

World Health Organization
International Labour Organization
United Nations Environment Programme

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY (IPCS)

WORKSHOP REPORT

TOXICOGENOMICS AND THE RISK ASSESSMENT OF CHEMICALS FOR THE PROTECTION OF HUMAN HEALTH

SUMMARY

*Held at the Federal Institute for Risk Assessment, Berlin, Germany
17-19 November 2003.*

Background

1. An IPCS Workshop on Toxicogenomics and the Risk Assessment for the Protection of Human Health was held 17-19 November 2003, hosted by the Federal Institute for Risk Assessment, Berlin, Germany. The Workshop was chaired by Dr Ursula Gundert-Remy, Germany.
2. The Workshop was organized by an international steering group (Vanessa Vu, US EPA, Mike Waters, US NIEHS; Tohru Inoue, Japan NIHS; Eisaku Toda, OECD; Terri Damstra, IPCS- Inter-regional Research Unit; Ursula Gundert-Remy, BfR, Germany and Lesley Onyon, IPCS).
3. Preparations for the Workshop were undertaken in collaboration with the Organisation for Economic Cooperation and Development (OECD) as a action from the 2002 Special Session of the OECD Joint Meeting. At this meeting it was concluded that sharing information and cooperation at a scientific level was an important first step to facilitate the future and development of strategies for the application of toxicogenomics in the risk assessment process. Information about the Workshop was distributed by the OECD Secretariat to National Coordinators of the Test Guidelines Programme.
4. The Workshop was attended by 38 scientific experts from OECD and non-OECD Member countries. Participants had experience in the generation and use of toxicogenomic data or were potential users of such information in the risk assessment process. They were drawn from governments, academia, research institutes and industry. The list of participants is given in [Annex1](#).

Objectives of Workshop

5. The focus of the IPCS Workshop was on the potential use of toxicogenomic information at different stages of the risk assessment process for the protection of human health. This focus was agreed in the anticipation that further OECD/IPCS collaborative activities would be taking place in 2004, particularly with respect to environmental effects.
6. The Workshop viewed the science of toxicogenomics as one which combines studies of genetics, genomic-scale mRNA expression (transcriptomics), cell and tissue-wide protein expression (proteomics), metabolic profiling (metabonomics) and bioinformatics along with conventional toxicology information in efforts to understand the modes-of-action of chemicals and the potential role of gene-environment interactions.
7. The specific objectives of the IPCS Workshop were to:
 - establish a scientific forum and dialogue between relevant experts including those with expertise in molecular biochemistry, genetic toxicology, epidemiology, public health, risk assessment, computational toxicology and clinical medicine;
 - share information about scientific-level activities involving toxicogenomics including any programmes at national, regional and international levels;

- discuss the potential of toxicogenomics to contribute to improvements in the risk assessment process for the protection of health from environmental exposure to chemicals, for understanding the mode-of-action of environmental toxicants and the relevance and scope of gene-environment interactions;
- identify the near-term needs and necessary steps for enhancing international cooperation to contribute to improving the scientific understanding and the potential contribution of toxicogenomic research for improving chemical safety; and
- identify and discuss any gaps in knowledge, issues and challenges that might hinder the enhancement of awareness and use of toxicogenomics for protecting human health from environmental chemical exposures.

8. The Workshop agenda is given in [Annex 2](#). The Workshop followed a structure that included both plenary presentations and break-out groups. Plenary presentations were aimed at encouraging a common level of understanding of both toxicogenomic technologies and risk assessment processes. This was considered important given the wide range of expertise represented at the meeting. Information about regional, national and other collaborative toxicogenomic activities was presented by US, Japan, European Union (DG Research), Republic of Korea and the ILSI Health and Environmental Sciences Institute. Participants were encouraged to consider what information and action was needed to make a bridge between toxicogenomics and traditional toxicity testing approaches.

9. Break-out groups were organized to facilitate discussion of three aspects of risk assessment.

- **Predictive models for identifying human health hazards**, including: screening and testing; investigation of modes-of-action of chemicals, and investigation of classes of chemicals and mixtures.
- **Human exposure and susceptibility**, including: biomonitoring of exposure and effect; variability of susceptibility between individuals and among population and sub-population groups.
- **Risk assessment**, including: cross-species extrapolation of dose-responses, extrapolation of low-dose exposures; and assessment of mixtures.

10. During discussion, participants were invited to identify relevant issues and uncertainties in current risk assessment processes which might be informed by toxicogenomic information and what possible actions could be taken to better inform and find solutions to these issues. A series of questions were used by the break-out groups to stimulate discussion. A copy of the break-out group questions used during the Workshop is given in [Annex 3](#). [Annex 4](#) provides the listing of background documents identified by the Steering Group.

Conclusions

11. The Workshop was successful in achieving its objectives and a number of areas of common ground were identified. Not all questions posed at the Workshop

were answered. This was largely because there are key information gaps and a consequent urgent need to establish and build an infrastructure for linking different types of information and expertise. The dialogue initiated by the Workshop at the international level was appreciated and it was considered that this should be continued.

12. The Workshop confirmed the widely-held view that toxicogenomics had the potential to improve the specificity and range of methods used to predict chemical hazards and inform and overcome a number of uncertainties involved in chemical-related risk assessment. Achieving a better understanding of the linkages and correlations between toxicological endpoints, conventional toxicology, biochemical and cellular toxicology and toxicogenomic information was considered a necessary first step before strategies and future applications for risk assessment purposes could be developed.

13. Most work on the development and application of toxicogenomics has taken place within separate institutes or companies, particularly in the area of drug discovery or in understanding the toxicological modes-of-action of selected chemicals. In order to foster the development and application of the science it was considered important to strengthen the dialogue across disciplines, particularly between those generating toxicogenomic information, those with experience in traditional toxicological approaches and risk assessors wishing to use the information. The need to include experts from other backgrounds was also considered essential, particularly molecular epidemiologists, experts in molecular and clinical genetics and bioinformatics experts. As the science of toxicogenomics is still developing there is also a need to involve academic institutions in the work and in discussion of the potential broader applications.

14. Initially, progress in increasing understanding and application of toxicogenomics in risk assessment will be best made by building on the foundation of existing toxicity testing protocols. However, in the future, it could be anticipated that the refinement and even a revolution in the testing of protocols and approaches could be possible. At this stage it is not likely to be useful generating large amounts of toxicogenomic data without relating it to the traditional toxicology knowledge base. Developing an understanding of which genes and gene products are involved in the modes-of-action of toxicants represents a knowledge gap to be filled.

15. Toxicogenomics in its broadest sense holds promise for identifying biomarkers of exposure with improved sensitivity and selectivity, and in easily accessible biological fluids and tissues (e.g. blood, urine, buccal epithelial cells). In the long term biomarkers of susceptibility and disease may also be identified. In pharmacogenomic studies this potential has already been demonstrated although it is recognized that in this area the mode-of-action of the pharmaceutical is already known and the objective is to identify the molecular basis of pharmaceutical efficacy and/or adverse effects in a patient population that is also well characterized. This information does not exist often in the risk assessment of chemicals where one is essentially trying to predict a lack of biological effect.

16. Toxicogenomics has the potential to result in the acquisition of large amounts of novel data. A fundamental need exists for data quality standards to ensure confidence in data from different sources and platforms. Mechanisms for sharing data and the development of bioinformatics and computational capacities also need to be addressed urgently.

Recommendations

17. The Workshop recommended further global collaboration be undertaken to develop case-studies involving chemicals with known modes-of-action and available toxicogenomic data; building up of associated knowledge bases such as by identifying sentinel genes or gene clusters involved in toxicological responses and investigating sources of human toxicology data including the potential of existing “bio-banks”.

18. In the area of hazard identification, it was recommended that possibilities for the design and execution of research to add toxicogenomic endpoints to existing test guideline protocols should be investigated.

19. For risk assessment it was also recommended that support be given for the development of improved biomarkers of exposure and protocols for their validation and continuing to develop a scientific understanding of factors associated with increased susceptibility to chemical risks. .

Next steps

20. The Workshop provided a good opportunity to discuss the potential uses of toxicogenomics tools and/or data . A number of recommendations on what first steps might be taken and what types of information or action is needed to further develop the application of toxicogenomics in risk assessment were made. The Workshop supported the publication of an article for publication in a peer-reviewed journal based on the full Workshop report and the planning of a follow-up workshop to establish collaborative work on case-studies.

**IPCS WORKSHOP ON TOXICOGENOMICS AND THE RISK
ASSESSMENT OF CHEMICALS FOR THE PROTECTION OF HUMAN HEALTH
Berlin, Germany**

17 - 19 November 2003

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**IPCS WORKSHOP ON TOXICOGENOMICS AND THE RISK ASSESSMENT OF
CHEMICALS FOR THE PROTECTION OF HUMAN HEALTH**

To be held 17 - 19 November 2003, starting at 08:30 on the 17th November

**Bundesinstitut für Risikobewertung
Thielallee, 88-92
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DRAFT AGENDA

Official Welcome

Official Welcome by representative of the Ministry of Environment, Germany

Welcome by representative of the Bundesinstitut für Risikobewertung,
Germany

Welcome by representative of International Programme on Chemical Safety
(IPCS), World Health Organization

1. **Overview of Objectives of Workshop, Election of Chair & Adoption of Draft Agenda**

Representative of Steering Group for Workshop
2. **Introduction of Participants**
3. **Overview of Toxicogenomics Technologies**
Dr Axel Oberemm, Bundesinstitut für Risikobewertung, Germany
4. **Overview of Chemical Risk Assessment Process**
Dr Kerry Dearfield, US Environmental Protection Authority
5. **Overview of Regional, National and other Collaborative Toxicogenomics**
 - 1) **Activities Related to Chemical Safety Evaluation and Risk Assessment**
 - **US, Dr Alex Merrick**, US National Centre for Toxicogenomics
 - **Japan, Dr Jun Kanno**, National Institute of Health Sciences, Tokyo, Japan
 - **European Union, Dr Fergal Donnelly**, Research and Technical Development, European Commission.

- **Republic of Korea**, Dr Ki-Hwa Yang, National Institute of Toxicological Research, Seoul
- **ILSI-HESI** Collaborative Research Programme, Dr Cyril Petit, ILSI-HESI
- Others

6. **Bridging between Toxicogenomics and Traditional Toxicity Testing**

Dr Lewis Smith, Syngenta International AG, Basel, Switzerland

7. **Plenary Discussion and Charge to Breakout Groups**

8. **Breakout Group discussions**

Breakout Group 1- Predictive Models for Identifying Potential Human Health Hazards

Co-chairs. **Dr Tohru Inoue**, National Institute for Health Sciences, Tokyo, Japan, and **Dr Hugh Tilson**, National Health and Environmental Effects Research Laboratory, US Environmental Protection Agency.

Possible items for presentation and discussion

- Toxicity profiling based on understanding of mode-of-action leading to screening potential of individual chemicals, classes of chemicals and mixtures;
- Alternative ways of identifying hazards
- Integration of genomics with other computational toxicology methods
- Cross-species extrapolation of toxic effects (including intra-species)

Breakout Group 2 - Human Exposure and Susceptibility

Co-chairs. **Dr Juergen Bolak**, Fraunhofer Institut für Toxikologie und Experimentelle Medizin and **Dr George Orphannides, Syngenta (standing in for Terri Damstra**, Inter-regional Research Unit, International Programme on Chemical Safety, WHO).

Possible items for presentation and discussion

- Identification and monitoring exposed individuals, human population and sub-populations
- Variability of human susceptibility
- Toxicogenomic data as a measure of exposure

Breakout Group 3 - Risk Assessment

Co-chairs.

Dr Alan Boobis, Experimental Medicine & Toxicology, Imperial College London, UK and Dr Vanessa Vu, Science Advisory Board Office, US Environmental Protection Agency

Possible items for presentation and discussion

- Cross-species extrapolation (Dose-response)
- Shape of dose-response curve at low dose and low-dose extrapolation methods
- Assessment of mixtures
- Use of toxicogenomics in determining chemicals-related disease risk factors

9. **Interim Reports and Continued Breakout Groups discussion**
10. **Breakout Groups to complete discussion and report their overall discussions and recommendations**
11. **Summary of Workshop and Discussion of Next Steps**
12. **Closure of Workshop**

QUESTIONS FOR BREAK-OUT GROUPS

IPCS Workshop on Toxicogenomics and the Risk Assessment of Chemicals for the Protection of Human Health

The following questions were drafted to provide a framework for discussion in break-out group sessions. The Co-chairs of each break-out group were requested to refine the questions as necessary in discussion with participants during the Workshop.

The questions were provided in draft form so that participants had something to focus on before the start of the Workshop. A collection of relevant journal articles were also provided.

The questions were not necessarily exclusive to any one group and there was expected to be some cross over of discussion between groups. The discussions attempted to focus on the current situation, and the challenges ahead. In some cases where it was not possible to answer the specific questions, it was attempted to identify what information, types of information or action would be needed in order to be able to answer the questions in future.

Participants in each group were encouraged to provide examples of their experience/research to help focus the discussions. Participants are asked to indicate to IPCS (Onyonl@who.int) in advance of the session if they wished to make a short presentation.

Breakout Group 1: Predictive Models for Identifying Human Health Hazards

- How do you envision genomics, proteomics and metabonomics (“omics”) information being used in hazard identification? For prioritization and ranking of chemicals prior to testing? To replace current testing protocols altogether? From the perspective of the chemical industry? From the perspective of a regulatory agency?
- What do we need to know before we can distinguish a biological change at the “omic” level from a toxicological effect?
- What do we need to know about the chain of biological events that are linked from exposure at a target site to manifestation of an adverse effect (i.e., toxicity pathway) in order to use “omics” data in a hazard identification context?
- Should “omics” information be used at the hazard identification step to address dose-response assessment, i.e., extrapolation from high-to-low dose, animal to humans, susceptible sub-populations, or should “omics” only be used to determine if a chemical poses a hazard?
- What science or research areas need to be developed before “omics” can be applied to hazard identification, i.e., more information about toxicity pathways, systems biological approaches, bioinformatics?
- Are there data quality and data reporting requirements that will pose major barriers for the use of “omics” in hazard identification?

Breakout Group 2: Human Exposure and Susceptibility

- What do we need to know before “omics” information can be used to quantify exposure of humans to environmental agents?
- What possibilities may exist for toxicogenomics to contribute to the development of indicators of chemicals related disease, rather than indicators of toxicological endpoints traditionally included in hazard and risk assessment ? What information may be needed to address this question ?
- What do we need to know before “omics” information can be used to elucidate the linkage between external exposure and internal dose. Is it necessary that the indicator of exposure be a component of the toxicity pathway?
- What do we need to know before “omics” information can be used to reduce uncertainty in extrapolation between individuals in the populations, i.e., susceptible sub-populations? Should these observations be included in the hazard identification process?
- Can “omics” information be used in surveillance programs to protect human health?

Breakout Group 3: Risk Assessment

- What do we need to know before “-omics” information can be used to inform the shape of the dose-response curve? To extrapolate from high to low dose?
- What do we need to know before “omics” information can be used to establish mode or mechanism of action for the purposes of risk assessment?
- What do we need to know before “omics” information can be used as a critical effect to set a NOAEL or LOAEL or establish an adverse effect for a Benchmark Dose?
- What do we need to know before “omics” information be used to reduce uncertainties associated with intra -and interspecies extrapolation?
- What do we need to know before “omics” information can be used to harmonize human health risk assessment approaches (i.e., cancer and non-cancer risk assessments)? How can “omics” information inform decisions about the presence or absence of a threshold?
- What do we need to know before “omics” information can be used to addresses issues related to cumulative risk? To aggregate risk?

RESOURCE LIST

Some recent review articles

IPCS Workshop on Toxicogenomics 17-19 November 2003

1. Butte A (2002)
The Use and Analysis of Microarray Data
Nature Reviews/Drug Discovery 1 951-960
2. Fielden M & Zacharewski T (2001)
Challenges and Limitations of Gene Expression Profiling in Mechanistic and Predictive Toxicology
Toxicological Sciences 60 (6-10)
3. Henry et al (2002)
Use of Genomics in Toxicology and Epidemiology: Findings and Recommendations of a Workshop
Environmental Health Perspectives 110 (10) 1047 – 1050
4. Ideker T et al (2001)
A New Approach to Decoding Life: Systems Biology
Ann Rev Genomics Hum Genet 2 243-72
5. Inoue T 2003
Toxicogenomics – a new paradigm in Toxicology
In Toxicogenomics T Inoue and W Pennie (Eds) Springer –Verlag Tokyo
6. Lesko et al (2003)
Pharmacogenomics and pharamcogenomics in drug development and regulatory decision-making: Report of the first FDA-PWG-PhRMA-DruSafe Workshop
J Clin Pharmacol 43(4) 342-58
7. Ophanides G & Kimber I (2003)
Toxicogenomics: Applications and Opportunities
Toxicological Sciences 75 1-6
8. Olden K et al (2001)
A Bold New Direction for Environmental Health Research
American Journal of Public Health 91(2) 1964- 1970
9. Petricoin W et al (2002)
Medical applications of microarray technologies: a regulatory science perspective
Nature Genetics supplement 32 476-479

10. Tennant R 2002
The National Center for Toxicogenomics: Using New technologies to Inform Mechanistic Toxicology
 Environmental Health Perspectives 110 (1) A8 – A10

11. Waters M et al (2003)
Systems Toxicology and the Chemical Effects in Biological Systems Knowledge Base
 Environmental Health Perspectives Toxicogenomics 111 (1T) 15 – 28

12. Yoon B et al 2003
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