INCLUSION OF "OMICS" DATA IN MODEL DEVELOPMENT FOR THE NERVOUS SYSTEM. Rory B. Conolly, *National Center for Computational Toxicology, U.S. EPA, Research Triangle Park, NC 27711, U.S.A.*

Physiologically based pharmacokinetic (PBPK) models quantify how anatomical, physiological, and biochemical factors influence the relationship between external dose and the amount of chemical reaching key target sites within the body. Systems biology and the "omic" technologies now provide a capability for describing at the biochemical level the pharmacodynamic relationship between a chemical at its target site and the ultimate biological effect. For example, computational models for signaling pathways such as MAPK and NF-κB have been developed. These models generate interesting dynamic behaviors including oscillations, bistability, history-dependence, and switch-like dose-response. While the available data describing the scale-up of these behaviors to all the cells in a tissue is limited, some reports suggest that signaling-mediated behaviors across large numbers of cells are coordinated. For example, the induction of hepatic CYP1A1 and 1A2 in rats exposed to TCDD spread from the central vein outwards as the dose of TCDD was increased. The interface between induced and uninduced cells was distinct, indicating that the responses of individual cells were coordinated. This behavior is consistent with bistable behavior of the network that controls CYP 1A1 and 1A2 levels in rat liver, with TCDD providing the extracellular signal that coordinates the responses of individual cells. Computational models of signal transduction pathways and other biochemical networks can thus be developed as natural extensions of PBPK models, providing more mechanistically-based descriptions of the entire exposure-tissue dose-response continuum. *This work was reviewed by EPA and approved for publication but does not necessarily reflect official Agency policy.*