A MODE-OF-ACTION-BASED QSAR APPROACH TO IMPROVE UNDERSTANDING OF DEVELOPMENTAL TOXICITY

Yang, Chihae[1]; Worth, Andrew P.[2;] Arvidson, Kirk B.[3]; Richard, Ann M.[4]

[1] Altamira, LLC, Columbus, OH, USA; [2] JRC-IHCP, Ispra, Italy; [3] CFSAN, OFAS, U.S. FDA, College Park, MD USA; [4] NCCT, ORD, U.S. EPA, Research Triangle Park, NC, USA

QSAR models of developmental toxicity (devtox) have met with limited regulatory acceptance due to the use of ill-defined endpoints, lack of biological interpretability, and poor model performance. More generally, the lack of biological inference of many QSAR models is often due to a disconnect between the training sets and modeling activities. To this end, we initiated a mode-of-action (MoA) QSAR approach in which biological context and interpretation guide the construction of training sets and selection of descriptors. We previously implemented the MoA concepts of DNA electrophilic reactivity and interactions involved in mutagenicity, clastogenicity, and rodent tumorigenicity into the FDA CFSAN Chemical Evaluation and Risk Estimation System (CERES). We here extend this approach to a new set of MoA QSAR models and chemotypes for developmental defects in prenatal devtox studies. A consolidated devtox database was created from several high quality databases, including ToxRefDB, FDA drugs/food additives, and ILSI DevTox. Based on these data, mechanistically-based QSAR training sets for particular phenotypic effects (e.g., cleft palate) were created by grouping chemicals using high-level biological events linked to putative toxicity pathways. An example is presented of MoA categories built from ToxCast and literature-based evidence of chemical interactions with nuclear hormone receptors, e.g. thyroid, androgen, estrogen, glucocorticoid, retinoid, and steroidogenic factors. These MoA categories are linked to offspring morphology phenotypes; classifiers (defined by structural rules and phys-chem properties) are developed for chemicals that were not maternally toxic at doses producing effects. Finally, the MoA classification models are combined to produce an overall weight-of-evidence prediction, which effectively conveys model results with mechanistic insights, compatible with the workflow of toxicologists in safety/risk assessment.
This abstract does not necessarily reflect EPA, FDA or JRC policy.