IVIVE: The Role of Pharmacokinetic Model Evaluation

Lisa Sweeney, Ph.D.
Naval Medical Research Unit Dayton
Jackson Foundation for the Advancement of Military Medicine

Emerging approaches in human health risk assessment rely on determination of biologically effective concentrations in a suite of high throughput screening (HTS) in vitro assays. Even in the absence of in vivo toxicity data to "anchor" in vitro biologically effective doses, it is possible to place in vitro toxicity data into a risk context by using pharmacokinetic models to estimate the human intake (e.g., mg/kg/day) that would produce a risk-relevant internal dose. Internal dosimetry can be computed either from validated pharmacokinetic models of varying complexity or predicted from relatively simplistic pharmacokinetic models parameterized via in silico predictive algorithms and limited in vitro data (e.g., plasma protein binding and clearance by hepatocytes). Since pharmacokinetic models are the key linkage to extrapolate from an in vitro effective dose to a real-world exposure of potential concern, it is important to consider the level of confidence in the model before using it in decision making. To assess model confidence, the following characteristics should be evaluated: suitability for the current intended use (e.g., exposure routes, suitable dose metrics), biological realism, adequately verifiable mathematical description and computational implementation, parameter analysis (e.g., basis and sensitivity) and validation (e.g., parallelogram approach, read-across), and anticipated variability/uncertainty in model predictions. While these considerations for model evaluation are not unique to the application of models to IVIVE, a greater reliance on in vitro and in silico data represents an important paradigm shift in toxicology and risk assessment, and therefore must be taken into consideration in assessing suitability of models for application to specific purposes.