Integrated Chemical Environment: An Advanced Platform Aiding NAM-based Chemical Assessments

A. Unnikrishnan[1], A.L. Karmaus[1], V. Hull[1], X. Chang[1], A. Borrel[1], K.T. To[1], A. Daniel[1], S. Cooper[1], J. Phillips[2], E. McAfee[2], D.G. Allen[1], W. Casey[3], N. Kleinstreuer[4]

[1]Inotiv, RTP, NC, United States; [2]Sciome, RTP, NC, United States; [3]NIH/NIEHS/DTT, RTP, NC, United States; [4]NIH/NIEHS/DTT/PTB/NICEATM, RTP, NC, United States

Traditional toxicological assessments have relied almost exclusively on results from in vivo toxicity testing approaches. With the development of new approach methodologies (NAMs), researchers can now integrate in vitro data, in silico predictions, legacy in vivo studies, and computational tools to make informed decisions. The Integrated Chemical Environment (ICE, https://ice.ntp.niehs.nih.gov/) provides toxicologically relevant data curated by the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Test Methods (NICEATM) and exploratory tools for interpreting these data. ICE has played a significant role in assisting the development, interpretation, and implementation of NAM-based projects, and is continuously evolving to address growing data needs and incorporate advanced features within its tools. The latest ICE update includes multiple new datasets and features to enhance the computational tool capabilities. One of the key updates in the latest ICE release (v3.8) is the integration of exposure predictions from the U.S. Environmental Protection Agency (EPA)'s SEEM3 model. Exposure predictions from SEEM3 can provide general population-level exposure predictions across multiple scenarios, including consumer, dietary, far-field industrial and pesticide sources. Exposure predictions for over 400,000 chemicals are included within the applicability domain of the model, with the median, 5th, and 95th percentile estimates reported for each chemical. These data are now accessible through the ICE Search tool and can also be compared to the equivalent administered doses predicted from the ICE In Vitro to In Vivo Extrapolation (IVIVE) tool. The ICE curated high-throughput screening (cHTS) dataset has also been updated to incorporate ~135,000 new sample-endpoint relationships, which can provide further data support for various in vitro bioactivity assessments and computational toxicology workflows. Several new technological interference warning flags have been added into the cHTS curation workflow, providing additional insight towards in vitro data confidence. Finally, chemical-use data have been updated to incorporate functional use categories that broaden the underlying data for the Chemical Characterization tool. These examples of new and updated ICE data sets offer additional context to provide comprehensive yet simple and interpretable outputs throughout the different ICE tools. With each release, ICE implements advanced features to its user interface and computational tools that aim to ease data exploration for all ICE end users. Key among the updates implemented in ICE v3.8 are the expanded Physiologically Based Pharmacokinetic (PBPK) and IVIVE tools, both of which now include a gestational model from the EPA's httk package. Additionally, the enhanced ICE Search tool now provides an option to search the ICE data repository using a chemical name along with other pre-existing chemical identifier input options. This update also provides a completely revised Search results page with new summary statistics and publication-quality result visualization options for all the data within ICE. Together, these ICE features allow its users to explore ICE's ever-growing data repository of over 1 million chemicals, supporting purposes like chemical analysis for NAMs-based assessments. This project was funded in whole or in part with federal funds from the NIEHS, NIH under Contract No. HHSN273201500010C.

Keywords: Bioinformatics, Alternatives to Animal testing, Computational Toxicology, Exposure Assessment