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Application of the ToxMiner Database: Network Analysis of Linkage between ToxCast Phase I Chemicals and Thyroid Related Disease Outcomes

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The US EPA ToxCast™ program is using *in vitro* HTS (High-Throughput Screening) methods to profile and model bioactivity of environmental chemicals. The main goals of the ToxCast program are to generate predictive signatures of toxicity, and ultimately provide rapid and cost-effective alternatives to animal testing. The chemicals selected for Phase I are composed largely by a diverse set of pesticide active ingredients, which had sufficient supporting *in vivo* data included as part of their registration process with the EPA. Other miscellaneous chemicals of environmental concern were also included. Application of HTS to environmental toxicants is a novel approach to predictive toxicology and health risk assessment, and differs from what is required for drug efficacy screening in that biochemical interaction of environmental chemicals are sometimes weaker than that seen with drugs and their intended targets. Additionally, the chemical space covered by environmental chemicals is much broader compared to that of pharmaceuticals.

The ToxMiner database has been created and added to the EPA's ACToR (Aggregated Computational Toxicology Resource) chemical database. One purpose of the ToxMiner database is to link biological, metabolic and cellular pathway data to genes and *in vitro* assay data for the initial subset of chemicals screened in the ToxCast Phase I HTS assays. Also included in ToxMiner is human disease information, which correlates with ToxCast assays that target specific genetic loci. We have implemented initial pathway inference and network analyses, which allow linkage of the types of adverse health outcomes with exposure to chemicals screened in Phase I. Initial pathway analyses, in conjunction with statistical inference, has indicated the prevalence of thyroid cancer and thyroid-related pathologies as outcomes of exposure to those chemicals. Here we explore the enrichment of the ToxCast HTS dataset for thyroid related outcomes, drawing from published gene-expression data on genes related to thyroid phenotypes, and characterize the structure and linkage between the ToxCast chemical set and thyroid cancer and related etiologies using a Bayesian analysis framework. *Although this work was reviewed by EPA and approved for publication, it may not necessarily reflect official Agency policy.*