

Testing quantitative adverse outcome pathway predictions using aromatase inhibitors in female fathead minnows

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To become more efficient and cost effective regulatory toxicology is increasingly averting from whole animal testing toward collecting data at lower levels of biological organization, through such means as in vitro high throughput screening (HTS) assays. When anchored to relevant adverse outcome pathways (AOP) such data may be used to predict apical impacts of chemical exposures. This study examines the utility and limitations of a quantitative AOP (Q-AOP) designed to translate HTS data on aromatase inhibition into quantitative predictions of reproductive impacts in fish. Eight chemicals, shown to be aromatase inhibitors in mammalian HTS assays, were selected for testing. First, in vitro exposures to fathead minnow ovary tissue were conducted and fish specific relative potencies compared to those based on the mammalian assays. The rank order of potency for inhibiting fish aromatase activity was [Fadrozole>Letrozole>Anastrozole>Imazalil>Epoxiconazole>Prochloraz>Propiconazole>4-Hexylresorcinol] which matched the mammalian-based rank order. However, AC50s determined in the fish-specific assay were 2-40 fold greater than in mammals. Relative potencies were used as input data in a series of biologically-based models used to predict potential impacts on plasma estradiol, vitellogenin production, oocyte development, and population dynamics under different exposure scenarios. Model predictions are being tested through 24h in vivo exposures. The latest, with imazalil, showed a 50% decrease in estradiol after 24h exposure to 100µM compared to an 80% reduction predicted by the models. This difference may be due to chemical specific differences in chemical uptake and elimination rates which were not accounted for in the Q-AOP modeling.