United States
Environmental Protection
Agency

ExpoCast:
Applications to Integrated Bioactivity - Exposure Ratios

John Wambaugh
National Center for Computational Toxicology
U.S. EPA, Office of Research and Development

Exposure Science in the 21st Century Grantee Kickoff Meeting
February 3, 2015
Research Triangle Park, NC

Introduction

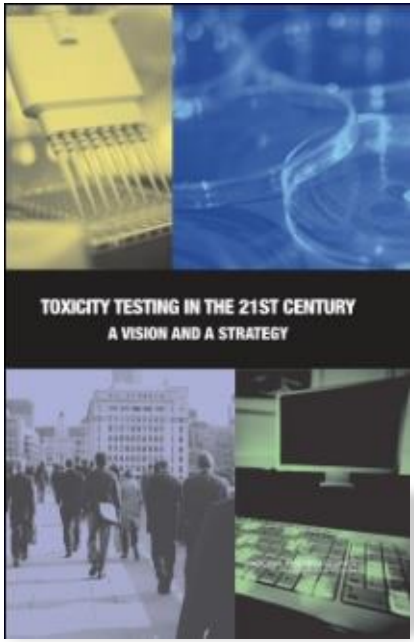
- The timely characterization of the human and ecological risk posed by thousands of existing and emerging commercial chemicals is a critical challenge facing EPA in its mission to protect public health and the environment

- While advances have been made in HT toxicity screening, evaluated **exposure** and **dosimetry** prediction methods applicable to 1000s of chemicals are needed

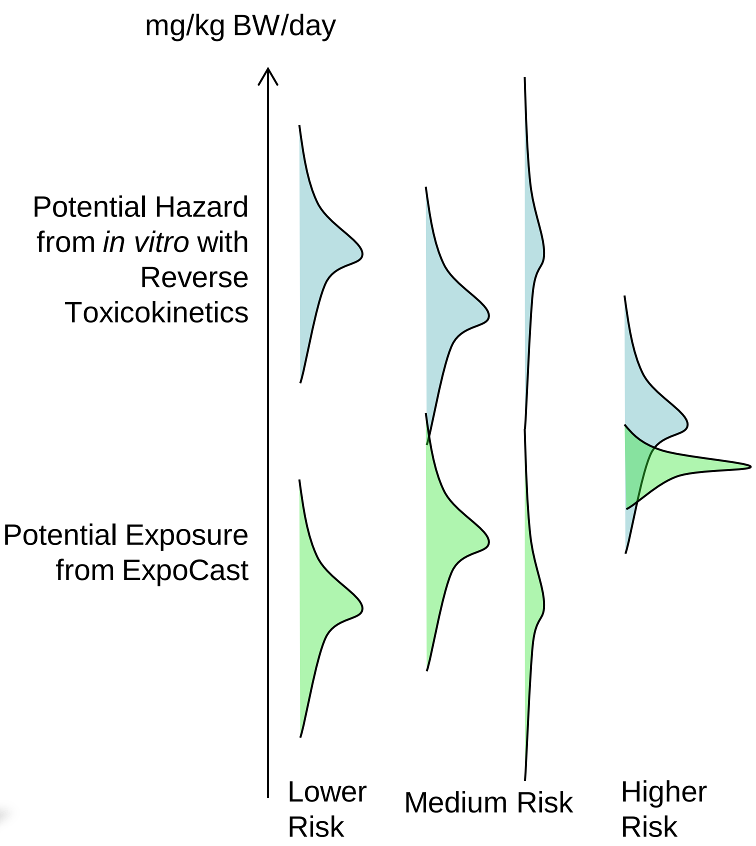
November 29, 2014

Prioritizing 1000’s of Chemicals for Further Study

- High throughput risk prioritization relies on **three components** – high throughput **hazard** characterization, high throughput **exposure** forecasts, and high throughput **pharmacokinetics**



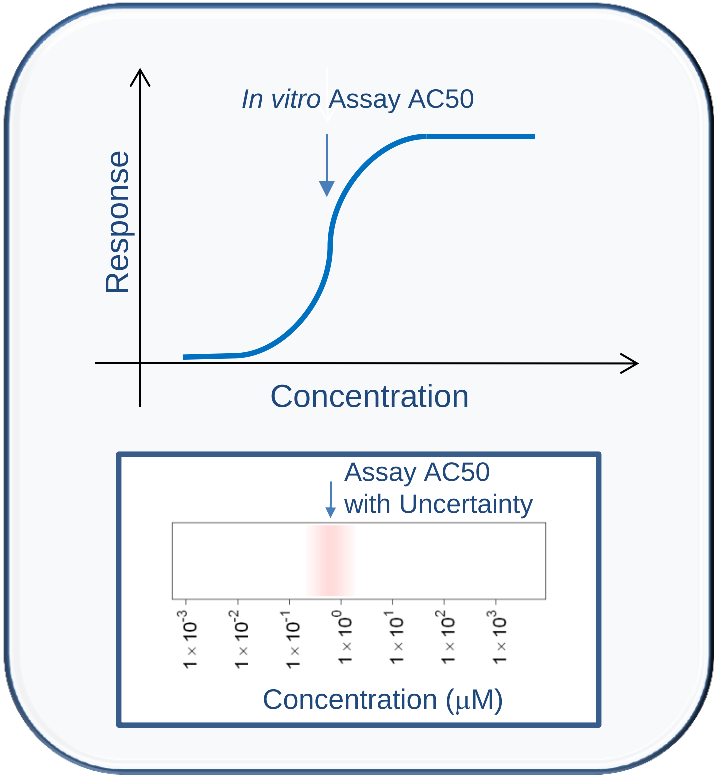
2007 NRC Report



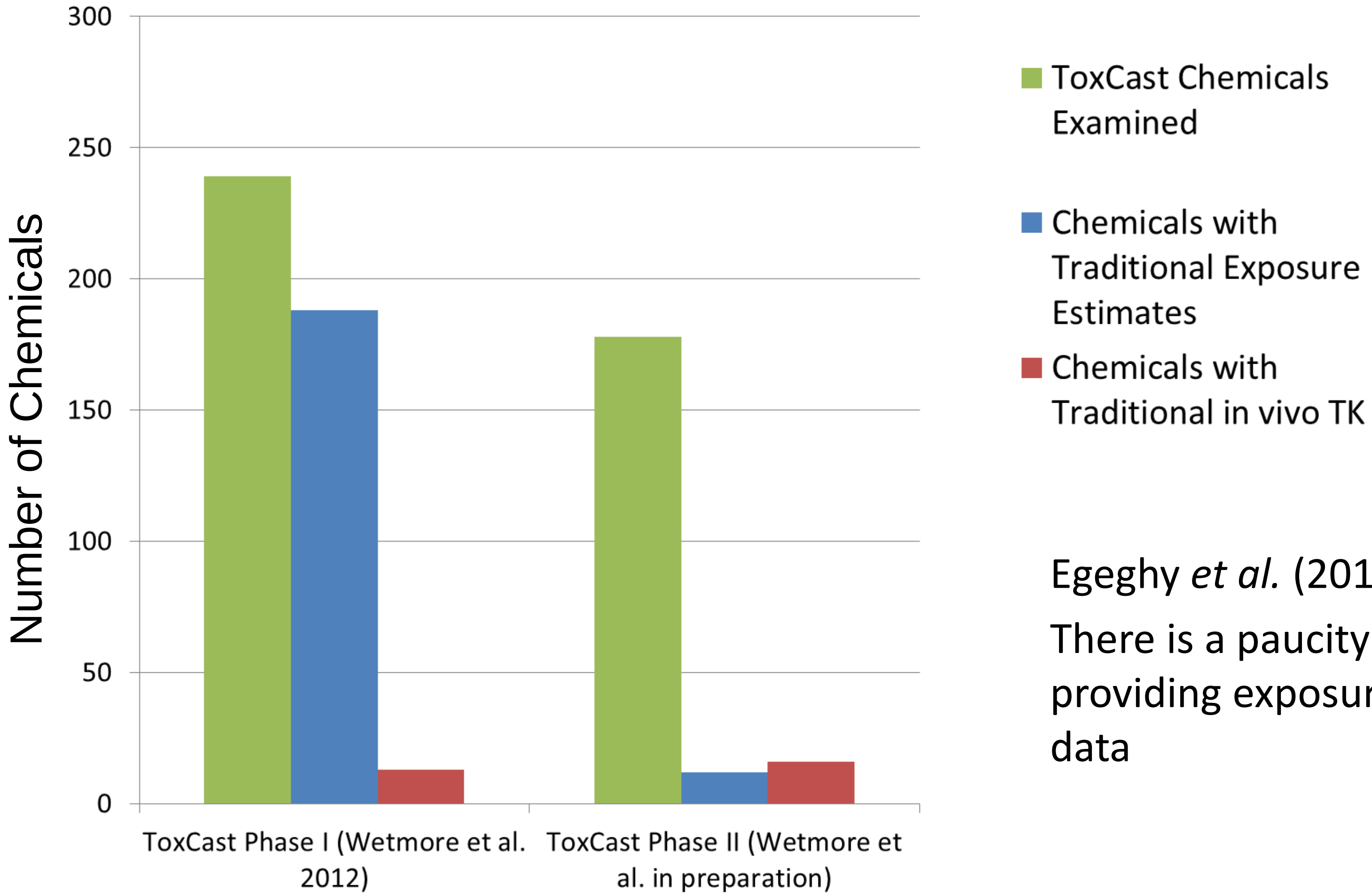
e.g. Judson *et al.*, (2011) Chemical Research in Toxicology

High-Throughput Bioactivity

- **Tox21**: Examining >10,000 chemicals using ~50 assays intended to identify interactions with biological pathways (Schmidt, 2009)
- **ToxCast**: For a subset (>1000) of Tox21 chemicals ran >500 additional assays (Judson et al., 2010)
- Most assays conducted in dose-response format (identify 50% activity concentration – AC50 – and efficacy if data described by a Hill function)
- All data is public: http://actor.epa.gov/



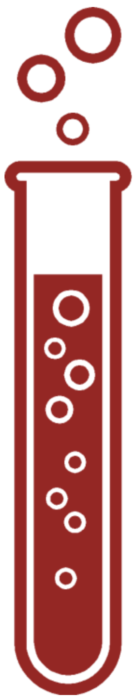
In Vitro Bioactivity, *In Vivo* Toxicokinetics, and Human Exposure



Egeghy *et al.* (2012):

There is a paucity of data for providing exposure context to HTS data

High Throughput Toxicokinetics (HTTK)



High Throughput *In Vitro* Bioactive Concentration

HTTK *in vitro* data

Simulated Human *In Vivo* Doses

Monte Carlo Simulation of Biological Variability

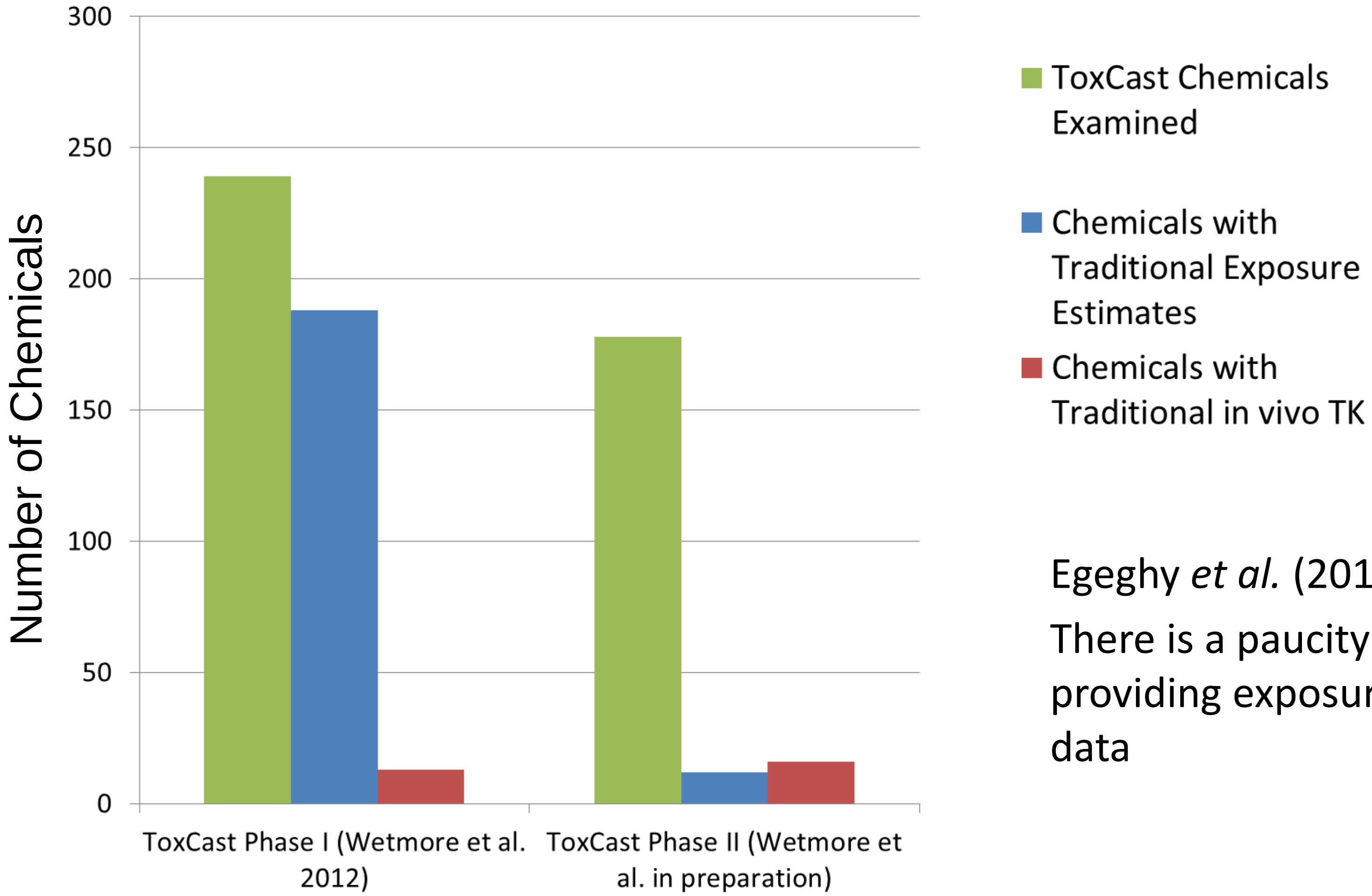
Combination of higher exposure and sensitivities

Populations that are More Sensitive

Images from Thinkstock

United States Environmental Protection Agency

In Vitro Bioactivity, *In Vivo* Toxicokinetics, and Human Exposure



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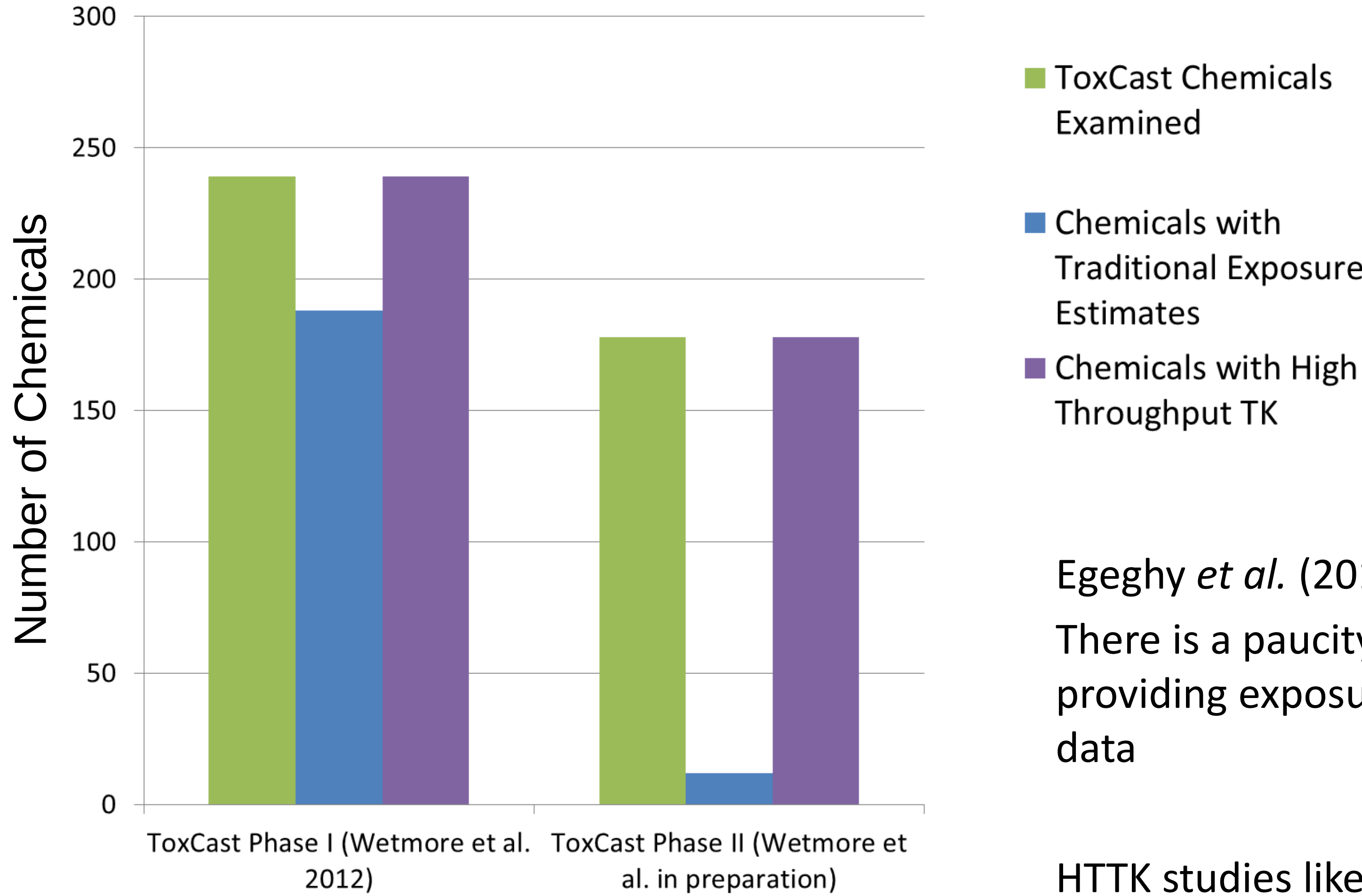
In Vitro Bioactivity, *In Vivo* Toxicokinetics, and Human Exposure



Egeghy *et al.* (2012):

There is a paucity of data for providing exposure context to HTS data

HTTK studies like Wetmore *et al.* (2012), can address the need for toxicokinetic data

High Throughput Exposure Forecasts

- New methods for Exposure Forecasting (ExpoCast) currently being considered for prioritization of chemical testing in the Endocrine Disrupter Screening Program (EDSP)
- Favorably reviewed by July 2014 Federal Insecticide, Fungicide, Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP)

https://federalregister.gov/a/2014-12593

Agency/Docket Numbers:

EPA-HQ-OPP-2014-0331
FRL-9910-22

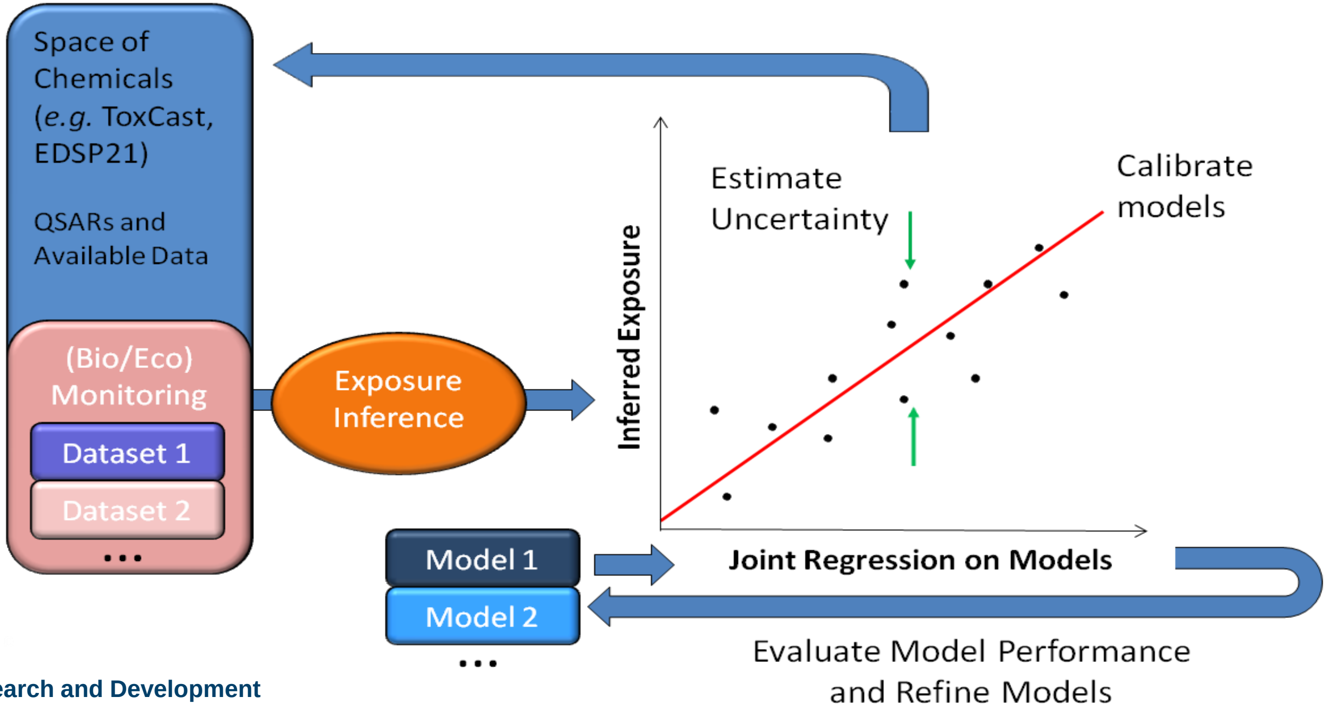
Exposure SAP White Paper

New High-throughput Methods to Estimate Chemical Exposure

Scientific Advisory Panel Meeting, July 2014

Consensus Model Building with the SEEM Framework

- Incorporate multiple models into consensus predictions for 1000s of chemicals within the **Systematic Empirical Evaluation of Models (SEEM) framework**
- Evaluate/calibrate predictions with available measurement data across many chemical classes
- Analogous efforts for both human and ecological exposures



Predicting NHANES exposure rates

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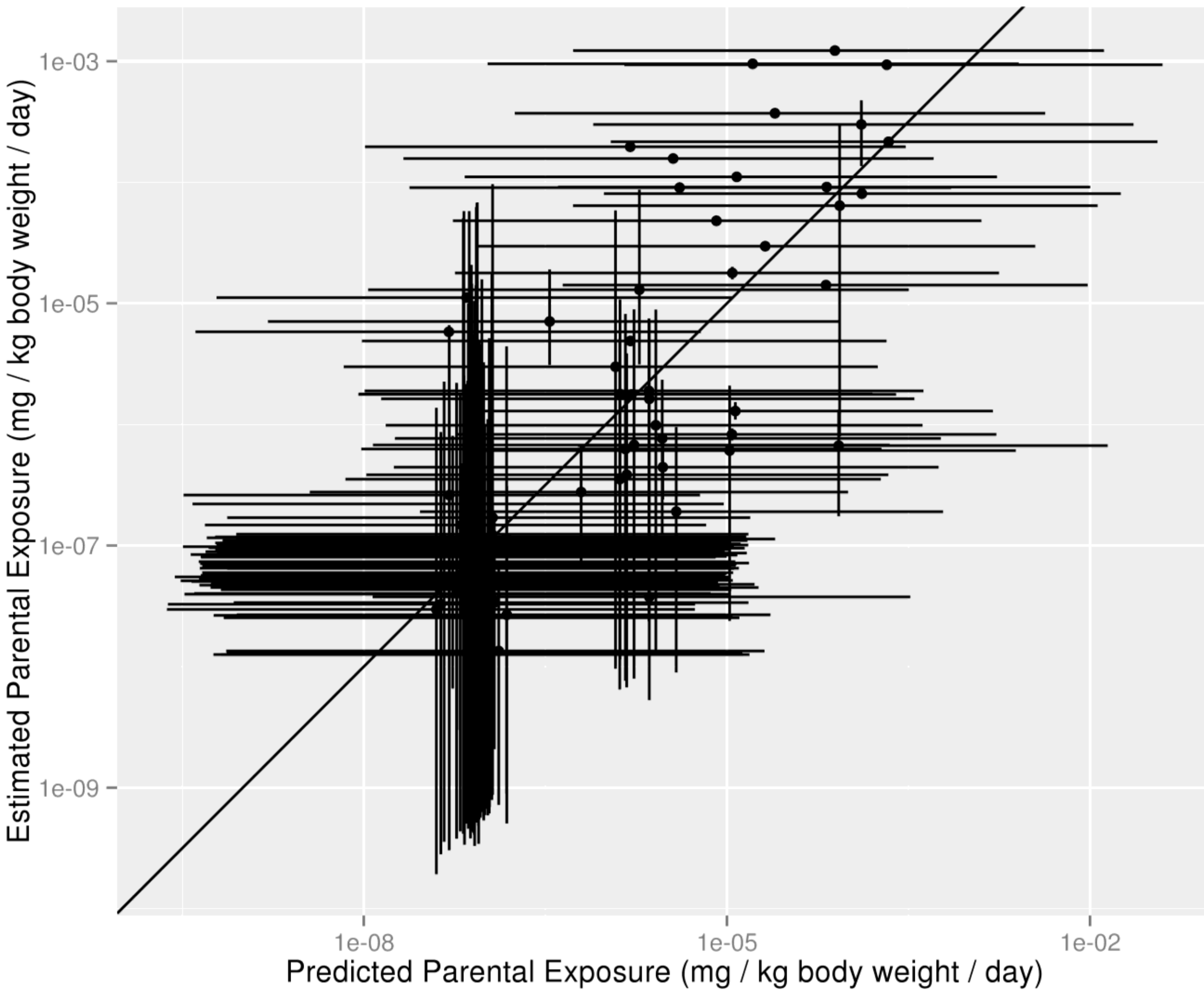


$R^2 \approx 0.5$ indicates that we can predict 50% of the chemical to chemical variability in mean NHANES exposure rates

Same five predictors work for all NHANES demographic groups analyzed – stratified by age, sex, and body-mass index

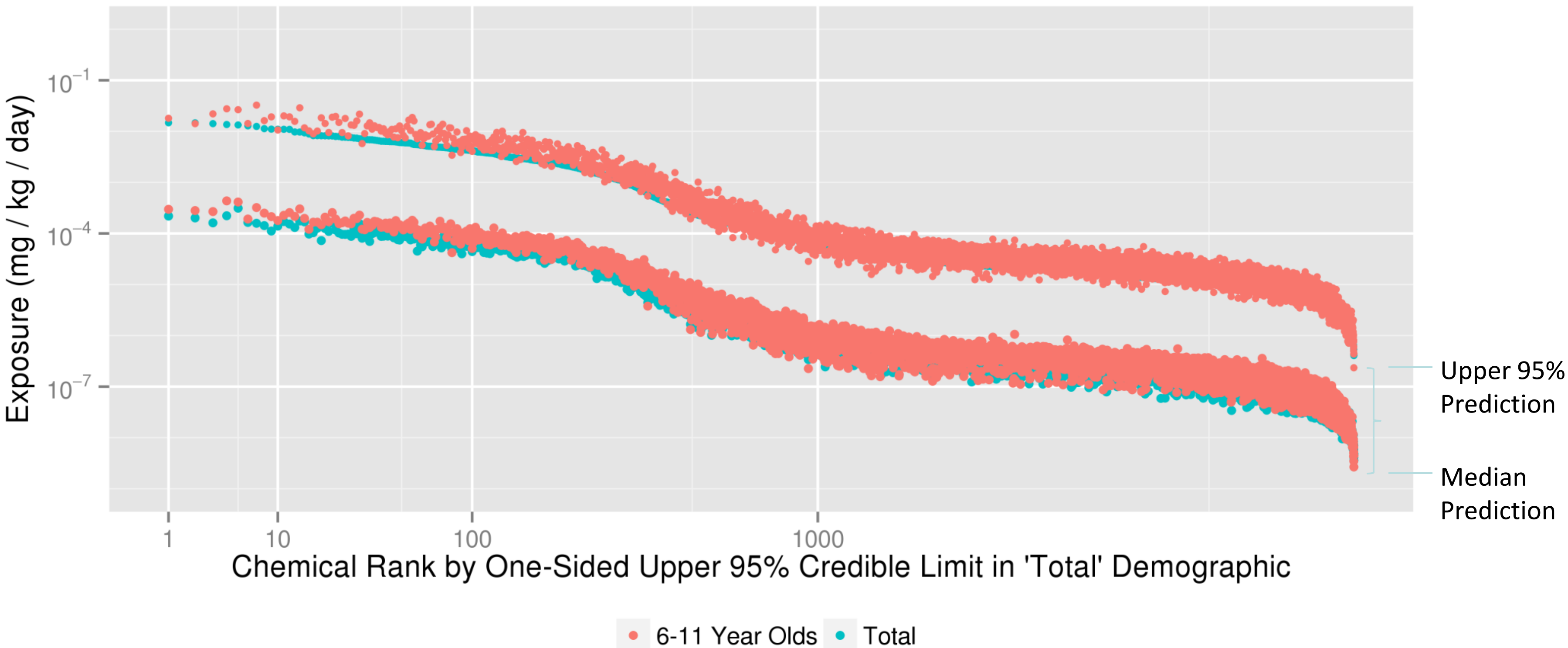
Wambaugh *et al.*, 2014

High-throughput exposure heuristics

Heuristic	Description	Number of Chemicals: Inferred NHANES Chemical Exposures (106)	Number of Chemicals: Full Chemical Library (7784)
ACToR "Consumer use & Chemical/Industrial Process use"	Chemical substances in consumer products (*e.g.*, toys, personal care products, clothes, furniture, and home-care products) that are also used in industrial manufacturing processes. Does not include food or pharmaceuticals.	37	683
ACToR "Chemical/Industrial Process use with no Consumer use"	Chemical substances and products in industrial manufacturing processes that are not used in consumer products. Does not include food or pharmaceuticals	14	282
ACToR UseDB "Pesticide Inert use"	Secondary (*i.e.*, non-active) ingredients in a pesticide which serve a purpose other than repelling pests. Pesticide use of these ingredients is known due to more stringent reporting standards for pesticide ingredients, but many of these chemicals appear to be also used in consumer products	16	816
ACToR "Pesticide Active use"	Active ingredients in products designed to prevent, destroy, repel, or reduce pests (*e.g.*, insect repellants, weed killers, and disinfectants).	76	877
TSCA IUR 2006 Total Production Volume	Sum total (kg/year) of production of the chemical from all sites that produced the chemical in quantities of 25,000 pounds or more per year. If information for a chemical is not available, it is assumed to be produced at <25,000 pounds per year.	106	7784

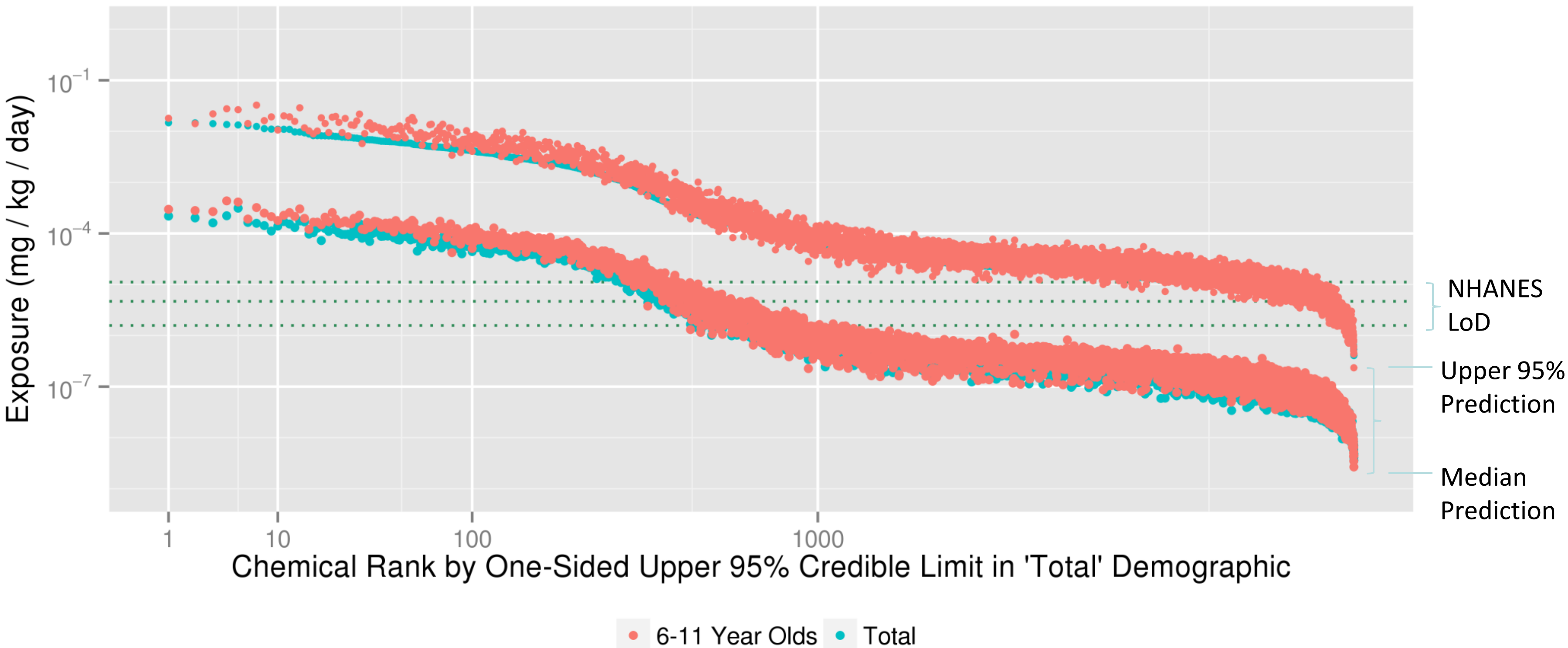
Wambaugh *et al.*, 2014

Calibrated Exposure Predictions for 7968 Chemicals



Wambaugh *et al.*, 2014

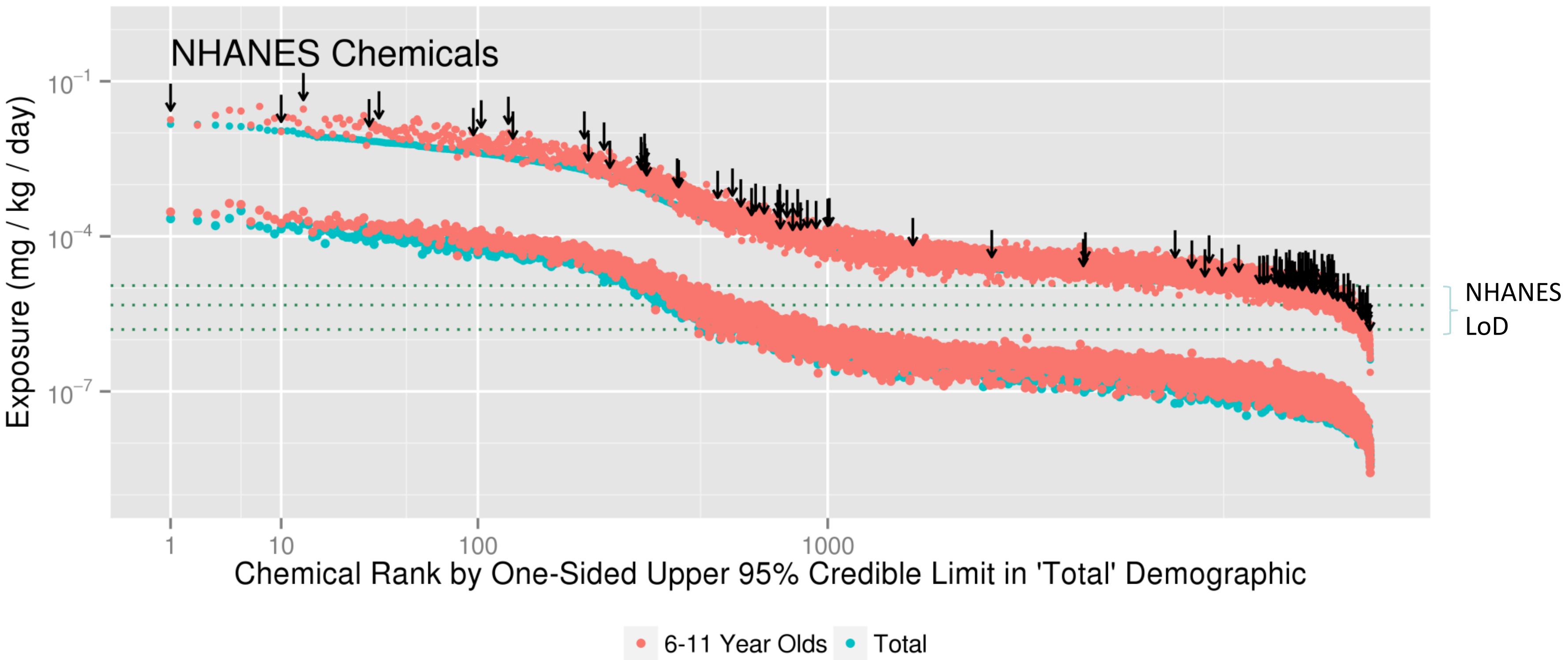
Calibrated Exposure Predictions for 7968 Chemicals



- We focus on the median and upper 95% predictions because the lower 95% is below the NHANES limits of detection (LoD)
- Dotted lines indicate 25%, median, and 75% of the LoD distribution

Wambaugh *et al.*, 2014

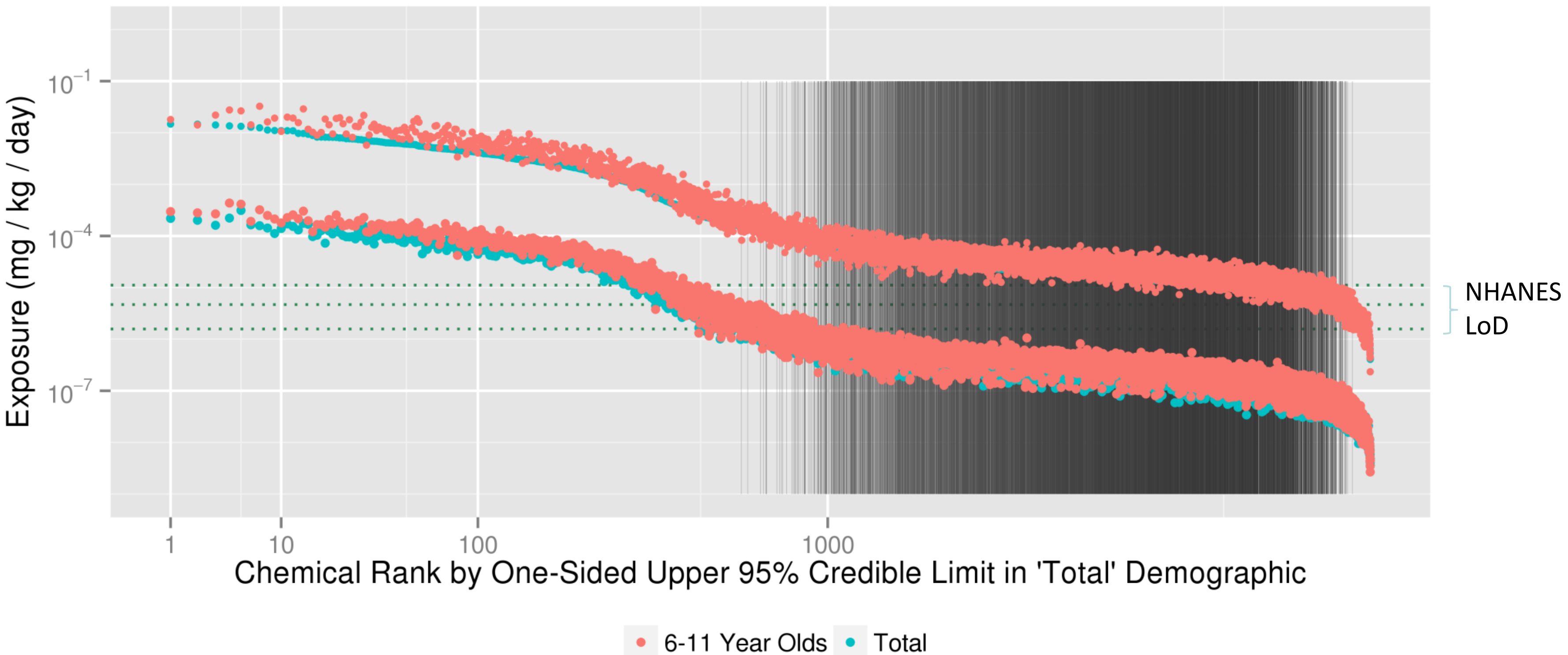
Calibrated Exposure Predictions for 7968 Chemicals



- Chemicals currently monitored by NHANES are distributed throughput the predictions
- Chemicals with the first and ninth highest 95% limit are monitored by NHANES

Wambaugh *et al.*, 2014

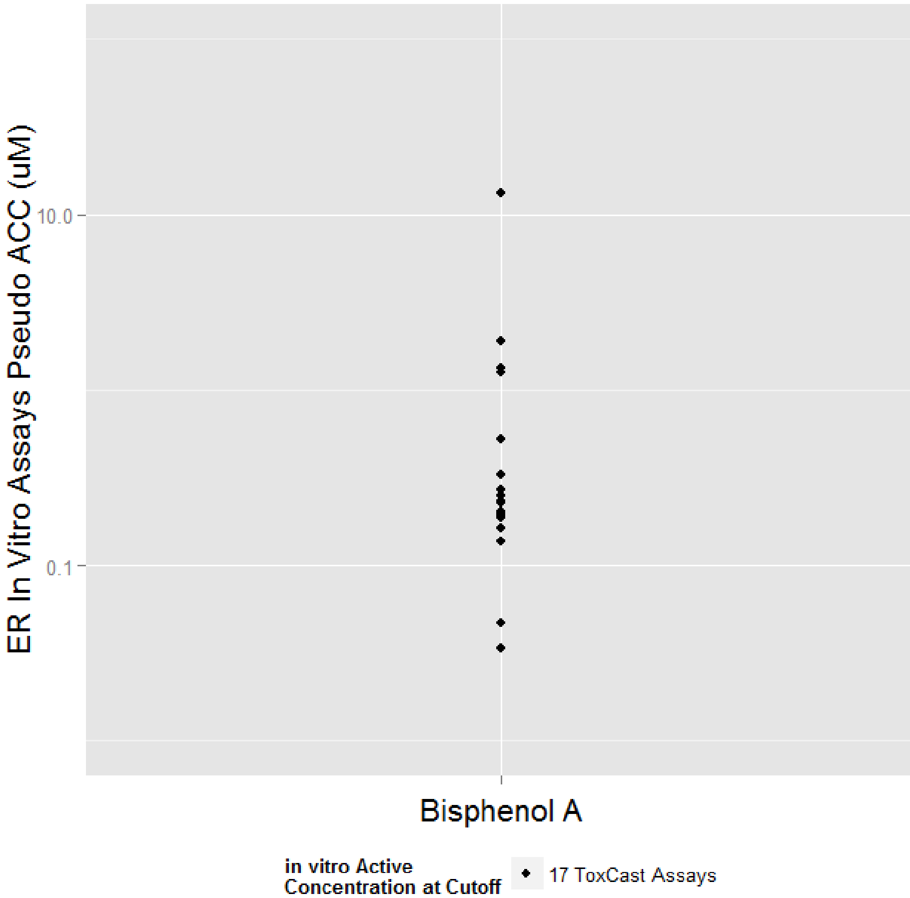
Calibrated Exposure Predictions for 7968 Chemicals



- The grey stripes indicate the 4182 chemicals with no use indicated by ACToR UseDB for any of the four use category heuristics

Wambaugh *et al.*, 2014

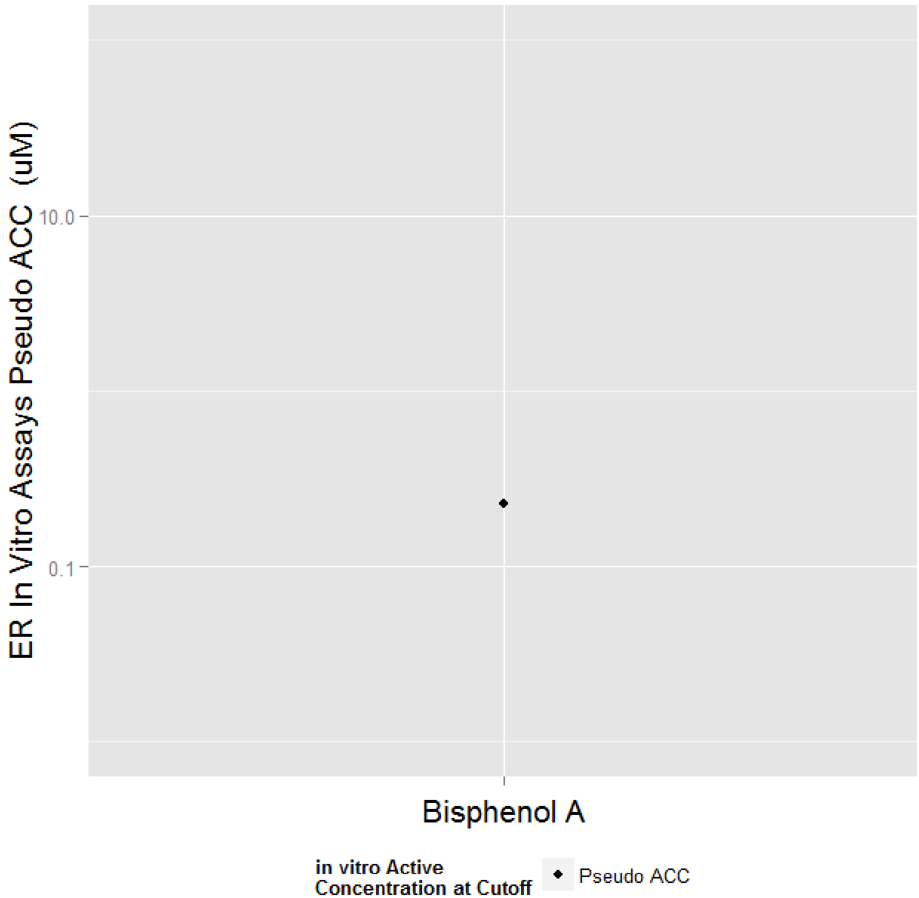
Integrated Bioactivity : Exposure Ratio (IBER)



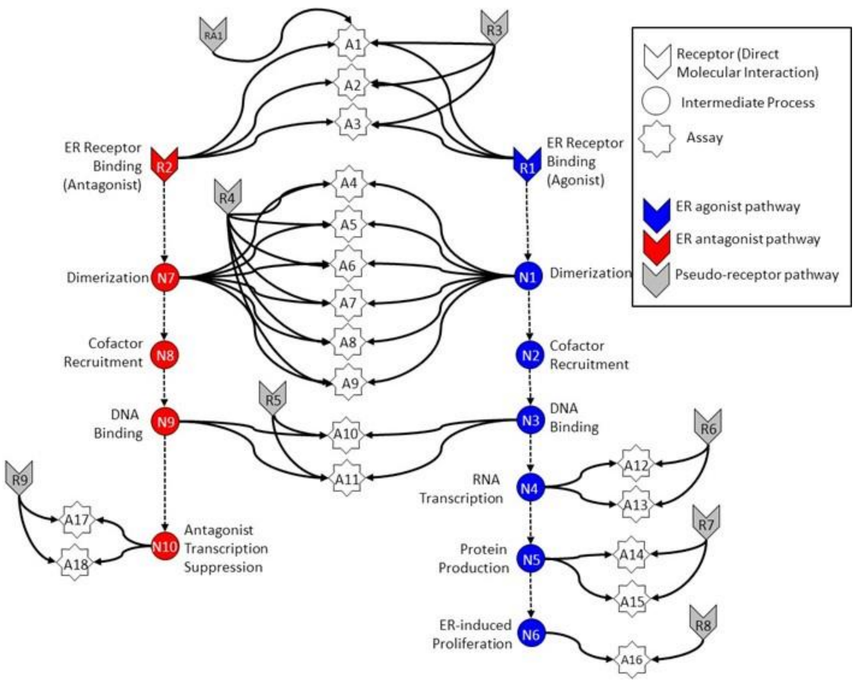
- Bisphenol A was active at some concentration for 17 of 18 ER-related assays

Assay	Conc.
NVS_NR_bER_ACC	0.19
NVS_NR_hER_ACC	0.20
NVS_NR_mERa_ACC	0.27
OT_ER_ERaERa_0480_ACC	1.27
OT_ER_ERaERa_1440_ACC	1.34
OT_ER_ERaERb_0480_ACC	0.23
OT_ER_ERaERb_1440_ACC	0.25
OT_ER_ERbERb_0480_ACC	0.23
OT_ER_ERbERb_1440_ACC	0.19
OT_ERa_EREGFP_0120_ACC	0.33
OT_ERa_EREGFP_0480_ACC	0.52
ATG_ERa_TRANS_up_ACC	0.03
ATG_ERE_CIS_up_ACC	0.05
Tox21_ERa_BLA_Agonist_ratio_ACC	1.88
Tox21_ERa_LUC_BG1_Agonist_ACC	0.14
ACEA_T47D_80hr_Positive_ACC	0.16
Tox21_ERa_BLA_Antagonist_ratio_ACC	13.27
Tox21_ERa_LUC_BG1_Antagonist_ACC	1000000

Integrated Bioactivity : Exposure Ratio (IBER)



- A mathematical model was used to integrate all assays into a single predicted active concentration



Judson *et al*., in preparation

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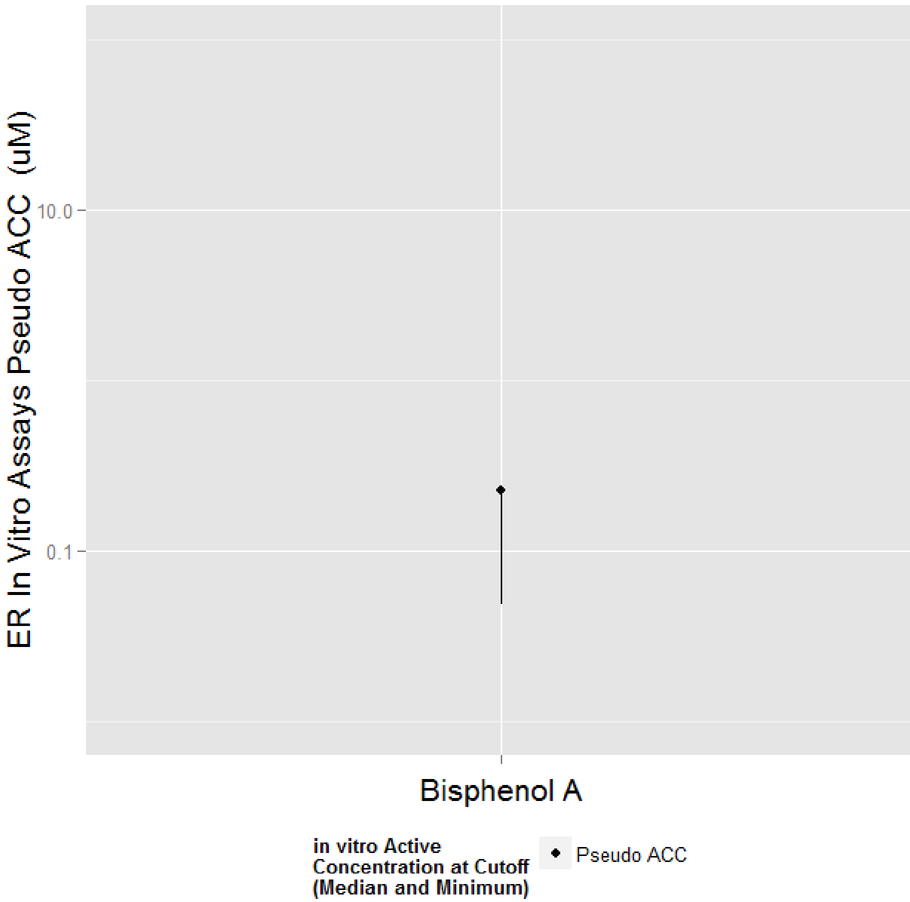
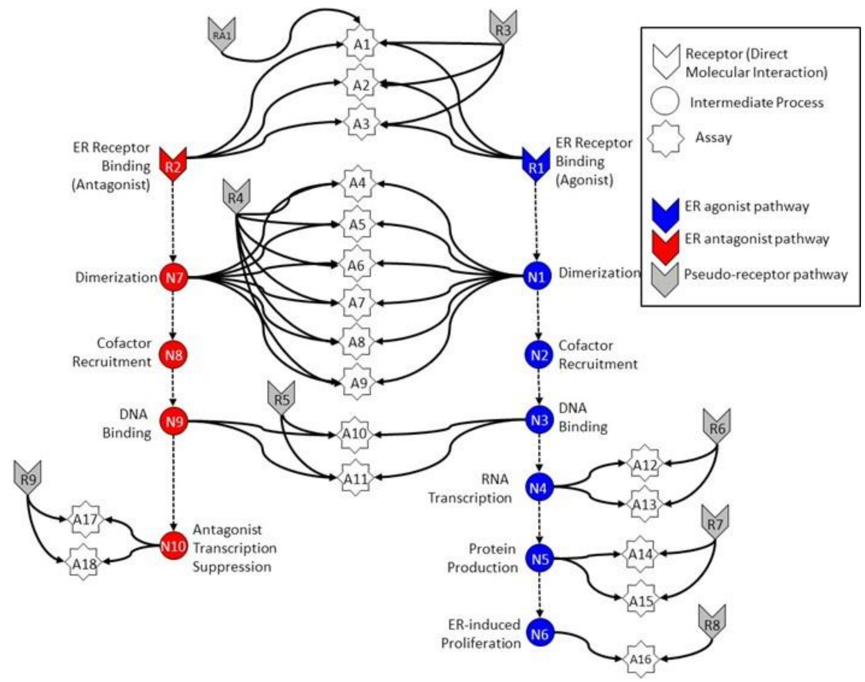
Integrated Bioactivity : Exposure Ratio (IBER)

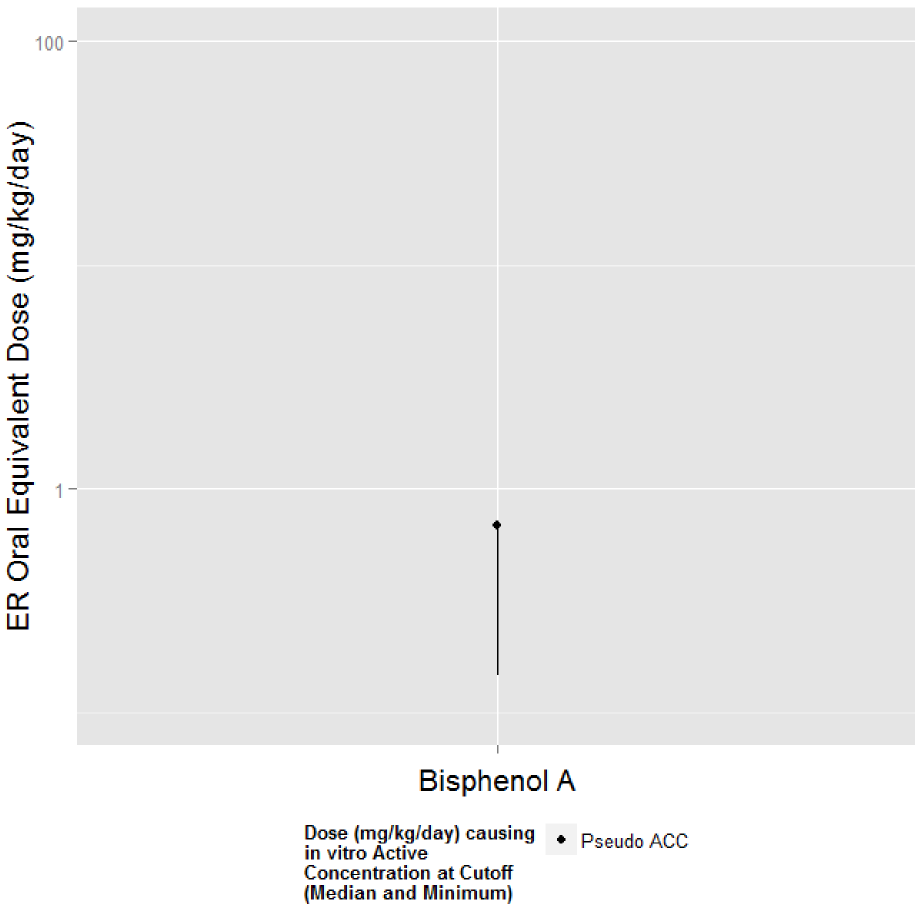


- The error bar indicates the span between the median and the minimum plausible active concentration

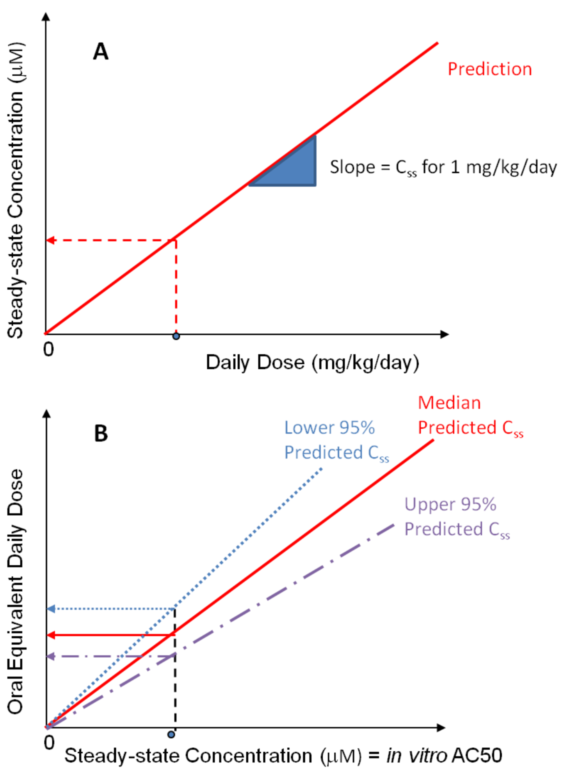


Judson *et al*., in preparation

Integrated Bioactivity : Exposure Ratio (IBER)

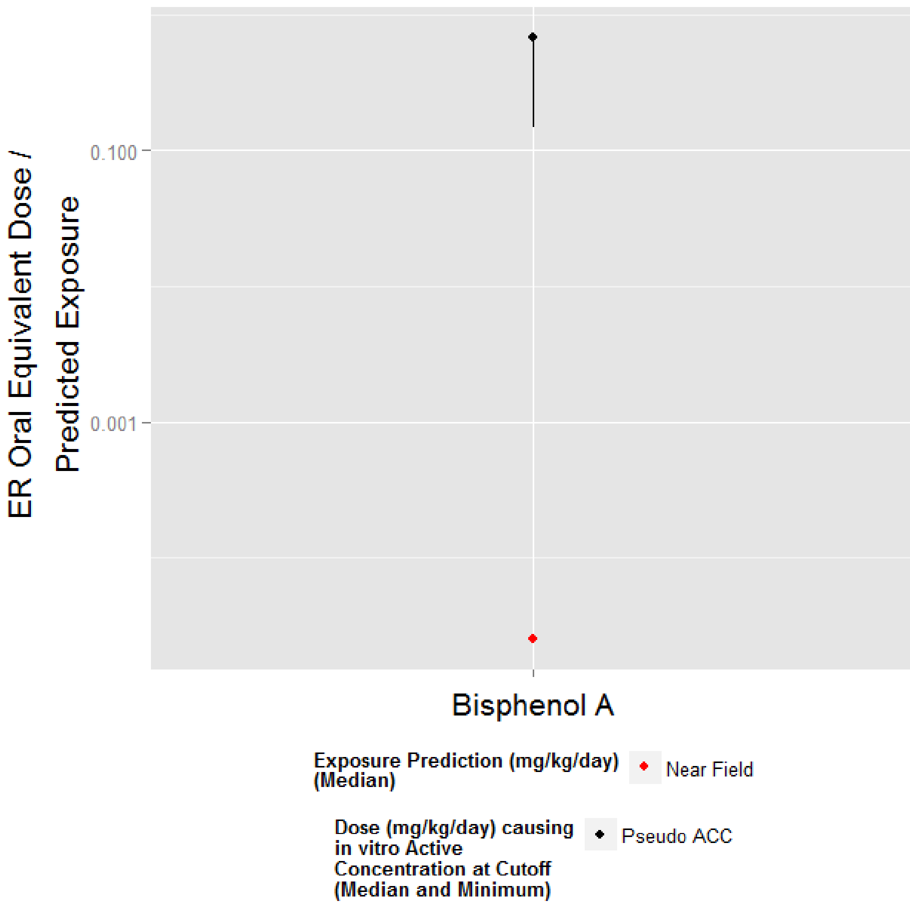


- Reverse dosimetry based on HTTK data was used to predict an oral equivalent dose that would cause the ACC in plasma for the 95-percentile, most sensitive adult



Wetmore *et al.*, (2012)

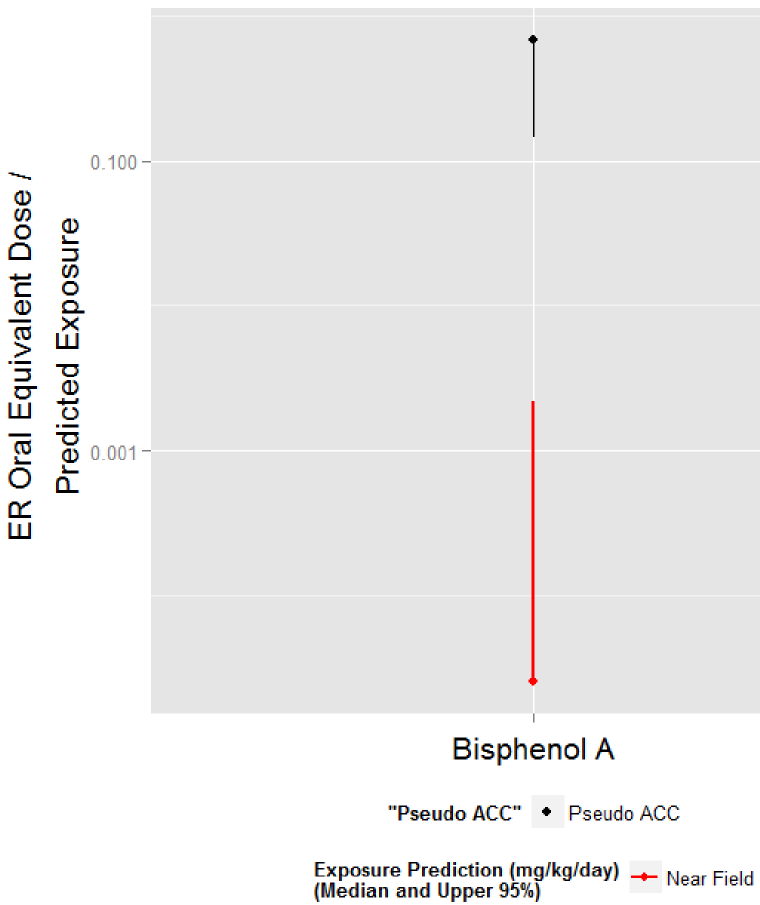
Integrated Bioactivity : Exposure Ratio (IBER)



- Based on the ACToR UseDB descriptors and production volume, a median exposure for similar NHANES chemicals can be predicted

Heuristic	Bisphenol A
Consumer & Industrial Use	Yes
Industrial Use Only	No
Pesticide Inert	No
Pesticide Active	No
Production Volume	> 1 billion lbs/year

Integrated Bioactivity : Exposure Ratio (IBER)



- Due to the large uncertainty, the upper 95% limit of the exposure estimate credible interval is used

Heuristic	Bisphenol A
Consumer & Industrial Use	Yes
Industrial Use Only	No
Pesticide Inert	No
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Production Volume	> 1 billion lbs/year

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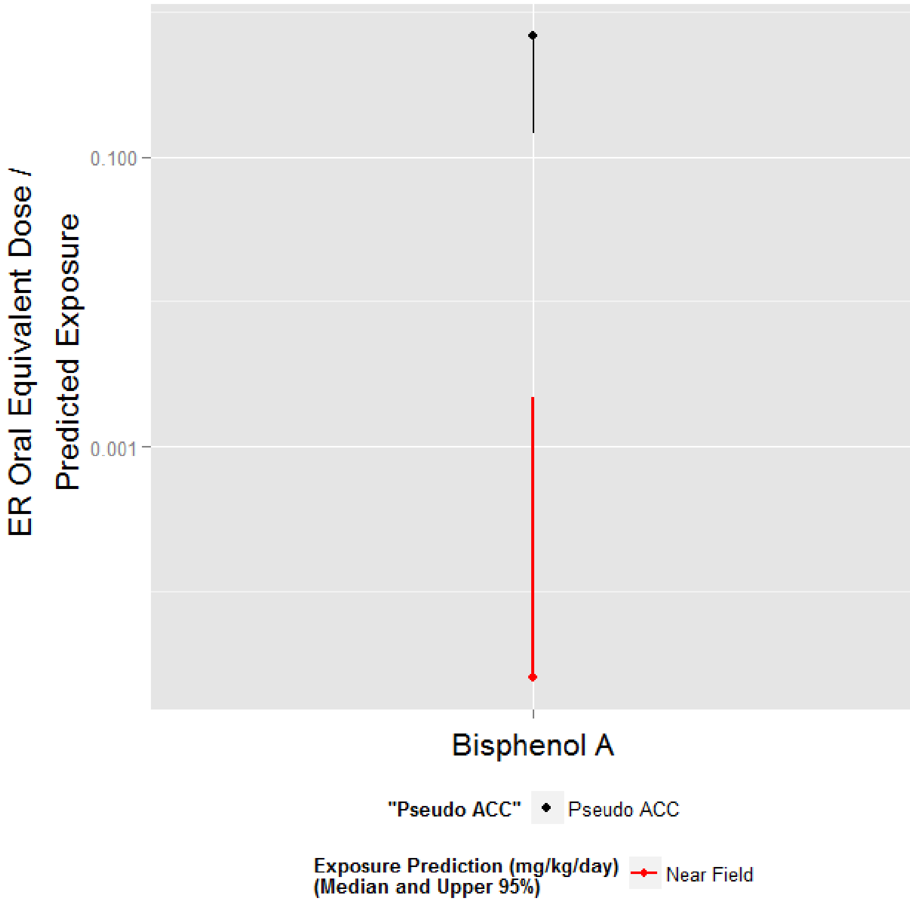
Integrated Bioactivity : Exposure Ratio (IBER)

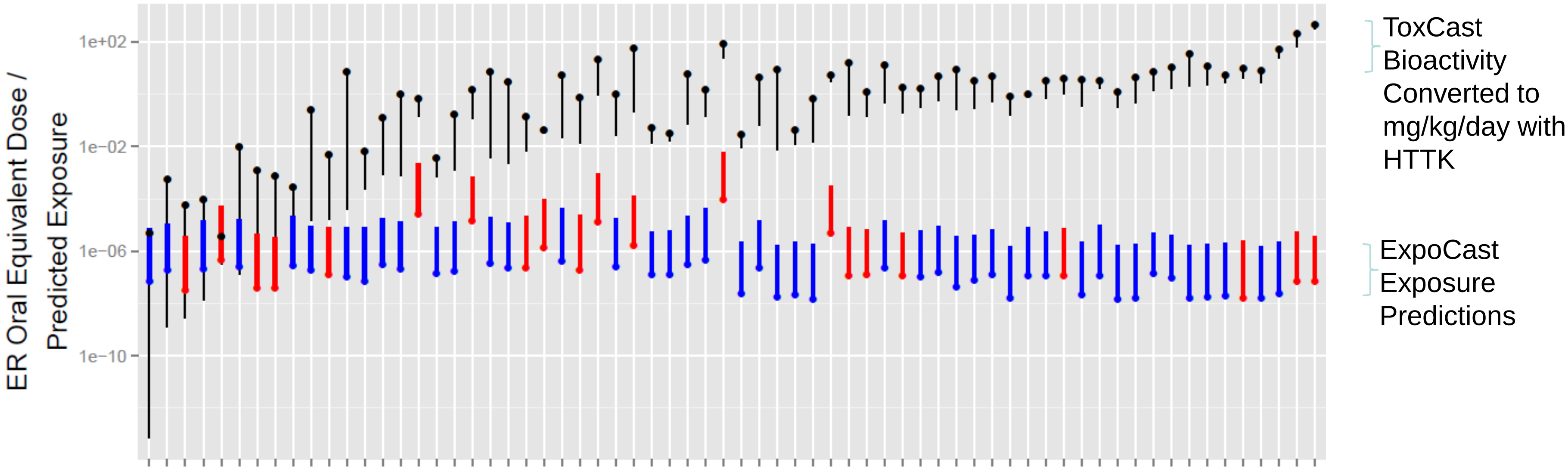


- ANSES (2013) BPA Receipts, 200 ng/kg BW/d (Workers) and 10 ng/kg BW/d (Consumers)
- LaKind and Naiman (2011) Estimated Exposure to BPA from NHANES data in ng/kgBW/day):

Demographic	LaKind and Naiman (2011)	ExpoCast Geometric Mean Median	ExpoCast Geometric Mean Upper 95%
Total	35.1	25.0	2193
Age 6-11y	54	63	4984
Age 12-19y	48	59	5169
Age 20-39y*	38.5	57	6056
Age 40-59y*	28.9	57	6056
Age >=60y	27.3	66	84221
Male	39.6	38	3132
Female	31.2	12	1125

*ExpoCast makes single prediction for Age 20-59y

IBER Scientific Advisory Panel (SAP)

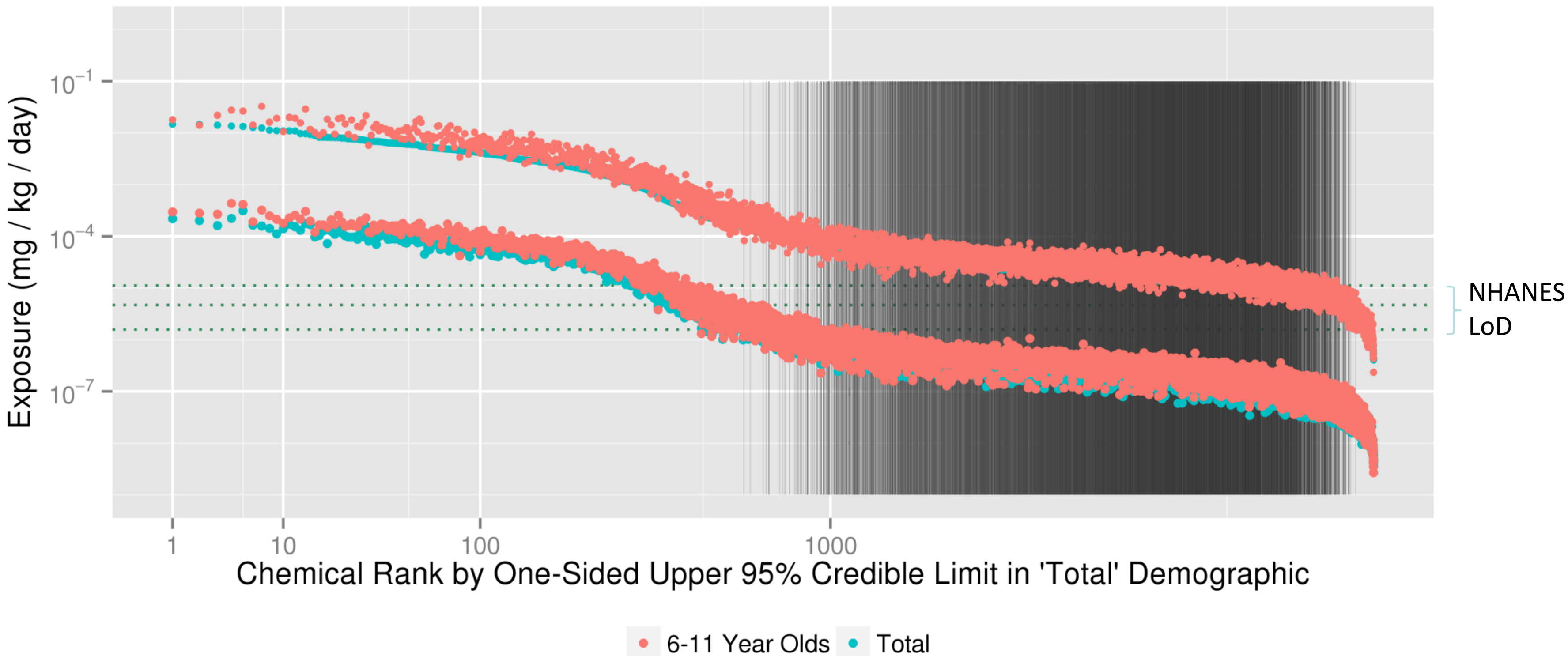


ToxCast Chemicals

December, 2015 Panel:
“Scientific Issues Associated with Integrated Endocrine Bioactivity and Exposure-Based Prioritization and Screening“

DOCKET NUMBER:
EPA–HQ–OPP–2014–0614

Calibrated Exposure Predictions for 7968 Chemicals



- The grey stripes indicate the 4182 chemicals with no use indicated by ACToR UseDB for any of the four use category heuristics

Wambaugh *et al.*, 2014

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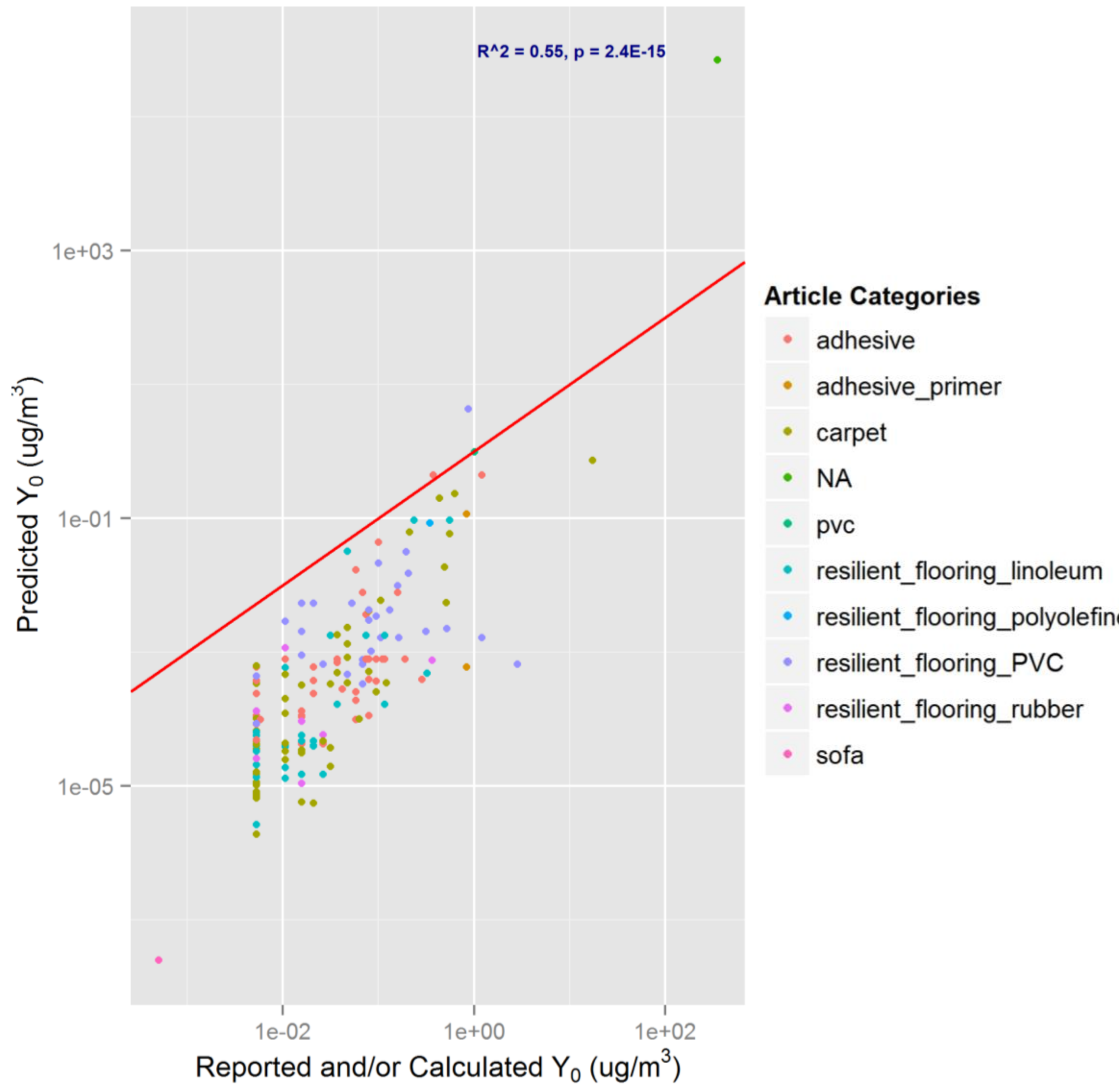
Gas-Phase Concentration Model

- 73 total chemicals in model including SVOCs[1] reported from Wilke *et al*. (2004)

- 4 chemicals reported from Little *et al.* (2012)

- 1 main physicochemical property that model data (VP). Other predictors include formulation descriptors.



Acronyms:
- SVOCs = Semivolatile Organic Compounds
- FRs = Flame Retardants
- VP = Vapor Pressure
- $Y_{\circ}$ = Gas-phase concentration

Slide from Chantel Nicolas

Refined Models and Better Data: SHEDS-HT

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Chemical to Chemical Variability of NHANES Biomonitoring

~10% Far field (Industrial) Releases
Wambaugh et al. (2013)

~50% Indoor / Consumer Use
Wambaugh et al. (2014)

Consumer product database and two new near field models

Contents lists available at ScienceDirect
Food and Chemical Toxicology
journal homepage: www

Development of a consumer produ
exposure screening and prioritizati

M.-R. Goldsmith[a,*], C.M. Grulke[a], R.D. Brook
R. Edwards[d], D.T. Chang[a], R. Tornero-Velez[a]
J. Mitchell[g], D.A. Vallero[a], L. Phillips[a], M. Ph
T.J. Buckley[a], C.C. Dary[a]

[a] United States Environmental Protection Agency (U.S. EPA), Office of Resear
[b] Student Services Contractor at U.S. EPA, RTP, NC, United States
[c] Lockheed-Martin Information Technology, RTP, NC 27711, United States
[d] North Carolina State University, 2200 Hillsborough St., Raleigh, NC 27695,
[e] Oak Ridge Institute for Science and Education Fellow, United States
[f] University of North Carolina at Chapel Hill, Chapel Hill, NC 27514, United
[g] Biosystems and Agricultural Engineering, Michigan State University, E. Lan

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Keywords:
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Ingredients
Product formulation
Near field exposure
Exposure prioritization

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Model for Screening-Level Assessm
Exposure to Neutral Organic Che

Xianming Zhang,*[,†,§] Jon A. Arnot,*[,†,‡] and Fran

[†] Department of Physical and Environmental Sciences, Univers
[‡] ARC Arnot Research and Consulting, Toronto, Ontario M4

Supporting Information

ABSTRACT: Screening organic chemicals for hazard and ri
health requires near-field human exposure models that ca
parametrized with available data. The integration of a mod
exposure, uptake, and bioaccumulation into an indoor mass b
provides a quantitative framework linking emissions in ind
ments with human intake rates (*iRs*), intake fractions (*iFs*)
state concentrations in humans (*C*) through consideratio
permeation, inhalation, and nondietary ingestion exposu
Parameterized based on representative indoor and a
characteristics, the model is applied here to 40 chemicals
in the context of human exposure assessment. Intake fraction
concentrations (C_U) calculated with the model based on a u
rate to air for these 40 chemicals span 2 and 5 orders o
respectively. Differences in priority ranking based on either *i*
elimination processes within the human body. The model
representative of many in-use chemicals to show how the
chemical properties and to illustrate the capacity of the

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Article
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SHEDS-HT: An Integrated Probabilistic Exposure Model for Prioritizing Exposures to Chemicals with Near-Field and Dietary Sources

Kristin K. Isaacs,*[,†] W. Graham Glen,[‡] Peter Egeghy,[†] Michael-Rock Goldsmith,[§,○] Luther Smith,[‡] Daniel Vallero,[†] Raina Brooks,[∥] Christopher M. Grulke,[⊥,○] and Halûk Özkaynak[†]

[†] U.S. Environmental Protection Agency, Office of Research and Development, National Exposure Research Laboratory, 109 T.W. Alexander Drive, Research Triangle Park, North Carolina 27709, United States
[‡] Alion Science and Technology, 1000 Park Forty Plaza Suite 200, Durham, North Carolina 27713, United States
[§] Chemical Computing Group, Suite 910, 1010 Sherbrooke Street West, Montreal, QC H3A 2R7, Canada
[∥] Student Services Contractor at U.S. Environmental Protection Agency, 109 T.W. Alexander Drive, Research Triangle Park, North Carolina 27709, United States
[⊥] Lockheed Martin, 109 T.W. Alexander Drive, Research Triangle Park, North Carolina 27709, United States

Supporting Information

ABSTRACT: United States Environmental Protection Agency

Consumer Product Data

Contracts Awarded in December 2014

Exposure Screening Tools for Accelerated Chemical Prioritization (ExpoCast)

- Solicitation posted May 22, 2013

- Two awardees:
  Battelle Memorial Institute (Columbus, OH) and
  Southwest Research Institute (San Antonio, TX)

- The EPA is interested in building models to quantitatively predict potential exposure for thousands of chemicals in commerce. Results will be used in the ExpoCast project to evaluate, calibrate and reduce uncertainty in exposure model predictions and for prioritizing compounds for more in-depth testing and risk assessment. To support computational models three kinds of exposure measurement data are required:

  (1) key physical-chemical properties
  (2) chemical emissions from consumer products used indoors
  (3) chemical occurrence in product, environmental, and biological media.

SEEM Evolution – Human Exposure

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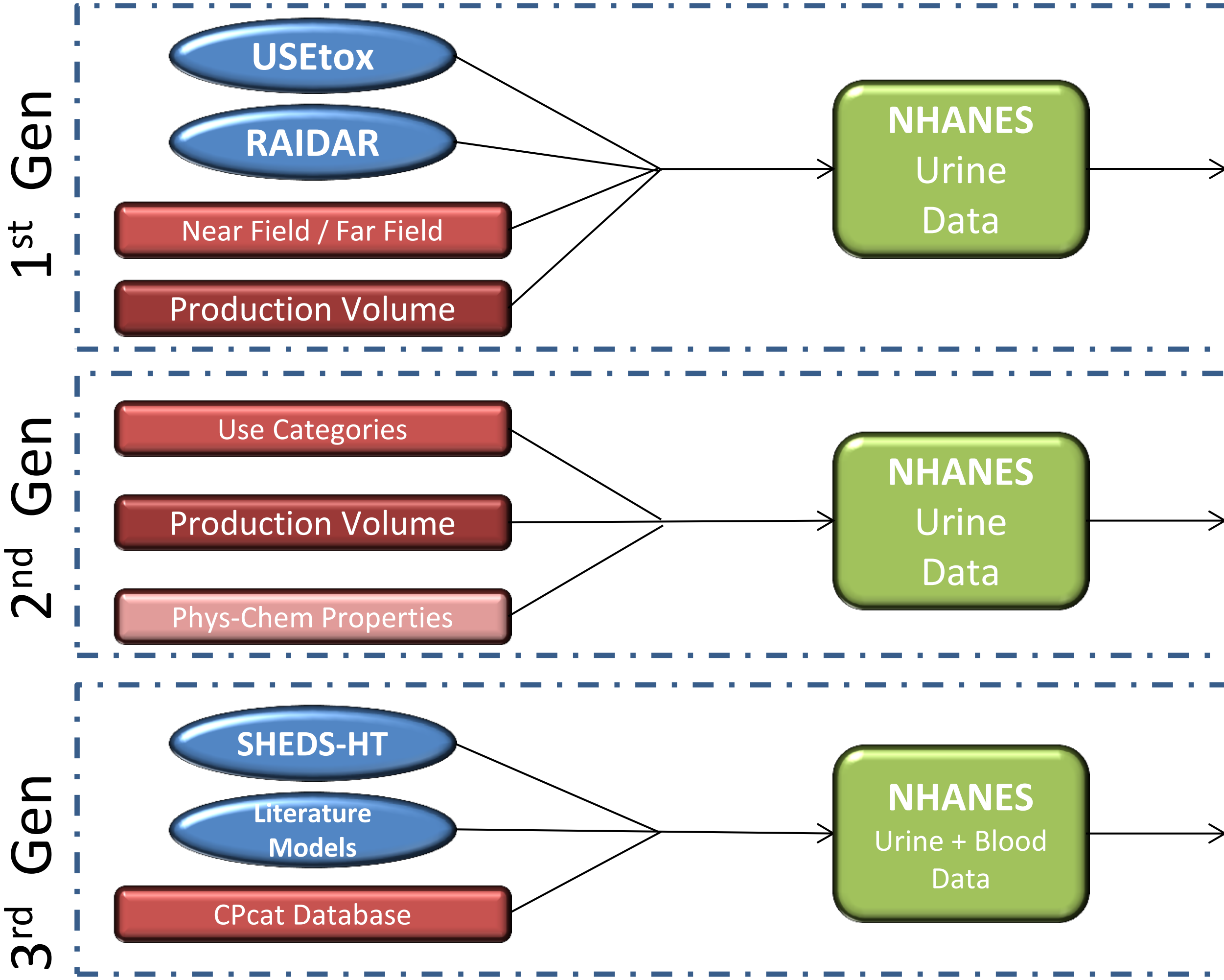
Model and Predictors | **Calibration/Evaluation Data** | **SEEM Conclusion**



1st Gen – SEEM Conclusion
- Existing complex fate and transport models have low correlation to measured exposures
- Near field factor most important

2nd Gen – SEEM Conclusion
- Simple, readily available data
- Better correlation to measured exposures
- Similar predictions across demographics

3rd Gen – SEEM Conclusion
- Analysis ongoing

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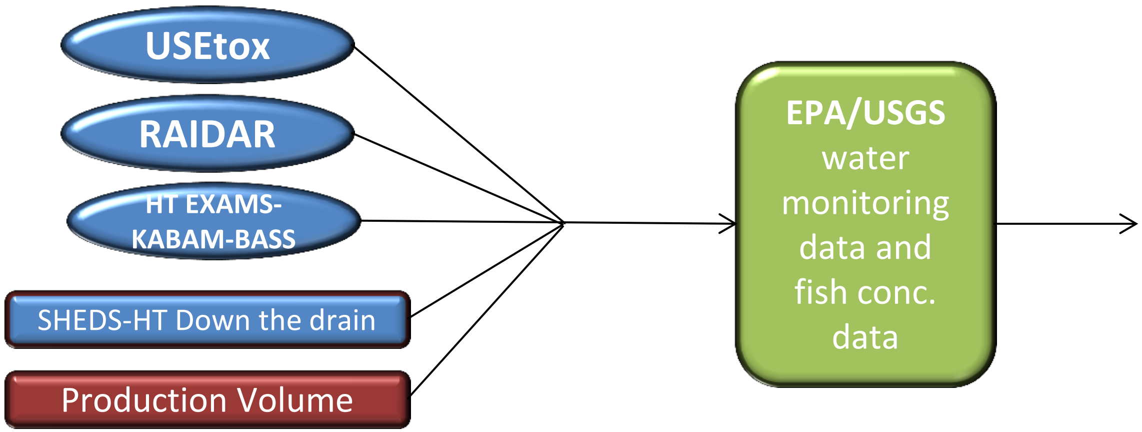
SEEM Evolution – Far-field Water
Eco (fish) and Human Exposure

Far-field Water

Model and Predictors | Calibration/Evaluation Data | SEEM Conclusion



- Analysis ongoing

Conclusions

United States Environmental Protection Agency

- High throughput risk prioritization relies on three components – high throughput hazard characterization, high throughput exposure forecasts, and high throughput pharmacokinetics
- Characterize uncertainty in chemical exposures by examining the predictive ability of models and the coverage (or lack thereof) of critical pathways
- Upcoming analysis:
  - Augment heuristics with calibrations of new mechanistic HT models for exposure from consumer use and indoor environment (*e.g.*, SHEDS-HT)
  - Develop new data sources with additional chemical descriptors (*e.g.*, CPcatDB)
  - Should help decrease uncertainties and increase confidence in extrapolation
  - Perform similar analysis for water concentrations

Collaborators

Chemical Safety for Sustainability (CSS) Rapid Exposure and Dosimetry (RED) Project

NCCT
Chris Grulke
Richard Judson
Thomas Knudsen
Chantel Nicolas*
Robert Pearce*
James Rabinowitz
Caroline Ring*
Woody Setzer
Imran Shah
Rusty Thomas
John Wambaugh

NRMRL
Xiaoyu Liu

NHEERL
Jane Ellen Simmons
Marina Evans
Mike Hughes

*Trainees

NERL
Craig Barber
Derya Biryol *
Dalizza Colon
Kathie Dionisio*
Peter Egeghy
Kim Gaetz
Kristin Isaacs
Julia Rager*
Mark Strynar
Jon Sobus
Mike Tornero-Velez
Dan Vallero

Arnot Research and Consulting
Jon Arnot
Chemical Computing Group
Rocky Goldsmith
Environmental Protection Agency
Alicia Frame
Hamner Institutes
Barbara Wetmore
Cory Strope
Indiana University
James Sluka
Michigan State University
Jade Mitchell
National Institute for Environmental Health Sciences (NIEHS)
Mike Devito
Nisha Sipes
Kyla Taylor
Kristina Thayer
Netherlands Organisation for Applied Scientific Research (TNO)
Sieto Bosgra
North Carolina State University
Anran Wang*
Research Triangle Institute
Timothy Fennell
Silent Spring Institute
Robin Dodson
University of California, Davis
Deborah Bennett
University of Michigan
Olivier Jolliet
University of North Carolina, Chapel Hill
Alexander Sedykh*
Alex Tropsha