Variability within Systemic *In Vivo* Toxicity Points-of-Departure

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In vivo studies have long been considered the gold standard for toxicology screening and deriving points of departure (POD). With the push to decrease the use of animal studies, predictive models using in vivo data are being developed to estimate POD. However, recent work has illustrated that currently available *in vivo* data are not without variability and error. This presents a challenge for predictive modeling efforts. The first goal of the current work was to characterize and quantify explained and unexplained variability within systemic *in vivo* POD values. The second goal was to characterize the degree to which groups based on chemical fingerprints can account for variance of PODs among studies. 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 National Toxicology Program, pharmaceutical industries, and publically available literature covering over 1,000 chemicals. We used multilinear regression and analysis of variance (ANOVA) to account for known variability due to study conditions (e.g., species, strain, study type, dose spacing) and estimate the unexplained variability of the $\log_{10}$(POD) to be 0.33. The variance among chemical treatments is about 0.46, while the other study conditions explain substantially less of the variance. Stratifying the dataset by chemical class showed similar results, indicating stability of the ANOVA. In the second analysis, chemicals where then grouped by toxprint chemotypes using k-means clustering. Replacing individual chemicals with unsupervised chemical groupings based on structural fingerprints produced greater unexplained variance across varied numbers of clusters. The naïve structural similarity only accounts for a small amount of variability and further supports the challenges of developing predictive models of conventional PODs. Our estimate of unexplained variance defines an upper bound on the precision that can be obtained on predictions from toxicity models trained on conventional PODs derived from *in* vivo data.

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