

Predicting Adverse Effects of Endocrine Disruptors on Male Sexual Differentiation: Challenges with Alternative Test Methods

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ABSTRACT

Male reproductive development relies on tightly regulated, spatiotemporal hormone signalling, from fetal life to puberty. While gonadal sex determination, leading to testis formation, is primarily driven by genetic cues, the development of male reproductive organs and secondary sex characteristics largely depends on androgen surges during the fetal masculinization programming window, albeit with other signalling pathways also playing important roles. Given this hormonal dependence, male reproductive development is particularly vulnerable to endocrine disruption at critical life stages, especially from chemicals with anti-androgenic or estrogenic effects. Despite substantial knowledge about the regulation of male sexual development by endocrine signalling, predicting *in vivo* effects from non-animal experimental data remains challenging. Some challenges stem from the inherent complexity of biological systems, which artificial or reductionist test systems struggle to replicate. Other obstacles arise from poorly designed test methods relative to desired effect outcomes. However, with the growing focus on new approach methodologies (NAMs) and deeper insights into interactions between endocrine-disrupting chemicals and biological systems, there are significant opportunities to enhance current testing frameworks. This could gradually reduce reliance on *in vivo* toxicity studies for chemical hazard identification and risk assessment.