Development of a Risk Assessment for Dibutylphthalate

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The goal of this research effort was to develop an approach for conducting a risk assessment for di-(n-butyl)-phthalate (DBP) that makes maximal use of the pharmacokinetic (PK), pharmacodynamic (PD), and mode-of-action research on this compound previously completed at The Hamner Institutes for Health Sciences (Hamner). Studies at the Hamner have demonstrated that the administration of sufficient doses of DBP to rats during late pregnancy [gestation days 12–21] causes adverse effects on the developing male reproductive tract, including hypospadias, nipple retention, cryptorchidism, and agenesis of accessory male sex organs. Hamner studies have also demonstrated that exposure of the rat to sufficient doses of DBP during gestation is associated with a decrease in fetal testosterone, with testosterone levels decreasing significantly as early as one hour after maternal dosing. This phthalate-induced decrease in fetal testosterone may be an initial step that leads to fetal adverse development and toxicity. The draft EPA risk assessment for DBP makes use of these Hamner studies; this risk assessment resulted in a proposed reference dose (RfD) of 0.3 milligrams per kilogram per day (mg/kg/day), as compared to the previous RfD for DBP of 0.1mg/kg/day based on a different study.

Previous studies at the Hamner have also characterized the PK of DBP in the rat, including the distribution of DBP and its metabolites monobutyl phthalate (MBP) and MBP-glucuronide (MBP-G) in maternal and fetal tissues following administration of DBP to pregnant rats. In parallel, a physiologically based pharmacokinetic (PBPK) model was developed to describe the metabolism of DBP to MBP and MBP-G, the dosimetry in the pregnant rat, and the transfer to the developing fetus. This research effort investigated the use of in vitro data on the metabolism of DBP in human tissues to support the development of a human PBPK model for DBP that can be used to derive a chemical-specific adjustment factor (CSAF) for PK in place of the default approach. The possibility of deriving a CSAF for PD based on in vitro data was also evaluated. This ACC-funded research project served as the basis for winning a USEPA STAR grant that is now supporting continuation of the research.

Implications: EPA risk assessments need to be adjusted to make use of extensive data relating to pharmacokinetics (PK), pharmacodynamics (PD), and genomic dose-response in test animals. The goal of this effort was to develop approaches for incorporating all of these types of data into a more accurate and less uncertain risk assessment. The development and demonstration of these approaches for DBP will provide an important precedent for the incorporation of PK, PD, and mode-of-action data into the risk assessments for other developmental toxicants and endocrine active compounds.

Key words: phthalates, risk assessment, PBPK

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