Use of Tier 0 Exposure and Bioactivity Predictions for Rapid Prioritization of Chemicals for Further Testing


The development of new tools and capabilities should be accompanied by case studies designed to evaluate their usefulness and to identify areas of needed improvement. This case study focuses on the first two tiers of our proposed tiered approach for risk-based chemical evaluation: the preliminary assessment (Tier 0) and the initial *in vitro* screening assessment (Tier 1) (see Figure 1). We apply cheminformatics tools, machine learning, and high-throughput *in vitro* to *in vivo* extrapolation (HT-IVIVE) modeling to support chemical triage prior to the selection of Tier 2 fit-for-purpose assays. We propose an initial triage based on the ratio between high-throughput exposure estimates and Thresholds of Toxicological Concern (TTCs), followed by automated read-across to identify suitable analogues for determining potential endpoints and potency estimates in lieu of further testing. We take advantage of curated structures for over 45,000 chemicals from the Collaborative Estrogen Receptor Activity Prediction Project (CERAPP, Mansouri et al., 2016), which includes all ToxCast and Tox21 compounds, among others. This effort is being conducted in collaboration with scientists at the EPA/NCCT.

We designed a plan for prioritizing chemicals of interest using margins of exposure (MoE) calculated from high throughput bioactivity and exposure prediction methodologies. Using the CERAPP chemical structure database, we identified ~300 chemicals with well-defined structures that also had bioactivity data in ToxCast/Tox21. Bioactivity for these compounds was estimated using two prediction methodologies: Threshold of Toxicological Concern (TTC) and oral equivalent dose (OED) based on ToxCast/Tox21 bioactivity data coupled with HT-IVIVE. Population level estimates of exposure were developed using NCCT’s ExpoCast SEEM model. Chemicals were then ranked based on MoE. The next phase of the project will focus on testing the utility of QSAR and bioactivity based read-across to predict chemical risk. We are taking a systematic approach to defining the compounds that will be evaluated in this case study. The >45,000 compounds in CERAPP, were binned into at least 17 chemical families of interest, and we have begun to evaluate which of these have adequate predictive and experimental data to be used as structural analogues for read across evaluation. We then interrogated combinations of descriptors (i.e. structural, physicochemical, reactivity) to identify those that are most useful for maximizing read-across capabilities. In doing this, we have illustrated the leveraging of existing and relevant tools to address real-world toxicology concerns that can be applied today, concurrent with of the development of new and improved prediction tools.

In 2018 we continued TTC evaluation by developing TTCs for the 45,000 chemicals in the CERAPP database. To provide these values in a publicly available portal, we developed an online interface for TTC and margin of exposure lookup for 45,000 compounds. ([https://scitovation.shinyapps.io/chemical_prioritization/](https://scitovation.shinyapps.io/chemical_prioritization/)).
Implications: The current chemical safety testing paradigm for new compounds entering commerce is expensive and inefficient, relying heavily on animal testing with questionable relevance to human safety. Currently there are ~15,000 chemicals in commerce lacking formal assessments on their impact on human health. With the recent changes to the TSCA regulations, there is a growing need for methods to support rapid, risk-based chemical prioritization. The recently enacted Lautenberg Chemical Safety Act involves an “inventory reset” of these chemicals, which will require EPA to explicitly declare the chemicals in commerce that require additional testing. New risk-based approaches can help to catalyze change from the current regulatory emphasis on hazard identification and will provide an improved scientific justification for (and confidence in) chemical read-across. Here, we demonstrate the use of a tiered framework for triaging this chemical universe, providing a means of prioritizing compounds identified as most likely to pose a health risk.

Collaborations: EPA NCCT

Key words: exposure, read-across, fit-for-purpose, PLETHEM, TTC, prioritization

Project start and end dates: January 2017 – December 2019

Peer-reviewed publication(s):


Presentation(s):


This abstract was prepared by the principal investigator for the project. Please see lri.americanchemistry.com for more information about the LRI.
Durham, NC, April 16-18, 2018.


Other publication(s): None to date.

Abstract revision date: July 2019

References: