(IIID-5) Mathematical Model of Steroidogenesis to Predict Dynamic Dose-Response to Endocrine Disruptors

Authors: Michael S. Breen[1], Daniel L. Villeneuve[2], Gerald T. Ankley[2], Rory B. Conolly[1]
[1]National Center for Computational Toxicology, U.S. EPA, RTP, NC; [2]Mid-Continent Ecology Division, U.S. EPA, Duluth, MN, USA

There is increasing evidence that exposure to endocrine disrupting chemicals (EDCs) in the environment can induce adverse effects on reproduction and development in both humans and wildlife, mediated through hormonal disturbances. These adverse effects induced in the tightly regulated endocrine pathways can be mediated through inhibition of the enzymes involved in steroidogenesis. We are developing a mechanistic mathematical model of the intratesticular and intraovarian metabolic network that mediates steroid synthesis, and the kinetics for enzyme inhibition by EDCs to predict the time and dose-response. The deterministic model describes the biosynthetic pathways for the conversion of cholesterol to the steroid sex hormones (e.g. testosterone and estradiol) and the gamete maturation inducing hormones (progestins) secreted by the testes and ovaries in fish. The model includes the intermediate metabolites and enzymatic reactions for the pathways involved in biosynthesis of the hormones. The initial concentrations and enzyme reaction rates were taken from the literature or set to biologically reasonable values. Computer simulations were performed to compare the model predicted time and dose-response with experimental data. Preliminary results show that the predicted response behavior of the secreted hormone concentrations is comparable to experimental data. This mechanistic model allows for an improved understanding of the dynamic dose-response behavior at the molecular level, and the identification of new predictive molecular biomarkers indicative of the ultimate adverse effects in support of risk assessments. Since the biosynthetic pathways for the steroid hormones are evolutionarily conserved in vertebrates to a significant extent, this computational model is likely to also be relevant for mammalian species. *This work was reviewed by the U.S. EPA and approved for publication but does not necessarily reflect Agency policy.*