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International (IPCS/OECD) Toxicogenomic Activities in the Context of a New Strategic Approach to International Chemicals Management

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The rapidly-evolving science of toxicogenomics and its accompanying tools are being integrated into many aspects of toxicology, epidemiology and risk assessment methodologies. Many entities in private enterprise, research institutions and government are currently addressing how this might best be undertaken. The agreement by the International Programme on Chemical Safety (WHO/ILO/UNEP) and the OECD Joint Meeting of the Chemicals Committee and Working Party on Chemicals, Pesticides and Biotechnology to collaborate from the outset on this issue has been an important driver to increase efforts to coordinate communication, data sharing and information exchange at the global level. IPCS and OECD work jointly to plan activities globally involving their respective constituents.

The direction for the joint work of IPCS/OECD was agreed in 2004 following collaborative workshops held in Berlin, Germany (2003) focusing on implications for human health effects risk assessment and in Kyoto, Japan (2004) focusing on environmental effects. It was a finding of these two workshops that there was no fundamental difference between the use of genomic methods for studying human health effects and for studying environmental effects, strengthening further the need for IPCS and OECD to work together.

Following the two initiating workshops described above, a Joint IPCS/OECD Advisory Panel was established which is currently developing workplans for how to deal with priority areas identified at the workshops. These areas cover application of toxicogenomics to category approaches in chemicals assessment, cross-species extrapolation, rapid screening methods, and new biomarkers of exposure, effect and susceptibility. A survey of the regulatory community is also being planned to further characterize the readiness of regulatory authorities to use toxicogenomics-derived data.

The negotiation process to develop a new Strategic Approach to International Chemicals Management (SAICM) is nearing completion, with the final high-level meeting being convened in Dubai, February 2006. SAICM aims to meet the commitments to chemicals management of the Rio Declaration on Environment and Development, Agenda 21, the Bahia Declaration on Chemicals Safety, the Johannesburg Plan of Implementation and the 2005 World Summit Outcome. The SAICM Global Plan of Action for countries includes a number of action items of direct relevance to the future use of toxicogenomics, in the context of work to support risk reduction and especially in vulnerable population groups. Specific mention is made of use of scientific advances in toxicogenomics in work areas addressing knowledge and information. Support at political level for further work on toxicogenomics, expressed in the context of SAICM, should add significantly to the current scientific momentum.

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Aims of the presentation

- To describe origin & evolution of joint IPCS/OECD activities on toxicogenomics
- To consider future IPCS/OECD toxicogenomics work plans
- To place in context of new Strategic Approach to International Chemicals Management (SAICM)

IPCS

- UN Conference on Human Environment, 1972
- IPCS established in 1980, with cooperative programme of work agreed by Executive Heads of WHO, ILO & UNEP
- Objectives:
  - To establish the scientific basis for safe use of chemicals
  - To strengthen national capabilities & capacities for chemical safety

International chemicals activities

- IPCS – provides focus for collaborative operational work of three UN organizations
- IOMC – coordinates work of nine IGOs (WHO, ILO, UNEP, FAO, OECD, UNIDO, UNITAR, World Bank, UNDP)

Much has been achieved ...

- Chemical assessment schemes in place in most countries worldwide
- Significant progress with:
  - standardised test guidelines
  - mutual acceptance of data
  - harmonised hazard & risk assessment guidelines
  - sharing burden of assessment work

Much has been achieved ...

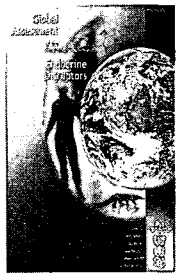
- Political commitment to test & assess all HPV chemicals
- In Europe, farREACHing proposals for evaluation & authorisation of chemicals
- However, regulatory toxicology is relatively new discipline & (potential) use of toxicogenomics is part of the continuum of evolution

Some lessons learnt ...

- Science of risk assessment continues to evolve ..... slowly
- Importance of mutual understanding of common principles
  - case studies particularly useful
- Value of international mechanism(s) to share information & develop common approaches
- Political commitment & economics determine priorities

... & from work on emerging issues

- Early action avoids need for subsequent retrospective harmonization efforts
- Value in establishing strong networks of health professionals, scientific researchers & risk assessment practitioners



Potential areas of toxicogenomic interest for regulatory risk assessment

- Re-focus & prioritise testing needs
  - *Size of the task (circa 300/5000 screening assessments completed)*
  - Strengthen & complement (Q)SAR approaches
- Deal with uncertainties in traditional toxicology approaches
  - In-depth assessments e.g. uncertainty factors, cross-species extrapolation, including modes-of-action
- Real-life toxicology
  - Linking exposure to disease
  - Susceptible/resistant populations & life stages
  - Emerging issues/recognition of effects not included in traditional testing approaches
  - Mixtures

Joint IPCS/OECD action

- Special OECD 33rd Joint Meeting session on toxicogenomics, February 2002
- IPCS/OECD workshop on human health aspects, Berlin, November 2003
- OECD/IPCS workshop on environmental aspects, Kyoto, October 2004

Berlin workshop

- Development of case studies of chemicals with known modes-of-action & available toxicogenomic data
- Establishment of knowledge bases (e.g. identification of sentinel genes/gene clusters involved in toxicological response & link to human toxicology data, including "bio-banks")

Berlin workshop

- For hazard identification, research to possibly add toxicogenomic endpoints to existing test guideline protocols
- For risk assessment, development of improved biomarkers of exposure with protocols for validation (to improve understanding of increased susceptibility)

Kyoto workshop

- *Comprehensive (eco)toxicogenomic* studies to differentiate compensatory & adaptive responses from adverse toxicological outcomes
- Extension of technological platforms for diverse taxa & development for use across species

Kyoto workshop

- Quality assurance & control of sequencing data & individual "omic" techniques, coupled to good data management & annotation
- Sequencing data & clones to be made publicly available
- Strategic plan to realise transfer of genomic-based techniques from fundamental research to potential regulatory use

Common views

- At this stage focusing on separate actions for environment & health not useful, issues being fundamentally the same
- Need to embrace data management & bioinformatics issues, including quality, quantity, sharing, validation
- Avoid implication of regulatory requirements – first need to build confidence & understanding
- Initial timeframes very optimistic

37th OECD Joint Meeting, November 2004

- IPCS & OECD to develop further plan of *action to explore & evaluate* regulatory application of genomic methods in chemical assessment
- IPCS – science & evidence base for toxicogenomics, linking to existing work on biomarkers, modes-of-action & ethical considerations
- OECD – needs & possibilities for application of toxicogenomics in regulatory context

38th OECD Joint Meeting, June 2005

IPCS/OECD Advisory Group reported back on proposals for further work, noting need to:

- merge human health & environment perspectives
- strengthen links between research & regulatory application
- build confidence among scientists & regulators in interpreting & using genomic data, with transparency of judgements made
- identify key messages for communication (given rate of development of science & technologies)

Possible areas for further international work

- Application of toxicogenomics to category *approaches in chemicals*
- Cross-species extrapolation
- Rapid screening methods
- New biomarkers
- Survey of regulatory needs & potential of toxicogenomics

Possible areas for further international work

- Further development of survey of existing toxicogenomic tools
- Publication of scientific report on IPCS/OECD toxicogenomic workshops
- Validation issues
- Refining current test methodologies for certain endpoints (e.g. genotoxicity, allergy)
- Identifying barriers to successful implementation of toxicogenomic techniques for regulatory decision-making

What is current status ?

- Joint IPCS/OECD Advisory Group to develop more defined action plans
- Progress report to 39th OECD Joint Meeting, February 2006
- Membership of Group
  - Joint Chair & Secretariat –IPCS & OECD
  - EC (JRC-ECVAM)
  - Germany (BfR)
  - Japan (MOE, MHLW-NIHS)
  - NGO (Environmental Defence, BIAC-ILSI)
  - Republic of Korea (KFDA)
  - UK (DEFRA-NERC)
  - US (US EPA-ORD/OPPTS, NIEHS, NCT)

Current focus of lead countries

- Molecular screening for characterizing individual chemicals & chemical categories (US)
- New biomarkers (Germany & IPCS/IRRU)
- Survey of regulatory needs & potential of toxicogenomics (Japan)

Molecular screening

- Utilisation of pharmaceutical screening methods to develop genomic "fingerprints" specific to given chemical categories, aiming to link genomic profiles from short-term *in vivo* or *in vitro* testing to longer-term effects
- Case studies from pharmaceutical applications to demonstrate proof-of-concept for molecular screening relevant to prioritization/grouping of environmental chemicals, with special emphasis on assays predicting mammalian health endpoints

New biomarkers

State-of-the-science review of validity & reliability of use of toxicogenomic tools in development of new biomarkers & relevance to IPCS definitions of biomarkers of exposure, effect & susceptibility *(IPCS EHC 222: Biomarkers in risk assessment: validity & validation)*

IPCS/OECD Advisory Group

- Given historical experience of development of (Q)SAR approaches, need to identify multiple countries to participate in initial work
- Joint IPCS-OECD activity will promote inter-Ministry & inter-agency engagement & cooperation at country level on project implementation

International chemicals management

- Rio Declaration on Environment & Development (Chapter 19, Agenda 21), 1992
- IFCS Bahia Declaration on Chemicals Safety, 2000
- WSSD & Johannesburg Plan of Implementation, 2002
- 2005 World Summit Outcome

International chemicals management

- Basel Convention on Control of Transboundary Movements of Hazardous Wastes & their Disposal, 1989
- Rotterdam Convention on Prior Informed Consent Procedure for certain Hazardous Chemicals & Pesticides in International Trade, 1998

International chemicals management

- Stockholm Convention on Persistent Organic Pollutants (POPs), 2001
- Globally Harmonized System of Classification & Labelling of Chemicals, 2002

Strategic Approach to International Chemicals Management (SAICM)

- UNEP GC agreed to develop SAICM, building on Bahia Declaration, working with IFCS & IOMC, 2002
- PrepComs 1-3, 2003-2005
- WHA resolution 56.22: SAICM & participation of global health partners, 2003

SAICM

- SAICM builds on previous international initiatives
- Promotes development of multi- & cross-sectoral & participatory approach
- Aims to achieve 2020 WSSD goal of use & production of chemicals in ways that lead to minimization of significant adverse effects on human health & environment

SAICM

- ICCM, Dubai, 4-6 February 2006
  - High-level declaration
  - Overarching policy strategy
  - Global plan of action
- Health sector input from > 60 countries
- WHA consideration for implementation, May 2005

Global plan of action

- Human health protection
  - new methods for assessment of dose-response relationships & risks to vulnerable groups
- Risk assessment, management & communication
  - use of molecular epidemiology, clinical & exposure data, scientific advances in toxicogenomics, methods relevant to real-life exposures

Conclusions

- Joint IPCS/OECD activity on toxicogenomics is leading to more congruent international work programme on part of countries
- Political commitment to SAICM & inclusion of toxicogenomics in GPA will add to current scientific momentum