Variability within Systemic *In Vivo* Toxicity Studies

Ly L. Pham[1]; Woodrow, Setzer[2]; Martin, Matt[2]

[1]ORISE Fellow, RTP/EPA

[2]National Center for Computational Toxicology, Office of Research and Development, U.S. Environmental Protection Agency, RTP, NC

Email: pham.lyly@epa.gov

In vivo studies have long been considered the gold standard for toxicology screening. Often time models developed in silico and/or using *in vitro* data to estimate points of departures (POD) are compared to the *in vivo* data to benchmark and evaluate quality and goodness-of-fit. However, recent work has illustrated that currently available in vivo data are not without flaws and inherent variance presents a challenge in predictive modeling. The goal of the current work was to characterize the amount of variance that exists within systemic *in vivo* data. The present study was done using the US EPA's Toxicity Reference Database (ToxRefDB) which contains around 5,000 *in vivo* toxicity studies from the Office of Pesticide Programs (registrant-submitted studies), National Toxicology Program, pharmaceutical industries, and publically available literature covering over 1,000 chemicals. Using multilinear regression to calculate the residual sum or squares, we accounted for known variability in study conditions to quantify the unexplained variance of the $\log_{10}$(POD) to be about 0.35. The leave-one-out method was used to assess the amount of variance explained by various study conditions (e.g., species, purity of test material) and chemicals were found to be the biggest contributor. Stratifying the dataset by species and administration methods showed similar results, indicating stability of the unexplained variance. Considering and quantifying the unexplained variance will provide a benchmark and lower bounds on the mean-square-error for predictive toxicity model development. This work provides an upper bound on the level of precision predictive models can attain when trained on conventional PODs.

This abstract does not necessarily reflect U.S. EPA policy.