

US EPA ARCHIVE DOCUMENT



Moving From Data Requirements to Knowledge Requirements to Inform Risk Assessment and Regulatory Decisions

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15 Years Illustrative Study

Future Risk Determination Vision

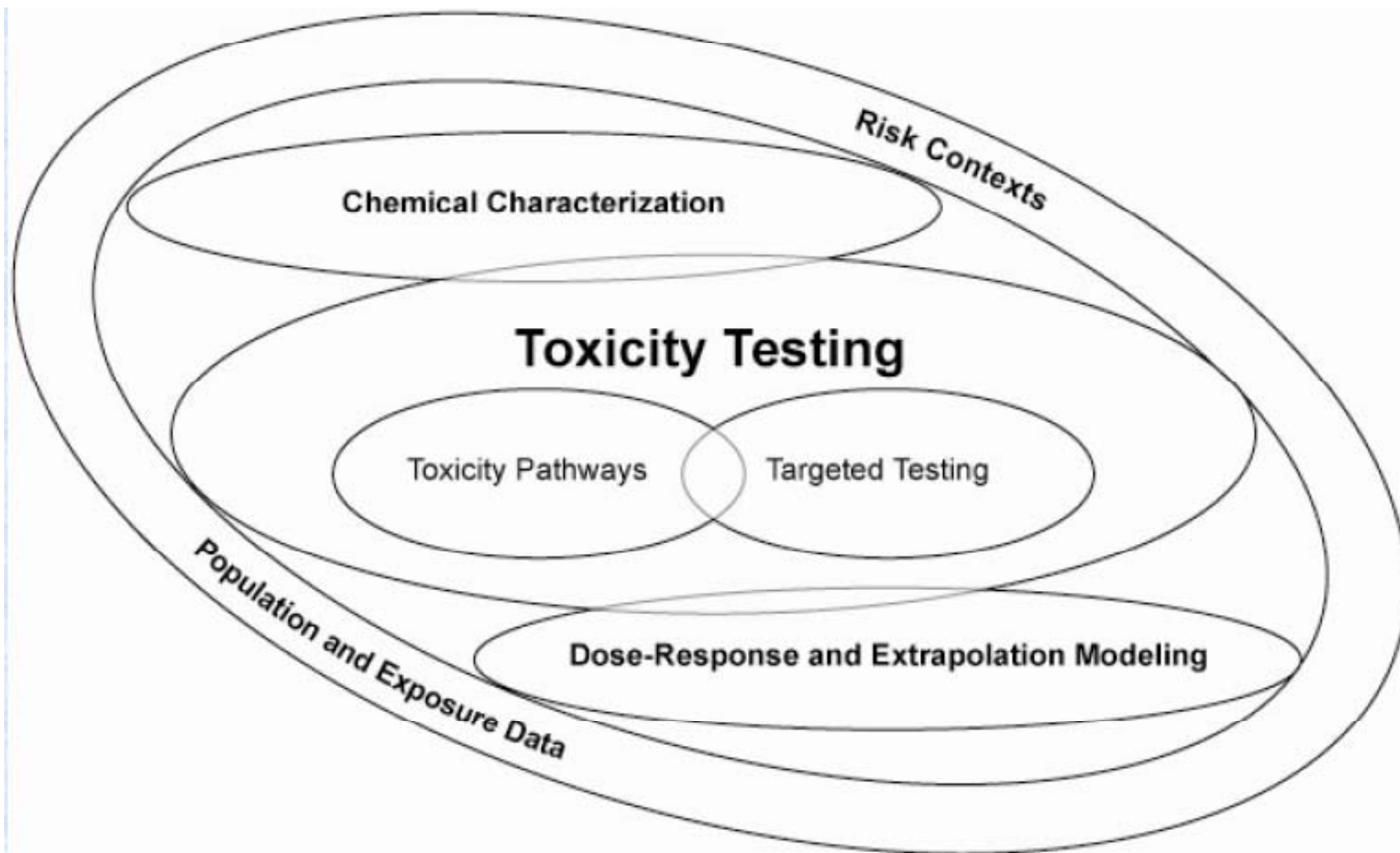


- Know what to test, when to test, and how to test
- Most decisions informed by the chemical's inherent properties
- Require tests only when necessary
- Animal testing only when absolutely necessary
- This Will Take Time



15 Years Illustrative Study

Toxicity Testing in 21st Century: A Vision and Strategy





15 Years Illustrative Study

Chemical Risk Management Vision

- Transition to science-based integrative, diagnostic, and predictive approaches to enhance efficiency and accuracy of risk assessment.
- Reduce reliance on animal testing
- Enhance the interpretation of data



15 Years Illustrative Study

EPA's Needs Expand the NAS Vision

- Include ecological as well as human effects
- Establish the process to bring new science into regulatory practice



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Goal

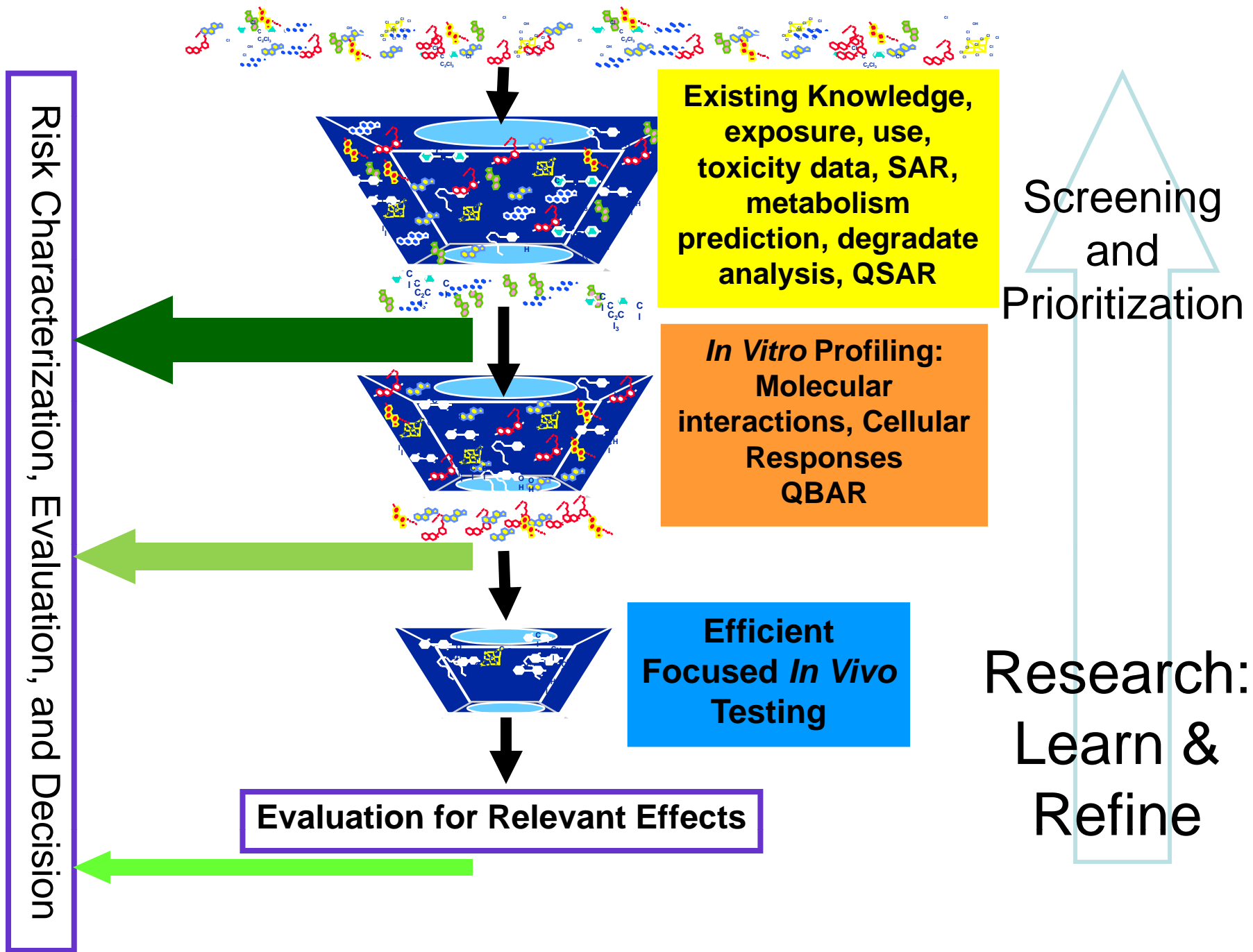
Integrated evaluation strategy that provides the **necessary scientific knowledge** to inform regulatory determinations of the potential for an adverse impact, **from the use** of a chemical, on public health and the environment with **speed, efficiency, and accuracy.**



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Understanding based on inherent properties

- For chemical: Inherency relates to chemical-specific properties associated with its impact on humans & environment (EPA perspective)
 - Physico-chemical and material properties, atomic composition, structure, size, surface area, solubility, surface charge, aspect ratio, etc.
 - Ability to interact with biological processes
 - How it is used, metabolized, and degrades

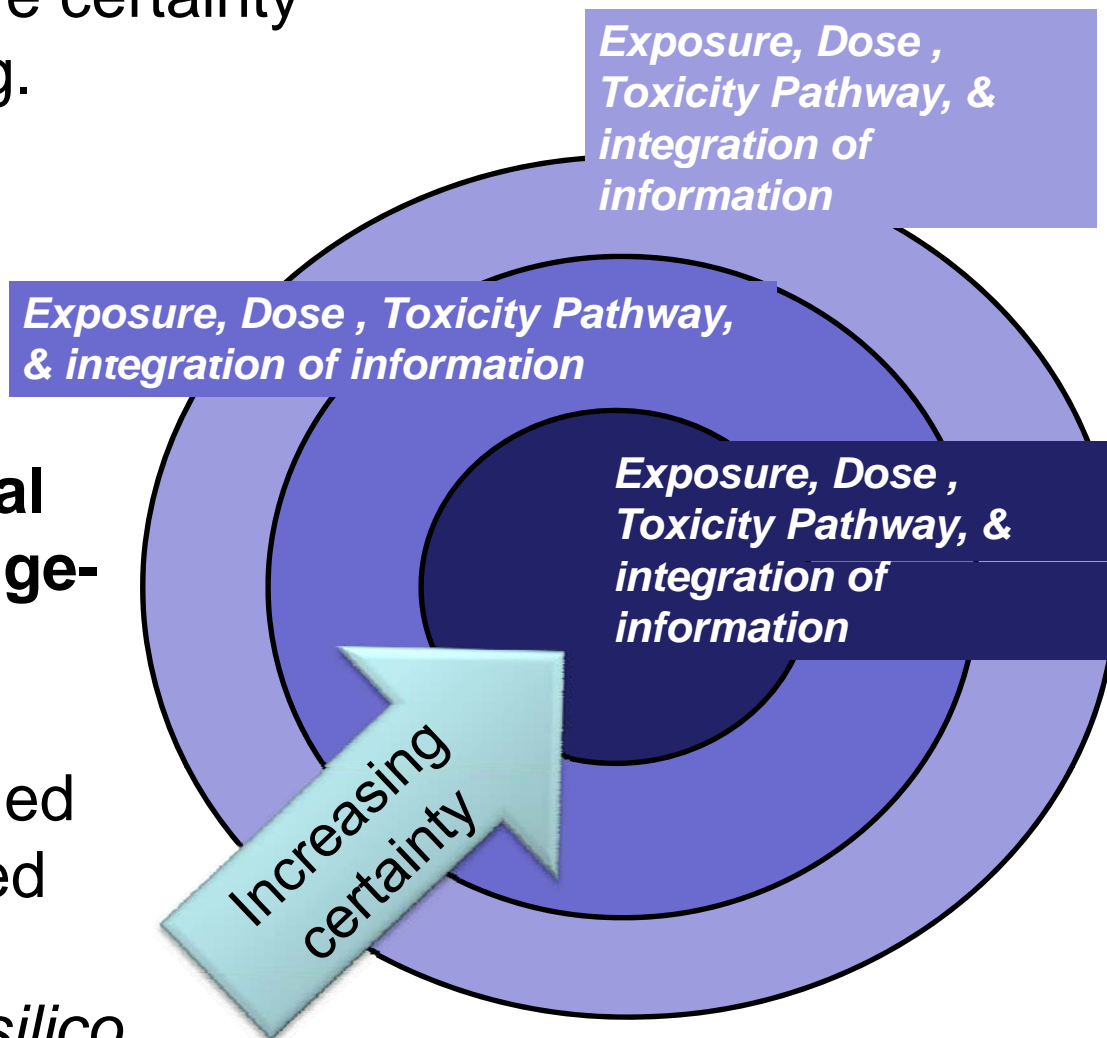


We typically equate more certainty with more animal testing.

This is the current model; the future will be different.

Less reliance on animal testing; more knowledge-based instead.

Could mean more detailed *in vitro* assays, enhanced exposure assessment, greater specificity of *in silico* models.



Greater certainty necessitates increased understanding, quantitative data, and greater integration at each level.



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Move Toward Evaluation of Clusters of Chemicals Based on Inherent Properties, Likely Use, and Common Adverse Outcomes

Group Chemicals by Similar Features

Inherent Properties of Chemicals and Chemical Classes

Chemical Structure
Biological profiles via HTS
Physical Chemical Properties
Lifecycle Information

Fill data gaps: Read-across (similar chemical structure) or QSARs
Predict endpoint: Shared chemical properties using information from one chemical in a class with a lot of data to predict effects of other chemicals in the class.

Situational and Toxicity Pathway Based Assessments

Risk Context/Lifecycle Assessment/Exposure Context

Chemical Structure and Physical Chemical Properties

Identify relevant adverse response in humans and wildlife

Describe Toxicity Pathways

Identify Key Events

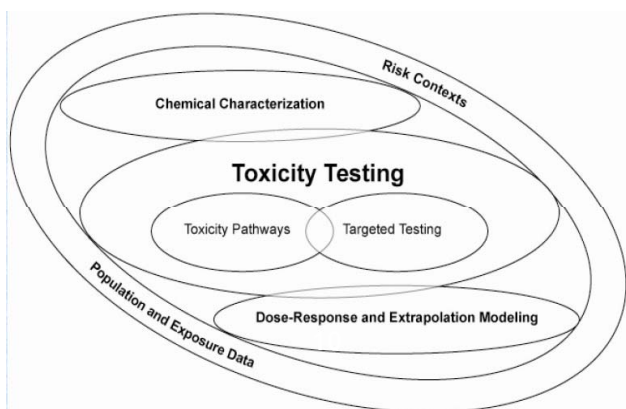
Develop and apply in vitro assays

Tissue and cellular dose

High-throughput screens

Additional targeted testing as needed based on results

Assessment of Risk



Enhanced interpretation of data



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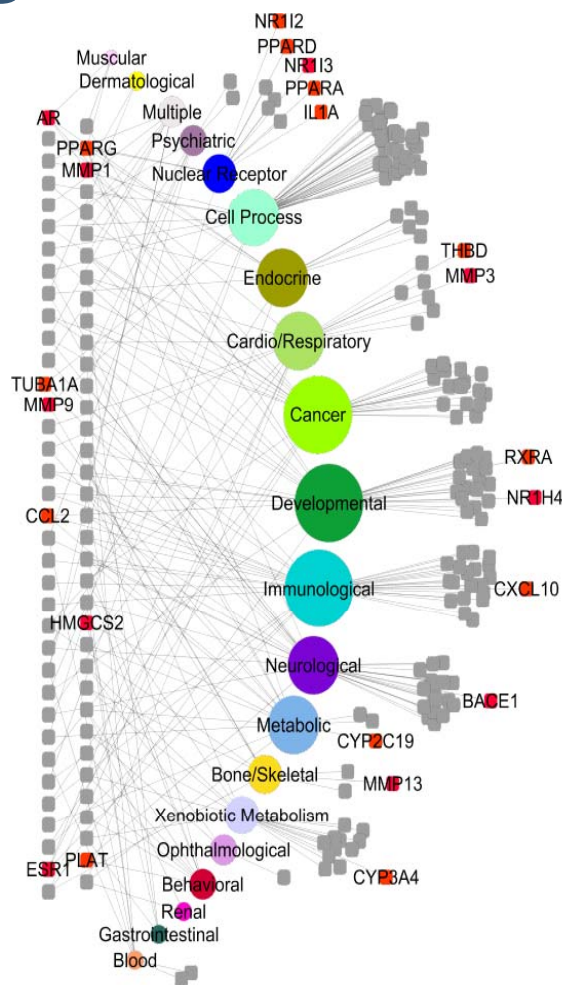
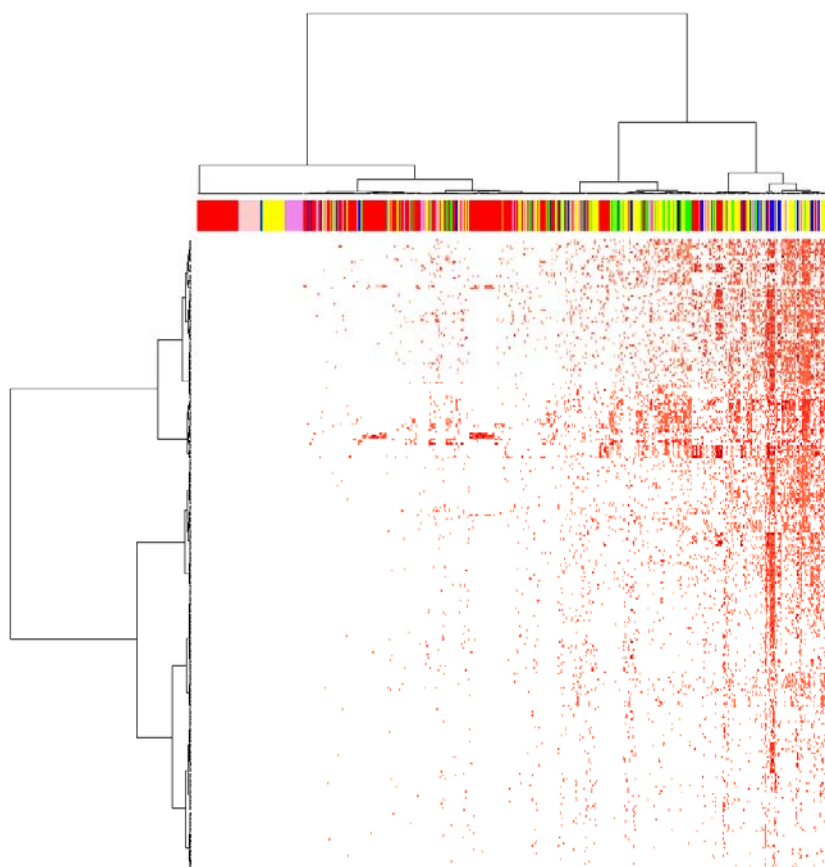
Use Quantitative Activity Relationships to Determine Additional Evaluation Needs

- Prioritize and target testing on toxic potential of chemicals based on structure and biological activity.

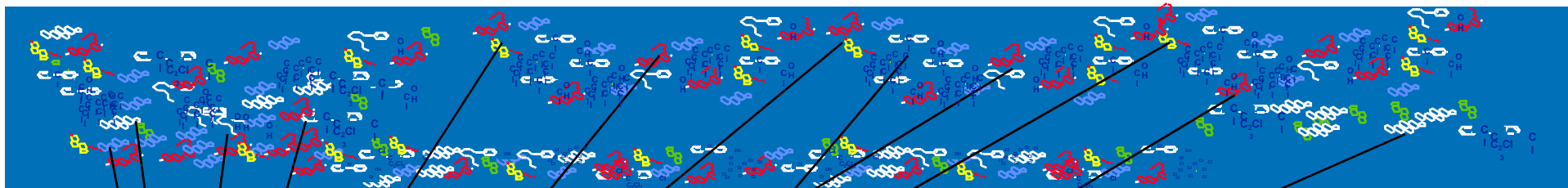


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Associating Bioactivity in vitro with Pathways and Diseases

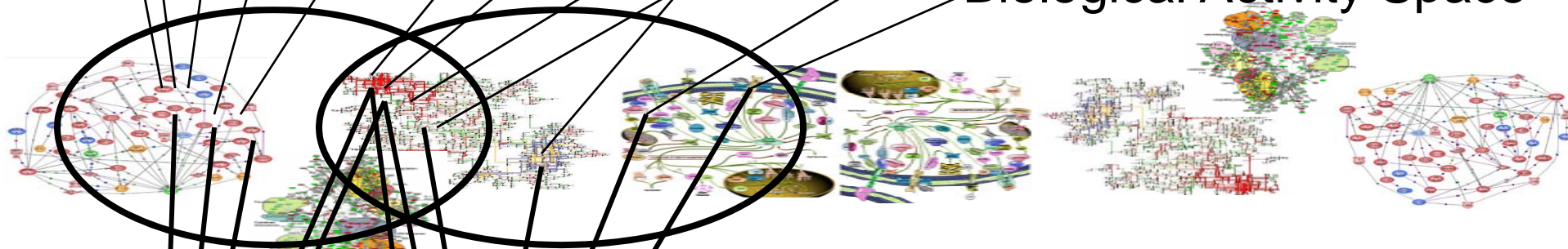


Chemical Space



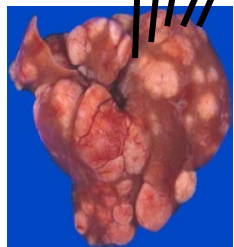
Quantitative Structure Activity Relationships

Biological Activity Space

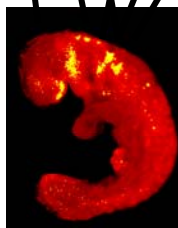


Quantitative Biological Activity Response

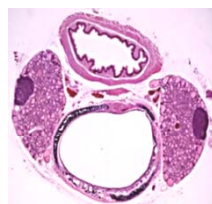
Adverse Outcome Space



Cancer



Developmental Defects



Endocrine Disruption



Respiratory Disease

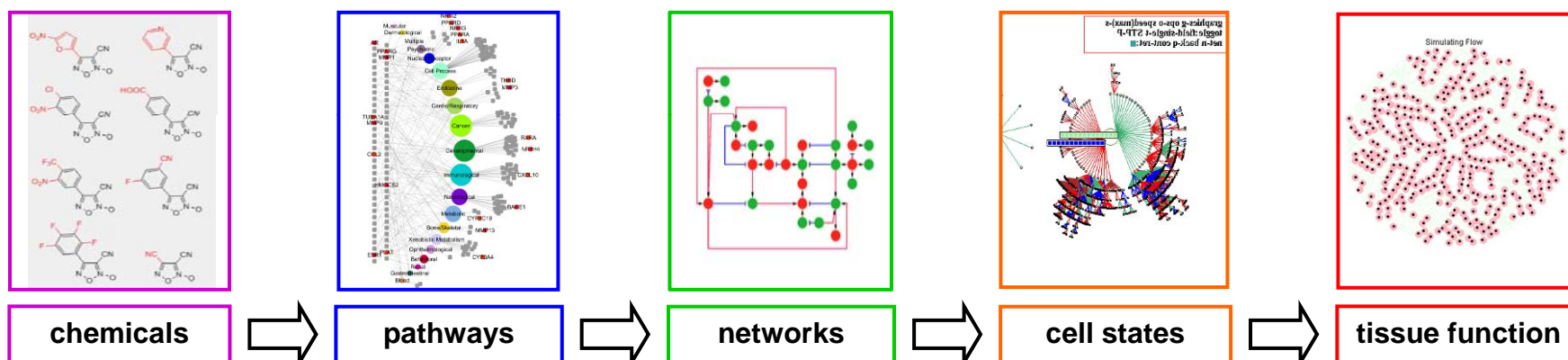


Neurologic Effects



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Modeling Toxicity: Pathways to Virtual Tissues



Identify Key Targets and Pathways

Moving beyond empirical models to multi-scale computer models of complex biological systems.

Quantitative Dose-Response Models

Risk Assessments



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Future Risk Determination

- Decision-based testing
- Inherent properties (hazard and exposure) of the chemical directs assessment strategy
- Testing only as necessary
- Testing in animals is rare

“To innovate is not to reform”

Edmund Burke (1729–1797), Irish philosopher, statesman.