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Biological modeling as a method for data evaluation and integration in toxicology

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Overview

- Biological Models
- Evaluating consistency of data and integrating diverse data
  - Examples
    - Pharmacokinetics & Response
    - Pharmacodynamics
- Conclusions & Challenges

This presentation does not necessarily reflect policy of the US Environmental Protection Agency.

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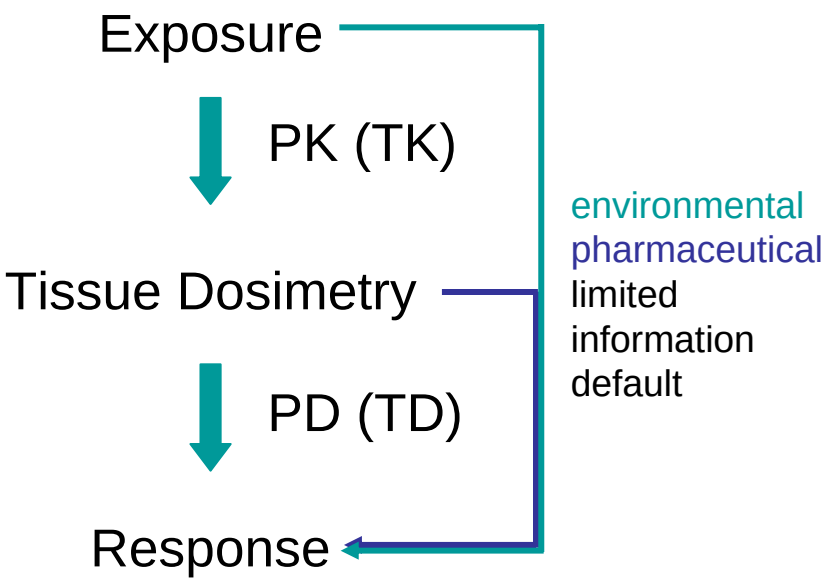
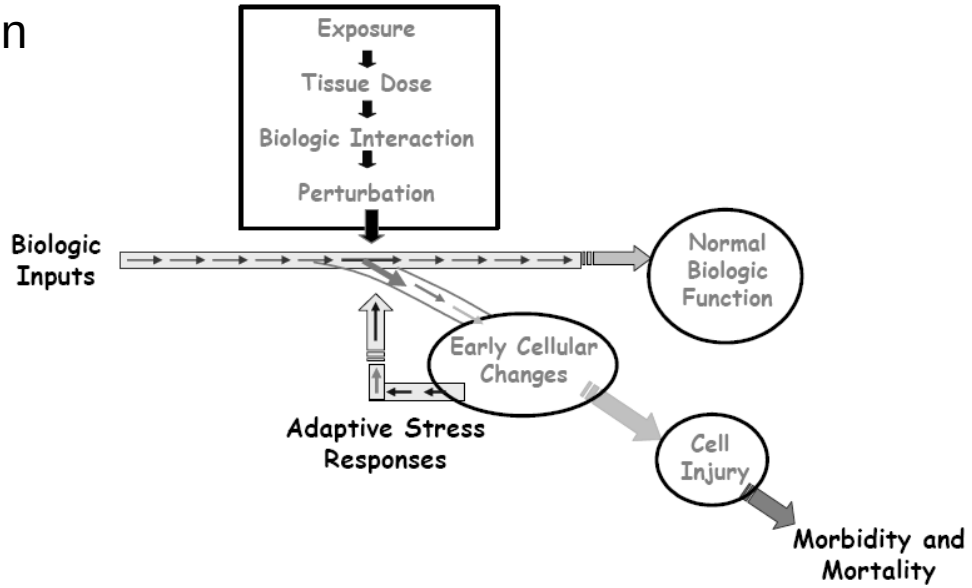
What is a biological model?

- Explicit mathematical representation of biological hypotheses, knowledge of the physical system
- Biological & Association Models Systems Biology & Bioinformatics
- Toxicological Context: Source to Outcome Continuum, Mode of Action
- Toxicity Pathway *(National Academy of Sciences 2007 Toxicity Testing in the Twenty-first Century: A Vision and a Strategy)*





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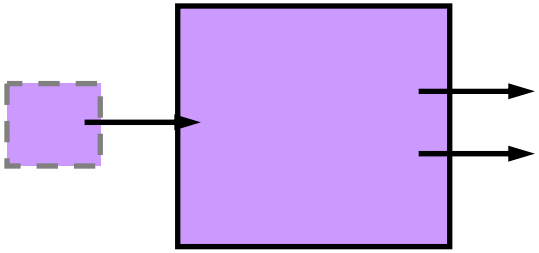
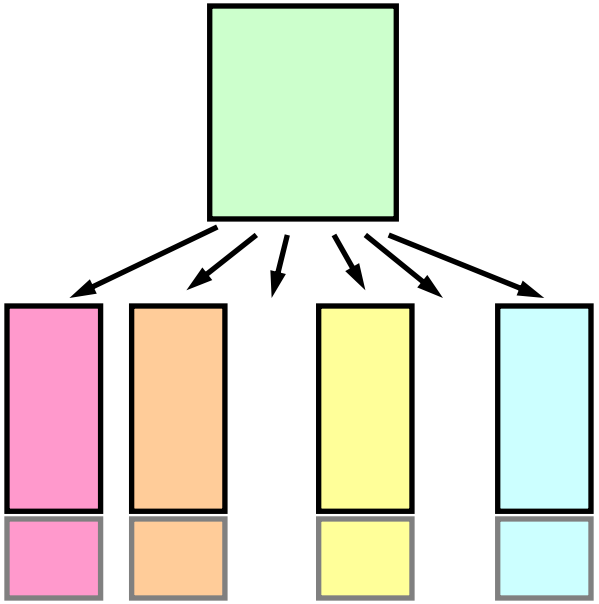
Models for full characterization of variability and uncertainty

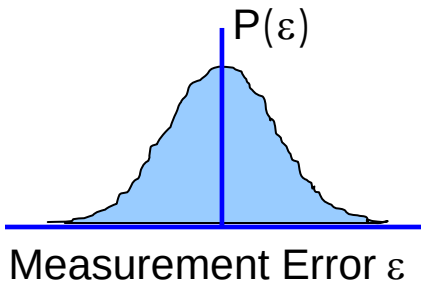
PK and/or PD Model



Hierarchical Statistical Model



Measurement Model



Estimate all parameters simultaneously

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Uses of Biological Models

- Analysis and Integration of Data
  - Multiple study designs (in vitro, in vivo)
  - Different measured endpoints
- Hypothesis Generation and Testing
  - Alternative biological structures/descriptions
- Predictions
  - Improved risk and safety assessments
    - Interspecies, dose, route-to-route extrapolations (predictions)
  - Evaluating population variability
    - Modeling populations (e.g., polymorphisms) versus individuals
    - Modeling life stages (e.g., children, elderly, ill)
  - Evaluating uncertainties

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Iterative processes

Draft Guidance on the Development, Evaluation, and Application of Regulatory Environmental Models

http://cfpub.epa.gov/crem/knowledge_base/knowbase.cfm

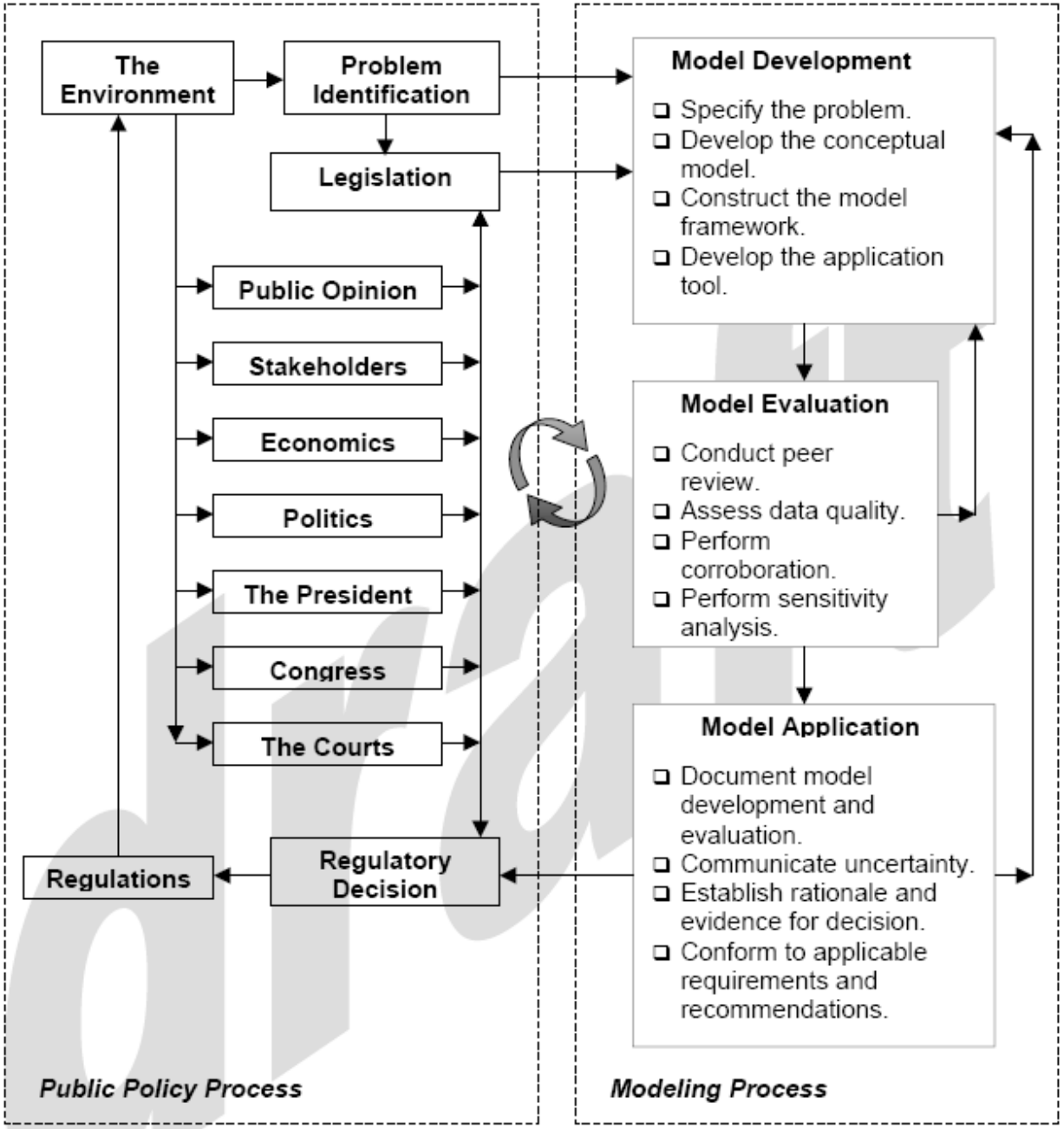

Figure 1. The Role of Modeling in the Public Policy Process. This guidance recommends best practices to develop, evaluate, and apply models that are to be used in the public policy process.

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Evaluating consistency of data and integrating diverse data

- Examples
  - Vinyl chloride liver angiosarcomas
  - Chloroprene lung cancer risk
  - Receptor mediated processes
  - Systems biology

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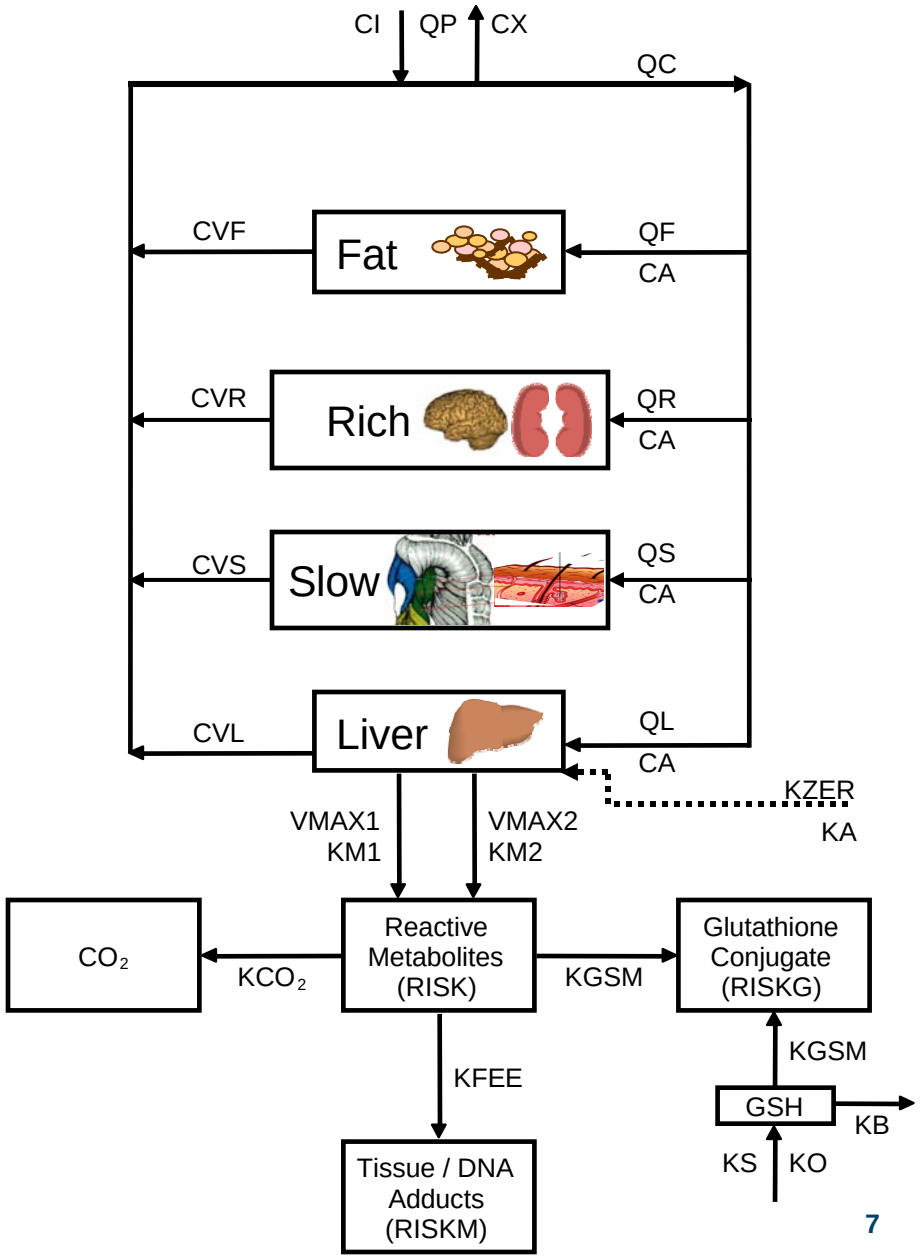
PBPK for Volatile Organic Compounds: Vinyl Chloride

Clewell HJ, Gentry PR, Gearhart JM, Allen BC, Andersen ME.

Comparison of cancer risk estimates for vinyl chloride using animal and human data with a PBPK model.

Sci Total Environ. 2001 Jul 2;274(1-3):37-66.



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Vinyl chloride Animal & Human Derived Risk Estimates

Animal Bioassay	95% UCL (Risk/million/ppb)	
	Males	Females
Maltoni – mouse inhalation	1.52	3.27
Maltoni – rat inhalation	5.17	2.24
Feron – rat diet	3.05	1.1
Maltoni – rat gavage	8.68	15.7

Human risk estimates (per million) for lifetime exposure to 1 ppb vinyl chloride in air based on the incident of liver angiosarcoma in animal bioassays or epidemiological studies.

Epidemiological Study	95% UCL (Risk/million/ppb)
Fox & Collier	0.71 – 4.22
Jones *et al.*	0.97 – 3.60
Simonato *et al.*	0.40 – 0.79

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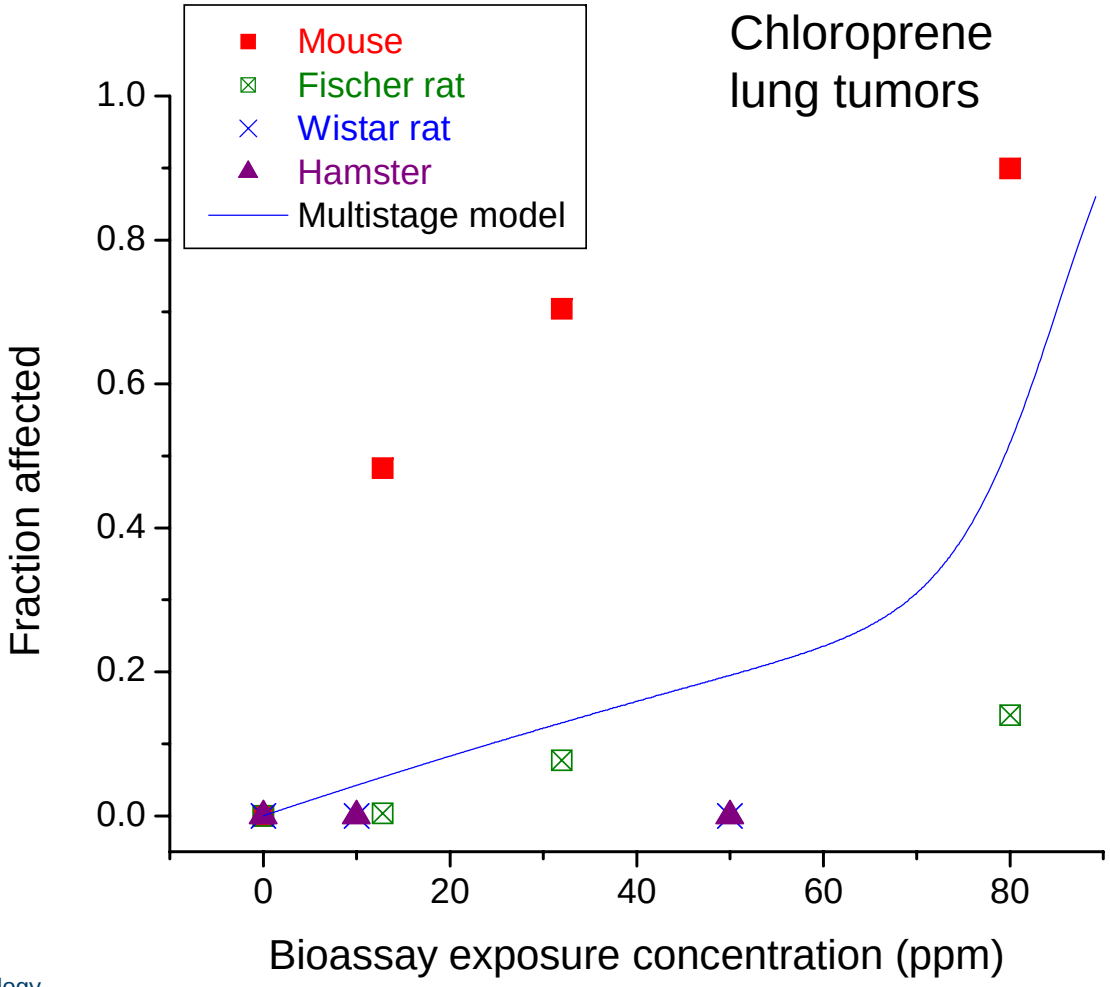
Why are such different incidences across species observed for the same exposures?

Himmelstein MW, Carpenter SC, Evans MV, Hinderliter PM, Kenyon EM.

Kinetic modeling of beta-chloroprene metabolism: II. The application of physiologically based modeling for cancer dose response analysis.

Toxicol Sci. 2004 79(1):28-37



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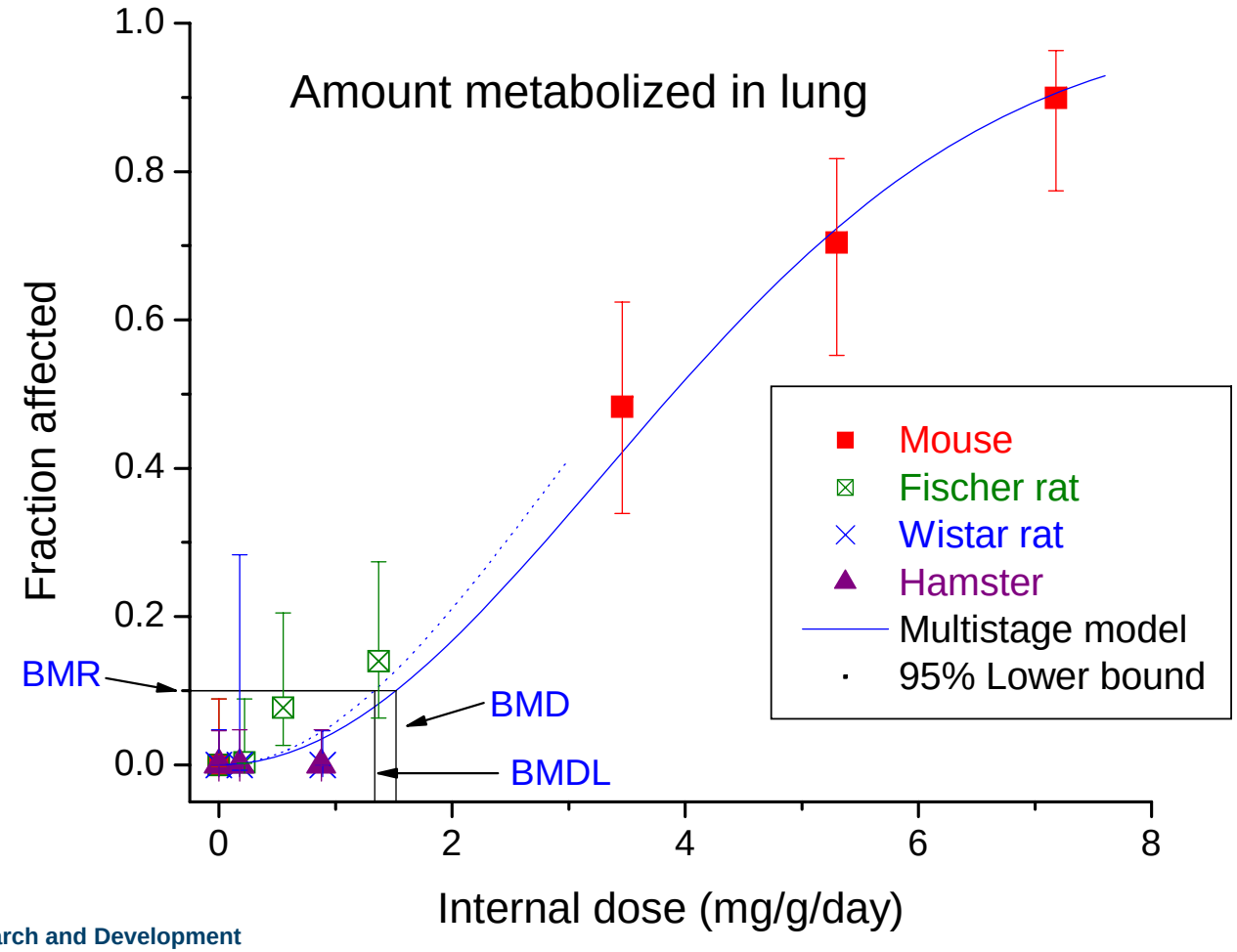

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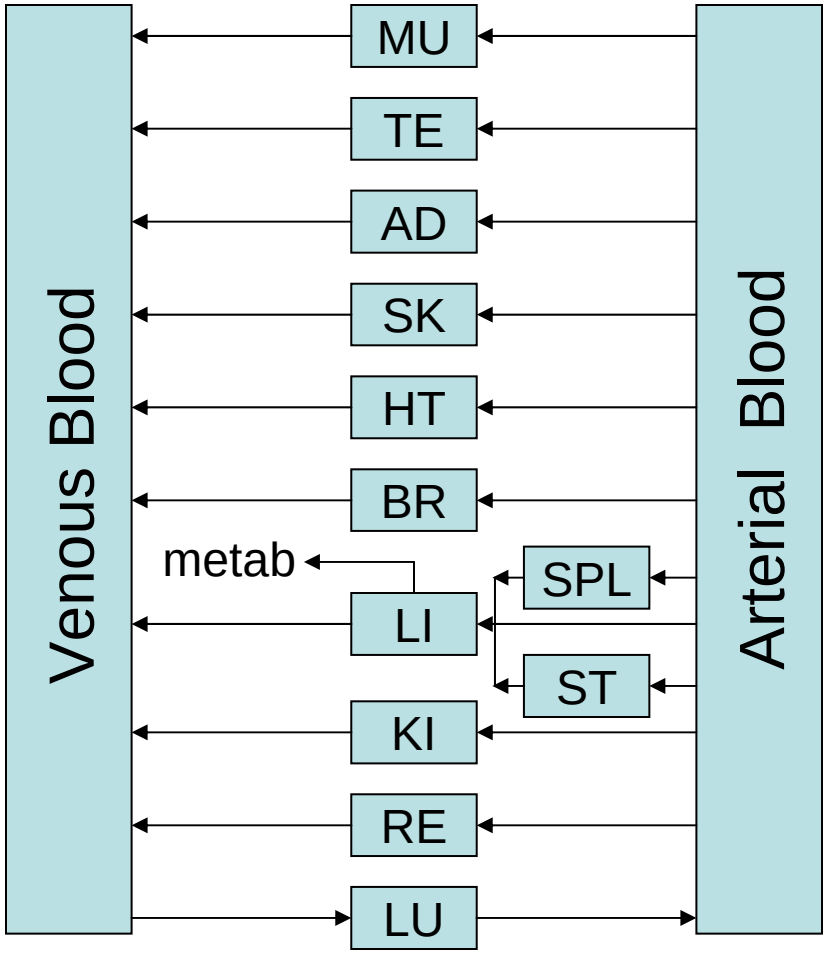
Pharmacological Agents: Diazepam



Wide range of statistical and mathematical analyses:

Gueorguieva I, Aarons L, Rowland M. Diazepam pharamacokinetics from preclinical to phase I using a Bayesian population physiologically based pharmacokinetic model with informative prior distributions in WinBUGS. J Pharmacokinet Pharmacodyn. 2006 Oct;33(5):571-94.

Gueorguieva I, Nestorov IA, Rowland M. Reducing whole body physiologically based pharmacokinetic models using global sensitivity analysis: diazepam case study. J Pharmacokinet Pharmacodyn. 2006 Feb;33(1):1-27.

Gueorguieva I, Nestorov IA, Rowland M. Fuzzy simulation of pharmacokinetic models: case study of whole body physiologically based model of diazepam. J Pharmacokinet Pharmacodyn. 2004 Jun;31(3):185-213.

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Endocrine System Modeling

- Pharmacokinetics
  - Classical compartmental model – luteinizing hormone (LH)
  - PBPK models – testosterone (T), dihydrotestosterone (DHT)
- Pharmacodynamics
  - Central axis – LH positively regulates T, T negatively regulates LH
  - Prostate – androgen (DHT) dependent function

Potter LK, Zager MG, Barton HA. Mathematical model for the androgenic regulation of the prostate in intact and castrated adult male rats. Am J Physiol Endocrinol Metab. 2006 291(5):E952-64

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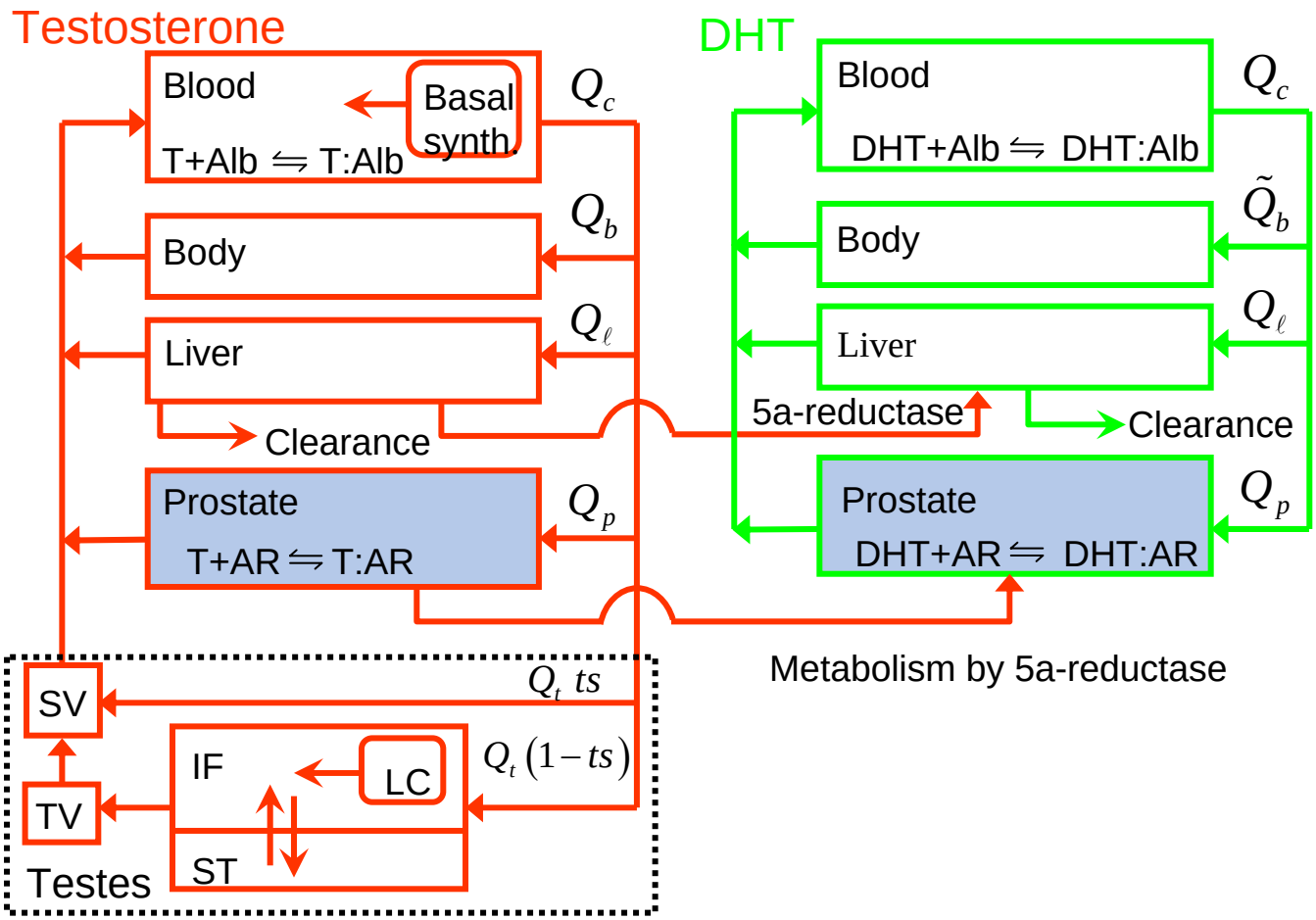
Prostate: Modeling Gene to Tissue Response



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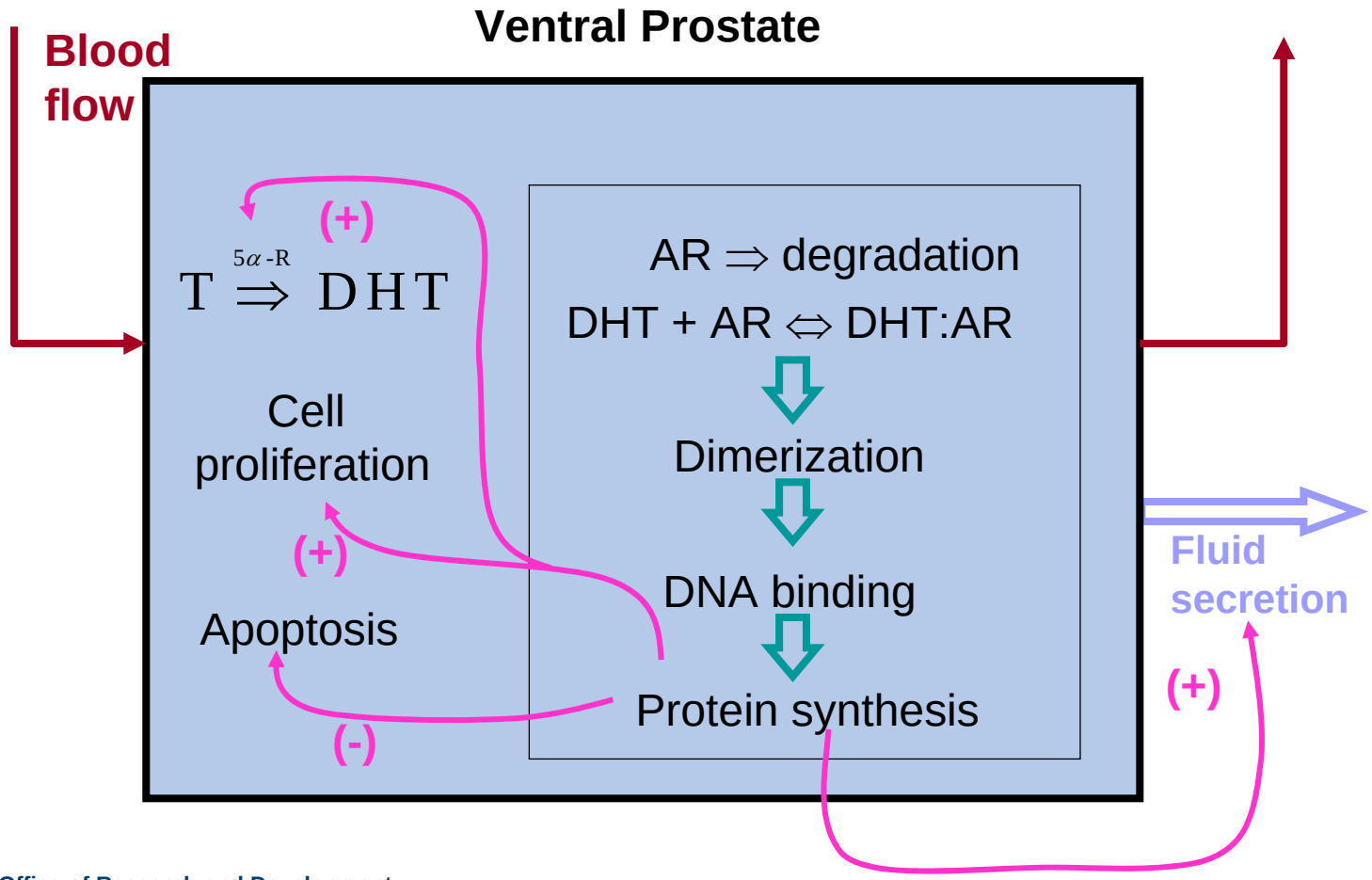
Prostate: Modeling Gene to Tissue Response



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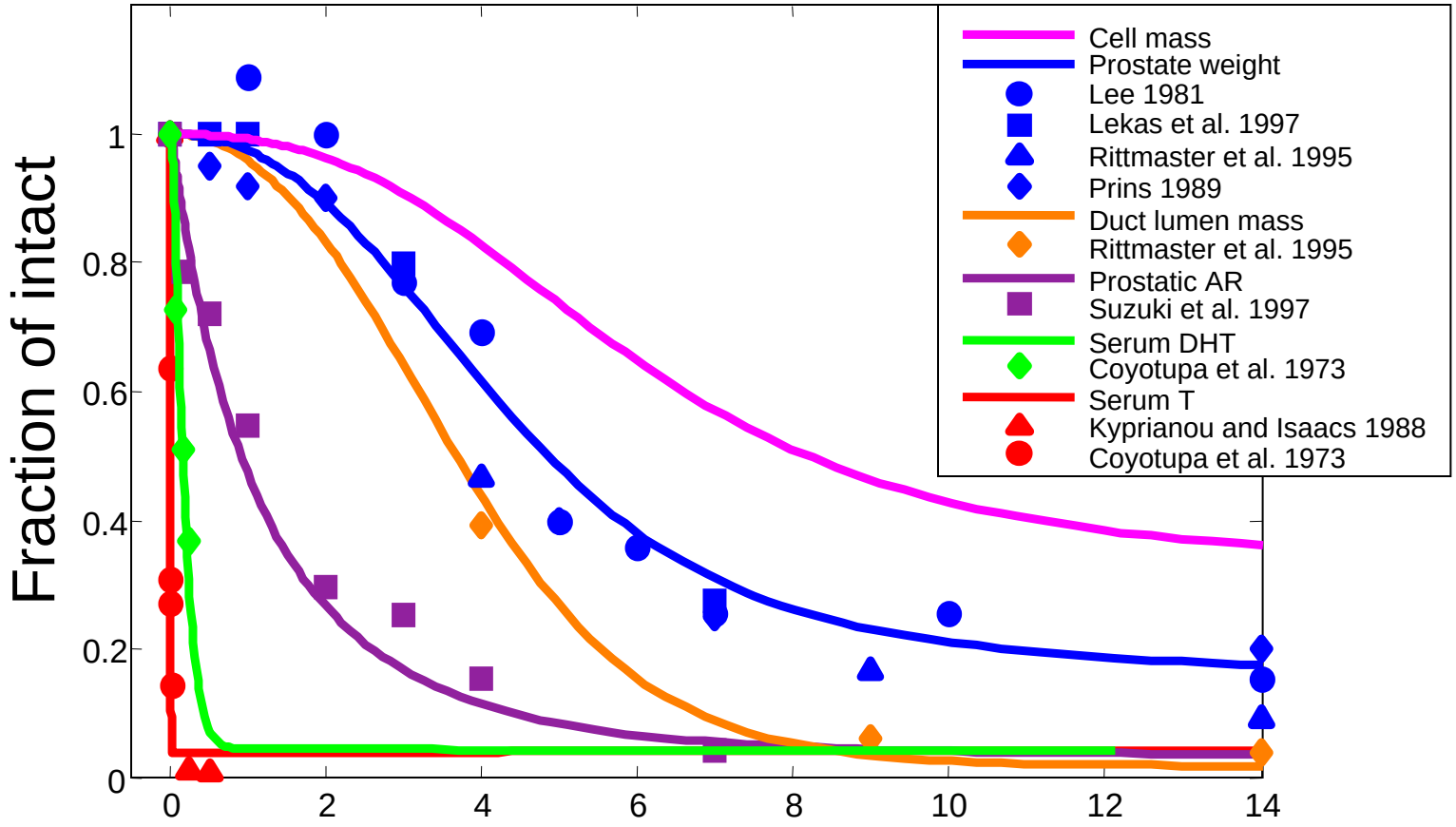
Predicted Prostate Regression Following Castration: Model Calibration and Validation



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Systems Biology Modeling

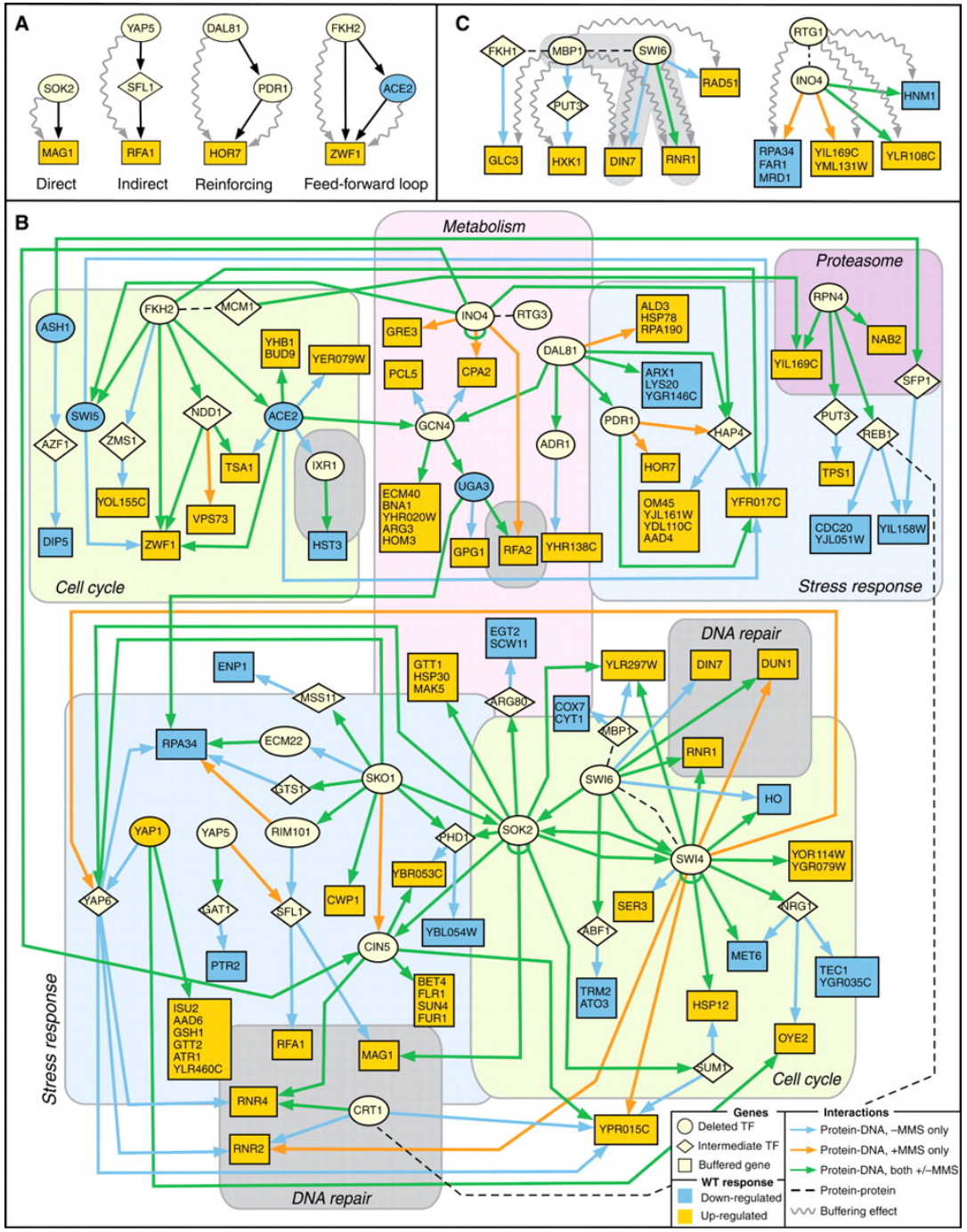
Bottom Up – from molecular reactions to network behavior, describe system & write equations

Top Down – from network behavior to molecular reactions – perturb system over range of dose & time, measure response, derive system

Workman CT, Mak HC, McCuine S, Tagne JB, Agarwal M, Ozier O, Begley TJ, Samson LD, Ideker T.

A systems approach to mapping DNA damage response pathways.

Science. 2006 May 19;312(5776):1054-9



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Kinds of Data

- In vitro measurements:
  - metabolism rates, protein binding, tissue partitioning
- In vivo measurements
  - Physiology: serum protein or receptor concentrations, blood flow rates, tissue volumes
  - Exposed: oral gavage, diet, inhalation at different dose levels for varying durations
  - Chemical in blood, urine, feces, tissues (time course)
  - Molecular, biochemical, cellular, tissue level responses
- Transcriptomics, proteomics, metabonomics, imagining – in vitro or in vivo, control and exposed (perturbed)

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Conclusions & Challenges

Mathematical models help evaluate consistency among datasets and integrate diverse kinds of data and information.

- Acceptance among trained toxicologists & other scientists.
- Acceptance process for application of models in public decision making.
- Transparency: One person's transparency (e.g., mathematical equations or biological descriptions) is another person's opacity.
- Technical challenges: systems biology for response processes, characterizing uncertainty in model outputs

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Acknowledgements

- Laura Potter, GSK
- Mike Zager, Pfizer
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- R. Woodrow Setzer, NCCT, US EPA

US EPA

National Toxicology Program Interagency Agreement

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EBT & NAS Vision of Toxicity Testing in 21st Century

Moves towards:

- Characterizing perturbations of toxicity pathways applicable to humans
- Data from human-derived materials
- In vitro assays of Toxicity Pathways
- Doses perturbing toxicity pathways
- Combine in vitro pathway data with computer models to predict in vivo

Moves away from:

- Data from animals
- In vivo assessments in animals except for targeted testing for specific purposes
- “High” dose toxicity studies
- Histopathology as dominant adverse endpoint to molecular perturbations of toxicity pathways

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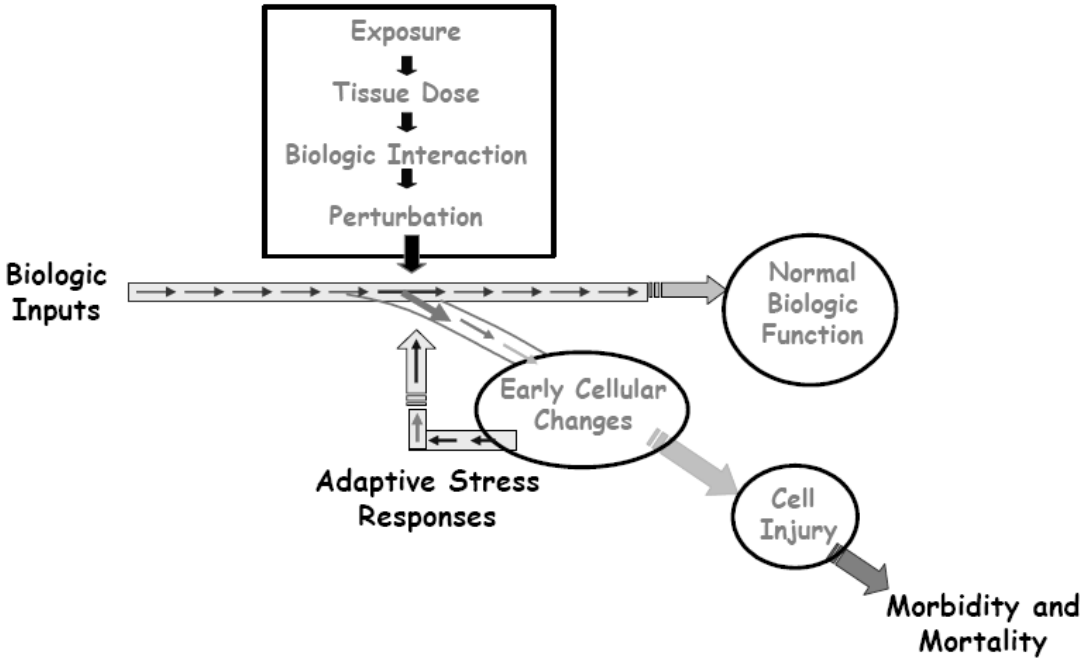
Toxicity Pathways



- Assessed using batteries of in vitro assays
- Need agreement on perturbations distinguishing normal biology from pathway to toxicity

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Challenges

- In vitro to in vivo extrapolation of toxicity pathways replaces cross-species extrapolation as dominant focus.
- Computational models integral to data analysis and interpretation.
- Demonstrating approach works
- Proposed as phased in over 20 years requiring substantial research & development budget

National Academy of Sciences 2007 Toxicity Testing in the Twenty-first Century: A Vision and a Strategy