Screening of plasticisers for their effects on the developing male reproductive system

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Human males exhibit a high incidence of reproductive disorders (cryptorchidism, hypospadias, low sperm counts, testicular germ cell dysplasia/cancer) that are suggested to constitute a testicular dysgenesis syndrome (TDS), with a common origin in fetal life. TDS disorders are hypothesized to result from dysfunction of the Leydig cells of the fetal testis. In rats, a TDS-like syndrome can be induced in male offspring by treatment in late pregnancy with high doses of certain phthalate esters, notably di(n-butyl) phthalate (DBP) or diethylhexyl phthalate (DEHP). Such treatment causes profound inhibition of fetal testicular testosterone levels through down-regulation of the transcription factor SF1 which, in turn, leads to down-regulation of the expression of genes involved in cholesterol uptake, transport and conversion into testosterone. This effect is thought to underlie the development of hypospadias, decrease in anogenital distance and nipple retention found in male offspring of DBP/DEHP-exposed dams. Suppression of testosterone, in combination with suppression of insulin-like factor 3 (Insl3), is also thought to account for the high incidence of cryptorchidism in rats exposed in utero to DBP or DEHP. In order to assess the potential of a novel plasticizer, tris(2-ethylhexyl)trimellitate (TOTM), to induce TDS, rats were exposed daily, in utero, to TOTM (500mg/kg). Exposure took place between gestational day 12 and 19 when animals were sacrificed, fetal testes removed, RNA extracted and analysed using whole genome microarrays. The effects of TOTM on the expression of genes in pathways involved in steroidogenesis and testes development were examined. The effects of TOTM were also compared with DEHP, mono(ethylhexyl)phthalate (MEHP, an active metabolite of DEHP) and 2-ethylhexanol (2-EH), which were used as controls, two positive and one negative, respectively. MEHP and DEHP (500mg/kg) caused a repression of genes in TMD pathways involved in cholesterol synthesis and transport (HMGCS, HMGCR, StAR, SCARB1, FDFT1, FDPS), steroidogenesis (CYP11a, HSD3B1, SC4MOL) and testes development (INSL3, INHA). 2-EH caused minor repression of some of the genes in the TMD pathways. TOTM did not cause a significant repression of genes in the TMD pathways. Therefore, it is highly unlikely that TOTM will cause testicular dysgenesis in rats under these treatment conditions.

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