IPCS Scoping Meeting to Address the Human Relevance of Animal Modes of Action in Assessing Cancer Risk

8-10 November 2000
TNO/BIBRA International
Carshalton, Surrey, UK

Introduction

Dr. D. Anderson, on behalf of the host institution, the Netherlands Organization for Applied Scientific Research (TNO)/British Industrial Biological Research Association (BIBRA), welcomed the participants to the Scoping Meeting which was then declared open by Ms C. Sonich-Mullin on behalf of IPCS. Ms Sonich-Mullin along with Mr J. D. Sandler, welcomed the participants on behalf of the secretariats. Ms. Sonich-Mullin began the meeting with the introduction of the participants (a full list is given in Annex 1). She informed the participants that the secretariat proposed Dr. L. Smith as the meeting Chair/Facilitator and Dr. E. Faustman as Rapporteur. These proposals were agreed upon by the participants.

Meeting Goals and Objectives

Ms. Sonich-Mullin presented the project goals and objectives which are to extend the IPCS conceptual framework for the evaluation of a mode of action (MOA) in animals, to address human relevance, increasing transparency in cancer risk assessments and identifying research and data needs.

Toward this end, the purpose of this meeting was:

- To discuss and confirm project goals and determine how best to reach them.
- To scope the project and develop a plan of action to achieve the project goals and objectives.

It was suggested that the best way forward was to develop a targeted overview of how we have reached this point, by focusing on what we have learned and how we can use this information to design the project. To facilitate this, a case study approach was used. Case examples were provided to the meeting participants prior to the meeting along with a series of questions to be considered in reviewing the cases and to be used as “thought starters” for discussion.

Ms Sonich-Mullin noted that the overall product of this effort will be a Mode of Action Framework that addresses human relevance to be used as a tool to provide a structured approach to determining the human relevance of an animal mode of action. However, it was also noted that as this work progresses, additional products will be developed at
various stages of the project and will include (but are not limited to):

2. White papers or position papers that document the discussion and conclusions reached on each issue/question addressed.
3. Research and data needs.
4. Communication and implementation plan.

It was stressed that the focus of this meeting was to develop the project scope and action plan, keeping in mind the additional products identified and the overall project goals. Ms Sonich-Mullin provided a brief overview of what brought the proposed IPCS/ILSI interaction to this point. A Planning Workgroup will be established to accommodate the identified project scope and recommendations of this scoping meeting. It was noted that all of the participants in the IPCS Cancer Planning Workgroup which developed the Conceptual Framework to evaluate an animal mode of action, had expressed interest in this follow-on effort. Ms Sonich-Mullin encouraged participants in this scoping meeting to think with an international perspective in both scoping the project and identifying additional experts for involvement. It was noted that the participants in this scoping meeting as a whole, were not fully representative of the international scientific community despite the attempt by IPCS to cover many regions and specific areas of expertise, as a number of invited experts were unable to participate. In particular, the absence of anyone trained in epidemiology or related disciplines was recognized. In the interest of transparency this “shortcoming” was recognized and noted. The meeting was then turned over to Dr. Smith who reiterated the need to think on the global scale, but recognized that the current European/North American focus on the science will likely make securing global participation a challenge.

Dr. Smith reviewed the meeting agenda (provided in Annex 2) noting that themes and outputs had been identified for each day beginning with a discussion of determining what is relevant, moving to discussions of what needs to be further explored or expounded upon as we begin to identify products or potential products, and culminating in a discussion surrounding how we are going to accomplish our goals and meet our needs, or more specifically, the development of an action plan. It was agreed that for this type of meeting, the agenda would remain flexible to accommodate discussions but keeping mindful of the final products to be developed.

**Background on the IPCS Harmonization Project**

Ms. Sonich-Mullin provided a brief history of the IPCS project on the *Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals*. The *Harmonization Project* was instituted in 1993 and formally initiated in 1994, following a recommendation at the United Nations Conference on Environment and Development (UNCED) in 1992 and the endorsement of the Intergovernmental Forum on Chemical Safety (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 3.

**Background on the IPCS Harmonization of Cancer Risk Assessment Activity**

Dr Fielder provided an overview and update on the IPCS Cancer Risk Assessment activity to date focusing on the background of the events and discussions that have lead us to this point. He provided a summary of the processes used in developing the IPCS Conceptual Framework for Evaluating an Animal Mode of Action for Chemical Carcinogenesis (Sonich-Mullin, C, R. Fielder, J. Wiltse, et. al., 2000). He noted the discussions and agreement on the priority given within the Harmonization Project to focus on the extension of this framework to include human relevancy. While the project is focusing initially on cancer, it is recognized that the issues discussed and products developed may also apply to other endpoints. In addition to the high priority placed on this project, Dr Fielder also noted the agreement by the Harmonization Steering Committee that this activity be undertaken in collaboration with the International Life Sciences Institute (ILSI). Additional background information on the IPCS Harmonization of Cancer Risk Assessment Activity is provided in Annex 4.

**Background on the ILSI Focus on Mechanisms of Action**

Dr. Smith provided a brief overview of current ILSI activities in the area of human relevance and its ongoing interest in this area. ILSI has conducted a number of activities examining mechanism of action and human relevance (i.e., peroxisome proliferation, mouse liver tumour, bladder and mammary carcinogenesis). The current focus began formally in 1999 with the formation of an ILSI project committee with a primary goal of ensuring that mode of action/mechanism of action data are useful and used in risk assessment. The ILSI project committee quickly noted the successful efforts of the IPCS focus on mechanisms of action and the development of the animal mode of action framework. ILSI recognized that a logical step might be a collaborative effort to bring the science into the arena of human health risk assessment.

**Process, Roles and Responsibilities**

The participants acknowledged and readily agreed that the overriding goal of this project is the protection of human health.

Ms Sonich-Mullin provided an overview of the roles and responsibilities of individuals and groups involved in the Harmonization Project. The purpose of the presentation was to provide a clear understanding of the roles, responsibilities and the processes identified for carrying out the work but also to review the expectations of IPCS in carrying this activity forward. The roles and responsibilities of the meeting chair, rapporteur and subgroup
chairs and rapporteurs for this meeting were reviewed. The participants acknowledged and readily agreed that the overriding goal of this project is the protection of human health.

**Scoping Meeting Plan**

In developing the plan for this meeting, the IPCS and ILSI secretariats convened an *ad hoc* meeting of experts to determine the best way forward. A case study approach was agreed to be the most effective. Keeping in mind the overall purpose of the meeting, a set of questions were developed and presented. The overall purpose of using these questions was to stimulate thinking to identify the questions and issues requiring harmonization, scope the project and develop an action plan to address the issues identified. The questions identified and provided to the participants prior to the meeting are provided in Table 1.

It was reiterated that the overall product of this effort will be a *Mode of Action Framework that addresses human relevance*. This framework will be used as a tool to provide a structured approach to determining the human relevance of an animal mode of action. In this regard, conclusions based on the available data and information, data needs, and scientific judgements will become transparent. It is envisioned that this tool could be used in a number of ways including: understanding of the scientific basis for (and of) decision-making, identification of data and research needs, and providing a structure to organize information and develop assessments.

**Case Studies**

With this background provided, case studies were presented to the group (cases and presenters are provided in Table 2). The meeting participants discussed each of these case studies. The purpose of using the case studies in this meeting was not to focus on these specific compounds but rather to illustrate general issues that need to be considered when a review of relevancy for humans is undertaken. For this purpose these compounds represented excellent examples where considerable thought, research and reviews had been undertaken by numerous international and national organizations in industry, regulatory bodies and academic institutions.

The animal cases (Thiazopyr and Vinclozolin) were presented using the IPCS conceptual framework to evaluate an animal mode of action. The purpose of the presentation of the cases in this format was to allow the participants to become familiar with the framework developed and comfortable with using it to evaluate animal data. This would then allow for consideration of the elements in expanding the framework to consider human relevance.
Table 1. Questions to be considered in Developing the Action Plan

1. Premise: we have animal cancer data that identifies a mode of action (MOA) in animals with confidence. Given this, how do we approach the question of the relevance of that MOA in humans?

2. What data do we need to decide that an animal MOA is also a human MOA?
   a. Address nature of data needs – what kind of data do we have/what kind of data do we need?
   b. How do “key events” in an animal MOA inform human relevance?
      i Qualitatively
      ii Quantitatively
   c. What level of information is useful/needed?
      i Population level
      ii Individual level
      iii Organ/tissue level
      iv Cellular level
   d. How do you use “key events” identified in an animal MOA to design the analysis of human relevance?
      i Review of literature/available data
      ii Experimental design
      iii Data collection
      iv Other
   e. How do “key events” identified in an animal MOA get used in assessing human relevance?
      i physiologic level
      ii biochemical level
      iii molecular level
      iv other
   f. How do we determine how much information is enough?
      i General population
      ii Sexes
      iii Sensitive life stage
      iv Individuals
   g. How do we most effectively arrive at the best judgement on the available data?

Additional Issues for Consideration were also identified, such as how far do we go? (e.g., do we consider the full extent of human variability?). In this regard, the participants were encouraged to identify other issues that should be considered.
All of the cases, but more specifically Saccharin and Tamoxifen, illustrated both qualitative as well as quantitative factors that need to be examined in deliberations on human relevancy. They also illustrated maximal use of human information (for example, measurements of DNA adducts in human liver biopsy material from women undergoing Tamoxifen therapy) as well as assessment of human epidemiology studies (available for both Saccharin and Tamoxifen). During the course of the discussion of these case studies, it was evident that in many situations the deliberations on these compounds was protracted and that the overall process would strongly benefit from a systematic approach and increased transparency in the assessment.

The meeting participants used the case examples and questions provided to begin to identify “What is relevant to relevance?” moving to discussions of “What needs to be further explored or expounded upon as we begin to identify products?” and culminating in a discussion of “How are we going to accomplish our goals and meet our needs?”

### Table 2. Case Studies

<table>
<thead>
<tr>
<th>Case</th>
<th>Issue</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazopyr</td>
<td>thyroid tumours - animals</td>
<td>J. Wiltse</td>
</tr>
<tr>
<td>Vinclozolin</td>
<td>hormonal disruption/Leydig cell tumours - animals</td>
<td>J. Dempsey</td>
</tr>
<tr>
<td>Saccharin</td>
<td>human relevance of bladder cancer in rats</td>
<td>S. Cohen</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>human relevance of liver tumours in rats; endometrial cancer in humans</td>
<td>L. Smith</td>
</tr>
</tbody>
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### Summary of Discussions

Throughout the ensuing discussions, a “Decision Tree” (Figure 1) was developed for determining the relevance to humans for cancer mode of action. As a part of this effort, issues to be addressed were identified. Recommendations were provided to IPCS on the scope of the project, the specific information needed as a starting point, and the process to be used.
Figure 1. Assessment of Relevancy to Humans Within the Overall Risk Characterization Framework

EFFECTS IN ANIMALS

MOA?

STOP
(Assume Human Relevance)

YES

Do Risk Assessment

KEY EVENTS

ADME  MOLEC/CELL  PHYSIOLOGY/organ  AVAILABLE human data  OTHER

•  •  •  •  •

QUALITATIVE DIFFERENCES

NOT RELEVANT TO HUMANS

EXPOSURE

RISK CHARACTERIZATION

QUANTITATIVE DIFFERENCES
The group reached agreement that IPCS and ILSI move forward together and in parallel as it is needed and as determined to be most efficient. It was noted that ILSI could be particularly helpful in the technical workgroups.

In determining next steps, the scoping meeting agreed on a **Charge to the Planning Workgroup:**

- Begin with basic premise that, in the absence of evidence to the contrary (e.g., from mode of action), tumors observed in animals are assumed to be relevant to humans; this is the default position.

- Develop a framework to address human relevance as an extension of the IPCS Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis using the identified elements or components to consider as provided by the Scoping Meeting (see below).

- Use case studies to develop and demonstrate the framework.

- Consider future data to be collected and generated in developing the framework.

- Ensure widespread input to and adoption of the framework.

- Develop a detailed Action Plan to carry out this work.

**Draft Action Plan/Decision Tree**

As a result of the discussions, a draft plan of action was developed to be presented to the Planning Workgroup. This plan is presented as both a simple “Decision Tree” (Figure 1) and through the identification of a number of “elements to consider” in developing a framework to address human relevance (Table 3).

**Overall Scope**

It was agreed that the framework should be flexible enough to deal with situations in which the available data may be more or less comprehensive and robust. In this regard, a number of scenarios may need to be addressed and could include the following:

1. Have positive animal data, but no (or inadequate) human data - - - basic assumption is that animal data are relevant to humans.
Table 3. Elements to Consider in Developing a Framework for Human Relevance

Compilation of inventory/bibliography
Identification of relevant data to be “mined” (look for non-traditional sources)
- address quality control
- look for data on different “levels” (i.e., cellular to population)

look for similarities in the mode of action identified comparing animal data with the “new” human data

look for similarities in mode of action between chemicals (cross compound coherence)
- look for information on exposure to similar chemicals or
- look for observed similar physiological or disease states of populations exposed to different chemicals

evaluate epidemiological studies in a weight of evidence assessment using information across as well as within chemicals along with case reports and clinical trials to develop an overall assessment of the human relevance of the postulated or evaluated animal mode of action.

Determine plausibility or feasibility in humans based on normal physiology occurrences in the context of the key events postulated in the observed or suggested mode of action
- do this both qualitatively and quantitatively
- look at all levels: overall physiology, similar pathways of manifestation, kinetics, molecular level, etc.
- evaluate both positive and negative findings as well as relative amounts
- look at outcomes at all levels: e.g., biochemical, cellular, organ, population

look at cross species coherence
- observations in more than one species may strengthen or weaken assessment of human relevance.
- Consistent with the IPCS conceptual framework for evaluating a mode of action in animals, consider strength, consistency and specificity
- coherence vs consistency (repeatability)

consider dose/response
- what is the expected outcome in human based on the observations in animals and considering the key factors in the human context?

Determine relevance with a level of confidence based on the above

Identify areas of uncertainties, inconsistencies and data gaps in both
- biology of the tumour type
- available database
- include relative magnitude and direction
- determine
- if data gaps are critical.
2. Have good human data, do not have good animal response data but do have good overall animal data to suggest a mode of action (in animals) - - basic assumption is that this is relevant to humans.

3. Have what appears to be non-positive data in animals - is this chemical likely to be a human carcinogen?

**Elements to Consider in Developing a Framework for Relevance to Humans- Mode of Action- Cancer**

Preamble -- The use of information from animal studies is essential for the protection of public health and avoidance of unnecessary harm in humans. The proposed components to be considered in developing a framework are designed to enhance the use of information from animal studies to improve our understanding of their relevancy for identifying potential human impacts. This should help to improve our overall development and use of scientific information in our risk characterizations (see Figure 1).

A prerequisite to the use of this framework for assessment of human relevancy is a clear statement of the mode of action (MOA) in animals with qualitative and quantitative information on the sequence of postulated key events in the MOA. Such information would result from the identification of key events in a postulated MOA resulting from application of the IPCS conceptual framework for evaluating a MOA for chemical carcinogenesis (Sonich-Mullin, C, R. Fielder, J. Wiltse, et. al., 2000). Step nine from these framework guidelines would result in the development of such a clear statement of the postulated MOA that would be defined in the context of doses and routes of exposure that produce the hazard in animals and with an indication of the level of confidence in the postulated MOA. A MOA would have evidence provided by robust mechanistic data that established a biologically plausible explanation. (Note, in contrast, mechanism of action relates to sufficient understanding of the molecular basis to establish causality and is at the other end of the spectrum of the continuum from little to no evidence of mode of action to scientific proof of mechanism of action (Sonich-Mullin, C, R. Fielder, J. Wiltse, et. al., 2000).

The meeting participants readily acknowledged that information is rarely sufficient to support a solely qualitative difference in mode of action between animals and humans. More often, differences are quantitative. Thus, for most of the components outlined below, there may be both qualitative and quantitative issues to consider. However, the meeting participants also recognized that not all chemicals will require nor will have available, information to allow for full consideration of every component of each of the key steps in the MOA.
In the absence of any data to support a plausible MOA the basic premise will be that the
tumours observed in animals are relevant to humans. There is no presumption in
development or application of the framework of the relative sensitivity of humans versus
animals. The meeting participants realized that the MOA information from animals could
both enhance as well as reduce our concerns about the potential relevance for humans.

1. Human Biology of Key Events

a) Consideration of Human Data

The meeting participants agreed that an important initial step is to identify all potential
sources of pertinent human data. In the process of identifying these data, it is necessary
to consider the broad database of available human information including use of
potentially non-traditional sources of human information.

As shown in Figure 2, relevant information can range from \textit{in vitro} information from
human tissues (for example, human hepatocytes in culture, or human breast cells cultured
to ascertain tumor receptor sensitivity) to biological surrogates that are measured in
humans (for example, diagnostic or clinical evaluations, DNA adducts, or
characterization of tissue pathology specimens), or to molecular epidemiological studies
of human populations which can include biomarkers of exposure and/or effect.

Figure 2: Examples of Human Data Sources

| cellular | \textit{in vitro} | biomarkers |
| organ/tissue | clinical diagnosis | epidemiology |
| individual population | \textit{in vivo} |

The meeting participants noted that epidemiology studies addressing the human evidence
for a causal association from effects of a compound would need to be evaluated in a
similar framework that was applied for reviewing animal studies (Sonich-Mullin, C. R.
Fielder, J. Wiltse, et. al., 2000). In this regard, the Bradford Hill criteria should be
considered. The evaluation would be accomplished using a weight of evidence
assessment considering factors such as power of detection, confounders, bias and
exposure levels and patterns. Participants felt that case studies may contribute to
assessment of the relevance of the postulated MOA. Clinical conditions or variations in
the human experience may also inform relevancy (for example, physiological conditions
or inborn errors of metabolism that might result in hyperthyroidism in humans have been
used to inform the discussion on thiazopyr).
b) Cross-compound coherence

Epidemiological data on related compounds with similar potential MOA should be considered for their cross compound coherence. Information from human experiences with such related compounds could be used to support or minimize both the qualitative and/or quantitative support for the human relevance of the postulated MOA.

Based on availability of human data, meeting participants agreed that they would need to ascertain if they could define the sequence of key events for the MOA in humans - i.e., are there specific data on the specific agents in humans or is there sufficient information for general human responses to such agents compared to animal responses to suggest that the mode of action in humans may be similar? Relevant data may include that for agents that have similar modes of action and may relate to the specific chemical itself or to some relevant physiological or disease state of the population that minimize the agent’s response.

c) Qualitative and Quantitative Considerations of Plausibility of Animal MOA for Humans

As the human data are evaluated, the assessment needs to determine if the mode of action based on weight of evidence in animals is plausible or feasible in humans. Meeting participants felt that this should be determined based on knowledge of comparative physiology and should be considered in the context of the key events postulated in the MOA. Examples of qualitative considerations that the participants discussed included questions on whether the postulated MOA would occur in humans. For example, if the postulated MOA in animals includes activation of some specific enzymes as a part of its key sequence of events in the MOA, then an appropriate question would be whether such enzymes or related enzymes are present and inducible in humans. If they are not present, then how might the absence of relevant enzymes in humans begin to provide a qualitative rationale for non-relevancy for humans. If present, but at different levels or activities, how might these enzymatic differences begin to provide a quantitative difference in human response (either increasing or decreasing response).

Is the response expected to be similar in humans (i.e., in the same system or organ)? If not, how might the response be manifested (for example, in relation to forestomach tumors, is the mechanism specific to the forestomach which would exclude its occurrence in humans or is it consistent with development of lesions in a comparable tissue at site of contact in humans)? Other questions included determining if relevant related pathways occur in humans - i.e., is a comparable pathway possible for which there are similar key events (both kinetic and dynamic components)? Examples of the type of questions relating to kinetics posed by the meeting participants included whether the putatively toxic metabolites postulated in the MOA are produced in humans. If so, at what levels?
Is an essential key event (e.g., production of the putatively toxic metabolite and interaction with specific receptor) precluded in humans? For example, at the molecular level, are the postulated receptors present in humans? If so, in which organs, at what life stages and in what amounts? What outcomes result from interactions with these receptors? Would stimulation of receptors in animals and humans result in potentially different outcomes? Have DNA adducts been identified and under what conditions and amounts?

At the biochemical level, participants recognized the need to identify activity and levels of relevant enzymes, hormones, etc., that were essential to the mode of action. At the cellular, tissue and/or organ levels, relevant considerations include amounts and types of cell damage or death in potential target organs. Relevant considerations could also include determining amounts of proliferation under normal or treatment conditions and determination of what histopathology would be observed or expected. At the individual level, participants identified the need to determine what types and how many tumors are produced or would be postulated to occur given the MOA. At the population level, they asked whether there was information about human variability that is relevant to the mode of action. For example, is there information on metabolism, polymorphisms or underlying disease states that could lead to an alteration of the mode of action or exacerbation of the outcome?

2. Cross-Species Coherence

The meeting participants discussed how the output from the IPCS framework for evaluating a mode of action for chemical carcinogenesis would interface with the framework for relevance in humans. In considering these issues, the participants suggested several actions: First, the initial framework would have a new section (Section 10) that would address cross-species coherence and common biology. Second, this section would be used to explicitly highlight when the proposed MOA would be relevant across species and would lead into Section 11 where human relevance of the postulated animal MOA would be ascertained for humans. Obviously, the human relevance framework would not be a “stand alone” section but would, when completed, be fully integrated into an overall framework.

Figure 3 emphasizes the need for an interactive process. In establishing the MOA for a given MOA within one species, an interactive process must be used to determine cross-species and human relevancy.

Meeting participants identified questions related to whether there is information from other strains and species that strengthen or weaken our assessment of human response potential. For example, are comparable pathways present in responsive animals that are not present in resistant animals? Can this explain susceptibility of species and response
Figure 3. Considerations of Coherence in Determining MOA Relevancy

- Reiterate comparisons for other MOAs
- Cross –species coherence
  - Reiterate MOA-A for other species
- Cross compound coherence
  - Reiterate MOA-A comparisons for other compounds

Mode of Action A in Species X
(Output from section 9 from original framework)

Mode of Action In Humans
(New framework for relevancy of MOA for humans)
of specific organs? Particularly in cases where data on humans are limited, do cross-species comparisons inform the human relevancy considerations? For example, observation of the relevant pathway in 3 or 4 other mammalian species suggests that it might be operative in humans. Also, do the animal studies indicate sex differences that might be relevant for human considerations?

As in the framework for considering MOA in animal carcinogenicity, participants determined that the relevant human data should be considered in the context of strength, consistency and specificity. Consistency, which addresses repeatability of key events in the postulated mode of action for cancer in different studies is distinguished from coherence, which addresses relation of the postulated mode of action with observations in the broader database. They felt that assessment of the weight of evidence for human relevance should be considered in the context of coherence, taking into account tumour types, metabolic differences, and compensatory mechanisms which may be present across species and compounds. Is the database on the agent internally consistent in supporting the purported mode of action, including that for relevant noncancer toxicities? Coherence, which addresses relation of the postulated mode of action with observations in the broader database would, for example, determine the association of mode of action for tumors with MOA for other endpoints. This was distinguished from consistency which addresses repeatability of key events in the postulated mode of action for cancer in different studies (Sonich-Mullin, C, R. Fielder, J. Wiltse, et. al., 2000). Information from this larger database would include tumor response and key events in same cell type, sites of action logically relate to event(s), multistage, multi-event studies, stop/recovery studies.

3. Dose-response Relationship

To inform considerations of the dose-response relationship, the participants felt it was necessary to understand how the expression of the mode of action is a function of route, timing, dose-rate, duration, sex, ADME. Would the dose-response in humans be expected to be similar, increase or decrease at different levels depending on knowledge of key factors in the human context?

4. Assessment of Relevance to Humans

The meeting participants felt that a conclusive statement, similar to that developed for the current MOA framework for animal studies, was needed for the evaluation of human relevancy. This section would include a clear statement of the outcome of the human relevance framework analysis of the MOA with an indication of the level of confidence in weight of evidence for human relevance. Figure 1 shows how the information from the assessment of relevance to humans would fit into overall risk characterization.
5. Uncertainties, Inconsistencies, Data gaps

Participants suggested that a discussion on uncertainties should include those related to the biology of tumour development and those for the database on the compound of interest. They also felt it should include an indication of what the relative magnitude or direction of uncertainty would have on the determination of human relevancy. Inconsistencies should be flagged and data gaps identified. For the identified data gaps, there should be some indication of whether they are critical for the postulated mode of action or simply serve to increase confidence therein. Participants suggested that reviewers consider novel techniques to generate relevant data.

Additional Needs for the Document:
The meeting participants felt strongly that terminology would need to be defined and a glossary prepared for the framework document. Examples of terms that need to be defined include exposure, dose, kinetics, dynamics, ADME, timing, duration, temporal, lifestage, mechanisms versus mode or action, etc. For example, dose response was used in relation to mode of action in animals. Exposure was defined by the working group to describe the nature of exposure to humans. The IPCS/OECD Terminology Project was noted and use will be made of the definitions provided but perhaps with added detail specific to this need.

Summary

In scoping the project and beginning to develop an action plan, the meeting participants developed elements to be considered when determining relevance to humans for a cancer MOA. Through the development of a simple Decision Tree, the meeting participants:

- Provided recommendations to IPCS on the scope of the project and the specific information needed as a starting point as well as the expertise needed to carry out the project.

- Reached agreement that IPCS and ILSI move forward together and in parallel as needed and as determined to be most efficient.

- Provided a charge to planning workgroup which is:
  1. Begin with the basic premise that we will assume tumours observed in animals are relevant to humans, however, strongly noting that this be used as a starting point and that all other relevant scenarios be considered in the framework development.
2. Oversee the development of a framework to address human relevance as an extension of the IPCS Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis (using the “elements to be considered”).

3. Use case studies to develop and demonstrate the framework, clearly indicating the use of the specific cases.

4. Consider future data to be collected and generated in developing the framework.

5. Ensure widespread input to and adoption of the framework.

6. Develop a detailed Action Plan to carry out this work.

Next steps

A number of next steps were identified, including the need to recommend members for the Planning Workgroup. It was agreed that to be efficient, the Planning Workgroup should consist of 10-12 members. In addition, the meeting participants suggested the identification of a Planning Workgroup “Executive Committee” consisting of 3-4 individuals in addition to the secretariat who could be more involved in project management and in providing short term advice and guidance. In addition, Technical Workgroups to be used to address specific scientific elements identified in the decision tree (see Table 3) can be established.

To facilitate the formation of these potential workgroups, the meeting participants were asked for specific recommendations. To facilitate the identification of Planning Workgroup members, the participants agreed on the following criteria:

Planning Workgroup - criteria for involvement

- Senior - influential, credible, strong network.
- Knowledge of mode of action/mechanism of action.
- Knowledge of risk assessment.
- Ability to devote time.
- Overall diversity in participants relative to discipline (we need a multi-disciplinary workgroup), chemical safety sector/stakeholder and geographic region.
The relative roles and responsibilities of the various groups were reiterated: It will be the charge of the Planning Workgroup to develop a scientific and detailed action plan and to move the project forward. Thus, the individuals should have a strong technical background yet they should be senior and have a strong network. The Harmonization Steering Committee members will also serve as ambassadors and help to effect the implementation of the products of this project. It will be the role and responsibility of the Technical Workgroup members to provide scientific input and recommendations on the specific issues or questions identified for the consideration of the Planning Workgroup members. In this regard, it is the overall charge to the Planning Workgroup to oversee the development of the framework and all the related technical aspects.

Immediate next steps for the Secretariat were discussed and included:

- Timely distribution of Scoping Meeting report.
- Receipt of recommendation of Planning Workgroup members from the Scoping Meeting participants (with input from the IPCS Harmonization Steering Committee).
- Formation of the Planning Workgroup.
- Convene conference calls of Planning Workgroup to review the “Elements to be considered.” These elements represent a combination of identified needs (e.g., inventory) and steps to be taken (e.g., evaluate the epidemiology studies) as elements of the framework leading to the final “assessment of relevance” with an indication of the level of confidence, uncertainties, and inconsistencies leading to the identification of additional research or information needs.
- Identify cases to be considered.
- Work through the decision tree with the identified cases.
- Develop position papers as determined appropriate.
- Milestone: possible meeting of Planning Workgroup and/or Technical Workgroup discussions in Brisbane, Australia, July 2001 (as a satellite to the IUTOX meetings to take advantage of a number of experts already participating in the international meeting).

The first task of the Planning Workgroup will be to review and discuss the “elements to be considered” and the decision tree developed. The group will then modify or add to them, if necessary and as considered appropriate. It is suggested that the first step in the process be to work through the elements and outlined decision tree with one or two cases.
As the cases are worked, modifications may be necessary and additional information or data needs may be identified. Following the evaluation of these cases, a new “way forward” can be identified and a more complete action plan can be developed. Using the information provided by the this Scoping Meeting and the experience of evaluating the cases, the Planning Workgroup should be able to translate the needs into a more detailed action plan that will be used to move us forward in developing a final framework to address human relevance.

**Additional Needs**

In addition to the above, the meeting participants suggested that the Planning Workgroup should also consider the following:

- Develop a communication plan consistent with the overall Communication Strategy of the Harmonization Project to help to acquire acceptance by a wide audience.

- Make full use of the IPCS Harmonization Project web site to update progress and seek continual and timely comments throughout the process (i.e., inform and communicate to the general risk assessment community and to ascertain their input).

- Determine appropriate training exercises to ensure implementation of the framework by all stakeholders.
Annex 1: List of Participants

IPCS/ILSI Project to Address the Human Relevance of Animal Modes of Action in Assessing Cancer Risk

Scoping Meeting, 8-10 November 2000, Carshalton, UK

List of Participants

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Annex 2: IPCS Scoping Meeting, November 2000, Carshalton, UK, Agenda

IPCS/ILSI Project to
Address the Human Relevance
of Animal Modes of Action in Assessing Cancer Risk

Scoping Meeting

8-10 November 2000
TNO/BIBRA
Carshalton, Surrey, UK

AGENDA

The purpose of the Scoping Meeting is:

- To discuss and confirm the project goals and determine how best to reach them.
- Scope the project and develop a plan of action to achieve the project goals and objectives.

Wednesday, 8 November

Theme: What is Relevant to Relevance?

10:00 Welcome/Logistics D. Anderson, TNO/BIBRA

Meeting Overview C. Sonich-Mullin, IPCS
Harmonization Project and D. Sandler, ILSI

Purpose: to set the stage and tone for this meeting and to provide necessary information regarding the logistics of the meeting

Introductions

Presentation of Meeting Chair, Rapporteur

Adoption of the Agenda

Targeted background presentation on IPCS Harmonization Project C. Sonich-Mullin
8 November (continued)

**Background presentation of the status of the IPCS Cancer Framework**  
*R. Fielder, Cancer Activity Lead*

*Purpose:* to provide sufficient background on the events and discussions that have lead us to this point; to review our progress on this activity both scientifically and the process used

**Background presentation on the ILSI focus on mechanisms of action**  
*L. Smith, Zeneca*

*Purpose:* to provide an overview of current ILSI activities in the area of human relevance the ongoing interest of ILSI in this scientific area

**Process, roles and responsibilities of future IPCS Human Relevancy Planning Work Group**  
*M. Younes, IPCS*

*Purpose:* to provide a clear understanding of the roles, responsibilities and expectations of IPCS in carrying this activity forward.

12:00  
**LUNCH**

13:00  
**IPCS/ILSI Scoping Meeting Plan**  
*C. Sonich-Mullin and D. Sandler*

*Purpose:* General presentation of ‘Scoping Meeting Plan” followed by discussion to address questions and issues provided as thought provokers

14:00  
**Introduction to case studies**

Thyazopur  
*J. Wiltse, USEPA*  
Vinclozolin  
*J. Dempsey, NOHSC, Australia*

8 November (continued)

15:00  
**Break-out sessions**

Using the case studies to address the “thought provoking” questions as a seed for discussion and identification of needs, each break-out group will focus on one of the case studies presented
Purpose: To focus discussion and evaluate the issues using real data and real cases.

16:30  Report from Breakout Groups
       Discussion of identified needs/ideas/issues
       Continue to look for common elements

Expected output for the day:
       Refined Thought-Provoker (goal is to obtain some agreement on a working draft of the questions/issues to be addressed)

17:30  Adjourn

Group Dinner in the evening - details to be announced

9 November 2000

Theme: What needs to be further explored or expounded upon as we begin to identify products?

9:00  Presentation of Human Relevance Case Studies - what have we learned?

9:00  Saccharin  
      S. Cohen, University of Nebraska
      (30 minutes presentation; 30 minutes discussion)

10:00  Tamoxophen  
       L. Smith
       (30 minutes presentation; 30 minutes discussion)

12:30  LUNCH

9 November (continued)

13:30  Break-out Sessions

       Break-out groups will focus on the three original case studies (each group will address a different case from yesterday afternoon), with additional consideration of the Human Relevance Case Studies presented this morning.

16:00  Presentations from each break-out group on their discussions
17:30  Adjourn

Expected product:

Identification of WHAT needs to be done; identify potential “whitepapers”

10 November 2000

**Theme**: *How are we going to accomplish our goals and meet our needs?*
How do we get it all done?

9:00  Summary presentations of identified needs, concerns etc
* C. Sonich-Mullin, D. Sandler

9:30  Breakout sessions

Begin brainstorming session to address “How?”

**Purpose**: Now that we have identified WHAT needs to be done, the remainder of the workshop is scheduled to address the important question of HOW we will get it all done.

11:00  Developing an Action Plan
Reconvene in plenary to review discussions and begin to develop a project scope and action plan (address implementation/communication)

12:30  LUNCH

13:00  Reconvene to finalize products of this workshop:

Identify what is relevant: What are the individual elements that can “turn the tide” on the relevancy question?

How do we address these elements and answer the questions?

Identify “whitepapers” that are needed

Discuss and determine the structure of the project and the activities Who will do them, how are they coordinated, identify roles

Develop a schedule/timetable

How is this communicated to the general scientific community?
Identify IPCS project workgroup

15:00 Next steps and commitments

15:30 Adjourn
Annex 3: Background Information on the IPCS Harmonization Project

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
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
- ensure a focus on priority setting and achievable outcomes
- ensure openness and transparency in its activities to promote the broadest participation possible
- 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 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.
Annex 4: Background Information on the IPCS Harmonization of Cancer Risk Assessment Activity

IPCS PROJECT ON THE HARMONIZATION OF APPROACHES TO THE ASSESSMENT OF RISK FROM EXPOSURE TO CHEMICALS

ACTIVITY UPDATE: CHEMICAL CARCINOGENESIS

Submitted to the 5th Meeting of the IPCS Harmonization Steering Committee
24-26 October 2000
Washington, D.C.

Background

Following a Scoping Meeting in 1995, the initial approach adopted to identify impediments to harmonization was to compare assessment by different countries/agencies using specific case examples to focus on issues. This was the basis for a workshop held in Hannover in 1998 which identified a number of generic issues relating to harmonization namely: transparency, terminology, weight of evidence, flexibility and accessibility/communication. It was felt that a priority for further work in the carcinogenesis area should be given to weight of evidence and within this, mode of action. A conceptual framework was proposed, based partly on the Bradford Hill criteria as modified by Faustman for developmental toxicity (Faustman et al., 1977).

This conceptual framework was further developed and refined at a workshop held in Lyon in February 1999 attended by many scientists involved at a senior level within or as advisors to, regulatory authorities involved in risk assessment of chemical carcinogens. Case examples to illustrate the use of the framework were prepared prior to the workshop. These were used by breakout groups to evaluate the framework. There was unanimous agreement amongst participants that the framework was useful for providing a structured and transparent approach to mode of action considerations. Also that it would be a useful tool in the overall hazard characterization of a chemical. Furthermore, it could also be used in identifying research needs. Participants recommended that the frameworks should be distributed as widely as possible, both to national and international agencies, so that its utility could be investigated. This was endorsed at the 4th Meeting of the IPCS Harmonization Steering Committee (Montreux, Switzerland, 1999).

Progress Made

Members of the Working Groups have submitted the framework to various national regulatory bodies and international agencies for use in their work.
A paper entitled: IPCS Conceptual Framework for Evaluating Mode of Action for Chemical Carcinogenesis, has been submitted for publication to the Journal of Regulatory Toxicology and Pharmacology.

It is recognized that the framework only addresses one stage of the overall characterization of the hazard of chemical carcinogens to humans. Another key step is the assessment of relevance to humans. The IPCS Harmonization Steering Committee has agreed that this area should be given the highest priority for further work in the Project. It was also agreed that IPCS should accept the offer of collaboration with ILSI in taking this activity forward.

The overall goals of the IPCS/ILSI project will be to extend the IPCS Conceptual Framework for the evaluation of mode of action (MOA) in animals, to address human relevance.

As a first step, a Scoping Meeting has been arranged for 8-10 November to be held in the UK. The purpose of the meeting will be two-fold:

- to discuss and confirm the project goals and to determine how best to reach the;
- to scope the project and develop a plan of action to achieve the goals and objectives.

It is envisaged that the initial product will be a mode of action framework that addresses human relevance that can be used as a tool to provide a structured approach to determining the human relevance of an animal mode of action. This should aid transparency in decision-making and also in identifying data and research needs.

**Participating Groups**

A range of regulatory agencies are covered by members of the Workgroup. Specifically, representation from ILSI, IARC and the European Chemicals Bureau (Commission of the European Communities).

**Impacts Identified**

The Conceptual Framework for identifying mode of action of chemical carcinogens is being used by regulatory agencies in a number of countries for both pesticides and general chemicals. It is also being used by JMPR when considering animal carcinogens.
References


