EPA
United States
Environmental Protection
Agency

Exposure Research in EPA's Chemical Safety for Sustainability Research Program

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Office of Research and Development

Presentation to American Chemistry Council (ACC)
Long-Range Research Initiative Strategic Science Team (LRI SST)

October 3, 2017

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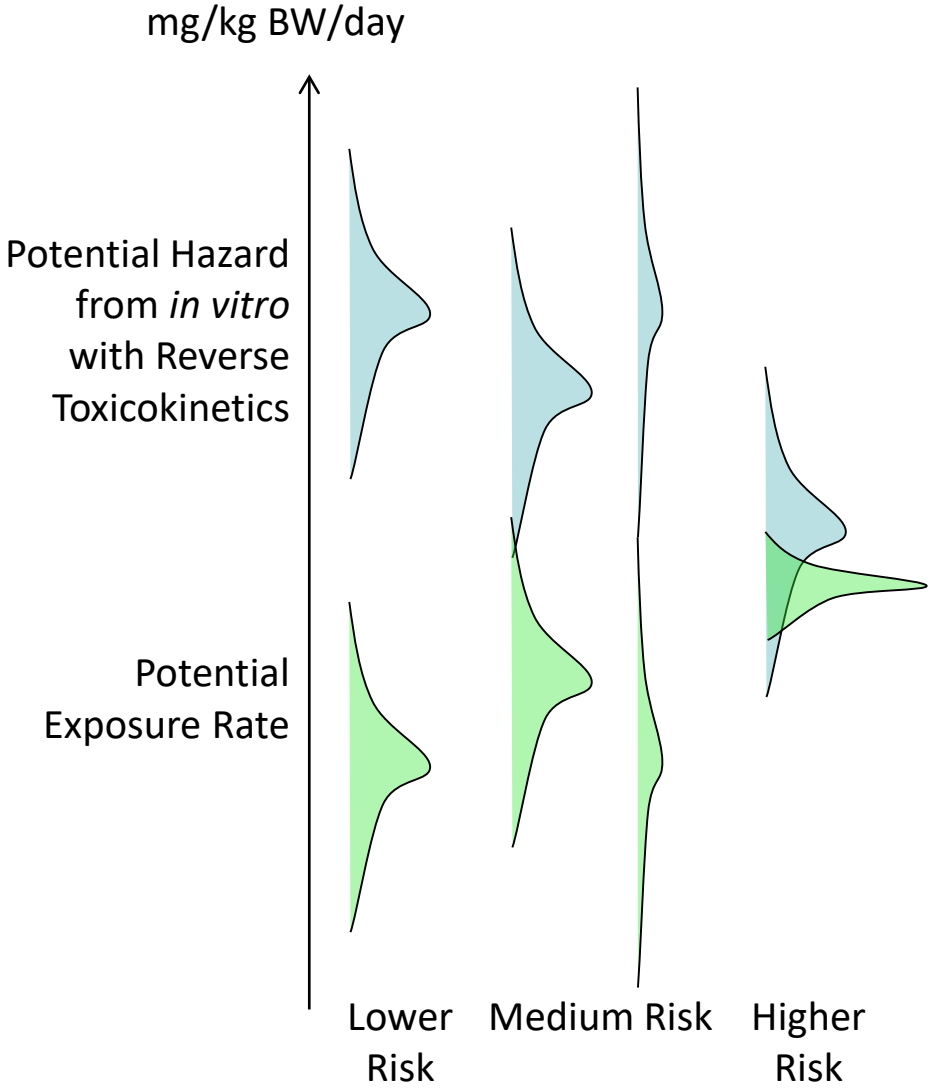
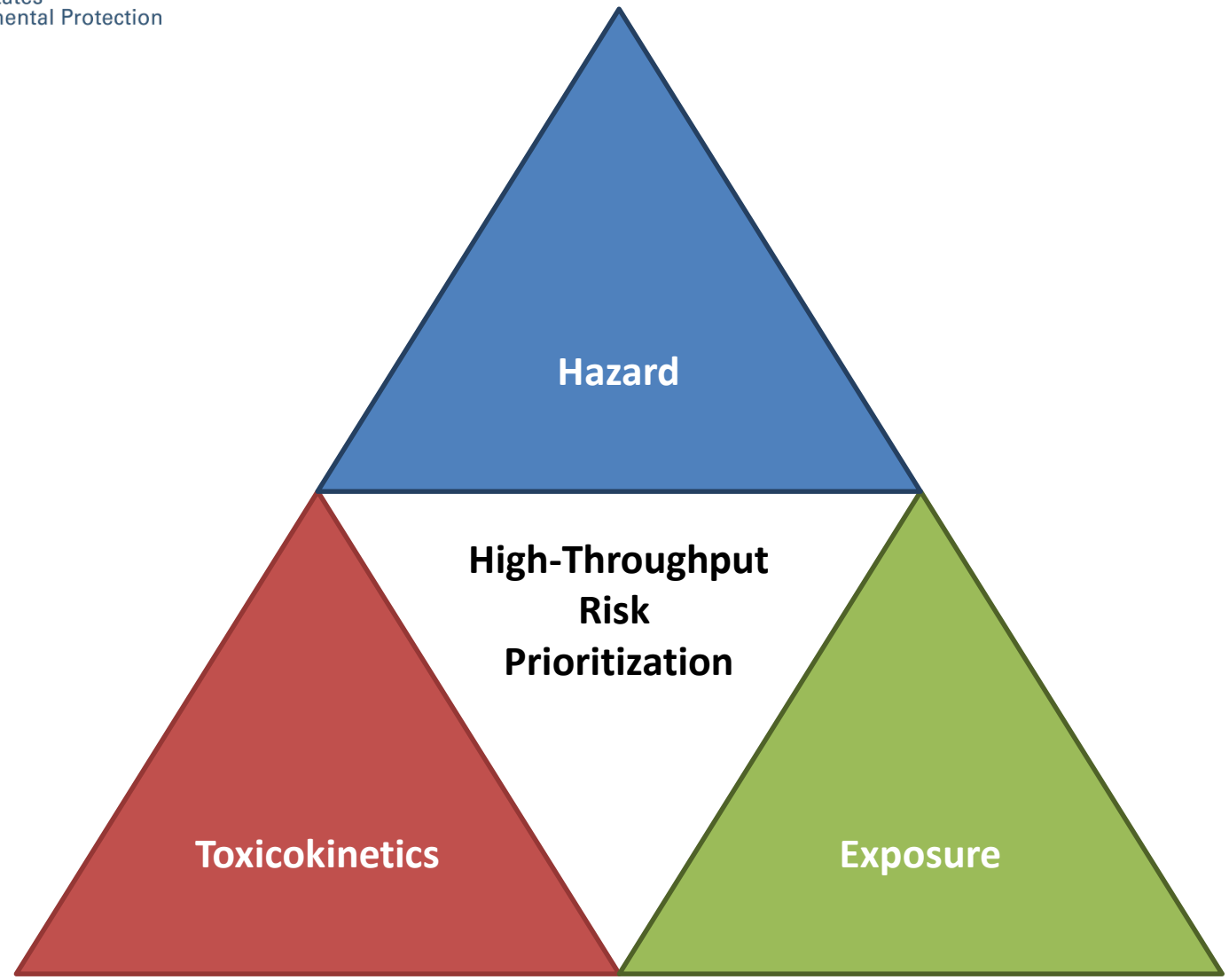
High Throughput Risk Prioritization

- **High throughput risk prioritization** needs:
  1. high throughput **hazard** characterization (e.g., ToxCast, Tox21)
  2. high throughput **exposure** forecasts
  3. high throughput **toxicokinetics** (*i.e.*, dosimetry)
- RED focuses on developing data and tools to address 2) and 3)
- We consider human AND ecological exposures!

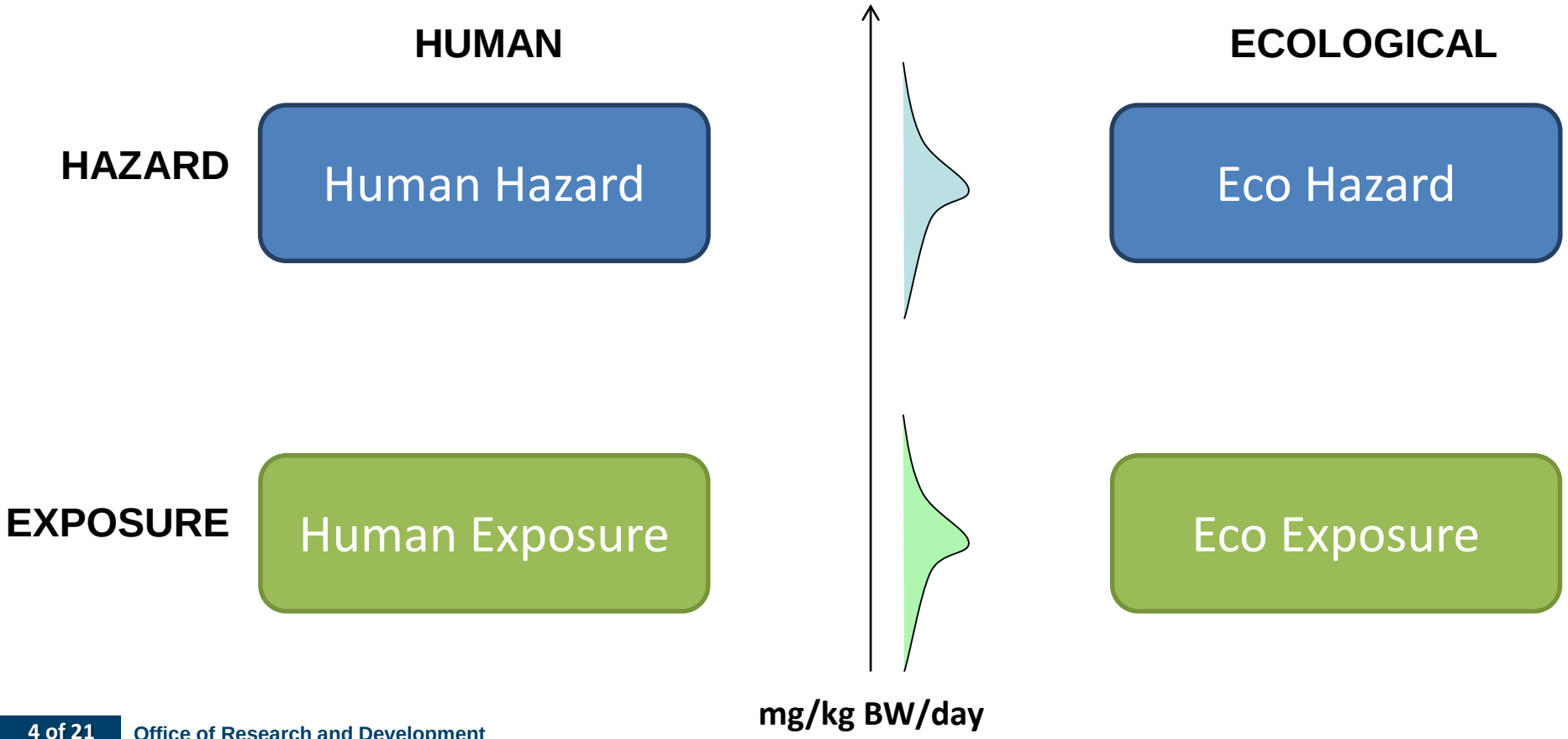


High Throughput Chemical Risk Prioritization



Application to U.S. EPA Endocrine Disruptor Screening Program (EDSP)

July and December 2014 FIFRA Scientific Advisory Panels reviewed research as it applies to the Endocrine Disruptor Screening Program



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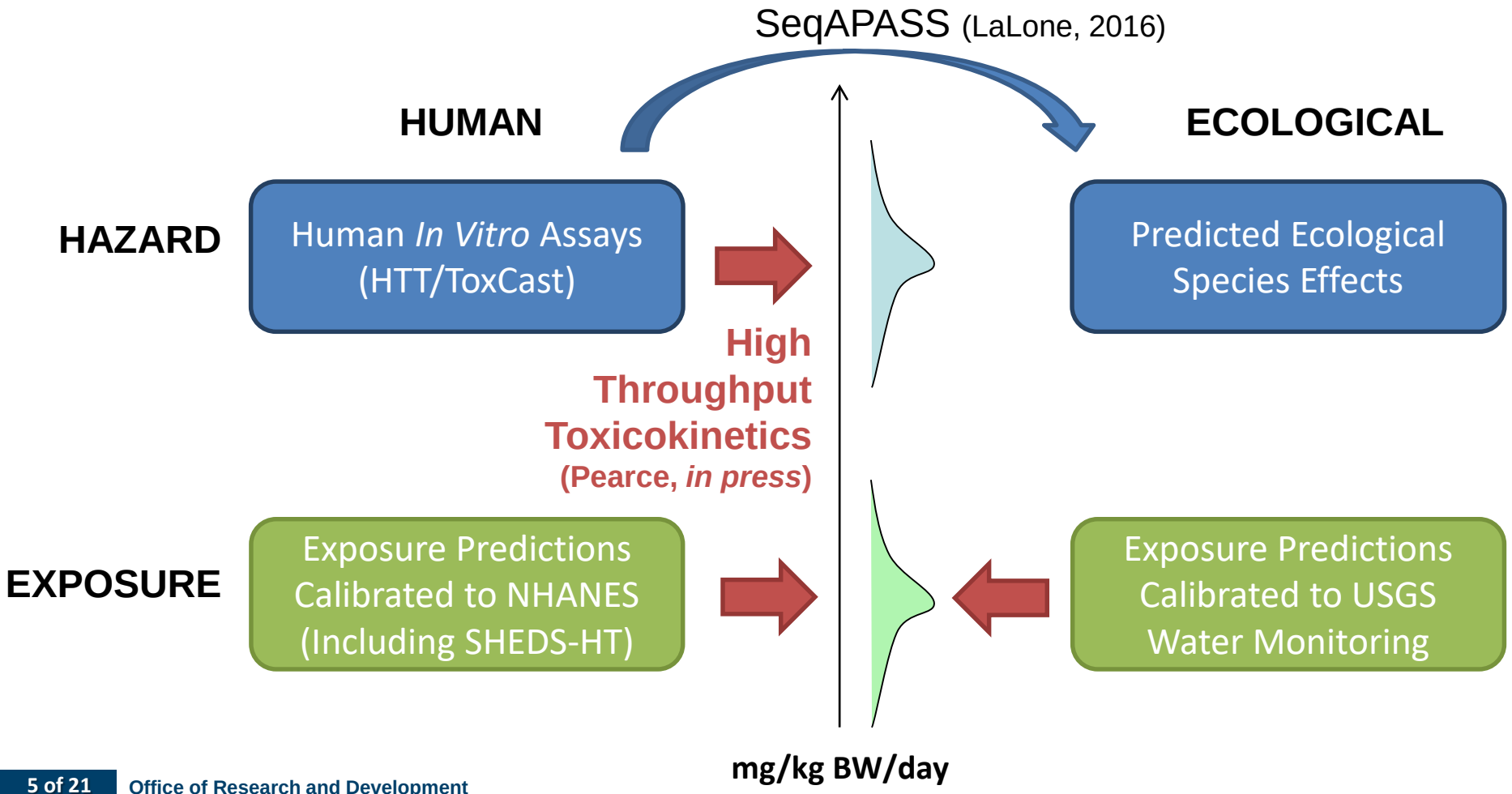
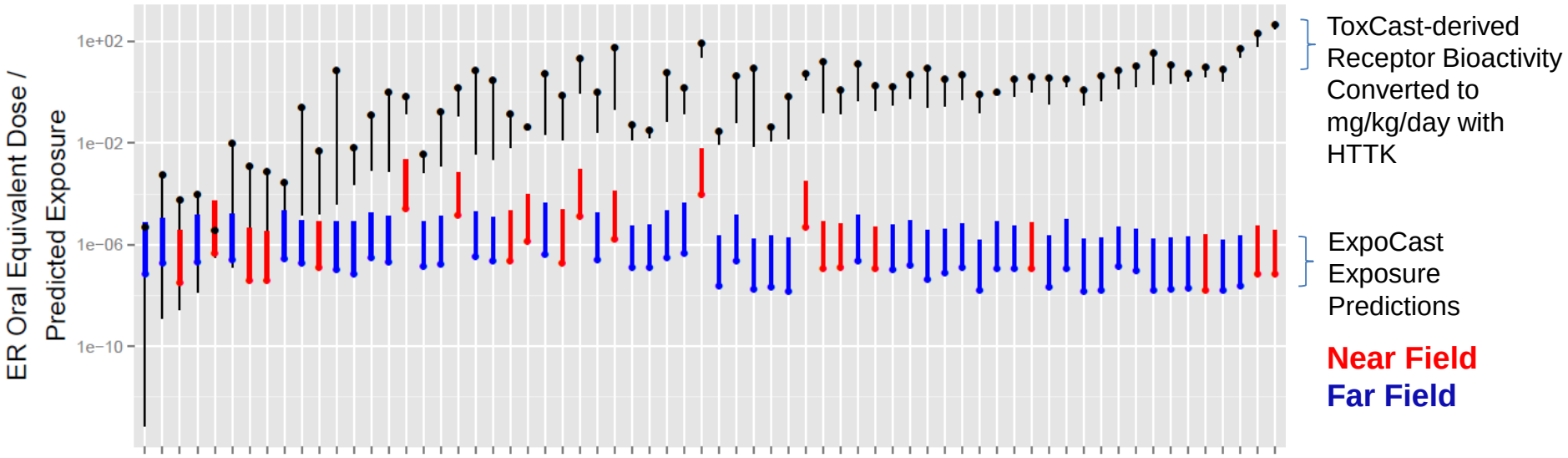


Application to U.S. EPA Endocrine Disruptor Screening Program (EDSP)



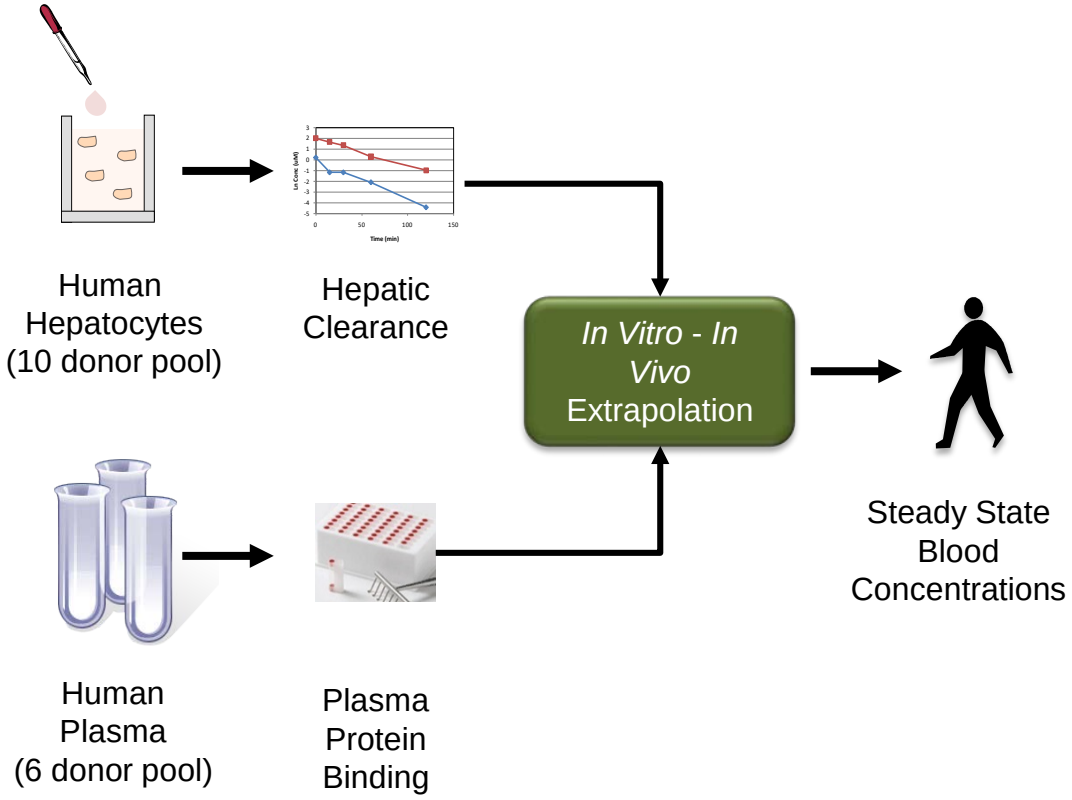
ToxCast Chemicals

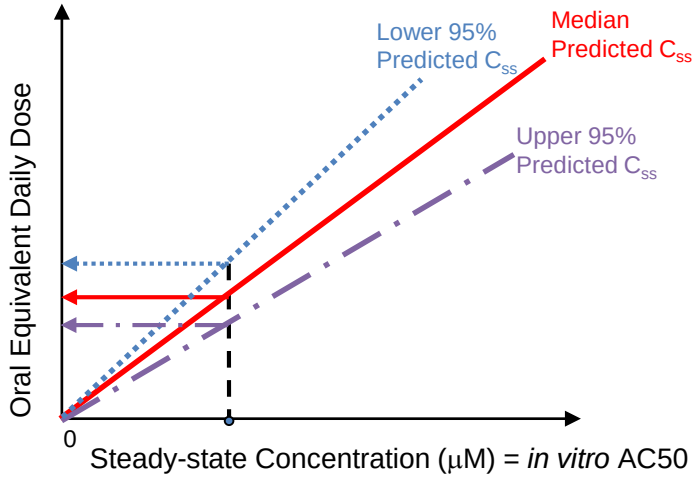
December, 2014 Panel: "Scientific Issues Associated with Integrated Endocrine Bioactivity and Exposure-Based Prioritization and Screening"

- Prioritization as in Wetmore et al. (2015)

Toxicokinetics: High-Throughput Approaches for Prioritization

United States Environmental Protection Agency

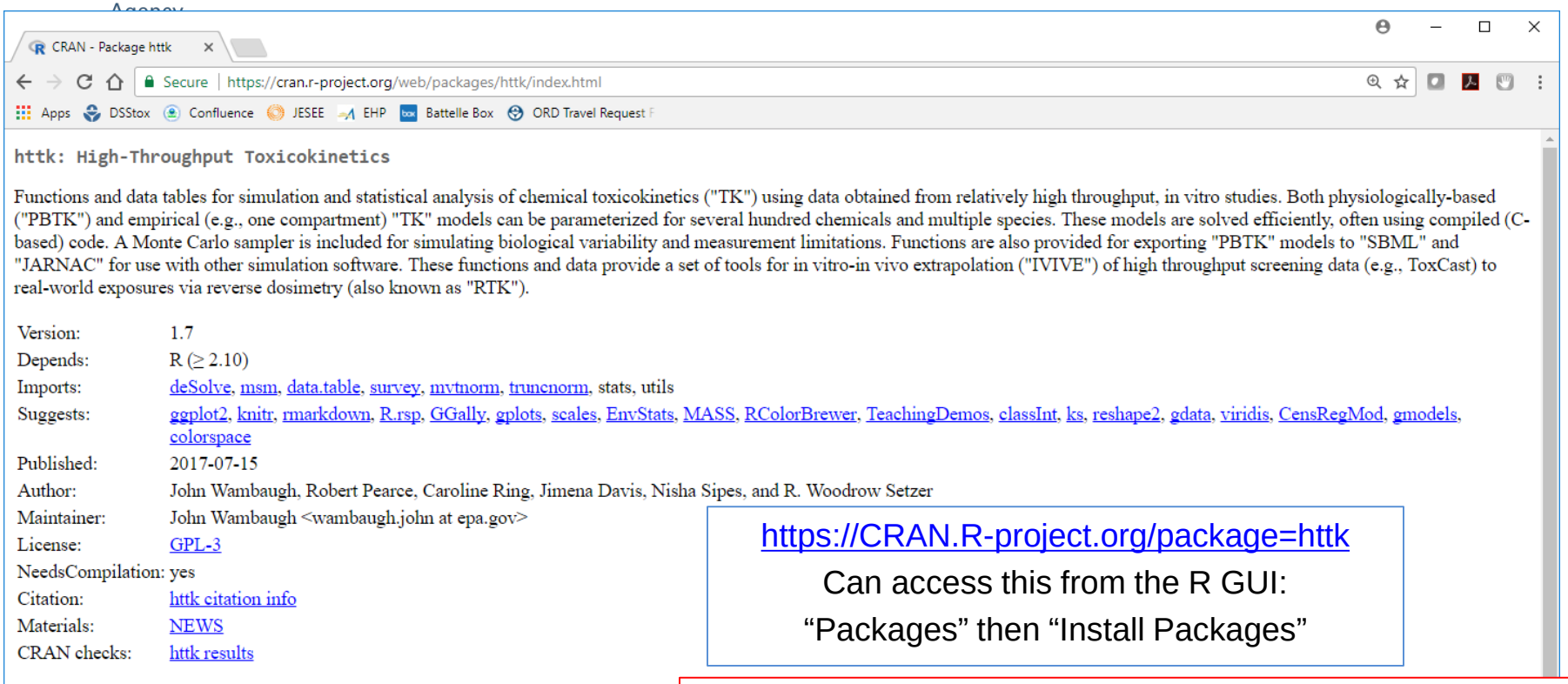




Wetmore et al., (2012, 2014, 2015)

High Throughput Toxicokinetics (HTTK) for Statistical Analysis

United States Environmental Protection Agency



CRAN - Package httk

Secure | https://cran.r-project.org/web/packages/httk/index.html

Apps DSStox Confluence JESEE EHP Battelle Box ORD Travel Request

httk: High-Throughput Toxicokinetics

Functions and data tables for simulation and statistical analysis of chemical toxicokinetics ("TK") using data obtained from relatively high throughput, in vitro studies. Both physiologically-based ("PBTK") and empirical (e.g., one compartment) "TK" models can be parameterized for several hundred chemicals and multiple species. These models are solved efficiently, often using compiled (C-based) code. A Monte Carlo sampler is included for simulating biological variability and measurement limitations. Functions are also provided for exporting "PBTK" models to "SBML" and "JARNAC" for use with other simulation software. These functions and data provide a set of tools for in vitro-in vivo extrapolation ("IVIVE") of high throughput screening data (e.g., ToxCast) to real-world exposures via reverse dosimetry (also known as "RTK").

Version:	1.7
Depends:	R (≥ 2.10)
Imports:	deSolve, msm, data.table, survey, mvtnorm, truncnorm, stats, utils
Suggests:	ggplot2, knitr, rmarkdown, R.rsp, GGally, gplots, scales, EnvStats, MASS, RColorBrewer, TeachingDemos, classInt, ks, reshape2, gdata, viridis, CensRegMod, gmodels, colorspace
Published:	2017-07-15
Author:	John Wambaugh, Robert Pearce, Caroline Ring, Jimena Davis, Nisha Sipes, and R. Woodrow Setzer
Maintainer:	John Wambaugh <wambaugh.john at epa.gov>
License:	GPL-3
NeedsCompilation:	yes
Citation:	httk citation info
Materials:	NEWS
CRAN checks:	httk results

Downloads:

Reference manual:	httk.pdf
Vignettes:	Creating Partition Coefficient Evaluation Plots
	Age distributions
	Global sensitivity analysis
	Global sensitivity analysis plotting
	Height and weight spline fits and residuals
	Hematocrit spline fits and residuals
	Plotting Css95
	Serum creatinine spline fits and residuals
	Generating subpopulations
	Evaluating HTTK models for subpopulations
	Generating Figure 2
	Generating Figure 3
	Plotting Howgate/Johnson data

https://CRAN.R-project.org/package=httk

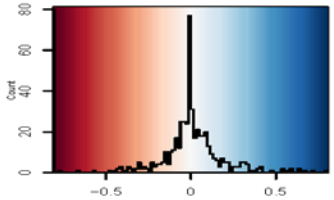
Can access this from the R GUI:

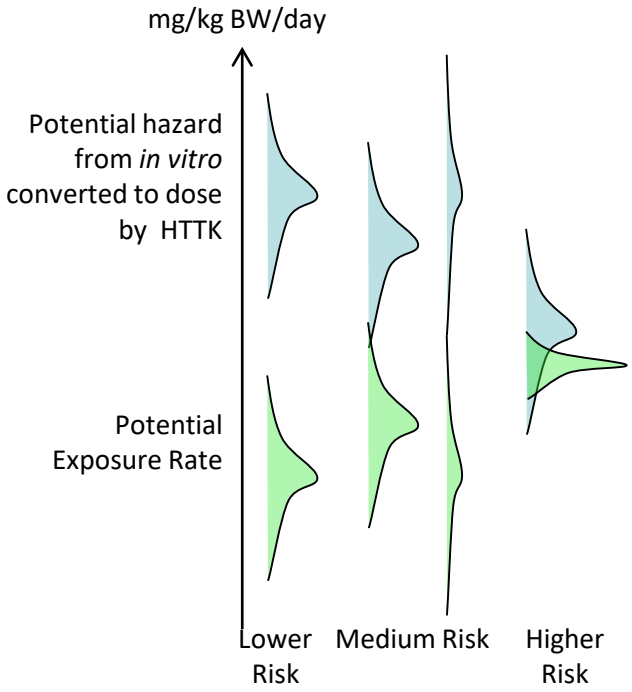
"Packages" then "Install Packages"

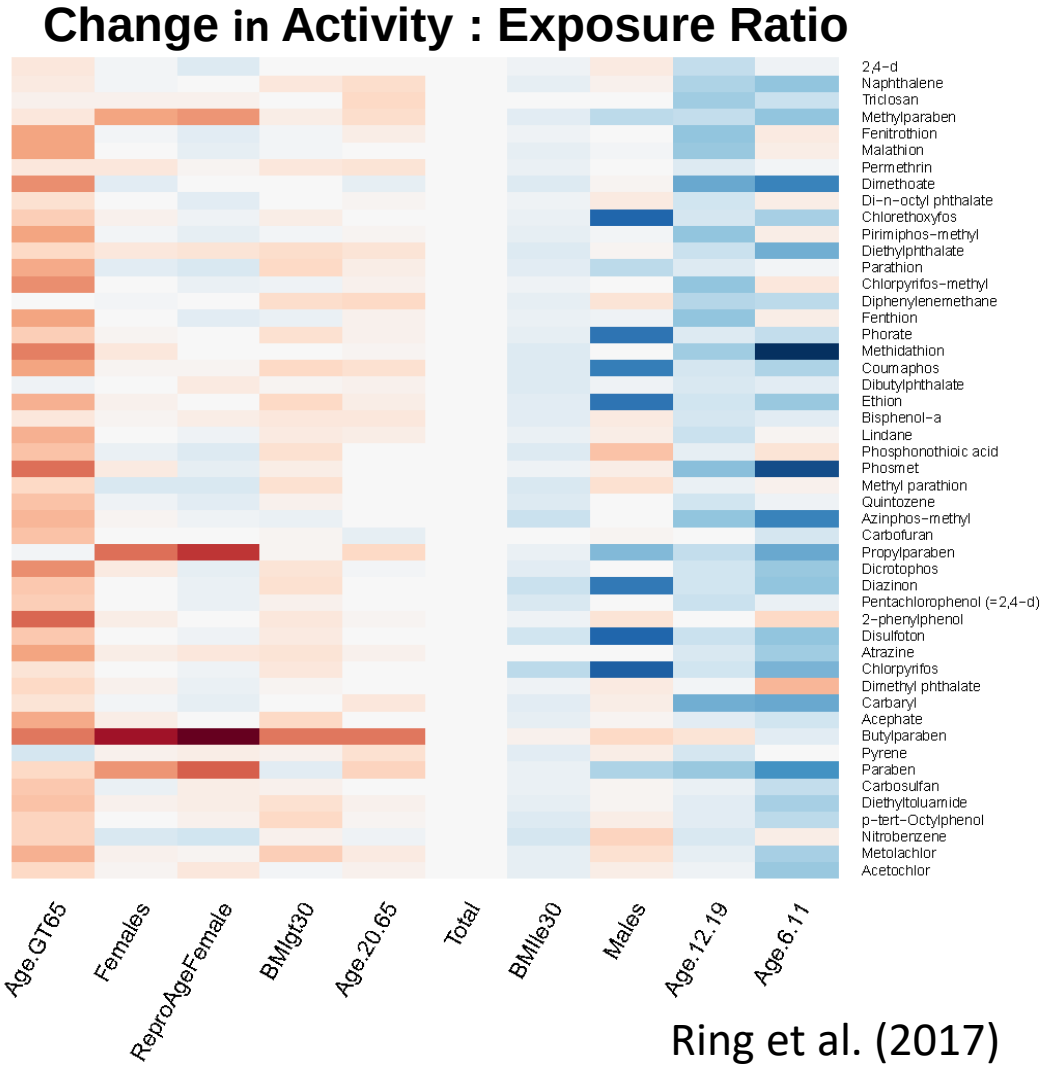
- "httk" R Package for *in vitro-in vivo* extrapolation and **PBTK**
- 553 chemicals to date
- 100's of additional chemicals being studied
- Pearce *et al.* (2017) provides documentation and examples
- Built-in vignettes provide further examples of how to use many functions

Toxicokinetic IVIVE:
Convert HTS µM to mg/kg/day

- We use HTTK to calculate margin between bioactivity and exposure for specific populations (CDC NHANES)

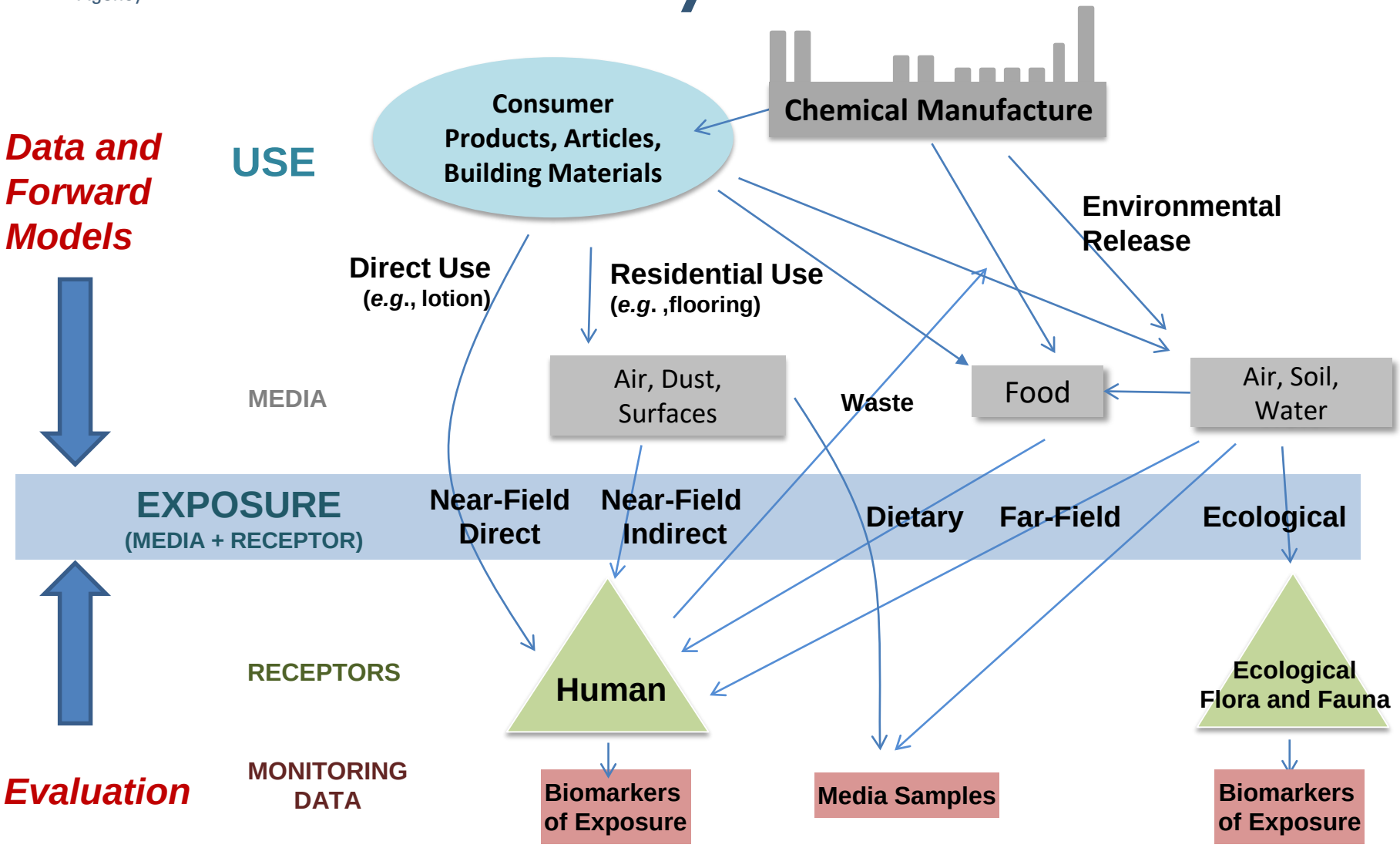






Ring et al. (2017)

Forecasting Exposure is a Systems Problem



Chemical Use: Chemicals and Products Database (CPDat)

EPA United States Environmental Protection Agency

MSDS Data

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Development of a consumer product ingredient database for chemical exposure screening and prioritization

M.-R. Goldsmith[a,*], C.M. Grulke[a], R.D. Brooks[b], T.R. Transue[c], Y.M. Tan[a], A. Frame[a,e], P.P. Egeghy[a], R. Edwards[d], D.T. Chang[a], R. Tornero-Velez[a], K. Isaacs[a], A. Wang[a,c], J. Johnson[a], K. Holm[a], M. Reich[f], J. Mitchell[g], D.A. Vallero[a], L. Phillips[a], M. Phillips[a], J.F. Wambaugh[a], R.S. Judson[a], T.J. Buckley[a], C.C. Dary[a]

Occurrence and quantitative chemical composition

Contents lists available at ScienceDirect

Toxicology Reports

journal homepage: www.elsevier.com/locate/toxrep

Exploring consumer exposure pathways and patterns of use for chemicals in the environment

Kathie L. Dionisio[a], Alicia M. Frame[b,1], Michael-Rock Goldsmith[a,2], John F. Wambaugh[b], Alan Liddell[c,3], Tommy Cathey[d], Doris Smith[b], James Vail[b], Alexi S. Ernstoff[e], Peter Fantke[e], Olivier Jolliet[f],

Broad "index" of chemical uses

CPCat (Chemical and Product Categories)

CPDat

Functional Use Data and Predictions

Green Chemistry

PAPER

View Article Online

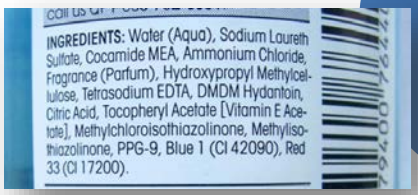
View Journal | View Issue

High-throughput screening of chemicals as functional substitutes using structure-based classification models†

Cite this: *Green Chem.*, 2017, **19**, 1063

Katherine A. Phillips,*[a,c] John F. Wambaugh,[b] Christopher M. Grulke,[b] Kathie L. Dionisio[c] and Kristin K. Isaacs[c]

Occurrence data



Ingredient Lists

EPA United States Environmental Protection Agency | Home

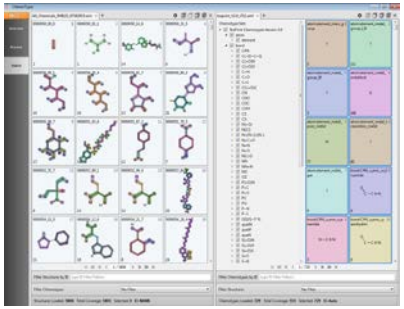
Chemistry Dashboard

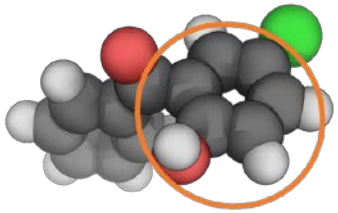
Package 'CPDat'

Classification Models for Chemical Function

United States Environmental Protection Agency

Chemical Structure and Property Descriptors

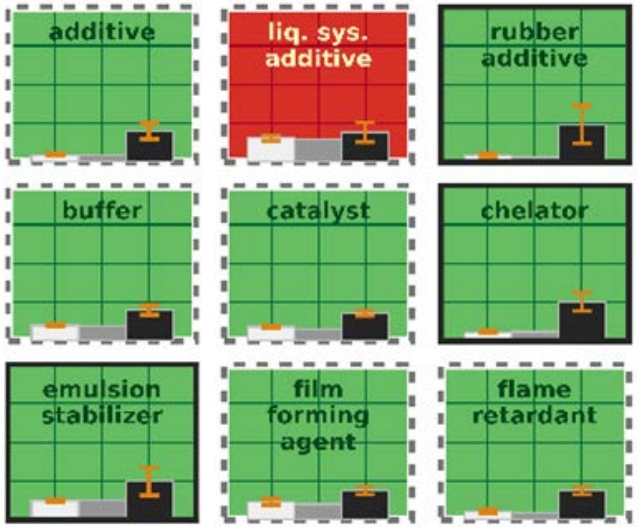




Physical and Chemical Properties

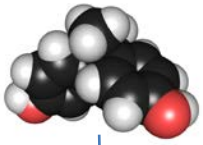
Chemical Function Information

FUse



Machine-Learning Based Classification Models

Prediction of Of Potential Functions for Unclassified Chemicals



YES NO

We have been able to build successful models **for 41 functions**

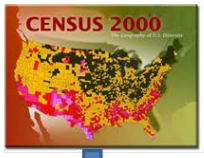
High-Throughput Forward Exposure Modeling

United States Environmental Protection Agency

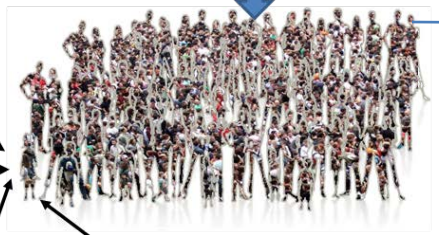
CPDat

Chemical Residues in Foods

Chemical Ingredients and Weight Fractions

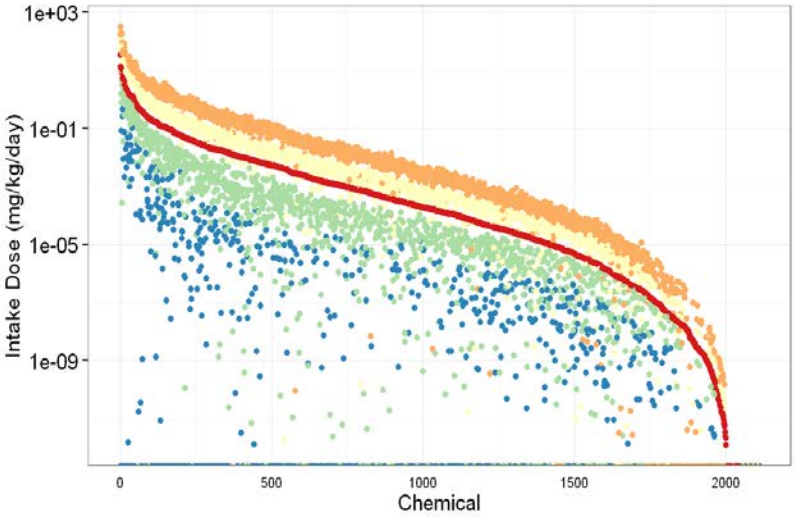


Consumer Product Use Patterns



Relevant exposure factors (e.g. weight, bathing and hand washing behaviors, hand-to-mouth behaviors)

Daily-level activity diary
- Time spent in microenvironments
- Energy expenditure (ventilation)



Stochastic Human Exposure and Dose Simulation Model

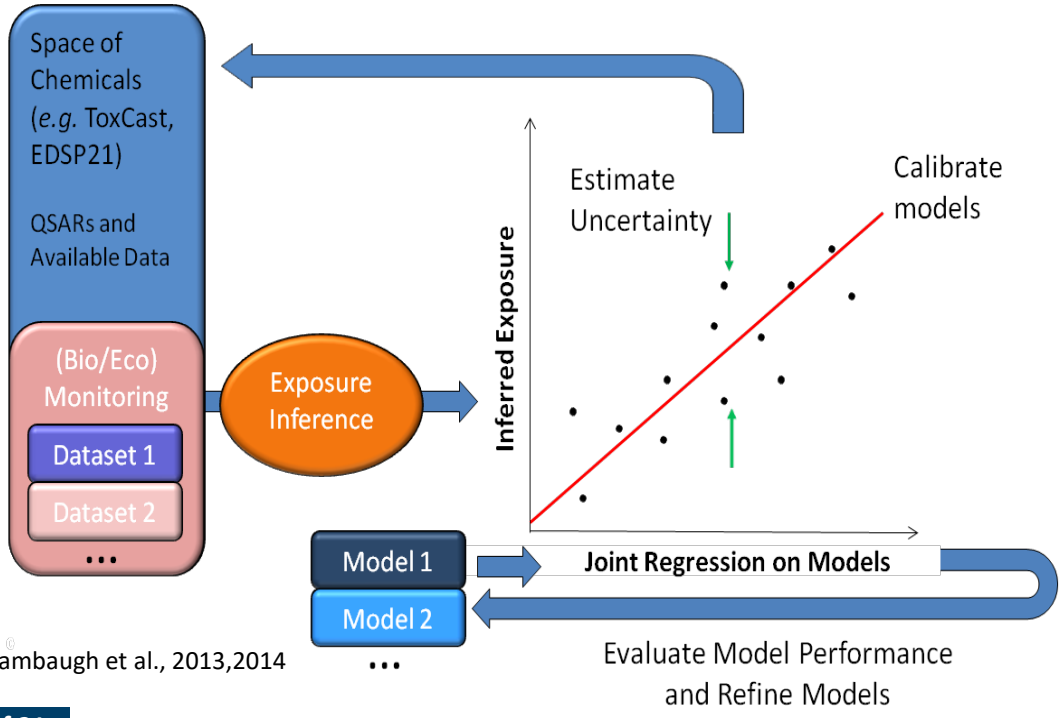
Public R Package "Sheds-HT"

Description The ShedsHT R package runs the Stochastic Human Exposure and Dose Simulation-High Throughput screening model which estmates human exposure to a wide range of chemicals.The people in SHEDS-HT are simulated individuals who collectively form a representative sample of the target population, as chosen by the user. The model is cross-sectional, with just one simulated day (24 hours) for each simulated person, although the selected day is not necessarily the same from one person to another. SHEDS-HT is stochastic, which means that many inputs are sampled randomly from user-specified distributions that are intended to capture variability. In the SHEDS series of models, variability and uncertainty are typically handled by a two-stage Monte Carlo process, but SHEDS-HT currently has a single stage and does not directly estimate uncertainty.

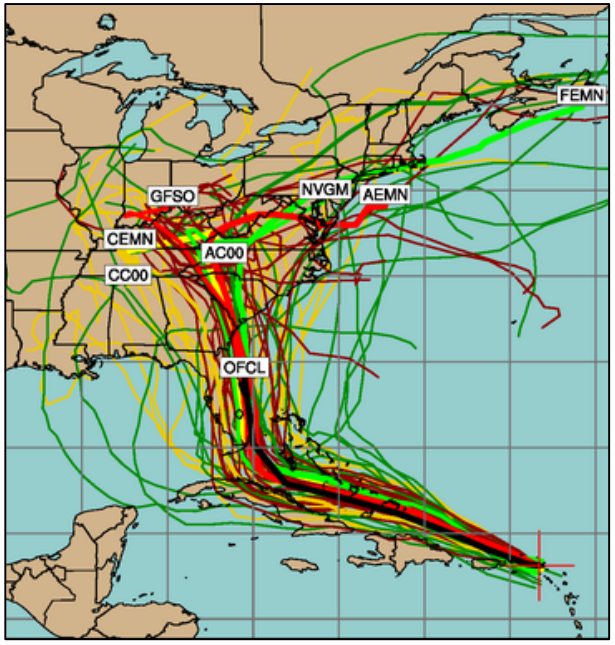
Isaacs et al. (2014), *Environmental Science and Technology*

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.
- To date we have relied on median U.S. population exposure rates only

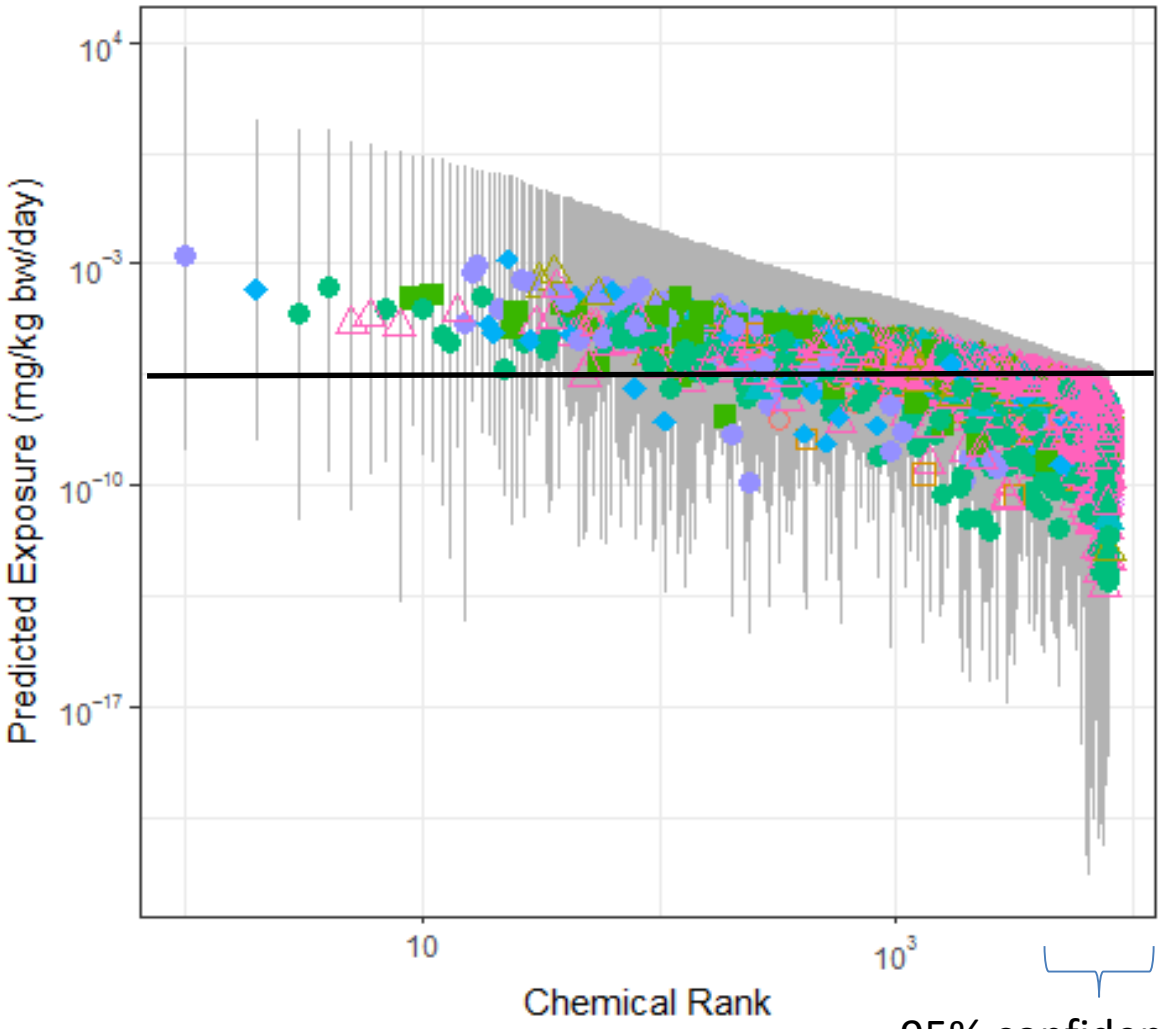


Wambaugh et al., 2013,2014



Integrating Multiple Models

SEEM Results: Human Exposure Predictions for 134,521 Chemicals



Lowest NHANES limit of detection (LOD) roughly corresponds to ~10^{-6} mg/kg BW/day

95% confident that median population would be <LOD for thousands of chemicals

Ring et al., in prep.

Improving Exposure Pathway Characterization and Model Evaluation: Non-Targeted Analyses of Monitoring Data

- Targeted Analysis:
  - We know exactly what we're looking for
  - 10s – 100s of chemicals
- Non-Targeted Analysis (NTA):
  - We have no preconceived lists
  - 1,000s – 10,000s of chemical
- Ongoing consumer product scanning and blood sample monitoring
- Development of significant in-house capabilities

- Goal is to develop tools, databases, and workflows for rapid analysis of any sample for chemicals of interest, i.e. ***exposure forensics***
- These monitoring data (and others) are being pushed into our public databases, along with other data being curated with program office partners

Non-Targeted Analysis Case Studies

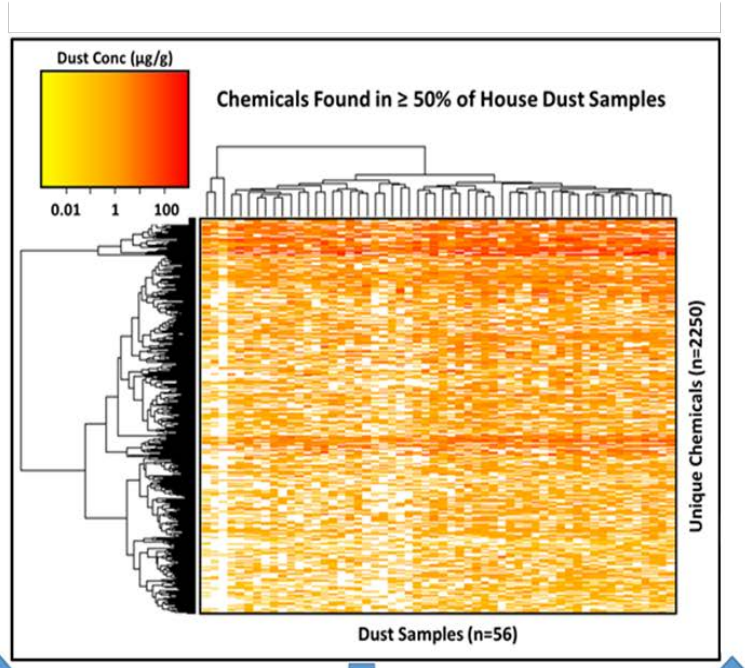
United States Environmental Protection Agency

House Dust:

- *56 houses*
- *45% of confirmed chemicals not previously studied in dust*

ORD Tools for Identifying Unknowns

- Chemistry Dashboard
- Models for Functional Use, Media Occurrence or Transformation Products
- Chemical and Products Database (CPDat)



Di(propylene glycol) dibenzoate:
35/56 samples
Med conc= 2 µg/g

C.I. Disperse Yellow 3:
33/56 samples
Med conc= 1 µg/g

Bisphenol S:
32/56 samples
Med conc= 0.5 µg/g

Rager *et al.* 2015 *Environment International*

Non-Targeted Analysis Case Studies

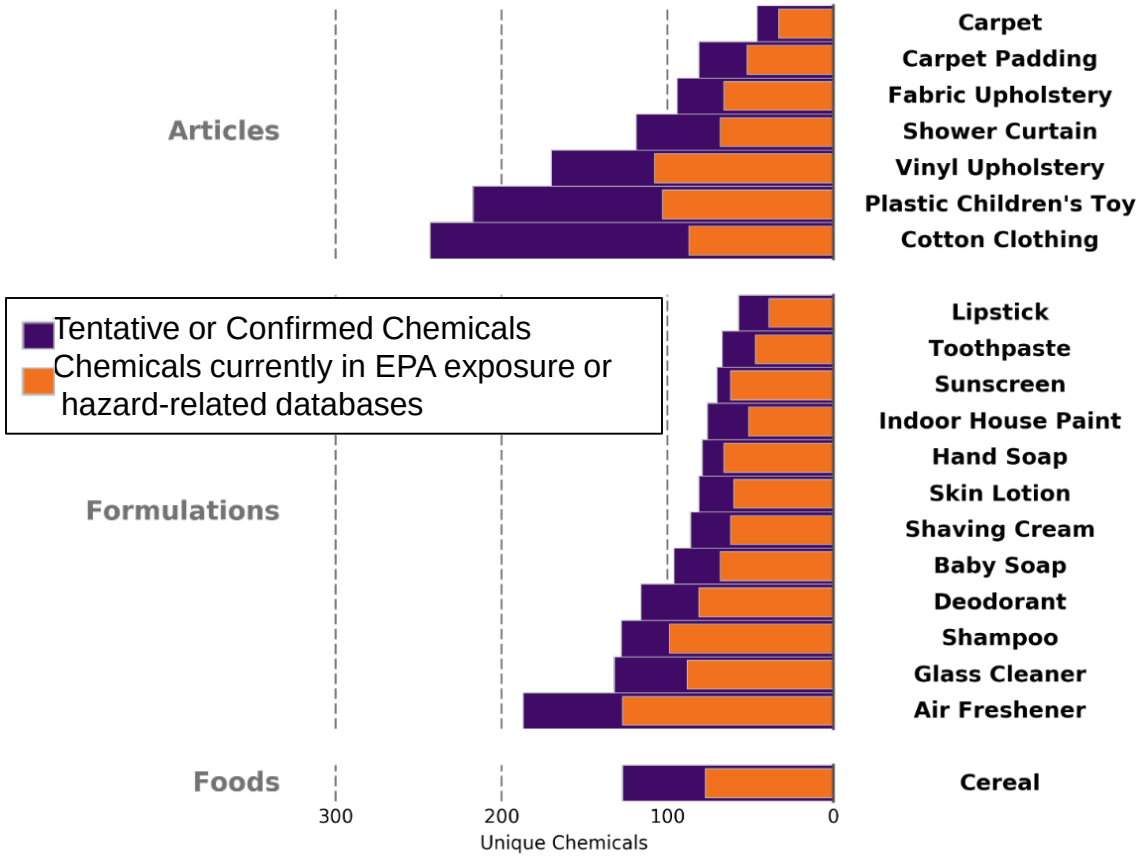
United States Environmental Protection Agency

Consumer Products:

- *5 examples each of 20 product types*
- *1,632 chemicals, 1,445 were not present in the Chemicals and Products Database*

ORD Tools for Identifying Unknowns

- Chemistry Dashboard
- Models for Functional Use, Media Occurrence or Transformation Products
- Chemical and Products Database (CPDat)



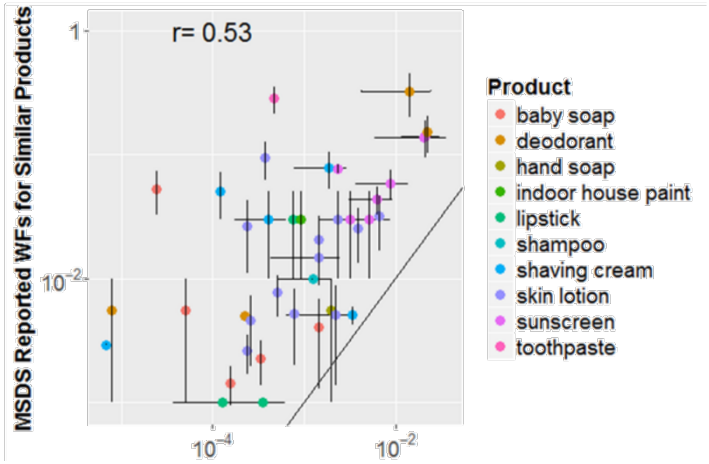
Phillips *et al.* (*submitted*)

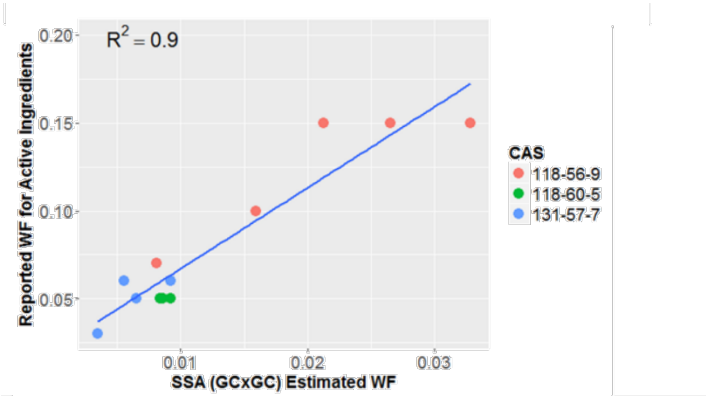
Caveats to Non-Targeted Screening

United States Environmental Protection Agency

- **Chemical presence in an object does not mean that exposure occurs**
- **Only some chemical identities are confirmed, *most are tentative***
  - Can use formulation databases and predictor models (e.g., Isaacs *et al.* (2016) and Phillips *et al.* (2017))
- **Chemical presence in an object does not necessarily mean that it is bioavailable**
  - Can build emission models (e.g., Biryol *et al.*, 2017)
- **Product de-formulation caveats:**
  - Samples are being homogenized and are extracted with a solvent (dichloro methane, DCM)
  - Only using one solvent (DCM, polar) and one method (GCxGC-TOF-MS)
- **Exposure alone is not risk, need hazard data**

Small range for quantitation may lead to lead inaccurate concentration

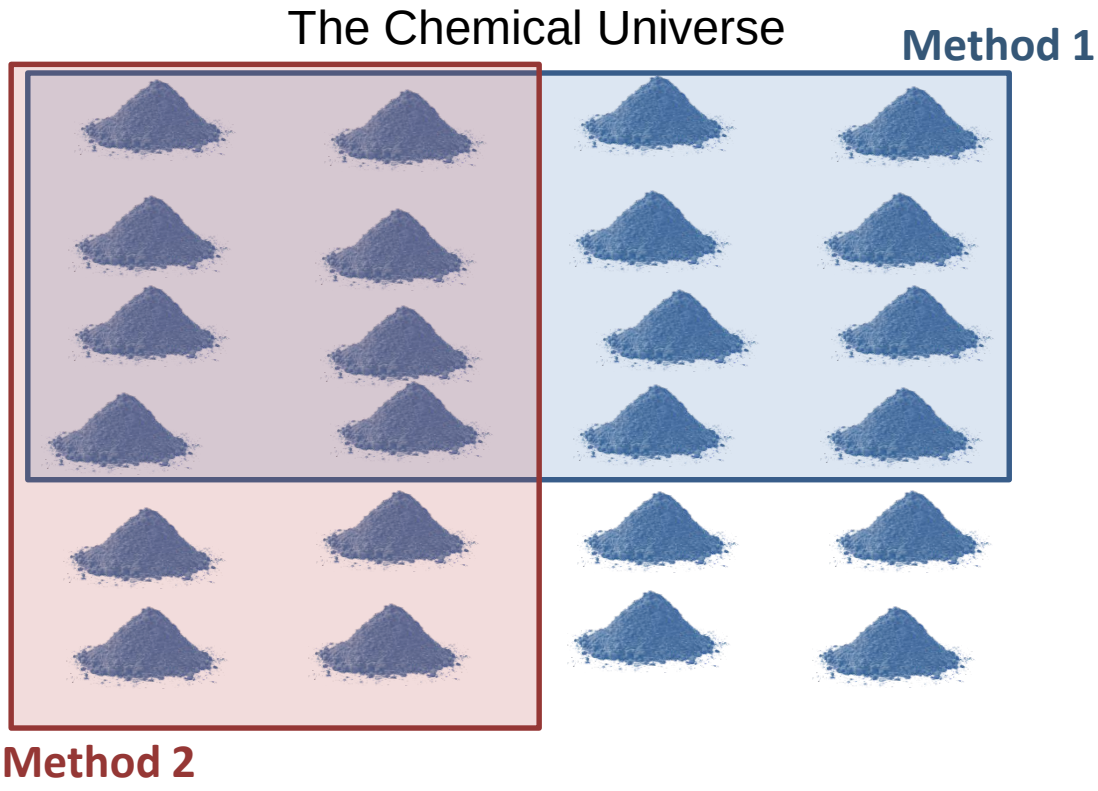




EPA's Non-Targeted Analysis Collaborative Trial (ENTACT)

United States Environmental Protection Agency

What NTA methods are available? What is the coverage of chemical universe and matrices? How do methods differ in their coverage?



Led by Jon Sobus and Elin Ulrich (EPA/NERL)

Phase 1:

- Collaborators provided 10 mixtures of 100-400 ToxCast chemicals each
- MS vendors provided with individual chemical standards

Phase 2: Fortified reference house dust, human serum, and silicone wristbands

See Sobus et al. "Integrating Tools for Non-Targeted Analysis Research and Chemical Safety Evaluations at the US EPA" (JESEE, *in press*)

Moving Forward from Prioritization to Risk Evaluation

EPA United States Environmental Protection Agency

Human Exposure Model

Population Characteristics

Residential Characteristics

Behavior and Product Use (Habits and Practices)

Product Composition (CPDat)

Source-to-Dose *(based on SHEDS-HT)*

Chemical Exposure
(days to years)

Chemistry Dashboard

Chemical Safety for Sustainability (CSS) Research Program

EPA United States Environmental Protection Agency

Rapid Exposure and Dosimetry (RED) Project

NCCT
Chris Grulke
Greg Honda*
Richard Judson
Andrew McEachran*
Robert Pearce*
Ann Richard
Risa Sayre*
Woody Setzer
Rusty Thomas
John Wambaugh
Antony Williams

NRMRL
Yirui Liang*
Xiaoyu Liu

NHEERL
Linda Adams
Christopher Ecklund
Marina Evans
Mike Hughes
Jane Ellen Simmons

NERL
Craig Barber
Namdi Brandon*
Peter Egeghy
Jarod Grossman*
Hongtai Huang*
Brandall Ingle*
Kristin Isaacs
Sarah Laughlin-Toth*
Seth Newton
Katherine Phillips
Paul Price
Jeanette Reyes*
Jon Sobus
John Streicher*
Mark Strynar
Mike Tornero-Velez
Elin Ulrich
Dan Vallero
Barbara Wetmore

Human Exposure Model Project

Cody Addington*
Namdi Brandon*
Nicholas Coco*
Kathie Dionisio
Peter Egeghy
Kristin Isaacs
Dave Lyons
Katherine Phillips
Paul Price
Steve Prince
Dan Vallero

Lead CSS Matrix Interfaces:
John Kenneke (NERL)
John Cowden (NCCT)

*Trainees

Collaborators

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Battelle Memorial Institute
Anne Louise Sumner
Anne Gregg
Chemical Computing Group
Rocky Goldsmith
National Institute for Environmental Health Sciences (NIEHS) National Toxicology Program
Mike Devito
Steve Ferguson
Nisha Sipes
Netherlands Organisation for Applied Scientific Research (TNO)
Sieto Bosgra
Research Triangle Institute
Timothy Fennell
ScitoVation
Harvey Clewell
Chantel Nicolas
Silent Spring Institute
Robin Dodson
Southwest Research Institute
Alice Yau
Kristin Favela
Summit Toxicology
Lesa Aylward
Tox Strategies
Caroline Ring
University of California, Davis
Deborah Bennett
Hyeong-Moo Shin
University of Michigan
Olivier Jolliet
University of North Carolina, Chapel Hill
Alex Tropsha

References

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- Dionisio, Kathie L., et al. “Exploring Consumer Exposure Pathways and Patterns of Use for Chemicals in the Environment.” Toxicology Reports (2015)
- Egeghy, Peter P., et al. "The exposure data landscape for manufactured chemicals." Science of the Total Environment 414: 159-166 (2012)
- Goldsmith, M-R., et al. "Development of a consumer product ingredient database for chemical exposure screening and prioritization." Food and chemical toxicology 65 (2014): 269-279.
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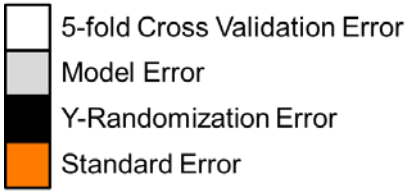
Classification Modeling Results

United States Environmental Protection Agency



Structural Descriptors

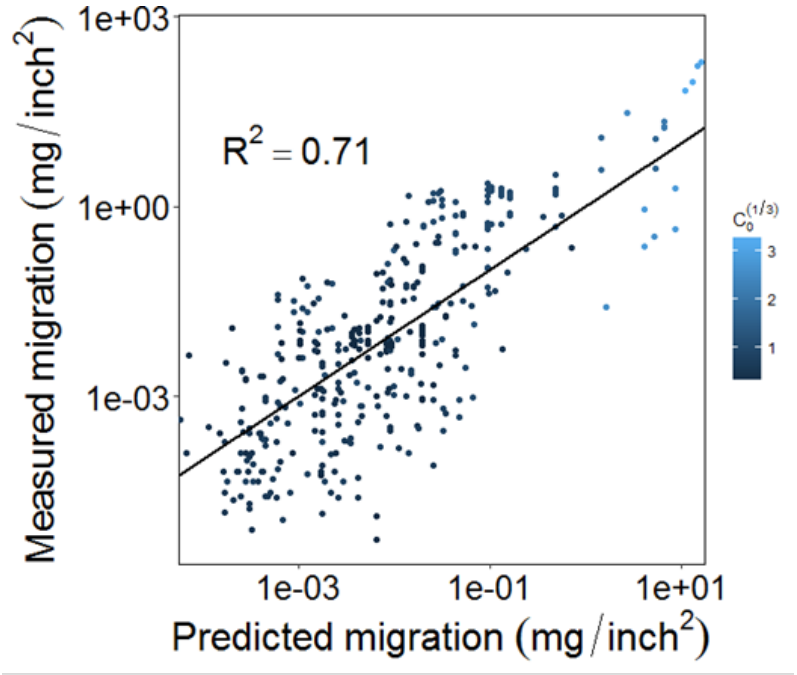
Structural and Physicochemical Descriptors

"Vague" categories yield worse validation results

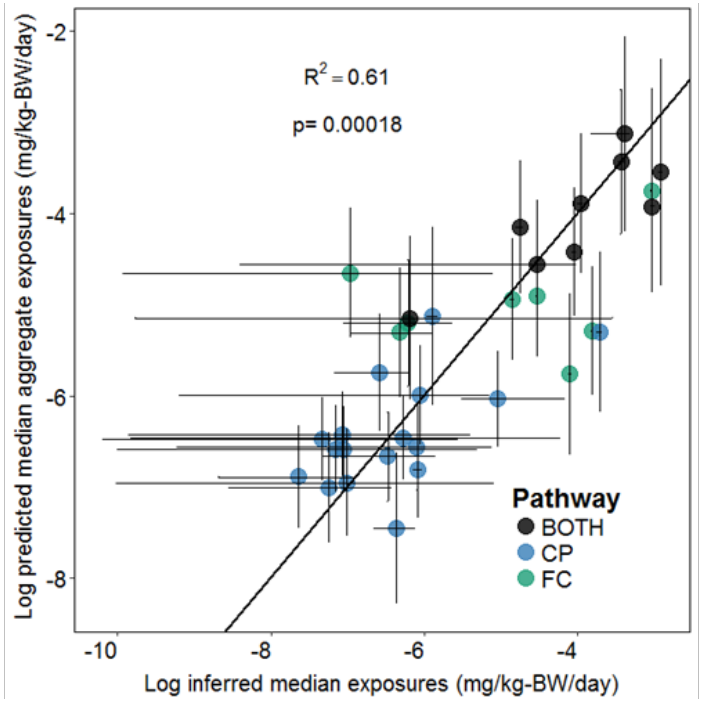
Phillips et al., Green Chemistry., 2017, 19, 1063.

Predicting Chemical Emissivity

- As we discover new chemicals in our environment, we need to characterize exposure potential
- A proof of concept model (Biryol, et al.) has been developed for food migration, but now modeling ExpoCast contract and NRMRL data for consumer products and articles of commerce



Results of the HT model for migration of packaging chemicals into food



SHEDS-HT Predicted aggregate exposures

Biryol *et al.* (*2017*)