PBPK Models, BBDR Models, and Virtual Tissues: How Will They Contribute to the Use of Toxicity Pathways in Risk Assessment? Rory Conolly, Imran Shah, and Thomas Knudsen. National Center for Computational Toxicology, Office of Research and Development, U.S. EPA, Research Triangle Park, NC 27711, USA.

Accuracy in risk assessment, which is desirable in order to ensure protection of the public health while avoiding over-regulation of economically-important substances, requires quantitatively accurate, *in vivo* descriptions of dose-response and time-course behaviors. This level of detailed characterization is desirable when substances are economically-important or environmentally persistent. The NAS toxicity testing report emphasizes *in vitro* studies, with bioinformatics and systems modeling approaches used to predict *in vivo* behavior. PBPK and BBDR models and virtual tissues (VT) will all be important in these extrapolations. PBPK models describe the relationship between external exposure and target site dose. BBDR models extend PBPK models to include the linkage between target site dose, key events and endpoint effect. These mathematical models typically have compartments that correspond to whole tissues (e.g. liver, kidney, lung) and typically contain limited tissue-specific data. VT models such as EPA's v-Liver^{TM} and v-Embryo^{TM} projects are computational models that will encode sufficient biological information to support significant predictive capabilities, with higher-level behaviors emerging from the structures encoded at more fundamental levels of organization. PPBK, BBDR and VT models are thus complementary to one another, with each having the ability to facilitate the interpretation of *in vitro* data with respect to *in vivo* significance and predicting dosimetry at finer levels of biological detail. This enhanced capability will help to identify (1) the doses or concentrations for *in vitro* studies that correspond to realistic levels of exposure *in vivo*, (2) relevant descriptions of the tissue dose-endpoint response continuum, and (3) will contribute to pathway-based assessment of specific biological processes and toxicities. *Although this work was reviewed by EPA and approved for publication, it may not necessarily reflect official Agency policy.*