Pharmacokinetic Modelling: A Potential Tool for Use in Risk Assessment

cr 5 Exposure Assessment in the Evaluation of Risk to Human Health

cr 6 From Risk Assessment to Risk Management: Dealing with Uncertainty

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