

Human Relevance of Developmental Responses to a Class of Endocrine Disruptors

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The effect of chemicals on the endocrine system is a major contemporary regulatory issue, with a significant challenge being how/whether to extrapolate data in rats to humans. This issue is prominent for a certain class of chemicals (anti-androgens), represented by phthalates. *In utero* exposure to some phthalates causes antiandrogenic-like effects on the developing male reproductive system of rats, but not mice. Thus, the question arises as to whether humans are susceptible like rats or resistant like mice. If susceptible, it is crucial to know whether effects are likely to occur at environmentally relevant concentrations. The Hamner Institutes will add a modeling component to a separately funded experimental component to address this issue.

This overall risk assessment project focuses on completing a mode-of-action based risk assessment, including genomic and interspecies mode-of-action studies, for compounds that impair the body's biochemical processes that produce steroid hormones, focusing on testosterone (steroidogenesis) in male rat fetuses. The work consists of developing both physiologically-based pharmacokinetic and dose-response models of experimental data produced separately. Impaired testosterone production from high-dose administration of some select phthalate esters is associated with altered male reproductive tract development. The relevance of these observations for inferring human risks is problematic in two ways: (1) the doses used in rat studies compared to environmental exposures in humans and (2) even mice appear to be resistant to some effects. A key question regarding the sensitivity of fetal tissues from diverse animal species will be examined to help decide whether the human fetal testes would be affected by these compounds or whether they are relatively insensitive as in mice. A xenotransplant model will be developed for comparison of fetal testicular response across species, including rats, mice, and rabbits.

The research will be published in the peer-reviewed literature to provide a credible basis for regulators to use the information. The work will also be presented at scientific venues to facilitate its broader application by both researchers and risk assessors.

Implications: Humans are conventionally considered as sensitive as the most sensitive animal species tests. Here, the sensitivity of fetal tissues from diverse animal species will be examined to help determine the pathways targeted by these compounds and the human relevance and sensitivity of the pathways targeted.

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