The Interdepartmental Group on Health Risks from Chemicals:

Annexes to
First report and
forward plan
to 2002
The Interdepartmental Group on Health Risks from Chemicals aims to stimulate the development of new, improved approaches to the assessment of risks to human health from chemicals.

The Group contributes to the work of the Interdepartmental Liaison Group on Risk Assessment as outlined in its second report to Ministers in 1998, 'Risk Assessment and Risk Management: Improving Policy and Practice within Government Departments'.

The Steering Committee of the Interdepartmental Group on Health Risks from Chemicals 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 Food Standards Agency, 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 Interdepartmental Group on Health Risks from Chemicals 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.
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LIST OF RISK ASSESSMENT AND TOXICOLOGY STEERING COMMITTEE PUBLICATIONS
Annexes

Annex 1 Remit and objectives of the IGHRC

Background

Chemicals are an integral part of our lives. They provide us with the consumer goods we have come to take for granted and the chemical industry is a vital part of the national economy. However, there are risks from the manufacture and use of chemicals, including risks to human health, and it is essential that these are managed sustainably. Government seeks to protect the health of those coming into contact with chemicals in a variety of ways, for example through advice, surveillance and regulation.

A necessary first step in deciding what measures may be needed to protect health is to carry out an assessment of the risks posed by exposure to the chemical. Risk assessment is carried out in a number of UK Government departments and agencies in various ways depending on the nature of the chemical, its use and the likely route and duration of exposure.

The process of risk assessment is subject to a number of limitations and uncertainties. In the vast majority of cases information is not available from human studies and has to be obtained instead either from experiments on other animal species or from in vitro studies. However the extrapolation of this information to the human situation carries with it various uncertainties, and these are then further compounded by uncertainties about the potential variations in interindividual susceptibility and uncertainties in estimating exposures to chemicals. Because of the uncertainties inherent in the process of risk assessment, the precise methods used may vary from department to department.

As well as the variations among the risk assessment methodologies used in different departments and agencies, there are also a number of uncertainties inherent in the data themselves and their interpretation. The development of techniques that would help to reduce these uncertainties would be of particular value in helping to increase confidence in the outputs of risk assessments, and in the risk management choices that flow from them. Improved scientific techniques might also help to reduce the need to rely on animal testing and/or help to bring about reductions in the number of animals needed for risk assessments, principles to which government departments and agencies are committed.

Modern thinking on risk analysis is that all the stages, including the risk assessment stage, need to be carried out in a transparent way with all the uncertainties clearly acknowledged and explained. It is important, therefore, that any research undertaken to help improve the process of risk assessment should take account of the need for transparency so that developments are discussed with stakeholders, including those expert committees which may wish to make use of new techniques in their own risk assessment work.

The Interdepartmental Group on Health Risks from Chemicals (IGHRC), acting as a sub-group of the Interdepartmental Liaison Group on Risk Assessment (ILGRA), comprises representatives from those UK Government departments and agencies involved in human health risk assessment of chemicals for regulatory purposes, and is uniquely placed to address these issues.

Remit

The IGHRC has the overall aim of reducing the uncertainties and limitations in the conduct of chemical risk assessment for human health as employed by government, in order to increase the robustness of and confidence in the outputs that emerge from its regulatory processes that rely on risk assessment.

The IGHRC has a remit, therefore, to consider ways of enhancing the risk assessment process for chemicals, by suggesting suitable research and providing guidance, as a part of the general drive...
to improve the basis of scientific advice and its translation into policy. The risk assessment of chemicals is of importance to a number of different departments and agencies, and by pooling expertise in the IGHRC, it is hoped to improve coherence between the procedures used in the different departments and agencies as well as securing improvements in risk assessment practice itself.

**Aims**

The IGHRC aims to:

- Promote the development of methods and techniques that will improve information used in the toxicological risk assessment process;
- Promote improved approaches to toxicological risk assessment for use in the regulatory context;
- Promote coherence and consistency in the practice of toxicological risk assessment as used within the different risk management and regulatory frameworks used in government;
- Act to disseminate and advance best practice within Government.

To address these aims the IGHRC has the following objectives:

**Primary objectives**

- To develop and publish for consultation a programme of work aimed at improving the conduct of risk assessments of chemicals in the UK;
- To promote through the identification of research needs the development of innovative methods and improved approaches;
- To provide a forum within government for discussing how greater coherence and consistency of approach can be achieved nationally, and, if feasible, internationally;
- To identify and disseminate best practice in collaboration with stakeholders and other national and international organisations.

**Secondary objectives**

- To report annually to ILGRA and funding bodies;
- To arrange for an independent evaluation of the IGHRC’s achievements after three years.

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**Annex 2a Research recommendations from the Risk Assessment and Toxicology Steering Committee publications cr2, cr3, cr4 and cr5**

**Risk assessment approaches used by UK Government for evaluating human health effects of chemicals, cr2**

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

2. 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.

3. 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.

4. 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.

**Risk assessment strategies in relation to population subgroups, cr3**

5. Further research is needed to increase knowledge on the response of specific subpopulations to toxicological insult, in order to determine whether, on the basis of scientific evidence, additional uncertainty factors may be needed to allow for the presence of such subgroups in a population.

6. Further work should be undertaken on interindividual variations in toxicokinetic and toxicodynamic parameters, in particular on the inherent variability within the human population due to genetic factors affecting the metabolism of chemicals. In particular, in vitro screens should be developed further to determine the metabolic pathways for chemicals and their regulation in humans, in order to estimate the size of population subgroups that have a genetic deficiency in metabolism.
7. Further information is needed on the interaction of nutritional status, nutrition and response to chemicals.

8. Research is needed on variations in immune response and on the importance of immunotoxicological endpoints, in order to increase understanding of immunologically mediated susceptibility and how this might be addressed in risk assessment.

Physiologically-based pharmacokinetic modelling: A potential tool for use in risk assessment, cr4

9. Research to develop expanded databases for basic morphological and physiological parameters, particularly for human populations, to be used for PBPK modelling, is to be encouraged; this could be carried out as part of other PBPK modelling research activities.

10. New ‘template’ models for defined structurally and/or functionally related chemicals, not already the subject of existing models, should be developed.

11. Specific research projects designed to bring together the experience and skills of researchers working on PBPK modelling of industrial chemicals and pesticides and related areas of pharmaceutical research should be undertaken, in order to explore issues of relevance to chemical risk assessment, such as human variability.

Exposure assessment in the evaluation of risk to human health, cr5

12. Generic exposure models should be developed for screening purposes, directed both at chemicals and at pathways of exposure. The value of personal exposure measurement rather than generic measurement should be considered.

13. Probabilistic methods, such as Bayesian, fuzzy arithmetic and simulation of the entire population, should be evaluated and developed to investigate whether these might have advantages over Monte Carlo approaches to risk assessment, either generally or in particular circumstances.

14. Exposure data should be collected on susceptible groups in the population and a survey of data sources should be conducted.

Annex 2b Policy recommendations from the Risk Assessment and Toxicology Steering Committee publications cr2, cr4, cr5 and cr6

Risk assessment approaches used by UK Government for evaluating human health effects of chemicals, cr2

1. 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.

2. 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.

3. 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.

4. 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.

5. 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.

Physiologically-based pharmacokinetic modelling: A potential tool for use in risk assessment, cr4

6. The application of PBPK modelling to risk assessment in non-human species should be investigated, to facilitate extrapolation between these species; this has direct application to human safety in relation to drug residues in animal tissues and would also have benefits to wider environmental considerations outside the remit of the Risk Assessment and Toxicology Steering Committee.

7. A cross-government interdepartmental group should be established to co-ordinate the application of PBPK methods and any government-sponsored research.

Exposure assessment in the evaluation of risk to human health, cr5

8. Models are needed for dealing with total exposures to particular chemicals and mechanisms should be developed for addressing mixtures, both in terms of evaluating their toxic effects and in terms of exposure estimation; models are also needed for dealing with bioaccumulation in estimating exposure and in risk assessment.

9. Models for dealing with uncertainty in exposure estimates and guidance on their interpretation should be developed.

10. Communication with the general public, including susceptible groups within the population, should be improved. Presentational aspects, for example visual displays, should be considered.

11. Government departments should establish a specific forum to address issues common to all departments. Suggested issues for such a forum include:

- harmonisation of approaches where feasible;
- development of guidelines;
- ensuring that total exposure to a chemical being examined is considered;
- the establishment of multidisciplinary groups, both in terms of media being addressed (e.g., food, occupational, environmental — water, air, soil), and the expertise involved (e.g., toxicology, epidemiology, chemistry, regulatory);
- common approaches to the use of expert judgement; and
- shared methods for communicating with the general public.

From risk assessment to risk management: Dealing with uncertainty, cr6

12. The degree of influence that available risk management options have on risk assessment, and vice versa, should be clearly explained when risk assessments or decisions about risk management are made publicly available.

13. Although uncertainty factors are often presented as single numbers, the scientific and non-scientific influences that contribute to deciding an uncertainty factor should be clearly set out when chemical risk assessments are made publicly available.
Annex 2c Comments on coherence and consistency (harmonisation) from the Risk Assessment and Toxicology Steering Committee publications cr2, cr4 and cr5

Risk assessment approaches used by UK Government for evaluating human health effects of chemicals, cr2

1. 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.

2. 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.

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

4. 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.

5. 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.

6. 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.

Physiologically-based pharmacokinetic modelling: A potential tool for use in risk assessment, cr4

7. A cross-government interdepartmental group should be established to co-ordinate the application of PBPK methods and any government-sponsored research.

Exposure assessment in the evaluation of risk to human health, cr5

8. Although consistency in data collection and analysis is desirable, harmonisation, where feasible and appropriate, is more important than standardisation of sampling and measurement methods and analysis. Clear and transparent guidelines should be developed to promote such harmonisation.

9. At all stages of the risk assessment process, from hazard identification and characterisation and exposure assessment to the overall risk assessment, better communication is needed between the experts involved. This will facilitate the optimal integration of all stages to produce the final overall assessment. Furthermore, the earlier stakeholders are included in the process the sooner limitations pertaining to clarity and transparency in the selection and use of methodologies and procedures can be identified and resolved.

10. Harmonisation of approaches and use of terminology (rather than standardisation) would benefit communication. There are a number of areas which could be harmonised, for example the definition of frequency distributions, the definition of cut-off points and approaches for dealing with lack of data.

11. Successful communication with the general public is vital. This is a two-way process and should include taking account of the concerns of the general public as well as providing information. Methods for communicating with the general public about the process of risk assessment and the issue of uncertainty should be improved. More openness about uncertainty issues and greater attempts to explain these to the public would be valuable. However, identifying uncertainties may be interpreted by some as ‘fudging’ and could lead to difficulties in acceptance of the subsequent risk assessment. The presentation of uncertainty must be transparent. Stakeholders should be involved, ideally throughout the process of communication.
to the public. Intermediaries such as health care workers and teachers might play a useful role.

12. Communication with the general public, including susceptible groups within the population, should be improved. Presentational aspects, for example visual displays, should be considered.

13. Throughout the exposure assessment process there is a need for a more harmonised approach and better pooling of expertise, and for improved clarity and transparency regarding both the choice of procedures, models and other factors to be used in the assessment and the communication of the outcome. To this end it is recommended that government departments establish a specific forum to address issues common to all departments. Suggested issues for such a forum include:

- harmonisation of approaches where feasible;
- development of guidelines;
- ensuring that total exposure to a chemical being examined is considered;
- the establishment of multidisciplinary groups, both in terms of media being addressed (e.g., food, occupational, environmental — water, air, soil), and the expertise involved (e.g., toxicology, epidemiology, chemistry, regulatory);
- common approaches to the use of expert judgement; and
- shared methods for communicating with the general public.

### Annex 3 Criteria for scoring and prioritising research recommendations

A scoring system was established to assist in weighting key criteria used to prioritise ten research areas (see Table) developed from the 14 research recommendations (see Annex 2a) from the Risk Assessment and Toxicology Steering Committee reports. The scoring system was used as an adjunct to decision making and a maximum score of five points was awarded per criterion.

#### Criteria for selection

1. Number of government departments interested
2. Novelty
3. Feasibility
4. Impact - applicability - ability to change current practice

Using these criteria, five research areas were selected to be taken forward for further consideration. Outlines of the research required in each area are presented in Annexes 4a–e, and a summary of current research, funded by individual departments and agencies, that meets any of these requirements is presented in Annex 5.

### Prioritising research recommendations

<table>
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<th>Research recommendation number (see Annex 2a) and research area title</th>
<th>Scores*</th>
<th>Criteria for selection</th>
<th>Comment</th>
<th>Total Score</th>
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<tr>
<td>1 Toxicology data needs</td>
<td>(1) No. of Gov't depts interested</td>
<td>(2) Novelty</td>
<td>(3) Feasibility</td>
<td>(4) Impact</td>
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<tr>
<td>2 Toxicology and uncertainty factors</td>
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<td>4</td>
<td>3</td>
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<td>3+4 Probabilistic risk assessment technique</td>
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<td>5</td>
<td>2-5</td>
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<td>2</td>
<td>4</td>
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<td>6 Genetic polymorphism in toxicity</td>
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<td>8 Immunotoxicology and susceptibility</td>
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<td>9-11 PBPK modelling</td>
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<td>12 Generic personal exposure estimates</td>
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<td>13 Probabilistic methods in exposure assessment</td>
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<td>14 Default exposure estimates</td>
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*Scores reflect degree of importance (5 highest, 0 lowest)
Annex 4a Specification for the research area: Toxicology and uncertainty factors

A number of UK Government departments and agencies have a responsibility for assessing risks to human health from chemicals in the air, soil, drinking water, food and the home or working environment. These assessments are usually based on the results of a range of studies in animals and/or studies in limited groups of humans. In order to use these results to estimate levels that would not be expected to cause adverse effects in the population, uncertainty factors are applied to the dose that was without adverse effects in the groups studied (no-observed-adverse-effect level; NOAEL). It has become widely accepted practice to divide uncertainty factors into two components (10 × 10): 10 to allow for interspecies differences and 10 to allow for intraspecies variation.

Both interspecies and intraspecies differences may result from differences in the absorption, distribution, metabolism and excretion (toxicokinetics) of the chemical or from differences in its activity at the target site (toxicodynamics). The uncertainty factors currently used are default values covering both these sources of variation; they could be refined and placed on a sounder scientific basis if more were known about toxicokinetic and toxicodynamic characteristics.

It is not realistic to expect data to be available for each individual chemical of interest and, therefore, there is a need to develop rules applicable to general classes of compounds. Generic research in the area of comparative toxicokinetics and toxicodynamics will help refine the uncertainty factors currently used, both nationally and internationally, in the risk assessment procedure. Such studies could also provide guidance on the appropriate additional uncertainty factors that should be applied to risk assessments based on deficient data.

The problem can be approached in a variety of ways and any one piece of research could not be expected to tackle all aspects. Ideally research should focus on approaches that could be applied to real risk assessment activities that are currently being undertaken.

Annex 4b Specification for the research area: Human variation and susceptibility

The assessment of chemicals for risks to human health is acknowledged as being subject to many uncertainties. A major factor contributing to the uncertainty is variability within the human populations of concern. Variability will exist within the exposed population in individual responses to a chemical once the body is exposed and in how organs/tissues respond when the chemical is delivered to the critical target site within an individual. This variability is likely to be determined in part by genetic factors but is also likely to be influenced by many other factors, such as age, gender and nutritional and pregnancy status, and combinations of these. There are often too few chemical-specific data available to allow the influence of these factors to be determined. Usually, the convention is to employ a default ‘uncertainty’ or ‘safety’ factor in the risk assessment process to allow for variability within the population. Although factors such as age (e.g. children and the elderly may respond differently from adults simply because of their biological age), gender and pregnancy status may influence the response of an individual within a population, there are relatively few data available by which to judge whether such factors would be covered by the default positions currently employed in risk assessment or whether additional defaults may be required to allow for population subgroups. Ideally research in this area would serve to increase the knowledge base available on the response of specific sub-populations, in order to determine whether, on the basis of scientific evidence, additional safety factors may be needed to allow for the presence of such groups in the general population.
Annex 4c Specification for the research area: Probabilistic modelling

Often, UK Government departments have to undertake risk assessments for chemicals found in the environment that arise from a range of sources. These assessments may be based on a variety of health endpoints, identified from human evidence or experimental observations in animal investigations. Furthermore, the environmental exposure data for humans or animals may be very limited or uncertain. Risk assessment is thus based on identification of the key hazard endpoints, combined dose–response relationships and exposure estimates. Classically, this has been done by using single point estimates for the most serious outcome(s) (often expressed as the NOAEL), applying an uncertainty factor, estimating exposure(s) and arriving at an overall risk of harm.

Probabilistic methods for risk assessment express the variation and uncertainty in an input factor as a probability distribution, which can be thought of as a frequency diagram of all the possible values of a variable in relation to the probability of each value occurring. The different components and stages of the risk assessment are linked together by mathematical relationships and the variabilities in the inputs at each stage are propagated throughout to the final output variable, which is also expressed in the form of a probability distribution. This may give a more realistic representation of the risk being assessed than the current tendency to use a single value. In addition, probabilistic methods allow sensitivity analysis of inputs, which indicates which are the factors most important to the result. This assists in prioritising the allocation of resources to further research on the factors that are most significant in influencing the overall outcome.

Research methodology is needed that will allow such novel approaches to be applied in a more generic way to a variety of situations where the risks arising from chemical exposures require assessment. Research may be of a translational nature, using existing techniques applied in imaginative or novel ways, or it may involve development of novel techniques which can be applied to a range of chemical related problems. Risk assessment must ultimately be a transparent process with all uncertainties made clear. It is, therefore, important that research on probabilistic methods should take account of the need for clarity and transparency, so that proposed approaches are readily understood both by the expert committees for whom the methodology will be an aid and by stakeholder groups.
Annex 4d Specification for the research area: Exposure models

Research on exposure models should review and evaluate key models and default values used to estimate, for screening purposes, human exposure to chemicals and should lead to recommendations on the applicability of such models and default values to the UK situation. Specifically, key exposure models used in the UK and elsewhere for predicting human exposure to contaminants (to include all media and routes of exposure) should be identified. The models should then be reviewed and assessed and guidance provided on their suitability to UK conditions. Relevant probabilistic methods to estimate exposure of populations and the applicability of such methods to human health risk assessment, either generally or in particular circumstances (e.g. for site-specific purposes), should be evaluated. A review and assessment of default values used in specific models (and elsewhere) should be included and would allow determination of the most representative parameters for the UK population. Ideally such a review would make recommendations on the suitability of the models and default values for predicting human exposure in the UK. A review would also help identify levels of uncertainties, data gaps, research needs to fill data gaps and any areas of development required for current models.

Annex 4e Specification for the research area: Physiologically-based pharmacokinetic (PBPK) modelling

PBPK models help evaluate the relationship between external exposure, target tissue dose and biological outcome.

There has been significant development of PBPK modelling, particularly in the USA where it has made a valuable contribution to the risk assessment process. Much of this work has focused on specific chemicals. The UK Government would like to explore the feasibility of drawing on this work to develop a generic model that can be used in the risk assessment of chemicals.

Appropriate PBPK research should explore the feasibility of developing a generic model that can be used in the risk assessment of chemicals, drawing on the work that has already been done in developing PBPK models. Research should identify the basic information about chemicals needed for use in a generic model (physicochemical properties, testing needs), the critical data gaps, the points at which assumptions have to be made, and the key uncertainties. Research should also identify a strategy for testing and validation of such a generic model and lead to recommendations for further studies.
Annex 5 Current research of relevance to the five IGHRC research areas, from the database on risk assessment methodology research

A database has been prepared comprising details of existing research (funded by individual departments or agencies) of relevance to the five project areas identified by the IGHRC (see Annex 3). Each of the individual research projects in the database has been tagged with one or more keywords. Thus some individual projects appear under more than one heading. Under each heading given below individual projects are listed by title, reference number (where supplied) and funding body. Funding bodies include the Biotechnology and Biological Sciences Research Council (BBSRC), the Department of Environment, Transport and the Regions (DETR), the Department of Health (DH), the Environment Agency (EA), the Food Standards Agency (FSA), the Health and Safety Executive (HSE), the Medical Research Council (MRC) and Natural Environment Research Council (NERC).

Toxicology and uncertainty factors

- Biomarkers, toxicokinetics and default safety factors (T01017 – FSA)
- Guidance on the characterisation of uncertainties in risk assessment of land contamination (P5B(99)/01 – EA)
- Uncertainty factors for chemical risk assessment (3783/R 51.158 – DH/HSE)

Variation and susceptibility

- A novel approach to the analysis of human genome variations investigating heterogeneity of both mutation and recombination (G09616/G09617 – BBSRC)
- A study of human interindividual variability: various physiological, anatomical and biochemical factors that influence chemical toxicokinetics (Loizou/CH EM /98/1 – DETR/DH)
- Absorption and metabolism of dietary phytoestrogens in humans — effect of age, gender, food matrix and chemical composition (T05010 – FSA)
- Biomarkers, toxicokinetics and default safety factors (T01017 – FSA)
- Can biomarkers be used to assess the carcinogenic potential of heterocyclic amines? (T01003 – FSA)
- Genetic susceptibility and resistance to xenobiotics (E370 – MRC)
- Genetic variations and organophosphates (3837/R 79.002 – HSE)
- Heterocyclic amines as risk factors in colon cancer (T01004 – FSA)
- Incorporating inter-individual variability in the interpretation of biological monitoring guidance values (9681/R 51.196 – HSE)
- Influence of genetic mutations on iron status linked to dietary intake from the UK women’s cohort study (N05023 – FSA)
- Influence of human gut microflora on dietary soya isoflavone phytoestrogen bioavailability in adults and children (T05011 – FSA)
- Measurement of the formation of MEIQx and DNA adducts in human colon cancer patients (T01005 – FSA)
- Occupational lead exposure, semen quality and endocrine status (3351/R 51.092 – HSE)
- Psychological effects of exposure to organophosphates (3794/R 51.160 – HSE)
- Regulation of iron absorption and effects of habitual diet on iron stores in heterozygote men with HFE mutations (N05022 – FSA)
- Teratological hazards associated with chemical exposure (3430/R 51.106 – HSE)
- The contribution of age and genotype to sensitivity to environmental genotoxins (Williams/CH EM /98/1 – DETR/DH)
- The neurotoxicity of paint solvents (3828/R 51.168 – HSE)
- Variations in sensitivity to chemicals among population subgroups (lifestyle factors) (Timbrell/CH EM /98/1 – DETR/DH)
Probabilistic modelling

- Application of non-linear mathematics and stochastic modelling to biological systems (814213 – BBSRC)
- CLEA Expert and computer codes (P5-09 – EA)
- Development of probabilistic models for describing individual intakes of chemical residues in food (T01013 – FSA)
- Expert elicitation of modelling parameters explicitly relevant to UK environmental and agricultural conditions (R01028 – FSA)
- Modelling agricultural processes and systems subject to uncertainty for decision making (0417 – BBSRC)
- Modelling inter- and intra- individual exposure to chemicals in food (T01014 – FSA)
- Models for decision support in agriculture (094 – BBSRC)
- Novel approaches to environmental modelling and risk assessment using concepts derived from statistics, entropy, chaos, and complexity theory (031566 – BBSRC)
- Proposal to facilitate probabilistic modelling in MAFF food chain models (R01010 – FSA)
- Risk based approaches to the derivation and expression of environmental quality standards (2062 – NERC)
- Scale and uncertainty in modelling phosphorous transfer from agricultural grasslands to watercourses: development of a catchment scale management tool (MAF12247 – BBSRC)
- Biological porous media modelling and measurement (0440 – BBSRC)
- CLEA Expert and computer codes (P5-09 – EA)
- Dangerous substances in sewerage networks (P2-197 – EA)
- Deposition of small particles from turbulent air flow (0422 – BBSRC)
- Dermal exposure measurements of indoor pesticide products (9484/R 51.116 – HSE)
- Development of a regional multi-media partition model for organic compounds (P4-S01 – EA/NERC)
- Development of a risk assessment model for exposure to occupational sensitisers (3997/R 51.183 – HSE)
- Development of critical level methodologies for toxic metals in soils and surface waters (1709 – NERC)
- Dislodgeable residues from surfaces treated with pesticides (R 51.150 – HSE)
- Dispersion and deposition of aerial pollutants and bio-aerosols emitted from agricultural structures (D11024 – BBSRC)
- Dispersion and deposition of gases and particulates for agricultural structures (0401 – BBSRC)
- Environmental modelling of antifouling biocides (R 51.143 – HSE)
- GIS applications in major hazard accident monitoring (3781/R 71.031 – HSE)
- INTErSECT Faraday Partnership (3769/R 48.112 – HSE)
- Mathematical modelling framework for screening the relative significance of pathways of human exposure to organic pollutants (Harrad/CH EM /98/1 – DETR/DH)
- Modelling of indoor and personal exposure to air pollution (EPG 1/3/110 – DETR)
- Modelling the fate and transport of particles in water - phase 2 (E1A(00)01 – EA)

Exposure models

- Air flow and spray droplet interactions with crops (0407 – BBSRC)
- Air flow through porous media (0420 – BBSRC)
- Analysis of soil vapour models for the contaminated land exposure assessment model (PSB(00)05 – EA)
- A assessment of the variability of critical group doses and implications for dose limitation (RP0142 – FSA)
• Novel approaches to environmental modelling and risk assessment using concepts derived from statistics, entropy, chaos, and complexity theory (031566 – BBSRC)

• Personal exposure monitoring and modelling (EPG 1/3/111 – DETR)

• Predictive dermal exposure model for contaminated land (3404/R 51.102 – HSE)

• Quantifying future exposures to dioxins and PCBs (reference number not supplied – DETR)

• Realistic modelling of atmospheric flows for dispersion (0438 – BBSRC)

• Standardised sampling protocols for human exposure monitoring following chemical contamination incidents - a feasibility study (White/CHEM/98/1 – DETR/DH)

• Strategy for assessing risk and assigning priorities to chemicals used to make food contact materials, a tiered approach with progressive refinement to calculate exposure level (A03023 – FSA)

• Studies of spray behaviour from a moving nozzle system in an airflow (JRE10877 – BBSRC)

• The further development of European Union system for the evaluation of substances (EUSES) (P2-175 – HSE)

• The variability in critical group doses and implications for control of radionuclides releases (R 01033 – FSA)

• Uncertainties in assessment of terrestrial food chain doses: sources and implications (RP0141 – FSA)

• Uncertainty analysis for the aquatic environment (R01037 – FSA)

• Validation of EASE model (3846/R 51.172 – HSE)

• Vapour transfer of soil contaminants (P5-018 – EA/Institute of Petroleum)

--- Annexes ---

### Physiologically-based pharmacokinetic modelling

- A study of human interindividual variability: various physiological, anatomical and biochemical factors that influence chemical toxicokinetics (Loizou/CHEM/98/1 – DETR/DH)

- Bioavailability of dietary phytoestrogens in man (2307051 – BBSRC)

- Biomarkers, toxicokinetics and default safety factors (T01017 – FSA)

- Department of Trade and Industry Government Chemist Programme (reference number not supplied – DTI)

- Developing a computer system to predict metabolism (METEOR) (3654/R 51.141 – HSE)

- Development of knowledge based system (KBS) (9555/R 51.145 – HSE)

- Food risk assessment fellowship (T01007 – FSA)

- Incorporating inter-individual variability in the interpretation of biological monitoring guidance values (9681/R 51.196 – HSE)

- Investigate and develop different modelling approaches in extending understanding and quantification of biological systems (144209 – BBSRC)

- Physiochemical and structural determinants of pharmacokinetic behaviour (99/A2/C/05310 – BBSRC)

- Predicting pharmacokinetic behaviour of compounds from structure and physicochemical information (95/A1/B/00754 – BBSRC)

- Quantifying future exposures to dioxins and PCBs (reference number not supplied – DETR)

- Refinement of health risk assessment processes using PB-PK modelling (reference number not supplied – DH/FSA)

- The development of assays for the determination of aluminium body-burden in man (Priest/CHEM/98/1 – DETR/DH)
Annex 6a Overview of current government-funded research contributing to toxicology and uncertainty factors, and variation and susceptibility

Background

Research needs specified in Annexes 4a and 4b, relate to the use, in risk assessment, of uncertainty factors to allow for uncertainties in extrapolating from limited data sets, usually derived from experimental animal models, to the whole or parts of the exposed human population. Due to the similarities between the two research areas of toxicology and uncertainty factors, and variation and susceptibility, the two topics have been combined in this analysis of currently funded individual research projects. For both specifications a key feature is that research should provide data that could be used to investigate the extent of variation between and within species in order to provide information on the use of uncertainty factors. In the analysis presented below, currently funded research has been included if it could contribute to the consideration of uncertainty factors, even if it has not been designed to address uncertainty factors per se.

Summation of government-funded research

Overall, 22 individual projects are listed in the database of current research (Annex 5) under the general headings ‘toxicology and uncertainty factors’ and ‘variation and susceptibility’. For two projects there appears to be no obvious link to the grouping (G 09616 and G 09617), for three projects the output is not designed to address the issue but the data generated may have the potential to do so (N05023, Timbrel/CH EM /98/1, T 05010 and T 05011), two are investigating xenobiotic metabolism (Loizou/CH EM /98/1, 9681/R 51.196) and one storage elemental Fe (N 05022). The projects on dietary uptake are likely to contribute to general knowledge about factors that influence uptake of specific classes of chemicals (e.g. phytoestrogens) or may contribute to increased understanding about the possible influence diet may have on responses to toxicants. One project should provide information on age and gender influences on dietary uptake, whilst two others will attempt to link intake/status with genetic variation directly. The studies on xenobiotic metabolism combine experimental and modelling approaches to investigate human variation in specific enzyme pathways; the outputs from these studies should be broadly applicable to the issue of variability and uncertainty factors.

Two (Williams/CH EM /98/1 and E 370) of the specific toxicodynamics projects relate to susceptibility and variability in the induction of genetic damage. One is looking specifically at the contribution of ageing and both are attempting to address genetic determinants of susceptibility. The third (3828/R 51.168) toxicodynamic project is investigating potential relationships between solvent exposure and chronic neurological disease and, if found, any genetic predisposition to development of the disease.

Three of the four projects that address both toxicokinetic and toxicodynamic aspects are linked joint centre work (T 01003, T 01004 and T 01005). These projects address dietary uptake, variability in metabolism and expression of genotoxic activity of heterocyclic amines in relation to potential links to colon cancer. The other project (3837/R 79.002) is investigating the influence genetic variation may have on potential health effects of sheep dips.
Conclusion

Analysis of the projects listed in the database indicates that most activity is focused on toxicokinetic issues. It is likely that the on-going work on kinetics will contribute positively to the research needs outlined, particularly in Annex 4a. Much of the research is likely to yield information that will be generally applicable at least within groups of substances (e.g. those with similar metabolic pathways). The results of the literature based analysis on inter-species and intra-human variability (3783/R51.158) are also likely to be useful in identifying gaps in knowledge and future directions for work on toxicokinetics.

Current research on toxicodynamic aspects is more limited and is focused on either genetic damage or neurotoxicity, reflecting primarily the interests of the funding bodies. Although the work on genetic damage may prove to have some general applicability to the identified research needs, the work on neurotoxicity may provide useful insight for that specific endpoint. However, in general, the breadth of ongoing activity on toxicodynamics is limited compared with that on toxicokinetics and will make a limited contribution to the research needs outlined in Annexes 4a and 4b.

Annex 6b Overview of current government-funded research contributing to probabilistic modelling

Background

The research needs outlined in Annex 4c address generic aspects of the use of probabilistic approaches to chemical risk assessment. Thus, appropriate research could apply to the overall risk assessment process or to individual components, such as exposure modelling or toxicological aspects. The key theme is the use of a probabilistic approach to make better use of a variety of disparate data and/or to establish better means of reducing uncertainty.

Summation of government-funded research

The current research database (Annex 5) includes 11 ongoing projects that broadly meet the requirements for research involving probabilistic methodology, although two (814213 and P5-09) do not directly address the use of probabilistic approaches. Most of the other projects are concerned with various ways of using probabilistic approaches to model exposure, either through food intake or through the environment. Only one study (2062) seems to take a holistic approach to the use of probabilistic methodology (using a Bayesian statistical framework) to address the difficult but critical area of prediction of harm from multi-species data. This study partly meets the research needs outlined in Annex 4c by focusing on the novel re-analysis of existing data. However, the project seems to address only ecological issues and thus would not be appropriate for human risk assessment, the main concern of the IGHRC.

Conclusion

There are a number of ongoing projects that address some aspects of probabilistic risk assessment (using either Bayesian or fuzzy logic approaches), but none of them directly relates to human risk from chemical exposure from either environmental or occupational sources. A recent publication entitled Probabilistic Approaches to Food Risk Assessment*, based on an expert workshop funded by MAFF (the project has now transferred to the Food Standards Agency) and as part of the Food Risk Assessment Fellowship (T01007), has

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* IEH (2000) Probabilistic Approaches to Food Risk Assessment (FORA 1), Leicester, UK, MRC Institute for Environment and Health
addressed the potential use of these approaches and may well stimulate research into other areas of human exposure from chemicals. Overall, research into the methodology of the use of probabilistic approaches for chemical risk assessment appears limited and should ideally be high on a priority list for future activities. However, research is only one means by which activity in this area can be stimulated and further workshops and teaching seminars may also be appropriate.

Annex 6c Overview of current government-funded research contributing to exposure modelling

Background

The objective of the research outlined in Annex 4d is to review key models and default values used to estimate human exposure to chemicals with a view to evaluating and making recommendations about their applicability to the UK situation.

Summation of government-funded research

The current research database (Annex 5) includes a total of 36 ongoing projects in this field, funded by several government departments, agencies and research councils. Various projects seek to develop generic models to predict human exposure to chemicals; these are generally to assess exposure from a particular pathway or chemical group and to address specific issues. Few of the models consider all routes of exposure (i.e. ingestion, inhalation and dermal). The projects most relevant to the research needs outlined in Annex 4d are outlined below.

Projects P4-S01 and 014 look at multimedia exposure to organic chemicals and provide for the estimation of current and future exposures. The models use equilibrium partitioning and allow for the screening of key pathways that may lead to increased human exposure to specific chemicals. Both projects estimate exposure via ingestion and inhalation among the general population. It is not clear whether P4-S01 considers dermal exposure.

Four projects relate to the development of generic models to be used for specific UK or European legislation (P5B(00)05, P5-09, P5-018, P2-175). CLEA and EUSES address multimedia exposures via inhalation, ingestion and dermal routes. CLEA (P5B(00)05, P5-09, P5-018) is used for the development of guideline values for organic and inorganic chemicals in contaminated land (UK), whilst EUSES (P2-175) is used for risk assessments of new and existing chemicals at the European level (mainly for organic chemicals). These can provide valuable information on several topics, including default values, most appropriate algorithms, and the use of probabilistic and deterministic approaches.
Other projects are developing models for specific media/routes of exposure:

- Dermal, mainly from occupational exposure (9484/R 51.116, R 51.150 and 3404/R 51.102)

- Dietary exposures (T 01007)

- Releases of chemicals to the water environment (R 51.143) or chemical migration to food from contact materials and subsequent bioaccumulation through the food-chain (A 03023)

- Indoor and personal exposure to air pollution (EPG 1/3/110 and EPG 1/3/111)

- Atmospheric deposition/critical loads to soils and surface waters of heavy metals (1709)

- Diffuse and unconsented sources of substances in sewerage systems (P2-197).

A number of projects aim to develop models that describe the dynamics of fluid and particulate flows. These generally relate to dispersion modelling techniques in agricultural environments (e.g. contamination of fields and buildings following agricultural spray of pesticides). Projects that fall under this category are 0407, 0402, 0440, 0422, D 11024, 0401, 0438 and JRE 10877.

Other projects aim to validate or update models or sub-modules of models. These include validation of EASE (project 3846/R 51.172) and validation of the soil vapour intrusion sub-module of CLEA (P5-018).

Conclusions

Some of the projects presented above relate to the development and validation of generic models for various purposes, including models developed for the purpose of screening key pathways for exposure to specific chemicals or groups of chemicals. From the information provided it is not possible to determine whether the default values used are appropriate to the UK situation or whether different models use different default parameters. Neither is it possible to determine whether part of the model development involves a review of other exposure models developed elsewhere.

Annex 4d outlines a need to identify key exposure models for predicting human exposure to contaminants and to review these. Some of the models currently under development are described briefly above. However, none of these research projects aim at specifically comparing key models and default values used or at making recommendations on the most appropriate models for the UK situation. Therefore this will still need to be addressed.

One of the objectives described in Annex 4d is to look at the value of personal exposure measurements. Currently there are two projects, EPG 1/3/110 and EPG 1/3/111, aimed at testing the performance of a model to estimate exposures from air pollution against measurements of indoor and outdoor concentrations and of personal exposures.
Annex 6d Overview of current government-funded research contributing to physiologically-based pharmacokinetic (PBPK) models

Background

PBPK models are intended to evaluate the relationship between external exposure, target dose and biological outcome. The specific areas identified in the development of a generic model for PBPK modelling as outlined in Annex 4e are to:

1. identify critical data gaps
2. identify points at which assumptions will have to be made
3. identify the basic information needed about chemicals to enter into a generic model
4. identify key uncertainties (i.e. which of 1 and 2 have most influence on the final assessment)
5. identify a strategy for testing and validation
6. recommend further research.

It is expected that most research projects will lead to recommendations for further research, so further comment on this is not given below.

Summation of government-funded research

Overall 13 individual projects are listed in the current research database (Annex 5) under the heading PBPK models. All the projects that seek to develop improved uncertainty factors will contribute to the development of PBPK models, but only those projects that specifically link findings to such models are included here. All projects considered relevant to the research needs outlined in Annex 4e are associated with one or more of the six requirements outlined above.

The study on food additives (T01017) contributes to points 1, 2 and 5. It is possible that information relating to 4 will also come from this study. Studies on diallyl sulphide and alcohol and meta-xylene (Loizou/CH E M/98/1) do not specifically address any of the six points but should provide information relevant to 1, 2, and 5 in relation to PBPK models for extrapolation from small samples of humans to large populations. The project on the variability in two enzyme systems in the human population (9681/R51.196) will contribute to 3, 4 and 5 and the DTI Government Chemist programme (reference not provided) may provide some information relevant to 3 in relation to chemicals with endocrine disrupting activity. The title of project 99/A 2/C/05310 suggests that it will provide information relevant to 3 but details of the project were not available.

The development of a computer system (3654/R51.141) that can predict metabolism may provide input to all six points of interest. Similarly the dermal and inhalation uptake study (9555/R51.145) will provide information relevant to the exposure component at all points, as will the project ‘Refinement of health risk assessment process using PBPK modelling’ (reference not provided).

The study looking at aluminium body-burden in man (Priest/CH E M/98/1) may provide some data relevant to certain types of chemicals, the wider applicability of the findings is uncertain.

HSE has included in its 2000/2001 Competition for Ideas a call for proposals for projects on physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) modelling. No specific proposal is yet available but the HSE intend to fund further work in the area of PBPK/PD modelling should suitable proposals be made.

Conclusions

All the research needs identified in Annex 4e are addressed to a greater or lesser extent by currently funded projects listed in the current research database.

There will be a need to encourage communication between groups working in relevant fields. The Risk Assessment and Toxicology Steering Committee has already conducted a workshop on PBPK modelling, therefore no benefit can be expected from repeating this exercise at present. Information obtained from the projects should be reported at the earliest opportunity to inform ongoing studies. There will be a need to re-evaluate further research requirements as the outputs from the various projects become available. A single time for optimal re-evaluation of the whole area is not obvious as the completion dates vary from project to project.

The IGHRC has approached the British Toxicological Society to encourage them to establish a PBPK modelling club, possibly under the umbrella of the Regulatory Toxicology speciality section.
### Annex 7a Analysis of policy recommendations from the Risk Assessment and Toxicology Steering Committee publications cr2, cr4, cr5 and cr6

<table>
<thead>
<tr>
<th>Number&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Recommendation</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>cr2 (1)</td>
<td>Incorporate information about human variability</td>
<td>Procedure&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>cr2 (2)</td>
<td>Procedures should be set up for assessing human exposure</td>
<td>Procedure</td>
</tr>
<tr>
<td>cr2 (4)</td>
<td>The areas where risk management affects risk assessment should be accurately identified; all should be clear about which are science based and which socially based</td>
<td>Procedure</td>
</tr>
<tr>
<td>cr2 (5)</td>
<td>Reporting of risk assessment to be logical and transparent</td>
<td>Procedure</td>
</tr>
<tr>
<td>cr4 (7)</td>
<td>Establish a cross department group to co-ordinate PBPK in RA</td>
<td>Procedure</td>
</tr>
<tr>
<td>cr5 (9)</td>
<td>Develop guidance for dealing with uncertainty</td>
<td>Procedure</td>
</tr>
<tr>
<td>cr5 (10)</td>
<td>Improve communication with the public</td>
<td>Procedure</td>
</tr>
<tr>
<td>cr5 (11)</td>
<td>Establish a forum to address issues common to departments</td>
<td>Procedure</td>
</tr>
<tr>
<td>cr6 (12)</td>
<td>Risk management options available for risk assessment should be explained</td>
<td>Procedure</td>
</tr>
<tr>
<td>cr6 (13)</td>
<td>Uncertainty factors need justification when communicated to the public</td>
<td>Procedure</td>
</tr>
<tr>
<td>cr2 (1)</td>
<td>Carry out research on human variability</td>
<td>Research&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>cr2 (3)</td>
<td>Statistical basis for worst case exposure assessment improved</td>
<td>Research</td>
</tr>
<tr>
<td>cr5 (8)</td>
<td>Models required for total exposure to particular chemicals</td>
<td>Research</td>
</tr>
<tr>
<td>cr5 (8)</td>
<td>Develop models for bioaccumulation</td>
<td>Research</td>
</tr>
<tr>
<td>cr5 (9)</td>
<td>Develop models for uncertainty</td>
<td>Research/review&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>cr2 (3)</td>
<td>Worst case assumptions about exposure should be discussed</td>
<td>Review</td>
</tr>
<tr>
<td>cr4 (6)</td>
<td>PBPK modelling should be investigated and applied to RA</td>
<td>Review</td>
</tr>
<tr>
<td>cr5 (8)</td>
<td>How do we address mixtures</td>
<td>Review</td>
</tr>
</tbody>
</table>

<sup>a</sup> Number refers to Annex 2b

<sup>b</sup> A procedure needs to be conducted to take forward the recommendations, for example, the production of a guidance document or the setting up of a specific-issue working group (see First Report and Forward Plan to 2002).

<sup>c</sup> Some of the policy recommendations (Annex 2b) require research to be taken forward.

<sup>d</sup> A critical literature review is required.
Annex 7b Analysis of coherence and consistency recommendations from the Risk Assessment and Toxicology Steering Committee publications cr2, cr4 and cr5

<table>
<thead>
<tr>
<th>Number&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Recommendations</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>cr2 (1)</td>
<td>Global harmonisation using minimum data via EU</td>
<td>Procedure&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>cr2 (2)</td>
<td>Guidance prepared for use and size of uncertainty factors</td>
<td>Procedure</td>
</tr>
<tr>
<td>cr2 (3)</td>
<td>Consistency in weight of evidence approach</td>
<td>Procedure</td>
</tr>
<tr>
<td>cr2 (4)</td>
<td>Share experience with modelling exposure</td>
<td>Procedure</td>
</tr>
<tr>
<td>cr2 (5)</td>
<td>Pool experience in exposure monitoring and sampling</td>
<td>Procedure</td>
</tr>
<tr>
<td>cr2 (6)</td>
<td>Default assumptions for exposure assessment should be shared and implemented where appropriate</td>
<td>Procedure</td>
</tr>
<tr>
<td>cr4 (7)</td>
<td>Interdepartmental group to co-ordinate application of PBPK modelling</td>
<td>Procedure</td>
</tr>
<tr>
<td>cr5 (8)</td>
<td>Clear and transparent guidelines for collection and analysis of exposure data</td>
<td>Procedure</td>
</tr>
<tr>
<td>cr5 (9)</td>
<td>Improve communication between experts</td>
<td>Procedure</td>
</tr>
<tr>
<td>cr5 (10)</td>
<td>Harmonisation of approaches and terminology</td>
<td>Procedure</td>
</tr>
<tr>
<td>cr5 (11)</td>
<td>Communicate with the public about process of risk assessment</td>
<td>Procedure</td>
</tr>
<tr>
<td>cr5 (11)</td>
<td>Involve stakeholders early in the process</td>
<td>Procedure</td>
</tr>
<tr>
<td>cr5 (13)</td>
<td>Harmonisation of exposure assessment approaches between departments — establish a forum</td>
<td>Procedure</td>
</tr>
</tbody>
</table>

<sup>a</sup> Number refers to Annex 2c  
<sup>b</sup> A procedure needs to be conducted to take forward the recommendations, for example, the production of a guidance document or the setting up of a specific-issue working group (see First Report and Forward Plan to 2002)
List of Risk Assessment and Toxicology Steering Committee publications*

Risk Assessment and Toxicology Steering Committee (1999a)
Developing New Approaches to Assessing Risk to Human Health from Chemicals (cr1), Leicester, U.K., Institute for Environment and Health

Risk Assessment and Toxicology Steering Committee (1999b)
Risk Assessment Approaches used by UK Government for Evaluating Human Health Effects from Chemicals (cr2), Leicester, U.K., Institute for Environment and Health

Risk Assessment and Toxicology Steering Committee (1999c)
Risk Assessment Strategies in Relation to Population Subgroups (cr3) Leicester, U.K., Institute for Environment and Health

Risk Assessment and Toxicology Steering Committee (1999d)
Physiologically-Based Pharmacokinetic Modelling: A Potential Tool for use in Risk Assessment (cr4) Leicester, U.K., Institute for Environment and Health

Risk Assessment and Toxicology Steering Committee (1999e)
Exposure Assessment in the Evaluation of Risk to Human Health (cr5) Leicester, U.K., Institute for Environment and Health

Risk Assessment and Toxicology Steering Committee (1999f)
From Risk Assessment to Risk Management: Dealing with Uncertainty (cr6) Leicester, U.K., Institute for Environment and Health

* Publications also available in a PDF format to download free from the IEH Web site: http://www.le.ac.uk/ieh/