Computational Approaches and Tools for Exposure Prioritization and Biomonitoring Data Interpretation

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research & development

Science Questions

The research addresses the following key science questions:

• What computational approaches can be developed to establish linkages along the source-exposure-dose-response continuum?

• How can these methods be used to identify exposures of greatest concern and to prioritize environmental chemicals for toxicity testing and/or risk assessment?

• Are these methods useful for interpreting biomarker data to estimate potential exposures and health risk?

Research Goals

• Develop the Environmental Fate Simulator (EFS) to parameterize and link environmental fate and transport models used to estimate environmental concentrations of chemicals.

• Develop screening-level PBPK models for congeneric series of chemicals, utilizing Quantitative Structure-Activity Relationship (QSAR) and other computational chemistry techniques, along with results from *in vitro/in vivo* studies to estimate chemical-specific parameters required for PBPK models.

• Refine computational tools to interpret biomonitoring data and to identify critical data gaps and uncertainties in assessing exposures and/or health impacts using biomonitoring data.

Impact and Outcomes

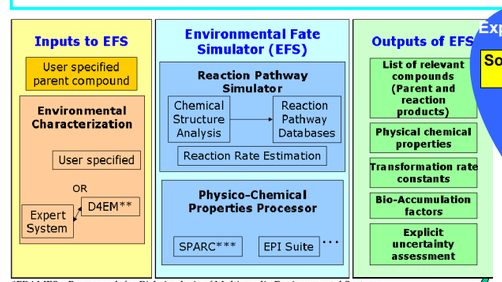
• Screening-level environmental and exposure/dose models and associated databases will couple with the NCCT toxicity models and databases to facilitate risk-based screening of environmental chemicals.

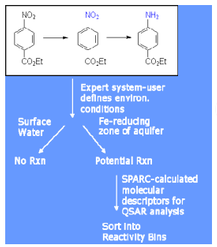
• Integrated PBPK models with comparative *in vitro/in vivo* data and QSAR/computational chemistry techniques will provide risk assessors enhanced understanding of how human exposures result in tissue dosimetry.

• Enhanced methods for interpreting biomarker data will be used to inform risk assessment and design future exposure and epidemiological studies. This work will serve as the basis for demonstrating the effectiveness of regulatory actions.

Computational Approaches and Tools

NERL research is developing Environmental Fate Simulator (EFS): A FRAMES*-supported computational tool for parameterizing environmental fate and transport models (e.g., EXAMS, PRZM) that estimate environmental concentrations of chemicals.

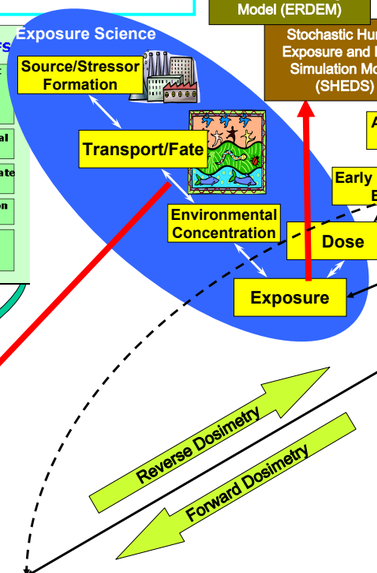




Parameterize and link environmental fate/transport models

Pesticide Root Zone Model (PRZM)

Exposure Analysis Modeling Systems (EXAMS)



Biomarker

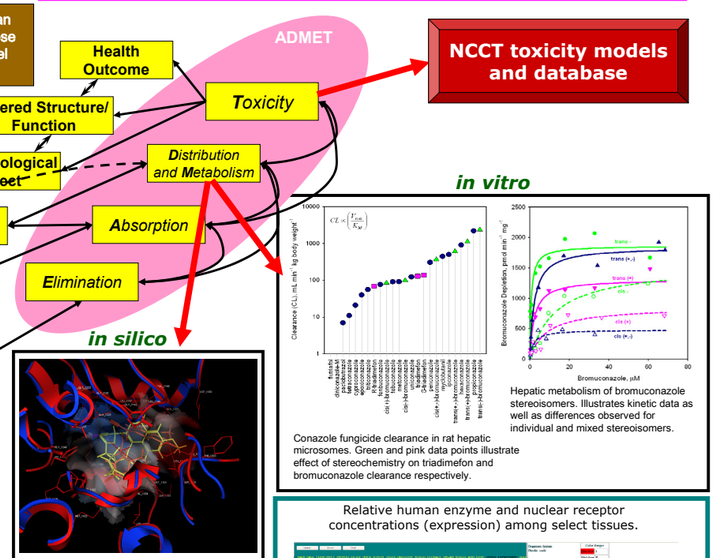
NERL research is refining computational approaches for assessing the quantitative relationships between biomarkers and human exposures to environmental chemicals. This work will ground truth the source-exposure-dose-response models developed by NERL and NCCT.

Forward dosimetry approach estimates an integrated internal dose from multiple sources and routes of exposure.

Reverse dosimetry approach estimates exposure levels that are consistent with observed biomarker levels.

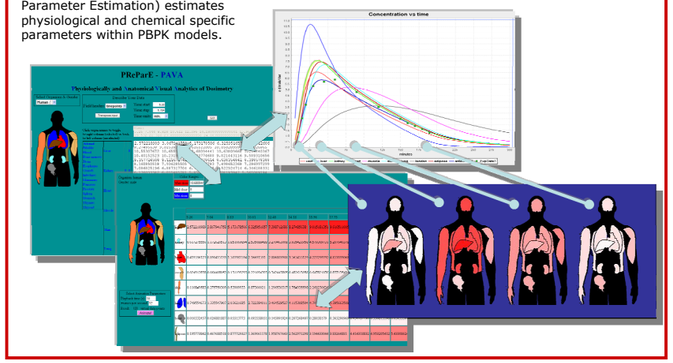
Both approaches require information regarding pharmacokinetics and exposure patterns.

NERL research is developing screening level PBPK models to link exposures to tissue doses for improved dose-response assessment. QSAR/other computational chemistry techniques and *in vitro* experiments are utilized to estimate chemical-specific parameters required for PBPK models.



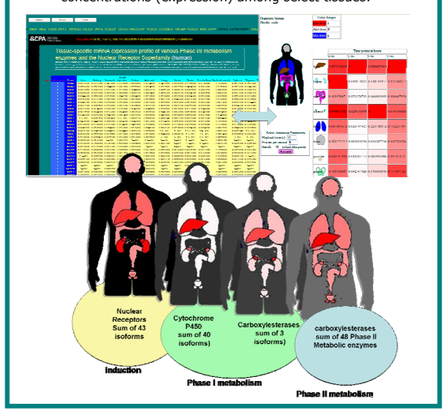
3D rendering of two poses obtained through molecular docking calculations of the high activity *trans* diastereomer of cypermethrin (in yellow and orange) within the backbone of human and preliminary rabbit carboxylesterase, rCE1(blue).

PReParE (Physiological Relevant Parameter Estimation) estimates physiological and chemical specific parameters within PBPK models.



Resulting visual analytics (Physiological and Anatomical Visual Analysis; PAVA) can be utilized to give further insight into PBPK/PD model development through CYP enzyme concentration across tissues, comparative and differential metabolism, inter-species and life stage analysis all through compact and intuitive visual representations.

Relative human enzyme and nuclear receptor concentrations (expression) among select tissues.



Results/Conclusions

Environmental Fate Simulator

Initial research has focused on predicting reaction pathways and rates for reductive transformation in anaerobic sediments.

• Functional groups that are susceptible to reductive transformation have been identified.

• SPARC calculators have been extended to calculate molecular parameters that describe the "willingness" of nitroaromatics and polyhalogenated methanes and ethanes to accept electrons.

•The predominant chemical reductants in anaerobic sediments have been identified.

Screening level PBPK models

Both *in silico* and *in vitro* approaches have been developed to estimate chemical specific parameters within a PBPK model.

• A simulation program PReParE has been developed to combine experimental and *in silico* knowledge base of chemicals for estimating physiological and chemical specific parameters.

• Specific enzyme inhibitors, purified human recombinant cytochrome P450s, induced microsomes, stable isotopes and series of analog compounds have been used to elucidate mechanisms of xenobiotic metabolism.

• Computational approaches utilizing molecular docking have also been employed.

Interpretation of biomonitoring data

A pilot study (Ex-R Study) conducted in Chapel Hill, NC has been initiated to estimate human exposures to pyrethroids using an exposure reconstruction approach. This study will assess the variability of pyrethroid metabolites in urine samples in non-occupationally exposed adults for a six week period of time. The exposure and absorbed doses of selected pyrethroids for study participants will be estimated based on their urinary biomarker levels using linked exposure and PBPK models.

Future Directions

• Develop and refine the EFS.

• Develop, evaluate, and apply innovative screening-level PBPK models to link exposures with tissue dosimetry.

• Link and apply NERL's EFS, exposure and dose models for selected chemicals.

• Integrate the NERL and NCCT computational approaches and tools to understand the key factors and uncertainties associated with exposures and risk along the source-exposure-dose-response continuum.

• Provide Agency risk assessors with both screening level and sophisticated computational approaches and tools for estimating environmental exposures and for prioritizing chemicals for toxicity testing and risk assessment.

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