Pathogenesis of Testicular Lesions Induced by Late Gestational Exposure to Di(n-butyl) Phthalate

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Di(n-butyl) phthalate (DBP) interferes with androgen-dependent development of the male reproductive tract when animals are exposed during a ten-day gestational window. Although DBP has antiandrogenic effects on the developing male reproductive tract, it has been previously shown that it does not bind to the androgen receptor in vitro. In utero exposure on gestation days (GD) 12–21 produces a range of reproductive tract malformations predominantly in the tissues derived from the Wolffian ducts, the epididymides and vasa deferentia, with less pronounced effects on the prostate, seminal vesicles, and external genitalia. When examined on postnatal day (PND) 100 the testes of exposed males had severe seminiferous tubular degeneration, Leydig cell hyperplasia, and several Leydig cell adenomas (adenomas were seen in two separate studies). Fetal testes examined on GD 18 and 21 contained lesions in the interstitial and tubular compartments. In the interstitium of males exposed to 500 mg/kg/day DBP there were multifocal areas of interstitial cell hyperplasia. On gestation day 21 seminiferous cords contained multinucleated gonocytes. In addition, androgen levels in the fetal testes were significantly decreased. In previous studies, animals exposed in utero were only examined on two gestation days, GD 18 and 21, and as adults on PND 100. To help fully elucidate the pathogenesis of lesions seen with in utero DBP exposure and to try to correlate the fetal and adult lesions a study was undertaken in which dams were dosed with 500 mg/kg/day DBP on gestation days 12–21 and male fetuses and pups were examined on GD 16–21 and on postnatal days (PND) 3, 7, 16, 21, 45 and 70. Data from these studies indicate that lesions in exposed male fetuses cannot be detected at the gross level. However, most of the fetal testes examined contained areas of Leydig cell hyperplasia and multinucleated gonocytes. The multinucleated gonocytes were not present in early postnatal life but by PND21 there were tubules with gonocyte degeneration. Small numbers of the areas of Leydig cell hyperplasia persist in the early postnatal period but are much less dramatic than those seen in the fetal testes. At PND 45, there were few testes with seminiferous epithelial degeneration, which was in sharp contrast to the testes examined at PND 70. It is believed that the complete or partial absence of the epididymides leads to blockage of fluid flow from the testis and that this significantly contributes to the development of seminiferous epithelial degeneration. Portions of this project have continued as part of CIIT’s ongoing antiandrogen program project.


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