Predictive Model of Systemic Toxicity

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In an effort to ensure chemical safety in light of regulatory advances away from reliance on animal testing, USEPA and L'Oréal have collaborated to develop a quantitative systemic toxicity prediction model. Prediction of human systemic toxicity has proved difficult and remains a gap in chemical safety assessment using alternative approaches. By leveraging multiple data sources including high-throughput screening (ToxCast HTS) and chemical descriptor and property (ToxPrint) data, a predictive model of systemic point-of-departures (POD, e.g., LOAEL or LEL) was developed. The model specifically predicts the study-level POD using data from roughly 3000 studies across nearly 600 chemicals. Systemic POD were curated in ToxRefDB from numerous study types, across multiple species and dose administration methods. Rather than attempt to adjust all POD to a single species or strain or dose duration or study type or administration method, these ToxRefDB parameters were included as covariates in the modeling process. Using Random Forest modeling, ToxRefDB covariates alone accounted for roughly 6% of the variance in the test set data. A model developed only with ToxCast HTS or ToxPrint data accounted for 44% of the variance, whereas a model developed using ToxRefDB covariates, ToxCast and ToxPrint data accounted for 53% of the variance; with a +/- 1-log confidence interval. The combination of covariates and features explain more variance in the data than either do individually, demonstrating the advantage of incorporating ToxRefDB covariates into the modeling process instead of adjusting POD a priori. The final resulting model was also enriched for features measuring xenobiotic metabolism gene expression as well oxidative stress markers demonstrating the importance for accounting for kinetics and non-specific bioactivity in predicting systemic toxicity. Herein, we have generated an externally predictive model of systemic toxicity capable of being used as a safety assessment tool. *This abstract does not necessarily represent EPA policy.*