Introduction

Dibutyl phthalate (DBP) is used as a plasticizer in a variety of commercial and consumer products (US EPA, 2014; Kavlock et al. 2002). The largest source of DBP exposure in humans is from inhalation and dermal exposures considered minimal (Kavlock et al. 2002). Epidemiological studies provide evidence of human exposure and altered androgen levels during fetuses, at which androgen production is critical for the normal development and function of the male reproductive system (WHO/UNEP, 2013), and experimental studies using rat models have reported that exposure to DBP is associated with adverse responses in the male reproductive system. Effects include decreased androgen production, agenesis of reproductive organs, and decreased fertility and sperm counts (CFPC, 2010; Makris et al. 2013; US EPA, 2008). Evidence from post-natal exposure studies also suggests that young animals are more sensitive to phthalate-induced testicular injury than adults (Boekelheide et al 2004). However, recent studies using ex-vivo human tissue culture preparations, or rodent and human testicular tissue xenografts report that human fetal tests are resistant to phthalate-induced disruption of testosterone production (Johnson et al., 2012; Albert, and Jegou, 2004).

Such findings raise questions about the human relevance of the androgen-related endpoints measured in experimental rodents exposed to phthalates. A mode of action framework was used to evaluate the available evidence from experimental and in-vitro studies according to lifestage of exposure. Studies considered for this analysis include:

- Exposures during the masculinization programming window (MPW; gestational period during which development of the male reproductive system occurs).
- Exposures during post-natal stages.

Methods

The experimental and mechanistic studies considered in this analysis were obtained from the literature search performed by the US EPA Integrated Risk Information System (IRIS). Studies for DBP or M BP were identified from online databases (PubMed, Web of Science, Toxline, and TSCATS2) using search terms designed to capture pertinent studies. The last update was performed in July 2017. Title/abstract screening followed by a full text review was performed to identify relevant studies on male reproductive effects and related mechanisms/pathways (See Figure 1 below). The types of in-vivo and in-vitro studies considered most informative were:

- Gestational DBP exposure studies that use mammalian in-vivo and in-vitro models, and human xenograft and ex vivo models tested during the masculinization programming window.
- A didactic in-vivo ex-studies that expose human fetal tissues to DBP or its metabolites in vivo.
- Studies aimed at characterizing the receptor for DBP at a molecular level.
- Post-natal DBP exposure studies that use mammalian model species, including in-vivo, xenograft, and cell culture models.

The available mechanistic and toxicological evidence was analyzed in concordance with the framework and levels of biological organization used for mode of action analyses for non-cancer endpoints in the Development of A Hierarchy Approach Pathways (Boobis et al., 2008; Edeards et al. 2016). A recommendations by US EPA’s Framework for Assessing Health Risk of Environmental Exposures to Children and the World Health Organization International Programme on Chemical Safety, the available mechanistic and toxicological studies and endpoints that inform the mode of action for DBP-induced male reproductive effects were evaluated according to the lifestage of exposure.

Gestational exposure studies:

- Fetal rats appear more sensitive to DBP-induced anti-androgenic effects than mice and may be more sensitive than other rodent species, non-primate humans, and human fetal testis xenografts and ex-vivo tissue cultures.
- DBP-induced androgen-independent effects in the seminiferous cord (SC & GC) are conserved among most mammalian models (rats, rabbits, mice, and human xenografts).
- DBP-induced Leydig cell effects are conserved in different mammalian species: (rats, rabbits, mice, gerbils, and guinea pigs, non-primate humans [in-vivo and xenografts]).
- DBP-induced effects in the seminiferous cord (SC & GC) are also conserved among most mammalian models (rats, mice, and non-human primate xenografts).

Results and discussion:

- Studies aimed at characterizing the receptor for DBP at a molecular level.
- Post-natal DBP exposure studies that use mammalian model species, including in-vivo, xenograft, and cell culture models.

The available mechanistic and toxicological evidence was analyzed in concordance with the framework and levels of biological organization used for mode of action analyses for non-cancer endpoints in the Development of A Hierarchy Approach Pathways (Boobis et al., 2008; Edeards et al. 2016). Recommendations by US EPA’s Framework for Assessing Health Risk of Environmental Exposures to Children and the World Health Organization International Programme on Chemical Safety, the available mechanistic and toxicological studies and endpoints that inform the mode of action for DBP-induced male reproductive effects were evaluated according to the lifestage of exposure.

- Fetal rats appear more sensitive to DBP-induced anti-androgenic effects than mice and may be more sensitive than other rodent species, non-primate humans, and human fetal testis xenografts and ex-vivo tissue cultures.
- DBP-induced androgen-independent effects in the seminiferous cord (SC & GC) are conserved among most mammalian models (rats, rabbits, mice, and human xenografts).
- DBP-induced Leydig cell effects are conserved in different mammalian species: (rats, rabbits, mice, gerbils, and guinea pigs, non-primate humans [in-vivo and xenografts]).
- DBP-induced effects in the seminiferous cord (SC & GC) are also conserved among most mammalian models (rats, mice, and non-human primate xenografts).

Discussion:

- Studies aimed at characterizing the receptor for DBP at a molecular level.
- Post-natal DBP exposure studies that use mammalian model species, including in-vivo, xenograft, and cell culture models.

The available mechanistic and toxicological evidence was analyzed in concordance with the framework and levels of biological organization used for mode of action analyses for non-cancer endpoints in the Development of A Hierarchy Approach Pathways (Boobis et al., 2008; Edeards et al. 2016). Recommendations by US EPA’s Framework for Assessing Health Risk of Environmental Exposures to Children and the World Health Organization International Programme on Chemical Safety, the available mechanistic and toxicological studies and endpoints that inform the mode of action for DBP-induced male reproductive effects were evaluated according to the lifestage of exposure.

- Fetal rats appear more sensitive to DBP-induced anti-androgenic effects than mice and may be more sensitive than other rodent species, non-primate humans, and human fetal testis xenografts and ex-vivo tissue cultures.

Selected references:


...