THE NATIONAL ACADEMIES
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 tests on laboratory animals are conducted to evaluate chemicals—including medicines, food additives, and industrial, consumer, and agricultural chemicals—for their potential to cause cancer, birth defects, and other adverse health effects. Information from toxicity testing serves as an important part of the basis for public health and regulatory decisions concerning toxic chemicals. Current test methods were developed incrementally over the past 50 to 60 years and are conducted using laboratory animals, such as rats and mice. Using the results of animal tests to predict human health effects involves a number of assumptions and extrapolations that remain controversial. Test animals are often exposed to higher doses than would be expected for typical human exposures, requiring assumptions about effects at lower doses or exposures. Test animals are typically observed for overt signs of adverse health effects, which provide little information about biological changes leading to such health effects. Often controversial uncertainty factors must be applied to account for differences between test animals and humans. Finally, use of animals in testing is expensive and time consuming, and it sometimes raises ethical issues.

Today, toxicological evaluation of chemicals is poised to take advantage of the on-going revolution in biology and biotechnology. This revolution is making it increasingly possible to study the effects of chemicals using cells, cellular components, and tissues—preferably of human origin—rather than whole animals. These powerful new approaches should help to address a number of challenges facing the

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field of toxicity testing. New tests should illuminate changes at the molecular level, helping scientists to better predict how chemical exposures do or do not lead to certain health effects and how they affect sensitive populations such as children. They should enable rapid screening of chemicals, which could reduce the backlog of the large number of industrial chemicals that have not yet been evaluated under the current testing system. They should also reduce animal use and suffering.

The U.S. Environmental Protection Agency (EPA), recognizing that the time has come for more innovative approaches to toxicity testing, asked the National Research Council to develop a long-range vision and a strategy to advance toxicity testing in the 21st Century. The committee's report presents that vision.

Current System Has Resulted in Expensive Patchwork Approach

Currently, companies seeking to register pesticides or federal agencies evaluating industrial or consumer chemicals carry out a series of tests by exposing animals to chemicals to screen for cancer, birth defects, and other adverse health effects. In the past, agencies have typically responded to scientific advances mostly by altering animal-based toxicity tests or adding more animal tests—such as studying offspring of exposed mothers—to existing toxicity-testing regimens. That approach has led to a testing system that is lengthy and costly and that uses many animals. In combination with the various legal authorities under which EPA operates, this system has resulted in many toxicants not being tested at all, despite potential human exposure to them—even as other contaminants receive significant research attention and decades of scrutiny.

How New Technologies Could Transform Existing Approaches

A number of emerging fields and techniques are contributing major new insights for understanding the biologic responses to chemicals in human tissues. For example, new high-throughput techniques developed by the pharmaceutical industry use efficient automated methods to test certain biologic activities of thousands of chemicals that used to be studied in animals.

Emerging fields also include systems biology, a powerful approach that uses computational models and laboratory data to describe and understand biologic systems as a whole and how they operate. Another important field is bioinformatics, which applies computational techniques to vast amounts of data to understand how cells and cell systems work.

Vision for the Future of Toxicity Testing

Systems biology, bioinformatics, and rapid assay technologies are helping scientists to better understand how cellular networks or pathways in the human body carry out normal functions that are key to maintaining health. When important pathways are significantly altered by chemical exposures, they can cause adverse health effects. But these effects only occur when exposures are of sufficient intensity or duration, or if they occur in susceptible individuals or during sensitive life-stages.

The report envisions a new toxicity-testing system that relies mainly on understanding "toxicity pathways"—the cellular response pathways that can result in adverse health effects when sufficiently perturbed. Such a system would evaluate biologically significant alterations without relying on studies of whole animals.

The key elements of the committee's vision

for the future of toxicity testing are identified in Figure 1 below. The figure encompasses both the assessment of toxicity pathways and "targeted testing," which is designed to clarify and refine information from toxicity pathway tests for use in chemical risk assessments.

For the foreseeable future, some targeted testing in animals will need to continue, as it is not currently possible to sufficiently understand how chemicals are broken down in the body using tests in cells alone. These targeted tests will complement the new rapid assays and ensure the adequate evaluation of chemicals.

At the bottom of the figure, dose-response and extrapolation modeling will enable the translation of cellular tests to whole human systems. Specifically, the modeling will estimate environmental exposures that would lead to significant perturbations of toxicity pathways observed in the cellular tests.

Population-based and human exposure data are also key elements of the vision. Collection of biomonitoring data—surveying levels of chemicals measured in human blood, hair or other tissues—is emphasized. As testing is developed and refined, other markers of human exposure, health effects, and susceptibility will be identified that can aid public-health authorities in assessing and responding to chemicals of concern in the environment.

The report emphasizes the importance of evaluating risk contexts—common decision-making scenarios—for which toxicity testing is being conducted. Some risk contexts require rapid screening of thousands of environmental agents, while others require highly refined dose-response modeling for an individual agent. Defining the risk context can often reduce the need to proceed in a stepwise manner from chemical characterization to testing to dose-response modeling, as set out in the figure—a lengthy process some stakeholder groups say has fallen short of addressing public health and environmental problems in a timely way.

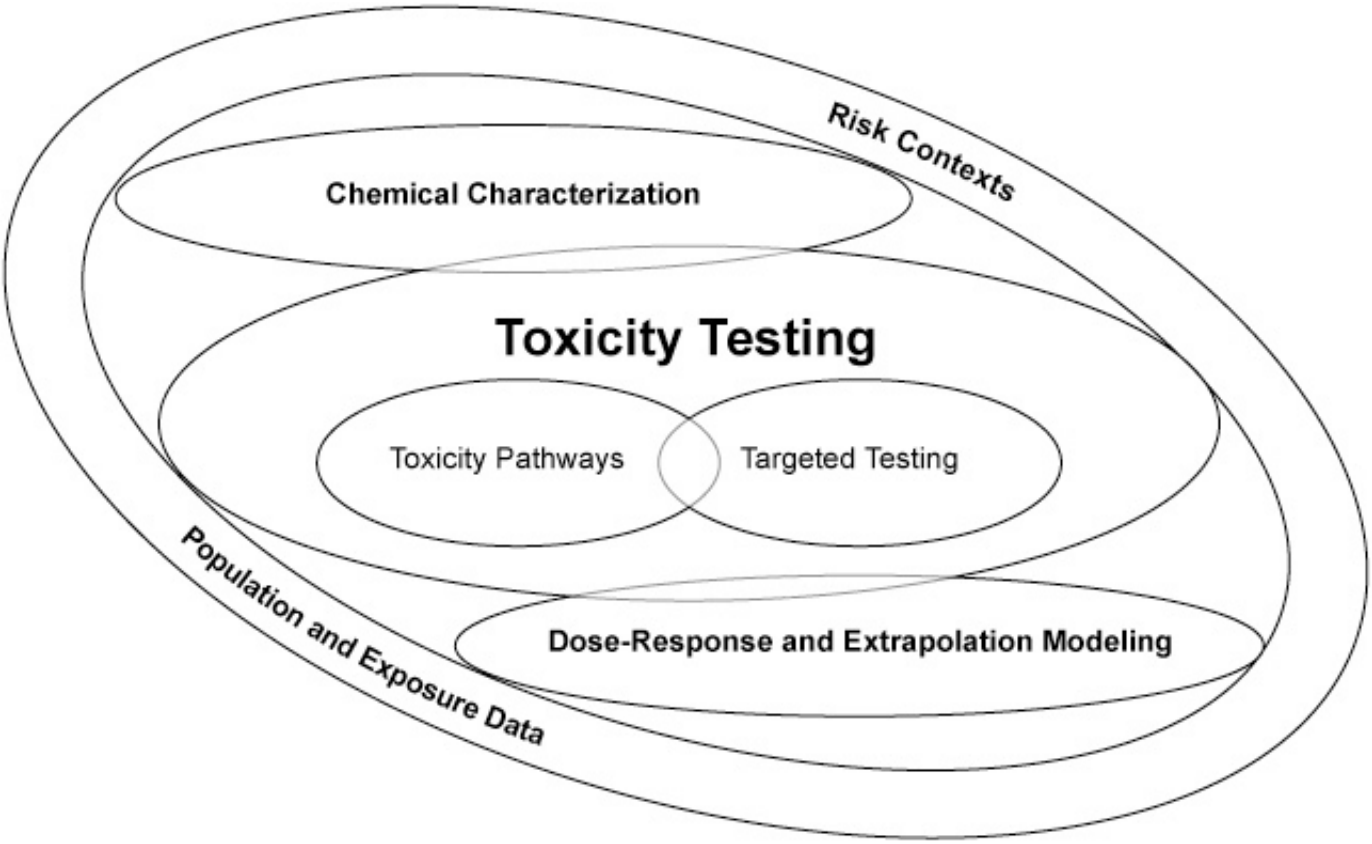

Figure 1. The committee's vision for toxicity testing is a process that can include chemical characterization, toxicity testing, and dose-response and extrapolation modeling as part of broader agency decision-making.

Achieving the Vision: Marshalling the Scientific Community

The report concludes that substantial benefits will result from achieving the vision but that it will require coordinated efforts and resources over the next several decades by scientists from government, industry, universities, consulting laboratories, and the public interest community. EPA has established a National Center for Computational Toxicology that is developing new software and methods for predictive toxicology. The National Institute of Environmental Health Sciences, through the National Toxicology Program's Roadmap for the Future has initiated a partnership with the Chemical Genomics Center of the National Institutes of Health to develop and begin carrying out high- and medium-throughput screening assays to test more chemicals in less time and at less cost. Long-standing problems, such as the backlog of untested or insufficiently tested chemicals, could be addressed while reducing the time-, resource- and animal-intensive nature of the current system that sometimes leaves decision-makers without clear guidance concerning the potential risks they must address.

To advance the science to realize these improvements, the committee recommends that a new institution be created to foster the kind of cross-disciplinary research that will be required to achieve the vision. The report says there would be far less chance of success within a reasonable timeframe if the research were dispersed among different locations and organizations without a core institute. Although resources to support such an institution may seem limited and current testing practices engrained in some sectors, using these new scientific tools to generate better information for decision-making will result in tangible environmental, public-health, and economic benefits.

The field of toxicity testing is at a pivotal juncture. The vision described in the report has the potential not only to improve current approaches, but to fundamentally transform them by making them quicker, cheaper, more scientific, and more responsive to existing and new challenges faced by environmental health authorities and the public.

Committee on Toxicity Testing and Assessment of Environmental Agents: Daniel Krewski (Chair), University of Ottawa; **Daniel Acosta, Jr.**, University of Cincinnati; **Melvin Andersen**, The Hamner Institutes for Health Sciences; **Henry Anderson**, Wisconsin Division of Public Health; **John Bailar III**, University of Chicago; **Kim Boekelheide,** Brown University; **Robert Brent**, Thomas Jefferson University; **Gail Charnley**, Health Risk Strategies; **Vivian Cheung**, University of Pennsylvania; **Sidney Green**, Howard University; **Karl Kelsey**, Harvard University; **Nancy Kerkvliet**, Oregon State University; **Abby Li**, Exponent, Inc.; **Lawrence McCray**, Massachusetts Institute of Technology; **Otto Meyer,** The National Food Institute; **D. Reid Patterson**, Reid Patterson Conculting; **William Pennie**, Pfizer, Inc.; **Robert Scala**, Exxon Biomedical Sciences (retired); **Gina Solomon**, Natural Resources Defense Council; **Martin Stephens**, The Humane Society of the United States; **James Yager**, Johns Hopkins University; **Lauren Zeise**, California Environmental Protection Agency. The project director was Ellen Mantus.

This report brief was prepared by the National Research Council based on the committee's report. For more information or copies, contact the Board on Environmental Studies and Toxicology at (202) 334-3060 or visit http://nationalacademies.org/best. Copies of *Toxicity Testing in the Twenty-first Century: A Vision and a Strategy* are available from the National Academies Press, 500 Fifth Street, NW, Washington, D.C. 20001; (800) 624-6242; www.nap.edu.

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