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Investigation of Adaptive Responses in Fathead Minnows (*Pimephales promelas*) Exposed to the Model Aromatase Inhibitor Fadrozole. Jensen, K.M.*, Cavallin, J.E., Durhan, E.J., Kahl, M.D., Makynen, E.A., Thomas, L.M., Villeneuve, D.L., Wehmas, L.C., and Ankley, G.T. Mid-Continent Ecology Division, U.S. Environmental Protection Agency, Duluth, MN, USA.

The vertebrate hypothalamic-pituitary-gonadal (HPG) axis is a highly dynamic system, which, through various feedback mechanisms, strives to maintain physiological conditions conducive to reproduction even in potentially stressful situations. The development of useful predictive models of toxicity involves an understanding of how chemicals interact with the HPG axis temporally, in terms of both direct impacts and potential mechanisms for compensation during dosing, as well as recovery after cessation of chemical exposure. Fathead minnows (*Pimephales promelas*) were exposed to the aromatase inhibitor fadrozole (0.5 or 30 µg/L) either continuously for 1, 8, 12, 16, 20, 24, and 28 d or exposed for 8 d and then held in control water (no fadrozole) for an additional 4, 8, 12, 16, or 20 d and the time-course of effects on ovarian steroid production, circulating 17β-estradiol (E2) and vitellogenin concentrations, and expression of steroidogenesis-related genes in the ovary were examined. Exposure to 30 µg fadrozole/L significantly reduced plasma E2 and vitellogenin concentrations after just 1 d and those effects persisted throughout 28 of exposure. In contrast, ex vivo E2 production was similar to that of controls on d 8-28 of exposure, while transcripts coding for aromatase and follicle-stimulating hormone receptor were elevated, suggesting a putative compensatory response. Following cessation of fadrozole delivery ex vivo E2 and plasma E2 concentrations exceeded and then recovered to control levels, but plasma vitellogenin concentration did not return to control levels, even after 20 d of depuration. Collectively these data provide several new insights as to the nature and time-course of adaptive responses of the HPG axis of a model vertebrate and its response to aromatase inhibitors, a class of endocrine-active chemicals of

regulatory concern. *The contents of this abstract neither constitute nor reflect official US EPA policy*.