LINKAGE OF EXPOSURE AND EFFECTS USING GENOMICS, PROTEOMICS, AND METABOLOMICS IN SMALL FISH MODELS

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Knowledge of possible toxic mechanisms/modes of action (MOA) of chemicals can provide valuable insights as to appropriate methods for assessing exposure and effects, thereby reducing uncertainties related to extrapolation across species, endpoints and chemical structure. However, MOA-based testing seldom has been used for assessing the ecological risk of chemicals. This is in part because past regulatory mandates have focused more on adverse effects of chemicals (reductions in survival, growth or reproduction) than the MOA through which these effects are caused. A recent departure from this involves endocrine-disrupting chemicals (EDCs), where there is a regulatory need for USEPA to understand both MOA and adverse outcomes. To achieve this understanding, advances in predictive approaches are required whereby mechanistic changes caused by chemicals at the molecular level can be translated into apical responses meaningful to ecological risk assessment, such as effects on development and reproduction, and ultimately population-level impacts.

This is a large, integrated project with collaborators from multiple ORD laboratories/centers, other Federal agencies, and several universities (originally through EPA's extramural grants program), that is employing two small fish models, the fathead minnow (*Pimephales promelas*) and zebrafish (*Danio rerio*), to develop better predictive tools for assessing the ecological risk of EDCs. For this work, a systems-based approach is being used to delineate toxicity pathways for 12 model EDCs (muscimol, fipronil, haloperidol, apomorphine, ketoconazole, trilostane, prochloraz, fadrozole, flutamide, vinclozolin, 17β-trenbolone and 17α-ethinylestradiol) with different known or hypothesized toxic MOA. The studies employ a combination of state-of-the-art genomic (transcriptomic, proteomic, metabolomic), bioinformatic and modeling approaches, in conjunction with whole animal testing protocols, to develop response linkages across biological levels of organization, ranging from molecular alterations to population impacts.

This abstract has been reviewed in accordance with the U.S. Environmental Protection Agency's peer and administrative review policies and approved for presentation and publication.