# A SYSTEMS BIOLOGY APPROACH TO TOXICOLOGY RESEARCH WITH SMALL FISH MODELS

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Increasing use of mechanistically-based molecular and biochemical endpoints and in vitro assays is being advocated as a more efficient and cost-effective approach for generating chemical hazard data. However, development of effective assays and application of the resulting data in quantitative risk assessment will require an improved understanding of the biology underlying response to chemical stressors. Over the past six years, our laboratory has employed a systems biology approach to study responses to endocrine active chemicals using small fish models. Initially, we constructed a graphical model depicting the current state of knowledge regarding regulatory control of the reproductive axis in fish. Eleven chemicals, selected specifically to interact with the reproductive axis via different targets/modes of action, were tested using a three-phased testing strategy. First, a 21 d fathead minnow reproduction assay was conducted and hypothesis-driven approaches to were used to establish linkages, across levels of biological organization, between the chemical mode of action, molecular and biochemical responses, and a reproductive outcome relevant to risk assessment. Second, short-term experiments were performed with zebrafish and Agilent 22k oligonucleotide microarrays were used to conduct unsupervised analyses of impacted pathways and functions, develop novel testable hypotheses, identify putative molecular biomarkers of exposure and/or effect, and reverse engineer transcription factor networks. Finally, time course experiments including both exposure and post-exposure sampling were used to evaluate temporal dynamics and robustness of transcriptomic and metabolomic responses and reverse engineer transcriptional networks for the fathead minnow ovary. Results of these studies are being used to: 1) elucidate adverse outcome pathways relevant for endocrine disrupting chemicals causing reproductive impairment in fish; 2) identify molecular responses with potential predictive or diagnostic utility; 3) evaluate the sensitivity, robustness (as a function of time, exposure concentration, species, etc.) and biological relevance of those responses; 4) improve systems-level understanding of mechanisms of toxicity including direct effects, indirect effects, compensation during exposure, and recovery following exposure; and 5) inform the development of biologically based computational models. This presentation will highlight results of these studies with an emphasis on understanding biological mechanisms that either modulate or manifest chemical toxicity. *This abstract does not necessarily reflect official Agency policy.*