NexGen Risk Assessment

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Professor and Director
McLaughlin Centre for Population Heath Risk Assessment
& Risk Sciences International

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Université d’Ottawa | University of Ottawa
Three Building Blocks for a NexGen Risk Assessment Framework

I) Toxicity Testing in the 21st Century (NRC, 2007) provides a vision for the future of toxicity testing based on the identification and prevention of perturbations of toxicity pathways.

II) McLaughlin Centre Framework for Population Health Risk Assessment (Krewski et al., 2007) integrates the fields of risk science and population health.

Cornerstone #1: Toxicity Testing in the 21st Century
Toxicity Testing

Targeted Testing

Chemical Characterization

Compile data on physical and chemical properties, use characteristics, environmental concentrations, possible metabolites and breakdown products, and possible toxic properties.

Answer key questions concerning compound’s stability, potential for human exposure and bioaccumulation, and toxicity of chemical and possible metabolites.

THE NATIONAL ACADEMIES
Advisers to the Nation on Science, Engineering, and Medicine
Toxicity Pathways

- Evaluation of perturbations in toxicity pathways rather than apical end points.
- Emphasis on high-throughput approaches using cells or cell lines, preferably of human origin.
- Use of medium-throughput assays of more integrated cellular responses.

Targeted Testing

- Testing conducted to evaluate metabolites, assess target tissues, and develop understanding of affected cellular processes at genomics level.
- Limited types and duration of in vivo studies, focusing on up to 14-day exposures.
- More extensive testing for representative compounds in novel chemical classes.
Endorsement by the Scientific Community

Reaction from Experts in Risk Assessment

Perspective

Toxicity Testing in the 21st Century: Implications for Human Health Risk Assessment

Daniel Krewski, Melvin E. Andersen, Ellen Mantus, and Lauren Zeise

“Suresh Moolgavkar, our Area Editor for Health Risk Assessment, asked six experts with different perspectives to comment on the paper. Each praises the vision and offers suggestions for making it more useful.”

Michael Greenberg & Karen Lowrie, Editors
Toxicity Testing in the 21st Century: Better Results, Less Use of Animals

Legal Obstacles Are Bumps, Not Roadblocks

Bret C. Cohen
Senior Associate
Willkie Farr & Gallagher LLP

“Agency rulemaking provides the legal flexibility to implement a new toxicity testing program using existing laws.”

Reaction from the Legal Community

The Environmental Forum

Volume 25, Number 2 • March/April 2008

Advancing Environmental Protection Through Analysis • Opinion • Debate
There is widespread support for the NAS vision. There are also real but surmountable challenges in moving the vision into routine regulatory practice. Progress is being made in producing the necessary science and knowledge base — we need to redouble our efforts to see that these insights carry over into the worlds of law and policy.

Paul Locke, Johns Hopkins University
Center for Alternatives to Animal Testing
US Environmental Protection Agency Strategic Plan and Strategic Goals

http://www.epa.gov/osa/spc/toxicitytesting/docs/toxtest_strategy_032309.pdf
I’ve spent nearly forty years as a toxicologist trying to relate high-dose animal studies to low-dose human risk. I now believe that’s impossible to do.

—Melvin E. Anderson
The Hamner Institutes for Health Sciences

Right now we’re prioritizing chemicals on the basis of other criteria, such as production volume, the likelihood for human exposure, or their structural similarity to other chemicals with known liabilities. By incorporating more biology into prioritization, we think we can do a better job selecting the right chemicals for animal testing.

—Robert Kavlock
National Center for Computational Toxicology

Human Toxicology Project Consortium

About the Consortium
What is the Human Toxicology Project Consortium?
The Consortium is a group of stakeholders currently drawn from the corporate and public interest communities that share the objective of accelerating implementation of the vision in the National Research Council’s 2007 report on “Toxicity Testing in the 21st Century.” The Consortium believes that the NRC vision is best implemented through a large-scale, international, coordinated effort analogous to the Human Genome Project of the 1990s. We call this needed effort the Human Toxicology Project.

Mission
Serve as a catalyst for the prompt, global, and coordinated implementation of “21st Century” toxicology, which will better safeguard human health and hasten the replacement of animal use in toxicology.

Vision
A global paradigm shift to an in vitro approach to the risk assessment of chemicals and drugs that is based on a modern understanding of human biology and disease pathways, yielding results more rapidly and more predictive of human health effects than current approaches.
JTEH Special Issue on Future Directions in Toxicity Testing

- **Part A**: NRC Report on Toxicity Testing in the 21st Century (reprint with permission)

- **Part B**: U.S. EPA Strategic Plan for Toxicity Testing (reprint)

- **Part C**: Individual contributions on future directions in toxicity testing
## Building the Scientific Toolbox

*(Andersen et al., 2010)*

<table>
<thead>
<tr>
<th>Tool</th>
<th>Application</th>
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<tbody>
<tr>
<td>High throughput screens</td>
<td>Efficiently identify critical toxicity pathway perturbations across a range of doses and molecular and cellular targets</td>
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<tr>
<td>Stem cell biology</td>
<td>Develop in vitro toxicity pathway assays using human cells produced from directed stem cell differentiation</td>
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<td>Functional genomics</td>
<td>Identify the structure of cellular circuits involved in toxicity pathway responses to assist computational dose response modeling</td>
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<tr>
<td>Bioinformatics</td>
<td>Interpret complex multivariable data from HTS and genomic assays in relation to target identification and effects of sustained perturbations on organs and tissues</td>
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<td>Systems biology</td>
<td>Organize information from multiple cellular response pathways to understand integrated cellular and tissue responses</td>
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<tr>
<td>Computational systems biology</td>
<td>Describe dose-response relationships based on perturbations of cell circuitry underlying toxicity pathway responses giving rise to thresholds, dose-dependent transitions, and other dose-related biological behaviors</td>
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<td>Physiologically-based pharmacokinetic models</td>
<td>Identify human exposure situations likely to provide tissue concentrations equivalent to in vitro activation of toxicity pathways</td>
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<td>Structure-activity relationships</td>
<td>Predict toxicological responses and metabolic pathways based on the chemical properties of environmental agents and comparison to other active structures</td>
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<td>Biomarkers</td>
<td>Establish biomarkers of biological change representing critical toxicity pathway perturbations</td>
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</table>
Case Study Prototypes
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<tr>
<th>Tool</th>
<th>Lung Injury and Ozone</th>
<th>Developmental Impairment and Thyroid Hormone Disruptors</th>
<th>Cancer and Polycyclic Aromatic Hydrocarbons</th>
<th>Cancer and Benzene</th>
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An Integrated Framework for Risk Management and Population Health

Daniel Krewski,1,2 Victoria Hogan,1 Michelle C. Turner,1 Patricia L. Zeman,1
Ian McDowell,2,3 Nancy Edwards,2,3,4 and Joseph Losos3

1McLaughlin Centre for Population Health Risk Assessment, Institute of
Population Health, University of Ottawa, Ottawa, ON, Canada; 2Department of
Epidemiology and Community Medicine, Faculty of Medicine, University of
Ottawa, Ottawa, ON, Canada; 3Institute of Population Health, University of Ottawa,
Ottawa, ON, Canada; 4School of Nursing, Faculty of Health Sciences, University of
Ottawa, Ottawa, ON, Canada
Risk assessment is a process to characterize risk using scientific methods.

Population health risk assessment is the comprehensive assessment of health risks in the general population based on genetic, environmental, social & behavioural determinants of health.

This forms the basis for evidence-based population health risk policy analysis, and, ultimately, cost-effective population health risk management decisions.
Chemically-induced perturbations

Susceptibility & Sensitivity Factors

Hereditary (Genetic & Epigenetic)
Lifestage
Non-chemical stressors
Nutrition
Health & Infection Status

Molecular Biomarkers of Disease Risk

Genes
Transcripts
Proteins
Metabolites

Gene Networks
Empirical Models
Pathways

Virtual Cells & Tissues
Empirical Models

Cells
Histological & Clinical Biomarkers & Effects

Biomonitoring Data & Models
Epidemiology
Clinical Research
Economic Valuation
Disease Definition

Cornerstone #3: Science and Decisions: Advancing Risk Assessment
- Enhanced framework
- Formative focus
- Four steps still core
- Matching analysis to decisions
- Clearer estimates of population risk
- Advancing cumulative assessments
- People and capacity building
"Risk-Based Decision-Making" Framework

Phase I: Formulating and Scoping Problem
For environmental condition:
- What’s the problem?
- What are the options for altering?
- What assessments are needed to evaluate options?

Phase II: Planning and Risk Assessing
Stage 1: Planning for:
- Options Assessment
- Uncertainty and Variability Analysis

Stage 2: Assessing

Stage 3: Confirming Utility of Assessment

Phase III: Risk Management
- Relative benefits of proposed options?
- How are other factors (e.g., costs) affected by options?
- Which option is chosen? What's the uncertainty and justification?
- How to communicate it?
- Should decision effectiveness be evaluated? If so, how?

Stakeholder involvement at each phase
FORUM SERIES, PART I

Toxicity Testing in the 21st Century: Bringing the Vision to Life

Melvin E. Andersen* †and Daniel Krewski†

*Hamner Institutes for Health Sciences, Research Triangle Park, North Carolina 27709; and †University of Ottawa, Ottawa, Ontario, Canada K1N 6N5

Received July 3, 2008; accepted November 6, 2008

8 + 1 Invited Commentaries 2009-2010
Recurring Themes in the Commentaries

• Definition of adversity

• Predicting *in vivo* results from *in vitro* toxicity pathway assay results

• Setting standards from results of *in vitro* assays

• How can the change from current practices to a new paradigm occur?
The “Swiss cheese” model of adverse effects

- Chemical Exposure
- Chemical is electrophilic
- Irreversible changes
- Abrupt dose-response transition
- Mitochondrial dysfunction
- Dose Response Extrapolation Modeling
- Latent Failures
- Toxicity Pathways Targeted Testing
- Latent Failures
- Chemical Characterization
- Latent Failures
- Apical Event
- Active Failures
- Adverse Effect
- Apoptotic cell

Adapted from Boekelheide and Campion, Toxicol. Sci., 2010.

McLaughlin Centre for Population Health Risk Assessment
Incorporating Human Dosimetry and Exposure into High-Throughput

_In Vitro_ Toxicity Screening


*National Center for Computational Toxicology, Office of Research and Development, United States Environmental Protection Agency, Research Triangle Park, North Carolina 27711; †Department of Environmental Sciences and Engineering, University of North Carolina, Chapel Hill, North Carolina 27514; ‡ The Hamner Institutes for Health Sciences, Research Triangle Park, North Carolina 27709; and §CellzDirect/Invitrogen Corporation (a part of Life Technologies), Durham, North Carolina 27703
Table 4. Potential Modifications of Risk Assessment Approaches in a NexGen Context

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<th>Risk Issue</th>
<th>Current Approach</th>
<th>NexGen Approach</th>
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<td>Defining Adversity</td>
<td>Adversity is presently defined in terms of observation of apical endpoints in mammalian systems.</td>
<td>Adversity will be defined in terms of critical perturbations of toxicity pathways, ultimately in the absence of information on apical outcomes. Defining adversity will require knowledge of dose response for various pathway assays and in vitro models that assess conditions leading to excessive pathway perturbations in relevant assays.</td>
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<td>Default assumptions</td>
<td>Current default assumptions used in risk assessment (such as a 10-fold variation in sensitivity within the human population) are usually based on limited empirical evidence.</td>
<td>Understanding toxicity pathways in more depth will permit a move away from default assumptions, towards a more mechanistic approach guided by scientific evidence and knowledge of the behaviour of the toxicity pathway in shifting from basal levels of activity to enhanced function with excessive perturbation. (It will likely be possible to characterize phenotypic variation with some precision using suites of human cell lines representing inherent differences in sensitivity and differences among life stages and through knowledge of pathway components and polymorphisms in these components that affect function).</td>
</tr>
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</table>
Selected Risk Issues to be Addressed

- Chemical mixtures
- Joint effects of multiple stressors
- Assessment of delayed effects
- Reversible or transient effects

- Analysis of various life stages
- Analysis of multiple exposure doses
- Assessment of exposures of different durations (e.g., acute, chronic, and intermittent exposures)
Towards a Framework for Next Generation Health Risk Assessment
New Directions in Toxicity Testing

Daniel Krewski,¹ Margit Westphal,¹ Mustafa Al-Zoughool,¹ Maxine C. Croteau,¹ and Melvin E. Andersen²

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²Program in Chemical Safety Sciences, Hamner Institutes for Health Sciences, Research Triangle Park, North Carolina 27709, USA; email: mandersen@thehamner.org

Toxicity Testing and Risk Assessment
(from Krewski et al., 2011, Annual Review of Public Health, in press)
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