Linking Exposure Measurements with Human Activity Data to Assess Dose in Human Tissues by Applying the Exposure Related Dose Estimating Model (ERDEM)

Curt Dary[1], Fred Power[1], Jerry Blancato[2], Miles Okino[1], Rogelio Tornero-Velez[2], and Stacy Harper[1]

U.S. Environmental Protection Agency, Office of Research and Development

1 National Research Exposure Laboratory (NERL), Las Vegas, NV • 2 National Research Exposure Laboratory (NERL), Research Triangle Park, NC

research and development

1 Science Questions

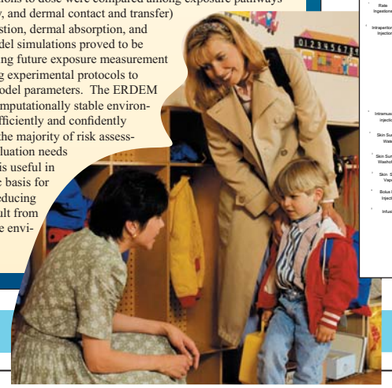
Can a physiologically based pharmacokinetic (PBPK) model be used to determine the interactions among, and individual contributions of, multiple chemicals from aggregate exposures on absorption, distribution, metabolism and excretion? Can the information from model-simulated aggregate exposures be used to estimate cumulative risk?

2 Research Goals

The Exposure Related Dose Estimating Model (ERDEM) was developed to enable researchers and risk assessors to estimate dose of parent chemicals and metabolites in various organs and tissues in humans. The ERDEM is fundamental to studies of aggregate exposure and cumulative risk because it allows for the examination of multiple exposure routes (e.g., oral, dermal and respiratory) simultaneously. The ERDEM pharmacokinetic modeling engine mathematically represents physiological, biological, and pharmacodynamic data in the form of differential equations. Physiological compartments include: arterial blood, brain, carcass, derma, fat, intestine, kidney, liver, ovaries, rapidly perfused tissue, slowly perfused tissue, spleen, static lung, stomach, testes, and venous blood. Metabolic parameters are estimated from human subject data. Allometric scaling is used to adjust for differences in organ and tissue volume among humans, by age and sex.

The ERDEM has been successfully used to assess risk in presumed sensitive populations to environmental agents, consumer products, and pesticides. In these case studies, time-histories of exposures were tested based on regulatory assumptions as specified under Federal Guidelines. For example, exposure time-histories that involve dermal contact rates with pesticide contaminated surfaces were used to derive dermal transfer coefficients (cm^2/hr) for input into the dermal absorption module. Inputs involving dermal transfer of residues via the oral pathway (hand-to-mouth activity) were allowed to simultaneously account for a portion of the mass transferred.

Ultimately, contributions to dose were compared among exposure pathways (i.e., oral, respiratory, and dermal contact and transfer) and routes (i.e., ingestion, dermal absorption, and inhalation). The model simulations proved to be instructive in preparing future exposure measurement studies and designing experimental protocols to augment or adjust model parameters. The ERDEM was found to be a computationally stable environment that could be efficiently and confidently modified to explore the majority of risk assessment and hazard evaluation needs of EPA. The model is useful in providing a scientific basis for characterizing and reducing human risks that result from exposures to multiple environmental stressors.



3 Methods/Approach

3a. Physiological Data Preparation

There must be a careful collection and verification of physiological data as it relates to:

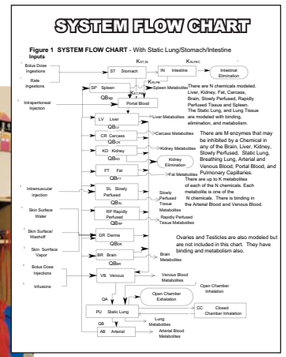
1. Exposure Chemicals and Metabolites (e.g., TCE to TCA metabolism)
2. Exposure Routes (Inhalation, Oral, Skin Surface, etc.)
3. Exposure Activity Scenarios (Sitting, Swimming, etc.)
4. Time Histories of Exposure Concentrations
5. Exposure Compartments (Liver, Kidney, etc.)

Physiological data is obtained either from experimental data or accepted literature. Comparison of experimental versus literature parameters can provide valuable information concerning differences introduced by additional factors such as species, gender or age. When there is no experimental data or literature available, estimation techniques (e.g., equations and Quantitative Structure Activity Relations (QSAR) software) can be used to obtain parameter values (e.g., organ partition coefficients and solubility parameter values).

Estimating Metabolic Parameters. Metabolic parameters are another class that needs to be prepared in order to conduct PBPK modeling. For volatile compounds, *in vivo* inhalation experiments can be used to obtain metabolic estimates in rodents. These estimates can then be extrapolated across species to obtain values for humans. For other chemicals, metabolic estimates can be derived from other similar compounds using QSAR techniques or software.

Estimating Organ Partition Coefficient (solubility). Partition coefficients are measured experimentally for volatiles, but need to be estimated for other classes of chemicals. One such approach makes use of the chemical's octanol/water partition coefficient as a starting point, calculating each organ's solubility based on its lipid content.

3b. Physiological & Mathematical Description of the ERDEM Model



Physiological Model Compartmental Structure. ERDEM is composed of a group of compartments representing different parts of the body in a series of stages: absorption, distribution, metabolism, and elimination. The accompanying system flow chart reveals the layout of this arrangement in terms of compartments. ERDEM consists of compartments for: Arterial Blood, Brain, Carcass, Derma, Fat, Intestine, Kidney, Liver, Ovaries, Rapidly Perfused Tissue, Slowly Perfused Tissue, Spleen, Static Lung, Stomach, Testes, and Venous Blood. The Static Lung compartment models breathing using a partition coefficient for blood-air exchange. ERDEM is capable of determining a relevant dose to certain organs of the human body.

Physiological Model Capability. ERDEM is specifically designed to simulate the exposure of a species to multiple chemicals and determine the dose of the exposure chemicals and their metabolites to each compartment or sub-compartment. It can be used to extrapolate from low dose to high dose, and to compare exposures for one exposure route to another. The exposure scenarios can be varied from a single exposure to multiple exposures, with multiple chemicals for each exposure. ERDEM accepts time histories for inhalation, dermal, and rate ingestion exposures. The parent exposure chemicals can have multiple metabolites, and these metabolites can have metabolites, and so on. All metabolites and parent chemicals can circulate throughout the body.

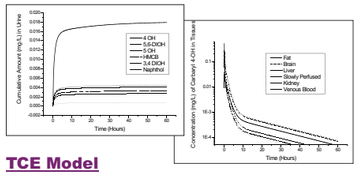
3d. ERDEM Carbaryl and TCE Dose Analysis

After data preparation activities and a PBPK model simulation have been completed, it is important to conduct model assessment on single and multiple run results.

The ERDEM system was designed to use a stochastic component (rudimentary interface exists for sensitivity and Monte Carlo analysis) that evaluates the uncertainty associated with input parameters and output model results. To date, ERDEM has been extensively used for simulating exposure to chloroform, carbaryl, and trichloroethylene (TCE). Currently, the ERDEM model is being used to estimate dose of MTBE and TBA in humans. In addition, model versions have been formulated for exposure to organophosphate pesticides and other chemicals and metabolites.

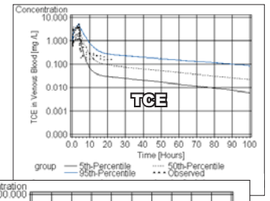
Carbaryl Model

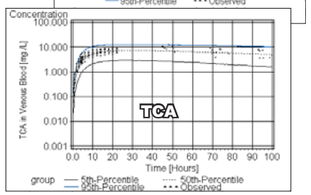
ERDEM Dose Response Curve Estimation for a Rat. Carbaryl runs were performed to determine dose response curves for a rat with an oral bolus dose ingestion (1mg/kg).



TCE Model

Uncertainty Analysis using Monte Carlo Techniques. An uncertainty analysis of trichloroethylene (TCE) human exposure for adult males was conducted from ERDEM output results. The model includes several circulating metabolites such as trichloroacetic acid (TCA) and trichloroethanol (TCOH). A modeling male population group between 25 and 35 years old was chosen with a mean body volume (μ=70 L) and cardiac output (μ=385.78, σ=96.195 mg/L). Using assumptions about parameter central tendency and natural variation, model runs were generated based on human subjects (Fisher et al., 1998) to perform Monte Carlo analysis with correlation adjustment amongst selected parameters.





TCE and TCA Model Run

Uncertainty Analysis with Experimental Data Versus Time With Percentile Overlays. For the most sensitive parameters, 1000 sets of random numbers were generated by SAS and 1000 ERDEM runs were conducted. Experimental venous blood concentration measurements for eight human male subjects are used to illustrate the model predictability.

3c. ERDEM Front End-GUI and Database Management System

Data Management

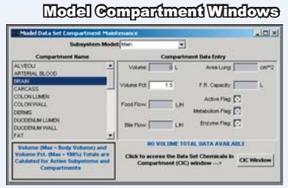
The ERDEM data entry and management PBPK modeling system is composed of an advanced Windows-based input management system—the ERDEM Front End Graphical User Interface (GUI)—using PowerBuilder, a rapid application development software. The ERDEM GUI uses Sybase Corporation's SQL AnyWhere relational database management system (DBMS) as the Model Data Set repository.

Managing Large Amounts of Physiological Data. The ERDEM Front End GUI and DBMS allow the user (risk assessor and toxicologist) to easily enter, edit and store the complex physiological (e.g., chemicals, metabolites, enzymes, compartments, exposure types and activities, time histories, and concentration parameters) data required for PBPK modeling. The ERDEM Windows environment is menu driven and requires that users enter data in order (i.e., Model, Activity, Chemical, Chemical Compartment, Enzyme, and Exposure menus).

Reporting, Exporting and Running ERDEM Simulations. The ERDEM GUI prepares a report of input parameters, exports a Model Data Set to an ACSL* command file, and then executes a simulation using the ERDEM model engine and ACSL Viewer. In addition, the ERDEM GUI also contains context driven online help, tutorial capabilities (audio/visual), and can be configured into custom versions for novices as well as experts in the PBPK modeling field.

** Advanced Continuous Simulation Language - Product of AEgis XCellon.*

Model Compartment Windows



4 Results/Conclusions

Implementing a comprehensive approach to PBPK modeling provides a user-friendly, productive environment or system for researchers (e.g., toxicologists, risk assessors, exposure scientists, and managers) to perform not only dose response estimation, but also uncertainly analysis and model assessment. When the comprehensive approach core activities, such as identification and implementation of the model design and performance criteria, the model hardware/software specifications, and the model testing and evaluation, are implemented correctly, users are then capable of carrying out the tedious and error prone modeling simulation activities with ease for any exposure and dose estimating model.

The ERDEM system represents a PBPK modeling and research environment that allows for implementation of the core activities including:

- A simulation data repository that promotes thorough data research and preparation activities that include requirements analysis and performance criteria for model inputs and outputs.
- Generic PBPK models that relieve the user of PBPK model design, coding and software interface planning so that attention can be placed on input data generation.
- Model run testing and evaluation activities that include applying sophisticated uncertainty analysis (sensitivity and Monte Carlo) techniques and publication reviews to simulation inputs and output results.

5 Impact and Outcomes

This research demonstrates the power of PBPK modeling for estimating the disposition of toxic substances and metabolites in human organs, tissue and excreta in relation to simulated exposure time-histories. This work also reveals how PBPK input parameter values might change for humans based on age, sex, body fat content, and overall physiological health. The results indicate the adaptability of the ERDEM platform to simultaneously test exposure along separate pathways and routes. Parent chemicals and specified metabolites for each chemical can be modeled to obtain cumulative risk calculations. Research versions of ERDEM are updated and modified as client based exposure applications might demand.

6 References

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Aggregate/Cumulative Risk

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