Assessing Interval Estimation Methods for Hill Model Parameters in a High-Throughput Screening Context

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The Hill model of concentration-response is ubiquitous in toxicology, perhaps because its parameters directly relate to biologically significant metrics of toxicity such as efficacy and potency. Point estimates of these parameters obtained through least squares regression or maximum likelihood are commonly used in high-throughput risk assessment, but such estimates typically fail to include reliable information concerning confidence in (or precision of) the estimates. To address this issue, we examined methods for assessing uncertainty in Hill model parameter estimates derived from concentration-response data. In particular, using a sample of ToxCast concentration-response data sets, we applied four methods for obtaining interval estimates that are based on asymptotic theory, bootstrapping (two varieties), and Bayesian parameter estimation, and then compared the results. These interval estimation methods generally did not agree, so we devised a simulation study to assess their relative performance. We generated simulated data by constructing four statistical error models capable of producing concentration-response data sets comparable to those observed in ToxCast. We then applied the four interval estimation methods to the simulated data and compared the actual coverage of the interval estimates to the nominal coverage (e.g., 95%) in order to quantify performance of each of the methods in a variety of cases (i.e., different values of the true Hill model parameters). In general, we found that although confidence intervals produced by the various methods tended to have similar widths, certain interval estimation methods tended to be more reliable (in that actual coverage matched nominal coverage) in certain categories of situations (which we have characterized). No single method, however, tended to be more reliable than others in all situations. This work demonstrates a framework for obtaining interval estimates for potency and efficacy parameters, and thus provides a better means for quantifying uncertainty in risk decisions. (This abstract does not necessarily reflect EPA policy.)

Keywords: Parameter estimation, confidence intervals, high-throughput screening, Bayesian methods, bootstrapping, concentration-response data