Title: “New Frontiers in Species Extrapolation: Tools for Toxicology”

Abstract: Cell-based high-throughput screening (HTS) and computational technologies are being applied as tools for toxicity testing in the 21st century. The U.S. Environmental Protection Agency (EPA) embraced these technologies and created the ToxCast Program in 2007, which has served as a screening and prioritization tool for thousands of chemicals. The rapid and automated screening methods take advantage of hundreds of (primarily) mammalian-based HTS assays for identifying biological activity suggestive of potential toxic effects. The data can aid in identifying chemicals that are most likely to impact biological pathways that lead to adverse health effects. To realize the full potential of the ToxCast data for predicting adverse effects to both humans and wildlife, it is necessary to understand how broadly these data may plausibly be extrapolated across species. Therefore, the U.S. EPA Sequence Alignment to Predict Across Species Susceptibility (SeqAPASS) tool was used to evaluate conservation of the 460 protein targets represented in the ToxCast assay suite. The SeqAPASS query sequence was selected based on the model organism used in the ToxCast assay (e.g., human, cattle, chimpanzee, guinea pig, rabbit, rat, mouse, pig, or sheep). Similarity of primary amino acid sequences and sequences from appropriate functional domains were compared across species to understand conservation of each assay target across taxa. To demonstrate application of the SeqAPASS data for extrapolation of ToxCast targets, case studies were developed that focus on the extrapolation of targets being evaluated as part of the Endocrine Disruptor Screening Program, including the androgen receptor, enzymes involved in steroidogenesis, and proteins in thyroid axis function. These case studies demonstrate the utility of SeqAPASS for informing the extrapolation of HTS data and identification of model organisms likely to be suitable for follow-up or complementary in vivo toxicity tests.