Gene Expression Profiling Following Exposure to Phthalate Esters: An Integrative Toxicogenomics Approach

Authors: Kevin W. Gaido¹, Banalata Sen², Susan Euling², Meric Ovacik³, Marianthi G. Ierapetritou¹, Panos G. Georgopoulos⁴, William Welsh⁴, Ioannis P. Androulakis³,⁵
¹The Hamner Institute for Health Research/CIIT Centers for Health Research (CIIT), United States
²U.S. EPA
³Rutgers University/Chemical Engineering, United States
⁴University of Medicine and Dentistry of New Jersey (UMDNJ)/Environmental and Occupational Health Sciences Institute (EOHSI), United States
⁵Rutgers University/Biomedical Engineering, United States

Keywords: di-butyl-phthalate, gene expression, singular value decomposition, pathway activity, steroidogenesis

Di-butyl-phthalate (DBP) is one of the widely used plasticizers, and studies have shown that DBP causes male reproductive tract abnormalities in rats. DBP does not bind to the androgen receptor (AR) as does flutamide, an antiandrogen drug, but interrupts testosterone synthesis by diminishing gene expression in cholesterol transport and steroid biosynthesis. However, the regulatory mechanism is still unknown. In this study, we propose a novel toxicogenomics approach to identify and characterize the molecular pathways that are being affected by DBP, other than the androgen-mediated male reproductive development toxicity pathway, and to relate different modes of actions of DBP. The methodology is based on a predefined collection of genes coding for proteins involved in specific metabolic or signaling pathways. The pathway activity levels, which were derived from singular value decomposition, form the basis for statistical comparisons for vehicle and DBP treated samples. We were able to determine active pathways other than those already identified in literature such as valine, leucine, isoleucine degradation, and glutathione metabolism. Pathway activity analysis suggests that DBP affected the cholesterol biosynthesis more compared to biosynthesis of testosterone. In addition, we expanded the pathway activity level methodology in order to identify “informative” subsets of genes that mostly contributed to overall pathway activity. The set of informative genes was used as the template in order to predict putative transcription factors that play an important role in DBP action. Furthermore, we predicted additional transcription factors using Ingenuity Pathway Analysis. The toxicogenomics approach we propose (i.e., the integration of bioinformatics and toxicology) was helpful to comprehend mechanism of repression of steroidogenesis due to DBP exposure.

Point of Contact:
Ioannis P. Androulakis
Assistant Professor
Rutgers University/Biomedical Engineering
Piscataway, NJ 08854
732-445-4500 ext.6212
yannis@rci.rutgers.edu