Abstract submitted for Society of Toxicology 2010 annual meeting Salt Lake City, UT March 8-11

Predictive Signatures from ToxCast Data for Chronic, Developmental and Reproductive Toxicity Endpoints

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The EPA ToxCast program is using in vitro assay data and chemical descriptors to build predictive models for in vivo toxicity endpoints. In vitro assays measure activity of chemicals against molecular targets such as enzymes and receptors (measured in cell-free and cell-based systems in binding, agonist and antagonist modes), in addition to cellular phenotypes and pharmacokinetic-related parameters. Over 600 separate assays were run in concentration response format to derive AC50 or LEC values for each chemical-assay combination. This collection of AC50 values were used to build statistically significant predictors of in vivo toxicity endpoints derived from chronic/carcinogenicity studies in rats and mice, prenatal developmental toxicity studies in rats and rabbits, and two-generation reproduction studies in rats. A collection of 309 unique chemicals were tested and used for predictive signature development. Several machine learning techniques were used to build multivariate predictive signatures: stepwise logistic regression, linear discriminant analysis, neural networks and support vector machines. K-fold cross validation was performed to quantify prediction accuracy. Three sets of mechanistic signatures will be presented. The first is for chronic rat liver proliferative lesions based on assays for targets in the peroxisome proliferator activating receptor (PPAR) pathway. The second is for prenatal cleft palate in rat fetuses based on assays targeting pathways for Wnt, retinoids, AhR, TGF-beta, glucocorticoids and chemokines. The third are for testicular toxicity seen in rat reproduction studies and based on in vitro assays, pathways and chemical descriptors. These models display high specificity (few false positives) but only moderate sensitivity (multiple false negatives). This behavior is expected because each model detects particular molecular-level mechanisms of toxicity, whereas multiple mechanisms of action can lead to the same overall animal-level phenotype. *This work may not necessarily reflect official Agency policy.*