USE OF TOXICOGENOMICS DATA IN RISK ASSESSMENT: A CASE STUDY ON DIBUTYL PHthalate AND MALE REPRODUCTIVE DEVELOPMENTAL EFFECTS

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ABSTRACT

A case study to incorporate toxicogenomics data qualitatively into an EPA health assessment has been performed for dibutyl phthalate (DBP). Focusing on the male reproductive developmental effects. Using EPA’s Integrated Risk Information System (IRIS) external peer review draft IRIS assessment as the starting point, we asked whether toxicogenomics data could further define the model(s) or mechanism(s) of action and insight interspecies extrapolation. The mode of action for dibutyl phthalate (DBP) is unknown, but the observed mode of action in rats is that of an androgen receptor (AR) agonist. The proposed mechanism of action is through an androgen receptor (AR) agonist, leading to increased testosterone levels, which in turn stimulates the development of the male reproductive system.

PROJECT GOALS:

1. Develop an approach for using toxicogenomics data most effectively in risk assessment.
2. Perform a case study using the approach.

DBP IRIS EXTERNAL PEER REVIEW DRAFT OF ASSESSMENT

Among the effects reported in the published literature, the developmental effects occur at the lowest doses. The Federal Pell Grants Program of the IRIS assessment selected the reduction in fetal testicular testosterone as the critical effect (US EPA 2003). The MOA for this endpoint was 20 mg/kg/day and the LOEL was 50 mg/kg/day. The 10x intersex and 10x intersex uncertainty factors were applied. The IRIS Assessment and this Case Study are separate activities with different goals.

CASE STUDY APPROACH

Evaluate Toxicity and Toxicogenomics Data in Conjunction to Identify Putative New Pathways and MOAs:

Using Toxicity and Toxicogenomics Data in Conjunction to Identify Putative New Pathways and MOAs:

Published DB Toxicogenomics Dataset

New Analyses of Toxicogenomics Data

Are Additional Pathways affected after in utero DBP exposure?

Flow Diagram for Analysis

Additional Pathways (not T or inst3 pathways) identified as Significant by

Weight of Evidence for Altered Genes and Pathways From the Published Toxicogenomics Dataset

Proposed DBP Mechanism of Action

Explained and Unexplained MOAs Among the Testicular Effects

DBP CASE STUDY

Male Reproductive Developmental Toxicity Dataset

Evaluated 24 in vivo studies that assessed male reproductive endpoints after development DBP exposure to:

1. Low incidence and low dose male reproductive effects?
2. MOA to explain each endpoint?

Proposed DBP Mechanism of Action

Explained and Unexplained MOAs Among the Testicular Effects

Organ Effect MOA
Reduced fetal testosterone T Reduced insulin signaling
Testes Multinucleated gonocytes; increased number of gonocytes in testes
Increased proliferation of Sertoli and peritubular cells; fewer Sertoli cells
Reduced sperm output; early postpubertal decrease in gonocyte number
Increased Leydig cell and interstitial cell numbers
Small increase of Leydig cell extent; aggregates, hyperplasia
Decreased number spermatogonia or tubular epithelial spermatogonia
Spermatozoa; abnormal testis size
Small or flaccid; other alternations; decreased or absent
Increased number or degeneration of interstitial cell layers
Identification of differentially altered genes

Identification of common and unique genes and pathways from EPA and Star St analyses

New molecular studies highlighted in yellow

Figure adapted from Barlow et al. (2000), Liu et al. (2005), Lehmann et al., 2004 (Clontech cDNA arrays). Shultz et al., 2001 (Affymetrix arrays), and White et al., 2004 (Clontech cDNA arrays).

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Dibutyl phthalate was selected for the case study because it has a relatively large toxicogenomics dataset with consistent findings and an ongoing risk assessment.

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