Using ToxCast/Tox21 Assays and QSAR Modeling to Predict Androgen Receptor Pathway Activity

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The Tox21 and ToxCast programs include *in vitro* assays conducted in a high-throughput screening (HTS) format. Many are relevant to the androgen receptor (AR) pathway and can identify substances with potential androgenic/anti-androgenic activity *in vivo*. Here we used nine of these assays to build a mathematical model to distinguish true AR pathway activity from technology-specific assay interference. The assay battery probed perturbations of the AR pathway at multiple points (receptor binding, cofactor recruitment, gene transcription and protein production) in multiple cell types. We compiled a list of putative AR reference chemicals from the ICCVAM and OECD reference chemical lists. Chemicals included agonists, antagonists, selective androgen receptor modulators (SARMs), and inactive chemicals. The model showed 96% (23/24) concordance with reference data, including successfully identifying multiple SARMs with both agonist and antagonist activity. The model identified as agonists or anatagonists all chemicals in the ToxCast library known to specifically target AR. However, fluoranthene, a SARM, was active in the cofactor recruitment assays but none of the other AR pathway assays, and was therefore mispredicted by the model as acting via an assay-specific interference pathway. We will discuss patterns of assay activity and pathway predictions across 1846 ToxCast chemicals and identify those predicted to be active against the AR pathway. The results from the AR pathway model were used to train and build a cross-validated quantitative structure activity relationship (QSAR) model for AR binding and used to make predictions for 30,000 chemicals. Where available, we compared *in vitro* and *in silico* predictions to toxicity data from the literature to identify potential trends relating to use case and exposure scenarios. *This project was funded in whole or in part with Federal funds from the NIEHS, NIH under Contract No.HHSN27320140003C and does not represent EPA or NIEHS policy.*