High Throughput Exposure Forecasts for Environmental Chemical Risk

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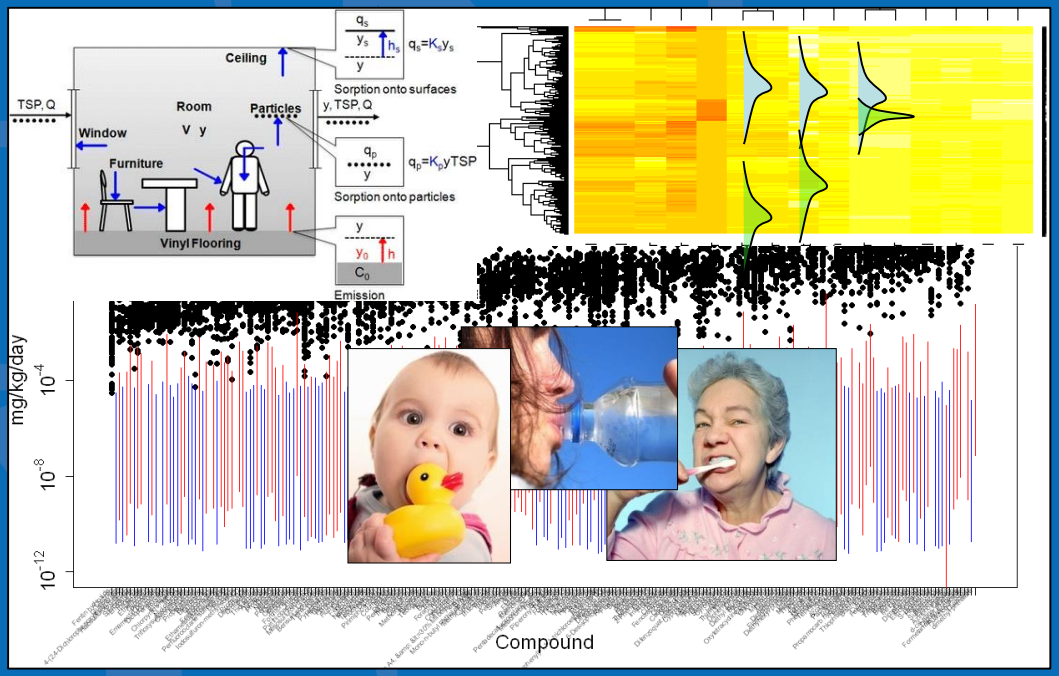


December 11, 2013

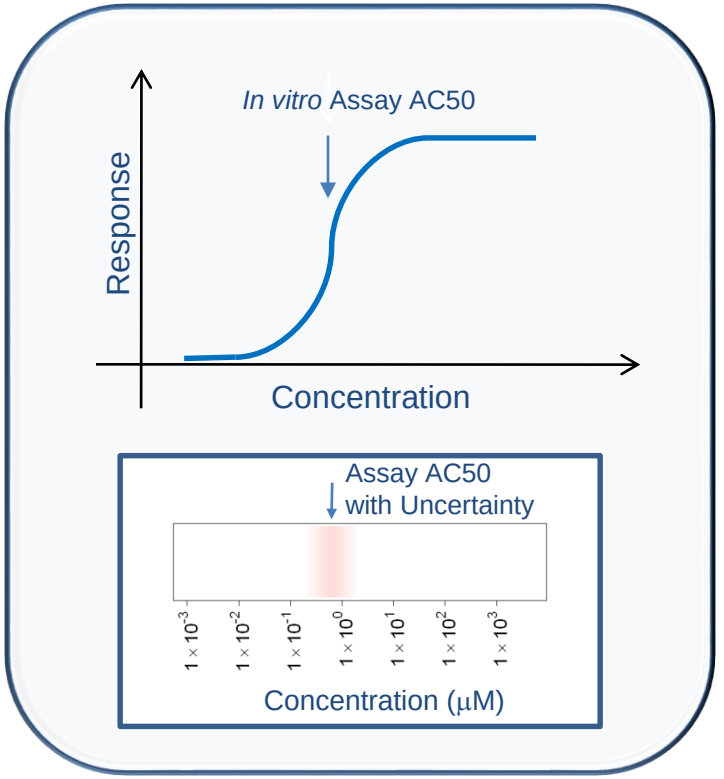
High-Throughput Toxicity Testing

Tox21: Examining >10,000 chemicals using ~50 assays intended to identify interactions with biological pathways (Schmidt, 2009)

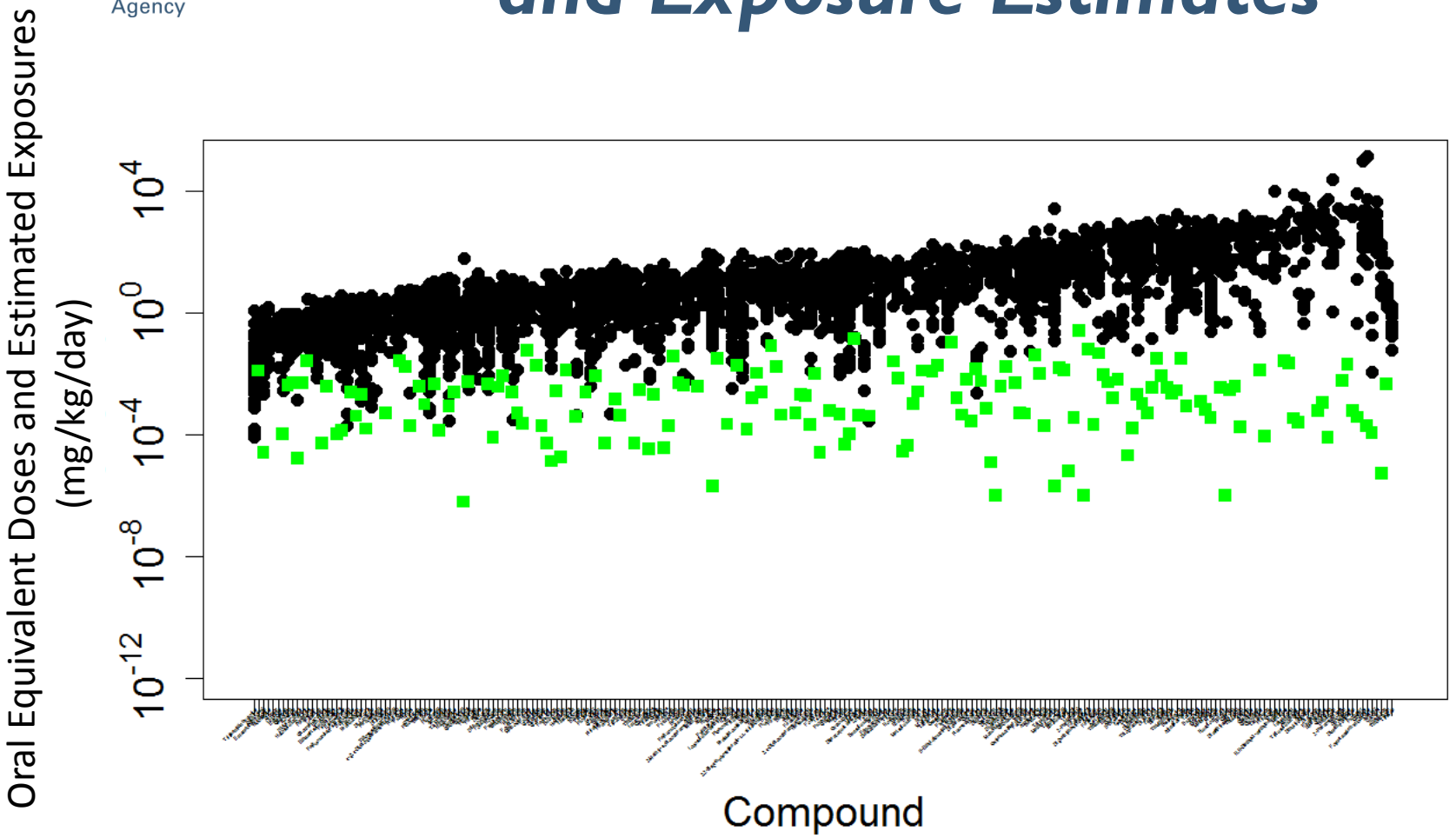
ToxCast: For a subset (>1000) of Tox21 chemicals ran >500 additional assays (Judson *et al.,* 2010)

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/



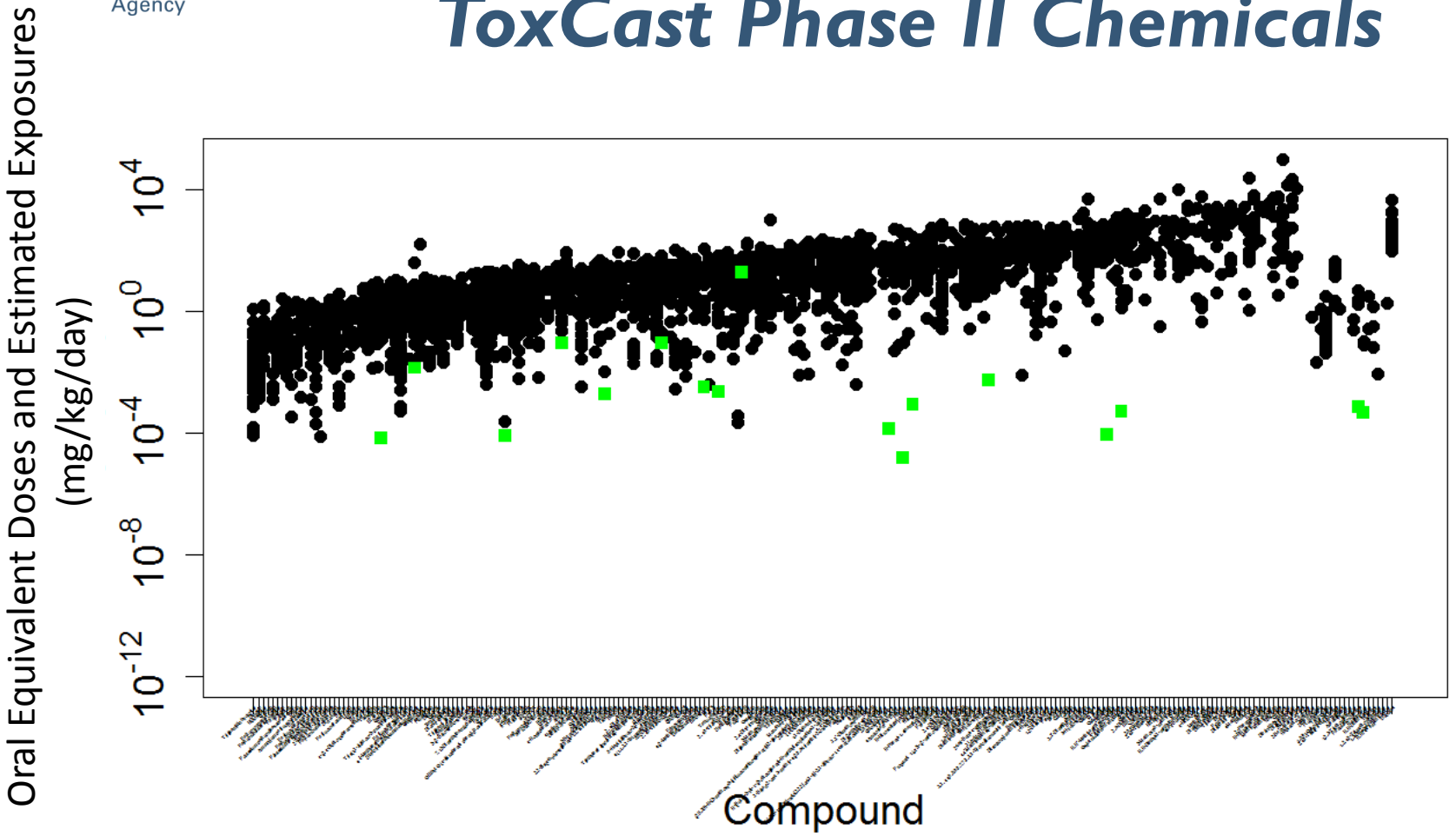
ToxCast Oral Equivalent Doses and Exposure Estimates



Green squares indicate highest estimated exposures from EPA REDs or CDC NHANES: ~71% of Phase I

Wetmore et al. *Tox. Sci (2012)*

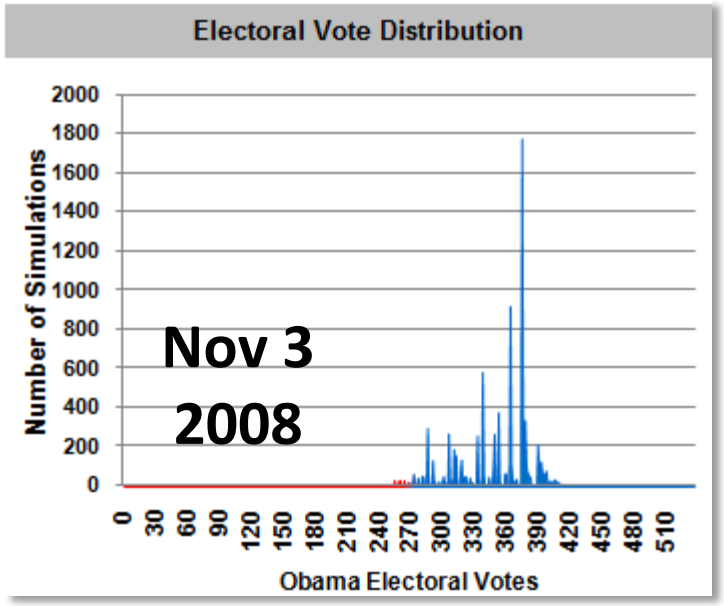
The Exposure Coverage of the ToxCast Phase II Chemicals

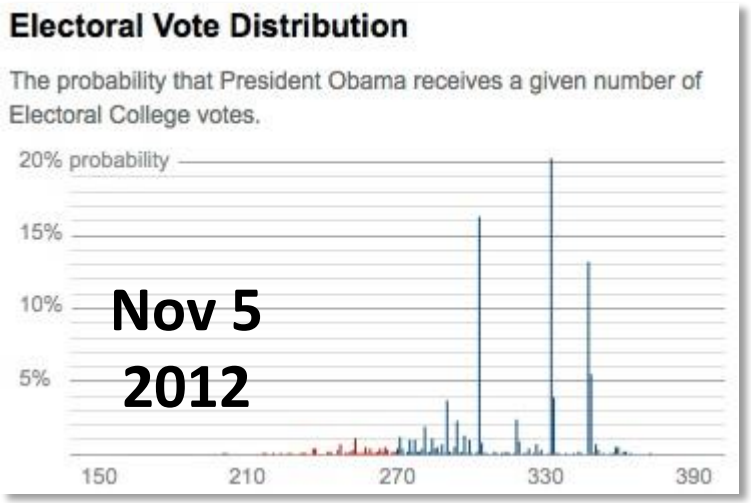


Green squares indicate highest estimated exposures from EPA REDs or CDC NHANES: ~71% of Phase I
~7% of Phase II

Unpublished data from Barbara Wetmore

The Signal and the Noise (2012)





Nate Silver (fivethirtyeight blog) has called the last two presidential elections correctly (a coin would do this one in four times)

He has called 99/100 state results correctly (a coin would do this one in ~10^{28} times)

Nate Silver: How to Make Good Forecasts

1) Think probabilistically

2) Forecasts change – today's forecast reflects the best available data today

3) Look for consensus – multiple models/predictions

In Nate Silver's terminology:
a ***prediction*** is a specific statement
a ***forecast*** is a probabilistic statement

Wikipedia (statistics): "when information is transferred across time, often to specific points in time, the process is known as forecasting"

High Throughput Exposure Predictions

Goal: A high-throughput exposure approach to use with the ToxCast chemical hazard identification.

Proof of Concept: Using off-the-shelf models capable of quantitatively predicting exposure determinants in a high throughput (1000s of chemicals) manner and then evaluate those predictions to characterize uncertainty (Wambaugh *et al.*, ES&T 2013)

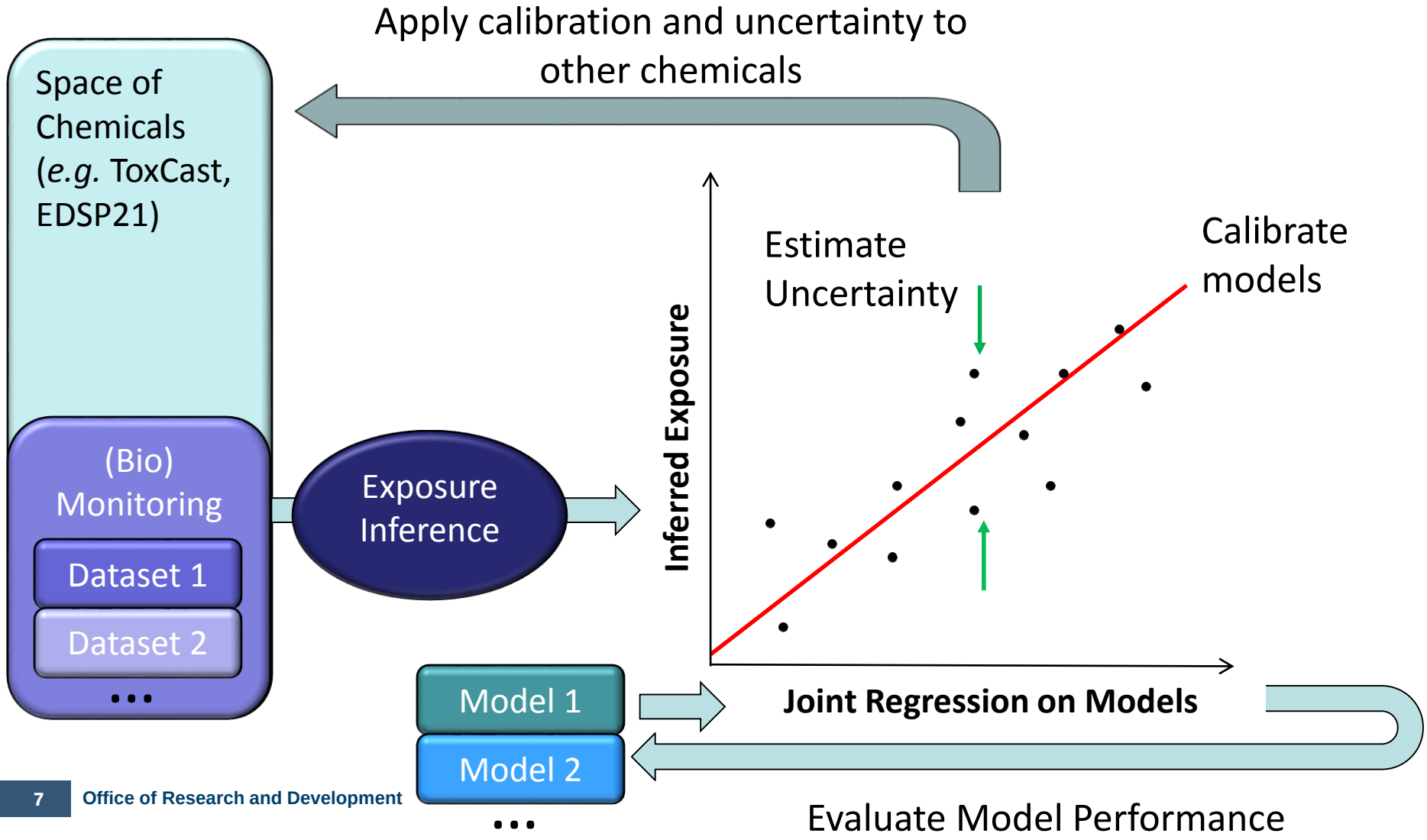
To date have found only fate and transport models to be quantitative and have sufficient throughput (Mitchell *et al.,* Science of the Total Environment 2013)

Also used a simple consumer use heuristic (Dionisio *et al., in preparation*)

Environmental Fate and Transport

Consumer Use and Indoor Exposure

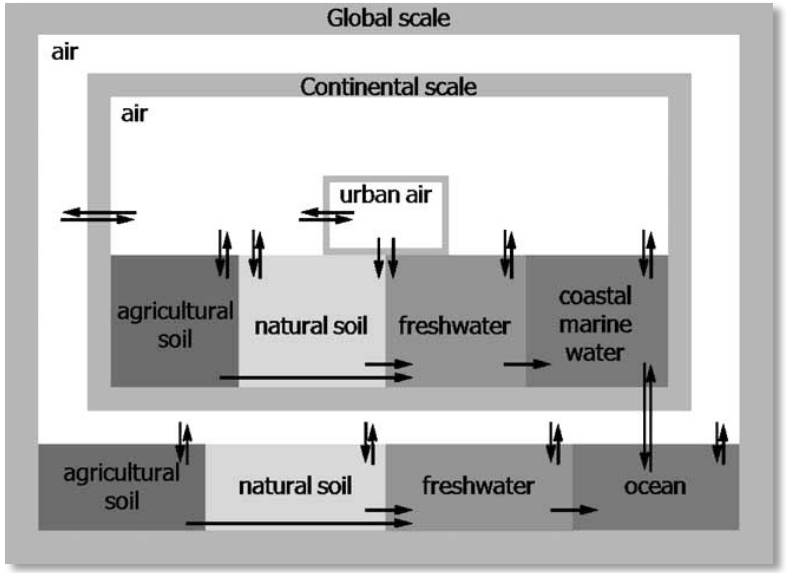
Framework for High Throughput Exposure Screening



Off the Shelf Models

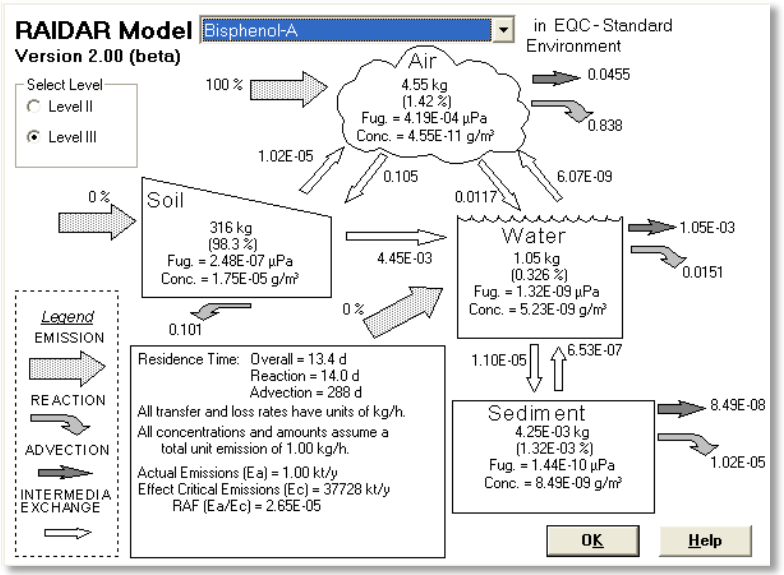
Treat different models like related high-throughput assays – consensus

USEtox



United Nations Environment Program and Society for Environmental Toxicology and Chemistry toxicity model Version 1.01
Rosenbaum *et al.* 2008

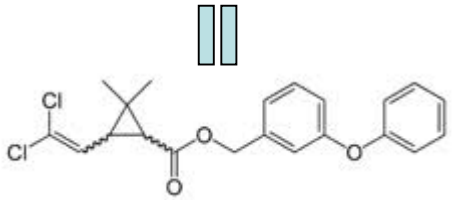
RAIDAR



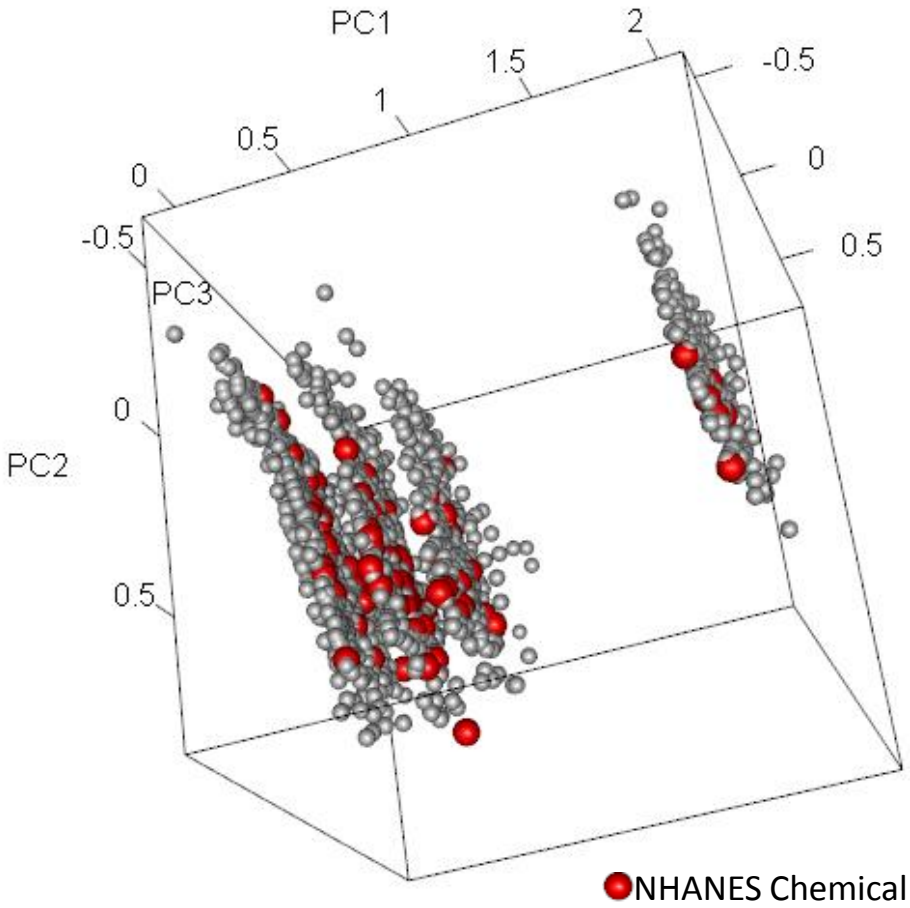
Risk Assessment IDentification And Ranking model Version 2.0
Arnot *et al*. 2006

Parameterizing the Models

Cl/C(Cl)=C/C3C(C(=O)OCc2cccc(O
c1ccccc1)c2)C3(C)C



Model parameters obtained from EPI Suite



EPI Suite contained experimental values for all parameters for ~5% of the chemicals

Many properties predicted from structure (SMILES), which failed 167 of 2127 chemicals

Dominant principal component (half life in environmental media) determined by expert elicitation

New data needed both to assess QSAR reliability and expand QSAR domain of applicability

Data Availability for Evaluating Predictions

CDC NHANES (National Health and Nutrition Examination Survey): covers a few hundred metabolites of environmental chemicals.

Observations: parent exposures for 82 chemicals estimated by Bayesian inference based on NHANES.

- parent exposures from urinary metabolites
- focusing on U.S. total geometric mean initially

Urinary Bisphenol A (2,2-*bis*[4-Hydroxyphenyl] propane)

Geometric mean and selected percentiles of urine concentrations (in µg/L) for the U.S. and Nutrition Examination Survey.

	Survey years	Geometric mean (95% conf. interval)	Selected pe (95% confiden 50th	75th
Total	03-04	2.64 (2.38-2.94)	2.80 (2.50-3.10)	5.50 (5.00-6.20)
	05-06	1.90 (1.79-2.02)	2.00 (1.90-2.00)	3.70 (3.50-3.90)
	07-08	2.08 (1.92-2.26)	2.10 (1.90-2.30)	4.10 (3.60-4.60)
Age group				
6-11 years	03-04	3.55 (2.95-4.29)	3.80 (2.70-5.00)	6.90 (6.00-8.30)
	05-06	2.86 (2.52-3.24)	2.70 (2.30-2.90)	5.00 (4.40-5.80)
	07-08	2.46 (2.20-2.75)	2.40 (1.90-3.00)	4.50 (3.70-5.50)
12-19 years	03-04	3.74 (3.31-4.22)	4.30 (3.60-4.60)	7.80 (6.50-9.00)
	05-06	2.42 (2.18-2.68)	2.40 (2.10-2.70)	4.30 (3.90-5.20)
	07-08	2.44 (2.14-2.78)	2.30 (2.10-2.60)	4.40 (3.70-5.50)
20 years and older	03-04	2.41 (2.15-2.72)	2.60 (2.30-2.80)	5.10 (4.50-5.70)
	05-06	1.75 (1.62-1.89)	1.80 (1.70-2.00)	3.40 (3.10-3.70)
	07-08	1.99 (1.82-2.18)	2.00 (1.80-2.30)	3.90 (3.40-4.60)

CDC, Fourth National Exposure Report（2011）

Data Availability for Model Predictions and Ground-truthing

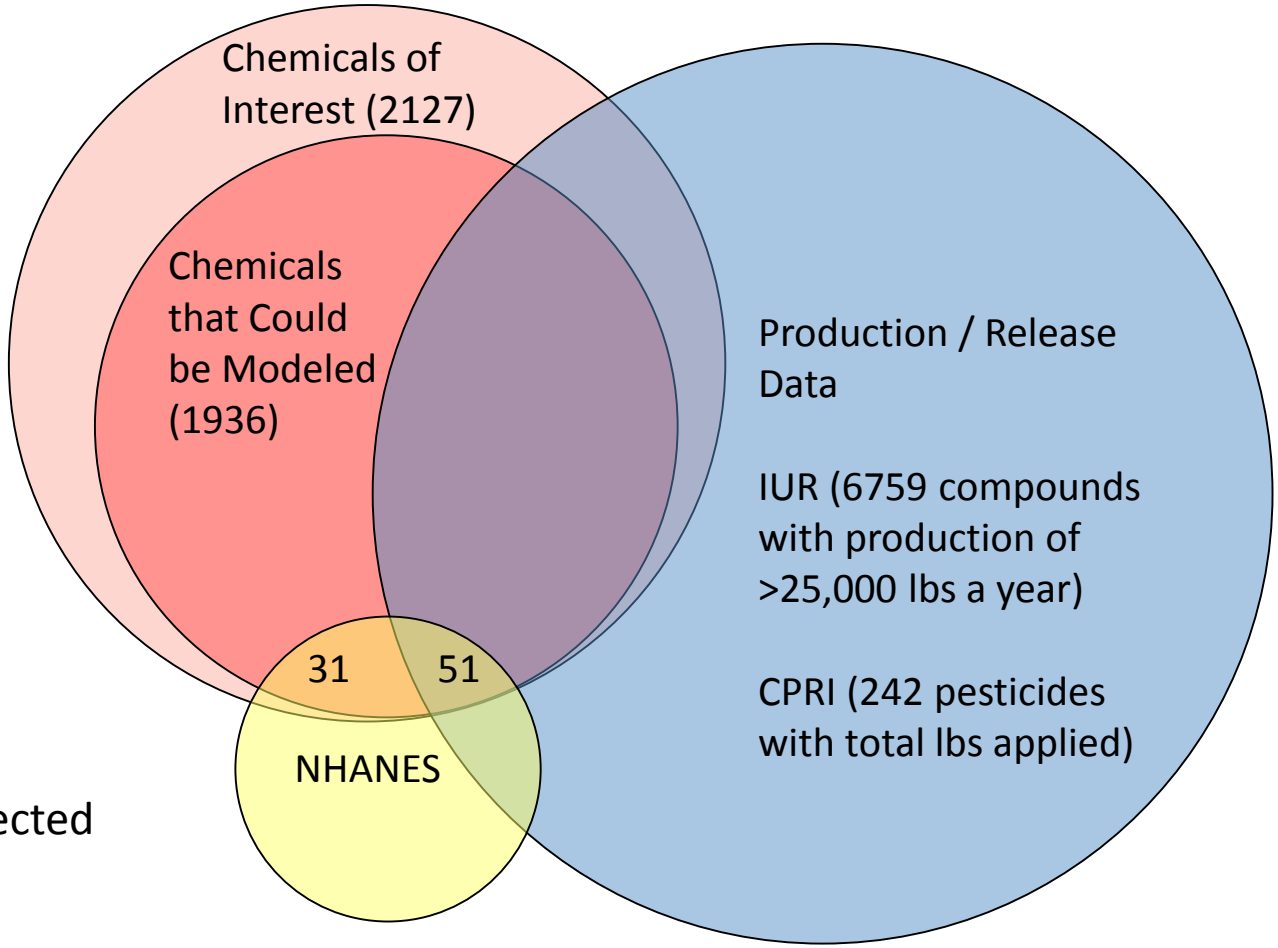
Ground-truth with CDC NHANES urine data

Many chemicals had median conc. below the limit of detection (LoD)

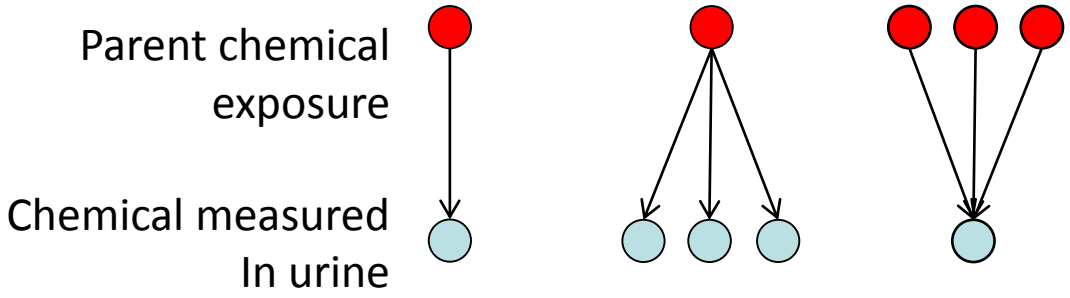
Most chemicals >LoD not high production volume

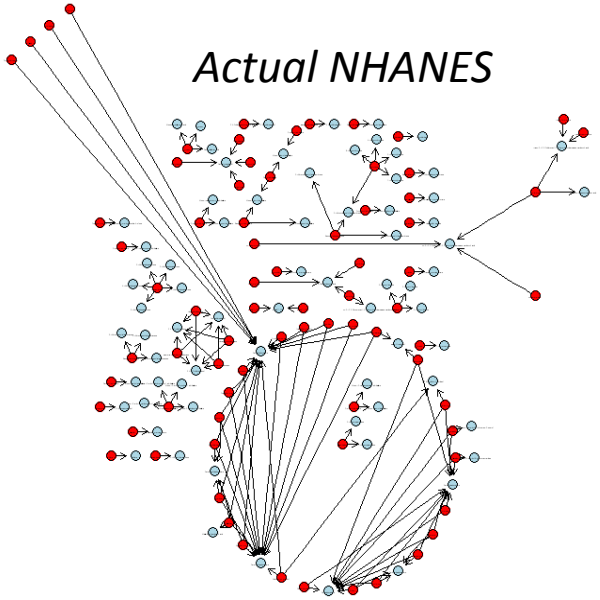
82 chemicals inferred for Wambaugh et al. (2013)

Adding more chemicals (103 currently), dozens more expected with serum model



Exposure Inference from Biomonitoring Data





A finite number of parent exposures are related to a finite number of urine products, and most of relationships are zero

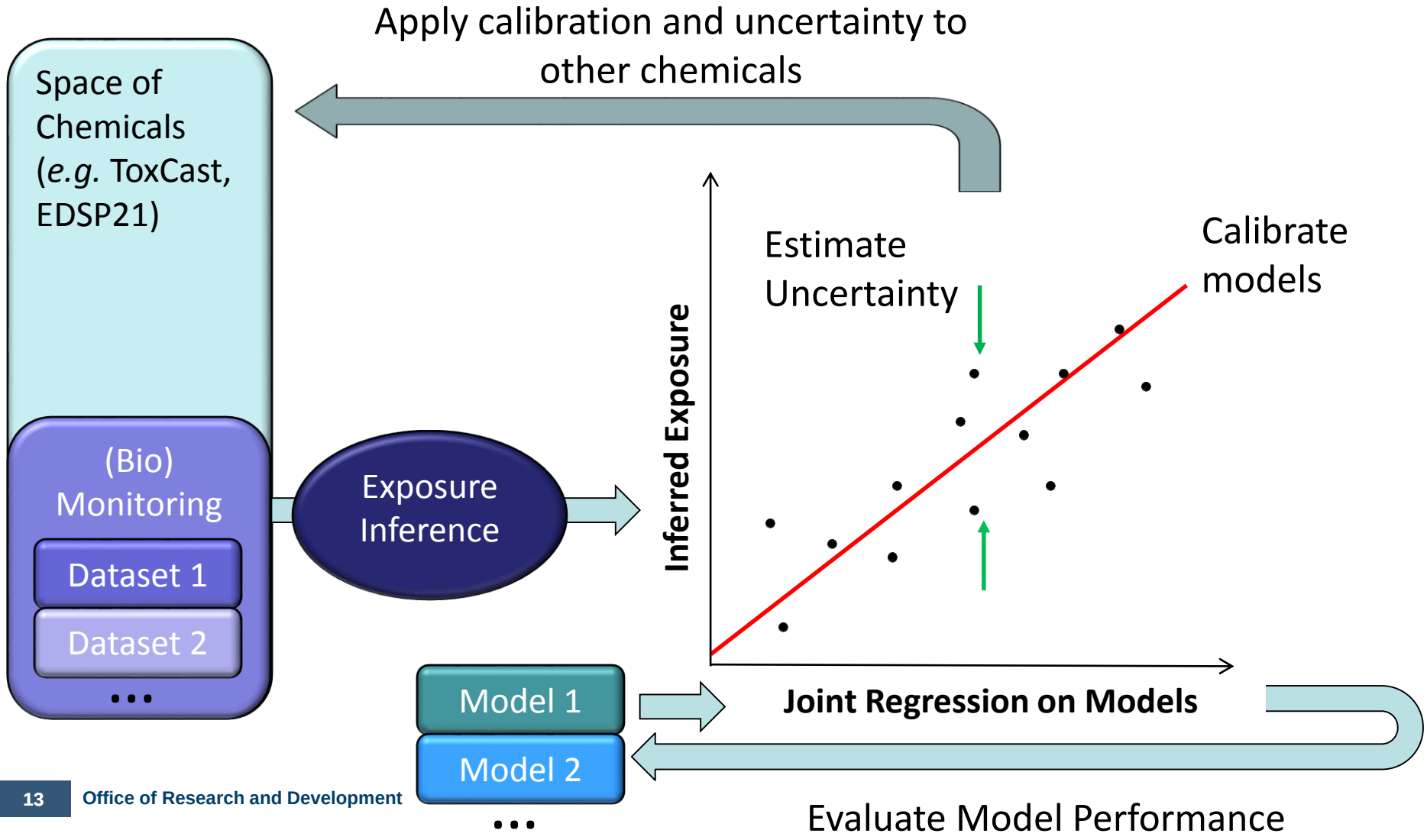
We can not determine the one "correct" combination of exposures that explains the urine concentrations for a given demographic:

Instead, we use Bayesian analysis via Markov Chain Monte Carlo to create a series of different explanations that covers all likely possibilities

Separate inferences need to be done for each demographic

Described in Wambaugh et al. (2013)
Additional work ongoing with Cory Strope, Jim Rabinowitz, Woody Setzer
Strope et al. *manuscript in preparation*

Framework for High Throughput Exposure Screening



Framework for High Throughput Exposure Screening

EPA United States Environmental Protection Agency

Space of Chemicals (*e.g.* ToxCast, EDSP21)

(Bio) Monitoring

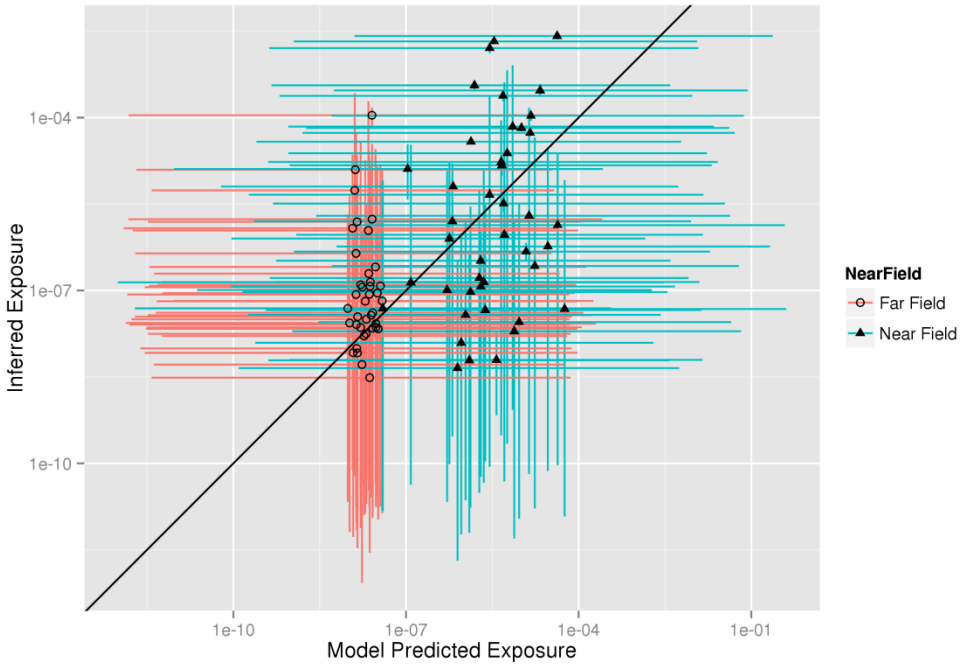
Dataset 1

Dataset 2

...

Exposure Inference

p-value 0.017



Model 1

Model 2

...

Joint Regression on Models

Evaluate Model Performance

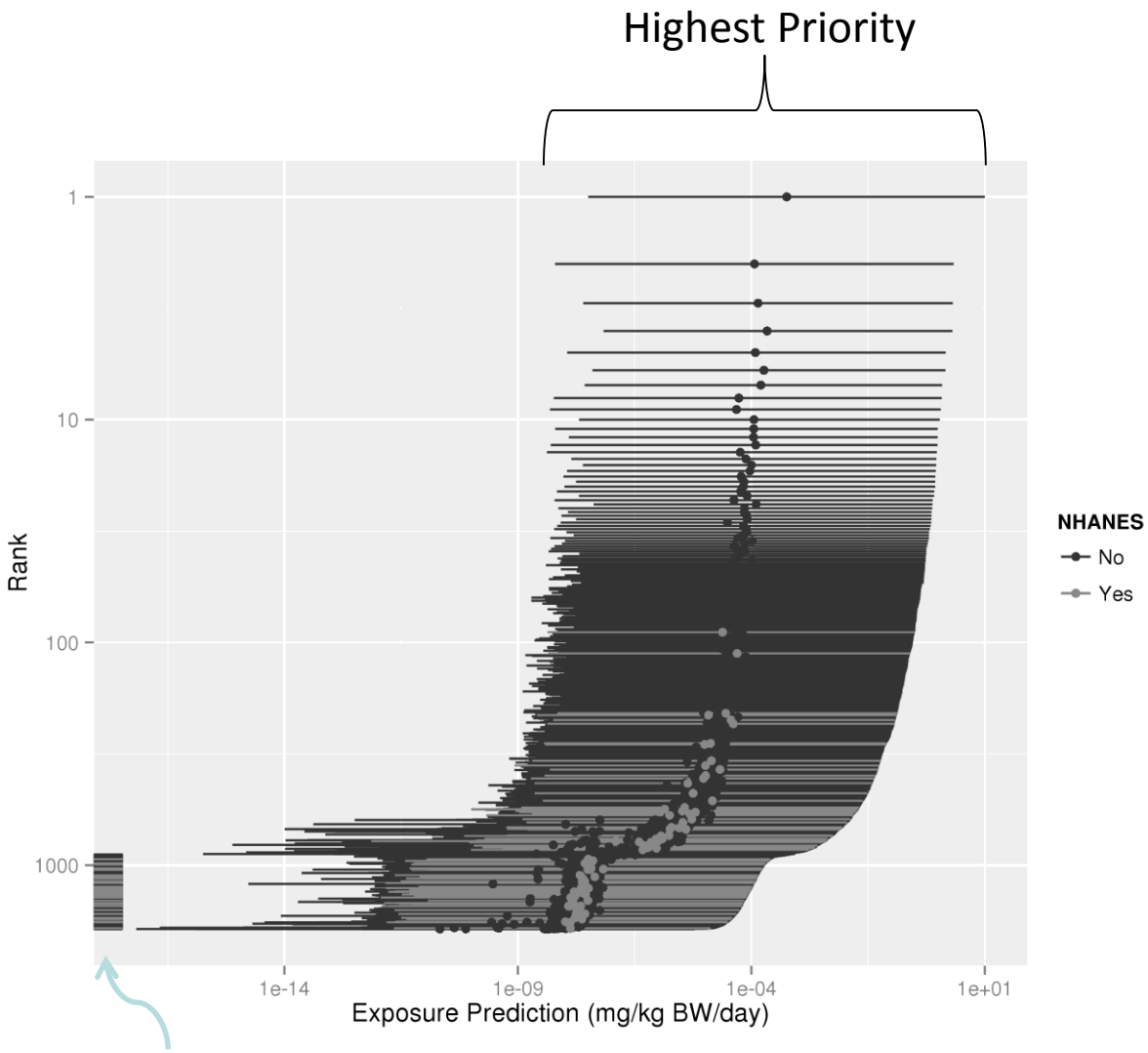
Forecasting Exposure for 1936 Chemicals

United States Environmental Protection Agency

Empirical calibration to exposures inferred from NHANES data for general population

Limited data gives broad uncertainty, but does indicate ability to forecast (R^2 = ~15%)

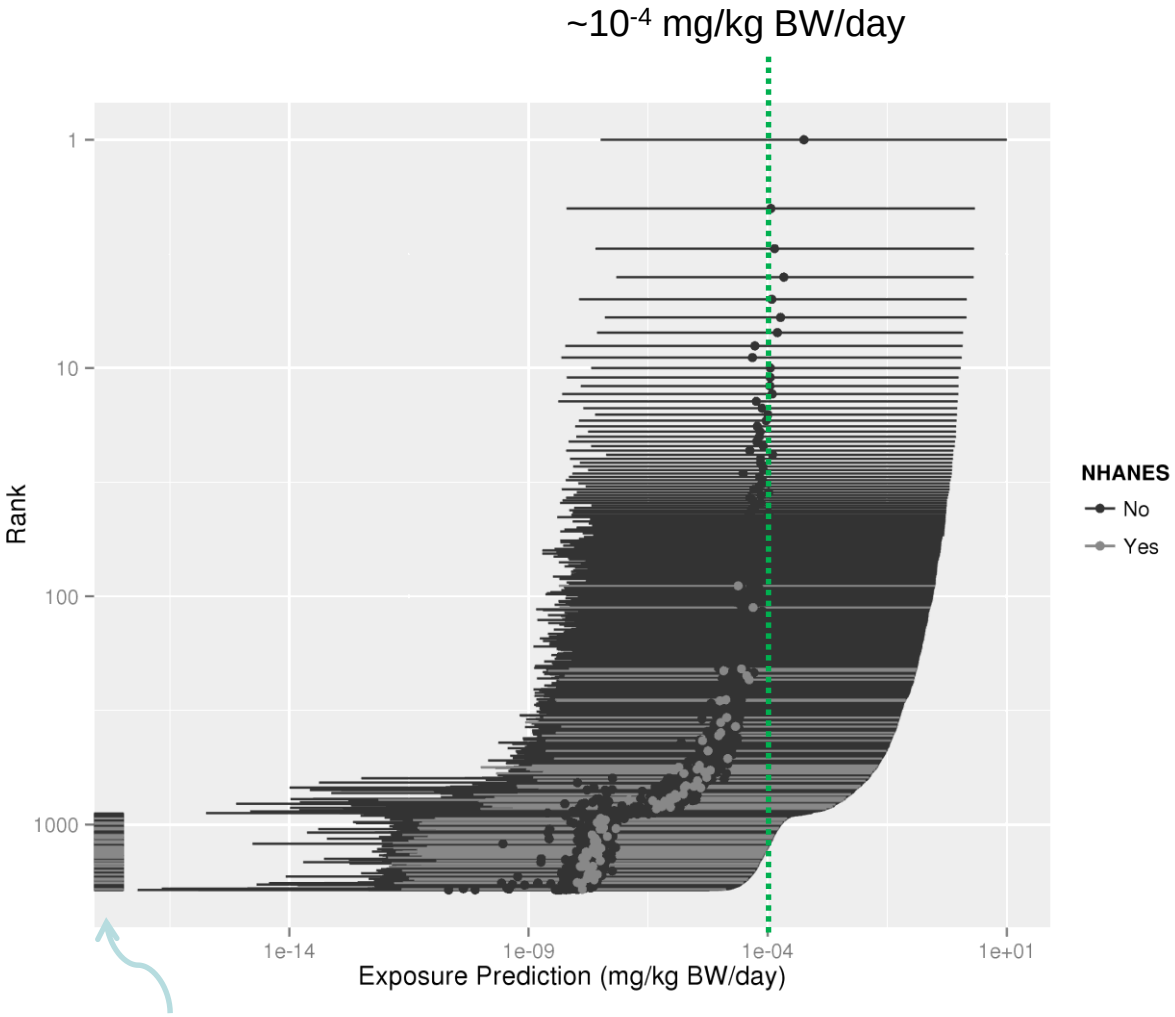
Importance of near field chemical/product use was demonstrated



For Some Chemicals, Eight is Enough

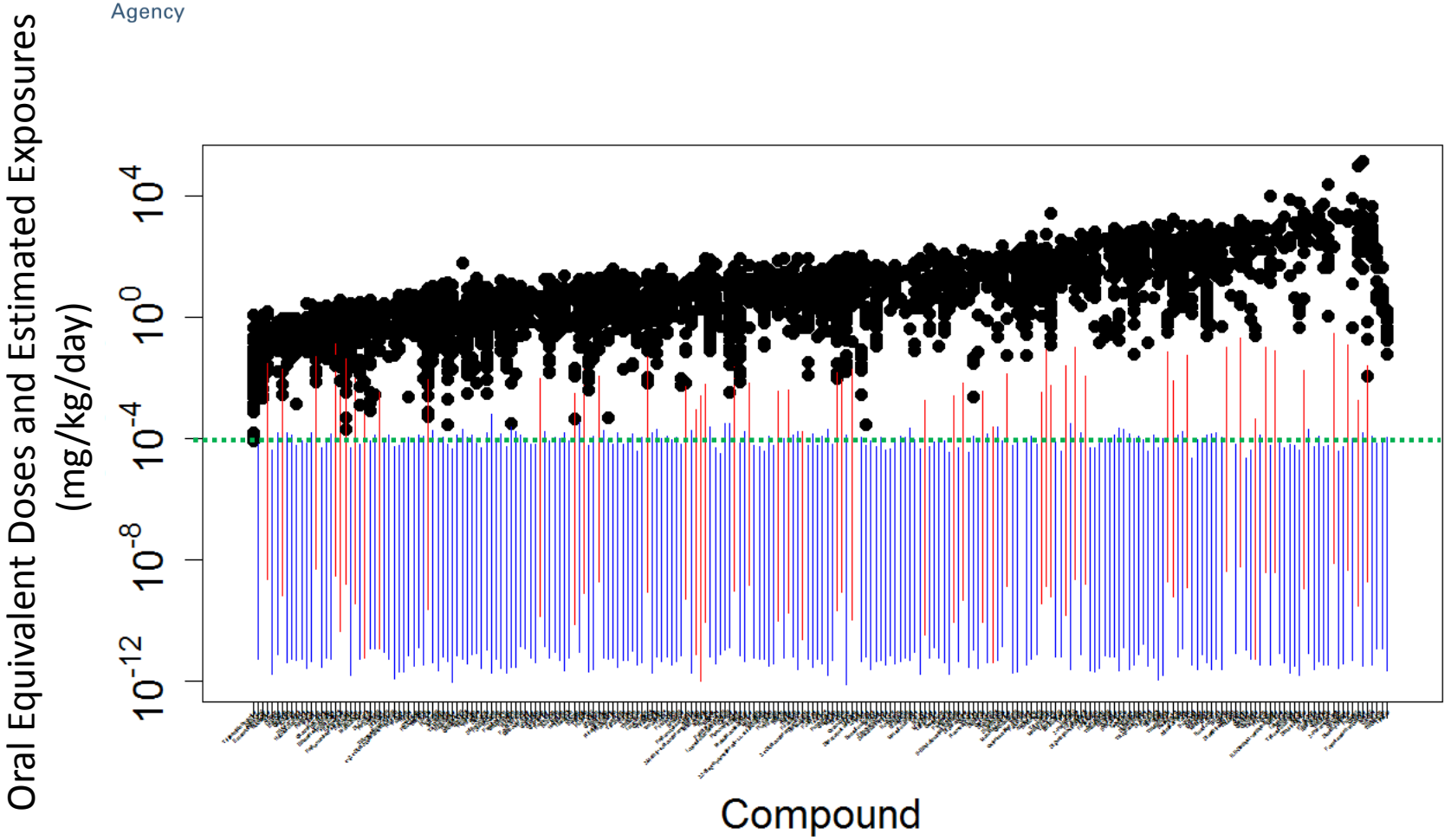
In Wetmore *et al.* the majority doses predicted to cause ToxCast bioactivities were in excess of 10^{-4} mg/kg/day

Even with large estimated uncertainty, that the upper-limit of the 95% confidence intervals for the bottom 668 chemicals are below this level



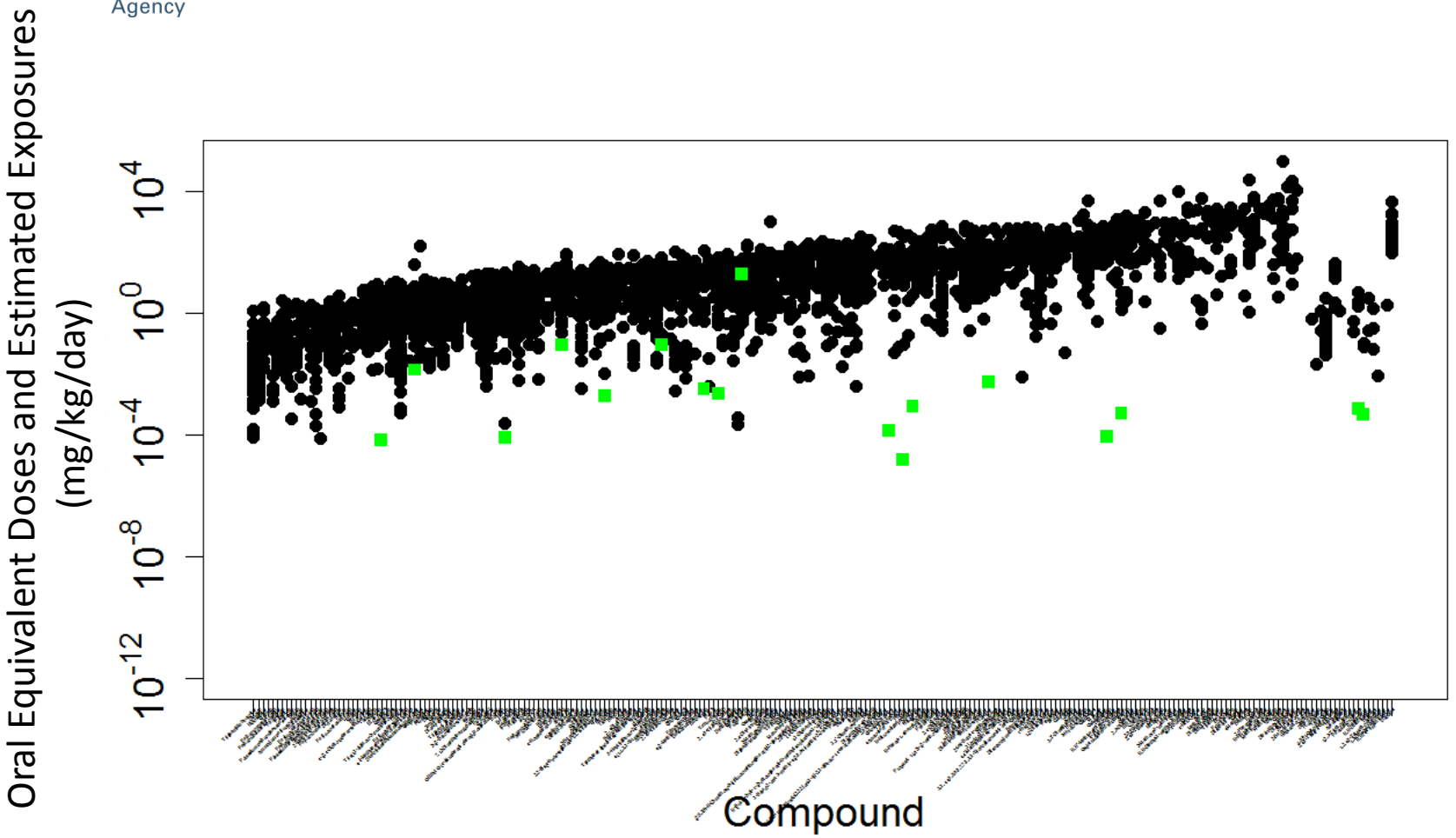
Far Field Chemicals

ToxCast + ExpoCast



Oral Equivalents from Wetmore et al. *Tox. Sci (2012)*

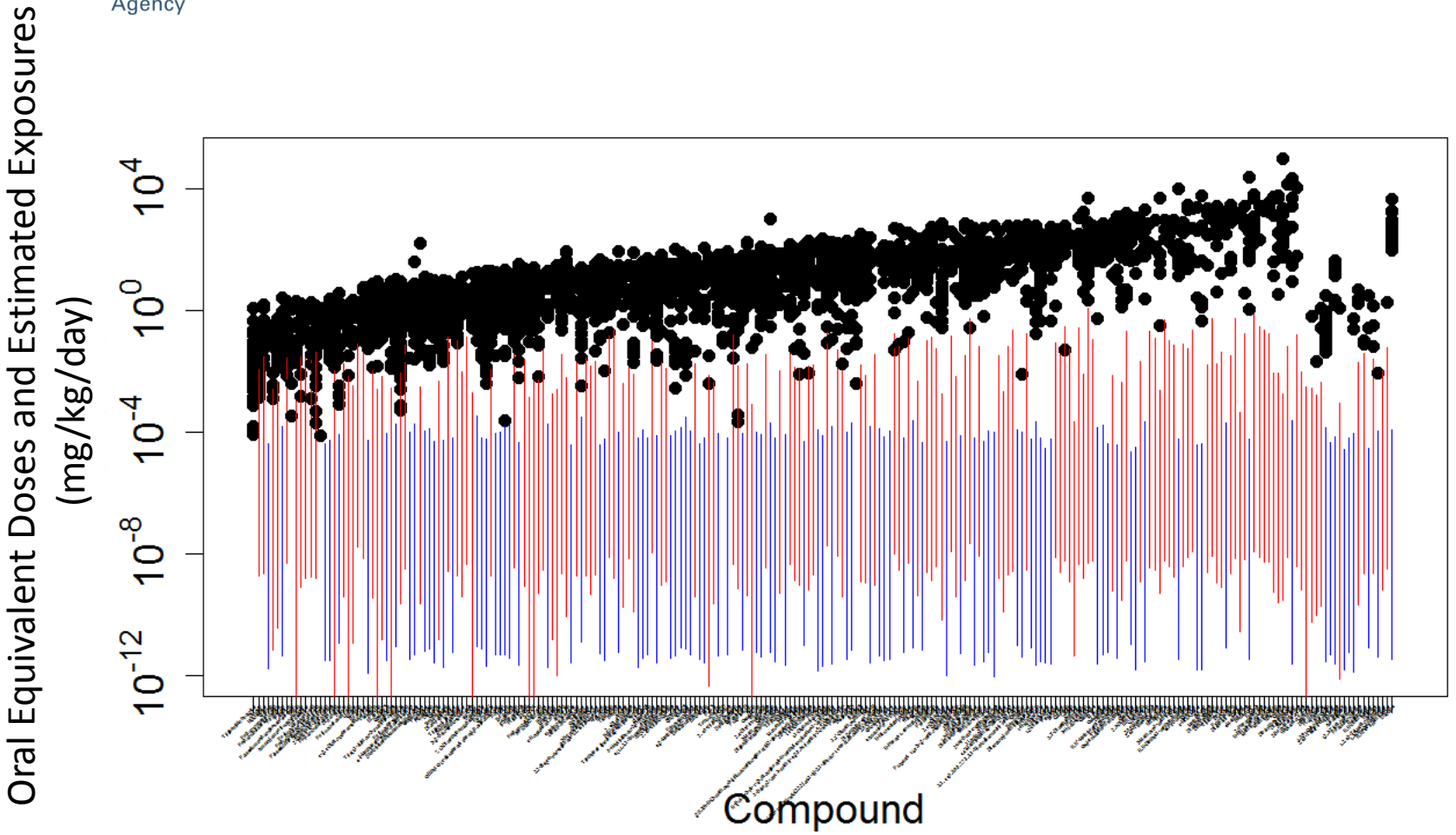
The Exposure Coverage of the ToxCast Phase II Chemicals



Green squares indicate estimated exposures from EPA REDs or CDC NHANES: ~71% of Phase I
~7% of Phase II

Unpublished data from Barbara Wetmore

ExpoCast Coverage of the ToxCast Phase II Chemicals



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Unpublished data from Barbara Wetmore

Statement of New Problem: Data Concerns

- If a simple near-field/far-field heuristic was most predictive so far, then do there exist other heuristics with the power to distinguish chemicals with respect to exposure?

- What we would like to know is:

    - What are the few, most-easily obtained exposure heuristics that allow for prioritization?

Statement of New Problem: Data Concerns

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- What we can answer is this:

    - Given a variety of rapidly obtained data (putative use categories and physico-chemical properties, largely from QSAR) which data best explain exposure inferred from the available biomonitoring data?

    - Hoping to find simple heuristics for exposure *e.g.,* use in fragrances, use as a food additive, octanol:water partition coefficient, vapor pressure

Heuristics for Chemical Use

Chemical Use Categories estimated from ACToR (chemical toxicity database):

- The sources for chemical data were assigned to various chemical use categories.
- Chemicals from multiple sources were assigned to multiple categories.

Table: Hits per use category for a given chemical

CASRN	Category 1	Category 2	…	Category 12
65277-42-1	0	10	…	1
50-41-9	31	7	…	3
…	…	…	…	…

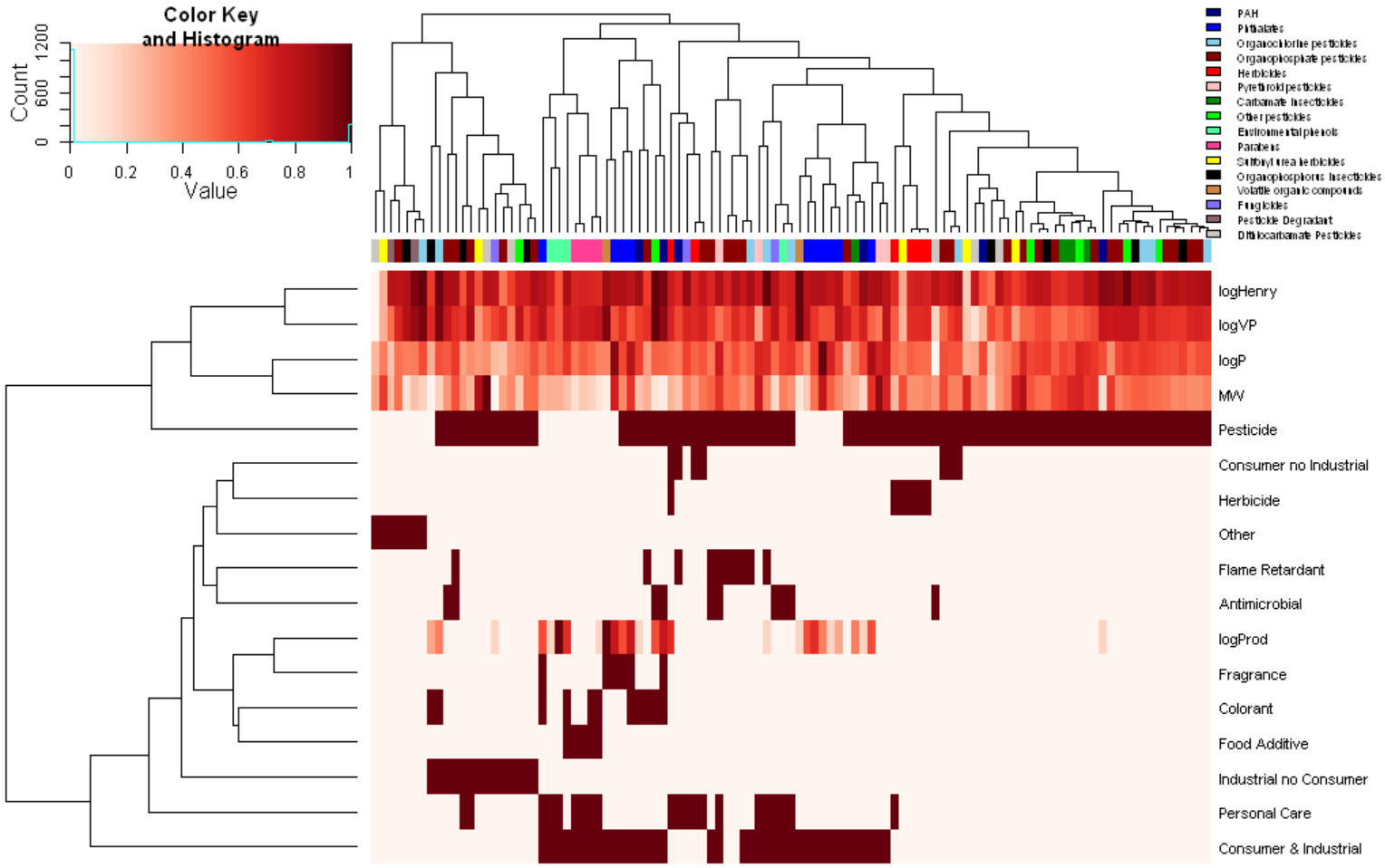
Binary matrix

CASRN	Category 1	Category 2	…	Category 12
65277-42-1	0	1	…	0
50-41-9	1	1	…	0
…	…	…	…	…

12 Chemical Use Categories
Antimicrobials
Chemical Industrial Process
Consumer
Dyes and Colorants
Fertilizers
Food Additive
Fragrances
Herbicides
Personal Care Products
Pesticides
Petrochemicals
Other

Work by Alicia Frame, Kathie Dionisio, Richard Judson
Dionisio et al. *manuscript in preparation*

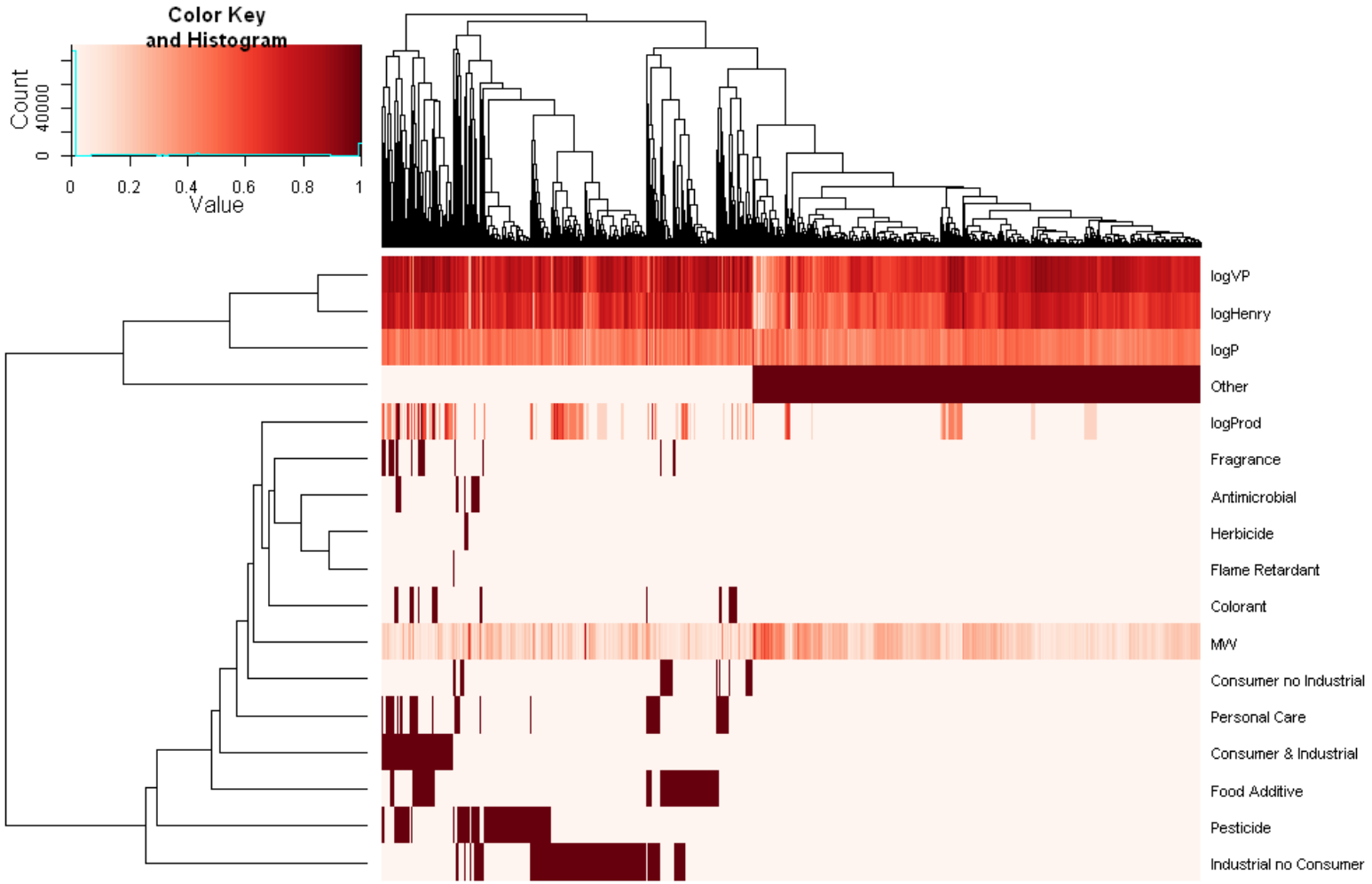
Heuristics for Chemical Use



NHANES Chemicals

Wang et al. manuscript in preparation

Heuristics for Chemical Use



>8000 Chemicals (including Tox21)

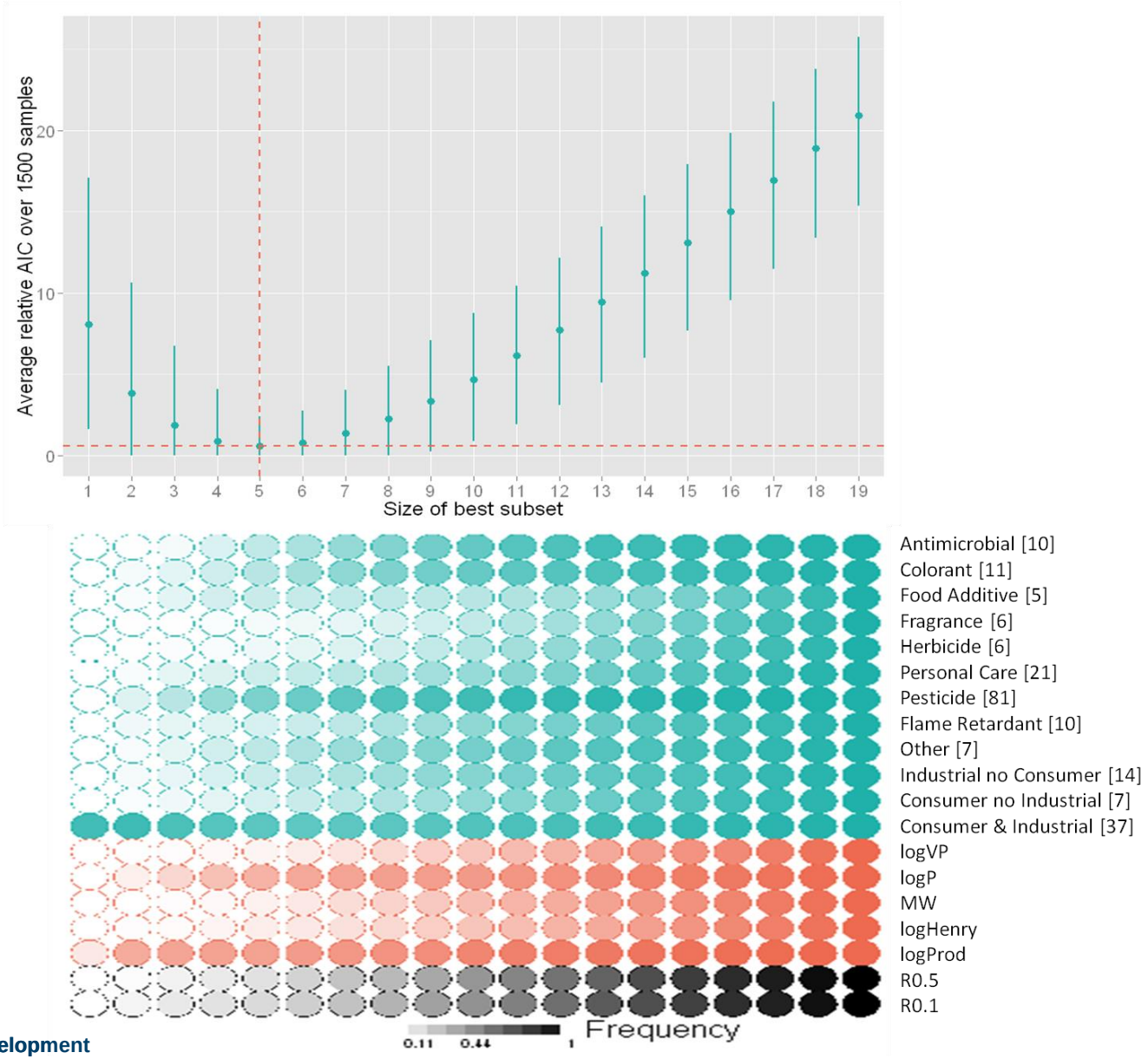
Wang et al. manuscript in preparation

Best Heuristics for General Population

United States Environmental Protection Agency

We used Bayesian methods to infer 1500 different exposure scenarios consistent with the NHANES data

We are looking for the most parsimonious explanation for the inferred exposures



Wang et al. manuscript in preparation

Better Models and Data Should Reduce Uncertainty

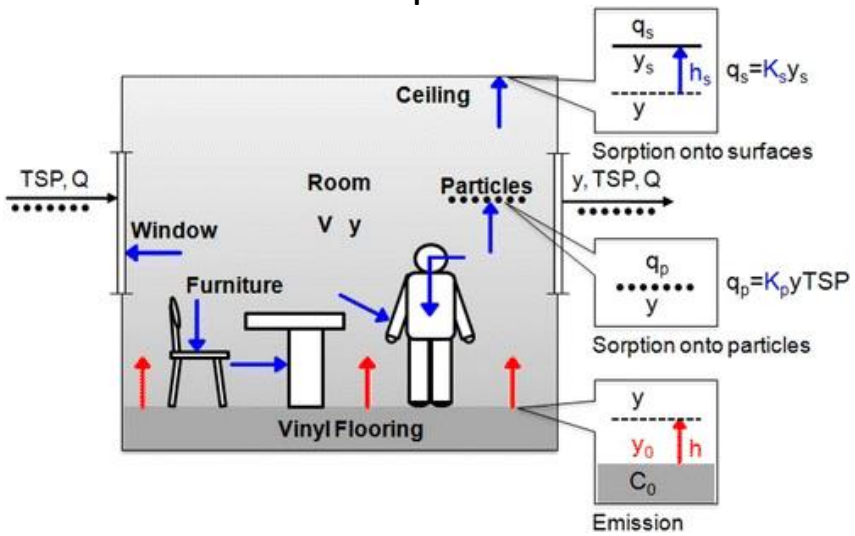
Uncertainty/Variability of NHANES Biomonitoring

~10% Far field (Industrial) Releases

~35% Indoor / Consumer Use

Indirect Exposure

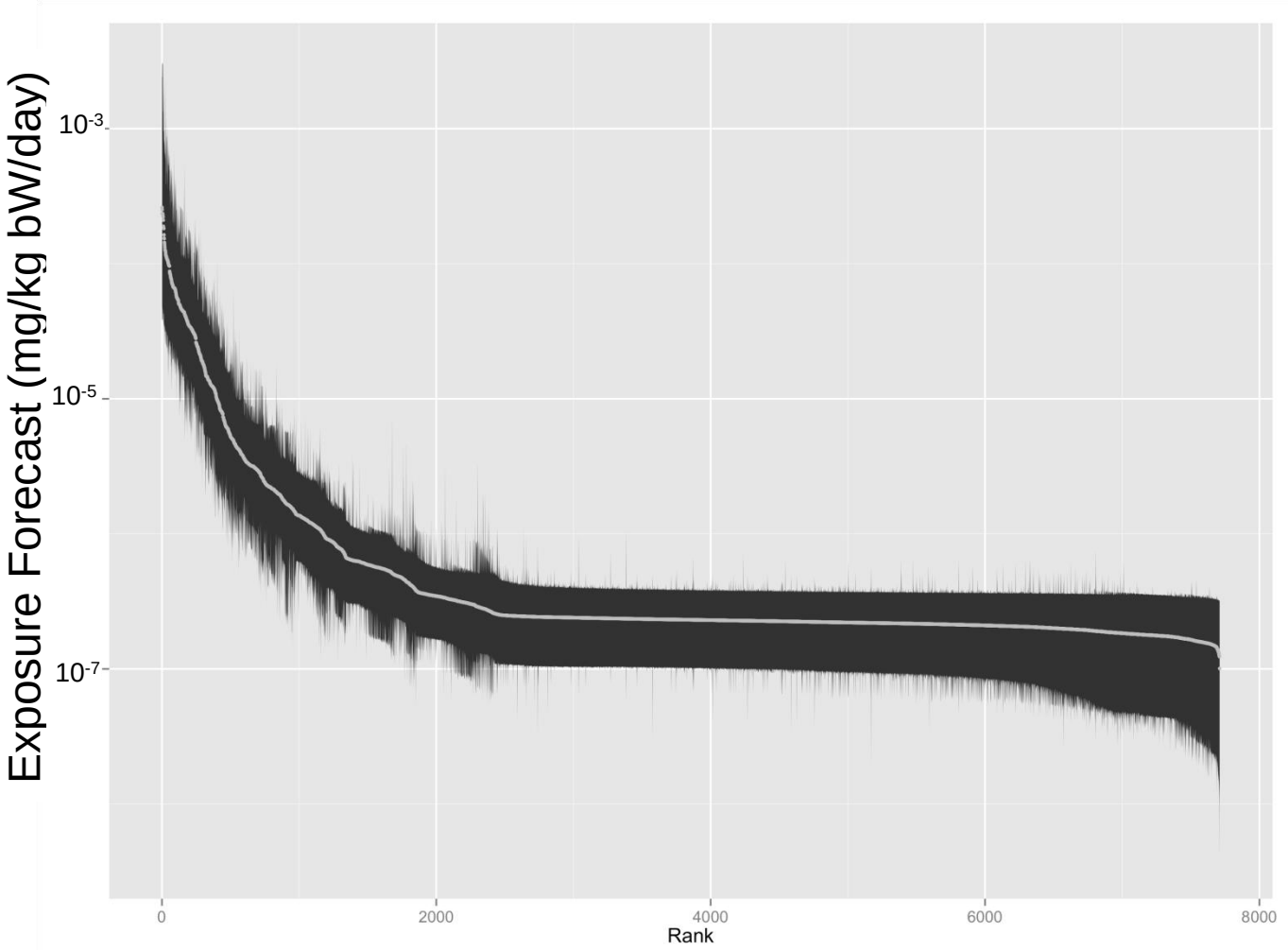
Direct Exposure



- Consolidated Human Activities Database (CHAD)
- Chemical Use Data
- Big Data (*e.g.* Google trends)

Image from Little *et al.* (2012), see also Nazaroff *et al.* (2012), Bennett *et al.* (2012), Wenger and Jolliet (2012)

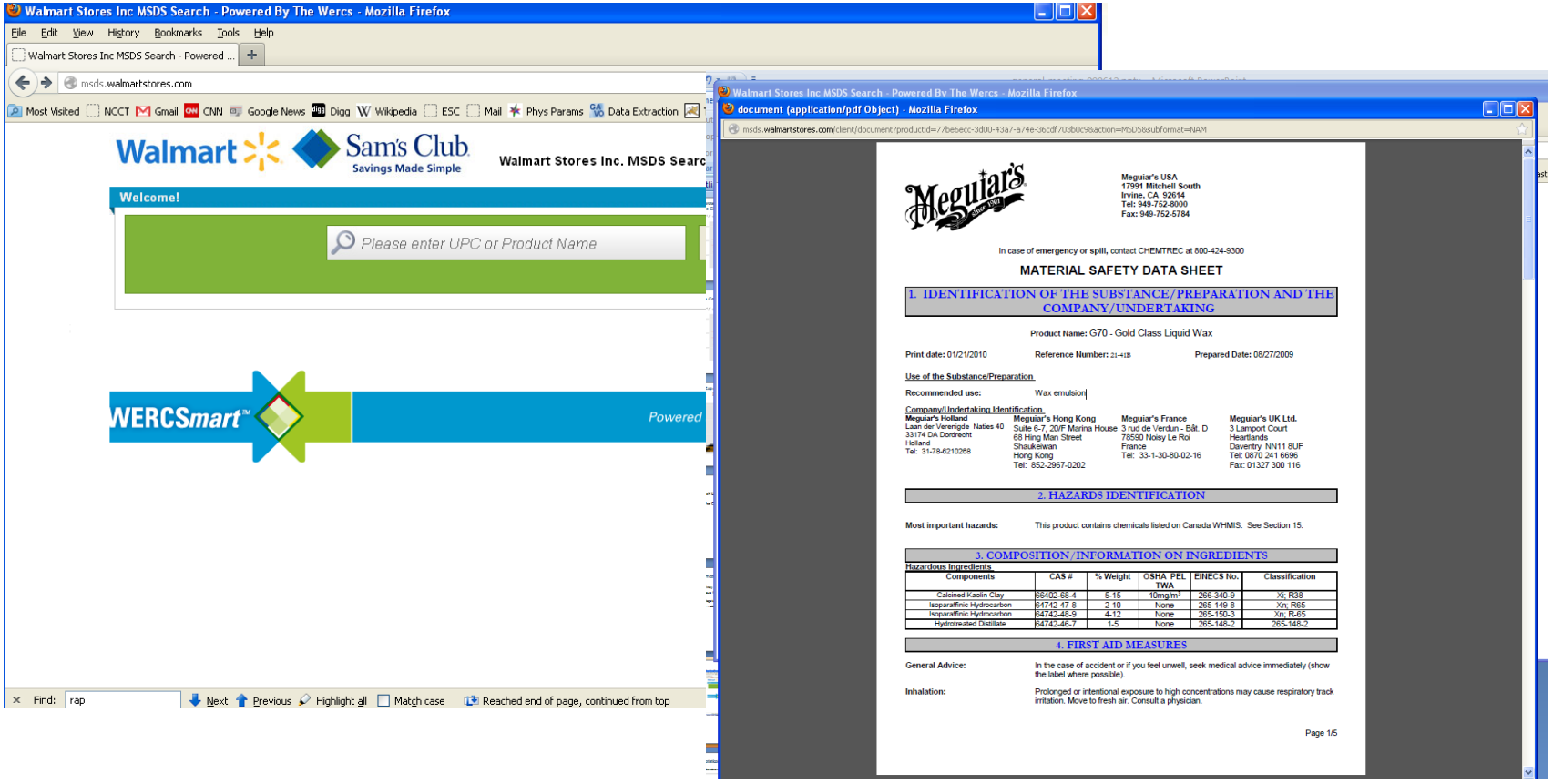
The Tox21 Chemicals



Wang et al. manuscript in preparation

Better Sources of Use Data

- Walmart provides Material Safety Data Sheets (MSDS) for all products it sells (msds.walmart.com)



Work by Rocky Goldsmith, Peter Egeghy, Alicia Frame, Amber Wang, Richard Judson
Goldsmith et al. manuscript (submitted)

Better Heuristics for Chemical Use

United States Environmental Protection Agency

Walmart provides Material Safety Data Sheets (MSDS) for all products it sells

	Product 1	Product 2	Product 3	Product 4	…
CAS 1	10%	Present			
CAS 2		50%			
CAS 3			0.001%		
…					

Approximate product classification (e.g. toys) as use

	Use 1	Use 2	Use 3	Use 4	…
Product 1	X		X		
Product 2		X			
Product 3				X	
…					

	Use 1	Use 2	Use 3	Use 4	…
CAS 1	X	X	X		
CAS 2		X			
CAS 3				X	
…					

Tentatively map chemicals to use categories

Work by Rocky Goldsmith, Peter Egeghy, Alicia Frame, Amber Wang, Richard Judson
Goldsmith et al. manuscript (submitted)

Exposure Research Priorities

United States Environmental Protection Agency

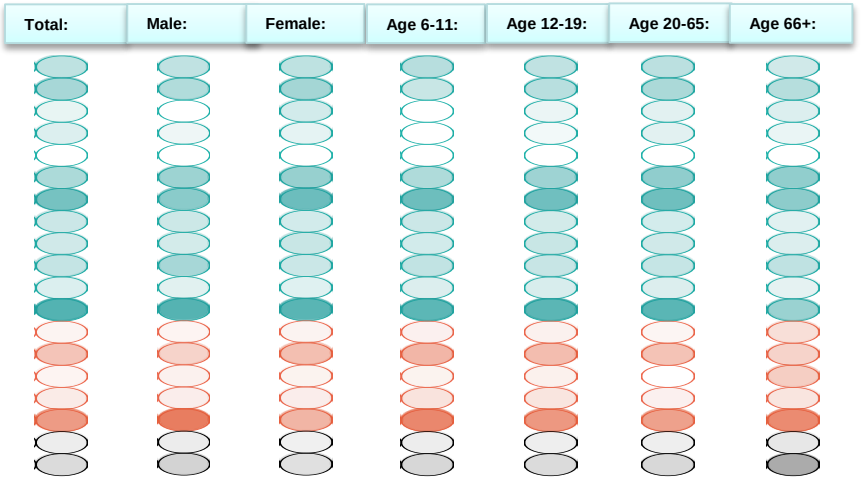
Obtaining new chemical data

- Measuring physico-chemical parameters
  - Characterizing QSAR appropriateness
  - Expanding QSAR domain of applicability
- Determining occurrence in articles, packaging, and products

New monitoring data

- Validation of predictions
- Characterization of chemical exposure
  - Specific demographics
  - Pooled samples

New indoor/consumer use models



EPA:

Empirical modeling of biomonitoring data
SHEDS-lite

ACC LRI:

USEtox and RAIDAR consumer use modules

Literature: Little *et al.* (2012) Nazaroff *et al.* (2012), Bennett *et al.* (2012), Wenger and Jolliet (2012)

Conclusions

"As far as the laws of mathematics refer to reality, they are not certain; and as far as they are certain, they do not refer to reality."

Albert Einstein, quoted in J R Newman, *The World of Mathematics* (1956).

- High throughput computational model predictions of exposure is possible
  - These prioritizations have been compared with CDC NHANES data, yielding empirical calibration and estimate of uncertainty
- Indoor/consumer use is a primary determinant of NHANES exposure
  - Developing and evaluating HT models for exposure from consumer use and indoor environment (*e.g.*, SHEDS-Lite)
- Can develop demographic-specific prioritizations
- Additional HTPK data anticipated and two new sources of use data (ACToR annotation and MSDS curation) available upon publication via ACToR – http://www.epa.gov/actor/

EPA Office of Research and Development

United States Environmental Protection Agency

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