Mathematical Model of Steroidogenesis:
Molecular Response to Endocrine Disruptor Exposures

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Scientists have identified alterations in the concentration dynamics of specific hormones as risk factors for common cancers such as breast cancer (estrogen, progesterone), endometrial cancer (estrogen), and prostate cancer (estrogen, testosterone) [1-2]. These adverse hormonal changes in the tightly regulated endocrine pathways can be induced from exposure to exogenous endocrine disruptors. Chemicals capable of acting as endocrine disruptors are ubiquitous with environmental sources that include household detergents, pesticides, plastics, pharmaceutical estrogens, industrial chemicals, and byproducts of incineration, paper production, and fuel combustion. Ecological exposures to endocrine disruptors are primarily from industrial and waste water treatment effluents, while human exposures are mainly through the food chain [3]. The adverse effects induced by exposure to endocrine disruptors can be mediated through alterations in the enzymes involved in steroid synthesis. We are developing a mechanistic mathematical model of the intratesticular and intraovarian metabolic network that mediates steroid synthesis to describe the dose-response for endocrine disruptors, and to identify and link new robust molecular biomarkers of exposure that are indicative of the ultimate adverse effects. The deterministic model describes the biosynthetic pathways for the conversion of cholesterol to the sex steroid hormones (progesterone, β-estradiol, testosterone, and 11-ketotestosterone) secreted by the testes and ovaries in fish. The model includes the intermediate metabolites and enzymatic reactions for the multiple pathways involved in the biosynthesis of the sex steroids. Changes in the concentration dynamics of the secreted hormones are used as an index of the endocrine disruption. The initial concentrations and enzyme kinetic reaction rates were taken from the literature or set to biologically reasonable values. Computer simulations were performed to examine the dose and time-response. This mechanistic model allows for an improved understanding of the source-to-outcome linkages and dynamic dose-response behavior at the molecular level for effective use of biomarkers for risk assessments with endocrine disruptors, including their possible effects on endocrine-induced cancers. Since the biosynthetic pathways for the sex steroids are evolutionarily conserved 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.*

References

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