The Interdepartmental Group on Health Risks from Chemicals:

Final report for Phase I 1999–2003

and

forward plan to 2006

cr11

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 Steering Committee of the Interdepartmental Group on Health Risks from Chemicals comprises participants from the Department for Environment, Food and Rural Affairs, the Department of Health, the Department of Trade and Industry, the Home Office, the Environment Agency, the Health and Safety Executive, the Food Standards Agency, the Medicines and Healthcare Products Regulatory Agency, the Pesticides Safety Directorate, the Veterinary Medicines Directorate, the Biotechnology and Biosciences Research Council, the Medical Research Council, and the Natural Environment Research Council.

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

This document has been prepared by the Interdepartmental Group on Health Risks from Chemicals. The opinions expressed do not necessarily represent the policies of the participating Departments, Agencies and Research Councils.

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Foreword

The Interdepartmental Group on Health Risks from Chemicals (IGHRC) is a group of representatives from UK government departments, agencies and research councils with an interest in chemical risk assessment. The group was originally established in 1996 as the Risk Assessment and Toxicology Steering Committee, but the name was changed in 1999 to reflect the broader remit of the group.

The overall aim of the IGHRC is to reduce uncertainties and limitations in the conduct of chemical risk assessment. To this end IGHRC develops and publishes reports and guidance documents aimed at improving the conduct of chemical risk assessments in the UK, establishes specific-issue working groups to develop and share expertise and runs training courses in the area of risk assessment. This report explains how the group carried out its work programme during the period October 1999 to September 2003 (Phase I) and how it intends to carry out its programme of activities during the period October 2003 to September 2006 (Phase II). The report is available for consultation, and can be accessed on the IGHRC website[1].

During Phase I two reports and two substantial guidance documents were published, with a third guidance document published in early 2004. IGHRC also funded a pilot project to define a human exposure model for use in chemical risk assessments in the UK, and a project investigating human variability in relation to toxicodynamics. A very successful course on presenting and publishing risk assessments was run in October 2001, and this was repeated in March 2004. An evaluation of the activities of IGHRC carried out in 2003 reported that the activities of the group provide high value for individuals, agencies and departments.

We hope, in reading this report, that you will feel IGHRC continues to make an important contribution in the field of chemical risk assessments.

Dr David R Harper
Chairman of IGHRC
Chief Scientist, Department of Health

[1] http://www.le.ac.uk/ieh/ighrc/ighrc.html

Contents

1 Introduction

The Interdepartmental Group on Health Risks from Chemicals (IGHRC) comprises participants from UK government departments, research councils and agencies, and aims to stimulate the development of new improved approaches to the assessment of risks to human health from chemicals, share experiences to achieve a more consistent and coherent approach on issues related to chemical risk assessment, and increase the clarity and transparency with which risk assessment documents are written. The IGHRC comprises two committees, a steering committee and an executive committee. The Members of both committees are listed in Annex 1. The Executive Committee meets every three months and is responsible for the day-to-day operation of the IGHRC including writing of reports, organising workshops, producing guidance documents, developing training courses and proposing future activities to the Steering Committee. The Steering Committee meets once or twice yearly to approve and oversee the work of the Executive Committee.

The group was originally established in 1996 as the Risk Assessment and Toxicology Steering Committee but changed its name in September 1999 to reflect its broader remit. The aims and objectives of the IGHRC are given in Annex 2. The purpose of this report is to summarise the activities of Phase I of the IGHRC for the period October 1999 to September 2003, and to outline the forward plan and work programme to September 2006 (Phase II).

2 Work programme 1999–2003

As part of the remit of the Risk Assessment and Toxicology Steering Committee (the forerunner of the IGHRC), six reports on different aspects of risk assessment were published in 1999 (Risk Assessment and Toxicology Steering Committee, 1999a–f). These committee reports (cr1–cr6) made a number of recommendations and the IGHRC was charged with taking these forward as a series of interdepartmental activities during the period 1999–2003.

The first task of the IGHRC was to produce a work programme for the period October 1999 to September 2002, for publication, followed by consultation. The programme was published as the *First Report and Forward Plan to 2002* with timescales and approximate costs, and distributed for consultation in December 2000 as committee reports cr7 and cr7A (IGHRC, 2000a,b). The original three-year period for the work programme for this phase (Phase I) was extended for a fourth year, to September 2003, and the original Gantt chart (IGHRC, 2000a) amended to portray all the activities of the IGHRC to September 2003 (Figure 1).

Phase I activities were grouped into four main areas: the initiation of research projects, the production of authoritative 'guidance' documents and reports, the formation of specific-issue working groups and the sharing of experience in order to initiate change.

Within these activities, the IGHRC proposed that it would:

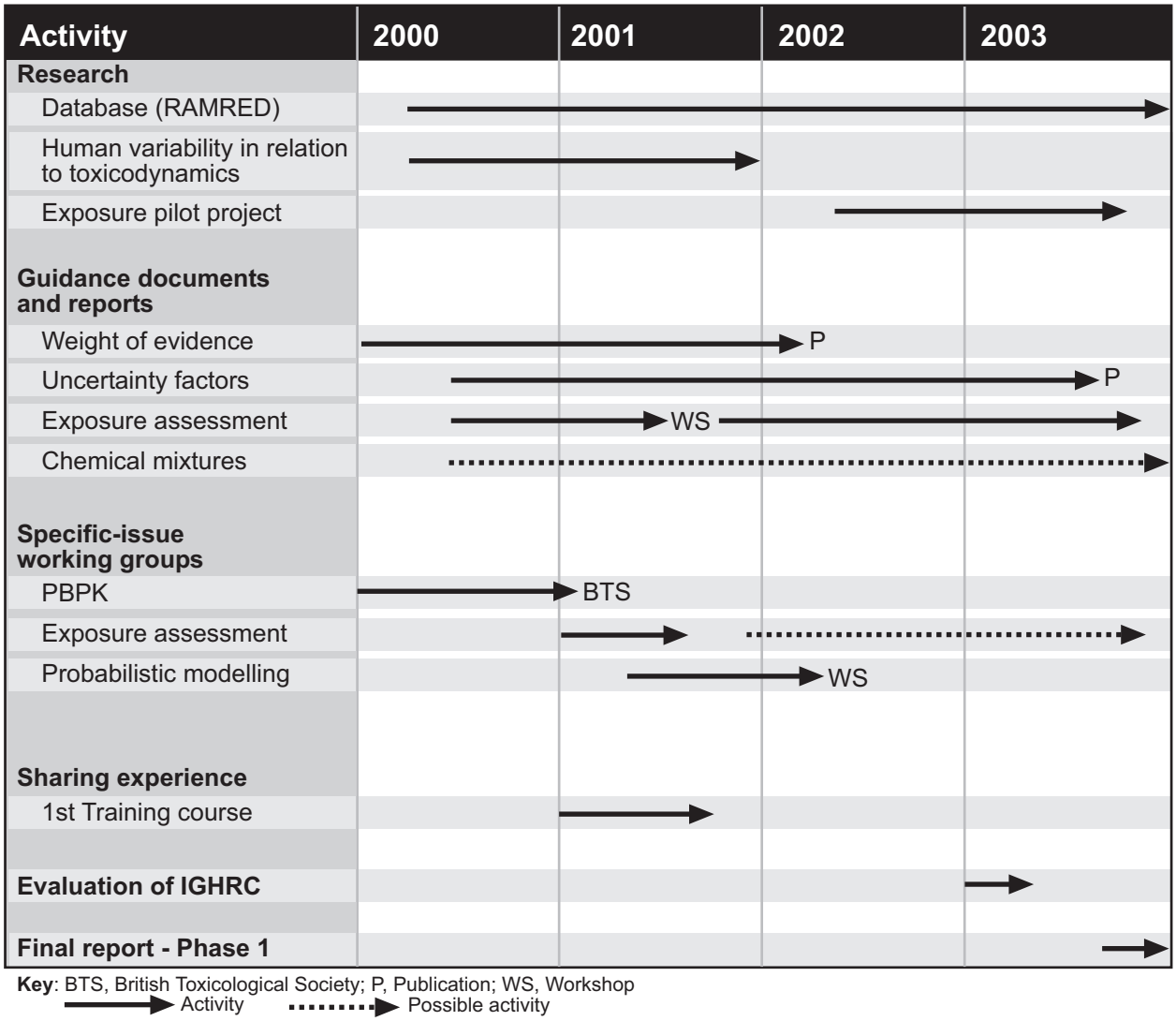
- fund a number of pilot research projects;
- update and maintain the risk assessment methodology research database (RAMRED);
- produce three guidance documents (on uncertainty factors, a weight-of-evidence approach to assessing chemical carcinogens and good exposure assessment practice);
- work in tandem with the British Toxicological Society (BTS) to set up a Physiologically Based Pharmacokinetic (PBPK) specific issue working group;
- convene a workshop to take forward probabilistic modelling in the UK; and
- hold courses for government scientists and policy makers to facilitate sharing experience and initiating change in the process of risk assessment.

In addition to the recommendations from the Risk Assessment and Toxicology Steering Committee reports, IGHRC also proposed exploring the impact of genomics and proteomics on future chemical risk assessment.

A limited number of replies were received during the consultative phase following publication of the *First Report and Forward Plan to 2002*. These were mainly supportive and encouraging of the work programme and recognised, in particular, the potential in sharing data and harmonising methodologies. Some suggestions were put forward for further activities, including looking at exposure to chemical mixtures, low dose effects of endocrine disrupting chemicals, multigenerational mammalian toxicity testing and reproductive toxicity. As there is extensive ongoing work outside of the IGHRC in the latter three areas, chemical mixtures alone was adopted by the IGHRC for potential future work.

The remainder of this section expands on the work programme outlined in the Gantt chart (Figure 1).

Figure 1 Schedule of activities, October 1999–September 2003



2.1 The research programme

The following five areas within chemical risk assessment were identified to take forward as research areas (IGHRC, 2000b):

- toxicology and uncertainty factors;
- human variation and susceptibility;
- the role of probabilistic modelling;
- exposure models; and
- PBPK models.

A database of ongoing research projects relevant to these five research areas was established and placed on the website of the IGHRC. This database, known as RAMRED, was produced and maintained by the MRC Institute for Environment and Health on behalf of the IGHRC. The database was updated once a year and could be searched by organisation, funding body, project or using free text or keyword search.

The IGHRC initially proposed sponsoring several research projects but it became clear that because of the differing research funding systems that exist between departments, agencies and research councils, it would not be realistic to attempt to establish a large common pool of funding. A document, *Priority Research Topics for Improving Chemical Risk Assessments* was produced to encourage government agencies, departments and research councils to consider funding research projects in these areas[1].

However, sufficient funding was made available to initiate the following two pilot research projects in areas identified by RAMRED as having minimal ongoing research.

[1] Available [January 2002] at http://www.le.ac.uk/ieh/pdf/prioritychems.pdf

2.1.1 A study on human variation in toxicodynamics

Following competitive tendering, this pilot project was awarded to Professor Andrew Renwick's group at the University of Southampton, and their final report received by the IGHRC in December 2002 (see Annex 3 for an Executive Summary and the report's main recommendations). It is anticipated that this report will also be published in a peer-reviewed journal.

2.1.2 Evaluation of currently used exposure models to define a human exposure model for use in chemical risk assessment in the UK

Following competitive tendering, IGHRC funded a one-year pilot project to review briefly the main existing exposure models that are currently being used in the UK and abroad, explore the development and use of a screening framework, and critically evaluate two relevant exposure models and propose how they might be modified to make them more applicable to chemical risk assessment in the UK. The project was awarded to Dr Mark Nieuwenhuijsen's group at Imperial College London. The final draft of the report was received in September 2003. The executive summary is given in Annex 4.

2.2 Guidance documents and reports

The IGHRC worked with government agencies and departments, as well as academic experts, to prepare the following guidance documents and reports on various aspects of chemical risks, with the purpose of making risk assessments more coherent and consistent.

- *Assessment of Chemical Carcinogens: Background to General Principles of a Weight of Evidence Approach* (IGHRC, 2002; committee report cr8)[1].
- *Uncertainty Factors: Their use in Human Health Risk Assessment by UK Government* (IGHRC, 2003; committee report cr9)[1].
- *Guidelines for Good Exposure Assessment Practice for Human Health Effects of Chemicals* (IGHRC, 2004; committee report cr10)[1].

[1] Full text version available [May 2004] at http://www.le.ac.uk/ieh/ighrc/igpublications.html

These documents have been approved by the agencies, departments and expert committees, thereby effectively producing a UK position on the topic in question.

In addition, IGHRC is very interested in the complex issue of how to undertake risk assessments on chemical mixtures and believes that guidance on how best to handle mixtures, from a regulatory perspective, would be very useful to UK Government departments and their expert committees. Further consideration of this document will take place following the outcome of a number of research projects initiated by the report: *Risk Assessment of Mixtures of Pesticides and Similar Substances* produced by the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (2002).

2.3 Specific-issue working groups

The IGHRC proposed establishing specific-issue working groups to develop and share expertise on a number of issues, including PBPK models, exposure assessment and probabilistic modelling. Initially these groups were to be interdepartmental, but the knowledge-base required made it necessary to go further afield for specific expertise.

The First Report and Forward Plan (IGHRC, 2000a) proposed a specific-issue working group on exposure assessment. However, when a workshop was convened in November 2001 to discuss exposure assessment and the content of the exposure guidance document, a separate specific-issue working group was considered unnecessary. In essence, the workshop participants became the specific-issue (exposure assessment) working group.

Specific-issue working groups were established for PBPK modelling and probabilistic modelling and their activities are outlined below.

2.3.1 Physiologically-based pharmacokinetic models

The IGHRC working group on PBPK modelling conducted a joint workshop with the British Toxicological Society on 'PBPK Modelling in Human Health Chemical Risk Assessment' in March 2001 at the Health and Safety Laboratories in Sheffield. Designed to appeal to individuals actively involved in risk assessment processes, it included presentations by key experts in the field and a 'hands-on' session with examples of data modelling using PBPK software. A total of 34 participants attended the workshop.

2.3.2 A practical introduction to probabilistic modelling of exposures for risk assessment

The IGHRC organised a one-day meeting 'Introduction to Probabilistic Modelling in Human Chemical Risk Assessment' at the University of Leicester in June 2002. The meeting was designed to introduce probabilistic modelling of exposures as a tool for improving the predictive value of chemical risk assessment and included presentations and case histories by key experts from government, academia and industry.

The meeting was well attended (58 participants) and stimulated a great deal of discussion on the use of probabilistic risk assessment in regulatory chemical risk assessment.

2.4 Sharing experience and initiating change

The IGHRC considers that sharing experiences across government agencies and departments on various issues will lead to a more consistent and coherent approach to risk assessment. Such sharing of experience may also initiate changes in procedure, or at the least lead to a better understanding of why different processes are used in different departments. Sharing of experience and initiating change may be achieved in a number of ways such as interdepartmental training, specific-issue working groups, workshops or running courses. The IGHRC proposed that the following areas would best be addressed by developing courses:

- reporting of risk assessment in a logical and transparent manner;
- improved communication with the public;
- explanation of risk management options; and
- uncertainty factors.

Following discussions it was agreed that the course on risk management was outside the remit of IGHRC and would not be taken forward, and, rather than running a course on uncertainty factors, the topic would best be covered through the production of a guidance document. Because courses on risk communication were run by a subcommittee of the Interdepartmental Liaison Group on Health Risks from Chemicals[1] it was felt that there was no requirement for IGHRC to conduct this course. Details of the remaining course are given below.

2.4.1 Presenting and publishing understandable and transparent risk assessments from chemical exposures

A two-day course on 'Presenting and Publishing Understandable and Transparent Risk Assessments from Chemical Exposures' took place at the MRC Institute for Environment and Health, in Leicester in October 2001. The aim of the course was not to teach individuals how to conduct chemical risk assessments but rather how to report them in a robust, logical and transparent manner. Discussion time was viewed as a very important part of the programme, with participants becoming actively involved and sharing their own experiences with colleagues from other UK Government agencies and departments. The course was attended by 18 scientists and policy makers, and participants unanimously agreed that the course was valuable and should be repeated[2]. The course outline is given in Annex 5.

2.5 Evaluation of the IGHRC initiative Phase I (October 1999–September 2003)

As part of the remit laid down in the *Annexes to the First Report and Forward Plan to 2002* (IGHRC, 2000b) the IGHRC proposed an independent evaluation of the activities and outputs of the group. Dr Sue Barlow, an independent consultant, was contracted to conduct the evaluation and her Executive Summary is given in Annex 6, and is also available on the IGHRC Website[3]. The full report may be obtained from the IGHRC Secretariat.

The evaluation was based on the views of scientists from eight Government agencies and departments participating in the IGHRC and on the views of seven advisory committees that had been provided with IGHRC publications and draft documents. Views were elicited from Government scientists by written questionnaire, for which the response rate was 46% (23/50), and from committees by structured, face-to-face or telephone interviews with chairpersons or other representatives. The evaluation of IGHRC courses was supplemented by written comments from non-Government participants.

[1] Now disbanded
[2] A second training course was held on 4/5 March 2004, with 24 participants
[3] http://www.le.ac.uk/ieh/ighrc/ighrc.html

2.5.1 Conclusions of the evaluation

The strongest aspects of the IGHRC initiative for individual participants have been the impact of the courses and workshops and the value of IGHRC in providing a forum for exchange of views on risk assessment practice across Government. There is a clear desire for these opportunities to continue.

The value of IGHRC to agencies and departments and their advisory committees has been its contribution, in synergy with other influences and pressures, to recognised improvements in risk assessment practice, particularly in the use of modelling, the treatment of uncertainty and the enhancement of transparency in published risk assessments.

The written documents, with the exception of the one on toxicological uncertainty, have had less impact. There have been few IGHRC publications to date, but there is clearly a wish for more written information and guidance, both among advisory committees and Government scientists, which could be separately directed at those relatively new to a topic and those with more advanced needs.

The collation of common priority research needs was delivered but the original aim of conducting jointly funded government research was not taken forward due to the difficulties in obtaining pooled funding. It would need a more pro-active strategy, beyond just publication of research needs, to bring joint funding to fruition. While IGHRC has promoted newer methods of risk assessment, it has not itself been instrumental in developing *de novo* approaches to risk assessment.

2.6 New issues for consideration

The main issue for consideration was that of genomics and proteomics and the impact of this new resource on chemical risk assessment. The IGHRC proposed to keep a watching brief on this area and to consider holding a workshop to explore the applicability of this technology to chemical risk assessment. Several meetings were held over the past two years to discuss this topic, the most recent being 'How Useful will Genomics, Proteomics and Metabonomics be to Assess Chemical Risk in Humans?', a discussion meeting held at the Society of Chemical Industry, London on 5 September 2003. A number of members of the Executive Committee of the IGHRC attended this meeting, and concluded that these techniques are several years away from being applicable to regulatory chemical risk assessment. The IGHRC will continue to keep a watching brief on this area over the next phase (Phase II) of its activities.

2.7 Summary of Phase I work programme

The aims and objectives of the IGHRC have been met in a number of ways through the above activities, and these are summarised in Annex 7.

3 Phase I financial statement (summary)

A summary of IGHRC income and expenditure for the period October 1999 to September 2003 is given in Table 1. This includes projected expenditure for Phase I activities carried over to Phase II, that is publication of the guidance document on exposure assessment, running a repeat of the first training course on risk assessment, and production of this final report of Phase I activities.

Table 1 Income and expenditure for IGHRC: Phase I actuals, period October 1999–September 2003 plus projected expenditure for activities in Phase I carried over to Phase II

A) Income	Oct'99–Sep'00	Oct'00–Sep'01	Oct'01–Sep'02	Oct'02–Sep'03	Total income Oct'99–Sep'03 Actuals £	
Balance b/f from RATSC contract	23 400				23 400	
Actual claims from IGHRC contract	115 897	102 406	104 788	N/A	323 091	
A) Total income	**139 297**	**102 406**	**104 788**	**N/A**	**346 491**	
B) Expenditure	Oct'99–Mar'01 (18 months)	Apr'01–Sep'01 (6 months)	Oct'01–Sep'02 (12 months)	Oct'02–Sep'03 (12 months)	Total actual expenditure	
Core staff costs	72 257	28 203	47 643	38 100	186 203	
Research programme and RAMRED	11 380	2 158	3 753	15 070	32 361	
B) Total expenditure (core activities)	**83 637**	**30 361**	**51 396**	**53 170**	**218 564**	
C) Schedule activities (to Sep'03)	Oct'99–Mar'01 (18 months)	Apr'01–Sep'01 (6 months)	Oct'01–Sep'02 (12 months)	Oct'02–Sep'03 (12 months)	Total actual expenditure	Expenditure carried over to Phase II activities
Guidance documents	0	2 204	0	33 676	35 880	11 390
Specific issues – Working groups	944	0	0	755	1 699	
Training courses × 2 (Oct'01 & Jan'04)				8 274	8 274	10 000
External review of IGHRC activities				10 785	10 785	
Final report (assume 20 page report, 400 copies)					0	5 100
C) Total expenditure (other scheduled activities)	**944**	**2 204**	**0**	**53 490**	**56 638**	**26 490**
Summary of income and expenditure	Oct'99–Mar'01 (18 months)	Apr'01–Sep'01 (6 months)	Oct'01–Sep'02 (12 months)	Oct'01–Sep'03 (12 months)	Total actuals	
Summary						
Total income to Sep'02	**139 297**	**102 406**	**104 788**	**N/A**	**346 491**	
Total expenditure to Sep'03 (core and scheduled activities)	**84 581**	**32 565**	**51 396**	**106 660**	**275 202**	

Total income	**£346 491**	
Total expenditure to date (Phase I)		£275 202
Funds allocated for Phase I carried over to Phase II		£26 490
Unallocated funds carried over to Phase II		£44 799
Total anticipated expenditure from Phase I		**£346 491**

Prepared 21 November 2003

RAMRED, risk assessment methodology research database; RATSC, Risk Assessment and Toxicology Steering Committee

The following government departments, agencies and research councils contributed towards the funding of IGHRC Phase I activities:

Biotechnology and Biosciences Research Council, Department of Health, Department of Trade and Industry, DETR, Environment Agency, Food Standards Agency, Health and Safety Executive, Home Office, MAFF, Medical Research Council, Pesticides Safety Directorate, Veterinary Medicines Directorate

4 Forward plan and work programme 2003–2006 (Phase II)

The forward plan and work programme for the period October 2003 to September 2006 (Phase II) was agreed at the Steering Committee meeting in January 2004.

4.1 Introduction

The purpose of this document is to outline the proposed strategy and programme of work of the Interdepartmental Group on Health Risks from Chemicals (IGHRC) for the period October 2003 to September 2006. This period represents the second phase of activities of IGHRC. The first phase (October 1999 to September 2002) is outlined in Sections 2 and 3. Annex 7 details specific IGHRC targets, and describes how these were achieved during Phase I, and how they will be achieved during Phase II.

Following a brainstorming session in February 2003 attended by members of both the Steering and the Executive Committees, the Executive Committee produced the first draft of the work programme. This was further discussed and expanded at the Sixth Steering Committee meeting in July 2003 and costings for the programme agreed. Individual 'champions' to take forward items within the programme were identified at the Fifteenth Executive Committee meeting in October 2003, and the updated programme agreed at the Steering Committee meeting in January 2004. At this meeting the Chairman emphasised the flexibility of the programme, which can be re-evaluated at any time should IGHRC committee members decide that a new project should take priority over, or be included alongside, existing projects.

4.2 Sharing experience/training

There was unanimous agreement by the Steering Committee that training for Government personnel involved in risk assessment from chemicals should be an essential part of future IGHRC activities. The purposes were manifold, but cited to be of particular importance was the need to bring people up to speed with general techniques and philosophy, and meeting and working with people from different departments in a learning atmosphere. Three particular courses were proposed.

4.2.1 Presenting and reporting transparent risk assessments

This course will be a modification of the one already successfully run by IGHRC in 2001, and comments from previous participants will be incorporated into the course design. The course, as before, will be a combination of presentations, case studies and interactive sessions[1].

The aim of this 2-day course is not intended to teach individuals how to conduct specific risk assessments but rather how to report them in a robust, logical and transparent manner and/or conduct a comprehensive analysis of such reports. Participants on the course will include scientists involved in the preparation of risk assessments (e.g. applicants seeking pre-market approval for products such as pesticides, medicines etc,) and decision-makers (e.g. expert advisory committee members and regulatory scientists involved in the setting of environmental standards, occupational exposure limits or licensing activities). Participants

[1] This course took place at the MRC Institute for Environment and Health, Leicester, 4/5 March 2004 with 24 participants. Course programme is available at http://www.le.ac.uk/ieh/ighrc/igcourses.html

will include a mixture of experienced risk assessors who would exchange experiences by a series of case studies and/or interactive sessions, and newer members to this area for whom the course would be a training exercise.

4.2.2 Basic aspects of exposure assessment

This course will be for non-experts who are required to use or understand exposure assessment as part of the overall process and will allow them some familiarity with the concepts and techniques used, as well as informing them of best practice. The course will be styled along similar lines to the elements covered in the exposure guidance document (IGHRC, 2004). The course will be divided into presentations and case studies, with plenty of opportunity for group discussions. Dr Peter Frier (LGC) has agreed to take the lead on this item, subject to Department of Trade and Industry (DTI) approval, with a timescale for holding the course at the end of 2004/early 2005.

4.2.3 A practical introduction to probabilistic modelling of exposures for risk assessment

This will be a hands-on course for experienced risk assessors and will follow on from some of the IGHRC work that has been successfully completed in this area. The course will consist of presentations explaining the theory and practical applications of probabilistic modelling and will include practical sessions using computers. The Food Standards Agency (FSA) run internal courses on probabilistic risk assessment and there is potential to liaise with them and to run the course in conjunction with a learned society such as the British Toxicological Society (BTS). It is hoped to run the course in 2005.

It was suggested that all IGHRC members should consult their departments with regard to other areas in which they may wish to receive training in chemical risk assessment.

4.3 Consistency and transparency – guidance documents

This was interpreted by the Steering Committee as a means of ensuring some level of harmonisation and openness between departments and agencies. In this context, harmonisation does not mean all departments undertaking risk assessments in the same way, but understanding where techniques might differ and being able to explain why this was the case. The IGHRC activity thought most useful to support this aim is through the production of guidance documents in the format of the three documents produced during Phase I: *Assessment of Chemical Carcinogens: Background to General Principles of a Weight of Evidence Approach* (IGHRC, 2002); *Uncertainty Factors: Their Use in Human Health Risk Assessment by UK Government* (IGHRC, 2003); *Guidelines for Good Exposure Assessment Practice for Human Health Effects of Chemicals* (IGHRC, 2004).

4.3.1 Route-to-route extrapolation in health risk assessment

The Steering Committee considered that a guidance document on route-to-route extrapolation would be very helpful for those working in assessing health risks of chemicals. Ideally data should be available on the specific route of concern. However, this was often not the case, and indeed it may not be necessary. In particular, consideration of generic advice on extrapolating oral toxicity data in animals (the information that is most likely to be available) to exposure via inhalation would be most helpful. Information on the minimum data requirements for any meaningful route-to-route extrapolation should be given. Similarly, extrapolation to dermal exposure should also be considered. Such guidance could reduce the need for animal studies to provide information, for example, on repeated dose studies by inhalation if such data were not available but information from oral studies was available and perhaps also an acute inhalation study.

Dr Robin Fielder (Department of Health, DH) has agreed to take this forward initially (until Summer 2004). The aim is for the document to be finalised in 2005.

The Steering Committee discussed the need for the production of a number of other guidance documents, but these would follow the completion of a number of existing activities. These are outlined in Sections 4.3.2 and 4.3.3 below.

4.3.2 Exposure modelling in chemical risk assessment

This document would be informed by the results of the exposure pilot project (which examined a number of existing exposure models, Section 2.1.2) and the guidance document *Guidelines for Good Exposure Assessment Practice for Human Health Effects of Chemicals* (IGHRC, 2004). The key issues would be to increase understanding of the differences and similarities of exposure models used by UK Government, to increase transparency on

why models are used in chemical exposure assessment and the default values used and also to increase transparency on how the information is presented. The document will concentrate on environmental exposure routes, and will be in a similar format to the IGHRC guidance document on uncertainty factors (IGHRC, 2003), that is it will map current methodology and guide users towards different approaches. The Environment Agency has agreed to take a lead on this document, which is anticipated to be completed by 2006.

4.3.3 Guidance on risk assessment for chemical mixtures

The IGHRC Steering Committee's view is that authoritative guidance on how best to deal with mixtures, from a regulatory perspective, is needed now.

The FSA has informed IGHRC that although it would be desirable to have authoritative guidance on how best to deal with mixtures from a regulatory perspective, they not think it possible to achieve this at present. A Science Group, led by the FSA, is in place working on guidelines for chemical mixtures to take forward work recommended in the WiGRAMP report (Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment, 2002). This Science Group is composed of officials from FSA, Veterinary Medicines Directorate (VMD) Pesticides Safety Directorate (PSD), DH and the Health and Safety Executive (HSE) and is chaired by Dr Tim Marrs. Their draft action plan is to take forward the recommendations of the WiGRAMP report on the risk assessment of mixtures and similar substances to produce a document that can be presented to the European Commission and other regulatory bodies to show how a regulatory system based on assessment of mixtures might operate. FSA are currently taking forward recommendations 11.2 and 11.3 of the WiGRAMP report, and are in the process of identifying groups of chemicals that may exert their effect via a common mechanism; this work will be of value for cumulative and aggregate risk assessment.

It was agreed that, in the first instance, it would be very useful and informative to collect from each regulatory body a view on how it currently deals with mixtures. This will produce a useful baseline against which to compare any future approaches that might be developed, and will inform the next stage of IGHRC activities in this area.

4.4 Specific-issue working groups

During Phase I specific-issue working groups were established to develop and share expertise in two areas: PBPK modelling and probabilistic modelling. The committee agreed that these were valuable activities, and workshops should continue to form part of the programme of activities during Phase II. A proposal for a workshop on chemical sensitisation was agreed.

4.4.1 Risk assessment for skin sensitisers

Suggestions for including respiratory and dietary sensitisation were discussed but it was agreed that their inclusion would dilute the focus of the workshop, and the proposal for a workshop specifically dealing with risk assessment for skin sensitisation was agreed. The risk assessment approach taken for skin sensitisers usually follows standard procedures for classification, with no account taken of potency. The workshop could explore the potential for introducing potency considerations into such risk assessments. The workshop would be informed by the following: a one-day symposium organised by the BTS on skin sensitisation in May 2004, specifically looking at the lymph node assay; a recent ECETOC report *Skin Sensitisation Testing for the Purpose of Hazard Identification and Risk Assessment* (Monograph 29, ECETOC, 2000) and a recent paper on classification of contact allergens according to potency (Kimber *et al.,* 2003). The HSE have agreed to take the lead on this workshop, which it is hoped to hold in Spring 2005.

4.5 Outline schedule of activities, October 2003–September 2006

The proposed IGHRC work programme up to October 2006, with outline timings, has been described in Sections 4.2–4.4. Figure 2 presents a summary schedule of activities in diagrammatic form, indicating the approximate start and finish dates and indicative costs. The total cost of the activities outlined in Figure 2 can be accommodated within the programme budget for the three-year period.

Figure 2 Schedule of activities, October 2003–September 2006

Activity	2003	2004	2005	2006	Costs £
Sharing experience/Training					
Presenting and reporting transparent risk assessment	→				10K
Basic aspects of exposure assessment		→			12K
A practical introduction to probabilistic modelling		→			20K
Guidance documents					
Route-to-route extrapolation		→			25K
Exposure modelling in chemical risk assessment		→			25K
Specific-issue working groups					
Risk assessment for skin sensitisers		→			25K
Chemical mixtures workshop (leading to preparation of a position document)					35K

5 References

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (2002) *Risk Assessment of Mixtures of Pesticides and Similar Substances*. Available [January 2004] on the Food Standards Agency website at http://www.food.gov.uk/science/ouradvisors/toxicity/COTwg/wigramp/

ECETOC (2000) *Skin Sensitisation Testing for the Purpose of Hazard Identification and Risk Assessment* (Monograph Number 29), Brussels, Belgium, European Centre for Ecotoxicology and Toxicology of Chemicals

IGHRC (2000a) *Interdepartmental Group on Health Risks from Chemicals: First Report and Forward Plan to 2002* (cr7), Leicester, UK, Institute for Environment and Health

IGHRC (2000b) *Interdepartmental Group on Health Risks from Chemicals: Annexes to First Report and Forward Plan to 2002* (cr7A), Leicester, UK, Institute for Environment and Health

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

Annexes

Annex 1
Members of the IGHRC Steering Committee

October 1999–September 2003

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Prof IFH Purchase

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Dr Len Levy
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Annex 2
IGHRC aims and objectives

The IGHRC is a committee made up of representatives of all the main government agencies and departments. The main focus of the IGHRC's activities is to seek ways to improve the procedures underpinning chemical risk assessment. In pursuit of this, the specific aims of the IGHRC are 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 a 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; and
- act to disseminate and advance best practice within government.

To address these aims the IGHRC has the primary and secondary objectives listed below.

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; and
- to identify and disseminate best practice in collaboration with stakeholders and other national and international organisations.

Secondary objectives

- To report annually to the Interdepartmental Liaison Group on Risk Assessment (ILGRA)[1] and funding bodies; and
- to arrange for an independent evaluation of the Group's achievements after three years (Phase I, October 1999 to September 2003).

[1] ILGRA has since been disbanded

Annex 3
A study on human variation in toxicodynamics

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A study funded by the Interdepartmental Group on Health Risks from Chemicals

Executive summary

Risk assessments for human exposure to chemicals are usually based on the results of toxicity studies in experimental animals. Uncertainty factors are applied to the animal dose–response data to allow for possible species differences and human variability in sensitivity. For chemicals present in food and drinking water an uncertainty factor of 100 is usually applied to the No Observed Adverse Effect Level (NOAEL) in animals studies to derive a 'safe' intake for humans. The 100-fold uncertainty factor comprises two separate factors of 10 with a 10-fold factor to allow for human variability in response to the chemical. Each 10-fold factor has to allow for differences in toxicokinetics, which is the delivery of the chemical to its site of action, and toxicodynamics, which is inherent target organ response to the presence of the chemical. Based on recent discussions and recommendations by the International Programme on Chemical Safety, it has been suggested that the 10-fold uncertainty factor for human variability should be regarded as comprising two factors, each of $10^{0.5}$ or 3.16 to allow for interindividual differences in toxicokinetics and toxicodynamics. The subdivision of the uncertainty factors was based on an analysis of human variability in pharmacokinetics and drug responses largely based on kinetic-dynamic modelling (in which the contribution of each can be separated and defined) and *in vitro* studies of pharmacological activities. Pharmacokinetic data on therapeutic drugs are relevant to the risk assessment of non-therapeutic compounds because they share common pathways of metabolism; however, most pharmacological responses are related to specific receptor binding characteristics and therefore the variability for such effects may not be representative of toxicological reactions.

The current project was undertaken to investigate the published data on human variability in toxicological response to the administration of compounds *in vivo* or from *in vitro* studies, in order

to allow a comparison with the default toxicodynamic variability factor of $10^{0.5}$ or 3.16. For *in vivo* studies the experimental method and analysis of data would have to separate out variability in overall response arising from toxicokinetic differences and from inherent variability in target organ sensitivity, usually by the use of a pharmacokinetic-pharmacodynamic model. For *in vitro* studies it was important that interindividual differences in metabolism of the compound *in vitro* did not give rise to differences in the duration of exposure to the active chemical and therefore differences in response which would have been related to the rate of metabolism rather than the inherent target organ sensitivity.

Literature searches were conducted using the electronic databases TOXLINE (1966–2001), BIDS-EMBASE (1981–2000) and MEDLINE (1966–2001) using a variety of search terms. Over 100 000 citations were identified and the abstracts scanned for potentially usable data.

Overall, the publications did not provide data describing *in vivo* interindividual variability in target organ sensitivity and response. Indeed many publications did not even adequately describe the interindividual variability in overall response to the external dose, let alone after allowing for kinetic variability. A major problem with the published *in vivo* studies was that the vast majority related to toxicity produced following administration of fixed doses of therapeutic agents. In order to define human variability in response, either to the external dose or at a target organ level, it is necessary to compare the doses required to produce the same level of response and not the differences in response to the same fixed dose. In addition to this fundamental problem, in the vast majority of the studies, the data presentation was inadequate with limited or no information on interindividual variability in response. In many cases the data were presented simply as the mean or median, sometimes with a range provided. Although there are a number of publications on the toxicity of cancer chemotherapeutic agents, these primarily reported the results as the numbers of individuals showing different grades of toxicity in relation to escalating doses, and it was impossible to determine the magnitude of individual responses with escalating doses from the published incidence data.

Major problems were also identified in the published *in vitro* studies on toxicity. Although many studies were identified in which cytotoxicity of various human cells was investigated in response to treatment with toxins, including non-therapeutic agents, the majority of studies gave no indication of the numbers of donors or the interindividual variability in the concentrations required to produce the same level of response. Many studies have been reported using human hepatocytes or other liver preparations, but the interpretation of variability for these was not possible because the majority of compounds would be subject to hepatic metabolism so that individual variability would reflect both metabolism (toxicokinetics) and target organ sensitivity. The vast majority of *in vitro* studies that described variability in response did not clarify whether such variability represented experimental error from pooled samples, or represented true human variability. Many studies did not even define the numbers of individuals from whom the samples were taken, or the processing of the samples prior to measurement of sensitivity. Only a very small number of studies adequately defined human variability in response, for example, by reporting the mean and coefficient of variation for the concentration causing a 50% response.

In conclusion, the analysis has shown that despite the large numbers of studies that have investigated responses of humans *in vivo* or *in vitro* using cell preparations, the data have not been analysed or reported such as to allow an assessment of human variability in sensitivity either in relation to the external dose or to target organ response. It is possible that many of the databases behind publications contain data suitable to define human variability in toxicodynamics but the analyses do not allow the abstraction of such information.

A number of recommendations can be made:

- It is recommended that all future investigations into human responses should, whenever possible, define the extent of human variability either in relation to external doses giving the same response, or to plasma or *in vitro* concentrations necessary to give the same level of response.

- It is important that *in vivo* studies use pharmacokinetic–pharmacodynamic models to define the variability in concentrations producing a fixed response.

- *In vivo* studies using sensitive biomarkers of effect could provide important information allowing an assessment of the validity of the uncertainty factors used to allow for human variability.

- While there will always be questions concerning the extrapolation of *in vitro* findings to the *in vivo* situation, it is important that future *in vitro*

studies using isolated human tissues or human cell lines should define not only the average level of response, but also interindividual variability in the concentrations required to produce a fixed level of response. Such information would require that samples from different subjects are maintained separately but under identical conditions and that they are not subject to techniques that would contribute *ex vivo* variability to the observations.

- The availability of information on interindividual variability in tissue responses to the presence of foreign compounds will be essential in the interpretation of potential genetically based differences in relation to risk assessment.

December 2002

Annex 4
Evaluation of currently used exposure models to define a human exposure model for use in chemical risk assessment in the UK

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Prepared for
the Interdepartmental Group on Health Risk from Chemicals

Executive summary

The risk assessment process involves hazard identification, exposure assessment, dose–response characterisation, and risk characterisation stages. Exposure models are commonly employed to quantify the exposure assessment stage. A variety of models have been developed in the UK and elsewhere to assess human exposures for chemical risk assessment purposes. This report sets out to define a human exposure model for use in chemical risk assessment in the UK. The report follows on from the *Review of Existing Exposure Models* by Fryer *et al*. (2003).

Two alternative approaches to exposure modelling are investigated, with respect to their suitability for chemical risk assessment in the UK. The first approach consists of using a single comprehensive exposure model. The Review of Existing Exposure Models document (Fryer *et al.*, 2003) describes and evaluates a total of 15 different existing exposure models. These models can be broadly classified as either source- or receptor-orientated in nature. Source-orientated models focus on predicting how chemicals from particular sources or release events come into contact with human populations. Receptor-orientated models focus on predicting how particular human populations or individuals come into contact with chemicals. The CalTOX and LifeLine™ models are selected as examples of source- and receptor-orientated models, respectively. These models are deemed to possess the greatest potential for use in a single exposure model approach.

The CalTOX and LifeLine™ models are assessed against a series of criteria to determine their suitability for use as comprehensive human exposure

Property	CalTOX	LifeLine™
Does the model account for all potential sources of exposure?	Limited	Limited
Does the model account for all potential pathways and routes of exposure?	Limited	No
Does the model have the ability to consider population subgroups with potentially high levels of exposure as well as general populations?	Limited	Yes
Dose the model consider/quantify variability and uncertainty?	Yes	Yes
Is the model applicable for appropriate temporal and spatial scales?	No	Limited
Is the model valid for its exposure remit?	Yes	Limited
Can the data requirements of the model be met for UK situations?	Limited	No
Is the model transparent and user-friendly?	Limited	Yes

models for chemical risk assessment in the UK. The table above summarises the results of this exercise.

The second approach to exposure modelling investigated in this report involves the use of a screening framework. The screening framework uses basic properties describing the relevant chemical and the exposure situation to screen a comprehensive range of potential exposure pathways and environmental processes. The user is then guided to existing exposure model(s) suitable for the exposure situation, as required. The essence of the screening framework approach is that the most appropriate method is identified for the exposure assessment situation. A working example of a screening framework is developed and tested against a series of scenarios representing a range of hypothetical exposure assessment situations involving a variety of chemicals. Arsenic, cadmium, benzene, isoproturon, and dioxins are selected as the chemicals to test the framework against since they cover a wide range of values for relevant physicochemical properties and they ensure that representative chemicals are included for all key pathways. The framework correctly identified the most significant exposure pathways and environmental processes for each of the exposure scenarios.

The two alternative approaches to exposure modelling discussed in this report are compared and contrasted in order to assess their relative suitability for chemical risk assessment in the UK. The single model approach to exposure modelling is relatively simple to use, consistent, and familiar for most users. However, single model approaches suffer from limited adaptability and an inherent trade-off between the comprehensiveness of the model and the amount of input data required. The use of a screening framework offers a transparent, flexible, consistent and comprehensive approach to exposure modelling but it is subject to the limitations of current exposure models and their lack of integration.

The findings of this report demonstrate that neither the existing versions of the CalTOX nor LifeLine™ models are suitable as single human exposure model approaches for chemical risk assessment in the UK. Modifications to the existing versions of these models are proposed but even if these modifications are adopted, limitations in the model methodologies will still exist relating to fundamental differences between source- and receptor-orientated models. It is concluded that the flexibility required to meet the wide range of exposure assessment needs for chemical risk assessment in the UK is best provided through the adoption of a screening framework approach to exposure modelling. The use of a screening framework also facilitates the process of model selection and it fits into a tiered approach to risk assessment. Possible future extensions of this work are discussed.

Final Draft, 16 September 2003

Annex 5
IGHRC training course programme outline

IGHRC
Presenting and publishing understandable and transparent risk assessments from chemical exposures

24th/25th October 2001

Time	Course session	Speaker/Session facilitator
Day 1		
9.30	Introduction	**Dr Carol Courage** Senior Toxicologist MRC Institute for Environment & Health
10.00	Using risk assessments Key steps in the risk assessment process	**Dr John Fowler** Independent Consultant
10.45	*Morning Coffee*	
11.00	Risk assessment from an NGO point of view	**Ms Jennie Oldham** Policy Officer, Green Alliance
11.45	Problem formulation	**Dr Carol Courage**
12.15	General question and answer session	**Dr Carol Courage**
12.30	*Lunch*	
13.30	Hazard identification and characterisation	**Dr Len Levy** Head of Toxicology and Risk Assessment Group MRC Institute for Environment & Health
15.15	*Afternoon tea*	
15.45	Exposure characterisation	**Dr David Tennant** Independent Consultant
17.30	Round up of Day 1	**Dr Carol Courage**
Day 2		
9.00	Introduction to aims and structure of Day 2	**Dr Len Levy**
9.15	Data quality	**Dr Sue Barlow** and **Dr David Tennant** Independent Consultants
10.45	*Morning Coffee*	
11.15	Risk characterisation	**Dr Steve Fairhurst** Head of Industrial Chemicals Unit Health & Safety Executive
13.00	*Lunch*	
14.00	Key features of communicating risk assessments	**Dr Len Levy**
14.45	Course round-up	**Dr Len Levy** and **Dr Carol Courage**
15.30	Course feedback and close	**Dr Len Levy**

Annex 6
Evaluation of the IGHRC initiative

Report prepared for the IGHRC Steering Committee by Dr Sue Barlow, Independent Consultant

Executive summary

Introduction

The objectives of this evaluation of the work of the Interdepartmental Group on Health Risks from Chemicals (IGHRC) were:

- To ascertain the value of the IGHRC initiative to the participants and to the departments/agencies carrying out chemical risk assessments.
- To assess its potential contribution to the development of chemical risk assessment approaches.

The evaluation was carried out against the background of the aims of the IGHRC initiative, which were to promote the development of improved methodologies, promote improved approaches to risk assessment, promote coherence and consistency in the practice of risk assessment, and disseminate and advance best practice.

Methods

The evaluation is based on the views of scientists from eight Government agencies and departments participating in IGHRC and on the views of seven advisory committees that have seen IGHRC publications and draft documents. Views were elicited from Government scientists by written questionnaire, for which the response rate was 46% (23/50), and from committees by structured, face-to-face or telephone interviews with chairpersons or other representatives. The evaluation of IGHRC courses has been supplemented by written comments from non-Government participants.

Findings

Courses and workshops

The courses and workshops covered the topics of PBPK modelling, probabilistic modelling, and presenting and publishing risk assessments. They were generally very well received, regarded as well organised, worth the time involved and good value. Ratings for speakers, value of the course to the individual participants and value to their agency/department were mostly 'excellent' or 'good'; a few rated these aspects as 'fair' but none rated them as 'poor'. There was enthusiasm for further courses with a number of suggestions made about future topics. It was suggested that the input should be broadened with more speakers drawn from outside Government.

The PBPK modelling and probabilistic modelling courses were rated as valuable both by those new to these topics and by those with some prior knowledge. Comments indicated that these courses had provided Government participants with good introductions to the science, practical applications and examples, in a way that equipped them to contribute to agency/department discussions on modelling and to respond when submissions or proposals included such modelling. The knowledge and experience gained was already being used within the agencies/departments, though IGHRC was not the only contributor to that process. Some indicated that the value to the agency/department was not clear as such models were not yet being used. Some also felt they still did not have enough information on how and when to use such models, nor on their limitations. This suggests that these courses might usefully be run at two levels, introductory and more advanced with plenty of time for 'hands on' sessions.

The course on presenting and publishing understandable and transparent risk assessments was also well received; it provided opportunities to compare approaches across Government, enhanced participants confidence in what they were currently doing, and gave non-toxicologists a better understanding of the various elements of risk assessment. The knowledge and experience gained on the course was being used, particularly in the preparation of risk assessments relevant to the general public.

A question was raised about whether IGHRC was the appropriate forum for running educational courses aimed at more junior staff and whether this was compatible with the aims of IGHRC to stimulate development of improved risk assessment methods.

Publications

Responses to the publications and draft publications varied depending on the topic and the level of the reader's prior knowledge. While the publications were generally well received by both Government scientists and advisory committees, comments suggested there was scope in the future both for more general, short documents aimed at the non-specialist and for longer documents containing guidance and more technical explanations aimed at specialist, day-to-day practitioners of risk

assessment. It was also clear that there is a delicate balance to be struck in trying to fulfil the aims of IGHRC to promote coherence and consistency in the practice of risk assessment and to disseminate and advance best practice. There is a very fine line to be drawn between the extent to which publications should go beyond merely describing the state of the science and the extent to which they could become overly prescriptive, particularly if they are to be acceptable to independent advisory committees and their secretariats.

The First Report and Forward Plan to 2002 and its Annexes was viewed as useful in describing the initiative's aims, albeit some thought it lengthy and repetitive.

The Assessment of Chemical Carcinogens was very well received for its content, clarity and conciseness. Other committees said they were comfortable with the approach used by the Committee on Carcinogenicity, outlined in the document.

The draft Framework Document on Toxicological Uncertainty, although lengthy, was welcomed as a very useful background document describing the national and international scene. It had stimulated good discussions in all the committees and, in particular, has been instrumental in triggering the development of a clearer, more structured approach to toxicological uncertainty in the occupational field.

An initial draft of the Guidelines for Good Exposure Practice became widely circulated, which was not the original intention. It is a topic which is not very amenable to simple generalisation and the detailed early version was considered lengthy and difficult to digest. Following input from a small group of exposure practitioners, a shorter final version is close to completion. It has not been seen by advisory committees.

Although there were only a limited number of Government respondents to the questionnaire and these were supposedly involved in IGHRC, the number who had not read the publications (about half for any one document) was somewhat surprising. This suggests that substantial effort is being put into the preparation of publications which are not very widely disseminated or read. Those involved in drafting IGHRC documents commented that it had taken considerable time and effort, but most considered the effort had been worthwhile. Most commented that the time between inception and publication was too long. The IGHRC may wish to review its target audience and dissemination of publications if future efforts are to be rewarded with a wider readership. For example, non-technical introductions to risk assessment that would be suitable for interested members of the general public and for new committee members, including 'lay' members, were among the suggestions for future publications from the advisory committees. Amongst risk assessment practitioners, there is clearly a desire for more detailed guidance, tailored, where necessary to the different chemical sectors. Other specific suggestions for topics for future publications were also made.

Influencing the conduct, presentation and publication of risk assessments

Just over half of the respondents considered that the IGHRC initiative had helped them to identify new or better approaches to risk assessment, for example, modelling approaches, questioning defaults for uncertainty, or highlighting the need for better transparency. Most respondents said that the IGHRC initiative has helped describe and make clear, for the first time, the similarities and differences in approaches between Government agencies/departments. This was welcomed and had prompted some useful exchanges of views. A number of suggestions were made about other risk assessment approaches the IGHRC might usefully pursue.

Just under half of the respondents said IGHRC had led to discussions in their agency/department about the way in which risk assessments are conducted and published, including the use of PBPK and probabilistic modelling, how uncertainty should be handled and how to be more transparent with consumers/end users about uncertainties. While other pressures for openness were noted, there was strong support from most respondents across all agencies/departments for the view that the IGHRC initiative had contributed to improving transparency in risk assessment. Nevertheless, few thought it had (yet) influenced the way their own agency/department presented risk assessments, commenting, for example, that some committees already have established approaches. Those who considered IGHRC had been influential cited increased emphasis on transparency in what is published and a welcome move away from phrases like 'no risk', 'no concern'. Transparency was also viewed as a spur to more robust risk assessment. There had been little feedback from other stakeholders about these changes. Those who thought the IGHRC had not contributed to improving transparency cited inertia to change and the fact that little has yet been published by IGHRC.

Two-thirds of respondents were satisfied, one-third dissatisfied with the way their agency/department currently conducts, presents and publishes risk assessments. There were both satisfied and dissatisfied respondents in every agency/department. Those satisfied cited as their reasons, *inter alia*, appropriate in-house expertise, thoroughness of data reviews, use of tiered approaches, transparency in what is published, and support from advisory committees and other stakeholders for the approaches put forward. Some, though generally satisfied, still saw room for improvement. Those dissatisfied cited, *inter alia*, slowness in preparation and publication of risk assessments, too much emphasis on spin in presentation, variable quality and lack of consistency, failure to address all areas of uncertainty, the need to move to more probabilistic approaches, make more use of toxicokinetic/toxicodynamic data and take more account of inherent human variability.

Influencing coherence and consistency in the practice of risk assessment

Most respondents thought the IGHRC initiative had contributed to coherence and consistency in risk assessment practice within Government agencies/departments, but found it difficult to judge whether it had had a significant impact in enhancing coherence and consistency across Government. Those who considered it had contributed cited as their reasons the raising of awareness of similarities and differences between agencies/departments, providing a peer-group forum for the sharing of practice, experience and ideas, and the potential of IGHRC documents as a good foundation for consensus building. The few respondents who considered it had not contributed to coherence and consistency in risk assessment practice thought that IGHRC had not yet generated anything that could promote it and did not have the stature to do so.

IGHRC had triggered discussions on coherence and consistency in four agencies/ departments. The outcomes of these discussions were somewhat nebulous with the exception of one, which had resulted in the agency/department resolving to move to greater transparency with a clear framework for dealing with uncertainty.

A number of suggestions were made about possible future activities the IGHRC might undertake on coherence and consistency (see main report for details).

Research needs in risk assessment

Around half the respondents had read the publication on Priority Research Topics. All but one thought IGHRC had been useful in identifying common research needs in risk assessment and the document had triggered discussions in five agencies/departments about taking the research needs forward. However, this had resulted in little concrete outcome and no joint funding of research, except for two pilot projects. A number of reasons for this were suggested, including logistical difficulties in agreeing joint funding across Government, lack of an identified person/organisation to push for such funding, and lack of common funding priorities among agencies and departments with differing business needs. Some commented that if the research was relevant it would be funded anyway by their agency/department, without pursuing joint funding.

The Risk Assessment Methodology Research Database (RAMRED) on the IEH website, outlining current projects funded by agencies and departments, had been accessed by only half the respondents. It has perhaps been more useful to those outside UK Government; over 500 organisations have accessed RAMRED from 42 countries in the 2 years since its launch. Government respondents regarded it as a potentially useful resource to find out what was being done and to prevent duplication. However, the database was considered limited, probably out of date, inadequate to enable others to follow up results, and time consuming and expensive to maintain. There was no support for its continuation and several thought it should be dropped from any future phase of IGHRC.

IGHRC as a forum for exchange of views

IGHRC was seen as a valuable forum for exchange of views, this aspect being viewed very positively by the great majority of respondents. IGHRC had provided useful opportunities for exchange of views, mainly via courses, workshops and committee meetings. It was noted that IGHRC had provided the first real opportunity for risk assessment practitioners across Government to get together. It had helped individuals gain access to expertise in other agencies/departments and had increased understanding of how other agencies/departments conduct risk assessments. All but one respondent said they would value continuing exchange with other agencies/departments. Views were mixed about the nature of any future activities; some desired a technical rather than a policy forum, others suggested broadening the group.

Value of IGHRC in international fora

Very few respondents were involved in international fora and only 3 had made use of aspects of IGHRC in international work, generally as background to discussions on risk assessment approaches and regulatory schemes. For example, it had helped to identify useful approaches to put forward at the European Union (EU) level. A number of suggestions were made on how to ensure that UK discussions and approaches to risk assessment were influential in a wider sphere, including encouraging/allowing the participation of knowledgeable UK Government people in international fora, having more Government agency/department publications and presentations at meetings on risk assessment, continuation of IGHRC with a dynamic programme and better publicity of its activities within and beyond the UK.

Views of advisory committees

All those consulted felt that the risk assessment methods currently available met their committee's needs and that their committee was adequately briefed on methodology, including newer approaches. An important issue for committees was recognising when it was appropriate to use newer methods. Some committees had already used newer methods, such as PBPK and probabilistic modelling, cumulative risk assessment, etc.

The difficulties of offering advice in situations where data were sparse were highlighted, particularly as they inevitably invoke a debate about precautionary approaches. Some future guidance on such situations would be welcomed. The development of alternative possibilities to ALARP/ALARA for giving advice on unavoidable exposures to genotoxic carcinogens would also be welcomed.

Guidance for new committee members on the principles of risk assessment would be welcomed, particularly now that most committees include several 'lay' members. A risk analysis framework with some parts common to all committees and other parts necessarily tailored to the individual committee situation was also suggested. More specific suggestions for future written guidance included integrating exposure across all routes (aggregate exposure) and estimating exposure of children.

Exposure assessments were regarded as the biggest area of uncertainty that committees had to contend with and toxicological uncertainty (lack of data) also featured large in the occupational field. Several of those consulted thought that transparency in dealing with uncertainties in published risk assessments by committees had greatly improved over recent years and that IGHRC had contributed to that process but they also considered that further progress was still needed and some committees had further to go than others.

Consistency in a committee's approach to risk assessment was viewed as very important. The safeguards to ensure this, that is reliance on input and historical memory of secretariat, members and observers, and reviewing of chemicals with similar structures and/or modes of action as groups, were considered to work well. There were mixed views about the need to know, and the value of, other bodies' opinions on particular chemicals.

The committees' views on the IGHRC documents have been included earlier under *Publications*.

The main value of IGHRC to date and possibly in the future was seen as contributing to providing a strong base for a scientifically justifiable risk assessment process that would underpin the ongoing work of the advisory committees. Encouragement of good practice and the emphasis on transparency helped to provide clear audit trails which stand up to scrutiny by outside parties. IGHRC was also seen as a useful forum for exchange of ideas and for pushing forward activities (e.g. research) which no single agency or department could do alone. If IGHRC continued, it was suggested that it would need to take more cognisance of international activities (e.g. by WHO/IPCS and the EU) covering similar ground.

Conclusions

The strongest aspects of the IGHRC initiative for individual participants have been the impact of the courses and workshops and the value of IGHRC in providing a forum for exchange of views on risk assessment practice across Government. There is a clear desire for these opportunities to continue.

The value of IGHRC to agencies and departments and their advisory committees has been its contribution, in synergy with other influences and pressures, to recognised improvements in risk assessment practice, particularly in the use of modelling, the treatment of uncertainty and the enhancement of transparency in published risk assessments.

The written documents, with the exception of the one on toxicological uncertainty, have had less impact. There have been few IGHRC publications to date, but there is clearly a wish for more written information and guidance, both among advisory committees and Government scientists, which could

be separately directed at those relatively new to a topic and those with more advanced needs.

The collation of common priority research needs was delivered but the initiative to stimulate jointly-funded research has not been successful. It would need a more pro-active strategy, beyond just publication of research needs, to bring joint funding to fruition. While IGHRC has promoted newer methods of risk assessment, it has not itself been instrumental in developing *de novo* approaches to risk assessment.

Other issues about the way in which IGHRC has worked have been raised during this evaluation, which might merit consideration in any discussions on the future of IGHRC. These include:

- Should IGHRC focus on continuing education covering existing risk assessment practice, or should it focus more on the development of new methodologies and approaches to risk assessment?

- Should IGHRC generate consensus documents, which take a long time and run the risk of being too general to be useful, or should it disseminate more focused or controversial documents authored by named people to stimulate discussion?

- Should IGHRC be more outward looking with respect to participants in its activities and related international developments on harmonisation of risk assessment, or should it focus on the immediate needs of UK Government scientists and the advisory committees?

2 June 2003

Annex 7
Ways in which the work programme addresses the aims of IGHRC

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. IGHRC has a remit, therefore, to consider ways of enhancing the risk assessment process for chemicals, by 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 IGHRC, and by promoting information dissemination and presentation of risk 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.

The aims of IGHRC can be summarised as follows:

- **Promote coherence and consistency** in the practice of toxicological risk assessment as used within the different risk management and regulatory frameworks used in Government.

- **Promote the development of methods and techniques** that will improve information used in the toxicological risk assessment process.

- **Act to disseminate and advance best practice** within UK Government and through EU and international fora.

Table 1 indicates how the activities during Phase I, and those proposed during Phase II, meet the aims and objectives of IGHRC.

Table 1 Phase I and Phase II IGHRC activities

October 1999–September 2003 (Phase I)	Promote coherence and consistency in toxicological risk assessment	Promote the development of toxicological risk assessment methods and techniques	Disseminate and advance best practice within government, sharing experience and initiating change
Risk assessment methodology research database (RAMRED)		√	√
Pilot project: Human variability in relation to toxicodynamics	√	√	
Pilot project: Human exposure model for use in chemical risk assessment in the UK	√	√	√
Guidance document: Assessment of chemical carcinogens (cr8, published 2002)	√	√	√
Guidance document: Uncertainty factors (cr9, published 2003)	√	√	√
Guidance document: Guidelines for good exposure assessment (cr10, published 2004)	√	√	√
Specific issue working group: Exposure assessment workshop (November 2001)	√	√	√
Specific issue working group: PBPK modelling (joint workshop with BTS, 2001)	√	√	√
Specific issue working group: Introduction to probabilistic modelling (meeting, June 2002)	√	√	√
Presenting and publishing understandable and transparent risk assessment from chemical exposures (two-day course, October 2001)	√	√	√
October 2003–September 2006 (Phase II)			
Guidance document: Route-to-route extrapolation in health risk assessment	√	√	√
Guidance document: Exposure modelling in chemical risk assessment	√	√	√
Specific issue working group: Risk assessment of skin sensitisers	√	√	√
Specific issue working group: Chemical mixtures	√	√	√
Presenting and publishing understandable and transparent risk assessments from chemical exposures (two-day training course, March 2004)	√	√	√
Basic aspects of exposure assessment (training course)	√	√	√
A practical introduction to probabilistic modelling (two-day training course)	√	√	√

BTS, British Toxicological Society; PBPK, Physiologically based pharmacokinetic modelling

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

The Interdepartmental Group on Health Risks from Chemicals (IGHRC) publications

cr 7 The Interdepartmental Group on Health Risks from Chemicals: First Report and Forward Plan to 2002

cr 7A The Interdepartmental Group on Health Risks from Chemicals: Annexes to First Report and Forward Plan to 2002

cr 8 Assessment of Chemical Carcinogens: Background to General Principles of a Weight of Evidence Approach

cr 9 Uncertainty Factors: Their use in Human Health Risk Assessment by UK Government

cr 10 Guidelines for Good Exposure Assessment Practice for Human Health Effects of Chemicals

cr 11 The Interdepartmental Group on Health Risks from Chemicals: Final Report for Phase I, 1999–2003 and Forward Plan to 2006

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