# Computational Toxicology Overview

"Pesticide Program Dialogue Committee Meeting"
October 29, 2003

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Office of Research and Development


RESEARCH & DEVELOPMENT
Building a scientific foundation for sound environmental decisions
A Framework for a Computational Toxicology Research Program in ORD
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Office of Research and Development
A Framework for
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COMPUTATIONAL TOXICOLOGY

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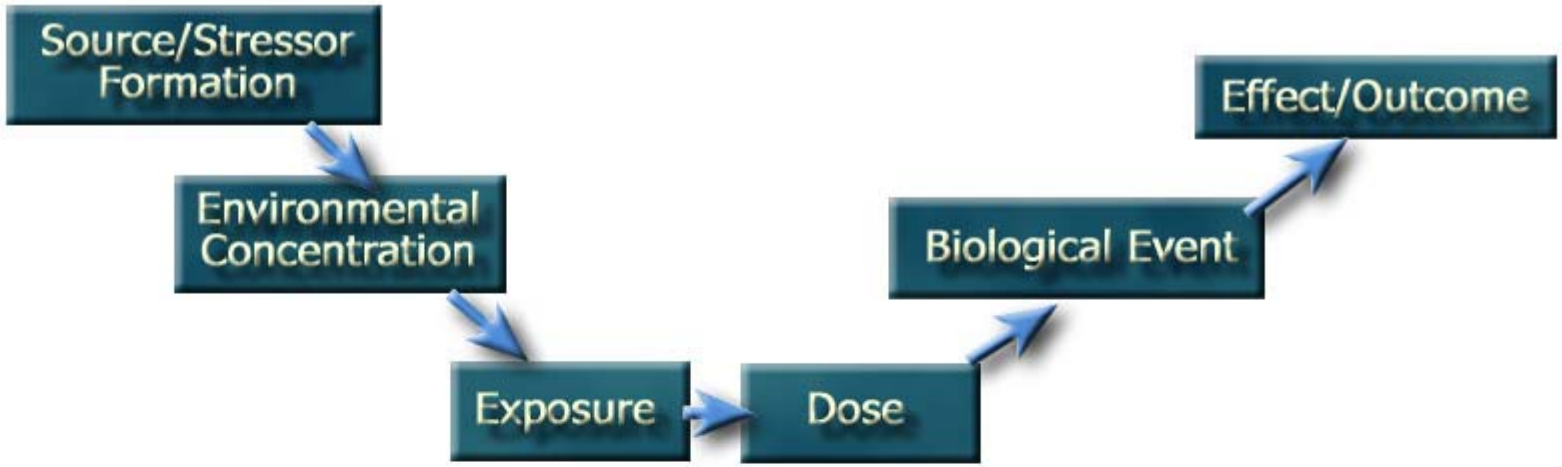


# EPA Context: Quantitative Risk Assessment/ Risk Management for Priority Pollutants

- Methods to Detect & Characterize
- Evaluate Single Chemical at a Time

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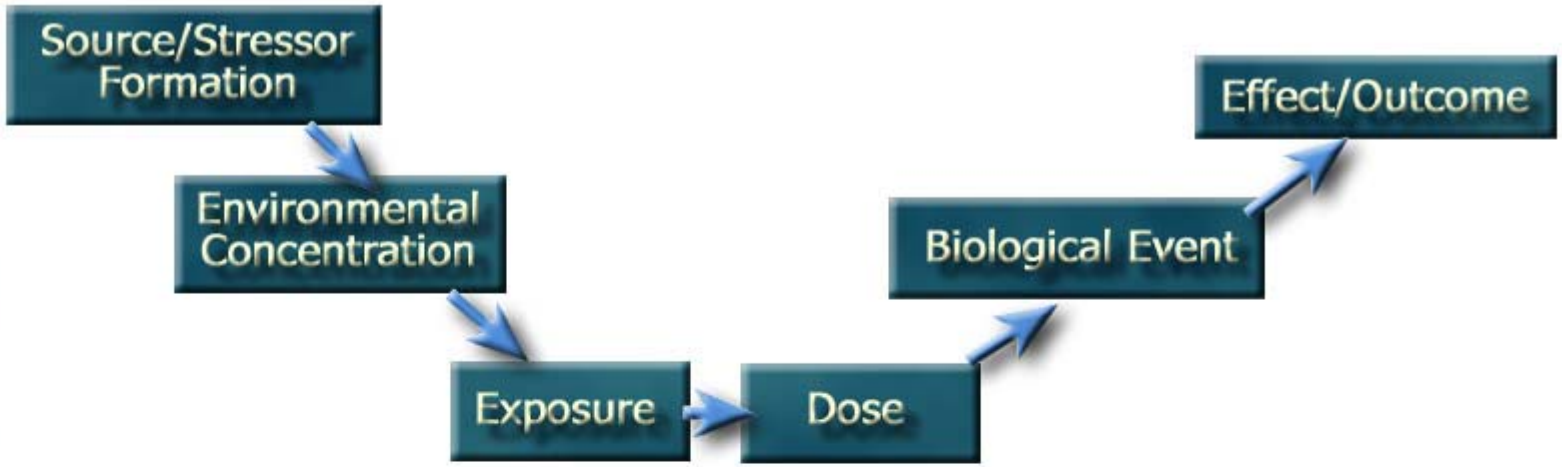


# PROGRAMMATIC CHALLENGES

- Many Priority Lists Already in Queue (e.g., EDC's, Pesticide Inerts, HPV's, CCL) with No Risk-Based Criteria for Setting Testing Priorities
- Different Authorities – Different Testing Requirements with No Scientific Basis for Flexible Testing Approaches
- Lack Data Needed to Reduce Uncertainties by Quantitative Risk Assessments (e.g., extrapolations)

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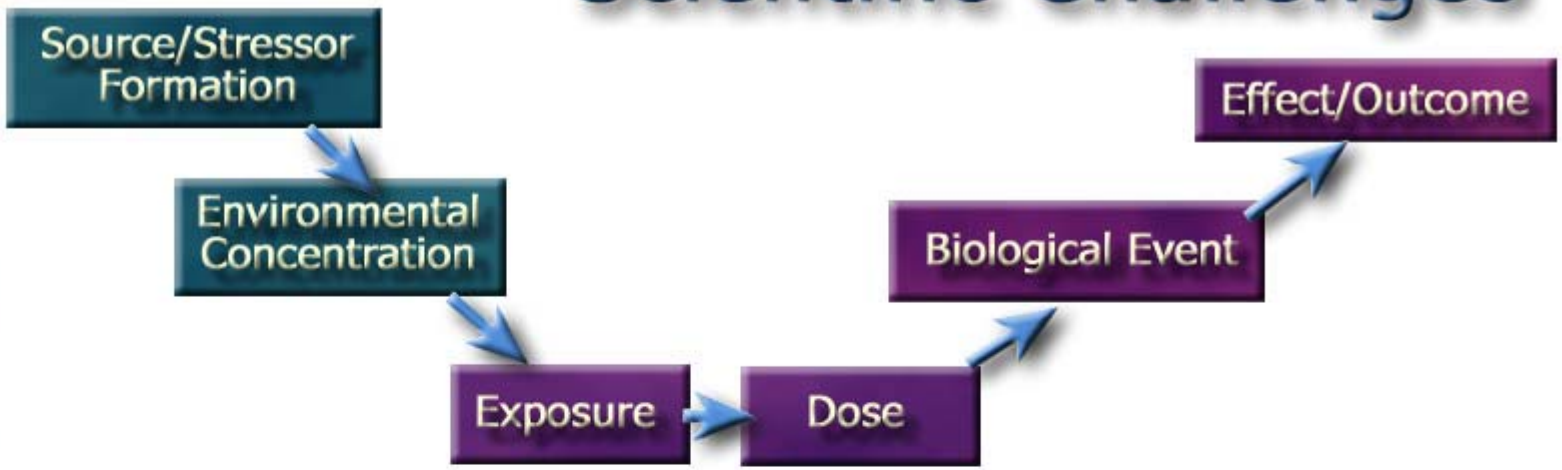
# Scientific Challenges




- Delineate Toxicity Pathways
- Extend Cross- and Within-Species Extrapolations
- Identify Endpoints for QSAR Models

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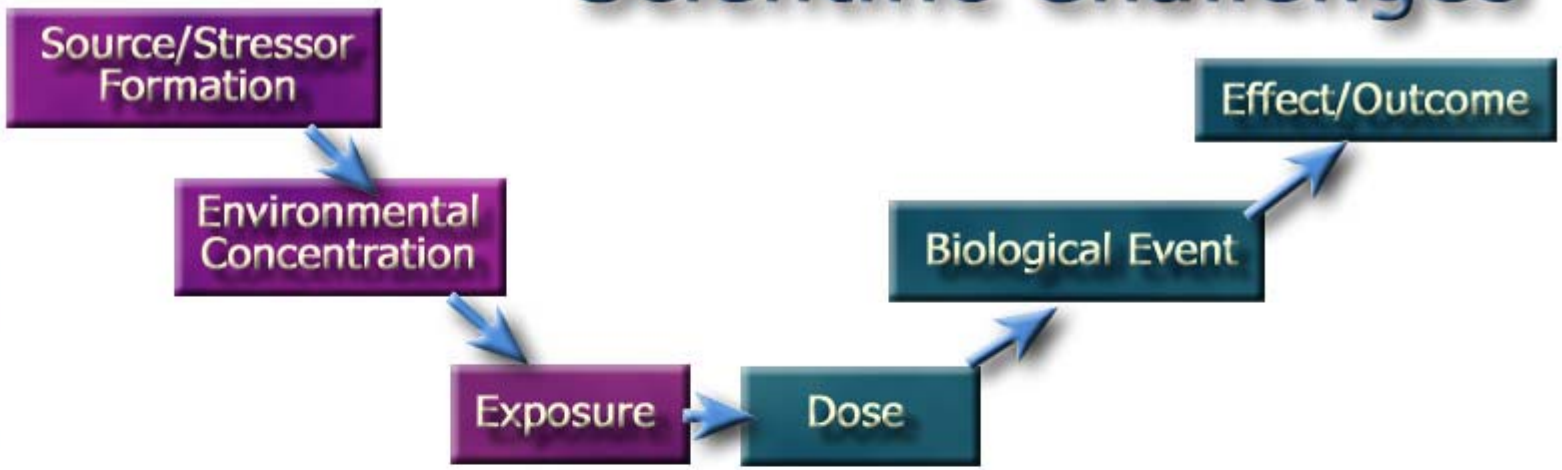
# Scientific Challenges




- Exposure Biomarkers
- Fate/Transport Models
- Exposure Models

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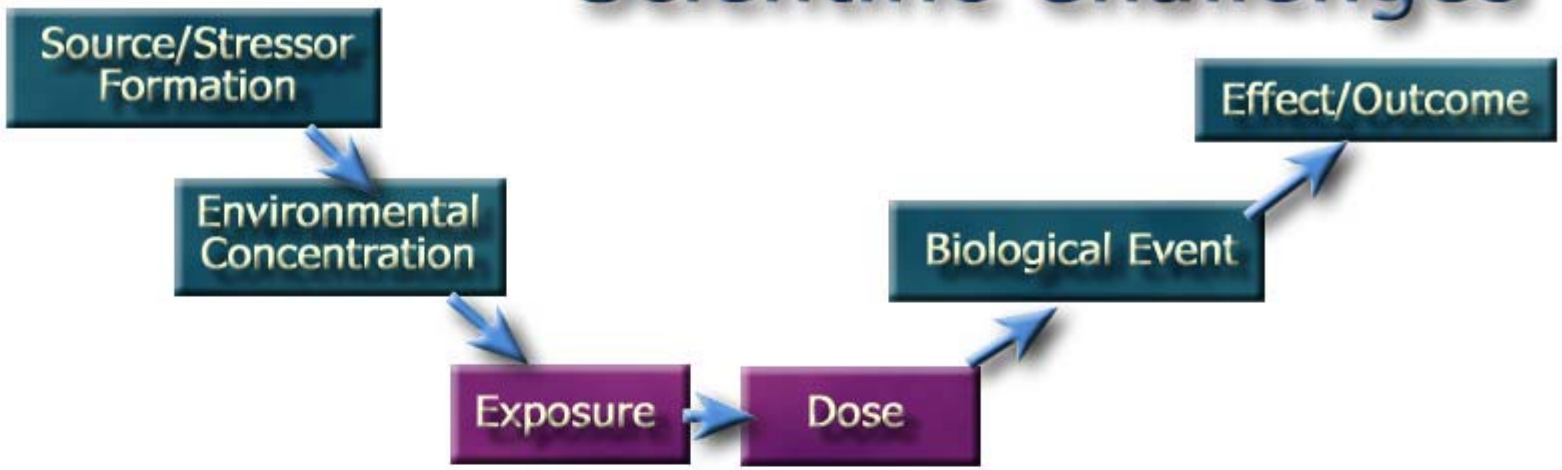
# Scientific Challenges




- Dose Metrics
- Understanding Cross- and Within-Species Variations in Pharmacokinetics

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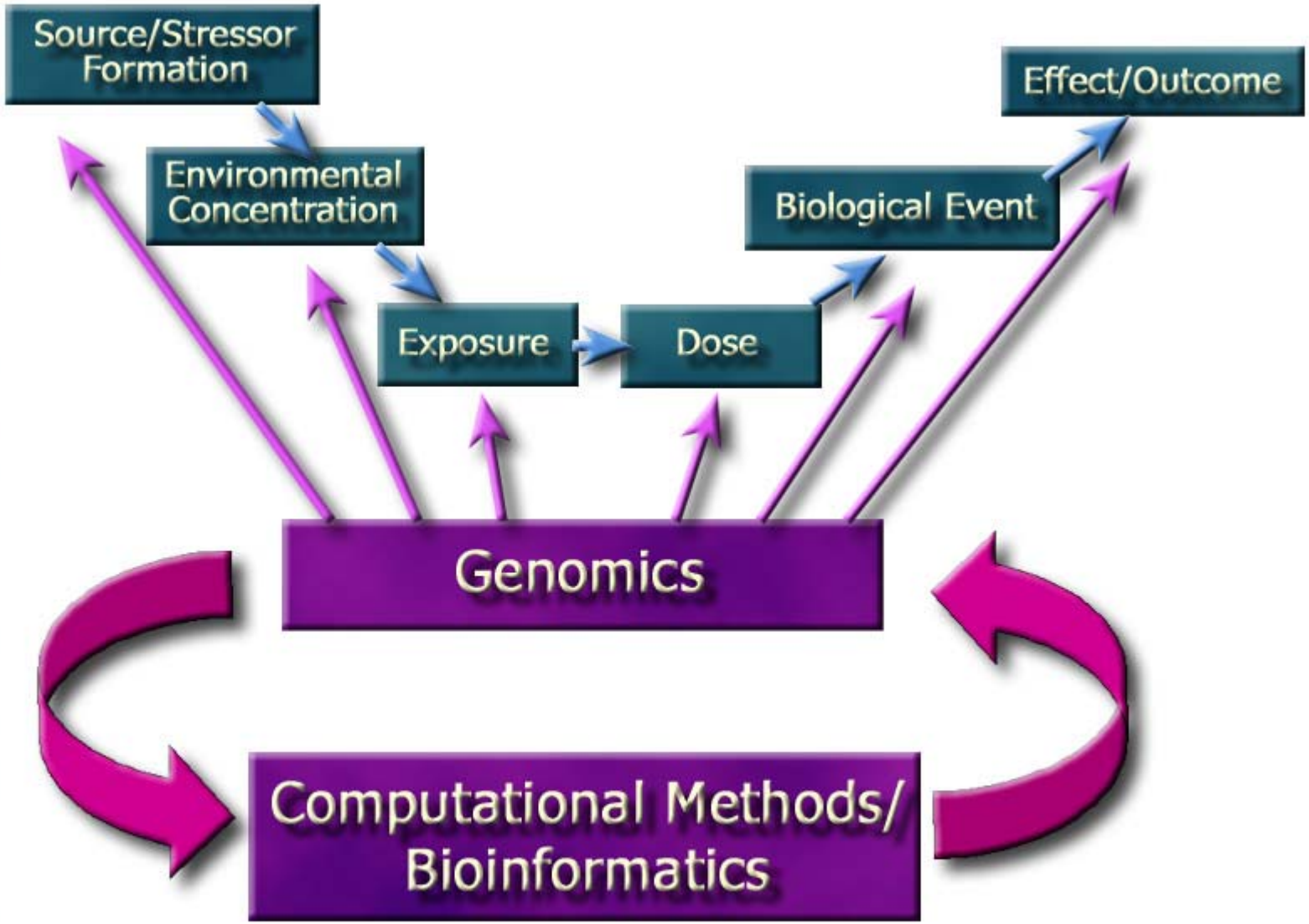


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To integrate modern computing and information technology with the technology of molecular biology and chemistry to improve EPA's prioritization of data requirements and risk assessments for toxic chemicals

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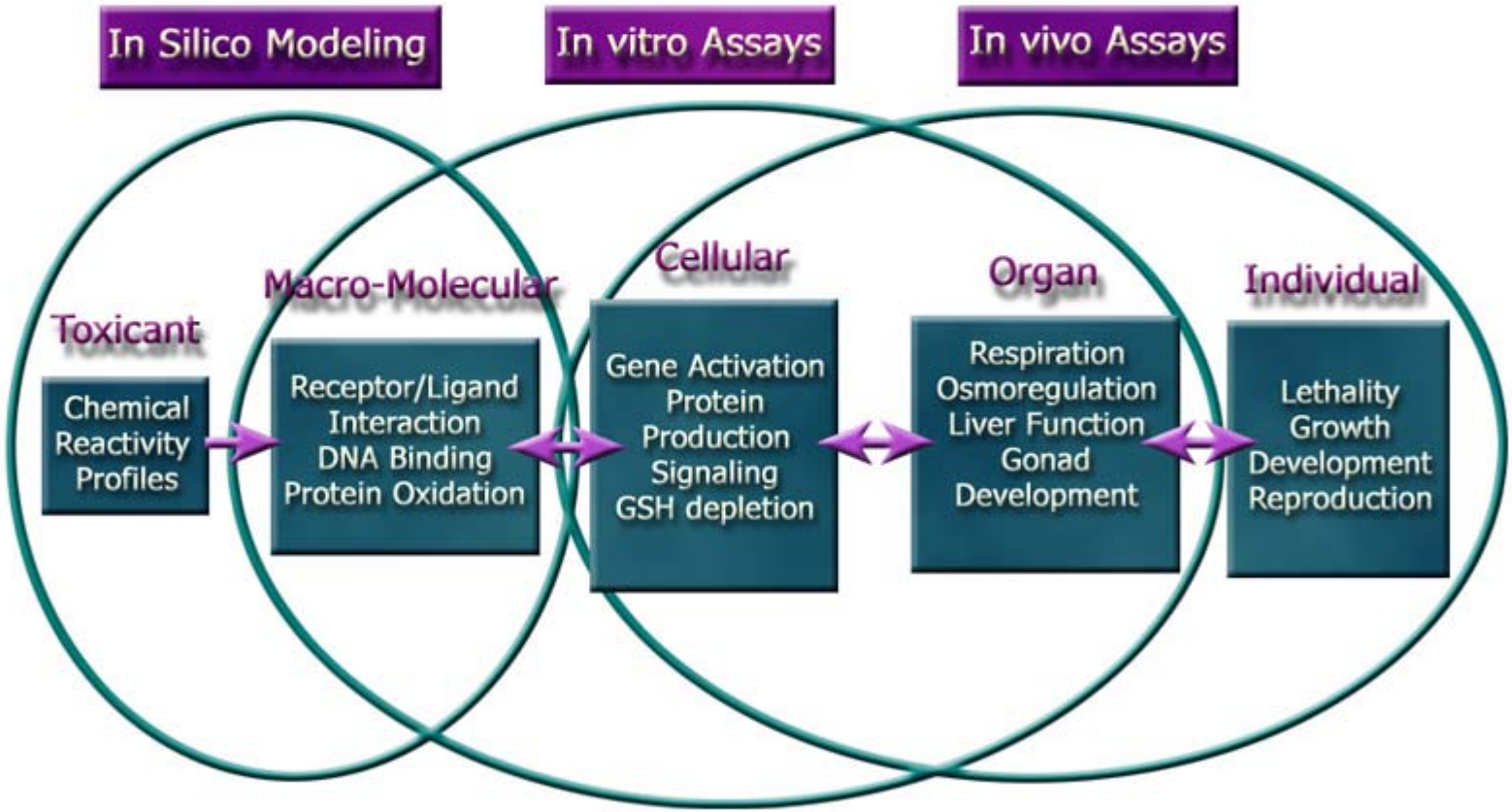
# Toxicity Pathways

## Linking Observations Across Levels of Biological Organization

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# Overarching Themes

- A technology-based, hypothesis-driven effort to increase the soundness of risk assessment decisions within EPA
- Build the capacity to prioritize, screen and evaluate chemicals by enhancing the predictive understanding of toxicity pathways
- Success measured by ability to produce faster and more accurate risk assessments for less cost relative to traditional means and to classify chemicals by their potential to influence molecular and biochemical pathways of concern

# General Objectives

I. Improve linkages in the source-to-outcome paradigm

II. Provide predictive models for screening and testing

III. Enhance quantitative risk assessment

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# I. Source to Outcome Linkages

- Chemical transformation and metabolism
- Diagnostic/prognostic molecular indicators (Exposure and Effects)
- Dose metrics
- Characterization of toxicity pathways
- Metabonomics
- Systems biology

# II. Predictive Models for Hazard Identification

- QSAR approaches
- Pollution prevention strategies
- High throughput screening

# III. Enhancing Quantitative RA

- Applying computational methods in quantitative risk assessments
  - Validation and development of protocols
  - Defining responses
  - Modifying Uncertainty factors
- Dose response assessments
- Cross species extrapolations
- Chemical mixtures

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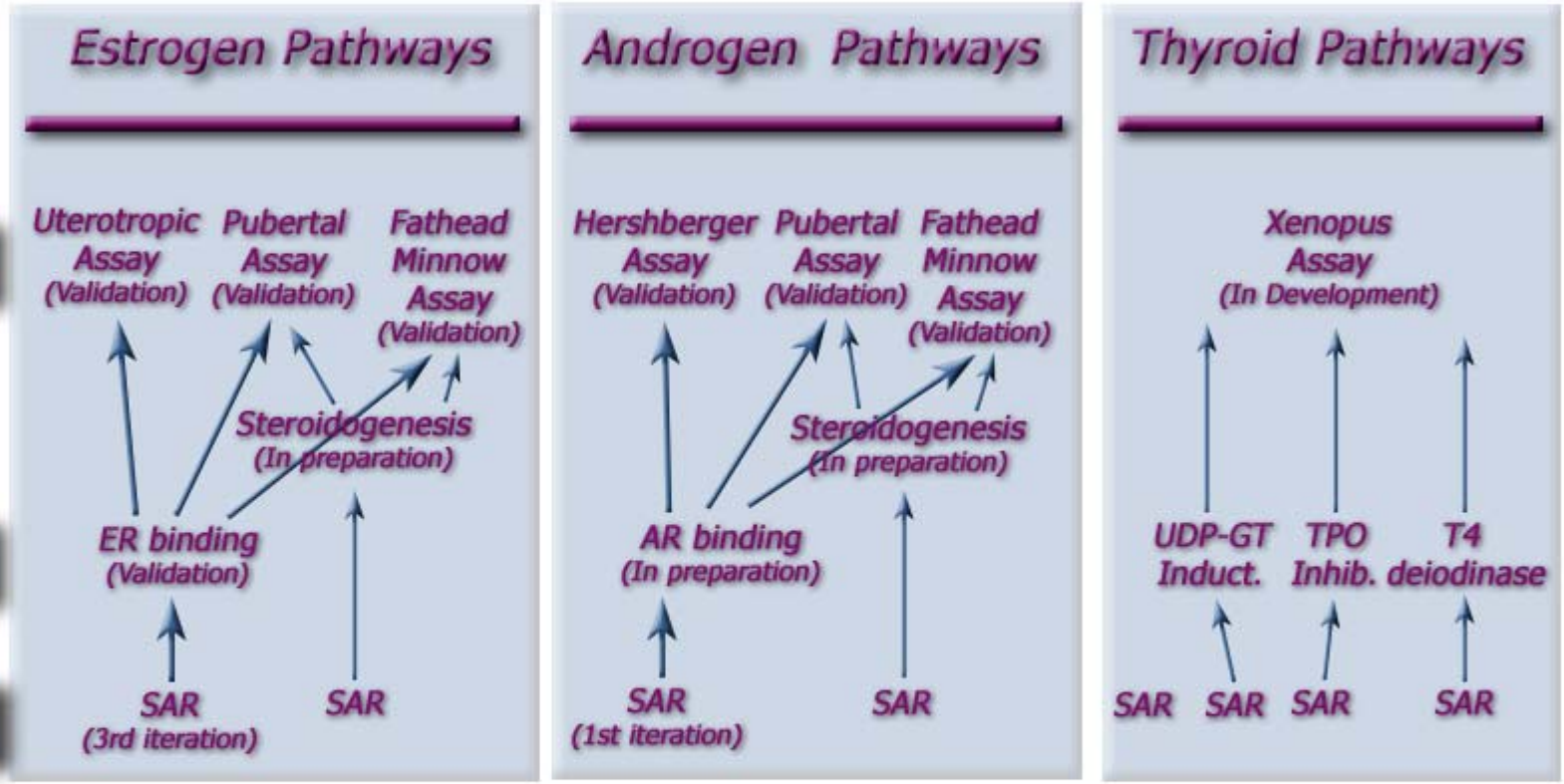
# Impaired Reproduction/Development

In vivo

In vitro

In silico





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# DNT Testing - Future

Long Term Goal: Move from expensive and time consuming in vivo testing batteries to faster and cheaper batteries that offer useful data for risk assessments

- Short-term: Refine current methods
- Mid-Range: Develop targeted testing based on predictive models
- Long-Term: Develop alternative methods
  - High-throughput *in-vitro*
  - Alternative species

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# Computational Toxicology Challenges

- Create a virtual escape from the EDC screening dilemma for EPA chemical lists and inventories
  - *in silico* identification of chemicals for further laboratory testing
  - balance exposure-toxicity risks in screening large inventories
- Develop a Systems Biology approach that links test-specific effects as localized symptoms of more global molecular events
  - Redefine chemical reactivity in a hazard identification context
  - add "likelihood estimates" to the spectrum of possible effects
- Provide a scientific foundation for a hypothesis-driven testing paradigm for EPA risk assessment processes
  - Introduce risk management thresholds along toxicity pathways
  - reduce animal testing by minimizing "negative" laboratory tests

# Challenges Continued

- Matching Expertise with Capabilities
  - Genomics
  - Informatics
  - High Performance Computing
- Coordinate/Partner with Others to Meet CompTox Objectives
- Interpretation, Interpretation, Interpretation
- Linking Science to Application
- Scientific Validation
- Harmonization
- Infrastructure
  - Organizational Roles
  - Transitions

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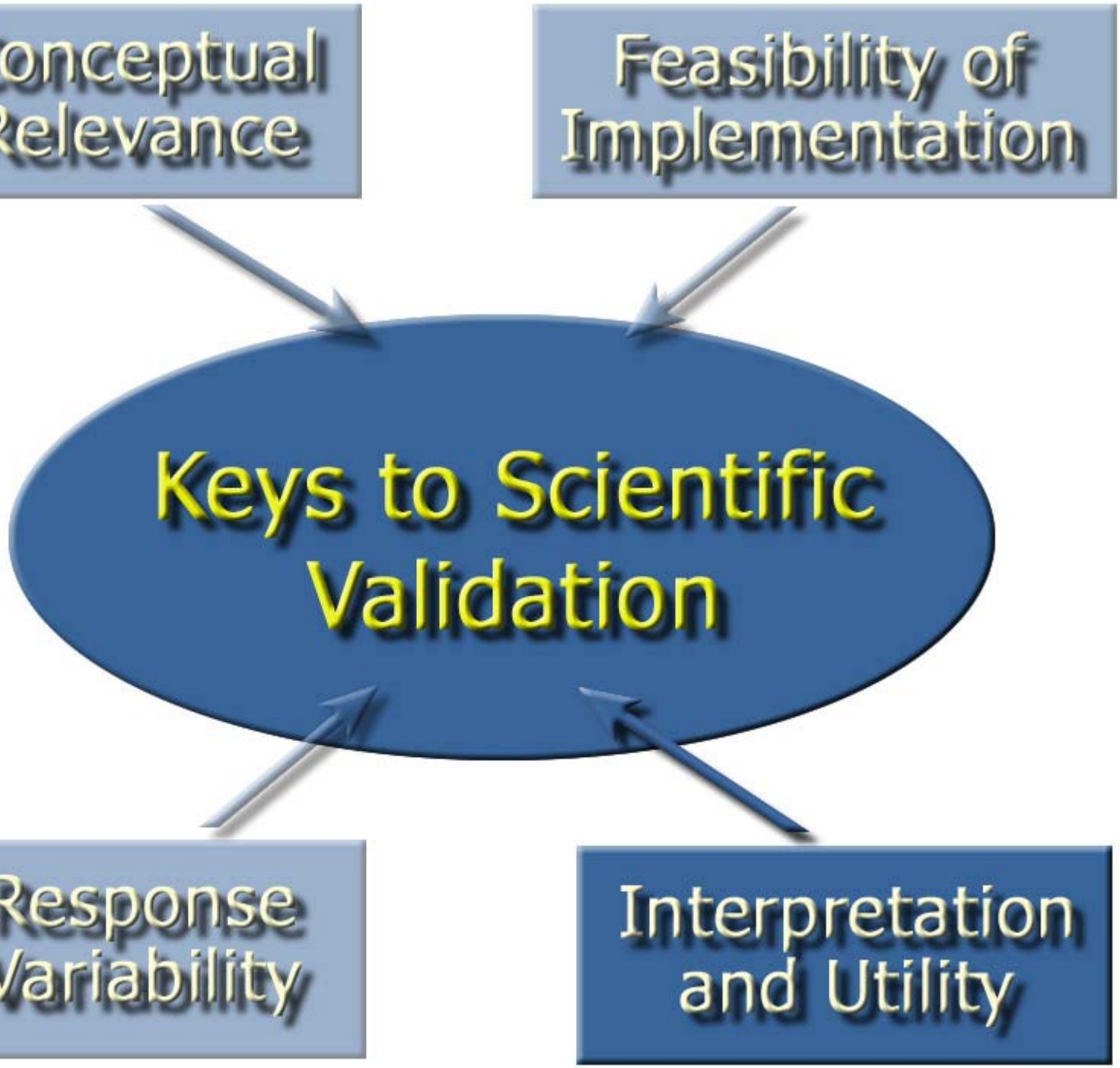


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# SUMMARY

- Completed Framework to guide development of research program
- Successful implementation will pose a number of challenges
  - Prioritization/Engagement
  - Coordination/Collaboration
- Workshop held September 29-30, 2003, to begin transition from Framework to research program
  - Communicate Framework
  - Identify/foster partnerships
  - Begin to shape research agenda