Abstract Title:

Adaptive Response in Female Fathead Minnows Exposed to an Aromatase Inhibitor: Computational Modeling of the Hypothalamic-Pituitary-Gonadal Axis

Authors:

Miyuki Breen - Biomathematics Graduate Program, Department of Mathematics, North Carolina State University, Raleigh, NC

Daniel L. Villeneuve - Mid-Continent Ecology Division, National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, Duluth, MN

Gerald T. Ankley - Mid-Continent Ecology Division, National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, Duluth, MN

David Bencic - Ecological Exposure Research Division, National Exposure Research Laboratory, U.S. Environmental Protection Agency, Cincinnati, OH

Michael S. Breen - National Exposure Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC

Karen H. Watanabe - Department of Environmental and Biomolecular Systems, Oregon Health & Science University, Beaverton, OR

Alun L. Lloyd - Biomathematics Graduate Program, Department of Mathematics, North Carolina State University, Raleigh, NC

Rory B. Conolly - Integrated Systems Toxicology Division, National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC

Abstract:

Exposure to endocrine disrupting chemicals can affect reproduction and development in both humans and wildlife. We are developing a mechanistic computational model of the hypothalamic-pituitary-gonadal (HPG) axis in female fathead minnows to predict dose-response and time-course (DRTC) behaviors for endocrine effects of the aromatase inhibitor, fadrozole. The model includes two feedback regulatory loops within the HPG axis that mediate adaptive responses to endocrine stress. One regulatory loop controls the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the brain, and the other regulates LH and FSH receptor recycling in the ovary. Data on plasma E2 and ovarian CYP19A mRNA from two

experiments with a post-exposure recovery phase were used to develop and evaluate the model. In the experiments, fathead minnows were exposed to fadrozole at 0, 3, or 30 µg/L for 8 days followed by a 8-day recovery phase (experiment 1) or to fadrozole at 0, 0.5, or 30 µg/L for 8 days followed by a 20-day recovery phase (experiment 2). Adaptive changes in plasma E2 levels occurred during exposure and overshoot occurred post-exposure. Initial efforts to identify parameter values providing good fits to the plasma E2 data were only partially successful, suggesting the possibility that additional regulatory loops in the HPG axis are needed in the model. Ongoing efforts are evaluating both this possibility and new approaches to parameter estimation for the current model structure. This study illustrates the value of computational modeling for (1) examining the possible dynamic behaviors of a given model structure and (2) exploration of modifications to model structure leading to novel hypotheses regarding the regulatory biology associated with the observed adaptive responses. *This abstract does not necessarily reflect US Environmental Protection agency policy.*