TERA
Toxicology Excellence for Risk Assessment
a nonprofit corporation dedicated to the best use of toxicity data for risk values

# Quantitative Risk Assessment

Quantitative risk analysis provides data based risk estimates derived using mathematical modeling and statistical analysis of experimental toxicity data. *TERA* scientists have extensive experience with the tools of quantitative risk analysis, and continue to research and develop new analytical methods to improve risk assessment.

## *Selected Capabilities*

### Biological Systems Modeling (Pharmacokinetics/Pharmacodynamics)

*TERA* has expertise in the mathematical modeling of complex biological processes using physiological-based pharmacokinetic (PBPK) models and pharmacodynamic (PD) or biologically-based dose-response (BBDR) modeling. PBPK models predict target tissue doses in response to chemical exposure allowing more accurate extrapolation across species, age groups, dose routes, or exposure durations. BBDR models are a mathematical description of the cellular mechanisms of toxicity that can improve low-dose and interspecies extrapolation. TERA scientists have recent experience with models for trichloroethylene (http://www.tera.org/news), nickel, methylene chloride, ethylene dichloride, warfarin, parathion, and others.

### Bayesian Population Analysis

*TERA* staff are proficient with Bayesian statistical techniques for analyzing uncertainty in mathematical models and population variability. Bayesian population analysis using Markov chain Monte Carlo (MCMC) simulation is a technique that is well suited for analysis of pharmacokinetic data using PBPK models and can enhance our understanding of interspecies and human variability using these highly parameterized models. *TERA* scientists recently performed Bayesian analysis of the harmonized PBPK models for trichloroethylene (http://www.tera.org/news), as well as other models for methylene chloride, ethylene dichloride, and methylene chloride. TERA staff have also played a significant role in identifying and addressing key uncertainties and issues that need to be addressed in order to more extensively incorporate the results of MCMC simulation into risk assessment.

### Biomarker Validation and Dose-Response

*TERA* scientists are currently developing methodology for validating biomarkers and performing biomarker-based dose-response for use in risk assessment using Bayesian networks. Network models are developed that link exposure, biomarkers of exposure and effects, and disease outcomes. This approach incorporates data spanning the exposure-early effects-disease continuum are analyzed, integrating complex data from emerging technologies (e.g., gene expression assays) with traditional toxicity data. This approach will reduce the need to

extrapolate from high doses that induce severe effects to more meaningful changes that occur at early time points and low doses.

## Benchmark Dose (BMD) Modeling

The benchmark dose (BMD) approach has a number of advantages over the traditional NOAEL/LOAEL approach. The greatest advantage is that the BMD approach responds appropriately to sample size, reflecting increased uncertainty in smaller sample sizes and yielding a lower point of departure. *TERA* scientists have conducted BMD analyses for numerous chemicals, published on issues related to the application of BMD methods, served on the peer review panel for the most recent BMD guidance, and participated in workshops on future development and issues of the BMD approach. *TERA* also offers training courses on the BMD approach. See http://www.tera.org/education.

## Categorical Regression Analysis

Categorical regression is a dose-response technique that incorporates not only information on how the incidence of response increases with dose, but also information on how the severity of response increases with dose. Categorical regression is a powerful tool for combining sparse data across studies or endpoints, for quantitative analysis of qualitative toxic severity data, and for integrating concentration-duration-response data for development of acute exposure guidelines, particularly for the inhalation route. *TERA* scientists have performed several categorical regression analyses, including the risk characterization of non-lethal weapons (http://www.tera.org/Research/nlw research.htm), and have published on the subject in the scientific literature (http://www.tera.org/Research/more dose response.htm).

## Occupational and Epidemiological Data Analysis

*TERA* scientists have experience conducting dose-response analysis of occupational exposure-response and epidemiological data. For example, in a published analysis of the lung cancer risk from inhalation exposure to hexavalent chromium, *TERA* staff used Poisson and Cox regression analysis of job-exposure matrix data to estimate cancer potency, and lifetable analysis to refine the extrapolation from the occupational data to environmental exposure scenarios and compute additional lifetime risks. As further examples, *TERA* staff have developed models to analyze odds ratios associated with occupations involving diesel exhaust and asbestos exposure.

**For more information visit us at www.tera.org**
**or contact Eric Hack at (513) 542-7475 x19; Hack@tera.org**