Building an Adverse Outcome Pathway Framework through HTS Data and Literature Mining Integration

N.C. Baker[1], N.S. Sipes[2], M.S. Hutson[3], T.B. Knudsen[2]

[1]Lockheed Martin, RTP, NC; [2]National Center for Computational Toxicology, Office of Research and Development, U.S. Environmental Protection Agency, RTP, NC; [3]Departments of Physics and Biological Sciences, Vanderbilt University, Nashville, TN

Interpreting EPA's ToxCast in vitro assay data in the context of Adverse Outcome Pathway (AOP) development is a significant challenge. While chemical activation in these assays may shed light on the molecular initiating event, the downstream effect of these activities at higher levels of biological organization (e.g., cellular, tissue, organ) leading to a potential toxicity endpoint can be difficult to identify. In this study we have used MeSH term annotations extracted from the biomedical literature to explore the relationship between the ToxCast assays significantly associated with cleft palate/cleft lip (CP/CL) toxicants and their possible downstream cellular, tissue, and organ level phenotypes. Approximately 60 ToxCast chemicals were identified as CP/CL toxicants either through the in vivo toxicity reference database, ToxRefDB, or literature reports. There were 29 ToxCast assays significantly ($p <= 0.05$) associated with these chemicals from univariate analyses. These 29 assays were associated with 18 unique genes and proteins. The MeSH terms for each of these genes and proteins were used to search a literature database of over 10 million articles to find the cellular, tissue, and organ MeSH annotation terms co-occurring with the genes and proteins. The co-occurrences counts calculated for the 66,275 resulting articles produced interesting significant connections. The ToxCast target leukocyte elastase, for instance, is highly co-annotated with the terms *Cell Adhesion*, *Extracellular Matrix*, and *Connective Tissue*, suggesting it should be examined for a possible role in extracellular matrix regulation during palate development. While cleft palate is used as an example, this robust literature mining technique has the potential to provide insight into AOP development for a broad range of toxicity endpoints.

This abstract does not necessarily reflect US EPA policy.