

## Testis Phthalate Target Cell Identification

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Understanding the risk of phthalates to human reproductive health requires knowledge of the critical molecular and cellular events following exposure. The long-term goal of this proposal was to produce a molecular and cellular pathway of the phthalate testis injury mechanism. While some late (dysgenetic testicular architecture) and early (altered testicular gene expression) manifestations of phthalate exposure are clear, the testicular cell initially targeted by phthalates is unknown. Based upon current data, we hypothesized that the Sertoli cell is the initial target cell following both fetal and pubertal phthalate exposure. To test the hypothesis, this proposal had three specific aims with the goal of determining the phthalate target cell: (1) identify early and sensitive *in vivo* genetic markers of phthalate exposure using microarray and *q*PCR; (2) map these genetic markers to testicular cell types using *in situ* hybridization; and (3) correlate microarray results from phthalate-exposed primary Sertoli and Leydig cells to microarray data previously obtained *in vivo*.

**Implications:** Phthalates are male reproductive toxicants with uncertain molecular mechanisms of action. To define the phthalate toxic mechanism, our short-term goal was to identify quantitative differences in susceptibility to phthalate-induced male reproductive injury among strains of genetically homogenous (inbred) mice. Once such mouse strains are identified, our longer-term goal was to use this information to discover regions of the mouse genome and specific genetic polymorphisms that are responsible for susceptibility differences. These data are important to understand the molecular mechanism of phthalate toxicity and as an aid in assessing risks of human phthalate exposure in a diverse human population.

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### Presentations:

Johnson, K. J. (2005). Protocadherins in spermatogenesis and the mechanism of phthalate-induced testicular injury. Invited presentation, North Carolina State University Environmental and Molecular Toxicology Department Seminar Series, Raleigh, NC, April 2005.

Johnson, K. J. (2005). Early molecular changes in the testis following pubertal phthalate exposure. Invited presentation, U.S. EPA Reproductive Toxicology Section Seminar, Research Triangle Park, NC, June 2005.

Johnson, K. J., Wallace, D., Hensley, J., Gaido, K., and Boekelheide, K. (2005). Phthalate-induced murine testicular dysgenesis and p53. Poster presentation, 2005 meeting of the NIEHS, Fetal Basis of Adult Disease Grantee Meeting, Duke University, Durham, NC, November 2005.

Johnson, K. J. (2006). Testicular molecules and cells targeted by endocrine-active phthalates. Invited presentation, Alfred I. duPont Hospital for Children, Wilmington, DE, October 2006.

Johnson, K. J., Wallace, D. G., Liu, D., Gaido, K. W., and Lahousse, S. A. (2006). Gene profiling of fetal and pubertal rat testis following acute phthalate exposure suggests a conserved genetic response. Poster presentation, Gordon Conference on Environmental Endocrine Disruptors, Il Ciocco, Italy, July 2006.

Johnson, K. J., Wallace, D., and Lahousse, S. (2006). Gene expression profiling suggests a conserved initial mechanism for fetal and pubertal phthalate testicular injury. *The Toxicologist* 90 (S-1): 252. (Abstract 1238).

**Peer-reviewed publications:**

Lahousse, S. A., Beall, S. A., and Johnson, K. J. (2006). Mono-(2-ethylhexyl) phthalate rapidly increases celsr2 protein phosphorylation in HeLa cells via protein kinase C and casein kinase 1. *Toxicological Sciences* 91: 255–264.

Lahousse, S. A., Wallace, D. G., Liu, D., Gaido, K. W., and Johnson, K. J. (2006). Testicular gene expression profiling following prepubertal rat mono-(2-ethylhexyl) phthalate exposure suggests a common initial genetic response at fetal and prepubertal ages. *Toxicological Sciences* 93: 369–381.

Johnson, K. J., Hensley, J. B., Kelso, M. D., Wallace, D. G., and Gaido, K. W. (2007). Mapping gene expression changes in the fetal rat testis following acute dibutylphthalate exposure defines a complex temporal cascade of responding cell types. *Biology of Reproduction* 77: 978–989.

**Other publication(s):** None to date.

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