High-throughput methods for estimating food contact substance exposures to support risk-based chemical prioritization

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Food Packaging Forum Workshop
Predicting the safety of food contact articles: New science and digital opportunities
Zurich, Switzerland
October 4, 2018

United States Environmental Protection Agency

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Chemical Regulation in the United States

- A tapestry of laws covers the chemicals people are exposed to in the United States (Breyer, 2009)

- Different testing requirements exist for food additives, pharmaceuticals, and pesticide active ingredients

- Most other chemicals, ranging from industrial chemicals to dyes to many consumer product chemicals, are covered by the **Toxic Substances Control Act** (TSCA) which is administrated by EPA

  - Thousands of chemicals on the market were either “grandfathered” in or were allowed without experimental assessment of hazard, toxicokinetics, or exposure

  - Thousands of new chemical use submissions are made to the EPA every year

- TSCA was updated in June, 2016 to allow ***risk-based*** evaluation of these and other chemicals

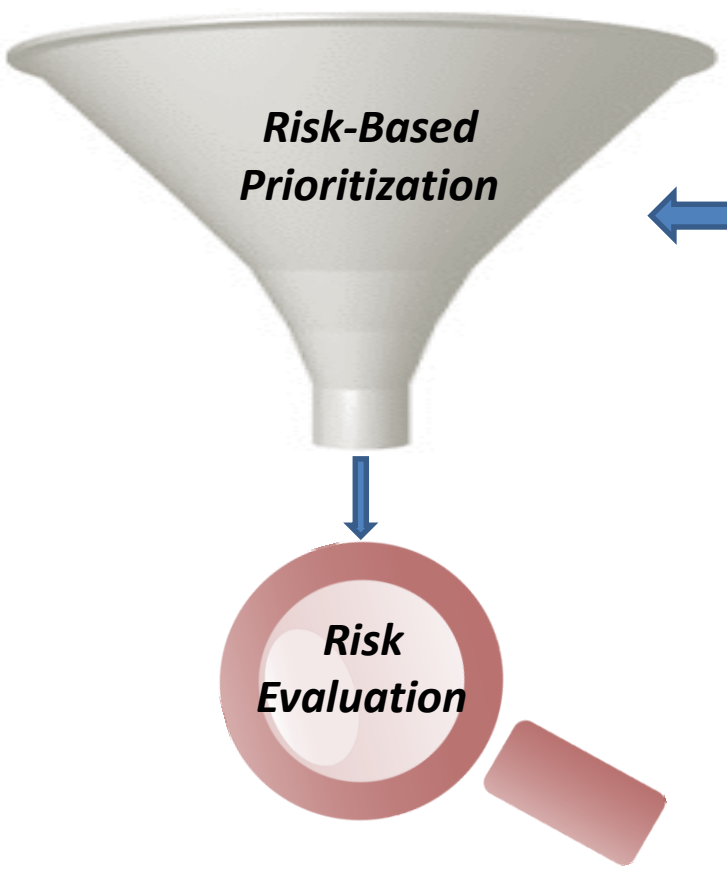
  - Methods are being developed to inform the ***prioritization of these existing and new chemicals for testing***

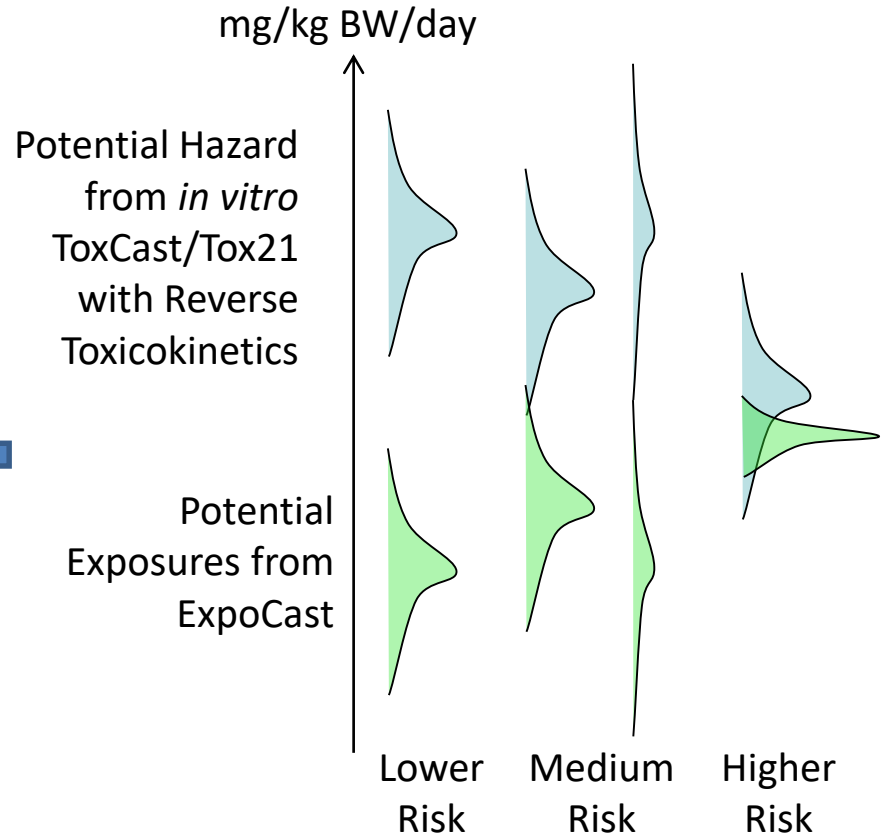
November 29, 2014

Adapted from John Wambaugh

High-Throughput Risk-Based Prioritization

June 2017: **67,709** Chemicals on the TSCA Inventory





High-Throughput Risk-Based Prioritization

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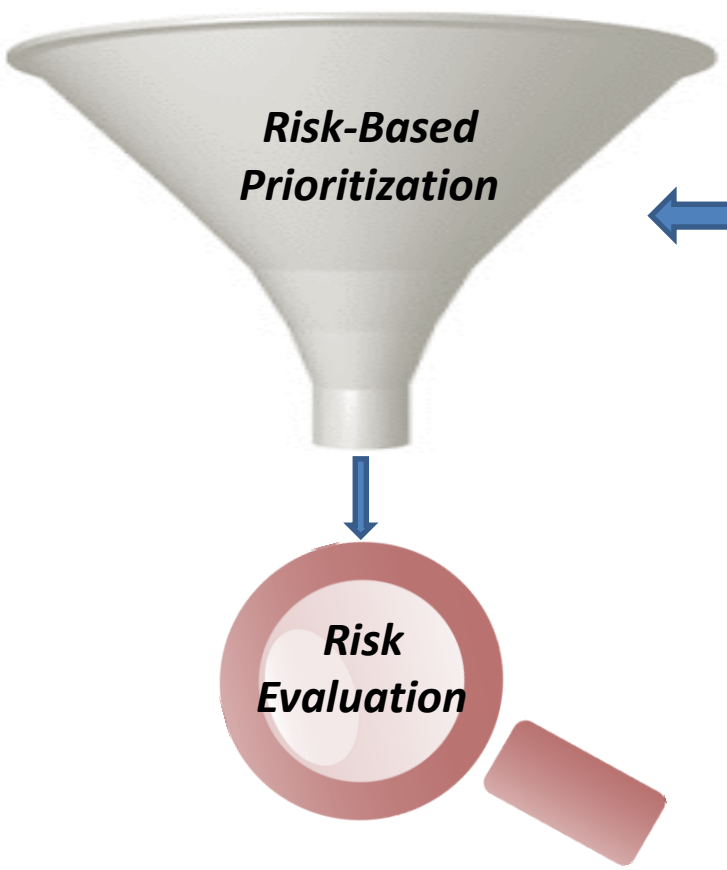

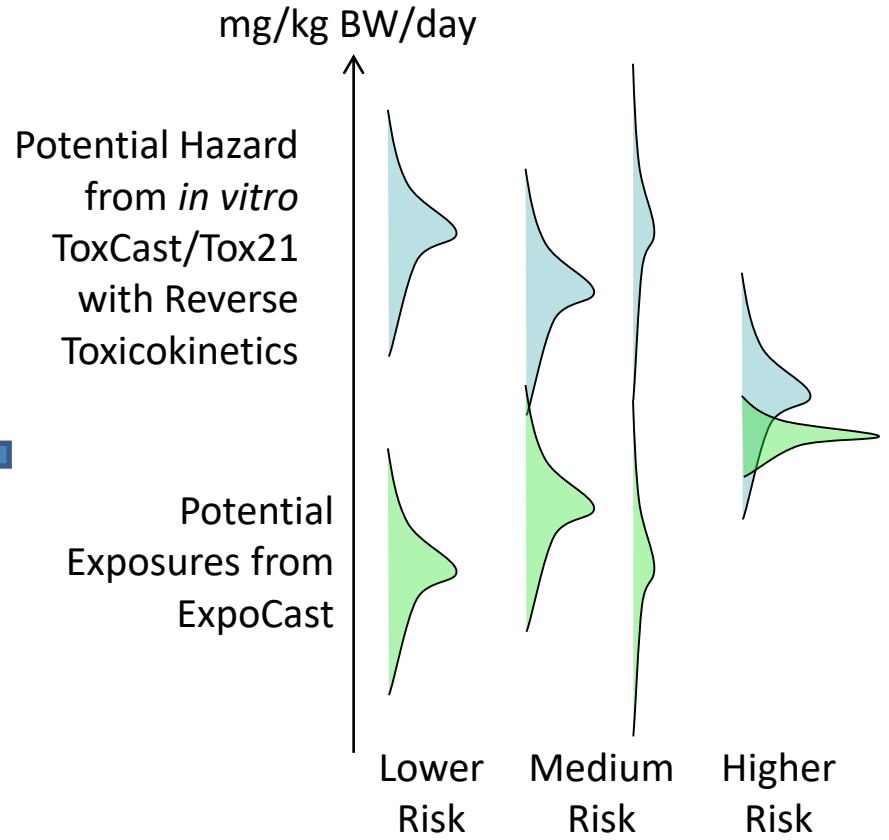

All of these methods are uncertain, but if that uncertainty can be quantified, we can make informed decisions:

No model is perfect, but still may be ***Fit for Purpose***

High-Throughput Risk-Based Prioritization

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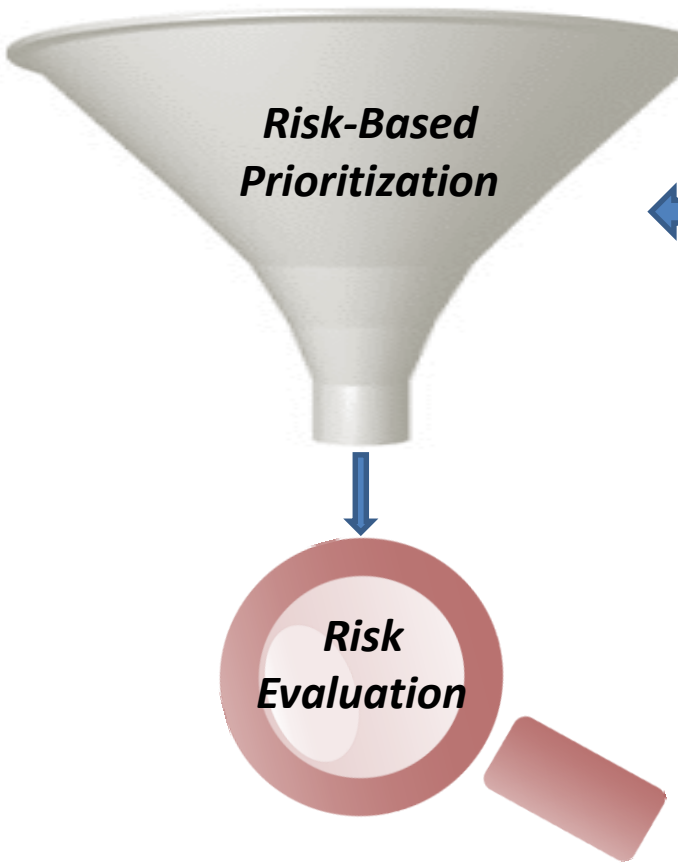
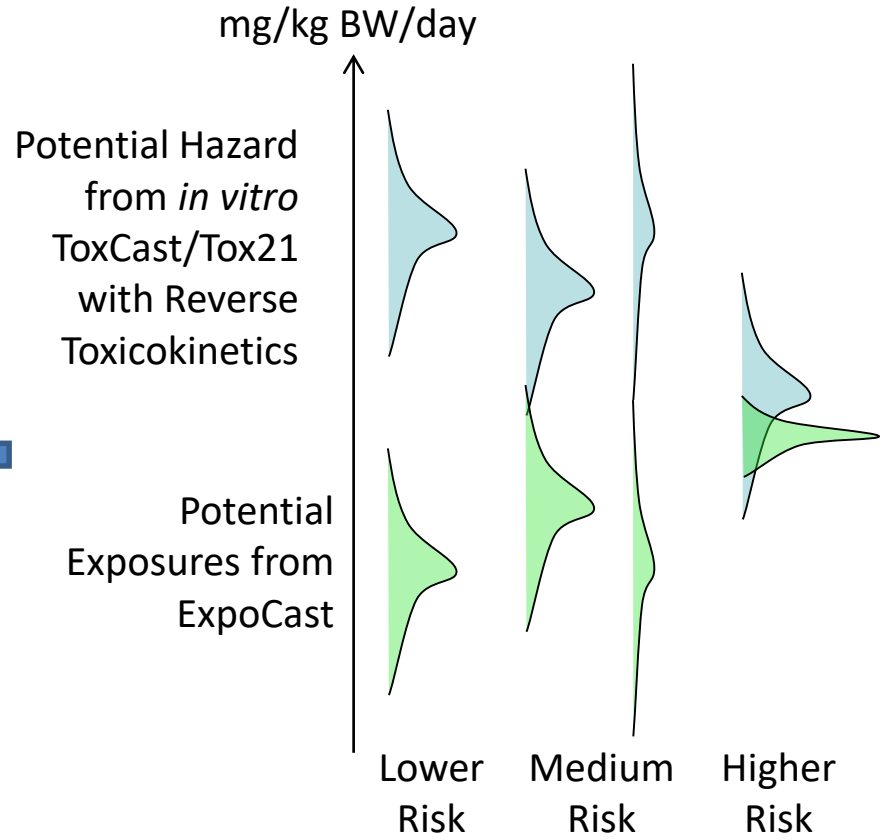




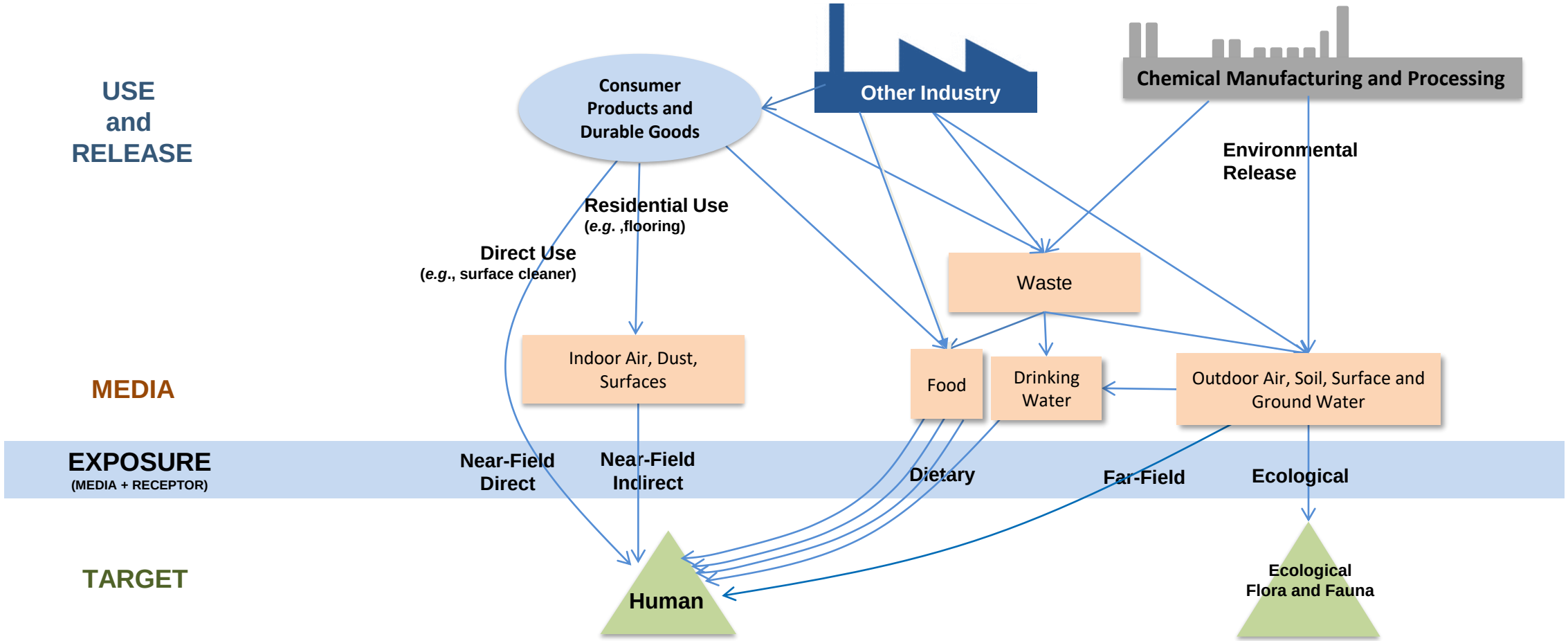
All of these methods are uncertain, but if that uncertainty can be quantified, we can make informed decisions:

No model is perfect, but still may be ***Fit for Purpose***

TSCA section 6(b)(1)(A):

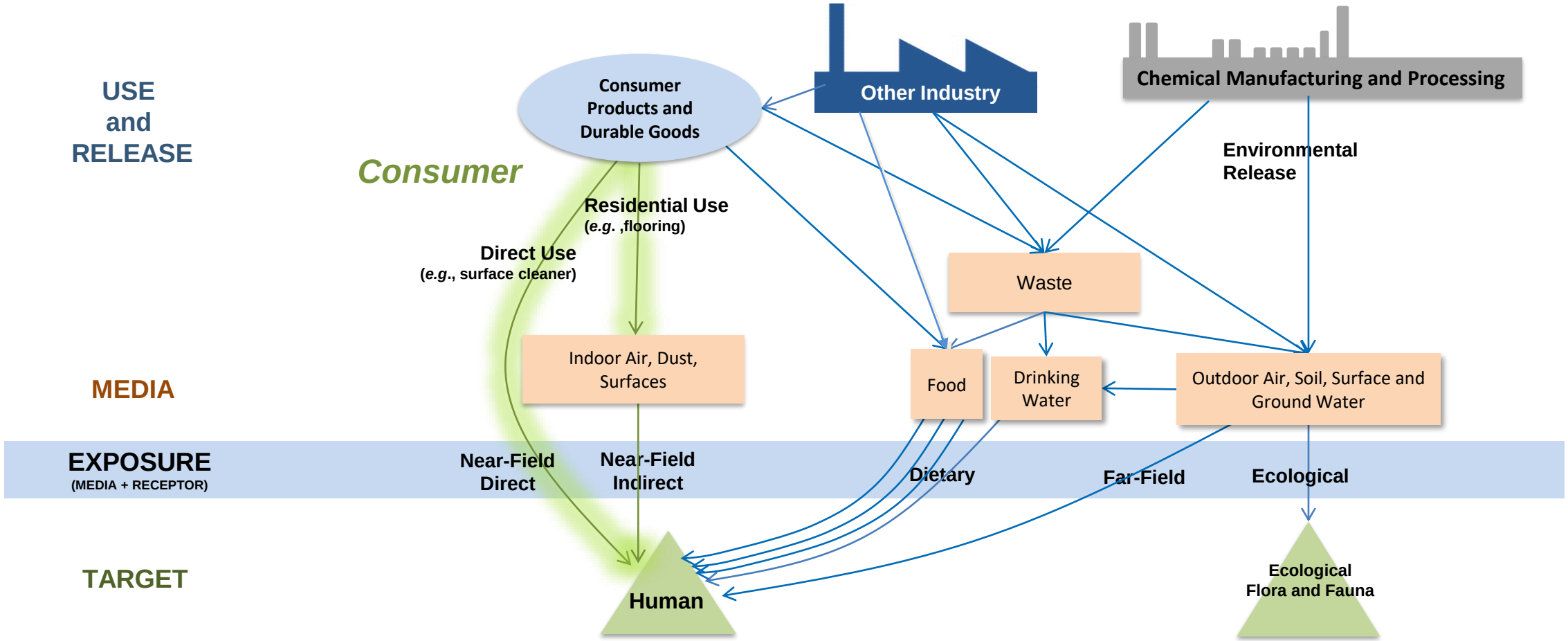
- Exposure potential of the chemical substance
- Must "consider conditions of use:" circumstances…under which a chemical substance is ***intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of.***

Exposure Forecasts Require Integrating Pathway-Specific Models and Data



"Exposure pathway": The course an agent takes from the source to the target (Zartarian et al, 2005)

Exposure Forecasts Require Integrating Pathway-Specific Models and Data



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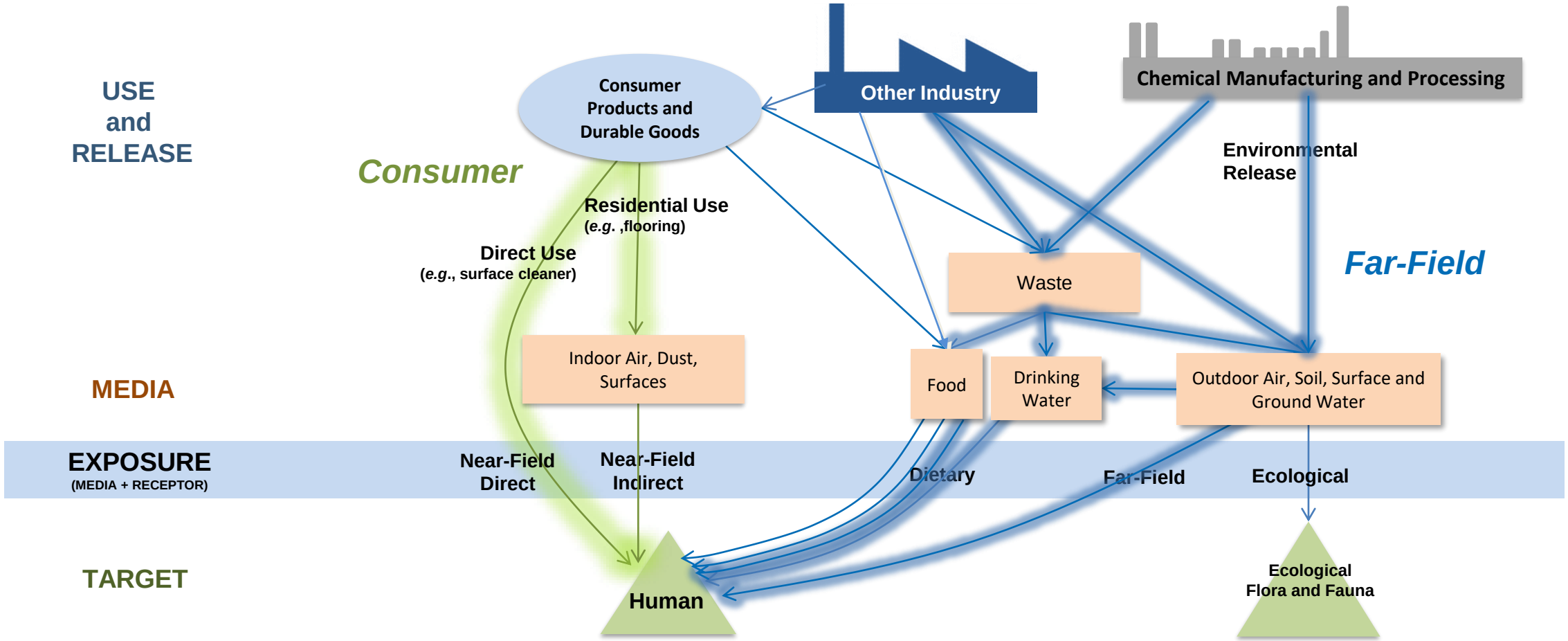

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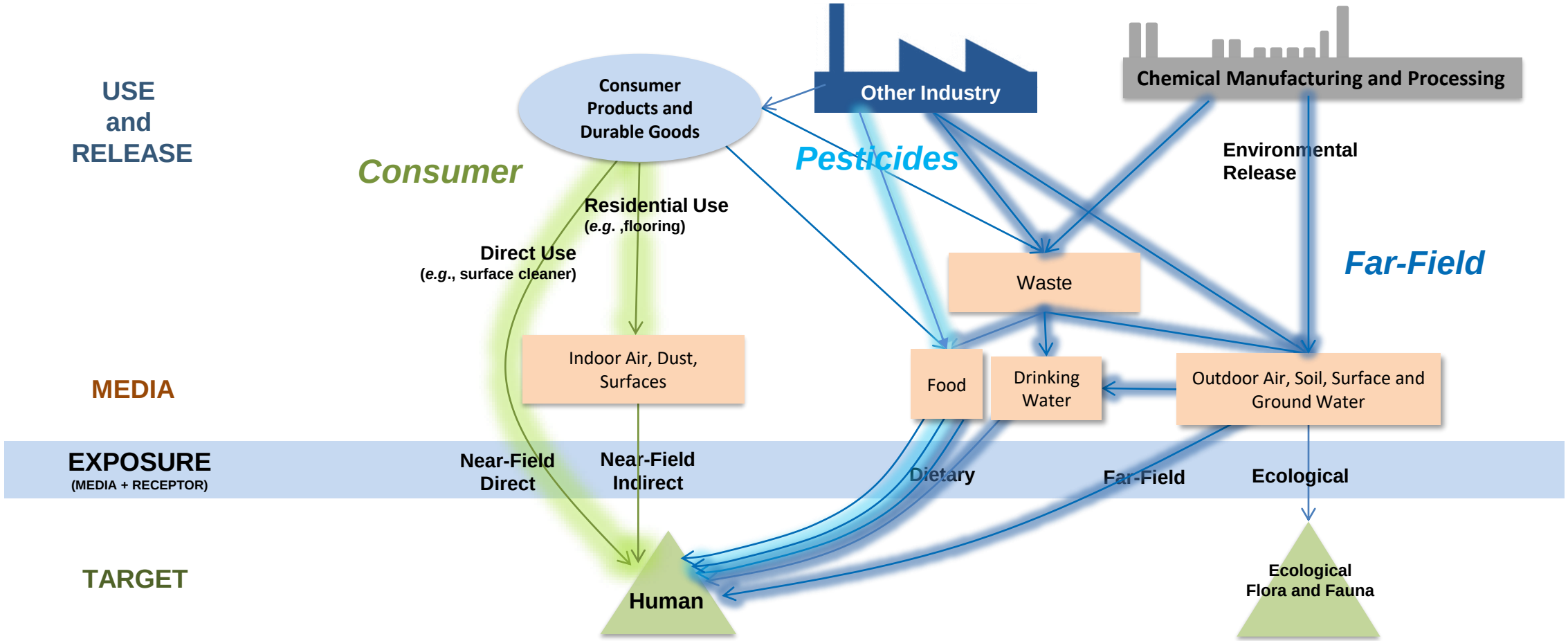

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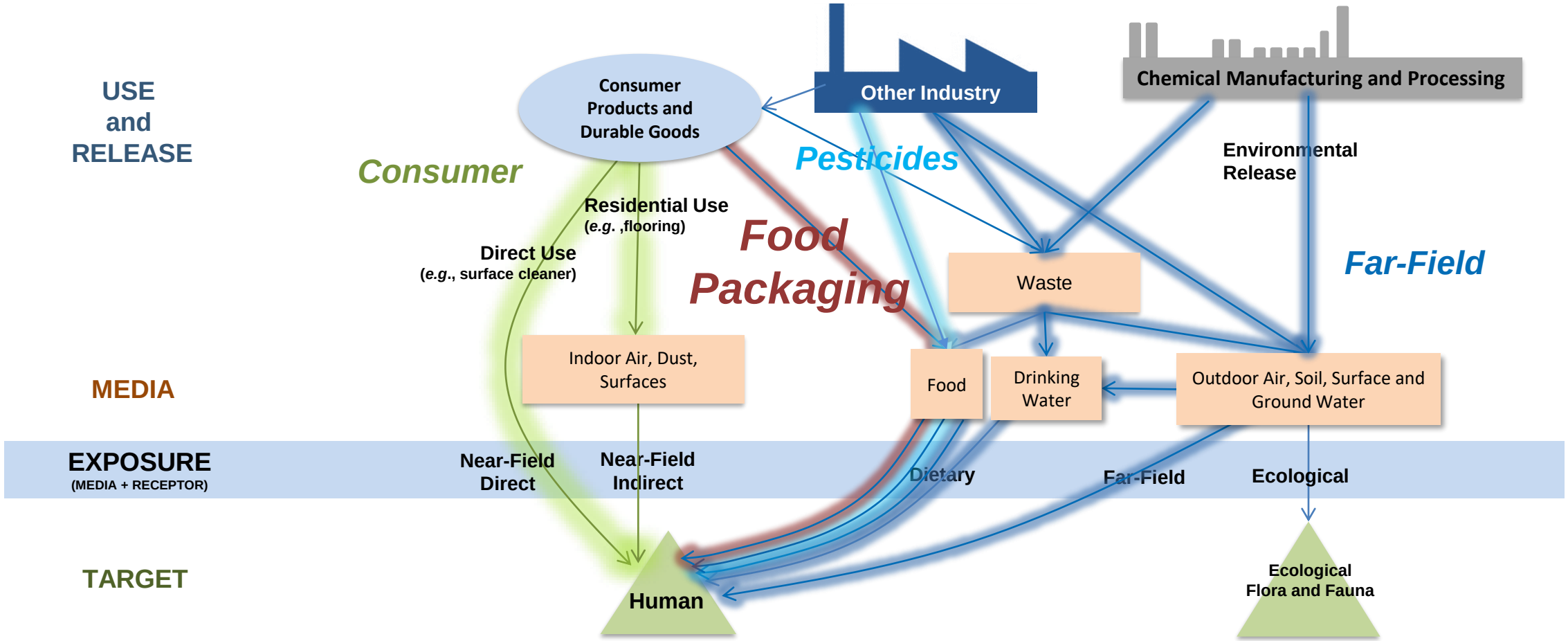

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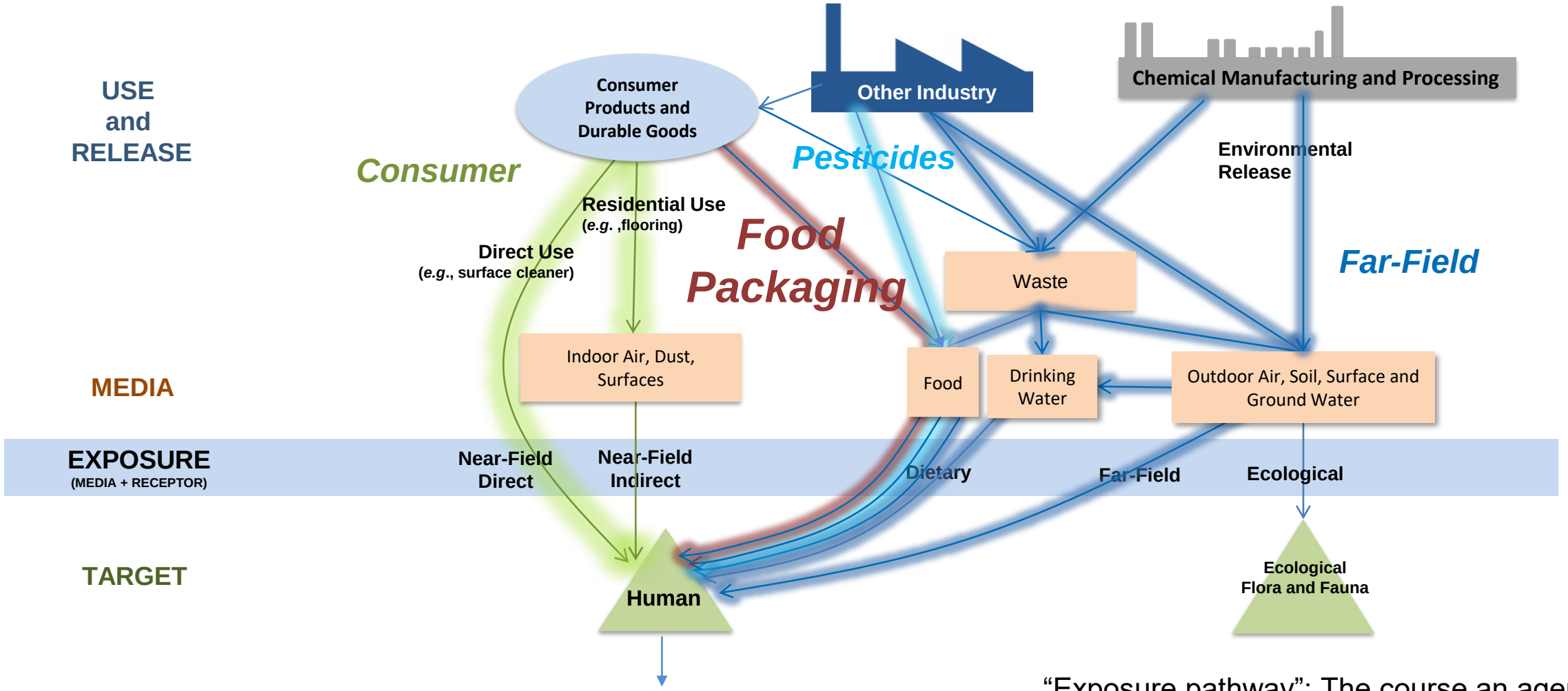
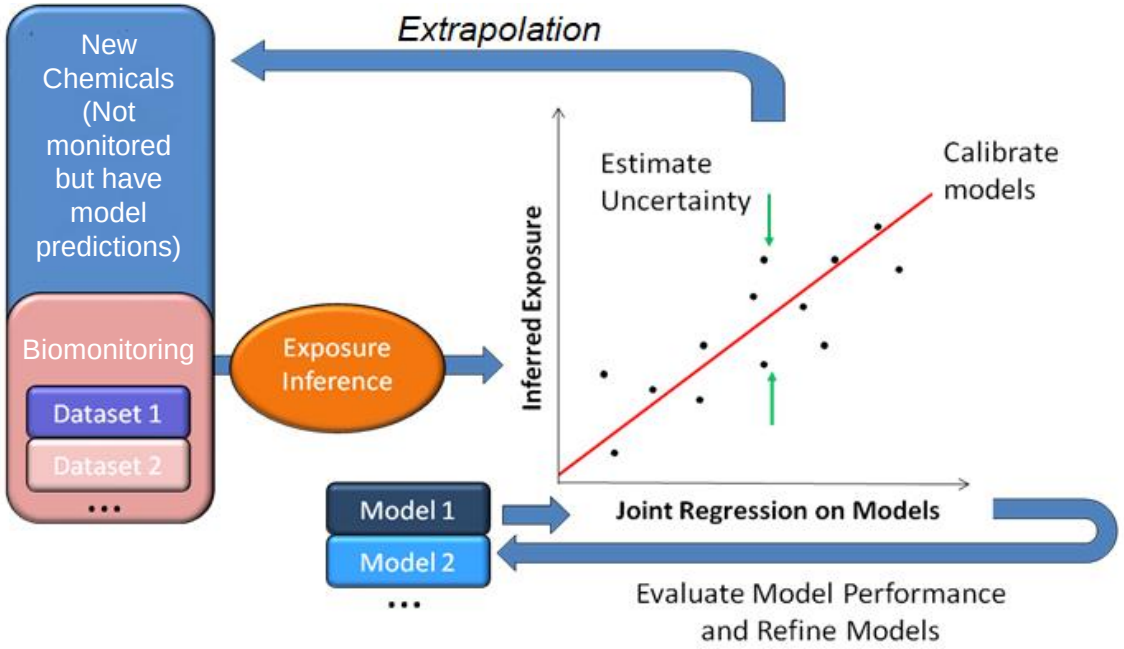


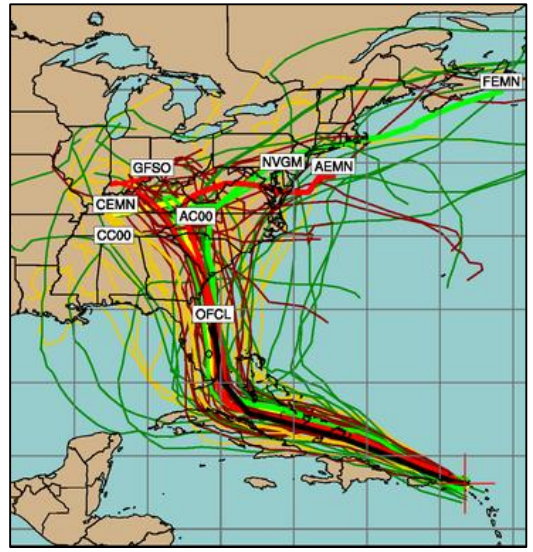
Evaluate and Calibrate with Monitoring Data

"Exposure pathway": The course an agent takes from the source to the target (Zartarian et al, 2005)

Consensus Exposure Predictions with the SEEM Framework

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

Adapted from John Wambaugh

Fit For Purpose Exposure Predictions in ExpoCast

- What are we doing: Trying to understand total exposure potential across many exposure pathways for tens of thousands of chemicals

- What are we NOT doing: In-depth exposure, risk, or safety assessments for individual chemicals

High-Throughput Exposure Predictions for Chemicals in Polymer Food Packaging

Food Concentration x ***Food Intake*** = ***Exposure***

High-Throughput Exposure Predictions for Chemicals in Polymer Food Packaging

United States Environmental Protection Agency

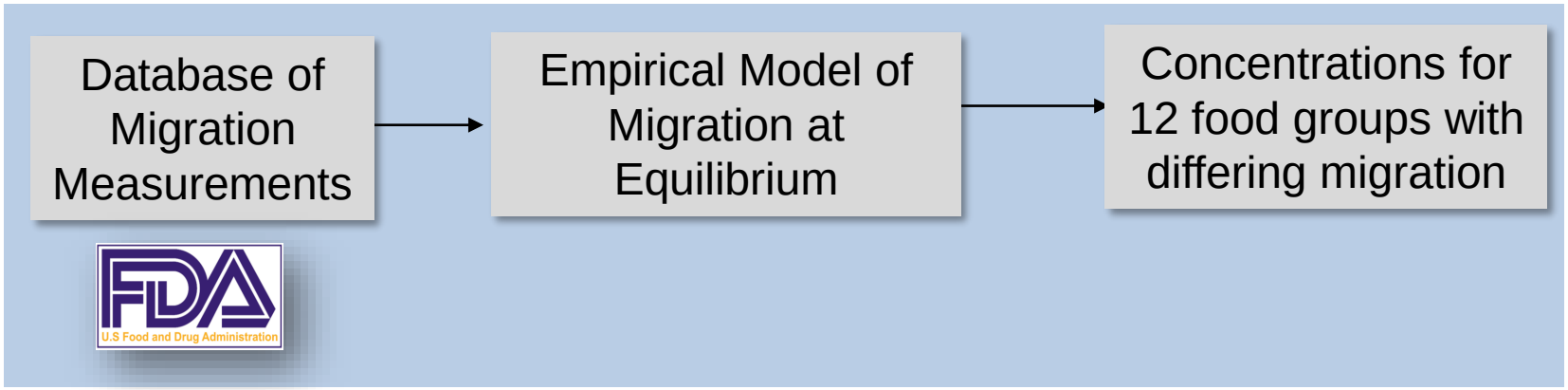
Food Concentration

Exposure

Food Intake

High-Throughput Exposure Predictions for Chemicals in Polymer Food Packaging

Food Concentration



Exposure

Food Intake

High-Throughput Exposure Predictions for Chemicals in Polymer Food Packaging

Food Concentration

Database of Migration Measurements → Empirical Model of Migration at Equilibrium → Concentrations for 12 food groups with differing migration

Exposure

National Health and Examination Survey What We Eat in America Food Diaries [7000 Food Codes] → Consumption patterns for 12 food groups by age and gender

Food Intake

High-Throughput Exposure Predictions for Chemicals in Polymer Food Packaging

Food Concentration

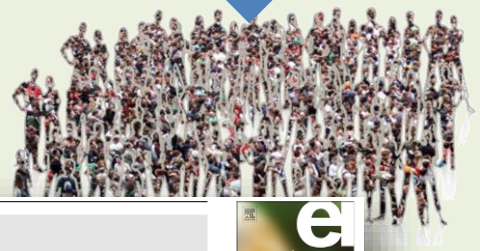
Database of Migration Measurements

Empirical Model of Migration at Equilibrium

Concentrations for 12 food groups with differing migration

Exposure

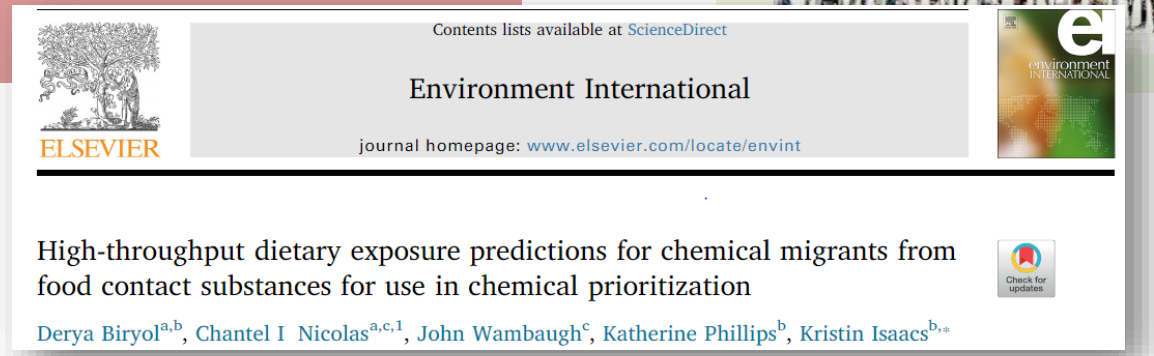
Population-Based Probabilistic Exposure Model (SHEDS-HT)



Food Intake

National Health and Examination Survey What We Eat in America Food Diaries [7000 Food Codes]

Consumption patterns for 12 food groups by age and gender



Contents lists available at ScienceDirect

Environment International

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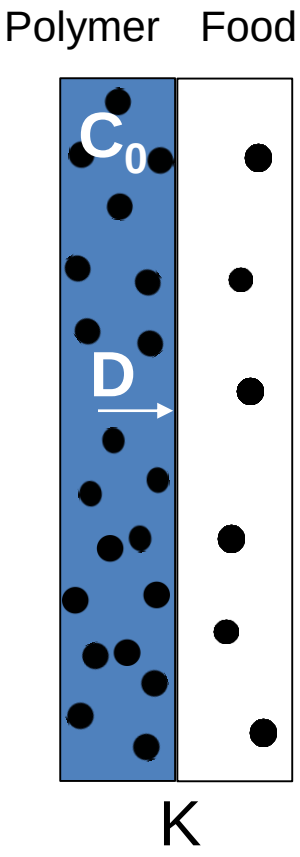
High-throughput dietary exposure predictions for chemical migrants from food contact substances for use in chemical prioritization

Derya Biryol[a,b], Chantel I Nicolas[a,c,1], John Wambaugh[c], Katherine Phillips[b], Kristin Isaacs[b,*]

Biryol et al., 2017

Empirical Model of Chemical Migration

System



Initial chemical concentration in polymer, C_0
Diffusion coefficient, D
Partition coefficient, K

Model

- Mechanistic/deterministic models (based on diffusion coefficient and portioning) currently cannot be applied for 1000's of chemicals
- Use empirical approach: Linear model for *log(Migration)* at equilibrium as a function of C_0, food type (e.g., fatty, aqueous), temperature, and chemical properties*
- Model selection was performed using the least absolute shrinkage and selection operator (LASSO) method to avoid model overfitting

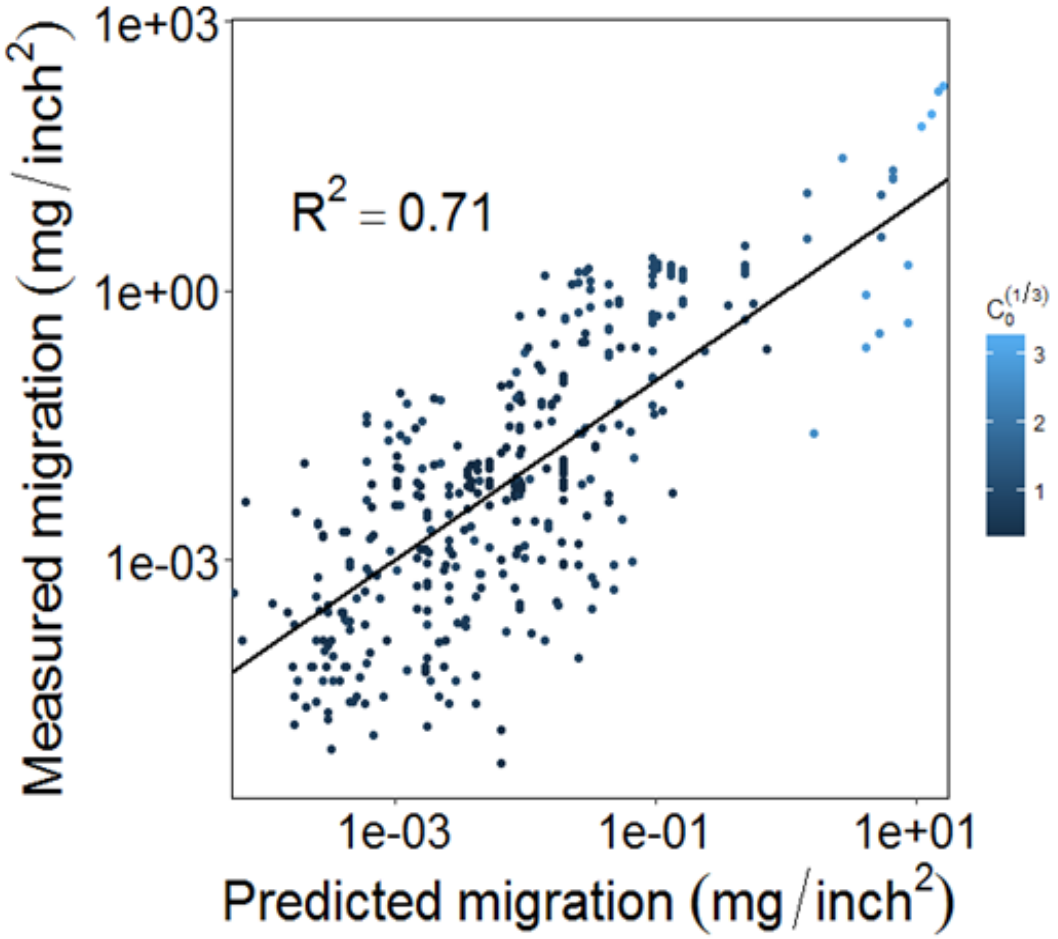
Data

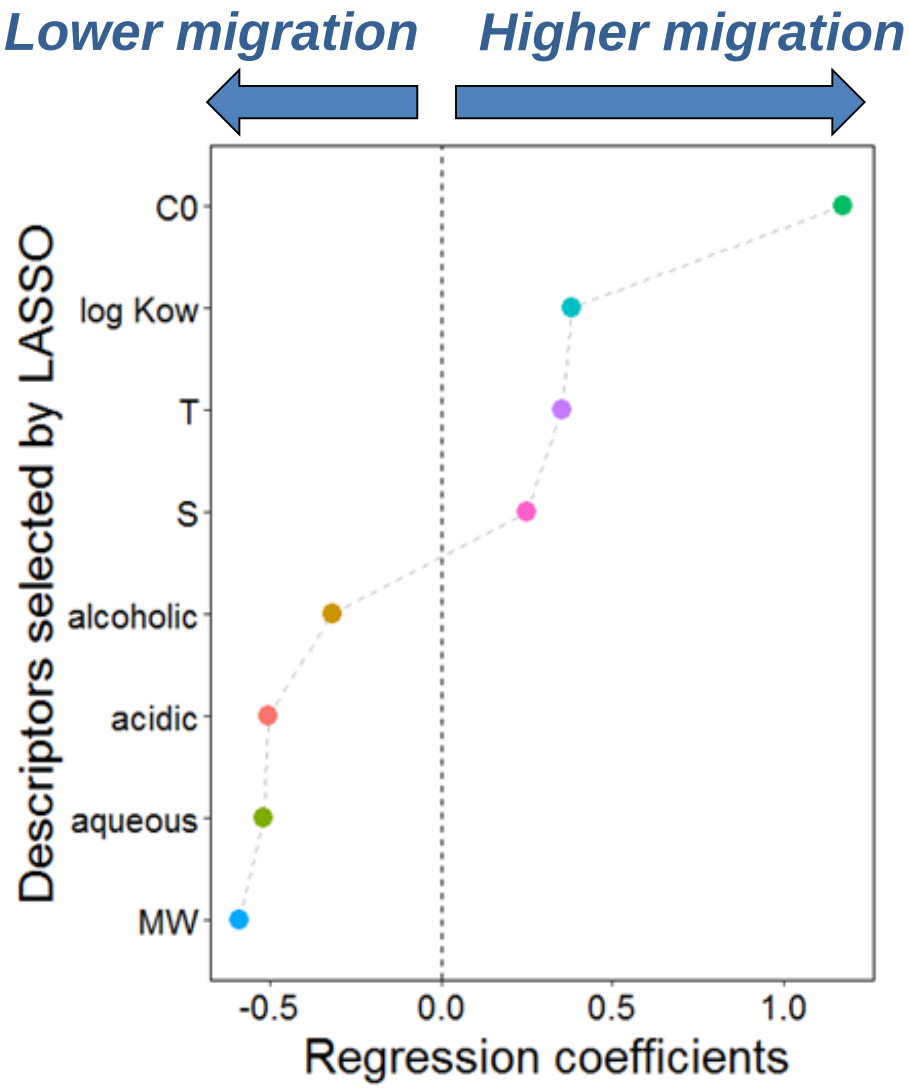
- *2583 migration experiments; 106 unique chemicals with various functions*
- *436 experiments (24 chemicals) with enough time course data to assume equilibrium had been reached*
- *Different food simulants, temperatures, and initial concentrations C_0*

U.S Food and Drug Administration

*EPA's OPERA QSAR predictions, Mansouri et al., 2018)

Empirical Model of Chemical Migration



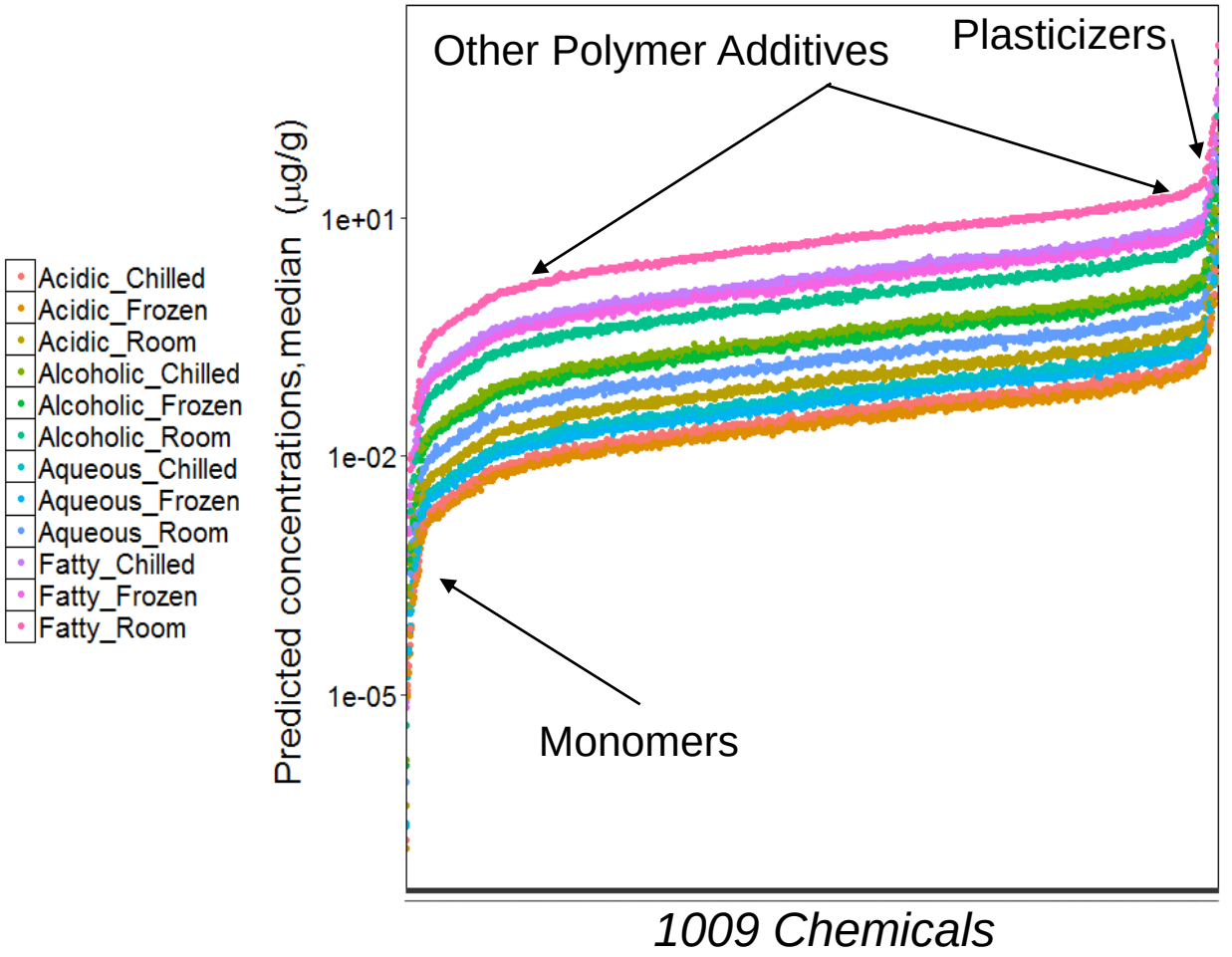


Biryol et al., 2017

Parameterizing the Migration Model to Estimate Food Concentrations

- Food concentrations estimated for 1009 chemicals identified in regulatory lists as present in food packaging (FDA, EU lists)
- C_0 from the literature, others estimated by matching reported chemical functions (e.g., plasticizers) to value ranges in experimental data
- Migration converted to concentration using standard packaging area-to-food mass ratio
  Regression model error incorporated as uncertainty
- 12 food groups (4 food types and 3 temperatures)

Median Concentrations for Food Groups



Biryol et al., 2017

Population-Based Dietary Exposure Predictions

- Consumption diaries generated
  - NHANES food consumption diary food codes mapped to the 12 food groups
  - Standard FDA *food type distributions* and *consumption factors* were applied
  - Final consumption of food (g) in each group calculated for each person

NHANES Mappings

Food Group	Food Type	Storage Temper-ature	Example NHANES Food Code	Example NHANES Food/Form Description
Fatty, Chilled	Fatty	4 ° C	11111000	Milk, cow's, fluid, whole
Fatty, Room	Fatty	27 ° C	11210050	Milk, evaporated
Fatty, Frozen	Fatty	0 ° C	11459990	Yogurt, frozen
Aqueous, Chilled	Aqueous	4 ° C	75113000	Lettuce, raw
Aqueous, Frozen	Aqueous	0 ° C	75233002	Squash, summer, cooked, from frozen, NS as to fat added in cooking
Aqueous, Room	Aqueous	27 ° C	75220023	Okra, cooked, from canned
Acidic, Chilled	Acidic	4 ° C	61210220	Orange juice, canned, bottled or in a carton
Acidic, Frozen	Acidic	0 ° C	61204600	Lemon juice, frozen
Acidic, Room	Acidic	27 ° C	63201110	Blackberries, cooked or canned
Alcoholic, Chilled	Alcoholic	4 ° C	93101000	Beer
Alcoholic, Room	Alcoholic	27 ° C	93201000	Cordial or liqueur
Alcoholic, Frozen	Alcoholic	0 ° C	93301500	Frozen daiquiri

Diaries for Modeling

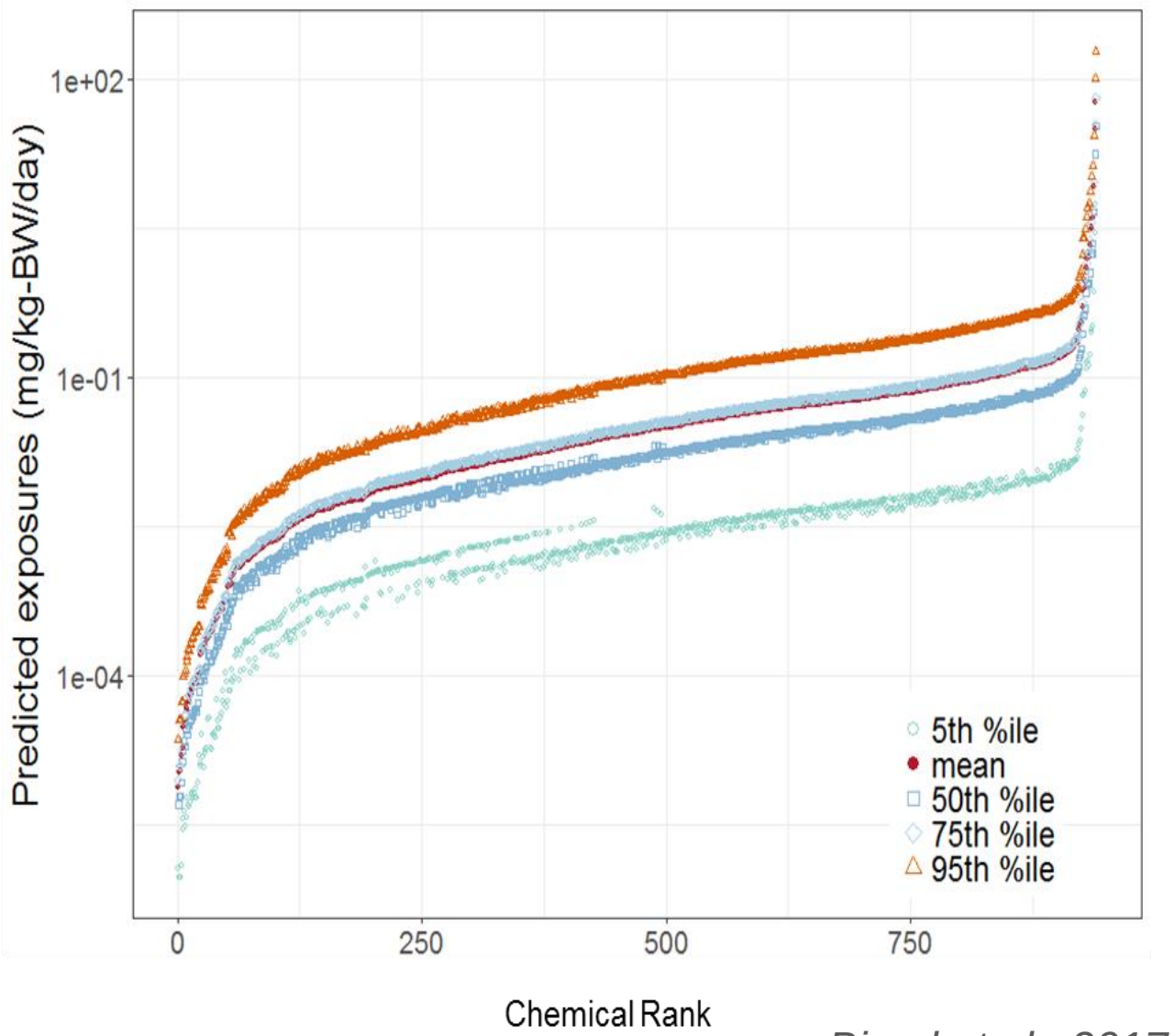
			Consumption (g)					
age	gender	wgt_kg	Alcoholic Chilled	Alcoholic Frozen	Dry Chilled	Dry Frozen	Dry Room	Fatty Chilled
26	M	97.6	15.552	0	0	0	51.3248	651.4006

etc.

Biryol et al., 2017

Population-Based Dietary Exposure Predictions

- Consumption diaries generated
  - NHANES food consumption diary food codes mapped to the 12 food groups
  - Standard FDA *food type distributions* and *consumption factors* were applied
  - Final consumption of food (g) in each group calculated for each person
- SHEDS-HT (Isaacs et al., 2014) model runs for 1009 chemicals
  - Consumption diaries assigned by age and gender to 35,000 simulated individuals representative of the U.S. population
  - Concentrations sampled for each person from migration model results (incorporating uncertainty)
  - Gut absorption estimated
  - Resulting population metrics for exposure estimated



Biryol et al., 2017

Key Assumptions and Uncertainties

- All packaging was assumed to be monolayer and in direct contact with foods; does not account for any chemical gradients in the polymer or food
- Migration model represents equilibrium concentration – estimate of maximum migration that will occur for food type and storage conditions
- Assumed that we can linearly extrapolate the results of experiments performed under temperatures designed to exaggerate migration to normal conditions
- Modeled migration during storage only, and does not model migration during heating
- Migration of chemicals into dry foods was assumed to be negligible

- Initial concentration of chemical in packaging (C_0) was a key parameter and the current method of estimation (using functional role) **imparts critical uncertainty**
- Model uncertainty: efforts to explicitly predict D and K (QSAR) would better reflect true migration patterns
- We assumed all modeled chemicals occurred in polymer packaging (no chemical-specific consideration of market, polymer type or food type distribution); **improved consumption factors are needed**
- Non-intentionally added chemicals are not considered

Use of the HT Food Contact Model in SEEM Collaboration on High Throughput Exposure Predictions

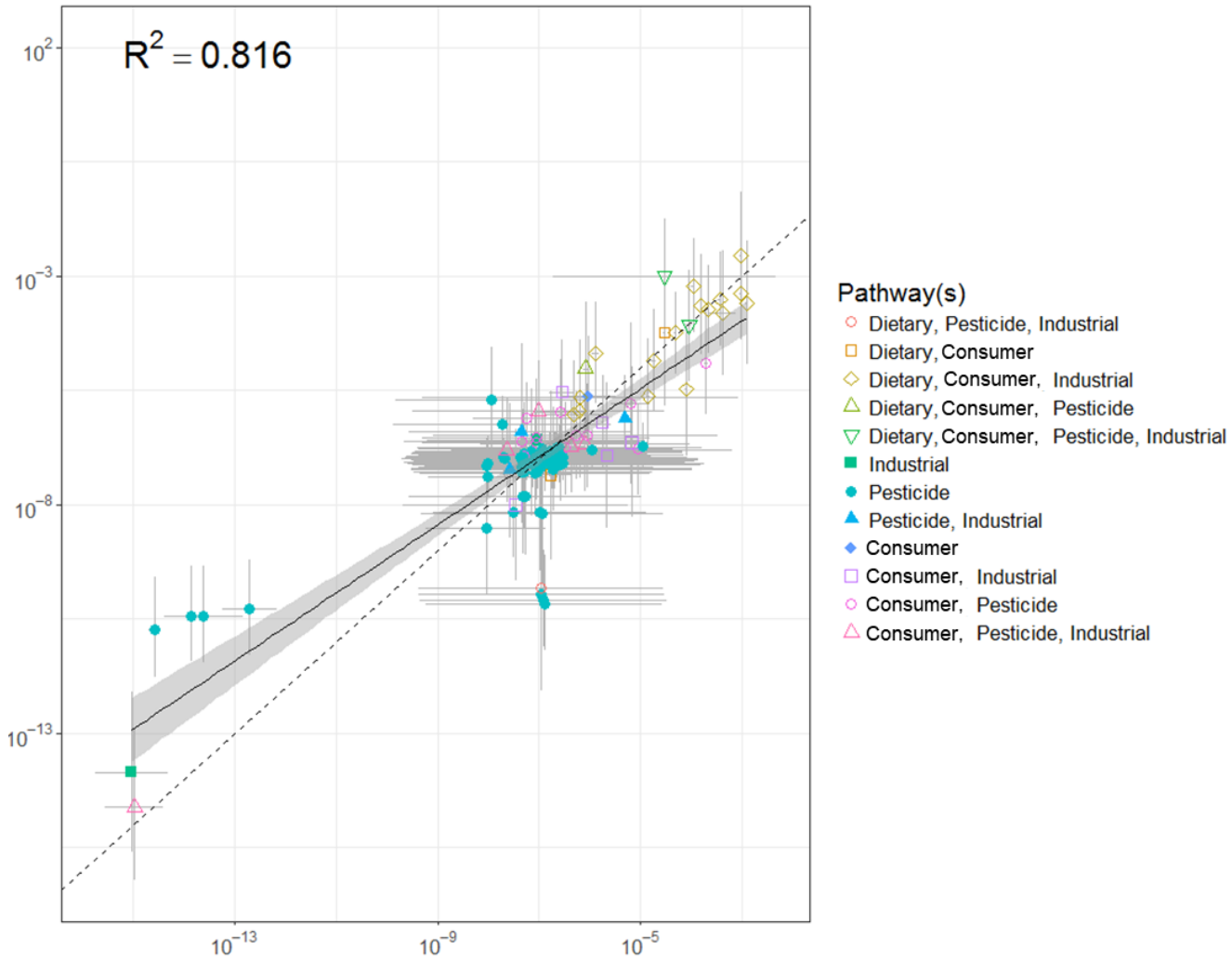
Predictor	Reference(s)	Chemicals Predicted	Pathways Covered by the Model/Predictor
EPA Inventory Update Reporting and Chemical Data Reporting (CDR) (2015)	US EPA (2018)	7856	All
Stockholm Convention of Banned Persistent Organic Pollutants (2017)	Lallas (2001)	248	Far-Field Industrial and Pesticide
EPA 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)	8167	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 Simulation Model- 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	Consumer
High-Throughput Dietary Exposure Model for Food Contact Substances (2017)	Biryol et al. (2017)	940	Dietary (Food Packaging)
Fugacity-based INdoor Exposure (FINE) (2017)	Bennett et al. (2004), Shin et al. (2012)	645	Consumer
RAIDAR-ICE Near-Field (0.803)	Arnot et al., (2014), Zhang et al. (2014)	1221	Consumer
USEtox Residential Scenario (2.0)	Jolliet et al. (2015), Huang et al. (2016,2017)	615	Consumer
USEtox Dietary Scenario (2.0)	Jolliet et al. (2015), Huang et al. (2016), Ernstoff et al. (2017)	8167	Dietary (Food Packaging)

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

Ring et al., submitted

Adapted from John Wambaugh

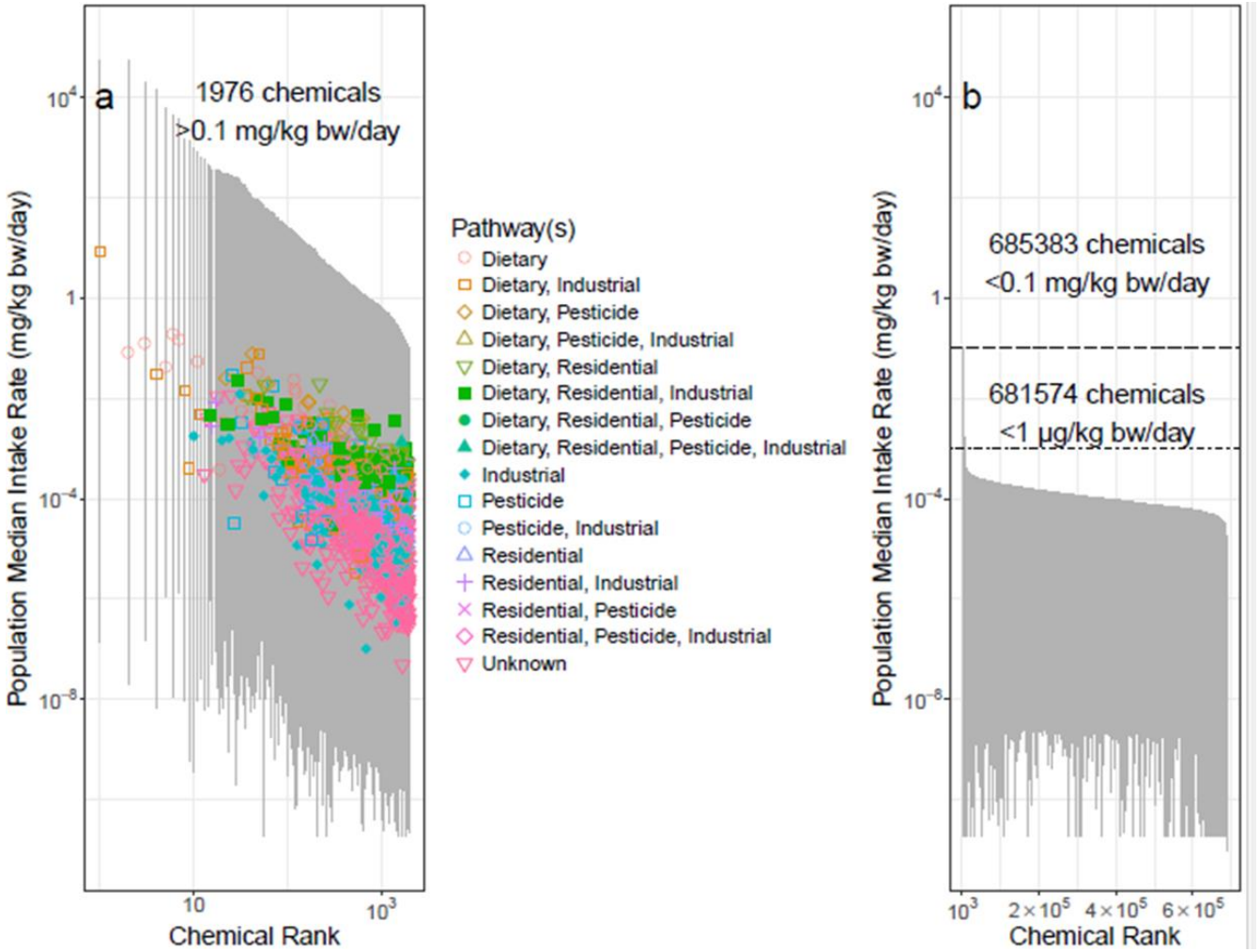
Pathway-Based Consensus Modeling in SEEM



- Bayesian multivariate regression using exposures inferred from NHANES biomonitoring data
- Regression incorporated pathway information
- Regression indicated chemicals with consumer and dietary pathways (N=24) had highest exposures relative to the mean
- The HT food contact model estimates were significantly predictive of exposures (only significant HT model for the dietary pathway)

Ring et al., submitted

Pathway-Based Consensus Modeling in SEEM



Ring et al., submitted

- Resulting regression model extrapolated to 687,359 chemicals
- Uncertainty quantified; majority of the chemicals had exposures (95% credible interval of population median) < 1 µg/kg bw/day
- Can be compared with bioactive exposures estimated from high-throughput screening for chemical prioritization

Conclusions

- EPA is charged with prioritizing thousands of chemicals for further testing and evaluation.
- In the ExpoCast project we are building high-throughput (HT) models for multiple exposure pathways, including food packaging, which we combine in a consensus model for population median exposure.
- A HT model to estimate chemical exposures from food packaging was developed by integrating a data-driven model for migration with food type-specific consumption patterns for the U.S. population.
- The biomonitoring-based SEEM evaluation framework allows us to quantify this uncertainty and the value of addition models and data.
- While HT models have many sources of uncertainty, they can still be fit for combination with HTS data for chemical prioritization.