1. This report provides a summary of a meeting held to explore the two parallel worlds of clinical and regulatory toxicology. A list of participants at the meeting is provided in Annex 1.

2. The meeting was funded by IPCS/UK domestic funds from the Department of Health, London, with additional support from the Scottish Executive. It was held at Edinburgh University Medical School from 20 to 21 September 2001. Dr Nick Bateman, Director of the Scottish Poisons Information Bureau, chaired the meeting. Ms Lesley Onyon (OECD) acted as rapporteur.

3. The adopted agenda for the meeting is provided in Annex 2.

BACKGROUND, PURPOSE AND SCOPE OF MEETING

4. Dr Tim Meredith, Coordinator, International Programme of Chemical Safety (IPCS), welcomed participants and summarised the background and objectives for the meeting.

5. The objectives for the meeting were:

   - for participants to obtain a better understanding of the two disciplines of clinical toxicology/poisons information and regulatory toxicology/risk assessment, and

   - to identify opportunities whereby clinical toxicologists/poisons centres and regulatory toxicologists/risk assessors could mutually improve the risk assessments used to protect human health from the use of industrial and consumer chemicals and products.

6. Historically, clinical toxicology/poisons information and regulatory toxicology/risk assessment have existed in two parallel worlds and have developed as separate disciplines sharing the common objective of protecting human health. The two disciplines face similar challenges, e.g. how to act in the absence of information on the effects and potential for exposure, and how to manage the increasing perception of deficiencies in the current chemical risk assessment processes.
7. At the global level major advances have been made in relation to risk assessment work and in particular the development of consistent risk assessment approaches. However there still remains a substantial shortfall in the number of existing chemicals that have been assessed and it is now widely accepted that to stand any chance of tackling the shortfall, as much risk assessment work as possible must be shared internationally. Efficiencies may also be gained by reaching a better understanding, refinement and acceptance of assessment methodologies being used.

8. Dr Meredith reported that recent international declarations have supported an increase in the collection and use of harmonised human exposure and poisoning data. The third meeting of the InterGovernmental Forum on Chemical Safety was held in Salvador da Bahia, Brazil, October 2000. At this meeting the challenges set for chemical safety in the 1992 Rio Declaration on Environment and Development were reconfirmed and priorities agreed for expanding and accelerating the international assessment of chemical risks, including:

- cooperation with developing countries and countries with economies in transition to ensure that all relevant data, including exposure data, required to assess human and environmental health are developed and assessed;

- establishing poisons centres in countries that do not yet have such centres and strengthening those that already exist; and

- making extensive progress on national systems for the collection of harmonised data, including categorisation by, e.g. poisoning case, chemical identity, structure and use.

9. These priorities align strongly with the objectives of the International Programme on Chemical Safety (IPCS) INTOX Programme [http://www.intox.org].

INTRODUCTION

10. Dr Stephen Corbett (Australia) introduced a draft background paper “Bridging the Gap between Clinical and Regulatory Toxicology”. Dr Corbett prepared the background paper for the meeting to help stimulate discussion and to identify areas of common interest.

11. Dr Corbett described the history of risk assessment and its application in regulatory practice, including both qualitative and quantitative approaches. He also described the worldwide development of poisons centres which provide toxicological information and advice on the management of poisoning cases, provision of laboratory analytical services, research, education and training in the management of poisoning.

12. The IPCS INTOX Programme was introduced and its key activities described. INTOX is an international activity designed to strengthen poisons centres by providing internationally evaluated data on the prevention, diagnosis and management of poisoning cases together with harmonised terminology for the recording and aggregation of human toxicology data.

13. Dr Corbett proposed three key areas as potentially benefiting from increased mutual understanding and activities between clinicians and regulatory toxicologists:

- Improving the evidence base in human toxicology – including epidemiological studies.
- Characterising individual susceptibility.
- Improving the surveillance of human exposure and disease.

14. Following initial discussion, the meeting agreed the following key questions should provide a framework for discussion and for the conclusions of the workshop:

- What is the level of common understanding between the two disciplines concerning the nature of regulatory risk assessment and the work of clinical toxicologists and poisons centres in collecting data on reports of human poisoning incidents?
- What are the uses of human data in making risk assessments for regulatory purposes, and what are the future possibilities?
- What information on the health effects and potential exposure of humans to industrial and consumer chemicals and products is collected. Is there any information that risk assessors currently lack?
- What is the potential for poisons centres to improve estimates of human exposure?
- Are there any immediate benefits that might result from clinical and regulatory toxicologists working more closely together?
- What would be some initial steps in starting to strengthen collaboration between the two disciplines?

**REQUIREMENTS AND USE OF HARMONISED HUMAN DATA IN RISK ASSESSMENT ACTIVITIES**

**The nature of risk assessment.**

15. The meeting found that there was not, in general, a good understanding between clinicians and risk assessors about the term “risk assessment”, the information needed to conduct a risk assessment, the methodologies and the possible uses of the risk assessment after completion. This lack of understanding needed to be addressed as a priority if the two disciplines were to work together.

16. Dr Ursula Gundert-Remy (Germany) explained, that, from the point of view of a risk assessment authority there were several reasons for performing a risk assessment, including:

- finding out the risks on a regular systematic basis associated with the manufacture, import, use and disposal of chemical substances under the auspices of a national or regional assessment scheme. An example of this would be the European regulation EC 793/93 on the evaluation and control of existing chemical substances.
- working cooperatively under an internationally agreed framework – such as the IPCS Concise International Chemical Assessment Documents (CICADS) or the Organisation for Economic Co-operation and Development (OECD) High Production Volume (HPV) Chemicals Programme to find out the risks associated with chemicals of international concern.
in response to an acute accidental release, e.g. fire and road accidents.

- in response to an accidental finding (e.g. residues in water, food, and waste) or a monitoring programme.

17. Participants agreed that the third and fourth examples should not be overlooked. If a comprehensive risk assessment already exists for a specific chemical it should provide a useful starting point for the information needed by emergency personnel. However a concern was expressed that often the assessment needed re-examining and putting in a local context to ensure its appropriateness for the emergency at hand.

18. Dr Gundert-Remy explained further, that, in all cases, the principles and components of risk assessment are broadly the same:

- **A hazard assessment** of the potential effects of the chemical - including the identification of effects on human health and the environment and characterisation of the dose(s) or concentration(s) at which critical effects are likely to be seen and identifying parameters such as the No-Observed Adverse Effect Level (NOAEL).

- **An assessment of the likely exposure(s)** to the chemical under various circumstances of use, including the hazard assessment and populations at risk. The exposure assessment would typically be based on how the chemical is normally used and on the possibilities for over-exposure including accidents. The exposure assessment involves using measured levels of exposure and/or estimates of exposure using model scenarios.

19. Undertaking the risk assessment involves integrating these two main components. A range of approaches can be used depending on the intended needs of the risk assessment. For example:

- comparing the dose at which critical effects might be expected with the estimated exposure, to give a “margin of safety” for particular exposure situations;

- deriving specific guidance values which can be used in the future for intentional or unintentional releases; or

- calculating quantitative estimates of risk effects for situations of interest.

20. Most developed countries have legislative requirements for the conduct of risk assessments for both new and existing industrial chemicals and the endpoints examined are specified in the legislation. For example, Member States of the European Union require acute toxicity, irritation and corrosive, sensitisation, repeated dose toxicity (28 days, 90 days), mutagenicity, carcinogenicity and reproductive toxicity data to be routinely provided before the marketing of the chemical.

21. The OECD specifies the minimum amount of information that should be available on chemicals produced in quantities of over 1000 tonnes per annum (High Production Volume or HPV). The IPCS Programme for producing Concise International Chemical Assessment Documents (CICADS) and Environmental Health Criteria (EHC) documents looks at all available information. However in spite of major efforts by many countries, industry and international
organisations throughout the last decade, over 70% of all HPV chemicals still lacked the most basic short term toxicity information about health and environmental hazards (US Environmental Defense, 1998, Toxic Ignorance). In response, the international chemical industry has launched a global initiative to ensure missing data are produced by 2004. Such an increase in activity will demand efficient means of accessing all existing data, including human data. Better use of existing data will avoid unnecessary animal tests and help maximise the resources available to meet the challenge. In the event that priorities would be useful, poisons centres might wish to be more actively involved in risk assessment programmes to identify those chemicals that result in most enquiries/calls. There might also be opportunities for clinicians, poisons centre professionals and emergency service personnel to participate in the development of certain risk assessments to ensure that they are as relevant as possible for protecting human health.

Use of human data in carrying out risk assessments.

22. Human data are currently mainly used to identify/confirm adverse effects predicted from animal toxicity studies, thereby improving the evidence base in toxicology, to establish specific guidance values and in classifying hazards. They are also currently used to provide alerts and prioritise potential chemicals of concern. The potential for using human data in the risk assessment process does not seem to have been fully reached.

23. Risk assessors seem to be generally unaware of the potential of poisons centre data and how to access them and so are often limited to the use of literature reports of ad-hoc cases. These reports are often inadequate in identifying the chemical involved, in providing an estimate of the exposure and for describing the symptoms and signs exhibited by the exposed person(s). In practice, this often leads to a reliance on animal data and the use of default uncertainty factors in making risk assessments.

24. Ms Bette Meek (Canada) described her experience in conducting assessments under the Canadian Environment Protection Act. She tended to agree with the commonly held view that the amount of effort in obtaining data on human experience was not always balanced by the usefulness of the data to the overall risk assessment. Although efforts to find relevant data continued, many difficulties were encountered with the available data including the presence of many uncontrolled variables, incomplete exposure estimations and the differing responses observed among individuals.

25. Ms Meek described the case of an in-depth assessment of ethylene glycol. Ethylene glycol is a very common cause of human poisoning. For example, the Scottish Poisons Information Bureau reported that ethylene glycol was its third most frequent cause of chemical poisoning in 1998.

26. In Canada, an attempt was made to try to use the human data that existed to improve the understanding of the relative sensitivity of rodents and humans to ethylene glycol. Unfortunately the information available for humans and animals was not fully compatible. Urinary concentrations of oxalate were absent in the reported human data, but this was the common metabolite measured in the rodent studies.

27. This example helped to highlight the potential usefulness in having an early dialogue with clinical toxicologists during the planning phase of risk assessments in order to understand the reasons for likely information gaps and to explore ways to overcome them. Risk assessors need a better appreciation that biochemical analyses taken during the treatment of a poisoning case were decided on the basis of whether the analytical information would help in the clinical management
of the case. In the case of ethylene glycol, the measurements used were typically acid-base balance and renal function tests and not the measurement of urinary oxalate concentrations. Improved dialogue with clinical toxicologists might also be helpful in identifying surrogate metabolites that could provide information to address critical information gaps, e.g. information from clinical trials where similar metabolites have been measured.

28. Other examples were identified where human data already drives the risk assessment process. These examples served to reinforce the need for improvements in the access to existing information and the importance of improved data collection by poisons centres/clinical toxicologists.

29. Dr Gundhert-Remy illustrated the importance of human data for the derivation of Acute Exposure Guidance Levels (AEGLs) by using the example of methanol, another important cause of human poisoning incidents.

30. AEGLs are defined as the concentrations of a substance in the air that cause a specific biological effect in a defined population in a specified period of time. They represent threshold exposure values for the general public. AEGLs provide guidance to those responsible for emergency planning and response to chemical accidents as well as for prevention of accidents with possible adverse health effects. The US has an active programme for the development of AEGLs and international participation is currently being considered.

31. Dr Gundhert-Remy reported that the acute and short-term toxicity of methanol varies greatly between different species due to pharmacokinetic differences. Rodents develop higher blood methanol concentrations than humans and monkeys. In addition, rodents did not accumulate the metabolite - formate - which can lead to blindness and death from metabolic acidosis in humans. The AEGLs for methanol therefore rely heavily on pharmacokinetic studies in human volunteers and data on acute lethal effects on humans after the ingestion of methanol.

32. Ms Onyon also illustrated the importance of human data in the classification of chemicals at the hazard identification stage of the risk assessment.

33. In June 2001, a global set of classification criteria was adopted by OECD Member countries as a contribution to one of the six priority issues addressed in Chapter 19 of Agenda 21 by the United Nations Conference on Environment and Development (UNCED). The agreed harmonized integrated classification system for human health and environmental hazards on chemical substances and mixtures is described in detail in OECD Monograph Number 33 [http://www.oecd.org/ehs].

34. Classification is intended to improve the identification and reporting of the inherent hazardous properties of chemical substances and mixtures so that their health hazards can be communicated more consistently. This can also help to improve information included on labels and safety data sheets and ultimately the safety measures for all users of the chemical, whether involved in manufacturing, formulation, transport, direct use or disposal.

35. The type of human data needed for classification includes reliable epidemiological data and experience of the effects on humans from occupational data, chemical accidents, clinical studies and well-documented case reports and observations.
36. For classification, human data of good quality and reliability have precedence over other data. While there is guidance on the conduct and interpretation of toxicity tests using laboratory animals there is little information available on where to find information about human cases and any guidance on how to use data if they exist. Classification cannot be made where information is equivocal or in the absence of data. This should compel clinical toxicologists/poisons centres and regulatory toxicologists/risk assessors to work more closely together. Without classification of the hazard at a certain level of severity, the details of that particular hazard would not necessarily be reported on the label or safety data sheet and therefore be known to the public, clinicians or poisons centres.

37. For some classification criteria, human data are particularly critical, e.g. those defining relatively low acutely toxic chemicals. These chemicals may present a danger to vulnerable populations. Animal testing for this hazard is not encouraged.

38. Classification criteria are also now being developed for “non-classical” toxicity endpoints. For some of these it is again vital to access existing human data. Two examples are chemicals that cause chemical pneumonitis and those that defat the skin. These are examples that are reported commonly to poisons centres, e.g. white spirit and other petroleum distillates. The experience of poisons centres in the diagnosis and treatment of such cases could be very useful in developing the new classification criteria themselves. This should help both disciplines because the risk of developing chemical pneumonitis will be more consistently reported by manufacturers on the product label and subsequently improved information would be available to the public and clinicians.

39. Dr Andrew Renwick (UK) introduced the IPCS work on the harmonisation of non-cancer risk assessment methodologies which focuses on the toxicokinetic and toxicodynamic data on the chemical under evaluation. He explained that the chemical 2-butoxyethanol provided a good example with a relatively large amount of comparative animal and human toxicokinetic data that could be used to refine the risk assessment. The work was aimed at developing meaningful uncertainty factors and challenged whether the traditional approach of using a factor of x10 for interspecies differences and another factor of x10 for individual differences was valid. The results so far have shown examples of chemicals where these default factors had been overprotective and others where they had been underprotective. Dr Renwick emphasised the importance of finding examples from both animal and human studies where data exist and of working closely with clinicians and poisons centres to identify suitable cases.

40. In the course of the meeting, Dr Renwick and Dr Monique Mathieu-Nolf (France) proposed a scheme for identifying those chemicals that could be useful for further discussion and study (Annex 3). The scheme consisted of working from list(s) of priority risk assessments and
comparing them with lists of chemicals frequently implicated in cases of human poisoning by poisons centres. Well-characterised cases of human exposure to these chemicals could then be:

- subject to dose-response evaluation looking for indicators of critical effects;
- analysed and related to chemical-specific, toxicokinetic or mode of action data; and
- further examined to evaluate the current default risk assessment approach.

41. Dr Renwick proposed that the development of case studies of this nature would also enable variation between individuals to be studied in future including the genetic variability of individuals.

42. Drs Steve Hankin and Colin Ramsay (UK) presented three case studies which had involved Scottish public health professionals: dioxins from animals being burnt to stem the recent epidemic of foot and mouth disease; hydrocarbons seeping into water supplies; and a chlorine exposure incident. These examples illustrated some of the difficulties faced by emergency personnel in obtaining information relevant to the incident and in making decisions based on the scarce information. They explained particular difficulties in knowing how to apply guidance values for chemical exposures, if indeed they existed. While they appreciated that guidance values were often developed for different reasons, e.g. low level lifetime exposure of the general public, rather than acute exposure of a selected group, the lack of information on the methodology used to develop them and the lack of transparency in identifying critical data could be particularly frustrating. In an emergency situation, decisions have to be made quickly and evacuating people from their homes or closing off the water supply must be justified by clear and authoritative sources of information. These examples drew attention to the need to ensure the usefulness of completed risk assessments for different audiences, for risk assessors to make their methodologies as clear as possible and for emergency personnel to explain their needs and any perceived limitations in current risk assessment reports.

OPPORTUNITIES FOR IMPROVED HUMAN DATA COLLECTION

43. This part of the meeting focused on describing the nature and variety of poisons centres, the current and planned role of the IPCS INTOX Programme, and opportunities for providing improved human data.

Data collected by poisons centres.

44. There are over 200 poisons centres which have been established worldwide since the 1950’s and plans internationally to support the establishment of a minimum of 30 centres in other countries.

45. Dr Lindsay Murray (Australia) explained that poisons centres collect different types of information depending on the level and type of services they are funded to provide. Accordingly, he wished to avoid any misunderstanding that all, or even selected, poisons centres could provide an infinite amount of data and information for risk assessment. The simplest level of data collected by poisons centres relates to the enquiries or calls received – these can be from the general public, from hospitals or general practitioners. The information gathered commonly includes the nature of the chemical or product involved, the timing and circumstances of exposure, an estimate of the dose and a summary of the symptoms and signs exhibited. The enquiries may or may not relate to an actual poisoning case.
46. Not all poisons centres are able to follow up enquiries to obtain further information. Those centres that are able to follow up enquiries can sometimes link the enquiries to a subsequent hospital admission. In this case the opportunity for obtaining more useful information for risk assessment and other purposes is increased. The number of cases able to be followed up in detail is however limited, and each poisons centre is likely to be unique in the extent and type of cases it is able to follow up routinely.

47. Other poisons centres admit patients with suspected poisoning for specialised treatment and/or monitoring. Others are closely linked to specialist treatment centres in nearby hospitals. These provide additional opportunities to monitor and collect information.

48. Poisons centres deal with the whole range of potential toxic exposures ranging from plants, pharmaceuticals, and veterinary medicines to venomous animals. Industrial chemicals and consumer chemicals make up a small percentage of the total number of enquiries. The percentage of the enquiries attributable to these chemicals varies depending on the geographical location of the poisons centre. Often in developing countries there is a greater emphasis on pesticide and other chemical exposures. The ability to aggregate information on cases of poisoning on a global basis is therefore important in getting better information on the extent and range of experience with specific chemicals.

49. The capacity of poisons centres to become further involved in follow-up, toxicovigilance and other surveillance activities depends on the priorities the poisons centres have been set up to meet. Many centres have been established to deal only with acute emergency situations and so would not necessarily have the resources to respond to questions from the regulatory community on chronic exposures. Some centres are currently developing such links so that they can provide practical information on the types of exposure situations causing concerns and the outcomes of exposure to certain chemicals. Some are already involved with national authorities preparing risk assessments and some feedback from those involved in this type of collaborative activity might be useful for others. If it was known in advance that there was an interest in obtaining follow-up information about certain exposures then these might be subject to special follow-up for a specific time period. The availability of specialised analytical services may also be available at some centres and could add to the depth of follow-up information available.

50. Poisons centres have built up a significant source of human expertise in retrieving and managing specialised information, diagnosing different types of poisoning, predicting outcomes and managing individual cases. In addition some centres have extensive product compositional databases, sometimes in the form of electronic product registers that are not available to risk assessors. The detailed information is lodged with such centres for use in an emergency and centres have obtained the information over a long period of time through building trust and confidence with product manufacturers. Regulatory assessors often lack this type of information and have to make time-consuming investigations to find out which products contain certain chemicals. More often than not, regulatory assessors are limited to dealing with the primary producer of the chemical under legislation and cannot easily access information from downstream product formulators and retailers. In the absence of appropriate information, risk assessors are often forced to make assumptions about exposure and in consequence, exposure estimation may be the weakest aspect of the risk characterisation process. Consequently, there may be opportunities for building links with poisons centres to obtain generalised information about product types and exposure situations encountered with certain types of chemicals. As the information lodged with poisons centres is held in trust, further discussion would be needed with the product manufacturers involved before such a dialogue could be initiated.
51. Dr Albert Nantel (Canada) suggested that poisons centres are often well placed to identify and develop exposure scenarios for frequently occurring types of exposure. Exposure to aerosols was one example which lacked a good model for predicting levels of human exposure. Other types of exposure not generally expected by the manufacturer of formulator, such as exposure of pregnant women to paints and glues in enclosed spaces could also be identified from information about enquiries to poisons centres. This information could be used to prioritise the development of generic exposure models for use in the risk assessment process.

52. Ms Joanna Tempowski (UK) described the development of the IPCS INTOX Programme as a tool for poisons centres and units concerned with the prevention, recording, evaluation, diagnosing, treating and reporting of chemical emergencies. INTOX has four key capabilities, providing:

- information on toxic exposures;
- an information management system;
- a gateway to a global network of poisons centres and other users of INTOX; and
- a forum for collaboration between experts and those responding to emergencies concerning toxic chemicals.

53. The INTOX Databank contains a series of detailed Poisons Information Monographs (PIMs) which provides information on the likely symptoms, signs, treatment and poisoning outcome for chemicals that are the subject of common enquiries to poisons centres. A candidate list of additional PIMs needed for the system is also available. Better awareness, and access to existing and planned international or regional risk assessments, might assist in the production of future PIMs and provide a possible future point of collaboration between the two disciplines.

54. Much effort had been given to the development of a standardised case/incident reporting form together with authority lists for recording symptoms and signs prior to consultation and at the time of consultation. Use of these by collaborating centres is necessary to allow human poisoning data to be aggregated globally. This is particularly important where there are few cases reported to many centres and also between centres where the circumstances of poisoning with the same agent may be different.

55. Ms Onyon circulated a template that is being considered for use within the OECD Existing Chemicals programme to help improve the reporting of human case studies. The aim was to incorporate the template into the guidance manual for those providing information in the OECD HPV Programme. It was suggested that clinical toxicologists/poisons centres might be able to provide comment on this template using the benefit of their experience in human poisoning cases. This comment can be provided directly to the OECD and the suggested reporting template can be found on the OECD’s password protected internet homepage (Contact: Dian.Turnheim@oecd.org).

56. Dr Murray suggested that one way for continuing dialogue about improving human data collection and any planned or ongoing collaborative activities might be to use existing INTOX email discussion groups (e.g. intox-general@ccohs.ca).
SUMMARY CONCLUSIONS

The level of common understanding between the two disciplines about risk assessment.

57. There is much scope for improving the level of common understanding about risk assessments between clinical toxicologists/poisons centres and regulatory toxicologists/risk assessors, and for the future involvement of other specialists such as occupational toxicologists, clinical toxicologists, geneticists and forensic and molecular toxicologists. Better understanding of the risk assessment process, methodologies, emerging issues and the challenges faced will be a necessary first step in establishing a continuing dialogue, both at a national level and internationally.

58. Existing networks such as the INTOX email discussion groups and network of risk assessors already involved in international activities might also be useful in promoting involvement in specific collaborative projects.

The uses of human data in making risk assessments for regulatory purposes and future possibilities.

59. There are a number of current uses for human data in existing risk assessment procedures but use in practice is hindered by a lack of awareness about information sources and their strengths and limitations. The main use of human data seems to be in identifying/confirming the toxicity of chemicals predicted from animal studies. Human data does not seem to have been used widely in the assignment of risk assessment priorities – again possibly due to the lack of dialogue between the relevant disciplines. Some authorities are beginning to engage poisons centres and clinicians in providing comment on assessments being undertaken and there seems to be great potential in the involvement of both disciplines in discussing and planning follow-up actions for high priority in-depth risk assessments.

60. There are possibilities for increased collaboration in the preparation of risk assessment reports. Poisons-centre professionals, clinicians and other emergency responders should consider assisting in these peer-review processes so that the completed reports can be as useful as possible in the preparation of PIMs, in establishing guidance values and aiding decision making in cases of emergency.

61. With the implementation of a global system for classifying the hazards of chemicals, an increased pace of the conduct of risk assessments for existing chemicals, poisons centres and clinical toxicologists should make every effort to improve access to existing information on human exposure to chemicals. This would reduce unnecessary animal testing and help to ensure that data not available from any animal studies, e.g. chemical pneumonitis are reported by manufacturers in a consistent way.

62. As well as ensuring that current uses of human data are improved, there may be value in using the systematic approach outlined in Annex 3 to identify chemicals which are of interest to both risk assessors/regulatory toxicologists and poisons centres/clinical toxicologists. Identifying these chemicals will be important in exploring and further developing collaborative projects.

63. Together, the two disciplines of clinical and regulatory toxicology are in a unique position to continue to develop and refine risk assessment methodologies applicable to human data. For example, improving knowledge and methodology relating to the susceptibility of certain human sub-populations to chemical effects, the extrapolation of animal toxicity data to
humans, and refining the use of uncertainty factors in the risk assessment process. Hypotheses derived from new disciplines such as genomics and proteomics hold great promise for future risk assessment activities but will require validation with human data before they can be a part of the general risk assessment machinery. Risk assessors and clinical toxicologists will have a significant role to play in the development, testing and validation of such developments.

**Information on the health effects, potential exposure to industrial and consumer chemicals and products that risk assessors lack.**

64. In addition to easily-retrievable information on cases of human poisoning, risk assessors currently lack good information on use patterns of specific chemicals, including their presence in formulated products. This information is often lodged with poisons centres or is available from product registers in some countries.

65. The identification of generic exposure scenarios for exposures of common concern to poisons centres/clinical toxicologists would be very helpful to the risk assessment community.

**First steps for the two disciplines to work more closely together.**

66. The first steps for the two disciplines to work more closely together are based on improving awareness of the availability of risk assessment reports and the methodologies used to produce them and how to access human data on poisoning cases. The feasibility of identifying chemicals which have both human and animal data available is important for establishing a basis for further collaboration.

67. The following specific initial products and activities were identified by the meeting:

- Investigating the specific sources of human data used by the risk assessment community and promoting information on how to access any supplementary sources, including specialist services available in certain poisons units/specialist treatment centres.

- Looking at any existing examples where regulatory authorities currently work with poisons centres in the risk assessment process, and evaluating the experience to date.

- Developing some case studies where there is information from both risk assessment and the management of poisoning perspectives, such as the example presented by Canada on ethylene glycol. Such case studies could be used for: investigating the feasibility for ongoing collaboration; exploring the use of INTOX among a limited number of collaborating poisons centres for follow-up of chemicals which have been given priority for in-depth risk assessment; considering indicators of critical effects; identifying chemical-specific data on toxicokinetics or mode of action and exploring the validity of using default uncertainty factors in the risk assessment. The feasibility of using the scheme shown in Annex 3 could be tested for identifying initial case studies – essentially those assigned priority for risk assessment and with the most experience and information from poisons centres.

- Exploring the possibility of collaborative meetings between clinicians and risk assessors involved in the review of specific risk assessments.
- Testing the use of existing networks such as INTOX for obtaining comment on topics common to both risk assessors and clinical toxicologists, and for highlighting issues of importance.

- Identifying exposure scenarios of concern to poisons centres to establish priorities for developing relevant exposure scenarios for estimating exposure to the public, consumers and workers and assessing whether or not there are adequate exposure scenarios available for these uses. Collaborating in the development of generic exposure models for these priorities, as appropriate.

- Identifying the needs of clinical toxicologists and emergency workers in using current risk assessments, including identifying any barriers for full use of existing risk assessments and questions about the methodology used and its application at the local level.
Annex 1

LIST OF PARTICIPANTS

Bridging the Gap between Clinical and Regulatory Toxicology
20-22 September 2001

Dr Stephen Corbett
Manager, Environmental Health
NSW Health
Gladesville Hospital
P.O. Box 798, Victoria Road
Gladesville 2111
Australia
Tel: +61-02-98160426
Fax: +61-02-98160377
E-mail: scorb@doh.health.nsw.gov.au

Dr Andrew Fraser
Deputy Chief Medical Officer
Health Department
Scottish Executive
St. Andrew’s House
Regent Road
Edinburgh EH1 3DG
United Kingdom
Tel: +44-131-2442270
Fax: +44-131-2442835
E-mail: andrew.fraser@scotland.gov.uk

Mrs Alison M Good
NPIS (Edinburgh),
Scottish Poisons Information Bureau
The Royal Infirmary,
Edinburgh, EH3 9YW
Tel: 0131 536 2298,
Fax: 0131 536 2304
Email: Alison.Good@LUHT.SCOT.NHS.UK

Dr Ursula Gundert-Remy
Federal Institute for Health Protection of Consumers & Veterinary Medicine (BgVV)
Postfach 33013
Thielallee 88-92
14191 Berlin 33
Germany
Tel: +49-30-84123300
Fax: +49-30-84123003
E-mail: u.gundert-remy@bgvv.de
Dr Steve Hankin  
Scottish Centre for Infection and Environmental Health (SCIEH)  
Clifton House  
Clifton Place  
Glasgow  G3 7LN  
United Kingdom  
E-mail: Steve.Hankin@scieh.csa.scot.nhs.uk

Dr Arthur Johnston  
Health Department  
Scottish Executive  
St. Andrew’s House  
Regent Road  
Edinburgh EH1 3DG  
United Kingdom  
Tel: +44-131-  
Fax: +44-131-  
E-mail: arthur.johnston@scotland.gov.uk

Dr Monique Mathieu-Nolf  
Centre Anti-poisons de Lille  
CHRU  
5 Avenue Oscar Lambert  
59037 Lille  
France  
Tel: +33-320444799  
Fax: +33-320445628  
E-mail: mmathieu@chru-lille.fr

Ms Bette Meek  
Head, Priority Substances Section  
Environmental Health Directorate  
Health Protection Branch, Add.Loc. 0802B1  
Health Canada  
Tunney’s Pasture  
Ottawa, Ontario K1A 0L2  
Canada  
Tel: +1-613-9573129  
Fax: +1-613-9542486  
E-mail: bette_meek@hc-sc.gc.ca

Dr Lindsay Murray  
Emergency Medicine  
Department of Surgery  
Queen Elizabeth II Medical Centre  
Nedlands, WA 6009  
Australia  
Tel: +61-8-93461943  
Fax: +61-8-93461665  
E-mail: Lindsay.Murray@health.wa.gov.au
Dr Albert J. Nantel  
Scientific adviser  
Institut national de santé publique du Québec (INSPQ)  
2400 d'Estimauville  
Beauport, Québec  
G1E 7G9  
Canada  
Tel: 1-418-666-7000 Ext. 501  
Fax: 1-418-666-2776  
E-Mail: albert.j.nantel@chuq.qc.ca (or) ajnantel@riq.qc.ca

Ms Lesley Onyon  
Environment, Safety and Health  
Environment Directorate  
Organisation for Economic Co-operation and Development  
2 rue André Pascal  
75775 Paris  
France  
Tel: +33-1-45249849  
Fax: +33-1-45241675  
E-mail: lesley.onyon@oecd.org

Dr Hans Persson  
c/o Swedish Poison Information Centre  
Karolinska Hospital  
Box 60 500  
S-104 STOCKHOLM  
Sweden  
Tel: +46-8-610-0511  
Fax: +46-8-327-584  
hans.persson@apoteket.se

Dr Colin Ramsay  
Scottish Centre for Infection and Environmental Health (SCIEH)  
Clifton House  
Clifton Place  
Glasgow G3 7LN  
United Kingdom  
Tel: +44-141-3001100  
Fax: +44-141-3001170  
E-mail: colin.ramsay@scieh.csa.scot.nhs.uk
Dr Andrew Renwick
Clinical Pharmacology Group
School of Medicine
University of Southampton
Bassett Crescent East
Southampton SO16 7PX
United Kingdom
Tel:  44-23-8059 4263/4261
Fax:  44-23-8059 4262
E-mail: A.G.Renwick@soton.ac.uk

Ms Joanna Tempowski
Medical Toxicology Unit
Guy’s & St. Thomas’ NHS Trust
Avonley Road
London SE14 5ER
United Kingdom
Tel:  +44-207-7715309
Fax:  +44-207-7715306
E-mail: Joanna.Tempowski@gstt.sthames.nhs.uk

Local Organizer

Dr Nick Bateman
Scottish Poisons Information Bureau
The Royal Infirmary
Lauriston Place
Edinburgh EH3 9YW
United Kingdom
Tel:  +44-131-5362303
Fax:  +44-131-5362304
E-mail: spib@luht.scot.nhs.uk

Secretariat

Dr Tim Meredith
Coordinator
International Programme on Chemical Safety
World Health Organization
20 Avenue Appia
1211 Geneva 27
Switzerland
Tel:  +41-22-7914348
Fax:  +41-22-7914848
E-mail: mereditht@who.int
INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

Bridging the Gap between Clinical and Regulatory Toxicology

To be held in the Henry Littlejohn Suite, Edinburgh University Medical School, Teviot Street, Edinburgh.

20 – 22 September 2001, commencing at 09.00 on the first day

Proposed Provisional Agenda

1. Introduction and welcome.

2. Approval of the agenda and election of officers.

3. Background, purpose and scope of the meeting.

4. Introduction to Background Paper “Bridging the Gap between Clinical and Regulatory Toxicology.

5. Discussion of requirements for, and utilisation of harmonised human toxicology data in the context of regulatory (and other) risk assessment activities at national and international level.

6. Discussion of opportunities for, and feasibility of, harmonised human toxicology data collection in the clinical and occupational environment, including lessons learned through the INTOX Programme.

7. Formulation of a provisional plan of action for structured interaction between the fields of regulatory and clinical toxicology, with a view inter-alia, to further exploring the utilisation of harmonised human data in the context of risk assessment.

8. Any other business.

9. Closure of the meeting.
Annex 3

Initial scheme for prioritising and identifying candidate chemicals with interest to both disciplines for further work

- Risk Assessment Priority List
- Poisons Information Centre Lists

Combined List

- Interrogate Clinical Toxicology Database
- Exclude low exposure/low hazard chemicals

- Interrogate Clinical Toxicology Database
- Identify well-characterised cases

- Dose Response Evaluation looking for indicators of critical effects
- Assess bio-analytical data related to chemical – specific, toxicokinetic or mode of action
- Explore the validity of the default risk assessment

Develop biomarkers of response

- Assess Variation
- Assess Genetic Variability
- Refine dose response