Development and Application of a Reference Database for Androgen Receptor Activity

N Kleinstreuer[1], P Ceger[1], P Browne[2], D Allen[1], J Hamm[1], W Casey[3]

[1]ILS, RTP, NC, USA; [2]EPA/OSCP, Washington DC, USA;
[3]NIH/NIEHS/DNTP/NICEATM, RTP, NC, USA

Mandated testing of thousands of chemicals to identify those that may act as androgen receptor (AR) agonists or antagonists will cost millions of dollars and take decades to complete using current validated methods. Alternative methods using high-throughput screening (HTS) and computational toxicology technologies, such as those developed in the ToxCast/Tox21 screening programs, can rapidly and inexpensively identify potential androgen-active chemicals. Evaluation of such alternative testing strategies requires high-quality in vitro and in vivo reference data. Here, we describe a literature search for reference data from in vitro AR binding and transactivation (TA) assays. A list of 127 putative androgen-active or inactive chemicals was compiled based on international AR test method validation efforts. We conducted semi-automated literature reviews for in vitro AR binding and TA assays on these chemicals, and extracted data from identified references into a single database. Detailed assay information and results were recorded using a standardized ontology. Data were analyzed for reproducibility and species specificity. Antagonist data were only considered if they included concurrent cytotoxicity evaluations (noted in 55% of assays). Based on quantitative data such as relative binding affinity and TA activity (or inhibitory) concentrations, chemicals with reproducible results were assigned potency ranges. The reference data were used to evaluate performance of nine HTS ToxCast/Tox21 assays that map to the AR pathway and an associated computational model integrating the assays. Reference chemical lists and supporting data will be made available to the public and submitted to OECD via the Validation Management Group-Non-Animal to facilitate international harmonization of AR test method evaluations. *This work does not reflect EPA policy.* *This project was funded in whole or in part with Federal funds from the NIEHS, NIH under Contract No. HHSN273201500010C.*

Keywords: Predictive toxicology, alternatives to animal testing, endocrine; androgens