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Toxicokinetics to identify nonlinearities in dose-response and implications for risk assessment.

Rory Conolly, Office of Research and Development, U.S. EPA, Research Triangle Park, North Carolina, USA.

Development of exposure guidelines that are health protective but not unnecessarily stringent requires a good understanding of nonlinearities in dose-response curves. The last 30 or so years have witnessed the development of physiologically based pharmacokinetic (PBPK) modeling as a powerful approach for identifying the biological bases of nonlinearities in dosimetry and for providing a predictive capability for scenarios when data are lacking. Nonlinearities are functions of (1) the inherent chemical characteristics of the toxicant (e.g., susceptibility to biotransformation) and (2) the organism-specific biology that determines target site dose and the pathway linking dose with an adverse outcome (e.g., inhibition of CYP19A, which converts testosterone to estradiol, is linked to altered fecundity). In this presentation I will describe the key steps in development of nonlinear PBPK models and consider how uncertainties in model structure and parameterization can be addressed. This latter point is crucial if PBPK and other types of biologically motivated computational models are to find routine acceptance by regulators. It is often the perception that model uncertainties are unacceptably large that fosters a reluctance to use the models to support regulatory decision making. I will argue that, rather than quantitative analysis of model uncertainty using, for example, Bayesian or Monte Carlo techniques, a more practical approach would be to simply rank the uncertainties of PBPK model and alternative default relative to each other. For example, how would we rank the relative uncertainty of rat to human extrapolation of chloroform dosimetry performed using (1) a PBPK model or (2) a default uncertainty factor? As long as development of the computational model is well documented, the computer code has been thoroughly checked, and the model has been shown to be able to predict data that were not used for model development, then this relative ranking approach should provide a practical route to more routine use of PBPK modeling in support of regulatory decision making. *This is an abstract or a proposed presentation and does not necessarily reflect EPA policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.*