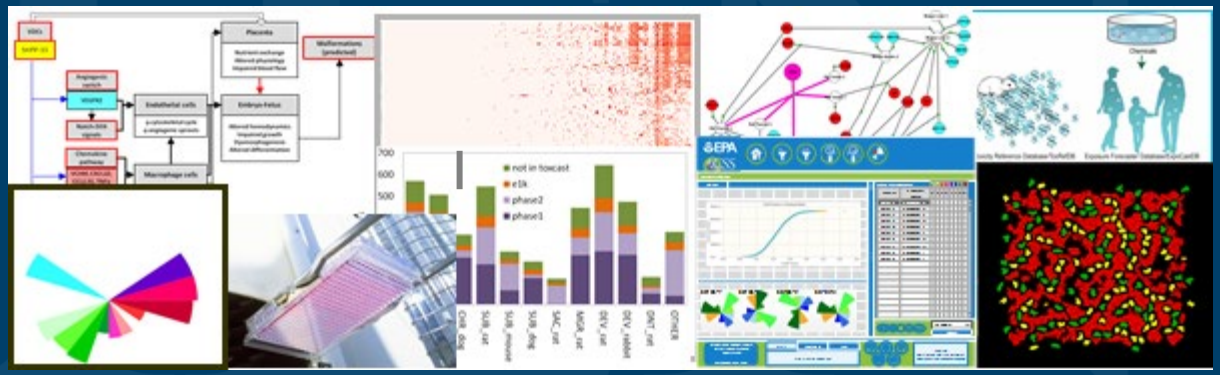
EPA United States Environmental Protection Agency

ToxCast/CompTox Update



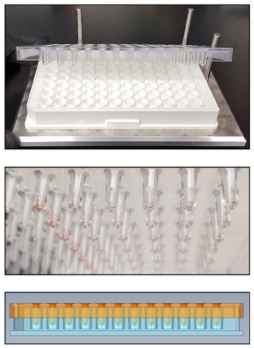
21st Century Toxicology Satellite Meeting

May 12, 2021

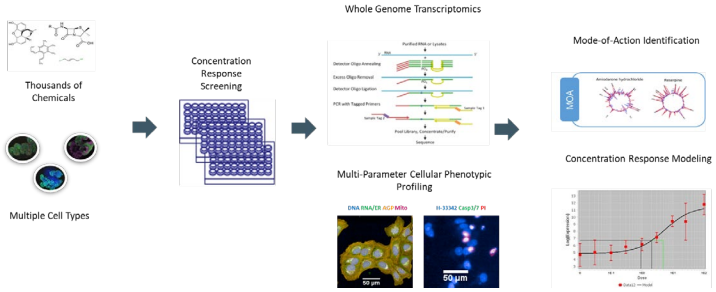
Maureen R. Gwinn
Center for Computational Toxicology and Exposure
Office of Research and Development
US Environmental Protection Agency

Some recent accomplishments

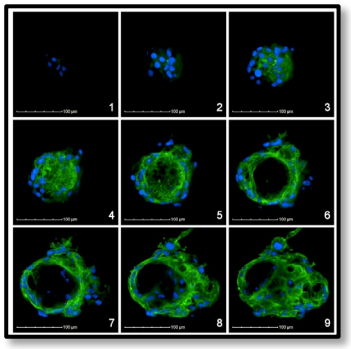
Metabolic Competence

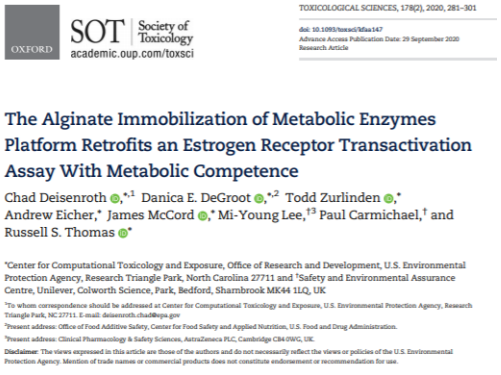


High Content/Coverage Screening



OCM Model for Thyroid

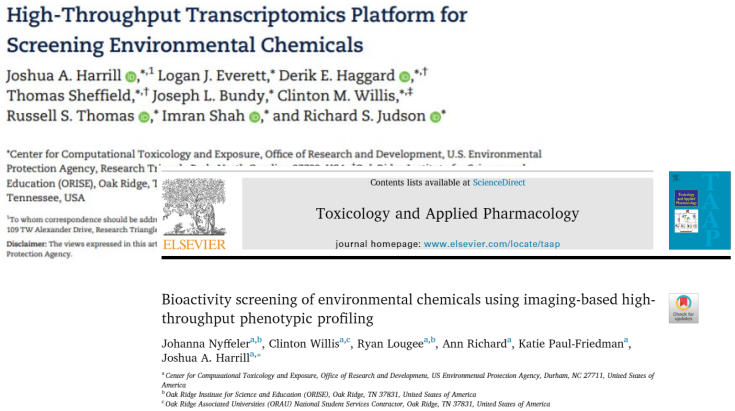




The Alginate Immobilization of Metabolic Enzymes Platform Retrofits an Estrogen Receptor Transactivation Assay With Metabolic Competence

Chad Deisenroth, Danica E. DeGroot, Todd Zurlinden, Andrew Eicher, James McCord, Mi-Young Lee, Paul Carmichael, and Russell S. Thomas

Deisenroth et al. Toxicological Sciences, Volume 178, Issue 2, December 2020, Pages 281–301, https://doi.org/10.1093/toxsci/kfaa147



High-Throughput Transcriptomics Platform for Screening Environmental Chemicals

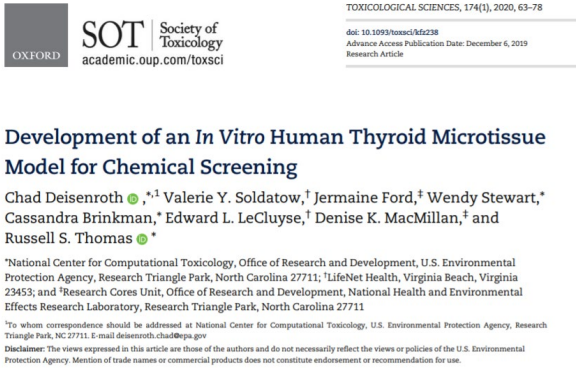
Joshua A. Harrill, Logan J. Everett, Derik E. Haggard, Thomas Sheffield, Joseph L. Bundy, Clinton M. Willis, Russell S. Thomas, Imran Shah, and Richard S. Judson

Toxicology and Applied Pharmacology

Bioactivity screening of environmental chemicals using imaging-based high-throughput phenotypic profiling

Johanna Nyffeler, Clinton Willis, Ryan Lougee, Ann Richard, Katie Paul-Friedman, Joshua A. Harrill

Nyffeler et al. SLAS Discov. 2021 Feb;26(2):292-308. doi: 10.1177/2472555220950245
Harrill et al. Toxicol Sci. 2021 Feb 4;kfab009. doi: 10.1093/toxsci/kfab009. Online ahead of print

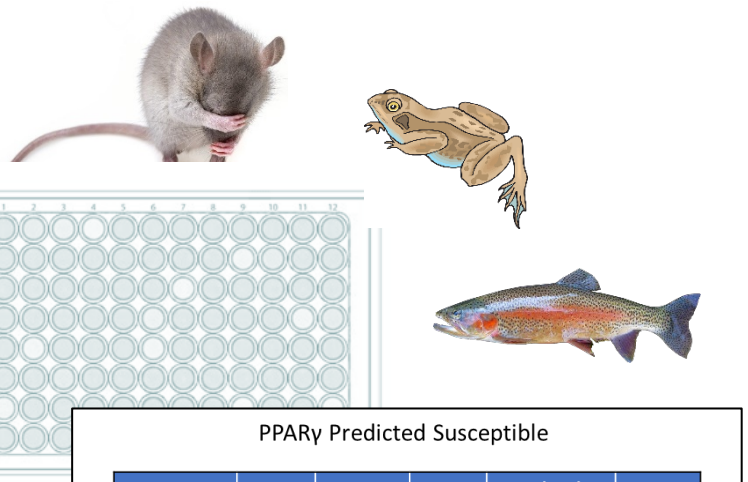


Development of an *In Vitro* Human Thyroid Microtissue Model for Chemical Screening

Chad Deisenroth, Valerie Y. Soldatow, Jermaine Ford, Wendy Stewart, Cassandra Brinkman, Edward L. LeCluyse, Denise K. MacMillan, and Russell S. Thomas

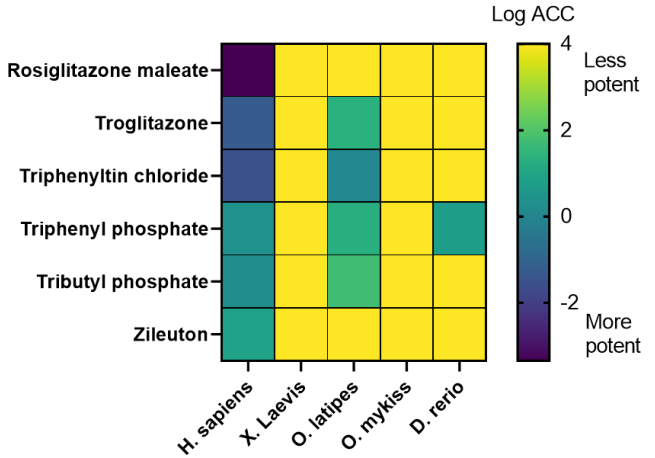
Deisenroth et al. Toxicological Sciences, Volume 174, Issue 1, March 2020, Pages 63-78, https://doi.org/10.1093/toxsci/kfz238

Evaluating Cross-species Differences in Nuclear Receptor-Ligand Interactions using a Multiplexed In Vitro Bioassay



PPARγ Predicted Susceptible

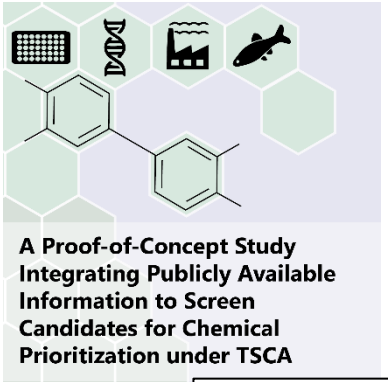
Taxa	Homo sapiens	Xenopus laevis	Oryzias latipes	Oncorhynchus mykiss	Danio rerio
Rosiglitazone	Y 1.0	N 0.06	N <0.006	N <0.006	N <0.006

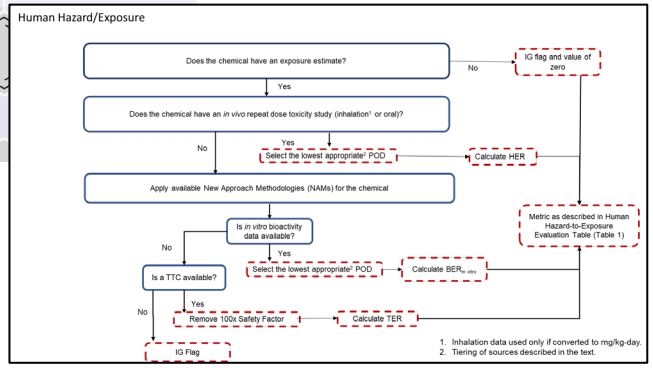


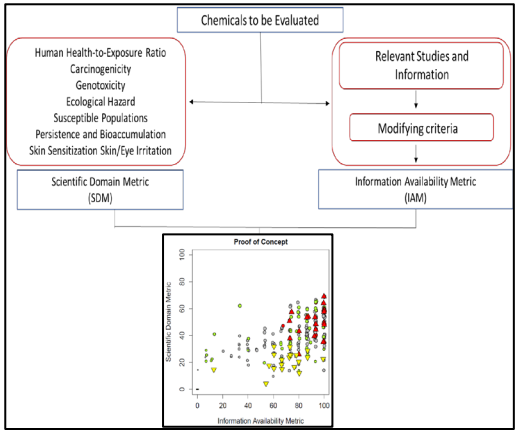
- Five species intended to capture maximum variability in PPARγ, PPARα, RXRβ, and GR sensitivity were selected for incorporation into a multiplexed in vitro bioassay.
- Species-specific differences in sensitivity were detected for all ligands tested as well as for environmental samples.
- Results suggest that effects-based monitoring employing human cell lines may misrepresent hazard to aquatic organisms for certain NRs.
- Screening of additional chemicals in the assay developed may provide new insights into predicting cross-species sensitivity based on amino acid sequence conservation.

Slide adapted from Dan Villeneuve

Implementation of the Proof-of-Concept Study for Integrating Publicly Available Information to Screen Candidates for Chemical Prioritization under TSCA







- Short and long-term approaches to identify a pool of potential candidates that inform selection of low and high priority candidates for prioritization
- Long-term approach uses both traditional and NAM data to bin chemicals based on a combination of risk-related scoring and information availability
- The approach was intended to:
  - Understand the landscape of publicly-available information on the over 33,000 substances on the active inventory
  - Provide a transparent and reproducible process for integrating available information and identifying potential information gaps
  - Increase efficiency and manage workload by focusing expert review on substances that may have a greater potential for selection as high- or low-priority candidates
  - Create a flexible and sustainable process that can adapt to scientific advances and continual generation of new safety-related information
  - Organize the process into modular workflows that can be readily updated or adapted to address scientific advances and prioritization needs under other mandates

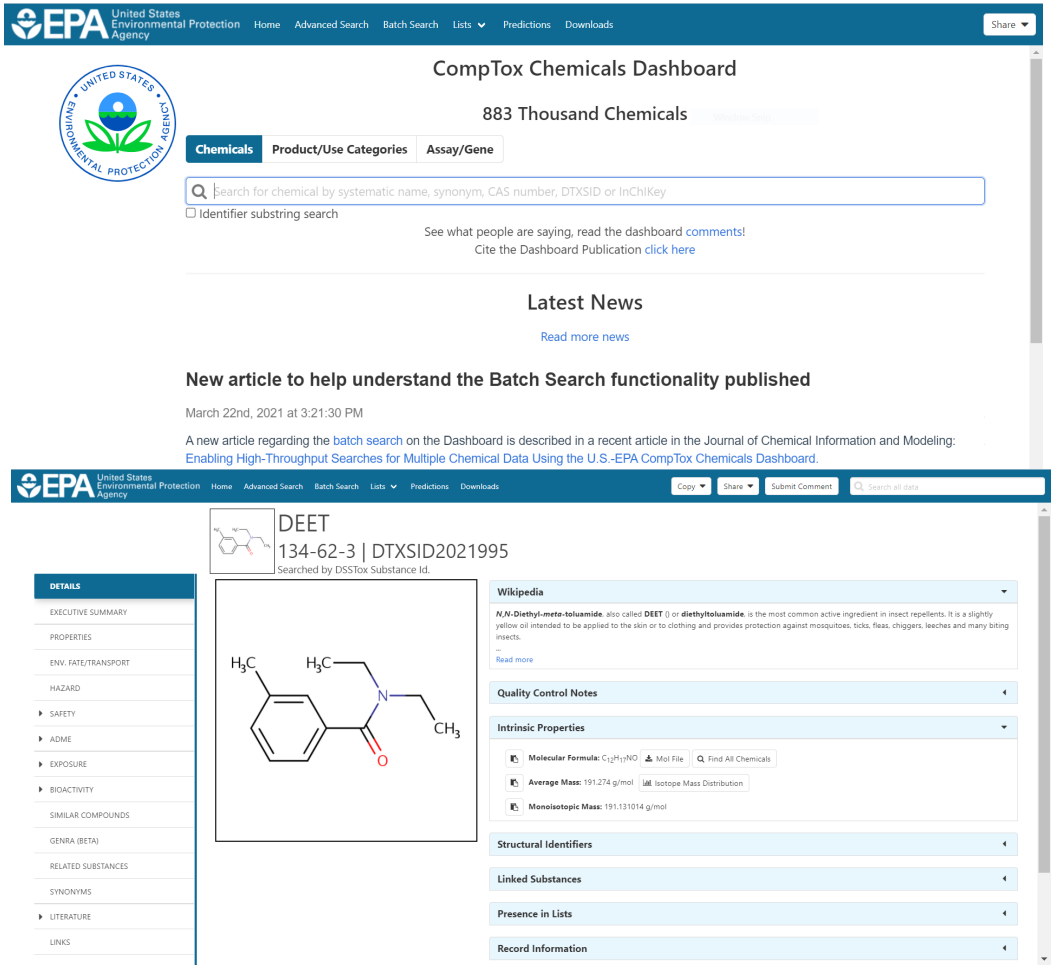
New Version of the CompTox Chemicals Dashboard – Later this Year!

Data

- Soon with >900,000 chemicals
- New version of ToxVal v9 and invitrodb 3.4

User Experience

- Replacement of tables in the application with more flexible table handling for data
- The Abstract Sifter and GenRA will be presented as separated tools in a modular way that have been plugged into the new Tools menu of the dashboard.
- Performance will be much enhanced in terms of download speed and the batch search will be able to handle much larger input sets.



https://comptox.epa.gov/dashboard

Acknowledgements and Questions

EPA Colleagues:
- CPHEA
- CEMM
- OCSPP
- OLEM
- Regions

Collaborative Partners:
- NTP
- FDA
- NCATS
- Health Canada
- ECHA
- JRC
- EFSA
- A*STAR