

# IPCS WORKSHOP ON DEVELOPING A CONCEPTUAL FRAMEWORK FOR CANCER RISK ASSESSMENT

Lyon, France, 16-18 February 1999

## Meeting Report

### INTRODUCTION

Dr J. Rice, on behalf of the host institution, the International Agency for Research on Cancer (IARC), welcomed participants to the Workshop which was later declared open by Ms Sonich-Mullin on behalf of the IPCS. She informed participants that the Cancer Planning Workgroup had proposed Dr A. Knaap as Chair of the Workshop and Dr R. Fielder as Rapporteur. These proposals were agreed upon. Dr Knaap began the meeting with the introduction of participants (a full list is given in Annex 1).

### Background to the Harmonisation Project

Ms C. Sonich-Mullin then gave a brief history of the IPCS project on the *Harmonisation of Approaches to the Assessment of Risk from Exposure to Chemicals*. The *Harmonisation Project* was instituted in 1993 following a recommendation at UNCED in 1992 and was endorsed by IFCS in 1994. The objective of this project is to improve understanding of the methods and practices used by various countries and organisations so as to develop confidence in, and acceptance of, assessments that use different approaches (convergence being the long term goal). Further details on the Harmonization Project are provided in Annex 2.

### Harmonisation of Cancer Risk Assessment

An overview of the activities specifically relating to cancer risk assessment was then provided by Ms Sonich-Mullin. This work started with a scoping meeting held in February 1995 where it was recommended that priority should be given to comparing chemical-specific risk assessments developed by different organisations. This was endorsed as a priority area by the Harmonisation Project Steering Committee and a second Scoping Meeting took place in March 1997. At this Meeting, it was agreed that the focus should be on issues that presented impediments to harmonisation, with the use of specific chemicals to illustrate these issues. This led to the Hannover Workshop to address specific issues in cancer risk assessment held in January 1998. (The report of this meeting was available as a background document: IPCS No. xxx). At the Hannover Workshop, a number of generic issues relating to harmonisation were identified. These were transparency, terminology, weight of evidence, flexibility and accessibility/communication. During discussion on criteria for deciding on mode of action/causality, a framework was proposed by Dr J Wiltse, as a generic approach. This was based partly on the Bradford-Hill criteria for causality as modified by E. Faustman for developmental toxicity. It was recommended that priority should be given to developing this framework.

Subsequently, a planning workshop was held in June 1998 to develop the framework using actual data. It was recommended that an effective way of providing peer review to critique and improve the framework would be to convene a workshop of 30-35 scientists from a wide range of relevant backgrounds to consider its applicability using case examples. This was the basis for the current meeting in Lyon.

### GOALS AND OBJECTIVES OF THE LYON WORKSHOP

Ms Sonich-Mullin informed participants that the purpose of the Workshop was to gain feedback on the conceptual framework, to identify improvements and also to receive comments on its potential implementation. Prior to the Workshop, participants were provided with the framework and case examples.

The objectives of the workshop were to provide IPCS with feedback on the framework. Participants were specifically asked to consider the following questions:

- Is the framework useful for analysis and transparency?
- Is it usable?
- It is applicable to risk assessments?

- It is applicable in the identification of research needs?
- What improvements are needed?

An additional objective was to gain the commitment of participants to use the framework. The question was raised as to whether they were willing to be ambassadors and provide additional input at a later meeting based on experiences.

## **OVERVIEW OF FRAMEWORK USING CASE EXAMPLES PREPARED BY PLANNING GROUP**

### **Outline of conceptual framework**

Dr J Dempsey outlined the paper on the conceptual framework for evaluating a postulated mode of action. Consideration was given to the following sections: scope; summary description of postulated mode of action; key events; strength, consistency and specificity of association of tumour response with key events, dose-response relationship; temporal association; biological plausibility and coherence; other modes of action; conclusions.

Dr Dempsey stated that it was hoped that the use and implementation of the framework would facilitate understanding by increasing transparency of the thought process, providing a common format for considering mode of action, and encouraging clear and consistent documentation. It should be of value in risk assessment documents which include analysis of carcinogenicity data either within, or prior to, the hazard characterisation section. The importance of regarding the framework as an analytical tool to facilitate the above and not a fixed check-list was emphasised.

Participants expressed a very positive attitude to the framework in general, and felt that it would be most helpful for the use intended. In the ensuing discussion, a major issue related to considerations of relevance of the mode of action to humans. This had also been of concern to, and was considered by, the planning group. It was felt, however, that the framework should be related solely to the mode of action of the induction of tumours in animals. It was recognised that relevance to humans was of critical importance in characterisation of hazard to humans. However the criteria for this stage in hazard would be different. This was a later stage in the overall process. A similar view had been taken at the Hannover workshop when the IARC and EPA criteria for considering that the 2 u globulin mechanism for male rat kidney tumorigenesis was specific to the male rat and not relevant to human had been discussed. This was viewed as a separate issue from the conceptual framework. The Workshop recommended that priority should be given to the consideration of a framework for relevance to humans in future work in this area. It was not appropriate as part of the mode of action framework.

The conclusion would need to include a clear statement on the results of the analysis regarding the postulated mode of action, having regard for the inconsistencies and uncertainties, and data gaps. The Workshop noted that interpretation of the data in this regard would depend on the use of which the hazard assessment was being put, and that the framework could not be used to identify what data were sufficient in a given instance. This section was more subjective being dependent on the specific circumstances. The value of the framework was in outlining in a transparent and structured way, the underlying thought process that had led to the conclusions drawn.

It was also felt that different weighting could be given to some sections; in particular it was noted that biological plausibility was not as fundamental a requirement as some of the other issues considered.

### **Considerations of Chemical T**

Dr Dempsey led the group through the framework on chemical T which had been prepared by the planning group as a worked example of a data rich chemical that induces thyroid tumours by thyroid hormone disruption. The emphasis was on the framework and the data set used, not on the specific chemical and for this reason it had been decided not to specifically state the chemical name, but to refer to it in code.

In the ensuing discussions the following points were raised which needed to be considered to improve the accuracy and completeness of the framework.

There were inconsistencies in the dose levels producing hyperplasia in the males and those producing tumours. In addition females appeared to be more sensitive to induction of hyperplasia, but they were insensitive to tumour induction.

Regarding the dose-response for hyperplasia vis a vis tumour induction, it needed to be recognised that this may be time dependent and it could be inappropriate to consider inconsistencies at a later time, ie, at tumour development. Quantitative data on hyperplasia were needed (radio label incorporation studies) to obtain a meaningful dose response.

It was noted that the bio-transformation data were inadequate and this warranted a mention in the framework.

In the mode of action section reference is made to renal adenomas even though the response lacked statistical significance. This was confusing, If these tumours are considered treatment-related they need to be included in the scope (or more appropriately in a separate framework).

Also in the mode of action section there was some discussion with reference to the statement that chemical T does not belong to a class that is expected to generate reactive metabolites. It was noted that this was equivalent to saying that it does not have structural alerts. The workshop felt that further clarification of what is meant by structural alerts would be helpful and perhaps this could be considered by the break-out groups.

In summary although there was agreement that this data set was reasonably complete there were inconsistencies.

### **Consideration of Chemical Z**

Dr Mangelsdorf led the workshop through the framework prepared by the planning group for Chemical Z. This compound produced bladder tumours at high dose levels in male rats. The key events were considered to be altered urinary physiology, formation of bladder stones, irritation and hyperplasia of the urothelium. The major metabolite monosodium phosphite did not produce any of the effects seen with compound Z. It was felt that the data supported the postulated mechanism and that there were no data gaps that would significantly detract from confidence in the data and conclusions.

The following comments were made during the discussion of this example. There were concerns that the framework had not flagged the uncertainties. For example some consideration was needed as to why effects appeared to be limited to the male rat. Furthermore it was unclear why the major metabolites did not produce any effects.

It was noted that the fact that there were no plausible alternative mechanisms did not, by itself, add significantly to confidence in the conclusions.

The need to recognise the importance of information on structurally related chemicals was raised. It was agreed that SAR data, if available, should be included in the section on coherence, and that the 'explanatory note' should give greater encouragement to the use of such data available.

### **BREAK-OUT GROUPS**

For the purposes of evaluating the framework, three break-out groups were identified. The Chairs were Professor Sir C. Berry, Dr B. Schwetz and Dr E. Dybing; the respective rapporteurs were Dr J. C. Larsen, Dr S. Munn and Dr F. Johannsen. Each member of the break-out groups were provided with the hazard data summaries and the postulated mode of action for each case example which they used to evaluate the framework.

It was stressed that the purpose of the break-out groups was to use the framework and identify improvement on the basis of the data provided in the examples. The focus should be on the framework itself, not the specific chemical. For this reason chemicals were referred to by a designated letter rather than their chemical names. In addition the groups were asked to specifically consider the questions relating to the goals of the Workshop noted earlier. In particular they were asked to consider if the framework was useful and applicable to risk assessment and for identifying research needs.

### **First Case Study: Chemical V**

Dr Dempsey outlined the data set and postulated mode of action on Chemical V which comprised the first case study. The tumour of concern was Leydig cell tumours in the rat and the postulated mode of action was hormone disruption by binding to the androgen receptor displacing testosterone binding.

These data were then considered by all the three break-out groups to gain 'hands on' experience with the framework. The areas of agreement, and the main points raised during the report back to plenary are summarised below.

There was agreement by all groups that the framework was useful as an analytical tool to provide a structural and transparent means of outlining the data supporting a postulated mode of action. It had general applicability as a component of the hazard identification/characterisation process. It should be based on analysis of as complete a data set as possible that was available in a given instance. In addition it could be used to identify research needs. It was important to recognise in this regard that the amount of information appropriate in a given instance would be dependent on the context of the use of the data. For example, the amount of data appropriate for an industrial chemical with limited exposure would be less than that for a pesticide leaving food residues. Also that there was a need, when determining data gaps, to distinguish data that were essential from those that were desirable (e.g., essential for regulatory purposes vs. desirable for research interests).

There was general agreement on the key events and that the postulated mode of action was supported with a reasonable level of confidence. It was noted that there were some deficiencies with regard to dose response but on the whole the data were supportive.

A number of specific points were raised regarding the framework and it was agreed these needed further consideration. These are mentioned below and will be considered in subsequent sections of this report:

A major point that hampered discussion was identified as the need to clarify the definition of key events and also the distinction between consistency and coherence.

Greater emphasis should be placed on SAR data where available. This is mentioned in the biological plausibility section of the framework, but it was felt that the use of such data should be more actively encouraged.

The title of the conclusions section needed rewording to reflect the fact that the 'results' of the analysis were based on judgement of the weight of evidence and that any comment as to whether there was sufficient data to support the postulated mode of action would be dependent on the context in which the data were used. The term conclusion was too definite in this context.

It was felt preferable to have a separate section on uncertainties, data gaps and degree of confidence rather than incorporate such considerations in the final sections.

There was a need for incidence tables for the critical events in the summary of the data. It was noted that persons using the framework should have direct access to the original/full data set, unlike the participants in this workshop (who used summary information for the purposes of expediting the case examples).

With regard to the order of sections in the framework it was thought better to consider the empirical data on dose-response (section 5) and on temporal relationships (section 6) prior to consideration of strength, consistency and specificity of data (section 4). When dealing with the subsequent case examples the Break-out groups were asked to consider using this revised order.

Finally the situation of multitissue/multispecies carcinogens was raised. It was noted that separate frameworks would be needed for each of the tissues of concern. The group felt that it was important that an overall assessment of the situation was made, since increasing numbers of sites and modes of action may increase the level of concern. However, it was recognised that this was a separate issue from the mode of action framework, and that it needed to be considered at the hazard characterisation stage.

### **Second Case Study: Chemical B**

Dr Mangelsdorf briefly outlined the data set and the postulated mode of action of Chemical B. This produced bladder tumours in the male rat as a consequence of the change in urinary physiology or precipitation of metabolites resulting in calculi formation, chronic irritation and hyperplasia leading to the bladder epithelial tumours.

All three break-out groups considered this compound. Although there was much consistency in the comments, there was no complete agreement as to whether the postulated mode of action had been convincingly demonstrated, with 2 of the groups believing that the mode of action was consistent with the

data with one believing that it had not been convincingly demonstrated. The main points in the discussion in plenary are summarised below.

Each group identified similar key events, namely calculi formation, irritation, hyperplasia of bladder epithelium.

Each group also noted that an alternative mode of action based on a genotoxic mechanism could not be ruled out and that further data from an in vivo assay in the target tissue was needed in this regard. It was pointed out that a weak genotoxic action together with promoter action (eg by high concentrations of a phenolic compound) could also be a plausible mechanism.

All felt that the postulated mode of action was plausible and two groups believed that the data essentially fitted this hypothesis. However one of the groups identified a major inconsistency namely that hyperplasia preceded the calculi formation. The lack of harmonisation in this regard may well have arisen from inconsistencies in terminology. It was recognised that the terminology used in the reports supporting the documentation on compound B were confusing in this regard (protein casts, crystals, micro calculi, calculi etc). The need to encourage uniform terminology was noted.

Other uncertainties discussed were that there was no clear understanding as to why effects appeared to be male rat specific and, whether the early events in calculi formation were due to physiological or chemical process.

The need for dose-response data on DNA synthesis and cell replication in the bladder epithelium was regarded as important because such data may provide convincing evidence to support the postulated mode of action.

In commenting on this case example, Dr Mangelsdorf noted that the nature of the micro calculi or calculi had been the most difficult part to capture due to lack of a clear, consistent description in the source publications. This was most likely due to the apparent production of hyperplasia prior to stone formation (the possibility of micro crystals being present that could act as source of irritation could not be ruled out).

### **Third Case Study: Chemical A**

Dr Meek briefly outlined the data set and postulated mode of action on Chemical A. This was that the brain tumours induced in glial cells were a consequence of the generation of active oxygen species.

All the break-out groups came to the same conclusions with this compound. There was no evidence to support the hypothesis that this type of DNA damage produced glial tumours. The key events should be demonstration of active oxygen species in brain by use of biomarkers for oxidative stress, together with precancerous histopathology. No data was provided on any such events that could be linked to this postulated mode of action.

The most likely mode of action related to genotoxicity but the in vivo data base was incomplete.

There was some discussion of the place of epidemiology data within the framework in view of the negative epidemiology. It was agreed that this was clearly important at a later stage in assessing relevance to humans, but was not part of this mode of action framework.

### **Fourth Case Study: Chemical E**

Dr Meek briefly outlined the data set and postulated mode of action of Chemical E. It was a multisite/multispecies animal carcinogen which produced a metabolite that reacted with DNA. The example was being considered to identify whether the framework could be used in a different way namely to consider multiple tumour sites induced by the same mechanism (genotoxicity).

There was good agreement amongst the break-out groups regarding this example. The key event was biotransformation via glutathione to an active metabolite which reacted with DNA. There was confidence in the postulated mode of action.

It was noted that the compound was also cytotoxic and that the resulting sustained cell proliferation was likely to enhance the initiating (mutagenic) effects. The framework should distinguish between alternative mechanisms and synergistic mechanisms.

It was noted that the in vitro mutagenic profile suggested direct acting properties but that this was probably due to the presence of glutathione transferase in the assay systems. It was pertinent that negative results were obtained in deficient strains of Salmonella. In addition the lack of genotoxic activity in vivo was probably due to the lack of significant amounts of active metabolite reaching the limited number of tissues examined.

## **PROPOSALS TO IMPROVE THE FRAMEWORK**

The Workshop participants then gave consideration to ways of improving the framework in the light of their experience with the case examples. This consolidated comments and recommendations made during earlier discussion at the meeting.

The following were agreed:

In order to reduce redundancy changes were recommended in the titles of section 1 (Scope) and 2 (Summary description of postulated mode of action). Section 1 should be 'introduction to framework' and section 2 'postulated mode of action'.

Although the framework is intended to analyse only one mode of action, recognition should be given to the need to discuss tumours with an inter-related mode of action within the same framework.

There was a need to clarify the description of key events. These are measurable events that are important in the postulated mode of action. Examples given to illustrate this should be specific, eg thyroid tumours, bladder, etc. Events should be a consistent sequence (not necessarily repeatable as suggested in the current document).

It would be better to consider sections 5 (dose-response relationship) and 6 (temporal association) before 4 (strength, consistency, and specificity of association).

There is a need to clarify the distinction between consistency and coherence. Consistency related to internal consistency of the data base for that chemical's mode of action. Coherence is much wider, bringing in the larger spectrum of relevant data from the scientific literature. It is important to consider whether the data fit with the accepted body of evidence.

A separate section was needed on uncertainties, inconsistencies, data gaps, rather than inclusion of these in the final section. There was a need to consider both uncertainties in database and on biology of tumour development.

The use of SAR data should be encouraged when available (this is included in biological plausibility).

There was a need to consider synergistic and alternate mechanisms (where possible).

The final section should be retitled. 'Assessment of postulated mode of action' (not conclusions since the framework is an analytical tool to facilitate understanding of the mode of action and transparency in the thought process; the end result is not a conclusion but rather an assessment). Within this section, there should be an explanation note providing a clear statement on outcome with an indication of the level of confidence in the postulated mode of action.

There was some debate about whether it would be possible to have a formal 'classification' or code for the level of confidence in the postulated mode of action. It was agreed that this was too early to consider and may not be appropriate since it would depend on the type of hazard characterization/risk assessment for which the framework is being considered as an analytical tool. A different level of confidence would be appropriate in different cases.

The summary document was viewed as helpful but not a substitute for looking at the original and full data set. It was noted that persons using the framework should have direct access to the original/full data set, unlike the participants in this workshop (who used summary information for the purposes of expediting the case examples).

It was recognised that it could be difficult to get a complete set of appropriate temporal data.

In presenting the information, in the framework, studies should be clearly identified.

The following additional comments were made:

### **GENERAL COMMENTS**

In the overall hazard characterization, increasing number of tumour sites and mode of action may increase the level of concern.

The framework is an analytical tool to facilitate one part only of hazard characterisation; clearly there are important other inputs. In this regard, high priority should be given to structured approach to considering relevance of mode of action to humans.

Another approach based on consideration of tumour biology at specific sites rather than focussing on chemicals was considered worthy of development. This could be complementary to and progressed simultaneously with the framework.

### **VALUE OF FRAMEWORK**

There was unanimous agreement that the framework was useful for analysis and transparency in providing a structured approach to mode of action considerations. It is useful as an analytical tool to facilitate part of the hazard characterisation stage in the risk assessment process.

It is also useful in identifying research needs. In this regard it was noted that it is important to distinguish what data were essential (e.g., from a regulatory perspective) and what data were desirable (e.g. for research interests) in any given situation.

### **NEXT STEPS**

It was envisaged that the report of this Workshop, together with an amended framework be circulated shortly (2-4 weeks) to all Workshop participants for comment.

The Workshop agreed that it was now a priority to seek as widespread application of this conceptual framework as possible and to gain feedback of its usefulness in practice.

A number of participants stated that they would be taking this forward in both national and international force. These included JMPR and JECFA, the EU pesticides (ECCO) and Existing Chemicals context, EPA, PMRA (Canada). This was to be welcomed and supported. Participants were encouraged to be ambassadors for the framework and to take it forward within their National regulatory process, once a final report of this meeting and a revised framework had been circulated.

The participants also suggested that they circulate the framework within and among their various organizations including its posting on their own websites. However, it was also stipulated that it be clearly indicated as an IPCS effort. The secretariat agreed to provide an introduction to be used in the presentation of the framework for consistency and clarity.

Some participants felt that it was important for a formal IPCS document to be issued before taking the framework forward. However, there was general agreement that participants could take the framework forward without the delay that would ensue if action is dependent on a formal document.

Nevertheless, rapid publication of a formal IPCS/WHO document was encouraged.

It was recommended that consideration be given to publishing the framework in the scientific literature. In this context the inclusion of the worked examples would be helpful, but there was concern that they would lead to some chemical specific comment. Any decision in this regard would have to be considered with some caution. Perhaps this area should be limited to those examples circulated with papers for this meeting, since these were already on the world wide web, but with a clear reference to IPCS.

The Workshop agreed that it would be useful to collect feedback following the use of the framework within different organizations and for different purposes (approximately in one year).

Future enhancements to the framework were discussed. The need to develop a framework to look at human relevancy was identified. Additionally, it was identified that further consideration be given to provide advice on structural alerts for genotoxicity.

There was general agreement that the use of the world wide web to circulate information and to facilitate communication was effective and that it be further used by this project.

## **CLOSING**

In closing the meeting the efforts of the chairs, rapporteurs and participants were recognized. Additionally, the IPCS Cancer Planning Workgroup was especially recognized for their efforts in revising the framework and preparing the workshop materials.

While much effort was required to organize the workshop, IPCS indicated their confidence that, in moving forward with this activity, the benefits will be realized through the sharing of work and information. It was indicated that it is IPCS' role to serve as a catalyst in this endeavor and encouraged the participants to use this workshop as a starting point in the sharing of information and in furthering communications with one another. The Harmonization Project was indicated as a high priority within IPCS; however, it was also recognized that the success of the project lies in the active participation and commitment of all participants. IPCS recognized and expressed gratitude for the support voiced at this workshop.

## **ANNEX 1**

### **IPCS WORKSHOP ON DEVELOPING A CONCEPTUAL FRAMEWORK FOR CANCER RISK ASSESSMENT**

Lyon, France, 16-18 February 1999

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## ANNEX 2

# **INTERNATIONAL PROGRAMME on CHEMICAL SAFETY project on the HARMONIZATION of APPROACHES to the ASSESSMENT of RISK from EXPOSURE to CHEMICALS**

## **Introduction**

As a direct response to the IFCS Priorities for Action Resolution adopted at Forum I in 1994, the International Programme on Chemical Safety (IPCS) has undertaken a project to harmonize approaches to the assessment of risk from exposure to chemicals. The overall goal of this project is to globally harmonize approaches to risk assessment, through increased understanding, focusing on specific issues and to strive for agreement on basic principles. Progress through all stages of this project will result in efficient use of resources and consistency among assessments.

The assessment of risk from exposure to chemicals in the environment is of global importance. Risk assessment activities are conducted on national, regional, and international levels. However, historically, minimal attempts have been made to systematically coordinate these assessments. Current regulatory requirements and research agendas coupled with limited resources indicate the importance and necessity of such coordination. Achieving harmonization of approaches will afford a number of opportunities including a framework for comparing information on risk assessment, an understanding of the basis for exposure standards for specific chemicals in different countries, progress toward common classification and labeling schemes for hazardous chemicals, savings of time and expense by sharing information leading to a potential non-requirement to repeat assessments, and credible science through better communication among organizations and peer review of assessments and assessment procedures.

## **Background**

The impetus for the current coordinated international, regional and national efforts on hazardous chemicals assessment and management was the UN Conference on Environment and Development (UNCED) held in 1992. UNCED saw the development of Agenda 21, the "blueprint" for sustainable development that has guided most international and national environment-related activities. Specifically, Chapter 19 of Agenda 21, which covers the environmentally sound management of toxic chemicals, is the agreed-upon, endorsed international program of action of governments for developing and implementing national programs for chemicals management within the principles of sustainable development. The principle that Member States should cooperate to strengthen capacity and capability for sustainable development by improving scientific understanding through exchanges of scientific and technological knowledge, forms a component of the work of IPCS. One of these is the project on the Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals.

IFCS has endorsed the 6 priority areas in Chapter 19 and have set fairly ambitious targets to be achieved by the year 2000. Programme area A relates to expanding and accelerating international assessment of chemical risks, an important component being the need for harmonised approaches for health and environmental risk assessments. As indicated:

"Harmonized approaches for performing and reporting health and environmental risk assessments should be agreed as soon as possible. Such protocols should be based on internationally agreed principles to permit the full use of risk assessments performed by both national authorities and international bodies."

This is the justification for the work of the Harmonisation Project. This work is crucial in facilitating the production of internationally agreed-upon risk assessments and thus enabling the most efficient use of limited resources. Thus, harmonization activities play a central role in the delivery of the programme of work within Chapter 19, and in particular result in burden sharing and better use of scarce assessment resources.

This ensures a global increase in the output of chemicals risk assessments, enhancing access to information on chemicals management issues. As such, harmonization provides new and cooperative ways of delivering sustainable outcomes from chemical assessment and management processes.

## **Developing Partnerships**

It is recognized that the success of this project lies in the commitment and active participation of a number of partners, both nationally and internationally. Thus, the role of IPCS in leading this effort, is not only to contribute to the resolution of the scientific issues raised, but perhaps more importantly, to develop partnerships and to coordinate activities among these partners. Such cooperation with a number of organizations is necessary to avoid duplication of effort, make use of limited resources, and allow the harmonization of risk assessment approaches to become a reality in the long term. In addition to the IPCS organizations (WHO, ILO and UNEP), coordination of the work on harmonization has begun with the Organization for Economic Cooperation and Development (OECD), Food and Agriculture Organization (FAO), and United Nations Industrial Development Organization (UNIDO), within the framework of the Inter-Organization Programme for the Sound Management of Chemicals (IOMC), as well as with regional/intergovernmental (e.g., European Commission) and national organizations.

As an example of "developing partnerships," IPCS and OECD have met to formally discuss the complementary nature of their efforts in the area of risk assessment methodology. The results of the discussions is provided in: *IPCS/OECD Intersecretariat Meeting on Cooperation in Activities in the Area of Risk Assessment Methodology, May 1995, revised June 1997.*

## **What is Harmonization?**

To understand the approach taken by this project, it is necessary to understand what is meant by harmonization. Harmonization, in the risk context, should not be equated with standardization. It is not a goal of this project to standardize risk assessments globally, as that would be neither appropriate nor feasible. Instead, harmonization can be thought of as an effort to strive for consistency among approaches. Thus, harmonization is defined, in a step-wise fashion, as an understanding of the methods and practices used by various countries and organizations so as to develop confidence in and acceptance of assessments that use different approaches. It further involves a willingness to work toward convergence of these approaches or methods as a long-term goal.

Thus, harmonization reflects a process that maximizes opportunities by identifying similarities and understanding the basis for differences. The ultimate goal of harmonization is to establish an openness and transparency within the risk assessment process so that scientific assessments of chemicals can be put to the greatest use in ensuring sustainable and scientifically sound use of chemicals. This can be achieved through processes such as assessment exchanges between regulatory agencies, through greater use of international assessments within national programs and through greater use of national assessments in international assessment programs. These activities ensure that more information on chemical risk is available to populations globally.

## **Focus**

The project is being pursued on two levels. The first focuses on sound scientific principles. The second bridges the gap (often wide) between policy/decision-making and scientific considerations. While sound science should govern our decisions, policy issues that will affect the implementation of the scientific recommendations made must also be considered. This should not imply that there must be standardization of management issues, but rather that inherent to any discussion of scientific principles used for risk assessment, is the need to facilitate the application of science in the policy arena. This can only be accomplished with a clear understanding of the management issues involved in that arena. For this reason, a Steering Committee, comprised of individual scientists knowledgeable of the approaches used in their organizations and who can affect necessary and agreed upon changes in such approaches, has been established. The Steering Committee provides input into the process and planning activities and provides comments on the recommendations of the scientific workshops with regard to their implementation.

In light of the far-reaching goals of this project, it was essential for IPCS to define some bounds. The focus is on human health rather than environmental risk assessment, although it is understood that such a distinction is not always possible, nor plausible as the lines are not so clearly drawn. It was agreed that together, IPCS and OECD embark on all aspects of harmonization through the collaboration mechanisms

already put into practice. In this way, "harmonization" can be broadened and issues such as integration of methodologies can be considered as we strive for harmonization. Given this initial focus, the project includes consideration of all aspects (qualitative and quantitative) of the National Academy of Sciences (NAS) risk assessment paradigm: hazard identification, dose-response assessment, exposure assessment and risk characterization.

### **Plan of Action**

A number of priority areas were identified, chosen on the following criteria: (1) potential public health impact; (2) availability of both national and international guidance documents; (3) probability of short-term success; (4) lack of consideration of the end point in any other fora; (5) existence of at least partial agreement on data requirements and study protocols.

Based on these criteria priority areas were identified as: reproductive and developmental toxicity, carcinogenicity, mutagenicity (germ cell), general qualitative issues for non-neoplastic endpoints, and more recently neurotoxicity and immunotoxicity. Following the establishment of priorities information was gathered about risk assessment and management approaches in many nations. This endeavor was identified as one that could be most beneficial if done as a joint activity with OECD. Thus, an ongoing effort is the *OECD/IPCS Inventory of Risk Assessment Methodologies*. This inventory will be used as a pointer of efforts worldwide and can be used to initiate analyses and comparisons of approaches.

While the collection and organization of information are quite simple and meet an important need, they had not previously been taken in the international sense. The importance of such simple steps to harmonization suggests that the most successful strategy may be to focus first on common sense approaches rather than the more complex scientific issues. These relatively simple but important efforts can then serve as the bases for further work toward harmonization.

Additionally, one common issue that was soon discovered to impact all aspects of this project and which, at times, is a barrier to harmonization, is the lack of consistent use of terminology. In this regard, the IPCS and OECD have collaborated on the harmonization of terminology. One result has been the initiation of the *IPCS/OECD Joint Project on the Harmonization of Chemical Hazard/Risk Assessment Terminology*.

It should be noted that both the *IPCS/OECD Joint Project on the Harmonization of Chemical Hazard/Risk Assessment Terminology* and *OECD/IPCS Inventory of Risk Assessment Methodologies* activities provide important tools for all other activities in the Harmonization Project.

### **Progress**

From the efforts thus far, a number of generic issues have been recognized as being important in facilitating risk assessment namely:

- openness and transparency regarding the underlying scientific basis,
- sound science to define and inform the methodology;
- broad and open participation in the process,
- need for effective communication through the consistent use of terminology.

In this regard, **the Harmonization Project aims to:**

ensure that its activities are outcome-oriented to promote health and the environment within the framework of sustainable development:

- (1) ensure a focus on priority setting and achievable outcomes
- (2) ensure openness and transparency in its activities to promote the broadest participation possible
- (3) ensure that information on activities and outcomes are broadly disseminated to key stakeholders.

**To achieve these aims, basic strategies have been identified:**

*Strategy 1: Use toxicological endpoint-specific topics to identify and develop the generic issues associated with harmonization.*

*Strategy 2: Gather information on chemical risk assessment methodology to promote greater awareness of the similarities and to assist in identifying the basis for differences.*

*Strategy 3: Develop an active and innovative information dissemination program which allows for rapid communication of project activities and outcomes to the broadest audience.*

*Toward this end, IPCS has convened a series of workshops focusing on the priority areas. Reproductive and developmental toxicity was the topic for the first workshop (which was a joint activity with OECD) and an additional workshop was convened as a follow up. It was from these activities that the terminology needs were defined and issues such as the elucidation of an 'adverse effect' as used in risk assessment and the need for efforts to achieve a common reporting format for assessments were clearly articulated and identified.*

*A scoping meeting was convened to discuss issues related to the harmonization of approaches to carcinogenicity and mutagenicity (germ cells), both separately and together. A number of recommendations for future efforts were identified. For cancer risk assessment, the need to discuss case examples became evident as guidelines alone do not provide a clear view of how assessments are actually conducted for chemicals of concern. Through an additional workshop and the establishment of a cancer planning workgroup, a session was convened to identify and discuss specific mechanistic issues identified as posing barriers to harmonization: bioactivation, enzyme induction, receptor mediation (including hormonal mechanisms, the Ah receptor, peroxisome proliferation and alpha-2u-globulin), effects on cell proliferation/apoptosis, and cytotoxicity. Following a discussion of these issues, work is now progressing toward the development of a conceptual framework for cancer risk assessment focusing on mode of action.*

*In the area of mutagenicity, a scheme for the qualitative assessment of mutagenicity was developed and published in Mutation Research in 1996. It appears to be accepted among the scientific community. Next steps will be to internationalize its acceptance among national and international organizations.*

Through these activities, *general qualitative risk assessment issues for non-neoplastic effects*, emerged and have been identified for future investigation in terms of the ability to harmonize approaches. However, one issue, the use of uncertainty factors, has been the subject of consultations and workshops alike. A future workshop focusing on case examples will complement the effort on carcinogenicity. Eventually, the integration of cancer and non-cancer approaches will be a topic for discussion.

The formation of the Steering Committee has occurred simultaneously to the ongoing scientific efforts. The purpose of the Steering Committee is to provide guidance and overall direction to the project and, in addition, to provide guidance on and work toward implementation of the scientific recommendations made by the workgroups, i.e., to put into practice the outputs of the projects. To accomplish these goals, the Steering Committee is composed of individuals with expertise in risk assessment and scientific fields, but more importantly, includes individuals who have a strong influence in their countries or organizations and thus can provide guidance that has a good chance of being translated into reality. The best scientific decisions will be of little significance if they cannot be implemented.

Three meetings of the Steering Committee have been held and members are consulted regularly for guidance, advice and priority setting for further work.

