Advanced Computational Methods in Dose Modeling: Application of Computational Biophysical Transport, Computational Chemistry, and Computational Biology

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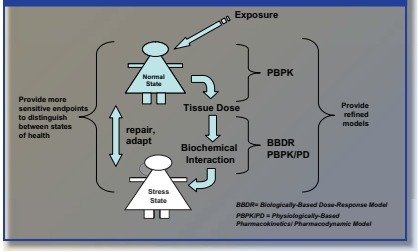
Issues:

- Extrapolation (e.g., high to low dose, animal to human, route to route) is a problem frequently confronted by the EPA during the risk assessment process.
- Data and information we use in risk assessments has inherent uncertainty and variability.
- These problems are compounded by the large number of chemicals that the EPA must consider under different regulations, particularly those that require the Agency to conduct multi-chemical ("cumulative") risk assessments.

Solution: Computational Toxicology will help improve:

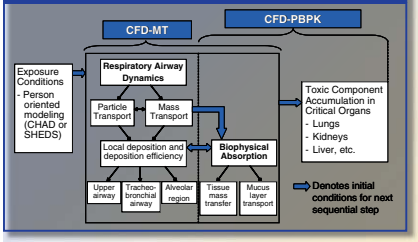
- Risk Assessment:
  - Delineate mode-of-action
  - Strengthen linkages between exposure, dose, effect
- Exposure Assessments:
  - Identify biomarkers of exposure and effect
  - Characterize susceptible sub-populations

Solution: Computational Toxicology will help improve risk assessments

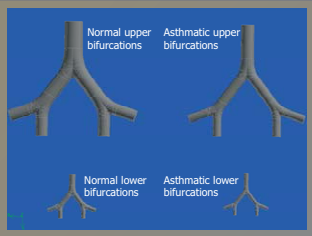


- **Computational Bio-Physics**
  … theory applies computational fluid dynamics (CFD) and mass transport methodologies to reduce uncertainties in inhalation dosimetry of aerosols and vapors. These computational approaches will strengthen the linkage between exposure and localized/systemic absorption of pollutants.
- **Computational Chemistry**
  … will be used to develop reduce uncertainties in dose-modeling by reducing bias and increasing precision in parameter estimation (i.e., equilibrium binding constant, metabolic rate constants, enzyme inhibition constants).
- **Computational Biology**
  … will involve the assessment of health effects as alterations in metabolic, protein and genomic profiles. Concurrent evaluation of standard toxicological endpoints will provide us with the information that we need to utilize 'omics technologies in modeling efforts for predictive toxicology. The goal is to provide an unbiased estimate of the differential organismal state even in the absence of other quantifiable health effects of exposure.

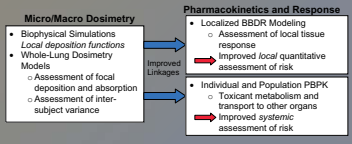
Role of Biophysical Modeling in Risk Assessments:



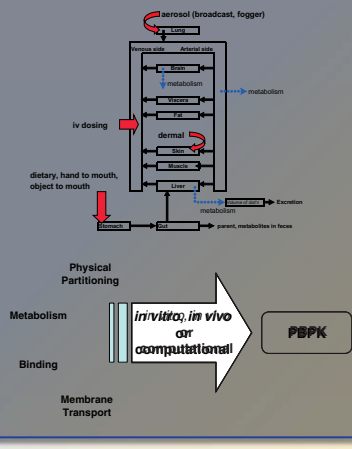
Models of normal and asthmatic pediatric bifurcations in the upper and lower airways



- Computational biophysical simulations will be used to develop a whole-lung dosimetry model for PM and air toxics
- The resulting microdosimetry model will be used to strengthen linkages in the risk assessment source-to-outcome continuum by providing initial conditions to *local dose response* and *systemic pharmacokinetic* models



Role of Computational Chemistry: PBPK Development



Role of Computational Chemistry: PBPK development

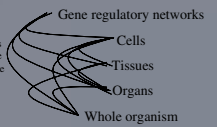
- We are applying computational methods to model P450- and carboxyesterase-dependent enzymatic reactions and determine rate constants for application in PBPK models.
- We plan to extend these applications to cumulative assessments, considering the joint action of mixtures of chemicals. These approaches will have direct application in current Food Quality Protection Act (FQPA)-driven assessments (e.g., carbamates, pyrethroids).
- We are also applying property-based quantitative structure-activity relationships to estimate physiochemical properties of equilibrium partitioning and dermal absorption.

Computational Biology: Systems Biology Approach

Integration of knowledge to represent and analyze the intact biological system.

Biological systems investigated at many levels:

Computational biology aims to mathematically define the relationships among multiple system level responses.



Integration of New Technologies ('omics) could provide:

- Indicators of early (subclinical) health effects
- Holistic view of biochemical status of organisms
- More sensitive endpoints for toxicological evaluation
- Non-invasive evaluation of exposure
- Improved understanding of mechanisms of action
- Unifying responses across species can be identified

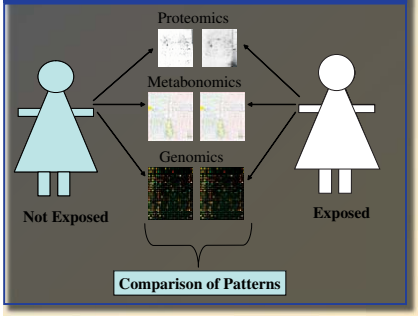
'Omics Technologies:

Metabonomics – provides the entire complement of all the small molecular weight metabolites inside a sample of interest determined using nuclear magnetic resonance (NMR)

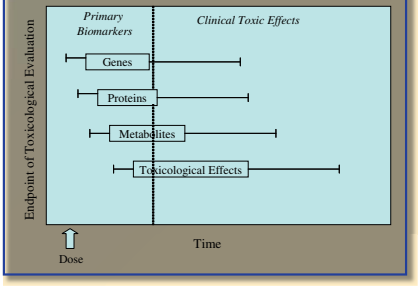
Proteomics – characterizes the dynamics of protein function on a global scale using two-dimensional gel electrophoresis of proteins followed by spot identification with mass spectrometry

Genomics – the expression of thousands of genes can be simultaneously evaluated for correlation with chemical exposure

Computational Biology: More Sensitive Endpoints of Evaluation



Computational Biology: Identification of Markers



Conclusion:

Through application of these CompTox disciplines we will:

- Delineate mode-of-action
- Strengthen linkages between exposure, dose, effect
- Identify biomarkers of exposure and effect
- Characterize susceptible sub-populations

Science and Innovation to Protect Health and the Environment