Integration of Technological Interference into Curated HTS Data

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Thousands of chemicals have been screened using in vitro high-throughput screening (HTS) assays in the Tox21and ToxCast programs, generating millions of data points that can be difficult to interpret and review in detail. Many Tox21/ToxCast assays use luminescence and fluorescence technologies to generate readouts and determine chemical activity; however, test substances can contain substructures that interfere with these technologies to generate false-positive outcomes. To identify these potential false positives, Tox21 includes a series of assays to test for interference between its chemical library and red, blue, and green fluorescence or luciferase luminescence detection technologies. For chemicals that have not been tested in Tox21, InterPred (https://sandbox.ntp.niehs.nih.gov/interferences/) provides QSAR predictions for chemical interference from a model trained on the Tox21 10k library. To increase confidence in HTS data in the Integrated Chemical Environment (ICE; https://ice.ntp.niehs.nih.gov/), we have integrated Tox21- and InterPred-derived alerts for potential autofluorescence interference into the ICE curated HTS (cHTS) pipeline. We first searched the assay technology annotation inventory in the EPA's InvitroDB v3.5 database and identified over 300 assays that use luminescence or fluorescence. We then cross-referenced the chemicals tested in those assays with interferent chemicals identified in Tox21 and InterPred. Warning flags were assigned to any potentially impacted assay endpoint-chemical pairs, and these flags were added to the cHTS workflow. The interference flags in the ICE cHTS pipeline help to further refine the accuracy and context provided for users to interpret cHTS bioactivity calls. Project was funded by NIEHS under Contract No. HHSN273201500010C.