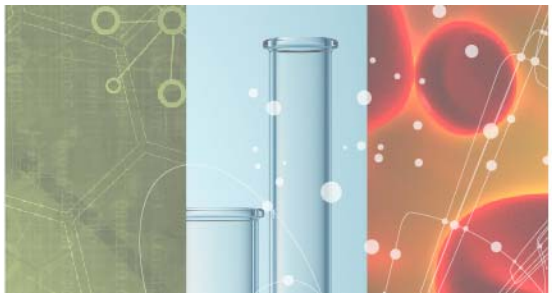

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ACC Science and Research Highlights

A Step Closer to Applying 21st Century Approaches for Risk-Based Priority Setting and Screening to Commodity Chemicals: Exposure-Activity Profiling

Risk is a function of both hazard and exposure. Use of 21st century *in vitro* toxicity screening methods for risk-based decision making requires:

1) relevant methods to quantify bioactivity (where these results can be used as a surrogate for potential toxicity),

2) methods to convert concentrations *in vitro* to equivalent human exposure levels (*in vitro* to *in vivo* extrapolation), and

3) measured or predicted human exposures.

Previous Research on Data-Rich Substances Demonstrated the Feasibility of Using High-Throughput *In Vitro* Results for Human Health Risk-Based Screening.

In previous research, investigators showed that ToxCast™ bioactivity results could be used for risk-based prioritization and screening for well-studied chemicals with rich data sources. For these substances, actual human exposures are fairly well established (or can readily be predicted) and these rich datasets support *in vitro* to *in vivo* extrapolation. Using a margin-of-exposure approach, results showed many substances exhibited large margins of exposure – that is, effects in the *in vitro* ToxCast assays occurred at equivalent human dose levels that were well above actual human exposures.

New Research Shows How to Overcome the Barriers Faced Due to Lack of Exposure Information and Toxicity Data for Commodity Chemicals.

For a large fraction of chemicals in commerce, quantitative human daily intake data are lacking and there is insufficient information available to support extrapolating from *in vitro* bioactivity levels to *in vivo* human exposure values. To tackle this challenge, scientists from The Hamner Institutes for Health Sciences collaborated with EPA scientists focused on ToxCast Phase II chemicals – substances which have limited reliable exposure information and sparse toxicity data.

The results of this collaboration have been recently published: "**Incorporating High-Throughput Exposure Predictions with Dosimetry-Adjusted In Vitro Bioactivity to Inform Chemical Toxicity Testing**." To judge risk and determine safety using this 21st century risk assessment methodology, activity-to-exposure ratios (AERs) are employed. AERs are analogous to margins of exposure and provide a way to make risk-based comparisons – the greater the distance between the (bio)activity and predicted exposure level, the greater the "safety."

Click here to learn more about the research programs at the Hamner Institutes for Health Sciences.

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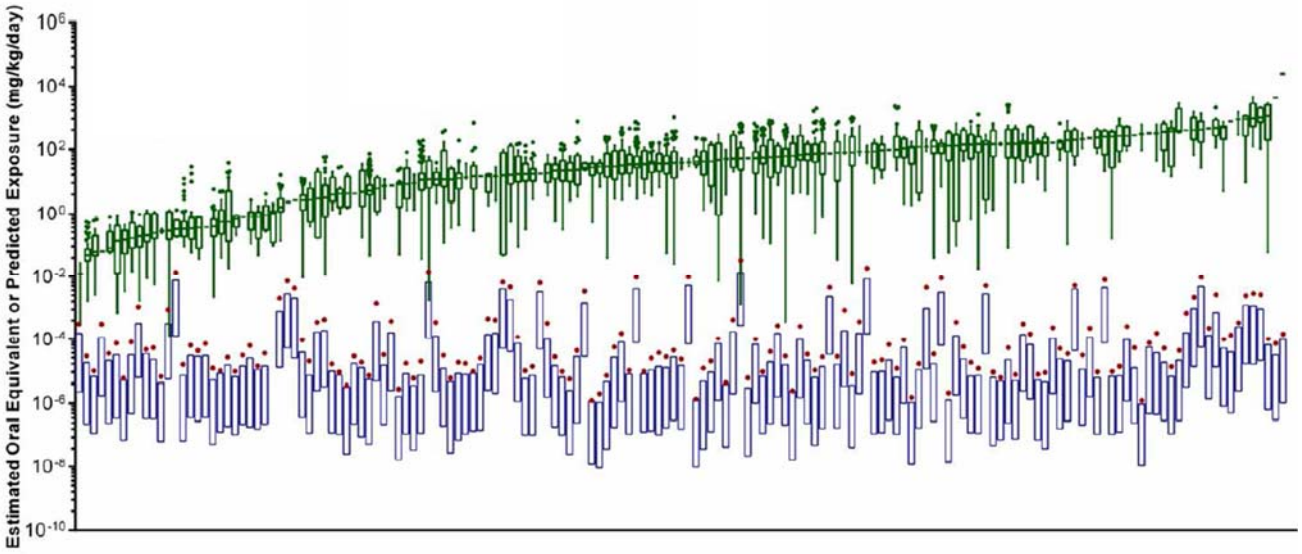
Comparison of human oral equivalent doses (OEDs) and exposure predictions for 163 ToxCast Phase II chemicals.
Figure 2 from Wetmore et al. 2015. Toxicol Sci. 148(1): 121–136. (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4620046/)



- Scientists extended the *in vitro* to *in vivo* extrapolation (IVIVE) methods pioneered by the Hamner to estimate human-equivalent doses for a subset of 163 ToxCast Phase II chemicals.
- EPA's recent high-throughput exposure predictions (ExpoCast™), generated using probabilistic modeling and Bayesian approaches, provided the human exposure estimates to enable calculating AERs. Values corresponding to the upper bound of the 95% confidence interval of the geometric mean for the exposure predictions were used.
- The results of this risk-based screening indicate that many of these substances would be a low priority for additional toxicity or risk evaluation.
  - Of the 163 chemicals assessed, approximately 90% (147) exhibited AERs >100, meaning the human-equivalent doses corresponding to the *in vitro* AC50s (or lowest effective concentrations) for these substances were more than 100-fold larger than predicted human exposures. In other words, exposures needed to achieve responses noted in the most sensitive in vitro ToxCast assays for each chemical are 2 or more orders of magnitude higher than predicted human exposures (i.e., exposures corresponding to the 95% confidence interval for an average person with non-occupational exposure).
- From the lens of risk based prioritization, those substances with AERS <100 (approximately 10% of the substances evaluated in this research project) would be candidates for further in-depth evaluation and/or toxicity testing.

The Path Ahead: Blazing a Trail for Use in TSCA Modernization

For substances that are not data rich, "Incorporating High-Throughput Exposure Predictions with Dosimetry-Adjusted In Vitro Bioactivity to Inform Chemical Toxicity Testing" demonstrates the feasibility of combing high-throughput bioactivity results with exposure forecasting for risk-based priority setting and screening-level risk determinations. Additional research is underway by the Long Range Research Initiative, the Hamner, and EPA to continue to improve, evolve, and build greater confidence in these methods. Focus is being given to developing additional assays to expand the biological space covered by high-throughput screening methods, improving exposure modeling and further refining IVIVE methods.

With respect to IVIVE, the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and EPA recently launched an initiative to engage the science community to (1) review the state of the science for using IVIVE, (2) identify areas that require additional data and/or research, and (3) highlight best practices and examples of how best to apply IVIVE in a tiered risk decision-making strategy. Dr. Barbara Wetmore of the Hamner, the lead author of the research article discussed above, is a key participant in this initiative and provided the opening webinar.

For more information on these scientific research projects please contact
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