Evaluating the Toxicity Pathways Using High-Throughput Environmental Chemical Data

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The application of HTS methods to the characterization of human phenotypic response to environmental chemicals is a largely unexplored area of pharmacogenomics. The U.S. Environmental Protection Agency (EPA), through its ToxCast™ program, is developing predictive toxicity approaches that use *in vitro* high-throughput screening (HTS) to profile and model the bioactivity of environmental chemicals. Current efforts draw from the extensive use of HTS technologies by pharma and biotech industries for the purposes of drug discovery, with notable similarities and differences. Output from the first phase of these experiments has been used to construct target gene lists that have been linked with publically available information on gene and protein annotation, molecular, biological, and cellular pathway/processes, as well as gene-disease association information. These data are integrated, and can be accessed and queried using the ToxMiner™ database. Currently there is no standard for analysis of available gene-pathway interaction data, and most studies to date have focused on a single data source; however, by looking across pathway data sources we illustrate, using computational network methods, previously undefined toxicity and toxicity-related pathway coverage in relation to global pathway space. Finally, we illustrate what pathways are being affected by the ToxCast™ chemicals screened in Phase I, and the relation of those pathways to human disease.