Dynamic Nature of Alterations in the Endocrine System of Fathead Minnows Exposed to the Fungicide Prochloraz

M. D. Kahl [1], J. E. Cavallin [1], K. M. Jensen [1], E. A. Makynen [1], D. Martinovic' [2], N. D. Mueller [1], D. L. Villeneuve [1], L. C. Wehmas [1], G. T. Ankley [1]

[1] U.S. EPA Mid-Continent Ecology Division, Duluth MN, [2] University of St. Thomas, St. Paul MN

The vertebrate hypothalamic-pituitary-gonadal (HPG) axis is controlled through various feedback mechanisms that ideally serve to maintain a dynamic homeostasis of the system in the face of changing environmental conditions, including exposure to chemical stressors. In these studies, we assessed the effects of prochloraz on HPG axis function in adults of a model small fish species, the fathead minnow (*Pimephales promelas*), in a study with multiple sampling times during both an 8-day exposure and 8-day recovery phase. Consistent with one anticipated mechanism of action of prochloraz, inhibition of activity of cytochrome P450 aromatase (CYP19A), exposure to the fungicide depressed *ex vivo* ovarian production and plasma concentrations of 17β-estradiol (E2) in female fish. At a low prochloraz water concentration (30 μg/L), inhibitory effects on E2 production were transitory, and did not persist during the 8-day exposure phase of the test. At a higher prochloraz concentration (300 μg/L), inhibition of E2 production was evident throughout the 8-day exposure, but steroid titers recovered within 1 day of cessation of the chemical exposure. Compensation and/or recovery of steroid production in the prochloraz-exposed females were accompanied by up-regulation of several ovarian genes associated with steroidogenesis, including CYP19A (aromatase), CYP17 (lyase), CYP11A (cholesterol side-chain cleavage) and follicle-stimulating hormone receptor. In male fathead minnows, the 8-day prochloraz exposure decreased testosterone (T) production, possibly through inhibition of CYP17 lyase. However, as observed for E2 in females, *ex vivo* testicular production and plasma concentrations of T recovered within 1 day after stopping the chemical exposure. Testicular genes involved in steroidogenesis up-regulated by prochloraz included CYP17 and CYP11A. Overall, these studies demonstrate the adaptability of the HPG axis to chemical stress, and highlight the need to consider the dynamic nature of the system when developing empirical or predictive approaches to assess potential risks of endocrine-active chemicals. *This Abstract does not necessarily reflect official Agency EPA Policy.*