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Effects of short time-course exposure to antiandrogen flutamide on steroidogenesis and gene expression in ovary of female fathead minnow (*Pimephales promelas*)

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Abstract: (2500 character limit including spaces)

Because the mechanisms through which antiandrogens disrupt reproduction in fish are not well-characterized, this work sought to identify genes and pathways affected by antiandrogen exposure, and to compare differentially expressed genes in the fathead minnow to those previously reported in zebrafish (*Danio rerio*). A time course study with continuous exposure to flutamide, a pharmaceutical antiandrogen, was conducted in the female fathead minnow. Sexually mature female fathead minnows were exposed to nominal (target) concentrations of 50 and 500 µg/L flutamide over 1, 2, 4 and 8 d, after which plasma and ex vivo steroid concentrations were determined. Changes in gene expression were evaluated in female ovary tissue using a custom 15000 feature fathead minnow microarray. Ex vivo estrogen and testosterone production, as well as plasma estrogen levels, were significantly reduced in fish exposed to 500 µg/L flutamide for 2 d. For the 1 d exposure, 337 genes were significantly altered ($\geq$1.3 fold change, $P<0.05$) in the 50 µg/L flutamide treatment group and 238 genes were significantly altered in the 500 µg/L group, as compared to time-matched controls. For the 2 d exposure, 337 genes were significantly altered in the 50 µg/L treatment group and 162 genes were significantly altered in the 500 µg/L group. In the 4 d exposure, 619 genes were significantly altered in the 50 µg/L treatment group and 219 genes were significantly altered in the 500 µg/L group. After pooling the gene expression data across 1, 2 and 4 d time points and across flutamide concentration level, 491 significantly altered genes were detected, as compared to pooled controls. Of these 491 genes, some were found to be in common with genes

previously reported to be altered in female zebrafish exposed to antiandrogens. The identification of genes and pathways impacted across fish species may aid in potential biomarker development for reproductive effects associated with antiandrogens. *The contents of this abstract neither constitute, nor necessarily reflect, official US EPA policy.*