Evaluating the applicability of read-across tools and high throughput screening data for food relevant chemicals

Jalissa L. Wynder1, Jerald Ovesen, PhD2, Andrew Maier, PhD2, Richard Judson, PhD3; 4 Nicole Kleinstreuer; Mansi Krishan, PhD1.

1ILSI North America, Washington, DC; 2University of Cincinnati, Cincinnati, OH; 3EPA, RTP, NC; 4NTP NICEATM, Durham, NC

jwynder@ilsi.org

Alternative toxicity assessment methods to characterize the hazards of chemical substances have been proposed to reduce animal testing and screen thousands of chemicals in an efficient manner. Resources to accomplish these goals include utilizing large in vitro chemical screening data from efforts such as the high-throughput (HT) Tox21/ToxCast programs and read-across tools such as the Organization for Economic and Cooperation Development (OECD) QSAR toolbox. The goal of this study is to compare the results from traditional toxicity studies with predictions from these proposed alternative testing methods. More specifically, we evaluated the utility of these emerging methods by using data from ToxCast combined with read-across tools to evaluate the hazards of current use food relevant chemicals. Briefly, computational models developed using Tox21/ToxCast HT data were used to predict estrogenic and/or androgenic activity of food relevant chemicals. We identified 94 putatively estrogen-or androgen-active food relevant chemicals in ToxCast. To reduce possible confounding from cytotoxicity and cell stress effects, the estrogen receptor (ER) and androgen receptor (AR) model results were filtered for any observed in vitro cytotoxicity, which resulted in 89 putatively active, non-cytotoxic food chemicals. To conduct our proof of concept study, we further shortlisted these 89 chemicals based on the availability of in vivo data related to developmental and reproductive toxicity (DART). This resulted in 10 putatively active, non-cytotoxic, endocrine disrupting chemicals. More specifically we identified 3 ER agonists, 1 ER antagonist, 1 AR agonist, and 9 AR antagonists. Structural similarity and similar mode of action were used to identify potential analogues for each of the 10 chemicals. We used read-across approaches to compare the pattern and potency of DART for the analogues identified to the known endocrine-disrupting potential of the target chemical. These methods helped us identify 3 target chemicals for which the analogue approach and computational models successfully predicted the putative endocrine disrupting potential of the food relevant chemicals. This study demonstrates that HT assay data and read-across tools can be used together to characterize the hazards of chemical substances, although limitations in the approaches are evident. This abstract does not necessarily reflect EPA policy.

Current word count: 346