ERD's Computational Toxicology Research Program

Objectives of ORD's CompTox Research Initiative

The ORD CompTox Research Initiative defines the "toxicity process" as: (1) formation of a chemical stressor, (2) the environmental concentration of the stressor, (3) the level of exposure of the stressor to a vulnerable organism, (4) the effective dose inside the organism, (5) a biological event triggered by the stressor, and finally, (6) a toxic effect. The objective of ORD's CompTox Research Initiative is to improve linkages across this continuum, resulting in improved approaches for prioritizing chemicals for subsequent screening and testing, and better methods for quantitative risk assessment. The overall success of the initiative is dependent on the development and coupling of new computational quantitative structure activity relationships (e.g., QSARs) and "omic" (i.e., genomic, proteomic and metabonomic) tools. This computational approach will significantly reduce EPA's dependence on animal testing to obtain chemical-specific toxicity data.

ERD's Role in the CompTox Research Initiative

At several points along the stressor formation-to-toxic effect continuum, it is critical to accurately model the environmental fate and metabolism of chemical stressors and to predict toxicity pathways. ERD has CompTox research in four major areas, to address these critical needs of the ORD CompTox Research Initiative:

- Development of computational tools and databases for environmental fate models
- Metabolism of xenobiotics: Enhancing the development of a metabolic simulator
- Metabonomics: The use of advanced analytical tools to identify toxicity pathways
- Development of software infrastructure to support the CompTox Program

Screening-Level Environmental Fate Models

Screening-level models require a chemical structure as input and will generate a set of daughter products that can form when the chemical is released into the environment. The models will comprise an expert system linking a library of possible transformations, physicochemical property calculators (e.g., SPARC), a database of rate constants and properties, and a set of QSARs. In addition to model development, research includes data mining activities in order to populate the database and derive QSARs. The database will also be supplemented with measurements from laboratory and field studies.

Metabolic Simulator

Metabolic simulators have been developed that provide the user with the metabolic pathways for many chemical structures. Due to the large number of potential metabolic pathways available to most chemicals, however, the generation of numerous metabolites during simulations is often problematic. The enhancement of these simulators for metabolism of xenobiotic chemicals in the liver and other target organs requires a high-quality database consisting of metabolic rate constants, metabolite formation, and

pathway elucidation. Towards this goal, a database will be populated with: (1) published literature values and other available data: (2) experimentally measured, in-house, *in vitro* metabolism studies; and (3) rate constants derived from in-house, mechanistic-based QSAR models.

Metabonomics: Identifying Toxicity Pathways

The application of metabonomics to toxicity pathway identification involves the elucidation of changes in metabolic patterns associated with chemical toxicity based on the measurement of component profiles in biofluids (e.g., urine), cells, or tissues, which enables the generation of spectral profiles for a wide range of metabolites. Once a series of fingerprints is defined for different toxicity pathways, the metabolite pattern for a toxic chemical of unknown mechanism can be compared to the database. This provides a very powerful tool for categorizing toxicants according to toxicity pathway. The goal is to: (1) establish high-resolution NMR spectroscopy-based metabonomic capabilities at ERD; (2) develop a metabonomics database for biofluids and tissues from various species exposed to different xenobiotics; and (3) integrate metabonomics data base with "omic" data to develop a holistic picture of xenobiotic metabolism and toxicity

Software Engineering

The CompTox Initiative requires a software infrastructure to achieve the stated goals. ERD will design and implement a modeling framework that will standardize the format and interchange protocols for all information generated via computer simulation. The technology will contain science-based models for simulating: the fate and transport of chemicals in a multimedia environment; human exposure as a function of activity; ecological exposure within specified habitats (terrestrial and aquatic); the fate and transport of chemicals within human and ecological receptors; and the expression of adverse health impacts.

NERL/ERD-Athens' Partnerships

The establishment of research partnerships with universities, federal agencies, and industry are a high priority for this research. Existing and planned partnerships include the *University of Georgia (UGA) Complex Carbohydrate Research Center (CCRC) NMR Facility*; *University of Georgia, Department of Chemistry*; *United States Dept. of Agriculture-Agricultural Research Service (USDA-ARS); Sections of Biological Chemistry and Molecular Toxicology, Biomedical Sciences Division, Imperial College, London; Procter and Gamble; Institute of Informatics and Dept. of Pharmacology, Rutgers University; and Sandia and Pacific Northwest National Dept. of Energy Laboratories.*

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