Development of a Risk Assessment for Dibutylphthalate

Harvey Clewell. *The Hamner Institutes for Health Sciences.*

The goal of this research effort is to develop an approach for conducting a risk assessment for di-(*n*-butyl)-phthalate (DBP) that makes maximal use of the pharmacokinetic, pharmacodynamic, and mode-of-action research on this compound completed at CIIT. Studies at CIIT 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. CIIT 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 recent draft EPA risk assessment for DBP makes use of these studies; this new risk assessment results 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 CIIT have characterized the pharmacokinetics (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 has been 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. The current research effort will investigate 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 pharmacodynamics (PD) based on *in vitro* data will also be evaluated.

Implications: EPA risk assessments need to be adjusted to make use of extensive data relating to pharmacokinetics, pharmacodynamics, and genomic dose-response in test animals. The goal of the present effort is 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 dibutylphthalate 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.

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Presentations:

Clewell, R. A., Kremer, J., Andersen, M. E., and Borghoff, S. (2006). Using a PBPK model to explore mechanisms of observed pharmocokinetic differences of phthalates across life-stages in rats. *Toxicologist* 95(1): 259. (Abstract 1270).

Campbell, Jr. J. L., Tan, Y.-M., Clewell, R. A., and Clewell, III H. J. (2007). Physiologically based pharmacokinetic model for monobutyl phthalate: Interpreting biomonitoring data to assess human exposure and risk. Oral presentation at the Society for Risk Analysis Annual Meeting, San Antonio, TX, December 9-12, 2007.

Clewell, R. A., Borghoff, S. J. and Andersen, M. E. (2007). Application of a unified PBPK model to two kinetically distinct pthalate esters - DBP and DEHP. *Toxicologist* 96(1): 348. (Abstract 1682).

Peer-reviewed publications:

Clewell, H. J., Tan, Y. M., Campbell, J. L., and Andersen, M. E. (2008). Quantitative interpretation of human biomonitoring data. *Toxicology and Applied Pharmacology* 231: 122-133.

Clewell, R. A., Kremer, J. J., Williams, C. C., Campbell, J. L., Andersen, M. E., and Borghoff, S. J. (2008). Tissue exposures to free and glucuronidated monobutylphthalate in the pregnant and fetal rat following exposure to di-n-butylphthalate: Evaluation with a PBPK model. *Toxicological Sciences* 10: 241-259.

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