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Emerging Technologies

Modeling Chemical Fate and Metabolism for Computational Toxicology

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Environmental Issue

The need to develop a scientifically credible approach for setting risk-based priorities for chemical testing requirements prior to having empirical data from which to estimate risks.

Computational Toxicology is the integration of modern computing and information technology with the technology of molecular biology and computational chemistry to improve EPA's prioritization of data requirements and risk assessments for toxic chemicals

Objectives of ERD-Athens CompTox Team

I. Modeling Chemical Fate in Ecosystems

- Perform laboratory and field experiments to fill data gaps
- Utilize input from genomic tools to:
  - determine "threshold concentration" for toxic event
  - identify the toxic chemical species (in a mixture)
- Utilize computational tools for fate model parameterization and speciation (e.g., SPARC - SPARC Performs Automated Reasoning in Chemistry)

II. Modeling Chemical Fate in Organisms (metabolism)

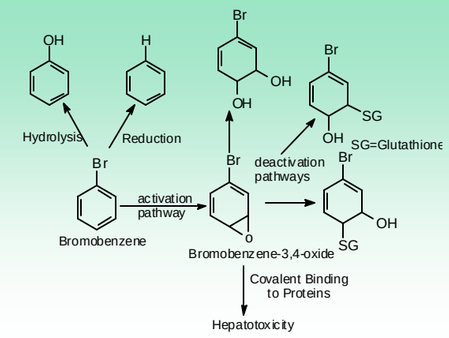
- Evaluate existing metabolic simulators
- Improve simulator database (e.g., add new pathways)
- Apply advanced analytical tools for testing / improving metabolic simulator (e.g., NMR, Raman)
- Utilize SPARC outputs to inform metabolic simulator of species of concern (hydrolysis, speciation, etc.)

III. Software Engineering

- Design and implement a modeling framework (e.g., FRAMES)
- Perform uncertainty and sensitivity analysis

The Problem

Environmental fate and metabolic pathways are often complex even for relatively simple chemicals (e.g., bromobenzene). Pathways must be elucidated and prioritized for environmental fate and metabolic simulators to be developed.

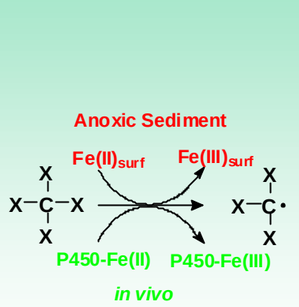


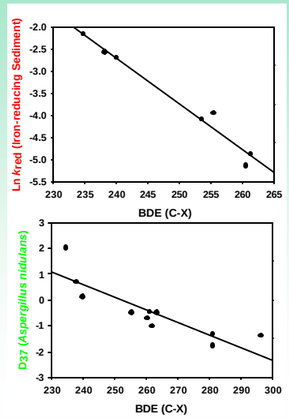
Scientific Approach

Experimental systems and tools for populating databases for environmental fate and metabolic simulators

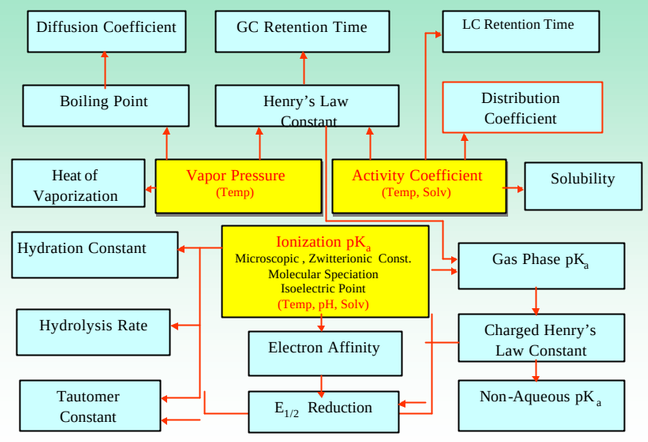
- Experimentally measured values. Systems include:
  - -Well characterized sediments and soils
  - -Intact liver
  - -Liver microsomes
  - -S9 fraction
- Rate constants and molecular descriptors derived from mechanistic-based SPARC and/or QSAR models
- Advanced spectroscopic techniques (e.g., wide-bore NMR) for measuring metabolic rate constants and identifying metabolites *in vivo* and *in vitro*

QSARs for the abiotic (surface bound Fe(II)) and biological (P450-Fe(II)) reduction of polyhalogenated methanes suggest commonalities in the process of developing and refining simulators for environmental transformation and metabolism.

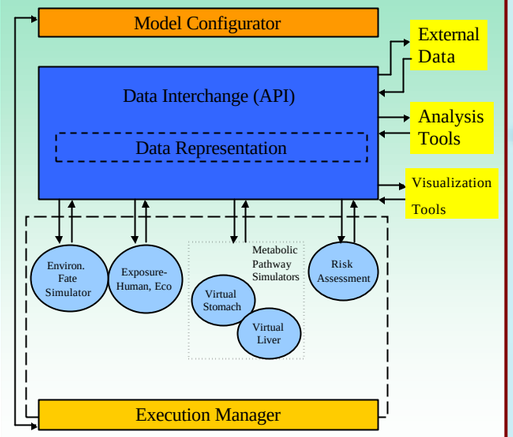




SPARC computational models will provide necessary parameterizati on and speciation data for transformation and metabolic simulators



Design concept for CompTox modeling framework is based on open-architectural, object oriented software



Clients for CompTox

- All EPA program offices that require toxicity testing for chemicals –OPP, OPPT, OW, OSW
- Other parts of EPA that perform risk assessment/management – NCEA, Regions, State EPDs

Impact

- CompTox will allow direction of limited resources for toxicity testing to regulated chemicals of highest potential risk
  - -lowers risk to humans and ecosystems
  - -reduces the need for animal testing
- CompTox goals are unobtainable without accurate modeling of chemical fate and metabolism

United States Environmental Protection Agency

Partnering to Protect Human Health and the Environment