Chemical Selection for NTP's High Throughput Screening Initiative - Round 1

C. S. Smith[1]; J. Bucher[1]; A. Dearry[1]; C. Portier[1]; R. Tice[1]; K. Witt[1]; B. Collins[1]
[1]Environmental Toxicology Program, NIEHS, Research Triangle Park, NC, USA.

In support of a new HTS Initiative, the NTP is collaborating with the NIH Chemical Genomics Center (NCGC) to use quantitative HTS (qHTS) assays to test compounds for activity against defined biological targets (see Tice et al. Poster). This collaboration benefits both programs by adding toxicity testing capabilities to the NIH Molecular Libraries Initiative (MLI), and by allowing rapid implementation of NTP,s HTS program designed to screen large numbers of compounds for activity against targets and pathways with toxicological relevance (e.g., oxidative stress, inflammation, apoptosis). The NTP will link HTS-produced toxicity data to data from traditional toxicity assays, with the goal of identifying mechanisms of action requiring additional investigation, developing predictive models for biological response, and prioritizing substances for further evaluation. For the first round of testing, the NTP provided 1408 compounds (1353 unique, 55 duplicates to assess assay reproducibility) selected because they were soluble in dimethylsulfoxide at 10 mM and because they were associated with publicly available bioassay results. Most of these compounds originated as nominations to the NTP for toxicity testing of various types, and of these, virtually all have been tested in the Salmonella mutagenicity battery, while many have been studied in reproductive and chronic rodent bioassays. Also, reference sets of compounds proposed for developing in vitro assays for endocrine disruption or ocular toxicity were included. The set sent to the NCGC include nearly every chemical class of small molecules imaginable. Molecular weights ranged from approximately 100 to 400. Functionally, the set includes solvents, fire retardants, preservatives, flavoring agents, plasticizers, therapeutic agents, inorganic and organic pollutants, drinking water disinfection byproducts, pesticides and natural products. A second

set of compounds is currently being chosen based on the knowledge gained from this first set.