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

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Welcome from Canada . . .

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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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Committee Roster

Daniel Krewski (*Chair*), University of Ottawa, Ottawa, ON
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
Sidney Green, Howard University, Washington, DC
Karl Kelsey, Harvard University, Boston, MA
Nancy Kerkvliet, Oregon State University, Corvallis, OR
Abby Li, Exponent, Inc.**,** San Francisco, CA
Lawrence McCray, Massachusetts Institute of Technology, Cambridge MA
Otto Meyer, Danish Institute for Food and Veterinary Research, Søborg, Denmark
D. Reid Patterson, Reid Patterson Consulting, Inc., Grayslake, IL
William Pennie, Pfizer, Inc., Groton, CT
Robert Scala, Exxon Biomedical Sciences (Ret.), Tucson, AZ
Gina Solomon, Natural Resources Defense Council, San Francisco, CA
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

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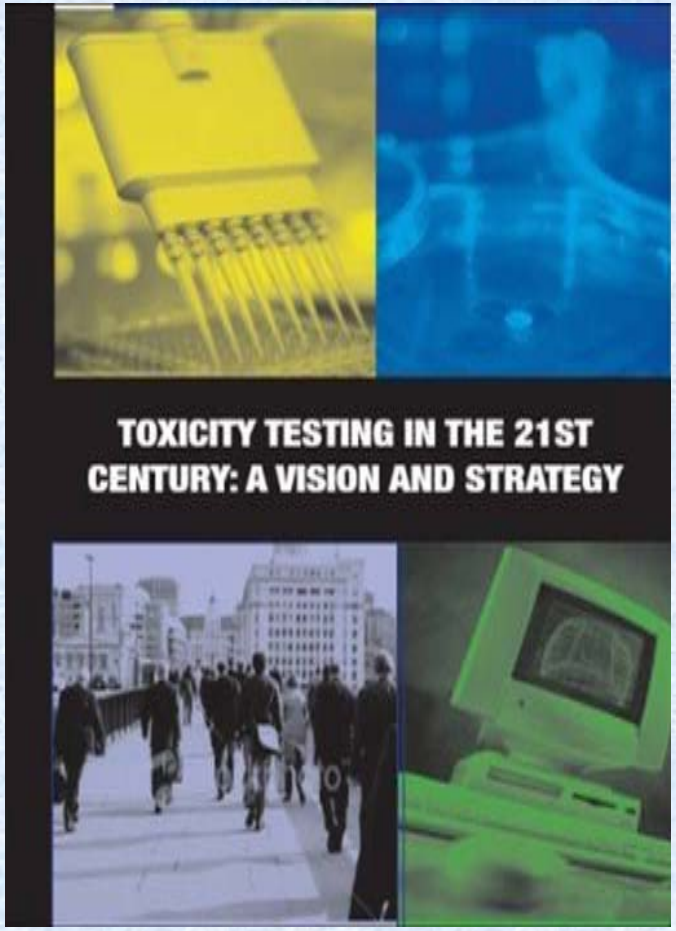
NRC Report (2007)



- Develop efficient, high throughput testing strategies to assess the potential health risks of large numbers of environmental agents to which people may be exposed
- Exploit scientific advances in biology and toxicology to achieve risk assessments that are more relevant to human populations

www.nas.edu

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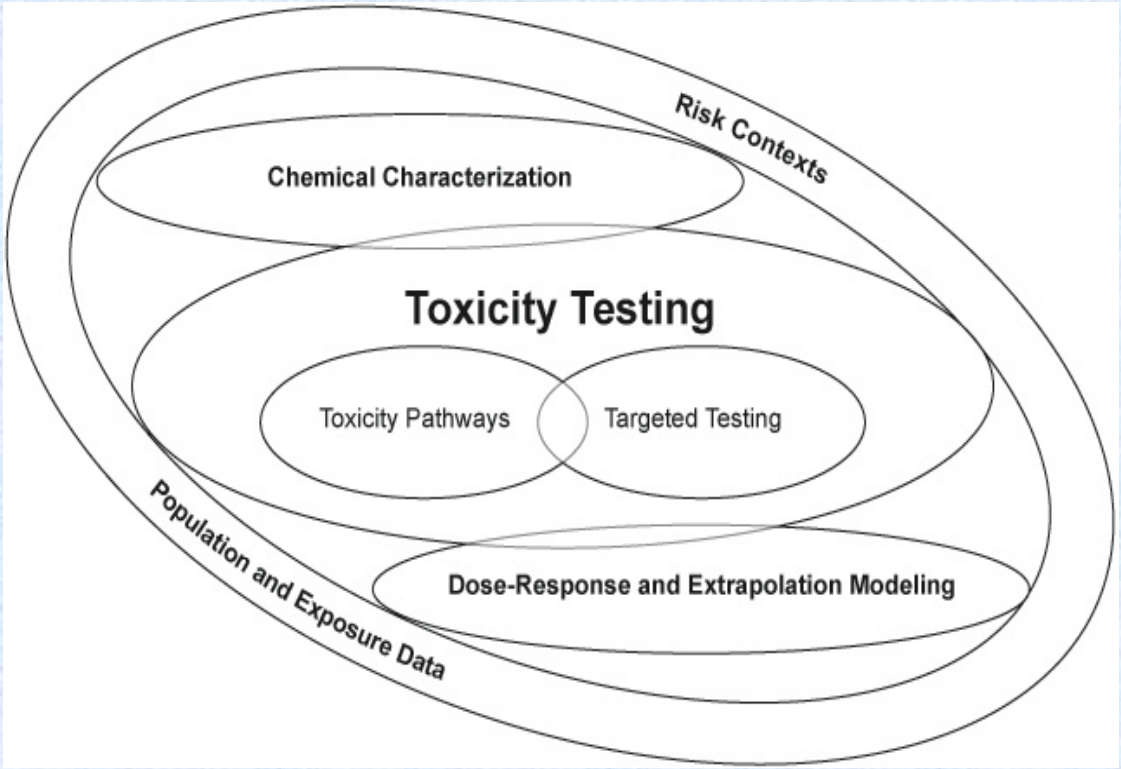
Perturbation of Toxicity Pathways

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

Components of the Vision



Computational toxicology

In vitro tests

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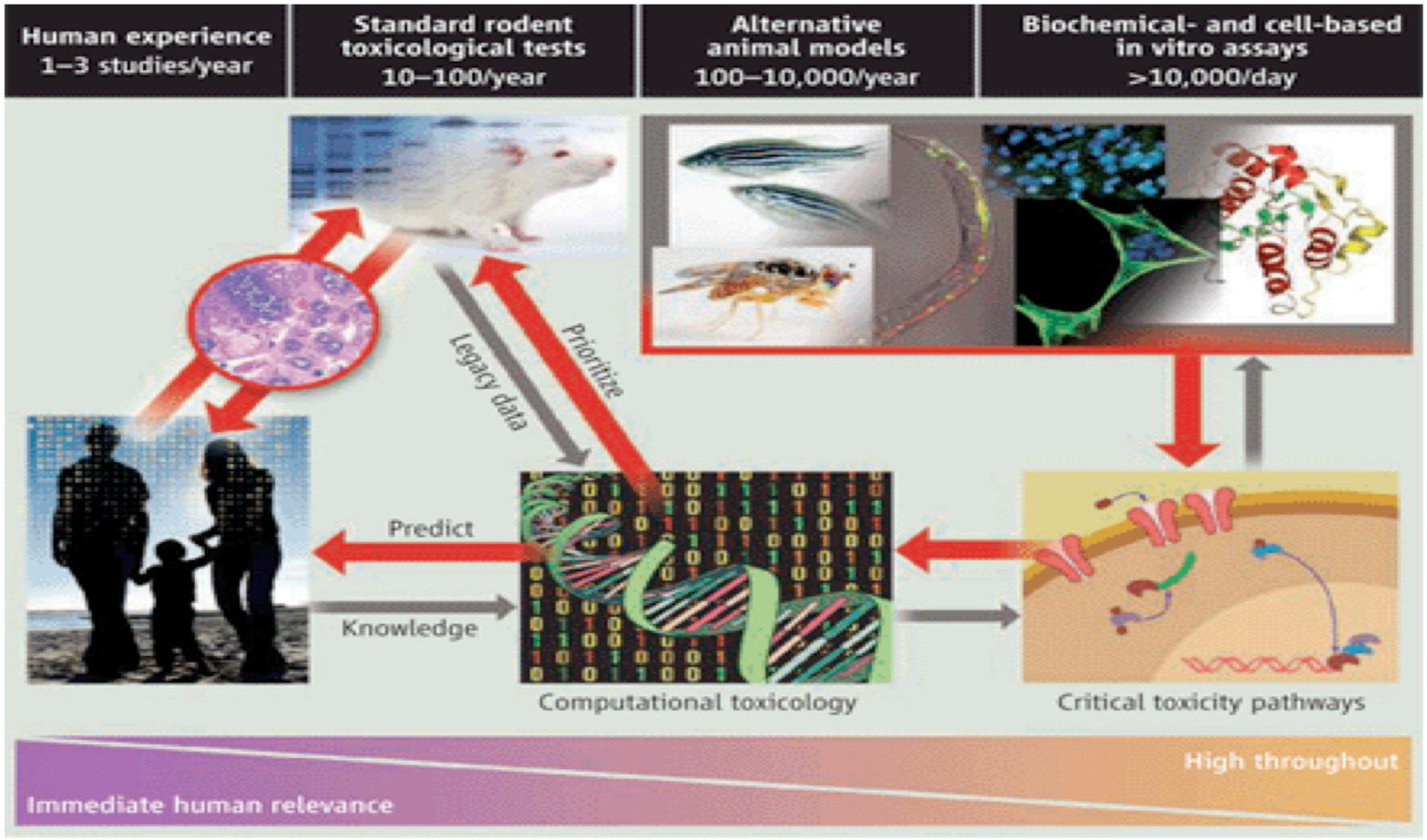
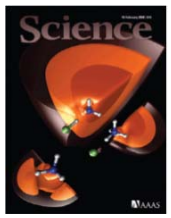
Progress since 2007

Endorsement by the Scientific Community





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

Further Debate
Within the Scientific Community

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†

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Received July 3, 2008; accepted November 6, 2008

Development of Scientific Toolbox

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

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

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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

June 29-30, 2009

September 12, 2009

November 5, 2009

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

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

Federal Agency Commitment

MEMORANDUM OF UNDERSTANDING

ON

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

BETWEEN THE

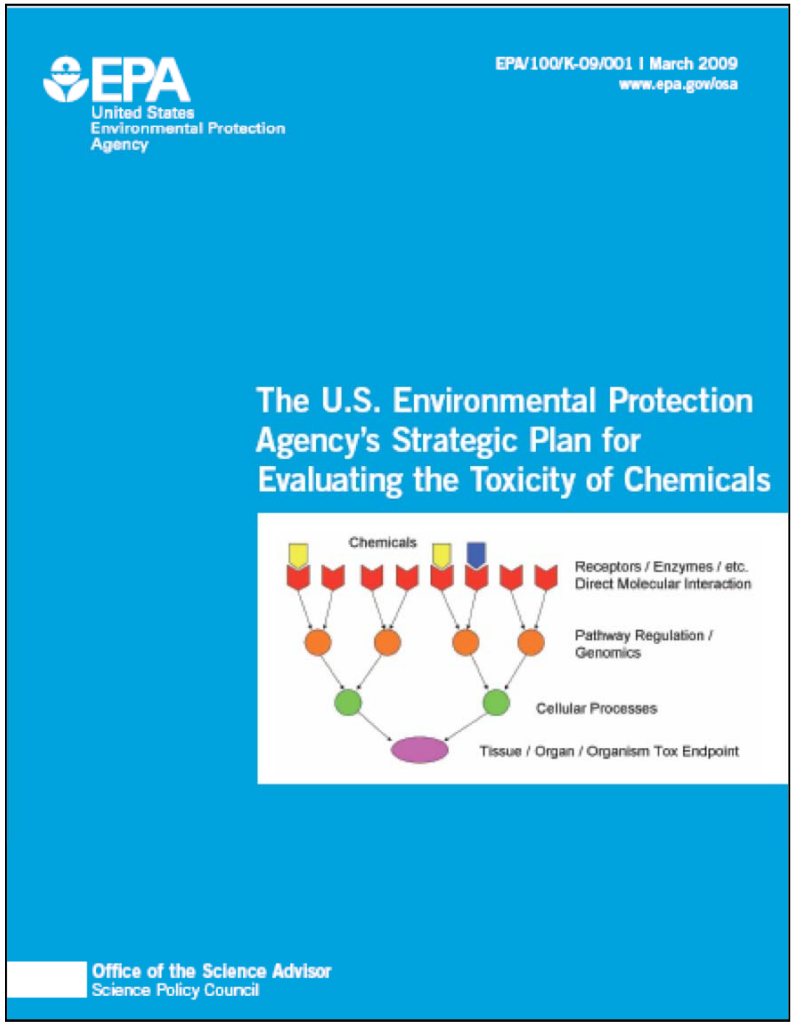
U.S. DEPARMENT OF HEALTH AND HUMAN SERVICES (HHS)
NATIONAL INSTITUTES OF HEALTH (NIH)
National Institutes of Environmental Health Sciences (NIEHS)/
National Toxicology Program (NTP)

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



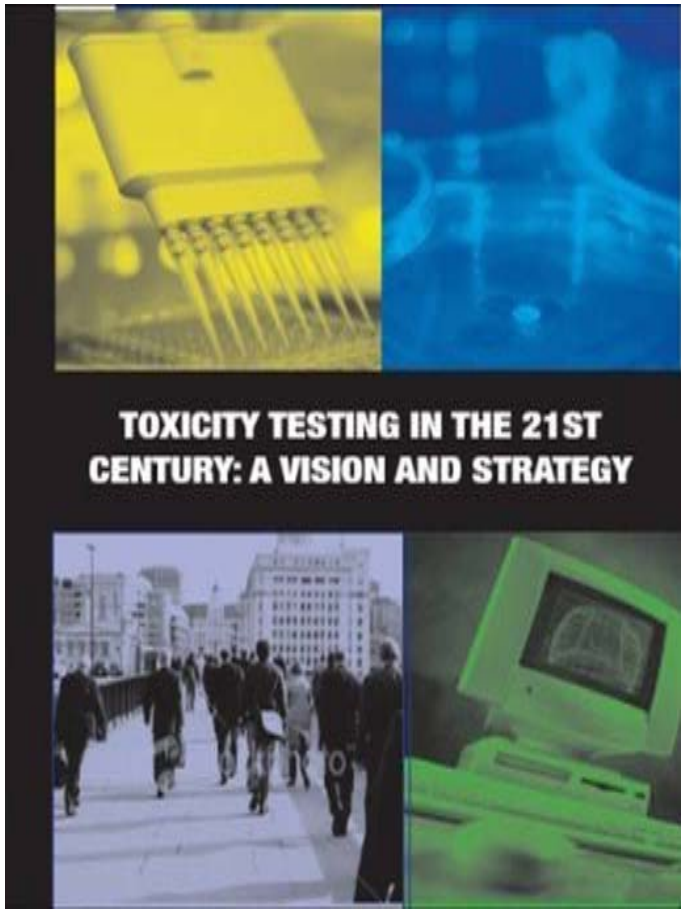
http://www.epa.gov/osa/spc/toxicitytesting/docs/toxtest_strategy_032309.pdf

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. EPA, 2009

Dual Motivation for Change



Better Science

Animal Welfare

Council of Canadian Academies
Conseil des académies canadiennes

Expert Panel on the Integrated Testing of Pesticides

"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."

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

Future Directions in the European Union

"This convergence of factors, coupled with the need to evaluate the safety of an increasingly large number of chemicals and their mixtures, has prompted some of the world's leading scientific authorities to call for a fundamental paradigm shift in toxicology . . . ."

http://cordis.europa.eu/documents/documentlibrary/106691831EN6.pdf

BEST

Board on Environmental Studies and Toxicology

Human and Environmental Exposure Science in the 21st Century

"An NRC committee will develop a long-range vision for exposure science . . . . It will include development of a unifying conceptual framework for advancement of exposure science to study and assess human and ecological contact with chemical, biological, and physical stressors in their environments. concern. The committee's report will be a potential companion document to previous NRC reports such as Toxicity Testing in the 21st Century."

http://www8.nationalacademies.org/cp/projectview.aspx?key=49180

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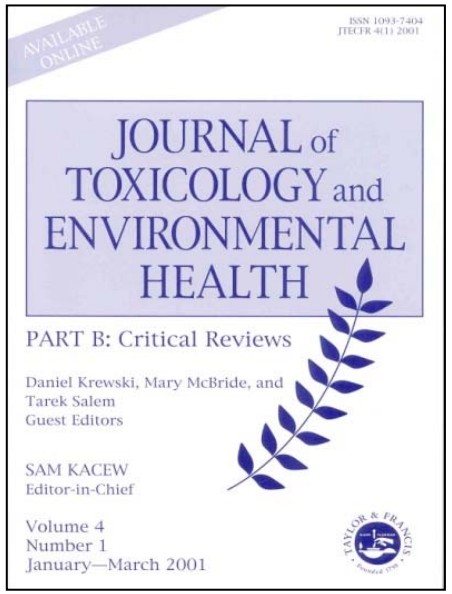
JTEH Special Issue on Future Directions in Toxicity Testing

- **Part A**: NRC Report on Toxicity Testing in the 21st Century (reprinted with permission)
- **Part B**: U.S. EPA Strategic Plan for Toxicity Testing (reprint)



- **Part C**: 12+ individual contributions on future directions in toxicity testing

Making the Vision a Reality

- Establishment of the science base on which the NRC vision rests
- Consideration of the implications of the vision for application of current and future regulatory statutes
- Re-orientation of risk assessment practice to focus on prevention of perturbation of toxicity pathways
- National/international coordination, and mid-course corrections over the next 5 – 10 years