

CIIT Center for Computational Biology and Extrapolation Modeling (CCBEM)

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The mission of the Center for Computational Biology and Extrapolation Modeling (CCBEM) is to further our understanding of the biological mechanisms that determine the shape of the xenobiotic exposure-adverse response curve in humans and laboratory animals. CCBEM promotes a Systems Biological approach to research with a focus on development of computational models of biological systems. These computational models are used for data evaluation, experimental design and for the extrapolations – route-to-route, between species, and from high to low doses – that are essential to science-based human health risk assessment. CCBEM promotes incorporation of biologically based modeling at the earliest feasible stages of laboratory research projects and also develops prototype, biologically motivated human health risk assessments. CCBEM promotes technology transfer both inside and outside of CIIT with the goal of maximizing the use of computational resources in support of research and health risk assessment. Training in computational modeling of biological systems is provided through seminars and special courses that include hands-on computer laboratories.

Start and end date: January 2003 – December 2005

Presentations:

Gentry, P. R., McDonald, T., Sullivan, D., Yager, J., Crump, K. S., and Clewell, H. J. (2006). Integration of the available genomic data for inorganic arsenic species to support the development of a nonlinear cancer dose-response modeling approach. *The Toxicologist* 90(S-1): 447. (Abstract 2182).

Andersen, M. E. (2005). Vinyl chloride: Establishing the role of dosimetry in risk assessment. *The Toxicologist* 84(S-1): 342. (Abstract 1676).

Conolly, R. (2005). Dose-additivity of mixtures: Where are we going with the science? *The Toxicologist* 84(S-1): 7. (Abstract 30).

Reddy, M. B., Plotzke, K. P., Looney, J. R., Utell, M. J., Jovanovic, M. L., McMahan, J. M., McNett, D. A., and Andersen, M. E. (2005). Physiological modeling of the dermal absorption of octamethylcyclotetrasiloxane (D4) and decamethylcyclopentasiloxane (D5). *The Toxicologist* 84(S-1): 192. (Abstract 940).

Andersen, M. E. (2003). Recasting the toxicology paradigm: a systems biology perspective. Presentation at the Annual Meeting of the International Life Sciences Institute, Miami, FL, January 17–23, 2003.

Conolly, R. B. (2003). Biological implications of adaptive responses and bystander effects for individual and population dose-response curves. Invited presentation at Annual Meeting of the Society of Toxicology, Salt Lake City, UT, March 11, 2003.

Conolly, R. B. (2003). Principles of physiologically based pharmacokinetic (PBPK) modeling. Presentation at Department of Pharmacology and Toxicology, University of Wurzburg, Wurzburg, Germany, February 17–20, 2003.

Conolly, R. B. (2003). Quantifying uncertainty: PBPK modeling, Monte Carlo. Presentation at Department of Toxicology, North Carolina State University, Raleigh, NC, February 6, 2003.

- Conolly, R. B. (2003). Principles of risk assessment. Presentation at Department of Toxicology, North Carolina State University, Raleigh, NC, January 30, 2003.
- Conolly, R. B. (2003). Clonal growth modeling. Workshop instructor at Colorado State University, Fort Collins, CO, January 6–8, 2003.
- Andersen, M. E. (2002). Systems biology approaches for assessing risks of endocrine active compounds. Invited presentation at Michigan Section of the Society of Toxicology, Michigan State University, East Lansing, MI, November 1, 2002.
- Andersen, M. E. (2002). Mechanistic approaches to mixture risk assessment. Plenary speaker at International Conference on Chemical Mixtures, Atlanta, GA, September 10, 2002.
- Conolly, R. B. (2002). Principles of risk assessment. Invited presentation at GlaxoSmithKline, Research Triangle Park, NC, June 18, 2002.
- Conolly, R. B. (2002). Biologically motivated computational modeling of dosimetry and mode of action: using mechanistic data to reduce risk assessment uncertainty. Invited presentation at U. S. Environmental Protection Agency Environmental Effects Research Laboratory, Duluth, MN, April 3, 2002.
- Conolly, R. B. (2002). Toxicology: moving from the qualitative to the quantitative. Invited presentation at Life Sciences 2002—First SIAM Conference on the Life Sciences, Boston, MA, March 8, 2002.
- Greenlee, W. F. (2002). Recasting the toxicology paradigm: a systems biology perspective. Invited presentation at Department of Pharmacology & Toxicology, The Brody School of Medicine, East Carolina State University, Greenville, NC, October 29, 2002.
- Greenlee, W. F. (2002). Risk assessment implications of non-linear dose-responses. Invited plenary presentation at Conference on Non-Linear Dose-Response Relationships in Biology, Toxicology, and Medicine, University of Massachusetts, Amherst, MA, June 11–13, 2002.
- Conolly, R. B. (2001). Pharmacodynamic modeling. Invited presentation and eight-hour lecture and computer laboratory, at Workshop on Physiologically-Based Pharmacokinetic/Pharmacodynamic Modeling and Risk Assessment, Colorado State University, Fort Collins, CO, July 25, 2001.
- Conolly, R. B. (2001). Biologically based modeling and uncertainty analysis in risk assessment. Invited presentation at 9th International Congress of Toxicology (ICT-IX), Brisbane, Australia, July 8–12, 2001.
- Conolly, R. B. (2001). The use of modelling and probabilistic approaches in risk assessment. Invited presentation at 9th International Congress of Toxicology (ICT-IX), Brisbane, Australia, July 8–12, 2001.
- Conolly, R. B. (2001). Biologically based modeling and risk assessment course. Instructor at National Industrial Chemical Notification and Assessment Scheme (NICNAS), Sydney, Australia, July 5–6, 2001.
- Conolly, R. B. (2001). Quantifying uncertainty: PBPK modeling, Monte Carlo. Lecture in Toxicology course, North Carolina State University, Raleigh, NC, February 8, 2001.

Peer-reviewed publication(s):

Clewell, H. J., Gentry, P. R., Kester, J. E., and Andersen, M. E. (2005). Evaluation of physiologically based pharmacokinetic models in risk assessment: An example with perchlorethylene. *Crit. Rev. Toxicol.* 35: 413–433.

Dennison, J. E., Andersen, M. E., and Yang, R. S. H. (2005). Pitfalls and related improvements of *in vivo* gas uptake pharmacokinetic experimental systems. *Inhal. Toxicol.* 17: 539–548.

Dybing, E., Farmer, P. B., Andersen, M., Fennell, T. R., Lalljie, S. P. D., Mueller, D. J. G., Olin, S., Petersen, B. J., Schlatter, J., Scholz, G., Scimeca, J. A., Slimani, N., Tornquist, M., Tuijtelaars, S., and Verger, P. (2005). Human exposure and internal dose assessments of acrylamide in food. *Food Chem. Toxicol.* 43: 365–410.

Clark, L. H., Schlosser, P. M., and Selgrade, J. F. (2003). Multiple stable periodic solutions in a model for hormonal control of the menstrual cycle. *Bull. Math. Biol.* 65: 157–173.

Other publications:

Andersen, M. E., Reddy, M. B., Clewell, H. J., III, and Yang, R. S. H. (2005). Conclusions and future directions. In *Physiologically Based Pharmacokinetic Modeling: Science and Applications* (Reddy, M. B., Yang, R. S. H., Clewell, H. J., III, and Andersen, M. E., editors), pp. 389–399, John Wiley & Sons, Hoboken, NJ.

Andersen, M. E., Yang, R. S. H., Clewell, H. J., III, and Reddy, M. B. (2005). Introduction: A historical perspective of the development and applications of PBPK models. In *Physiologically Based Pharmacokinetic Modeling: Science and Applications* (Reddy, M. B., Yang, R. S. H., Clewell, H. J., III, and Andersen, M. E., editors), pp. 1–18, John Wiley & Sons, Hoboken, NJ.

Bae, D. S., Andersen, M. E., and Clewell, H. J., III. (2005). Halogenated alkenes. In *Physiologically Based Pharmacokinetic Modeling: Science and Applications* (Reddy, M. B., Yang, R. S. H., Clewell, H. J., III, and Andersen, M. E., editors), pp. 55–78, John Wiley & Sons, Hoboken, NJ.

Dennison, J. E. and Andersen, M. E. (2005). Reactive vapors in the nasal cavity. In *Physiologically Based Pharmacokinetic Modeling: Science and Applications* (Reddy, M. B., Yang, R. S. H., Clewell, H. J., III, and Andersen, M. E., editors), pp. 119–140, John Wiley & Sons, Hoboken, NJ.

Lutz, W. K., Gaylor, D. W., Conolly, R. B., and Lutz, R. W. (2005). Nonlinearity and thresholds in dose-response relationships for carcinogenicity due to sampling variation, logarithmic dose scaling, or small differences in individual susceptibility. *Toxicol. Appl. Pharmacol.* 27: S565–S569.

Reddy, M. B., Yang, R. S. H., Clewell, H. J., III, and Andersen, M. E. (2005). *Physiologically Based Pharmacokinetic Modeling: Science and Applications*. (Reddy, M. B., Yang, R. S. H., Andersen, M. E., and Clewell, H. J., III, editors), John Wiley & Sons, Inc., Hoboken, NJ, 420 pp.

Yang, R. S. H. and Andersen, M. E. (2005). Mixtures. In *Physiologically Based Pharmacokinetic Modeling: Science and Applications* (Reddy, M. B., Yang, R. S. H., Clewell, H. J., III, and Andersen, M. E., editors), pp. 349–373, John Wiley & Sons, Hoboken, NJ.

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