# NexGen Risk Assessment

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&
Risk Sciences International

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Université d'Ottawa | University of Ottawa

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## 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.

**III) Science and Decisions: Advancing Risk Assessment (NRC, 2009)** describes new methods and approaches for human health risk assessment.

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

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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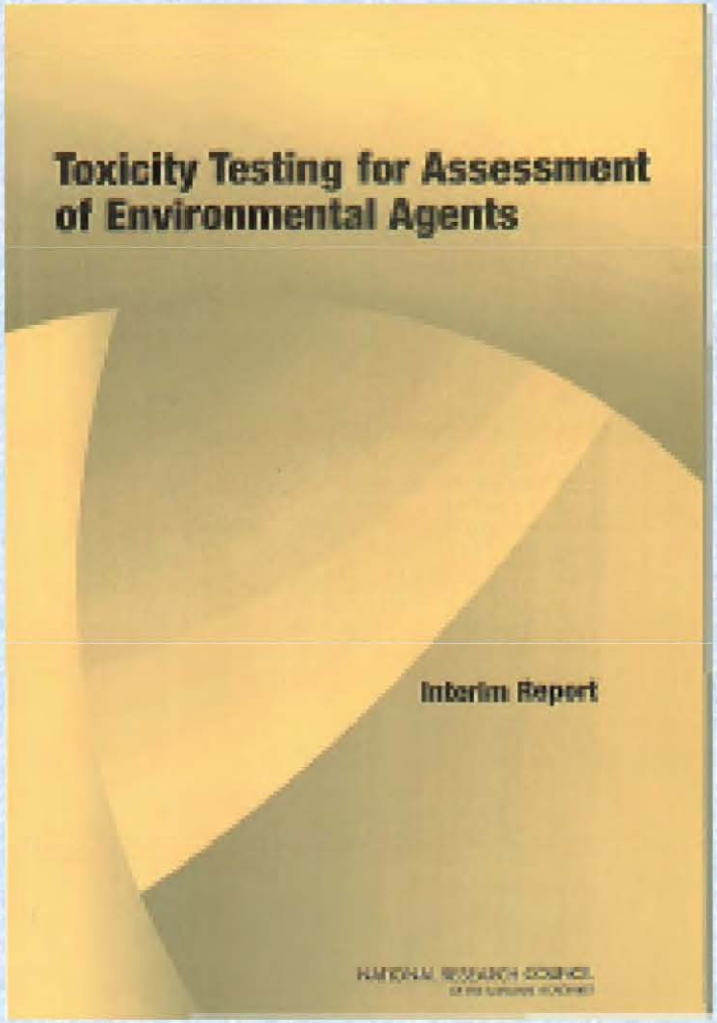
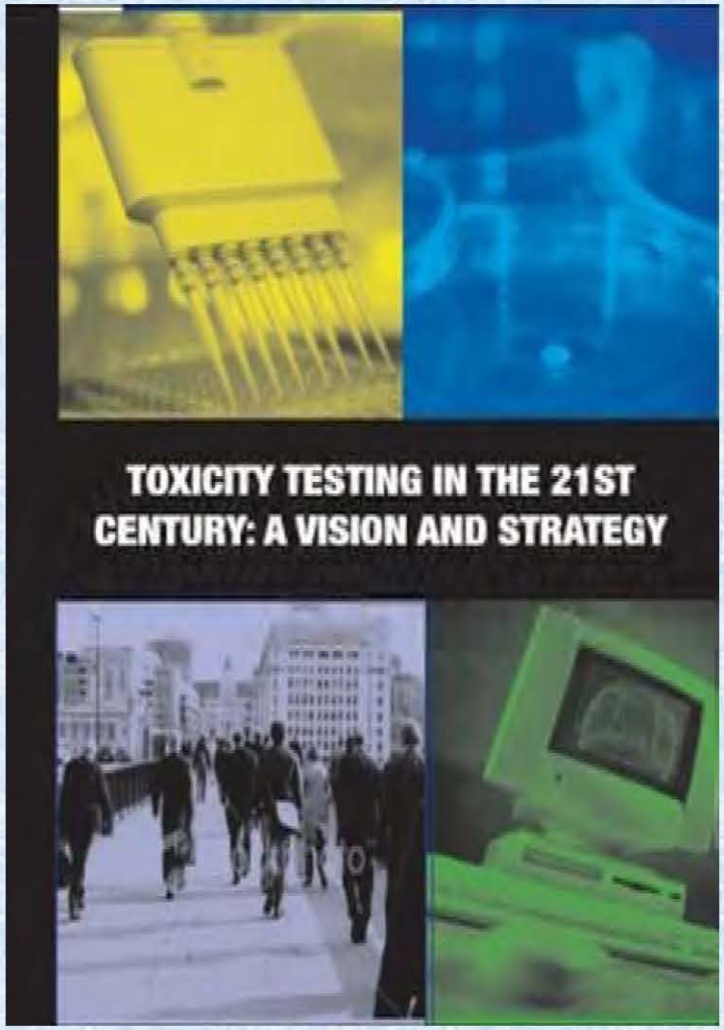
# Interim and Final Reports




www.nas.edu

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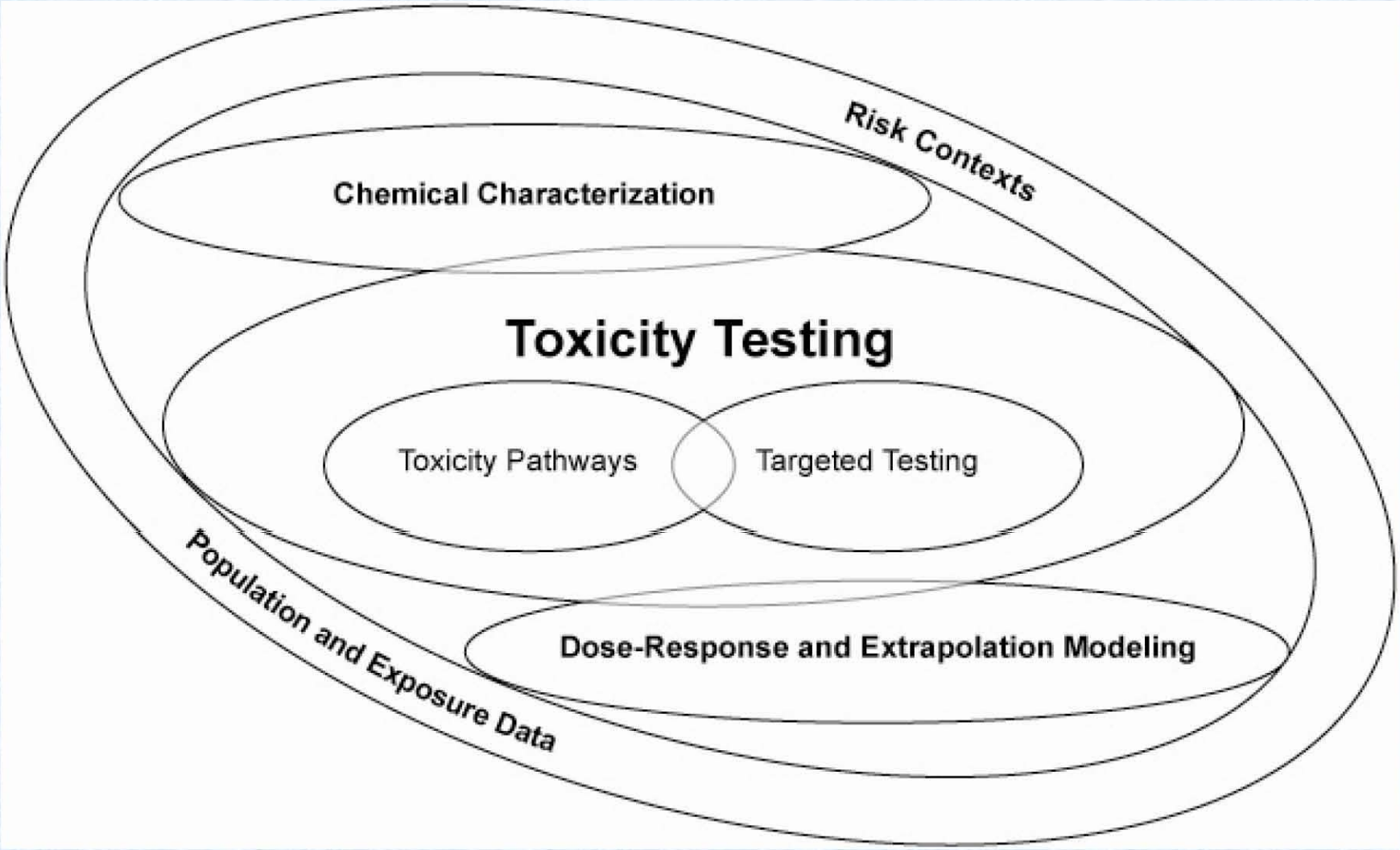
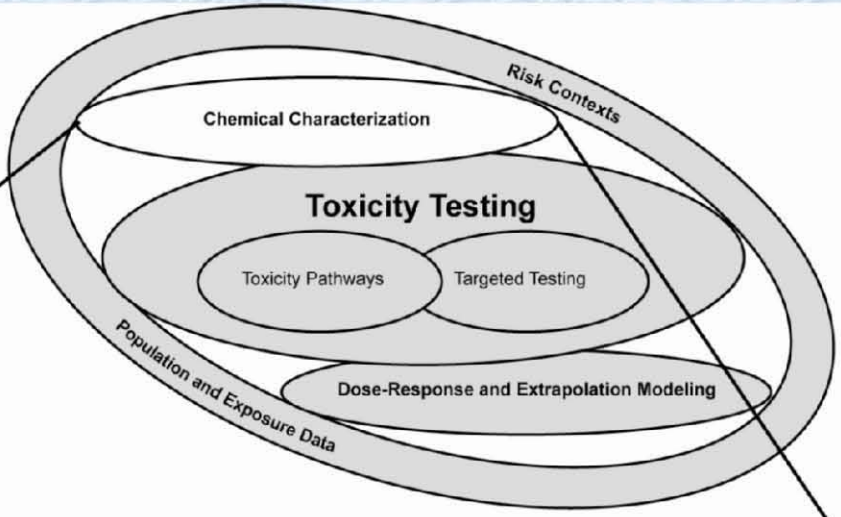
# Components of the Vision



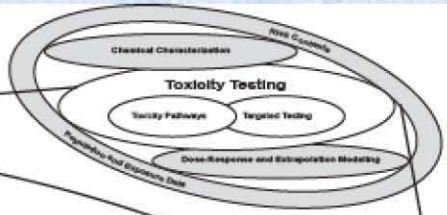
# Chemical Characterization




## Chemical Characterization

- Compile data on physical and chemical properties, use characteristics, environmental concentrations, possible metabolites and breakdown products, and possible toxic properties.
- Predict properties and characteristics, where possible and appropriate, by using computational tools.
- Answer key questions concerning compound's stability, potential for human exposure and bioaccumulation, and toxicity of chemical and possible metabolites.

# Toxicity Testing



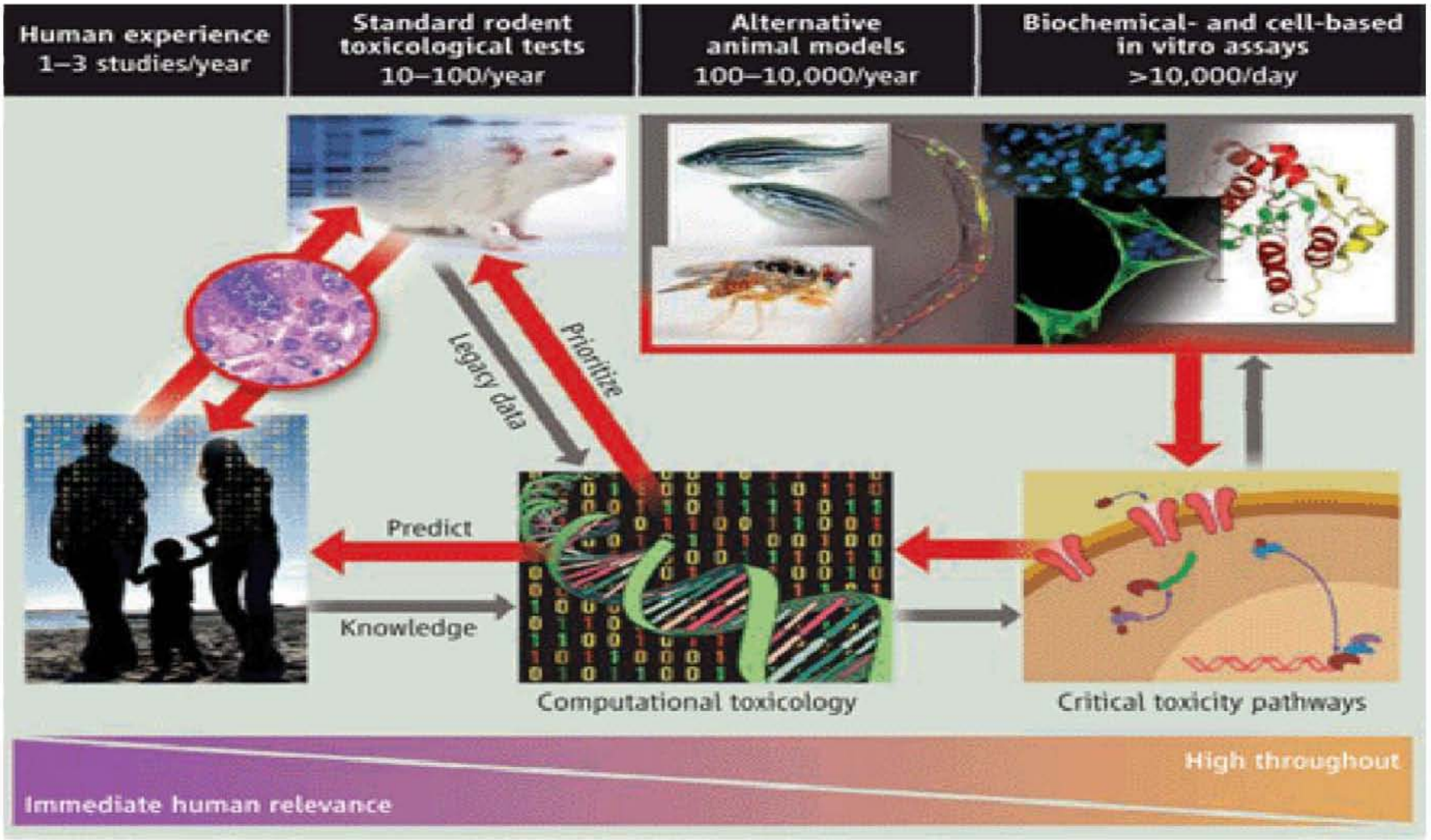

## Toxicity Pathways

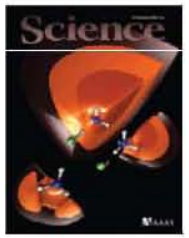
- Evaluation of perturbations in toxicity pathways rather than apical end points.
- Emphasis on high-throughput approaches using cells or cell lines, preferably of human origin.
- Use of medium-throughput assays of more integrated cellular responses.

## 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.

# Endorsement by the Scientific Community




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

# Reaction from Experts in Risk Assessment

*Risk Analysis, Vol. 29, No. 4, 2009* DOI: 10.1111/j.1539-6924.2008.01150.x

*Perspective*

## 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]**

"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

# Reaction from the Legal Community

## 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®

# Reaction from the Animal Law Community

## *International Symposia on Challenges and Opportunities in Implementation*

uOttawa — June 29-30, 2009

CENTER FOR ANIMAL LAW STUDIES AT LEWIS & CLARK — September 12, 2009

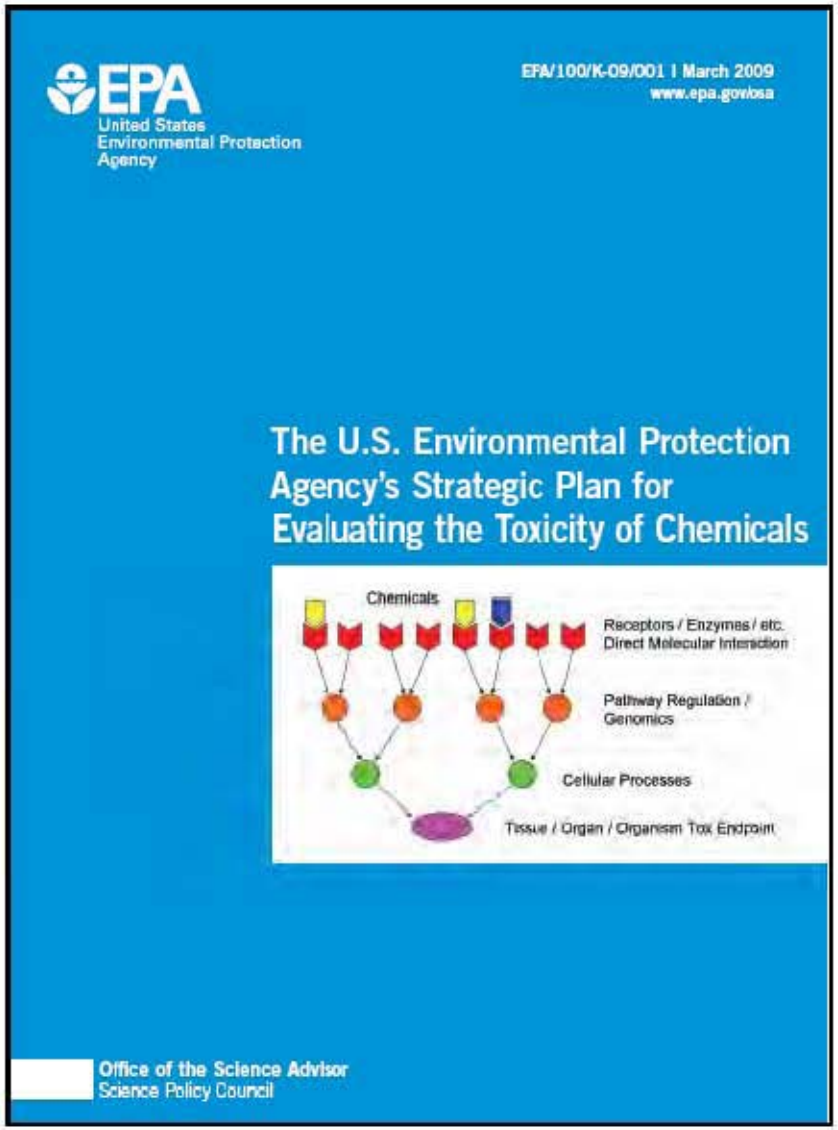
THE UNIVERSITY OF CHICAGO THE LAW SCHOOL — November 5, 2009

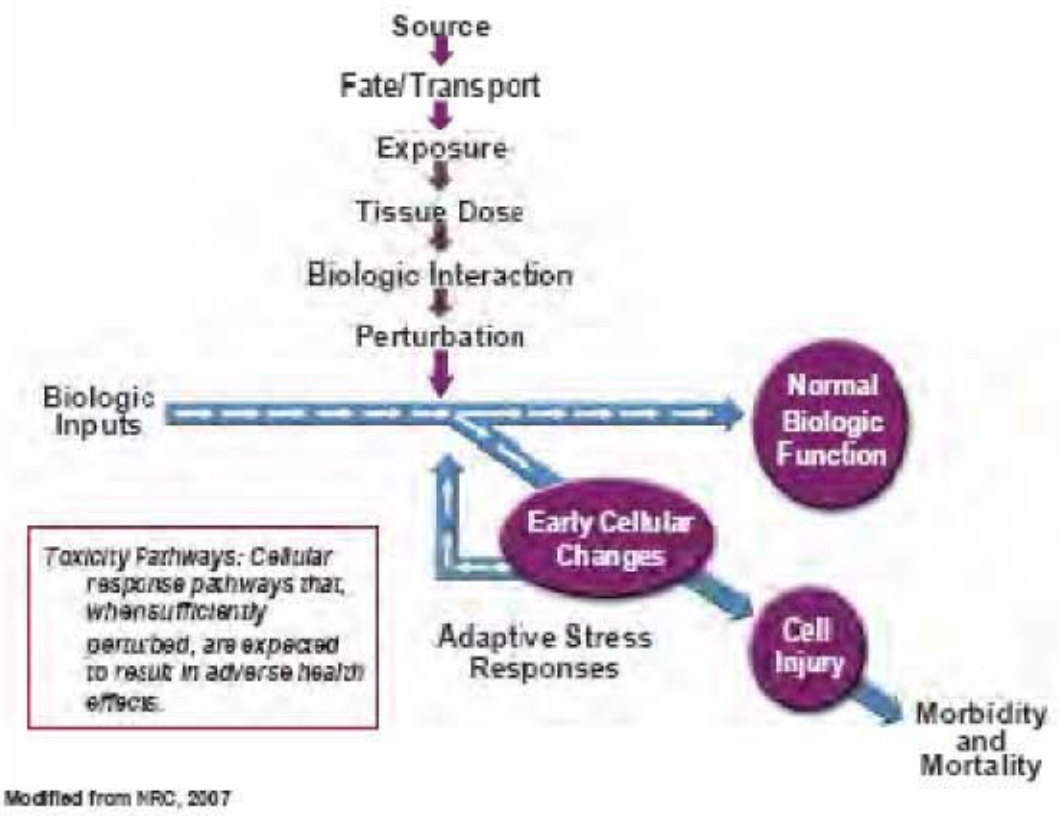
ENVIRONMENTAL LAW • INSTITUTE — June 21-23, 2010

"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

Tox21

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

NIEHS National Institute of Environmental Health Sciences

National Human Genome Research Institute

NCGC NIH Chemical Genomics Center

FDA

# TOX21

## New Dimensions of Toxicity Testing

On the ground floor of the National Institutes of Health Chemical Genomics Center (NCGC) in Rockville, Maryland, a $10-million automated laboratory spends all day and night screening chemicals at speeds no team of human researchers could ever match. In a week, depending on the nature of the assay, it can yield up to 2.2 million molecular data points derived from thousands of chemicals tested at 15 concentrations each.

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

*Schmidt CW (2009) TOX 21: new dimensions of toxicity testing. Environ Health Perspect 117: A348-A353*

Consortium Members

DOW

DUPONT The miracles of science

ExxonMobil

The Hamner Institutes for Health Sciences

THE HUMANE SOCIETY OF THE UNITED STATES

HUMANE SOCIETY INTERNATIONAL

HUMANE SOCIETY LEGISLATIVE FUND

Johnson & Johnson Pharmaceutical Research & Development L.L.C.

L'ORÉAL Research & Innovation

P&G

Unilever

Consortium Partners

CAAT JOHNS HOPKINS Center for Alternatives to Animal Testing

# 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**

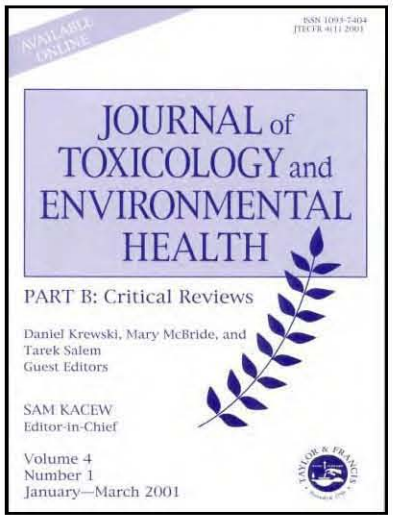
Serve as a catalyst for the prompt, global, and coordinated implementation of "21st Century" toxicology, which will better safeguard human health and hasten the replacement of animal use in toxicology.

**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)*

| 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 |

# Case Study Prototypes

| Tool | Lung Injury and Ozone | Developmental Impairment and Thyroid Hormone Disruptors | Cancer and Polycyclic Aromatic Hydrocarbons | Cancer and Benzene |
|---|---|---|---|---|
| High throughput screens | | ✓ | ✓ | |
| Stem cell biology | | | | |
| Functional genomics | ✓ | ✓ | ✓ | ✓ |
| Bioinformatics | ✓ | ✓ | ✓ | |
| Systems biology | ✓ | ✓ | ✓ | ✓ |
| Computational systems biology | ✓ | ✓ | | |
| Physiologically-based pharmacokinetic models and Dosimetry | ✓ | | | |
| Structure-activity relationships | ✓ | ✓ | ✓ | |
| Biomarkers | | ✓ | ✓ | ✓ |
| Molecular and genetic epidemiology | ✓ | | | ✓ |
| Exposure assessment | | | ✓ | |

# *Cornerstone #2: Population Health Risk Assessment*

Human and Ecological Risk Assessment, 13: 1288–1312, 2007

ISSN: 1080-7039 print / 1549-7680 online
DOI: 10.1080/10807030701655798

# An Integrated Framework for Risk Management and Population Health

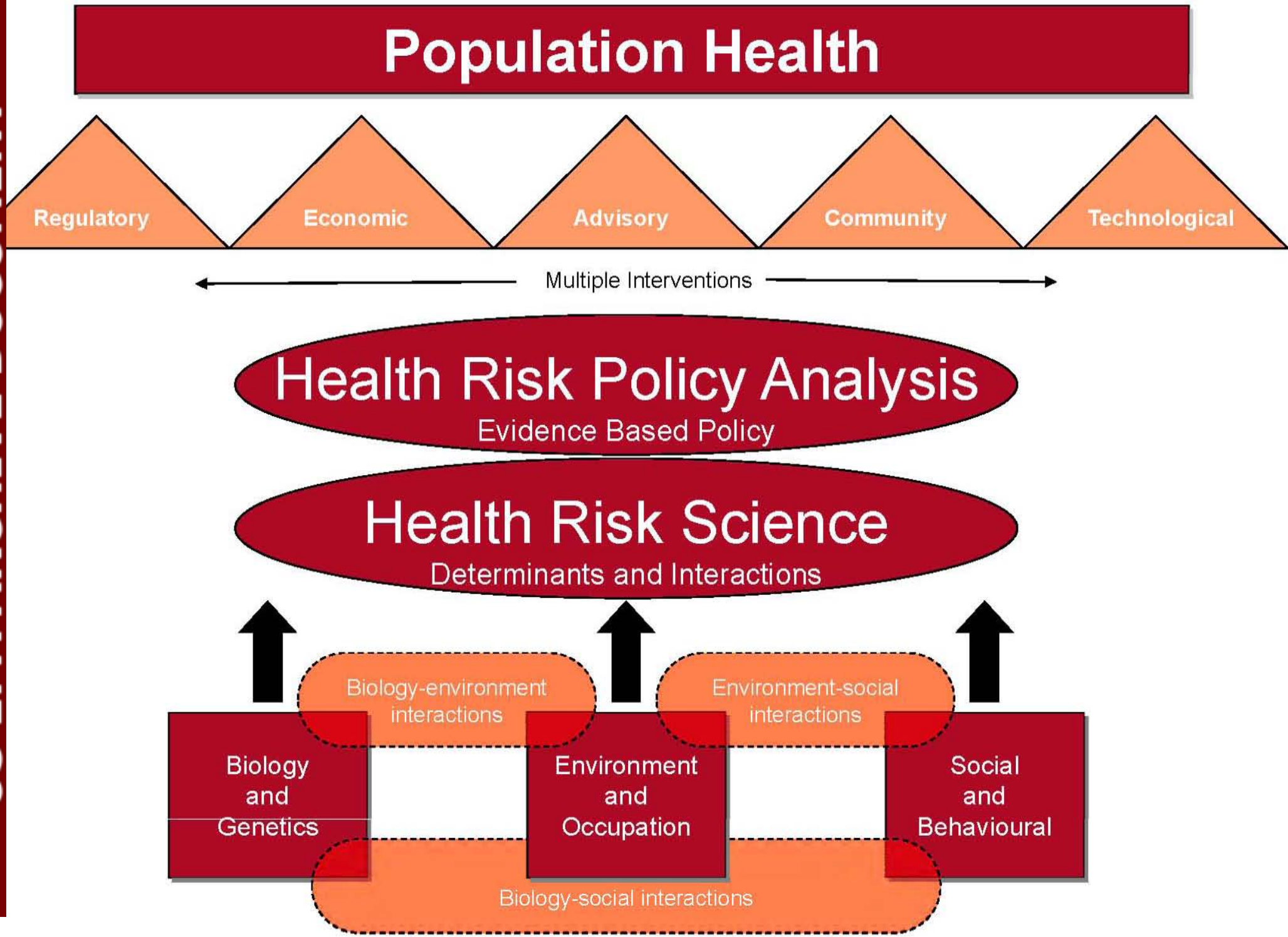
**Daniel Krewski,[1,2] Victoria Hogan,[1] Michelle C. Turner,[1] Patricia L. Zeman,[1] Ian McDowell,[2,3] Nancy Edwards,[2,3,4] and Joseph Losos[3]**
[1]McLaughlin Centre for Population Health Risk Assessment, Institute of Population Health, University of Ottawa, Ottawa, ON, Canada; [2]Department of Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada; [3]Institute of Population Health, University of Ottawa, Ottawa, ON, Canada; [4]School of Nursing, Faculty of Health Sciences, University of Ottawa, Ottawa, ON, Canada

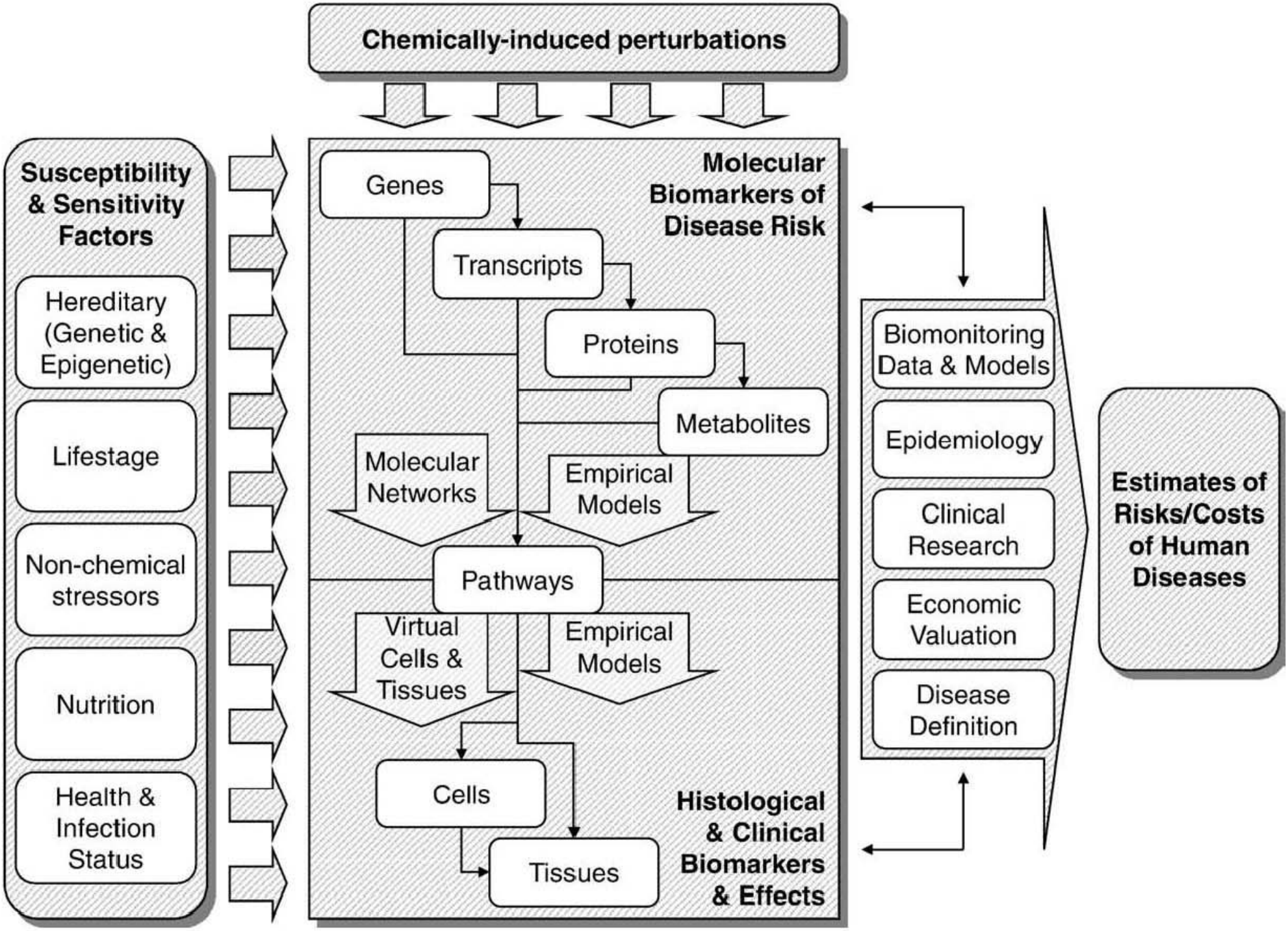
# What is "Population Health Risk Assessment"?

***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*.**






*Chiu, W.A., et al., Approaches to advancing quantitative human health risk assessment of environmental chemicals in the post-genomic era, Toxicol. Appl. Pharmacol. (2010), doi:10.1016/j.taap.2010.03.019*

# *Cornerstone #3: Science and Decisions: Advancing Risk Assessment*

# KEY MESSAGES


- Enhanced framework
- Formative focus
- Four steps still core
- Matching analysis to decisions
- Clearer estimates of population risk
- Advancing cumulative assessments
- People and capacity building

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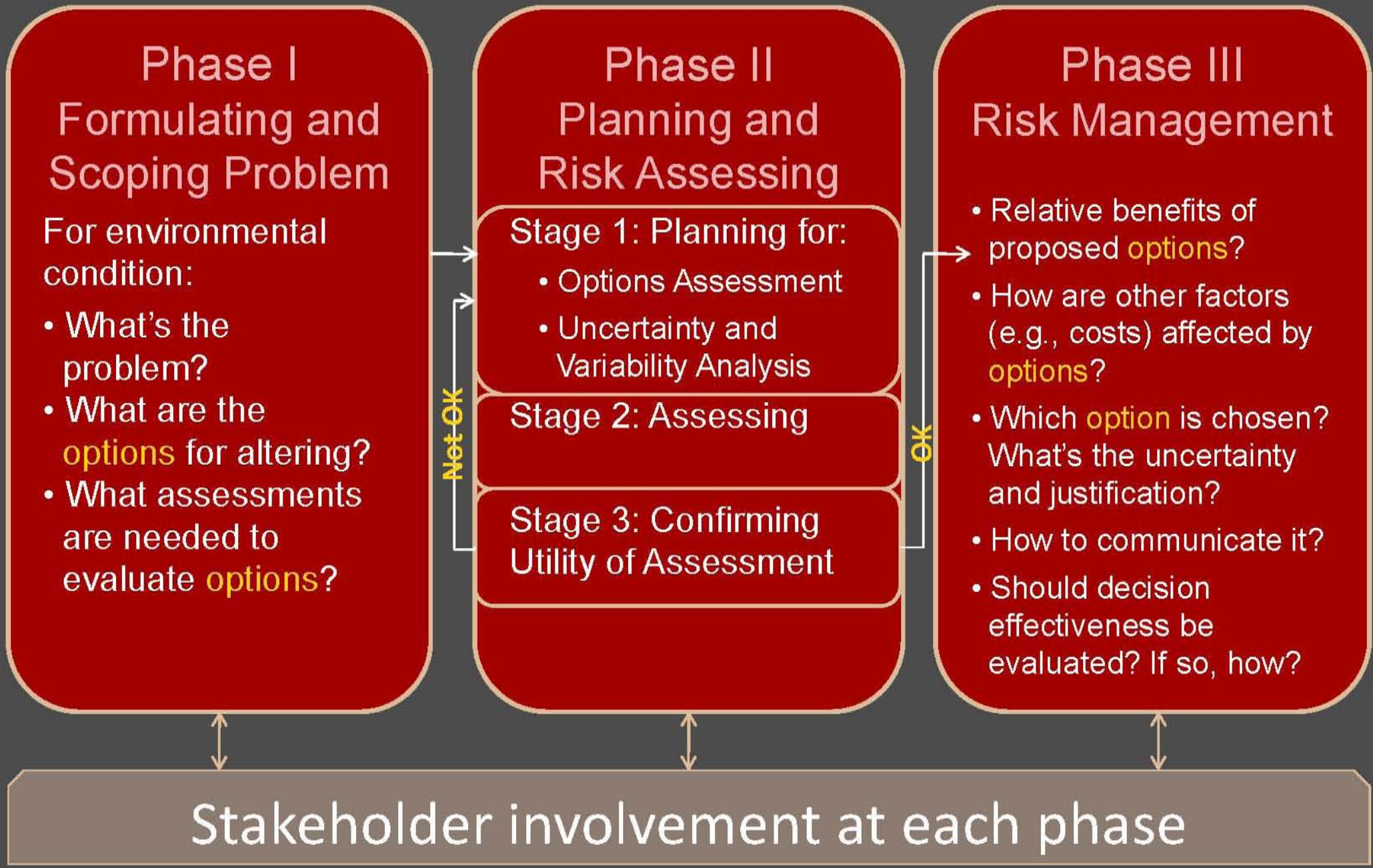
# "Risk-Based Decision-Making" Framework



*Original Editorial*

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

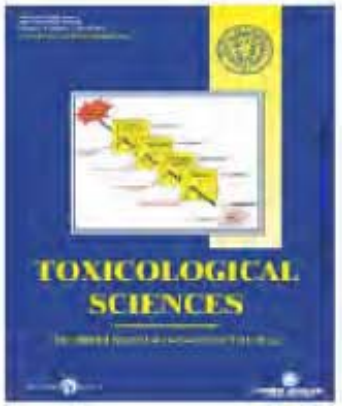
Received July 3, 2008; accepted November 6, 2008

*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







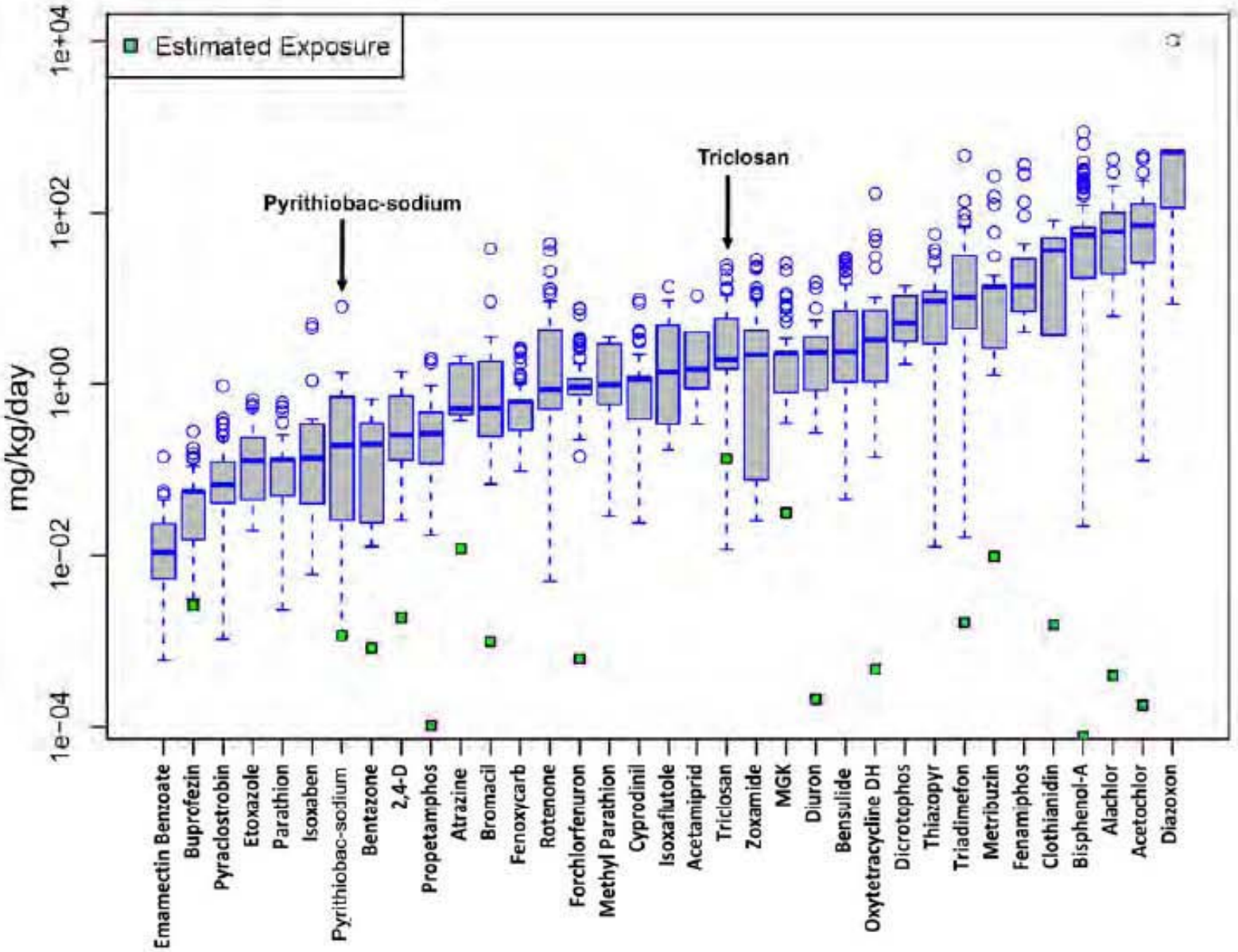
Adapted from Boekelheide and Campion, Toxicol. Sci., 2010.

TOXICOLOGICAL SCIENCES 117(2), 348–358 (2010)
doi:10.1093/toxsci/kfq220
Advance Access publication July 16, 2010

# Incorporating Human Dosimetry and Exposure into High-Throughput *In Vitro* Toxicity Screening

Daniel M. Rotroff,*† Barbara A. Wetmore,‡ David J. Dix,* Stephen S. Ferguson,§ Harvey J. Clewell,‡ Keith A. Houck,* Edward L. LeCluyse,§ Melvin E. Andersen,‡ Richard S. Judson,* Cornelia M. Smith,§ Mark A. Sochaski,‡ Robert J. Kavlock,* Frank Boellmann,‡ Matthew T. Martin,* David M. Reif,* John F. Wambaugh,* and Russell S. Thomas‡,[1]

*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




*Rotroff DM, Wetmore BA, Dix DJ, Ferguson SS, Clewell HJ, Houck KA, Lecluyse EL, Andersen ME, Judson RS, Smith CM, Sochaski MA, Kavlock RJ, Boellmann F, Martin MT, Reif DM, Wambaugh JF, Thomas RS (2010) Incorporating human dosimetry and exposure into high-throughput in vitro toxicity screening. Toxicol Sci 117: 348-358*

# **Table 4**. Potential Modifications of Risk Assessment Approaches in a NexGen Context

| Risk Issue | Current Approach | NexGen Approach |
|---|---|---|
| **Defining Adversity** | Adversity is presently defined in terms of observation of apical endpoints in mammalian systems. | 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. |

# **Table 4**. Potential Modifications of Risk Assessment Approaches in a NexGen Context

| Risk Issue | Current Approach | NexGen Approach |
|---|---|---|
| **Default assumptions** | 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. | 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). |

# 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)

*Background Paper #2*

# Towards a Framework for Next Generation Health Risk Assessment

McLaughlin Centre for Population Health Risk Assessment

uOttawa


# New Directions in Toxicity Testing

Daniel Krewski,[1] Margit Westphal,[1] Mustafa Al-Zoughool,[1] Maxine C. Croteau,[1] and Melvin E. Andersen[2]

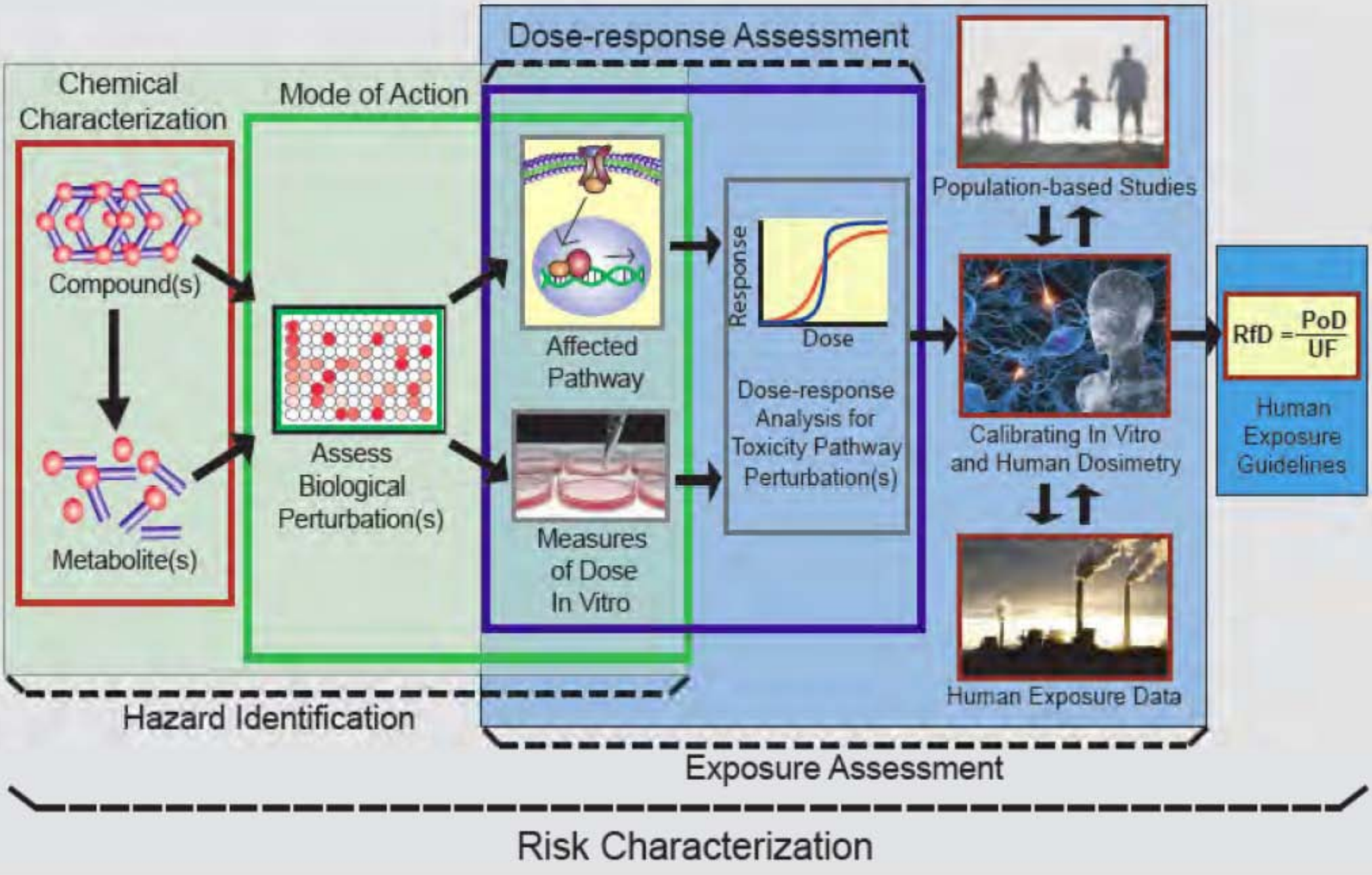
[1]McLaughlin Center for Population Health Risk Assessment, University of Ottawa, Ottawa, Ontario, Canada K1N 6N5; email: dkrewski@uottawa.ca, mgeister@uottawa.ca, malzough@uottawa.ca, mcroteau@uottawa.ca

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

*To appear in Annual Review of Public Health (2011)*

# Toxicity Testing and Risk Assessment

*(from Krewski et al., 2011, Annual Review of Public Health, in press)*



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