Conceptual systems models as tools for hypothesis generation and testing in ecotoxicogenomics research.

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Microarray, proteomic, and metabonomic technologies are becoming increasingly accessible as tools for ecotoxicology research. Effective use of these technologies will depend, at least in part, on the ability to apply these techniques within a paradigm of hypothesis driven research. We propose that conceptual systems models can serve as powerful tools that facilitate hypothesis-based conduct of –omics research. In cases where some *a priori* knowledge of a likely mechanism of action (MOA) is available, conceptual systems models can be used to develop testable hypotheses regarding the effects of chemical exposure on tens to hundreds of genes, proteins, and/or metabolic products. Conceptual systems models can also be used to cluster genes or proteins into functional groups representing various regulatory nodes within the system of interest. Examination of effects on such functional clusters can be used to generate hypotheses regarding the likely MOA of unknown or poorly characterized compounds and/or the likely effect of the –omic changes on higher level function. Examples of these applications are provided using a conceptual model of the teleost brain-pituitary-gonadal (BPG) axis and empirical results from fathead minnow microarray experiments in which reproductively active fathead minnows were exposed to 17β-estradiol or the aromatase inhibitor fadrozole, for 24 h and 7d. Gene expression in gonad and liver was examined using two prototype fathead minnow microarrays, one with 30-mers for 125 unique genes, the other with 60-mers for around 1000 unique genes. We conclude that conceptual systems models represent important tools that can help realize the research potential provided by –omics technologies. Furthermore, application of conceptual systems models in –omics research has potential to generate more accurate and predictive systems models to support ecological risk assessments as well as basic research. *This abstract does not necessarily reflect U.S. EPA policy.*