# Toxicity Testing in the 21st Century: Making the Vision a Reality

Daniel Krewsk, PhD, MHA
Professor and Director
McLaughlin Centre for
Population Heath Risk Assessment

October 27, 2009

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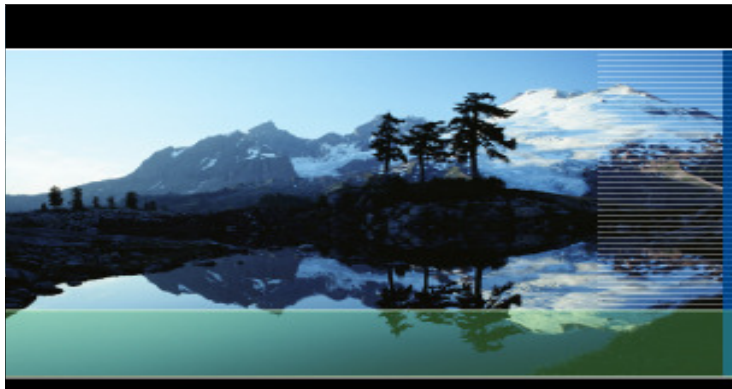

BEST

Board on Environmental Studies and Toxicology

# Toxicity Testing in the 21st Century: A Vision and A Strategy


Committee on Toxicity Testing and Assessment of Environmental Agents

Board on Environmental Studies and Toxicology

Institute for Laboratory Animal Research

Division on Earth and Life Studies

National Research Council



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**Daniel Acosta, Jr.**, University of Cincinnati, Cincinnati, OH
**Melvin Andersen**, CIIT Centers for Health Research, Research Triangle Park, NC
**Henry Anderson,** Wisconsin Division of Public Health, Madison, WI
**John Bailar III,** University of Chicago, Chicago, IL
**Kim Boekelheide,** Brown University, Providence, RI
**Robert Brent,** Thomas Jefferson University, Wilmington, DE
**Gail Charnley,** HealthRisk Strategies, Washington, DC
**Vivian Cheung,** University of Pennsylvania, Philadelphia, PA
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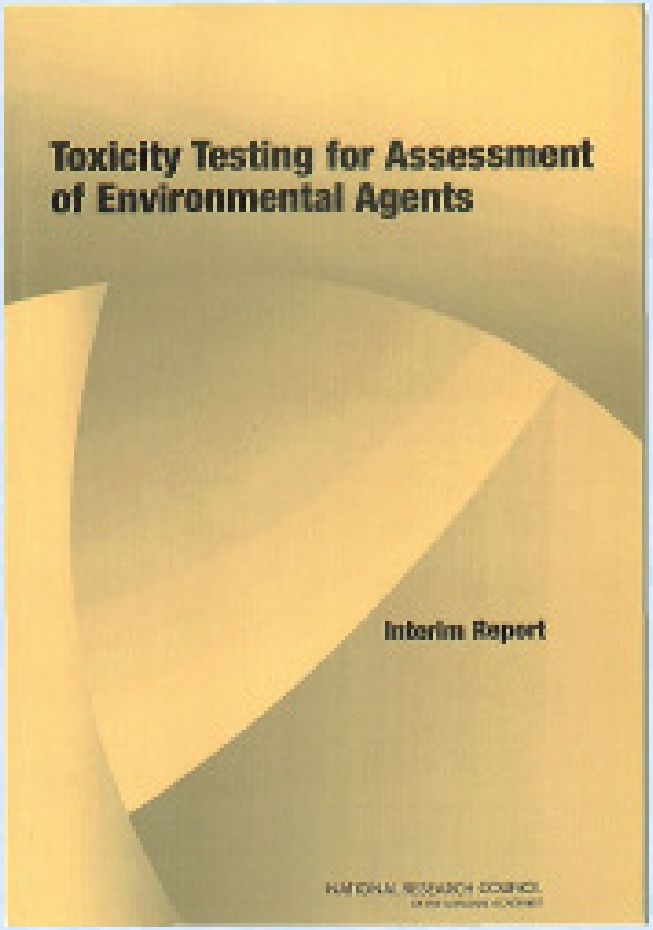
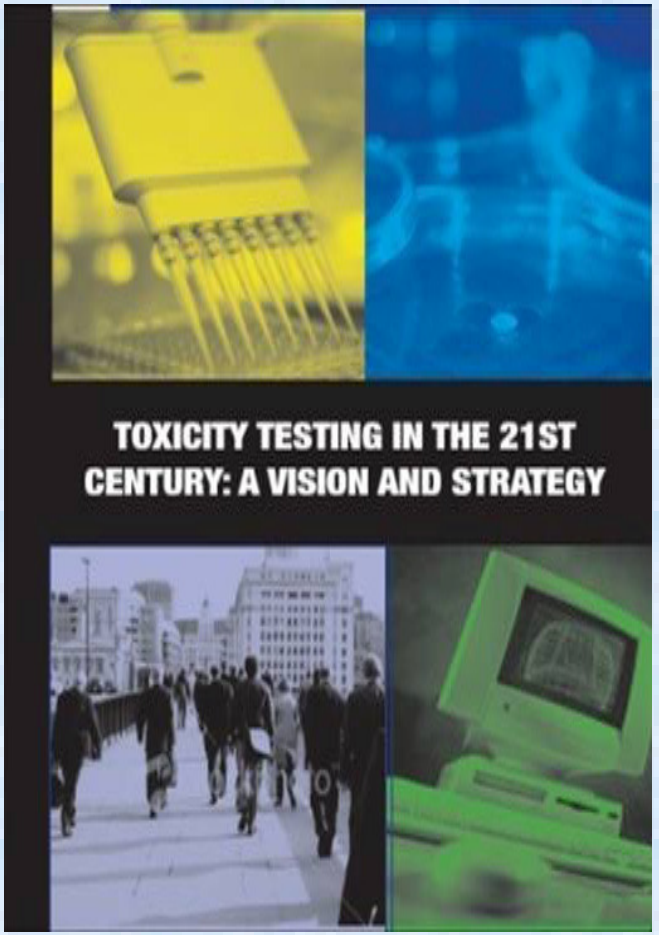
**Martin Stephens,** The Humane Society of the United States, Washington, DC
**James Yager, Jr.,** Johns Hopkins University, Baltimore, MD
**Lauren Zeise,** California Environmental Protection Agency, Oakland, CA

# Interim and Final Reports

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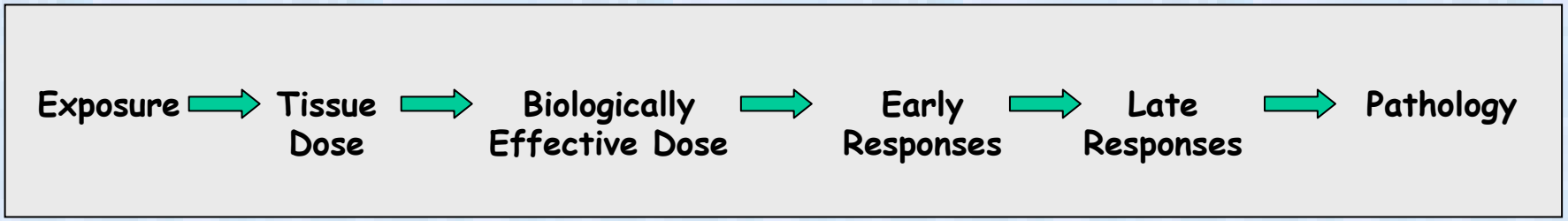
# Current Paradigm: The Exposure-response Continuum




Physiologically Based Pharmacokinetic Models

Tissue Dose Metric

Mode of Action

Pharmacokinetics

Pharmacodynamics

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# A Transformative Vision

**Make no little plans. They have no magic to stir men's blood and probably themselves will not be realized**

**Make big plans; aim high in hope and work, remembering that a noble, logical diagram once recorded will never die, but long after we are gone will be a living thing, asserting itself with evergrowing insistency.**

*Daniel Hudson Burnham, Architect*
*Designer of the 1893 Chicago World's Fair*

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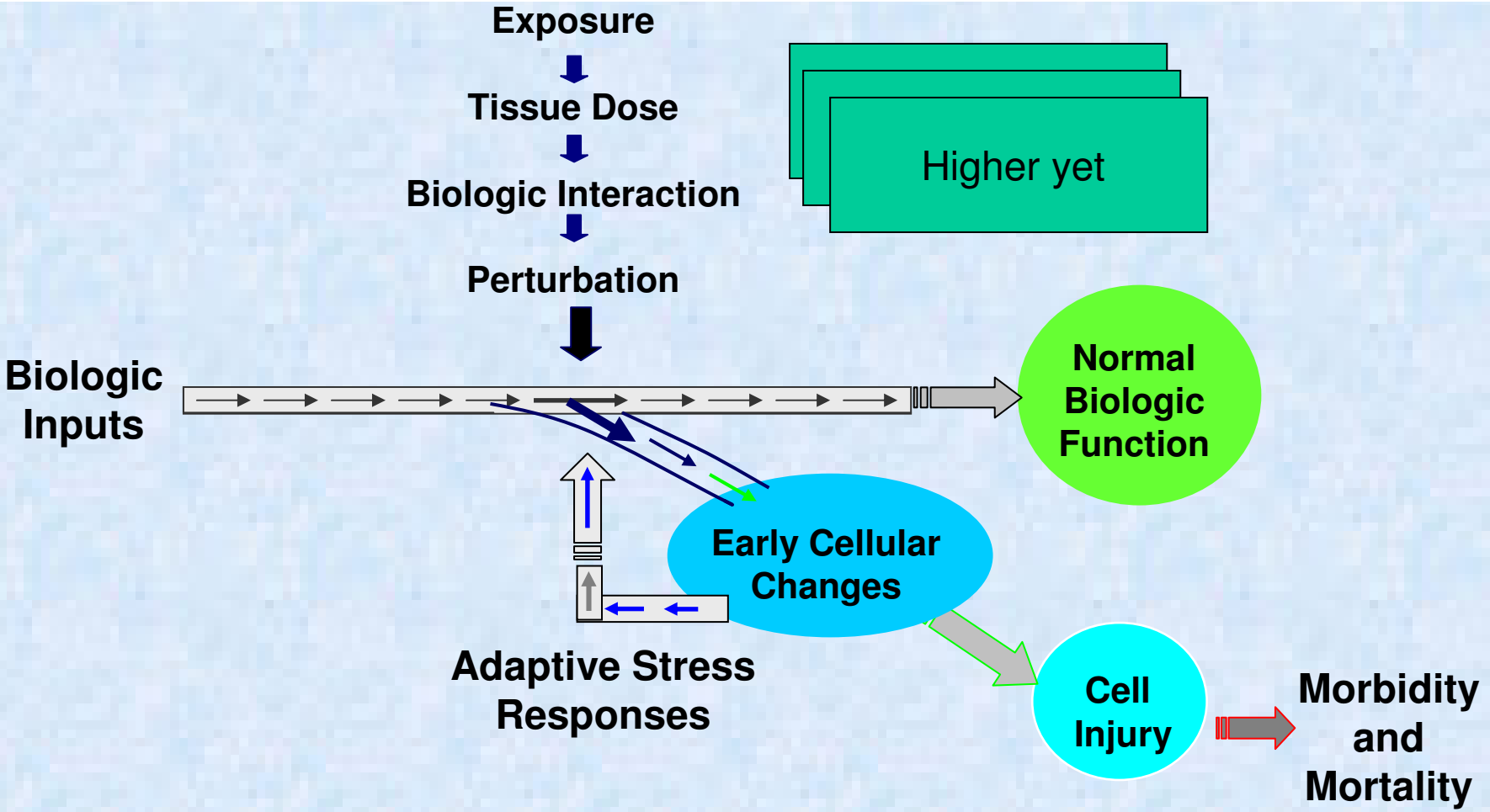
# A New Paradigm: Activation of Toxicity Pathways

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# Toxicity Pathways

***Toxicity Pathway: A cellular response pathway that, when sufficiently perturbed, is expected to result in an adverse health effect.***

# Toxicity Response Pathways

*Endogenous hormones*

*DNA damage*

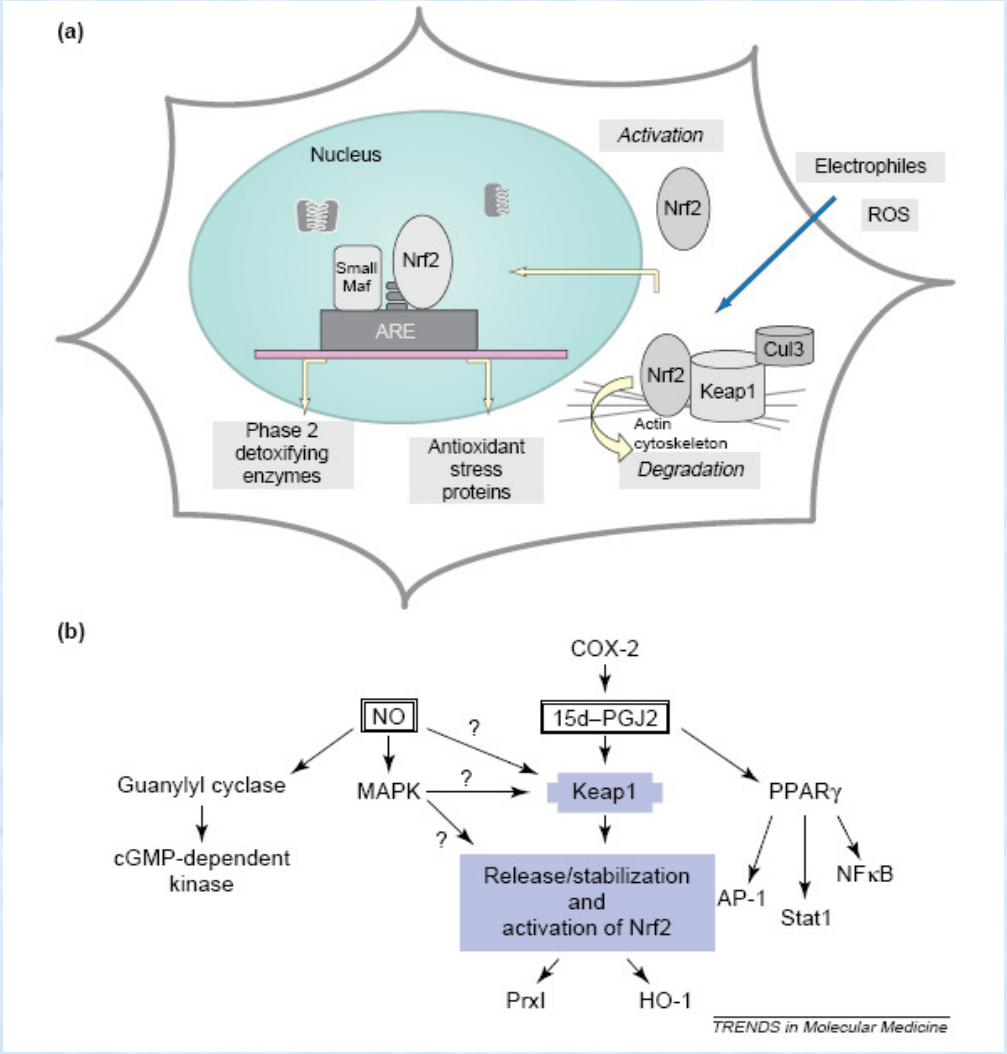
*PXR, CAR, PPAR and AhR receptors*

*Hypo-osmolarity*

*Nrf2 oxidative stress*

*Heat-shock proteins*

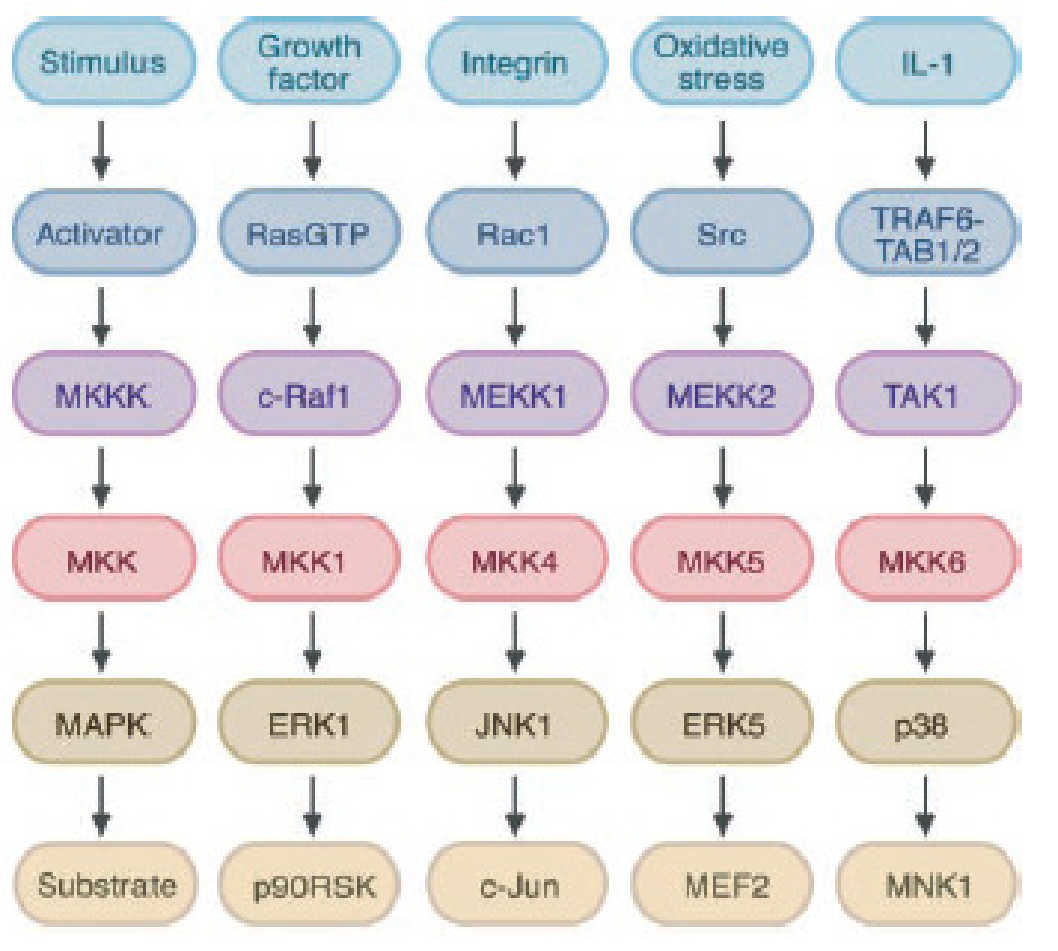
# Nrf2 Antioxidant Response Pathway




In non-toxic environments, Nrf2 is bound to the cytoplasmic protein Keap1

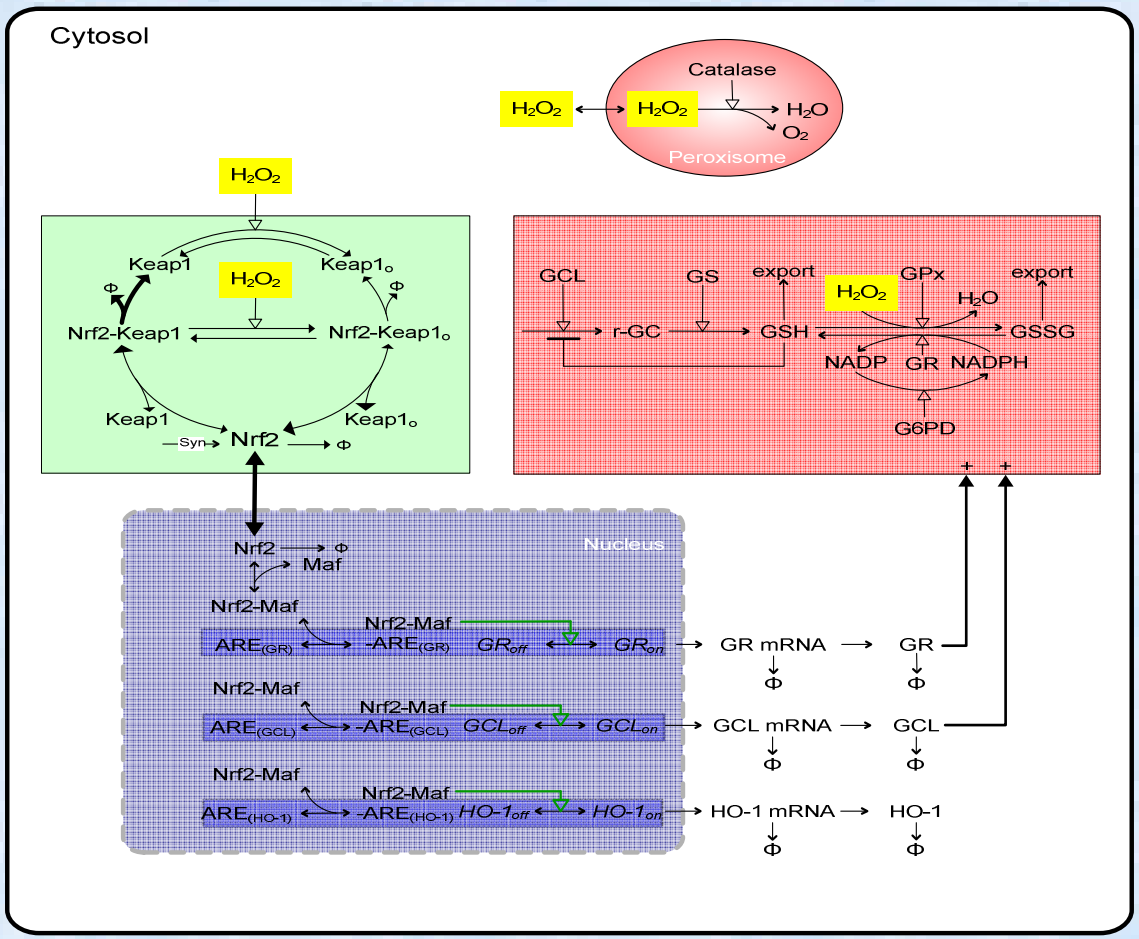
In toxic environments, Nrf2 is released into the nucleus, leading to expression of antioxidant stress proteins

# Integration of Cell Signaling Pathways




Mitogen-activated protein kinase (MAPK) cascades integrate cell signaling pathways that govern cell kinetics

# Computational Systems Biology




Feedback controlled adaptive stress responses govern activation and perturbation of signaling pathways

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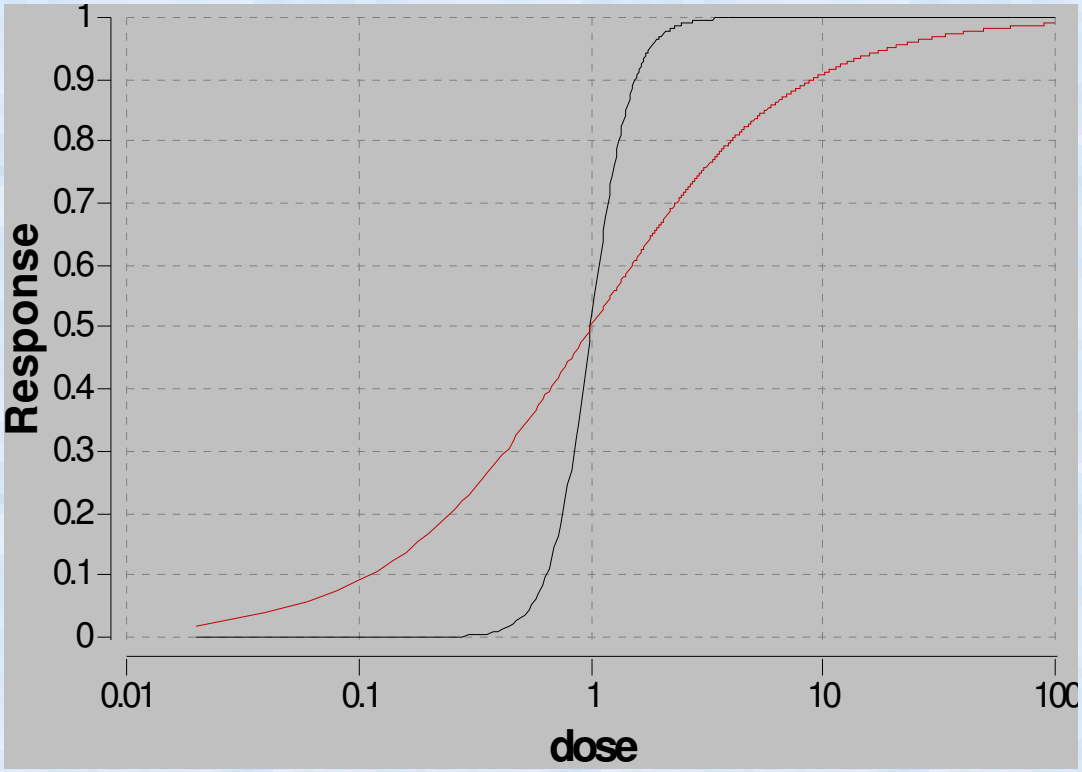
# Dose-response Modeling of Nrf2 Pathway Activation




Nfr2 activation represents an important biological perturbation of a general toxicity pathway

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# Options for Future Toxicity Testing Strategies

| **Option I**<br>**In Vivo** | **Option II**<br>**Tiered In Vivo** | **Option III**<br>**In Vitro/In Vivo** | **Option IV**<br>**In vitro** |
|---|---|---|---|
| Animal biology | Animal biology | Primarily human biology | Primarily human biology |
| High doses | High doses | Broad range of doses | Broad range of doses |
| Low throughput | Improved throughput | High and medium throughput | High throughput |
| Expensive | Less expensive | Less expensive | Less expensive |
| Time consuming | Less time consuming | Less time consuming | Less time consuming |
| Relative large number of animals | Fewer animals | Substantially fewer animals | Virtually no animals |
| Apical endpoints | Apical endpoints | Perturbations of toxicity pathways | Perturbations of toxicity pathways |
| | Some *in silico* and *in vitro* screens | *In silico* screens possible | *In silico* screens |

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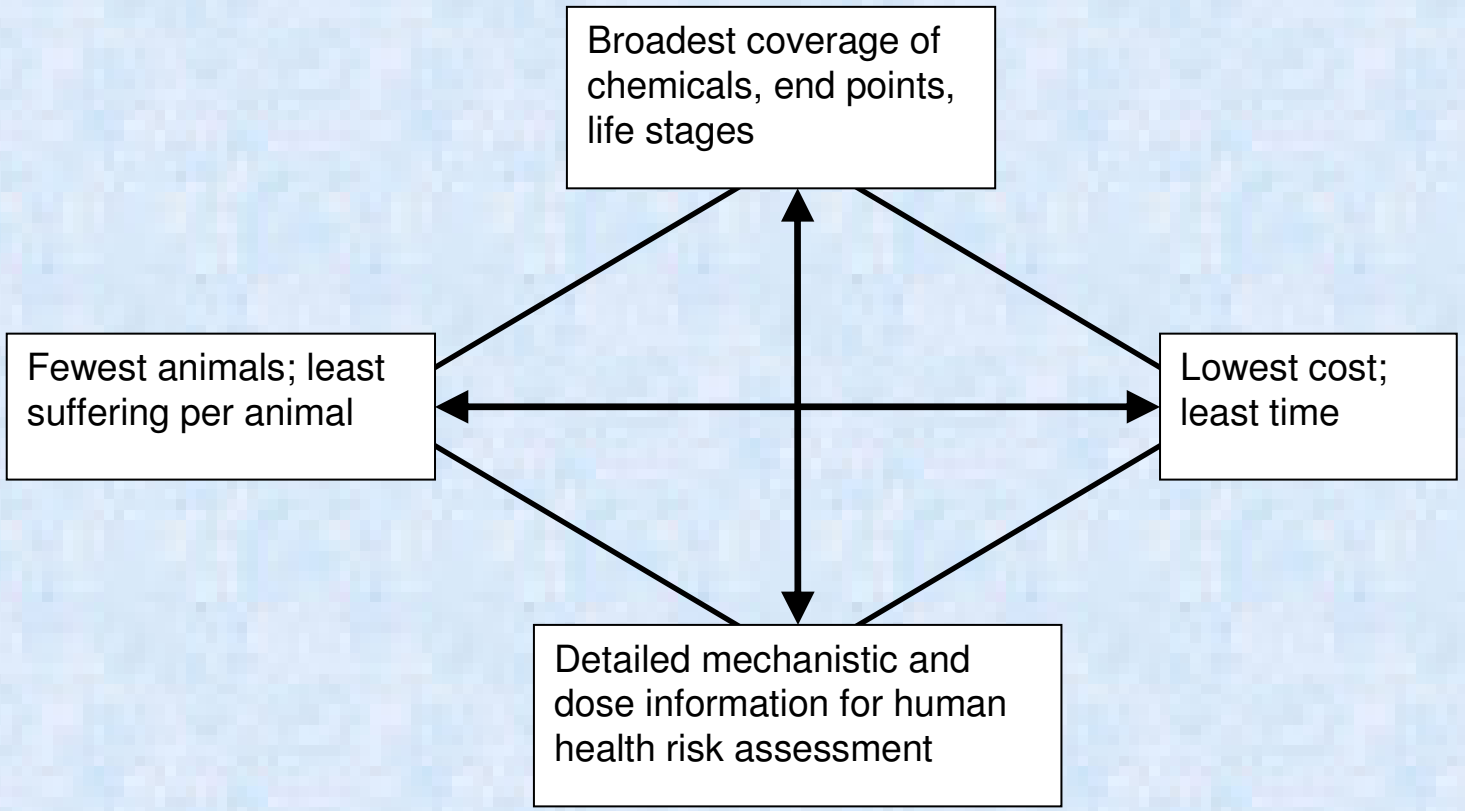
# Design Criteria: Objectives of Toxicity Testing

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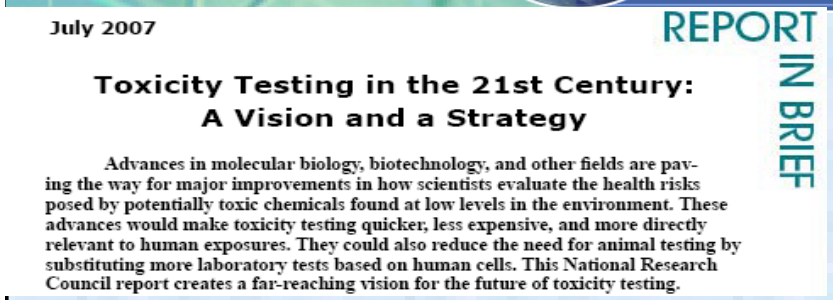
# The Committee's Vision



July 2007

REPORT IN BRIEF

**Toxicity Testing in the 21st Century: A Vision and a Strategy**

Advances in molecular biology, biotechnology, and other fields are paving the way for major improvements in how scientists evaluate the health risks posed by potentially toxic chemicals found at low levels in the environment. These advances would make toxicity testing quicker, less expensive, and more directly relevant to human exposures. They could also reduce the need for animal testing by substituting more laboratory tests based on human cells. This National Research Council report creates a far-reaching vision for the future of toxicity testing.

# Toxicity Testing in the 21st Century: A Vision and A Strategy

*Final Report Released June 12, 2007*

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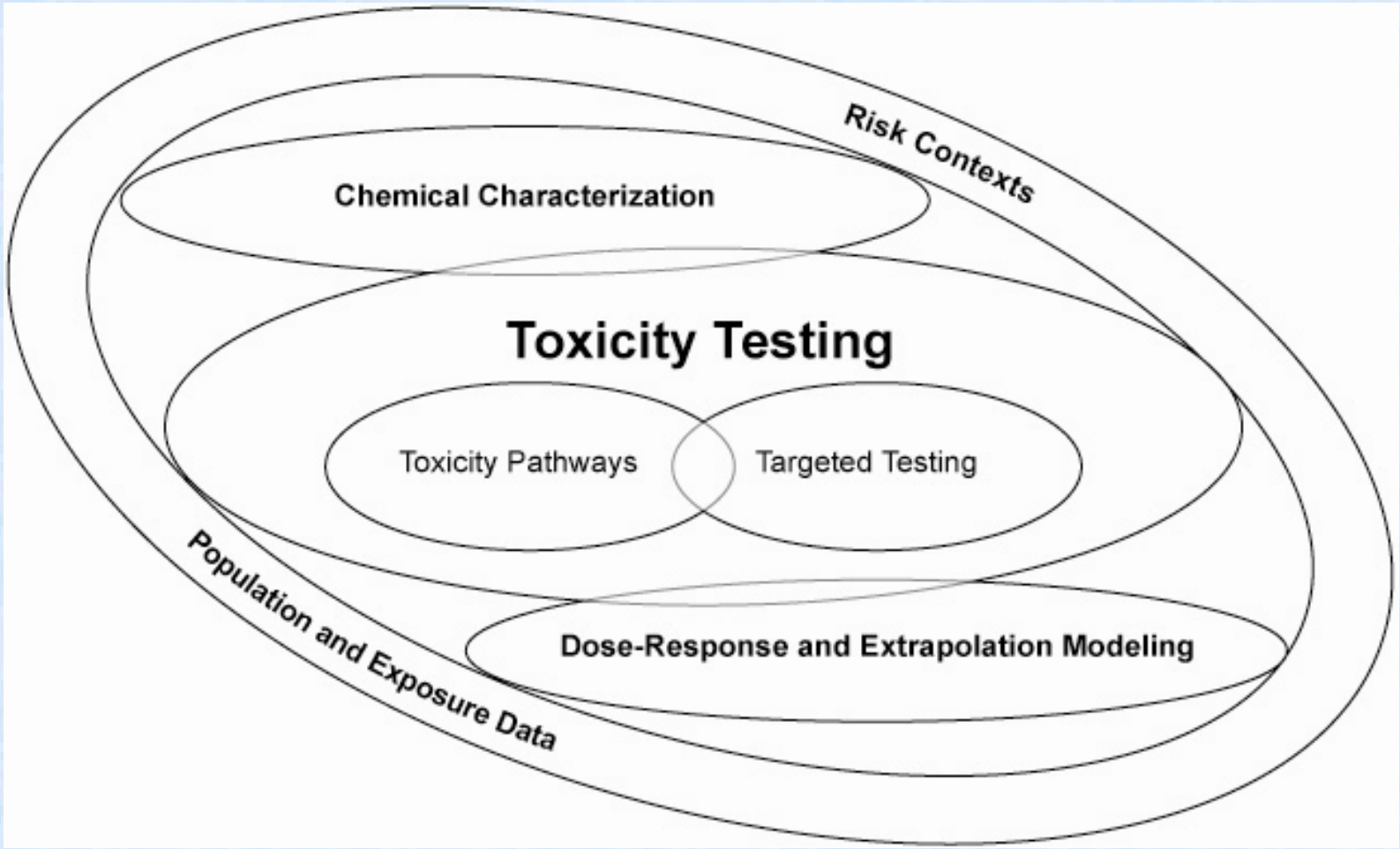
# Components of the Vision

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# Chemical Characterization




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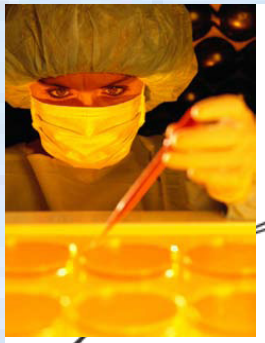
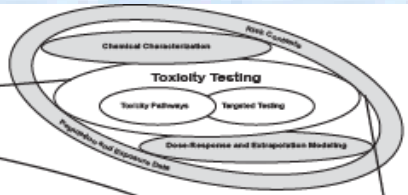
# Toxicity Testing





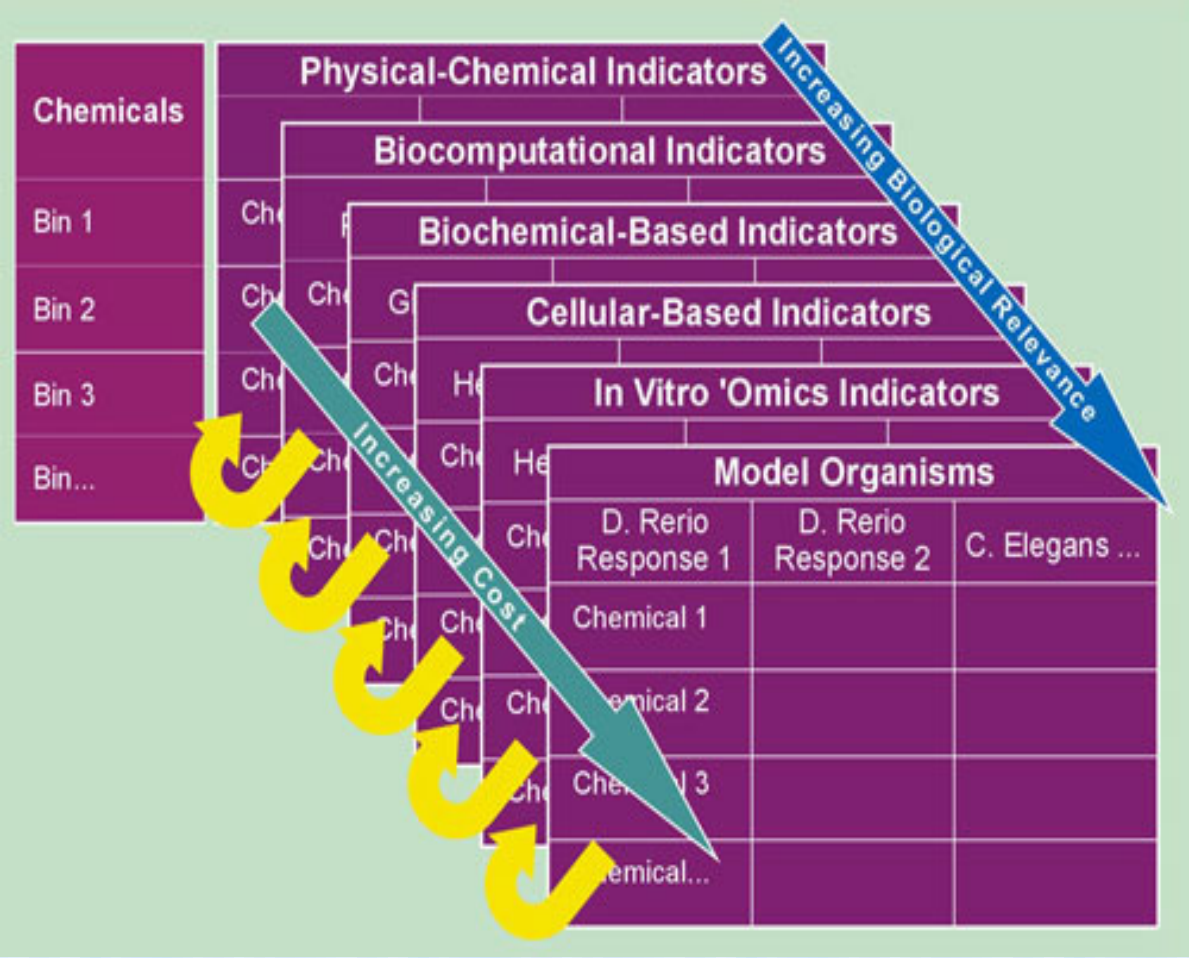

## Toxicity Pathways

- 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.

# Implementing the Vision: EPA's ToxCast™ Program




Forecast toxicity based on bioactivity profiling

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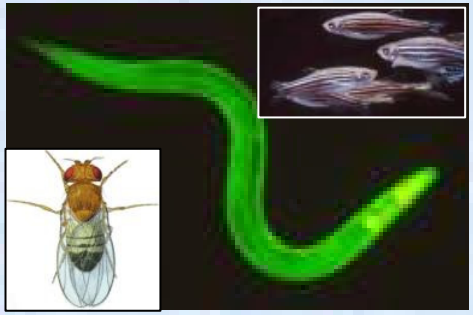
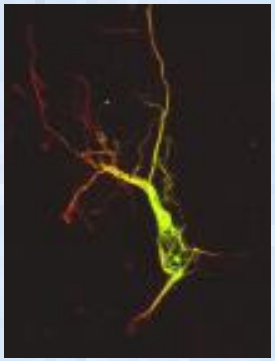
# Implementing the Vision: NIEHS High Throughput Screens

1-3/year

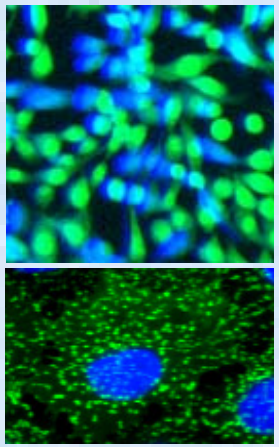
10's/year

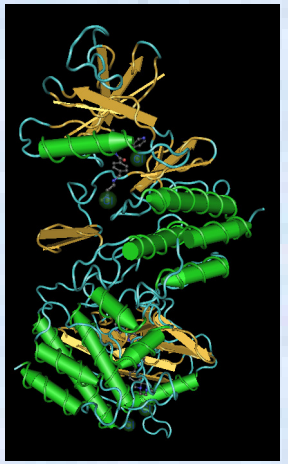


100's/year



10,000's/day





100,000's/day

**High Throughput**
**Molecular mechanism**

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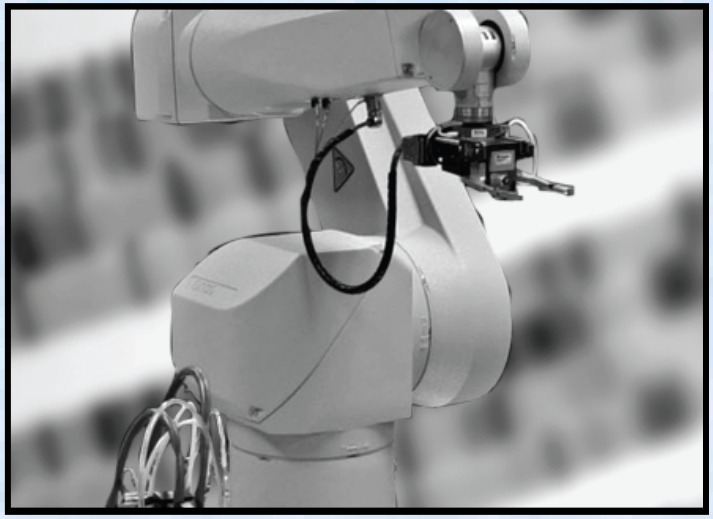
# Implementing the Vision: NIH National Chemical Genomics Center



- Enzymatic assays
- Receptor binding assays
- GTPγS binding Assays
- Tissue culture assays
- Cell-based Elisa and Western Blots (for quantitative antigen detection )
- FLIPR™ Assays (GPCR and ion channel targets)
- Immunoassays

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# Progress since 2007: *Regulatory Implications*

# Toxicity Testing in the 21st Century: Better Results, Less Use of Animals

## Legal Obstacles Are Bumps, Not Roadblocks

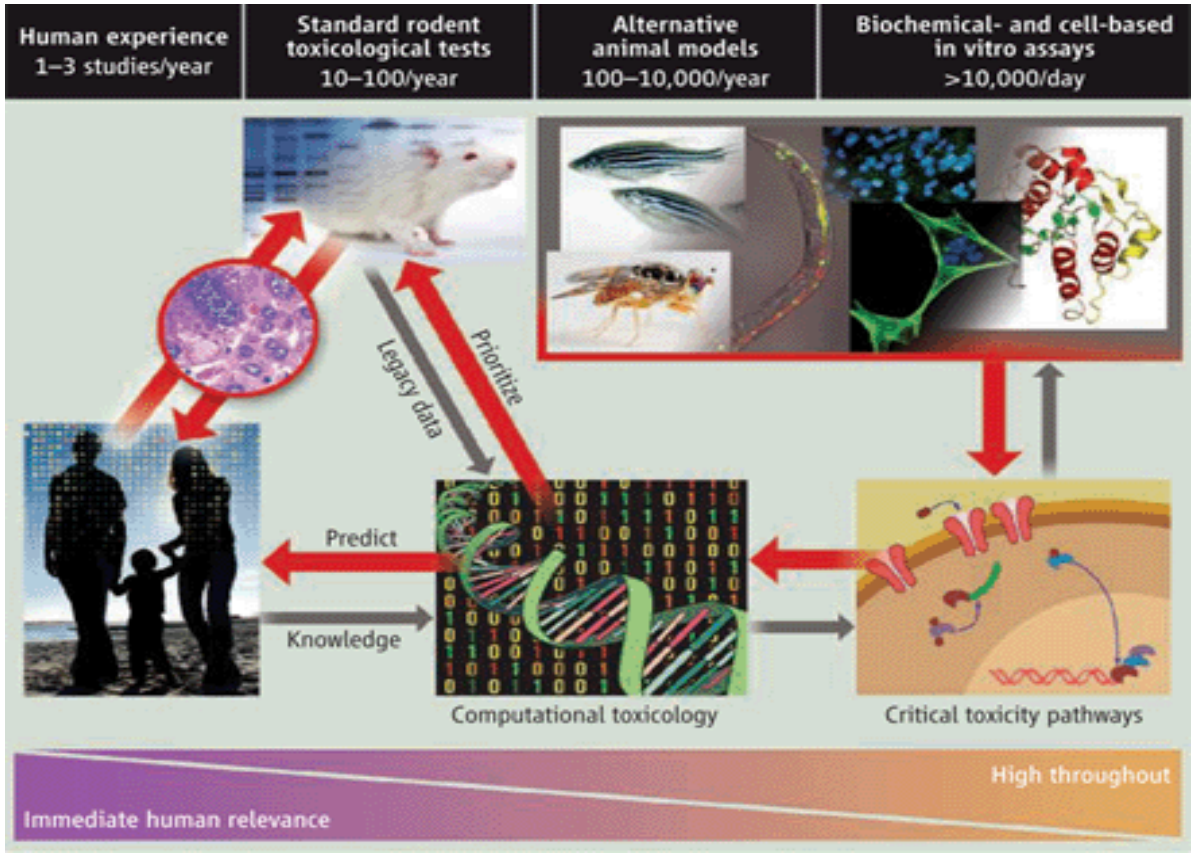
*"Agency rulemaking provides the legal flexibility to implement a new toxicity testing program using existing laws."*

**Bret C. Cohen**
*Senior Associate*
Willkie Farr & Gallagher LLP

THE Environmental Forum®
Volume 25, Number 2 · March/April 2008
Advancing Environmental Protection Through Analysis · Opinion · Debate
ENVIRONMENTAL LAW · INSTITUTE®

# Progress since 2007: *Endorsement by Scientific Community*

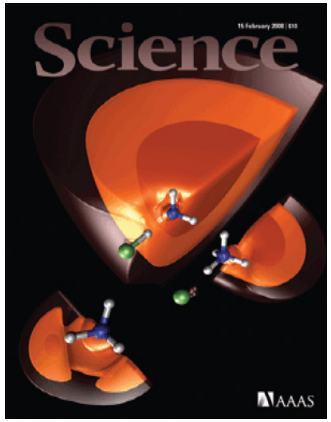
# Transforming Environmental Health Protection*




*Collins, F.S., Gray, G.M. & Bucher, J.R. (2008), Science (Policy Forum). Vol. 319. pp. 906 - 907

# Making it Happen*

"We propose a shift from primarily in vivo animal studies to in vitro assays, in vivo assays with lower organisms, and computational modeling for toxicity assessments."




*Collins, F.S., Gray, G.M. & Bucher, J.R. (2008), Science (Policy Forum). Vol. 319. pp. 906 - 907

# Progress since 2007:
# *Implications for Risk Assessment*

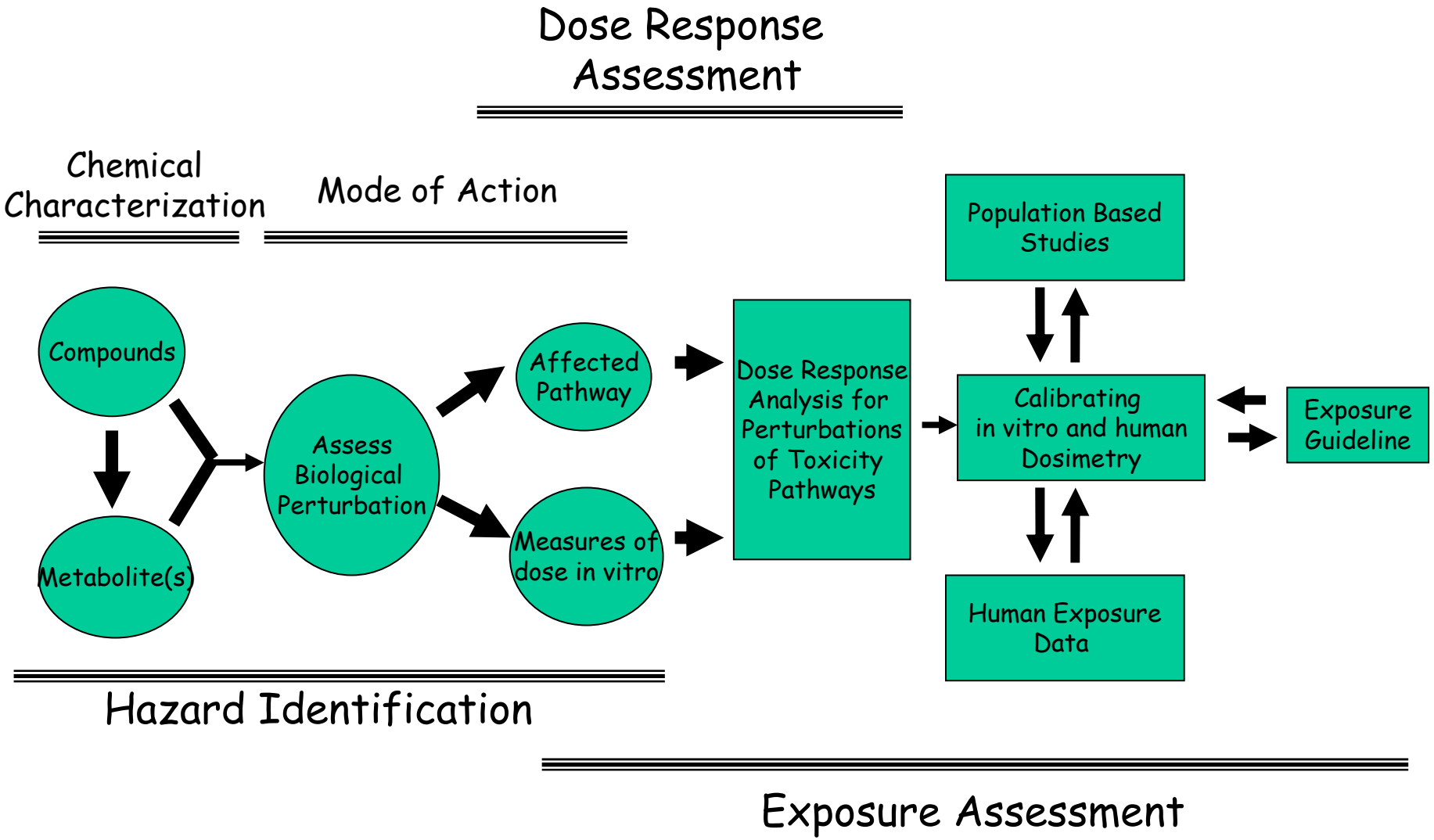
*Risk Analysis* DOI: 10.1111/j.1539-6924.2008.01150.x

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

**Daniel Krewski,[1]* Melvin E. Andersen,[2] Ellen Mantus,[3] and Lauren Zeise[4]**

At the request of the Environmental Protection Agency, the National Research Council (NRC) recently completed a major report entitled *Toxicity Testing in the 21st Century: A Vision and a Strategy*. The terms of reference for this report were to develop a long-range vision and strategic plan to advance the practices of toxicity testing and human health assessment of environmental agents. The report describes how current and anticipated scientific advances can be expected to transform toxicity testing to permit broader coverage of the universe of potentially toxic chemicals to which humans may be exposed, using more timely and more cost-effective methods for toxicity testing. The report envisages greatly expanded use of high- and medium-throughput *in vitro* screening assays, computational toxicology, and systems biology, along with other emerging high-content testing methodologies, such as functional genomics and transcriptomics. When fully implemented, the vision will transform the ways toxicity testing and chemical risk assessment are conducted, moving away from measuring apical health endpoints in experimental animals toward identification of significant perturbations of toxicity pathways using *in vitro* tests in human cells and cell lines. Population-based studies incorporating relevant biomarkers will also be useful in identifying pathway perturbations directly in humans and in interpreting the results of *in vitro* tests in the context of human health risk assessment. The present article summarizes and extends the NRC report and examines its implications for risk assessment practice.

# Toxicity Testing and Risk Assessment



# Highlights of Invited Commentaries I

- **Tsuji & Garry (Exponent Corporation)**
  - Consider background exposures, mixed exposures and sensitive subpopulations

- **Rory Connolly (U.S. EPA)**
  - Consider accuracy of risk predictions
  - Microdosimetry to aid in in vitro to in vivo extrapolations, including use of PBPK models
  - Development of virtual tissues to integrate across molecules, pathways, cells and tissues

# Highlights of Invited Commentaries II

- **Donald Elliot (Yale Law School)**
  - Legal challenges in implementing the vision
  - Establishment of what constitutes an 'adverse effect'

- **Dale Hattis (Clark University)**
  - Challenges in using HTS results based on the current EPA regulatory framework
  - Consider expected 'value of information' of successively adding additional toxicological test data

# Highlights of Invited Commentaries III

- **Lorenz Rhomberg (Gradient Corporation)**
  - NRC report will require pervasive changes in both toxicity testing and risk assessment
  - Effective risk assessment needs to consider underlying causative pathways in animals and humans, and at high and low doses

- **Robert Kavlock (U.S. EPA), Chris Austin (NCGC), and Ray Tice (NIEHS)**
  - Interagency memorandum of understanding
  - Develop efficient test batteries for identifying human health hazards, and for prioritizing chemicals for further more in-depth evaluation

# Progress since 2007: *Rethinking Toxicity Testing*

TOXICOLOGICAL SCIENCES **107(2)**, 324–330 (2009)
doi:10.1093/toxsci/kfn255
Advance Access publication December 12, 2008

FORUM SERIES, PART I

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

Melvin E. Andersen*,[1] 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

## Table 1. Toxicity Testing Tools and their Application in Risk Assessment

| Tool | Application |
|---|---|
| **High throughput screens** | Efficiently identify critical toxicity pathway perturbations across a range of doses and molecular and cellular targets |
| **Stem cell biology** | Develop in vitro toxicity pathway assays using human cells produced from directed stem cell differentiation |
| **Functional genomics** | Identify the structure of cellular circuits involved in toxicity pathway responses to assist computational dose response modeling |
| **Bioinformatics** | Interpret complex multivariable data from HTS and genomic assays in relation to target identification and effects of sustained perturbations on organs and tissues |
| **Systems biology** | Organize information from multiple cellular response pathways to understand integrated cellular and tissue responses |
| **Computational systems biology** | 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 |
| **Physiologically-based pharmacokinetic models** | Identify human exposure situations likely to provide tissue concentrations equivalent to in vitro activation of toxicity pathways |
| **Structure-activity relationships** | Predict toxicological responses and metabolic pathways based on the chemical properties of environmental agents and comparison to other active structures |
| **Biomarkers** | Establish biomarkers of biological change representing critical toxicity pathway perturbations |

# Progress since 2007:
# *Federal Agency Commitment*

# MEMORANDUM OF UNDERSTANDING

ON

High Throughput Screening, Toxicity Pathway Profiling,
and Biological Interpretation of Findings

BETWEEN THE

U.S. DEPARMENT OF HEALTH AND HUMAN SERVICES (HHS)
NATIONAL INSTITUTES OF HEALTH (NIH)
National Institutes of Environmental Health Sciences (NIEHS)/
National Toxicology Program (NTP)

AND THE

U.S. DEPARMENT OF HEALTH AND HUMAN SERVICES (HHS)
NATIONAL INSTITUTES OF HEALTH (NIH)
National Human Genome Research Institute (NHGRI)
NIH Chemical Genomics Center (NCGC)

AND THE

U.S. ENVIRONMENTAL PROTECTION AGENCY (EPA)
Office of Research and Development

EPA 100/K-09/001
March 2009

# The U.S. Environmental Protection Agency's Strategic Plan for Evaluating the Toxicity of Chemicals

Office of the Science Advisor
Science Policy Council
U.S. Environmental Protection Agency
Washington, DC 20460

# Strategic Goals

- **Toxicity Pathway Identification and Chemical Screening and Prioritization**
- **Toxicity pathway-based risk assessment**
- **Institutional Transition**

# Resources Needed to Implement EPA's Strategic Plan*

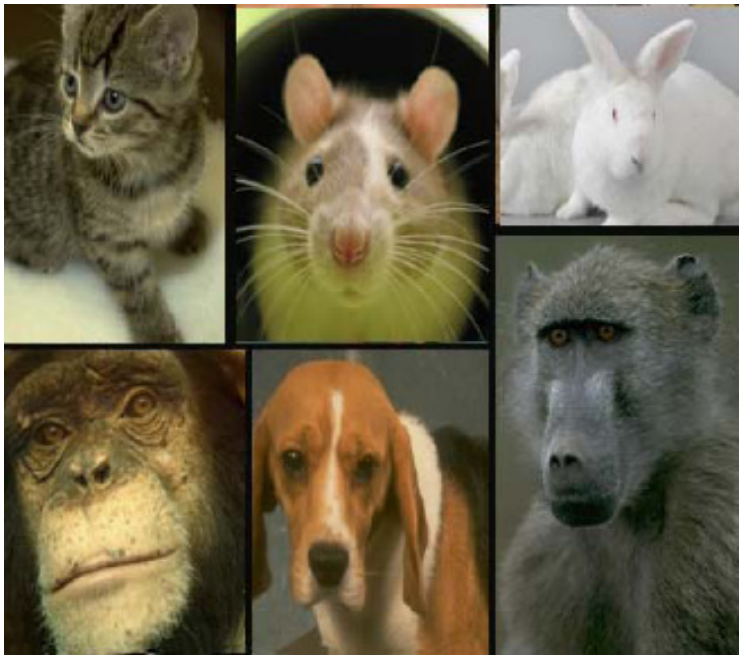
"This strategic plan describes an ambitious and substantive change in the process by which chemicals are evaluated for toxicity. The NRC (2007) suggested that such a transformation would require up to $100 million per year in funding over a 10 - 20 year period to have a reasonable chance of reaching its goals."

*U.S. Environmental Protection Agency (2009). Strategic Plan for the Future of Toxicity Testing at the U.S. Environmental Protection Agency. (www.epa.gov/osa/spc/toxicitytesting/)

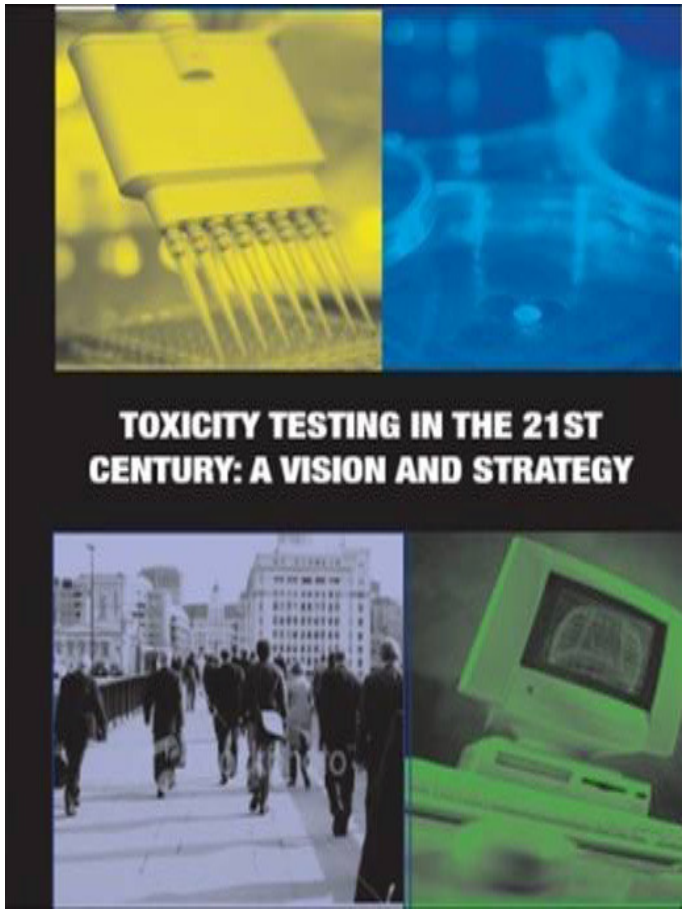
# Progress since 2007:
# *Animal Welfare*

# Animal Rights Perspective: Humane Society of the United States

- **Long-term goal: eliminate use of animals in harmful research**
- **Promote 3 R's: Replacement, Reduction, Refinement**



# Dual Motivation for Change




**Better Science**


**Animal Welfare**

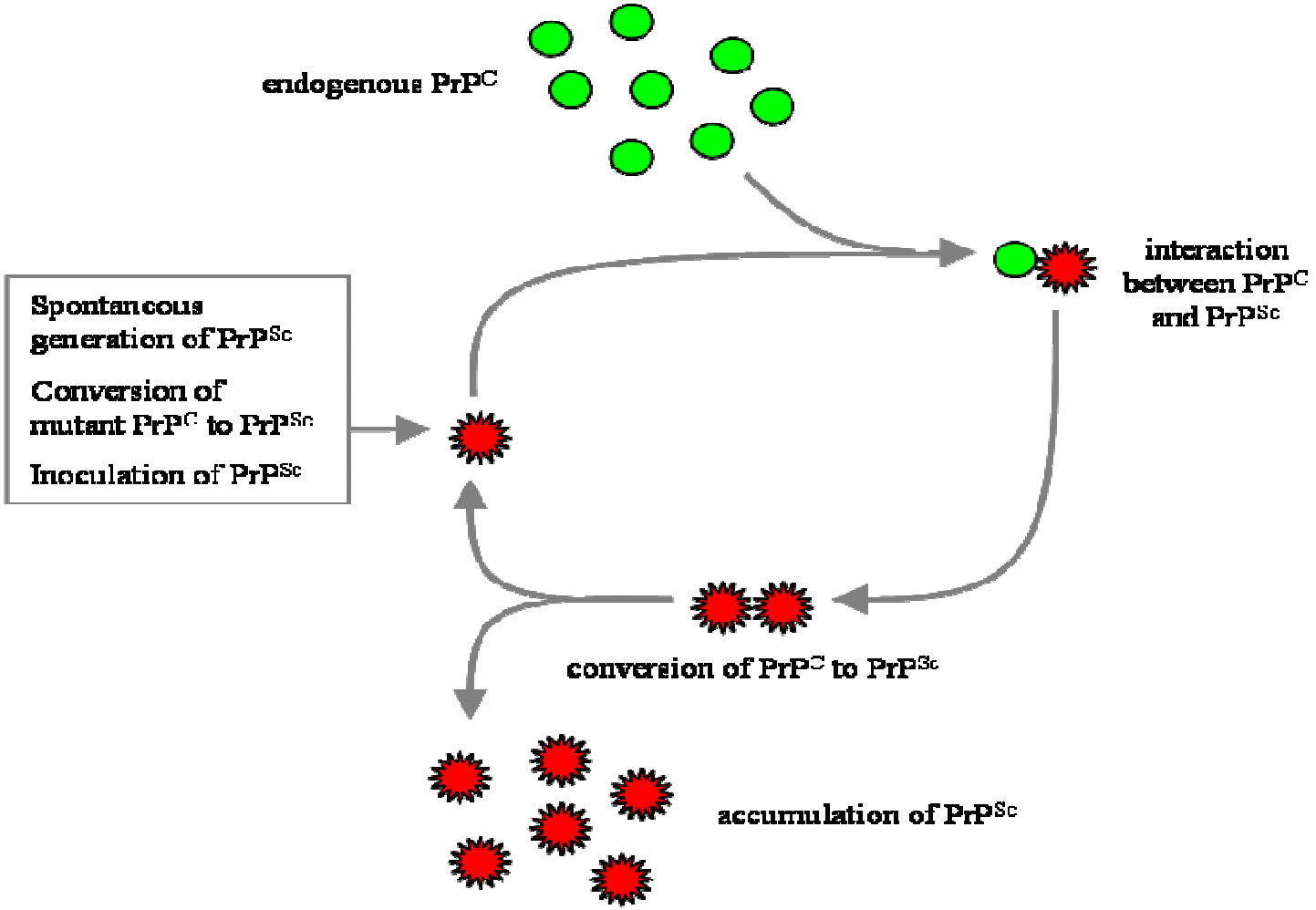
# Progress since 2007: *UnderstandingToxicity Pathways (Prion Diseases)*

# PrioNet Canada

- A Network of Centres of Excellence in Canada established in 2005 to respond to Canada's BSE crisis
- Budget of $35 million over seven years
- Five research themes
  - Bovine spongiform encephalopathy
  - Chronic wasting disease and scrapie
  - Creutzfeldt-Jakob disease
  - Prion protein structure and function
  - Prion disease risk management
- The Network of Centes of Excellence involve:
  - 60 principal investigators
  - 150 graduate students
  - 300+ attendees at the annual meeting
- International collaboration key to success

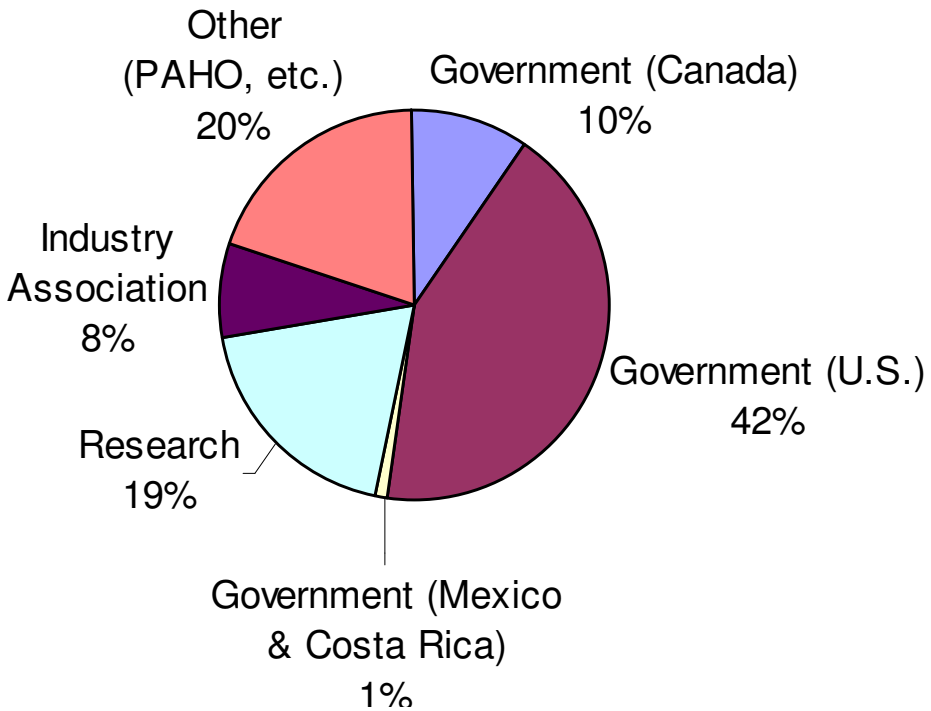
Neil Cashman
Scientific Director
*University of British Columbia*

# Prion Misfolding as a Toxicity Pathway



# International Collaboration

## Attendee Demographics




**Attendees = 50**

THE Environmental Forum

ADVANCING ENVIRONMENTAL PROTECTION THROUGH • ANALYSIS • OPINION • DEBATE

# A Shift to "Anticipate and Prevent"

DANIEL KREWSKI

The U.S. National Research Council's 1983 report *Risk Assessment in the Federal Government: Managing the Process* heralding the beginning of modern risk management. Although the fundamental principles of both risk assessment and risk management are now well-established, guidance provided by risk science is better suited to the assessment and management of well-known risks, such as those associated with toxic chemicals or infectious disease. Risk science is less well suited to deal with emerging risks issues, such as those posed by prion diseases, a broad class of rapidly progressive, untreatable, and fatal neurodegenerative syndromes. Prion diseases share a common cause or origin, based on a mis-folded version of a ubiquitous, normal protein that propagates by making copies of itself. The result is spongiform change (microcavitation) of the brain.

Looking to the future, an integrated approach to risk management may afford new opportunities to "anticipate and prevent" the spread of other animal prion diseases, such as chronic wasting disease, to humans. CWD is a new animal prion disease in North America, which has been diagnosed in both wild and captive cervids (deer and elk) in Canada in the United States. The risk posed by CWD to domestic ruminants (cattle and sheep) or caribou and moose is unknown, as is the risk to humans, although transmission to primates has been demonstrated experimentally. Learning from the BSE experience internationally may help to address this emerging prion disease risk issue in a proactive manner.

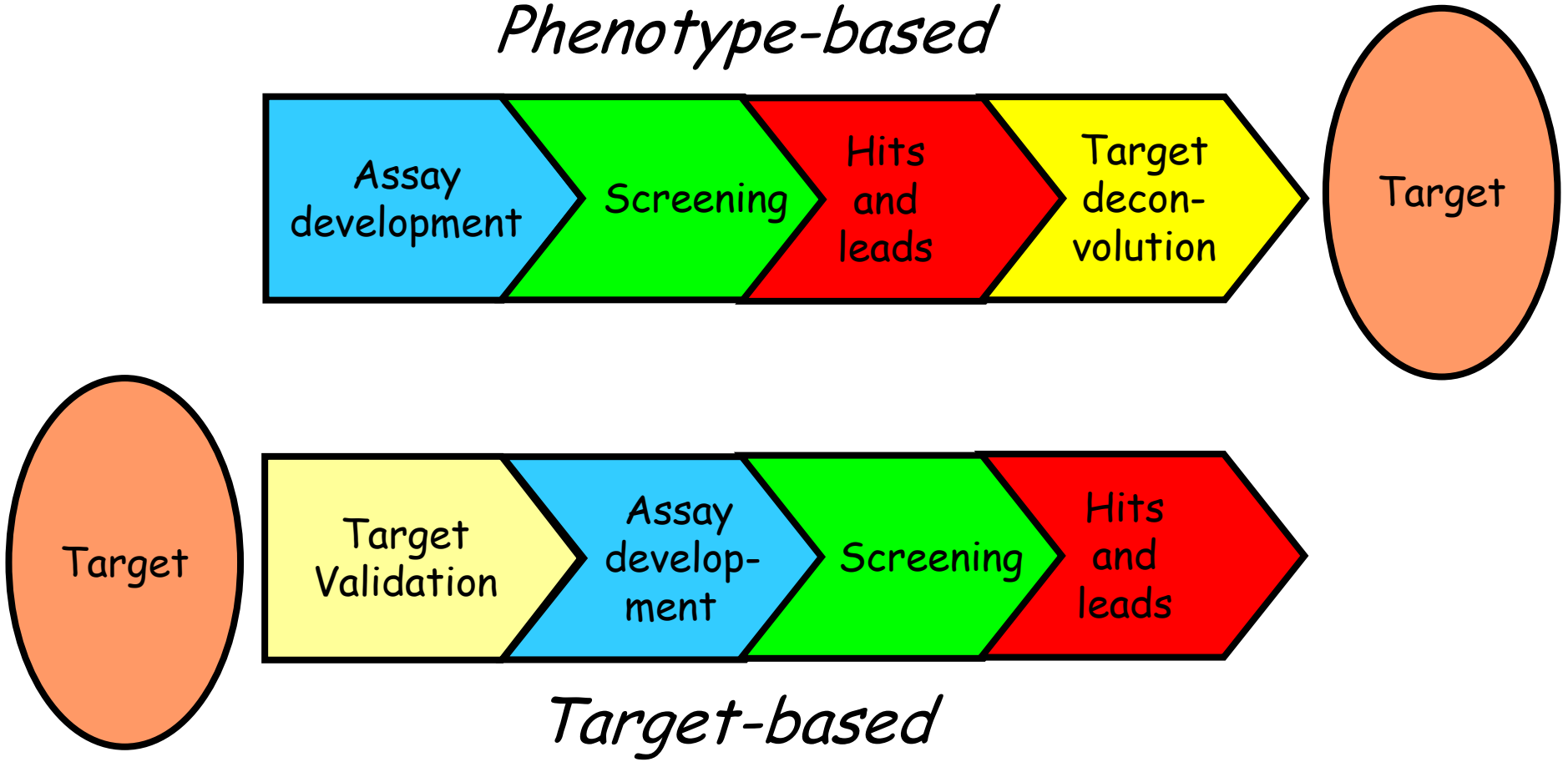
**Daniel Krewski**, Ph.D., M.PH., is Director of the R. Samuel McLaughlin Centre for Population Health Risk Assessment at the University of Ottawa.

# Progress since 2007:
# *Linkages to Pharmaceutical Risk Assessment*

# Applications in the Pharmaceutical Industry?

- Drug safety
- Drug efficacy

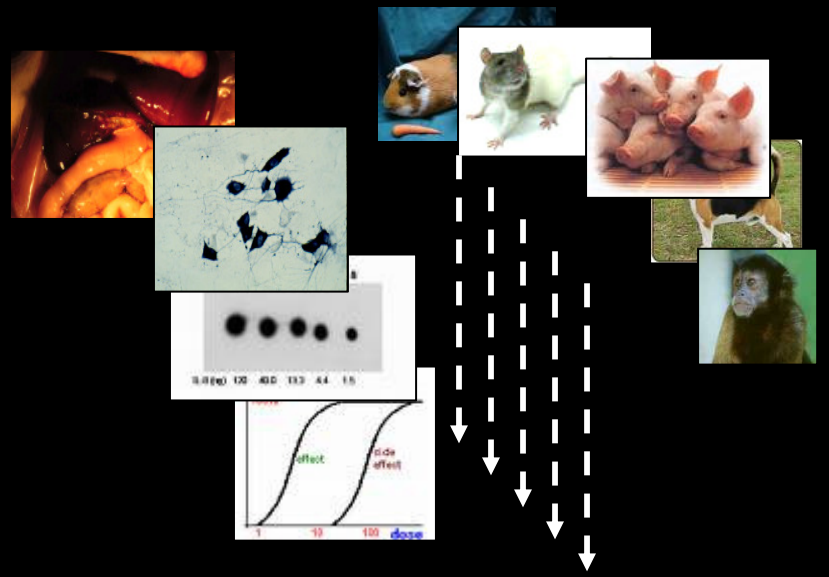
# Applications in Drug Design




[Adapted from: Terstappen, Schulpen, Raggiaschi & Gaviraghi (2007), Nature Reviews/Drug Discovery, 6, 891-903]

# *Linking Population Based and Laboratory Studies*

Pharmacovigilance | Pharmacotoxicology




Understand biological mechanisms of suspected ADRs

Investigate toxicological effects of drugs under real world conditions

# Progress since 2007:
# *Building the Science Base*

# Toxicity Testing Literature Search Criteria Example: High-throughput Screening

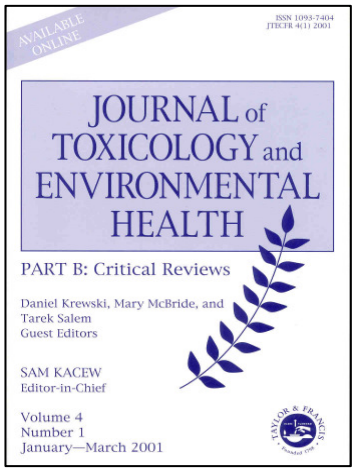
- (toxicity **OR** toxicology **OR** toxicity testing)
- AND (2000-2009)
- AND (high-throughput screens OR high-throughput in vitro screens)

# Review Papers on Selected Topics, 2000-2009

| Number | Topic | Medline | Scifinder |
|---|---|---|---|
| 1 | High-throughput in vitro screening | 2 | 32 |
| 2 | Stem cell biology | 6 | 71 |
| 3 | Functional genomics | 33 | 285 |
| 4 | Bioinformatics | 36 | 215 |
| 5a | Systems biology | 12 | 318 |
| 5b | Systems toxicology | 3 | 298 |
| 6 | Computational systems biology | 1 | 11 |
| 7 | Physiologically based pharmacokinetic models | 0 | 53 |
| 8a | Structure-activity relationships | 95 | 263 |
| 8b | Quantitative structure-activity relationships | 109 | 330 |
| 9 | Computational toxicology | 9 | 122 |
| 10 | Computational biology | 64 | 151 |
| 11a | Biomarkers | 53 | 201 |
| 11b | Exposure biomarkers | 0 | 344 |
| 11c | Susceptibility biomarkers | 0 | 70 |
| 11d | Effect biomarkers | 1 | 201 |

# 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:** 15+ individual contributions on future directions in toxicity testing



# Progress since 2007:
# *Regulatory Applications*

Council of Canadian Academies
Conseil des académies canadiennes


# Expert Panel

# on the

# Integrated Testing of Pesticides

Council of Canadian Academies
Conseil des académies canadiennes

# Integrated Testing

*"Integrated testing, using in vitro data from diverse fields of study, represents an exciting means by which we can refine and reduce in vivo toxicity testing requirements. By this approach, it may be possible to avoid the need for full batteries of animal-based toxicity tests for each pesticide under assessment, while still maintaining defensibility of the assessments."*

Council of Canadian Academies
Conseil des académies canadiennes

# Assessment Questions

1. What is the current status of the use of integrated testing strategies for the risk assessment of pesticides, pharmaceuticals, industrial chemicals and other chemical substances by regulatory agencies around the world?
2. What is the state of the science of the tools and data sources associated with integrated testing strategies?
3. Could there be potential impacts on the public's perception and confidence in regulatory risk assessment and risk management decisions for pesticides if integrated testing strategies were implemented?

http://www.scienceadvice.ca/pesticides.html

# Progress since 2007:
# *Implementing the Vision*

# Symposium on International Implications of the U.S. National Research Council Report on Toxicity Testing in the 21st Century: Challenges and Opportunities in Implementation

**University of Ottawa,**
**Desmarais Building,**
**55 Laurier St. East, Room 1150**
**June 29-30, 2009**

The Johns Hopkins Bloomberg School of Public Health, Center for Alternatives to Animal Testing (Baltimore, Maryland, USA) and the McLaughlin Centre for Popultion Health Risk Assessment at the University of Ottawa organized this symposium, which examined from an international perspective the scientific, risk assessment and implementation challenges and opportunities generated by the vision contained in the US National Research Council's Toxicity Testing report.

http://www.mclaughlincentre.ca/events/toxicity/index.shtml