Current State-of-the-Science use of QSURs to support exposure and risk estimation

EPA's Systematic Empirical Evaluation of Models (SEEM) Framework

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The views expressed in this presentation are those of the author and do not necessarily reflect the views or policies of the U.S. EPA

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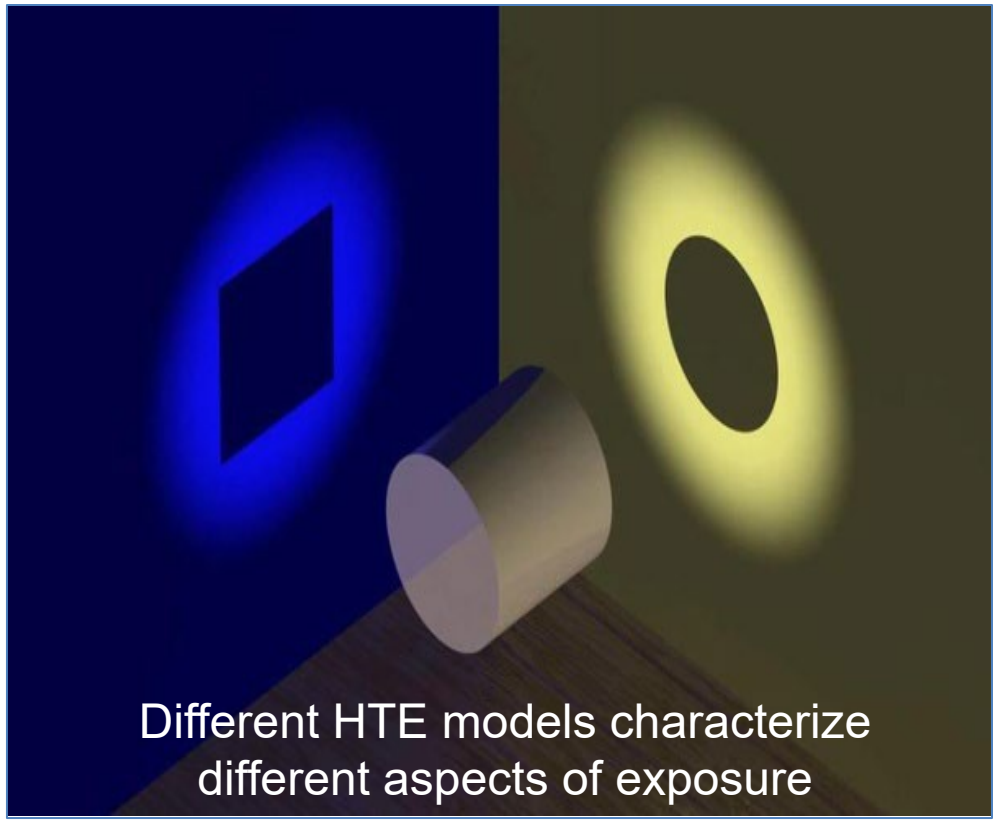
High Throughput Exposure (HTE) Models

- Various HTE models provide the predictions for different aspects (pathways, chemistries) of exposure
  - Each model incorporates different assumptions
  - No one predictor is expected to the whole picture
- Monitoring data can indicate “reference” exposures
- At EPA we build a probabilistic, consensus prediction of daily intake rate (mg/kg BW/day) using multiple HTE models and other predictors
  - **Properly combining the models relies on prediction of chemical use from structure**



High Throughput Exposure (HTE) Models

- To be considered an HTE model, a model must:
  1. Be applicable to and capable of handling many chemicals with minimal descriptive information
  2. Cover one or more relevant exposure routes (for example, inhalation, food ingestion, mouthing, and dermal contact) and sources (for example, industrial and residential use), accounting for the influential parameters relevant for the considered pathways
  3. Allow for integration with models for other pathways
  4. Be scientifically plausible, respecting mass-balance principles and accounting for competing processes (for example, volatilization versus dermal uptake)
  5. Allow for the assessment of interindividual and intraindividual variation in exposure and impact of such variation on acute and chronic doses as the required input data become available
  6. Be amenable to integration within statistical frameworks that quantify uncertainty for propagation into risk evaluations
  7. Remain parsimonious, that is, no more complicated than necessary to describe the data

Huang and Jolliet, 2016 and Wambaugh et al., 2019

Knowledge of Exposure Pathways Limits High Throughput Exposure Models

"…The assumption that 100% of [quantity emitted, applied, or ingested] is being applied to each individual use scenario is a very conservative assumption for many compound / use scenario pairs."

Environmental Science & Technology

Article

pubs.acs.org/est

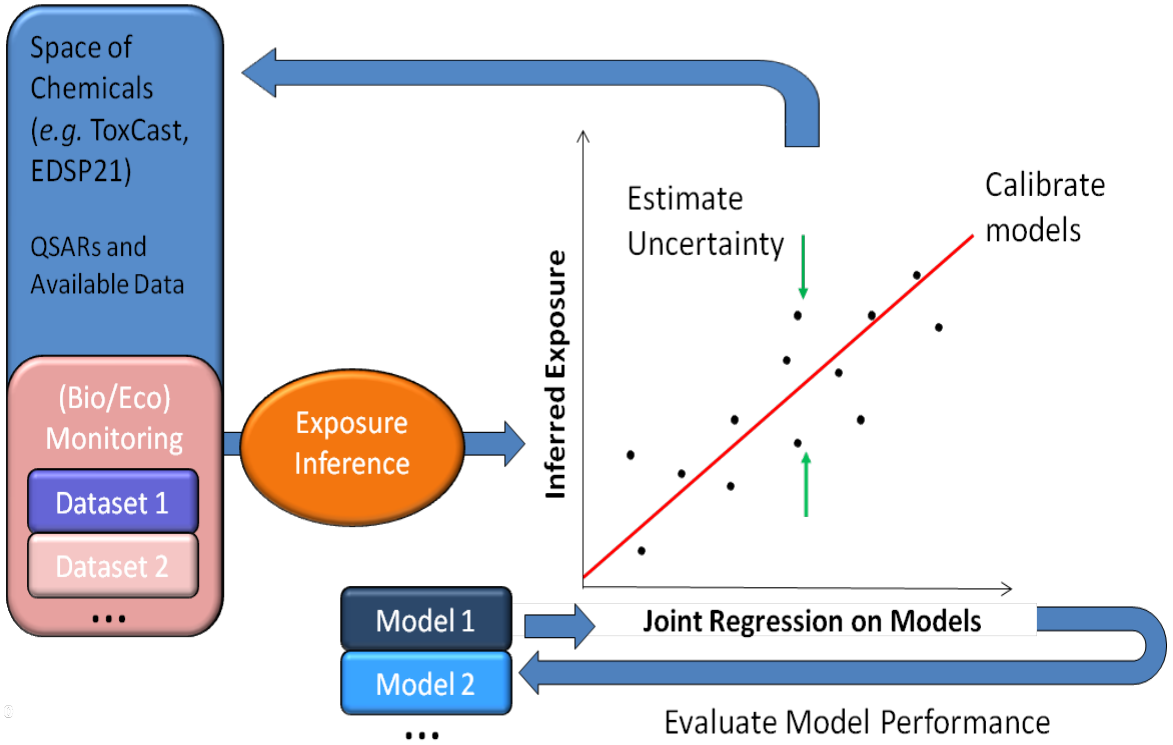
Environ. Sci. Technol. 2015, 49, 11, 6760−6771

Risk-Based High-Throughput Chemical Screening and Prioritization using Exposure Models and in Vitro Bioactivity Assays

Hyeong-Moo Shin,[*,†] Alexi Ernstoff,[‡,§] Jon A. Arnot,[∥,⊥,#] Barbara A. Wetmore,[▽] Susan A. Csiszar,[§] Peter Fantke,[‡] Xianming Zhang,[○] Thomas E. McKone,[◆,¶] Olivier Jolliet,[§] and Deborah H. Bennett[†]

Consensus Exposure Predictions with the SEEM Framework

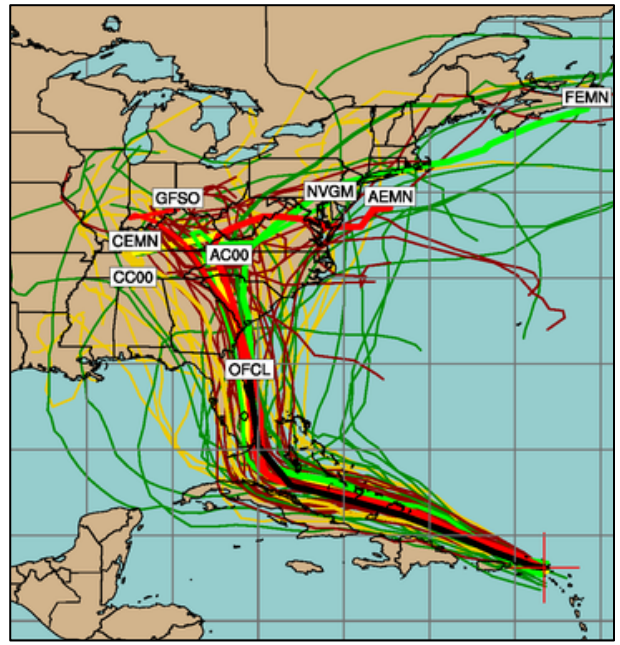
- Different exposure models incorporate **knowledge**, **assumptions**, and **data**
- We incorporate multiple models into consensus predictions for 1000s of chemicals within the **Systematic Empirical Evaluation of Models (SEEM)** (Wambaugh et al., 2013, 2014)



Wambaugh et al., 2019

- Evaluation is similar to a sensitivity analysis: What models are working? What data are most needed?

Hurricane Path Prediction is an Example of Integrating Multiple Models



Evaluating Exposure Models with the SEEM Framework

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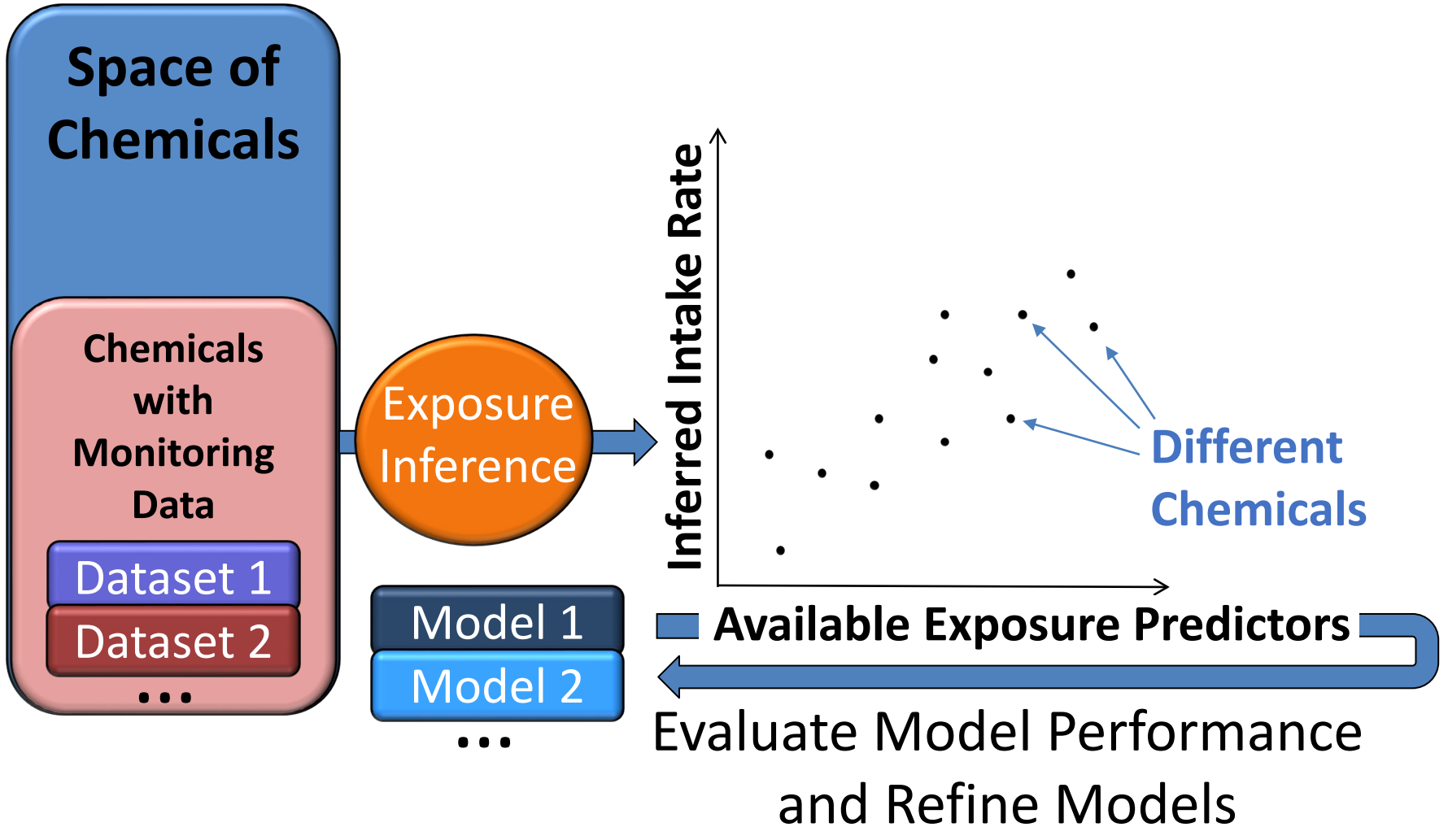

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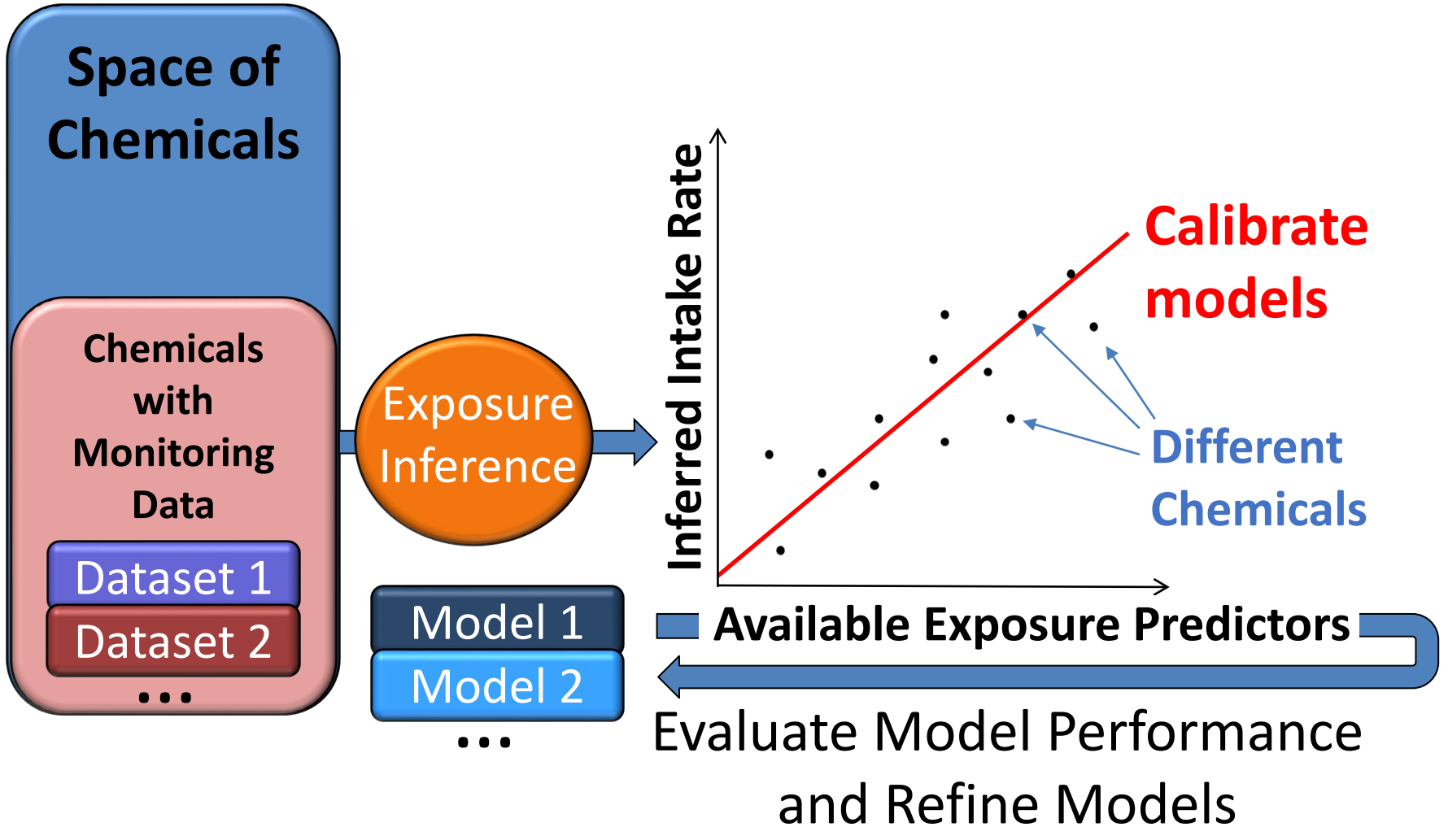

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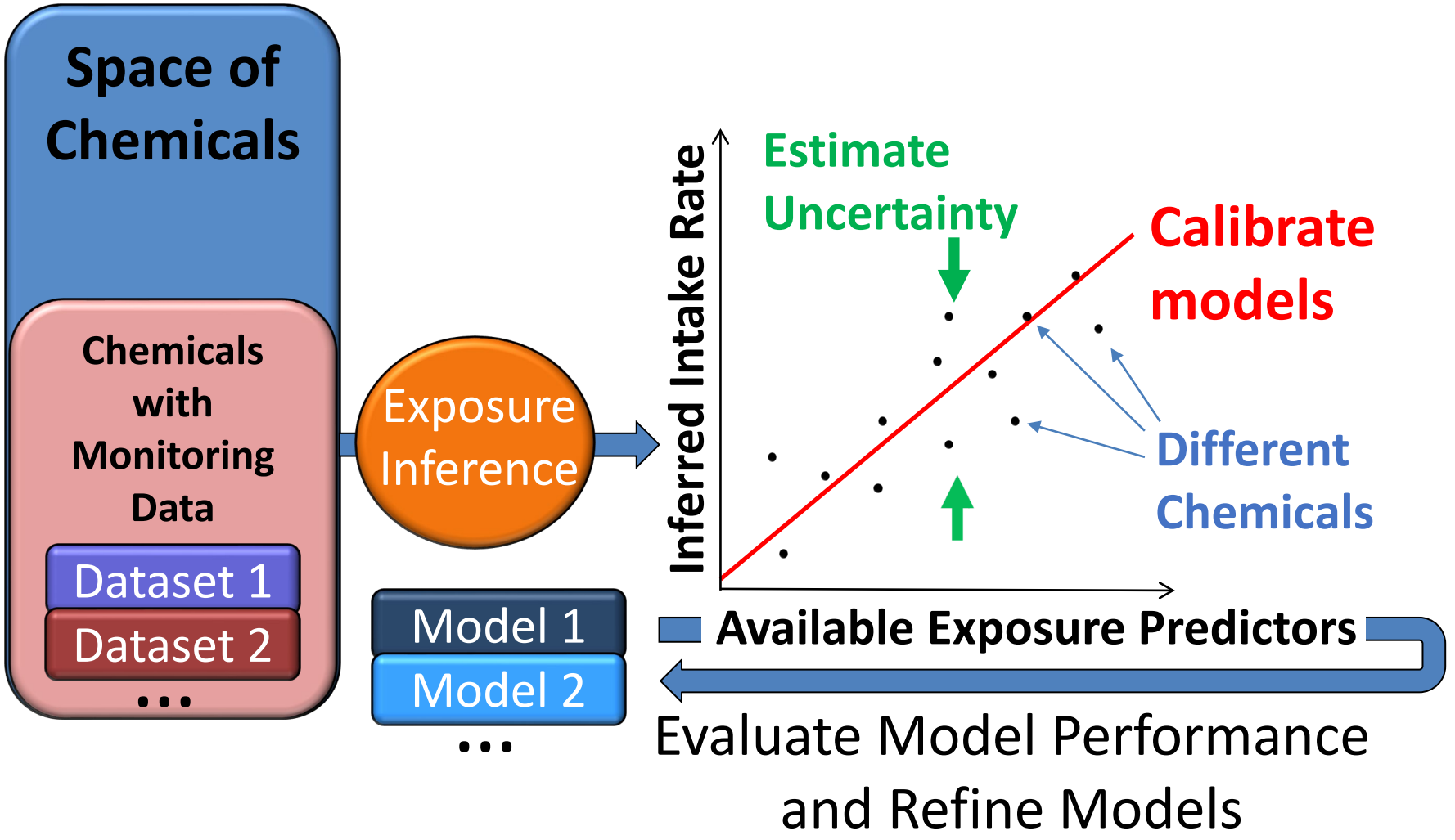

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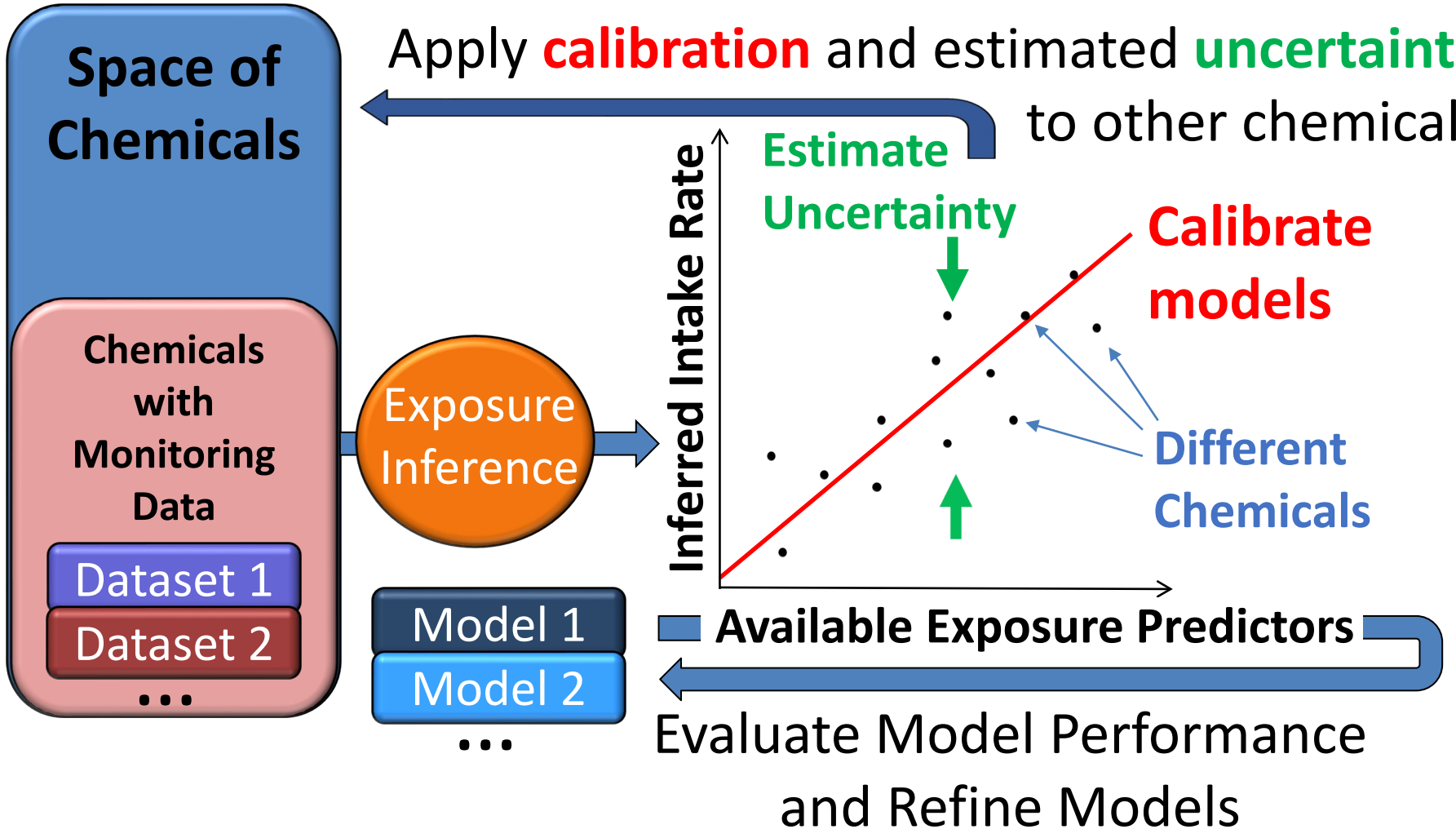
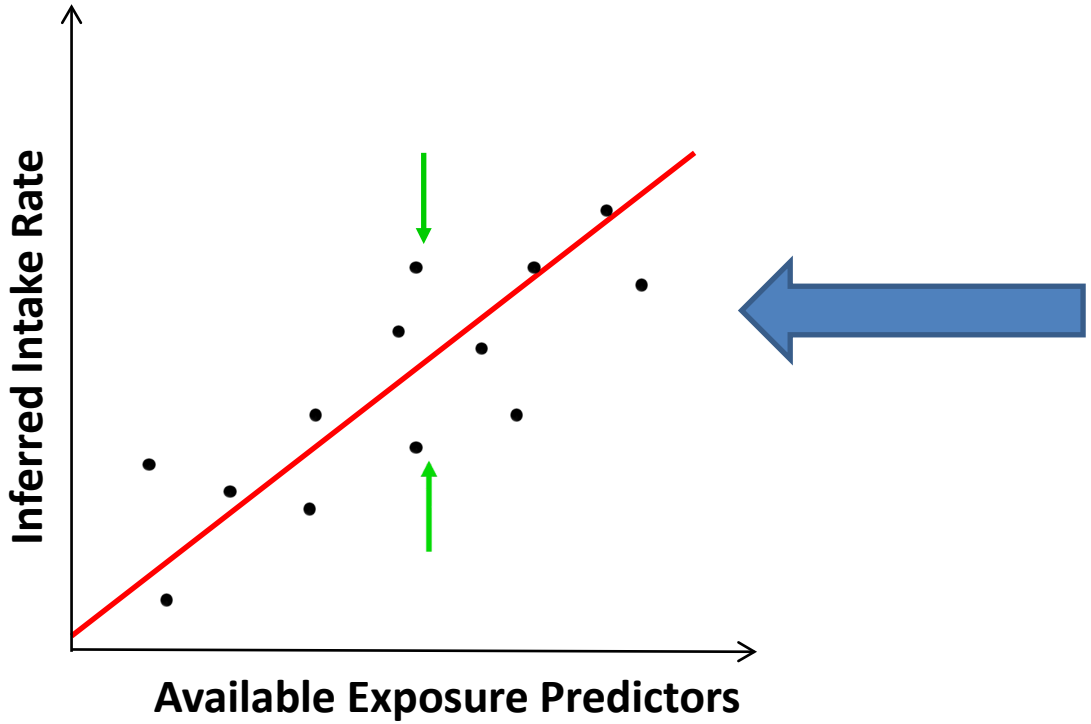


Wambaugh et al., 2019

SEEM is a Linear Regression

Multiple regression models:

$$\text{Log(Parent Exposure)} = a + m * \log(\text{Model Prediction}) + b * \text{Near Field} + \varepsilon$$

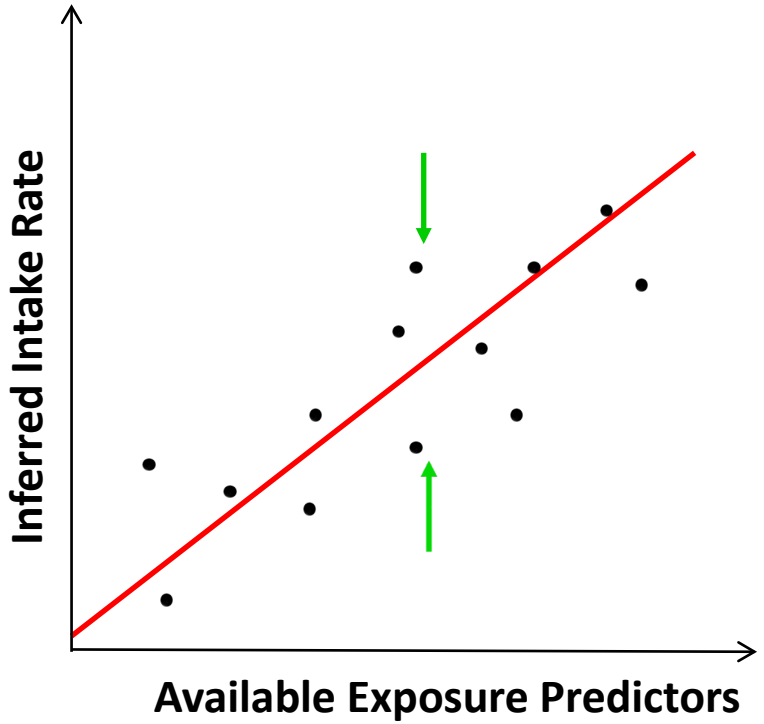


$\varepsilon \sim N(0, \sigma^2)$
Residual error, unexplained by the regression model

SEEM is a Linear Regression

Multiple regression models:

Log(Parent Exposure) = a + m * log(Model Prediction) + b* Near Field + ε



Not all models have predictions for all chemicals

- We can run SHEDS-HT (Isaacs et al., 2014) for ~2500 chemicals

What do we do for the rest?

- Assign the average value?
- Zero?

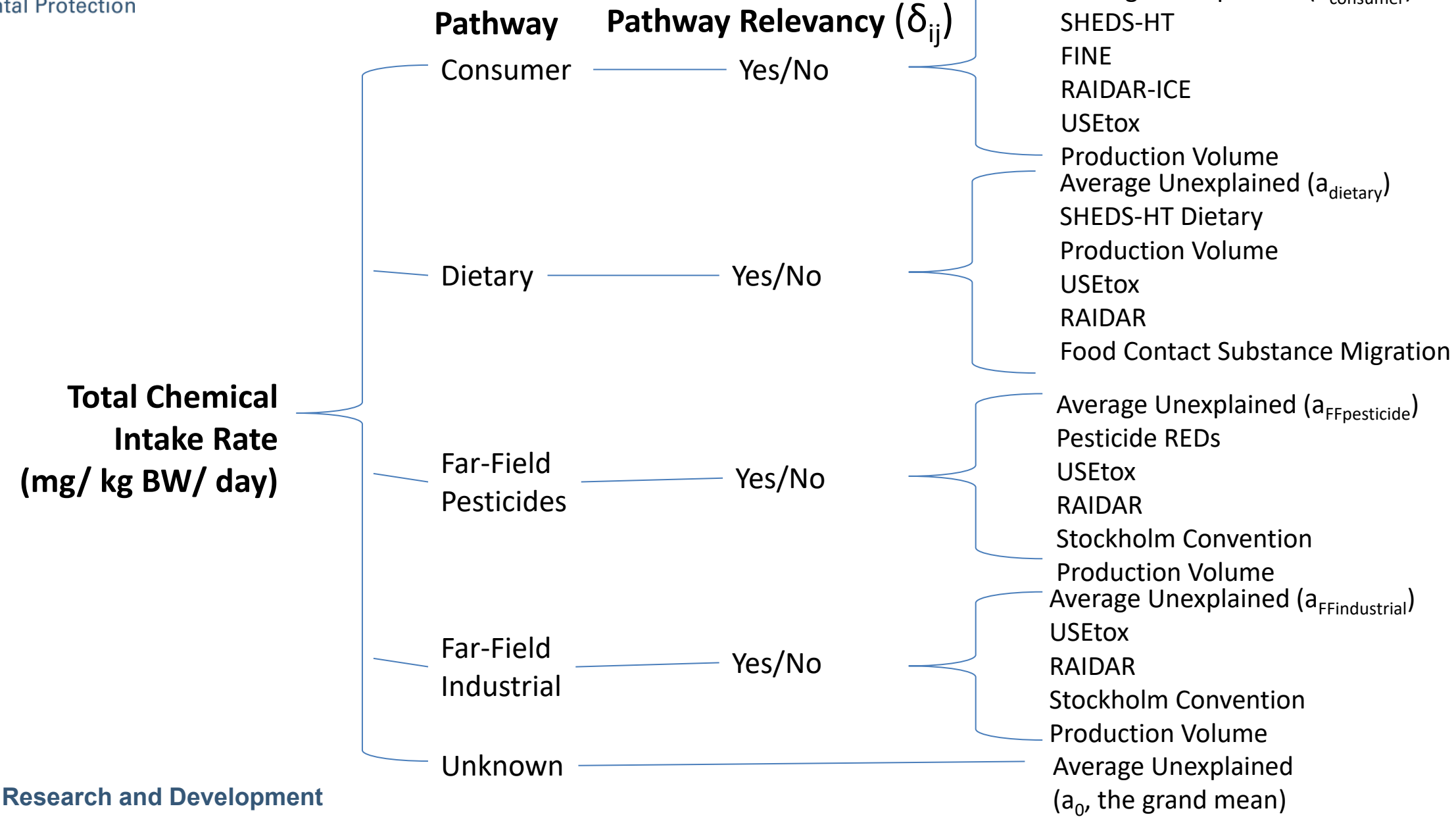
Ring et al., 2019

Collaboration on High Throughput Exposure Predictions

Jon Arnot, Deborah H. Bennett, Peter P. Egeghy, Peter Fantke, Lei Huang, Kristin K. Isaacs, Olivier Jolliet, Hyeong-Moo Shin, Katherine A. Phillips, Caroline Ring, R. Woodrow Setzer, John F. Wambaugh, Johnny Westgate

Predictor	Reference(s)	Chemicals Predicted	Pathways
EPA Inventory Update Reporting and Chemical Data Reporting (CDR) (2015)	US EPA (2018)	7856	All
Stockholm Convention of Banned Persistent Organic Pollutants (2017)	Lallas (2001)	248	Far-Field Industrial and Pesticide
EPA Pesticide Reregistration Eligibility Documents (REDs) Exposure Assessments (Through 2015)	Wetmore et al. (2012, 2015)	239	Far-Field Pesticide
United Nations Environment Program and Society for Environmental Toxicology and Chemistry toxicity model (USEtox) Industrial Scenario (2.0)	Rosenbaum et al. (2008)	8167	Far-Field Industrial
USEtox Pesticide Scenario (2.0)	Fantke et al. (2011, 2012, 2016)	940	Far-Field Pesticide
Risk Assessment IDentification And Ranking (RAIDAR) Far-Field (2.02)	Arnot et al. (2008)	8167	Far-Field Pesticide
EPA Stochastic Human Exposure Dose Simulator High Throughput (SHEDS-HT) Near-Field Direct (2017)	Isaacs (2017)	7511	Far-Field Industrial and Pesticide
SHEDS-HT Near-field Indirect (2017)	Isaacs (2017)	1119	Residential
Fugacity-based INdoor Exposure (FINE) (2017)	Bennett et al. (2004), Shin et al. (2012)	645	Residential
RAIDAR-ICE Near-Field (0.803)	Arnot et al., (2014), Zhang et al. (2014)	1221	Residential
USEtox Residential Scenario (2.0)	Jolliet et al. (2015), Huang et al. (2016,2017)	615	Residential
USEtox Dietary Scenario (2.0)	Jolliet et al. (2015), Huang et al. (2016), Ernstoff et al. (2017)	8167	Dietary

SEEM3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Pathway
Chemical-Specific Pathway Relevancy (δ_{ij})
Predictors
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Yes/No
Average Unexplained ($a_{consumer}$)
SHEDS-HT
FINE
RAIDAR-ICE
USEtox
Production Volume
Dietary
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Production Volume
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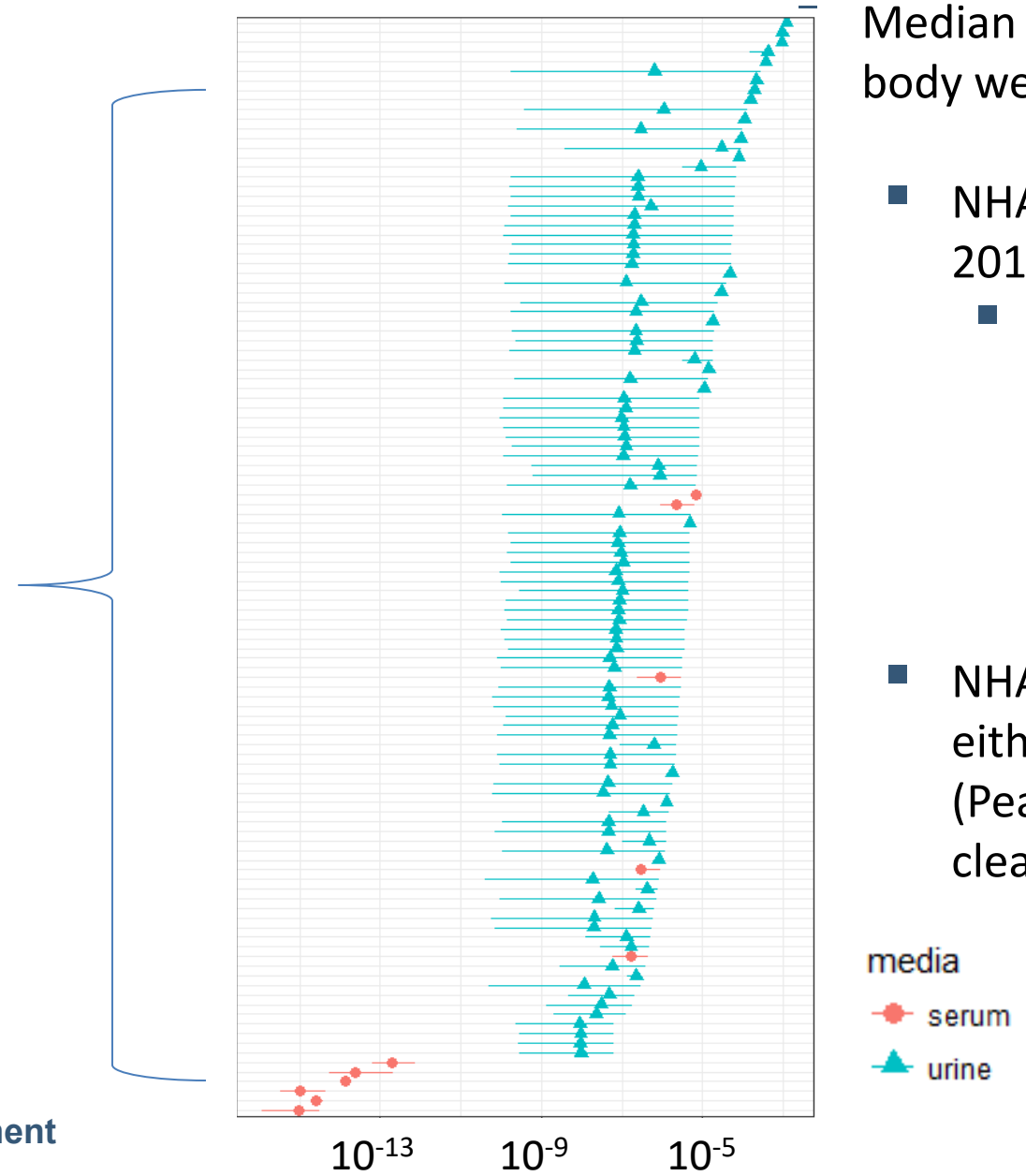
Average Unexplained (a_0, the grand mean)

Evaluation Data

Intake Rates Inferred from NHANES

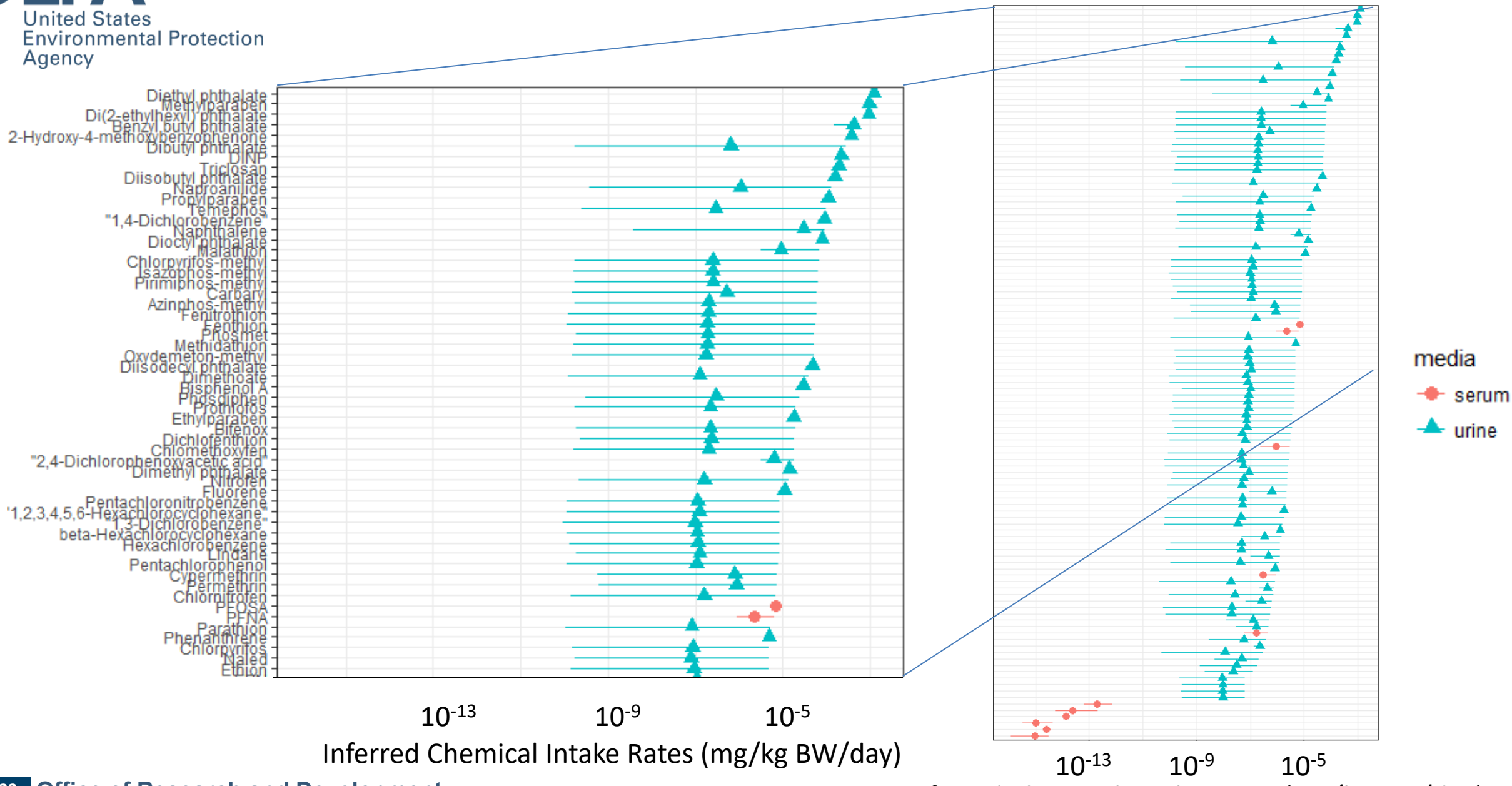


Median chemical intake rates (mg / kg body weight /day) were inferred from:

- NHANES urine (Wambaugh et al, 2014, Ring et al. 2017)
  - ORD provides its Bayesian tool for inferring exposure from biomonitoring (Stanfield et al., 2022) publicly via R package "bayesmarker" available on GitHub
- NHANES serum/blood either using either HTTK-predicted clearance (Pearce et al., 2017) or literature clearance estimates for chemicals suited to HTTK

Ring et al., 2019

Reverse Dosimetry (Tan et al., 2006)



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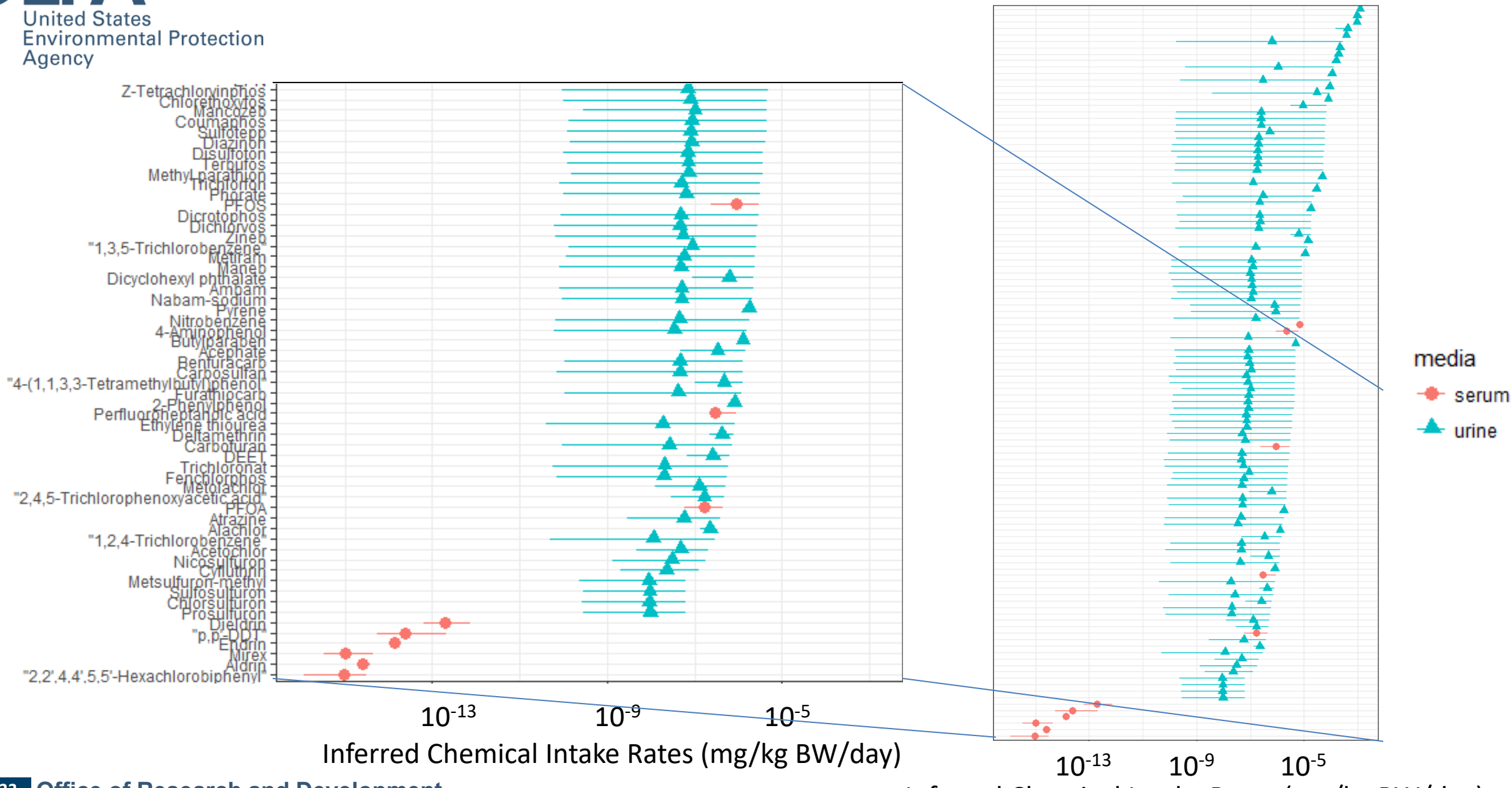
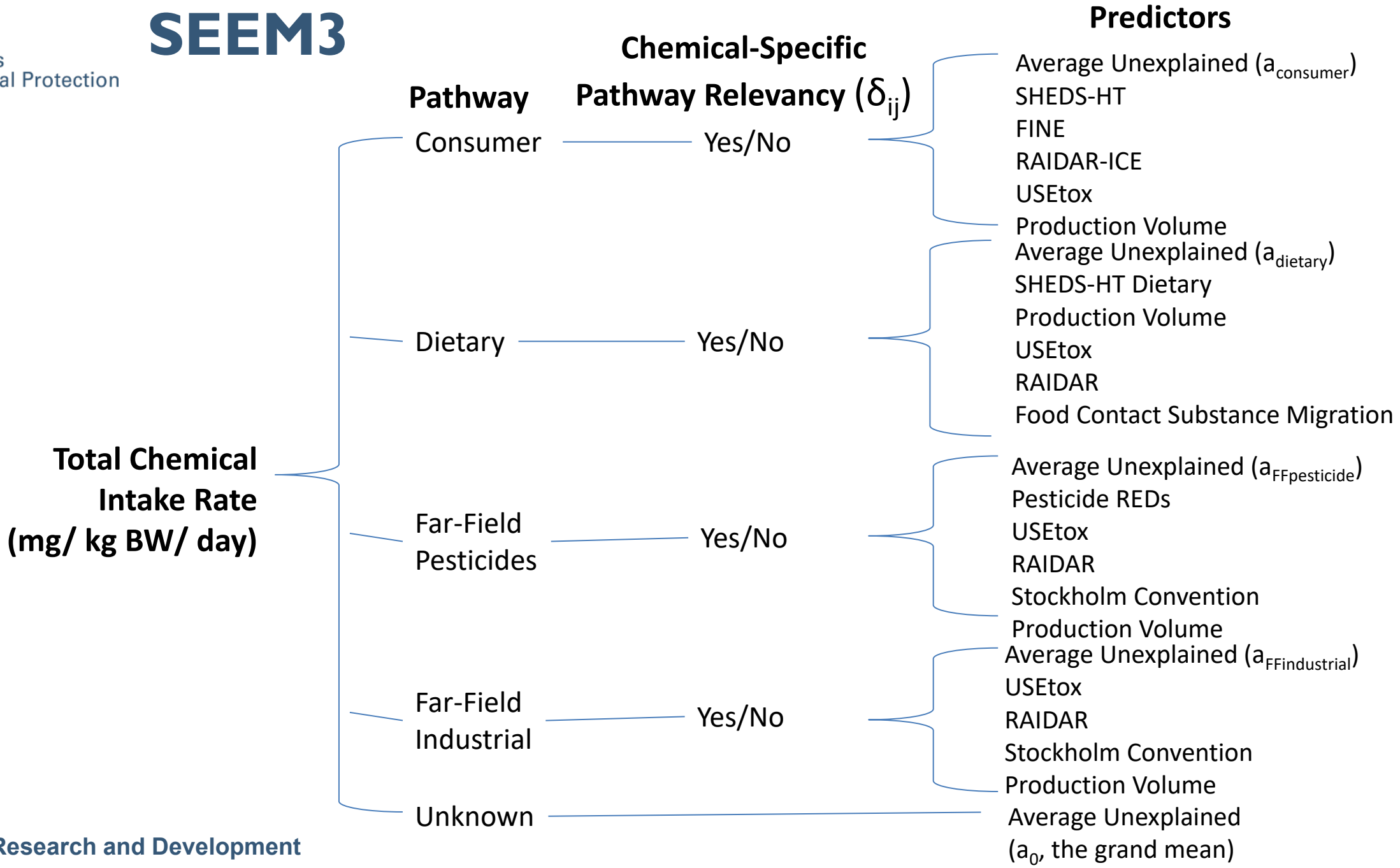
United States Environmental Protection Agency



SEEM3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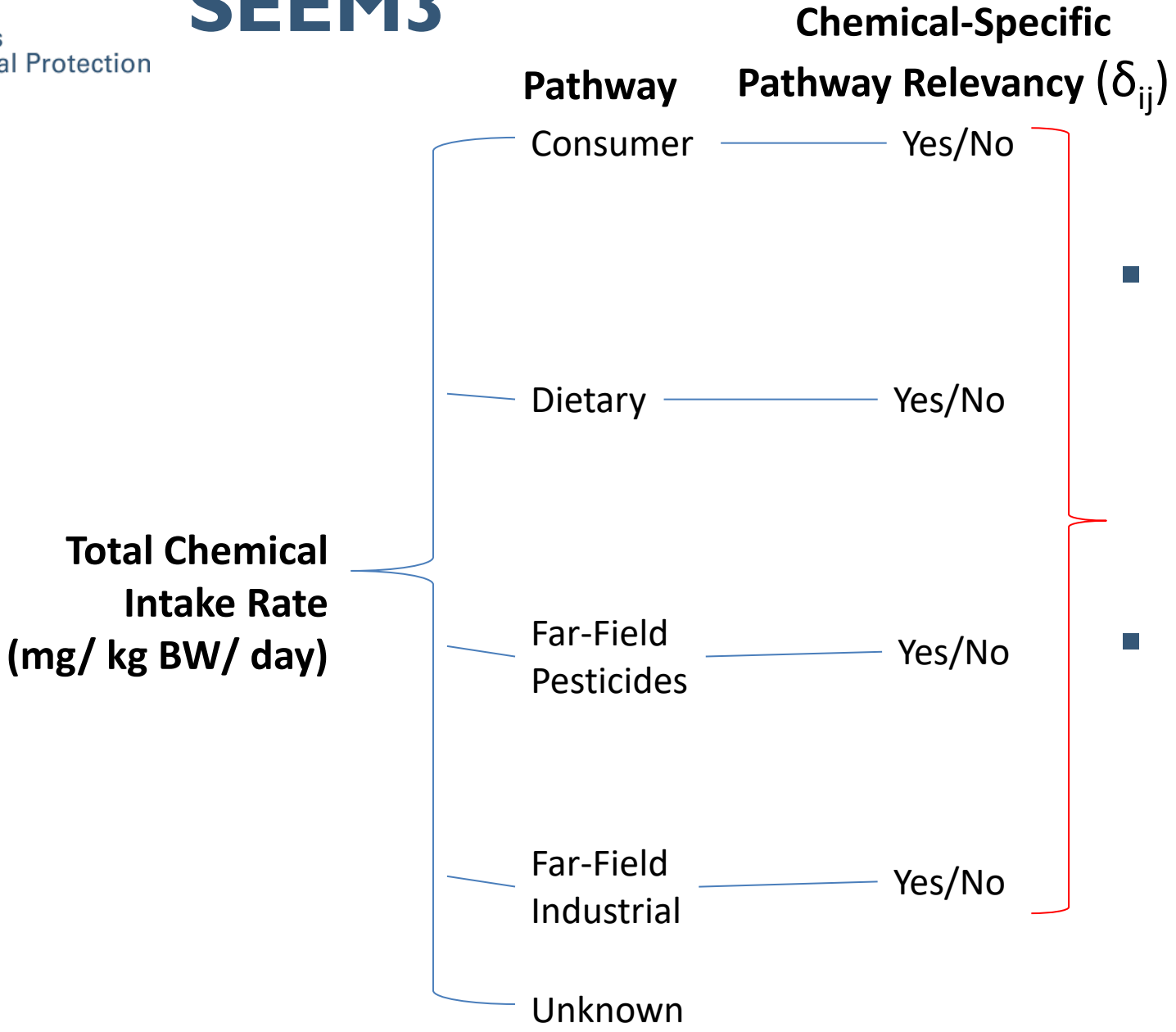
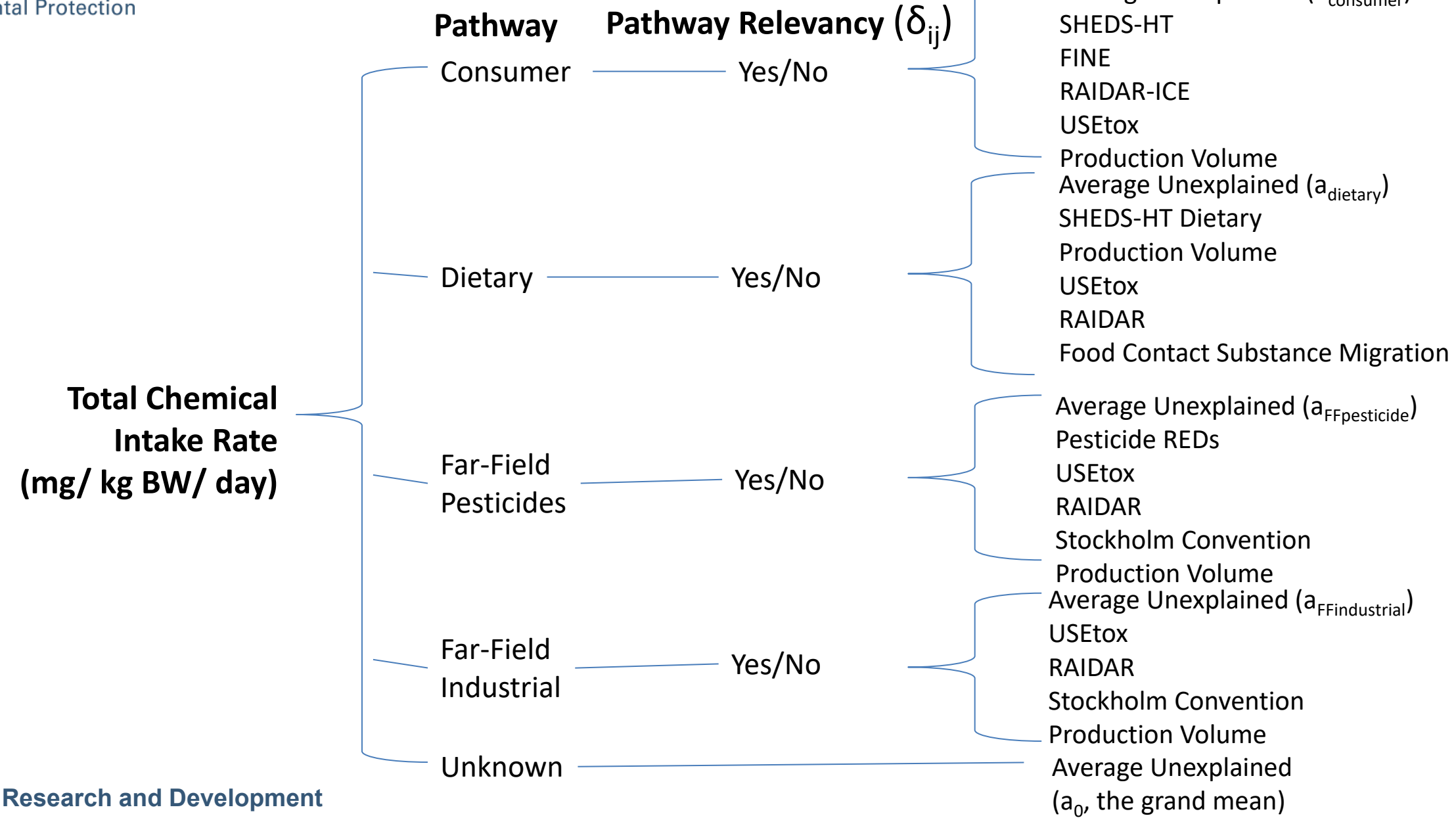


- Likelihood of exposure via various source-based pathways is predicted from production volume, OPERA physico-chemical properties and ToxPrint structure descriptors
- Machine learning (Random Forest) – generates a chemical specific probability of exposure by that pathway (which is then used as a Bayesian prior)

SEEM3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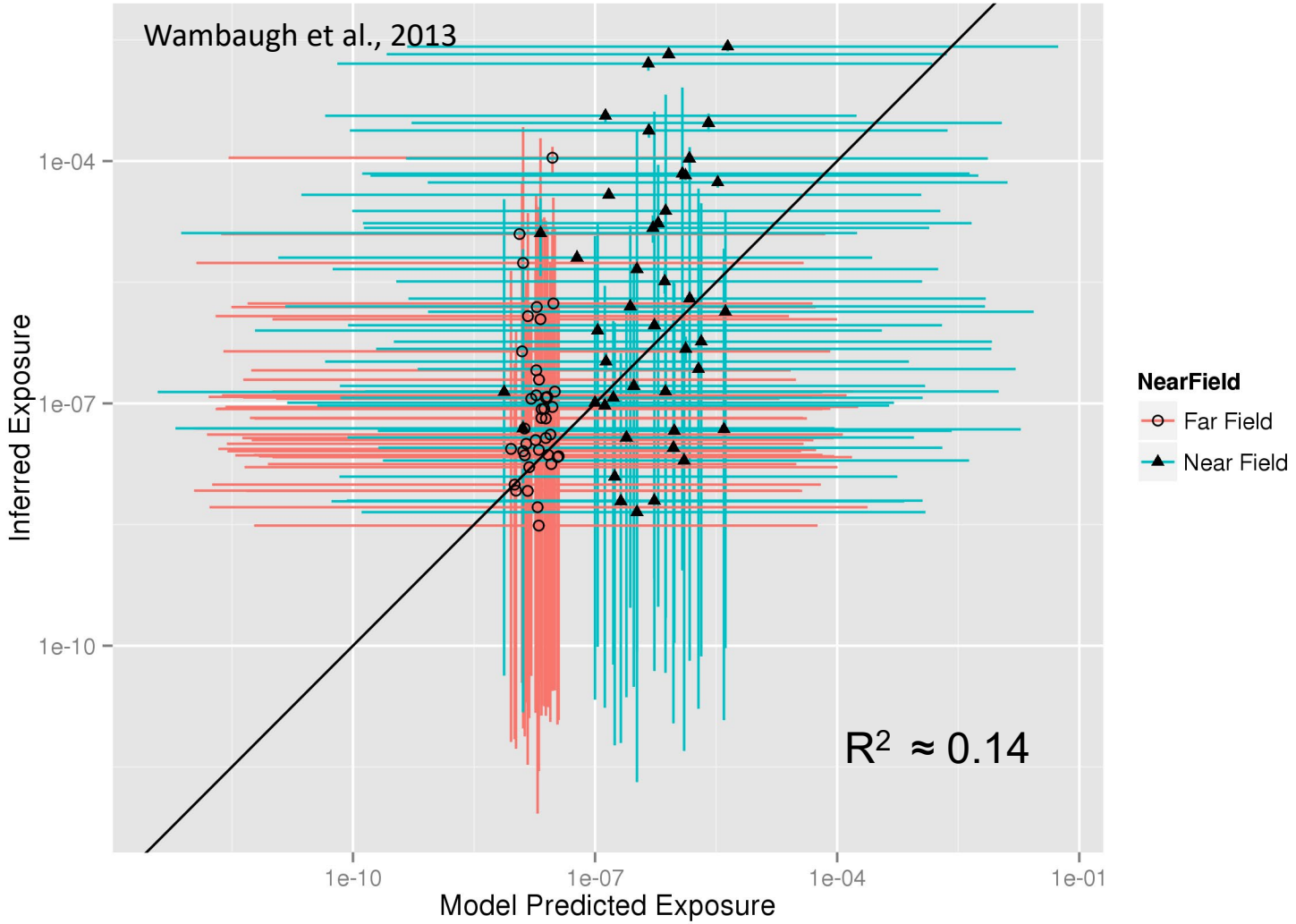
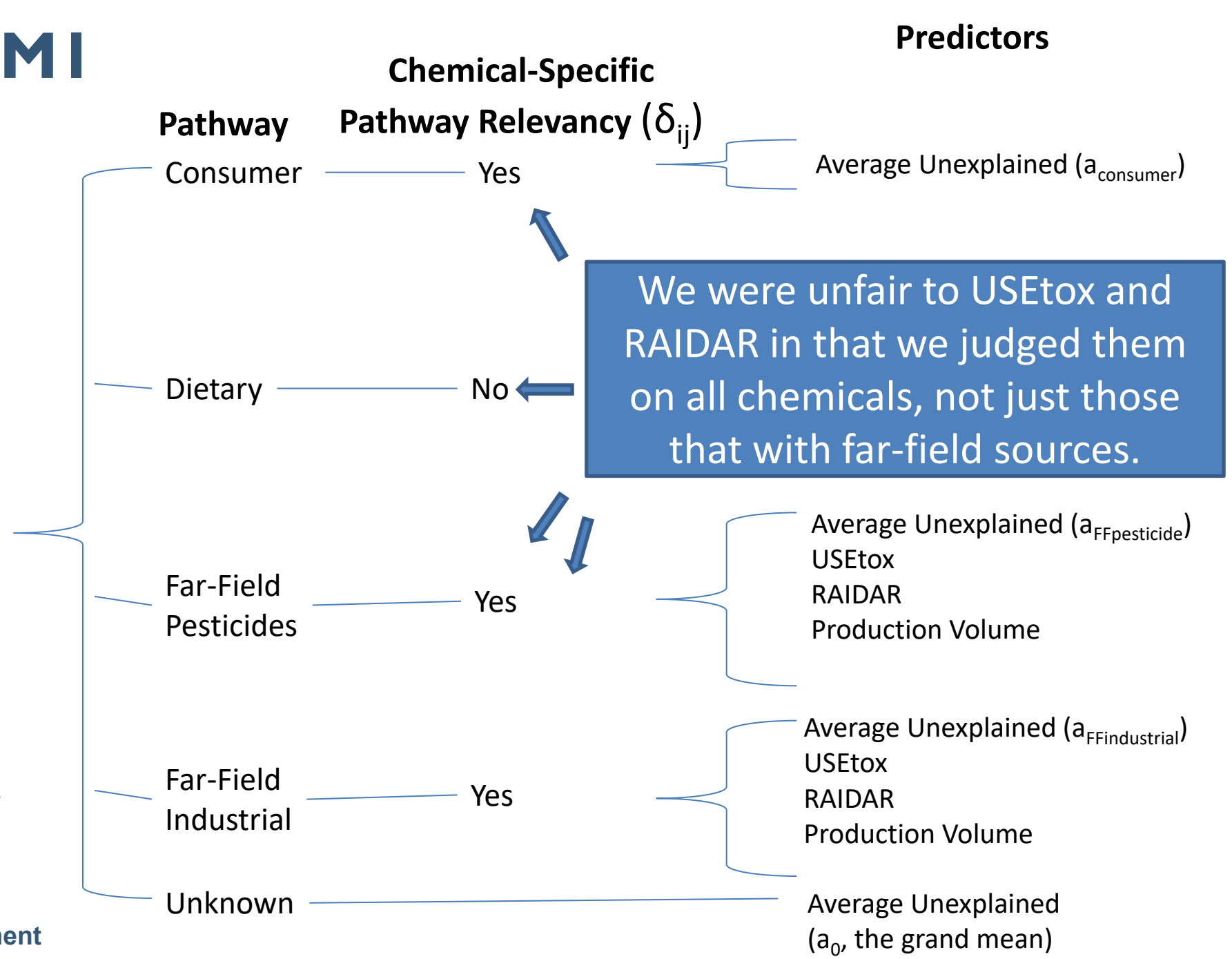
First Generation SEEM



- Those chemicals with "near-field" – proximate, in the home, sources of exposure – had much higher rates of exposure than those with sources outside the home (Wallace et al., 1986)
- The only available high throughput exposure models in 2013 were for far-field sources

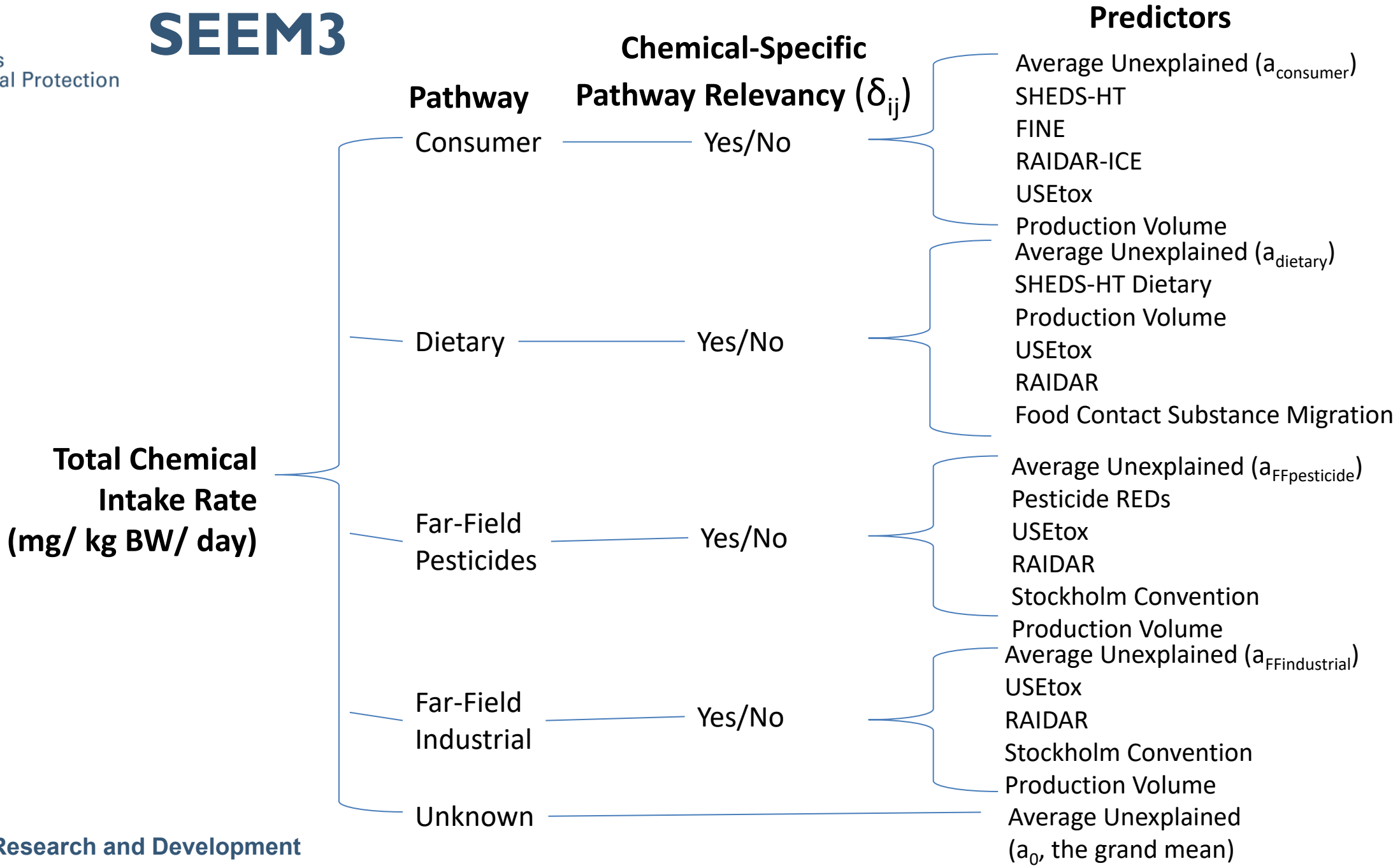
EPA United States Environmental Protection Agency

SEEM I



The 3rd Gen. SEEM framework incorporates the previous models

SEEM3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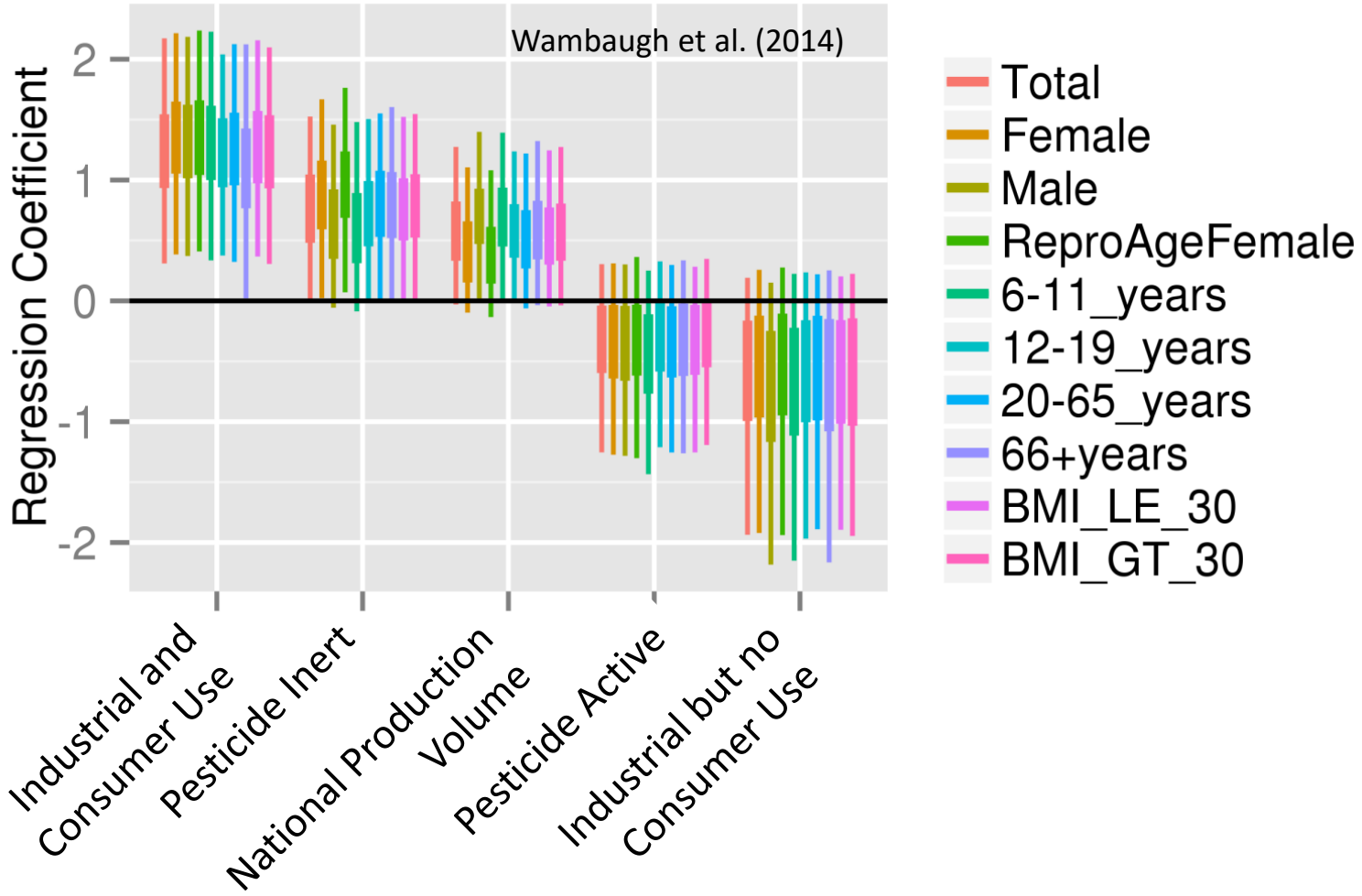
Heuristics of Exposure



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

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

- Industrial and Consumer use
- Pesticide Inert
- Pesticide Active
- Industrial but no Consumer use
- Production Volume

SEEM2

Predictors

Chemical-Specific Pathway Relevancy (δ_{ij})

Pathway

Total Chemical Intake Rate (mg/ kg BW/ day)

Consumer — Yes/No — Average Unexplained ($a_{consumer}$)

ACToR UseDB gave us chemical pathway predictions (Yes/No) and we estimated the average exposure for each pathway

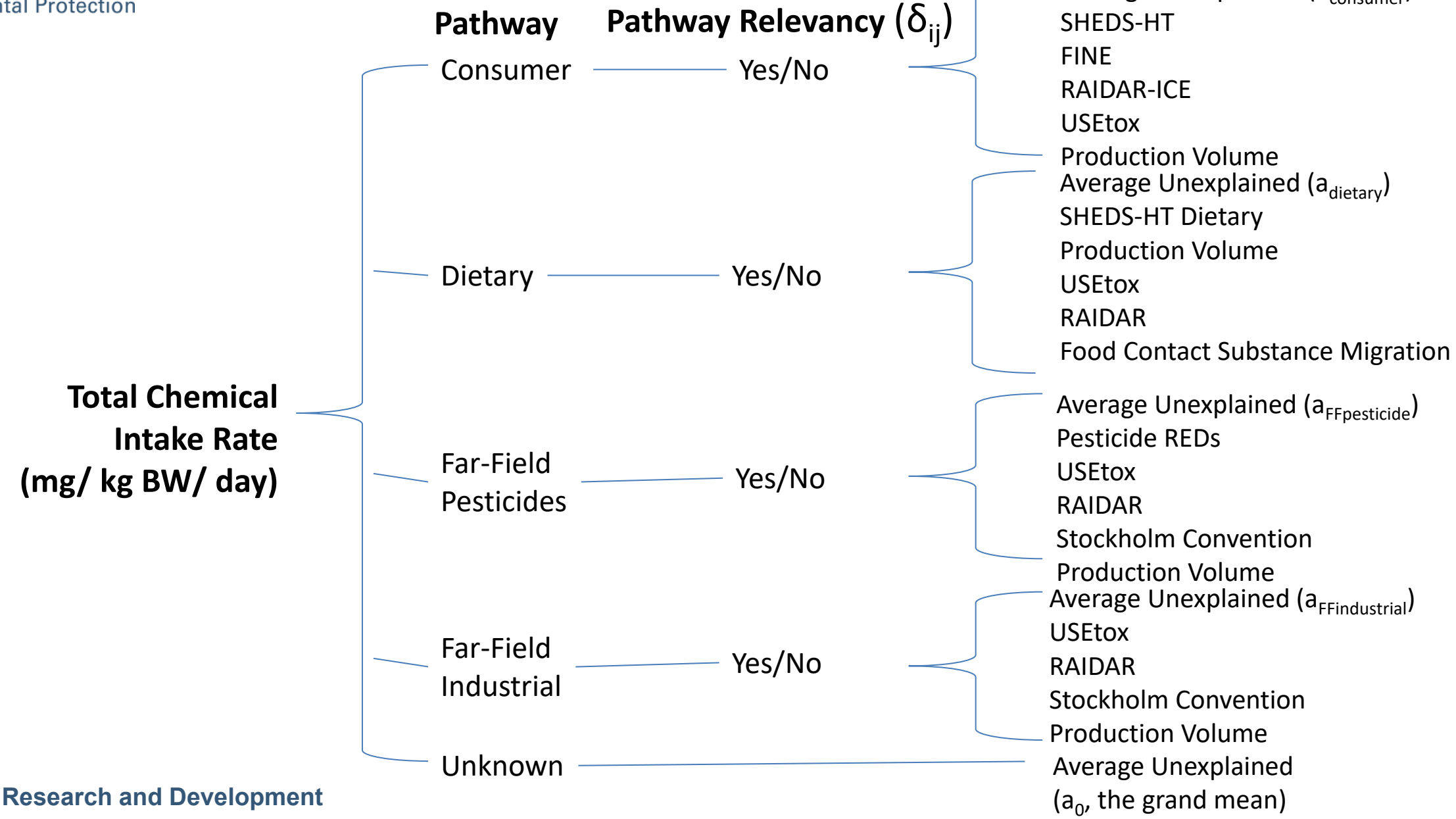
Far-Field Pesticides — Yes/No — Average Unexplained ($a_{FFpesticide}$)

Far-Field Industrial — Yes/No — Average Unexplained ($a_{FFindustrial}$)

Unknown — Average Unexplained (a_0, the grand mean)

The 3rd Gen. SEEM framework incorporates the previous models

SEEM3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SEEM3

- We have many models/predictors, but we have many more chemicals (CompTox Chemicals Dashboard has > 1,000,000 as of November 2022)
  - What do we do for chemicals without model predictions?
- One trick from quantitative structure-activity relationship (QSAR) modeling is to use the average value when a prediction is missing
  - But should every chemical be treated as an average consumer product chemical AND average pesticide AND average industrial compound?
  - *This is the Shin et al. (2015) problem!*
- "Pathway models" for chemical use scenario:
  - Predict whether a chemical gets used for a certain exposure scenario
  - Only assign average values for the models relevant to that pathway

Predictors

- Average Unexplained ($a_{consumer}$)
- SHEDS-HT
- FINE
- RAIDAR-ICE
- USEtox
- Production Volume

- Average Unexplained ($a_{dietary}$)
- SHEDS-HT Dietary
- Production Volume
- USEtox
- RAIDAR
- Food Contact Substance Migration

- Average Unexplained ($a_{FFpesticide}$)
- Pesticide REDs
- USEtox
- RAIDAR
- Stockholm Convention
- Production Volume

- Average Unexplained ($a_{FFindustrial}$)
- USEtox
- RAIDAR
- Stockholm Convention
- Production Volume

- Average Unexplained (a_0, the grand mean)

QSUR's for Exposure Pathway

Ring et al. (2019) used the method of Random Forests to relate chemical structure and properties to exposure pathway

	NHANES Chemicals	Positives	Negatives	OOB Error Rate	Positives Error Rate	Balanced Accuracy	Sources of Positives	Sources of Negatives
Dietary	**24**	2523	8865	27	32	73	FDA CEDI, ExpoCast, CPDat (Food, Food Additive, Food Contact), NHANES Curation	Pharmapendium, CPDat (non-food), NHANES Curation
Near-Field	**49**	1622	567	26	24	74	CPDat (consumer_use, building_material), ExpoCast, NHANES Curation	CPDat (Agricultural, Industrial), FDA CEDI, NHANES Curation
Far-Field Pesticide	**94**	1480	6522	21	36	80	REDs, Swiss Pesticides, Stockholm Convention, CPDat (Pesticide), NHANES Curation	Pharmapendium, Industrial Positives, NHANES Curation
Far Field Industrial	**42**	5089	2913	19	16	81	CDR HPV, USGS Water Occurrence, NORMAN PFAS, Stockholm Convention, CPDat (Industrial, Industrial_Fluid), NHANES Curation	Pharmapendium, Pesticide Positives, NHANES Curation

Ring et al., 2019

SEEM3

Total Chemical Intake Rate (mg/ kg BW/ day)

Pathway	Chemical-Specific Pathway Relevancy (δ_{ij})	Predictors
Consumer	Yes/No	Average Unexplained ($a_{consumer}$) SHEDS-HT FINE RAIDAR-ICE USEtox Production Volume

Bayesian analysis via Markov Chain Monte Carlo assigns each chemical either a "Yes" or "No" according to predicted probability

If the pathway is no for a chemical, nothing is added to the intake rate

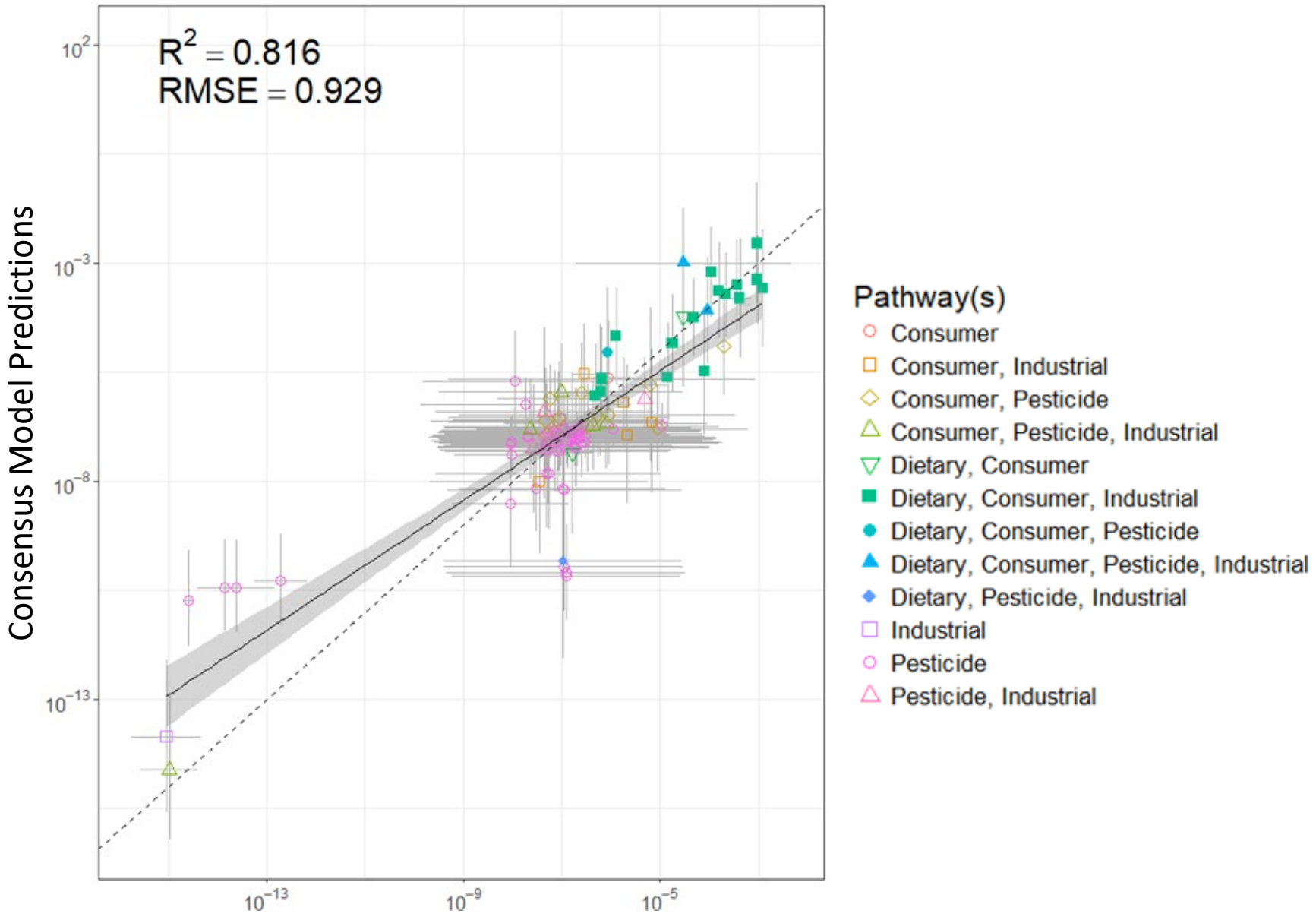
Linear regression is used to estimate the average unexplained exposure (intercept) and loadings (slopes, or predictive ability) for each model

Model predictions are centered at zero – **if there is no prediction for a chemical, the average value "zero" is added**

Pathway-Based Consensus Modeling of NHANES

United States Environmental Protection Agency

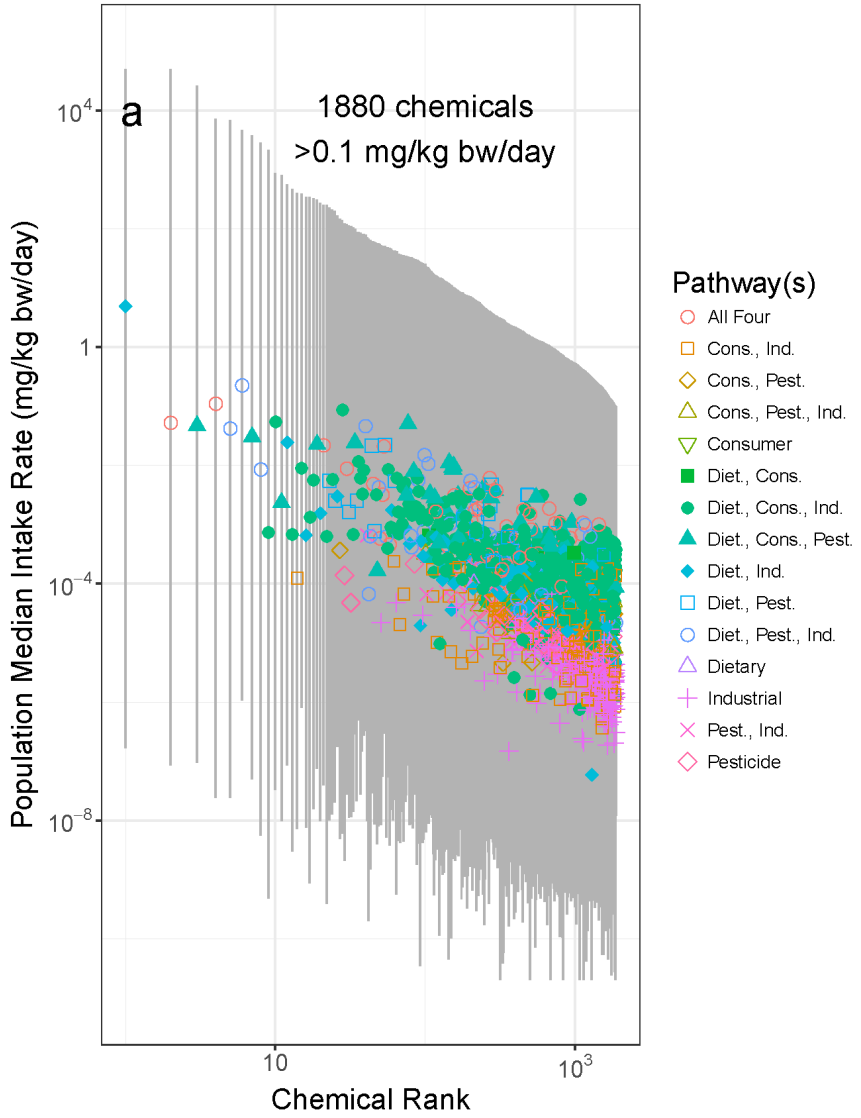
- Machine learning models were built for each of four exposure pathways
- Pathway predictions can be used for large chemical libraries
- Use prediction (and accuracy of prediction) as a prior for Bayesian analysis
- Each chemical may have exposure by multiple pathways



Ring et al., 2019

Consensus Modeling of Median Chemical Intake

- We extrapolate to predict relevant pathway(s), median intake rate, and credible interval for each of 479,926 chemicals
- Of 687,359 chemicals evaluated, 30% have less than a 50% probability for exposure via any of the four pathways and are considered outside the “domain of applicability”
- This approach identifies 1,880 chemicals for which the median population intake rates may exceed 0.1 mg/kg bodyweight/day.



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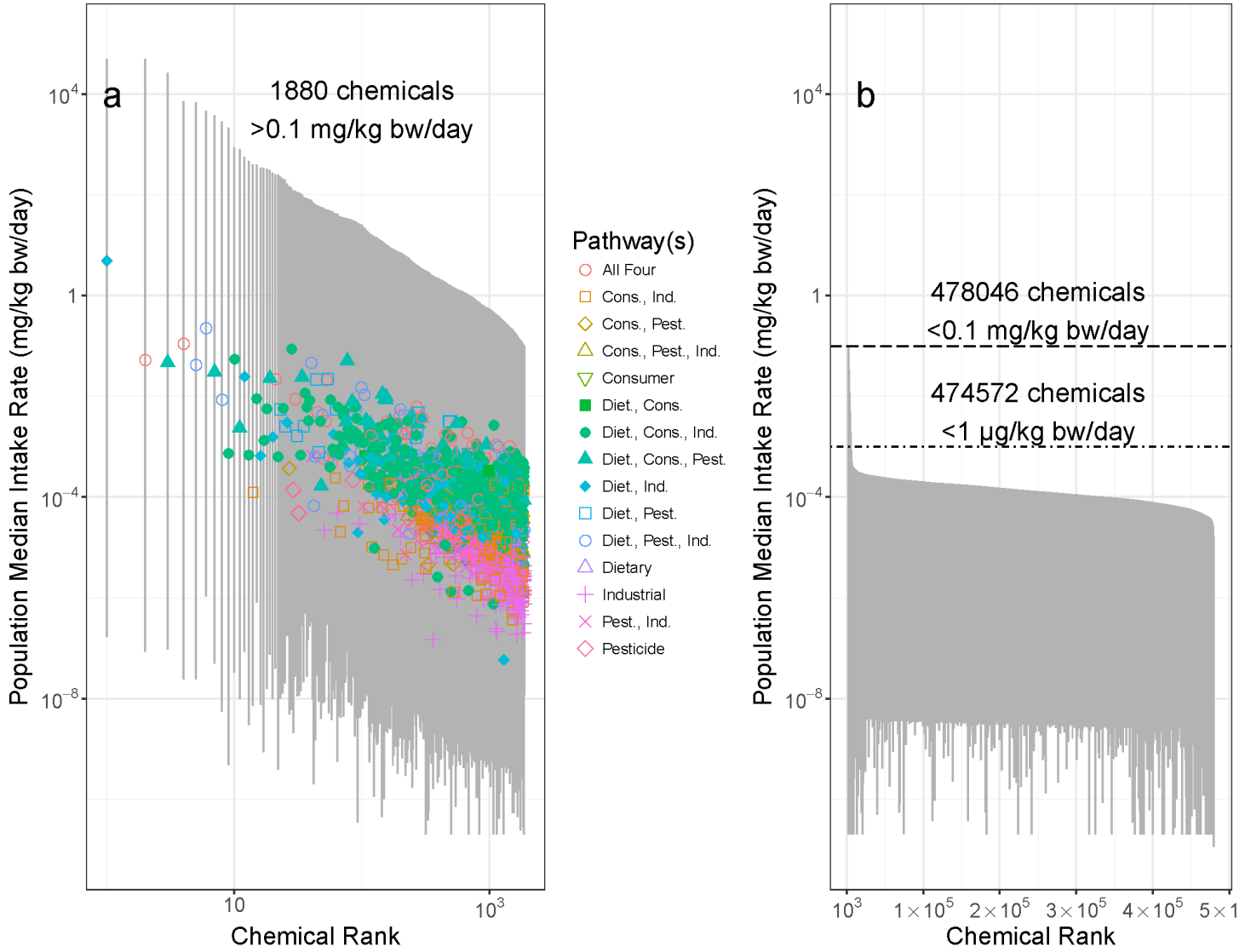
- This approach identifies 1,880 chemicals for which the median population intake rates may exceed 0.1 mg/kg bodyweight/day.
- There is 95% confidence that the median intake rate is below 1 µg/kg BW/day for 474,572 compounds.

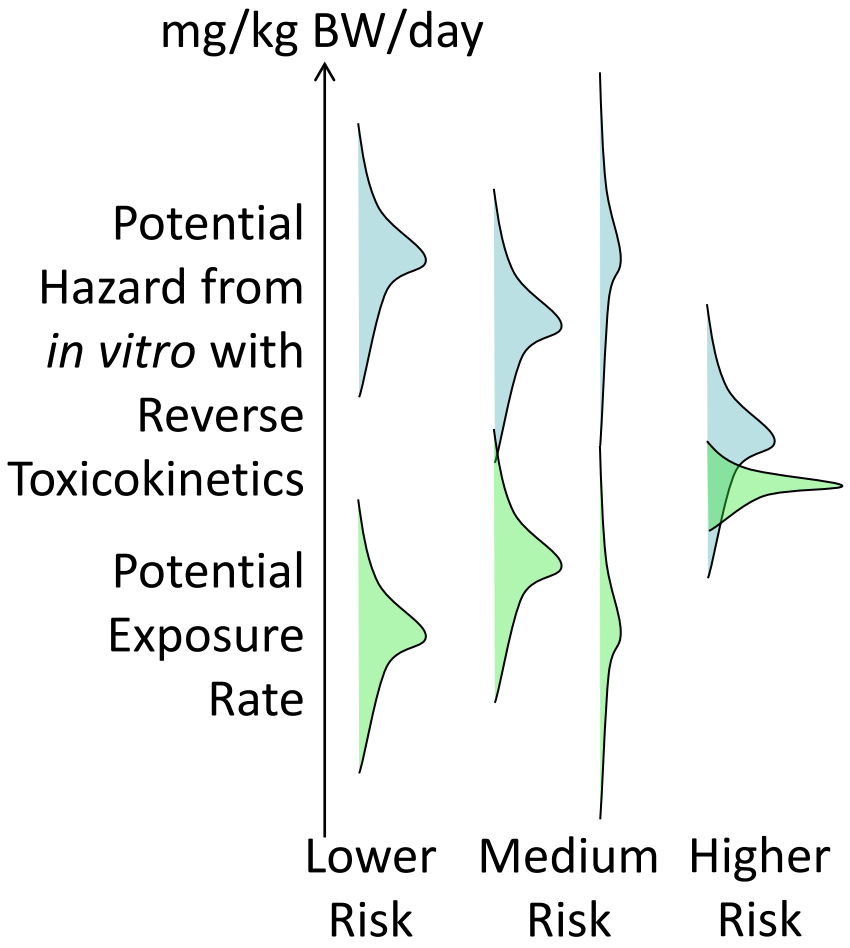


Ring et al., 2019

Propagating Uncertainty Into Chemical Risk Prioritization

- When compared with ranges of potentially adverse dose rates (for example, ToxCast *in vitro* bioactivities converted via reverse dosimetry) it is possible to identify the margin between “hazard” and “exposure“ even with the presence of uncertainty

- Carefully quantifying uncertainty is key and requires appropriate evaluation data and relevant models



Bioactivity : Exposure Ratio (Risk)
For example, Wetmore et al. (2015)

Figure from Wambaugh et al., 2019

Conclusions

Please send questions to:
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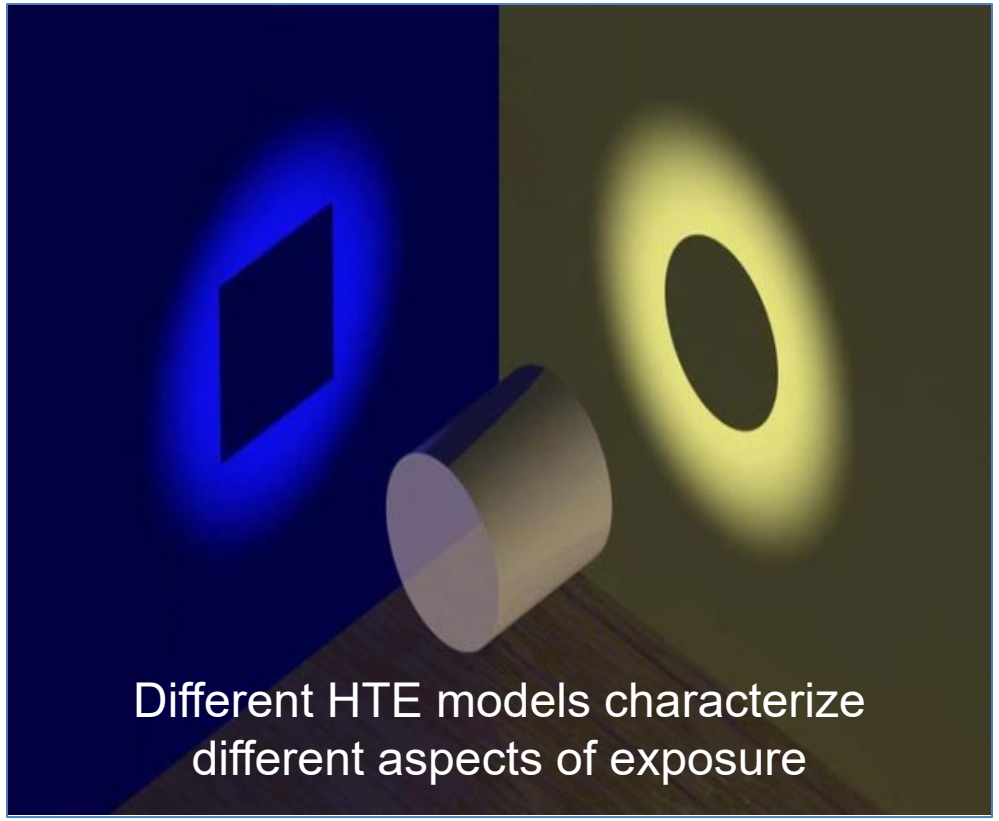
- SEEM is a probabilistic, consensus prediction using multiple HTE models and other predictors
  - Various HTE models provide the predictions for different aspects of exposure
  - Monitoring data provides our “reference” exposures
- QSUR “pathway models” provide exposure model “domain of applicability”
  - Allow us to know which model to use and when
  - Of 687,359 chemicals evaluated, 30% have less than a 50% probability for exposure via any of the four pathways and are considered outside the domain of applicability



ExpoCast Project (Exposure Forecasting)

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- Arnot, J. A.; et al., Develop Sub-Module for Direct Human Exposures to Consumer Products. Technical Report for the U.S. Environmental Protection Agency; ARC Arnot Research & Consulting, Inc.: Toronto, ON, Canada, 2014.
- Bennett, D. H.; Furtaw, E. J., Fugacity-based indoor residential pesticide fate model. Environmental Science & Technology 2004, 38, (7), 2142-2152.
- Ernstoff, A. S., et al.., High-throughput migration modelling for estimating exposure to chemicals in food packaging in screening and prioritization tools. Food and Chemical Toxicology 2017, 109, 428-438.
- Huang, Lt al.., A review of models for near-field exposure pathways of chemicals in consumer products. Science of The Total Environment 2017, 574, 1182-1208.
- Huang, L.; Jolliet, O., A parsimonious model for the release of volatile organic compounds (VOCs) encapsulated in products. Atmospheric Environment 2016, 127, 223-235.
- Jolliet, O. et al. Defining Product Intake Fraction to Quantify and Compare Exposure to Consumer Products. Environmental Science & Technology 2015, 49, (15), 8924-8931.
- Pearce, Robert G., et al. "Httk: R package for high-throughput toxicokinetics." Journal of statistical software 79.4 (2017): 1.
- Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating toxicokinetic variability." Environment International 106 (2017): 105-118.
- Ring, Caroline L., et al. "Consensus Modeling of Median Chemical Intake for the US Population Based on Predictions of Exposure Pathways." Environmental science & technology 53.2 (2019): 719-732
- Shin, H.-M.; McKone, T. E.; Bennett, D. H., Intake Fraction for the Indoor Environment: A Tool for Prioritizing Indoor Chemical Sources. Environmental Science & Technology 2012, 46, (18), 10063-10072.
- Shin, Hyeong-Moo, et al. "Risk-based high-throughput chemical screening and prioritization using exposure models and in vitro bioactivity assays." Environmental science & technology 49.11 (2015): 6760-6771.
- Stanfield, Zachary, et al. "Bayesian inference of chemical exposures from NHANES urine biomonitoring data." Journal of Exposure Science & Environmental Epidemiology (2022): 1-14.
- Tan, Yu-Mei, Kai H. Liao, and Harvey J. Clewell III. "Reverse dosimetry: interpreting trihalomethanes biomonitoring data using physiologically based pharmacokinetic modeling." Journal of Exposure Science and Environmental Epidemiology 17.7 (2007): 591.
- Wallace et al., “The TEAM Study: Personal exposures to toxic substances in air, drinking water, and breath of 400 residents of New Jersey, North Carolina, and North Dakota .” Environmental Research 43: 209-307 (1987)
- Wambaugh, John F., et al. "High-throughput models for exposure-based chemical prioritization in the ExpoCast project." Environmental science & technology 47.15 (2013): 8479-848.
- Wambaugh, John F., et al. "High Throughput Heuristics for Prioritizing Human Exposure to Environmental Chemicals." Environmental science & technology (2014).
- Wambaugh, John F., et al. "New approach methodologies for exposure science." Current Opinion in Toxicology 15 (2019): 76-92.
- Wetmore, Barbara A., et al. "Integration of dosimetry, exposure and high-throughput screening data in chemical toxicity assessment." Toxicological Sciences (2012): kfr254.
- Wetmore, Barbara A., et al. "Incorporating High-Throughput Exposure Predictions with Dosimetry-Adjusted In Vitro Bioactivity to Inform Chemical Toxicity Testing." Toxicological Sciences 148.1 (2015): 121-136.
- Zhang, X.; Arnot, J. A.; Wania, F., Model for screening-level assessment of near-field human exposure to neutral organic chemicals released indoors. Environmental science & technology 2014, 48, (20), 12312-12319.