

International Workshop on Toxicity Testing in the 21st Century: Summary of Day 1

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Purpose of Symposium

Paul Locke, Johns Hopkins University

- Bring together international experts in toxicology, risk assessment, and regulatory policy
- Discuss scientific, risk assessment, and regulatory policy challenges and opportunities regarding NRC vision for toxicity testing
- Launch series of five symposia that will examine these issues in detail over the next year



Introduction

Maria Trainer, Council of Canadian Academies

- Council of Canadian Academies established in 2006 to conduct independent, expert assessments on science that is relevant to issues of public interest
- Eight assessments completed to date
- New assessment on 'Integrated Testing of Pesticides' being done for PMRA will provide an opportunity to explore the potential application of the new directions outline in the NRC vision
- Assessment to examine the question: what is the scientific status and use of integrated testing strategies in the human and environmental regulatory risk assessment of pesticides?



Toxicity Testing

Thomas Hartung, Johns Hopkins University

- Need to find balance among:
 - Product safety, agent discovery, basis research
 - Animal suffering, quality of prediction, throughput
- EU REACH program will require assessment of over 37,000 chemicals
- Ban on animal testing of cosmetics sold in EU as of March, 2009
- Evidence-based toxicology can help to meet future challenges in toxicity testing
- Global approach needed to modernizing toxicity testing



Commentary: Implementation of NRC Vision

Mel Andersen, Hamner Institutes for Health Sciences

- Focus on evaluating perturbations of cellular responses in a suite of toxicity pathway assays
- Initial step: Select series of prototype pathways and chemicals to define key technology areas needed to develop appropriate pathway assays



Commentary: U.S. Interagency Strategy

Ray Tice, NIEHS

- 2004: NTP Roadmap (moved away from disease endpoints)
- 2004: NCGC established
- **2004: NRC panel formed**
- 2005: HTS collaboration
- 2007: EPA ToxCast™ Program
- **2007: NRC report complete**
- 2008: Tox21 collaboration based on MoU with NIEHS, EPA, NCGC)



Chemical Risk Assessment

Bette Meek, University of Ottawa

- Increasingly, legislation is requiring consideration of *all* chemicals
- Priorities have been established for 23,000 chemicals in Canada on the Domestic Substances List
- Similar requirements EU (REACH) and US (ChAMP)
- Simple and complex priority setting tools focusing on exposure and hazard have been developed in Canada to address DSL chemicals: exposure often more discriminating than hazard)



Commentary

Richard Judson, US EPA

- Will likely need several assays for a given pathway perturbation to demonstrate reproducibility
- Major challenges facing NRC vision:
 - Find the toxicity pathways
 - Obtain HTS assays for these pathways
 - Screen chemical libraries
 - Link in vitro and in vivo results
- Building the science base: Need to relate molecular targets (pathway perturbations) to endpoints (adverse health outcomes)



Commentary

Greg Paoli, Risk Sciences International

- NRC Report on *Science and Decisions: Advancing Risk Assessment* released in 2008
- Left unchecked, risk analyses can become ‘overwhelming’
- Risk assessments can extend for protracted periods (e.g., dioxin): need ‘stopping criteria’
- Also need ‘starting criteria’ (when is a detailed risk assessment needed, what are risk assessment priorities)
- ‘Value of information’ analysis may be helpful in deciding what risk assessment information is needed in specific contexts



Panel Discussion: Challenges in International Implementation of Risk Assessment and Toxicity Guidelines



Panel Commentary

Vicki Dellarco, US EPA

- Transition towards new integrative and predictive 21st century techniques to increase efficiency of testing and risk assessment
 - Near term – improve chemical prioritization
 - Long term – less reliance on animal testing, using more mechanistic assessments (including SAR, QSAR, in vitro testing)
- Need to build libraries of toxicity pathways to support long term goal



“There is flexibility in current regulatory process.”

Panel Commentary

David Blakey, Health Canada

- How will the new paradigm be validated?
 - Need to define what we are trying to predict
 - Classical evaluation criteria include: reproducibility, repeatability, and predictive value
 - International Cooperation on Alternative Test Methods may be helpful, ICATM (ICCVAM, ECVAM, JaCVAM, Canada)



Panel Commentary

David Blakey, Health Canada

- How will the data be interpreted?
 - Will the new methods be more sensitive?
 - When is a response a toxicological effect?
- What regulatory instruments will be used?
 - Regulations can be inflexible, and can take time to change
 - Ideally want a nimble regulatory system to accommodate change



“Changing regulations is a bit like watching a supertanker change course.”

Panel Commentary

Gail Charnley, HealthRisk Strategies

- Validation will be critical to implementation of new toxicity testing paradigm
- Need to identify important cellular response pathways involved in toxic response
- Need to distinguish between adaptive response and toxic response
- Development of risk assessment guidelines has historically taken considerable time (this may be even more challenging with the future paradigm)
- Interpretation of pathway data may differ from the scientific, legal, and regulatory perspective, due to differences in 'standards of evidence'



Panel Commentary

Manfred Liebsch, ZEBT

- BfR now organized into institutes for risk assessment and risk management
- New in vitro toxicology department planned
- Contributes to development of OECD test guidelines (requires 100% consensus)
- OECD open to Tox21 Vision, if member countries are supportive
- OECD will require that non-proprietary methods be used
- *What should the role of OECD be in implementing Tox21?*



Risk Assessment Guidelines

John Geraldez, Treasury Board of Canada

- Treasury Board Secretariat responsible for the establishment of government wide guidelines on regulatory issues
- TBS is currently developing government wide risk assessment guidelines for use by departments
- TBS consults with other jurisdictions, particularly the US and EU, in developing policies that will be both state of the art and promote international harmonization



Progress and Opportunities

- NRC report provides a blueprint for transforming toxicological practice to meet current testing needs
- Considerable progress has, and is being made to develop the science base needed to support the NRC vision
- Discussions about the regulatory and risk implications of this paradigm shift are needed to support the implementation of the vision
- Broad stakeholder participation, including the public, is needed to ensure success



“Nothing is so powerful as an idea whose time has come.”

Victor Hugo

