A Systems Biology Approach to Small Fish Ecotoxicogenomics

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At present, a large and integrated effort in the area of ecotoxicogenomics within US Environmental Protection Agency (EPA), Office of Research and Development is a research program titled *Linkage of exposure and effects using genomics, proteomics, and metabolomics in small fish models*. The effort involves collaboration across five EPA divisions and centers, several academic partners, and other US government agencies, notably the Army Engineer Research and Development Center (ERDC). Eleven chemicals known or hypothesized to disrupt reproductive function in fish, through different modes of action, were tested using a three-phased testing approach. 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 abstract does not necessarily reflect official Agency policy.*