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CHEMICAL TOXICITY DISTRIBUTIONS AS AN APPROACH TO ASSESS AND COMPARE SENSITIVITIES OF COMMON *IN VITRO* AND *IN VIVO* ASSAYS OF ENVIRONMENTAL ESTROGENICITY

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ABSTRACT: A number of emerging contaminants in municipal effluent discharges and effluent-dominated streams are estrogen agonists to fish. Various *in vitro* and *in vivo* techniques have been developed to assess the relative estrogenicity of individual compounds or mixtures in ambient samples. Although several attempts have been made to compare the relative sensitivities of various combinations of these assays, we performed a novel assessment of common *in vitro* and *in vivo* assays for evaluating estrogenicity using probabilistic ecological hazard assessment estimations (PEHAs). Specifically, the relative sensitivities of three common *in vitro* methods, YES (yeast estrogen screen reporter gene assay), MCF-7 (human breast ademocarcinoma cell lines) and rainbow trout (*Oncorhynchus mykiss*) hepatocyte assays, and vitellogenin (VTG) induction in three common *in vivo* fish models (*O. mykiss, Pimephales promelas, Oryzias latipes*) were assessed. PEHAs utilizing chemical toxicity distributions for EC50 values from in vitro studies and VTG Lowest Observable Effect Concentrations from *in vivo* models were obtained from literature data for estrogen agonists. The *in vitro* distributions predicted an 8.5%, 6.3% and 1.9% probability for MCF-7, YES and hepatocyte assays, respectively, of finding a compound in aquatic systems that will elicit an estrogenic agonist response at a concentration below 0.1 µg L^{-1}, a common regulatory trigger value. Using this technique, the MCF-7 assay was the most sensitive *in vitro* assay for evaluating estrogenicity. The probabilities of eliciting significant VTG induction in *O. mykiss, P. promelas, and O. latipes* at a concentration less than 0.1 µg L^{-1} were 27.3%, 26.2% and 20.1%, respectively, implying that *O. mykiss* VTG induction was the most sensitive *in vivo* model for estrogen agonists. Based on the PEHA approach presented here, three common *in vivo* models provided a more conservative estimate of estrogen agonist hazards to fish than the *in vitro* assays.

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