Dosimetry in Risk Assessment and a bit More

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QSAR and Aquatic Toxicology &
Risk Assessment
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Outline

- Key components in toxicological evaluations
- Where are we likely to go with PK and PD models and how might SAR methods be helpful
- Hand-off to Greg Lien

Key Ideas in Toxicology CSU 2000

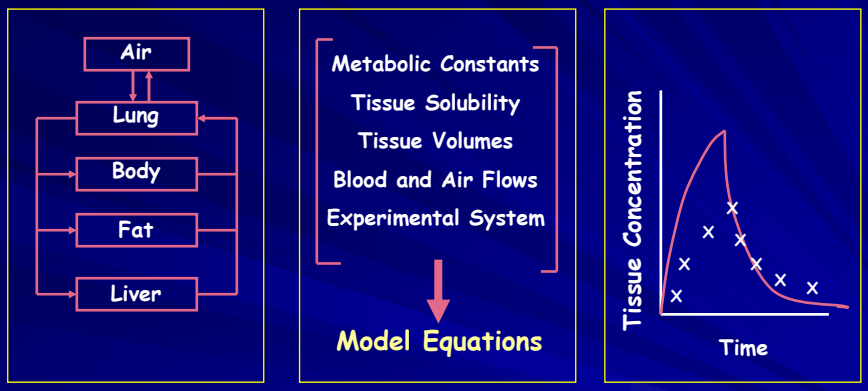
- Mode of Action - more specifically 'Chemical Mode of Action'
- Target Tissue Dosimetry
- Dose-Response/Risk Assessment

What tools help us evaluate these relationships?

Pharmacokinetic models – calculate the tissue dose of active forms of the toxic chemical for various doses, dose-routes, and animal species

Pharmacodynamic models – calculate the degree of response for any level of tissue dose in different species for differing exposure scenarios

Physiologically Based Pharmacokinetic (PBPK) Modeling



Define Realistic Model → Collect Needed Data → Make Predictions

Refine Model Structure

Using PBPK models – The Process 1987

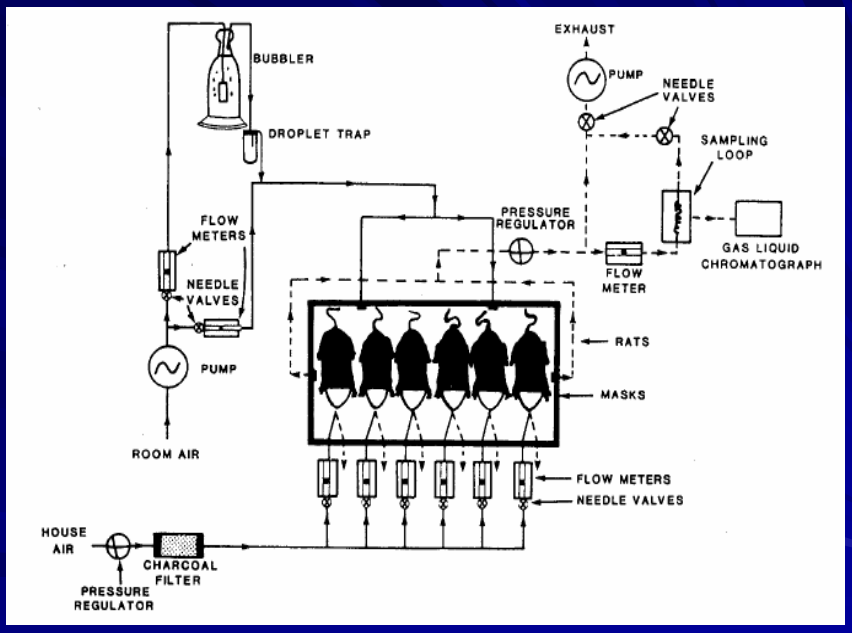
- Identify toxic effects in animals and people
- Evaluate available data on mode(s) of action, metabolism, chemistry of compound, metabolites and related chemicals
- Describe potential **mode(s) of action**
- **Propose relationship between response and tissue dose**
- Develop a PBPK model to calculate tissue doses
- Estimate tissue dose during toxic exposures with PBPK model

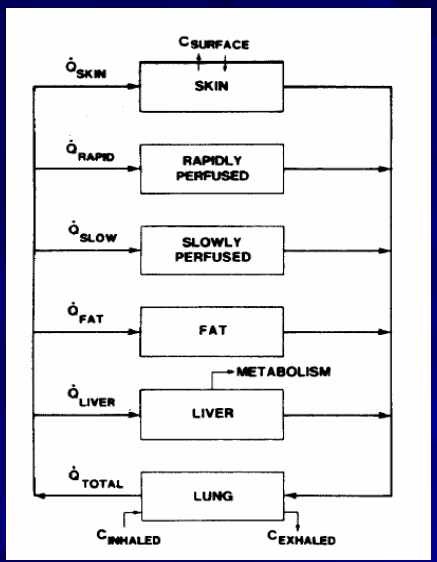
Mode of Action

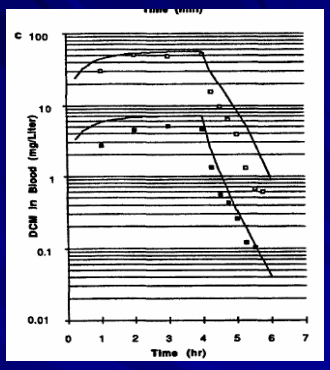
- As in 'Clue', i.e., the butler in the pantry using the pipe wrench
- The reactive intermediate in the hepatocytes creating DNA-adducts
- The estrogenic compound binding the ER in the uterus to enhance cell proliferation.

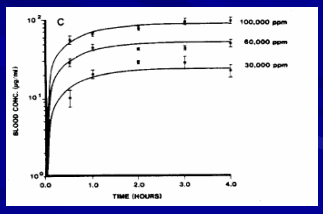
Extrapolations supported by these models

- High doses to low doses
- Dose route – inhalation, oral, dermal
- Among species
- Across classes of chemicals
- **Dosing scenarios**
- ***in vitro* to *in vivo***



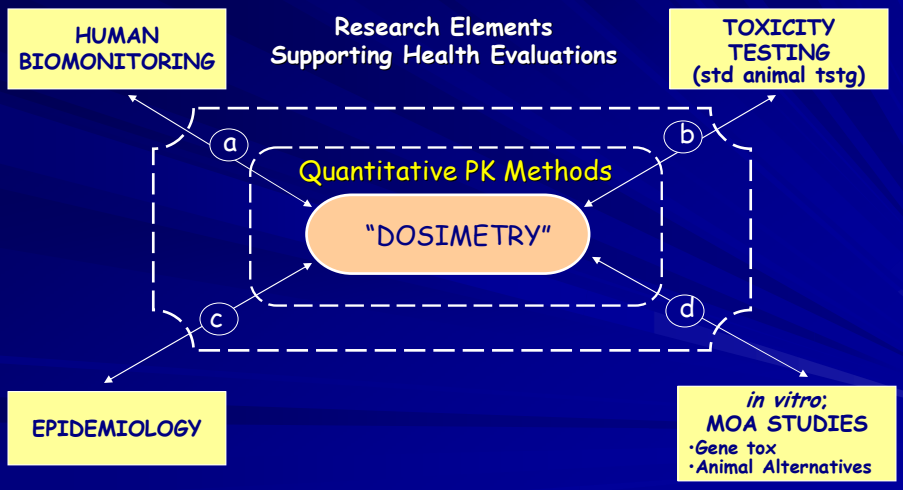


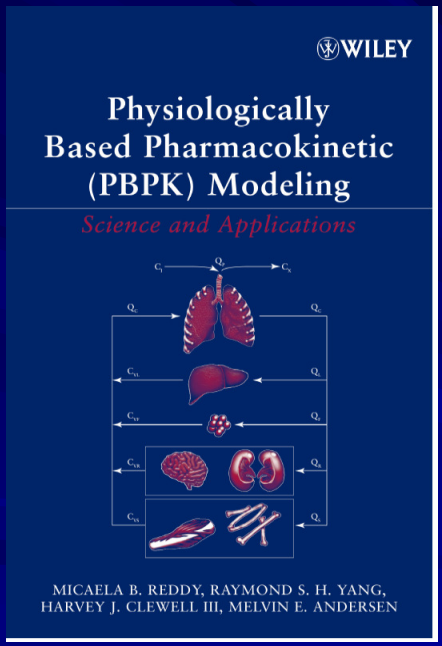




McDougal et al., 1986. Toxicol. Appl. Pharmacol.,85, 286-294.

Improving Use of Dosimetry for Evaluating Health Risks-ILSI/HESI





Coverage of between 700 and 900 papers.

- Volatiles
- Persistent organics
- Drugs
- Inhaled Irritants
- Dioxin-like Compounds
- Metals
- Siloxanes, etc.

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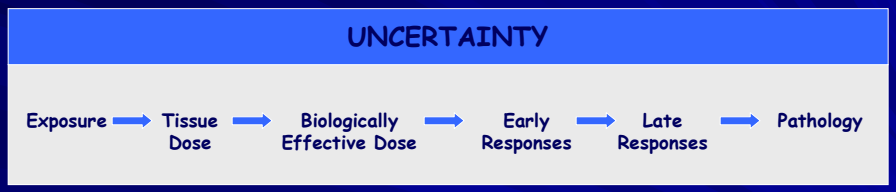
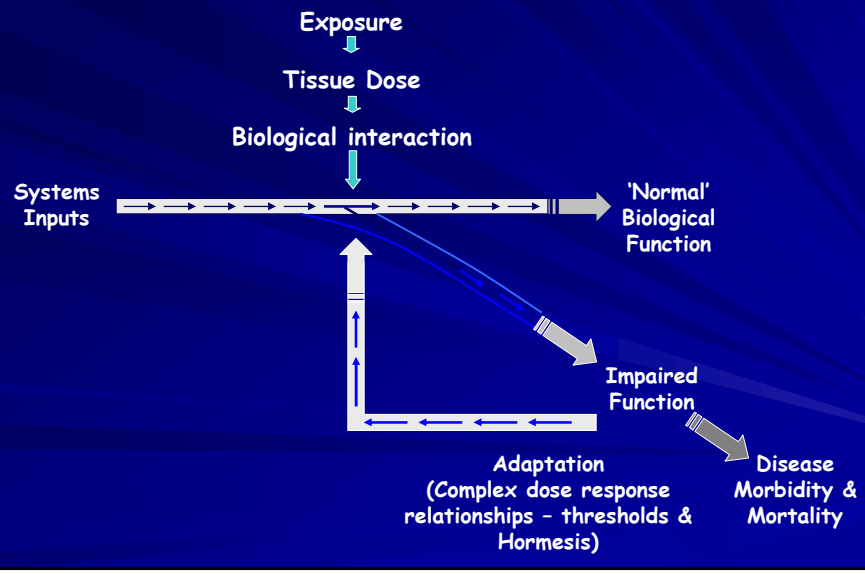
Dosimetry Directions

- Develop parameter data bases for human PBPK models including improvements in QSAR approaches parameter estimation
- Expand suite of 'validated' human PBPK models for biomonitoring research – human studies issues here
- **Extend quantiative approaches (experience) to study basic biological processes perturbed by chemical exposures**

Exposure----Dose-----Response Circa 1985



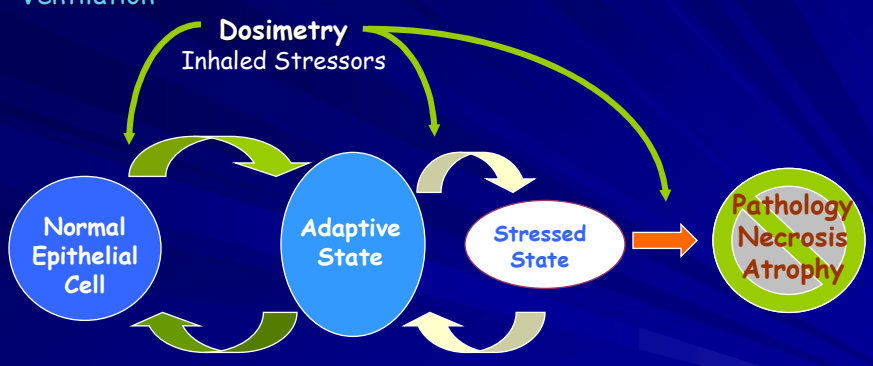
Perturbation of Biological Processes



Conceptual model for cellular toxicity

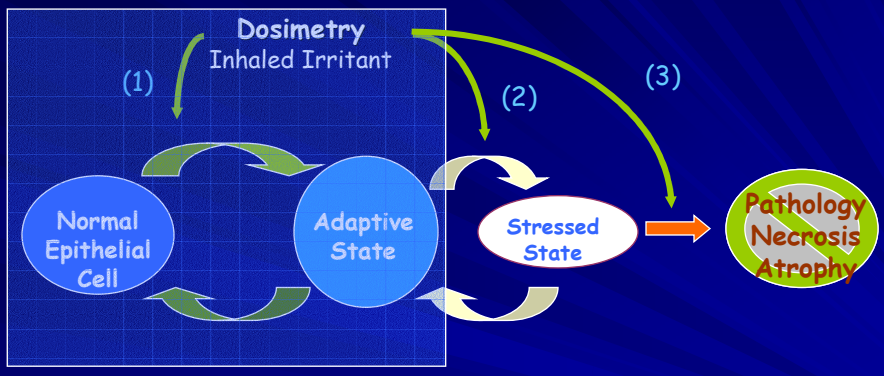
Tissue Phase Reactions

Cl_2 → HOCl + HCl



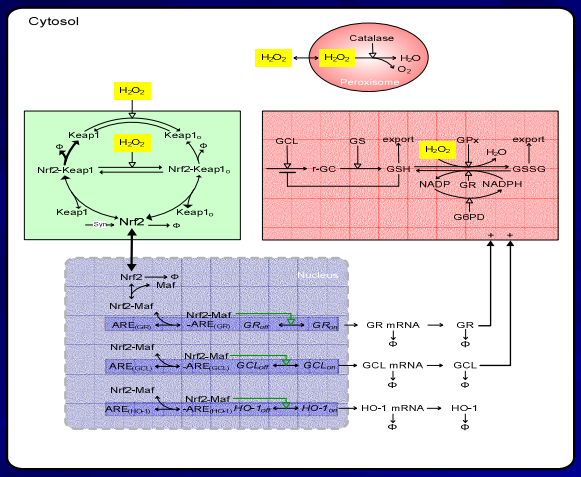
Developed for Diesel Exhaust Particle (DEP) toxicity – referred to as hierarchical oxidative stress (Andre Nel)

Mechanistic Dose Response Models and Genomic Data



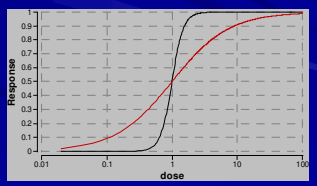
- Use specific in vivo studies to develop a dose response model for activation of **oxidative stress pathway** following irritant exposures and **differentiate dose regions** that activate adaptive processes from those associated with inflammation and apoptosis (high concentrations)

A model for oxidative stress in Pathway Assist- automated model building and dose response



HOCl and Nrf2 and Keap-1

Dose-Responses



Response Models Directions

- Focus on initial cellular responses and evaluate dose-response characteristics for these initial events mechanistically….for me these models focus on the chemical mode of action and accessible 'quantitative biology'

- **Develop data bases on cell response systems including dose response in a manner to enhance value for QSAR**