Proposal for publication on analysis of male reproductive data from Saillenfait (2008)

Title: Analysis of male reproductive effects related to the phthalate syndrome

Background: Saillenfait et al. (2008) studied the effect of gestational DIBP exposure on numerous endpoints of male reproductive development in Sprague-Dawley rat offspring. Dr. Saillenfait provided EPA with individual data on developmental malformations of the male reproductive system, growth, anogenital distance, and age of preputial separation as well as adult male organ histopathology effects and reproductive organ weights. Sue Euling and Todd Blessinger are co-assessment managers of DIBP.

The DIBP toxicological review includes a dose-response analysis of phthalate syndrome (PS), limited to a collection of dichotomous male reproductive effects. Continuous PS endpoints were considered but were not included because data on clinical or biological cutoffs for the endpoints is not available in order for these endpoints to be dichotomized. For the analysis, an animal was designated as having PS if it exhibited at least one of these effects, as discussed in NRC's report on Phthalate Cumulative Assessment and demonstrated in Gray et al. (2009).

Purpose: We will investigate the relationships among the male reproductive effects that constitute PS, how the pattern of effects is related to DIBP dose, and individual endpoint contribution to the incidence rate of PS, such as whether there is one or a subset of effects that dominate the syndrome (i.e., are the most sensitive to DIBP exposure).

Authors (contribution): Todd Blessinger (model design and analysis), Susan Euling (biology/toxicology of PS), Anne-Marie Saillenfait, Institut National de Recherche et de Sécurité (provided individual animal data; reproductive and developmental toxicology), Lily Wang (modeling of patterns of PS endpoints), Karen Hogan (initial PS modeling), Christine Cai (initial PS modeling).

Institutions: U.S. EPA and France's Institut National de Recherche et de Sécurité (INRS)

Details:

We propose to evaluate the male reproductive effects of DIBP using multivariate analysis, as follows.

- For continuous outcomes, investigate the effect of dose using a multivariate regression model. To account for small sample sizes, a permutation test may be used. In addition, we may apply principal component analysis to investigate the relationship among the continuous outcomes.
- For dichotomous outcomes, use logistic principal component analysis to investigate the relationship among the outcomes. This type of analysis is relatively new, but there are references that address the topic (de Leeuw, 2006; Landgraf & Lee, 2015). To model the effect of dose on these outcomes, we will also explore applying a multivariate analysis for dichotomous outcomes (e.g., Glonek & McCullagh, 1995) or extending logistic principal component analysis to incorporate dose and litter effect.
- A multivariate analysis combining dichotomous and continuous outcomes will be explored. This analysis would allow the determination of the degree of contribution of the continuous effects to PS. The development of such an analysis will first require an assessment of resources and tools available.

Potential Impact of Work:

- Provide a more thorough understanding of the phthalate syndrome, including the drivers for RfD development and relationships among the syndrome's endpoints. In addition, an alternative definition of the syndrome may be developed. This investigation is responsive to the NRC's Phthalates Cumulative Risk Assessment Report. This work supports the IRIS Phthalate Assessments and the scientific interests of multiple stakeholders. Specifically, if the findings suggest that one or a subset of endpoints is the drivers for PS, then this is valuable information for research scientists and risk assessors. A followup study would be to explore whether the drivers are similar or different among phthalate esters.
- Development of modeling methods that can be broadly applied to dose-response modeling in IRIS assessments when there are a set of related endpoints. This work supports HHRA goals, including Project 6 on Cumulative Risk Methods, and the IRIS program in particular.

References:

De Leeuw, J. (2006). Principal component analysis of binary data by iterated singular value decomposition. Computational Statistics and Data Analysis 50, 21–39.

Glonek, G. F. V. and McCullagh, P. (1995). Multivariate logistic models. Journal of the Royal Statistical Society, Series B 57, 533-546.

Gray LE Jr, Barlow NJ, Howdeshell KL, Ostby JS, Furr JR, Gray CL. (2009) Transgenerational effects of Di (2-ethylhexyl) phthalate in the male CRL:CD(SD) rat: added value of assessing multiple offspring per litter. Toxicol Sci. 2009 Aug;110(2):411-425.

Landgraf, Andrew J. and Lee, Yoonkyung (2015). Dimensionality Reduction for Binary Data through the Projection of Natural Parameters. Technical Report 890, Department of Statistics, The Ohio State University.

National Research Council (NRC), 2008. Phthalate and cumulative risk assessment: The tasks ahead. Committee on the Health Risks of Phthalates, Board on Environmental Studies and Toxicology, Division on Earth and Life Sciences. The National Academies Press, Washington, DC.