

# IPCS WORKSHOP ON ISSUES IN CANCER RISK ASSESSMENT

Fraunhofer Institute of Toxicology and Aerosol Research,  
Hannover, Germany, 27-30 January 1998

## Meeting Report

1. The Workshop was opened by Ms Sonich-Mullin who welcomed participants on behalf of IPCS. Prof Dr Heinrich, Director of the Fraunhofer Institute of Toxicology and Aerosol Research, as the host of the Workshop, welcomed participants to the Institute. Prof Dr Heinrich provided an introduction of the work of the Fraunhofer Institute especially highlighting its ongoing contribution to the IPCS. Mr Quarg, representing Prof Dr Schlottmann of the German Federal Ministry of Environment, Nature Conservation and Nuclear Safety, also welcomed participants and highlighted the value of the IPCS Harmonization Project as an important process towards ensuring sound and common approaches to chemicals risk assessment. Ms Sonich-Mullin expressed the appreciation of the IPCS to the German Ministry, for their support of this Workshop and their longstanding contribution to, and support of, the activities of the IPCS. She further thanked the Fraunhofer Institute for organizing the meeting on behalf of IPCS as well as their commitment to the goals and objectives of the IPCS activities.

2. Following the introduction of participants (a full list is provided in Annex 1), Ms Sonich-Mullin presented proposals for the Chair and Rapporteur for the consideration of the Workshop. This Workshop is a logical progression and follow on to earlier harmonization workshops on cancer risk assessment and has been the result of much planning. Given this, Ms Sonich-Mullin presented the Planning Workgroup's recommendations for the Workshop Chair and Rapporteur. Nominated and accepted by the Workshop were Dr Ada Knaap, The Netherlands, as the Workshop Chair and Dr Margaret Hartley, Australia, as the Workshop Rapporteur. Drs Knaap and Hartley accepted the nominations and then assumed their roles. The draft agenda was accepted for the Workshop (Annex 2).

3. Dr Knaap welcomed the opportunity and expressed the importance of, and her support for, the overall goals of the harmonization efforts. Dr Knapp then asked Ms Sonich-Mullin to provide an overview of the Harmonization Project.

### **Background: IPCS Harmonization Project**

4. Ms Sonich-Mullin indicated her intent to provide a brief background on, and overview of, the Harmonization Project. As a beginning, she provided an introduction to the IPCS, focusing on its roles and activities through which the need for the **Harmonization Project** was identified. The Harmonization Project was initiated in 1993 following the recommendation of UNCED, 1992, and the support of the IFCS.

5. The initial planning meeting in 1993 was significant in that it acquired the commitment of a number of representatives of national, multinational and international regulatory and other scientific and research organizations to move forward toward harmonization and to implement its recommendations. It further was instrumental in defining harmonization as: understanding the methods and practices used by various countries and organizations so as to develop confidence in and acceptance of assessments that use different approaches. The Project involves a willingness to work toward convergence as a long-term goal. It was stressed that harmonization is not standardization.

6. To move forward the initial approach taken is an endpoint-specific approach. Priorities were reviewed but of particular importance was the high priority placed on methods of cancer risk assessment. The current focus will be on human health using the 1983 National Academy of Science (US) risk assessment paradigm.

7. The accomplishments to date and ongoing efforts were briefly reviewed (a full report of activities can be found in IPCS/97.x), noting the work of the Terminology Project and the Inventory Project. The Terminology Project is considering generic and technical terms used in risk assessment. The

Inventory is a index of recent developments in risk assessment methodology and guidelines and will serve as a invaluable tool for risk assessors through information sharing.

8. The advantages of harmonization were presented. These include: that it allows a framework for the comparison of information; allows for the understanding of the basis of exposure standards; enables progress toward common classification and labelling schemes; allows for savings of time and expense through information sharing; and allows for credible science.

9. It was noted that harmonization cannot be dictated. Rather, it will eventually result from scientific discussions, information exchange and the understanding of each others goals and objectives. Finally, we should strive not to harmonize the past but rather to create the future.

10. Discussions raised the view that in the short term standardization is not the goal but that in the longer term this may be achieved in some aspects of risk assessment as appropriate. It was recognised that different risk assessment methodologies may all have validity as the type of approach chosen will be dictated by the purpose of the risk assessment. Further, standardization may impose too rigid a process onto approaches to risk assessment and the need for flexibility was agreed upon.

### **Harmonization of Cancer Risk Assessment**

11. Dr Karl Baetcke presented an overview of the specific activities on the harmonization of approaches to cancer risk assessment. To date, two workshops on cancer risk assessment have been convened. The initial workshop, convened in February 1995 (IPCS 95.x), outlined general issues and recommendations for action which were subsequently agreed upon by the Steering Committee in their first meeting (June, 1995 IPCS/95.y). Given the lack of very specific guidelines and the role of scientific judgement in the risk assessment process, the initial workshop recommended that for carcinogenicity, the best information would come from comparing chemical-specific risk assessments developed by different organizations. Thus, based on these recommendations, a second workshop was convened in March 1997.

12. The purpose of the second workshop was to select chemicals for comparison, identify if specific criteria could be stipulated to allow for full comparison and to receive the commitment of individuals and organizations to participate in this activity. The stated goals of the workshop were:

- to develop assessments on chemicals which cover a variety of issues/circumstances encountered in cancer risk assessment to allow for full comparison of the approaches being used; and
- to determine the status of the harmonization of such approaches.

13. Specific objectives of the workshop were to:

- review the recommendations of the previous workshop;
- determine if the recommendations made were currently appropriate given any recent developments;
- identify specific chemicals for use in case studies to compare different country approaches;
- delineate the processes necessary for success in furthering this effort.

14. Early in the workshop, the participants agreed that, rather than selecting chemicals as a focus for comparing and contrasting different regulatory approaches taken to the assessment of carcinogenicity data, where generic issues have already been identified these would serve as a useful tool to progress discussions in this area. Therefore the approach was to focus on the main scientific issues encountered which may lead to differing approaches, then identify and select specific chemicals as case examples to illustrate these generic issues.

15. Given this agreement, a number of specific issues that arise in cancer risk assessment, and for which there are differing scientific approaches were identified and agreed upon. These included:

- mode of action / relevance to humans
- genotoxic / non-genotoxic
- receptor mechanism: (i.e hormonal, Ah receptor, peroxisome proliferation)
- cell proliferation / apoptosis/cytotoxicity
- toxicokinetics / metabolism

16. With these key issue in mind, the workshop identified chemicals which could be used to illustrate these differences. Criteria used in selecting chemicals were that they:

- illustrate more than one of the issues;
- have been evaluated by more than one country/organization
- have been evaluated recently (within the last three years).

The intention was to include chemicals that reflect a number of data scenarios, i.e., those that are data-rich or data-poor and relatively easy to assess vs. those more complicated to assess. It was agreed that issues papers be developed on each issue with a defined content. Individuals present at the workshop agreed to prepare specific issues papers. For pragmatic reasons, it was agreed to restrict this effort to about 10-12 compounds. Other issues also discussed included: maximum tolerated dose (noting the ILSI work group on dose selection and possible need for follow-up), the relevance of effects in organs that are not present in humans, statistical methods for bioassays, and specific issues associated with metals and inorganics. However, it was decided that these latter issues would not be specifically addressed in the Hannover Workshop.

18. In order to further discuss harmonization aspects associated with the generic issues of cancer risk assessment, the preparation of a series of issues papers for the case study chemicals was undertaken. For each chemical, a lead person was assigned the task to produce a summary paper outlining Generic Issues (not focusing on assessment of specific chemicals).

19. The summary issues papers follow a common format along the lines:

- evidence for genotoxicity;
- evidence for considering mechanism irrelevant to humans;
- key factors in deciding if adequate/partially adequate or inadequate;
- evidence to depart from default approach to dose response risk assessment;
- are there common approaches in different countries?
- what are reasons for the differences?
- different "threshold" for "adequate" data. Different time "cut-offs" for the database;
- can further data be identified that will facilitate harmonization?

20. The issues agreed upon, and the chemicals chosen for the comparisons, are outlined in the report: *IPCS/9 7.13, "IPCS Workshop on Chemical-Specific Risk Assessment for Carcinogens - Chemical Selection, " 3-5 March 1997.*

21. Following the drafting of issues papers a planning meeting of the issue writers was convened 2-3 October 1997 in Lyon France, to:

- review the issues papers
- identify any additional issues
- to finalize plans for the Hannover Workshop, Germany, 26-30 January 1998;
- define possible future efforts past the Hannover Workshop.

22. It was felt important to ensure that the Hannover Workshop be comprised of individuals, drawing on the scientific and regulatory community of experts in the area of cancer risk assessment. The goals were to focus on the issues identified and to work toward reaching consensus on the scientific approaches to dealing with the issues identified. Further, the results of the Hannover Workshop will be presented in full to the September 1998 meeting of the Project Steering Committee for comment on determining the ability to implement the agreements reached, in national and agency/organization decision-making activities.

23. Presentation of the issues papers was to provide a general overview of the issue, clarify approaches used in developing papers; highlight concerns/problems identified; follow a standard format, highlight transparency issues. In addition, the issues of the use of weight of evidence (how much mechanistic data needed?) and the role of different science/regulatory policies should be raised.

## Hannover Workshop Goals and Objectives

24. Ms Sonich-Mullin presented the specific goals and objectives for the present Workshop. These were:

- **Identify and discuss specific issues.** Identify factors that facilitate or detract from the ability of individual regulatory organizations to reach international harmonization on the preparation of risk assessments and risk assessment documents.
- **Use chemicals as case examples only.** Chemicals identified to illustrate issues. Purpose is NOT to focus on the chemical in question nor to come to international consensus on the chemical-specific risk assessments
- **Identify areas of current agreement.**
- **Identify areas of divergence.** Through understanding differences greater harmonization is possible.
- **Identify mechanisms by which differences may be resolved.** What can we do? Scope plan of action that will allow the international regulatory community to move towards preparing assessment documents that are useful to multiple regulatory/assessment bodies.

## Issues Papers/ Summaries

25. Issues papers were prepared with the sole purpose being to stimulate discussions at the workshop. Issues papers were prepared by individual members of the Planning Group and circulated to all members of the planning group, as well as to the Harmonization Project Steering Group, for comment. While they are provided as an annex to this report (Annex 3), the reader is requested to keep in mind, the specific purpose of these papers. They are not complete reviews of the issues nor do they represent an exhaustive comparison of the data. Rather, they represent a risk assessor's view based on a review of the information available and following a specific framework to identify generic issues in cancer risk assessment.

26. Dr Bette Meek provide an overview of the experiences the issue writers had in the preparation of the issues papers and highlighted the high level of similarity should be made accessible to other regulatory agencies as a means of facilitating harmonization efforts.

71. The Workshop had considerable discussion on the issue of peer review and decisions made by expert committees, noting that these mechanisms need to be fully articulated and transparent in associated documentation. For example, the level and type of peer review processes, whether peer review had a specific focus and the role of the expert committee in the risk assessment approach, if clearly articulated, can assist in the further understanding of how decisions are reached.

72. Further, the identification of which data sets are actually utilized in risk assessments and the possibility of establishing formal exchange mechanisms of to assist in the identification of key data may assist in ensuring that key data are available to all agencies conducting assessments on the same substance.

73. There were several issues raised concerning occurrence of multiple tumours associated with exposure to a non-genotoxic compound. For example, should there be concern when there are multiple tumours at multiple sites (though some may occur through a related mechanism) even though all might have a plausible mode of action to support a non linear approach to the risk assessment?

74. The question of approaches to cases where there are multiple tumours at multiple sites, the significant ones of which all have a plausible mode of action to support a non linear / margin of exposure approach, but where there may be remaining small increases (albeit small) in tumour incidence which might not have been considered as adequate evidence of carcinogenicity in their own right, were raised. These issues of approaches to multi-site tumours were not discussed fully but were considered appropriate as possible subjects for future deliberations.

75. The Workshop discussed the approaches to criteria for determining relevance of thyroid tumours in rats and noted the existence of criteria developed by IARC, EPA and others. Parallels for possible harmonization activities were drawn from earlier discussions on criteria for male rat kidney tumours and mouse liver tumours. It was suggested that further work to prioritize these criteria in terms of which would be considered necessary (Level I- establish mode of action) and those considered desirable (Level II- further criteria to establish mechanism of action) would further enhance harmonization efforts in cancer risk assessment. Further, the issues of criteria were highlighted as useful for "test cases" for validation of the proposed conceptual framework for establishing mode of action in cancer risk assessment (see discussion on Conceptual Framework below).

76. The Workshop again drew attention to the issues associated with the presentation, within assessment reports of qualitative versus quantitative interspecies **variations in the tumour response**. This again highlighted the need for enhanced clarity in the assessment report to ensure that where consideration of the size of a quantitative difference was deemed large enough to be considered effectively a qualitative difference.

#### *Multi-Site Cytotoxicity/Cell Proliferation and Enzyme Induction - Case Study: Fenbuconazole*

77. Fenbuconazole was presented as a case study illustrating approaches used by the Ministry of Agriculture, Fisheries, and Food, UK and the US Environmental Protection Agency in evaluating data on two tumour types, thyroid and liver, and potentially two different components in the mode of action in the liver, cell proliferation and enzyme induction.

78. Significant differences identified in the comparison of reviews where the US EPA recommended using linear extrapolation for risk assessment whereas the UK recommended a non-linear/ margin of exposure approach, the application of results of genotoxicity test results to the choice of risk quantification and the weight given to data from two year bioassays on liver toxicity versus data from "mode of action" studies. Overall, the reviewer of the two evaluations felt that the clarity and scope of each evaluation was such that the reviews would be useful to other organizations and that with the exception noted, there was substantial agreement on the significance of data on genotoxicity, the induced mechanism of thyroid carcinogenesis, and on data from supporting studies. It was unclear what weight was given to genotoxicity data as to what extent mechanistic data influenced the approach to quantitative risk assessment by the two organisations or how much information was needed to reach a decision that a plausible mode of action had been demonstrated.

79. In subsequent discussions, two major issues were identified, namely: the need to develop criteria for determining if a carcinogenic response in thyroid tissue was a result of a secondary mechanism and a need to develop criteria for determining relationships among liver weight increases, enzyme induction, and hepatocellular carcinogenesis.

80. It was noted that the US EPA has drafted a Science policy document on thyroid tumours which will be available shortly. Discussions identified that these criteria may also be useful for further considerations for possibly harmonizing the use of criteria for these tumour types similar to the proposals noted for criteria for rat male kidney tumour responses.

81. It was also noted that clear definitions of cell proliferation and cell replication are required, linked to observations which can measure apoptosis and define the cell populations involved in cell replication. Finally, it was stated that there were species differences in the sensitivity of liver cells to P450 induction which should be considered in evaluations of cancer risk.

## **Cytotoxicity/Proliferation and DNA Protein Cross-Links**

### ***Case Study: Formaldehyde***

82. The case study is an example of a carcinogen for which cytotoxicity/proliferation in the respiratory tract and interaction with DNA (DNA protein cross links) are associated with carcinogenesis.

83. There were differences in the extent to which the available data on mode of action were considered to be sufficient to deviate from default approaches to quantitative estimation of dose-

response. The EHC concluded that if respiratory tract tissue is not repeatedly damaged and exposure of humans is low then non cytotoxic concentrations of formaldehyde can be assumed to represent a negligible cancer risk. This was based primarily on the observation that tumours are induced only at cytotoxic concentrations. The US and Canadian assessments did not attribute as much weight to this evidence. While incorporating variations among species in delivered dose in calculating risk estimates (recent US assessment), it was acknowledged that the uncertain role of cytotoxicity was probably not adequately addressed by these approaches. It should be noted, however, that while this approach is reflected in a peer reviewed publication of US EPA staff published more recently (1994), the IRIS (1987) entry has not been updated and estimated risk, therein, is based on direct extrapolation of tumour incidence by the default linearized multistage model.

84. In the ensuing period since these assessments were completed, considerable additional **data** have been generated on the mechanism of toxicity of formaldehyde which, upon review and in light of the proposed revised Cancer Guidelines in the US, may lead to greater consistency among agencies in approach. In that regard, Health Canada and the US EPA are currently jointly coordinating external peer review of dose response modelling, which takes into account results of recent mechanistic studies for formaldehyde. This activity will clearly lead to harmonization.

85. The Workshop discussed a number of issues including the relationship of the weight of evidence of genotoxicity in *vitro* and *in vivo* to genotoxic effects at the target site. Further, the "discomfort" in the US and Canadian assessments about whether genotoxicity at the target site adequately addressed in assessments based solely on cytotoxicity was noted.

86. A commonly accepted BBDR model for formaldehyde may have more general application with respect to other aldehydes (with similar genotoxic and irritant properties). Cross agency methods for evaluation of BBDR models could also aid in the harmonization of these model types.

87. A number of comments on the confining nature of current classification systems for hazard identification were made especially when the data was such that clear classification was easy. The Workshop agreed that inclusion of narrative statements on hazard characterization, in addition to classification would greatly facilitate harmonization.

88. Further, the Workshop discussed and agreed that epidemiological data was useful for bounding estimates of BBDR.

## **Hormonal (antiandrogen) induced tumours**

### ***Hormonal antiandrogen induced tumours - Case Study: Vinclozolin, Procymidone and Iprodione***

89. The issue was expressed as the implication of hormonally induced tumours. Using US EPA and Australian documents, there was general consensus that none of the compounds was genotoxic. The carcinogenic response was clearly induction of Leydig cell **tumours in rats, and** liver tumours in mice. The main difference in the evaluations arose from interpretation of the mode of action studies. While Australia accepted the biological plausibility of the Leydig cell tumours in all substances as arising from one of several possible anti-androgen mechanisms, the US EPA accepted this approach only for vinclozolin, and regarded the studies as inadequate/inconclusive for iprodione and procymidone. Australia regarded the liver tumours as not being significant evidence of carcinogenicity based on dose response considerations, hormonal disturbance, and human exposure considerations (ie hazard characterization). The US EPA, in their hazard identification, considered the liver tumours induced by procymidone and iprodione to be significant. The other main difference arose from the different approaches to the interpretation of the relevance of Leydig cell tumour in rats to humans.

90. The Workshop commented that, in general, most underlying modes of action for Leydig cell tumours involving hormonal disruption are likely to display a non-linear dose response.

91. The Workshop discussed that an adequate understanding of the mode of action of Leydig cell tumorigenesis is necessary in order for regulatory authorities who assume linearity of dose-response at low doses as the default in such cancers to adopt a non linear/margin of exposure

approach. In this respect, the findings of the 1995 EPA/AIHC/NIEHS workshop on rat Leydig cell tumours were identified and discussed as a useful source of information and proposal which may assist further work in this area.

92. It was noted that there was uncertainty with respect to the nature and status of the rat Leydig cell tumours with reference to man, where these tumours are very rare. At present it would appear that there was no identified mode of action which supports a potential to induce other testicular tumours in man but that excess androgen production may have adverse effects either carcinogenic or non carcinogenic.

93. The Workshop agreed that normal endocrine system function relies on periodic fluctuations in hormone levels and that these normal variations maybe a significant confounder when attempting to understand the potential for exogenous substances to disturb endocrine functions.

94. Further activities specific to the Leydig cell tumours should include the development of criteria for characterization of the mode(s) of action by which these tumour types arise. As identified above, the Workshop considered that the US EPA/AIHC/NIEHS report is a good starting point for this work. It was noted that the US has recently begun work on this issue and the Workshop suggested that, if possible, peer review and participation by the broader scientific and regulatory communities in this process was a prime opportunity to ensure a harmonized approach.

## **Interspecies Differences in Metabolism**

### ***Case Study: Methylene Chloride***

95. Five full risk assessment documents were compared, i.e. those from The Netherlands (1987), US EPA (1990), IPCS (EHC, 1996), Government of Canada (1994;1996), and US.OSHA (1997). The data package for these assessments were essentially the same, except for two papers: one concerning genotoxicity *in vitro* (1990) and a mouse bioassay (1993); both these studies showed positive results. Given the date of assessment, neither of these studies were seen by the Dutch. However, despite more recent evaluations, only the IPCS assessment referred to the mouse bioassay.

96. Methylene chloride is rapidly absorbed both after inhalation and after oral exposure. There are mainly two metabolic pathways, for which there are clear species differences. Epidemiological data were limited and did not demonstrate a statistically increased cancer risk with exposure. From the seven bioassays performed, tumours, observed after inhalation exposure, included lung and liver tumours in both male and female mice and benign mammary tumours essentially in female rats. Also an increase was seen in salivary gland tumour in rats, but these were considered to be associated with viral infections. The chemical was mutagenic in prokaryotes, negative in gene mutations but positive for chromosomal aberrations in assays with eukaryotes, and negative in all performed *in vivo* studies, except the one published in 1990. Studies on DNA adduct formation were all negative.

97. The US and Canadian agencies classified methylene chloride as a probable human carcinogen, though interspecies metabolic differences were accounted for through PBPK modelling. In the IPCS assessment, methylene chloride was considered a carcinogen in mice, with no, or at most, low potency for man. Risk assessment was, therefore, based on a noncancer endpoint.

98. In the Dutch assessment, it was concluded that methylene chloride was not a carcinogen in humans based primarily on tumours being observed only at doses which produce cytotoxicity at sites where the spontaneous incidence was relatively high. Additionally, genotoxicity was considered weak and was not demonstrated *in vivo* but only *in vitro* at high doses. Additionally, gene mutation tests in eukaryotes and tests for DNA adducts were negative. Therefore non-cancer effects were considered critical for the risk assessment.

99. Since there was no apparent cytotoxicity at levels which induced tumours, this rationale for considering tumours not relevant for humans in this context was unclear.

100. During discussions, members again questioned when are interspecies variations sufficiently large to consider them qualitative rather than quantitative? This is particularly relevant when the margin between exposure (in the workplace, for example) and the doses to which the animals were exposed in carcinogenicity bioassays are relatively small (less than one order of magnitude).

101. Issues of how polymorphism can be factored into the consideration of interspecies extrapolations was discussed as a general issue.

102. With respect to PBPK modelling, the question of how much is enough information for confident characterization of interspecies variations in metabolism (e.g., number of **human** liver tissue samples)? was posed. It was noted that PBPK modelling obviates the need for the body surface area correction for interspecies variation in rates of metabolism. In addition to interspecies variations, nonlinear pharmacokinetics (i.e., dose-dependent variations) should also be taken into account. It was also noted that additional strength can be gained if negative tumour data from apparently non-susceptible species are used to evaluate the PBPK model. The Workshop agreed that the documentation of PBPK modelling should be sufficiently transparent to enable critical evaluation and source code should be provided, wherever possible. Further, modelling should be evaluated to insure consistency with data available for all species.

103. The Workshop agreed that a more uniform format for the description of data and their interpretation would further facilitate harmonization. As such, the doses and conditions at which specific relevant effects are observed should also be specified.

104. Finally, the Workshop noted that harmonization of terminology is desirable and that classification systems are generally less informative than narrative descriptions of hazard characterization. Further, it was agreed that assessments should clearly delineate hazard identification processes from risk characterization.

## KEY ISSUES

105. Throughout the presentations and discussions of the various case studies, a number of generic issues emerged which were identified by the Workshop as important to harmonization efforts. These issues fell essentially into five areas although it is noted that these issues often relate to each other and need to be considered collectively to further enhance harmonization efforts. These five main areas were:

- transparency;
- terminology;
- weight of evidence considerations;
- flexibility;
- accessibility/communication.

## Transparency

106. A continuing theme throughout the four days of deliberations was the need to improve the transparency of risk assessment documents and in the decision making processes.

107. It was noted by many of the authors of the issues papers that what initially appeared to the major difference in the interpretations of, and conclusions reached on, specific components of a number of these risk assessments in fact often reflected a lack of transparency, **and hence** understanding, of the science policy and/or regulatory constraints (eg classifications) which guided the assessments. However, a number of these differences were resolved through open discussion among workgroup members.

108. This was further demonstrated during the workshop when additional information was provided on certain case studies from participants led to a greater understanding of apparent differences in approaches based on identical data sets.

109. The case studies highlighted transparency issues such as a lack of detail on the overall risk assessment process, a lack of information on such features as the use of guidelines, criteria, and peer review processes followed, timing differences in the preparation of reviews, and differences in the data sets available to different organizations.

110. The Workshop agreed that a sufficient level of detail in describing data sets (including age of studies) was important in ensuring transparency. The question of how much detail is enough? was not fully resolved but reports should include summaries of the raw data sufficiently detailed to allow independent evaluation of risk. However, the Workshop warned against adopting a too prescriptive approach on the level of detail, noting that a "minimum requirement" would allow individual agencies/organizations to add more detail depending upon their particular needs.

111. The Workshop drew attention to ongoing activities in addressing level of detail and formatting of assessment reports for pesticides through the OECD Pesticide Forum and the IPCS CICADs (Concise International Chemicals Assessment Documents) programme and noted that these, and other similar activities, would be invaluable in informing the general issue of the appropriate level of detail in assessment reports.

112. In addition to the issue of level of detail, the Workshop agreed that the use of a narrative on the risk assessment approach, in addition to the application of criteria and/or classification systems, would greatly enhance understanding and hence harmonization efforts. This is further highlighted by the fact that many participants believed that classification systems used in isolation can be restrictive in cancer risk assessment.

113. When PBPK modelling is used, the Workshop agreed that the purpose and the information sources (including human data) being used in the model need to be clearly articulated to enhance understanding and use of such approaches. The use of narratives was again highlighted.

114. Discussions also focussed on the need for transparent reporting of peer review processes including the need for detail on the level, purpose and type of peer review used in the risk assessment. Distinctions were drawn between independent expert peer review as a final step as opposed to peer input during the assessment process itself. Further, the group felt that the level of peer review and the task assigned (eg. consideration of a single issue within the risk assessment consideration) to a peer review committee needs to be clearly articulated.

115. The Workshop agreed that in general the moves towards the use of narratives on the weight of evidence and decision making in cancer risk assessment should be strongly encouraged. The Workshop also noted that this issue is equally applicable to the non cancer risk assessment work of the Harmonization Project.

Overall, it was agreed that transparency in cancer risk assessment processes and assessment reports is a critical factor to maximize the usefulness of assessment reports and to **achieve** harmonization.

## **Terminology**

116. As highlighted in paragraphs 28-29 above, the presentations and discussions highlighted a number of key terminology issues. One issue which provided a useful framework to facilitate understanding of the apparent differences in risk assessment approaches between various agencies/organizations was the delineation of the evidence base required for risk assessment and decision making within different regulatory agencies and organizations.

117. One particularly useful framework developed during discussion in the Workshop was the concept of a **mode of action - mechanism of action continuum**. This facilitated understanding of the different data and evidential needs in different approaches in risk assessment. For example, the differences in risk assessment approaches of regulatory agencies and other organizations were often explained by where an agency was on the continuum of evidence required to establish a mode of action (sufficient evidence to establish a biologically plausible explanation) or to establish a mechanism of action (sufficient evidence to establish scientific proof of causality).

118. During discussions, a number of general and specific terminology issues arose which the Workshop identified as needing attention in order to enhance harmonization efforts. These included:

- the definition of hazard identification and hazard characterization;
- the use of terms such as threshold/non linear and linear default approaches;
- greater clarity in the terms: relevant and non relevant (through the use of narrative);

- issues of shifting terminology, eg in classification systems which highlight the need for enhanced transparency and communication;
- the need for consistent use of terms such as cell proliferation, **cell replication** and apoptosis;
- the use of the terms quantitative and qualitative differences (including how big does a quantitative difference need to be to be considered qualitative?).

Overall, it was agreed that consistent use of terms in cancer risk assessment would assist to maximize the usefulness of assessment reports and facilitate harmonization and that issues highlighted at the Hannover Workshop should be communicated to the Terminology Project for further consideration.

## Weight of Evidence Considerations

119. The role of scientific judgement and the need for flexibility in the risk assessment process was noted. Further, considerations of the amount of information and data required for decision making as well as the weight placed on critical data were discussed throughout the Workshop. It was noted that risk assessment decisions may often have to be made without full data sets being available and that further data needs are often articulated within the risk assessment.

120. The Workshop agreed that where further mechanistic data is requested, it should be clearly articulated what is the purpose of the requested data, what priority (eg: essential or desirable) such data has and when data become available they must be incorporated into the risk assessment. Other discussions on data needs focussed the weight given to multi-tumours occurring at multi-sites in multi-species even when the critical tumours may have established mode(s) of action. The "lack of comfort" by some regulatory agencies in dismissing the relevance of tumours in such situations was noted.

121. Further, the use of exposure considerations in risk assessment was discussed. The Workshop noted that where data was lacking, regulatory agencies in practice may use margin of exposure considerations to determine whether additional data needs to be generated. In addition, it was noted that there needed to be transparency in how and when exposure issues were considered in the risk assessment.

122. The fact that risk assessment is an iterative process and that science must continue to inform the risk assessment was noted by the Workshop. As increased scientific knowledge and understanding emerge, the more the weight of evidence considerations can move along the mode of action - mechanism of action continuum (with a parallel decrease in the level of uncertainty).

123. Discussions highlighted that need to consider population variability/polymorphism in the risk assessment process. This was particularly true for responses to hormonal modes of action where individuals may display hormonal modulation with time and for accounting for metabolic differences.

124. The Workshop noted that there was a need for regulatory agencies to define or delineate the weight given to the evidence for genotoxicity in relation to the mode of action. The issue of how the entire genotoxicity data set is incorporated into the risk assessment was considered worthy of further consideration.

125. The Workshop also recognized that elucidation of species differences could be assisted by PBPK modelling noting however, that this would not normally be considered a requirement but should be used for chemicals requiring priority risk assessment. Again, the need for **transparency in the** application of the PBPK was noted.

126. The use of criteria for establishing the mode of action, and the weight given by various agencies/organizations to criteria and other information in establishing mode of actions for tumour formation, were discussed for the various case studies. It was agreed that harmonization of criteria would greatly assist in common approaches to cancer risk assessment. Further, the Workshop considered that the criteria for the male rat kidney tumours (alpha 2u mode of action) used by the US EPA (purple book) and those proposed by IARC could be harmonised using a two tier approach (see paras 39 & 40 **above**). **It was** considered that similar approaches could be taken for other tumour types (rat thyroid, mouse liver, and rat Leydig cell).

### **Conceptual Framework: Critical Events in Evaluating Causal Factor(s) in Carcinogenicity**

127. These considerations of criteria for deciding mode of action/causality and the diversity of case studies presented highlighted the commonalities of approaches in considering the mode of action of different tumour types. This facilitated the development during the workshop of a generic approach to the principles for evaluating the mode of action/causality for tumour formation in cancer risk assessment; termed by the workshop as the **Conceptual Framework**.

128. The Conceptual Framework was presented to the workshop by Dr Jeanette Wiltse, based on the identification of general principles and issues associated with determining mode of action of various tumour types. The Framework is based on the Bradford-Hill criteria for causality, as modified by E. Faustman (*Fausinan et al, 1997. Experimental Approaches to evaluate mechanisms of developmental toxicity. Handbook of Developmental Toxicity, CRC Press 3-41*), for developmental toxicity. The Framework presents a pathway for presentation of observed data linked to points of analysis against a set of guidelines/criteria and key questions.

129. The key guidelines and questions are generic in nature with the observations being specific to each tumour case. The level of observation to fulfill the questions will reflect whether mode(s) or mechanism(s) of action are being established, ie whether sufficient evidence exists to establish biological plausibility or scientific proof of causality. The flexibility of this issue within the framework was welcomed.