Welcome and Opening of Meeting.

1. The WHO/IPCS Scoping meeting was officially opened by Monique Middlehof, External Affairs, RIVM, who welcomed participants to RIVM and stressed the highly relevant and broadly based collaboration between RIVM and WHO. On behalf of WHO, Carolyn Vickers (Secretariat) thanked the RIVM and the Head of the Collaborating Centre, Henk van Loveren, for hosting the meeting and working with WHO on this new activity. She outlined the purpose of the meeting, to plan the development of guidance for risk assessors for immunotoxicity risk assessment for chemicals. Participants (with the exception of the representative of the ECB) were reminded that they had been appointed as WHO Temporary Advisers, invited in their personal capacities as international experts, with the responsibility of serving and advising the World Health Organization, and not as representatives of their governments, institutes, or any other organization. The list of participants is at Annex 1.

2. Henk van Loveren was elected meeting Chair. The meeting agreed that the Secretariat take the record.

Adoption of the Agenda

3. The provisional agenda was adopted (Annex 2).

Introduction to the Work

4. The Secretariat provided an overview of the WHO/IPCS Harmonization Project and the Environmental Health Criteria Series, both of which have produced guidance documents relevant for the immunotoxicity work. The following were specifically identified in discussion: IPCS Mode of Action (MOA) Framework; Chemical-specific Adjustment Factors (CSAF); IPCS Risk Assessment Terminology; EHC180 (Immunotoxicity); EHC 212 (Allergic Hypersensitization); EHC236 (Autoimmunity) and EHC237 (Evaluating Health Risks in Children Associated with Exposure to Chemicals). In addition, projects planned or
underway on life stages, and interpretation of effects that may be modest or adaptive were mentioned.

5. Henk van Loveren introduced the approved proposal including the overall aims of the project to provide guidance for risk assessors and as a result to improve risk assessment practice. The specific outcomes expected from this meeting were to develop an outline for the guidance, provide advice on expertise needed to develop the guidance, and develop a timeline for the work.

Development of annotated outline for the guidance document

6. A series of short presentations were then delivered by participants on pre-assigned topics, followed by discussion.

- Henk van Loveren: Presentation on the EHCs 180, 212, and 236
- Rolaf van Leeuwen: The Risk Assessment Paradigm: Consequences for Immunotoxicity
- MaryJane Selgrade: Issues in Risk Assessment of Immunosuppressive Chemicals
- Peter Griem: Issues in Risk Assessment of Sensitizing Chemicals
- Dori Germolec: Issues in Risk Assessment of Chemicals Inducing Autoimmunity
- Nursen Basaran: Clinical Experience with Immunotoxicity (use of human data in risk assessment)
- Rodney Dietert: Developmental Immunotoxicity: Consequences for Risk Assessment
- Geert Houben: The Threshold of Toxicological Concern Approach. Food allergy as an example
- Andy Rooney: Draft US Guidance on Risk Assessment for Immunotoxicity
- George Fotakis: Developments in the EU concerning Risk Assessment for Immunotoxicity: In relation to chemicals, including REACH

7. Informed by the discussion and using the "Straw Outline" as a starting point, the meeting developed a detailed outline for the document (Annex 3). In the final discussion of this agenda item, the meeting clarified that the document developed should aim to set the agenda for discussion between the risk assessor and immunotoxicity experts (and should not be a comprehensive/text book on the issue). For example, it should convey triggers (effects that may be observed in a dataset) that might lead a risk assessor to consult an expert.

Development of case studies

8. The meeting discussed the development of case studies, and agreed that this would be useful: to test the guidance during its development; to illustrate the guidance; and for subsequent education and training purposes. A short list of possible cases was developed, and is included in outline at Annex 3. Possible authors for the case studies were identified. The meeting agreed not to include any therapeutics in the examples, given the main audience for the document was chemical risk assessors and that this would dictate the consultation process. The
cases would probably not be anonymised as it might limit their usefulness, and it would be preferable therefore not to choose controversial cases. It was further agreed that the case study topics should be decided when a first draft of the document is available, and the number should be manageable as additional cases could always be developed later.

**Planning the Drafting of the Guidance and Next Steps**

9. The meeting discussed the process for drafting the guidance and agreed on the next steps. Authors were assigned to prepare the first draft of the chapters (Annex 4). Authors were charged with preparing first drafts by the end of May 2008, to be followed by a teleconference (scheduled for mid June) to discuss the drafts. Following this, second drafts will be prepared and circulated. A face-to-face meeting will then be needed to discuss the document in detail and finalize the public review draft. Following public review an international workshop will be held to discuss and finalize the document.

**Communication, engagement and uptake issues.**

10. Participants discussed the need for early communication with the risk assessment community regarding the development of the document and engagement of experts in the process (e.g. in peer review) in order to facilitate eventual uptake and use of the guidance. A number of key events (international conferences etc) were identified that could help in this regard. The Secretariat was requested to prepare some short promotional materials that could be used to alert people to the document (eg. at SOT 2009 specialty section meetings). EUROTOX, SRA, Society of Teratology and the Japanese Society of Immunotoxicology meetings were other possible venues to promote the work. Noting that training and continuing education materials will be needed to support the guidance, SOT 2010 was mentioned as a possible venue to launch a Continuing Education Course.

**Closure.**

11. In closing the meeting on 29 February, the Chair and WHO thanked participants for their contributions at the meeting and for their commitment to the future work plan. WHO thanked Henk van Loveren for his expert Chairmanship of the meeting.
Annex 1

List of Invited Participants

Prof Dr. Nursen Basaran, Hacettepe University, Department of Toxicology, Ankara, Turkey

Dr Rodney Dietert, Professor of Immunotoxicology, Department of Microbiology and Immunology, Cornell University, Ithaca, USA

Dr Dori Germolec, Integrative Toxicology Group, NIEHS, Research Triangle Park, USA

Dr Peter Griem, Clariant Produkte (Deutschland) GmbH, Corporate Product Safety, Germany

Dr Geert Houben, Manager Research, BU Quality and Safety, TNO, The Netherlands

Prof Dr FX Rolaf van Leeuwen, Centre for Substances and Integrated Risk Assessment, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands

Prof. dr. Henk van Loveren (Meeting Chair), National Institute of Public Health and the Environment (RIVM), Bilthoven, The Netherlands

Dr Andrew A Rooney, U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Integrated Risk Information System, Research Triangle Park, USA

Dr MaryJane Selgrade, Chief, Immunotoxicology Branch, US EPA, Research Triangle Park,

Representatives

JRC/ECB
Dr. George Fotakis, Joint Research Centre - Ispra, Institute for Health and Consumer Protection, European Chemicals Bureau, Italy

Secretariat

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY
Project on the Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals

WHO/IPCS Scoping Meeting for the Development of Guidance for Immunotoxicity Risk Assessment for Chemicals

28-29 February 2008, (commencing at 9.00 on 28 February)
WHO Collaborating Centre for Immunotoxicology and Hypersensitivity, RIVM, Bilthoven, The Netherlands

**Annotated Agenda**

1. **Welcome and Opening of Meeting.**
   
   Official meeting opening, followed by opening remarks from the WHO/IPCS Secretariat.
   
   The meeting will be invited to agree on its Chair and arrangements for recording the meeting outcomes.

2. **Adoption of the Agenda**
   
   The Chair will invite participants to adopt the agenda, amended as necessary.

3. **Introduction to the Harmonization Project**
   
   Short presentation by the Secretariat about the WHO/IPCS Harmonization Project.

4. **Aims of this Immunotoxicity Activity and expected outputs from this Scoping Meeting**
   
   *Documents: Proposal approved by the Harmonization Steering Committee*
   
   Henk van Loveren will introduce the approved proposal including the overall aims of the project (and what will be produced). The specific outcomes expected from this meeting will be explained (outline for guidance, expertise needed to develop guidance, timeline for the work). There will be an opportunity for questions and discussion.

5. **Development of annotated outline for the guidance document**
   
Short presentations (5 mins max.) by meeting participants on their assigned topics, covering: state-of-the-science relevant to the development of the guidance document; issues and questions for this meeting to discuss.

6. Development of case studies

General discussion about the development of case studies, which can be useful to test the guidance during its development, to illustrate the guidance (e.g. as annexes or examples in the guidance document), and for education and training purposes. The selection of case studies can follow later in the process.

7. Planning the Drafting of the Guidance and Next Steps

The meeting will discuss the process for drafting the guidance and agree on next steps. This will include: timeline, format, meetings/teleconferences needed etc..

8. Communication, engagement and uptake issues.

Discussion about early communication with the risk assessment community regarding the development of the document and engaging experts in the process (e.g. in peer review) to facilitate eventual uptake and use of the guidance. Key events (international conferences etc) could be identified. It is envisaged that training and continuing education materials will be needed to support the guidance.

9. Any other business.

Participants will be invited to raise any other business.

10. Closure.

Participants are asked to be available until 13.00 on 29 February November.
Guidance for Immunotoxicity Risk Assessment for Chemicals

Outline for Document developed at Scoping Meeting 28-29 February 2008

FOREWORD
ACKNOWLEDGEMENTS
MEMBERS OF THE WHO/IPCS WORKING GROUP
LIST OF ACRONYMS AND ABBREVIATIONS

EXECUTIVE SUMMARY

1. INTRODUCTION
   Objectives of the document
   Existing guidance or guidelines (international, national)

2. BACKGROUND
   Risk assessment of chemicals for immunotoxicity
   The immune system as a special case
      Challenge required for expression, pathogenicity
      Characteristics of dose response curves
      Induction of tolerance
      Individual responsiveness (allergy, autoimmunity)
      Thresholds or not
   The developing immune system
      Early in life exposure, later in life effects
   Current practices
   Newer approaches (genomics)

3. FRAMEWORK FOR IMMUNOTOXICITY RISK ASSESSMENT FOR CHEMICALS
   Overarching guidance and entry point for chemical risk assessors, following which, subsequent steps in the risk assessment can be taken in a transparent fashion
      Framework for considering information available to direct what immunotoxicity to consider
      Can a tiered approach to assessment be used, based on data available or objective (screening assessment, in depth evaluation, etc.)
      To then proceed with the different parts of the assessment as indicated below
      Refer to EHCs on immunotoxicity
      Benchmark/NOAEL
      Data gaps
      Involvement of experts

4. ASSESSMENT OF IMMUNOSUPPRESSION
   Clinical data
   Epidemiological data
5. ASSESSMENT OF IMMUNOSTIMULATION

Clinical data
Epidemiological data
Animal data
Local vs systemic effects
(Ir)reversibility of effects
Biological plausibility
  Weight of evidence, decision tree
  Biological relatedness of different outcomes
  Include example linking specific effects to infections
  Adversity, significance of mild to moderate immunosuppression
  Mode of action/mechanisms
Groups at risk (developing immune system, elderly, immunocompromised)
Early in life exposure, later in life effects
Dose response relationship, thresholds
Acute vs chronic exposure
Uncertainty factors
Exposure assessment
Risk characterization in terms of reduced resistance to infections/tumors
Refer to case study

6. ASSESSMENT OF SENSITIZATION AND ALLERGIC RESPONSE

Clinical data
Epidemiological data
Animal data
Skin, respiratory, oral
Systemic vs local
Mode of action/mechanisms
Biological plausibility
Induction vs elicitation
Groups at risk (developing immune system, elderly, immunocompromised)
Early in life exposure, later in life effects
Acute vs chronic exposure
Dose response relationship, thresholds, limitations of data sets, hazard
identification vs hazard characterization
Uncertainty factors
Exposure assessment
Risk characterization in terms of sensitization and allergic disease
Refer to case study

7. ASSESSMENT OF AUTOIMMUNITY AND AUTOIMMUNE DISEASE
Clinical data
Epidemiological data
Animal data
Mode of action/mechanisms
Self reactivity to new, altered or cryptic antigens
Biological plausibility
Groups at risk (developing immune system, elderly, immunocompromised,
allergic/autoimmune)
Early in life exposure, later in life effects
Acute vs chronic exposure
Dose response relationship, thresholds
Uncertainty factors
Exposure assessment
Risk characterization in terms of induction of autoimmunity
Refer to case study

8. CONCLUSIONS/PRINCIPLES/ETC.

REFERENCES

GLOSSARY

ANNEXES, E.G. ILLUSTRATIVE CASE STUDIES
Case studies to be decided later after having a first draft of the guidance. The
following short list was developed:
Coplanar PCBs (immunosuppression)
Platinum (sensitization)
A fragrance (sensitization)
HCB (Immunostimulation)
Mercury (Autoimmunity)
List of section authors for first draft

FOREWORD (Secretariat)

ACKNOWLEDGEMENTS (Secretariat)

MEMBERS OF THE WHO/IPCS (WORKING GROUP) (Secretariat)

LIST OF ACRONYMS AND ABBREVIATIONS (WHO Editor)

EXECUTIVE SUMMARY (To be prepared later)

INTRODUCTION (George Fotakis, Andy Rooney, Secretariat)
   Objectives of the document (see project outline)
   Mention Existing guidance or guidelines (international, national)

BACKGROUND (Rodney Dietert)

FRAMEWORK FOR IMMUNOTOXICITY RISK ASSESSMENT FOR CHEMICALS (Geert Houben, Rolaf van Leeuwen)

ASSESSMENT OF IMMUNOSUPPRESSION (Andy Rooney, Dori Germolec)

ASSESSMENT OF IMMUNOSTIMULATION (Bob Luebke, Mary-Jane Selgrade)

ASSESSMENT OF SENSITIZATION AND ALLERGIC RESPONSE (Peter Griem, Mary-Jane Selgrade)

ASSESSMENT OF AUTOIMMITY AND AUTOIMMUNE DISEASE (Dori Germolec)

CONCLUSIONS/PRINCIPLES/ETC. (To be prepared later)

REFERENCES

GLOSSARY

ANNEXES, E.G. ILLUSTRATIVE CASE STUDIES (Case studies to be decided later after having a first draft of the guidance)