Harmonization & Communication of PBPK models using the Exposure Related Dose Estimation Model (**ERDEM**) system: Trichloroethylene

EPA Science Forum 2004 — Healthy Communities and Ecosystems

Miles S. Okino[1], Fred W. Power[1], Jerry N. Blancato[1]
Weihsueh Chiu[2], Chao Chen[2], & John C. Lipscomb[3]

1. National Exposure Research Laboratory (NERL), US EPA, Las Vegas, NV
2. National Center for Environmental Assessment (NCEA), Washington DC
3. National Center for Environmental Assessment (NCEA), Cincinnati, OH

1. ABSTRACT

In support of the trichloroethylene (TCE) risk assessment for the Office of Air and Radiation, Office of Solid Waste and Emergency Response, and Office of Water, NERL and NCEA are developing an updated physiologically-based pharmacokinetic (PBPK) model. The PBPK modeling effort is being coordinated with a workgroup co-sponsored by EPA and the U.S. Air Force and facilitated by Toxicology Excellence for Risk Assessment (TERA). The workgroup includes researchers from EPA, academia, the Air Force, and private consulting.

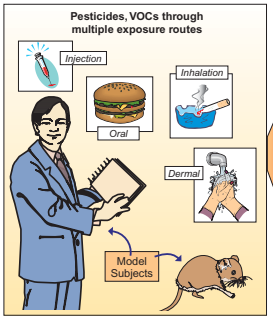
PBPK models are powerful computational tools that can be used to link exposure to the internal concentrations of parent compounds and/or active metabolites at the target site(s) of toxicity. Challenges in model development are the comparison and harmonization of existing models, management of multiple diverse datasets, and characterization of the uncertainties. The implementation and documentation of a mathematical model in a general structure addresses these issues by managing the chemicals, compartments, and parameters in a consistent manner. The Exposure Related Dose Estimating Model (ERDEM) platform, developed by NERL, provides an appropriate structure.

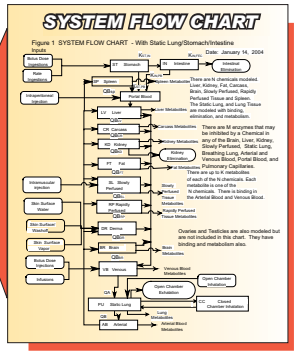
The EPA Science Advisory Board has stressed the importance of transparency in the updated assessment of TCE. The development of the updated PBPK model in the ERDEM system addresses this charge through its graphical user interface (GUI), standard report generation, and availability to the public. Evaluation of the model can be done at a high level – standard reports or simulations of new scenarios through the GUI – and at varying levels of detail down to the actual FORTRAN code. This enables use and review by researchers of diverse backgrounds.

http://www.epa.gov/heasdweb/erdem/erdem.htm

2. PBPK MODELS & ERDEM

PBPK models represent the physiological processes associated with chemical absorption, distribution, metabolism and excretion (ADME)





- ERDEM provides a general platform for PBPK models
- Demonstrated applicability to a wide range of chemicals

Liver Mass Balance Equation

$$V_{LI}\frac{dC_{LI}}{dt} = \frac{dA_{LIVA}}{dt} + \frac{dA_{LIVB}}{dt} + \frac{dA_{LIVR}}{dt} + Q_{LI,1}C_{ART,1} + Q_{LI,2}\frac{C_{GUT,1}}{R_{LIVR}} - \frac{dA_{LI,1}}{dt} - \sum_{j=1}^{N_{LI}}\frac{dA_{LIVB,j}}{dt} + \sum_{k=mol}\frac{dA_{LIVR,k}}{dt_k}\tau_{LIR}$$

where

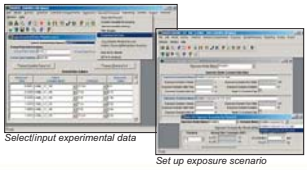
$I_{GUT,m}$ is the circulating compound that is the m^{th} metabolite of the i^{th} circulating compound.

r_{LIR} is 1.0 if the mass units are millimoles, and is the ratio of the molecular weight of the i^{th} chemical to that of the parent chemical, the i^{th} chemical, if the mass units are milligrams.

3. PUBLISHED MODELS

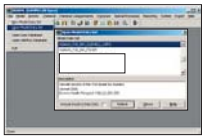
The general structure of ERDEM enables the implementation of published models

- J.W. Fisher et. al. and H.J. Clewell have published TCE PBPK models with different structures evaluated against different data sets



Select/input experimental data

Set up exposure scenario

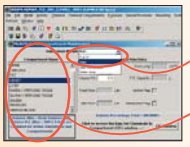


- ERDEM enables rapid evaluation and comparison of the models against identical scenarios and data
  - J.W. Fisher model can be run under scenarios evaluated by Clewell
  - H.J. Clewell model can be run under scenarios evaluated by Fisher

4. TCE PBPK MODEL

EPA and the Air Force are co-sponsoring a workgroup facilitated by TERA to develop a TCE PBPK model harmonizing previously published models

- NERL and NCEA are participating in the workgroup, with H.J. Clewell (Environ Corp.) and J.W. Fisher (University of Georgia)
- The risk assessment for TCE may require evaluation of additional metrics, or against additional studies, resulting in further refinement, augmentation, and/or modification of the model by EPA
- ERDEM is a valuable platform for model evaluation and development

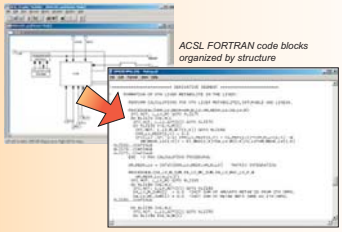


Alternative systems can be activated to account for other physiological processes (i.e. enterohepatic recirculation of glucuronides)

Additional compartments can be activated for TCE or its metabolites

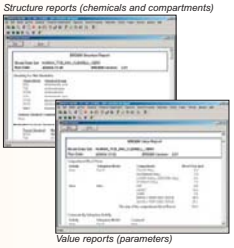
5. MODEL REVIEW

ERDEM facilitates model review by providing standard reports, output and code structure



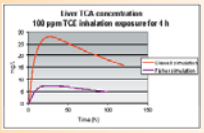
ACSL FORTRAN code blocks organized by structure

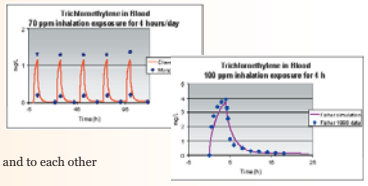
Structure reports (chemicals and compartments)



Value reports (parameters)

6. PBPK MODEL CHARTS





- Model results can be compared to data and to each other

7. MODELING INVESTIGATIONS

ERDEM also facilitates other PBPK modeling investigations

- Rapid evaluation of hypotheses
- Uncertainty analysis through Monte Carlo simulations (Tsang et. al. 2000)
- Future directions
  - Hierarchical Bayesian approaches (e.g., using Markov Chain Monte Carlo)
  - Parameter estimation from linked QSAR database

8. REFERENCES

Clewell, H.J. *Development of a Physiologically Based Pharmacokinetic Model of Trichloroethylene and Its Metabolites for Use in Risk Assessment*, Environ Health Perspect 108(suppl 2): 283-305 (2000).

Fisher J.W., Mahle, D., Abbas, R. *A Human Physiologically Based Pharmacokinetic Model for Trichloroethylene and Its Metabolites, Trichloroacetic Acid and Free Trichloroethanol*, Toxicol Appl Pharmacol 152: 339-359 (1998).

Tsang, A.M., Brown, R.N., Power, F.W., Blancato, J.N., Scott, C.W. *Uncertainty Analysis of TCE Using the Dose Estimating Exposure Model (DEEM) in ACSL*. 2000 Annual Meeting of the Society of Toxicology, Philadelphia, PA, March 19 - 23, 2000.

9. DISCLAIMER

Although this work was reviewed by EPA and approved for publication, it may not necessarily reflect official Agency policy.

Delivering Science-Based Information to Decision Makers