

## PBPK Tools for Interpreting Biomonitoring Studies

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Biomonitoring of chemicals in human blood and urine samples is becoming commonplace and has aided in identifying the presence of small amounts of chemicals in many human populations. The degree of risk posed by these chemicals is estimated based on levels of exposure and the relationship of these exposure levels to those that are known to cause toxicity in test animals or in more highly exposed human populations. This project develops quantitative, pharmacokinetic models for several classes of compounds, where the classes are distinguished by differences in persistence and chemical characteristics. These models utilize simulation and variability approaches to conduct reverse dosimetry (i.e., estimating exposure intensity from biomonitoring test results).

The initial, short-term research products are (1) a paper for publication describing the use of these reverse dosimetry approaches to interpret biomonitoring results, and (2) a brief Congressional staff policy paper communicating the importance of these models in interpreting and communicating biomonitoring results to the general public. Longer-term products will focus on applications of these methods to a broader suite of compounds. Our work has already developed a novel approach for applying physiologically-based pharmacokinetic (PBPK) modeling within the framework of Monte Carlo uncertainty analysis to perform reverse dosimetry of biomonitoring data on volatile compounds. The next phase of research will apply the PBPK/Monte Carlo modeling approach to interpret biomonitoring data for non-persistent, non-volatile chemicals (e.g., phthalates) as well as for persistent chemicals (e.g., perfluorinated compounds). Each of these classes of chemicals is expected to present different challenges for the interpretation of biomonitoring data. In addition, the Center for Human Health Assessment used this research to develop a short course titled, "Pharmacokinetic Models for Interpreting Biomonitoring Results" which was offered to ACC-member company employees and other interested parties in the fall of 2006.

**Implications:** Biomonitoring studies i.e., finding low levels of commercial chemicals in blood and urine, have fueled concerns about the dangers of these chemicals. New tools are desperately needed to interpret these studies in a risk context. Our research used pharmacokinetic modeling, physiologically based pharmacokinetic modeling in particular, to interpret biomonitoring data in relation to exposure reconstruction and risk characterization. A general approach, referred to as reverse dosimetry, was developed to estimate distributions of environmental exposure levels that would produce measured biomarker concentrations. Our work refocused biomonitoring issues to emphasize the minimal risks expected for most of these compounds.

**Start and end date:** June 2005 – December 2008

### Presentations:

Clewell, H., Tan, C., and Andersen, M. (2006). Application of pharmacokinetic modeling to estimate PFOA exposures associated with measured blood concentrations in human populations. Presentation, 2006 Annual Meeting of the Society for Risk Analysis, Baltimore, MD, December 3–6, 2006.

Clewell III, H. J., Andersen, M. E., and Tan, C. (2006). Interpreting biomonitoring data using physiologically based pharmacokinetic (PBPK) modeling. Workshop, CIIT Centers for Health Research, Research Triangle Park, NC, February 6–10, 2006.

**Peer-reviewed publications:**

Liao, K. H., Tan, Y. M., and Clewell, III, H. J. (2007). Development of a screening approach to interpret human biomonitoring data on volatile organic compounds (VOCs): Reverse dosimetry on biomonitoring data for trichloroethylene. *Risk Analysis* 27: 1223–1236.

Tan, Y. M., Liao, K. H., and Clewell, H. J. (2007). Reverse dosimetry: interpreting trihalomethanes biomonitoring data using physiologically based pharmacokinetic modeling. *Journal of Exposure Science and Environmental Epidemiology* 71(7): 591–603.

Clewell, H. J., Tan, Y. M., Campbell, J. L., and Andersen, M. E. (2008). Quantitative interpretation of human biomonitoring data. *Toxicology and Applied Pharmacology* 231L: 122–133.

**Other publications:**

Tan, C., Liao, K., and Clewell, H. (2005). Physiologically based pharmacokinetic modeling as a tool to interpret human biomonitoring data. *CIIT Activities* 25(4).

PBPK Tools for Interpreting Biomonitoring Data. (2007). Short course at International Society for Exposure Analysis: Update. One week coursebook.

PBPK Modeling and Risk Assessment. (2008). One week coursebook.

Clewell et al. (2008). Exposure assessment: Exposure modeling and measurement – Toxicokinetic modeling. In *Encyclopedia of Environmental Health*. (Submitted).

Tan, Y.-M. and Clewell, H. (2008). Probabilistic reverse dosimetry modeling for interpreting biomonitoring data. In *Quantitative Modeling in Toxicology*. John Wiley. (Submitted).

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