Adding Context to Tox21/ToxCast Data: Linking In Vitro Assays to Toxicity Outcomes

AL Karmaus[1], SM Bell[1], DG Allen[1], WM Casey[2], NC Kleinstreuer[2]

[1]ILS, RTP, NC, United States; [2]NIH/NIEHS/DNTP/NICEATM, RTP, NC, United States

The rapidly increasing inventory of publicly available in vitro high-throughput screening (HTS) assay data is facilitating the development of computational approaches for chemical hazard assessment. With HTS assays for more than 1,000 endpoints, the United States Environmental Protection Agency's ToxCast program provides insight into a wide variety of molecular and cellular targets. While ToxCast data is annotated to include information about technology platform, assay design, and gene target (where appropriate), it remains a challenge to place assay outputs into a toxicological context. Here we present a framework for mapping ToxCast HTS assay endpoints to toxicological adverse outcomes, moving beyond assay annotations to molecular biological targets to provide a more robust assay grouping schema. To date, 168 ToxCast assay endpoints have been manually mapped to "acute systemic toxicity" by linking them to distinct modes-of-action (MOA) known to be relevant to acute systemic toxicity. Acute systemic toxicity MOAs rich in ToxCast data include mitochondrial inhibition (20 assay endpoints), altered ion flow (23 assay endpoints), and oxidative stress (27 assay endpoints). Likewise, 154 assay endpoints have been mapped to "developmental toxicity", for which MOA groupings include neural crest cell disruption (26 assay endpoints), endocrine disruption (49 assay endpoints), and vascular disruption (23 assay endpoints), among others. To demonstrate the utility of MOA mapping for toxicity outcomes, we present a case study using the ToxPi prioritization approach, which leverages weighted relationships across various MOAs to yield insight into the potential of a chemical to elicit developmental toxicity. This approach provides a linkage of in vitro HTS assays to toxicological MOAs, which can facilitate chemical prioritization (i.e., with ToxPi), inform predictive modeling, or even aid in developing the foundation for adverse outcome pathways. This project was funded in whole or in part with federal funds from the NIEHS, NIH under Contract No. HHSN273201500010C.

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