Male reproductive toxicity in animal studies of diisobutyl phthalate (DIBP): a case study application of systematic review approaches

Erik E. Yost1, Susan Y. Euling1, James A. Weaver1, Brandiee E. J. 1, Beverly1, Nagalakshmi Keshava1, Anuradha Mudipalli1, Xiaohui Arzouga2, Todd Blessinger2, Laura Dishaw2, Andrew Hotchkiss3, Susan L. Makris4

1 US EPA National Center for Environmental Assessment, Research Triangle Park, NC; 2 US EPA National Center for Environmental Assessment, Washington, DC

Introduction

Diisobutyl phthalate (DIBP) is used as a plasticizer in a variety of industrial and consumer products. Although DIBP has been less widely studied compared to other phthalates, there is evidence that DIBP and its primary metabolite, monoisobutyl phthalate (MIBP), cause male reproductive toxicity. A recent systematic review of endocrine-related low-dose toxicity by the National Academies of Sciences (NAS) evaluated the effects of DIBP on three anti-androgenic outcomes [testosterone, anogenital distance (AGD), and hypospadias], and concluded that DIBP is a presumed human hazard based on decreased fetal testosterone in rodents exposed during gestation. The Integrated Risk Information System (IRIS) performed a systematic review of male reproductive effects of DIBP exposure that considered all outcomes and all life stages of exposure, following recommendations in the 2014 NAS review of the IRIS program. Here, we use studies that evaluated testosterone in male rodents exposed during gestation. The Integrated Risk Information System (IRIS) performed the synthesis of results for testosterone is summarized in an evidence profile table (Table 2). Gestational exposure studies provided robust evidence for effects on testosterone, whereas evidence from postnatal exposure studies was found to be indecisive. Evidence judgments for other male reproductive endpoints identified in this systematic review are summarized in Table 3.

Methods

Aimal studies for DIBP or MIBP were identified by searching four online databases (PubMed, Web of Science, Toxline, and TSCATS), using search terms designed to capture all potentially pertinent studies. The last update was in July 2017. Title/abstract screening was used to identify primary health effect studies that exposed non-human mammalian animals to any administered dose of DIBP or MIBP via oral, dermal, or inhalation routes. These studies were evaluated by at least two reviewers using the approach in Figure 1. The synthesis of results for testosterone is summarized in an evidence profile table (Table 2). Gestational exposure studies provided robust evidence for effects on testosterone, whereas evidence from postnatal exposure studies was found to be indecisive. Evidence judgments for other male reproductive endpoints identified in this systematic review are summarized in Table 3.

Results

Table 1. Animal studies of testosterone and DIBP or MIBP exposure. Of the 11 studies that evaluated testosterone in male rats or mice, 7 exposed animals during gestation and/or until weaning, and 4 were postnatal exposures of males near the time of puberty. The postnatal exposure studies had higher risk of bias because of reporting limitations, including uncertainty about the pubertal status of the test animals at the time of exposure.

Table 2. Evidence profile table for animal studies of testosterone and DIBP exposure.

Discussion

Overall, the results from animal studies of male reproductive effects provide robust evidence of a hazard from DIBP exposure. Conclusions for testosterone are consistent with those of NAS (2017). The NAS review was limited to gestational exposure studies and excluded studies that exposed animals to a single high dose (≥500 mg/kg/day); therefore, NAS only considered two fetal testosterone studies, and had inadequate evidence to evaluate the effects of DIBP on AGD or hypospadias. The IRIS systematic review included all dose levels and life stages of exposure, and was able to evaluate a wider range of androgen-dependent and -independent male reproductive outcomes. Disclaimer: The views expressed in this poster are those of the author(s) and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.