The McKim Conferences for the Strategic Use of Testing

Gitchee Gumee Conference Center
Duluth, Minnesota
June 27-29, 2006

Test Methods for Every Hazard

- The matrix of species, hazards and exposure routes resulted in hundreds of test guidelines
- The search for “alternative” in vitro methods has added significantly to the batteries of tests to interpret
- The number of chemicals reviewed is a small percentage of chemicals being produced and used
- Our assessment infrastructure limits the number of chemicals which can be assessed for safety

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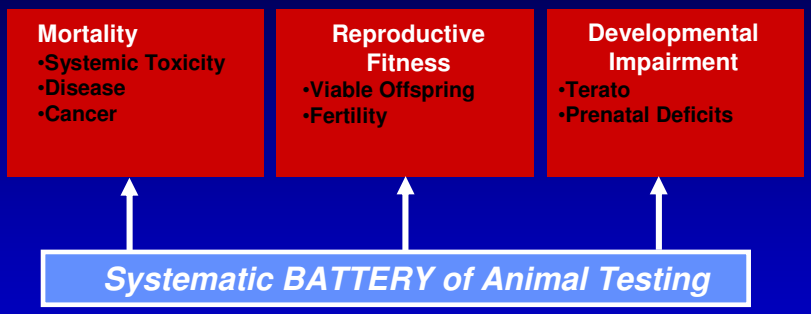
Battery-Driven Paradigm

"We toxicologists are the interpreters of data!"

EPA risk assessor



Current Perspective -- "What test data involving all possible adverse effects would I need to see before I would be willing to consider this chemical to be safe?"

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Hypothesis-Driven Paradigm

- The purpose of models is to improve our ability to generate hypotheses and prescribe tests
- Screening of untested chemicals requires a new generation of extrapolation tools
- The core of extrapolation is the development of classes, categories, and mechanistic analogues

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The CHALLENGE

- 30 Years of developing alternative methods has not reduced the use of animals or costs of testing
- One reason is a serious mismatch of the domains of alternative methods involving *in vivo* tests
- For untested chemicals, the primary priority-setting approach to date is production volume and not risk
- We need a new paradigm where testing sequences are driven by hypotheses from models/existing data

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The BARRIERS

- One major obstacle is that test data are scattered throughout the literature or in private databases
- Even in comprehensive and critiqued databases like AQUIRE, existing data may be for different chemicals, species or endpoints
- The bridge is a systematic approach to modeling chemical interactions within virtual animal models

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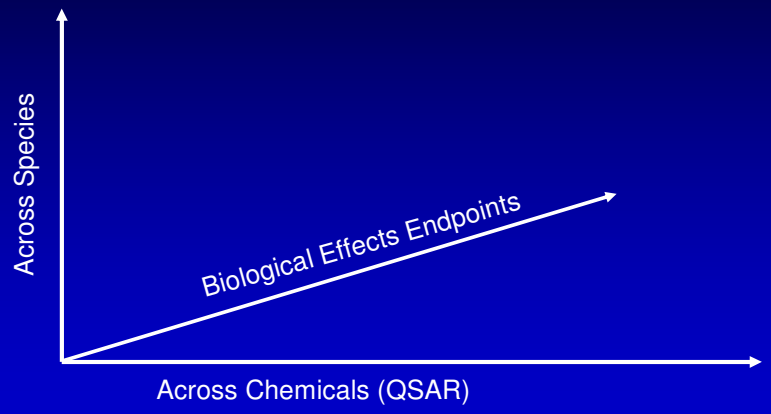
Extrapolation of Test Data



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Major Hurdles

- Chemical Speciation
  - Reactivity
  - Hydrogen Bonding
- Comparative Metabolism
  - Species
  - Populations
- Selective Toxicity
  - Species Biological Models
  - Biochemical Vulnerability

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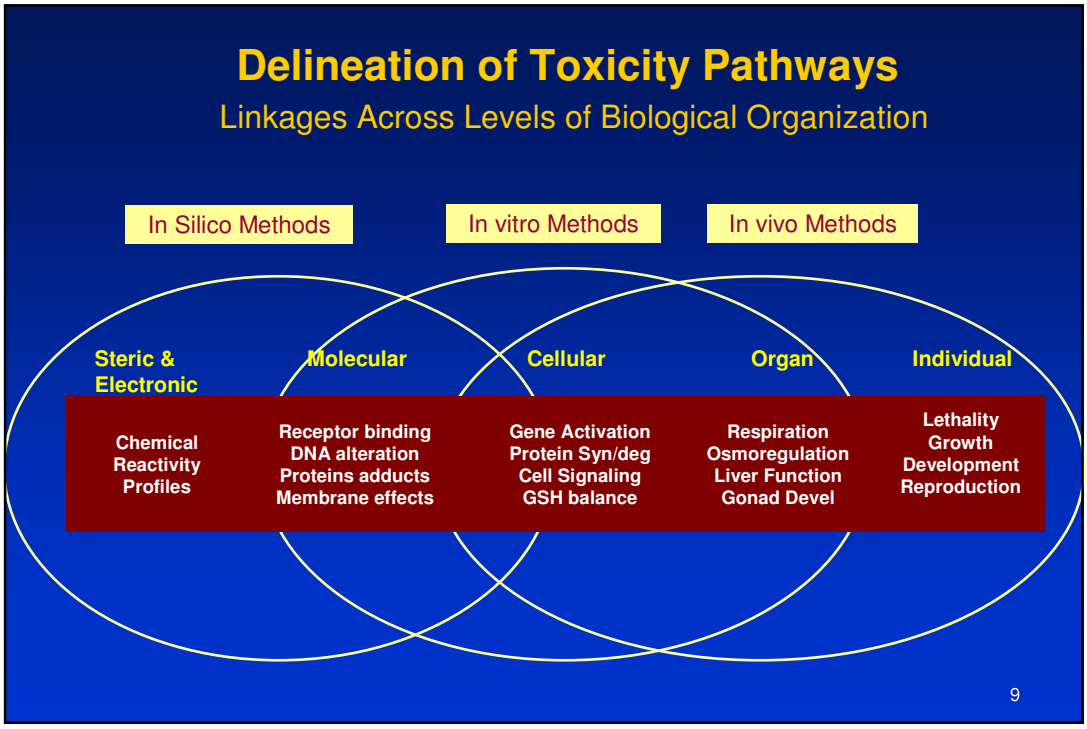
Delineation of Toxicity Pathways

Linkages Across Levels of Biological Organization



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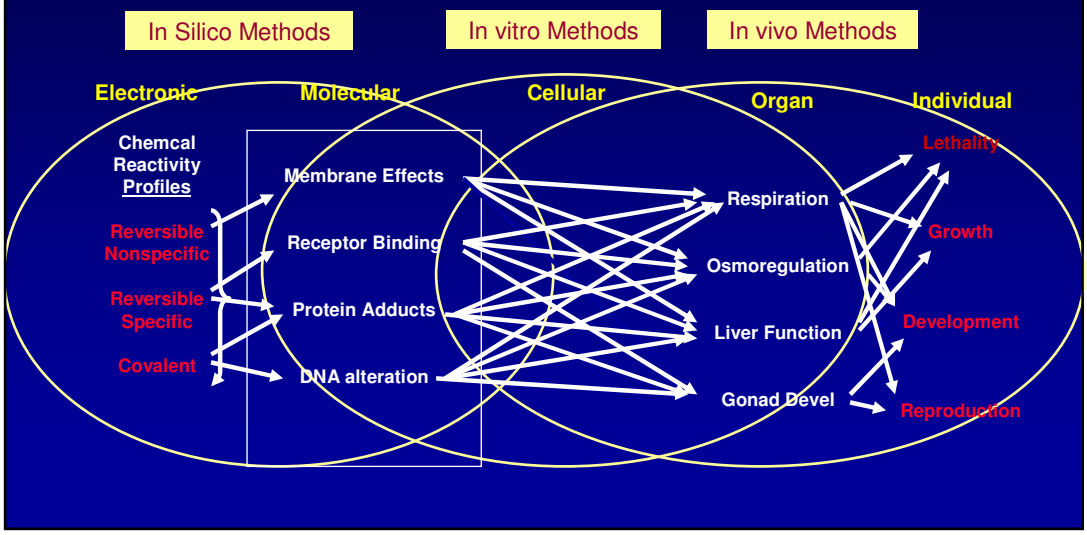

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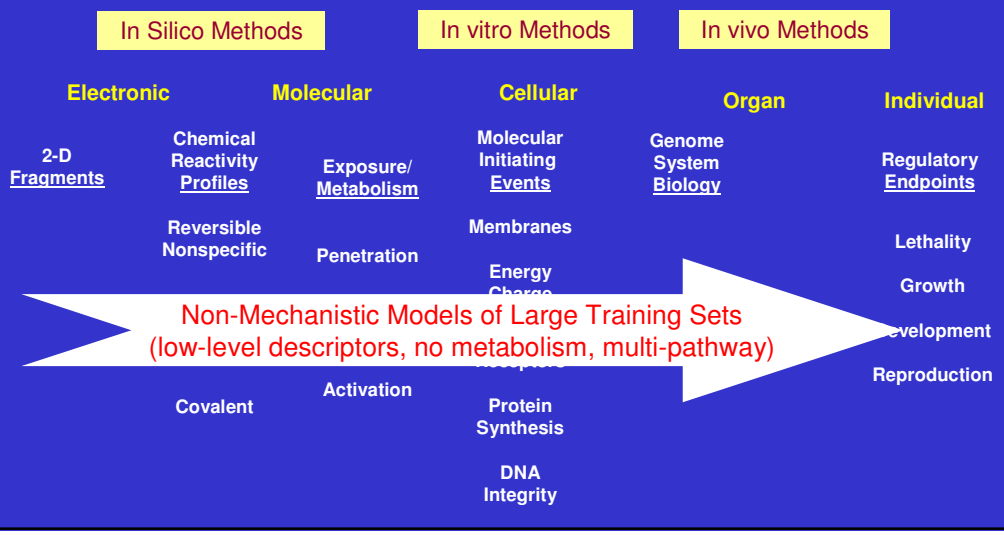
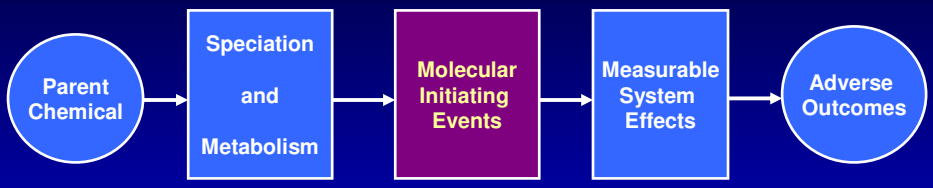


Knoxville Workshop Framework for Predicting Reactive Toxicity



Rather than developing statistical models of complex endpoints, molecular initiating events are identified as well-defined QSAR endpoints…..and used to estimate the probabilities for important downstream biological effects based on transparent assumptions

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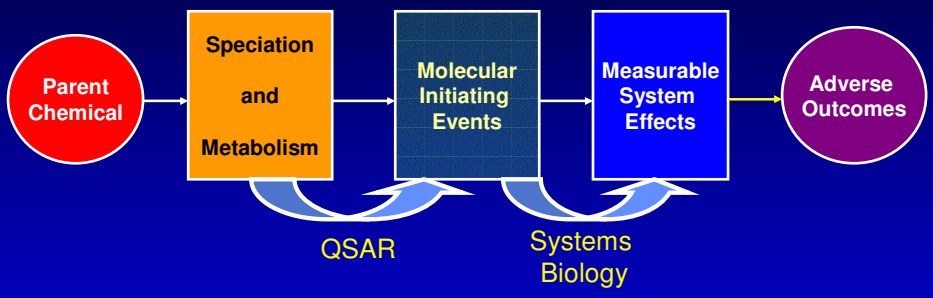
Delineating the Models for Toxicity Pathways



1. Establish Plausible Molecular Initiating Events
2. Design Database for Abiotic Binding Affinity/Rates
3. Explore Correlations/Pathways to Downstream Effects

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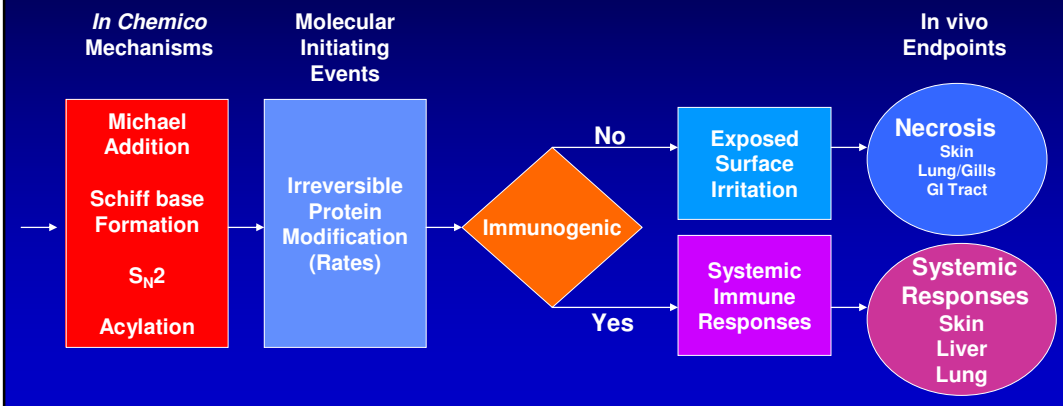
Major Pathways for Reactive Toxicity from Soft Electrophiles



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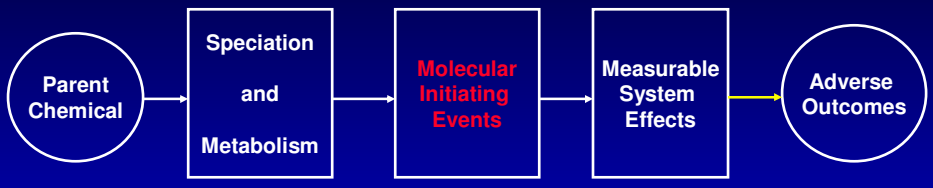
IQF Framework for Reactive Toxicity



Using Glutathione Thiol Reactivity as a Model Soft Nucleophile:

1. Correlate R(GSH) with Excess Toxicity in EcoTox Data
2. Correlate R(GSH) with Mammalian Skin Sensitization
3. Correlate R(GSH) with Mammalian Inhalation Toxicity
4. Correlate R(GSH) with Chemical Induced Liver Failure

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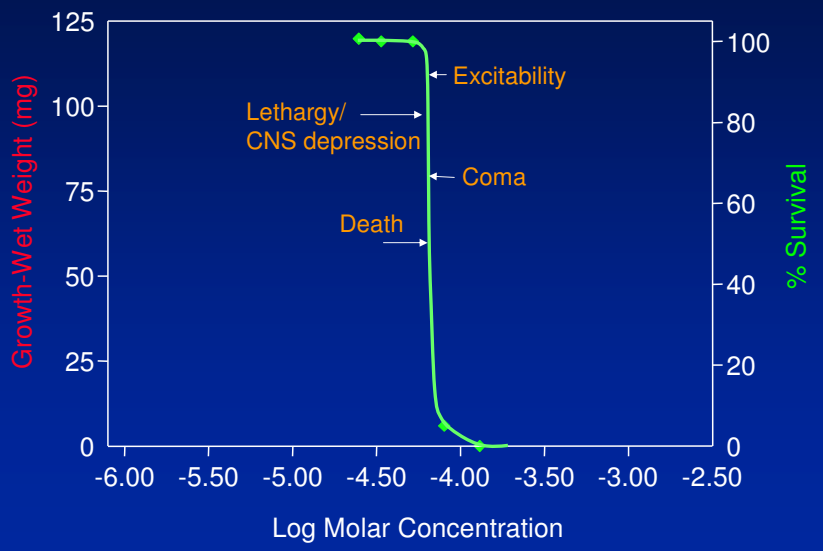
Octanol



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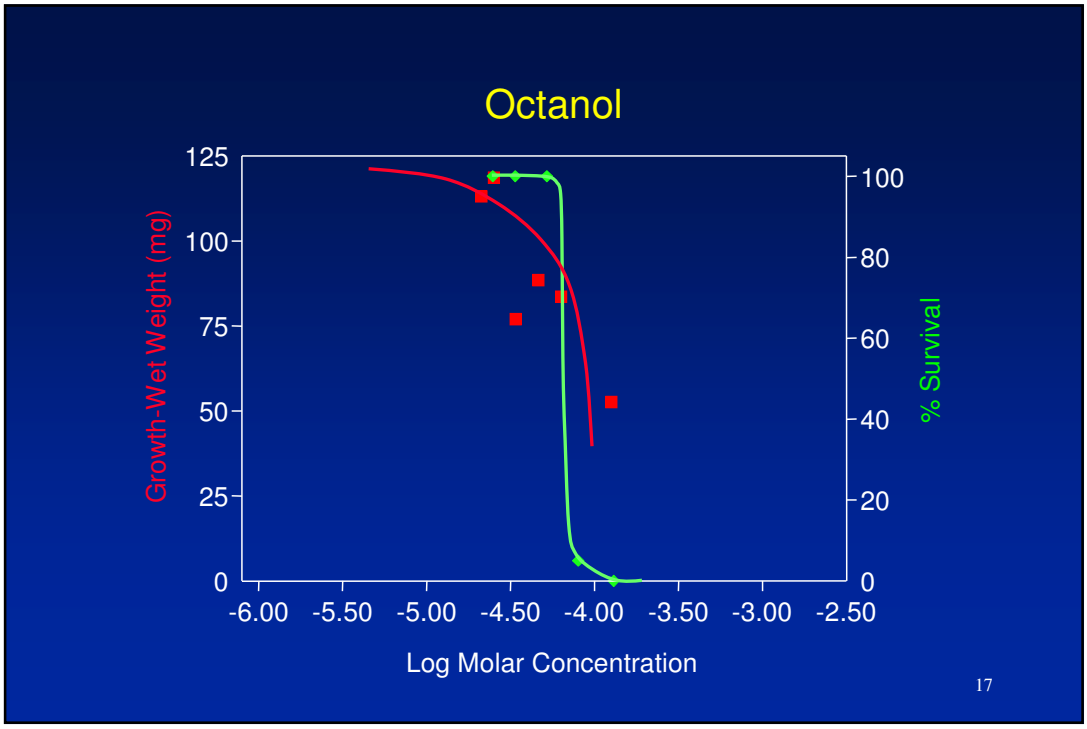
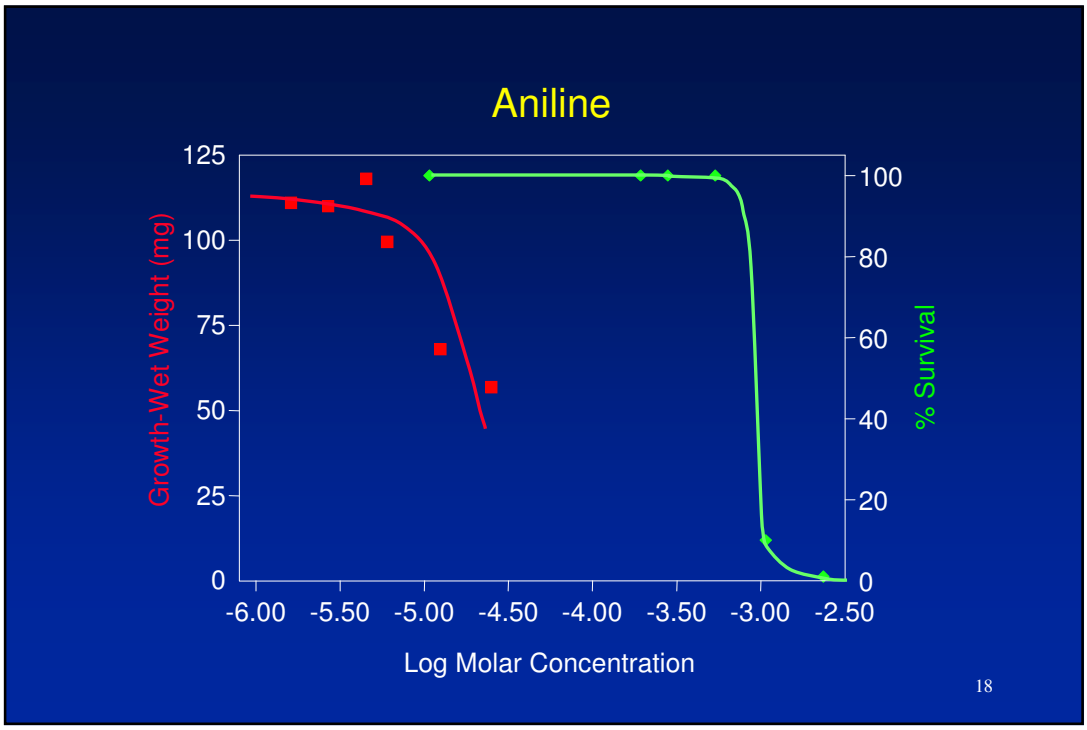
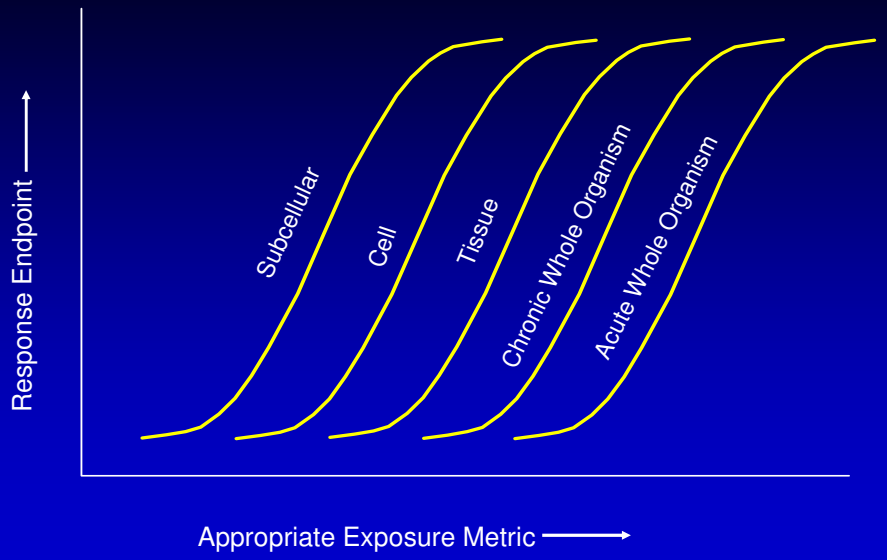

Octanol
Growth-Wet Weight (mg)
% Survival
125
100
75
50
25
0
100
80
60
40
20
0
-6.00
-5.50
-5.00
-4.50
-4.00
-3.50
-3.00
-2.50
Log Molar Concentration
17


Aniline
Growth-Wet Weight (mg)
% Survival
125
100
75
50
25
0
100
80
60
40
20
0
-6.00
-5.50
-5.00
-4.50
-4.00
-3.50
-3.00
-2.50
Log Molar Concentration
18

Is this really the Order for Industrial Chemicals?



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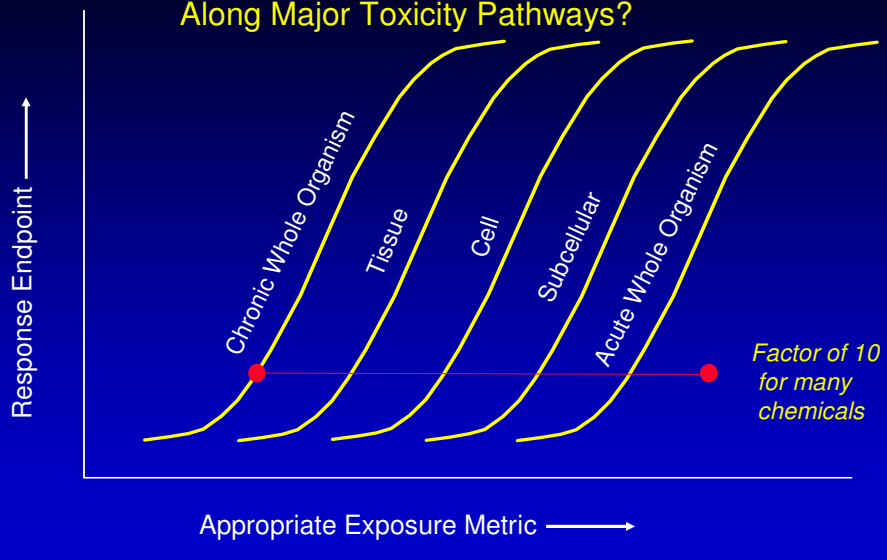
Can We Predict the Order of Effects Along Major Toxicity Pathways?



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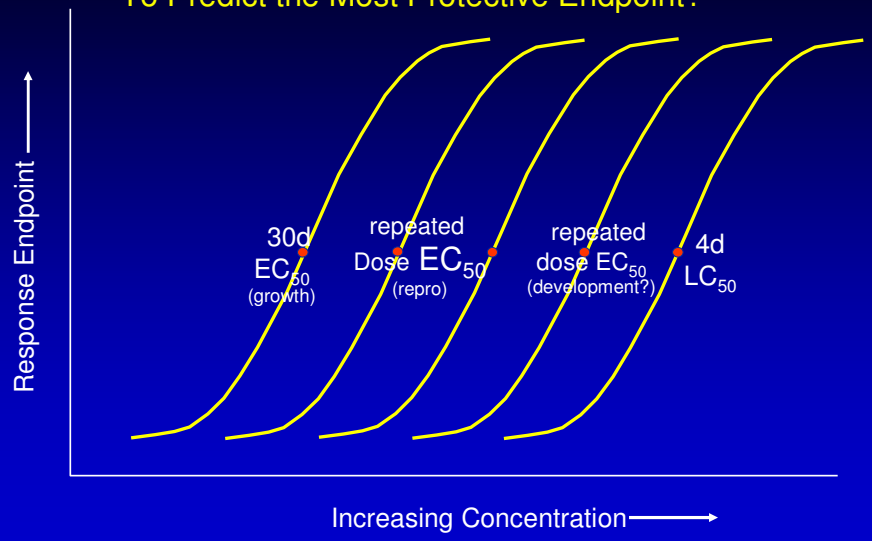
Can We Use Knowledge About Mechanisms To Predict the Most Protective Endpoint?



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Goals for Predictive Toxicology

- Develop QSAR and Biological Models for screening and initial testing hypotheses
- Integrate In-vitro and HTP capabilities to test hypotheses and generate new hypotheses downstream
- Reduce time and cost by focusing resources

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