

Computational Toxicology: A 21st Century Approach for Conducting Chemical Risk Assessments

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Outline for Today's Presentation

- Defining computational toxicology
- Addressing the need for this emerging technology
- Relationship to the Source-to-Outcome continuum
- Examples of high through-put screening for the prioritization of chemicals for further testing
 - -Environmental Fate Simulator
 - -Metabolic Simulator
 - -Metabolomics
 - -Virtual Liver

Computational Toxicology:

The application of mathematical and computer models and molecular biological approaches to improve the Agency's prioritization of data requirements and risk assessments.

Computational Toxicology Involves:

- **Computational chemistry**: physical-chemical mathematical modeling at the molecular level
- Molecular Biology: application of a wide coverage of technologies such as genomics, proteomics, and metabolomics
- **Computational Biology:** development of molecular biology data bases and analysis of the data
- Systems Biology: application of mathematical modeling and reasoning to the understanding of biological systems

The Source-to-Outcome Continuum



A Primary Goal: To improve the linkages in the Source-to-Outcome Continuum

High Throughput Screening

- Rapid, efficient means to provide preliminary data

 Prioritize those chemicals that require further testing
 Minimize dependence on animal testing
- Vast chemical inventory not tested
 - 87,000 chemicals currently the inventory
 - $\sim 2,500$ new chemicals being added each year
- Initial focus is on identifying Endocrine Disruptors

Development of Environmental Fate Simulators

- Identify reactive functional groups
- Provide reaction pathways and products as a function of environmental conditions
- Provide relevant physical-chemical data for parent and reactions products





Metabolism

- Develop simulator for chemical metabolism
- Addresses one of the largest uncertainties in toxicity assessment
 - Identifying pathways and metabolites
 - Prioritizing metabolic pathways

The Challenge:

Metabolic pathways are complex.

Pathways must be identified and prioritized.



The Omics in Computational Toxicology: Genomics/Proteomics/Metabolomics

- Genomics and proteomics measure responses to chemicals on the genetic and cellular protein level, respectively.
- Metabolomics measures the metabolic status (i.e. metabolite profile) of the whole organism, providing a connection between genomics/proteomics and histopathology.
- Information-rich spectroscopic techniques (primarily high-resolution NMR or MS) are used for metabolomics.

NMR spectrum of trout liver extract



Portion of the spectrum of a control liver extract (polar fraction) with several metabolites labeled.

What is Metabolomics? (in one slide)

NMR Spectra of Urine Samples from Mice Treated with Tissue-Specific Toxins



Changes in *endogenous* metabolites are specific for the site and pathway of toxicity

These metabolic profiles can be used:

- 1) to define toxicity pathways
- 2) as indicators of exposure (for reconstruction)
- 3) to link varying exposure scenarios (magnitude, timing, duration) to likelihood of risk
- 4) to evaluate the impact of exposure to multiple stressors (i.e., mixtures)
- 5) and much more!

Metabolomics Can Help Define Toxicity Pathways

proof of concept – male and female fathead minnows exposed to the model estrogen mimic 17α-Ethynylestradiol (EE2)

EE2 is known to feminize male fish

Sampling timeline (in days) for 3 dose levels (0, 10, 100 ng/L)



192 fish - 8 of a given "class", where class is defined by gender, exposure level, and sampling time

Defining Toxicity Pathways : Spectral Fingerprints

One "Snapshot" in Time and Concentration Day 4, 100 ng/L Polar liver extracts



- Impact of exposure is greater for males
- Males are more like females after exposure
- Glutamate and alanine are the two most abundant amino acids in fathead minnow vitellogenin (i.e., egg yoke precursor)

The Virtual Liver Project (v-Liver™):

A computational system for simulating chemical-induced injury in hepatic tissues

The Main Components of the v-Liver[™] Project:

- A Liver Knowledgebase (KB) to describe the biological components, connections and the overall wiring diagram
- A simulation engine to analyze the independent/integrated behavior of selected molecular, cellular and tissue level components
- Novel experimental models to build, calibrate and evaluate the tissue model

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