ExpoCast Framework for Rapid Exposure Forecasts

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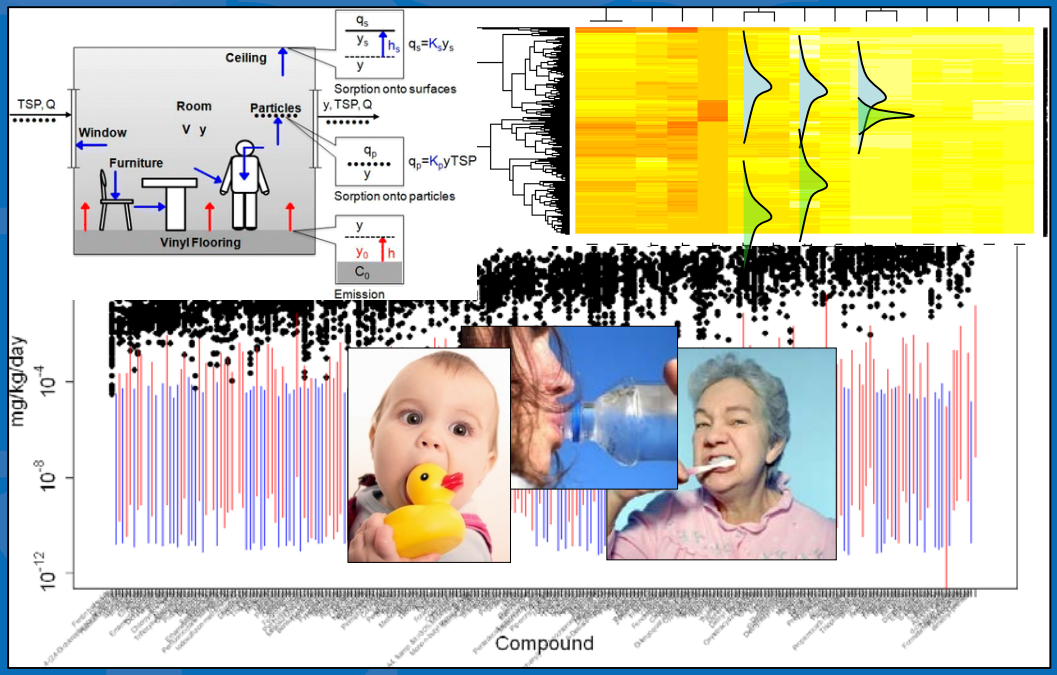

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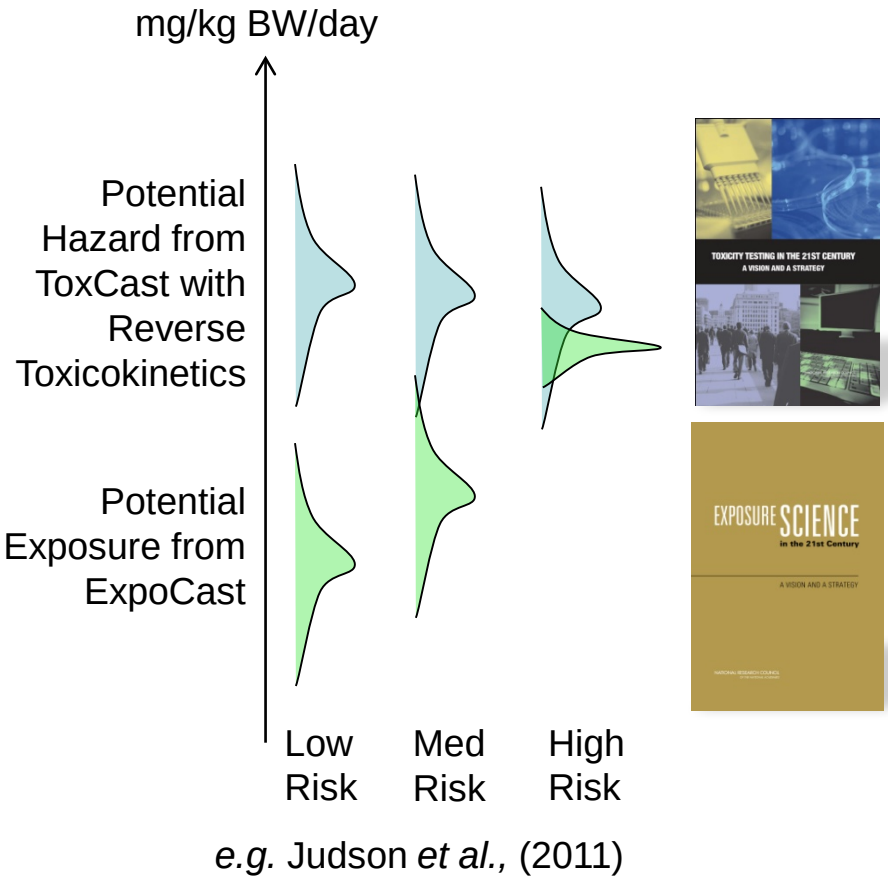
Cincinnati, OH

Risk Prioritization Requires Exposure

- **Tox21/ToxCast**: Examining thousands of chemicals using high throughput screening assays to identify *in vitro* concentrations that perturb biological pathways (Schmidt, 2009)

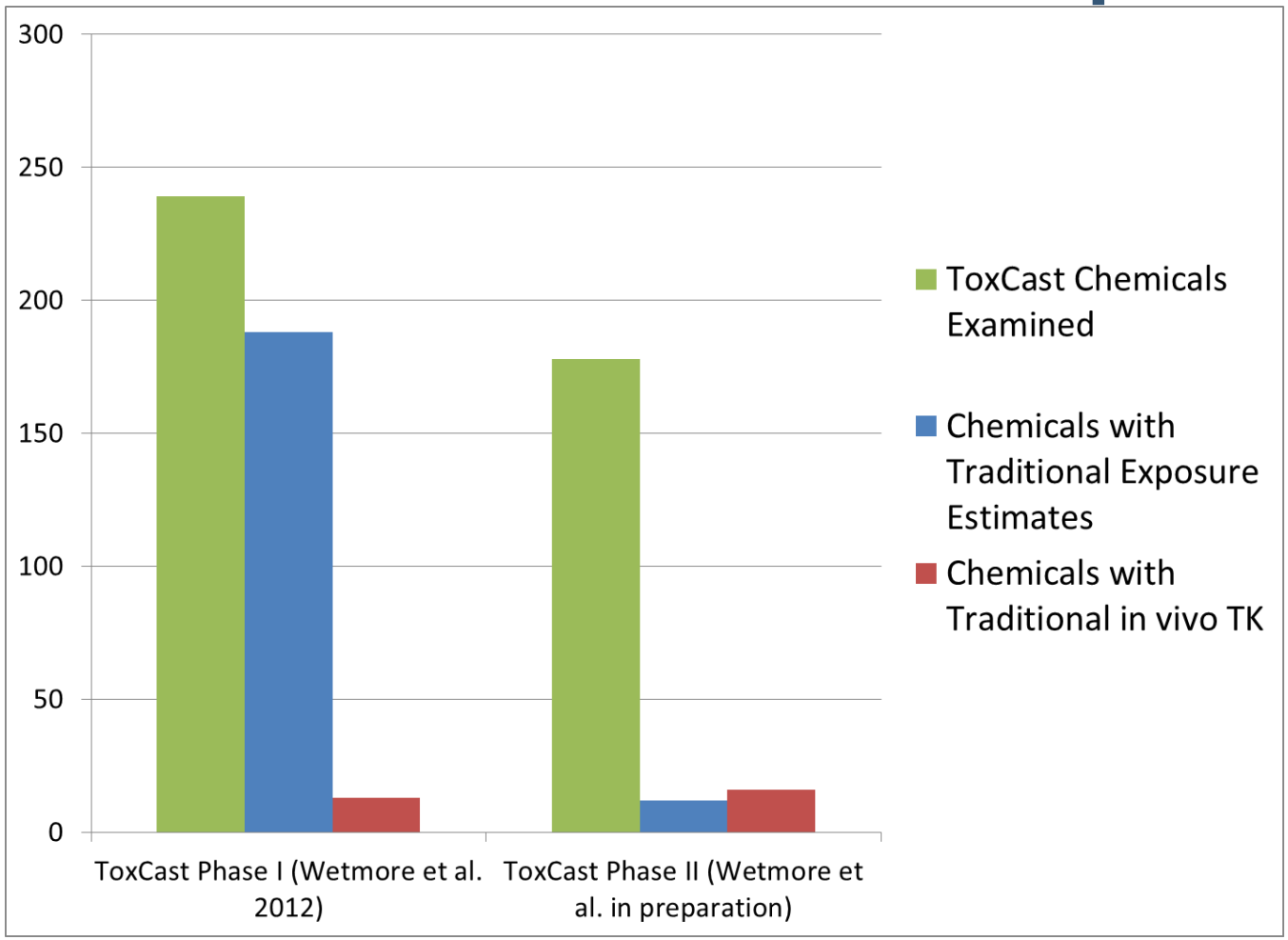
- In Wetmore *et al.* (2012), High throughput toxicokinetic *in vitro* methods are used to approximately convert *in vitro* bioactive concentrations (µM) into daily doses needed to produce similar levels in a human (mg/kg BW/day)

- These doses can then be directly compared with exposure rates, ***where available***



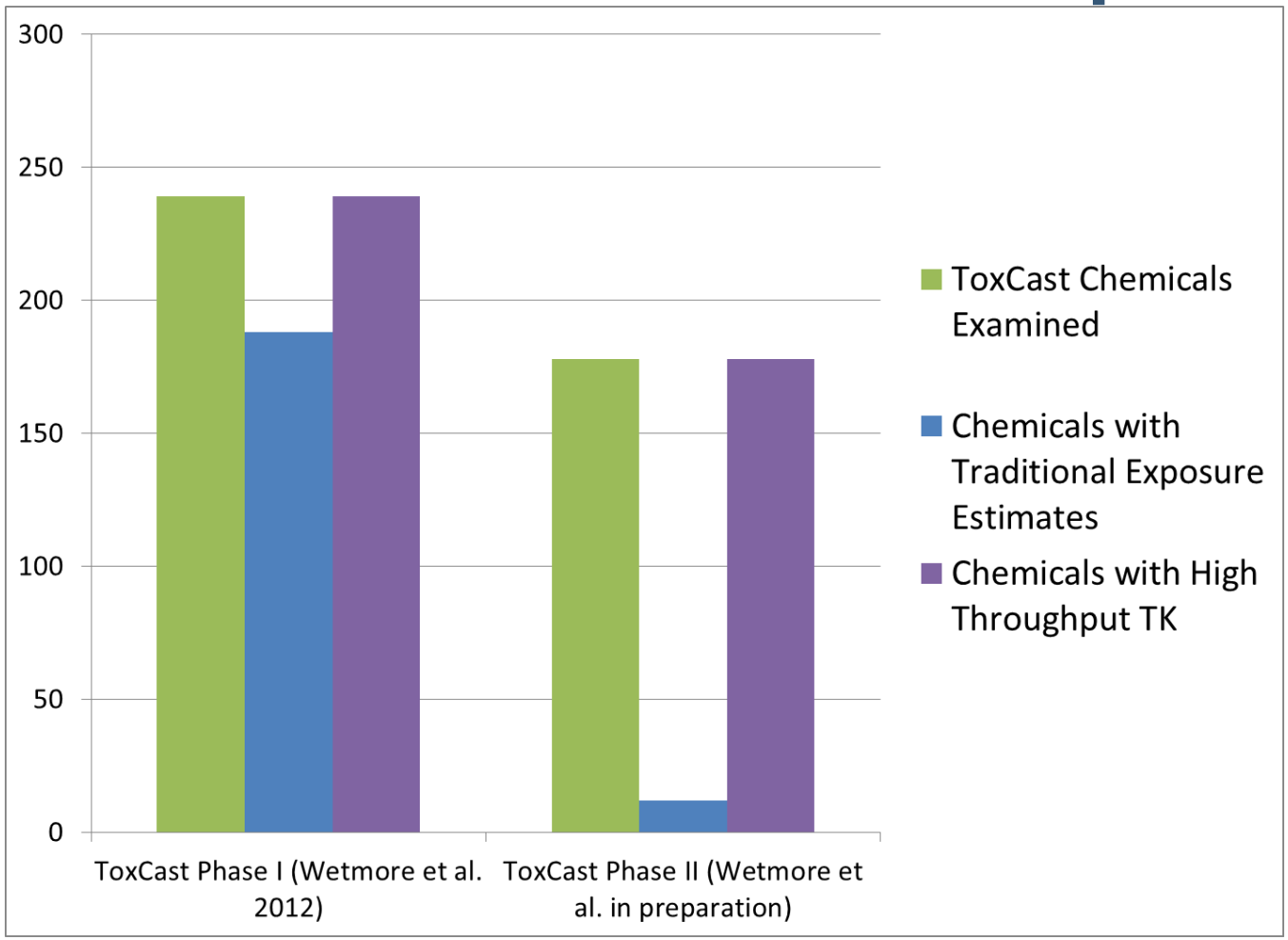
e.g. Judson *et al.*, (2011)

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



- Studies like Wetmore et al. (2012),addressed the need for toxicokinetic data

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



- As in Egeghy *et al.* (2012), there is a paucity of data for providing context to HTS data

Goals for High Throughput Exposure

- Incorporate multiple models into consensus predictions for 1000s of chemicals
- Evaluate/calibrate predictions with available measurement data across many chemical classes
- Empirically estimate uncertainty in predictions

Exposure Space

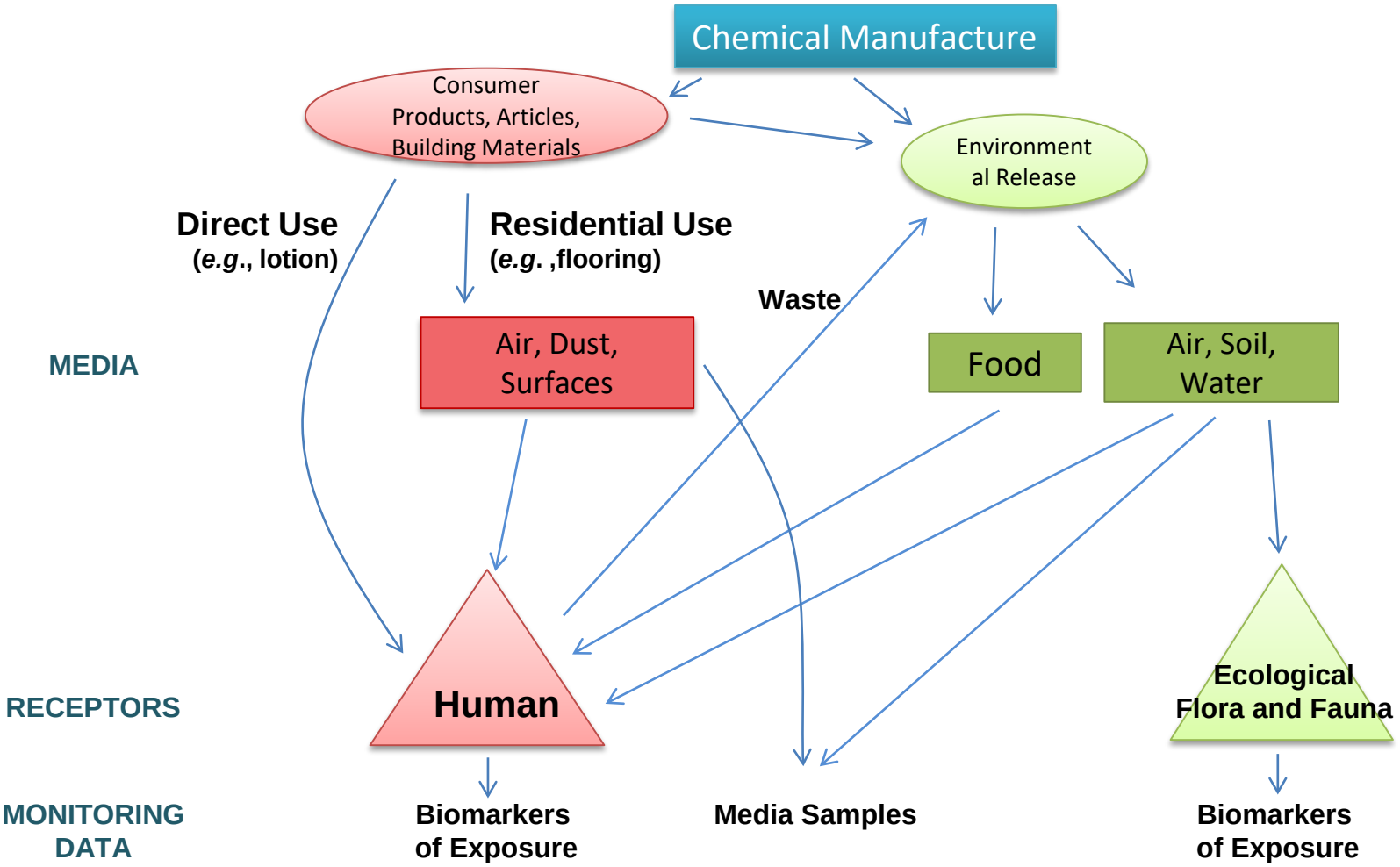


Figure from Kristin Isaacs

Exposure Pathways

United States Environmental Protection Agency

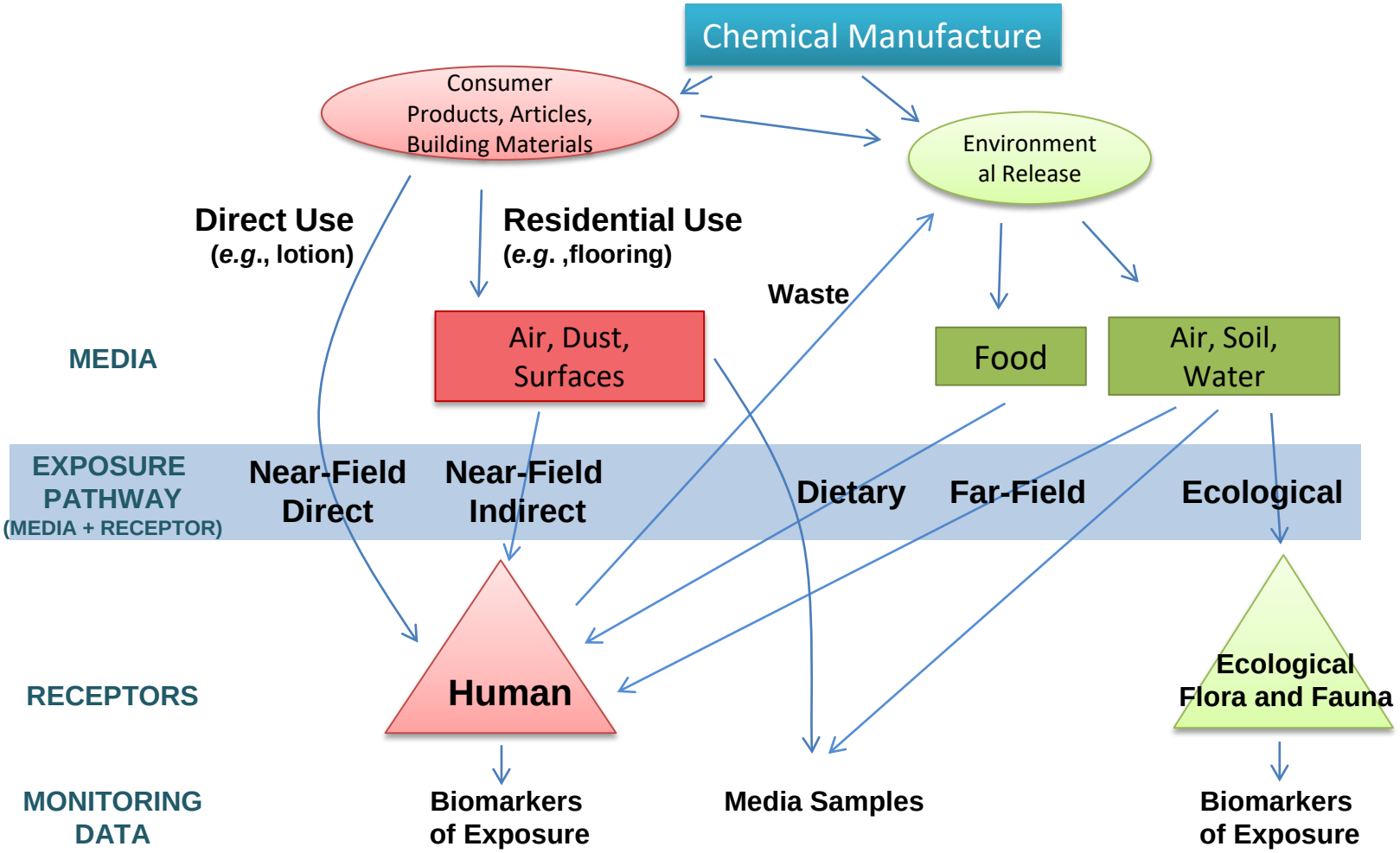
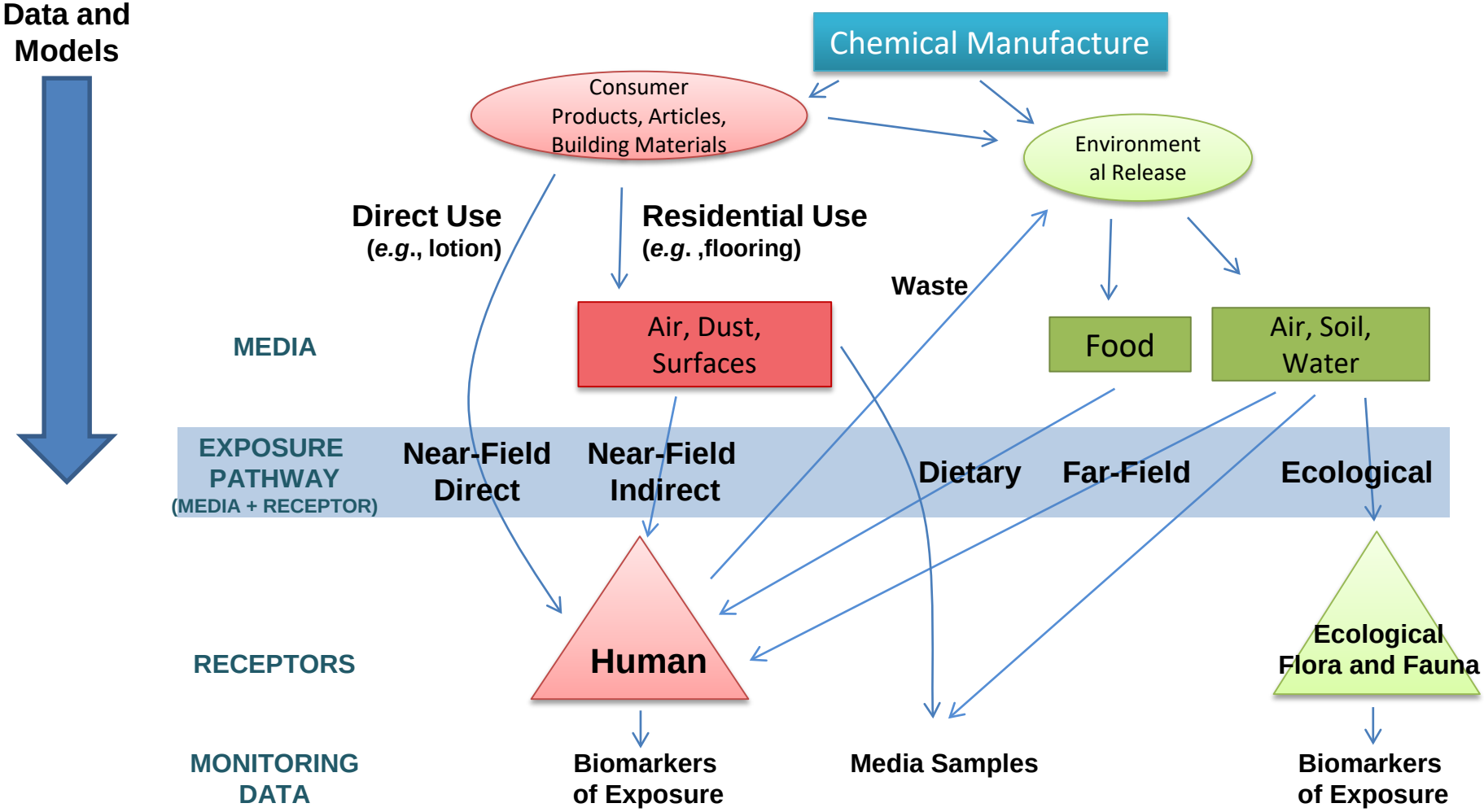


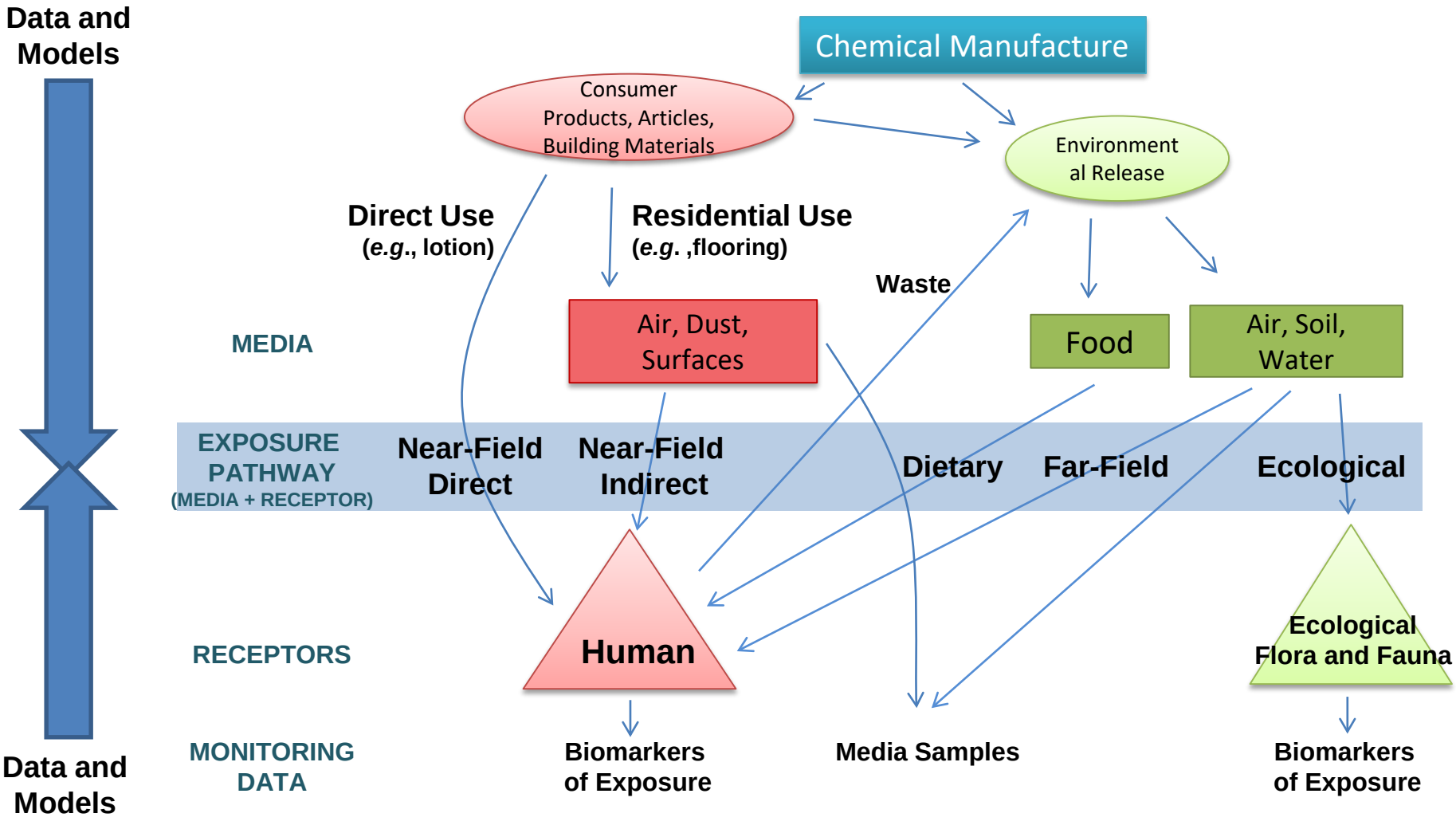
Figure from Kristin Isaacs

Forward Modeling of Exposure Pathways

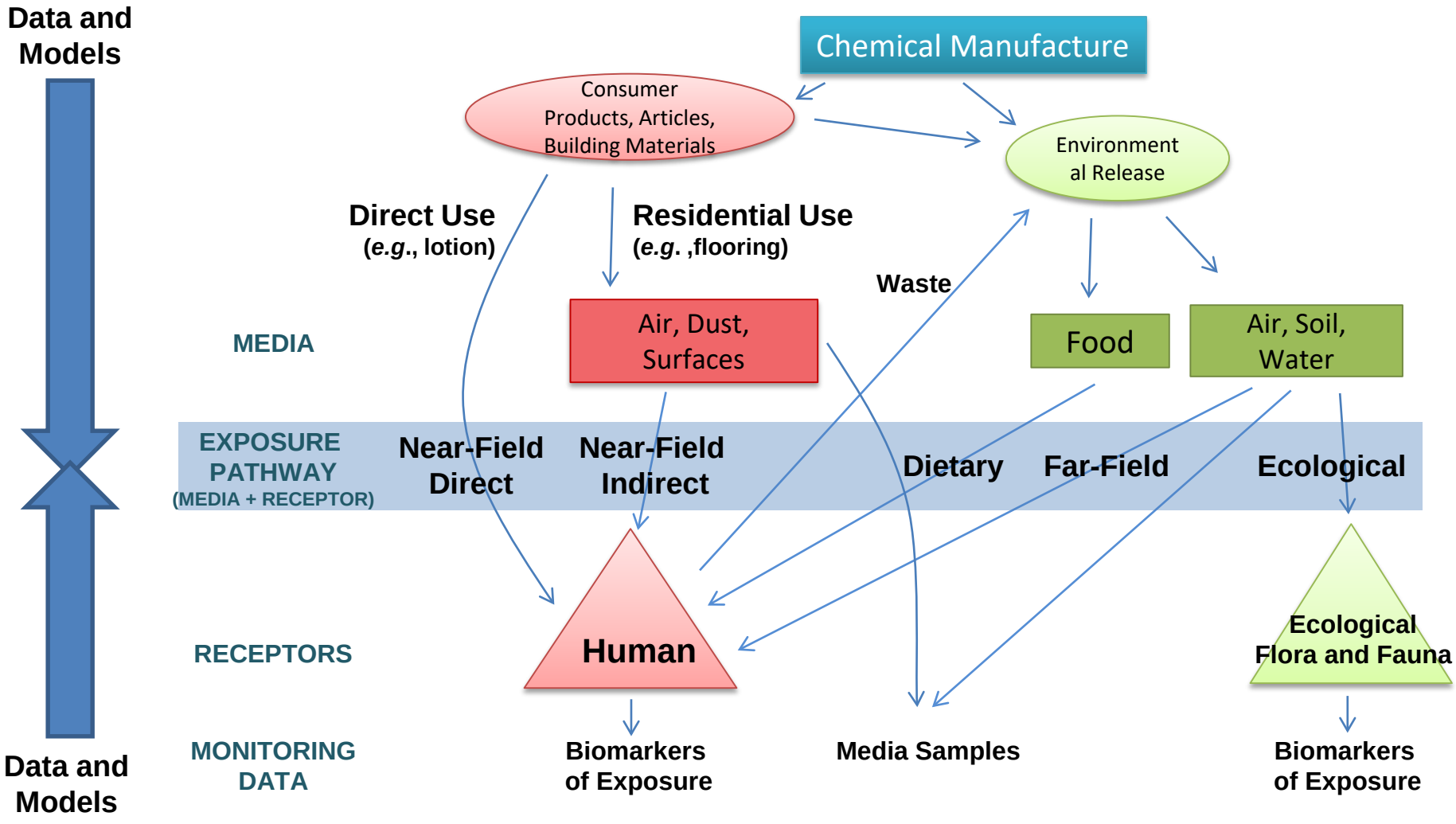
United States Environmental Protection Agency



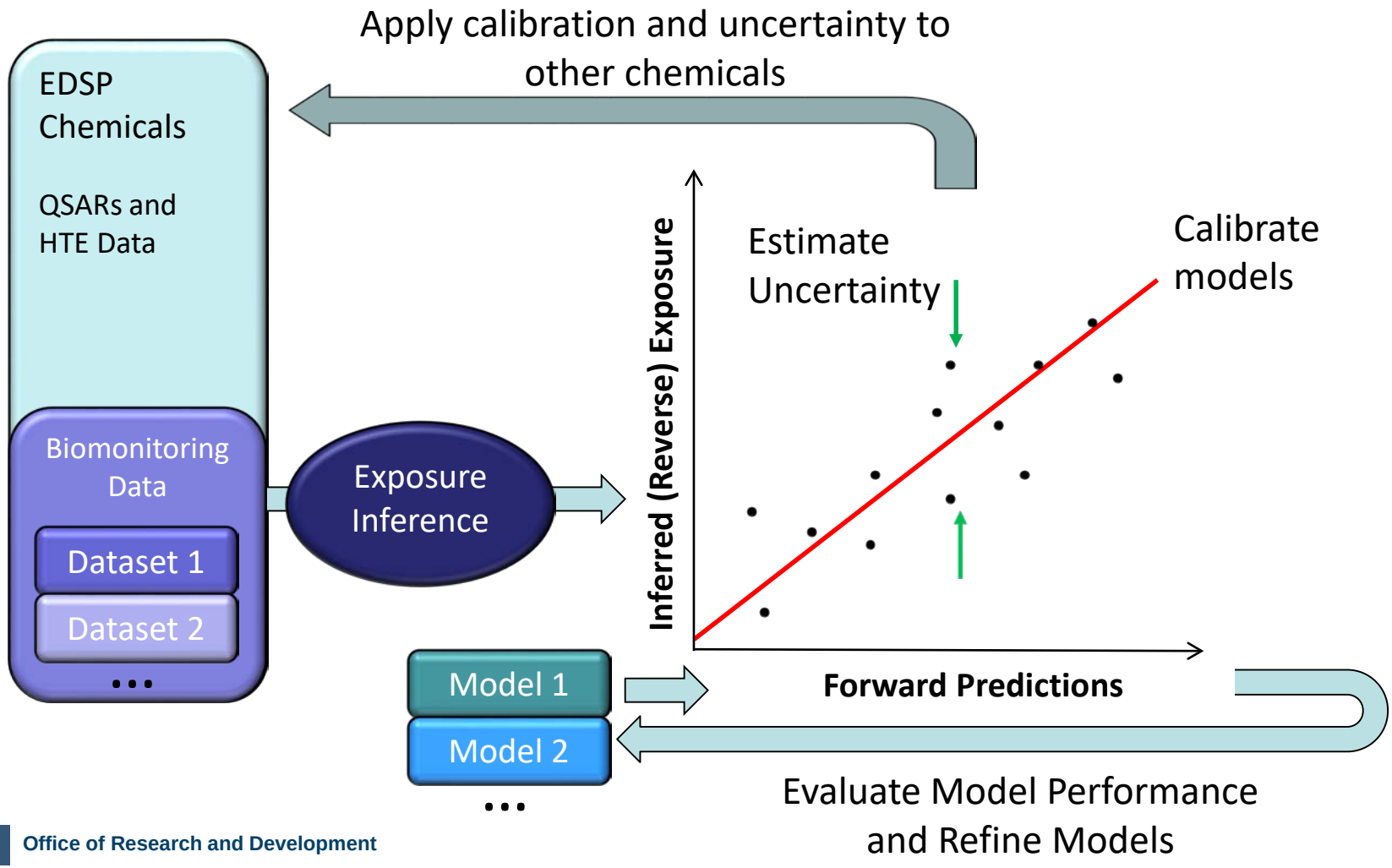
Inference of Exposure Pathways



Evaluation of Forward Predictions with Inferred Exposure

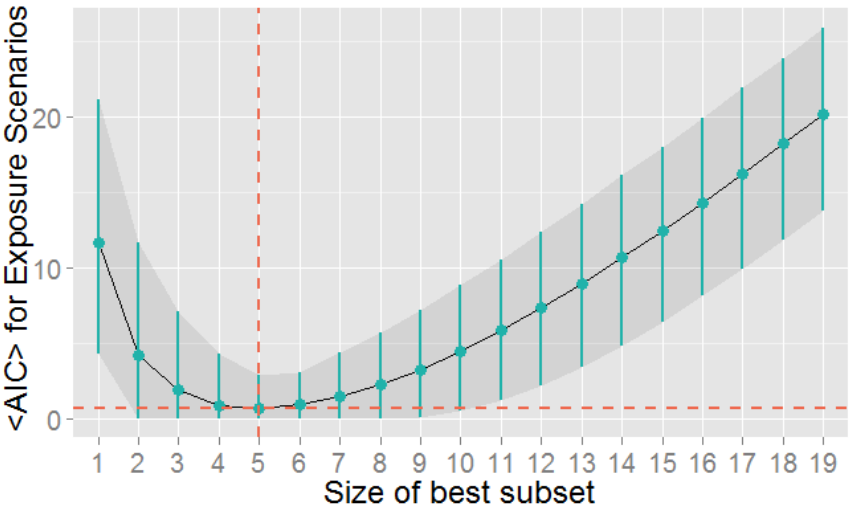


Systematic Empirical Evaluation of Models



High Throughput Descriptors for Exposure

United States Environmental Protection Agency

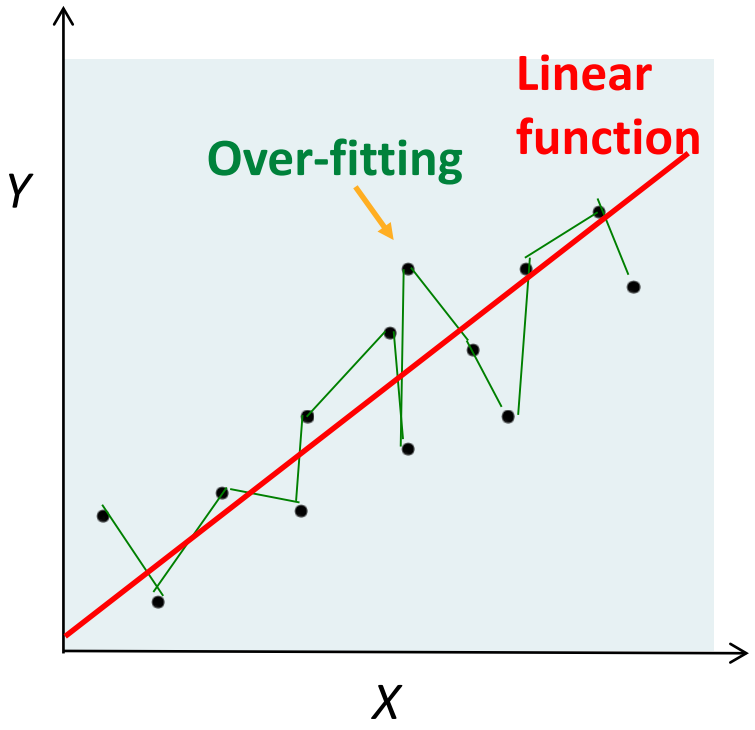


- Antimicrobial
- Colorant
- Food Additive
- Fragrance
- Herbicide
- Personal Care
- Pesticide Active
- Pesticide Inert
- Flame Retardant
- Other
- Industrial no Consumer
- Consumer no Industrial
- Consumer & Industrial
- log(Vapor Pressure)
- log(Hydrophobicity)
- Molecular Weight
- log(Production Volume)
- Random 50%
- Random 10%

Yes / No Use Descriptors

Physico-chemical Properties (EPI Suite)

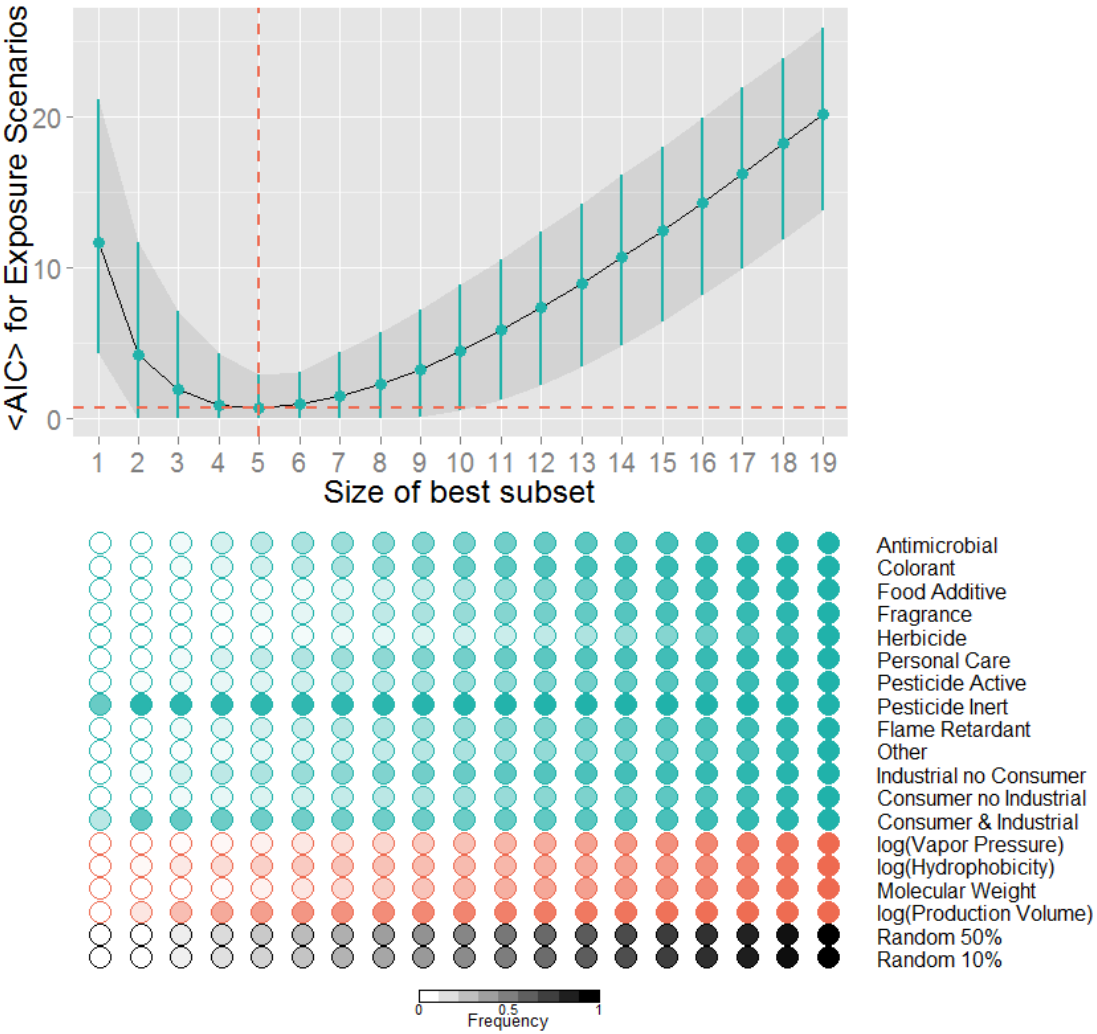
- The average relative AIC (smaller is better) for models made with different numbers of parameters for explaining 1500 different combinations of chemical exposures



Noisy data and the danger of over-fitting

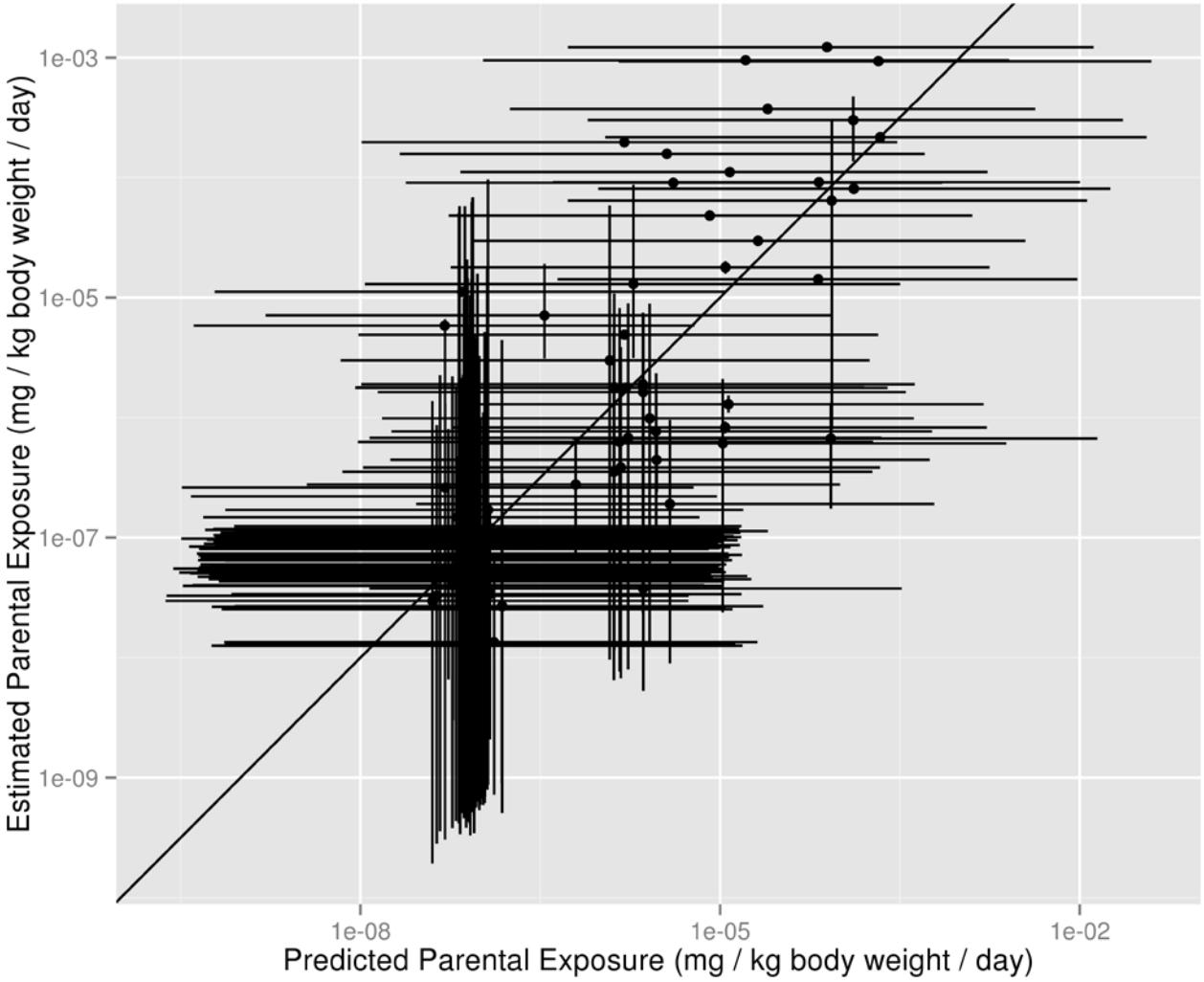
Not All Descriptors Are Useful

United States Environmental Protection Agency



- The average relative AIC (smaller is better) for models made with different numbers of parameters for explaining 1500 different combinations of chemical exposures
- The predictors involved in the optimal model with higher frequencies are represented by darker circles, and those with lower frequencies by lighter circles
- As a sanity check, two random variables generated from binomial distribution with probability 50% and 10% of obtaining 1, are not selected as optimal descriptors in the five factor model

Predicting NHANES exposure rates



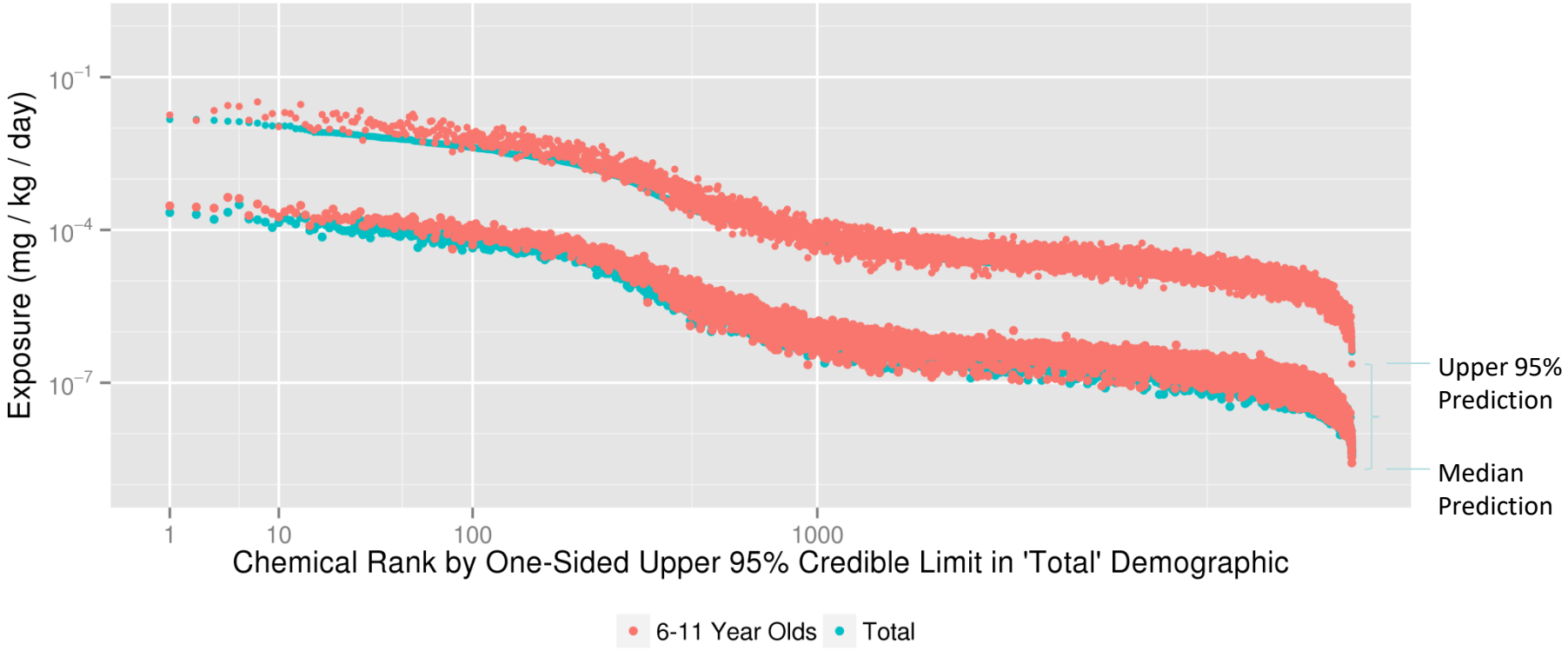
$R^2 \approx 0.5$ indicates that we can predict 50% of the chemical to chemical variability in mean NHANES exposure rates

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

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

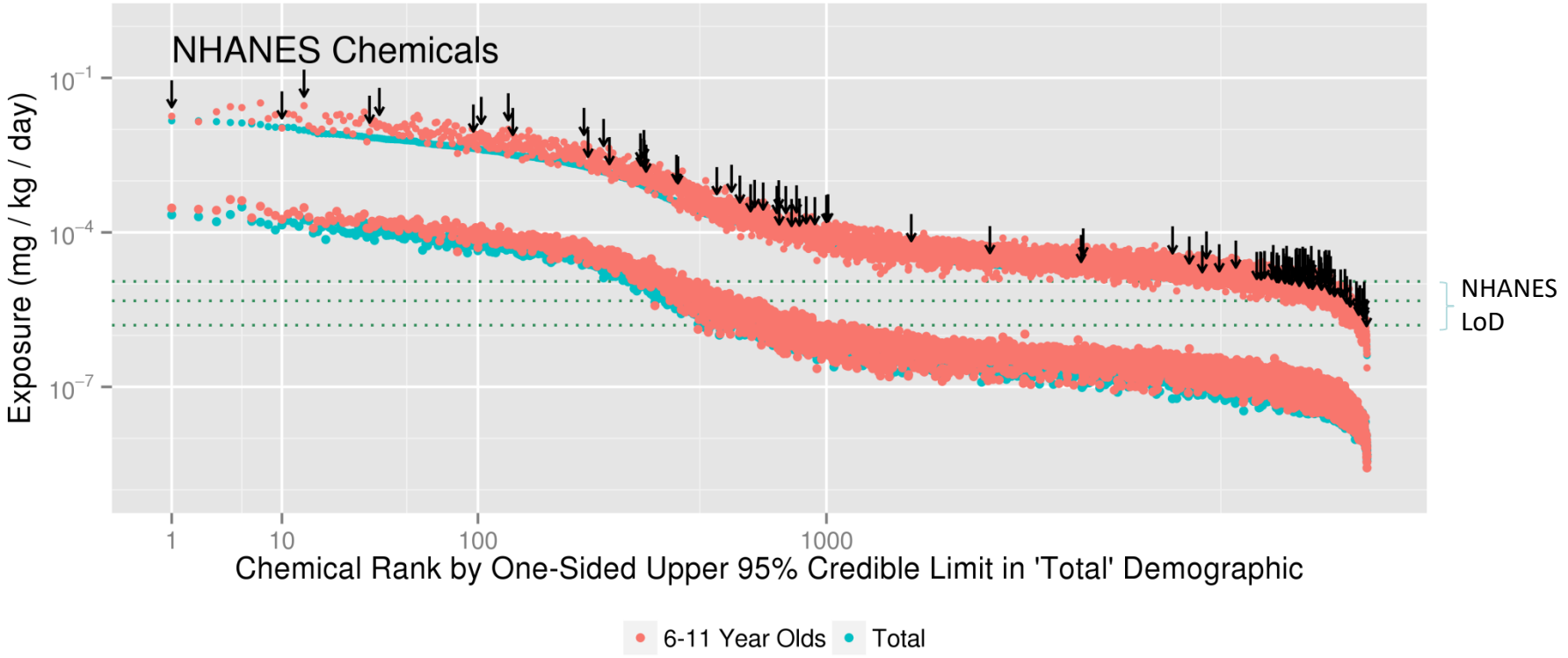
Calibrated Exposure Predictions for 7968 Chemicals



Calibrated Exposure Predictions for 7968 Chemicals

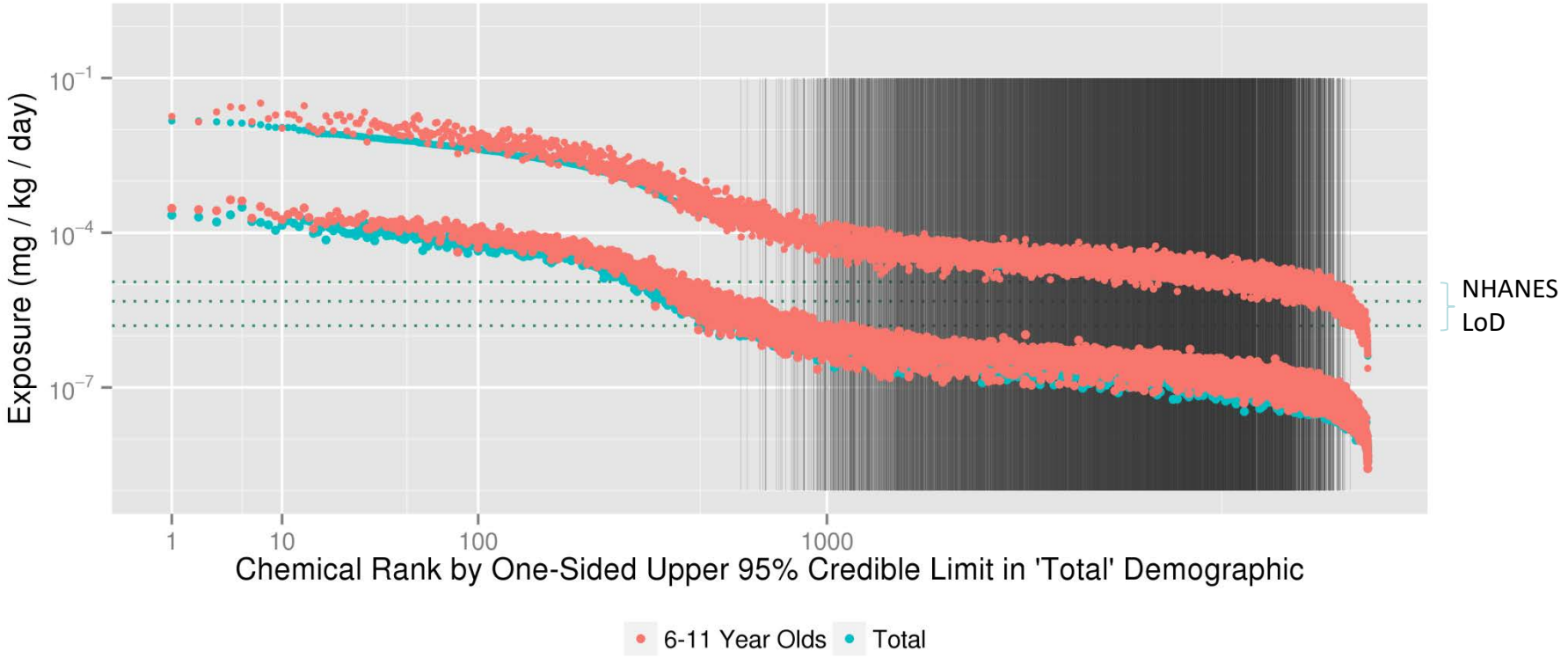
- We focus on the median and upper 95% predictions because the lower 95% is below the NHANES limits of detection (LoD)
- Dotted lines indicate 25%, median, and 75% of the LoD distribution

Calibrated Exposure Predictions for 7968 Chemicals



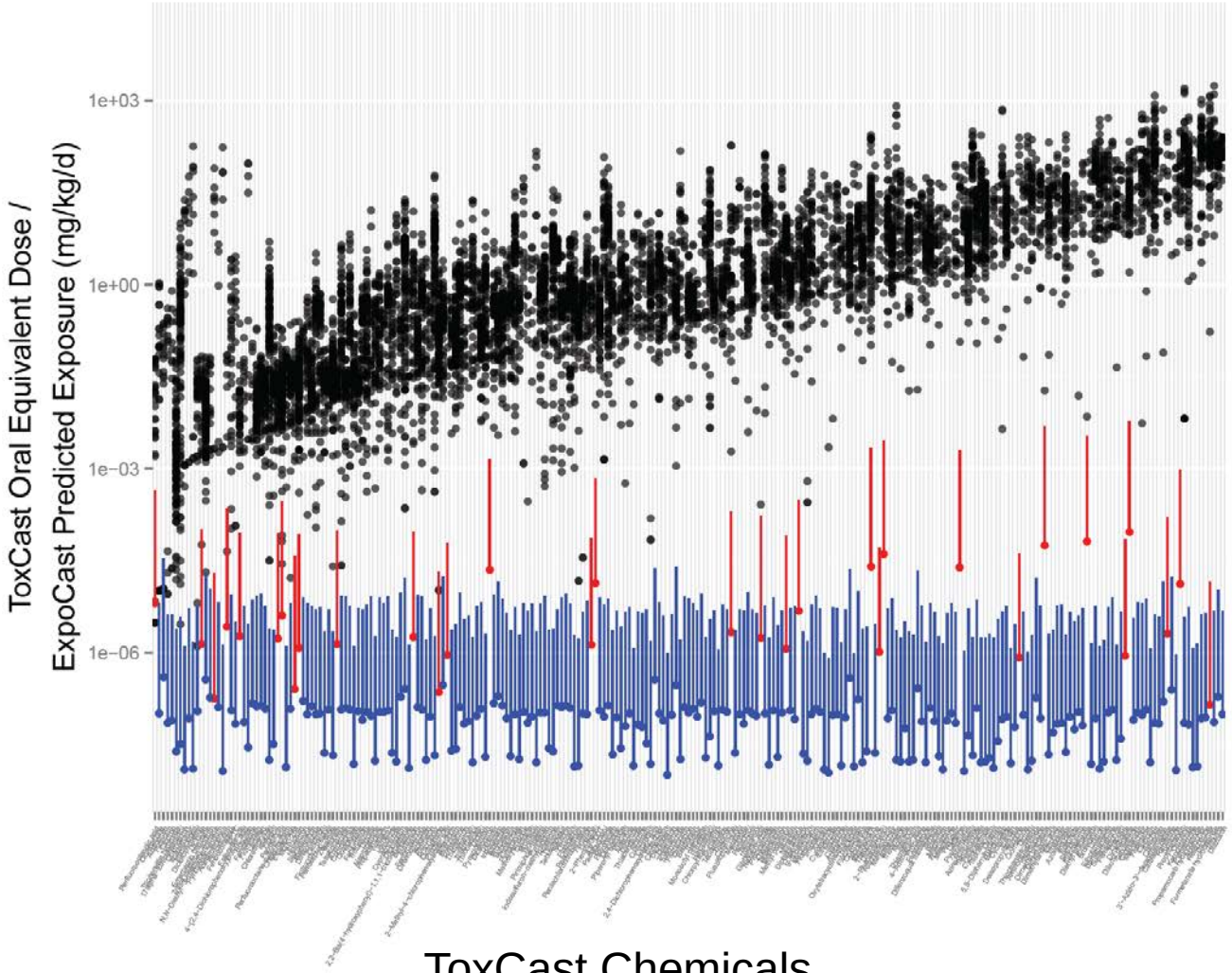
- Chemicals currently monitored by NHANES are distributed throughput the predictions
- Chemicals with the first and ninth highest 95% limit are monitored by NHANES

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

High Throughput Risk Prioritization



ToxCast Bioactivity Converted to mg/kg/day with HTTK

ExpoCast Exposure Predictions

ToxCast Chemicals

Prioritization as in Wetmore *et al*. (2012) Bioactivity, Dosimetry, and Exposure Paper

Conclusions

- We identify those HTE factors that correlate with the NHANES data and estimate uncertainty
- The calibrated meta-model can estimate relative levels of chemical exposures for 7968 chemicals
  - This includes thousands of chemicals with no other data on human exposure
  - Same factors are predictive (R^2 ~ 0.5) across demographics characterized by NHANES
- Different demographics have different mean (overall) exposures:
  - There are demographic-specific aspects not currently described by available HTE factors
- Upcoming analysis:
  - Replace 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

Acknowledgements

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