

# Linkage of Exposure and Effects using Genomics, Proteomics, and Metabolomics in Small Fish Models

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U.S EPA, ORD, Computational Toxicology Research Program

## Science Question

- How can we improve extrapolation across life stages/endpoints (biological levels of organization), species (including under-represented taxa) and from the lab to field for single chemicals and complex mixtures?
- Can we establish functional linkages between changes at the molecular level and phenotypic outcomes relevant for risk assessment for multi-organ biological systems well conserved among vertebrates?
- Can we develop integrated, biologically-based computational models that use mechanism of action as a basis for predicting adverse outcomes?

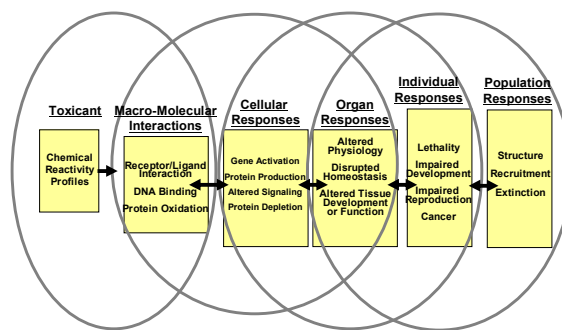
## Research Goals

- Identify novel molecular markers of effects of exposure to chemicals representing different mechanisms of action (MOA) within the vertebrate hypothalamic-pituitary-gonadal (HPG) axis
- Link these biomarkers to responses relevant to ecological risk assessment
- Support development of integrated modeling approaches that utilize MOA as a basis for prediction of adverse outcomes

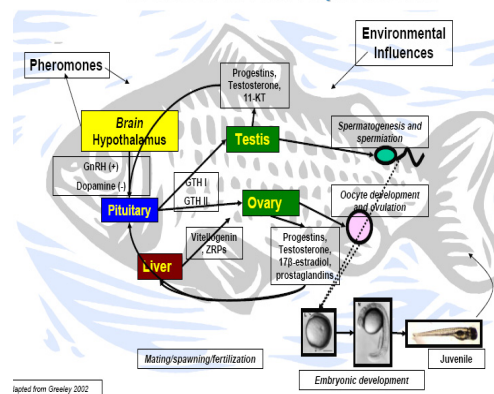
## Specific Approach

- Investigate effects of chemical probes on the HPG axis using definitive tests in the fathead minnow to establish initial toxicity pathways and ecologically-relevant responses (Phase 1)
- Identify transcriptomic, proteomic, metabolomic, and other whole-animal responses to the same chemicals using short-term zebrafish exposures (Phase 2)
- Validate genomic markers in the fathead minnow with an emphasis on time-course of responses and/or compensation and recovery after exposure (Phase 3)
- Concurrently integrate data from above in a systems modeling context, as well as relevant population modeling

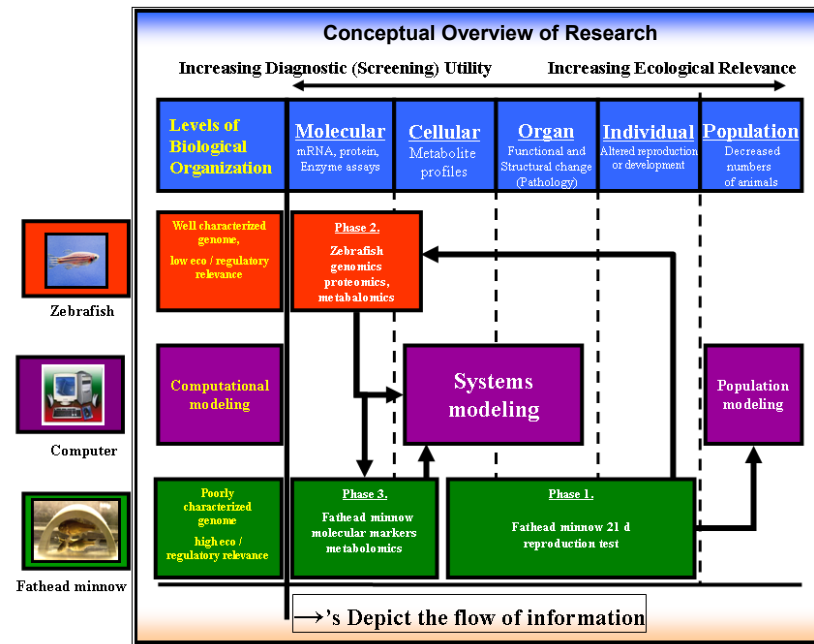
## Defining Toxicity/Adverse Outcome Pathways



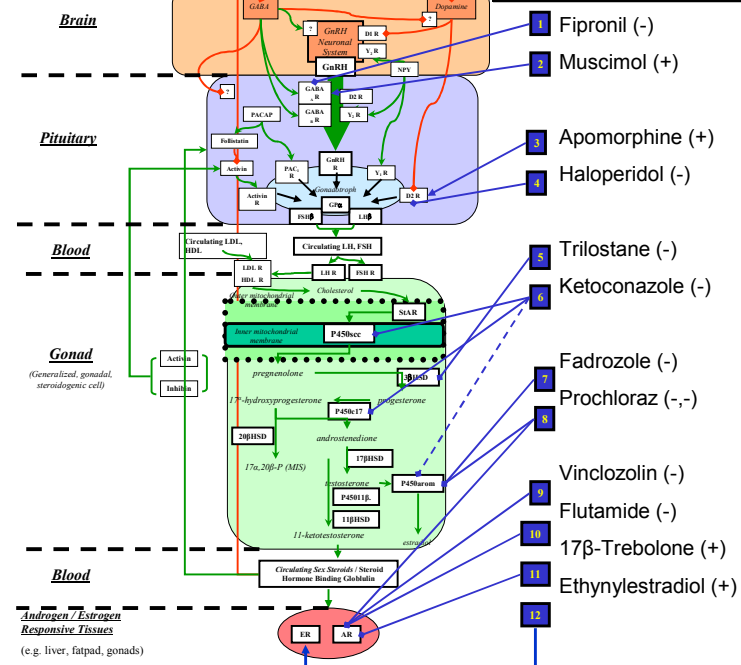
## Overview of Fish Reproduction



## Methods/Approach

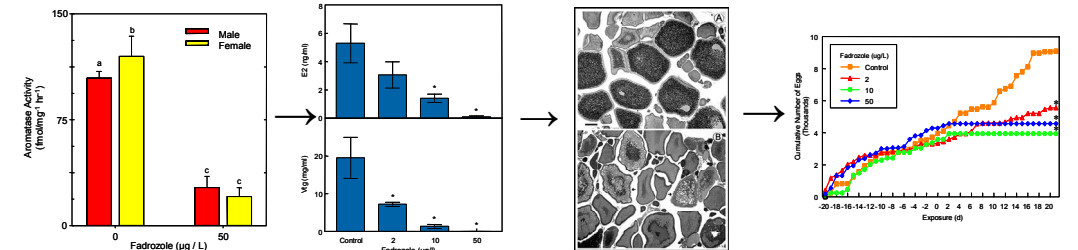


## Chemical "Probes"

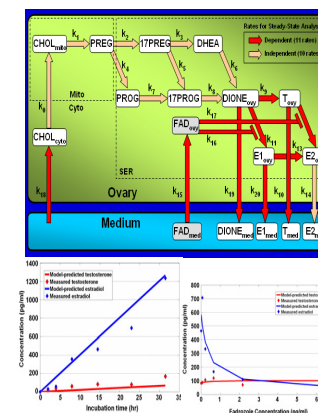


## Results/Conclusions

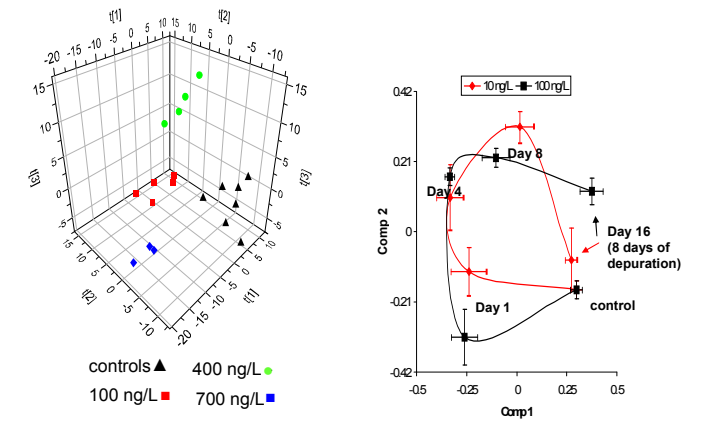
### Definition of Novel Toxicity/Adverse Outcome Pathways (Ankley et al. 2009)



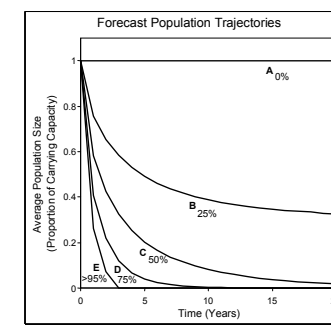
### Computational Model of Vertebrate Steroidogenesis (Breen et al. 2007)



### Metabolomics for Defining Pathways and Exposure Reconstruction (Ekman et al. 2008; 2009)



### Translating Biochemical Alterations into Population-Level Responses (Miller et al. 2007)



### Physiologically-Based Model for Predicting Estrogen Effects on HPG Axis Function (Watanabe et al. 2009)

