UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

COMPUTATIONAL TOXICOLOGY

PBPK Models, BBDR Models, and Virtual Tissues: How Will They Contribute to the Use of Toxicity Pathways in Risk Assessment?

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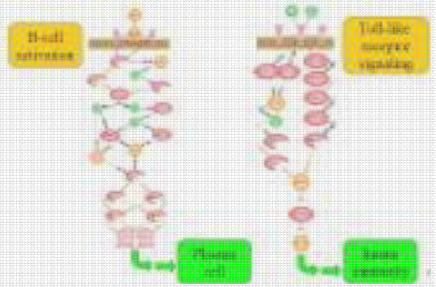
Introduction

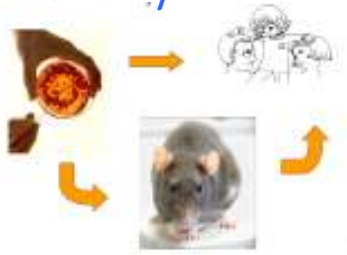
Poster #13 by Edwards et al., "Toxicity Pathway-Based Model of Action Modeling for Risk Assessment" describes the overall strategy being used by the EPA to develop a toxicity pathway-based approach to risk assessment. In this poster we consider (1) the similarities and differences between toxicity pathways and modes of action and (2) the relative capabilities of the main types of biologically based computational models (PBPK, BBDR, and virtual tissues) that will be used in this effort.

Toxicity pathways



Two examples of toxicity pathways. These are canonical B-cell differentiation, Toll-like receptor signaling pathways, which are associated with specific adverse effects in humans (e.g. immune deficiency, chronic inflammatory disorders). Though not shown here, crosstalk between pathways also may be important in the development of health effects. HTS *in vitro* assays can identify chemicals (e.g., TCDD) that perturb these pathways and present potential human risks.

Extrapolations

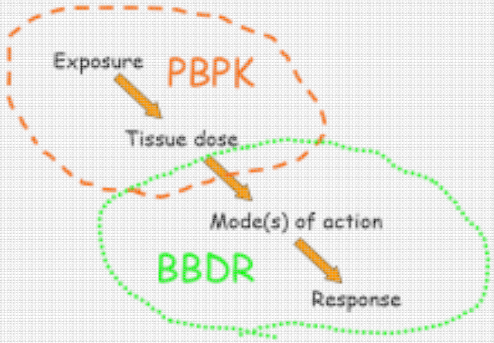


Toxicity pathway assays using human cells would only require *in vitro* → *in vivo* extrapolation to assess human risk. For assays derived from laboratory animals, however, validation of the *in vitro* → *in vivo* extrapolation would be facilitated by the relative ease of obtaining data *in vivo*, and by the availability of genetic models. The challenge of cross-species extrapolation would remain.

Modes of action and toxicity pathways

A mode of action (MoA) is defined as a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation (or a noncancer toxicity). A mode of action thus links dose with adverse health effect, while a toxicity pathway starts with dose but extends only to a key event that can be measured *in vitro* and that is a surrogate for an *in vivo* health effect. The mode of action thus encompasses and extends the toxicity pathway. A major challenge in implementing the NAS vision will be to understand how to extrapolate accurately from measurements of key events measured in toxicity pathways to *in vivo* health effects endpoints.

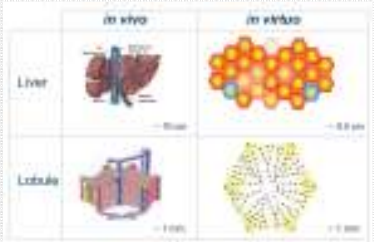
PBPK and BBDR models



Physiologically based pharmacokinetic (PBPK) and biologically based dose response (BBDR) models. PBPK models use the environmental concentration or applied dose as an input and predict tissue dose. This information can be used to help ensure the relevance of toxicant concentrations used *in vitro* to measure perturbations of key events in toxicity pathways. A BBDR model extends a PBPK model by linking from tissue dose to a sequence of one or more key events in a toxicity pathway and from the final key event in the sequence to the adverse health effect. The sequence of key events and related health effect together comprise the mode of action. Since BBDR models encompass the complete exposure-response continuum, they can predict dose-response and time-course behaviors to support risk assessments.

Virtual tissues

A sufficiently detailed description of a biological system at a given level of organization – molecular, cellular, etc. – will generate emergent behavior at the next higher level of organization. Research to develop a virtual tissue focuses on identifying the critical components (agents) of the tissue at, for example, the molecular level, then specifying how they are arranged spatially and how they interact with each other. When encoded in a computer program as a dynamical system, biological behaviors at higher levels of organization will emerge. The fidelity of these emergent behaviors is a test of the validity of the lower-level description. In this manner we conduct research *in silico* to better understand biological structure and function. Virtual tissues will provide coverage of multiple toxicity pathways and will provide a capability for predicting modes of action and the adverse health effects of toxicants.



Capabilities of PBPK and BBDR models and virtual tissues

	PBPK	BBDR	Virtual tissue
Tissue dose	++++	++++	++++
Cellular-level dose	-	-	++++
Representation of toxicity pathways	+	++	++++
Representation of mode of action	-	+++	+++
Data requirements	+	++	++++
Chemical-specific	+++	+++	-
Generate emergent behaviors that provide insight into normal biology and mechanisms of toxicity	+	++	++++
Use in extrapolation across species	+++	+++	++++
Use in risk assessment	++++	++	-

Virtual tissues, PBPK and BBDR models

Virtual tissues will recapitulate tissue structure and function and, to some extent, provide predictive capabilities currently only available from tissue-based experiments. Since both PBPK and BBDR models depend heavily on data from *in vitro* and *in vivo* experiments, virtual tissues hold the promise of becoming powerful tools to support tissue dosimetry and dose-time-response modeling in support of risk assessments. We can also expect that virtual tissues, as they increase in sophistication, will be able to predict qualitative and quantitative, tissue-specific aspects of toxicity directly, without reference to whole-body PBPK or BBDR models.