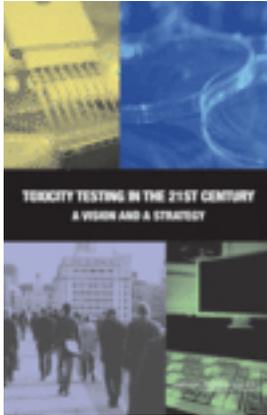


Free Executive Summary



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

Committee on Toxicity Testing and Assessment of Environmental Agents, National Research Council

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Advances in molecular biology and toxicology are paving the way for major improvements in the evaluation of the hazards posed by the large number of chemicals found at low levels in the environment. The National Research Council was asked by the U.S. Environmental Protection Agency to review the state of the science and create a far-reaching vision for the future of toxicity testing. The report finds that developing, improving, and validating new laboratory tools based on recent scientific advances could significantly improve our ability to understand the hazards and risks posed by chemicals. This new knowledge would lead to much more informed environmental regulations and dramatically reduce the need for animal testing because the new tests would be based on human cells and cell components. Substantial scientific efforts and resources will be required to leverage these new technologies to realize the vision, but the result will be a more efficient, informative and less costly system for assessing the hazards posed by industrial chemicals and pesticides.

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Summary

Change often involves a pivotal event that builds on previous history and opens the door to a new era. Pivotal events in science include the discovery of penicillin, the elucidation of the DNA double helix, and the development of computers. All were marked by inauspicious beginnings followed by unheralded advances over a period of years but ultimately resulted in a pharmacopoeia of life-saving drugs, a map of the human genome, and a personal computer on almost every desk in today's workplace.

Toxicity testing is approaching such a scientific pivot point. It is poised to take advantage of the revolutions in biology and biotechnology. Advances in toxicogenomics, bioinformatics, systems biology, epigenetics, and computational toxicology could transform toxicity testing from a system based on whole-animal testing to one founded primarily on *in vitro* methods that evaluate changes in biologic processes using cells, cell lines, or cellular components, preferably of human origin. Anticipating the impact

of recent scientific advances, the U.S. Environmental Protection Agency (EPA) asked the National Research Council (NRC) to develop a long-range vision for toxicity testing and a strategic plan for implementing the vision.

This report of the NRC Committee on Toxicity Testing and Assessment of Environmental Agents, prepared in response to EPA's request, envisions a major campaign in the scientific community to advance the science of toxicity testing and put it on a forward-looking footing. The potential benefits are clear. Fresh thinking and the use of emerging methods for understanding how environmental agents affect human health will promote beneficial changes in testing of these agents and in the use of data for decision-making. The envisioned change is expected to generate more robust data on the potential risks to humans posed by exposure to environmental agents and to expand capabilities to test chemicals more efficiently. A stronger scientific foundation offers the prospect of improved risk-based regulatory decisions and possibly greater public confidence in and acceptance of the decisions.

With those goals in mind, the committee presents in this report a vision for mobilizing the scientific community and marshaling scientific resources to initiate and sustain new approaches, some available and others yet to be developed, to toxicity testing. This report speaks to scientists in all sectors—government, public interest, industry, university, and consulting laboratories—who design and conduct toxicity tests and who use test results to evaluate risks to human health. The report also seeks to inform and engage decision-makers and other leaders who shape the nature and scope of government regulations and who establish budgetary priorities that will determine progress in advancing toxicity testing in the future. The full impact of the committee's wide-ranging recommendations can be achieved only if both scientists and nonscientists work to advance the objectives set forth in the vision.

THE VISION

The current approach to toxicity testing relies primarily on a complex array of studies that evaluate observable outcomes in whole animals, such as clinical signs or pathologic changes, that are indicative of a disease state. Partly because that strategy is so time-consuming and resource-intensive, it has had difficulty in meeting many challenges encountered today, such as evaluating various life stages, numerous health outcomes, and large numbers of untested chemicals. The committee debated several options for improving the current system but concluded that a transformative paradigm shift is needed to achieve the design criteria set out in the committee's interim report: (1) to provide broad coverage of chemicals, chemical mixtures, outcomes, and life stages, (2) to reduce the cost and time of testing, (3) to use fewer animals and cause minimal suffering in the animals used, and (4) to develop a more robust scientific basis for assessing health effects of environmental agents.¹

The committee considered recent scientific advances in defining a new approach to toxicity testing. Substantial progress is being made in the elucidation of cellular-response networks—interconnected pathways composed of complex biochemical interactions of genes, proteins, and small molecules that maintain normal cellular function, control communication between cells, and allow cells to adapt to changes in their environment. For example, one familiar cellular-response network is signaling by estrogens in which initial exposure results in enhanced cell proliferation and tissue growth in specific tissues. Bioscience is enhancing our knowledge of cellular-response networks and allowing scientists to begin to uncover how environmental agents perturb pathways in ways that lead to toxicity. Cellular response pathways that, when sufficiently perturbed, are expected to result

¹For a further discussion of the options considered by the committee, see Chapter 2, "Options for a New Toxicity-Testing Paradigm."

in adverse health effects are termed *toxicity pathways*. The committee envisions a new toxicity-testing system that evaluates biologically significant perturbations in key toxicity pathways by using new methods in computational biology and a comprehensive array of in vitro tests based on human biology.

COMPONENTS OF THE VISION

Figure S-1 illustrates the major components of the committee's vision: chemical characterization, toxicity testing, and dose-response and extrapolation modeling. The components of the vision, which are described in the sections that follow, are distinct but interrelated modules involving specific sets of technologies and scientific capabilities. Some chemical evaluations may proceed in a stepwise manner—from chemical characterization to toxicity testing to dose-response and extrapolation modeling—but such a sequential evaluation need not always be followed in practice. A critical feature of the new vision is consideration of the risk context (the decision-making context that creates the need for toxicity-testing information) at each step and the ability to exit the strategy at any point when sufficient data have been generated for decision-making. The vision emphasizes the generation and use of population-based and human exposure data where possible for interpreting test results and encourages the collection of such data on important chemicals with biomonitoring, surveillance, and epidemiologic studies. Population-based and human exposure data, along with the risk context, will play a role in both guiding and using the toxicity information that is produced. Finally, the vision anticipates the development of a formal process to phase in and phase out test methods as scientific understanding of toxicity-testing methods expands. That process addresses the need for efficient testing of all chemicals in a timely, cost-effective fashion.

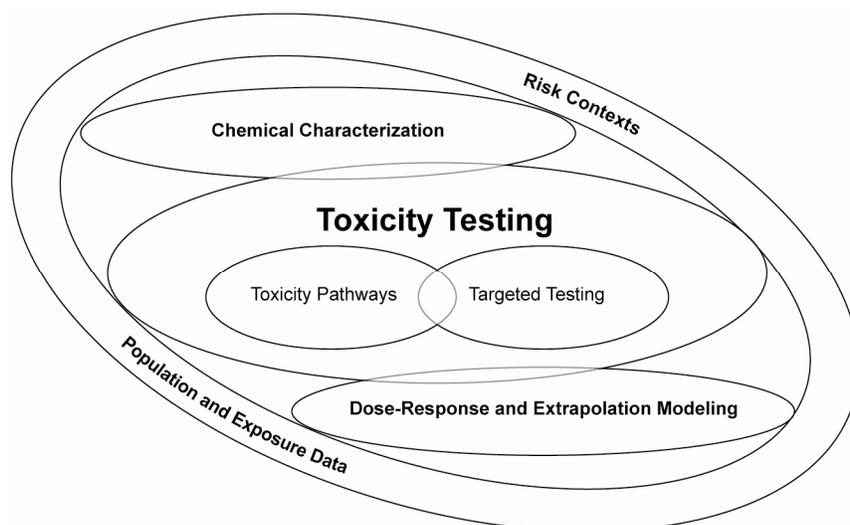


FIGURE S-1 The committee's vision for toxicity testing is a process that includes chemical characterization, toxicity testing, and dose-response and extrapolation modeling. At each step, population-based and human exposure data are considered, as is the question of what data are needed for decision-making.

Chemical Characterization

Chemical characterization is meant to provide insights to key questions, including a compound's stability in the environment, the potential for human exposure, the likely routes of exposure, the potential for bioaccumulation, possible routes of metabolism, and the likely toxicity of the compound and possible metabolites based on chemical structure or physical or chemical characteristics. Thus, data would be collected on physical and chemical properties, use, possible environmental concentrations, metabolites and breakdown products, initial molecular interactions of compounds and metabolites with cellular components, and possible toxic properties. A variety of computational methods might be used to predict those properties and characteristics. After chemical characterization, decisions might be made about what further testing is required or whether it is needed at all. In most cases,

chemical characterization alone is not expected to be sufficient to reach decisions about the toxicity of an environmental agent.

Toxicity Testing

In the vision proposed (see Figure S-1), toxicity testing has two components: toxicity-pathway assays and targeted testing. The committee expects that when the vision is achieved, predictive, pathway-based assays will serve as the central component of a broad toxicity-testing strategy for assessing the biologic activity of new and existing compounds. Targeted testing will serve to complement the assays and support evaluation.

Toxicity Pathways

Figure S-2 illustrates the activation of a toxicity pathway. The initial perturbations of cell-signaling motifs, genetic circuits, and cellular-response networks are obligatory changes resulting from chemical exposure that might eventually result in disease. The consequences of a biologic perturbation depend on its magnitude, which is related to the dose, the timing and duration of the perturbation, and the susceptibility of the host. Accordingly, at low doses, many biologic systems may function normally within their homeostatic limits. At somewhat higher doses, clear biologic responses occur. They may be successfully handled by adaptation, although some susceptible people may respond. More intense or persistent perturbations may overwhelm the capacity of the system to adapt and lead to tissue injury and possible adverse health effects.

The committee's vision capitalizes on the identification and use of toxicity pathways as the basis of new approaches to toxicity

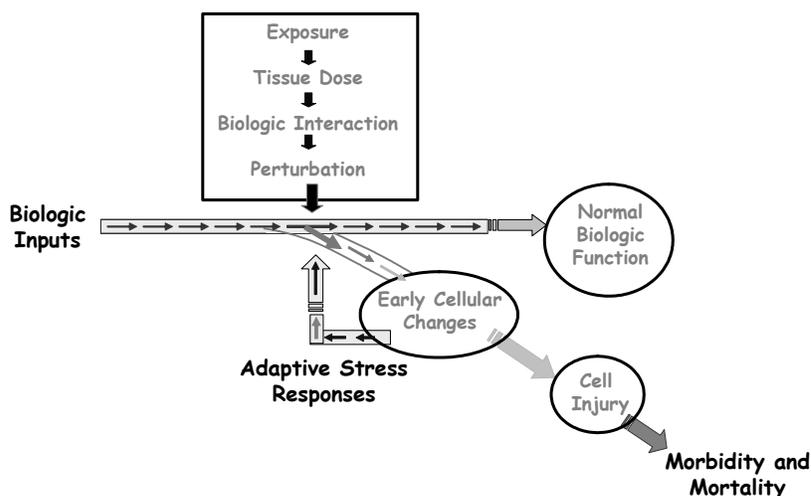


FIGURE S-2 Biologic responses viewed as results of an intersection of exposure and biologic function. The intersection results in perturbation of biologic pathways. When perturbations are sufficiently large or when the host is unable to adapt because of underlying nutritional, genetic, disease, or life-stage status, biologic function is compromised, and this leads to toxicity and disease. Source: Adapted from Andersen, M.E., J.E. Dennison, R.S. Thomas, and R.B. Conolly. 2005. New directions in incidence-dose modeling. *Trends Biotechnol.* 23(3):122-127. Reprinted with permission; copyright 2005, *Trends in Biotechnology*.

testing and dose-response modeling. Accordingly, the vision emphasizes the development of suites of predictive, high-throughput assays² that use cells or cell lines, preferably of human origin, to evaluate relevant perturbations in key toxicity pathways. Those assays may measure relatively simple processes, such as binding of environmental agents with cellular proteins and changes in gene expression caused by that binding, or they may measure

²High-throughput assays are efficiently designed experiments that can be automated and rapidly performed to measure the effect of substances on a biologic process of interest. These assays can evaluate hundreds to many thousands of chemicals over a wide concentration range to identify chemical actions on gene, pathway, and cell function.

more integrated responses, such as cell division and cell differentiation. Although the majority of toxicity tests in the vision are expected to use high-throughput methods, other tests could include medium-throughput assays of more integrated cellular responses, such as cytotoxicity, cell proliferation, and apoptosis. Over time, the need for traditional animal testing should be greatly reduced and possibly even eliminated.

Targeted Testing

Targeted testing would be used to complement toxicity-pathway tests and to ensure adequate evaluation. It would be used (1) to clarify substantial uncertainties in the interpretation of toxicity-pathway data; (2) to understand effects of representative prototype compounds from classes of materials, such as nanoparticles, that may activate toxicity pathways not included in a standard suite of assays; (3) to refine a risk estimate when the targeted testing can reduce uncertainty, and a more refined estimate is needed for decision-making; (4) to investigate the production of possibly toxic metabolites; and (5) to fill gaps in the toxicity-pathway testing strategy to ensure that critical toxicity pathways and end points are adequately covered. One of the challenges of developing an *in vitro* test system to evaluate toxicity is the current inability of cell assays to mirror metabolism in the integrated whole animal. For the foreseeable future, any *in vitro* strategy will need to include a provision to assess likely metabolites through whole-animal testing.

Targeted testing might be conducted *in vivo* or *in vitro*, depending on the toxicity tests available. Although targeted tests could be based on existing toxicity-test systems, they will probably differ from traditional tests in the future. They could use transgenic species, isogenic strains, new animal models, or other novel test systems and could include a toxicogenomic evaluation

of tissue responses over wide dose ranges. Whatever system is used, testing protocols would maximize the amount of information gained from whole-animal toxicity testing.

Dose-Response and Extrapolation Modeling

In the vision proposed (see Figure S-1), dose-response models would be developed for environmental agents primarily on the basis of data from mechanistic, *in vitro* assays as described in the toxicity-testing component. The dose-response models would describe the relationship between concentration in the test medium and degree of *in vitro* response. In some risk contexts, a dose-response model based on *in vitro* results might provide adequate data to support a risk-management decision. An example could involve compounds for which host-susceptibility factors in humans are well understood and human biomonitoring provides good information about tissue or blood concentrations of the compound and other related exposures that affect the toxicity pathway in a human population.

Extrapolation modeling estimates the environmental exposures or human intakes that would lead to human tissue concentrations similar to those associated with perturbations of toxicity pathways *in vitro* and would account for host susceptibility factors. In the vision proposed, extrapolation modeling has three primary components. First, a toxicity-pathway model would provide a quantitative, mechanistic understanding of the dose-response relationship for the perturbations of the pathways by environmental agents. Second, physiologically based pharmacokinetic modeling would then be used to predict human exposures that lead to tissue concentrations that could be compared with the concentrations that caused perturbations *in vitro*. Third, human data would provide information on background chemical exposures and disease processes that would affect the same toxic-

ity pathway and provide a basis for addressing host susceptibility quantitatively.

Population-Based and Human Exposure Data

Population-based and human exposure data are important components of the committee's toxicity-testing strategy (see Figure S-1). Those data can help to inform each component of the vision and ensure the integrity of the overall testing strategy. The shift toward the collection of more mechanistic data on fundamental biologic perturbations in human cells will require greater use of biomonitoring and human-surveillance studies for data interpretation. Moreover, the interaction between population-based studies and toxicity tests will improve the design of each study type for answering questions about the importance of molecular, cellular, and genetic factors that influence individual and population-level health risks. Because the vision emphasizes studies conducted in human cells that indicate how environmental agents can affect human biologic responses, the studies will suggest biomarkers (indicators of human exposure, effect, or susceptibility) that can be monitored and studied in human populations.

As toxicity testing shifts to cell-based studies, human exposure data from biomonitoring studies (such as those recommended in the NRC report *Human Biomonitoring for Environmental Chemicals*³) may prove pivotal. Such data can be used to select doses for toxicity testing that can provide information on biologic effects at environmentally relevant exposures. More important, comparison of concentrations that activate toxicity pathways with concentrations of agents in blood, urine, or other tissues from human populations will help to identify potentially important expo-

³NRC (National Research Council). 2006. *Human Biomonitoring for Environmental Chemicals*. Washington, DC: The National Academies Press.

asures to ensure an adequate margin of safety in setting human exposure guidelines.

Risk Context

Toxicity testing is useful ultimately only if it can be used to facilitate more informed and efficient responses to the public-health concerns of regulators, industry, and the public. Common scenarios, defined by the committee as “risk contexts,” for which toxicity testing is used to make decisions include evaluation of potential environmental agents, existing environmental agents, sites of environmental contamination, environmental contributors to a human disease, and the relative risk of different environmental agents. Some risk contexts require rapid screening of tens of thousands of environmental agents; some require highly refined dose-response data, extending down to environmentally relevant exposure concentrations; and some require the ability to test chemical mixtures or to use assays focused on specific mechanisms. Some risk contexts might require the use of population-based approaches, including population health surveillance and biomonitoring. With its emphasis on high-throughput assays that use human cells, cell lines, and components to evaluate biologically significant perturbations in key toxicity pathways, the vision presented here will assist the decision-making process in each risk context.

IMPLEMENTATION OF THE VISION

Implementation of the vision will require (1) the availability of suites of *in vitro* tests—preferably based on human cells, cell lines, or components—that are sufficiently comprehensive to evaluate activity in toxicity pathways associated with the broad

array of possible toxic responses; (2) the availability of targeted tests to complement the in vitro tests and ensure an adequate toxicity database for risk-management decision-making; (3) computational models of toxicity pathways to support application of in vitro test results to predict exposures in the general population that could potentially lead to adverse changes; (4) infrastructure changes to support the basic and applied research needed to develop the tests and the pathway models; (5) validation of tests and test strategies for incorporation into chemical-assessment guidelines that will provide direction in interpreting and drawing conclusions from the new assay results; and (6) evidence justifying that the results of tests based on perturbations in toxicity pathways are adequately predictive of adverse health outcomes to be used in decision-making.

A substantial and focused research effort will be needed to meet those requirements. The research will need to develop both new scientific knowledge and new toxicity-testing methods. Key questions that need to be addressed regarding knowledge and method development are highlighted in Box S-1.

The research and development needed to implement the vision would progress in phases whose timelines would overlap. Phase I would focus on elucidating toxicity pathways; developing a data-storage, -access, and -management system; developing standard protocols for research methods and reporting; and planning a strategy for human surveillance and biomonitoring to support the toxicity-pathway testing approach. Phase II would involve development and validation of toxicity-pathway assays and identification of markers of exposure, effect, and susceptibility for use in surveillance and biomonitoring of human populations. Phase III would evaluate assays by running them in parallel with traditional toxicity tests, on chemicals with large datasets, and on chemicals that would not otherwise be tested as a screening process. Parallel testing will allow identification of toxicities that might

BOX S-1 Key Questions to Address in Implementation

Knowledge Development

Toxicity-Pathway Identification—What are the key pathways whose perturbations result in toxicity?

Multiple Pathways—What alteration in response can be expected from simultaneous perturbations of multiple toxicity pathways?

Adversity—What adverse effects are linked to specific toxicity-pathway perturbations? What patterns and magnitudes of perturbations are predictive of adverse health outcomes?

Life Stages—How can the perturbations of toxicity pathways associated with developmental timing or aging be best captured to enable the advancement of high-throughput assays?

Effects of Exposure Duration—How are biologic responses affected by exposures of different duration?

Low-Dose Response—What is the effect on a toxicity pathway of adding small amounts of toxicants in light of pre-existing endogenous and exogenous human exposures?

Human Variability—How do people differ in their expression of toxicity-pathway constituents and in their predisposition to disease and impairment?

Method Development

Methods to Predict Metabolism—How can adequate testing for metabolites in the high-throughput assays be ensured?

Chemical-Characterization Tools—What computational tools can best predict chemical properties, metabolites, xenobiotic-cellular and molecular interactions, and biologic activity?

Assays to Uncover Cell Circuitry—What methods will best facilitate the discovery of the circuitry associated with toxicity pathways?

Assays for Large-Scale Application—Which assays best capture the elucidated pathways and best reflect in vivo conditions? What designs will ensure adequate testing of volatile compounds?

(Continued on next page)

BOX S-1 Continued

Suite of Assays—What mix of pathway-based high- and medium-throughput assays and targeted tests will provide adequate coverage? What targeted tests should be developed to complement the toxicity-pathway assays? What are the appropriate positive and negative controls that should be used to validate the assay suite?

Human-Surveillance Strategy—What surveillance is needed to interpret the results of pathway tests in light of variable human susceptibility and background exposures?

Mathematical Models for Data Interpretation and Extrapolation—What procedures should be used to evaluate whether humans are at risk from environmental exposures?

Test-Strategy Uncertainty—How can the overall uncertainty in the testing strategy be best evaluated?

be missed if the new assays were used alone and will compel the development of assays to address these gaps. Surveillance and biomonitoring of human populations would also begin during Phase III. Finally, the validated assays would be assembled into panels in Phase IV for use in place of identified traditional toxicity tests.

Validation will be a critical component of the research and development phases. Establishing the validity of any new toxicity assay can be a formidable process—expensive, time-consuming, and logistically and technically demanding. For several reasons, validation will be especially challenging for the mechanistically based tests envisioned by the committee. First, the test results to be generated in the new paradigm depart from the traditional data used by regulatory agencies to set health advisories and guidelines. Second, the many new technologies developed will need to be standardized and refined before specific applications are validated for regulatory purposes. Third, because new technologies are evolving rapidly, the decision to halt optimization of

a particular application and begin a formal validation study will be somewhat subjective. Fourth, the committee envisions that a suite of new tests will typically be needed to replace a specific traditional test. Fifth, existing guidelines focus on concordance between the results of new and existing assays; the difficulty will be to find standards for comparison that can assess the relevance and predictivity of the new assays. Sixth, because virtually all environmental agents will perturb signaling pathways to some degree, a key challenge will be to determine when such perturbations are likely to lead to toxic effects and when they are not.

A long-term, large-scale concerted effort is needed to bring the committee's vision for toxicity-testing to fruition. A critical factor for success is the conduct of the transformative research to establish the scientific basis of new toxicity-testing tools and to understand the implications of test results and their application in risk assessments used in decision-making. The committee concludes that an appropriate institutional structure that fosters multidisciplinary intramural and extramural research is needed to achieve the vision. The effort will not succeed merely by creating a virtual institution to link and integrate organizations that perform relevant research and by dispersing funding on relevant research projects. Mission-oriented intramural and extramural programs with core multidisciplinary activities within the institute to answer the critical research questions listed above can foster the kind of interdisciplinary activity essential for the success of the initiative. There would be far less chance of success within a reasonable time if the research were dispersed among different locations and organizations without a core integrating and organizing institute to enable the communication and problem-solving required across disciplines.

Research frequently brings surprises, and today's predictions about the promise of lines of research might prove to be too pessimistic or too optimistic in some details. Therefore, the committee recommends that an independent scientific assessment of the

research program supporting implementation of the vision be conducted every 3-5 years to provide advice for midcourse corrections. The interim assessments would weigh progress, evaluate the promise of new methods on the research horizon, and refine the committee's vision in light of the many scientific advances that are expected to occur in the near future.

Regulatory acceptance of the new toxicity-testing strategy will depend on several factors. New testing requirements will be expected to reflect the state of the science and be founded on peer-reviewed research, established test protocols, validated models, and case studies. Other factors affecting regulatory acceptance stem from administrative procedures associated with rule-making, such as documenting scientific sources; providing opportunities for scientific experts, stakeholders, and the interested public to participate; and consulting with sister agencies and international organizations. Implementing the vision will require improvements and focused effort over a period of decades. However, given the political will and the availability of funds to adapt the current regulatory system to take advantage of the best possible scientific approaches to toxicity testing in the future, the committee foresees no insurmountable obstacles to implementing the vision presented here.

Resources are always limited, and current toxicity-testing practices are long established and deeply ingrained in some sectors. Thus, some resistance to the vision proposed by this committee is expected. However, the vision takes full advantage of current and expected scientific advances to enhance our understanding of how environmental agents can affect human health. It has the potential to greatly reduce the cost and time of testing and to lead to much broader coverage of the universe of environmental agents. Moreover, the vision will lead to a marked reduction in animal use and focus on doses that are more relevant to those experienced by human populations. The vision for toxicity testing in the twenty-first century articulated here is a para-

digm shift that will not only improve the current system but transform it into one capable of overcoming current limitations and meeting future challenges.

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

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Preface

Over the past few decades, several toxicity-testing strategies have emerged for evaluating the hazards or risks associated with exposure to drugs, food additives, pesticides, and industrial and other chemicals. New testing technologies, methods, and approaches also have emerged in recent years. The U.S. Environmental Protection Agency (EPA) recognized the need to conduct a comprehensive review of toxicity-testing methods and strategies and requested that the National Research Council (NRC) conduct such a review and propose a long-range vision and strategy for toxicity testing.

In its 2006 interim report, the NRC Committee on Toxicity Testing and Assessment of Environmental Agents reviewed current toxicity-testing methods and strategies and selected aspects of several reports by EPA and others that described initiatives or proposals to improve current methods or strategies. The committee now presents its long-range vision and strategic plan to advance toxicity testing and considers its vision within the current regulatory framework. Although the committee was not charged to review government programs related to toxicity testing, some federal programs that are relevant to the subject of this report may be of interest to readers. For example, EPA has established a National Center for Computational Toxicology (<http://www.epa.gov/comptox/index.html>) 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 (<http://ntp.niehs.nih.gov/files/NTPrdmp.pdf>), has initiated a partnership with the Chemical Genomics Center of the National Institutes of Health to develop and carry out high- and medium-throughput screening assays to test more chemicals in less time and at less cost.

Preface

This report has been reviewed in draft form by persons chosen for their diverse perspectives and technical expertise in accordance with procedures approved by the NRC's Report Review Committee. The purposes of this independent review are to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards of objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following for their review of this report: Cynthia Afshari (Amgen, Inc.), Frederic Bois (INERIS), James Bus (Dow Chemical), Vincent James Cogliano (International Agency for Research on Cancer), David Dorman (The Hamner Institutes for Health Sciences), Alan Goldberg (Johns Hopkins University), Carole Kimmel (consultant), Gilbert Omenn (University of Michigan), Lorenz Rhomberg (Gradient Corporation), Joseph Rodricks (ENVIRON), Leslie Stayner (University of Illinois), and Helmut Zarbl (Fred Hutchinson Cancer Research Center).

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by the review coordinator, Rogene Henderson (Lovelace Respiratory Research Institute), and the review monitor, Donald Mattison (National Institutes of Health). Appointed by the NRC, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the committee and the institution.

The committee gratefully acknowledges the following for making presentations to the committee: Thomas Hartung (ECVAM), William Greenlee (The Hamner Institutes for Health Sciences), Carl Barrett (Novartis Institute for Biomedical Development), Robert Chapin (Pfizer, Inc.), Michael Festing (private consultant), William Stokes (National Institute of Environmental Health Sciences), Edward Calabrese (University of Massachusetts-Amherst), John Doull (University of Kansas Medical Center), Bette Meek (Health Canada), Michael Firestone (EPA), Clifford Gabriel (EPA), Lee Hoffman (EPA), Jim Jones (EPA), Deidre Murphy (EPA), Rita Schoeny (EPA), and Charles Auer (EPA). The committee especially thanks Dorothy Patton (retired from EPA) for her contributions to the report and consultation on toxicity testing in regulatory contexts.

The committee is also grateful for the assistance of the NRC staff in preparing this report. Staff members who contributed to the effort are Ellen Mantus, project director; Joanne Zurlo, director of the Institute for Laboratory Animal Research; James Reisa, director of the Board on Environmental Studies and Toxicology; Jennifer Obernier, program officer; Ruth Crossgrove, senior editor; Norman Grossblatt, senior editor; Mirsada Karalic-Loncarevic, manager of the Tech-

Preface

nical Information Center; Jordan Crago, senior project assistant; and Radiah Rose, senior editorial assistant.

I would especially like to thank all the members of the committee for their efforts throughout the development of this report.

Daniel Krewski, *Chair*
Committee on Toxicity Testing
and Assessment of Environmental Agents

Contents

SUMMARY	1
1 INTRODUCTION	18
Historical Perspective of Regulatory Toxicology, 19	
Risk Assessment, 23	
The Committee's First Task and Key Points from its Interim Report, 25	
The Committee's Second Task and Approach, 29	
Organization of the Report, 32	
References, 33	
2 VISION	35
Limitations of Current Testing Strategies, 38	
Design Criteria for a New Toxicity-Testing Paradigm, 42	
Options for a New Toxicity-Testing Paradigm, 43	
Overview of Committee's Long-Range Vision for Toxicity Testing, 48	
References, 53	
3 COMPONENTS OF THE VISION	56
Component A: Chemical Characterization, 57	
Component B: Toxicity Testing of Compounds and Metabolites, 60	
Component C: Dose-Response and Extrapolation Modeling, 68	
Component D: Population-Based and Human Exposure Data, 75	
Component E: Risk Contexts, 80	
Toxicity-Testing Strategies in Practice, 84	
Toxicity Testing and Risk Assessment, 90	
References, 91	
4 TOOLS AND TECHNOLOGIES	98
Tools and Technologies for Chemical Characterization, 98	
Mapping Toxicity Pathways, 102	
Tools and Technologies for Dose-Response and Extrapolation Modeling, 110	
References, 113	

Contents

5	DEVELOPING THE SCIENCE BASE AND ASSAYS TO IMPLEMENT THE VISION	120
	Scope of Scientific Knowledge, Methods, and Assay Development, 122	
	Strategy for Knowledge and Assay Development and Validation, 132	
	Building a Transformative Research Program, 155	
	Concluding Remarks, 162	
	References, 163	
6	PREREQUISITES FOR IMPLEMENTING THE VISION IN REGULATORY CONTEXTS	166
	Institutional Change to Meet the Vision, 167	
	Regulatory Use of New Methods, 171	
	References, 181	
APPENDIX		
	BIOGRAPHIC INFORMATION ON THE COMMITTEE ON TOXICITY TESTING AND ASSESSMENT OF ENVIRONMENTAL AGENTS.....	184
BOXES		
S-1	Key Questions to Address in Implementation.....	13
2-1	Key Terms Used in the Report	38
3-1	Example of Components of Signaling Pathway That Could Be Modeled	73
5-1	Key Research Questions in Developing Knowledge to Support Pathway Testing.....	124
5-2	Main Questions in Developing Tests and Methods	128
5-3	Some Science and Technology Milestones in Developing Toxicity-Pathway Tests As the Cornerstone of Future Toxicity-Testing Strategies.....	134
FIGURES		
S-1	The committee's vision for toxicity testing is a process that includes chemical characterization, toxicity testing, and dose-response and extrapolation modeling	5
S-2	Biologic responses viewed as results of an intersection of exposure and biologic function	7
2-1	The exposure-response continuum underlying the current paradigm for toxicity testing.....	39
2-2	Biologic responses viewed as results of an intersection of exposure and biologic function	49

Contents

2-3	The committee's vision is a process that includes chemical characterization, toxicity testing, and dose-response and extrapolation modeling	50
3-1	Overview of chemical characterization component	58
3-2	Toxicity-testing component, which includes toxicity-pathway testing in cells and cell lines and targeted testing in whole animals	61
3-3	Overview of dose-response and extrapolation modeling component	69
3-4	Nrf2 antioxidant-response pathway schematic	73
3-5	Overview of population-based and human exposure data component	76
3-6	Overview of risk contexts component	81
3-7	Risk-assessment components	91
5-1	Progression of some important science and technology activities during assay development	136
5-2	Screening of chemicals that would not otherwise be tested or be subject to only limited testing	149
 TABLES		
2-1	Options for Future Toxicity-Testing Strategies	44
6-1	Definitions of Adverse Effect	178

TOXICITY TESTING IN THE 21ST CENTURY

A VISION AND A STRATEGY

