**Application of computational and high-throughput *in vitro* screening for prioritization**

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**Abstract**: There are tens of thousands of man-made chemicals to which humans are exposed, but only a fraction of these have the extensive *in vivo* toxicity data used in most traditional risk assessments. This lack of data, coupled with concerns about testing costs and animal use, are driving the development of new methods for assessing the risk of toxicity. These methods include the use of *in vitro* high-throughput screening assays and computational models. This talk will review a variety of high-throughput, non-animal methods being used at the U.S. EPA to screen chemicals for their potential to be endocrine disruptors as part of the Endocrine Disruptor Screening Program (EDSP). These methods all start with the use of *in vitro* assays, e.g. for activity against the estrogen and androgen receptors (ER and AR) and targets in the steroidogenesis and thyroid signaling pathways. Because all individual assays are subject to a variety of noise processes and technology-specific assay artefacts, we have developed methods to create consensus predictions from multiple assays against the same target. The goal of these models is to both robustly predict *in vivo* activity, and also to provide quantitative estimates of uncertainty. This talk will describe these models, and how they are validated against both *in vitro* and *in vivo* reference chemicals. The U.S. EPA has deemed the *in vitro* ER model results to be of high enough accuracy to be used as a substitute for the current EDSP Tier 1 *in vivo* uterotrophic assay. Issues with developing these reference chemical sets will also be discussed – this is a critical component in the validation of any new method. Because the data on which reference chemical activity is based is itself variable, consistent and objective approaches to develop reference chemical sets need to be developed. Given the validated models for endocrine-related endpoints, we have also worked with a broad set of collaborators to develop multiple QSAR models of ER activity using the consensus *in vitro* model predictions as training data. We find that, just as for *in vitro* assays, the performance of a consensus of QSAR models is more accurate than that of the individual models. By using a combination of these *in vitro* and QSAR models, we have been able to make first-order predictions of the estrogenicity potential for the large majority of the EDSP universe (beyond even what is practical for testing using the in vitro methods), and are currently developing similar methods for the other endocrine-related pathways. *Disclaimer: This abstract does not necessarily reflect U.S. EPA policy.*

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