



**INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY
HARMONIZATION PROJECT**

Report of the First Meeting of the Cancer Working Group

3-5 March 2004, Arlington, Virginia, United States

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY (IPCS)

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WELCOME, OPENING OF MEETING AND INTRODUCTIONS.

1. The first meeting of the Harmonization Project Cancer Working Group was convened from 3-5 March 2004, in Arlington, Virginia. The meeting was opened for the International Programme on Chemical Safety (IPCS) by Ms Carolyn Vickers. Ms Vickers welcomed participants to the first meeting of the Working Group, and thanked them for the preparatory work that they had done. The invited participants list is at Annex 1.
2. Ms Vickers informed the Working Group that they had been tasked with extending the *IPCS Conceptual Framework for the Evaluation of an Cancer Mode of Action in Animals* (MOA Framework), to humans. The extended framework would not be specific to a particular category of chemicals, and hence should be applicable in the assessment of industrial chemicals, pesticides, food additives and contaminants, industrial byproducts, etc. The IPCS Harmonization Project aims to harmonize approaches to the assessment of risk from exposure to chemicals, and hence the documents produced are generally in the form of guidance that can be adopted for use by regulatory schemes. In extending the IPCS MOA Framework, Ms Vickers mentioned that this original piece may need to be amended so that the final product or products work as a whole. She also mentioned that other existing IPCS guidance may be relevant and if so should be referred to, for example the *IPCS Guidance Document for the Use of Chemical-Specific Adjustment Factors for Inter-species Differences and Human Variability in Dose/Concentration Response Assessment* (CSAF). The Working Group was also made aware of IPCS plans to extend the MOA Framework to non-cancer end-points. Finally, she mentioned the success of the workshop approach that had been used in developing the MOA Framework, in particular, in reaching the broader regulatory community.
3. Ms Vickers reminded participants (other than the representative of the OECD), that they had been invited to the meeting in their personal capacities as international experts, with the responsibility of serving and advising IPCS, and not as representatives of governments, institutes, or any other organization.

¹ The issue of this document does not constitute a formal publication. It should not be reviewed, abstracted or quoted without the written permission of the Coordinator, International Programme on Chemical Safety, WHO, Geneva, Switzerland.

WORKING GROUP CHAIR AND ARRANGEMENTS FOR MEETING REPORT.

4. In response to a proposal of IPCS, the meeting decided that Dr Bill Farland take on the role of Working Group Chair. Dr Farland assumed the Chair, and welcomed participants to Arlington. He explained the key documents for the meeting included: the IPCS MOA Framework²; the published reports on the human relevance framework (HRF) that had resulted from the International Life Sciences Institute (ILSI) Risk Sciences Institute (RSI) project³; and the two issues papers prepared for IPCS by Dr Jerry Rice titled *Human relevance of animal neoplasms: Site concordance between humans and experimental animals for cancers caused by exposure to chemical carcinogens* and *Human relevance of animal neoplasms: Significance of life stage at time of exposure to environmental carcinogens*. He then drew participants' attention to the need for the meeting to decide on the tools that would be needed to further the work beyond the meeting, including at the proposed workshop.

ADOPTION OF THE AGENDA.

5. The adopted summary and annotated agenda are at Annex 2. In accordance with Steering Committee procedures the Secretariat undertook to prepare the full meeting report, and it was noted that the main conclusions and recommendation of the Working Group would need to be agreed before the close of the meeting.

HARMONIZATION PROJECT AND WORKING PARTY PROCEDURES

6. The Working Group noted the Terms of Reference for the Harmonization Steering Committee, the specific Roles and Responsibilities established for the Harmonization Project, and the ongoing role of the Cancer Working Group in planning and execution of the work on human relevance.

REVIEW OF PREVIOUS HARMONIZATION PROJECT WORK ON CANCER.

7. Ms Cindy Sonich-Mullin delivered a presentation to the meeting, outlining the history of the Harmonization Project, focusing on the development of the MOA Framework (reproduced at Annex 3). She mentioned the value of the case study approach, whereby worked examples of chemical assessments applying the draft MOA Framework were developed and considered in a workshop setting. She also outlined the planning discussion for work on human relevance at the IPCS Scoping meeting to address the human relevance of animal MOA in assessing cancer risk, October 2000, Carshalton, United Kingdom.

² Sonich-Mullin C et al (2001). IPCS Conceptual framework for evaluating a MOA for chemical carcinogenesis. *Regulatory Toxicology and Pharmacology*. 34: 146-152.

³ Meek E et al (2003). A framework for human relevance analysis of information on carcinogenic modes of action. *Critical Reviews in Toxicology*. 33(6): 591-653. Also see accompanying articles in Volume 33, Issue 6.

REVIEW OF PROJECT DESCRIPTION AND OUTCOMES.

8. The Working Group noted the project description and expected outcomes, which had also been provided to the Group previously.

REVIEW OF (PUBLISHED) HUMAN RELEVANCE FRAMEWORK (HRF).

9. At the invitation of IPCS, Dr Penelope Fenner-Crisp, Executive Director, ILSI RSI attended this agenda item to deliver a presentation on the outcomes of the ILSI work on human relevance. Dr Fenner-Crisp explained the HRF contained in this publication, and noted that further work was underway on DNA-reactive carcinogens which could be made available to the Working Group. The Working Group's views and conclusions resulting from their discussion are included in the meeting report under the following item on IPCS work on a mode of action framework to address human relevance.

IPCS WORK ON A MODE OF ACTION FRAMEWORK TO ADDRESS HUMAN RELEVANCE.

10. Dr Jerry Rice presented to the Working Group the following two issues papers that he had been commissioned to prepare on life stage and site concordance. Dr Rice thanked Working Group members for their comments on the draft papers prior to the meeting and explained how the comments received had been addressed. The views and conclusions of the Group on the issues raised in the papers are recorded in the meeting report section titled "Why is it important to consider site concordance and life stages?".
11. After considering the information provided to the meeting and in the agenda papers, the meeting agreed on the views, conclusions and next steps set out in the below paragraphs 12 to 39.
12. In 2000, an IPCS Harmonization Project Cancer Planning Work Group⁴ convened in Carshalton, United Kingdom. Among the recommendations of that meeting was the suggestion that IPCS and ILSI move forward together and in parallel on the development of the extension of the IPCS MOA Framework toward addressing human relevance. It was recognized that ILSI could provide much help in technical workshops. In June 2001, ILSI RSI with support from the US EPA and Health Canada formed a working group to examine key issues in the use of mode of action information to determine the relevance of animal tumours. These efforts have resulted in several published reports⁵. This IPCS Cancer Working Group, convened on 3-5 March 2004 in Arlington, agreed that that these reports should form the starting point for further exploration of the issue of human relevance of animal tumours by IPCS with the goal of developing a unified framework for use of MOA information in risk assessment for regulatory and other purposes.

⁴ This initial Working Group differed in membership from the current group convened to work on the human relevance project.

⁵ Refer to footnote 3.

Evolution of the IPCS MOA Framework to consider human relevance

13. The Working Group discussed the type of document that would be produced as a result of its task to extend the MOA Framework to address human relevance. It was recognized that one integrated guidance document (a "unified framework") that worked as a whole would be needed to facilitate uptake and use by regulatory and other risk assessment bodies. The guidance could be supplemented by including in the publication the other materials generated through the process (e.g. issues papers and case studies).
14. Presentation of the previous work on development of the IPCS MOA Framework for animals and the ILSI human relevance framework prompted discussion of the evolution of definitions based on increasing experience, with focus on those for "mode" versus "mechanism" of action. The IPCS definitions published in Sonich-Mullin et al (2001) are: "A supported *mode of action* would have evidence provided by robust mechanistic data to establish a biologically plausible explanation. *Mechanism of action*, in contrast, relates to sufficient understanding of the molecular basis to establish causality; it is at the other end of the continuum from little or no evidence of *mode of action* to scientific proof of *mechanism of action*. Sonich-Mullin et al further states: "The support or rejection of the postulated MOA for tumour induction by a chemical carcinogen in animals is a key step in the overall hazard characterization/risk assessment. Another key step, but done at a later stage in the overall process, is the assessment of relevance to humans." It was noted that the definition of MOA in the HRF had evolved somewhat to encompass the identification of key events which are critical to considering not only the weight of evidence for mode of action in animals but also its relevance to humans.
15. Thus, in the HRF, MOA is a plausible hypothesis for the sequence of events leading to observed effect/s based on robust mechanistic data which involves identification of key events and comparison between animals and humans. Key events are measurable changes associated with critical steps in the mode of action, for which dose-response relationships, temporal associations, etc. can be examined. Mechanism of action, on the other hand, implies sufficient understanding of the molecular basis of effect to establish causality. Such mechanisms are rarely fully known.
16. Describing a mode of carcinogenic action is a key step in using more science in the hazard characterization process. In addition, MOA approaches are being relied upon more frequently than in the past to address questions regarding the human relevance of animal data. This has raised the question of what process can or should be used to gain "acceptance" of a MOA. This basic question can be broken down into two underlying questions: Acceptance by whom? and How is this generally accomplished?
17. In answering these questions, the Working Group recognized that there is widespread agreement among risk assessment practitioners that the acceptance by the "general scientific community" is an important attribute for MOA to be used in the risk assessment process for regulatory purposes. The "general scientific

community” is understood to include scientists from a number of scientific disciplines who are familiar with the risk assessment process. Acceptance does not mean that unanimity is required but that a majority of the scientists reviewing a MOA agree that underlying scientific information has been identified and appropriately analyzed, that the “key events” have been identified and supported by the information presented, that their relationship to carcinogenesis has been clearly and transparently articulated in the hypothesized MOA, and that alternate MOAs have been considered and rejected.

18. While there is no specific guidance for the sequence of steps that leads to acceptance of the MOA, it appears that extensive scientific peer participation is a prerequisite for acceptance. Peer participation includes both peer involvement and peer review. Peer involvement means that the hypothesized MOA should generally be the product of the collective efforts of a number of scientists who have identified, reviewed and analyzed data and formulated the MOA hypothesis. Peer review means that the product has been subjected to critical review by independent scientists. That is, it has been reviewed by those not involved in the process of development of the hypothesized MOA. In many cases, this peer review is extended through the publication of the hypothesized MOA and its underlying analysis in the scientific literature, allowing for widespread review and comment. Presentations and discussion at scientific meetings and workshops also constitute peer involvement that contributes to acceptance by the scientific community.
19. The Working Group does not anticipate that any more formal process of acceptance of a hypothesized MOA will be required in the future but that the activities described above will generally be sufficient to constitute “acceptance” of a MOA. The Working Group members agreed that MOAs should be viewed as flexible and able to evolve with emerging scientific information.
20. A case study approach and discussion at a larger workshop was considered appropriate to further the work. The Harmonization Project Stocktake was identified as one potential source of case studies, as the survey questionnaires employed will ask respondents to provide any examples of use of the MOA Framework. These could provide interesting cases to further develop by including consideration of human relevance. The Secretariat was asked to actively follow up sources of case studies, including by contacting regulatory bodies directly, as part of preparation for the planned workshop.

Application of a human relevance framework to genotoxic carcinogens

21. In discussing efforts to apply the HRF, Working Group members agreed that the framework could apply equally well to genotoxic and non-genotoxic carcinogens. The participants agreed that while the relevance to human carcinogenicity of several MOAs have been rigorously explored, the current efforts to apply the HRF do not explore the issue of genotoxic carcinogenicity to a sufficient extent and further efforts are needed. The difficulty is that beyond the mutation theory of carcinogenesis there is no agreed MOA or at least there is not a series of well-defined key events through which human relevancy can be explored. Hence, at

present, for many genotoxic carcinogens, it may be concluded that there is no clear MOA beyond genotoxicity per se, and thus human relevancy is assumed. Identification of a series of key events would reward diligence in investigating the effects of such compounds. By including detailed MOA considerations for genotoxic carcinogens, the applicability and generality of the framework would be extended.

22. Genotoxicity is essentially an operational definition in that compounds cause effects in relevant test systems. These effects include mutagenicity, clastogenicity, and aneugenicity. Further, a genotoxicity may arise by several mechanisms including direct interaction with DNA, generation of reactive oxygen species and epigenetic effects, e.g. inhibition of topoisomerase II. In exploring human relevance, it will be clearly valuable to determine which of these mechanisms is involved. Mechanisms that do not involve direct interaction with DNA can be accommodated within the HRF and are not considered further here.
23. The participants were informed that ILSI RSI is currently exploring the applicability of the HRF to DNA-reactive genotoxic carcinogens and in particular is seeking to identify key events that may be involved in the MOA of such compounds. It was agreed that when available, this document would be extremely useful in furthering this issue.
24. The participants concluded that there is still a lack of understanding of how DNA-reactive genotoxic carcinogens cause cancer. Whilst DNA binding and mutation are often critical events, many such compounds can affect DNA in more than one way, for example, adduction, strand break. There can also be more than one outcome, e.g. point mutation, chromosomal loss, failure of normal DNA repair mechanisms. The relevance of all such effects to cancer outcome is still debated, making identification of key events for an MOA problematical.
25. On-going and imminent studies involving global expression analysis have considerable potential to resolve some of these issues and to identify those events that are critical in the MOA for such compounds.
26. The participants felt unable to give clear guidance at this time on the key events that might be involved in such MOA. Events that might be key include whether the parent compound or a metabolite is responsible for the genotoxicity, whether adduction of DNA occurs, the identity of any DNA adducts, or whether adduction results in mutation.
27. The emphasis should be on identifying key events that will help in exploring the relevance of any tumours to humans and where kinetic or dynamic factors might influence their significance, for example, whether a metabolite is responsible for genotoxicity.
28. As it has not yet been possible to identify the key events in the MOA for DNA-reactive genotoxic carcinogens, it is not possible to provide guidance as to the types of the experimental data that might help in such evaluations. However the investigation of suitable examples may help clarify this situation. Working Group

members recommended that suitable worked examples be considered at the workshop, taking into account the imprecision of the distinction between genotoxic and non-genotoxic carcinogens.

Use of frameworks

29. Members discussed experiences regarding the application of the MOA Framework and the HRF and noted that there were lessons to be learned that were specific to the MOA Framework and the HRF, and to use of frameworks in general.
30. Overall, the experiences in using the MOA Framework have been very positive and the Working Group suggested an active process to collect information on its use. Based on experience obtained, minor refinements could be made and these should be considered during the development by IPCS of an integrated framework to address human relevance.
31. Members agreed that frameworks in general had several purposes, many of which were well described in the IPCS MOA Framework publication. The purposes discussed by the Working Group, included:
 - To provide a harmonized generic approach to the analysis of data.
 - To ensure transparency of the use of available data and reasons for the conclusions drawn.
 - To provide guidance in the presentation of data.
 - To learn from others' application of the framework.
 - To identify data gaps and needs.
32. However members noted some organizations have used the MOA Framework without documenting the process, which limited the transparency, sharing of experiences and harmonization.
33. Members also noted that the presentation of data and the analyses within the frameworks should not be prescriptive (as this depended on factors such as the type of data), as long as the data, context and thought processes are sufficiently described to ensure transparency in presentation. Case studies presented with both frameworks provided examples of the level of detail that is useful.

Comments on the (published) Human Relevance Framework (HRF)

34. Overall, there was general agreement among Working Group members that the questions identified as the critical components of the HRF were important and appropriate for addressing the issue of human relevance of a mode of action determined in animals. However, several issues were identified that could benefit from additional clarification, development or expansion. These issues need to be addressed in the IPCS effort and will likely require modification of the HRF. The issues requiring clarification and modification include:

- **Confusion as to how exposure (dose) considerations fit into the HRF.** For the IPCS effort, this issue should be clarified, and in particular, highlighting the point that exposure is to be taken up as part of the final risk assessment analysis, rather than part of the HRF analysis.
 - **Answering the three critical questions comprising the HRF in absolute terms (Yes or No).** It was recognized that there is an intentional bias in the answers to the three questions that comprise the HRF⁶. For question #1 (is the weight of evidence sufficient to establish the MOA in animals?), the default answer is no if an adequate dataset cannot be provided. Perhaps, “not yes” would be a more appropriate alternative. On the other hand, for questions #2 and #3 (are key events plausible in humans? and taking into account kinetic and dynamic factors, are key events plausible in humans?), the default answer will be “yes” if a data set does not provide convincing evidence that the answer should be “no.” Given this bias in the default answers, it was suggested that questions #2 and 3 should be answered as “no” or “not no” to more accurately reflect the confidence in the evaluation.
 - **Precise wording of questions 2&3.** It was recognized that evaluation of each key event was critical in reaching the conclusions regarding “plausibility in these questions. Alternate wording was discussed and should be the focus of additional thinking prior to the IPCS workshop. Workshop participants would benefit from some documented rationale for proposed changes to the HRF questions.
 - **The use of “unlikely” in the HRF schematic.** Working Group participants felt that the use of the term “unlikely” in an otherwise absolute scheme needed further consideration.
35. Working Group participants felt that addressing these and other issues at the IPCS Workshop would assist in the further evolution of an HRF.

Why is it important to consider site concordance and life stages?

36. Risk assessments in the past have generally not assumed that the tumour sites observed in animals would be the sites expected in humans. Newer risk assessments based on MOA have sometimes implicitly assumed that site concordance would hold. This assumption, however, has never been examined empirically. Some MOA in experimental animals are tissue-specific (e.g. thyroid follicular cell tumours arising from hormonal dysregulation, alpha-2u male rat kidney tumours), while others are more general (e.g. mutagenicity, immune suppression).
37. One can also distinguish between local and systemic tumour formation. Whereas good site concordance is generally found between humans and experimental animals in the case of local tumours, reflecting the most intense exposure to the

⁶ Figure 2, at page 601 in: Meek E et al (2003). A framework for human relevance analysis of information on carcinogenic modes of action. *Critical Reviews in Toxicology*. 33(6): 591-653.

target site, the concordance in the case of tumours following systemic exposure is often not that good, depending on the MOA, and frequently requires bridging MOA arguments from pharmacokinetics and pharmacodynamics.

38. As an example, DNA-reactive bladder carcinogens may be mentioned. A number of human bladder carcinogens also produce bladder tumours in experimental animals, while others do not and cause tumours at other sites. The difference in MOA in these cases is mostly of pharmacokinetic nature, as the mechanisms of bioactivation and detoxification of the respective carcinogens (e.g. aromatic amines) are complex and vary between species.
39. Differences in tumour susceptibility between life stages may be qualitative or quantitative in nature. Qualitative differences may result from the intrinsic susceptibilities of cells in different states of differentiation, quantitative differences result from variations in metabolic functions and capacities, and these should be reflected in the definitions of key events in the carcinogenic process.

FINALIZATION OF ISSUES PAPERS AND CONSIDERATION OF PUBLICATION.

40. The Working Group agreed that the issues papers on site concordance and life stage should be revised based on the comments received, and that they would be a useful contribution to the papers for the future workshop. Publication could be discussed at a later date and may involve preparation of a summarized public version.

FUTURE WORK.

Process for completion of the IPCS documents.

41. The meeting discussed the tools and processes necessary for the workshop and the final IPCS publication. The following papers would be prepared in advance of the workshop:
 - Revised versions of the issues papers on site concordance and life stage (Dr Rice). It was noted that further peer review would be a prerequisite for publication.
 - Text of an introduction putting into context the earlier work on the MOA Framework and the HRF and some additional analysis of these two frameworks (Dr Bolt).
 - Some case studies. The meeting noted that the development of case studies had proved resource-intensive in the ILSI exercise, and cautioned that adequate time would need to be set aside, including possibly convening pre-meeting/s. The case studies would be worked as far as the MOA framework for the chemical, and then contain the data inputs necessary for the workshop to prepare the human relevance section of the case. It was suggested that the case studies could be drawn from: PPAR alpha agonists; Diethylstilboestrol; a

genotoxic substance (e.g. an aromatic amine); the original MOA framework cases; and examples identified in the IPCS Harmonization Stocktake. It was noted that there will need to be examples where the animal MOA is generally well accepted.

- A draft unified IPCS framework addressing human relevance (i.e. incorporating the IPCS MOA Framework). A pre-meeting of a few members of the Working Group may be needed to prepare this document.
42. The workshop would use its experience of working through the case studies to refine the draft IPCS unified framework. It was suggested that this could be achieved over three days if the workshop materials are sufficiently developed beforehand. Hence the timing of the workshop will depend on completion of the preparatory work. It was thought that at a minimum four breakout groups containing approximately six participants would be needed for the case study work. More participants may be needed to ensure geographical plus sectoral representation.
 43. Subsequent to the workshop, the IPCS unified framework and the case studies would be subject to the IPCS peer review process applied generally in the Harmonization Project, that is, posted on the internet for public comment and sent to a list of identified experts, WHO Collaborating Centres and IPCS Participating Institutions.
 44. The Working Group felt that, if feasible, the annual SOT meeting would provide an ideal venue for presentation of the unified framework and discussion.
 45. It was agreed that the Chair and the Secretariat would need to plan the work in detail. It was noted that the main next steps were to decide on the case studies and who will prepare them and prepare the draft unified framework document.

Discussion of possible other future work.

46. The Working Group noted that a Stocktake of the IPCS Harmonization Project would take place in 2004, presenting an opportunity to identify aspects of cancer risk assessment that may benefit from future harmonization work. The Group agreed to participate in the Stocktake, in particular, through answering a survey questionnaire.

ANY OTHER BUSINESS

47. The Secretariat invited participants to provide feedback on the preparations for the meeting, which could be provided out of session to Carolyn Vickers.

CLOSURE

48. The timing of the next meeting/s of the Working Group or any sub-group/s formed will be dictated by detailed planning to be undertaken by the Secretariat in conjunction with the Chair, consulting as appropriate with the Working Group out-of-session.

49. In closing the meeting, the Chair thanked participants for their valuable input to the discussions. On behalf of IPCS, Ms Vickers thanked Dr Farland for his expert Chairmanship and his staff for their efficient organization of the local arrangements for the meeting.

**List of Invited Participants
IPCS Harmonization Project
1st Meeting of the Cancer Working Group, 3-5 March 2004, Arlington, USA.**

Professor Sir Colin Berry*
UNITED KINGDOM

Professor Hermann Bolt
Institut für Arbeitsphysiologie
GERMANY

Prof Alan R. Boobis OBE
Director of the Department of Health Toxicology Unit
Imperial College London
UNITED KINGDOM

Dr John Bucher
NIEHS
USA

Dr Samuel M. Cohen⁺
Professor and Chair, Pathology and Microbiology
Havlik-Wall Professor of Oncology
University of Nebraska Medical Center
USA

Dr William Farland
Office of Research and Development (810IR)
US Environmental Protection Agency
USA

Dr Jun Kanno⁺
Head, Division of Cellular & Molecular Toxicology
National Institute of Health Sciences
JAPAN

Dr E. Dinant Kroese*
Department of Toxicological Risk Assessment
TNO Chemistry
THE NETHERLANDS

Dr Lois D. Lehman-McKeeman
Bristol-Myers Squibb
USA

* Invited, unable to participate

⁺ Unable to participate on 3 March.

* Invited, unable to participate.

Ms Bette Meek
Health Canada
CANADA

Ms Deborah Willcocks
NICNAS
AUSTRALIA

Representatives

Laurence Musset+
Environment, Health and Safety Division, OECD
FRANCE

Secretariat

Dr Vincent Cogliano
Chief, Unit of Carcinogen Identification
and Evaluation
International Agency for Research on Cancer
FRANCE

Dr Jerry Rice (Consultant)
USA

Ms Cindy Sonich-Mullin
International Programme on Chemical Safety
World Health Organization
USA

Ms Carolyn Vickers
International Programme on Chemical Safety
World Health Organization
SWITZERLAND

IPCS/HSC-CWG-1/04/Agenda

**WORLD HEALTH ORGANIZATION
INTERNATIONAL LABOUR ORGANIZATION
UNITED NATIONS ENVIRONMENT PROGRAMME**

**INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY
Harmonization Project**

**First Meeting of the Cancer Working Group
Marriott Crystal City Hotel, 1999 Jefferson Davis Hwy,
Arlington, VA, United States, 3-5 March 2004
Commencing at 10 am on 3 March**

Summary Adopted Agenda

1. Welcome, opening of meeting and introductions.
2. Working Group Chair and arrangements for meeting report.
3. Adoption of the agenda.
4. Harmonization Project and Working Party procedures.
5. Review of previous Harmonization Project work on cancer
6. Review of project description and outcomes.
7. Review of ILSI Human Relevance Framework.
8. IPCS work on a mode of action framework to address human relevance.
9. Finalization of issues papers and consideration of publication.
10. Future work.
11. Any other business.
12. Closure.

Annotated Adopted Agenda

1. Welcome, opening of meeting and introductions. (Invited participants list)⁷

The meeting will be opened by Ms Carolyn Vickers on behalf of WHO/IPCS. Participants will be invited to introduce themselves.

2. Working Group Chair and arrangements for meeting report.

A Chair for the Working Group will be proposed for decision by the Group. In accordance with IPCS current practice the Secretariat will prepare the draft meeting report, which is then agreed by the Working Group members participating in the meeting.

3. Adoption of the agenda. (IPCS/HSC-CWG-1/04/Agenda)

The Chair will invite participants to adopt the agenda, amended as necessary.

4. Harmonization Project and Working Party procedures.

(Roles and responsibilities document, November 2002)
(Steering Committee terms of reference, November 2002)

The Secretariat (Ms Carolyn Vickers) will introduce the IPCS papers which explain the roles and responsibilities of the various bodies and individuals involved in the Harmonization Project, and the Terms of Reference of the Steering Committee for the Project. These papers are for noting.

5. Review of previous Harmonization Project work on cancer

(IPCS/HSC-CWG-1/04.2: IPCS Cancer MOA framework)
(IPCS/HSC/2000/Meeting Report: IPCS Scoping Meeting report)

The Secretariat (Ms Cindy Sonich-Mullin) will give a presentation on previous work the Harmonization Project has undertaken on cancer, in particular, the development of the IPCS Cancer Mode of Action Framework, and a scoping meeting on the human relevance project that took place in Carshalton in 2000. This will be followed by discussion time.

6. Review of project description and outcomes. (IPCS/HSC-CWG-1/04.1)

The project description and outcomes have the endorsement of the Harmonization Project Steering Committee. The meeting will be invited to review these documents, so that any necessary clarification can be made. In-depth discussion of the work to be done, including preparation of more detailed document/s, will take place under Agenda Item 8.

⁷ Brackets indicate agenda papers. Agenda papers available from the project e-community site, with the exception of the ILSI Framework report which was distributed in hard copy).

7. Review of ILSI Human Relevance Framework.

(ILSI Framework on human relevance: Critical Reviews in Toxicology)

Dr Penny Fenner-Crisp will give a presentation on the ILSI Risk Science Institute project, the results of which were published in Critical Reviews in Toxicology Volume 33/Issue 6/2003. This will be followed by discussion time.

8. IPCS work on a mode of action framework to address human relevance.

(IPCS/HSC-CWG-1/04.2: IPCS Cancer MOA framework)

(IPCS/HSC/2000/Meeting Report: IPCS Scoping Meeting report)

(ILSI Framework on human relevance: Critical Reviews in Toxicology)

(Draft issues papers (refer below))

Consideration of this item is expected to commence in the afternoon of the first day, beginning with development of a list of issues to be tackled during the course of the meeting. This could include further definition of scope, the type of document to be produced by the Working Group, and issues to be taken forward from the Issues Papers. Dr Jerry Rice will be invited to introduce the Issues Papers for this purpose, however the in-depth discussion required to finalize those papers will take place at Agenda Item 9. It is anticipated that a draft document would be developed and included in the meeting report.

9. Finalization of issues papers and consideration of publication.

(IPCS/HSC-CWG-1/04.3: Issue Paper 1 Draft 2)

(IPCS/HSC-CWG-1/04.4: Issue Paper 2 Draft 2)

Dr Jerry Rice will outline the comments received, revisions made, and any outstanding comments. These will be discussed, in order that the documents can be finalized. Publication options will be discussed.

10. Future Work

10.1 Process for completion of the IPCS document/s.

The meeting will consider arrangements for completion of the IPCS document/s that will be the project outcomes. This could include convening of a workshop (as per the timetable previously circulated to the Group), and any additional meetings of the Working Group. Timelines will be agreed.

10.2 Discussion of possible other future work

A Stocktake of the IPCS Harmonization Project is being undertaken in 2004, with a view to informing the future workplan for the Project. The Working Group will be invited to discuss possible additional areas of work on cancer, including relative priorities.

11. Any other business.

Participants will be invited to raise any other business.

12. Closure.

The IPCS Conceptual Framework for Cancer Risk Assessment

Framework Guidelines: Suggested Section Headings

1. Introduction

This section describes the cancer endpoint or endpoints that have been observed and identifies which of these is addressed in the analysis. (The nature of the framework is such that only one mode of action is analysed at a time; hence, for example, tumour types associated with a different mode of action, even if recorded in the same animals, will require separate framework analyses). However, where different tumours are induced by related mode of action, they are best addressed in a single analysis. It should also be noted that some modes of action will involve multiple contributing components.

2. Postulated mode of action (theory of the case)

This section comprises a brief description of the sequence of events on the path to cancer for the postulated mode of action of the test substance. This explanation of the sequence of events leads into the next section which identifies the events considered “key” (*i.e.* measurable) given the data base available for the analysis.

3. Key events

This section briefly describes the “key events” — *i.e.* measurable events that are critical to the induction of tumours as hypothesised in the postulated mode of action. To support an association, a body of experiments needs to define and measure an event consistently. Pertinent observations: *e.g.* tumour response and key events in same cell type, sites of action logically relate to event(s), increased cell growth, specific biochemical events, organ weight, histology, proliferation assays, hormone or other protein perturbations, receptor-ligand changes, DNA or chromosome effects, and cell cycle effects. For example, key events for tumours hypothesised to be associated with prolonged regenerative proliferation might be cytotoxicity as measured histopathologically and an increase in labelling index. As another example, key events for induction of urinary bladder tumours hypothesised to be due to formation of bladder stones composed primarily of calcium phosphate might include elevated urinary calcium, phosphate and pH and formation of bladder stones followed by irritation and regenerative hyperplasia of the urothelium.

4. Dose–response relationship

This section should detail the observed dose–response relationships and discuss whether the dose–response for the key events parallels the dose–response relationship for tumours. Ideally, one should be able to correlate increases in incidence of a key event with increases in incidence or severity (*e.g.* lesion progression) of other key events occurring later in the process, and with the ultimate tumour incidence.

Comparative tabular presentation of incidence of key events and tumours is often helpful in examining dose–response.

5. Temporal association

This section should detail the observed temporal relationships or sequence of events and discuss whether the key events precede the tumour response. One should see the key events before tumour appearance; this is essential in deciding whether the data support the postulated mode of action. Observations of key events at the same time as the tumours (*e.g.* at the end of a bioassay) do not contribute to temporal association, but can contribute to analysis in the next section. Most often, complete data sets to address the criterion of temporality are not available.

6. Strength, consistency and specificity of association of tumour response with key events

This section should discuss the weight of evidence linking the key events, precursor lesions and the tumour response. Stop/recovery studies showing absence or reduction of subsequent events or tumour when a key event is blocked or diminished are particularly important tests of the association. Consistent observations in a number of such studies with differing experimental designs, increases that support since different designs may reduce unknown biases or confounding. Consistency, which addresses repeatability of key events in the postulated mode of action for cancer in different studies is distinguished from coherence, however, which addresses relation of the postulated mode of action with observations in the broader database (see point 7). Pertinent observations are, *e.g.*, tumour response and key events in same cell type, sites of action logically relate to event(s), initiation–promotion studies, and stop/recovery studies.

7. Biological plausibility and coherence

The postulated mode of action and the events that are part of it need to be based on current understanding of the biology of cancer to be accepted, though the extent to which biological plausibility as a criterion against which weight of evidence is assessed is necessarily limited, due to considerable gaps in our knowledge in this regard. One should consider whether the mode of action is consistent with what is known about carcinogenesis in general (biological plausibility) and in relation to what is also known for the substance specifically (coherence). For the former, likeness of the case to others for structural analogues may be informative (*i.e.* structure–activity analysis). Additionally, this section should consider whether the database on the agent is internally consistent in supporting the purported mode of action, including that for relevant non-cancer toxicities. Some modes of action can be anticipated to evoke effects other than cancer, *e.g.* reproductive effects of certain hormonal disturbances that are carcinogenic. Moreover, some modes of action are consistent with observed lack of genotoxicity. Coherence, which addresses relation of the postulated mode of action with observations in the broader database — for example, association of mode of action for tumours with that for other endpoints — needs to be distinguished from consistency (addressed in Point 6 above) which addresses repeatability of key events in the postulated mode of action for cancer in different studies.

8. Other modes of action

This section discusses alternative modes of action that logically present themselves in the case. If alternative modes of action are supported, they need their own framework analysis. These should be distinguished from additional components of a single mode of action which likely contribute to the observed effect, since these would be addressed in the analysis of the principal mode of action.

9. Assessment of postulated mode of action

This section should include a clear statement of the outcome with an indication of the level of confidence in the postulated mode of action — *e.g.* high, moderate or low.

10. Uncertainties, Inconsistencies, and Data Gaps

Uncertainties should include those related to both the biology of tumour development and those for the database on the compound of interest. Inconsistencies should be flagged and data gaps identified. For the identified data gaps, there should be some indication of whether they are critical as support for the postulated mode of action or simply serve to increase confidence therein.