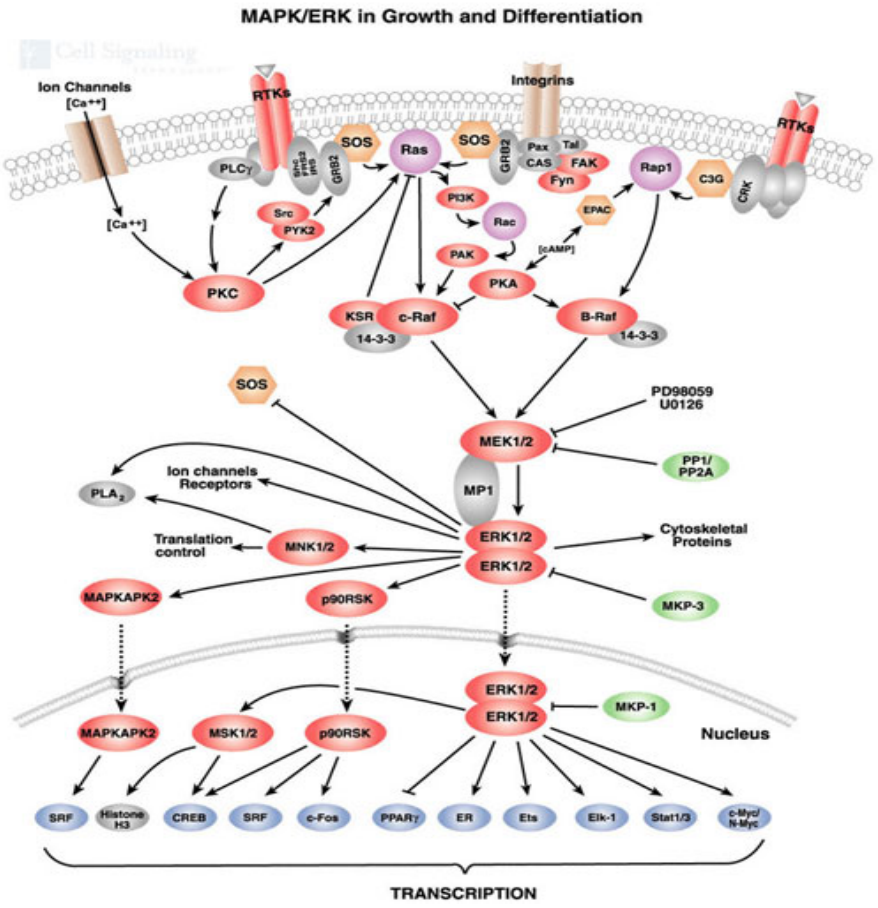
Toxicity Testing for Risk Assessment in the 21st Century

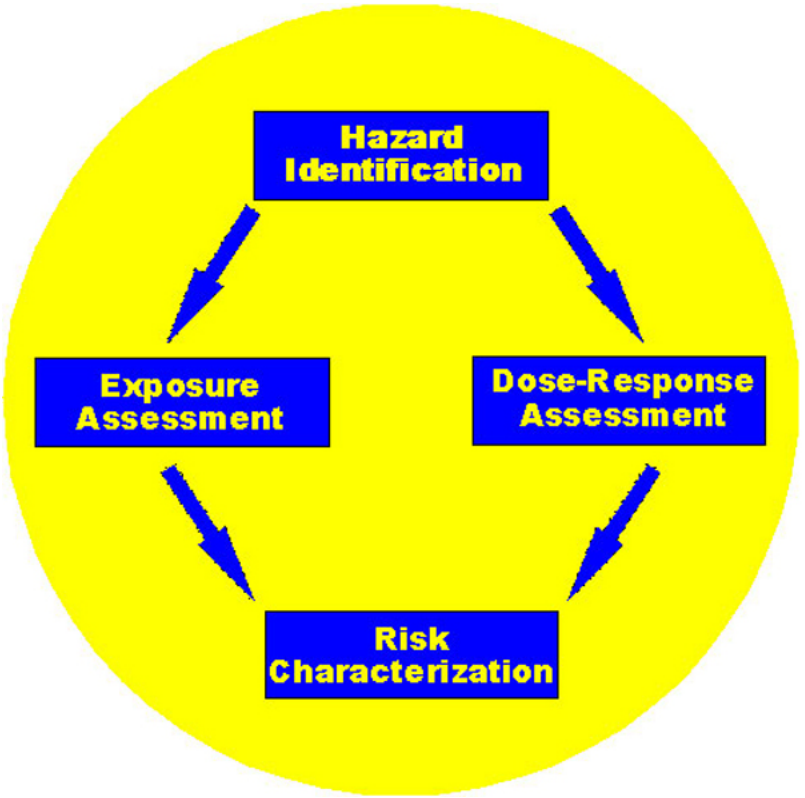
NOW

THE FUTURE



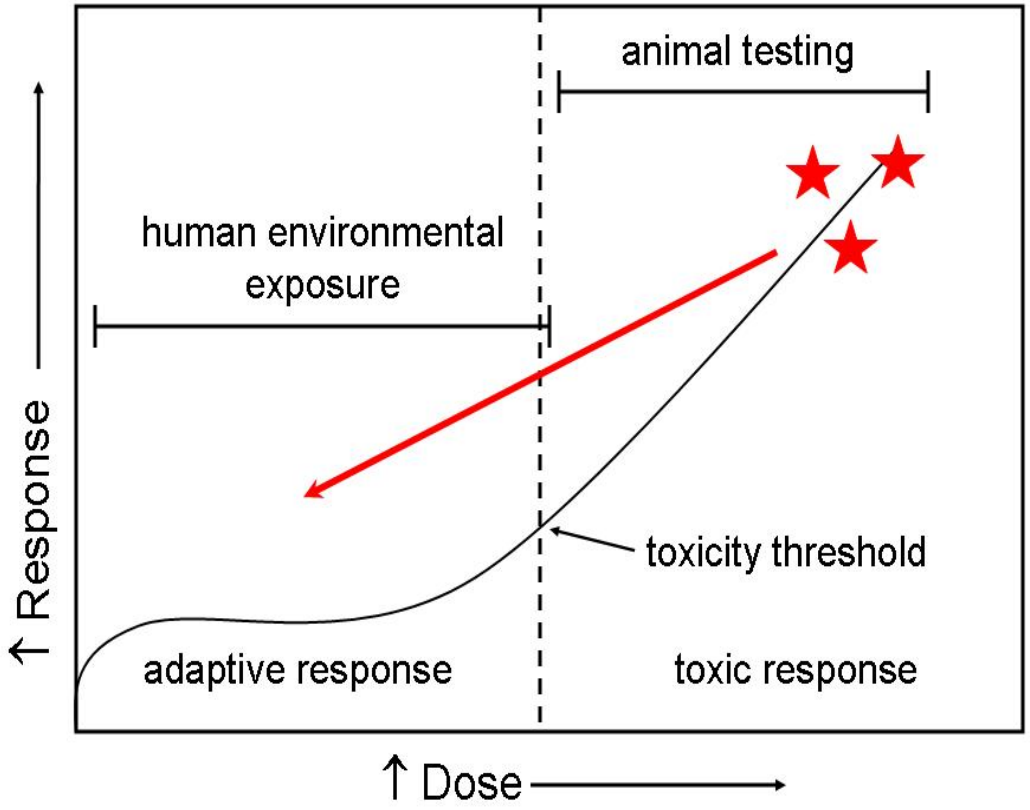
Risk Assessment Paradigm — The "Red Book" Approach (1983)

- Hazard identification – animal studies
- Dose-response assessment – animal studies
- Exposure assessment – field studies
- Risk characterization – hazard x exposure
- Risk Management – exposure standard depends on context, risk-benefit analysis



The Current Approach

- High doses in animals
- Large number of animals
- Low throughput
- Expensive
- Time consuming
- Pathology endpoints
- Dose response extrapolations over a wide range
- Application of uncertainty factors



How good is the current system?

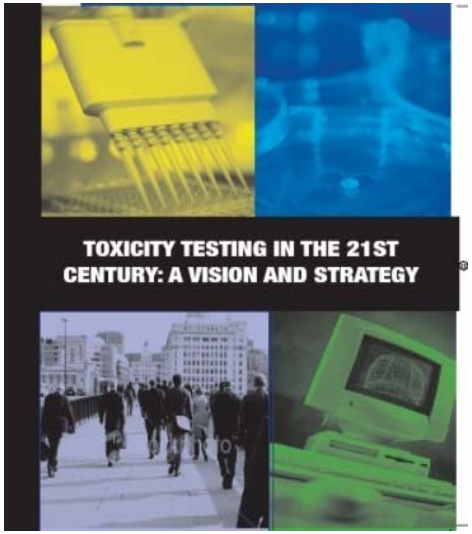
This is a difficult question to answer!

For pharmaceuticals, some insight:

Olson, H et al. “Concordance of Toxicity of Pharmaceuticals in Humans and Animals,” Regul Toxicol Pharmacol 32, 56-67, 2000

- 12 companies provided coded data to ILSI to examine how well preclinical animal studies predict actual human toxicities (150 compounds)
- Overall true positive human toxicity concordance of 71% (non-rodents alone 63%, rodents alone 43%)
- Concordance varied a lot among different tissues
- Differences in metabolism don’t explain non-concordance


THE SCIENTIFIC COMMUNITY
IS DIVIDED.
SOME SAY THIS STUFF IS
DANGEROUS, SOME SAY
IT ISN'T.



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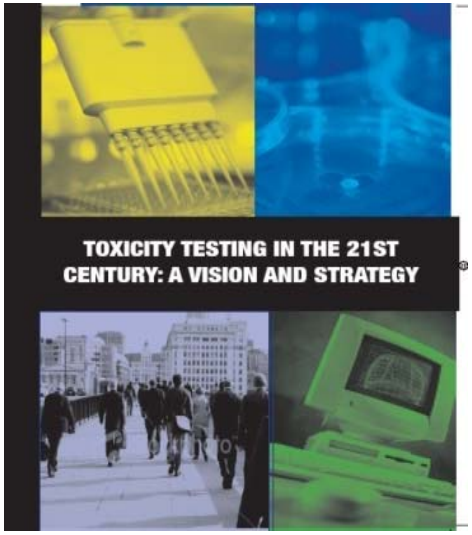
Toxicity Testing in the 21st Century
A Vision and a Strategy

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

Committee Roster

Daniel Krewski (*Chair*), University of Ottawa, Ottawa, ON
Daniel Acosta, Jr., University of Cincinnati, Cincinnati, OH
Melvin Andersen, CIIT Centers for Health Research, 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
Robert Brent, Thomas Jefferson University, Wilmington, DE
Gail Charnley, HealthRisk Strategies, Washington, DC
Vivian Cheung, University of Pennsylvania, Philadelphia, PA
Sidney Green, Howard University, Washington, DC
Karl Kelsey, Harvard University, Boston, MA
Nancy Kerkvliet, Oregon State University, Corvallis, OR
Abby Li, Exponent, Inc.**,** San Francisco, CA
Lawrence McCray, Massachusetts Institute of Technology, Cambridge MA
Otto Meyer, Danish Institute for Food and Veterinary Research, Søborg, Denmark
D. Reid Patterson, Reid Patterson Consulting, Inc., Grayslake, IL
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
Lauren Zeise, California Environmental Protection Agency, Oakland, CA

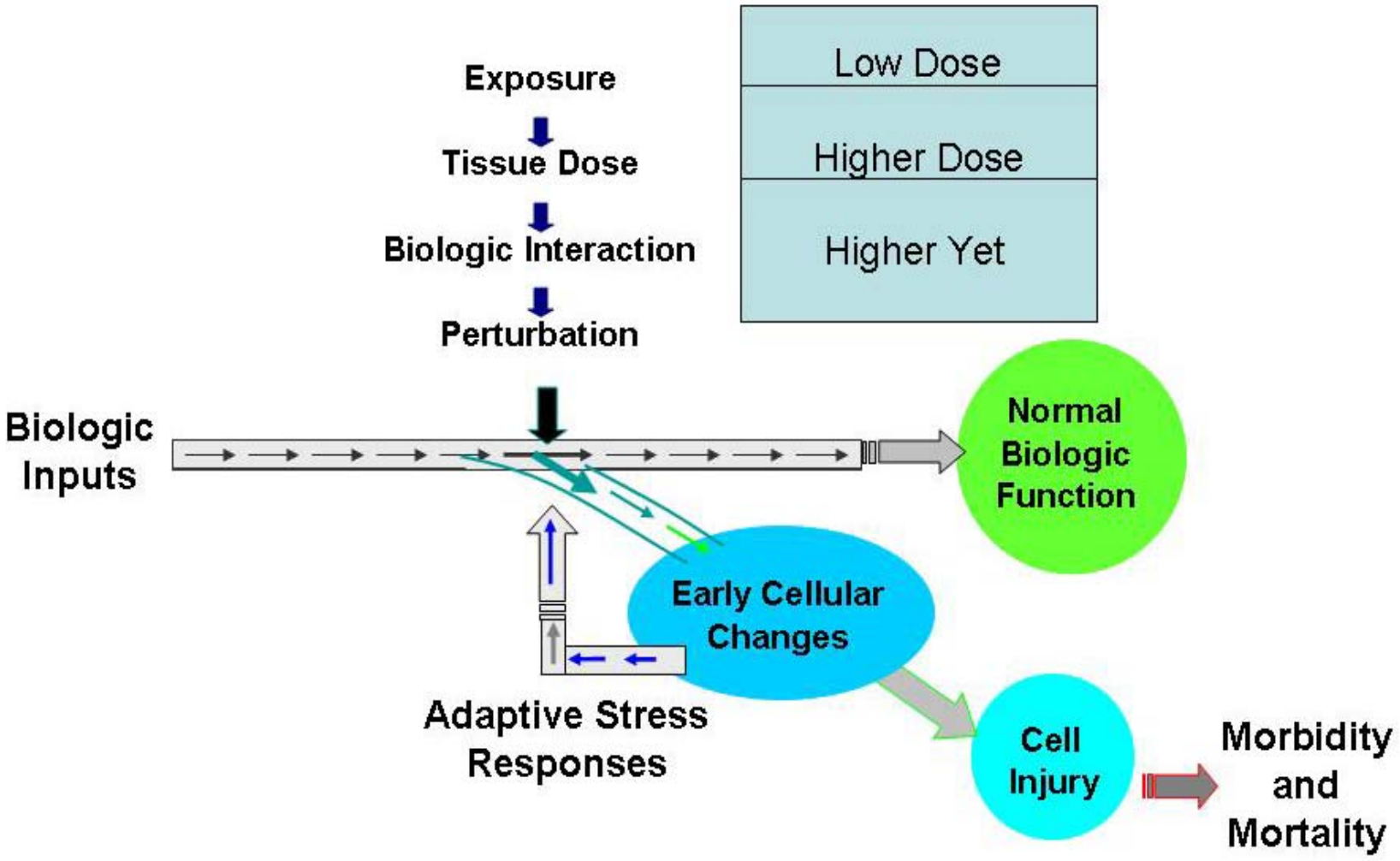


Proposed new direction based on “Toxicity Pathways”

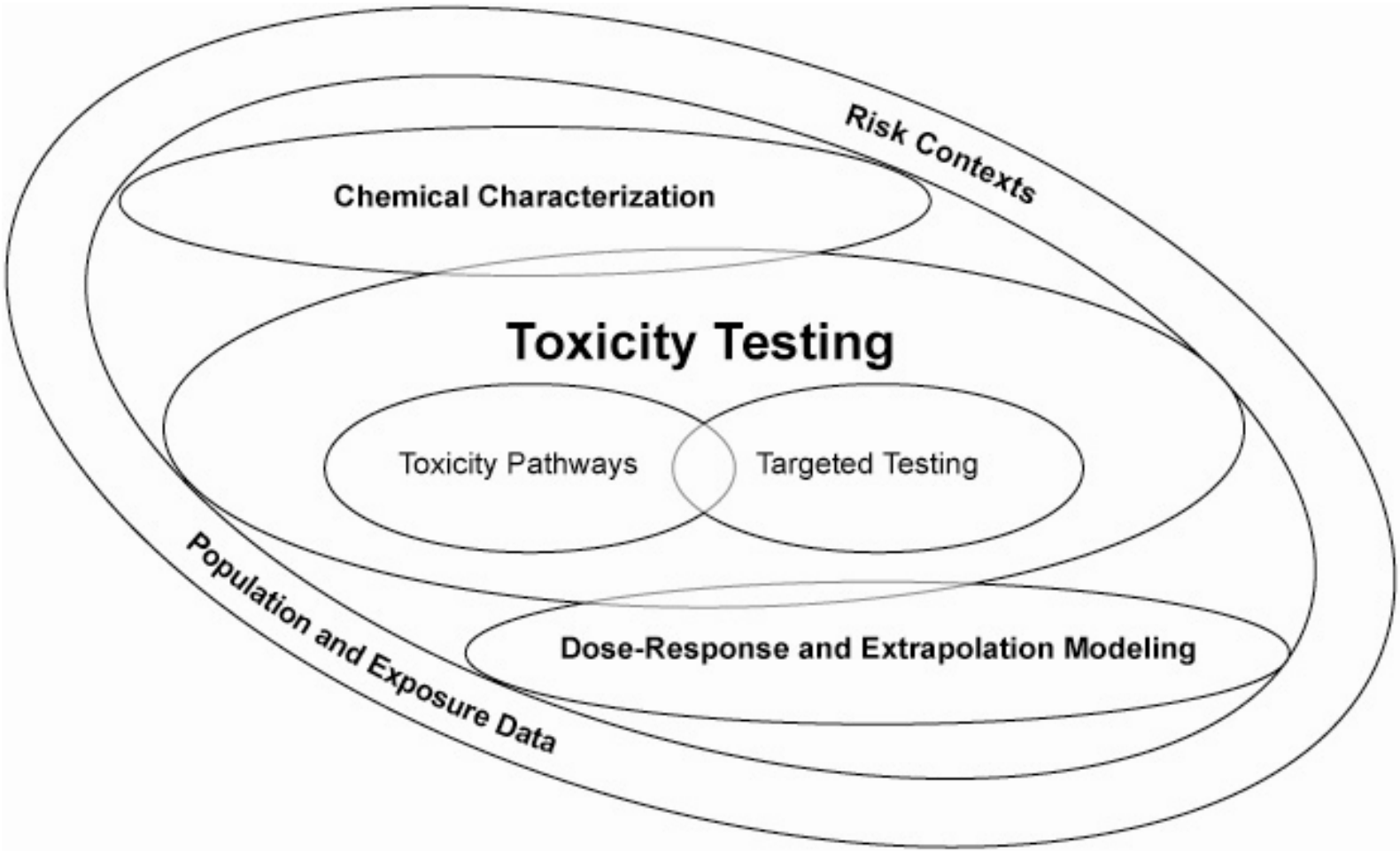
TOXICITY PATHWAYS:

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

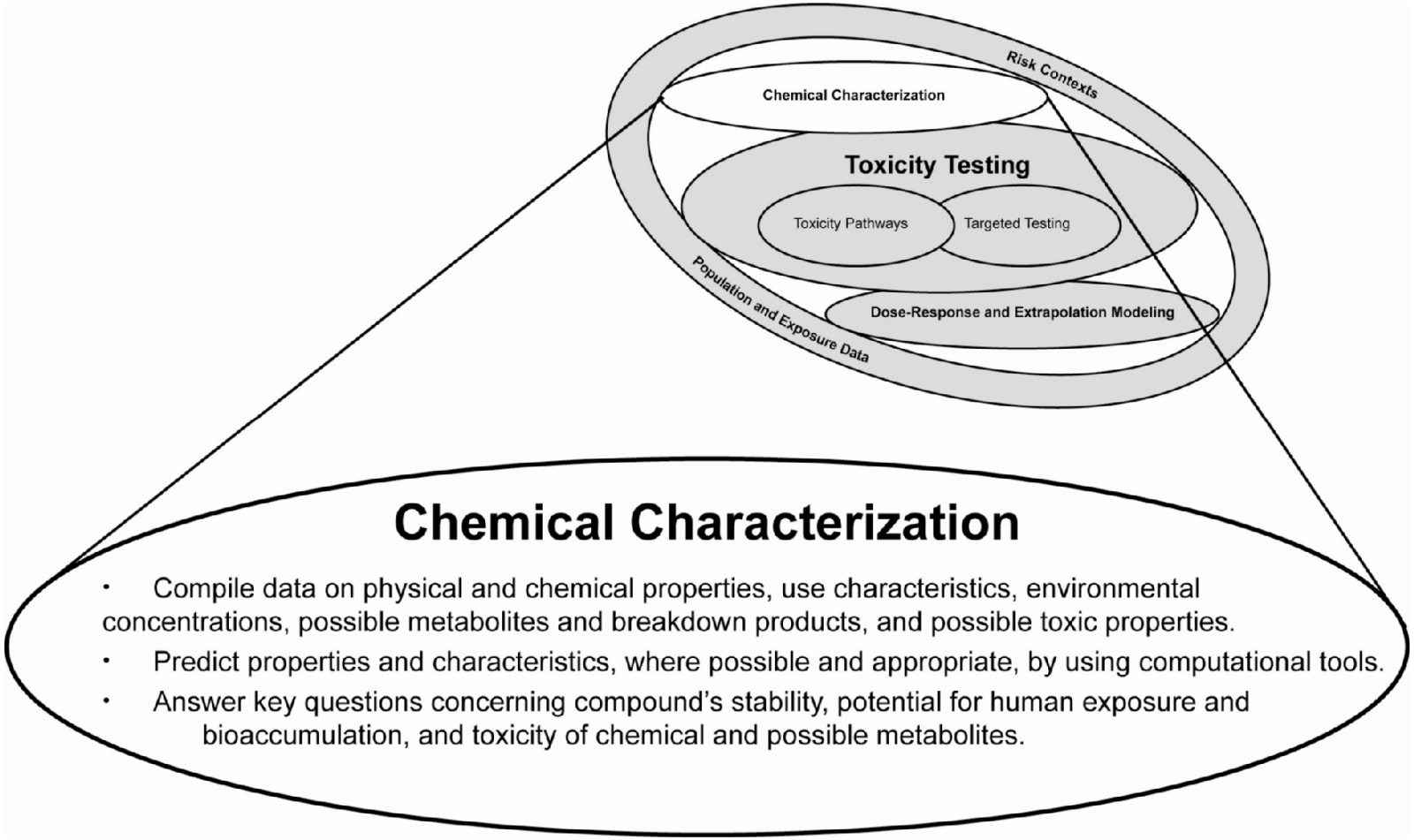
Activation of Toxicity Pathways



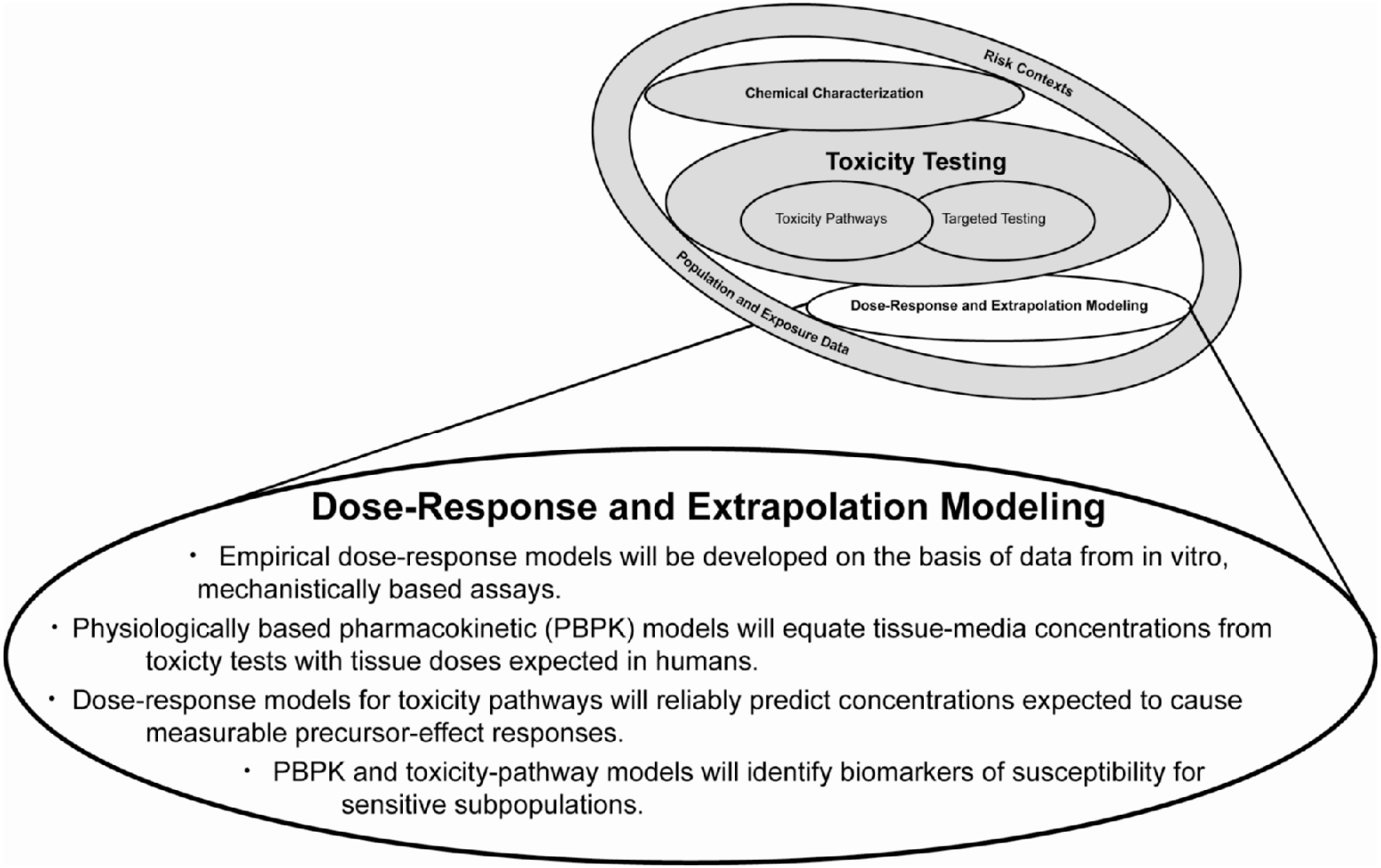
The Vision


Risk Contexts
Chemical Characterization
Toxicity Testing
Toxicity Pathways
Targeted Testing
Dose-Response and Extrapolation Modeling
Population and Exposure Data

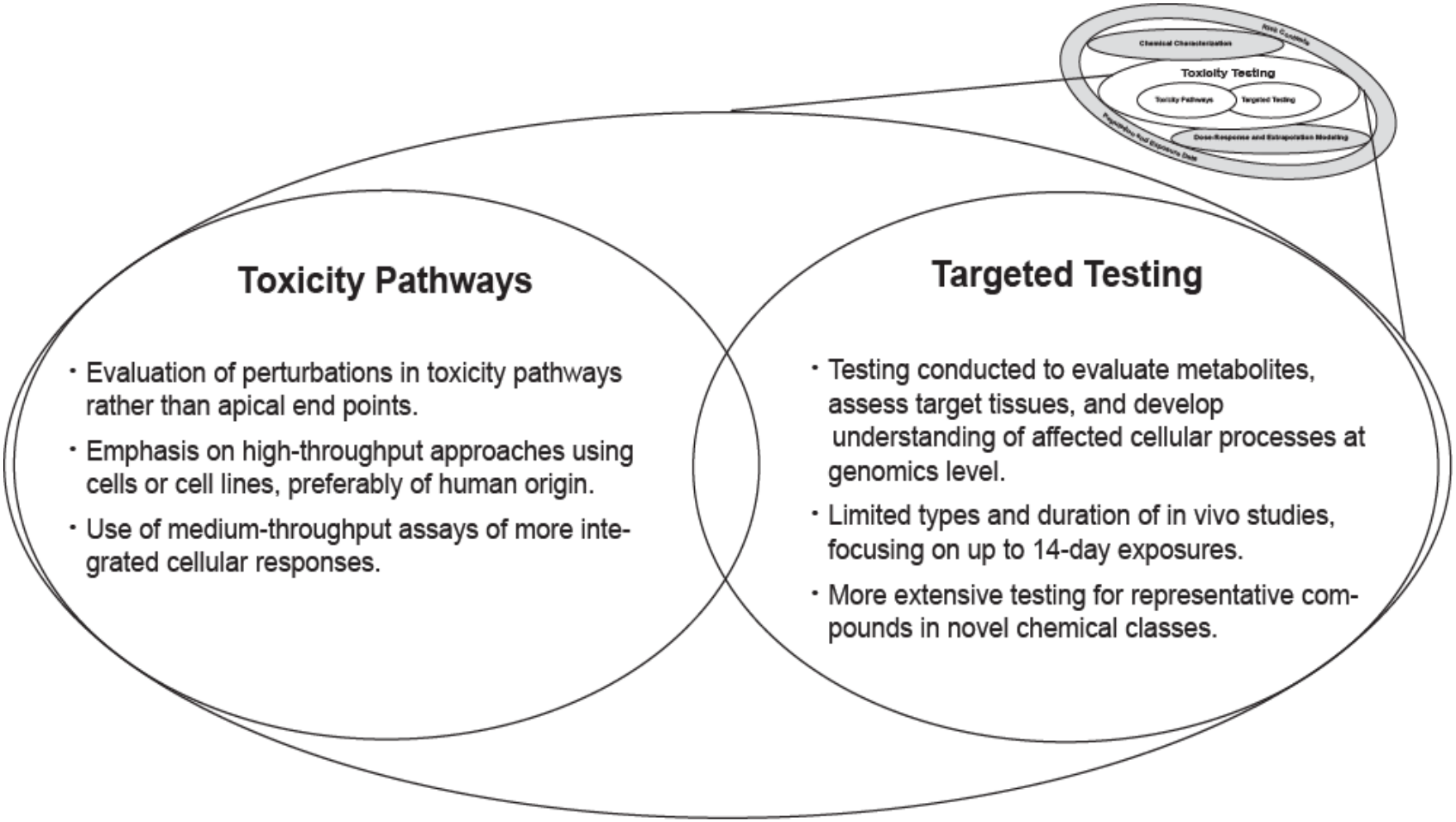
Chemical Characterization



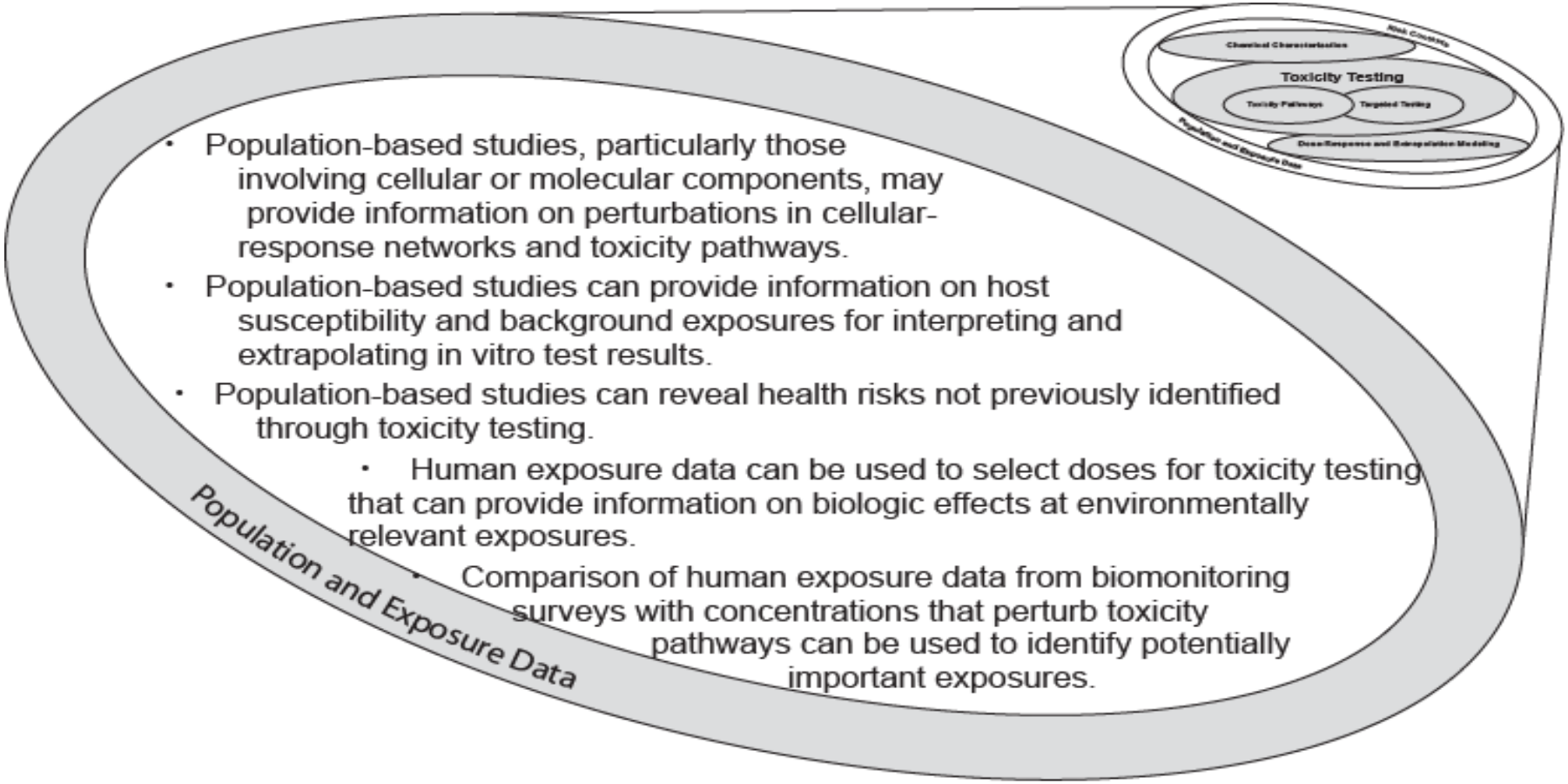
Dose-Response and Extrapolation Modeling



Toxicity Testing

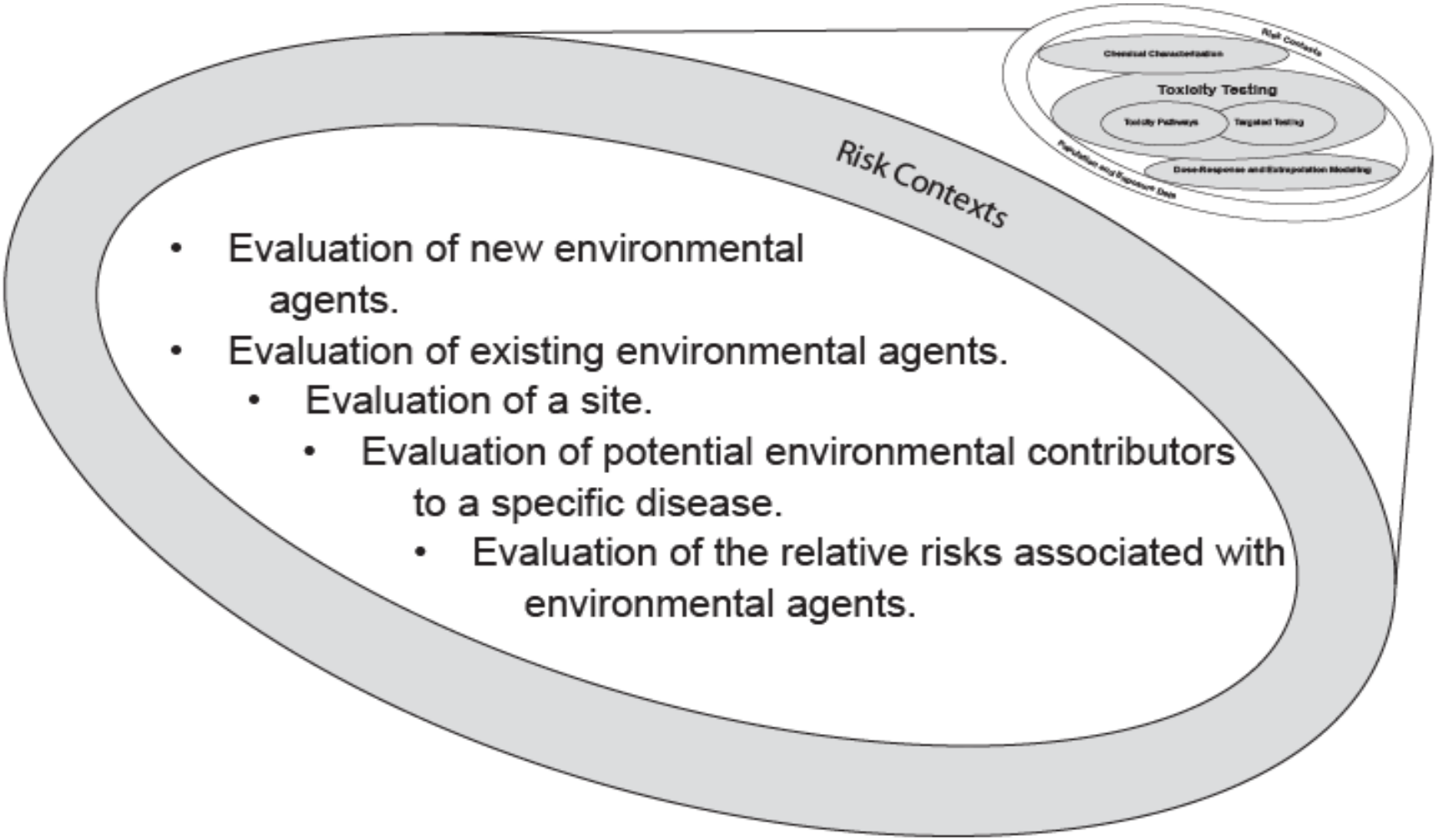


Population and Exposure Data

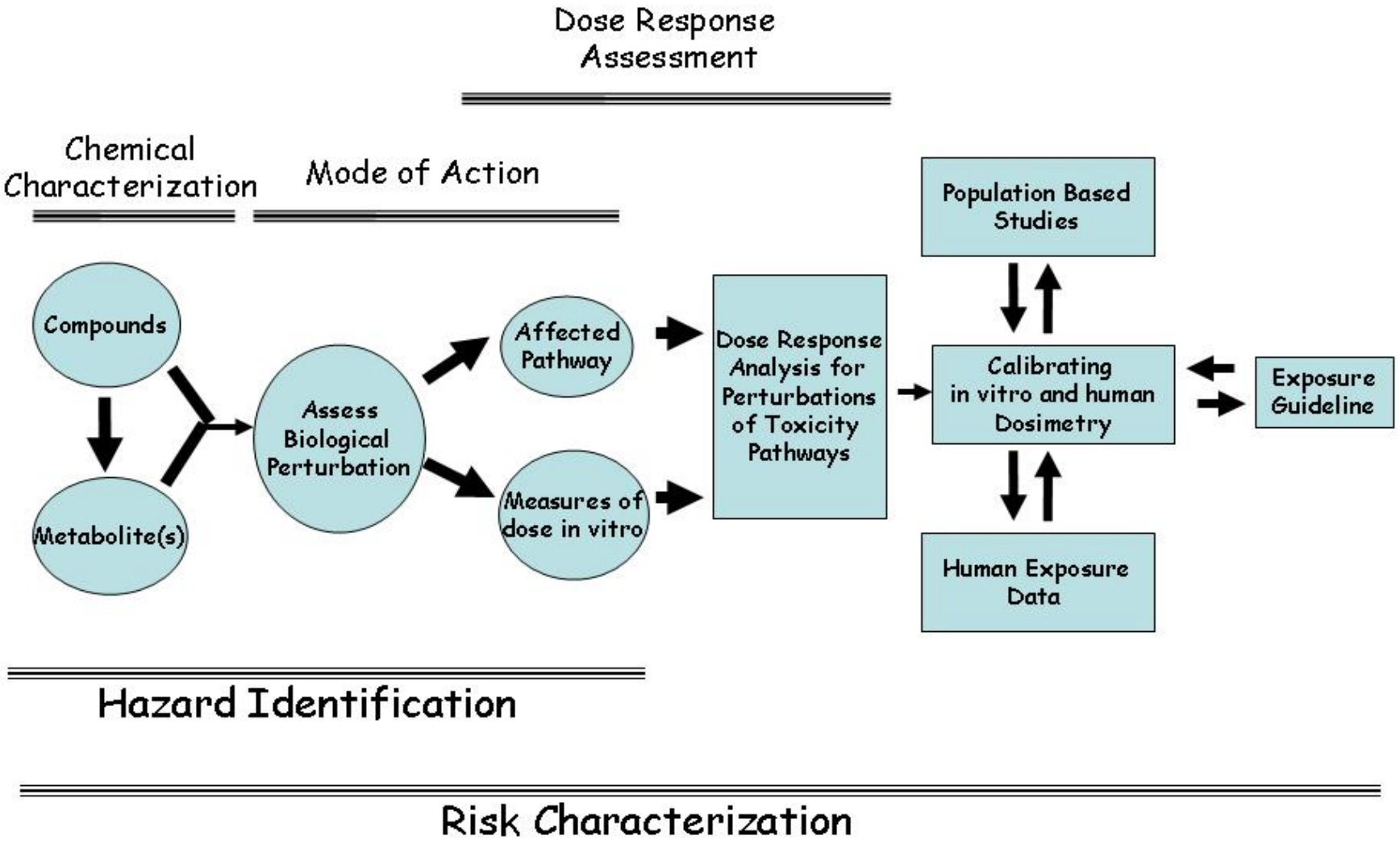


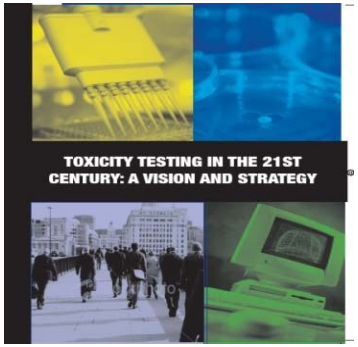
- Population-based studies, particularly those involving cellular or molecular components, may provide information on perturbations in cellular-response networks and toxicity pathways.
- Population-based studies can provide information on host susceptibility and background exposures for interpreting 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.

Risk Contexts



Toxicity Testing and Risk Assessment





Implementation of Strategy

- Comprehensive suite of in vitro tests, preferably based on human cells, cell lines, or components.
- Computational models of toxicity pathways to support application of in vitro test results in risk assessments.
- 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.

PROMISES

- Human relevance
- Dose relevance
- Chemical coverage
- Mechanistic focus: mode of action based
- Cost effective
- Fast
- The 3 Rs: replacement, reduction, refinement

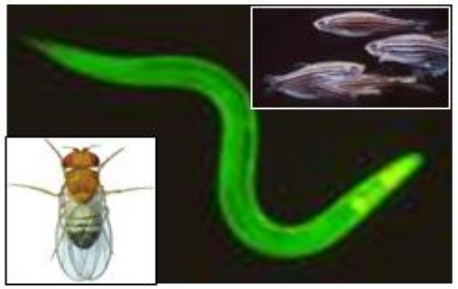
CONUNDRUMS

- Screening tool or stand-alone test system?
- Validation: to what? Animals at high doses?
- Human cell lines have a lot of abnormal biology
- Mixtures
- Metabolism
- Epigenetics, and other unknown mechanisms
- Cell-cell and organ interactions
- Distinguishing “adaptive” from “adverse” responses
- Toxicogenomics – overpromised and underperformed
- Use of an ‘unfamiliar’ surrogate (rats look more like people than cells look like people)
- Is this another “war on cancer?”

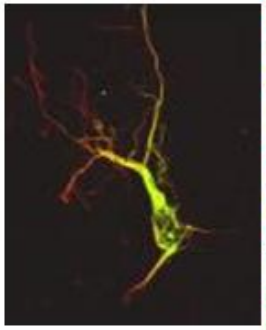
NIEHS: High Throughput Screens

1-3/year

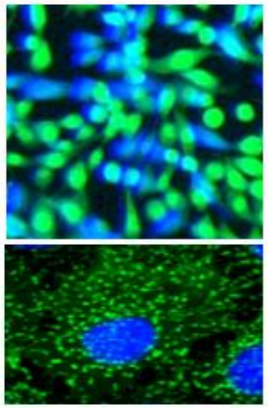
10's/year

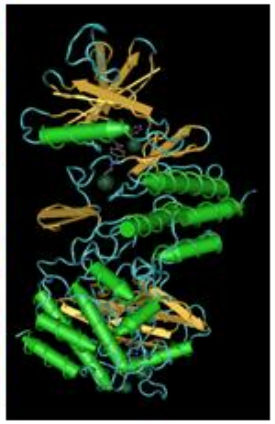


100's/year



10,000's/day



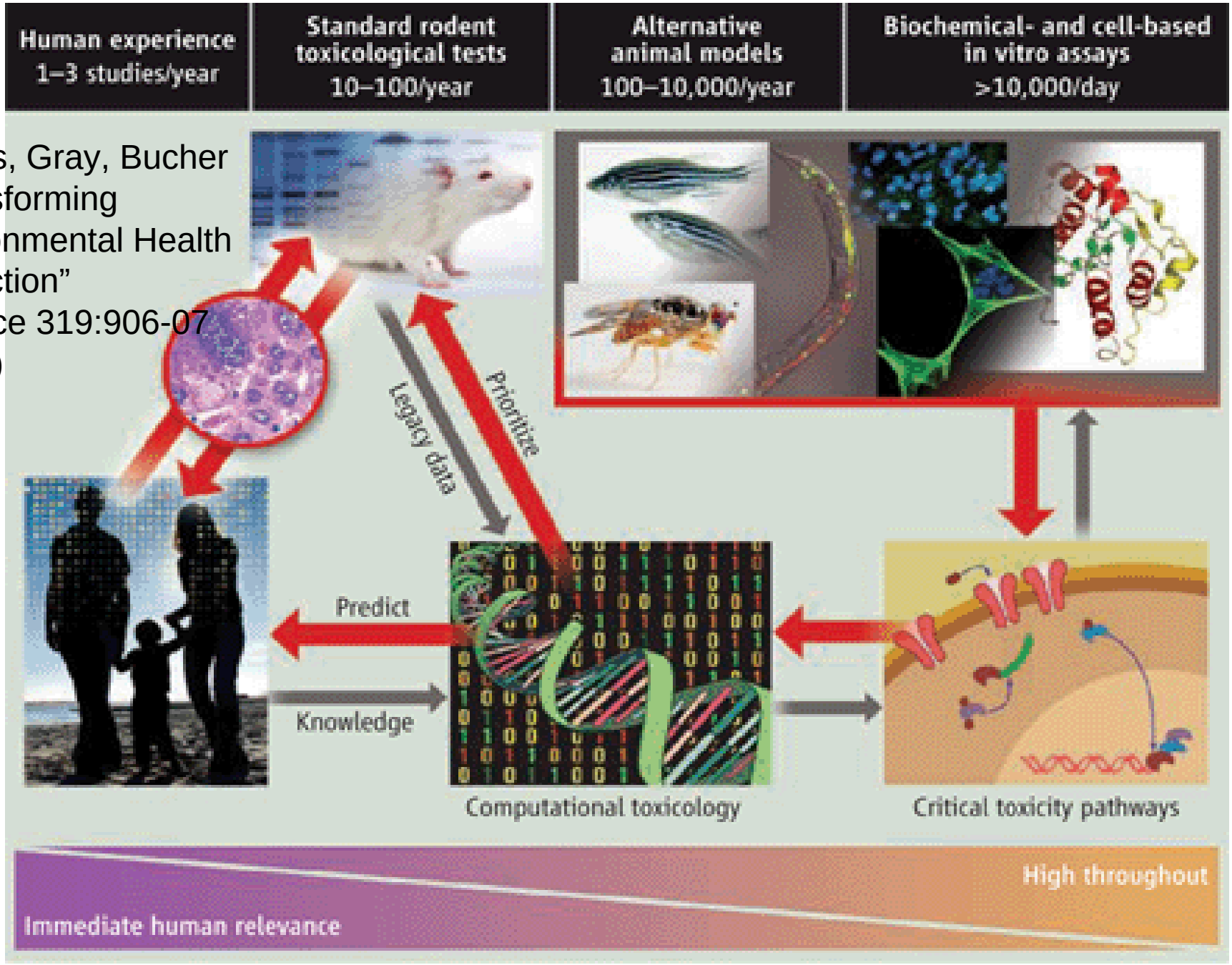


100,000's/day

High Throughput
Molecular mechanism

Immediate Human Relevance

Collins, Gray, Bucher
"Transforming Environmental Health Protection"
Science 319:906-07 (2008)



Déjà view: A look back at a Dwane Powell cartoon that has resonance today.

Thanks to Mel Andersen and Dan Krewski

1. The NRC report puts forth a new toxicity testing approach.
    - What are potential advantages and limitations of the proposed approach?
    - What impact might this new approach have on regulatory decision-making?
2. What role might ICCVAM and NICEATM serve in implementing the vision and strategy described in the report?
3. How might ICCVAM and NICEATM help ensure that the development and validation of assays described in the report will be applicable to and valid for regulatory safety testing, and further reduce, refine, and replace animal use for safety testing?