Effects of Di(n-butyl)phthalate on Reproductive Development

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Di(n-butyl)phthalate (DBP), a common plasticizer and solvent, was investigated for its potential to interfere with androgen dependent male reproductive development in rats. Previous work has shown that a variety of male reproductive malformations may be induced by in utero DBP treatment, with the most sensitive tissues being the developing Wolffian ducts, particularly the epididymis and vas deferens, although dihydrotestosterone mediated development was affected to a lesser extent (external genitalia, prostate). The overall goals of this project were to define the dose response for the induction of changes in male reproductive development (the most dose-sensitive toxicity produced by DBP) and if possible to ascribe a no-observed-adverse-effect level (NOAEL) for potential risk assessment purposes. In addition, the project examined the early events occurring in the fetal testis (the source of fetal androgen for male reproductive development) to determine any early changes that could be noted in morphology, immunolocalization of androgen receptor (AR), and testosterone levels. Adult rats (100 days old) exposed from gestation day (gd) 12 to 21 to DBP have previously been shown to have decreased sperm production, interstitial cell hyperplasia and adenomas, as well as reproductive tract malformations. The pattern of effects resembles that elicited by antiandrogens, but DBP (not its major metabolite) does not interact directly with the androgen receptor (AR). An indirect mechanism is proposed through which DBP alters androgen-dependent male sexual differentiation by disrupting the androgen status in the fetal testis. These studies have provided important new information about molecular mechanisms by which DBP induces malformations in the male reproductive tract. Elements of this project have continued within CIIT’s ongoing antiandrogen program project.

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