Overview of the National Center for Computational Toxicology at the U.S. Environmental Protection Agency

Rory Conolly

National Center for Computational Toxicology

US EPA, ORD, RTP, NC

Workshop on Systems Biology and the Human Health Risks of Environmental Chemicals

ICSB 7, Yokohama, Japan

October 12, 2006

Outline

- EPA and the NCCT
- Issues and challenges leading to formation of the NCCT
- Risk assessment paradigm
- Role of computation
- Overview of NCCT research and development activities

U.S. EPA

- The mission of the Environmental Protection Agency is to protect human health and the environment.
- EPA employs 18,000 people across the country, including headquarters offices in Washington, DC, 10 regional offices, and more than a dozen labs.
- http://www.epa.gov/epahome/aboutepa.htm

EPA - RTP

National Center for Computational Toxicology (NCCT)

"…to integrate modern computing and information technology with molecular biology to improve Agency prioritization of data requirements and risk assessment of chemicals"

NCCT

- Use mathematical and computational tools to advance the science needed to protect human health and natural ecosystems from pollutants.
- Leadership in efforts to improve understanding of the environmental transport and fate of pollutants.
- Setting priorities for future studies.
- http://www.epa.gov/comptox/

Why did EPA create the NCCT?

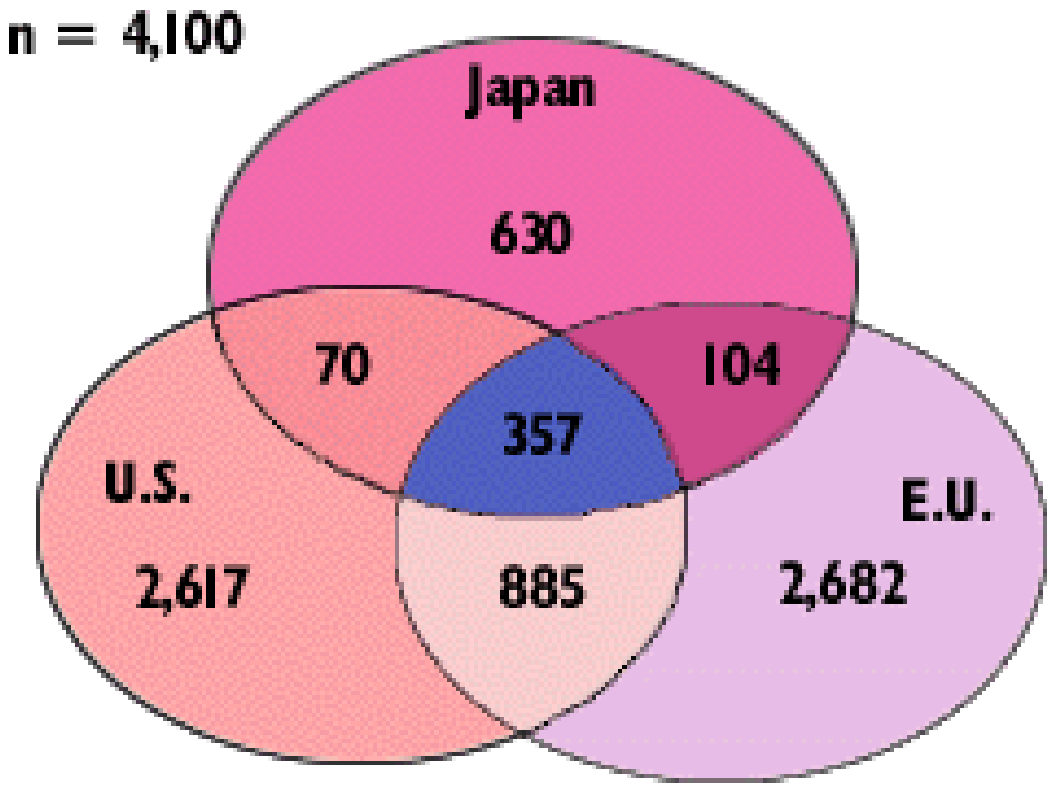
Issues and challenges

- 10’s of thousands of chemicals in commerce
- Concern for health risk
- Prioritization for testing
- Human and ecological health risk assessment
- Effective communication

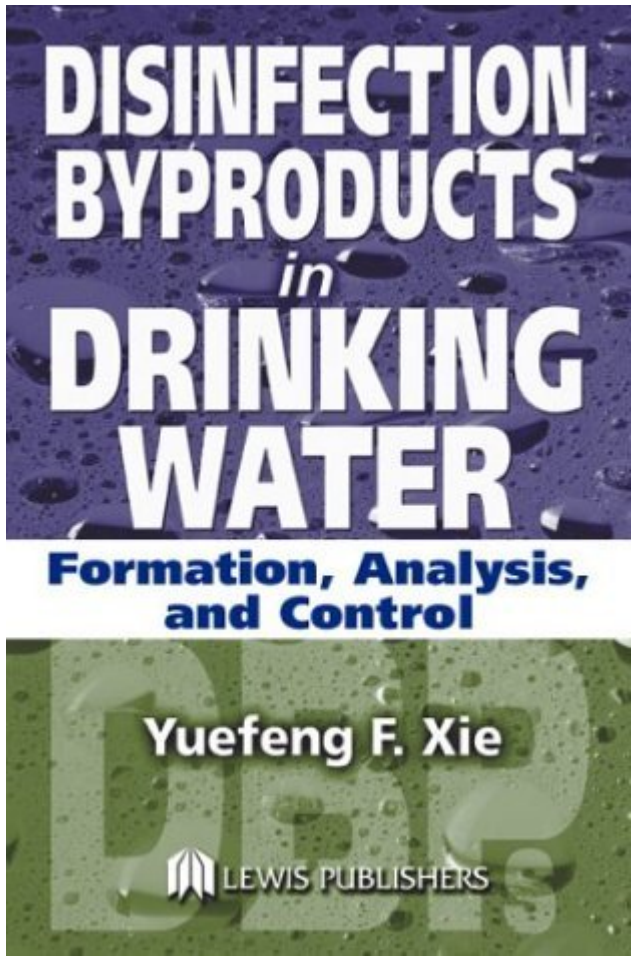
Chemicals in commerce

High production volume (HPV) chemicals

The U.S. high production volume (HPV) chemicals are those which are manufactured in or imported into the United States in amounts equal to or greater than one million pounds per year.

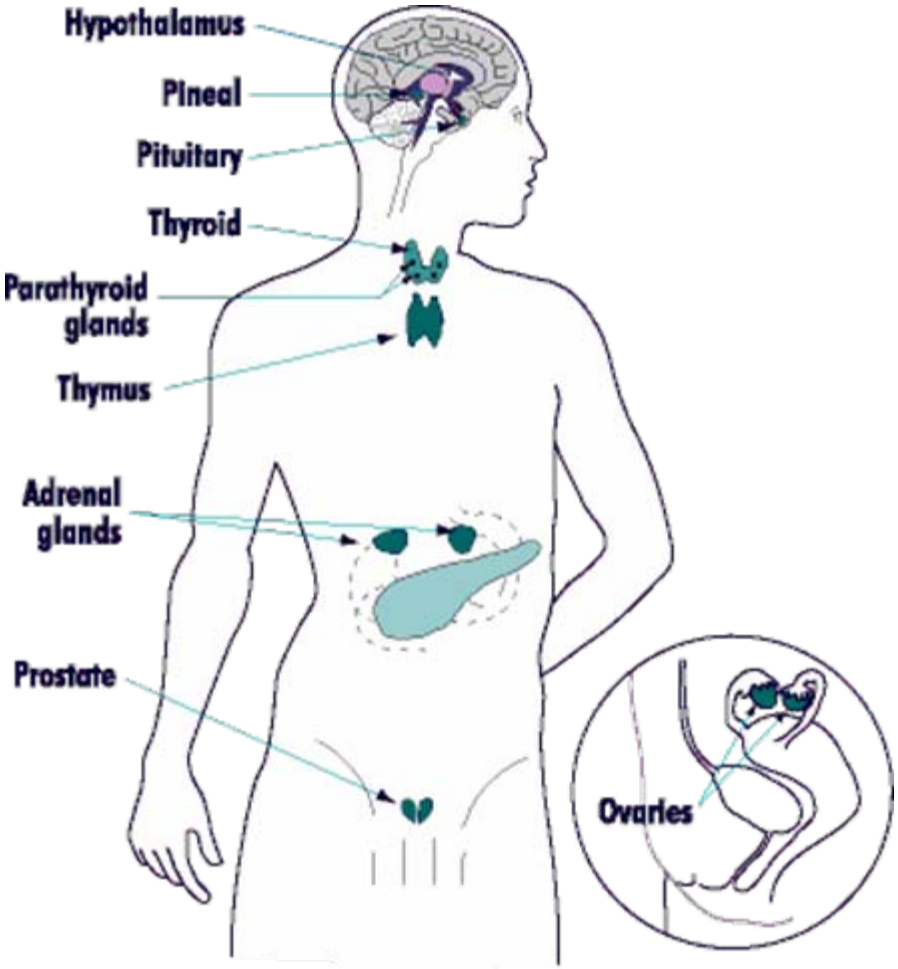


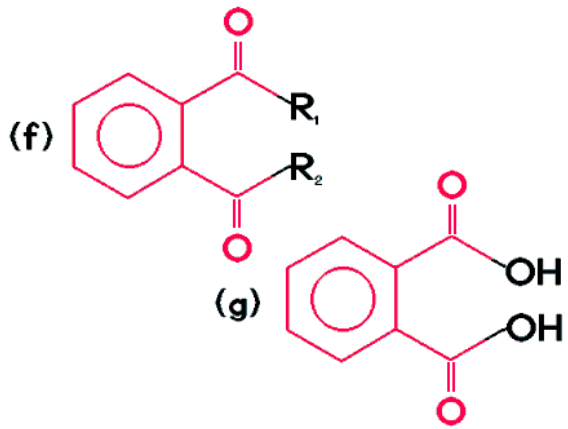
Water disinfection byproducts



Pesticide inerts

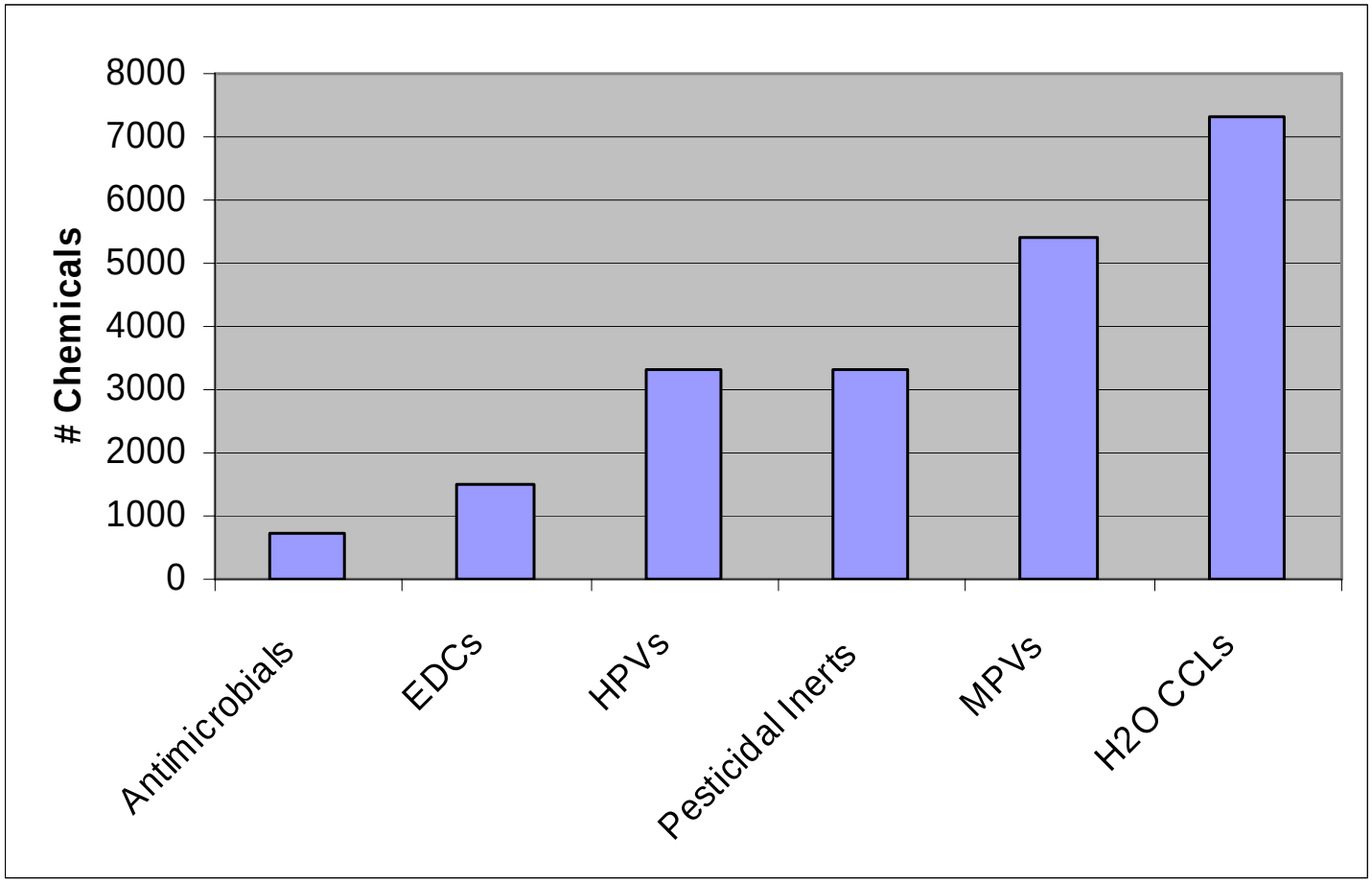
Endocrine disruptors



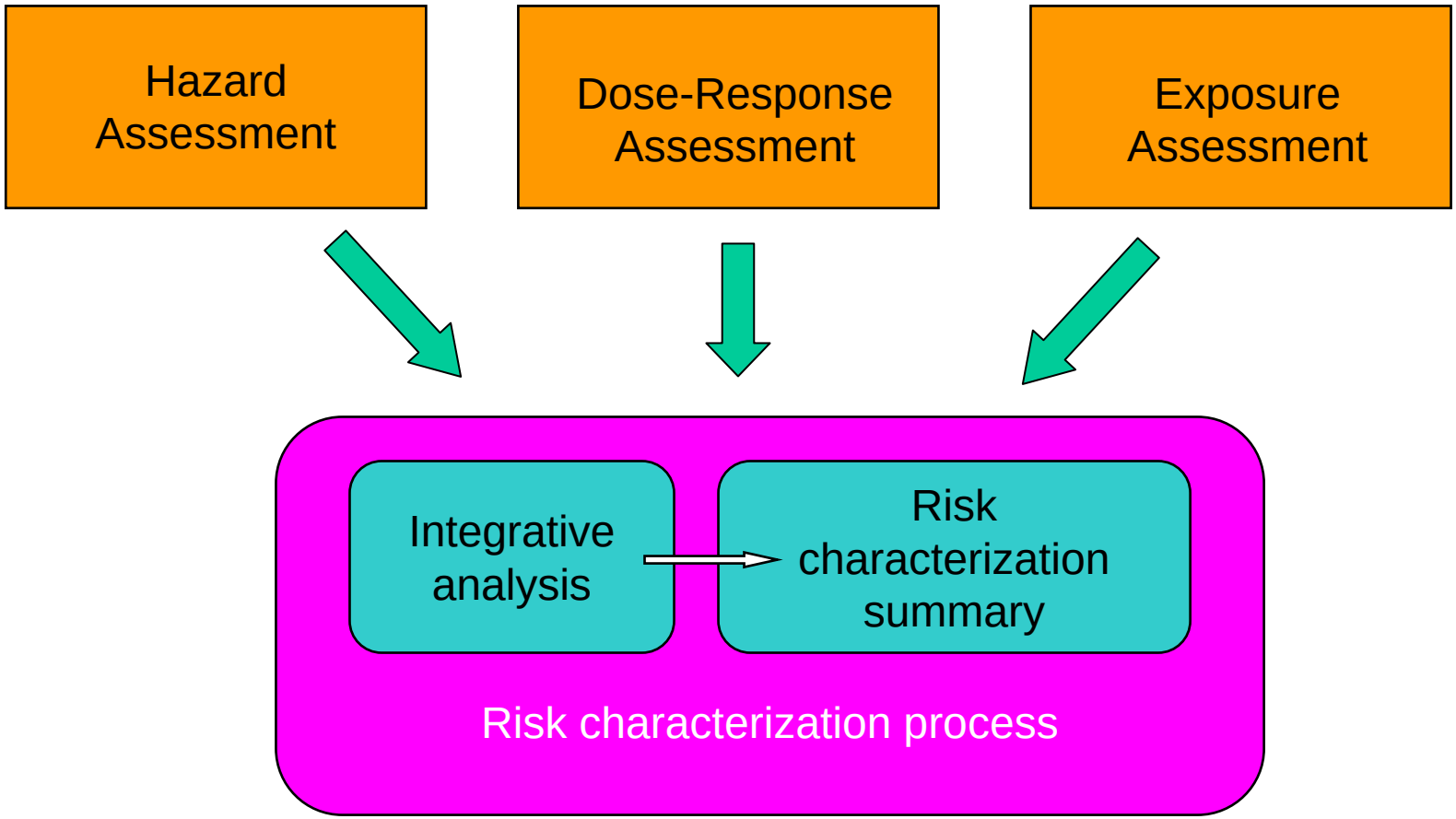


Phthalic acid

Numerical Challenges to Prioritization



Health risk assessment



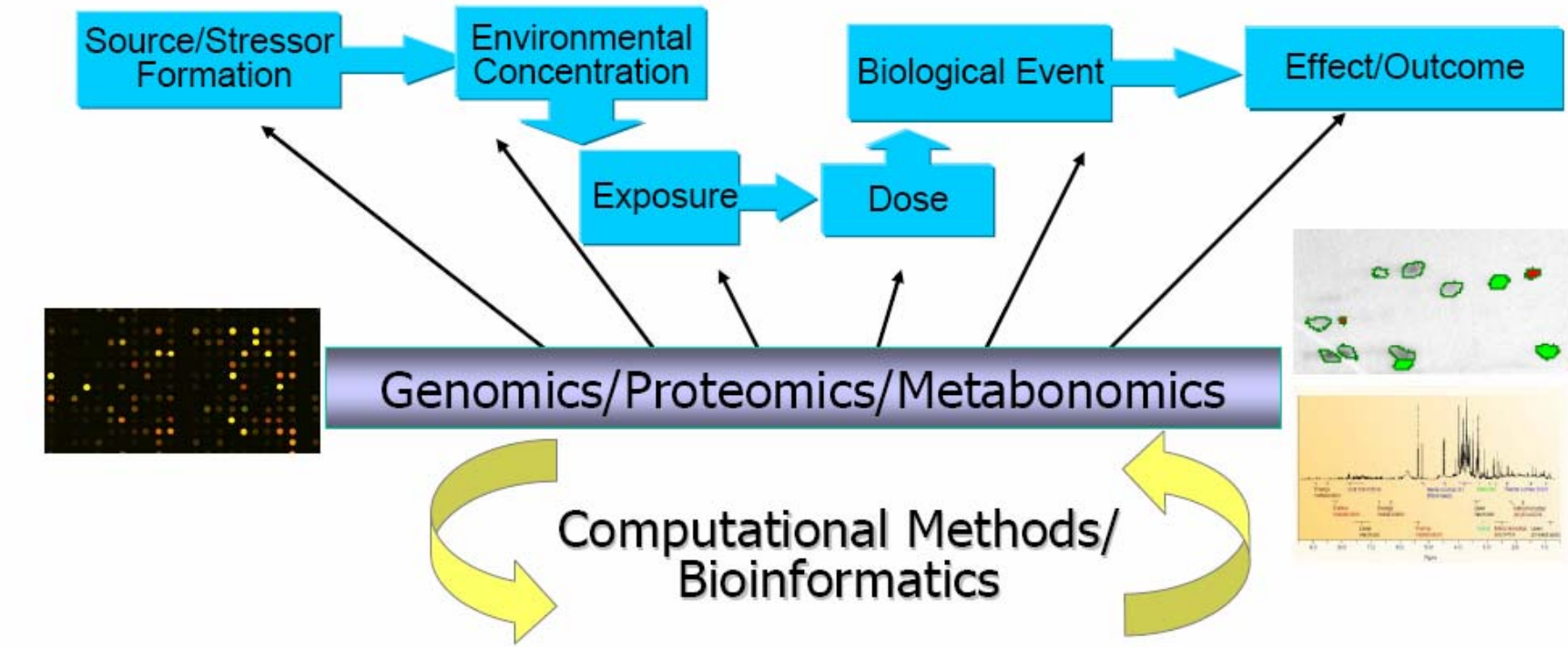
Hazard identification

- Is it toxic?
- A necessary but insufficient basis for management actions.
- Will produce valuable data for prioritization and possible acceleration of risk assessments by Governments as well by Industry.

ToxCast program for prioritizing environmental chemicals based on predicted toxicity

David Dix
NCCT ORD/USEPA
dix.david@epa.gov

ToxCast



Genomics, proteomics and metabonomics can provide useful information along the source-to-outcome continuum when appropriate bioinformatic and computational methods are applied.

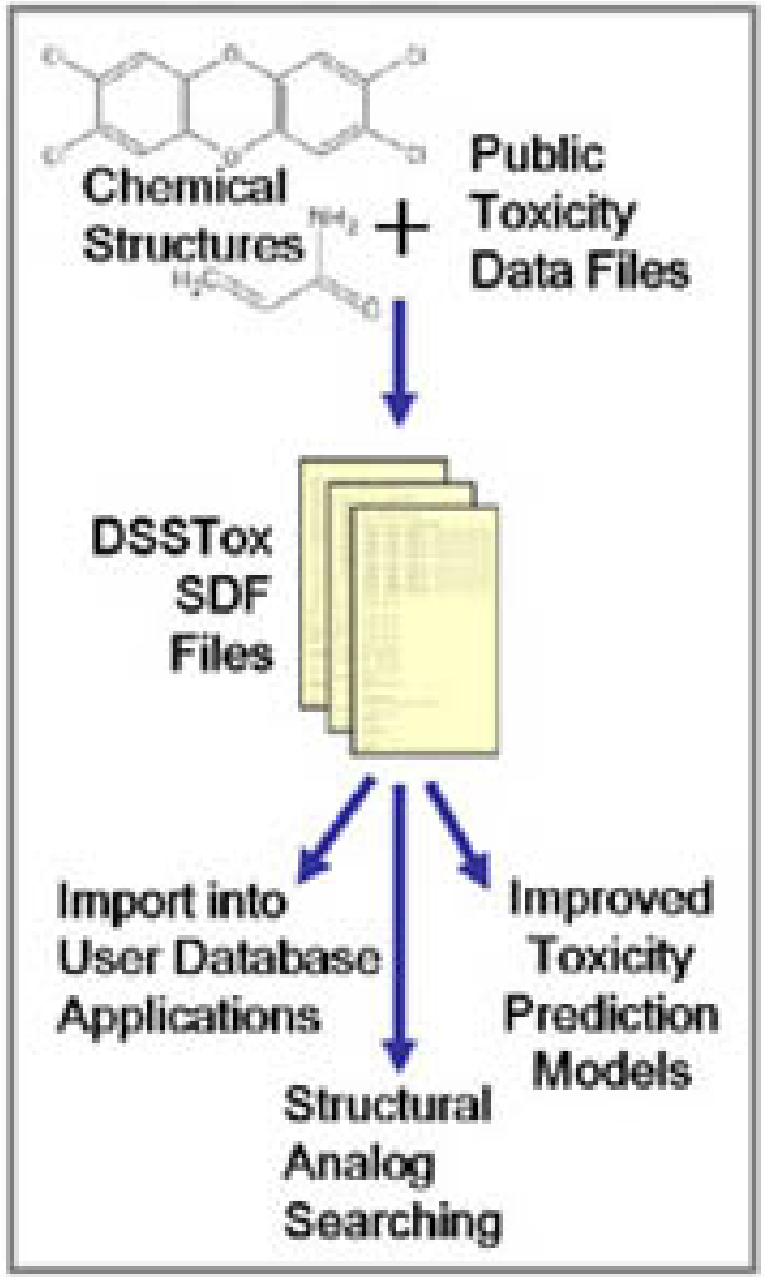
David Dix, Nat'l Ctr Computational Toxicology, ORD/USEPA dix.david@epa.gov

ToxCast- Potential Outcomes

- Provide EPA Program Offices with a relatively inexpensive predictive tool box that heretofore has been lacking.
- Improve the efficiency and effectiveness of the use of animals in hazard identification and risk assessment.

Distributed Structure-Searchable Toxicity (DSSTox) Database Network

DSSTox



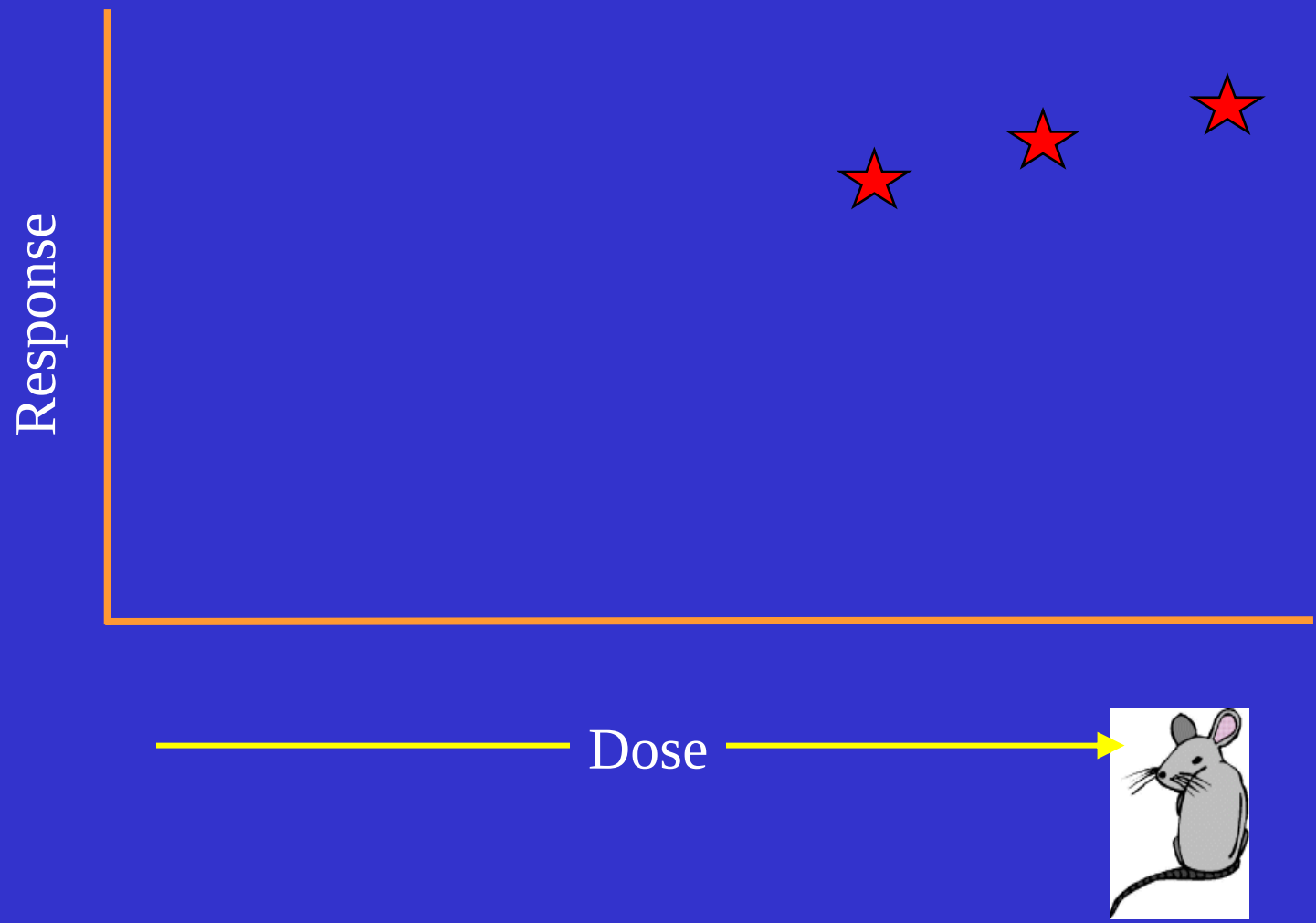
Ann Richard

DSSTox

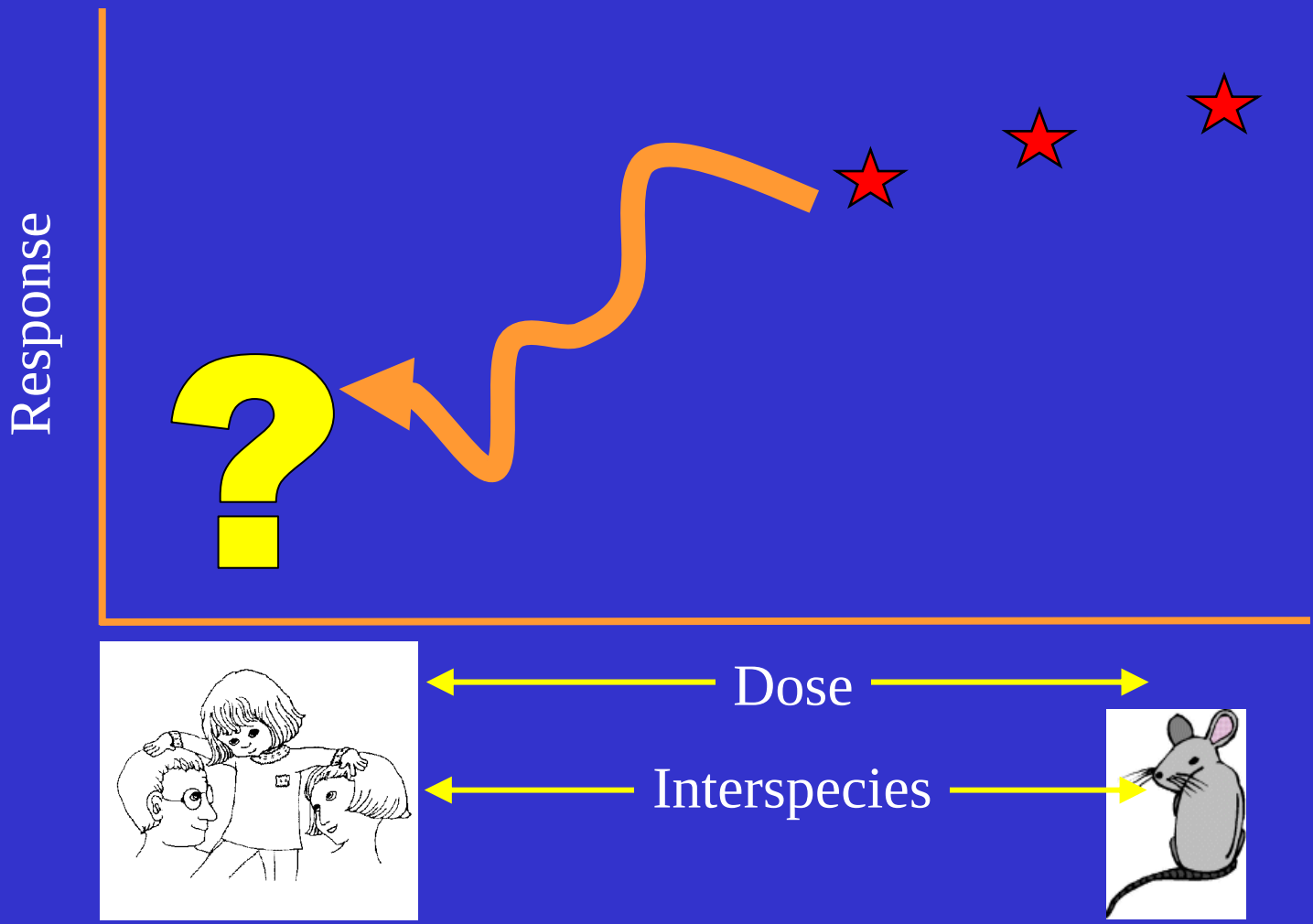
- Helping to build a public data foundation for improved structure-activity and predictive toxicology capabilities.
- The DSSTox website provides a public forum for publishing downloadable, standardized toxicity data files that include chemical structures.
- http://www.epa.gov/nheerl/dsstox/

Predicting health risks: Dose-response and exposure assessments

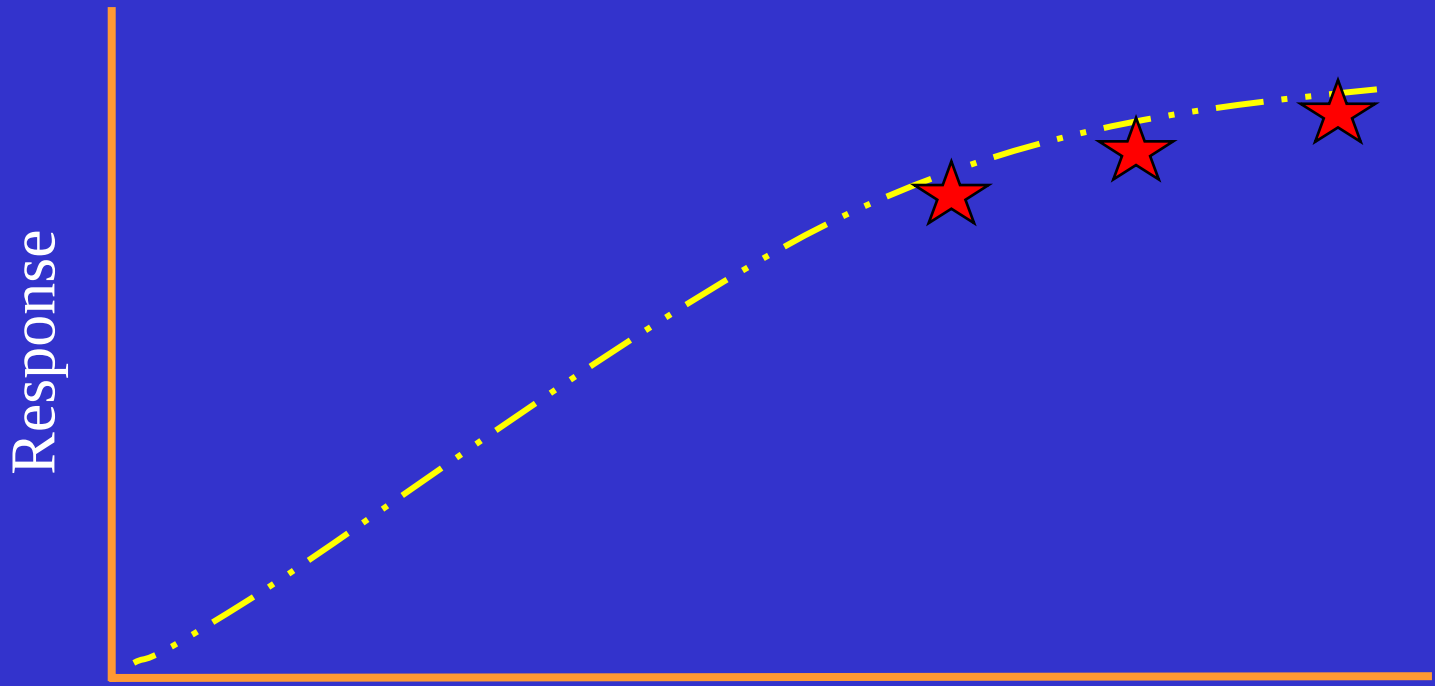
Typical high dose rodent data – what do they tell us?

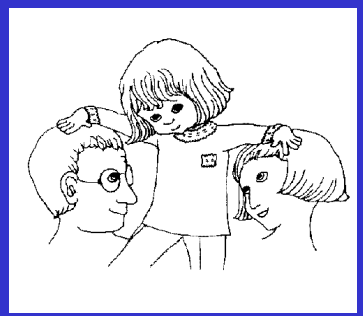


Not much!



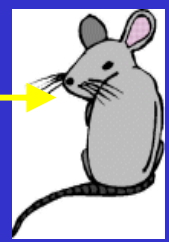
Possibilities





Dose

Interspecies



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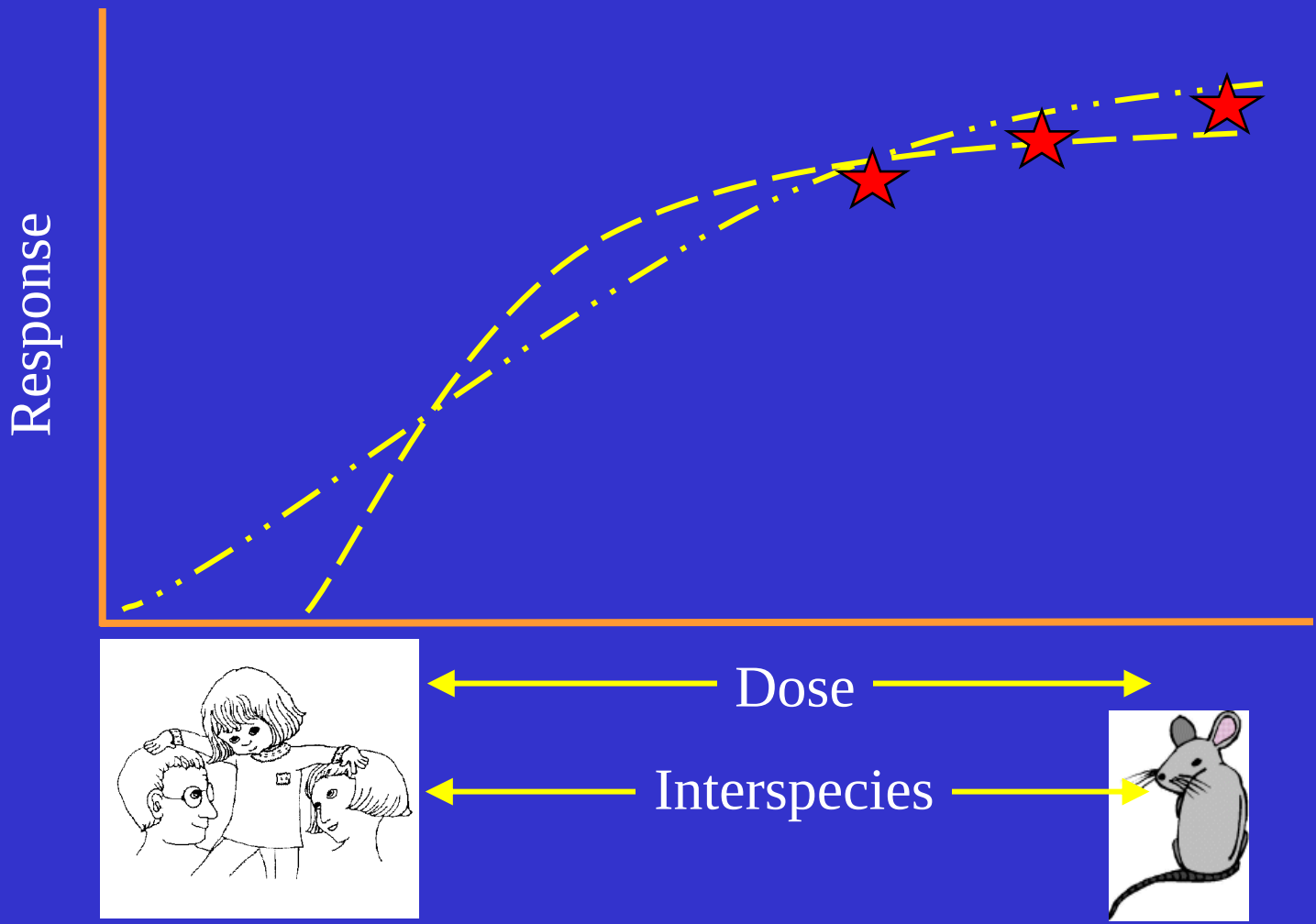

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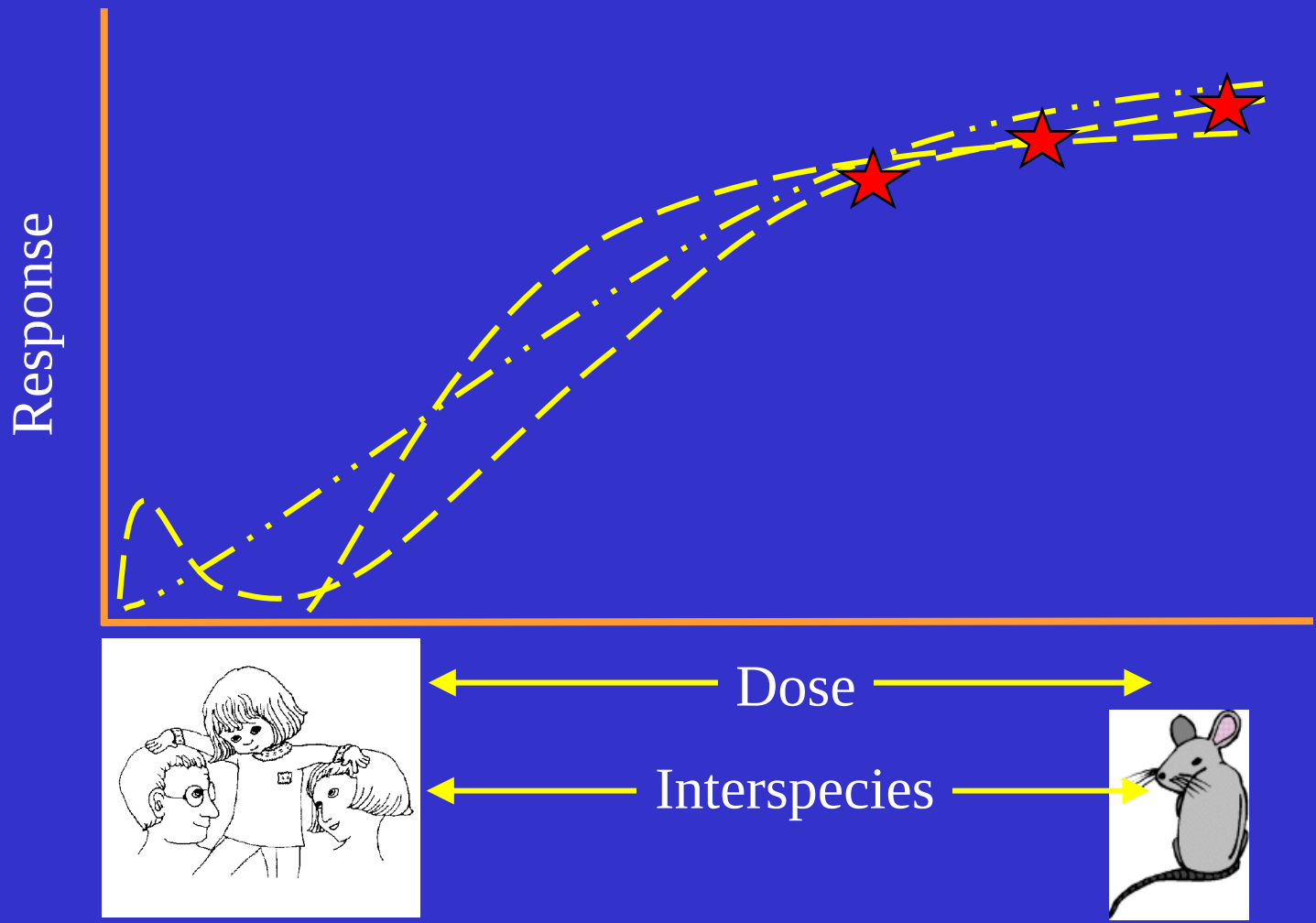

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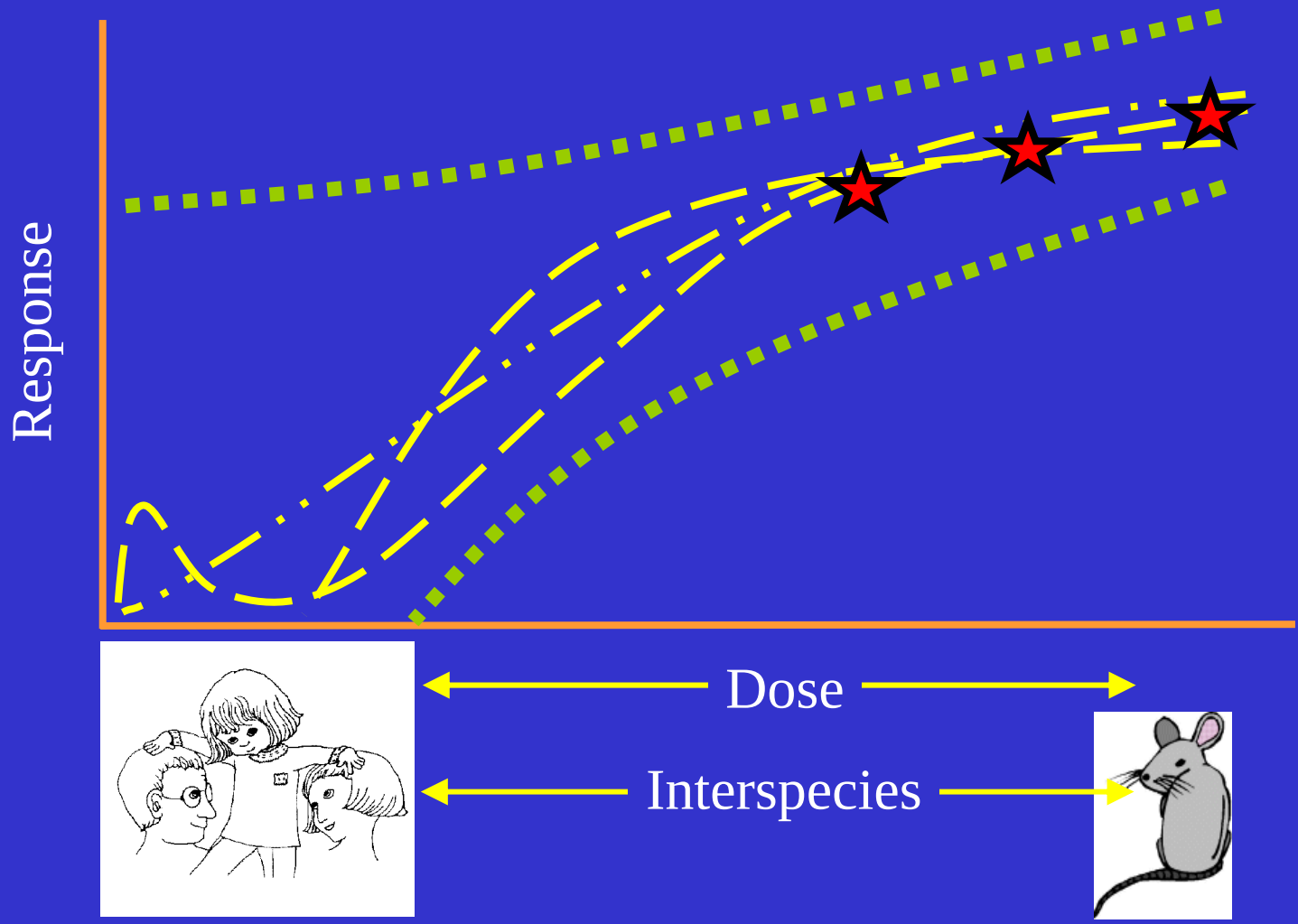
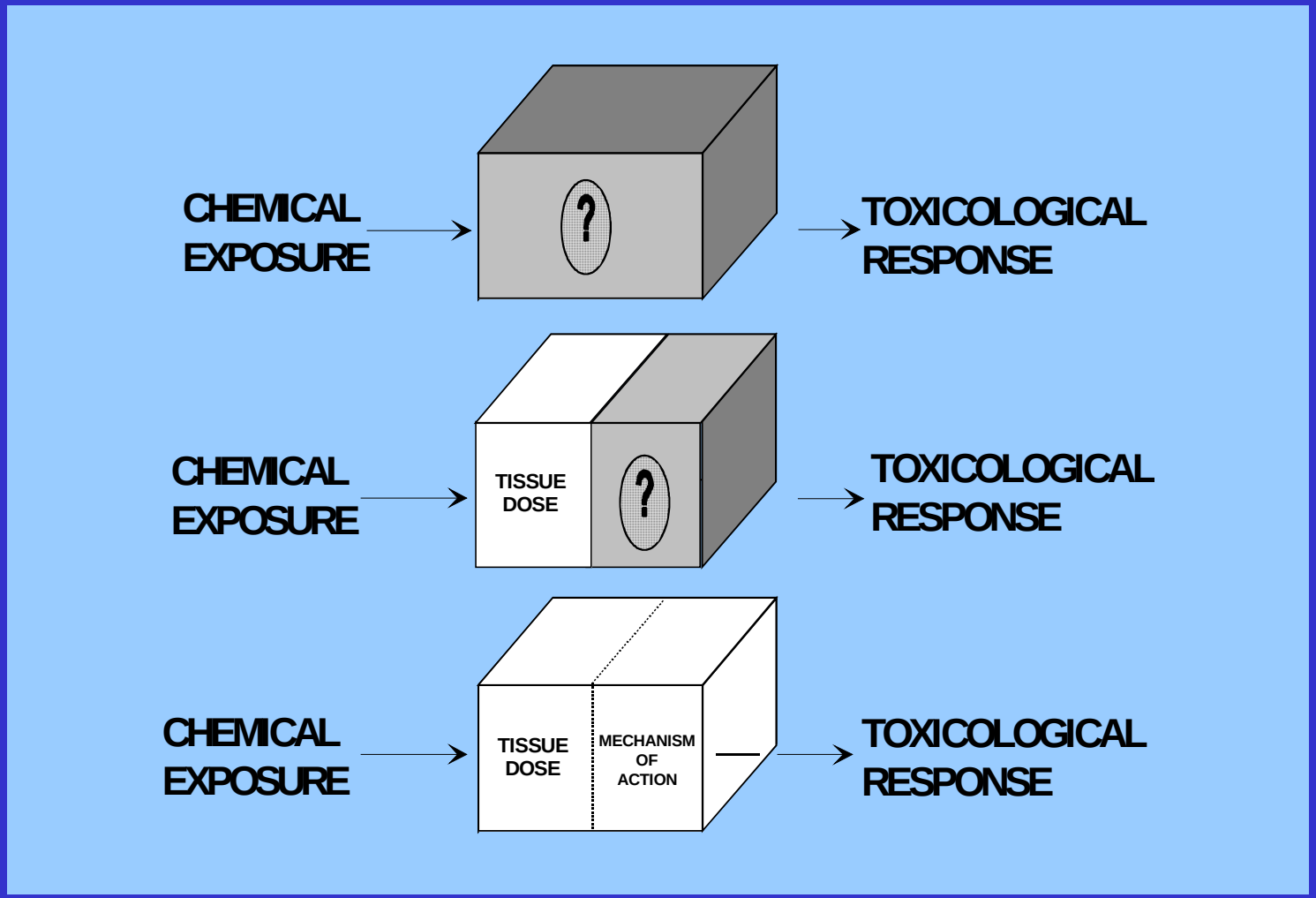
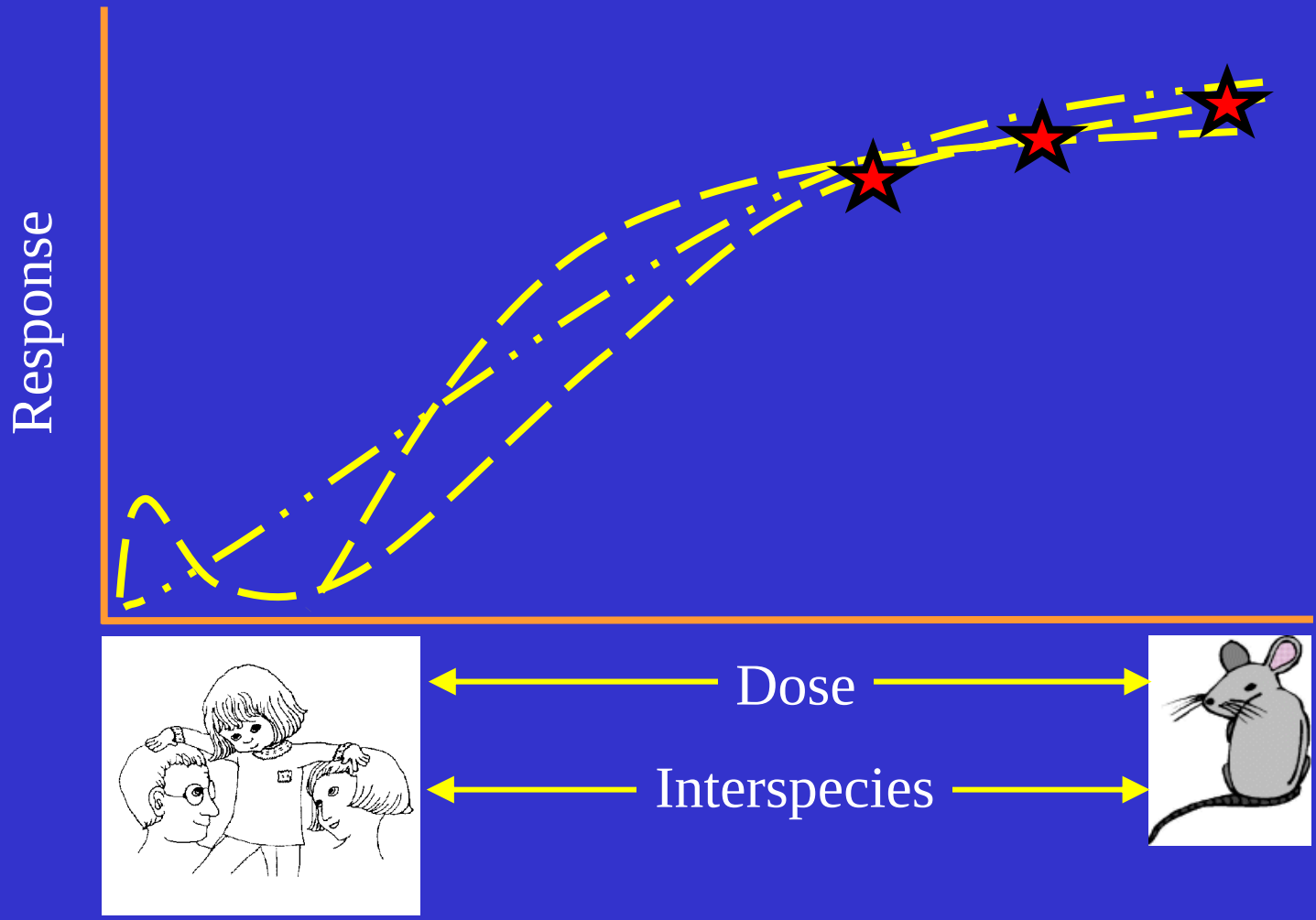


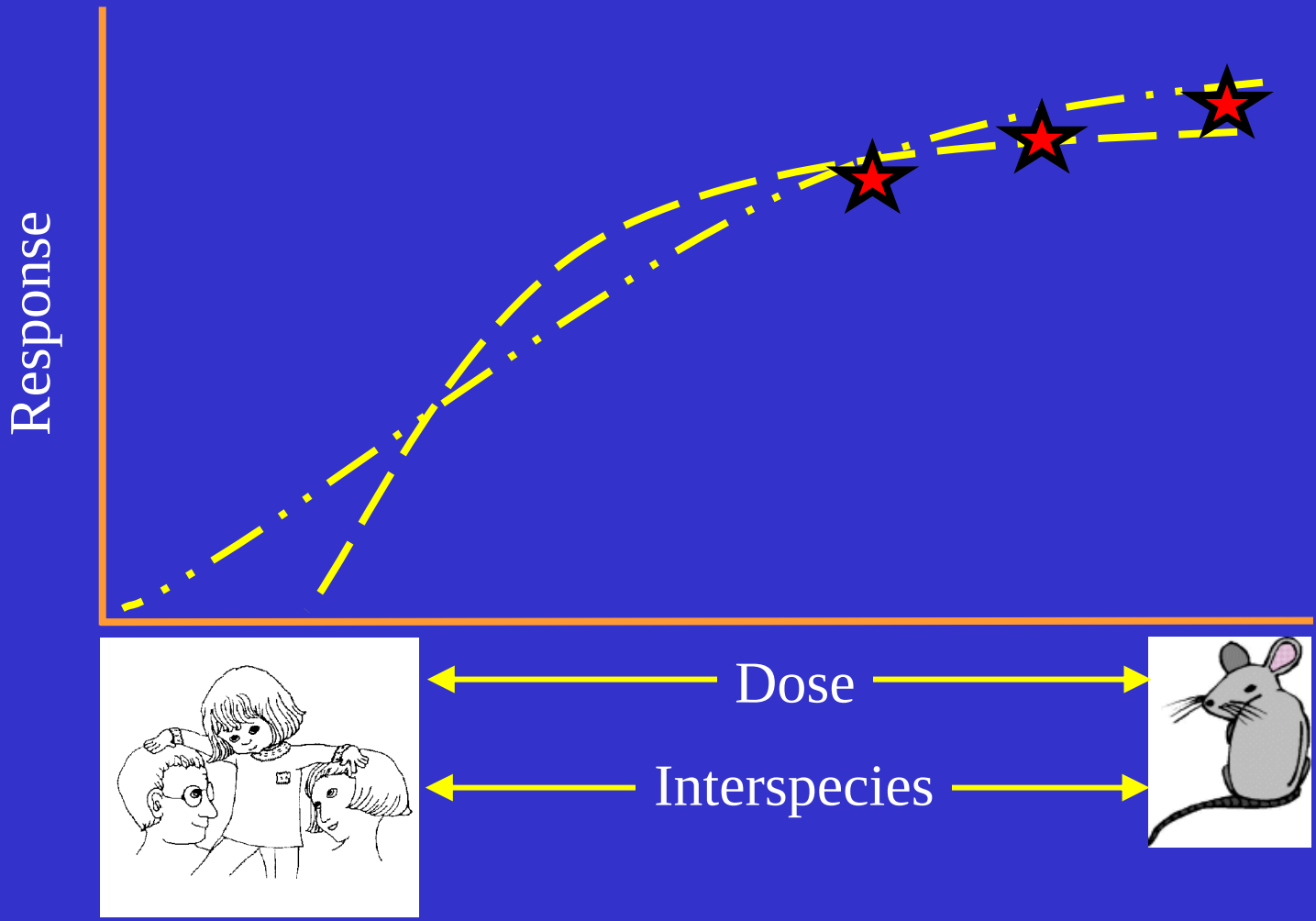
Biological mechanisms determine dose-response



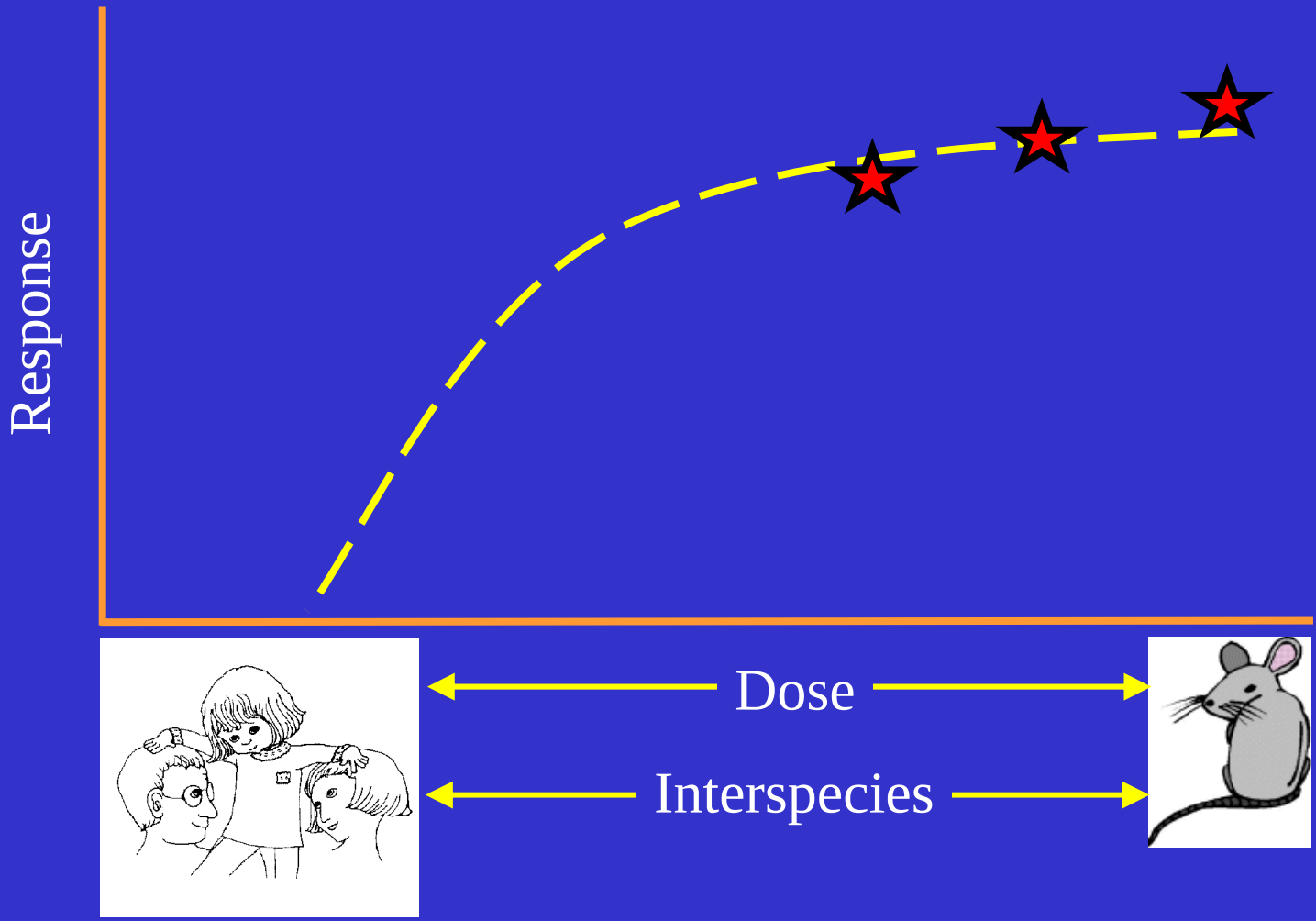
Refining the description with research on mechanisms



Refining the description with research on mechanisms



Refining the description with research on mechanisms



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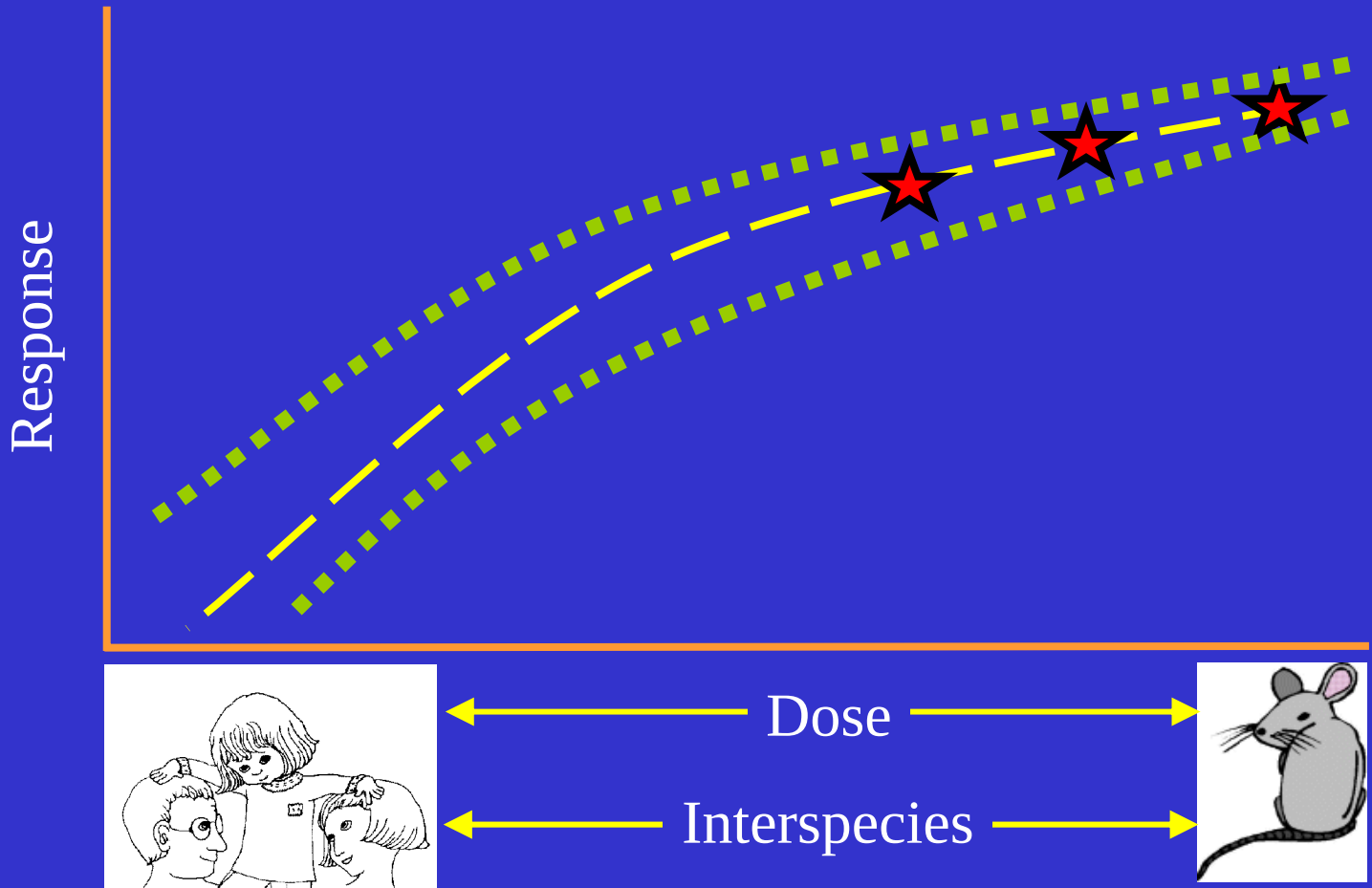
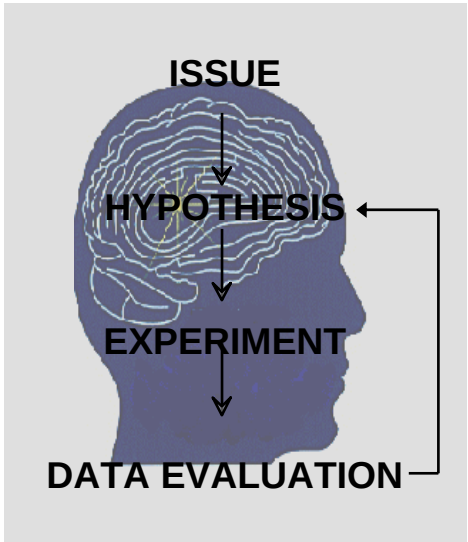


The role of computational toxicology in research on mechanisms

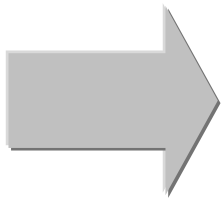
Computational modeling

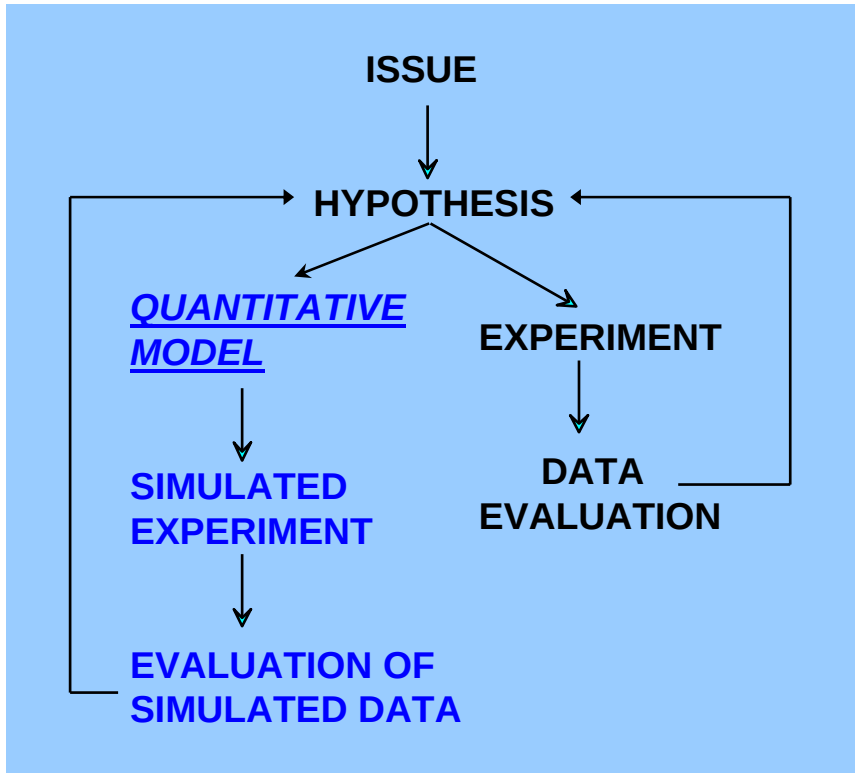
- Organize and integrate data
- Study dynamic behavior
- Analysis
  - Are model predictions consistent with existing data?
- Predictions
  - Suggest new experiments
  - Risk assessment

Computational modeling complements laboratory research



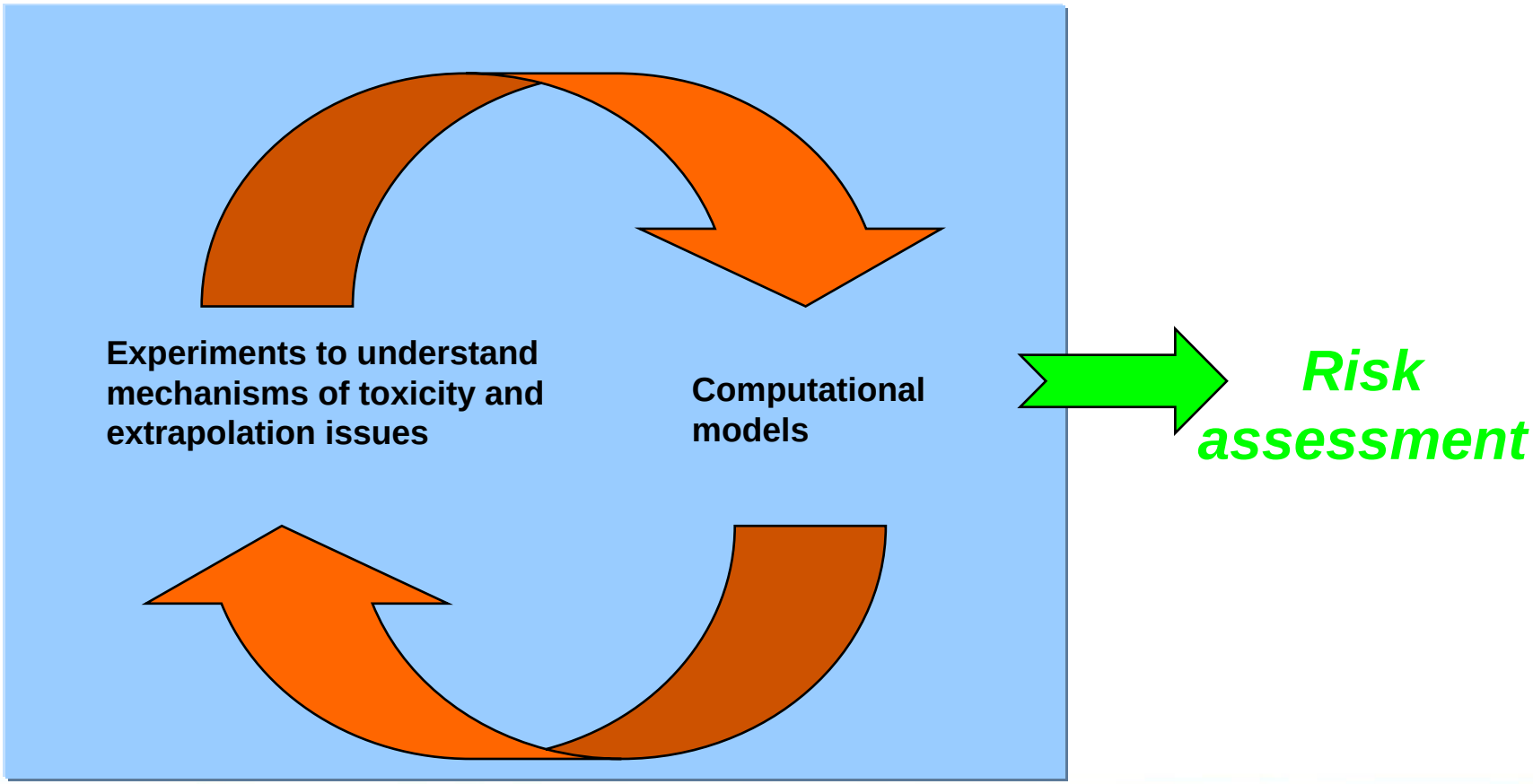
(Intuitive modeling)





(Formal + intuitive modeling)

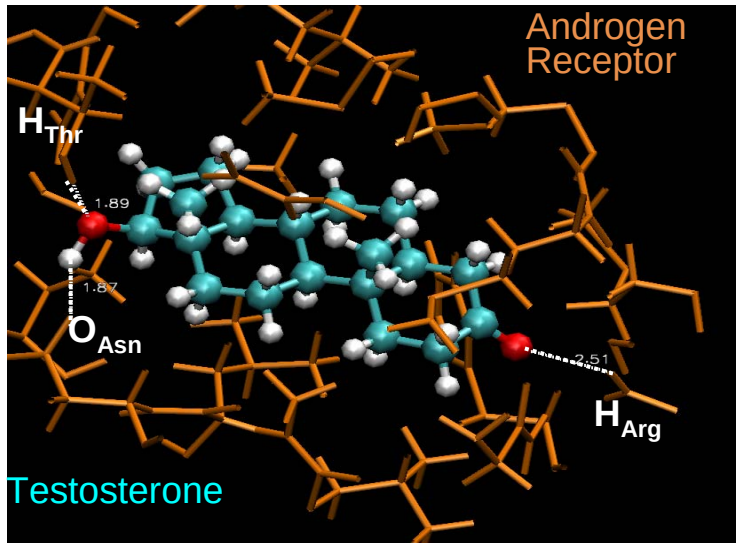
Biologically-based computational models: Natural bridges from research to risk assessment



Overviews

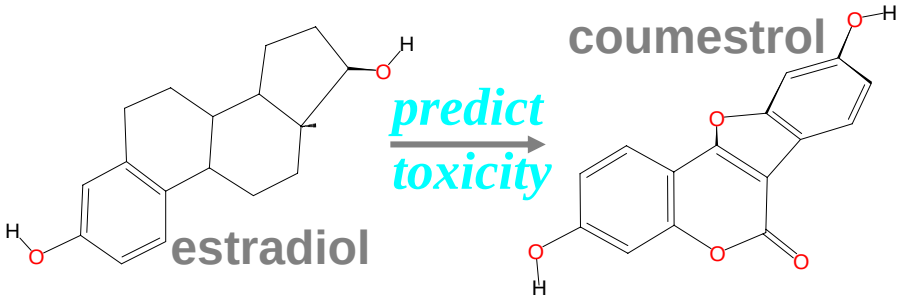
Molecular modeling as a tool for hazard identification

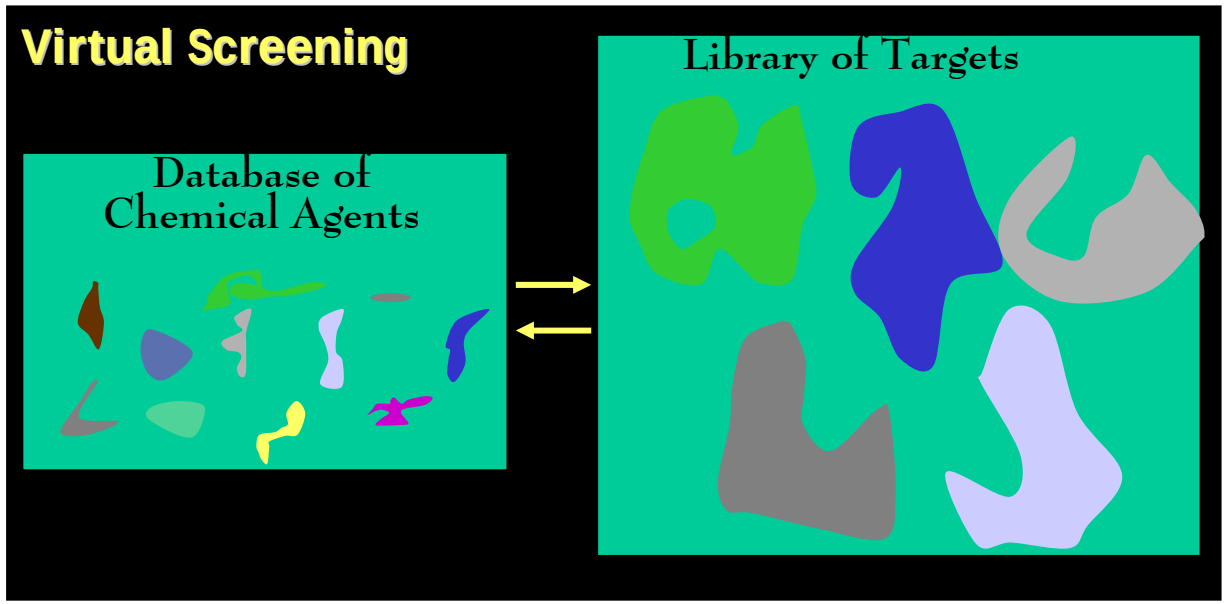
- Predict a potential toxicological effect of an environmental chemical based on knowledge of the effects of “similar” chemicals.
- Atomic-level details about interactions between environmental chemicals and molecules in the body, such as proteins or DNA.



Molecular Modeling

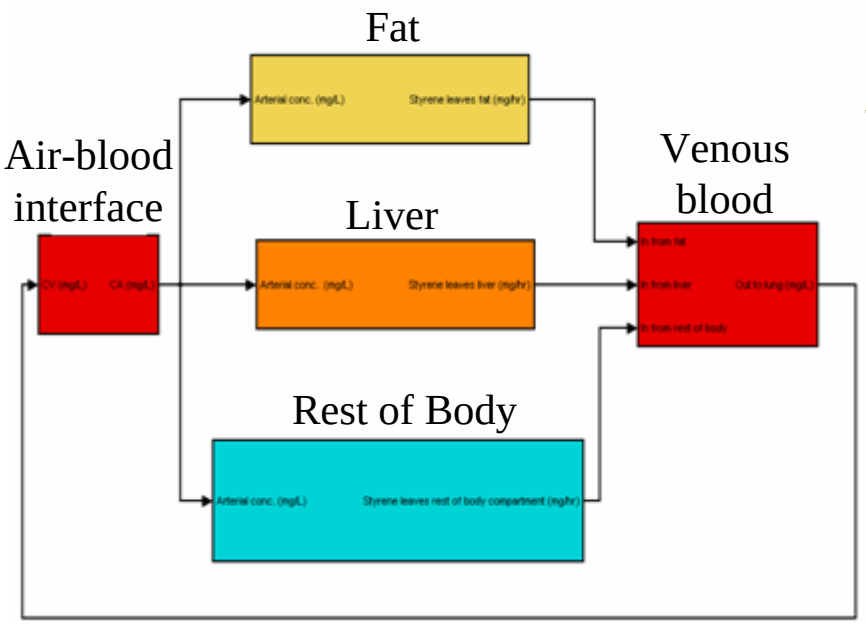
Aids the categorizaton and prioritization of chemicals for experimental testing

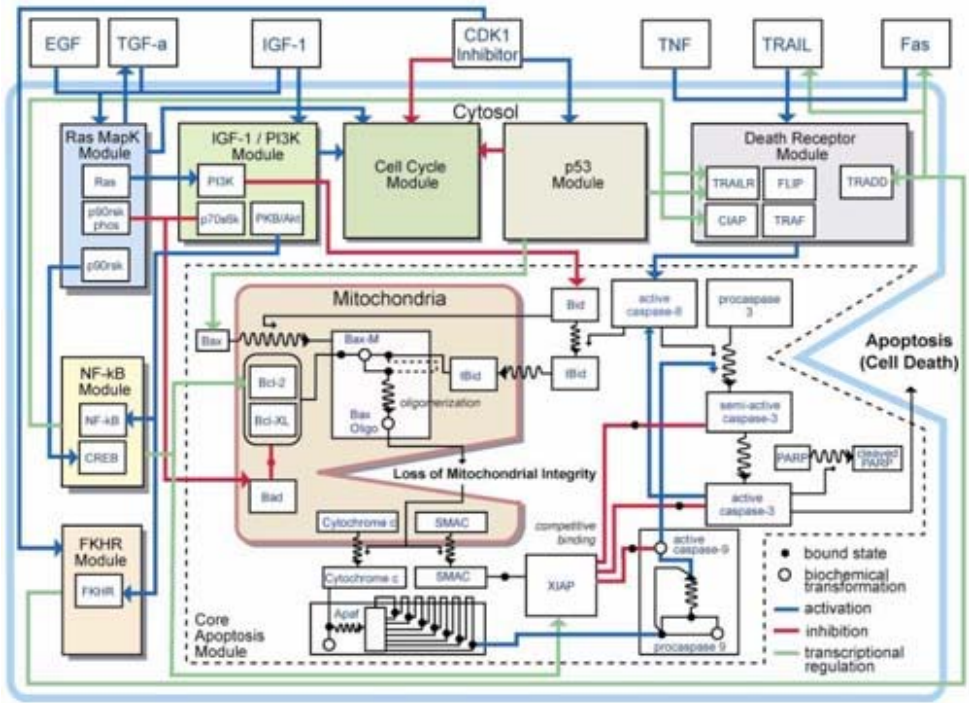




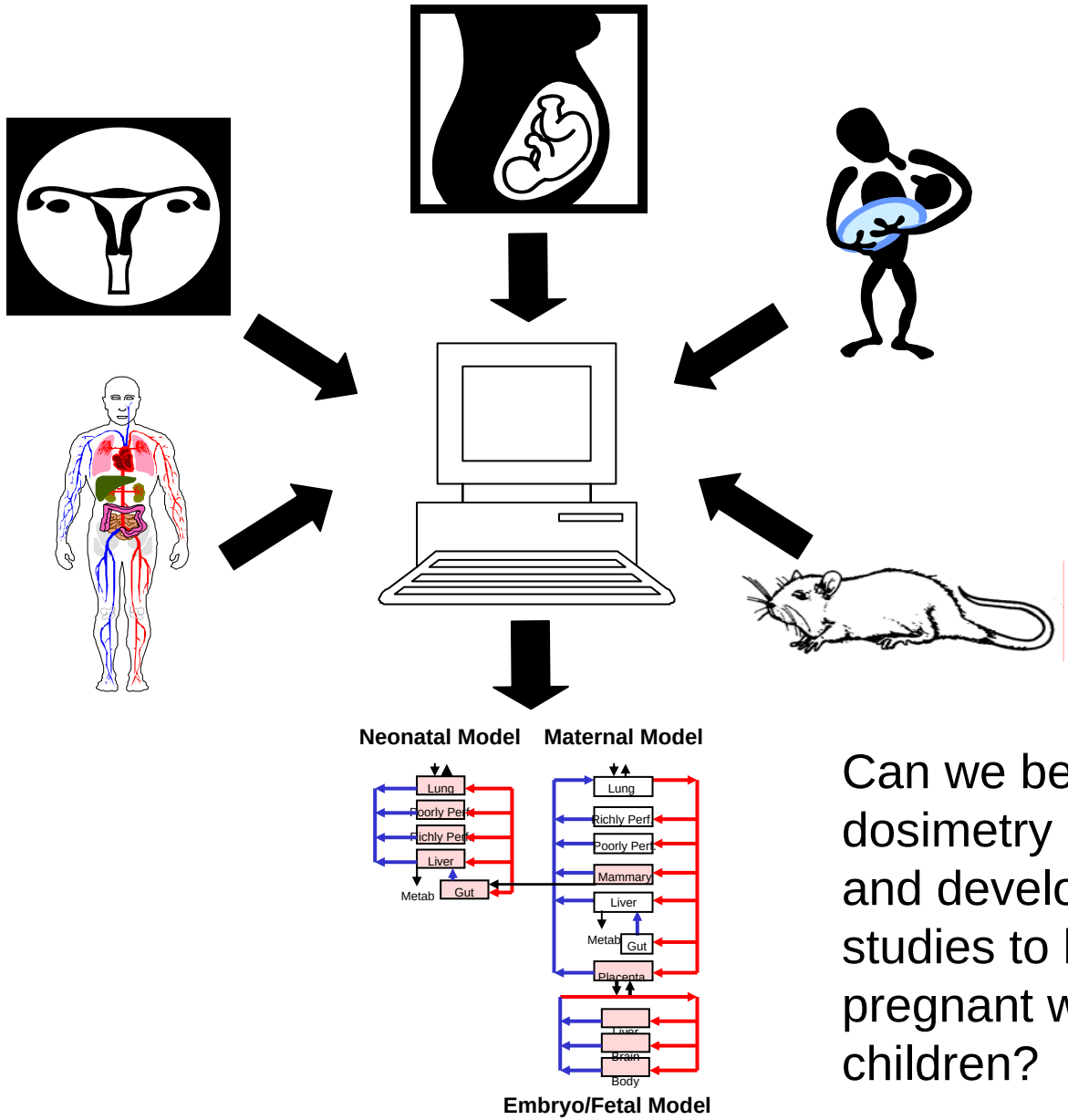
Jim Rabinowitz
Melissa Pasquinelli

Systems Modeling





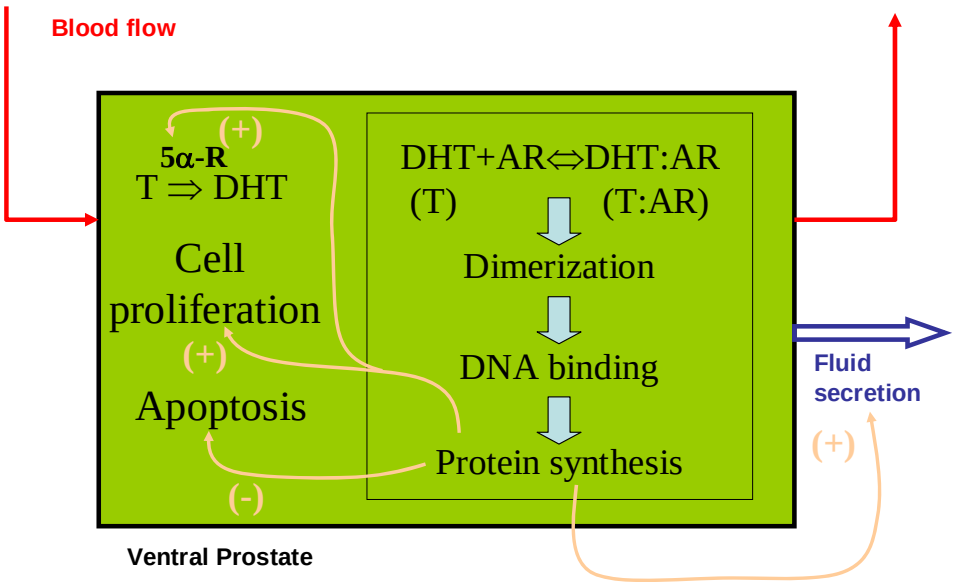
Predicting PK Across Lifestages & Species

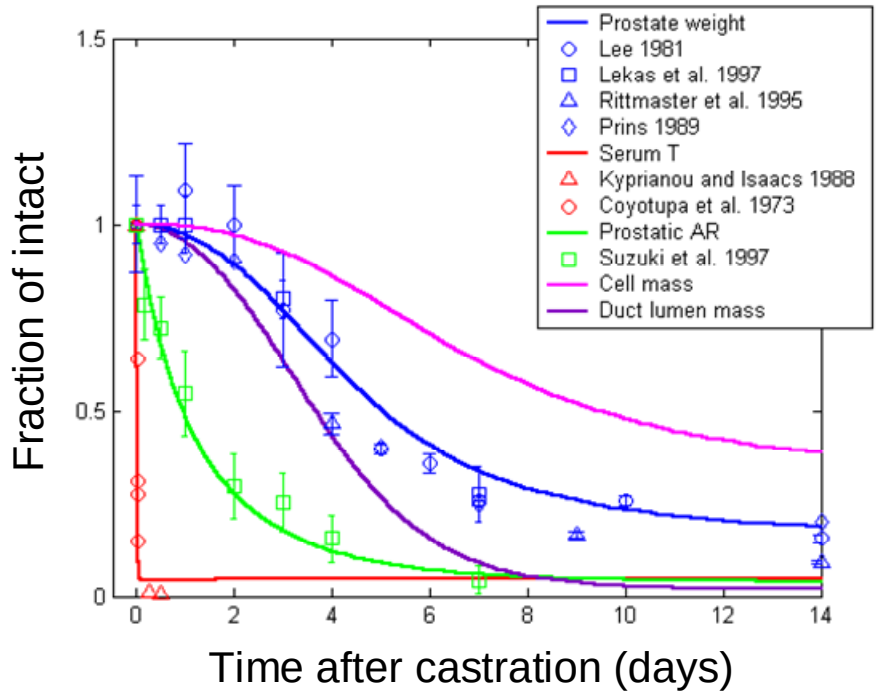


Can we better describe dosimetry in reproductive and developmental toxicity studies to better protect pregnant women and children?

Hugh Barton

Biologically based response modeling
Prostate: Gene to tissue response





Hugh Barton

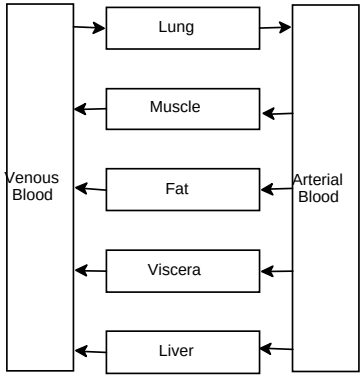
Modeling normal prostate regulation, strong perturbations (e.g., castration), and perturbations by environmental or pharmacological antiandrogens.

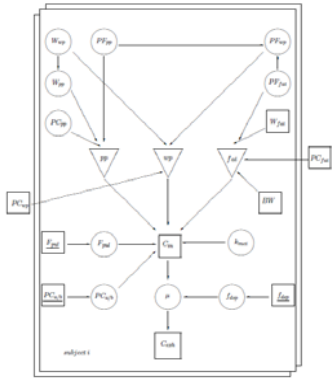
Statistical Analysis for Systems Models

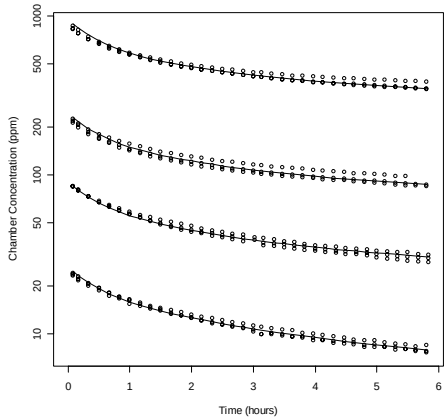
- NHEERL – Experimental Toxicology Division
- NCEA
- NIEHS
- UNC Dept. of Biostatistics – Joe Ibrahim

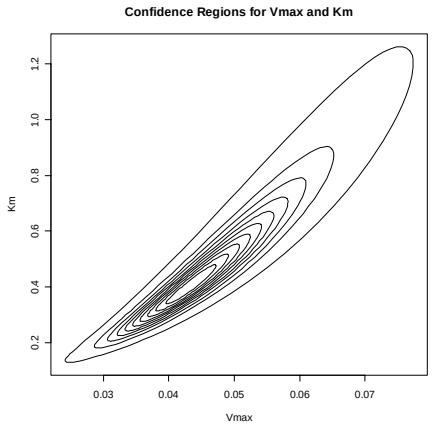
Goals

- Explore and develop statistical methodology for estimating parameters and evaluating alternative models
- Develop guidance for assessing uncertainty in systems models









Woody Setzer

Some of my own work

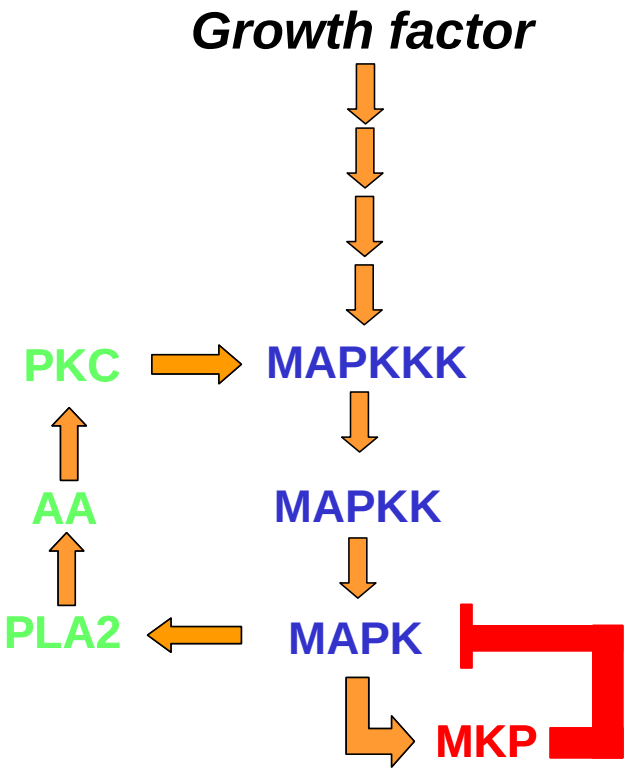
What do biological mechanisms tell us about dose-response?

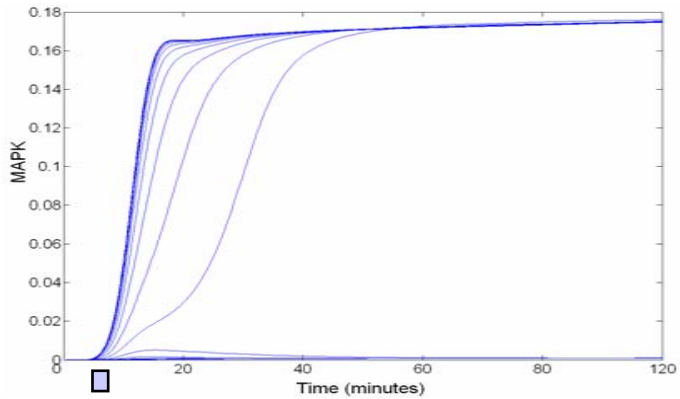
Goal:

To understand the role of MAPK signaling in neurodevelopmental toxicity in CG cells

Collaborator:

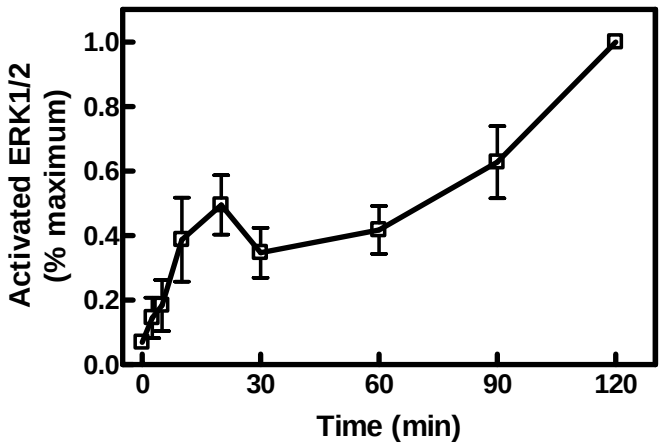
NTD - NHEERL





Input pulse

NMDA

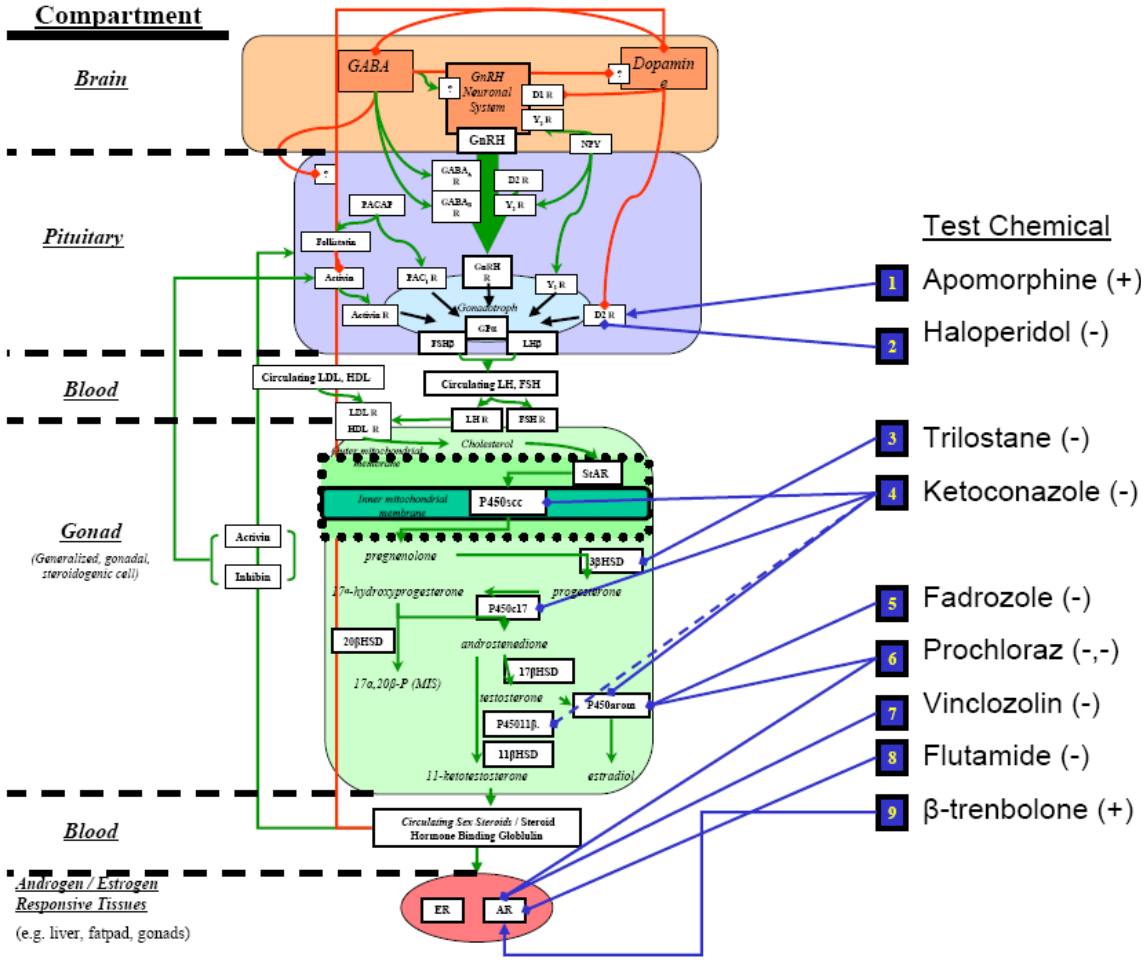


Goal:

Systems biology characterization of the HPG axis
in small fish.

Collaborators:

MED/NHEERL – Ankley
NERL
NCCT



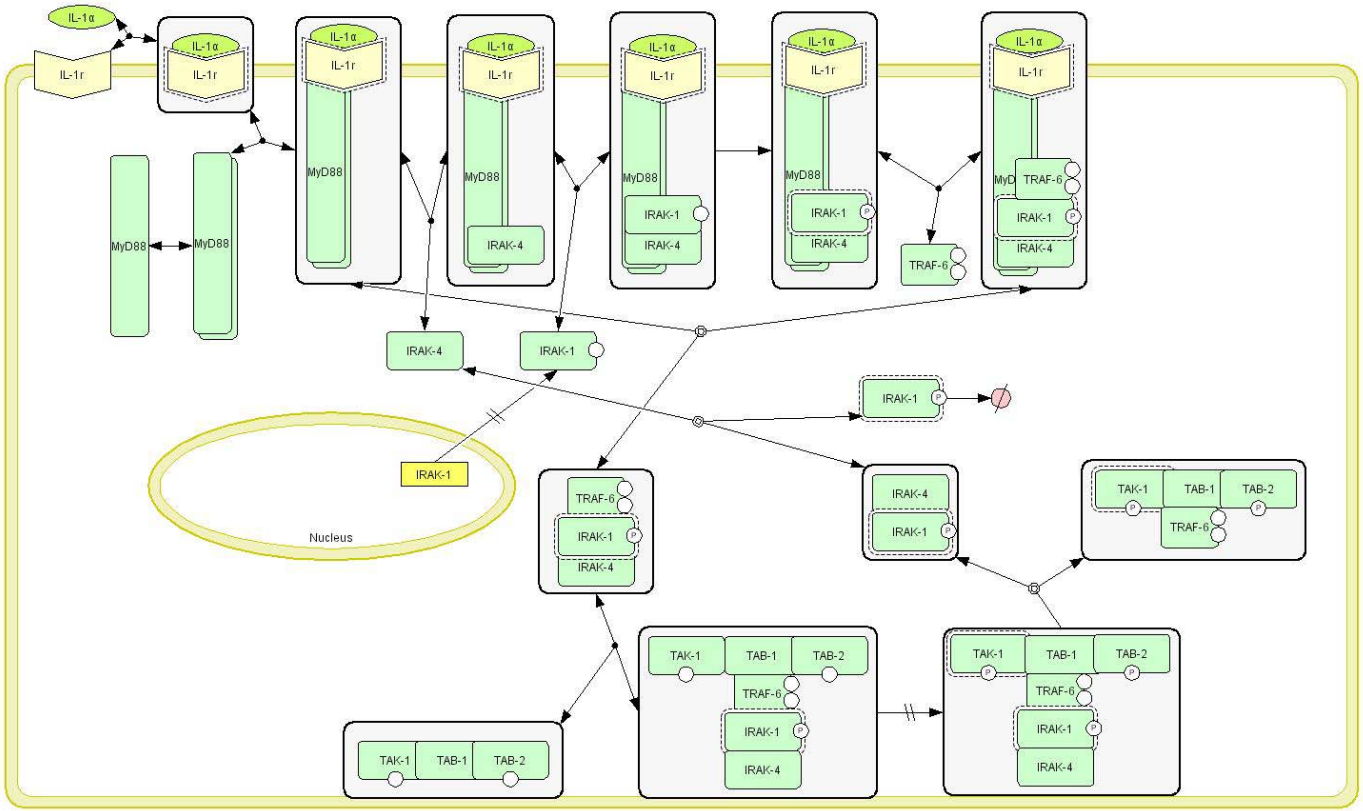
<u>Rory Conolly</u>
<u>Michael Breen</u>

Goal:

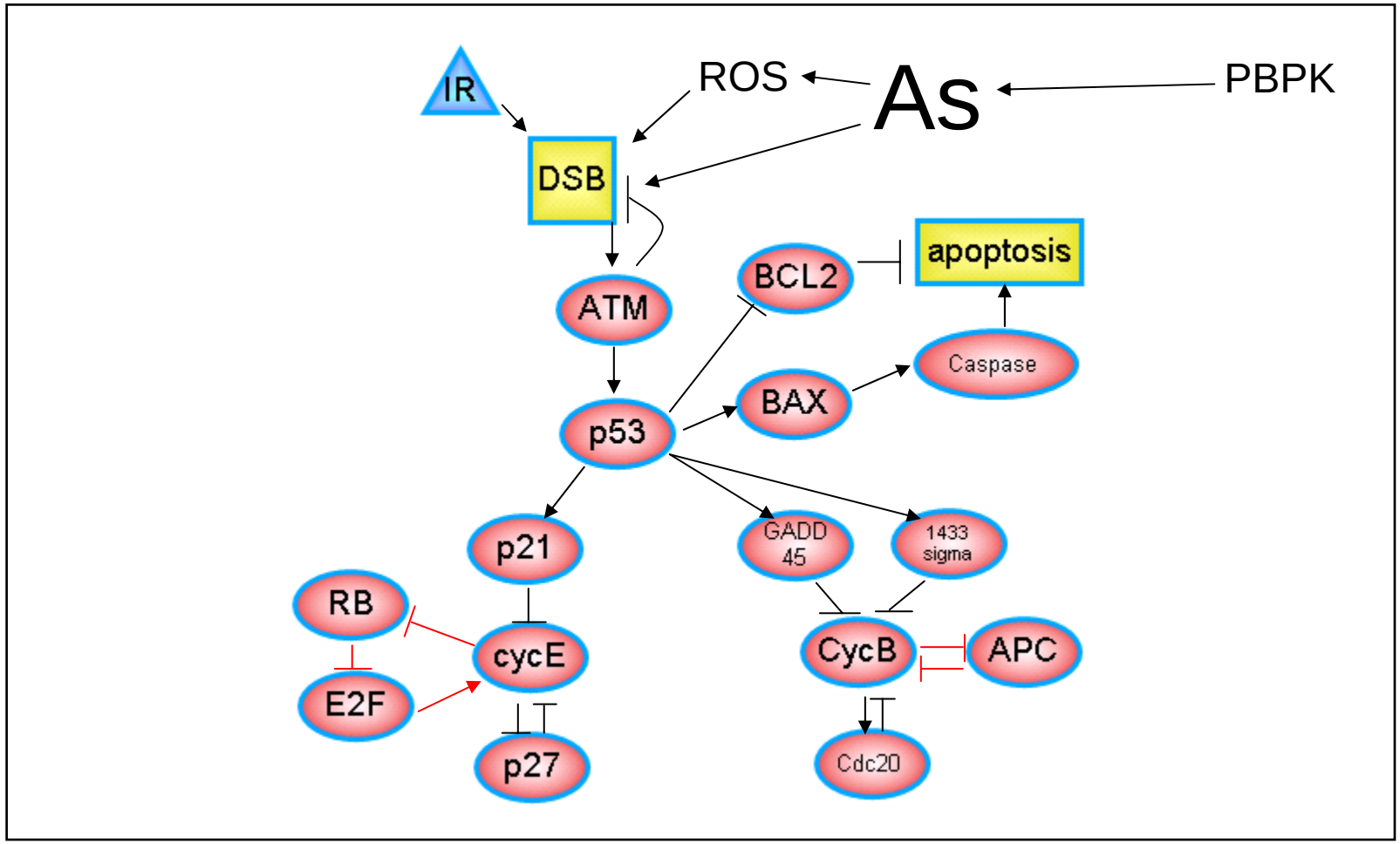
Systems biology characterization of dose- and time-responses in the dermal acute inflammatory reaction.

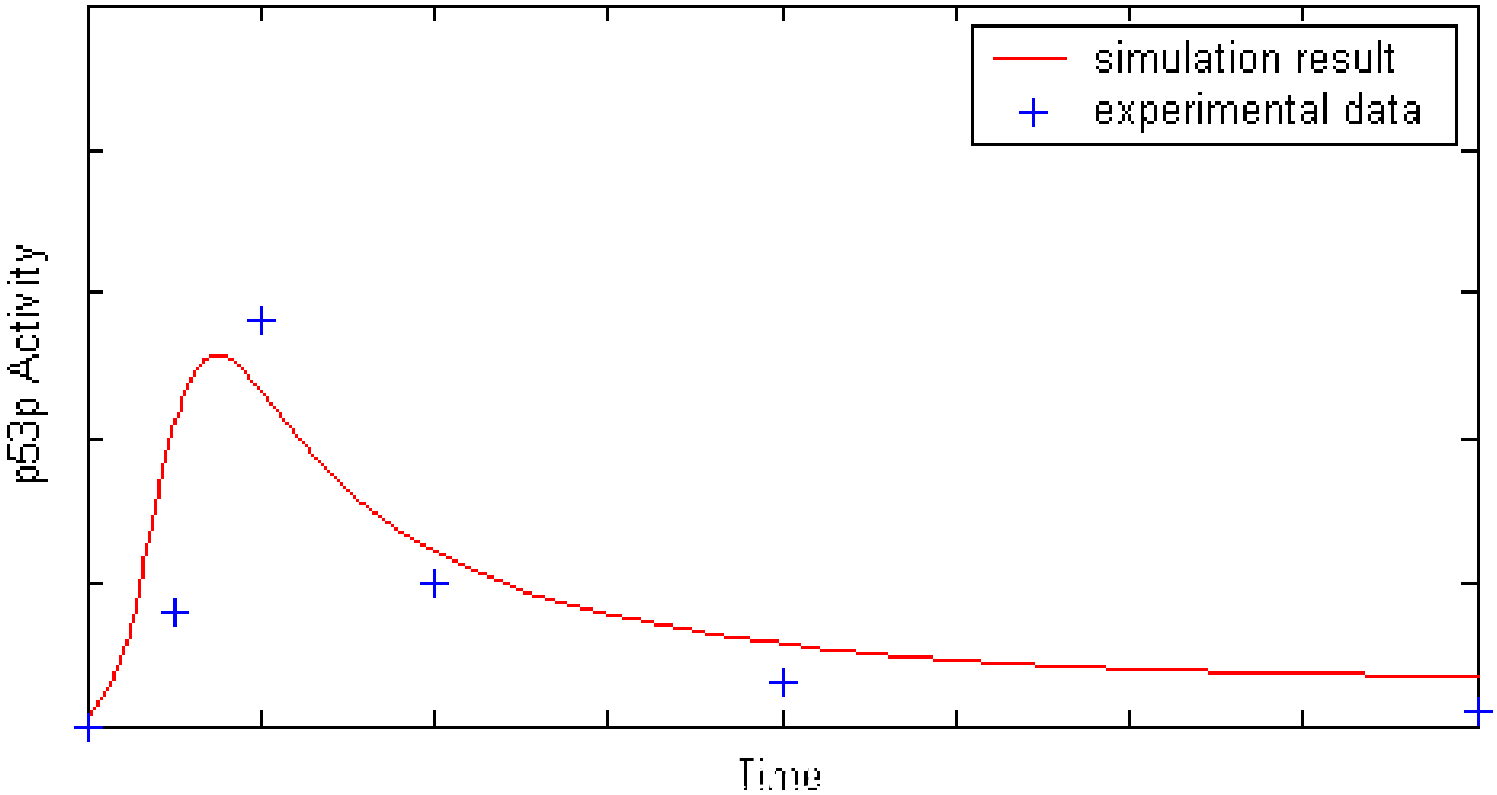
Collaborator:

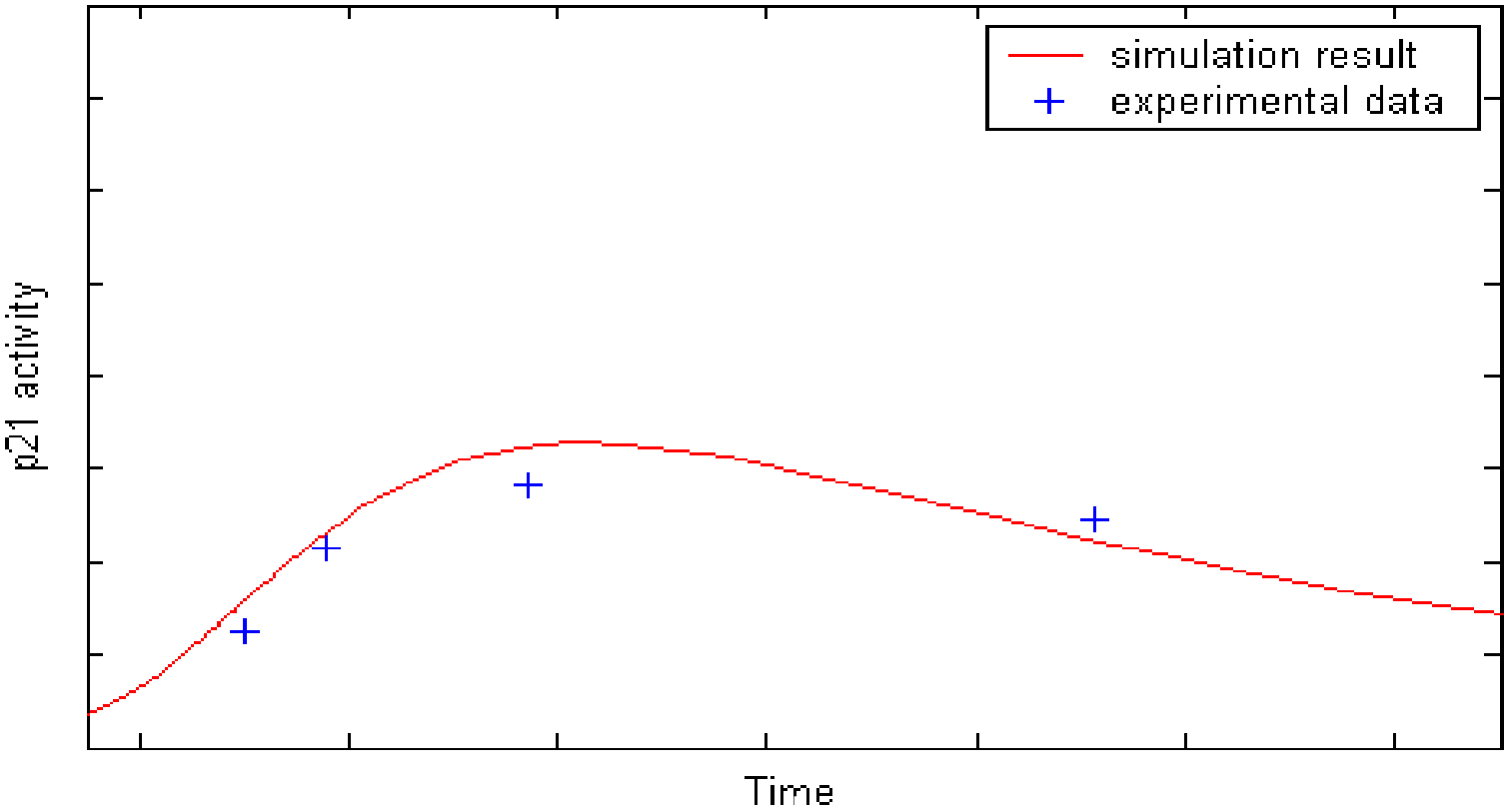
Jim McDougal, Wright State University



Ionizing radiation and arsenic




simulation result
experimental data
p53p Activity
Time


simulation result
experimental data
p21 activity
Time

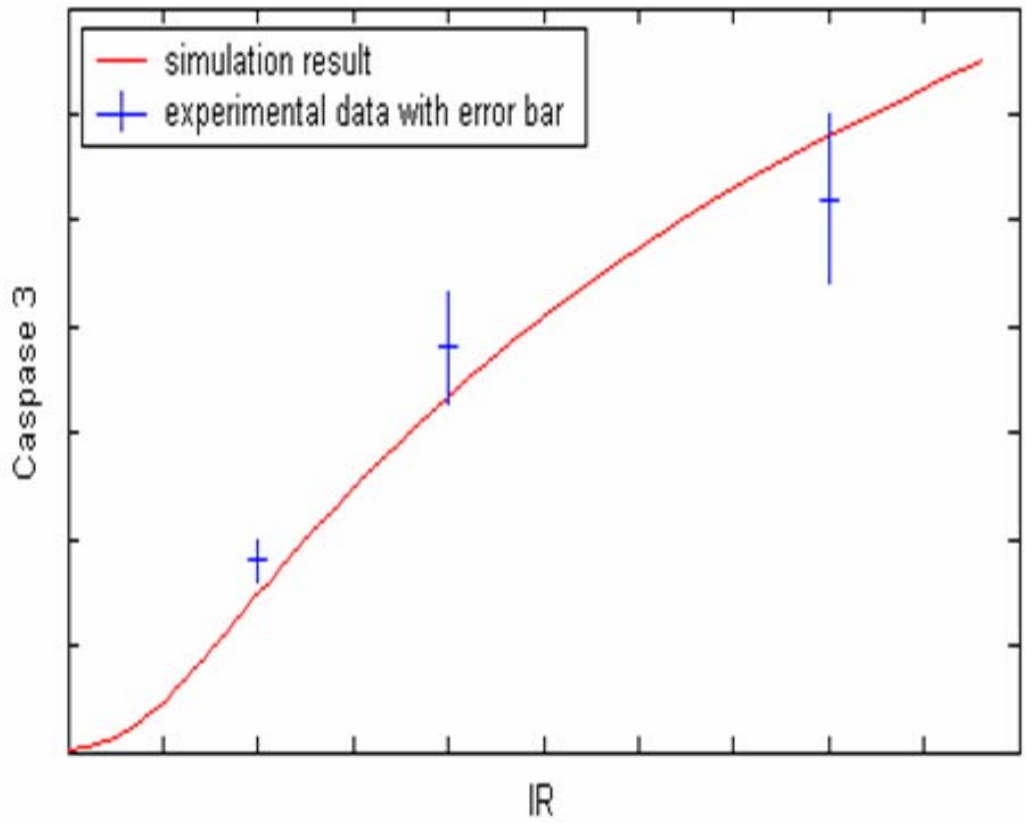


Figure 12. Comparison of simulated and experimentally measured dose-responses for caspace 3 after IR exposure (*Fernet et al, 2003*).

Goal:

Develop a multi-scale computational liver. This integrated, collaborative effort will address multiple issues.

Spatial
- -Regional dosimetry

Multiscale
- -Cells to tissue

Aging
- -Oxidative stress

Susceptibility
- -diabetes

Nuclear receptor biology

Arsenic

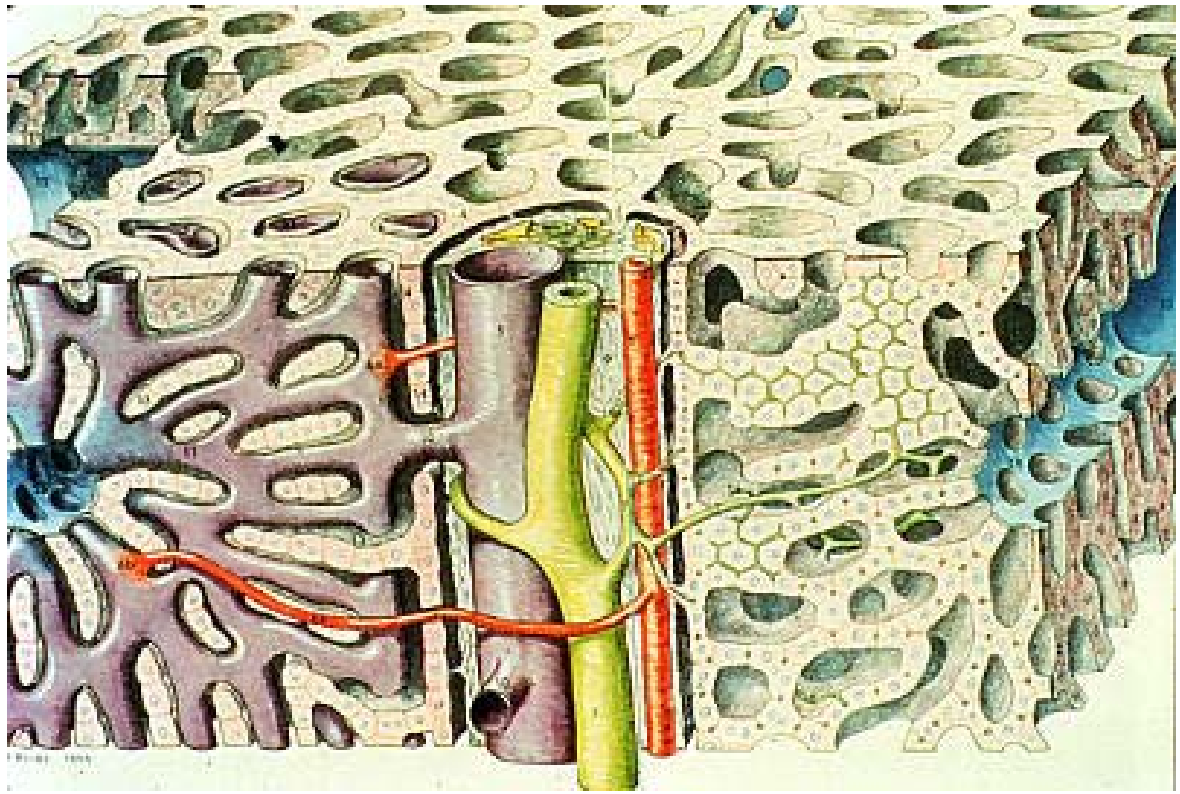
Collaborators:

NCCT - Conolly

ETD, ECD - NHEERL

HEASD - NERL

NCEA

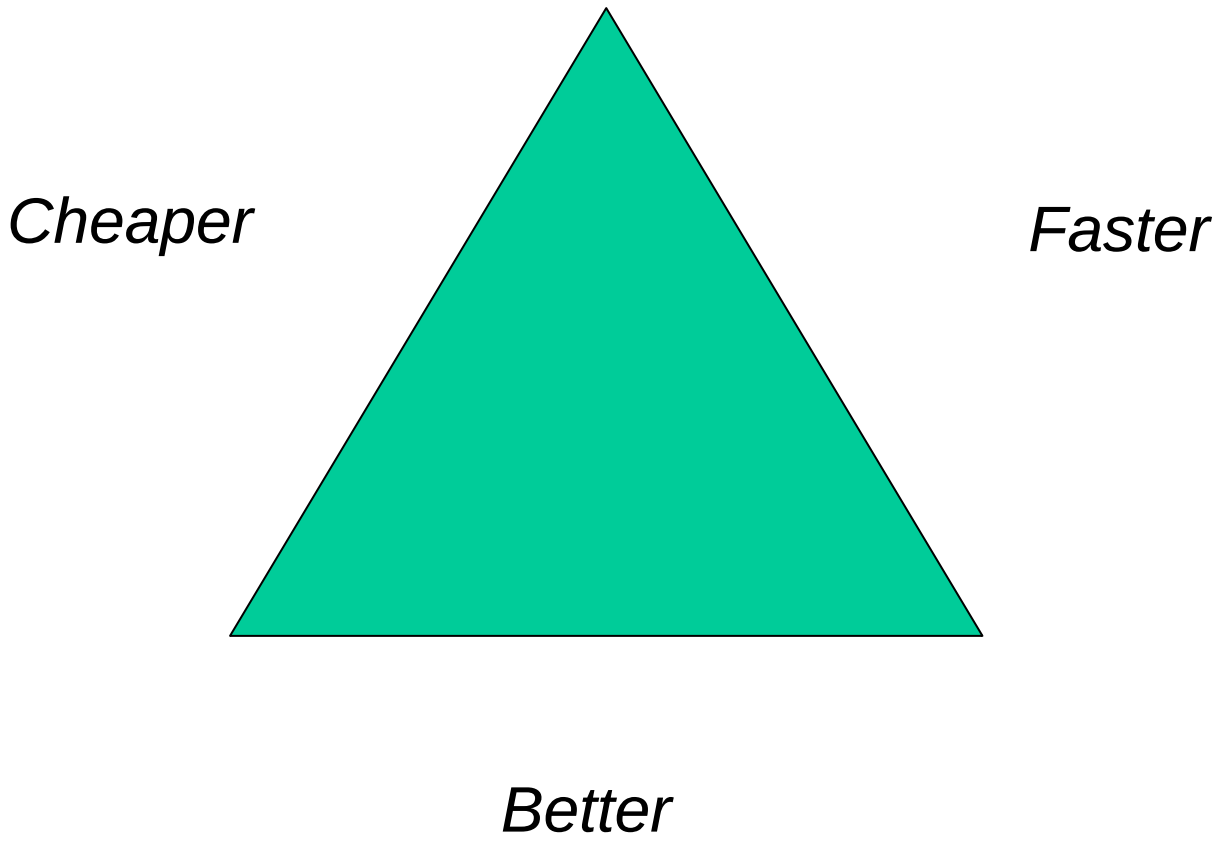


Toxcast → Multi-scale model of liver

Garbage in – garbage out

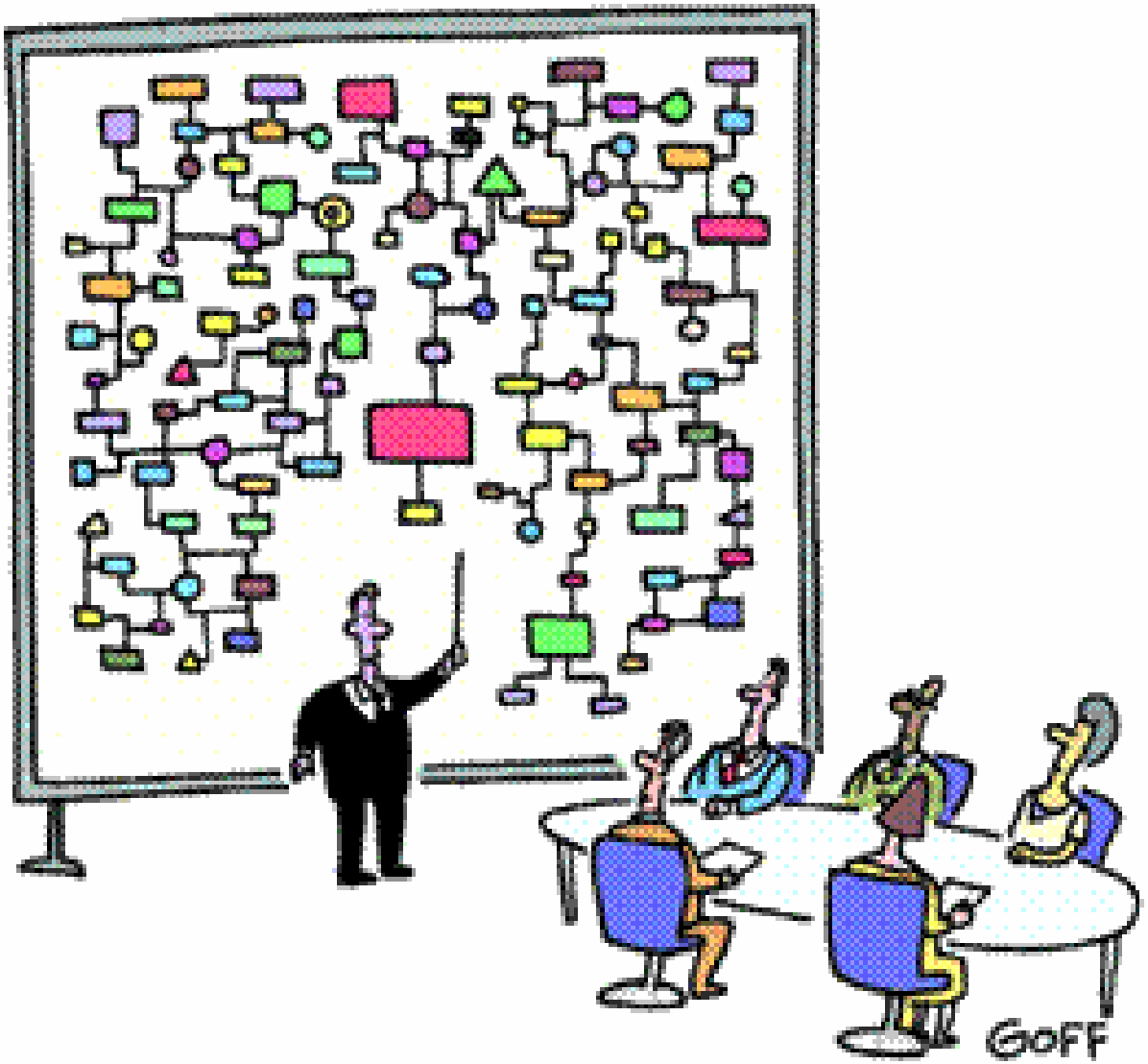
- Computational modeling and laboratory experiments must go hand-in-hand.

The Triad of Tradeoffs



Acknowledgements

- **NCCT**
  - Bob Kavlock
  - Jerry Blancato
  - David Dix
  - Hugh Barton
  - Melissa Pasquinelli
  - Ann Richard
  - Michael Breen
- **EPA**
  - Bill Mundy
  - David Villeneuve
- **University of New Mexico**
  - Tudor Opera
- **CIIT Centers for Health Research**
  - Maggie Zhao
  - Qiang Zhang



"And that's why we need a computer."

End