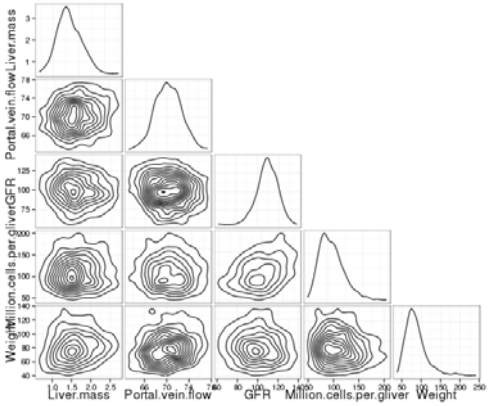
Human variability in high-throughput risk prioritization of environmental chemicals



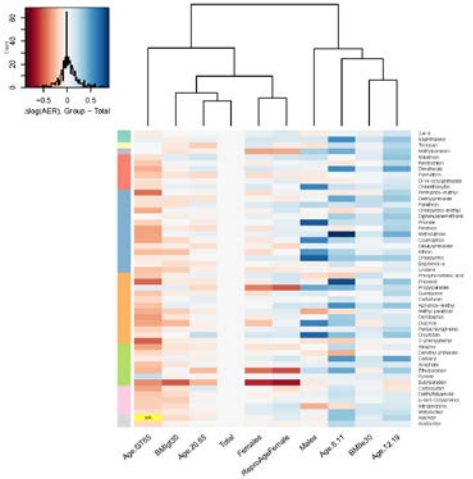
Dr. Caroline Ring

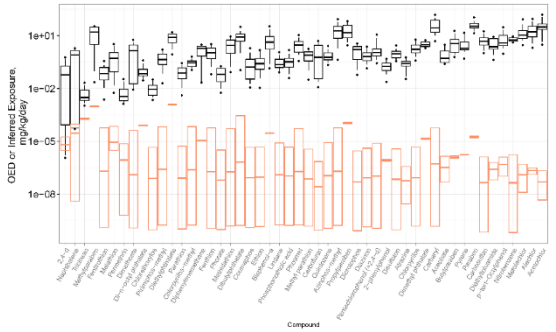
ORISE Postdoctoral Fellow

National Center for Computational Toxicology

US EPA, Office of Research and Development

20 January 2015





Need for risk prioritization: Too many chemicals

- Approx. 30,000 chemicals in wide commercial use[1]
- Approx. 700-1000 new chemicals on the market every year[1]
- Not feasible to do full *in vivo* tox studies on all of them[2]
- Need to triage: which chemicals should be prioritized for further testing?[3]
- Need low-cost, high-throughput methods of risk prioritization

High throughput risk prioritization

Risk can be described as function of hazard and exposure

- Exposure: HT model frameworks (*e.g.* ExpoCast)[4]
  - Estimate how much of a dose you get
- Hazard: *in vitro* HTS bioactivity assays (*e.g.* ToxCast)[5]
  - Dose-response data

How to relate *in vitro* bioactivity to *in vivo* toxicity and risk?

In vitro-in vivo extrapolation (IVIVE)[6] —

using reverse toxicokinetics approach[7]

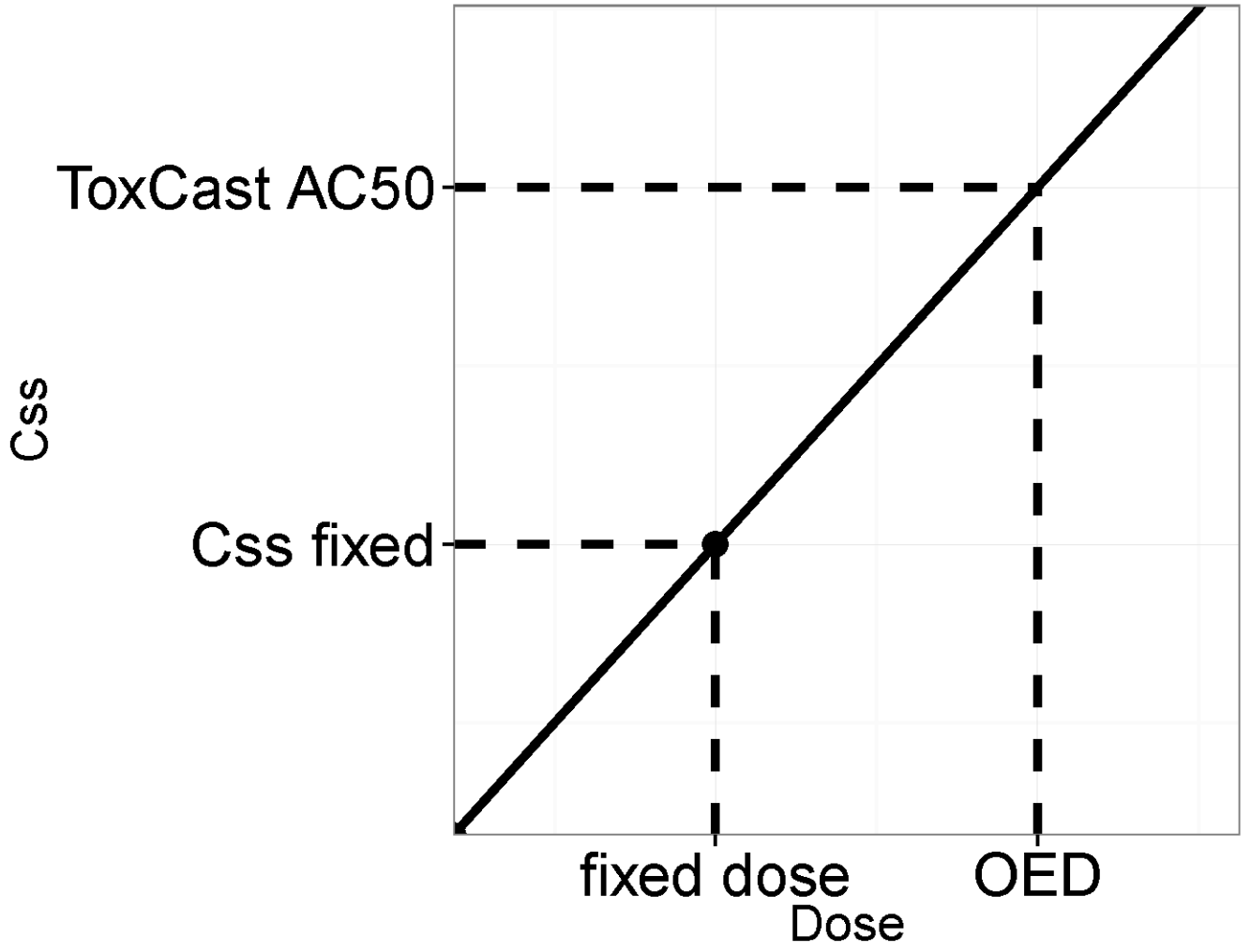
Reverse toxicokinetics

Assume first-order metabolism[8]

Work with steady-state plasma concentration (C_{ss})[8]

(assumptions for long-term, ambient exposures)

$$\text{Oral Equiv. Dose} = \text{Fixed dose} \times \frac{\text{ToxCast } AC_{50}}{C_{ss} \text{ from fixed dose}}$$



HTTK: High-throughput TK models

- Open-source R package `httk`, available on CRAN[9] (Pearce *et al.*, *J Stat Soft* 2016)
- General TK models can be parameterized for many chemicals using HT *in vitro* assays[8,10,11]
  - At present, 554 chemicals
- General TK models:
  - 1-compartment
  - 3-compartment
  - PBTK (physiologically-based TK)
  - 3-compartment steady-state

HTTK: High-throughput TK models

- Open-source R package `httk`, available on CRAN[9] (Pearce *et al.*, *J Stat Soft* 2016)
- General TK models can be parameterized for many chemicals using HT *in vitro* assays[8,10,11]
  - At present, 554 chemicals
- General TK models:
  - 1-compartment
  - 3-compartment
  - PBTK (physiologically-based TK)
  - 3-compartment steady-state
    - No tissue partitioning
    - First order hepatic metabolism
    - Passive renal clearance

HTTK parameters

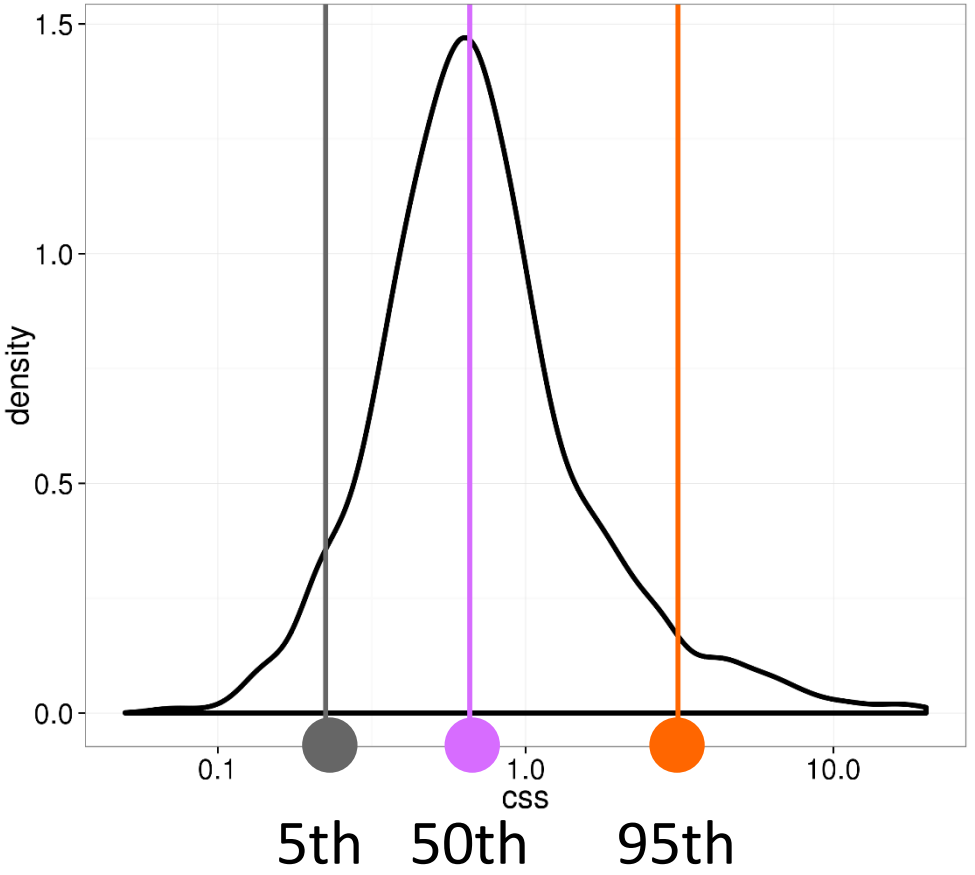
Chemical-specific parameters	
Fraction unbound in plasma (Fub) Intrinsic clearance rate (CLint)	Measured in HT *in vitro* assays (Wetmore *et al.* 2012, 2014, 2015)
Tissue-plasma partition coefficients	Predicted from phys-chem properties; not included in 3-compartment steady-state model
Physiological parameters	
Body weight Tissue volumes & blood flows Glomerular filtration rate (GFR) Hematocrit Hepatocellularity	By default: “average” human values

Simulating population variability: Monte Carlo

Same dose of a given chemical →

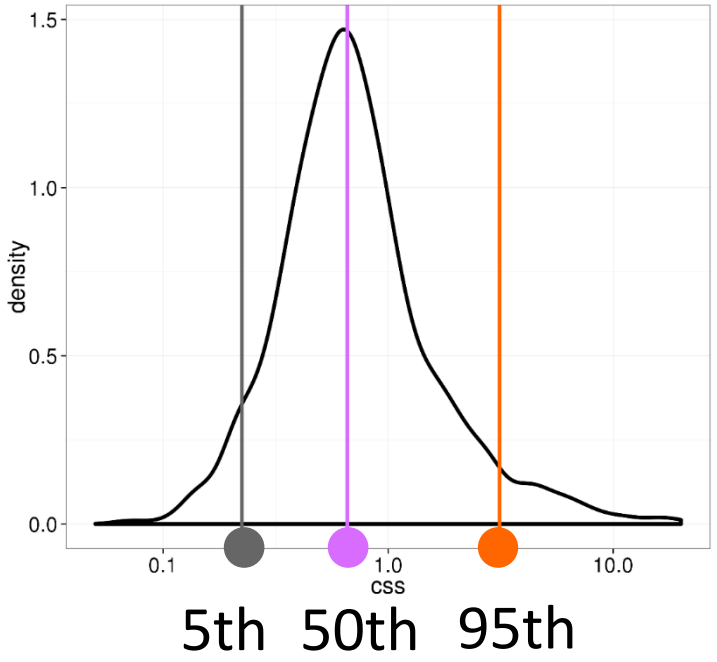
HTTK model parameters representing each individual

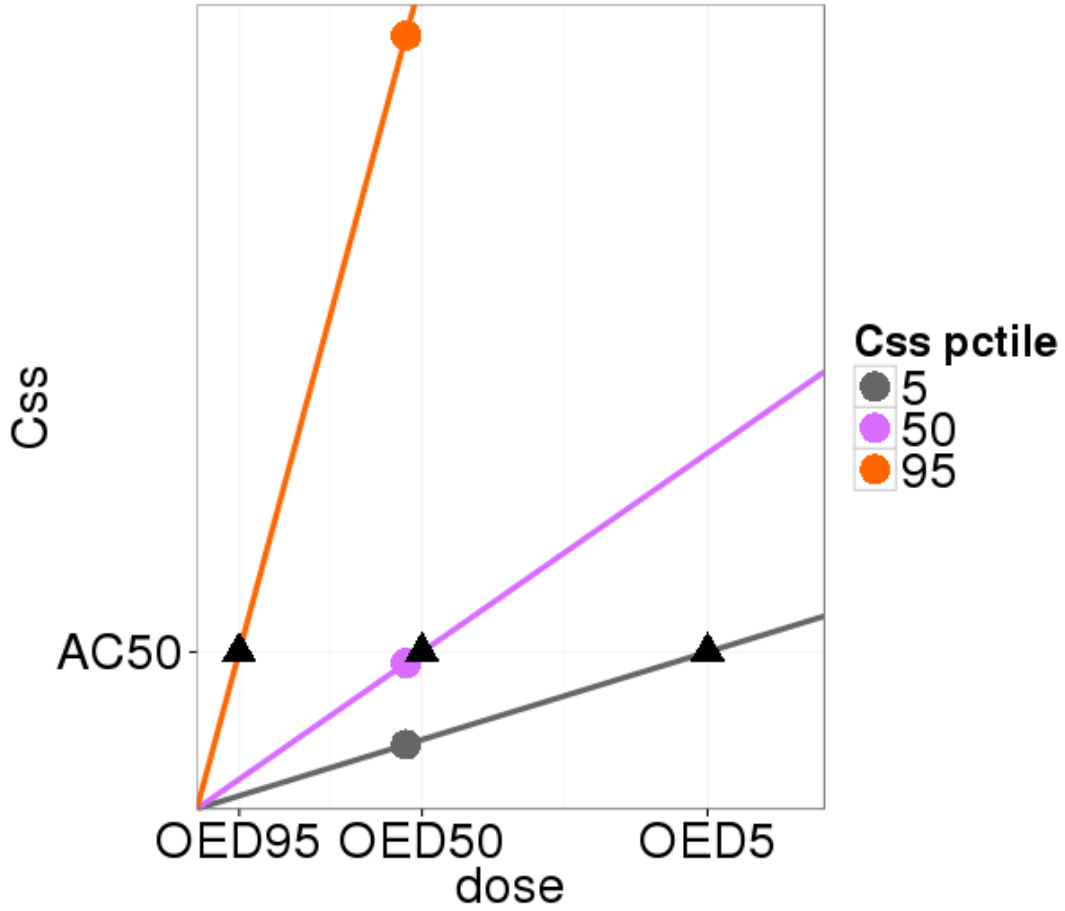
Varying C_{ss}



Population variability in reverse TK

C_{ss} from fixed dose

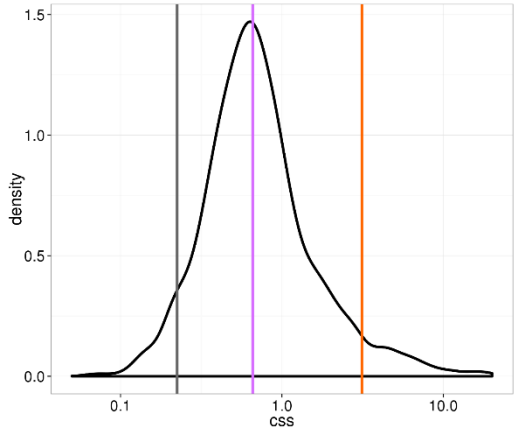




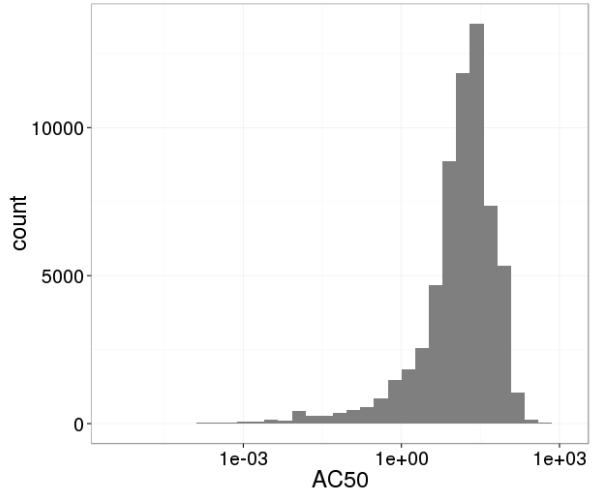
● Css95 = conservative OED

Range of OEDs for each chemical

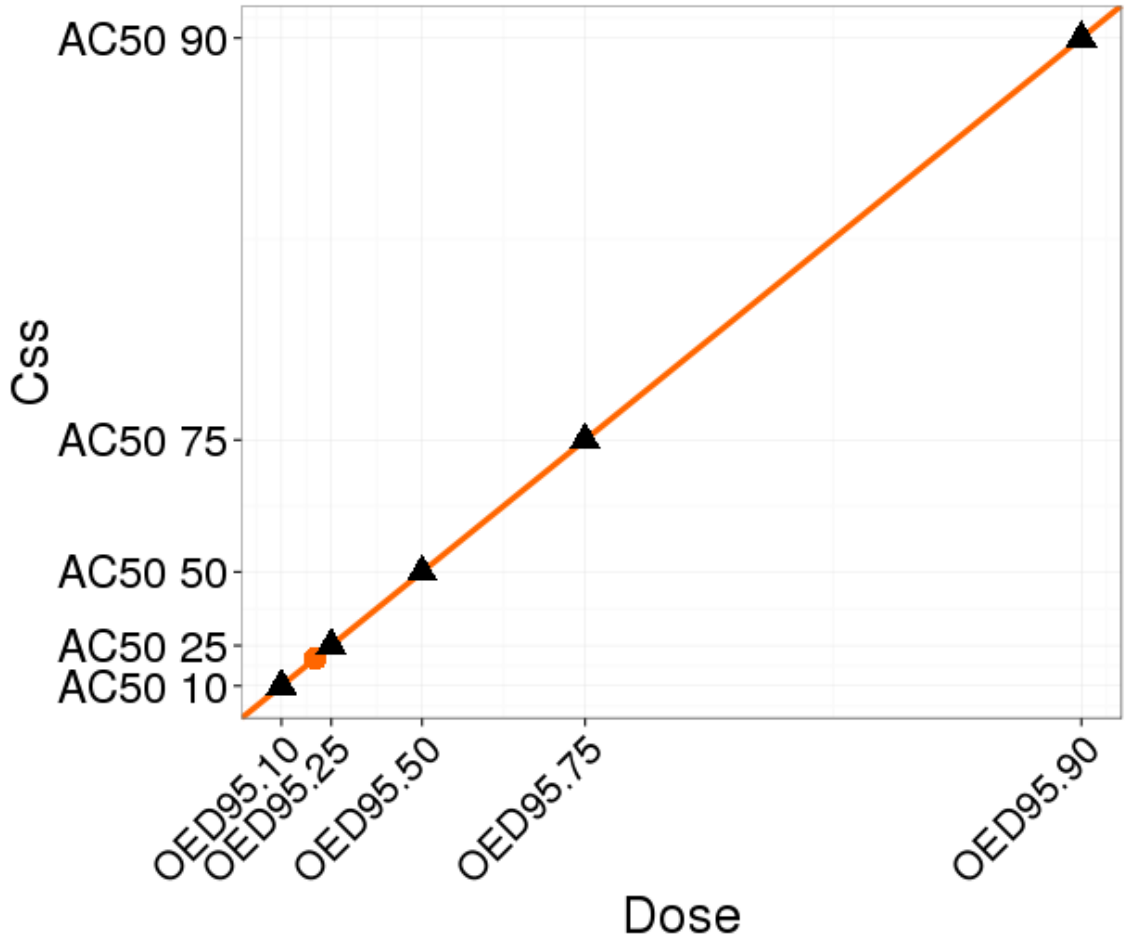
C_{ss} distribution – 95th percentile



ToxCast AC50 percentiles across assays



Range of OEDs for range of AC50s



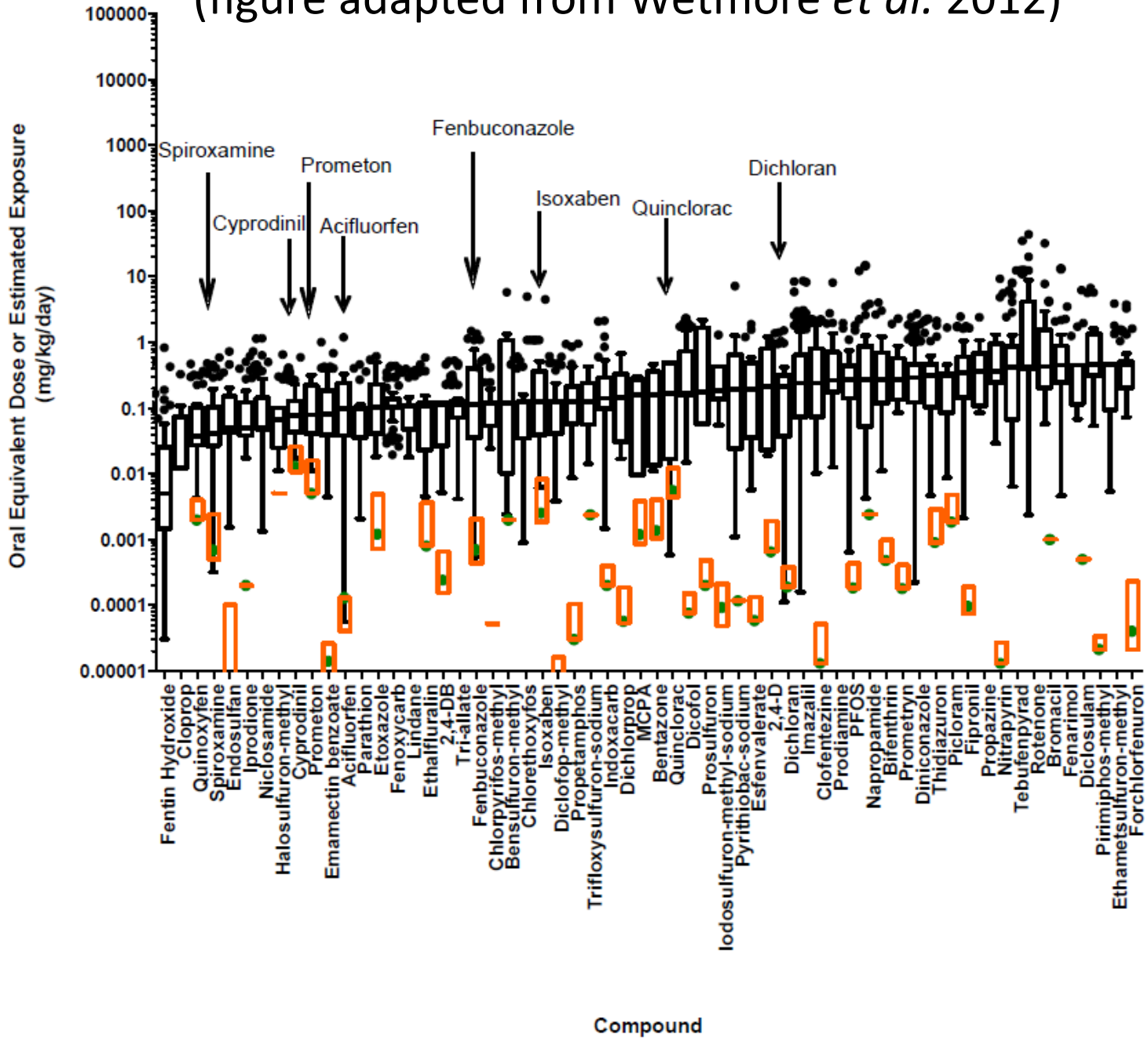
Activity-exposure ratio: compare OED to estimated exposure[8,10,11]

$$\text{AER} = \frac{\text{Oral Equiv. Dose}}{\text{Estimated exposure}}$$

AER <=1 : Exposure may be high enough to cause bioactivity

AER >> 1: Exposure less likely to be high enough to cause bioactivity

(figure adapted from Wetmore *et al.* 2012)



HT risk prioritization for potentially sensitive life stages [US EPA 2006, "A Framework for Assessing Health Risks of Environmental Exposures to Children"]

- Is AER higher/lower for certain demographic groups?
- To use AER approach:
  - Need exposure estimates by demographic group
  - Need estimates of C_{ss} variability by demographic group

ExpoCast: Exposures inferred from NHANES urine biomonitoring data

For 10 demographic groups:

1. Total
2. Age 6-11
3. Age 12-19
4. Age 20-65
5. Age >65
6. BMI <= 30
7. BMI > 30
8. Males
9. Females
10. Reproductive-Age Females (ages 16-49)

106 compounds; 50 HTTK compounds

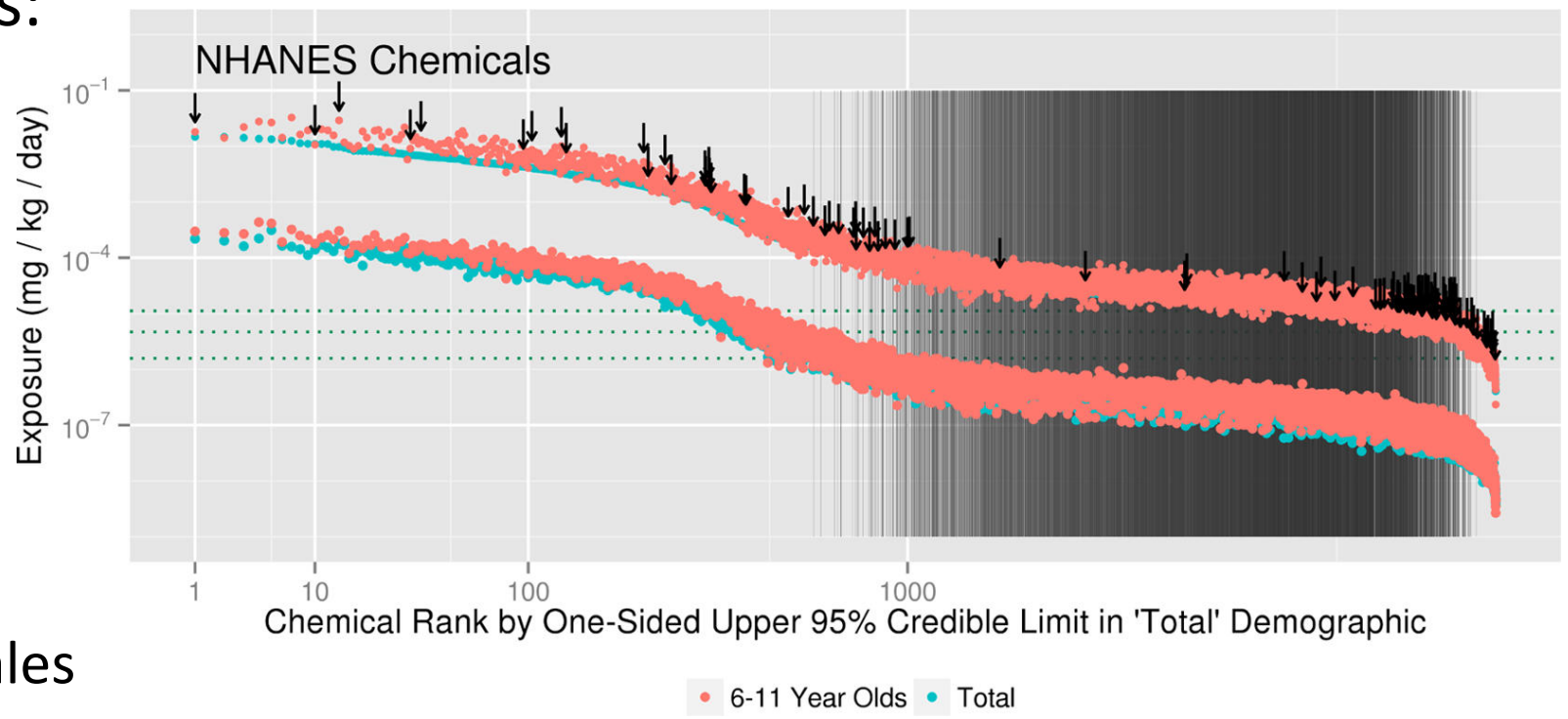
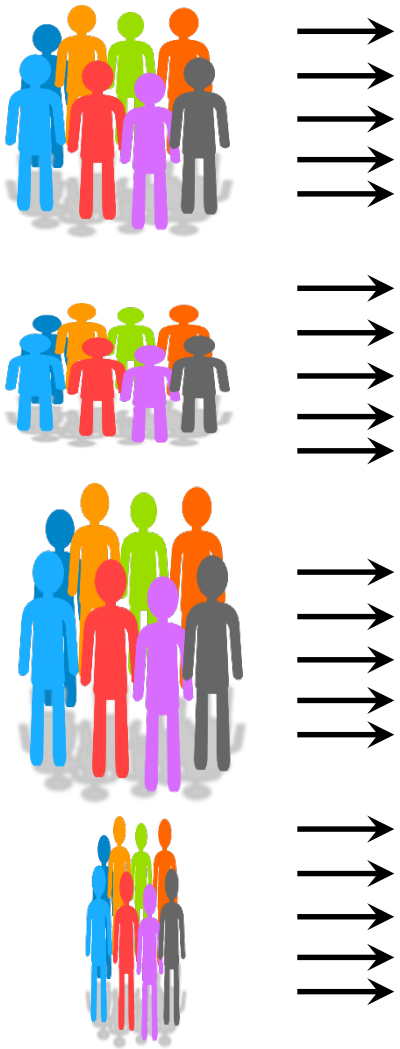


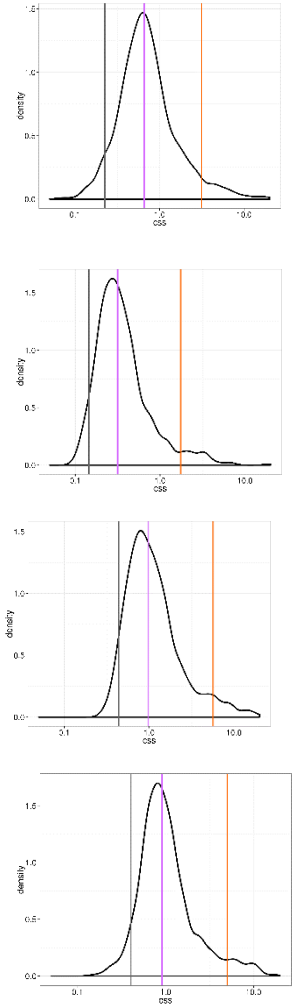
Figure adapted from Wambaugh *et al., Environ Sci Technol* 2014
See also Wambaugh *et al.*, *Environ Sci Technol* 2012

Goal: AERs by demographic group

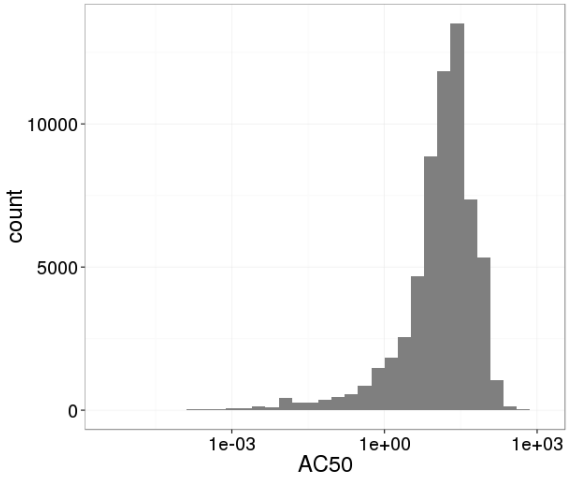
Physiology



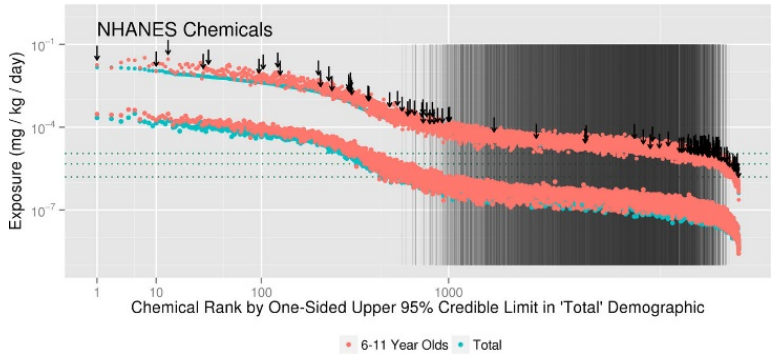
C_{ss}



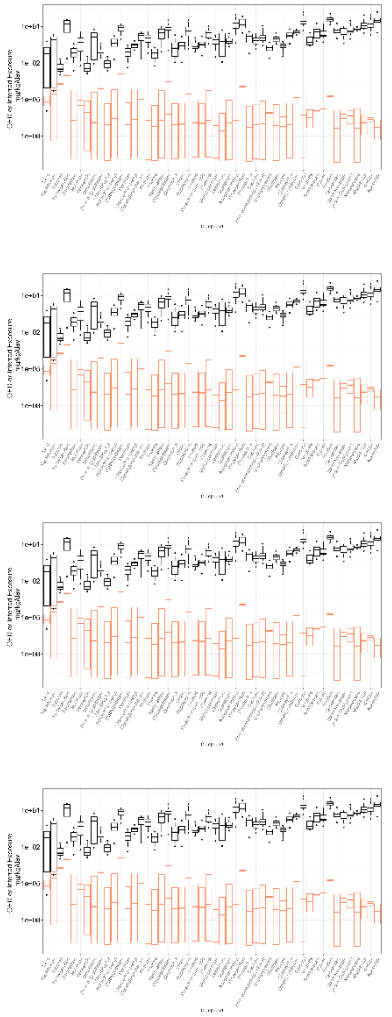
ToxCast AC50s across assays



Exposures by group



AERs



HTTK-Pop: Virtual population generator for HTTK

Demographics and body measurements

Sex
Race/ethnicity
Age
Height
Weight

Physiological quantities

Tissue masses
Tissue blood flows
GFR (kidney function)
Hematocrit
Hepatocellularity

(+ residual marginal variability)

Need population distribution with correlation structure

Source of demographic & body measures data: NHANES

Large, ongoing CDC survey of US population: demographic, body measures, medical exam, biomonitoring (health and exposure), ….

Designed to be representative of US population according to census data

Data sets publicly available (on the web)

NHANES quantities used in HTTK-Pop:

- Sex
- Race/ethnicity
- Age
- Height
- Weight
- Hematocrit (age 1 and older)
- Serum creatinine (age 12 and older) (can be used to predict GFR)

HTTK-Pop: population generation

Sample from subset of NHANES respondents specified by:

- Age limits (default 0-79 years)
- Sex (default: NHANES proportions of males and females)
- Race/ethnicity (default: NHANES proportions)
- BMI categories (default includes all)

Predict physiological parameters using allometric scaling, literature regression equations; add residual marginal variability

Generated virtual populations matching the 10 demographic groups

- Each with 1000 individuals

HTTK-Pop:
five physiological parameters, Ages 20-65

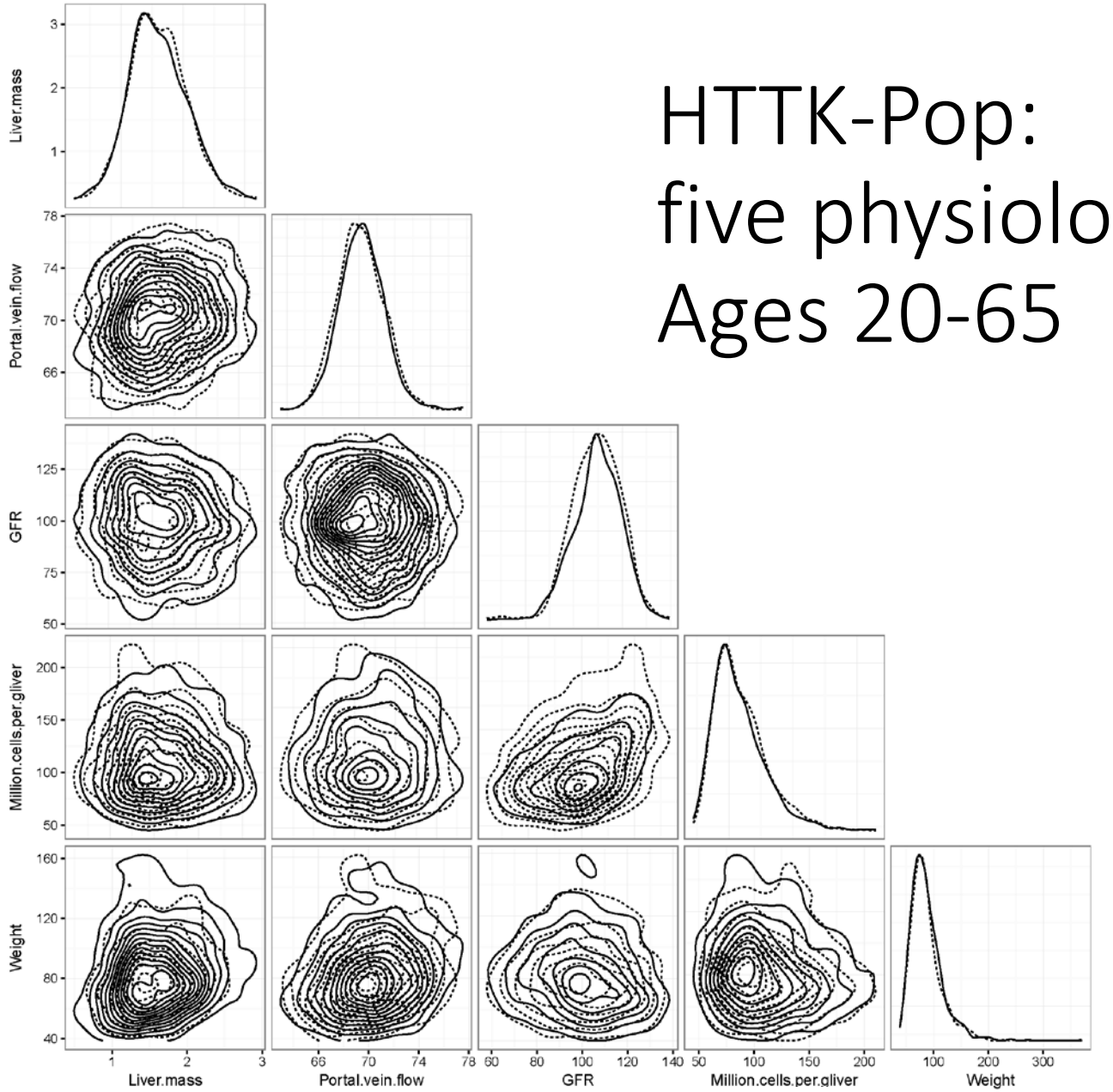
Liver mass

Portal vein flow

GFR

10^6 cells/g liver

Weight



Liver mass

Portal vein flow

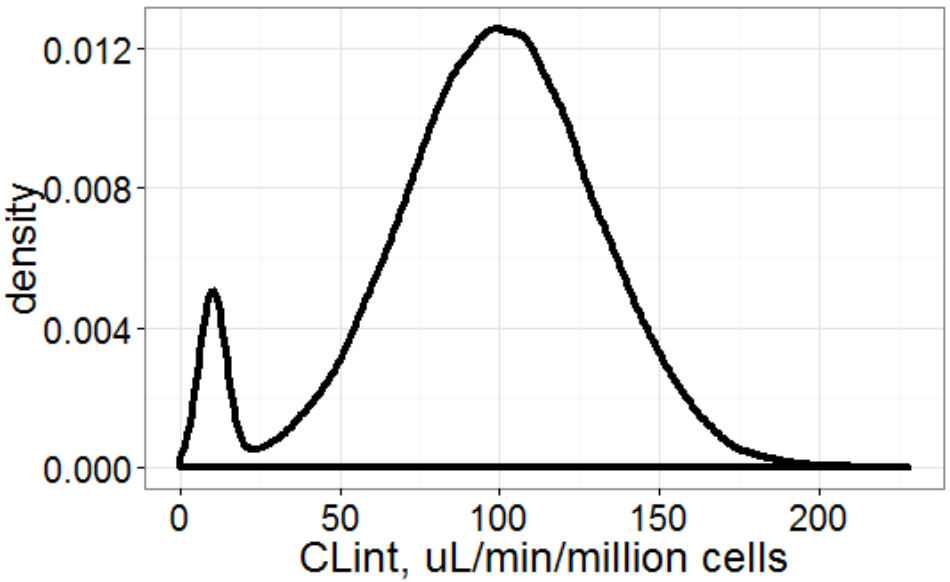
GFR

10^6 cells/g liver

Weight

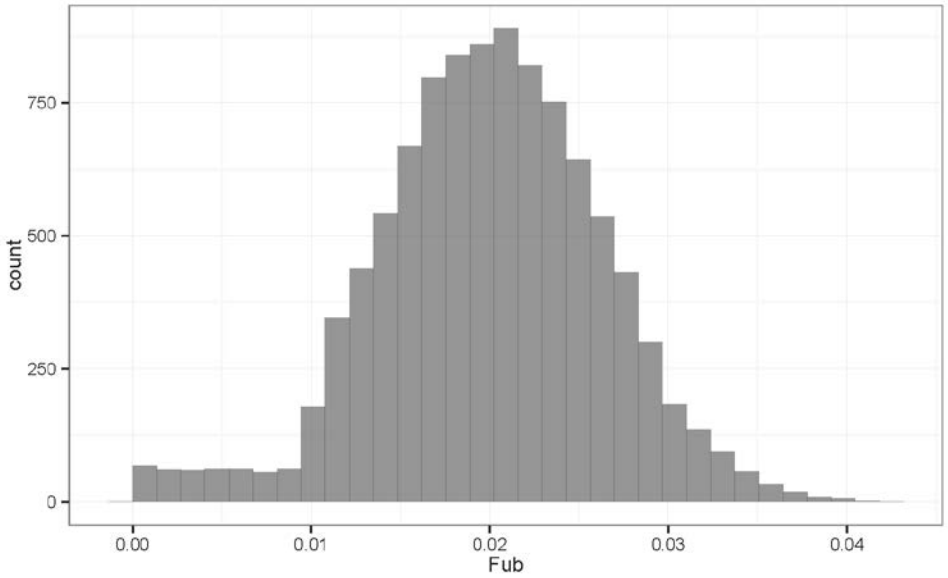
Chemical-specific parameters: assume distributions about *in vitro* measured values

Intrinsic clearance



Assume 5% of population are poor metabolizers (Gaussian mixture distribution)

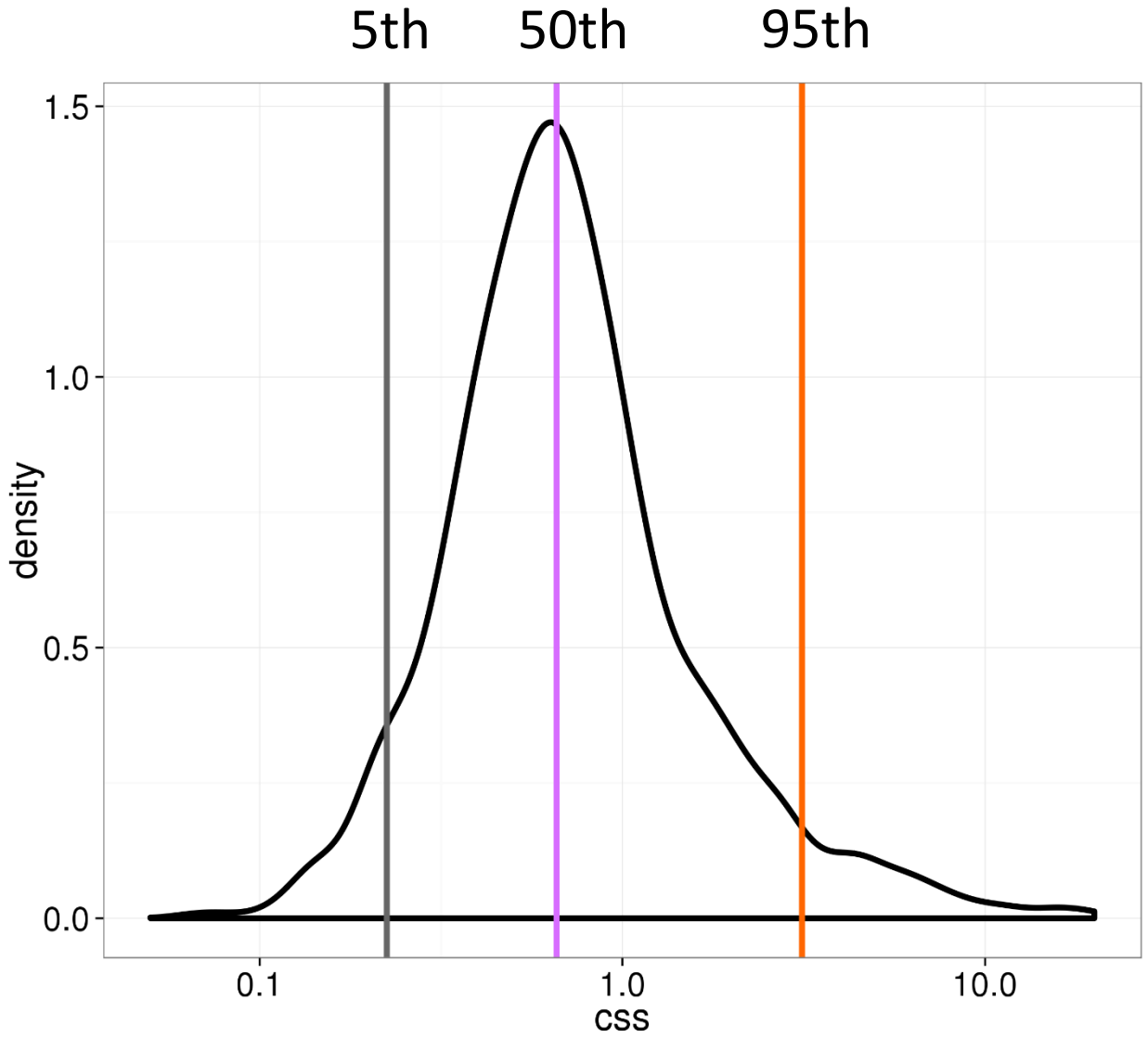
Fraction unbound in plasma



Assume Fub distribution censored below average LOD (0.01)

See: Wambaugh *et al. Toxicol Sci* 2015

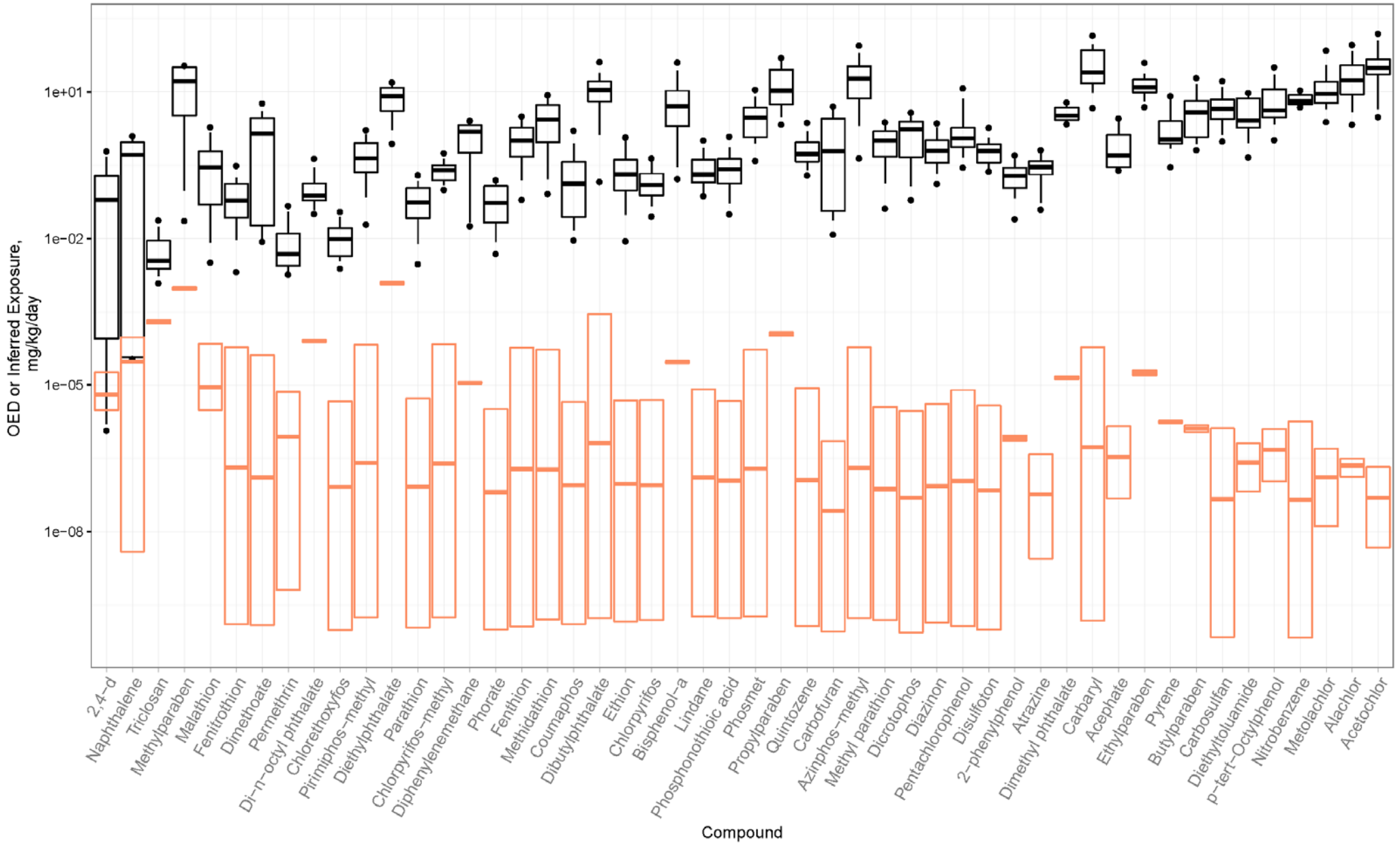
Evaluate HTTK model to get Css distribution



Example:
Bisphenol-A
Ages 20-65
Dose 1 mg/kg/day

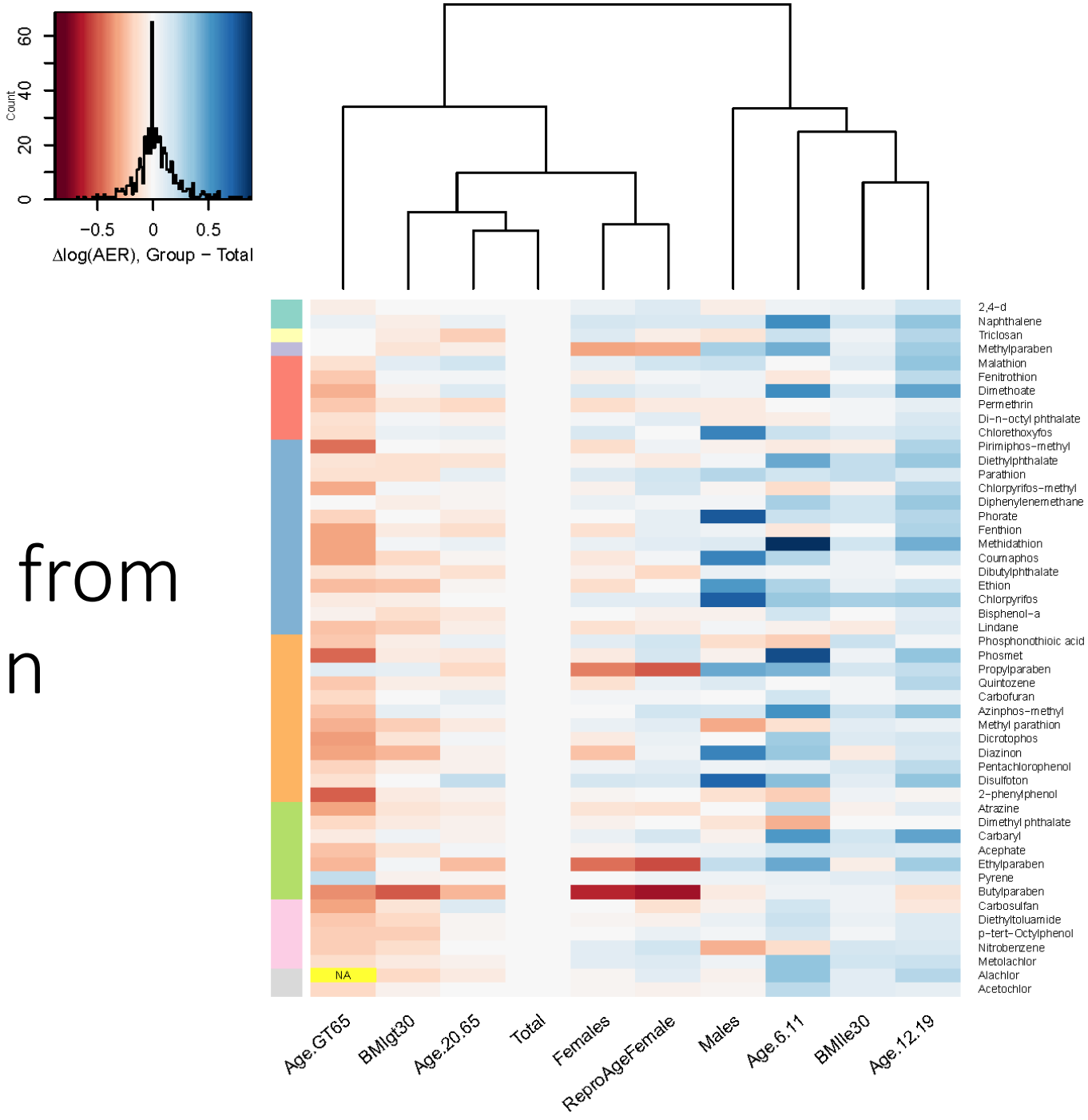
× 554 HTTK chemicals
× 10 demographic groups

OEDs and inferred exposures for total population



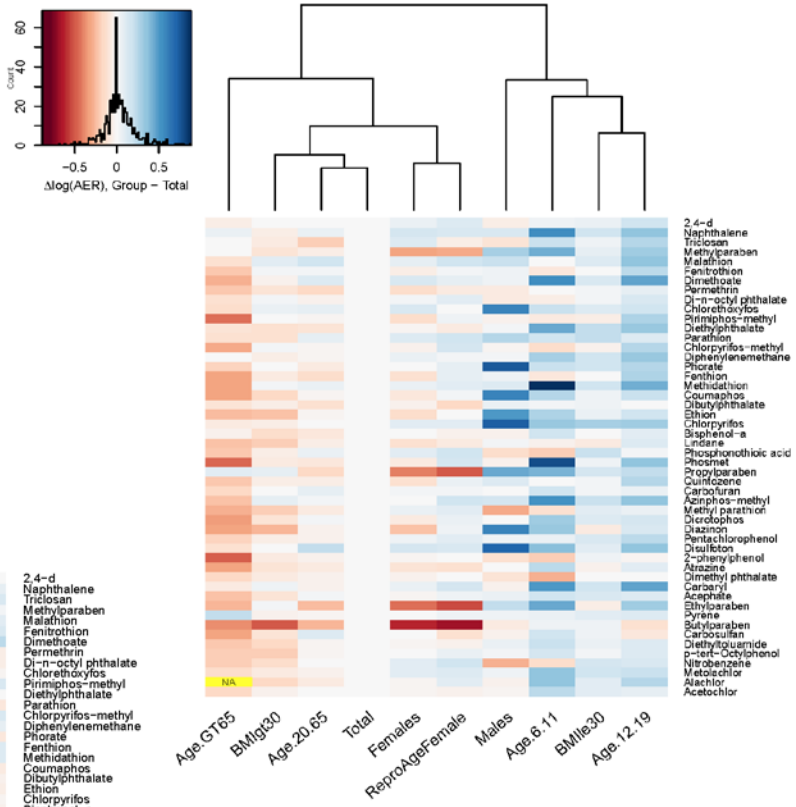
AER

Subgroups:
AER difference from total population

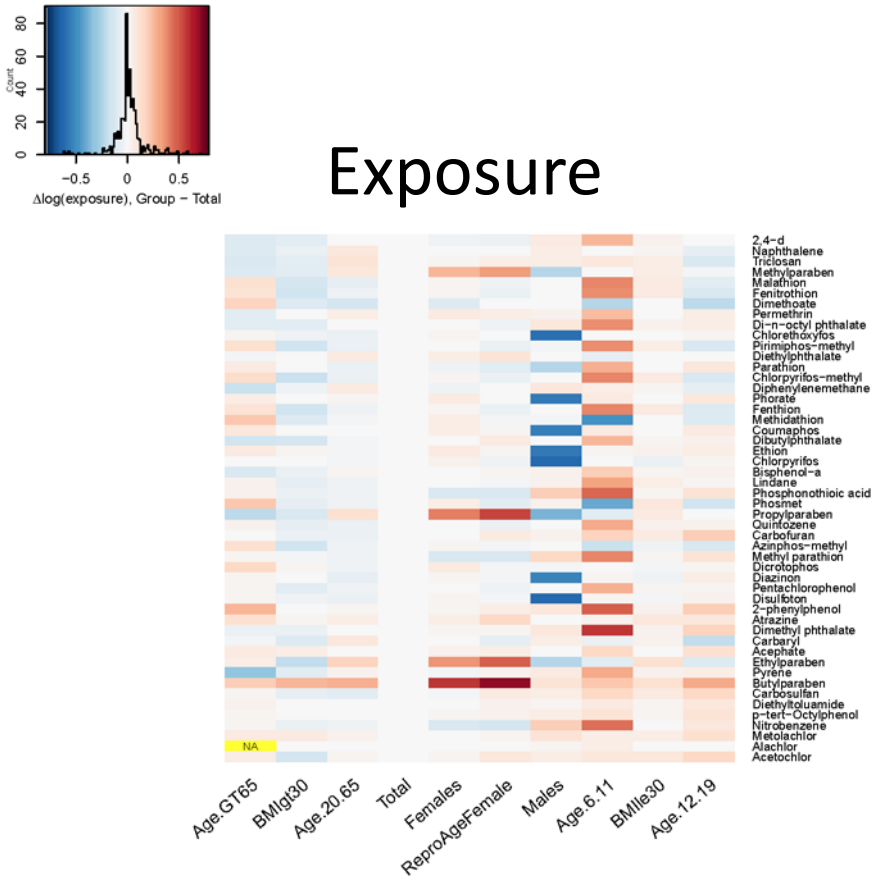


Chemicals by increasing AER for Total population

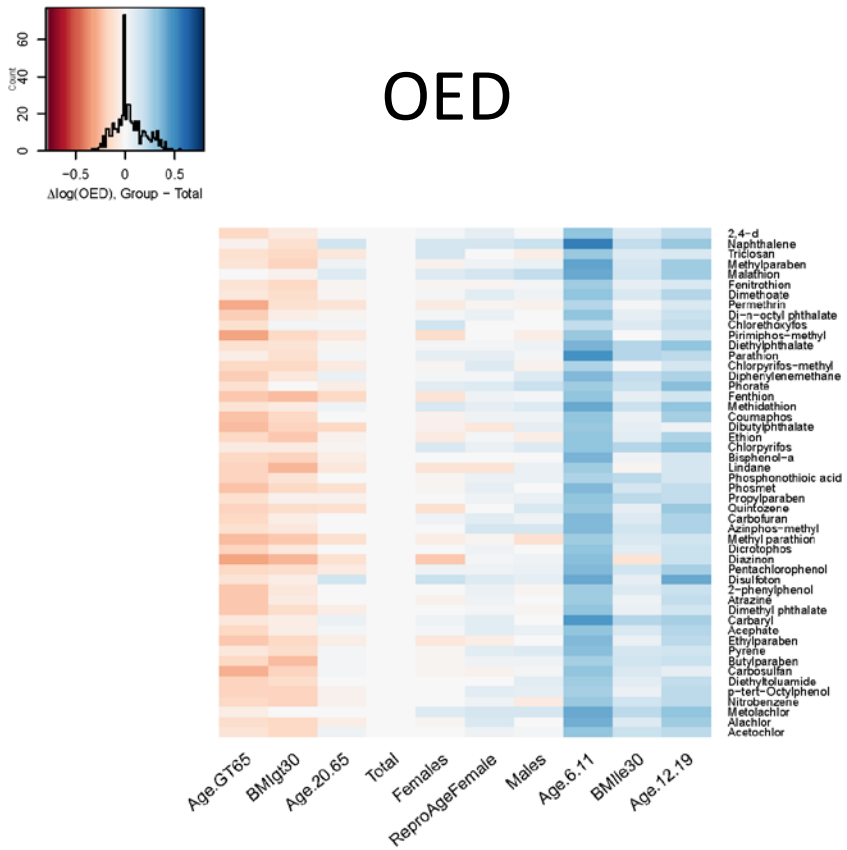
AER



Exposure



OED



Conclusions

- HTTK-Pop lets us simulate population physiology for various demographic groups, for use with HTTK models
- Prioritization based on AER for potentially sensitive groups
  - IVIVE for different groups, to compare with inferred exposures
- AERs for subgroups differ from total population, up to 6-fold
  - AER differences are driven by OED differences for some groups, exposure differences for others
  - Oral equivalent dose changes up to 3-fold (for 95^{th} percentile Css and 10^{th} percentile AC50)
  - Exposure changes up to 5-fold (for upper bound of 95% CI on median)
  - Ages > 65 and BMI > 30: lower AER across many chemicals
  - Ages 6-11 and Ages 12-19: higher AER across many chemicals
  - Other subgroups: AERs different for a few chemicals with big exposure differences

Caveats

- Steady-state assumption
- First-order hepatic-only metabolism assumption
- Toxcast AC50s assumed = *in vivo* bioactive/toxic plasma concentrations
  - Assay endpoints represent perturbations that may or may not lead to adverse effect
  - Plasma concentration vs. tissue concentration
- Median inferred exposures only

Future improvements?

- More realistic Fub distribution?
  - Plasma protein concentration variability: age, gender, disease state…?[12]
  - Albumin or AAG binding?[13]
- More realistic CLint distribution?
- Isozyme abundances and activity: varies with age, ethnicity (at least)[14,15]
- Isozyme-specific data & modeling[10]
  - Isozyme-specific metabolism assays not HT
  - *In silico* predictions of isozyme-specific metabolism? Not easy!
    - Existing data is mostly for pharmaceuticals
    - CYPS are complicated!

Thank you!

References

[1]Judson, R.; Richard, A.; Dix, D.J.; Houck, K.; Martin, M.; Kavlock, R.; Dellarco, V.; Henry, T.; Holderman, T.; Sayre, P.; Tan, S.; Carpenter, T.; Smith, E. The toxicity data landscape for environmental chemicals. Environmental health perspectives. 117:685-95; 2009

[2]Judson, R.; Houck, K.; Martin, M.; Knudsen, T.; Thomas, R.S.; Sipes, N.; Shah, I.; Wambaugh, J.; Crofton, K. In vitro and modelling approaches to risk assessment from the U.S. Environmental Protection Agency ToxCast programme. Basic Clin Pharmacol Toxicol. 115:69-76; 2014

[3]Wambaugh, J.F.; Wetmore, B.A.; Pearce, R.; Strope, C.; Goldsmith, R.; Sluka, J.P.; Sedykh, A.; Tropsha, A.; Bosgra, S.; Shah, I.; Judson, R.; Thomas, R.S.; Setzer, R.W. Toxicokinetic Triage for Environmental Chemicals. Toxicological sciences : an official journal of the Society of Toxicology; 2015

[4]Wambaugh, J.F.; Setzer, R.W.; Reif, D.M.; Gangwal, S.; Mitchell-Blackwood, J.; Arnot, J.A.; Joliet, O.; Frame, A.; Rabinowitz, J.; Knudsen, T.B.; Judson, R.S.; Egeghy, P.; Vallero, D.; Cohen Hubal, E.A. High-throughput models for exposure-based chemical prioritization in the ExpoCast project. Environmental science & technology. 47:8479-88; 2013

[5]Judson, R.; Houck, K.; Martin, M.; Knudsen, T.; Thomas, R.S.; Sipes, N.; Shah, I.; Wambaugh, J.; Crofton, K. In vitro and modelling approaches to risk assessment from the U.S. Environmental Protection Agency ToxCast programme. Basic Clin Pharmacol Toxicol. 115:69-76; 2014

[6]Bois, F.Y.; Jamei, M.; Clewell, H.J. PBPK modelling of inter-individual variability in the pharmacokinetics of environmental chemicals. Toxicology. 278:256-67; 2010

[7]Rotroff, D.M.; Wetmore, B.A.; Dix, D.J.; Ferguson, S.S.; Clewell, H.J.; Houck, K.A.; Lecluyse, E.L.; Andersen, M.E.; Judson, R.S.; Smith, C.M.; Sochaski, M.A.; Kavlock, R.J.; Boellmann, F.; Martin, M.T.; Reif, D.M.; Wambaugh, J.F.; Thomas, R.S. Incorporating human dosimetry and exposure into high-throughput in vitro toxicity screening. Toxicological sciences : an official journal of the Society of Toxicology. 117:348-58; 2010

References, continued

[8]Wetmore, B.A.; Wambaugh, J.F.; Allen, B.; Ferguson, S.S.; Sochaski, M.A.; Setzer, R.W.; Houck, K.A.; Strope, C.L.; Cantwell, K.; Judson, R.S.; LeCluyse, E.; Clewell, H.J., 3rd; Thomas, R.S.; Andersen, M.E. Incorporating High-Throughput Exposure Predictions with Dosimetry-Adjusted In Vitro Bioactivity to Inform Chemical Toxicity Testing. Toxicological sciences : an official journal of the Society of Toxicology; 2015

[9]Pearce, R.; Strope, C.; Setzer, W.; Sipes, N.; Wambaugh, J. httk: R Package for High-Throughput Toxicokinetics. Journal of Statistical Software; 2016

[10]Wetmore, B.A.; Allen, B.; Clewell, H.J., 3rd; Parker, T.; Wambaugh, J.F.; Almond, L.M.; Sochaski, M.A.; Thomas, R.S. Incorporating population variability and susceptible subpopulations into dosimetry for high-throughput toxicity testing. Toxicological sciences : an official journal of the Society of Toxicology. 142:210-24; 2014

[11]Wetmore, B.A.; Wambaugh, J.F.; Allen, B.; Ferguson, S.S.; Sochaski, M.A.; Setzer, R.W.; Houck, K.A.; Strope, C.L.; Cantwell, K.; Judson, R.S.; LeCluyse, E.; Clewell, H.J., 3rd; Thomas, R.S.; Andersen, M.E. Incorporating High-Throughput Exposure Predictions with Dosimetry-Adjusted In Vitro Bioactivity to Inform Chemical Toxicity Testing. Toxicological sciences : an official journal of the Society of Toxicology; 2015

[12]Israili, Z.H.; Dayton, P.G. Human alpha-1-glycoprotein and its interactions with drugs. Drug Metab Rev. 33:161-235; 2001

[13]Routledge, P.A. The plasma protein binding of basic drugs. British journal of clinical pharmacology. 22:499-506; 1986

[14]Yasuda, S.U.; Zhang, L.; Huang, S.M. The role of ethnicity in variability in response to drugs: focus on clinical pharmacology studies. Clin Pharmacol Ther. 84:417-23; 2008

[15]Howgate, E.M.; Rowland Yeo, K.; Proctor, N.J.; Tucker, G.T.; Rostami-Hodjegan, A. Prediction of in vivo drug clearance from in vitro data. I: impact of inter-individual variability. Xenobiotica; the fate of foreign compounds in biological systems. 36:473-97; 2006