Abstract

This study was designed to develop and validate a short-term in vivo protocol termed the Fetal Phthalate Screen (FPS) to detect phthalate esters (PEs) and other chemicals that disrupt fetal testosterone synthesis and testis gene expression in rats. We propose that the FPS can be used to screen chemicals that produce adverse developmental outcomes via disruption of the androgen synthesis pathway more rapidly and efficiently, and with fewer animals than a postnatal one-generation study. Pregnant rats were dosed from gestational day (GD) 14 to 18 at one dose level with one of 27 chemicals including PEs, PE alternatives, pesticides known to inhibit steroidogenesis, an estrogen and a potent PPARα agonist and ex vivo testis testosterone production (T Prod) was measured on GD 18. We also included some chemicals with "unknown" activity including DMEP, DHeP, DHEH, DPHCH, DAP, TOTM, tetrabromo-diethyl hexyl phthalate (BrDEHP), and a relatively potent environmental estrogen BPAF. Dose-response studies also were conducted with this protocol with 11 of the above chemicals to determine their relative potencies. CD-1 mice also were exposed to varying dose levels of DPeP from GD 13 to 17 to determine if DPeP reduced T Prod in this species since there is a discrepancy among the results of in utero studies of PEs in mice. Compared to the known male reproductive effects of the PEs in rats the FPS correctly identified all known "positives" and "negatives" tested. Seven of eight "unknowns" tested were "negatives", they did not reduce T Prod, whereas DAP produced an "equivocal" response. Finally, a dose-response study with DPeP in CD-1 mice revealed that fetal T Prod can be inhibited by exposure to a PE in utero in this species, but at a higher dose level than required in rats.Key words. Phthalate Syndrome, Fetal endocrine biomarkers, Phthalate adverse outcome pathway, testosterone production, fetal rat testis.