Experimental approaches to systematic discovery and development reproductive adverse outcome pathways in fish.

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Adverse outcome pathways (AOPs) are conceptual frameworks that portray causal and predictive linkages between key events at multiple scales of biological organization that connect molecular initiating events and early cellular perturbations (e.g., initiation of toxicity pathways) to adverse outcomes of regulatory significance (i.e., at the individual and/or population level). Proposals to make greater use of high throughput in vitro screening, quantitative structure-activity relationships, and other types of alternative data for screening, prioritization, and hazard assessment are dependent, in part, on the ability to identify major adverse outcome pathways, and develop associated assays and computational tools for predicting and ranking chemical hazards. This presentation will describe a systematic program of research that was undertaken to systematically discover, characterize, and develop AOPs for reproductive toxicity in fish and other vertebrates. Specifically, it illustrates how hypothesis-based experimentation, anchored to conceptual systems, models can guide AOP development. It also examines ways in which toxicogenomic data (i.e., transcriptomics, metabolomics) can be used to accelerate discovery of novel AOPs and improve our understanding of AOPs in a dynamic systems context that considers feedback processes and intersections/interactions between multiple pathways. Although the examples will focus on AOPs for reproductive toxicity in fish, the concepts employed are broadly applicable to a wide range of other adverse outcomes and model systems. *The contents of this abstract neither constitute nor reflect official US EPA policy.*