Mixed Model Inference in the Analysis Of cDNA Array Data.

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Non-parametric and parametric approaches were compared in order to examine the effect of 100 nM 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) treatment on gene expression in mouse Hepa 1c1c7 cells using a commercially available membrane cDNA array and radiolabeled probes. Hybridization signal intensities (HSI) from two replicate experiments were quantified using a phosphorimager and analyzed using conventional non-parametric methods of analysis and the General Linear Mixed model (GLMM), a more powerful parametric approach. Rank correlation between replicates was 0.002 ($P > 0.1$), indicating poor reproducibility between experiments. Using a GLMM, the variation in HSI was partitioned into replicates as a classification effect and the random effects of genes. Least Squares Means (LS-means) for the genes were computed and ranked according to their magnitude. The GLMM accounted for 61% of the variation in HSI with all terms in the model being significant ($P < .001$). Although the two methods gave different rankings for the effects on gene expression, both reported Cyp1a1 as the most induced gene. However, the probability of observing a treatment effect on each gene could not be calculated using the non-parametric analysis, while the GLM approach provides a mechanism for hypothesis testing. We demonstrate that the above approaches can be used to examine dose-dependent and temporal associations between effects of xenobiotics on endocrine function and gene expression. We illustrate that these data acquisition and statistical methods can be used to investigate dose-dependent and temporal associations between effects of xenobiotics on endocrine function and gene expression.