Computational Toxicology Framework – Objective 1: Improving Linkages in the Source to Outcome Paradigm

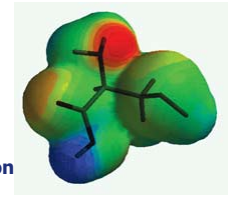
EPA Science Forum 2004
Healthy Communities and Ecosystems

FIRST OF THREE COMPTOX OBJECTIVES HAS SIX FOCUS AREAS – A CRITICAL PARTNERSHIP FOR MOLECULAR INDICATORS RESEARCH IS HIGHLIGHTED

I. CHEMICAL TRANSFORMATION AND METABOLISM

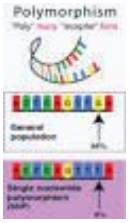
1. Chemical Fate Models
- Determine minimal concentrations at which biological events occur
- Determine biologically relevant chemical in mixtures
- Focus studies on crucial biotransformation

2. Metabolic Simulation
- Libraries of relevant metabolic transformation
- High quality data metabolic maps
- Probability indices for substructural units



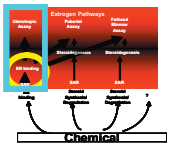
II. DEVELOPMENT OF DIAGNOSTIC/PROGNOSTIC MOLECULAR INDICATORS
- Few environmental stressors have specific or sensitive indicators
- Exposure indicators are poorly correlated with effects
- Molecular indicators could validate fate and transformation models
- Crucial for mixtures risk assessment
- Essential for integrated approach to risk assessment

III. DOSE METRICS
- Dose is often inferred from stressor uptake
- Dose models stand to be enhanced with specific data on stressor interactions with molecules initiating toxicity pathways
- Genetic polymorphism data will reduce uncertainty stemming from assumptions of homogeneous populations.
- Susceptibility indicators will be developed for input into exposure models



Partnership with Department of Energy Joint Genome Institute

IV. CHARACTERIZATION OF TOXICITY PATHWAYS
- Identification of discrete molecular initiating events
- Linking adverse outcomes to molecular alterations
- Elucidating linkages across biological levels of organization
- Biological basis for cross-species extrapolation
- Prediction of possible interactions for untested chemicals and mixtures



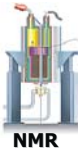
- Genomics research with wildlife organisms suffers from the lack of extensive DNA sequence data
  - Fathead minnow (Pimephales promelas) is critical aquatic toxicology model

  - Frog (Xenopus tropicalis) is an excellent thyroid disruption model

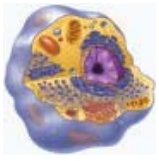
  - Aquatic invertebrate (Daphnia pulex) provides important monitoring and toxicology resource in collaboration with the Daphnia Genome Consortium

- February 18, 2004 - EPA Administrator Michael O. Levitt and DOE Secretary Spencer Abraham sign MOU to expand research and computing collaboration between the agencies
  - DOE's Joint Genome Institute to provide sequence data for Pimephales promelas cDNA libraries generated across life stage and stressor exposure, Xenopus cDNA libraries and the complete Daphnia pulex genome
- As of May, 2004, EPA/ORD has gained access to hundreds of gene sequences and has made plans with JGI for several additional cDNA libraries
- OUTPUT – EPA/ORD is constructing DNA microarrays for toxicogenomics research to address CompTox linkage research area II – "molecular indicators."

V. METABONOMICS
- Elucidate changes in metabolic patterns for range of endogenous metabolites
- Generate NMR spectral profiles for chemicals
- Build models to evaluate effect of novel chemicals on endogenous metabolites



VI. SYSTEMS BIOLOGY
- Computational models that reconstruct a cell, organ or organism's function from component parts
- Allows validation and simulator experiments that build confidence in predictive ability of adverse effects



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