

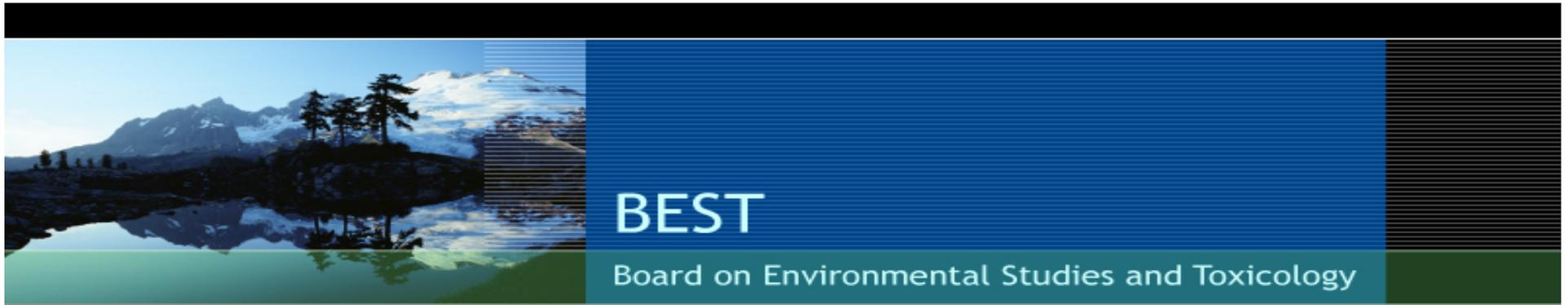


The Future of Toxicity Testing: Findings of the NRC Committee on Toxicity Testing and Assessment of Environmental Agents

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Cal/EPA Office of Environmental Health Hazard
Assessment

OEHHA-COEH Workshop:
Practical Decision-Making Tools for Identifying Safer Alternatives

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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

Division on Earth and Life Studies

National Research Council

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Advisers to the Nation on Science, Engineering, and Medicine



Committee Roster

Daniel Krewski (*Chair*), University of Ottawa, Ottawa, ON

Daniel Acosta, Jr., University of Cincinnati, Cincinnati, OH

Melvin Andersen, The Hamner Institutes for Health Sciences, Research Triangle Park, NC

Henry Anderson, Wisconsin Division of Public Health, Madison, WI

John Bailar III, University of Chicago, Chicago, IL

Kim Boekelheide, Brown University, Providence, RI

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William Pennie, Pfizer, Inc., Groton, CT

Robert Scala, Exxon Biomedical Sciences (Ret.), Tucson, AZ

Gina Solomon, Natural Resources Defense Council, San Francisco, CA

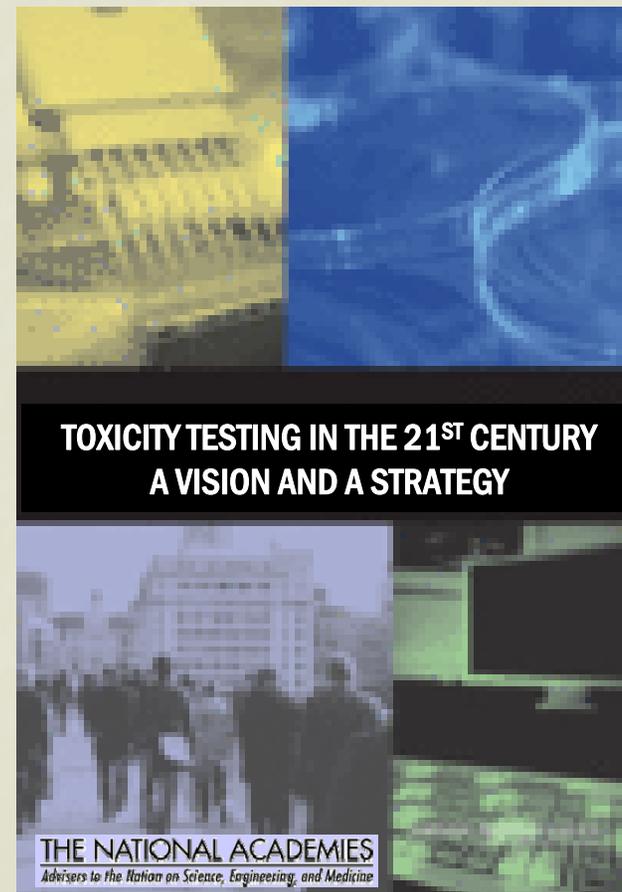
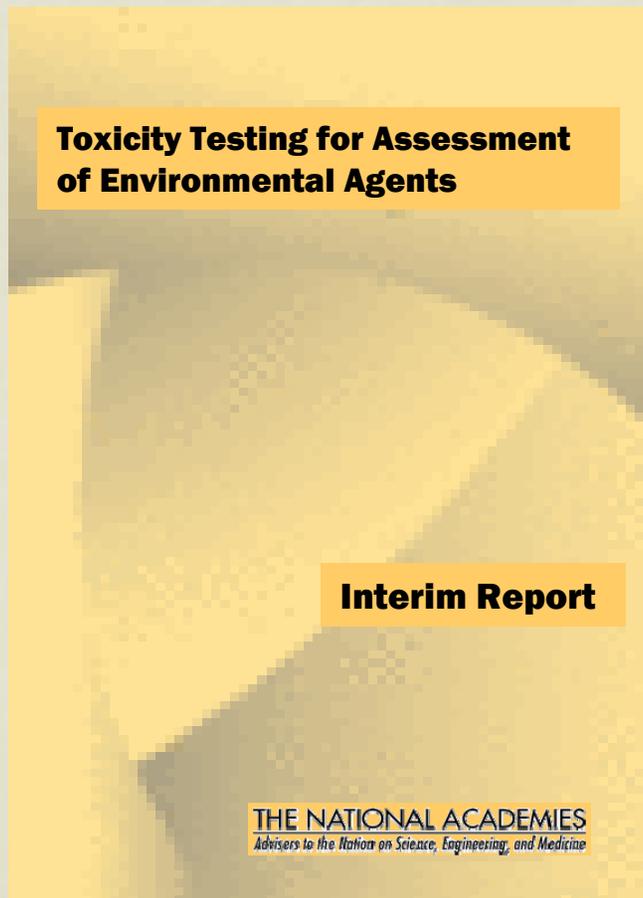
Martin Stephens, The Humane Society of the United States, Washington, DC

James Yager, Jr., Johns Hopkins University, Baltimore, MD

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Committee Reports



Interim Report

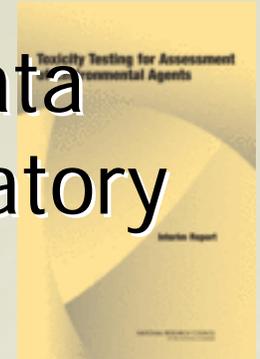


- Reviewed current toxicity-testing protocols and strategies
- Determined data needs from EPA cancer and noncancer guidelines
- Reviewed various documents and initiatives proposing improvements to toxicity-testing:
 - U.S. EPA *A Review of Reference Dose and Reference Concentration Processes*
 - NTP *Roadmap for the Future*
 - ILSI-HESI proposed modifications to pesticide testing
 - EU's REACH



Some Interim Report Conclusions

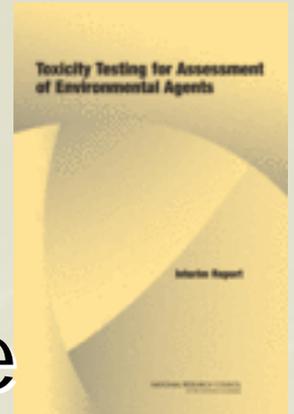
- Testing should be guided by the decisions to be made and assessments needed to support them
- ...be cautious in adding test requirements for the sake of theoretical thoroughness



- There can be a **disconnect** between data needed for risk assessment and laboratory data, e.g.:

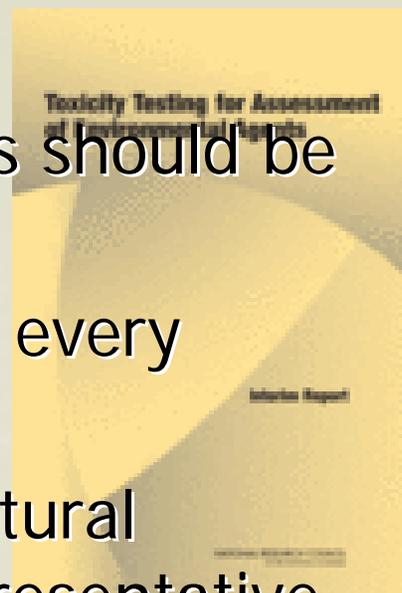


- Absent **direct** animal or human cancer evidence, chemicals generally treated as non-carcinogens and posing no cancer risk
- Test strategies not systematic in developing data to assess human variability
- Ad hoc generation of data for mode of action and pharmacokinetic evaluation (except genotoxicity data)

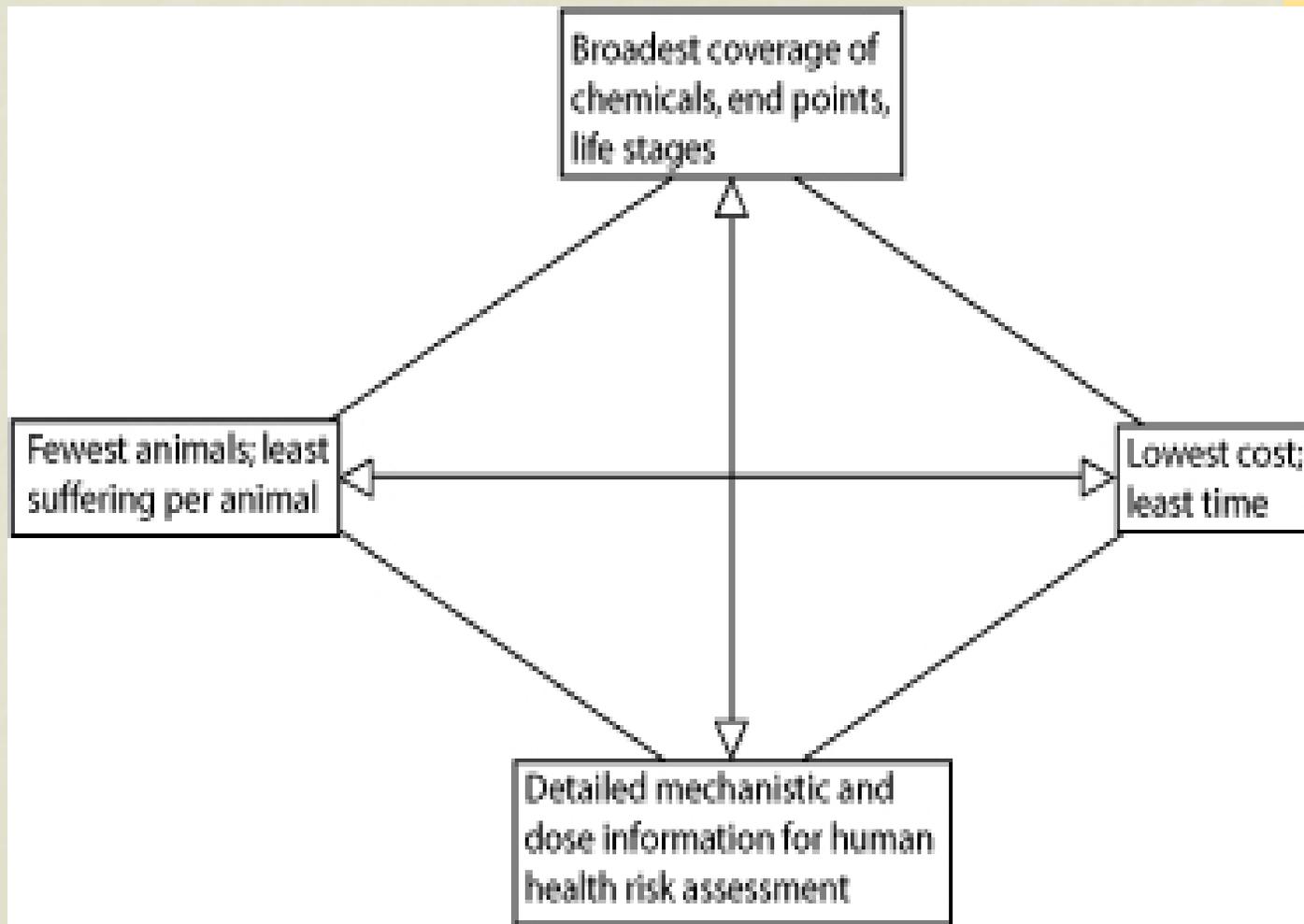
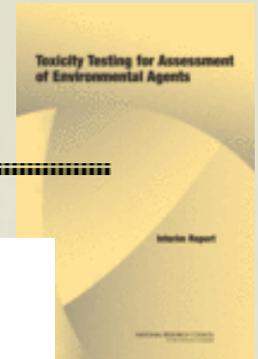


- “Ideally, regulations and risk assessment guidelines will evolve with testing capabilities and scientific understanding. That issue will increase in importance with greater use of screening approaches... that produce indirect evidence on both cancer and noncancer endpoints.”

- All new and existing environmental agents should be evaluated.
- It is impractical to test every chemical for every possible health effect over all life stages.
- Chemicals can be grouped in similar structural classes with in-depth testing of a few representative chemicals
- NTP near term efforts to refine and extend its tests
 - will increase depth of toxicity information and provide insight
 - **but** will be resource intensive and incapable of addressing large numbers of chemicals that should be assessed



- Fundamental Toxicity Test Strategy Problem:
Competing Objectives





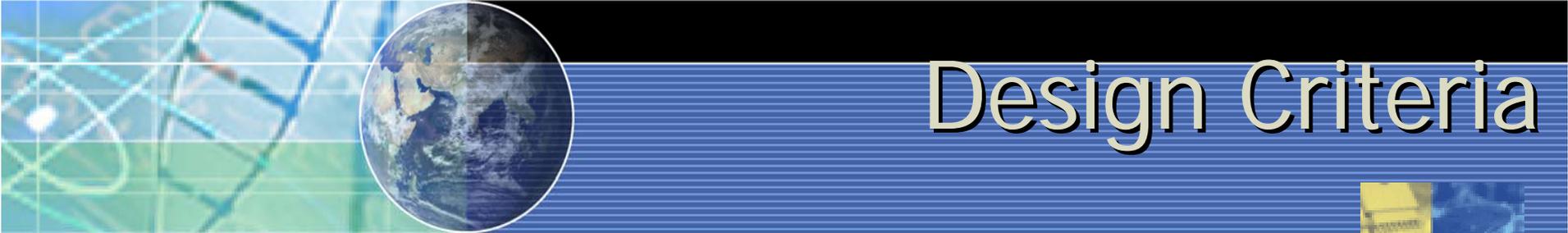
Statement of Task: Final Report

Develop a long-range vision and strategic plan to advance the practices of toxicity testing and human health assessment of environmental contaminants.

Consider the following:

- Assessment of key exposures and toxicity outcomes.
- Incorporation of state-of-the-science testing and assessment procedures.
- Methods for increasing efficiency in design and reducing animal use.
- Potential uses and limitations of new or alternative testing methods.
- Application of emerging computational and molecular techniques.





Design Criteria

A transformative paradigm needed to achieve the following design criteria:

- To provide broad coverage of chemicals, chemical mixtures, outcomes, and life stages.
- To reduce the cost and time of testing
- To use fewer animals and cause minimal suffering in the animals used.
- To develop a more robust scientific basis for assessing health effects of environmental agents.



More robust scientific basis – considerations:

- Animal – human relevance
 - High dose testing
 - Adequate coverage of sensitive humans
-



Options Considered

Option I In Vivo	Option II Tiered In Vivo	Option III In Vitro and In Vivo	Option IV In Vitro
Animal biology	Animal biology	Primarily human biology	Primarily human biology
High doses	High doses	Broad range of doses	Broad range of doses
Low throughput	Improved throughput	High and medium throughput	High throughput
Expensive	Less expensive	Less expensive	Less expensive
Time-consuming	Less time-consuming	Less time-consuming	Less time-consuming
Use of relatively large numbers of animals	Use of fewer animals	Use of substantially fewer animals	Use of virtually no animals
Based on apical end points	Based on apical end points	Based on perturbations of critical cellular responses	Based on perturbations of critical cellular responses
	Some screening using computational and in vitro approaches; more flexibility than current methods	Screening using computational approaches possible; limited animal studies that focus on mechanism and metabolism	Screening using computational approaches



Current Paradigm: The Exposure-Response Continuum



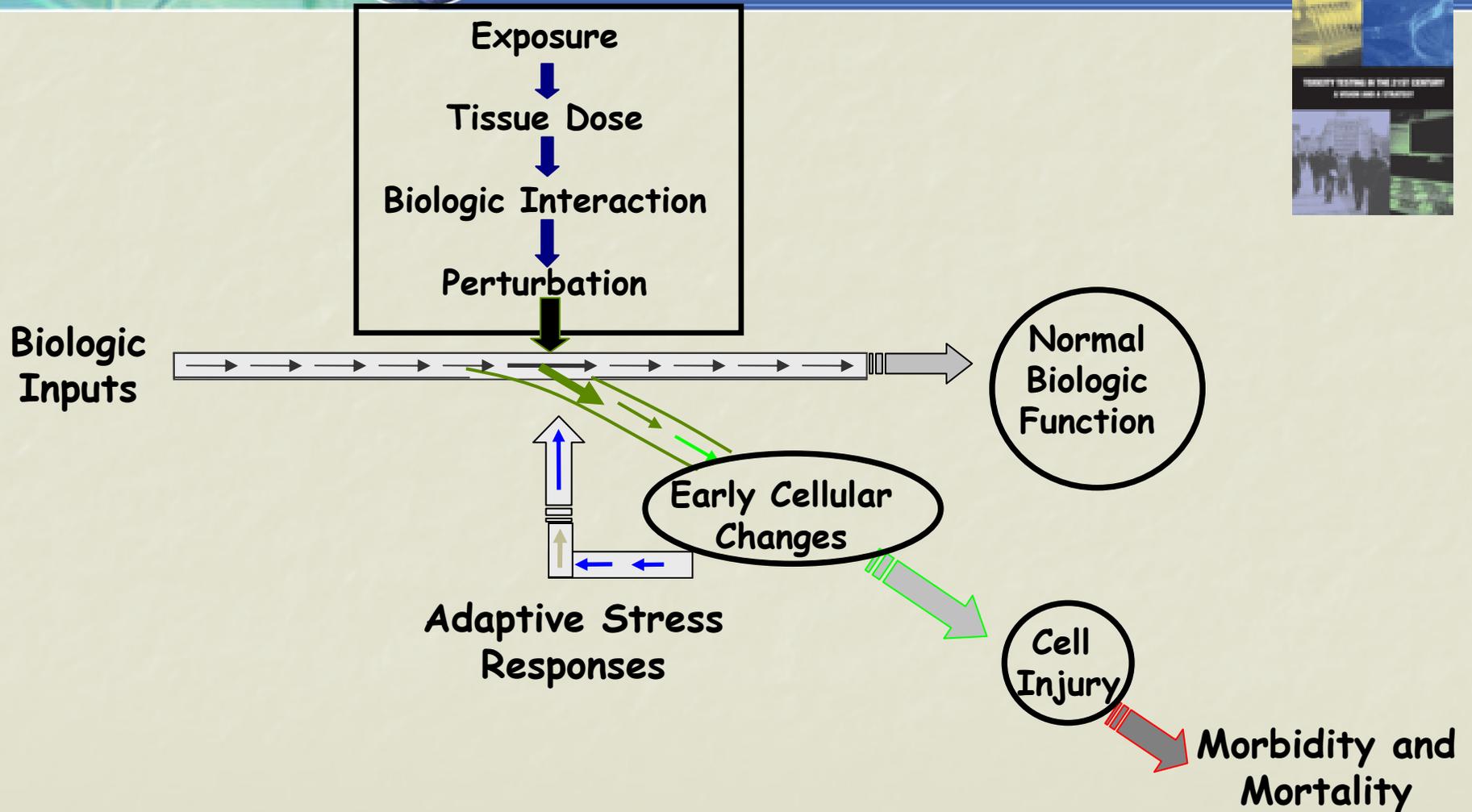


Toxicity Pathways



Toxicity Pathways:
Cellular response pathways that, when sufficiently perturbed, are expected to result in adverse health effects.

A New Paradigm



Perturbations and Disease

- Biologic responses viewed as results of an intersection of exposure and biologic function.
- Toxicity and disease results from:
 - Sufficiently large perturbations
OR
 - When the host is unable to adapt because of underlying nutritional, genetic, disease or life-stage status



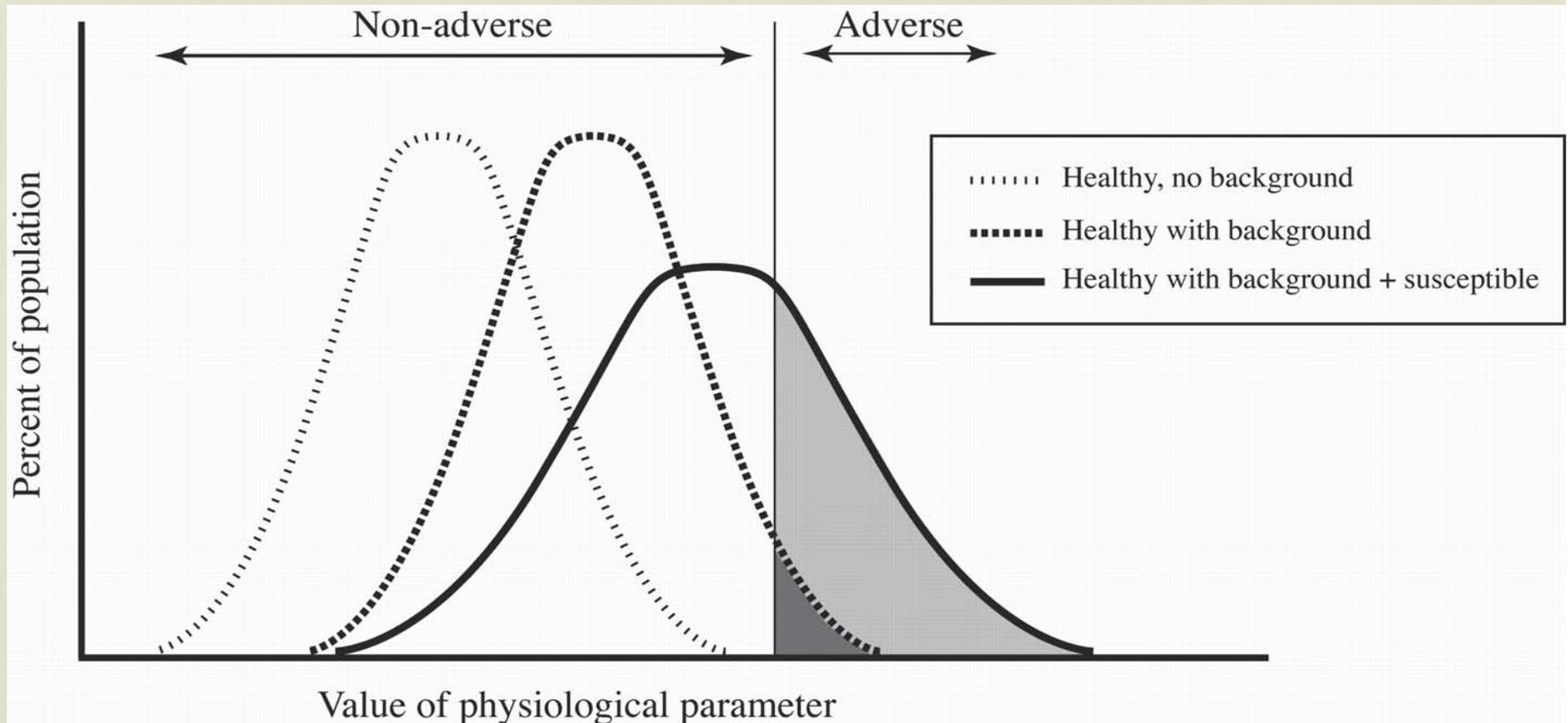
Paradigm Accounts for Impact of Background and Vulnerability on Risk

- Background

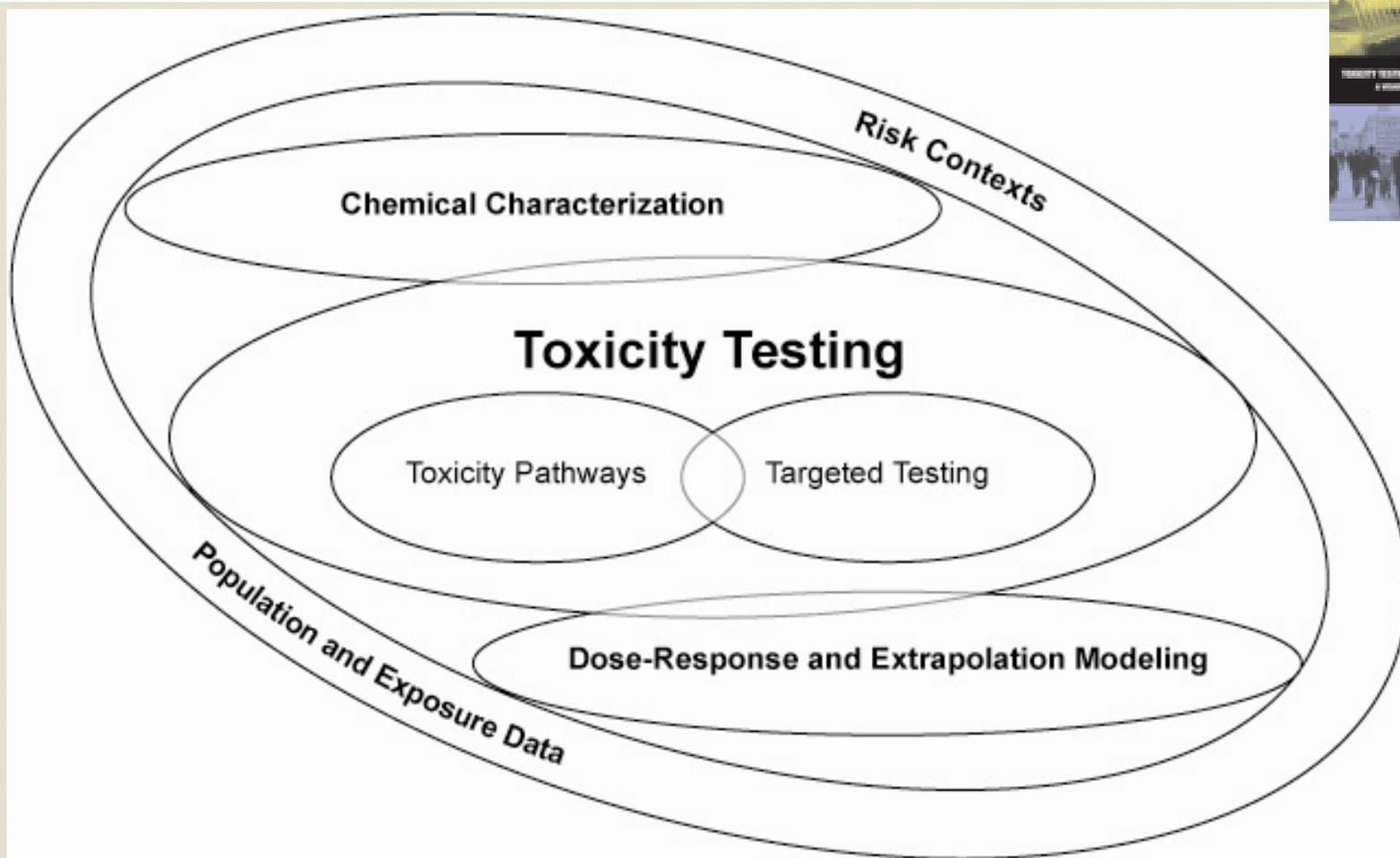
- Biological
- Exposure

- Vulnerability, e.g., from

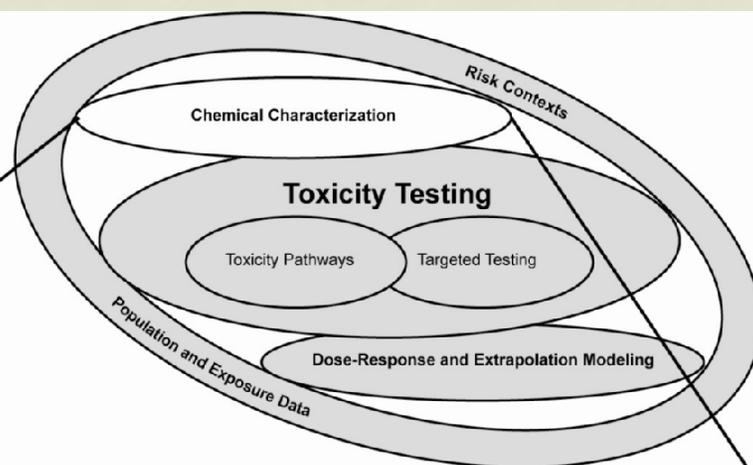
- Life stage
- Genetics
- Health disease status



Components of Vision



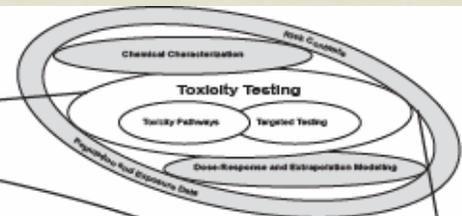
Chemical Characterization



Chemical Characterization

- Compile data on physical and chemical properties, use characteristics, environmental concentrations, possible metabolites and breakdown products, and possible toxic properties.
- Predict properties and characteristics, where possible and appropriate, by using computational tools.
- Answer key questions concerning compound's stability, potential for human exposure and bioaccumulation, and toxicity of chemical and possible metabolites.

Toxicity Testing



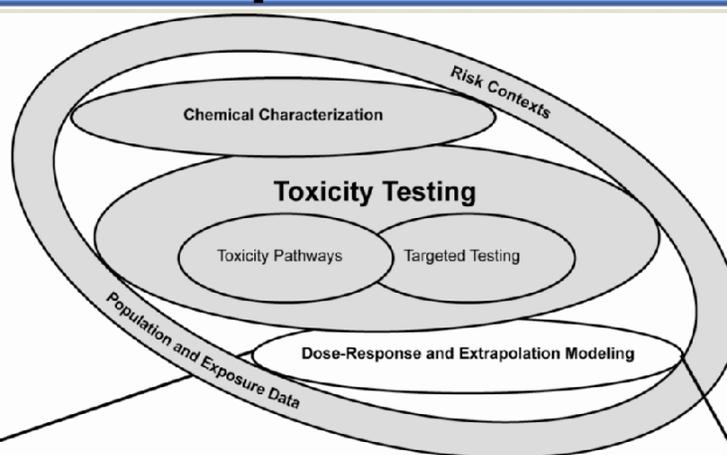
Toxicity Pathways

- Evaluation of perturbations in toxicity pathways rather than apical end points.
- Emphasis on high-throughput approaches using cells or cell lines, preferably of human origin.
- Use of medium-throughput assays of more integrated cellular responses.

Targeted Testing

- Testing conducted to evaluate metabolites, assess target tissues, and develop understanding of affected cellular processes at genomics level.
- Limited types and duration of in vivo studies, focusing on up to 14-day exposures.
- More extensive testing for representative compounds in novel chemical classes.

Dose-Response and Extrapolation Modeling



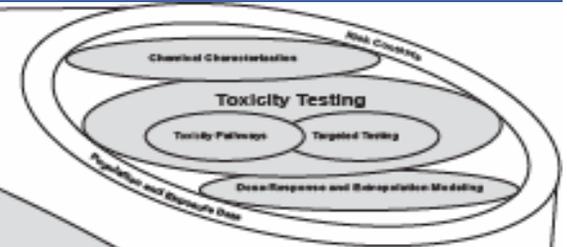
Dose-Response and Extrapolation Modeling

- Empirical dose-response models will be developed on the basis of data from in vitro, mechanistically based assays.
- Physiologically based pharmacokinetic (PBPK) models will equate tissue-media concentrations from toxicity tests with tissue doses expected in humans.
- Dose-response models for toxicity pathways will reliably predict concentrations expected to cause measurable precursor-effect responses.
 - PBPK and toxicity-pathway models will identify biomarkers of susceptibility for sensitive subpopulations.

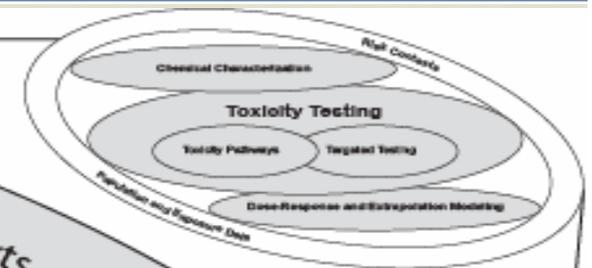
Population and Exposure Data

- Population-based studies, particularly those involving cellular or molecular components, may provide information on perturbations in cellular-response networks and toxicity pathways.
- Population-based studies can provide information on host susceptibility and background exposures for interpreting and extrapolating in vitro test results.
- Population-based studies can reveal health risks not previously identified through toxicity testing.
 - Human exposure data can be used to select doses for toxicity testing that can provide information on biologic effects at environmentally relevant exposures.
 - Comparison of human exposure data from biomonitoring surveys with concentrations that perturb toxicity pathways can be used to identify potentially important exposures.

Population and Exposure Data

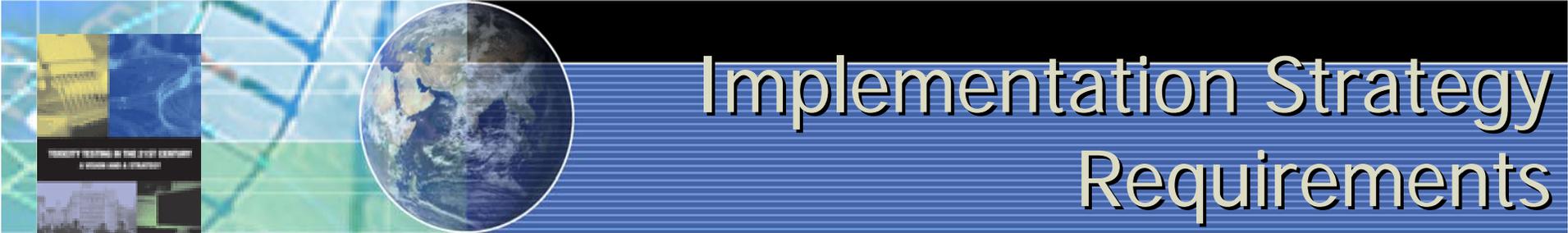


Risk Contexts



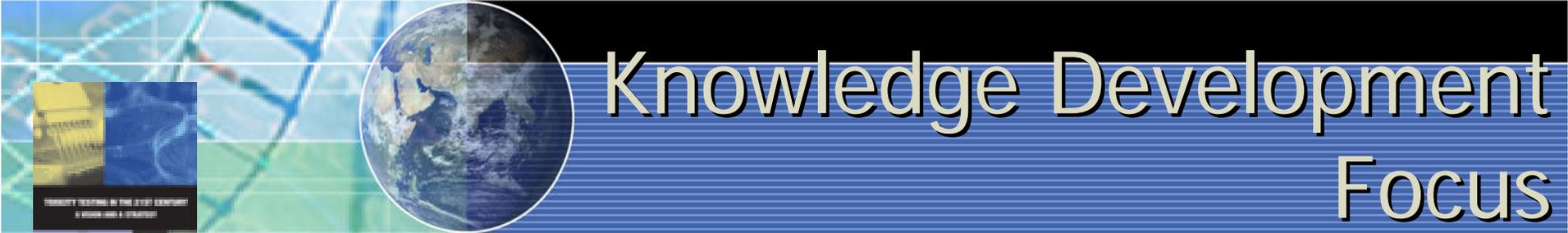
- Evaluation of new environmental agents.
- Evaluation of existing environmental agents.
 - Evaluation of a site.
 - Evaluation of potential environmental contributors to a specific disease.
 - Evaluation of the relative risks associated with environmental agents.





Implementation Strategy Requirements

- Comprehensive suite of in vitro tests, preferably based on human cells, cell lines, or components.
- Targeted tests to complement in vitro tests.
- Computational models of toxicity pathways to support application of in vitro test results.
- Infrastructure changes to support basic and applied research needed to develop the tests and pathway models
- Validation of tests and test strategies
- Evidence justifying that toxicity-pathway approach is adequately predictive of adverse health outcomes to use in decision-making.



Knowledge Development Focus

- Toxicity-pathway identification
- Multiple pathways
- Adversity
- Life stages
- Effects of exposure duration
- Low-dose response
- Human variability



Method Development Focus

- Methods to predict metabolism
- Chemical-characterization tools
- Assays to uncover cell circuitry
- Assays for large-scale application
- Suites of assays
- Human-surveillance strategy
- Mathematical models for data interpretation and extrapolation
- Test-strategy uncertainty





Program Time Line

Phase I

- Elucidate toxicity pathways.
- Establish data-storing and -management systems.
- Establish practices for assay conduct and reporting.
- Plan human-surveillance and -biomonitoring strategy.

Phase II

- Develop suite of representative human cell lines and cultures.
- Develop and validate high- and medium-throughput assays.
- Develop biomarkers for exposure, susceptibility, and effect for human surveillance and biomonitoring.

Phase III

- Gain experience through testing mechanistic assays
 - In parallel with traditional apical tests.
 - On chemicals with large datasets of apical tests.
 - By screening chemicals that would not otherwise be tested.
- Begin biomonitoring and surveillance of human populations.

Phase IV

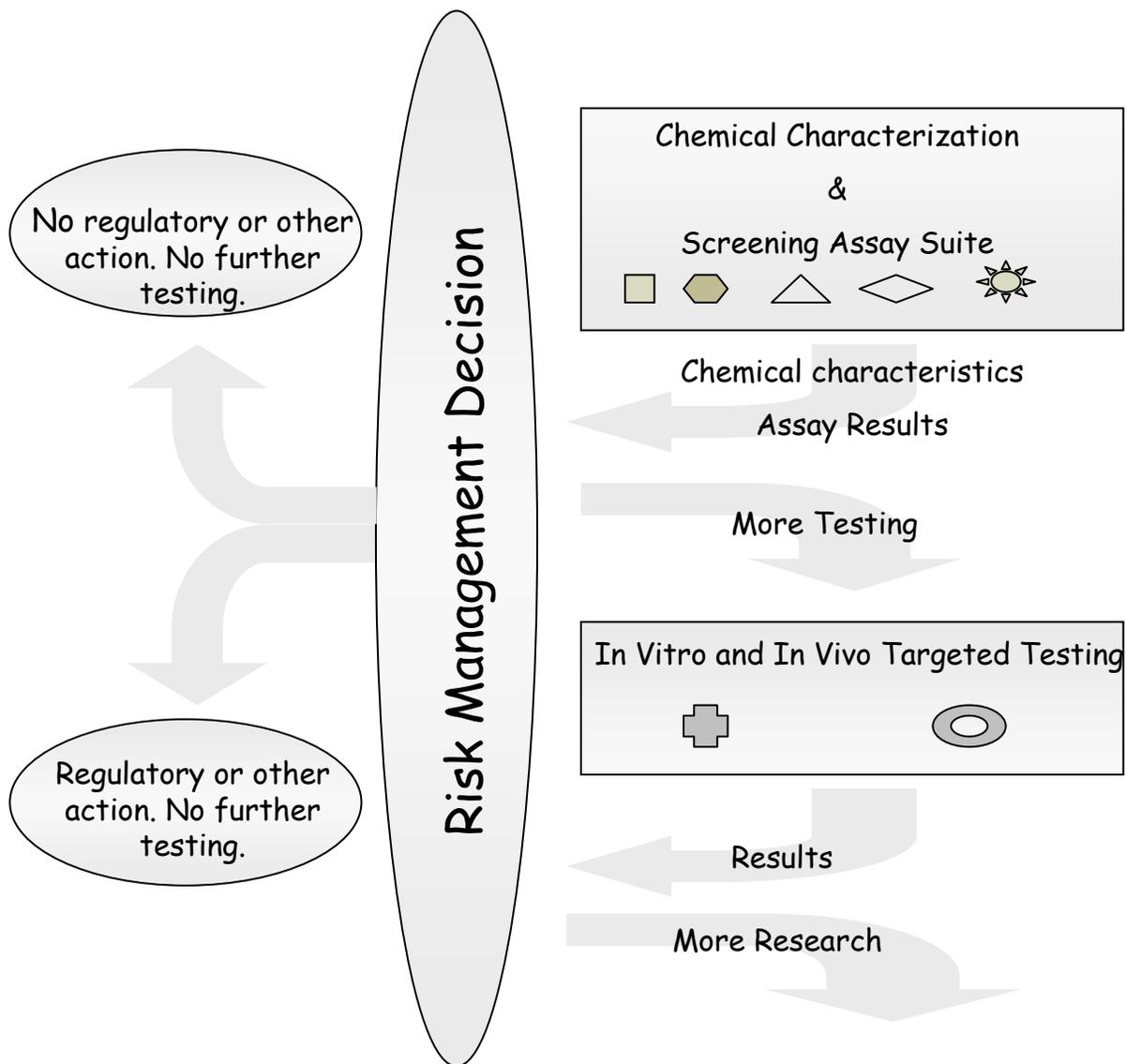
- Propose then validate suites of assays for use in place of identified apical tests.

Time



In Phase III: Assay Relevance and Validity Trial:

- For chemicals that otherwise would not be tested, a possible improved framework for chemical evaluation





Building a Transformative Research Program

- Long-term, large-scale concerted effort needed to bring vision to fruition.
- Appropriate institutional structure that fosters multidisciplinary intramural and extramural research needed to achieve vision.
- The effort will not succeed merely by creating a virtual institution to link and integrate organizations that perform relevant research.





The Institute

- Interdisciplinary research program
- Intramural and extramural research
- High-level coordination
- Cross-institution and cross-sector linkages
- Substantial funding
- Funded and coordinated primarily by federal government
- Midcourse corrections





Concluding Remarks

Some resistance to the vision is expected. However,

- The vision takes full advantage of current and expected scientific advances.
- It has the potential to greatly reduce animal use and the cost and time of testing.
- It will lead to much broader coverage – assessment of many more chemicals and end points.
- Testing will allow assessment of environmentally relevant doses.

“The vision is a paradigm shift that will not only improve the current system but transform it into one capable of overcoming current limitations and meeting future challenges.”



Moving Upstream

