Validation, acceptance, and extension of a predictive model of reproductive toxicity using ToxCast data

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The EPA ToxCast research program uses a high-throughput screening (HTS) approach for predicting the toxicity of large numbers of chemicals. Phase-I tested 309 well-characterized chemicals (mostly pesticides) in over 500 assays of different molecular targets, cellular responses and cell-states and Phase-II is testing another roughly 700 chemicals. Using ToxCast Phase-I data, a predictive model of reproductive toxicity was generated capable of externally predicting rodent reproductive toxicity, as observed in multigeneration toxicity tests, with over 75% accuracy (Martin et al. Biology of Reproduction, under final review). New ToxCast Phase-II chemicals and assays are being used to further validate the model, identify strengths and weaknesses, and, where appropriate, update the model with additional assays covering existing molecular targets in the model or new targets associated with reproductive toxicity. The current model is a classification model sufficient for large-scale chemical testing prioritization and begins to infer modes of action, e.g., estrogenicity, anti-androgenicity, or altering steroid metabolism. The model also has transparent inputs and outputs that are biologically translatable improving the chances for the model's acceptance and use in chemical testing prioritization and targeted testing applications. Extension of the model toward risk assessment applications requires incorporation of toxicokinetic and cell-level information where quantitative and dynamic outputs of dose and time can be placed into a systems modeling framework. This abstract does not necessarily reflect US EPA policy.