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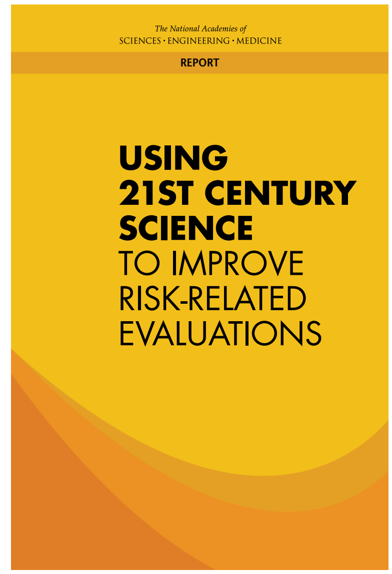
Using 21st Century Science to Improve Risk-Related Evaluations



Tools for assessing human health risks from exposure to chemicals have expanded rapidly in the 21st century. For example, new personal sensors and sampling techniques offer unparalleled opportunities to characterize individual exposures, new in vitro assays can now evaluate a number of cellular processes and responses, and -omics technologies have advanced molecular epidemiology, which focuses on underlying biology (pathogenesis) rather than observations from population studies alone.

Over the last decade, several large-scale US and international programs and collaborations have been initiated to develop and advance new technologies and methods, and data are being generated from government, industry, and academic laboratories at an overwhelming pace. For example, the Tox21 collaboration among several US federal agencies that uses high-throughput screening assays has generated a wealth of information on biological responses to chemical exposures in humans, and complementary information is being generated apace in academic laboratories. This report provides guidance on how data from the various emerging techniques can be integrated into and used to improve risk-related evaluations that support decision-making.

RELEVANT SCIENTIFIC ADVANCES

Chapters 2–4 of the report describe advances in exposure science, toxicology, and epidemiology that are increasing the scope of the data available for risk assessment.

Exposure science is being transformed by many scientific and technological advances that are enhancing the quality, expanding the coverage, and reducing the uncertainty of exposure estimates. Remote sensing and personal sensors can be combined with global positioning systems to provide a more complete understanding of human exposures. Computational exposure tools are expected to play a crucial role in providing exposure estimates for risk assessment when exposure-measurement data are not available. Advances in analytical chemistry methods are facilitating the identification of chemicals present in complex environmental samples. And biological matrices, such as teeth, nails, and the placenta, are being used to estimate exposures during particularly sensitive life stages, such as gestation.

In toxicology, -omics technologies are being used to investigate biological responses to environmental stressors at a molecular level by profiling, for example, messenger RNA (transcriptome), proteins (proteome), and cellular metabolites (metabolome). Other advances include large banks of immortalized cells collected from genetically diverse populations that can be used for toxicological research; large compilations of publicly available biological data that can be mined to develop hypotheses about relationships between chemicals, genes, and diseases; and genetically diverse mouse strains and alternative species that can be used to answer questions related to interindividual susceptibility or sensitivity to toxicants.

The scientific advances that have propelled exposure science and toxicology onto new paths have also substantially influenced the direction of epidemiology. One of the most important developments has been the incorporation of -omics technologies into epidemiological research.

POTENTIAL APPLICATIONS OF 21ST CENTURY SCIENCE

The report identifies a number of activities that could benefit from the incorporation of 21st century science. They include the following:

1. **Priority Setting.** Tens of thousands of chemicals are used in commerce in the United States in building materials, consumer products, and many other items. Being able to identify the chemicals that pose the most risk requires a way to prioritize them for testing. A risk-based approach that uses high-throughput exposure and hazard identification information provides one approach.
2. **Chemical Assessment.** This activity encompasses a broad array of analyses. Some cover chemicals that have a substantial database for decision-making. For those assessments, scientific and technical advances can be used to reduce uncertainties around key issues and to address unanswered questions. Other assessments cover chemicals that have few data. One approach for evaluating data-poor chemicals is to use toxicity data on well-tested chemicals (analogues) that are similar in their structure, metabolism, or biological activity in a process known as read-across. The assumption is that a chemical of interest has the same or similar biological activity to structurally similar compounds for which risks have been addressed. High-throughput assays can be used to strengthen confidence in the identification of the best analogue.
3. **Site-specific assessment.** Understanding the risks associated with a chemical spill or the extent to which a hazardous-waste site needs to be remediated depends on understanding three elements—the chemicals present, their toxicity, and the toxicity of the mixture. A combination of targeted and nontargeted analytical chemistry approaches, analogue-based methods, and high-throughput screening methods can be used to assess chemicals present and their toxicity and to determine what risks various mixtures might pose.
4. **Assessment of new chemistries.** Some new chemicals have chemical structures that differ substantially from chemicals that have been well studied toxicologically. Modern toxicological methods can help to identify chemical features that have greater or less potential for toxicity, and modern exposure science methods can help identify chemicals that have the highest potential for widespread exposure and bioaccumulation.

CASE STUDIES

The report's authoring committee developed several case studies in Appendices B, C, and D that show how 21st century science can be used in risk assessment.

Case studies related to chemical assessment are detailed in Appendix B. The first case study illustrates the use of read-across methods to derive a health reference value for a data-poor alkylphenol. The data -poor chemical is compared with two data-rich alkylphenols (analogues) that are similar in chemical structure and physicochemical properties. High-throughput in vitro data from ToxCast (an EPA program) are used to add confidence in the selection of the analogues. Data from in vivo rat multigenerational studies of the data-rich alkylphenols are used as a starting point for deriving the health reference value, and ToxCast data are used to make adjustments.

A case study on air pollution illustrates how 21st century science can be used to address outstanding issues for a well-defined hazard or chemical and to evaluate emerging concerns about them. The consequences of exposure to air pollution have been extensively investigated, and the evidence concerning a causal relationship between air pollution and lung cancer is strong. However, there are still unanswered questions, such as which components are primarily responsible for carcinogenicity, whether there are interactions or synergies among the various components, what effects might occur at low exposures, and which groups might be at greater risk because of particular characteristics, such as smoking tobacco. The case study describes how advances in exposure science and toxicology can be used to characterize adverse effects, refine exposure further, identify mechanisms and groups at risk, and investigate emerging concerns.

Case studies related to understanding the risk associated with a spill or a hazardous waste site are detailed in Appendix C. A large historically contaminated site with land and surface water near a major population center is considered; targeted and nontargeted chemical analyses that could be used at the site are described. Next, a chemical spill is detailed, and exposure and toxicity screening tools that could help to understand the human risk are described. Finally, a toxicity assessment of complex mixtures observed in environmental samples, tissues, and biofluids is considered, and a biological read-across approach that could be used to conduct an assessment is illustrated.

Appendix D describes a hypothetical scenario in which there are three choices of "new" chemicals for use in the manufacture of a product that will result in human exposure. The committee describes in vitro high-throughput data available on the chemicals and what those data might mean. It then considers several scenarios in which human exposure could occur and calculates indoor air releases that correspond to the in vitro bioassay data. The case study concludes with a discussion of how the data could be used in the decision-making process.

A NEW DIRECTION FOR RISK ASSESSMENT

The advances in exposure science, toxicology, and epidemiology support a new direction for risk evaluations—one based on biological pathways rather than observations in animal studies and one incorporating the emerging exposure science. The exposure aspect of the new direction focuses on estimating or predicting exposures to multiple chemicals and stressors, characterizing human variability in those exposures, providing exposure data that can inform toxicity testing, and translating exposures between test systems and humans. The toxicology and epidemiology elements of the new direction focus on the multifactorial and nonspecific nature of disease causation; that is, stressors from multiple sources can contribute to a single disease, and a single stressor can lead to multiple adverse outcomes. Although the 21st century tools provide the means to pursue the new direction, there are challenges that will need to be addressed.

THE NEED TO INTEGRATE AND INTERPRET DIVERSE DATA STREAMS

The diverse, complex, and very large datasets being generated pose challenges related to analysis, interpretation, and integration of data and evidence for risk assessment. In fact, technology has evolved far faster than the approaches for those activities. The committee emphasizes that insufficient attention has been given to analysis, interpretation, and integration of various data streams from exposure science, toxicology, and epidemiology. It proposes a research agenda that includes developing case studies that reflect various scenarios of decision-making and data availability; testing case studies with multidisciplinary panels; cataloguing evidence evaluations and decisions that have been made on various agents so that expert judgments can be tracked and evaluated, and expert processes calibrated; and determining how statistically based tools for combining and integrating evidence, such as Bayesian approaches, can be used for incorporating 21st century science into all elements of risk assessment.

The committee concludes that the data that are being generated today can be used to address many of the risk-related tasks that the agencies face. Although the challenges to achieving the visions of earlier reports often seem daunting, 21st century science holds great promise for advancing risk assessment and ultimately for improving public health and the environment. The committee emphasizes, however, that communicating the strengths and limitations of the approaches in a transparent and understandable way will be necessary if the results are to be applied appropriately and will be critical for the ultimate acceptance of the approaches. In addition, exposure scientists, toxicologists, epidemiologists, and scientists in other disciplines need to collaborate closely to ensure that the full potential of 21st century science is realized to help to solve the complex environmental and public-health problems that society faces.

This report builds on two previous reports from the National Research Council. *Toxicity Testing in the 21st Century: A Vision and a Strategy* envisioned a future in which toxicology relies primarily on high-throughput in vitro assays and computational models based on human biology to evaluate potential adverse effects of chemical exposures. Similarly, *Exposure Science in the 21st Century: A Vision and a Strategy* articulated a long-term vision for exposure science motivated by the advances in analytical methods, sensor systems, molecular technologies, informatics, and computational modeling. That vision was to inspire a transformational change in the breadth and depth of exposure assessment that would improve integration with and responsiveness to toxicology and epidemiology.

COMMITTEE ON INCORPORATING 21ST CENTURY SCIENCE INTO RISK-BASED EVALUATIONS

Jonathan M. Samet (*Chair*), University of Southern California, Los Angeles; **Melvin E. Andersen**, ScitoVation, Research Triangle Park, NC; **Jon A. Arnot**, ARC Arnot Research & Consulting, Toronto, ON; **Esteban Burchard**, University of California, San Francisco; **George P. Daston**, Procter & Gamble, Mason, OH; **David B. Dunson**, Duke University, Durham, NC; **Nigel Greene**, AstraZeneca, Waltham, MA; **Heather B. Patisaul**, North Carolina State University, Raleigh; **Kristi Pullen Fedinick**, Natural Resources Defense Council, Washington, DC; **Beate R. Ritz**, University of California, Los Angeles; **Ivan Rusyn**, Texas A&M University, College Station; **Robert L. Tanguay**, Oregon State University, Corvallis; **Justin G. Teeguarden**, Pacific Northwest National Laboratory, Richland, WA; **James M. Tiedje**, Michigan State University, East Lansing; **Paolo Vineis**, Imperial College London, UK; **Michelle Williams**, Harvard School of Public Health, Boston, MA; **Fred Wright**, North Carolina State University, Raleigh; **Lauren Zeise**, California Environmental Protection Agency, Oakland; **Ellen K. Mantus** (*Project Director*), **Marilee Shelton-Davenport** (*Senior Program Officer*), **Norman Grossblatt** (*Senior Editor*), **Mirsada Karalic-Loncarevic** (*Manager, Technical Information Center*), Radiah Rose-Crawford (*Manager, Editorial Projects*), **Ivory Clarke** (R*esearch Assistant*), National Academies of Sciences, Engineering, and Medicine

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