

A review of the National Research Council report

Toxicity testing in the 21st century: A vision and a strategy

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Abstract

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. This National Research Council report creates a far-reaching vision for the future of toxicity testing.

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Information from toxicity tests conducted to evaluate chemicals for their potential to cause birth defects, loss of IQ points, cancer and other adverse health effects serves as an important part of the basis for public health and regulatory decisions concerning chemicals.

Today, toxicological evaluation of chemicals is poised to take advantage of the on-going revolution in biology, biotechnology, and other fields. This revolution is making it possible to study the effects of chemicals using cells, cellular components, and tissues – preferably of human origin – rather than whole animals. 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. They should also enable rapid screening of chemicals, which could reduce the backlog of the large number of industrial chemicals that have not yet been evaluated for their environmental effects under the current testing system.

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.

1. Current system has resulted in expensive patchwork approach

Currently, companies or agencies seeking to evaluate chemicals carry out a series of tests by exposing animals to chemicals to screen for birth defects, cancer 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.

2. 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.

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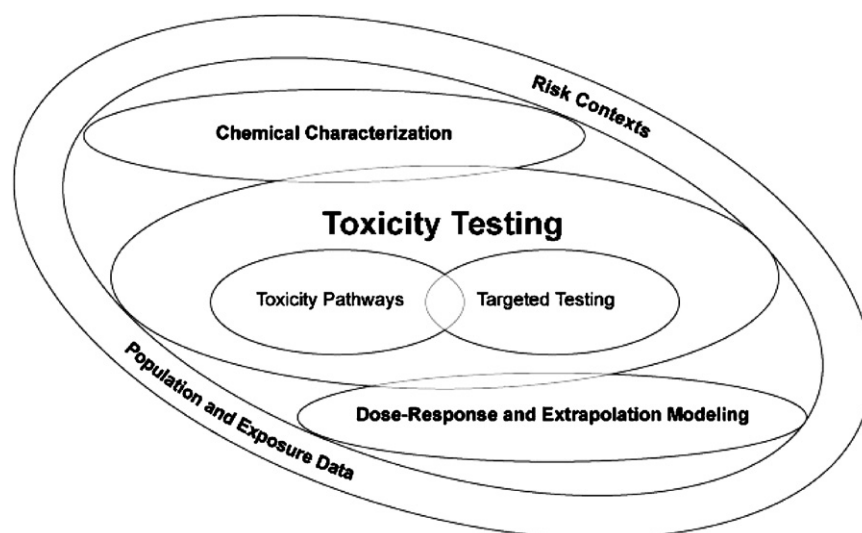


Fig. 1. The committee's vision for toxicity testing is a process that can include chemical characterization, toxicity testing, and dose–response and extrapolation modeling as part of broader agency decision-making.

Emerging fields also include systems biology, a powerful approach that uses computational models and laboratory data to understand interacting systems of biologic components 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.

3. 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 key to maintaining health. When important pathways are significantly altered by chemical exposures, they can cause adverse health effects. But only when exposures are of sufficient intensity or duration, or if they occur in susceptible individuals or during sensitive life-stages, do these effects occur.

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.

The key elements of the committee's vision for the future of toxicity testing are identified in Fig. 1. 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 understand sufficiently how chemicals are broken down in the body using tests in cells alone.

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 – sur-

veying levels of chemicals measured in human blood, hair, or other tissues – will aid in identifying markers of human exposure, health effects, and susceptibility that can aid scientists 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.

4. 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 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. 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 single core institute be created to foster the kind of cross-disciplinary research that will be required to achieve the vision. 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.

This summary was prepared by the National Research Council based on the committee's report. Copies of *Toxicity Testing in the 21st Century: A Vision and a Strategy* are available from the National Academies Press. Tel.: +1 800 624 6242; <http://www.nap.edu>.