Integrating Toxicity, Toxicokinetic, and Exposure Data for Risk-based Chemical Alternatives Assessment

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International Society of Exposure Science
"Quantitative High-Throughput Exposure Methods for Chemical Alternatives and Comparative Risk Assessment"
Research Triangle Park, NC
October 18, 2017

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EPA Office of Research and Development

- The Office of Research and Development (ORD) is the scientific research arm of EPA

- Research is conducted by ORD's three national laboratories, four national centers, and two offices
  - Includes **National Center for Computational Toxicology** and **National Exposure Research Laboratory**

- 14 facilities across the country and in Washington, D.C.

- Six research programs
  - Includes **Chemical Safety for Sustainability**

- Research conducted by a combination of Federal scientists; contract researchers; and postdoctoral, graduate student, and post-baccalaureate trainees

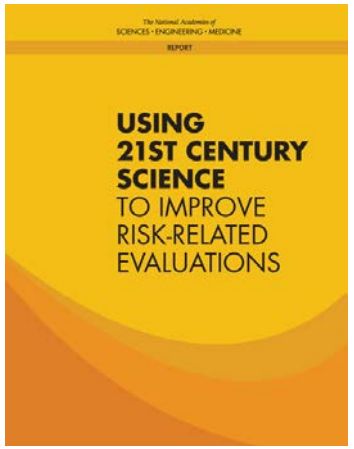
ORD Facility in Research Triangle Park, NC

Chemical Regulation in the United States

- Park *et al.* (2012): At least 3221 chemicals in pooled human blood samples, many appear to be exogenous
- A tapestry of laws covers the chemicals people are exposed to in the United States (Breyer, 2009)
- Different testing requirements exist for food additives, pharmaceuticals, and pesticide active ingredients (NRC, 2007)
- Most other chemicals, ranging from industrial waste to dyes to packing materials are covered by the recently updated Toxic Substances Control Act (TSCA)
  - Thousands of chemicals on the market were either "grandfathered" in or were allowed without experimental assessment of hazard, toxicokinetics, or exposure
  - Thousands of new chemical use submissions are made to the EPA every year
  - **Methods are being developed to prioritize these existing and new chemicals for testing**

November 29, 2014

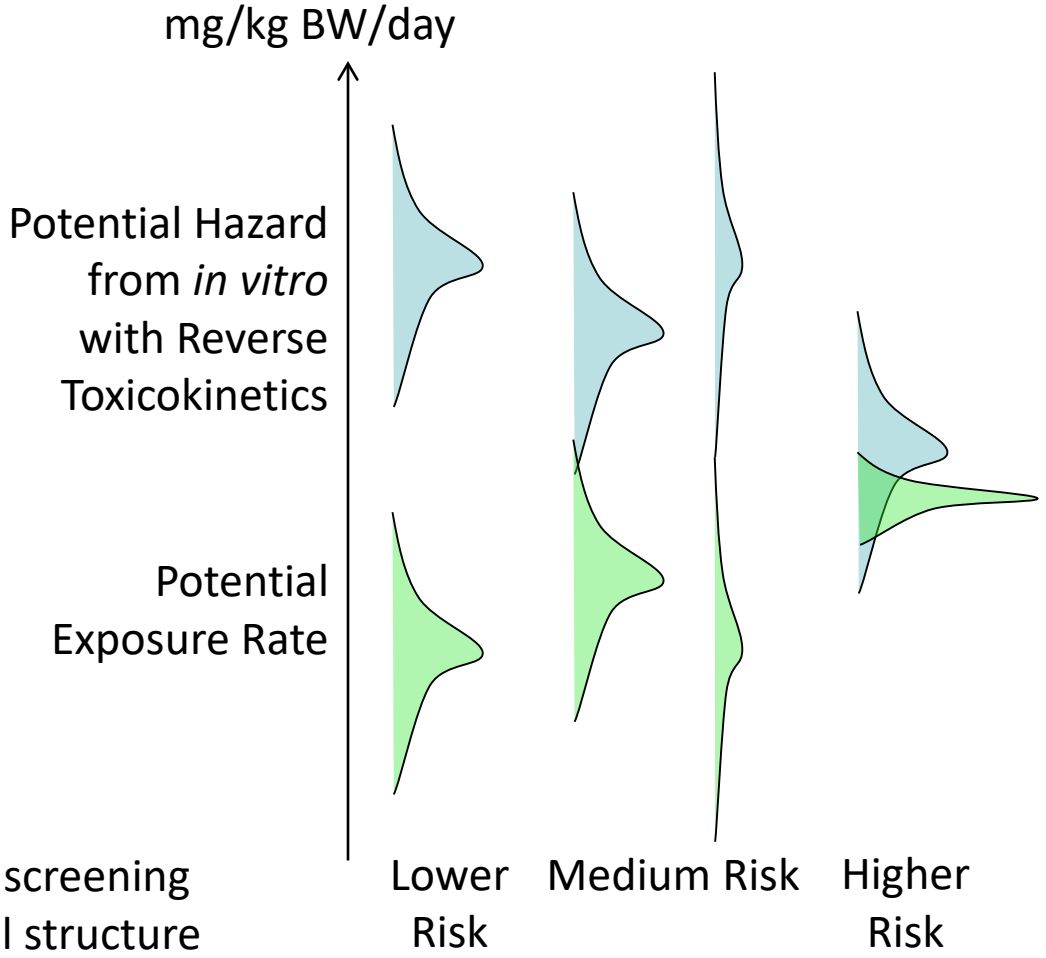
High-Throughput Risk Prioritization



National Academy of Sciences, January, 2017:
"Translation of high-throughput data into risk-based rankings is an important application of exposure data for chemical priority-setting. Recent advances in high-throughput toxicity assessment, notably the ToxCast and Tox21 programs… and in high-throughput computational exposure assessment… have enabled first-tier risk-based rankings of chemicals on the basis of margins of exposure…"

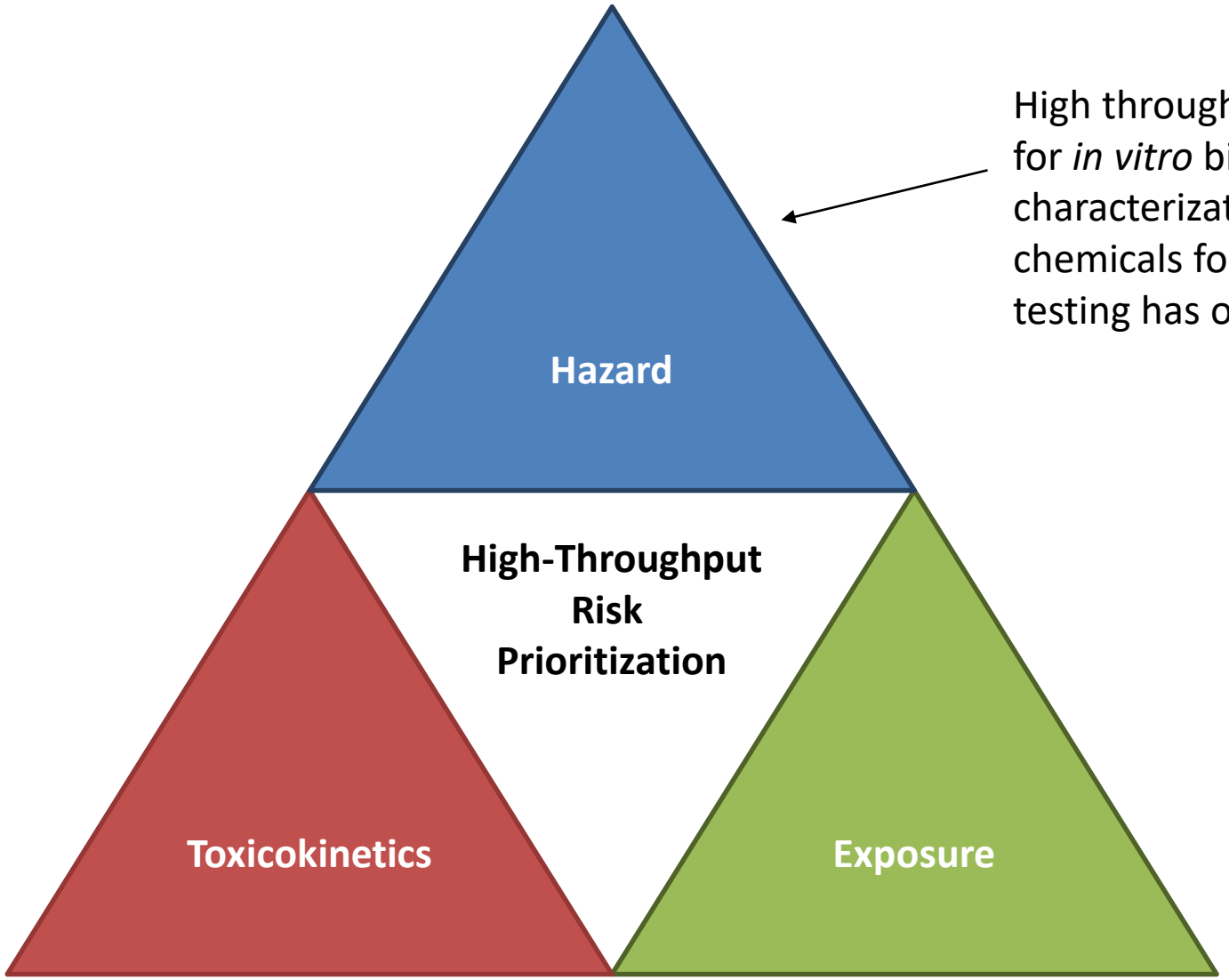
High throughput risk prioritization needs:

1. high throughput **hazard** characterization
2. high throughput **exposure** forecasts
3. high throughput **toxicokinetics** (*i.e.*, dosimetry)



Providing predictions for novel compounds will need to rely on screening massive chemical libraries and drawing inference from chemical structure (*e.g.*, quantitative structure activity relationships, QSAR)

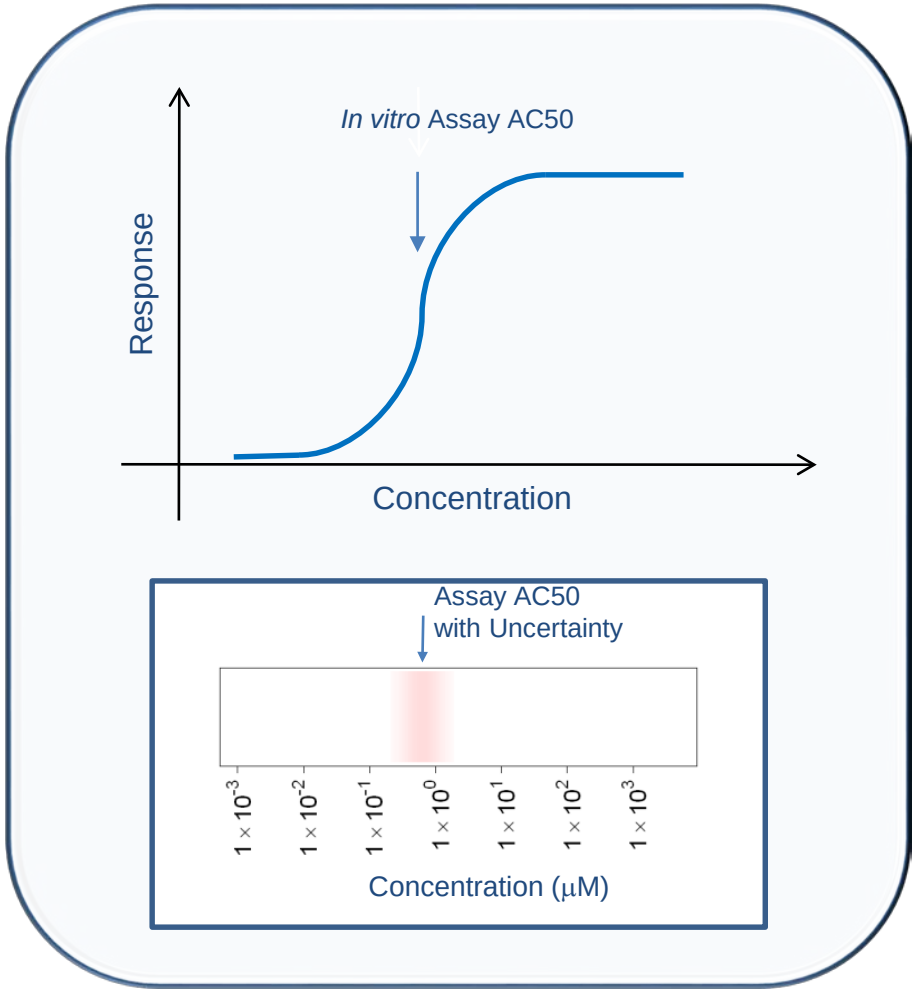
High-Throughput Risk Prioritization



High throughput screening (HTS) for *in vitro* bioactivity allows characterization of thousands of chemicals for which no other testing has occurred

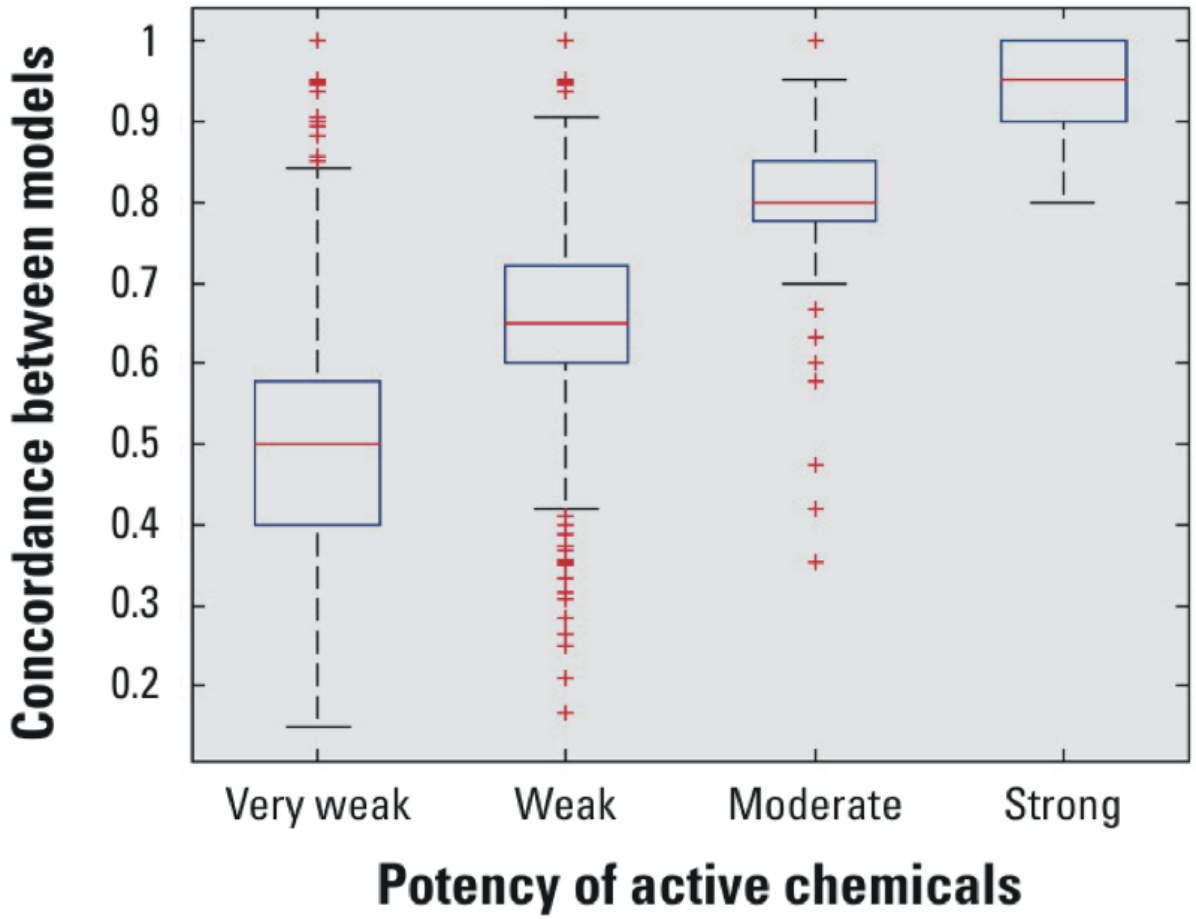
High-Throughput Screening

- **Tox21**: Examining >8,000 chemicals using ~50 assays intended to identify interactions with biological pathways (Schmidt, 2009)
- **ToxCast**: For a subset (>2000) of Tox21 chemicals ran >1100 additional assays (Kavlock *et al.*, 2012)
- Most assays conducted in dose-response format (identify 50% activity concentration – AC50 – and efficacy if data described by a Hill function, Filer *et al.*, 2016)
- Bioactivity profile for untested chemicals can be compared with profiles observed for reference chemicals with known toxicities



CERAPP: Collaborative Estrogen Receptor Activity Prediction Project

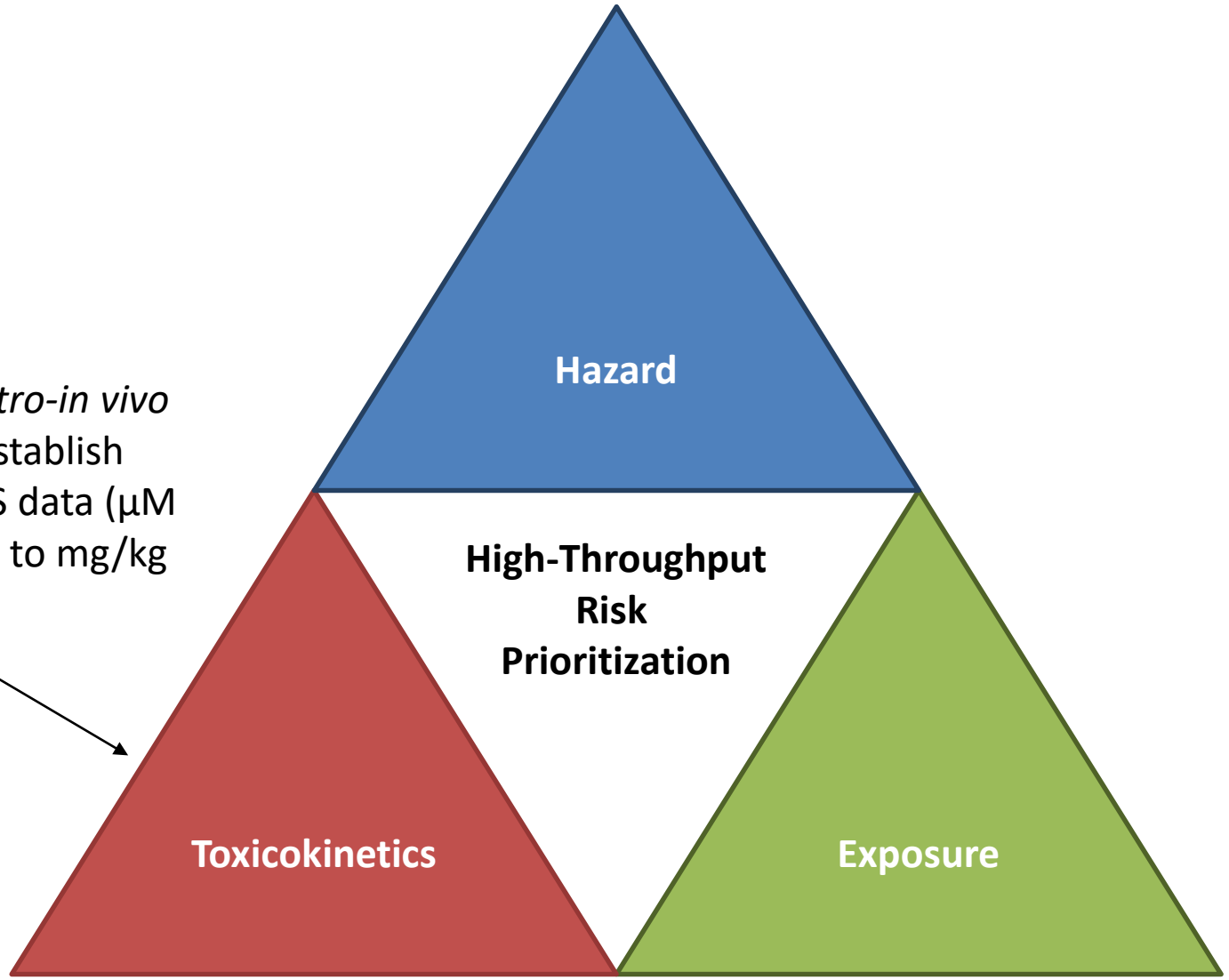
- ToxCast can only test those compounds that can be procured in relatively pure form and are not volatile
  - Need QSAR models
- CERAPP combined multiple models developed in collaboration with 17 groups in the United States and Europe to predict estrogen receptor (ER) activity
- Mostly used a common training set of 1,677 chemicals tested by ToxCast to make predictions for 32,464 chemical structures
- Predictions were evaluated on a set of 7,522 chemicals curated from the literature
- A consensus model was built by weighting models on scores based on their evaluated accuracies



Mansouri *et al.*, (2016)

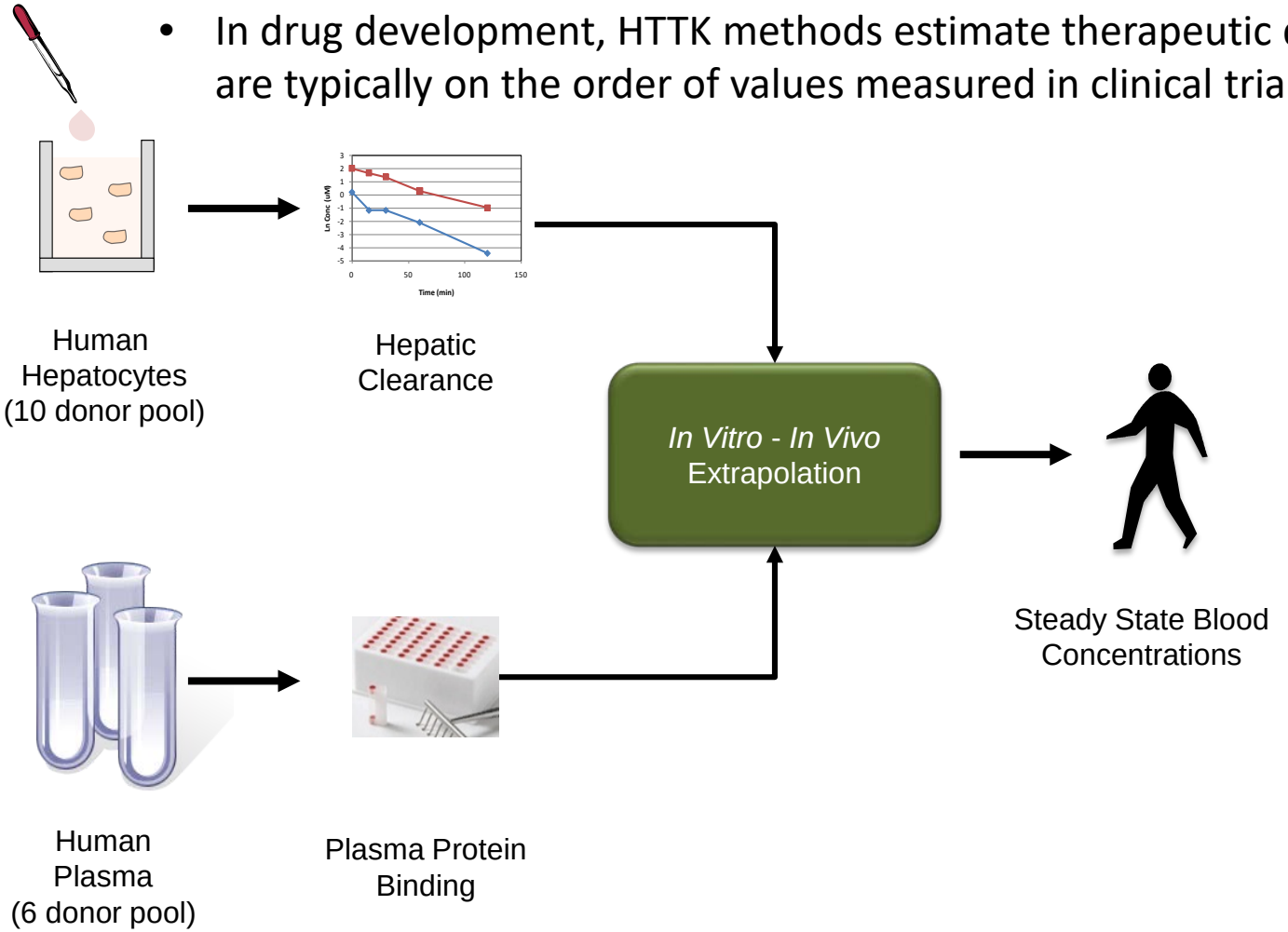
High-Throughput Risk Prioritization

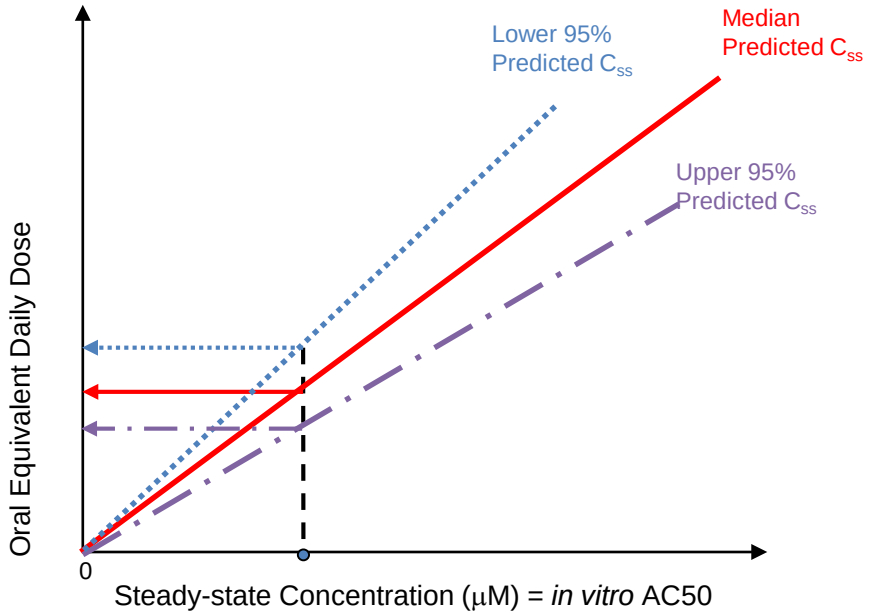
Toxicokinetics allows *in vitro-in vivo* extrapolation (IVIVE) to establish real world context for HTS data (µM concentrations converted to mg/kg BW/day dose rates)



High-Throughput Toxicokinetics (HTTK)

- Toxicokinetics describes chemical absorption, distribution, metabolism and excretion (ADME) by the body
- **Most chemicals do not have TK data** – we use *in vitro* methods adapted from pharma to fill gaps (i.e., HTTK)
- In drug development, HTTK methods estimate therapeutic doses for clinical studies – predicted concentrations are typically on the order of values measured in clinical trials (Wang, 2010)

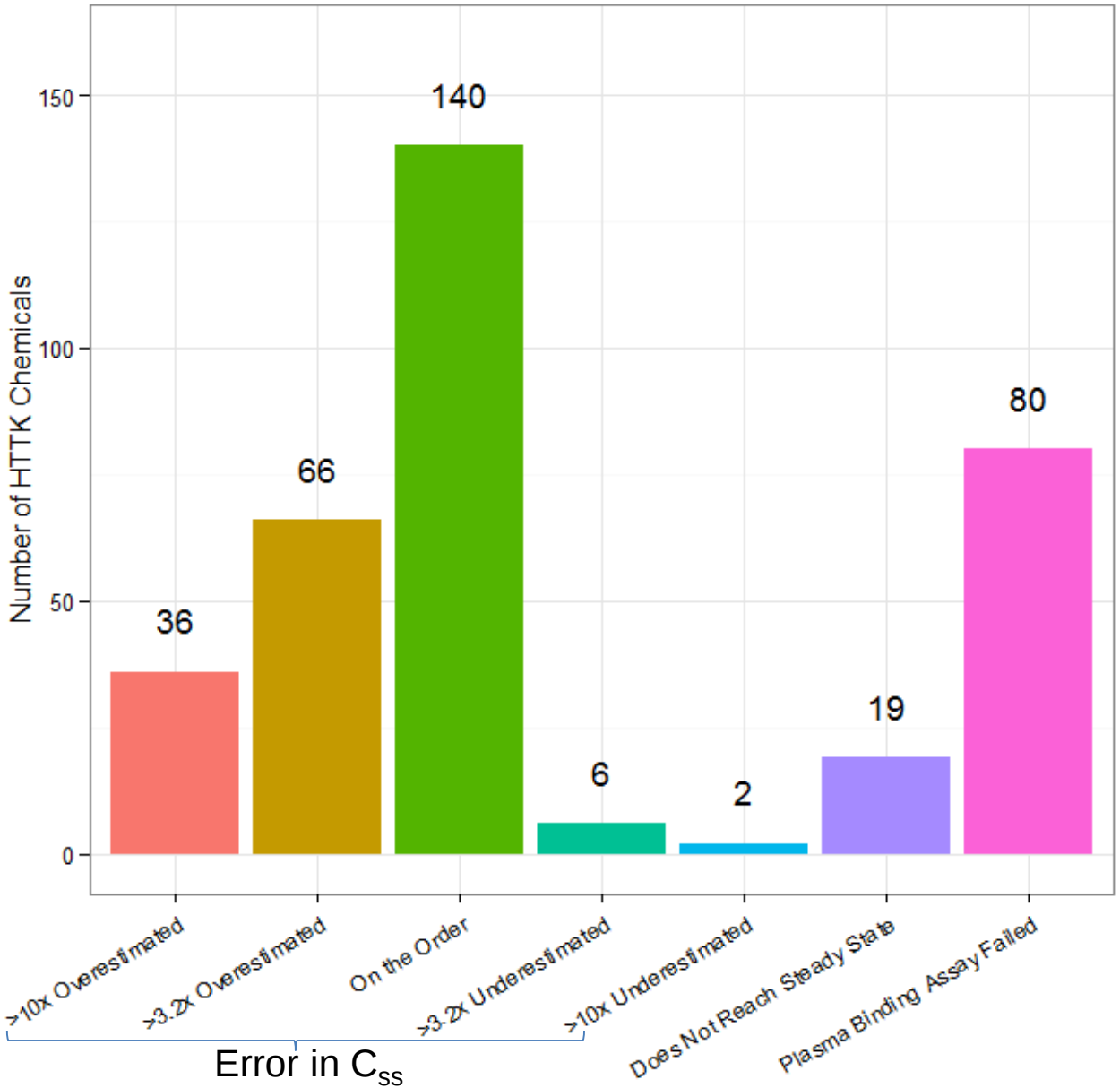




Wetmore et al., (2012, 2014, 2015)

Predicting Error in HTTK Predictions

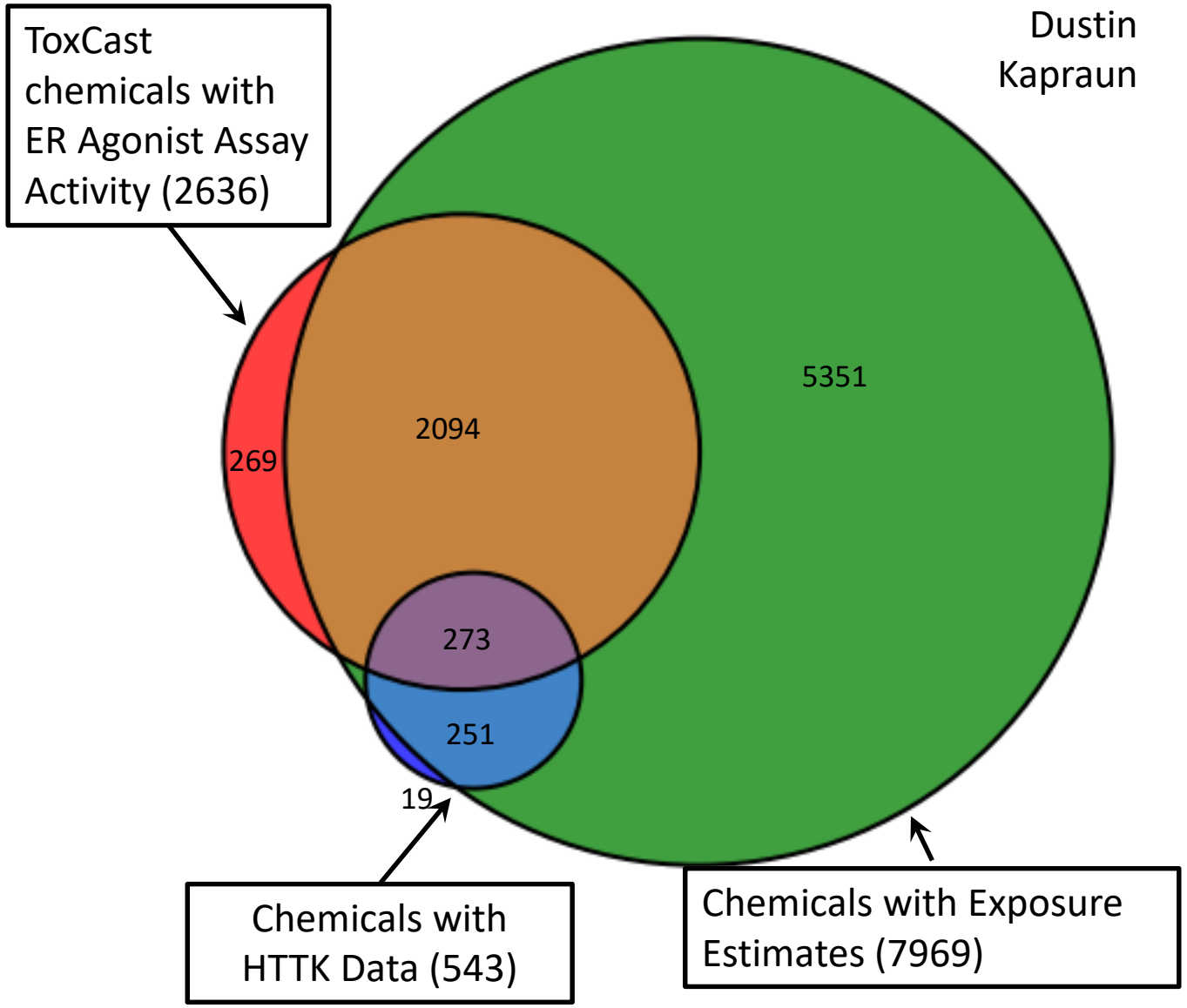
- For most compounds in the environment there will be no clinical trials
- Uncertainty must be well characterized
  - We compare to *in vivo* data to get **empirical estimates of HTTK uncertainty**
  - Any approximations, omissions, or mistakes should work to increase the estimated uncertainty when evaluated systematically across chemicals
- Through comparison to *in vivo* data, a cross-validated predictor of success or failure of HTTK has been constructed (Wambaugh et al., 2015)
- We also have categories for chemicals that do not reach steady-state or for which plasma binding assay fails



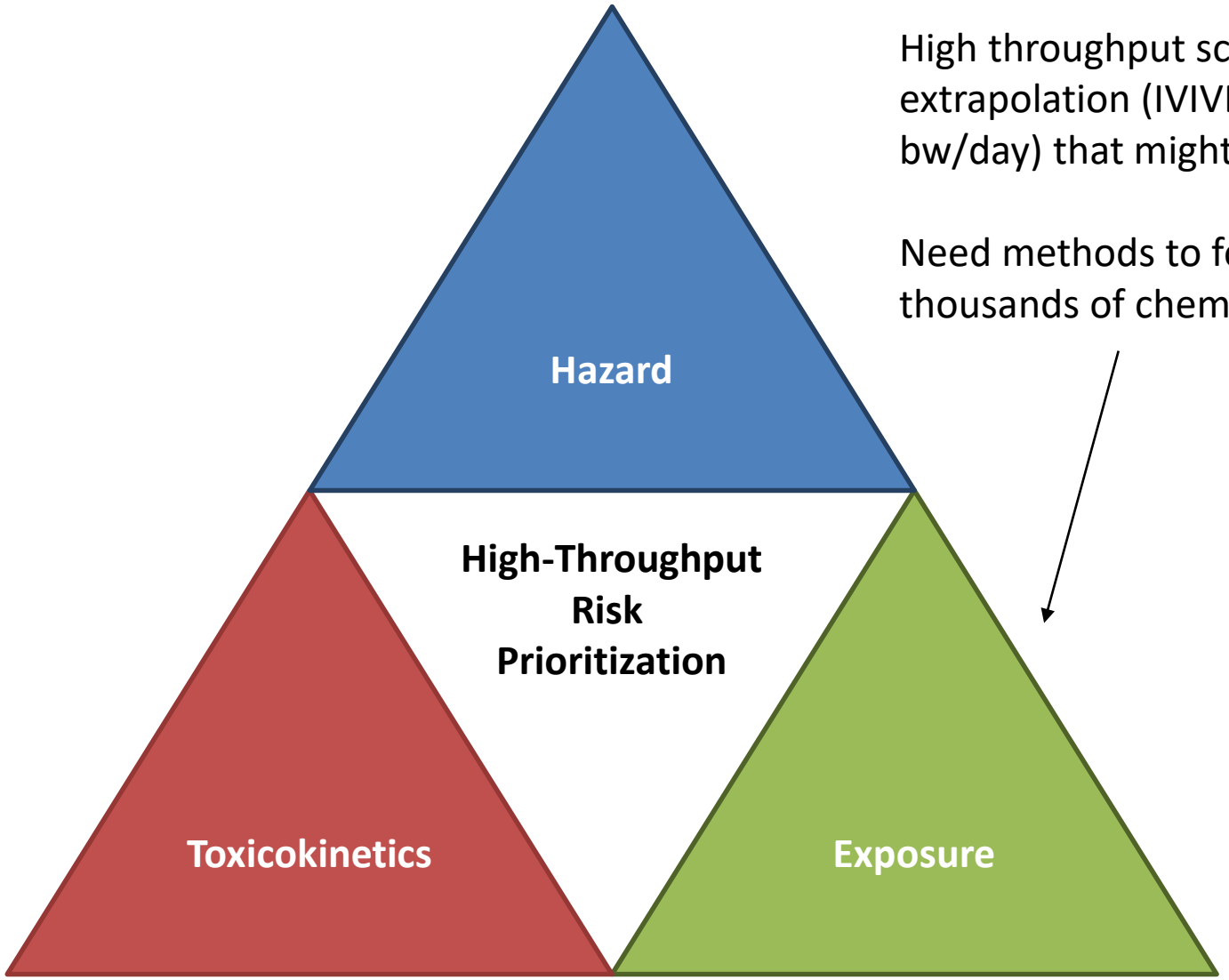
Predicting Critical TK Parameters

- Two parameters currently are key to HTTK model:
  - Plasma protein binding (PPB)
  - Hepatic clearance (metabolism)
- Unfortunately, chemical specific-analytical chemistry methods are needed, and these take time and resources to develop
- Ingle *et al.* (2016) developed QSAR models for PPB that was shown to work for environmental chemicals
- If a hepatic clearance model can be developed we can provide tentative TK predictions for thousands of more chemicals

Figure from Dustin Kapraun



High-Throughput Risk Prioritization

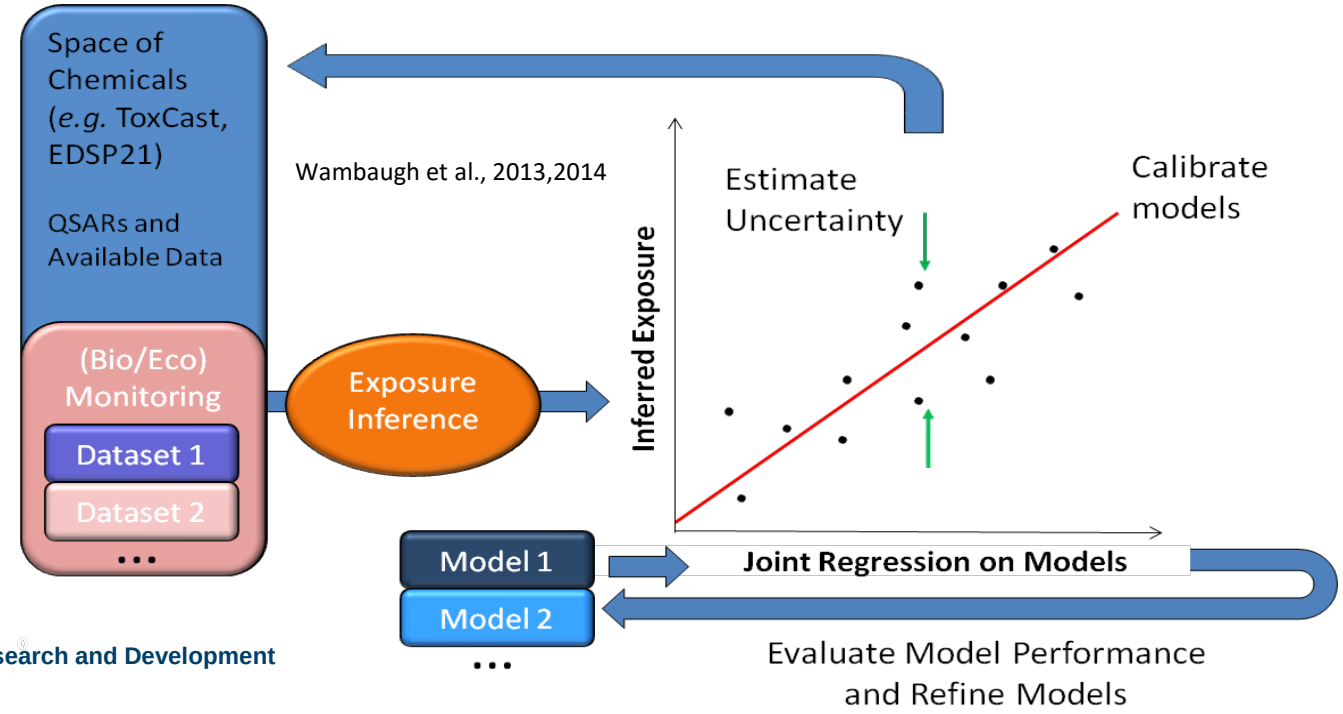


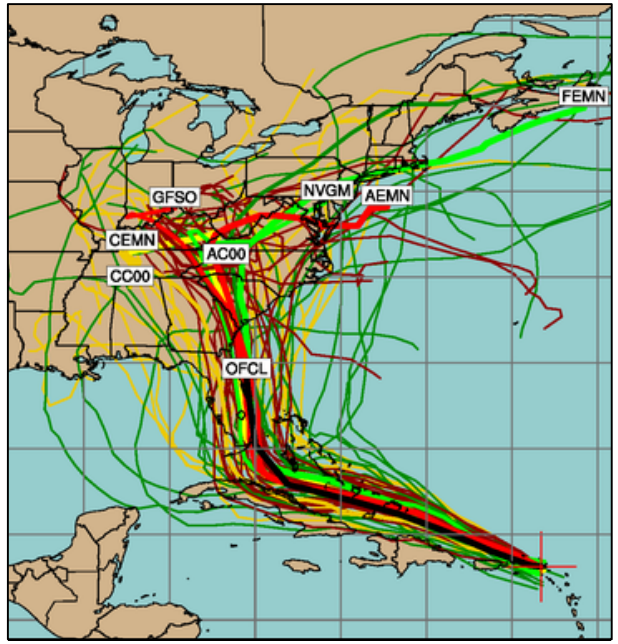
High throughput screening + *in vitro-in vivo* extrapolation (IVIVE can predict a dose (mg/kg bw/day) that might be adverse

Need methods to forecast exposure for thousands of chemicals (Wetmore *et al.*, 2015)

Consensus Exposure Predictions with the SEEM Framework

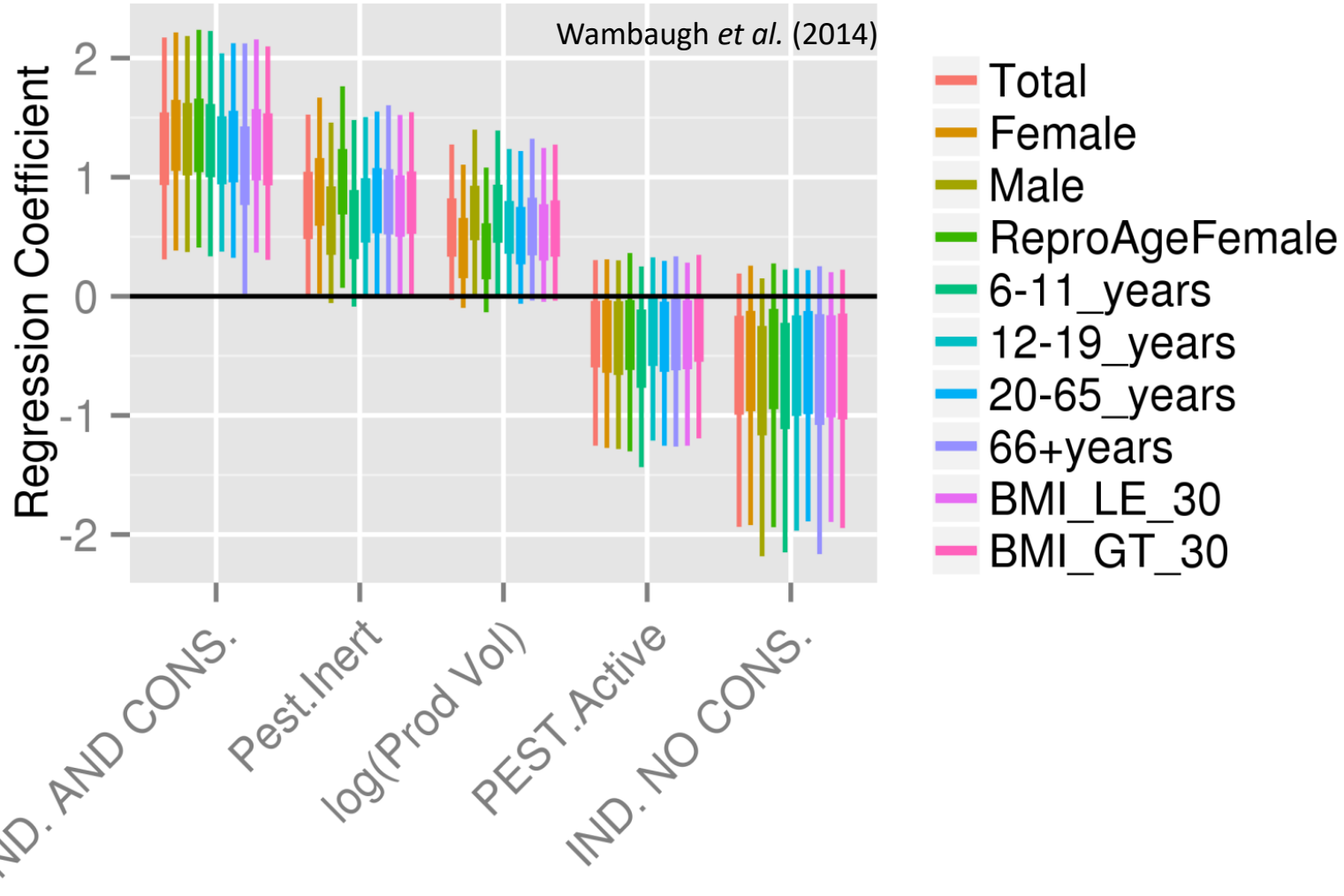
- We incorporate multiple models (including SHEDS-HT, ExpoDat) into consensus predictions for 1000s of chemicals within the **Systematic Empirical Evaluation of Models (SEEM) framework**
- We evaluate/calibrate predictions with available monitoring data
- This provides information similar to a sensitivity analysis: What models are working? What data are most needed? This is an iterative process





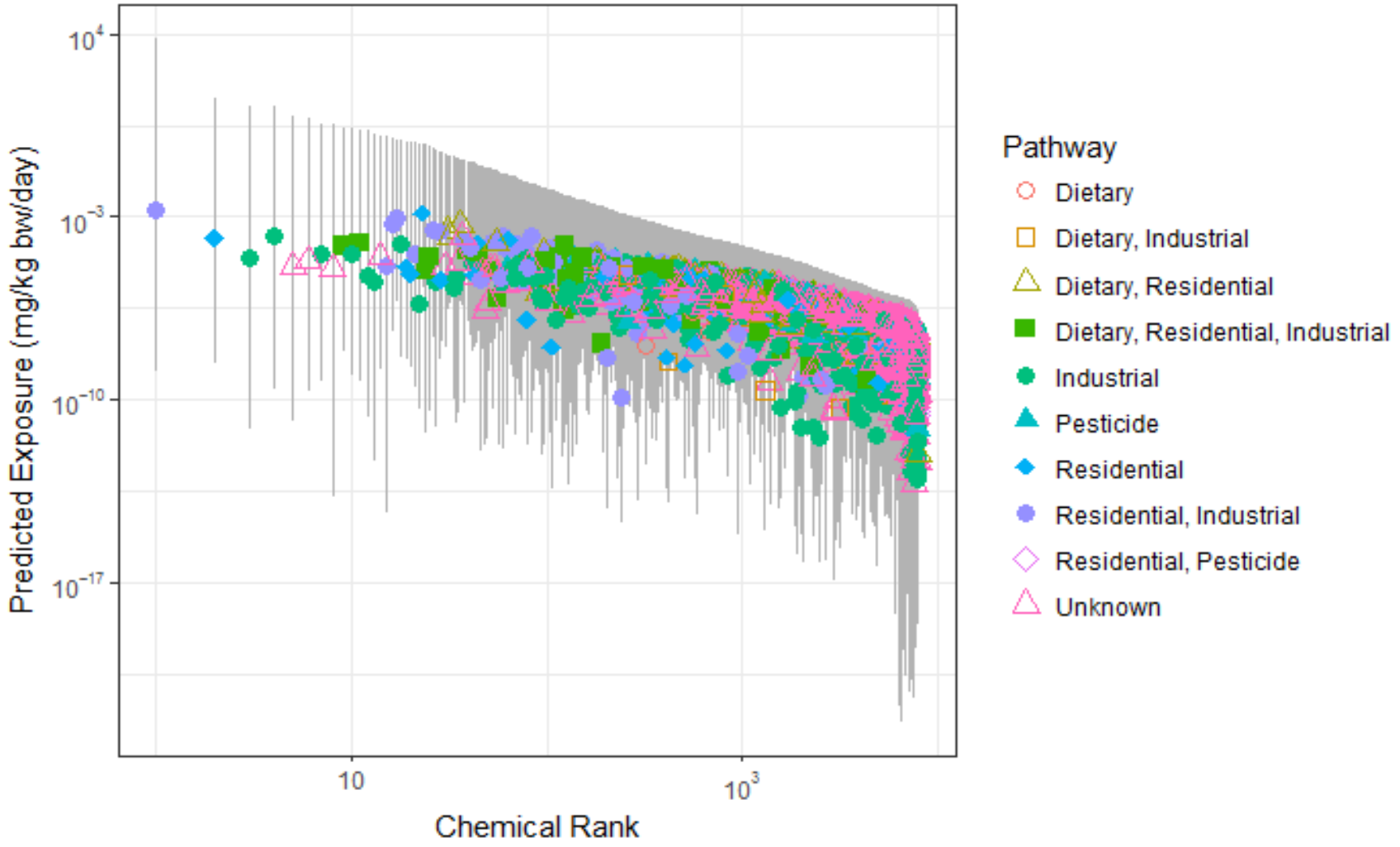
Integrating Multiple Models

Heuristics of Exposure



- Five descriptors explain roughly 50% of the chemical to chemical variability in median National Health and Nutrition Examination Survey (NHANES) exposure rates
- Same five predictors work for all NHANES demographic groups analyzed
- What we are really doing is identifying chemical exposure pathway
- Chemical-Product Database (https://actor.epa.gov/cpcat/) provides chemical use information (Dionisio et al., 2015)
- Data is incomplete, use quantitative structure-property relationships (QSPR) fill in the gaps (Phillips et al., 2017)

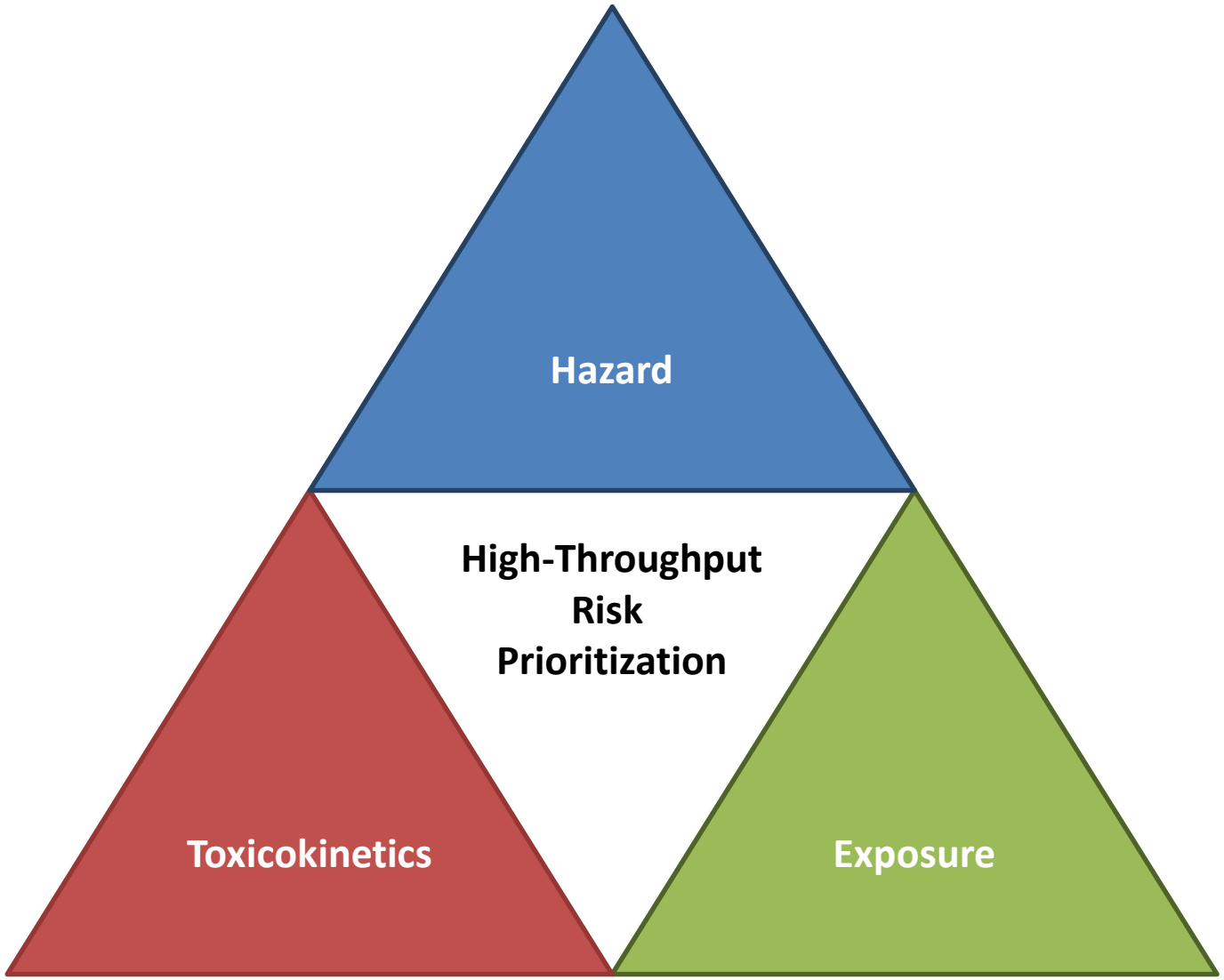
Human Exposure Predictions for 134,521 Chemicals



- Machine learning models were built for each four exposure pathways
- Pathway predictions can be used for large chemical libraries
- Use prediction (and accuracy of prediction) as a prior for Bayesian analysis
- Each chemical may have exposure by multiple pathways

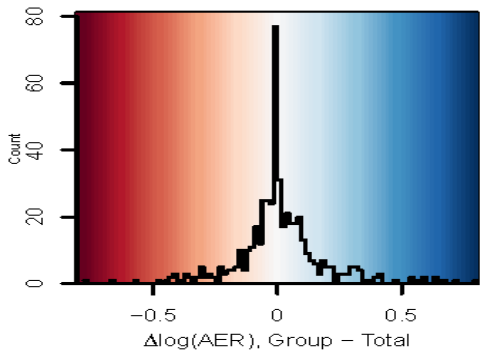
Ring et al. (*in prep.*)

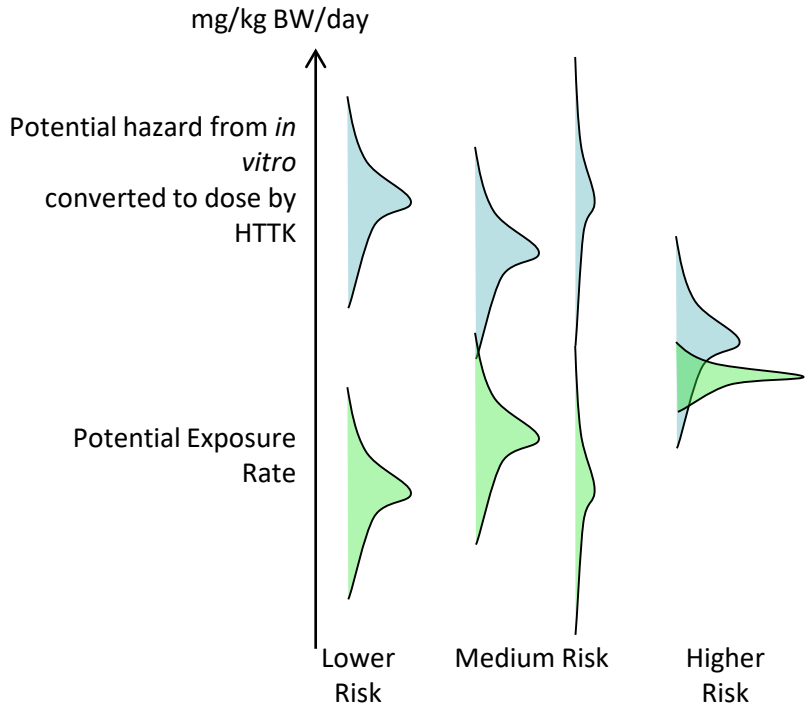
High-Throughput Risk Prioritization

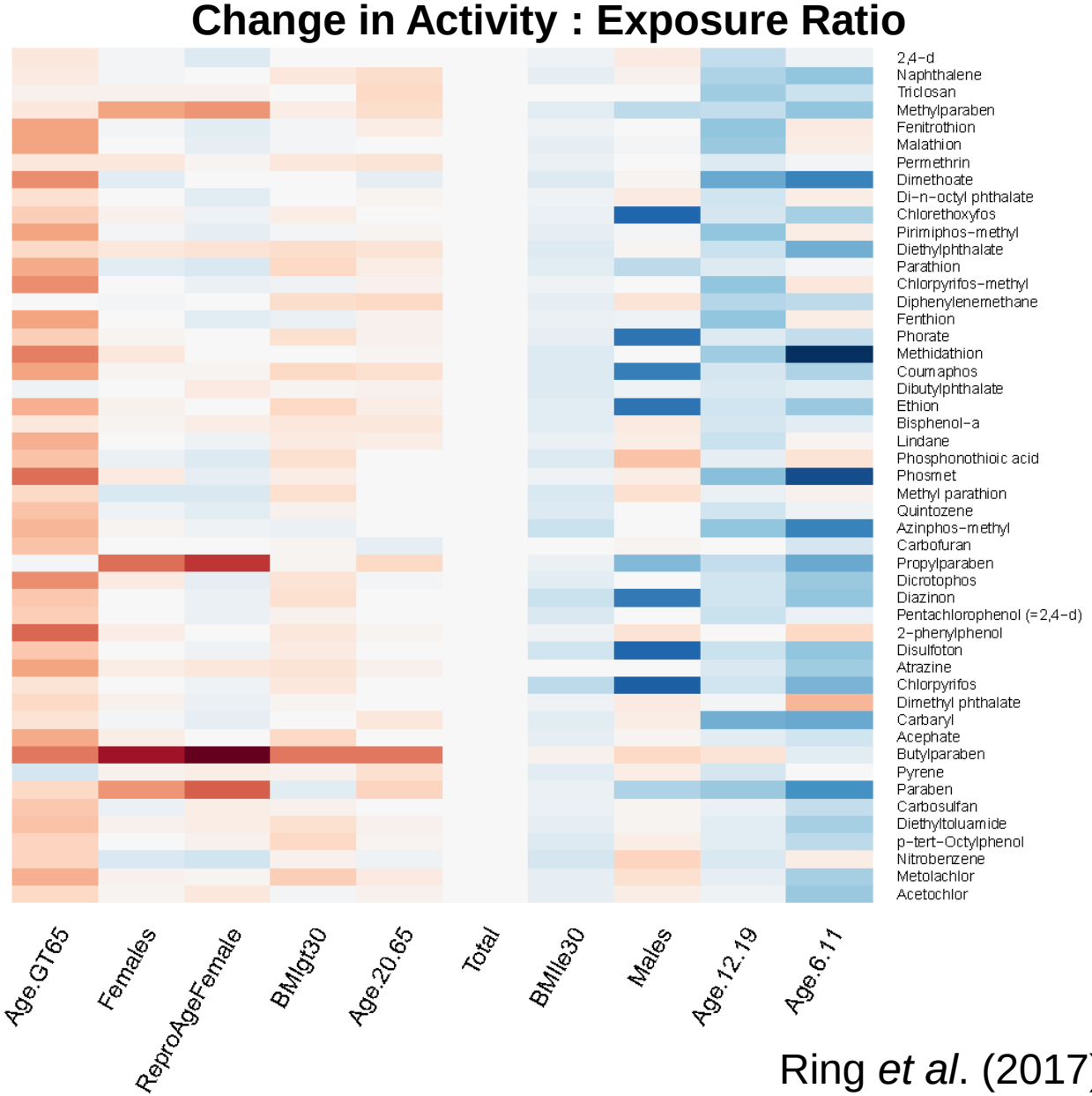


Life-stage and Demographic Specific Predictions

- We use HTTK to calculate margin between bioactivity and exposure for specific populations







Ring *et al*. (2017)

Conclusions

- We are close to being able to predict potential risk as a function of hazard, toxicokinetics, and exposure from chemical structure alone

- High throughput screening (HTS) provides bioactivity data for thousands of chemicals as a surrogate for hazard

- Toxicokinetics for IVIVE provides real world context to hazards indicated by HTS
  - Using *in vitro* methods developed for pharmaceuticals, we can predict TK for large numbers of chemicals, but we are currently limited by analytical chemistry

- Using high throughput exposure approaches we can make coarse predictions of exposure
  - We are actively refining these predictions with new models and data
  - In some cases, upper confidence limit on current predictions is already many times lower than predicted hazard

- All data being made public:
  - R package “httk”: **https://CRAN.R-project.org/package=httk**
  - The Chemistry Dashboard (A “Google” for chemicals) **http://comptox.epa.gov/**

EPA United States Environmental Protection Agency

Chemical Safety for Sustainability (CSS) Research Program

Rapid Exposure and Dosimetry (RED) Project

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