BEST

Board on Environmental Studies and Toxicology

Using 21st Century Science to Improve Risk-Related Evaluations

Committee on Incorporating 21st Century Science into Risk-Based Evaluations

Board on Environmental Studies and Toxicology

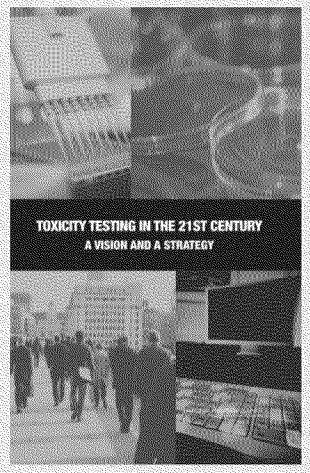
Division on Earth and Life Studies

The National Academies of

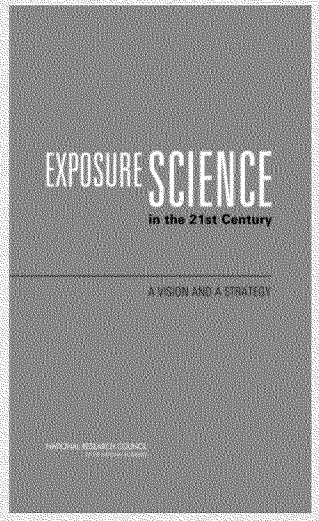
SCIENCES · ENGINEERING · MEDICINE

Tox21 and ES21 Reports

- ***Toxicity Testing in the 21st Century: A Vision and a Strategy*** was published in 2007 and envisioned a future in which toxicology relied primarily on high-throughput in vitro assays and computational models based on human biology to evaluate potential adverse effects of chemical exposure.



- ***Exposure Science in the 21st Century: A Vision and a Strategy*** was published in 2012 and provided a vision that was hoped to inspire transformational changes in the breadth and depth of exposure assessment that would improve integration with and responsiveness to toxicology and epidemiology.



The National Academies of
SCIENCES · ENGINEERING · MEDICINE

Statement of Task

Overall, the committee was asked to provide recommendations on integrating new scientific approaches into risk-based evaluations.

The committee was asked to consider the following:

- The advances that have occurred since publication of Tox21 and ES21 reports.
- Whether a new paradigm is needed for data validation.
- How uncertainty evaluations might need to change.
- What approaches are needed for communicating new science.
- Barriers and obstacles impeding integration of new science.

EPA-HQ-2018-0008760047428

Sponsors

- US Environmental Protection Agency
- US Food and Drug Administration
- National Institute of Environmental Health Sciences
- National Center for Advancing Translational Sciences

EPA-HQ-2018-0008760047429

Committee

JONATHAN SAMET, Chair, University of Southern California
MELVIN ANDERSEN, ScitoVation
JON ARNOT, ARC Arnot Research & Consulting
ESTEBAN BURCHARD, University of California, San Francisco
GEORGE DASTON, Proctor & Gamble
DAVID DUNSON, Duke University
NIGEL GREENE, AstraZeneca
HEATHER PATISAUL, North Carolina State University
KRISTI PULLEN FEDINICK, Natural Resources Defense Council
BEATE RITZ, University of California, Los Angeles
IVAN RUSYN, Texas A&M University
ROBERT TANGUAY, Oregon State University
JUSTIN TEEGUARDEN, Pacific Northwest National Laboratory
JAMES TIEDJE, Michigan State University
PAOLO VINEIS, Imperial College London
MICHELLE WILLIAMS, Harvard School of Public Health
FRED WRIGHT, North Carolina State University
LAUREN ZEISE, California Environmental Protection Agency

The National Academies of
SCIENCES · ENGINEERING · MEDICINE

Committee's Approach to Task

- The committee assessed scientific and technological advances in exposure science, toxicology, and epidemiology that could be integrated into and used to improve any of the four elements of risk assessment—hazard identification, dose-response assessment, exposure assessment, and risk characterization.
- It described applications and provided case studies for using the advances and the data being generated.
- It discussed problems arising from interpreting and integrating the new science and provided some recommendations for addressing the challenges.

EPA-HQ-2018-0008760047431

The Report

- Advances in Exposure Science
- Advances in Toxicology
- Advances in Epidemiology
- A New Direction for Risk Assessment and Applications of 21st Century Science
- Model and Assay Validation and Acceptance
- Interpretation and Integration of Data and Evidence for Risk-Based Decision-Making

The National Academies of
SCIENCES · ENGINEERING · MEDICINE

Common Theme

- Multidisciplinary approach is needed.

Exposure scientists, toxicologists, epidemiologists, and other scientists need to collaborate closely to ensure that the full potential of 21st century science is realized.

The National Academies of
SCIENCES · ENGINEERING · MEDICINE

ADVANCES IN EXPOSURE SCIENCE, TOXICOLOGY, AND EPIDEMOLOGY

The National Academies of
SCIENCES · ENGINEERING · MEDICINE

Exposure Science Advances

- Remote Sensing, Personal Sensors, and Other Sampling Techniques
- Computational Exposure Tools
- Targeted and Nontargeted Analyses
- –Omics Technologies
- Novel Exposure Matrices for Life-Span Research
- Physiologically Based Pharmacokinetic Models

EPA-HQ-2018-0008760047435

Expanding and Coordinating Exposure-Science Infrastructure

- An infrastructure is needed to improve the organization and coordination of the existing and evolving components for exposure science and ultimately to improve exposure assessment.
- Infrastructure development should include creating or expanding databases that contain information on chemical quantities in and chemical release rates from products and materials, on chemical properties and on processes, and analytical features that can be used in chemical identification.

The National Academies of
SCIENCES · ENGINEERING · MEDICINE

Aligning Environmental and Test-System Exposures

- Concentrations in test-system components need to be quantified by measurement, which is preferred, or by reliable estimation methods.
- Knowledge of physical processes, such as binding to plastic and volatilization, and of biological processes, such as metabolism, needs to be improved.

EPA-HQ-2018-0008760047437

Integrating Exposure Information

- Integration and appropriate application of exposure data on environmental media, biomonitoring samples, conventional samples, and emerging matrices constitute a scientific, engineering, and big-data challenge.
- The committee emphasizes that integration of measured and modeled data is a key step in developing coherent exposure narratives, in evaluating data concordance, and ultimately in determining confidence in an exposure assessment.

EPA-HQ-2018-0008760047438

Toxicology Advances

- ***Probing interactions with biological molecules***. In vitro assays that probe chemical interactions with cellular components can provide reliable and valid results with high agreement among laboratories and can be applied in low-, medium-, and high-throughput formats.

- ***Detecting cellular response***. Cell cultures can be used today to evaluate a number of cellular processes and responses, including receptor binding, gene activation, cell proliferation, mitochondrial dysfunction, morphological changes, cellular stress, genotoxicity, and cytotoxicity.

EPA-HQ-2018-0008760047439

Toxicology Advances

- ***Investigating effects at higher levels of biological organization***. The last decade has seen advances in engineered 3-D models of tissues, which recapitulate at least some of the physiological responses that the tissue or organ exhibits in vivo.

- ***Predicting organism and population response***. Transgenic rodents can be used to investigate specific questions, for example, related to susceptibility or gene-environment interactions. Genetically diverse rodent strains provide another approach for addressing questions related to interindividual sensitivity to toxicants. Alternative species provide viable animal models for hazard identification and investigation of biological mechanisms.

EPA-HQ-2018-0008760047440

Challenges to Toxicology

- Accounting for metabolic capacity in assays.
- Understanding and addressing other limitations of cell systems.
- Addressing biological coverage.

EPA-HQ-2018-0008760047441

Epidemiology in the 21st Century

- Factors reshaping epidemiology include expansion of the interdisciplinary nature of the field; the increasing complexity of scientific inquiry; emergence of new data sources and technologies for data generation; advances in exposure characterization; and increasing demands to integrate new knowledge from basic, clinical, and population sciences.

- -Omics technologies have substantially transformed epidemiological research and advanced the paradigm of molecular epidemiology.

EPA-HQ-2018-0008760047442

Challenges to Epidemiology

- -Omics assays can generate extremely large datasets that need to be managed and curated in ways that facilitate access and analysis. Databases, robust statistical techniques, and standard approaches to describe data are needed.

- Movement from fixed, specific cohorts to large cohorts enrolled from healthcare organizations that incorporate biospecimen banks and use healthcare records emphasize need for multidisciplinary teams for epidemiological research.

EPA-HQ-2018-0008760047443

USING 21ST CENTURY SCIENCE

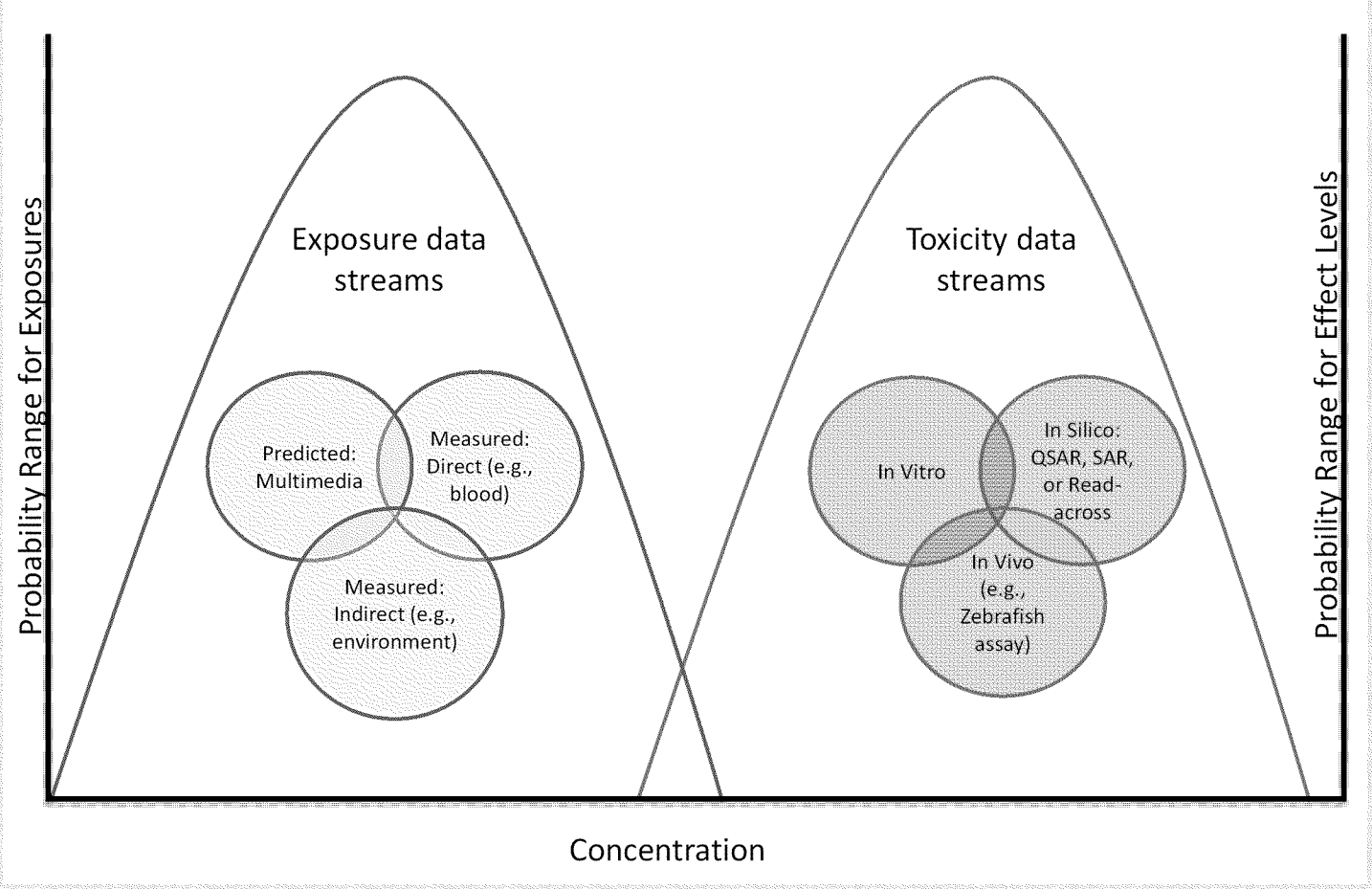
The National Academies of
SCIENCES · ENGINEERING · MEDICINE

Application Areas

- **Priority-setting** – Can be based on hazard, exposure, or risk.
- **Chemical assessment** – Can include IRIS assessments, PPRTVs, NTP OHAT hazard assessments, and assessments of various regulated substances, such as pesticides, drugs, and food additives.
- **Site-specific assessments** – Can involve selection of geographic sites or chemicals at a site to evaluate.
- **Assessment of new chemistries** – Can involve assessment of green chemistry, new-to-the-world technologies, and unexpected environmental degradation products of chemicals in commerce.

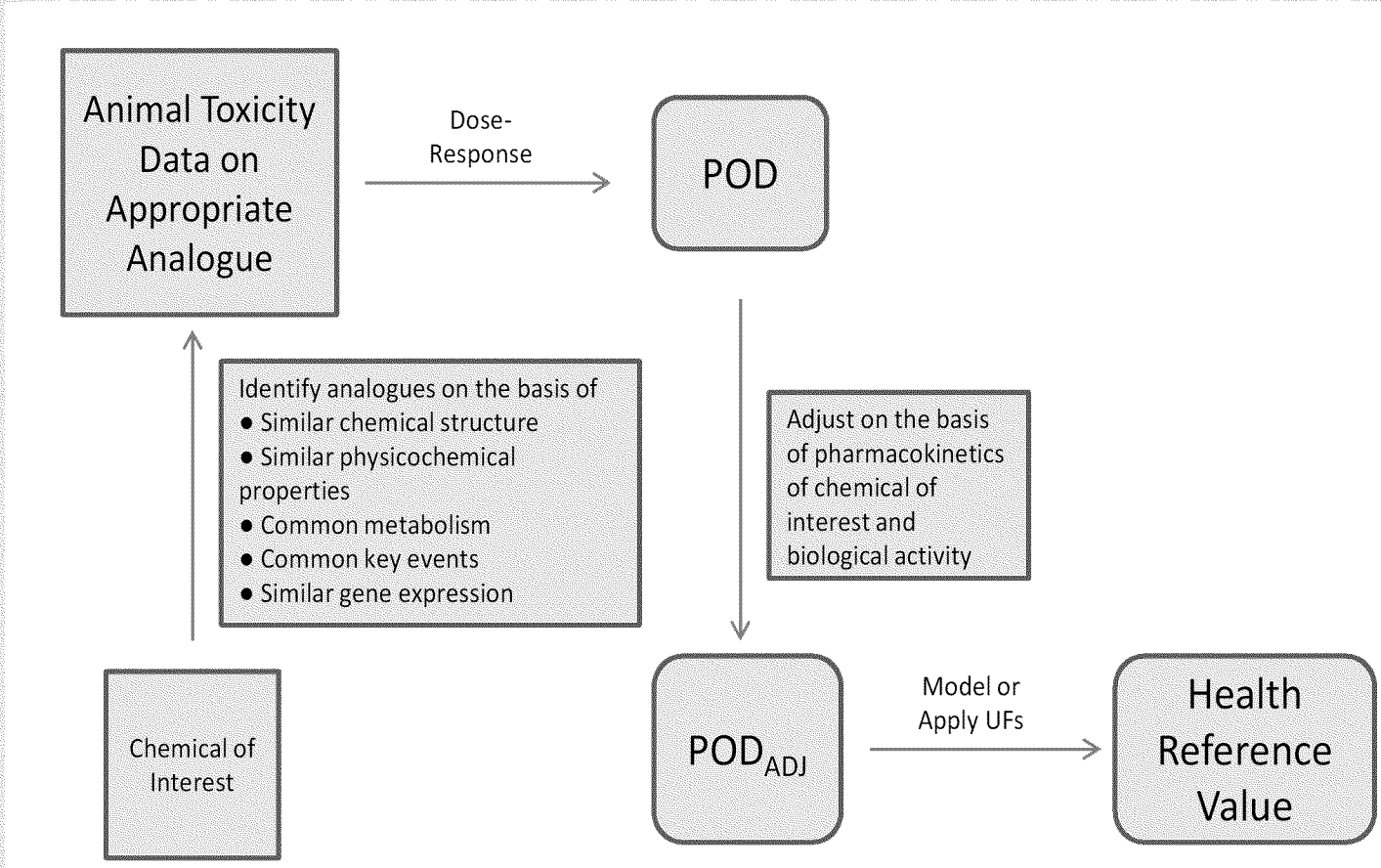
EPA-HQ-2018-0008760047445

Priority-setting



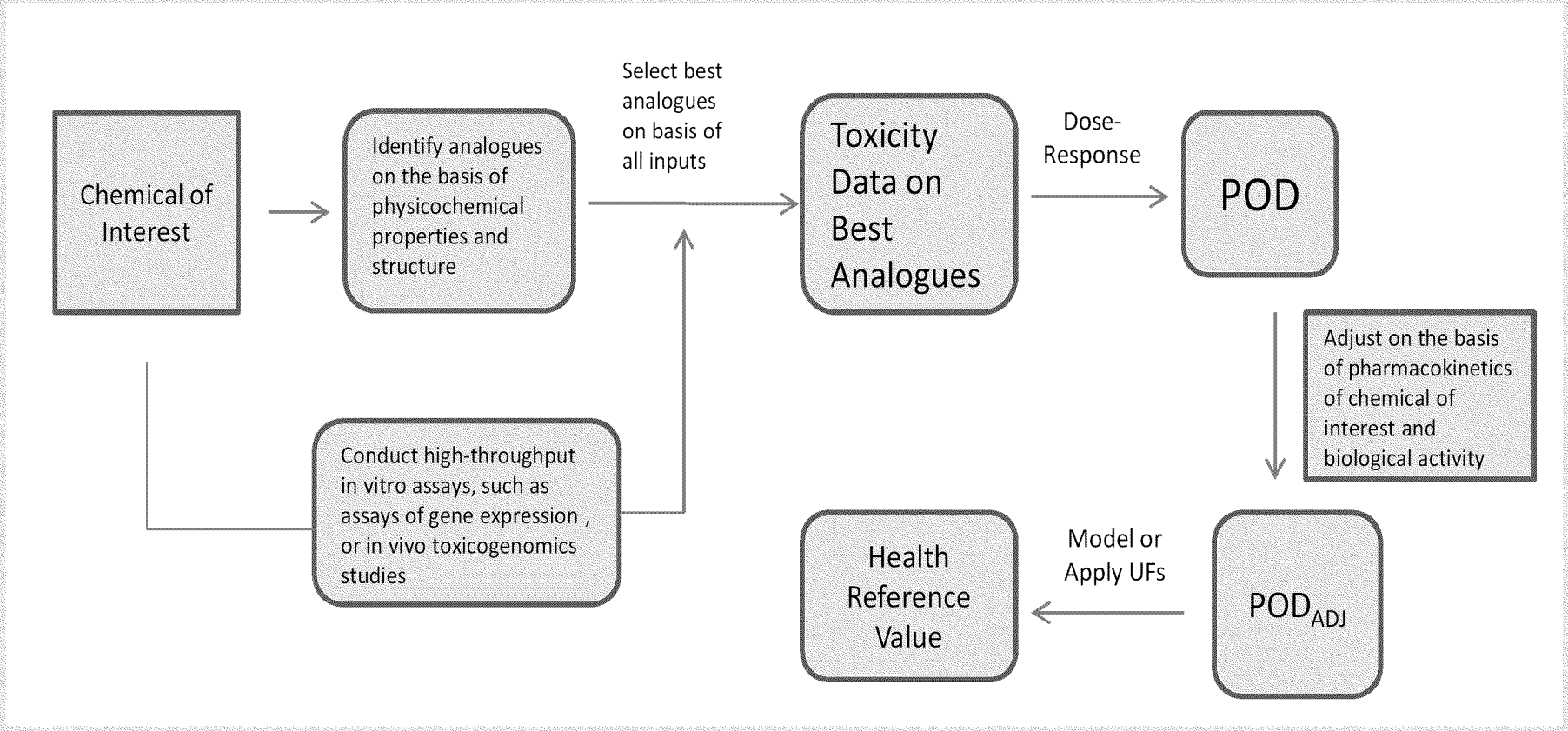
The National Academies of
SCIENCES · ENGINEERING · MEDICINE

Chemical Assessment



The National Academies of
SCIENCES · ENGINEERING · MEDICINE

Chemical Assessment



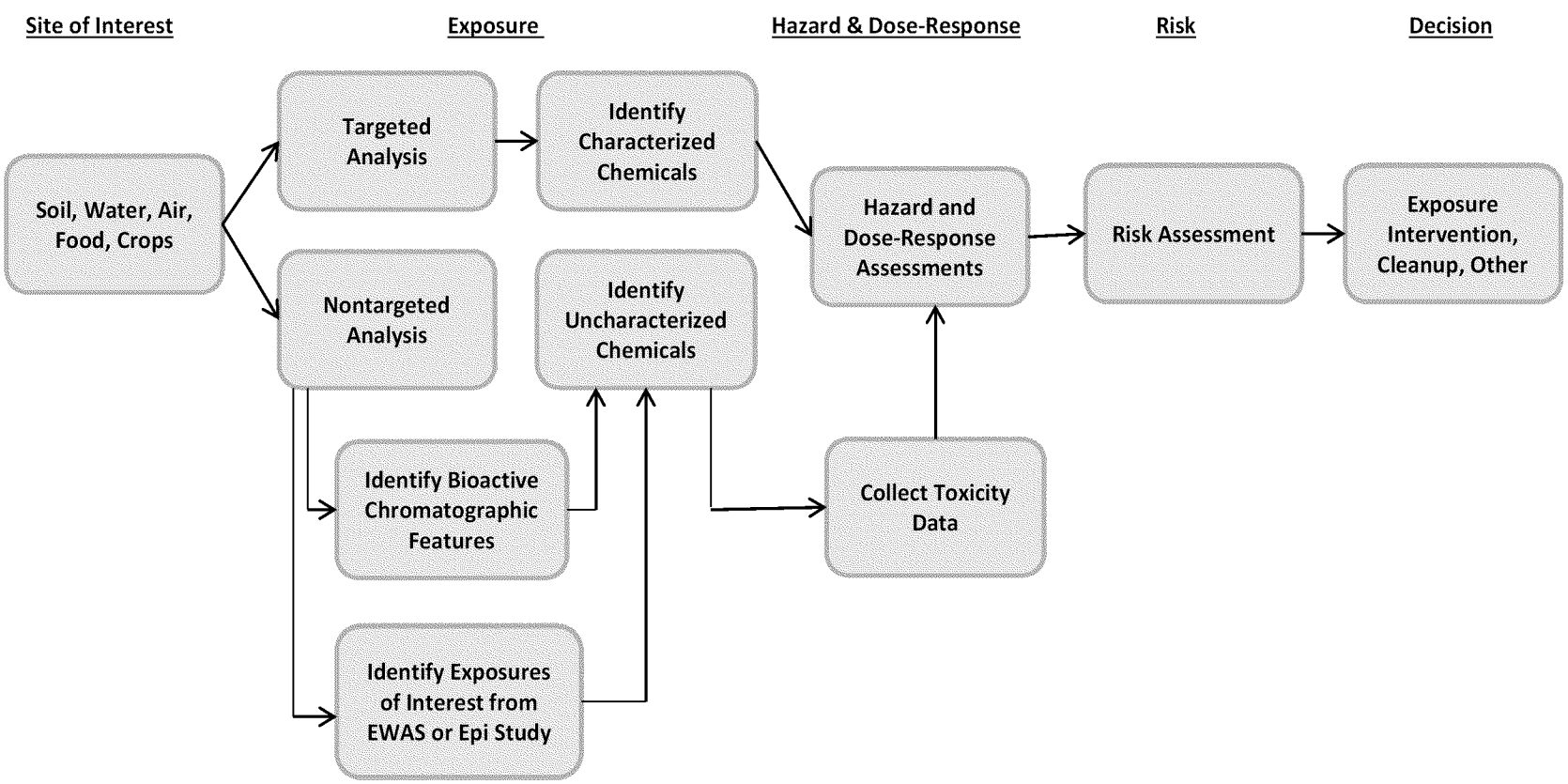
The National Academies of
SCIENCES · ENGINEERING · MEDICINE

Case Studies for Chemical Assessment

- ***Characterization of Data-Poor Chemical*** – The committee uses read-across to illustrate derivation of a health reference value for a data-poor alkylphenol.
- ***Air Pollution and Lung Cancer*** – The committee describes advances in exposure science and toxicology, specifically -omics technologies, that can help to characterize adverse effects, refine exposure further, and identify mechanisms and groups at risk
- ***Air Pollution and Neurotoxicity*** – The committee describes approaches to improve epidemological studies with new exposure tools and -omics technologies and to investigate the association using Tox21 approaches.

EPA-HQ-2018-0008760047449

Site-Specific Assessments



The National Academies of
SCIENCES · ENGINEERING · MEDICINE

Case Studies for Site-Specific Assessments

- ***Identifying chemicals present***. The committee describes how targeted and untargeted analyses of chemicals can be used at a large historically contaminated site.
- ***Characterizing toxicity***. The committee considers a chemical release and describes exposure and toxicity screening tools that could help to understand the human risk.
- ***Characterizing mixture toxicity***. The committee considers a toxicity assessment of complex mixtures observed in environmental samples, tissues, and biofluids and illustrates how a biological read-across approach could be used to conduct an assessment.

EPA-HQ-2018-0008760047451

Case Study for Assessing New Chemistries

Comparative assessment of 3 chemicals intended for new product use.

- Highlights the use of in vitro assays for hazard assessment and ES21 tools for exposure assessment.
- Information is used to provide risk characterization of new chemicals to inform decision-making.

EPA-HQ-2018-0008760047452

Validation

The current processes for validation cannot match the pace of development of new assays, models, and test systems, and the validation processes need to evolve.

EPA-HQ-2018-0008760047453

Elements That Need To Be Addressed

- Appropriate comparators for enabling fit-for-purpose validation of new test methods need to be identified.
- Assay utility and how assay data should be interpreted need to be defined.
- Performance standards for assays and clear reporting standards for testing methods need to be established.
- Methods for validating batteries of assays that might be used to replace toxicity tests need to be determined.

EPA-HQ-2018-0008760047454

THE NEW DIRECTION FOR RISK ASSESSMENT

The National Academies of
SCIENCES · ENGINEERING · MEDICINE

The New Direction for Risk Assessment

The advances in exposure science, toxicology, and epidemiology described in this report support the new direction for risk assessment,

- one based on biological pathways and processes rather than on observation of apical responses and
- one incorporating the more comprehensive exposure information emerging from new tools and approaches in exposure science.

EPA-HQ-2018-0008760047456

Questions to Address

- Can an identified pathway, alone or in combination with other pathways, when sufficiently perturbed, increase the risk of an adverse outcome or disease in humans, particularly in sensitive or vulnerable individuals?
- Do the available data support the judgment that the chemical or agent perturbs one or more pathways linked to an adverse outcome?
- How does the response or pathway activation change with exposure? By how much does a chemical or agent exposure increase the risk of outcomes of interest?
- Which populations are likely to be the most affected? Are some more susceptible because of co-exposures, pre-existing disease, or genetic susceptibility? Are exposures of the young or elderly of greater concern?

EPA-HQ-2018-0008760047457

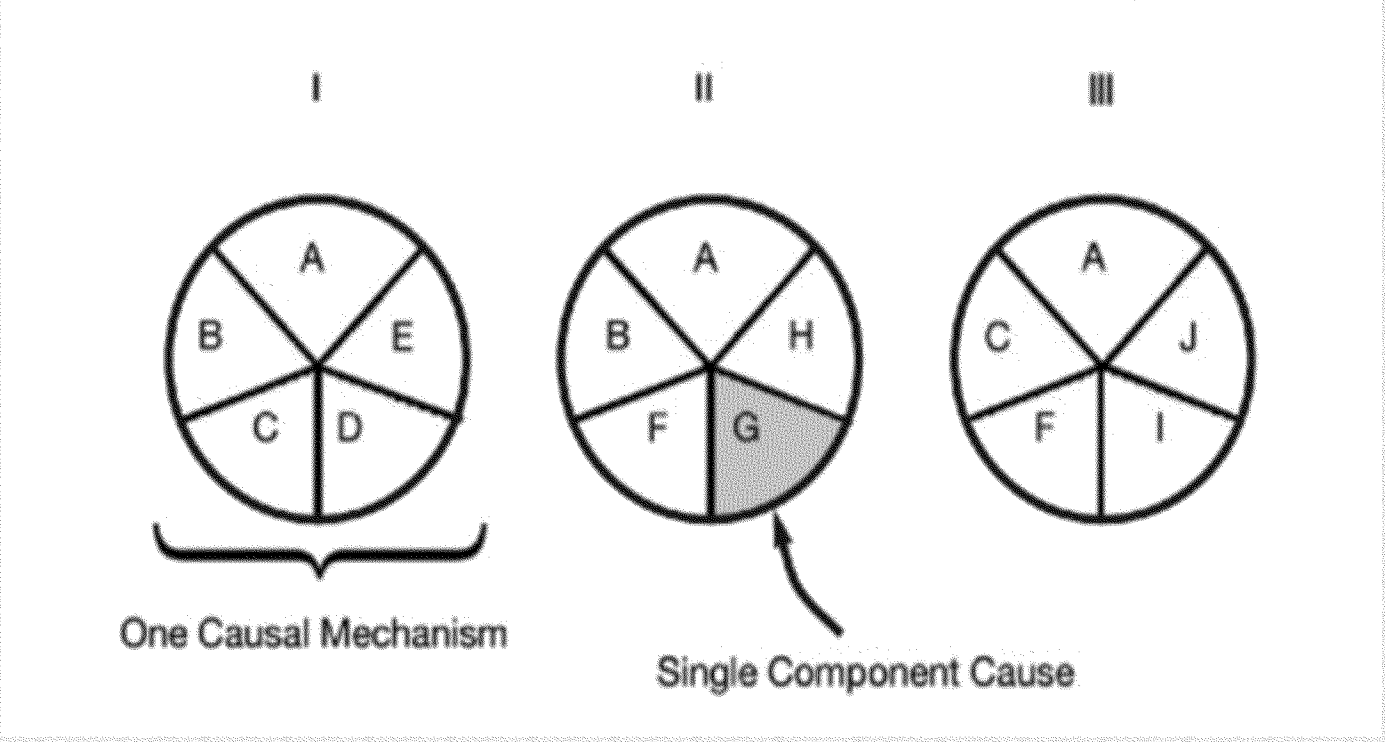
Multifactorial Nature of Disease

With the shift from observing apical responses to understanding biological processes or pathways comes the recognition that a single adverse outcome might result from multiple mechanisms, which can have multiple components.

EPA-HQ-2018-0008760047458

Sufficient-Component-Cause Model

The committee found the sufficient-component-cause model to be a useful tool for conceptualizing the new direction.



The National Academies of
SCIENCES · ENGINEERING · MEDICINE

Causal Guidelines and Data Integration

- The committee found that Bradford-Hill causal guidelines could be extended to help to answer such questions as whether specific pathways, components, or mechanisms contribute to a disease or outcome and whether a particular agent is linked to pathway perturbation or mechanism activation.
- Although the committee considered various methods for data integration, it concluded that guided expert judgment should be used in the near term for integrating diverse data streams for drawing causal conclusions.

EPA-HQ-2018-0008760047460

Challenges for the New Direction

- The 21st century science with its diverse, complex, and very large datasets, however, poses challenges related to analysis, interpretation, and integration of data and evidence for risk assessment.

- ***The committee emphasizes that insufficient attention has been given to analysis, interpretation, and integration of various data streams from exposure science, toxicology, and epidemiology.***

EPA-HQ-2018-0008760047461

Components of a Research Agenda

- Develop case studies that reflect various scenarios of decision-making and data availability.
- Test case studies with multidisciplinary panels.
- Catalogue evidence evaluations and decisions that have been made on various agents so that expert judgments can be tracked and evaluated, and expert processes calibrated.
- Determine 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.

EPA-HQ-2018-0008760047462

Concluding Remarks

- The data that are being generated today can be used to help to address many of the risk-related tasks that agencies face.
- Although the challenges to achieving the visions of the earlier reports often seem daunting, 21st century science holds great promise for advancing risk assessment and ultimately for improving public health and the environment.

EPA-HQ-2018-0008760047463