Continuous Toxicological Dose-Response Relationships Are Pretty Homogeneous

R. Woodrow Setzer, National Center for Computational Toxicology, US Environmental Protection Agency, Research Triangle Park, NC, USA; Wout Slob, National Institute of Public Health and the Environment (RIVM), Bilthoven, The Netherlands

Dose-response relationships for a wide range of in vivo and in vitro continuous datasets are well-described by a four-parameter exponential or Hill model, based on a recent analysis of multiple historical dose-response datasets, mostly with more than five dose groups (Slob and Setzer, 2014). Furthermore, the estimated shape parameters for the sigmoid models fall within narrow ranges that depend on endpoint and whether the study was in vivo or in vitro. Based on this work, we suggest that the bulk of model uncertainty for continuous endpoints can be covered by parameter uncertainty in Hill or four-parameter exponential models. Using the observed regularity of shape parameters as prior information in Bayesian fits allows sigmoid models to be fit even to datasets with inadequate numbers of doses, or suboptimal dose placement. Additionally, among-dose-group variability was evident over all the datasets. This renders conventional goodness-of-fit tests unreliable, and may unduly influence BMD estimates unless an appropriate error model which includes a hierarchical error component is used. We demonstrate some examples of fitting such a model to simulated and real datasets. This abstract does not necessarily reflect U.S. EPA policy.