An Introduction to Chemical Exposure Estimation

Jon Arnot, PhD

ARC Arnot Research and Consulting

Toronto, ON, CAN

May 25, 2023

SOT Webinar Series

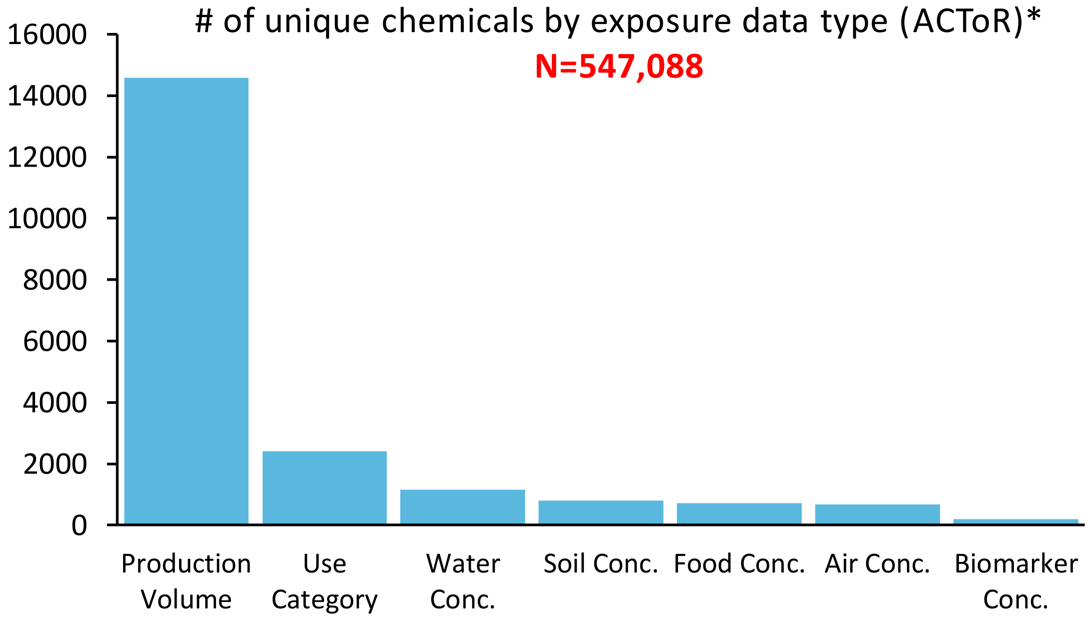
Presentation Overview

- Exposure science "101" (reader's digest version)
- Basic concepts and case examples of:
  - Mechanistic (first-principles) mass-balance models, e.g., PBK, fate and transport, exposure
  - Model parameterization, application and evaluation
- Fostering confidence in chemical exposure assessment
- Exposure And Safety Estimation (EAS-E) Suite:
  - Free public access to exposure data, models and tools

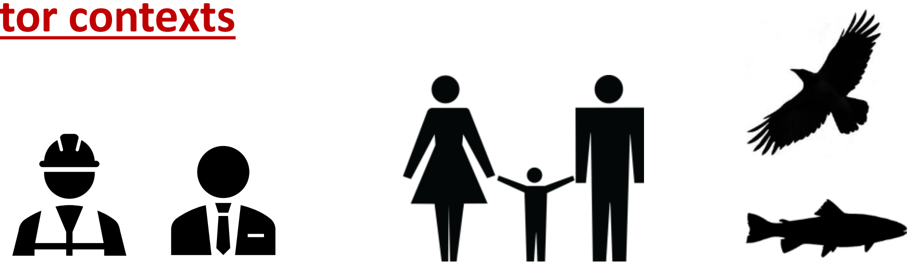
Current Regulatory Landscape

- Many diverse chemicals and use contexts require regulatory assessment, e.g., REACH, TSCA/LCSA, CEPA,
- Limited information → uncertainty (i.e., **exposure**)
- Need to develop and evaluate **databases** and **models** for different receptors and decision contexts

Exposure data gaps



Receptor contexts

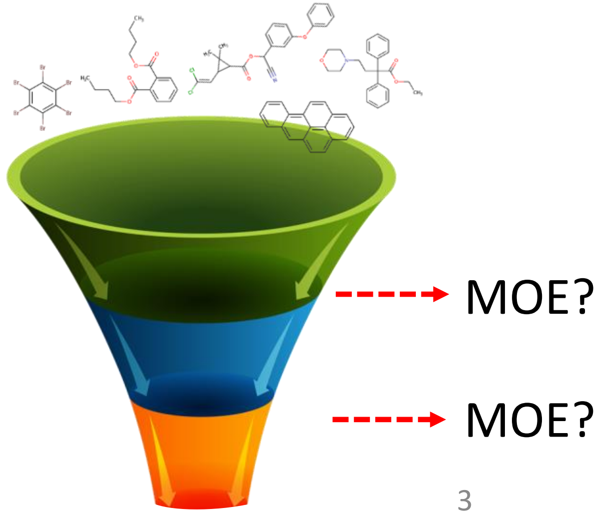


Decision contexts

Priority setting

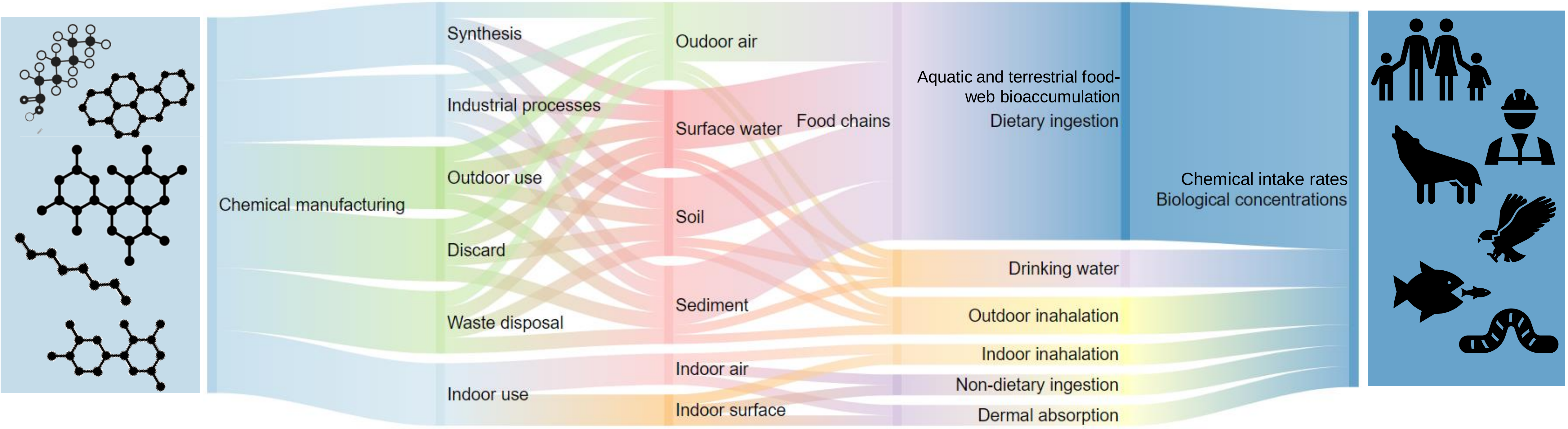
Screening-level

Higher tiered



*USEPA's Aggregated Computational Toxicology Online Resource; Egeghy et al., 2012

The Scope of Exposure Science: Production to Exposure



Chemical properties, production volumes & use information

Life Cycle Assessment (LCA), emission rates

Physiologically-based BioKinetic (PBK) models for various receptors

Food-web bioaccumulation models

Multi-media environmental fate & exposure models (outdoor **and indoor**)

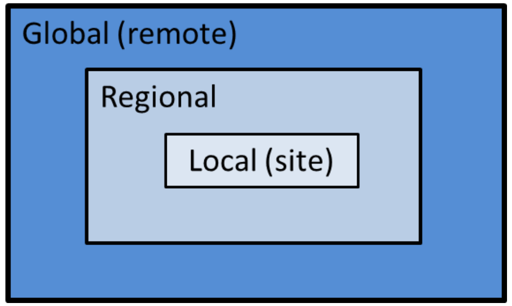
Exposure pathways, single route and **aggregate exposure** estimates

Exposure Assessment

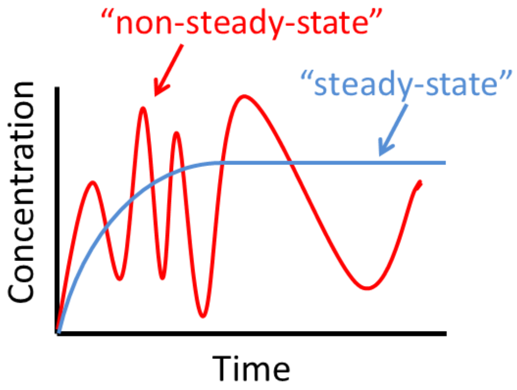
- Quantitative evaluation of the chemical concentration that reaches an organism
  - *Nature*
  - *Magnitude*
  - *Frequency*
  - *Duration*
  - *Route*
- External or internal exposure
- Aggregate or cumulative
- Describes how organisms come into contact with a stressor and the relevant media and exposure routes -> “the exposure narrative”
- Provides metrics of exposure to compare with hazard data to characterize potential risk

Know your system
Know your chemical

Spatial Scale



Temporal Scale



Decision Context

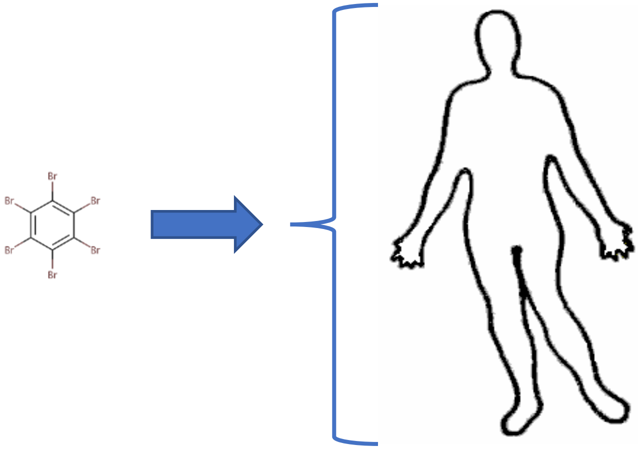
Priority setting

Screening

Comprehensive

Quantifying External Exposure: Chemical Intake Rates

Exposure route intake rates (mg-chemical/kg-bw/d)	Media contact rates (m^3-medium/kg-bw/d)	Multimedia concentrations (mg-chemical/m^3-medium)
Inhalation exposure =	Inhalation rate ×	Air concentration
Ingestion exposure =	Ingestion rate ×	Food & beverage (water) concentrations
Non-dietary ingestion exposure =	Non-dietary rate ×	Dust & surface concentrations
Dermal exposure =	Dermal deposition rate ×	Air, dust, surface concentrations, application rates
Total intake rate (aggregate exposure)		



Function of:

- Body size (age)
- Behaviour/activity

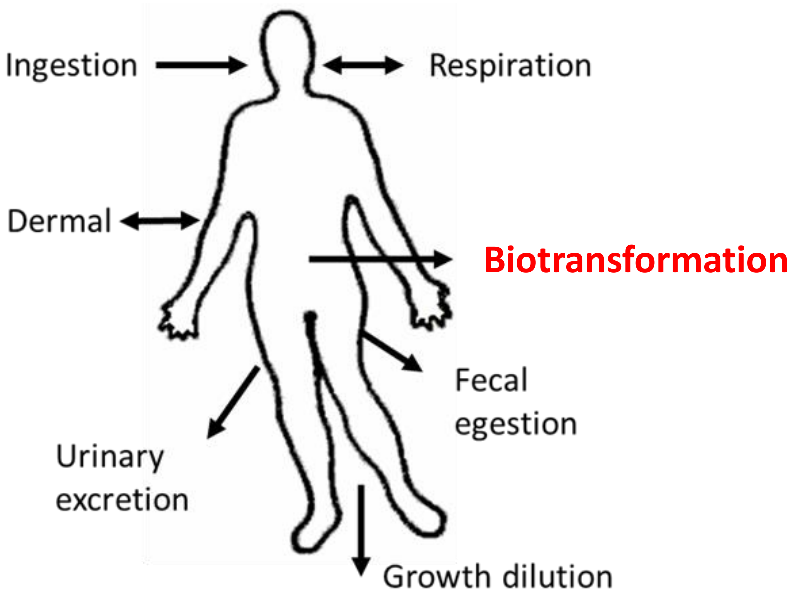
Function of:

- Chemical use/application rates
- Chemical degradation rates
- Product formulations
- Media composition
- Media volumes
- Media flow rates, residence times

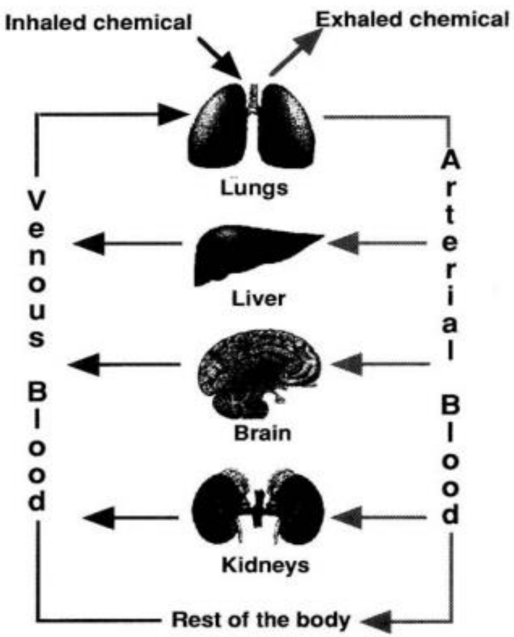
What if you don't have measured multimedia chemical concentrations???

Physiologically-Based Biokinetic (PBK) Models

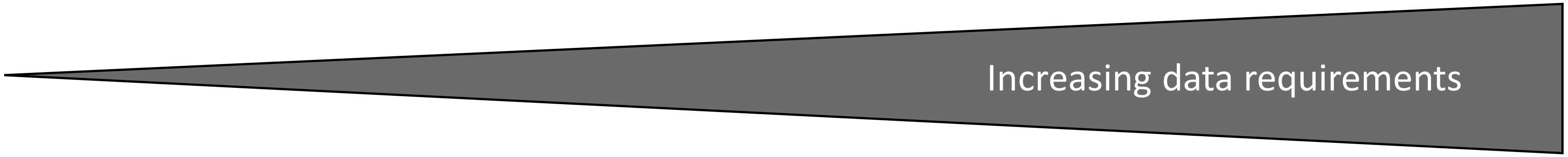
<u>One-compartment PBK model:</u>
organs, tissues, cells assumed at chemical equilibrium



<u>Multi-compartment PBK:</u>
each compartment defined with volumes, composition, blood flow rates, etc

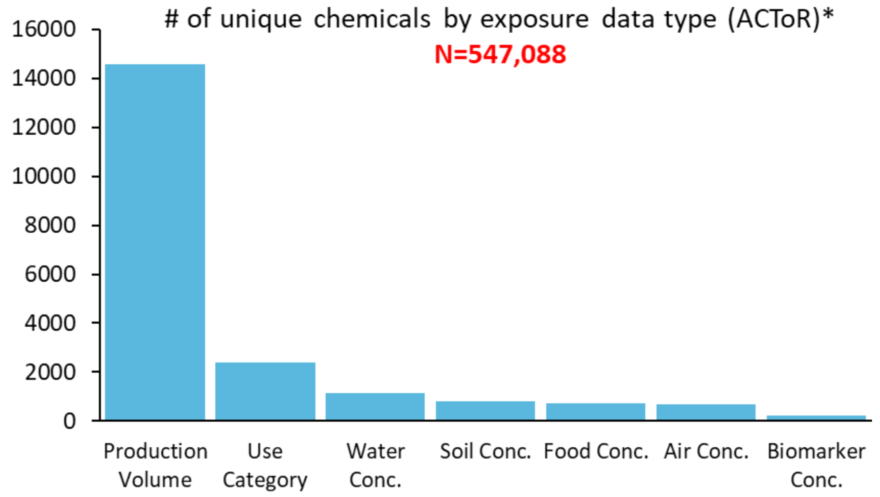


Measurements or predictions for TK properties, i.e., **<u>biotransformation rates</u>**, required for using all PBK models



Merits and limitations of all models…"fit-for-purpose"

Not Feasible To Measure All Chemicals In All Systems



<u>Need models to</u>:

1. Integrate and organize available measured data
2. Address data gaps, generate hypotheses (predictions)
3. Identify key processes influencing exposure
4. Forecast future time trends
5. Identify priority substances
6. Allocate resources accordingly

- Different models incorporate different knowledge, assumptions and data and range from relatively simple to complex
- Different models for different objectives: "right tool for the job" – **problem formulation**
- **Mass balance models**: General considerations for model development & parameterization
  - System information (environmental and biological parameters)
  - Chemical information (parameters and properties)

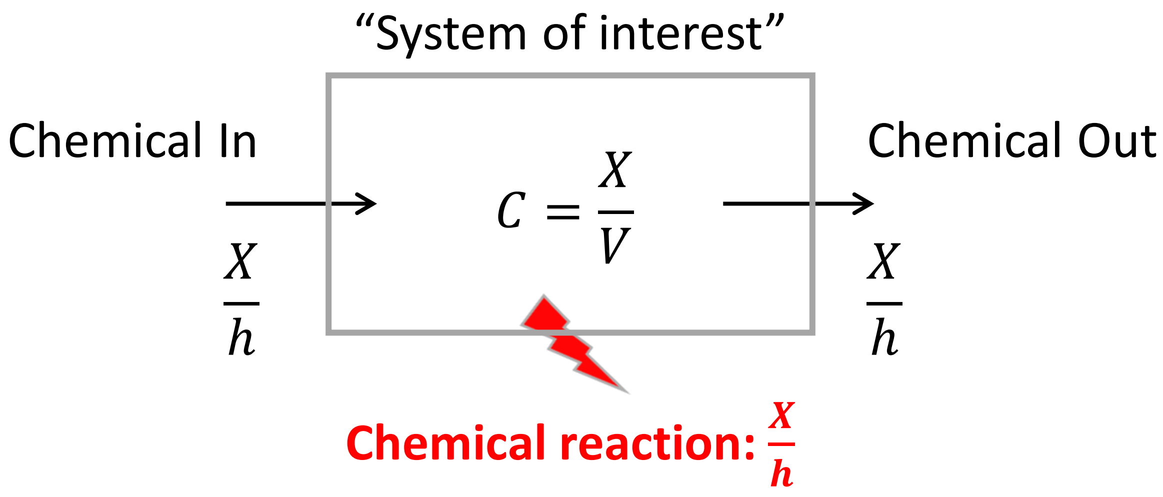
*USEPA's Aggregated Computational Toxicology Online Resource; Egeghy et al., 2012

System Information -> Building a Mass-Balance Model

Defining the "system of interest" based on its properties:

- Volumes
- Composition
- Flow rates
- Temperature
- pH, etc

- Considerations for different processes and their rates…



- Develop mass balance equation(s)

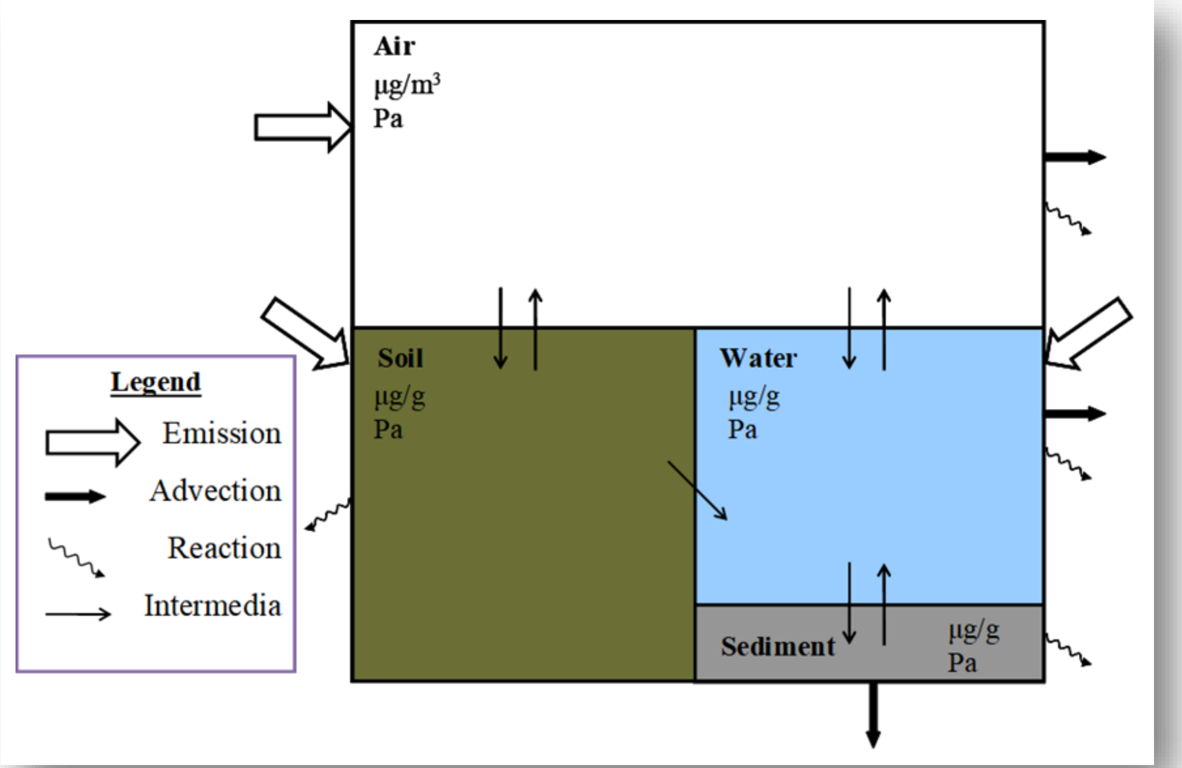
Simple mass balance for a **one compartment model**

$$\frac{\partial C}{\partial t} = In - Out - Reaction$$

Multimedia Mass-Balance Models: Conceptual Overview

Multimedia models describe and quantify the processes and partitioning determining chemical fate, transport and distribution in a system, e.g., in vivo and in vitro toxicokinetics, indoor environments, or natural environments

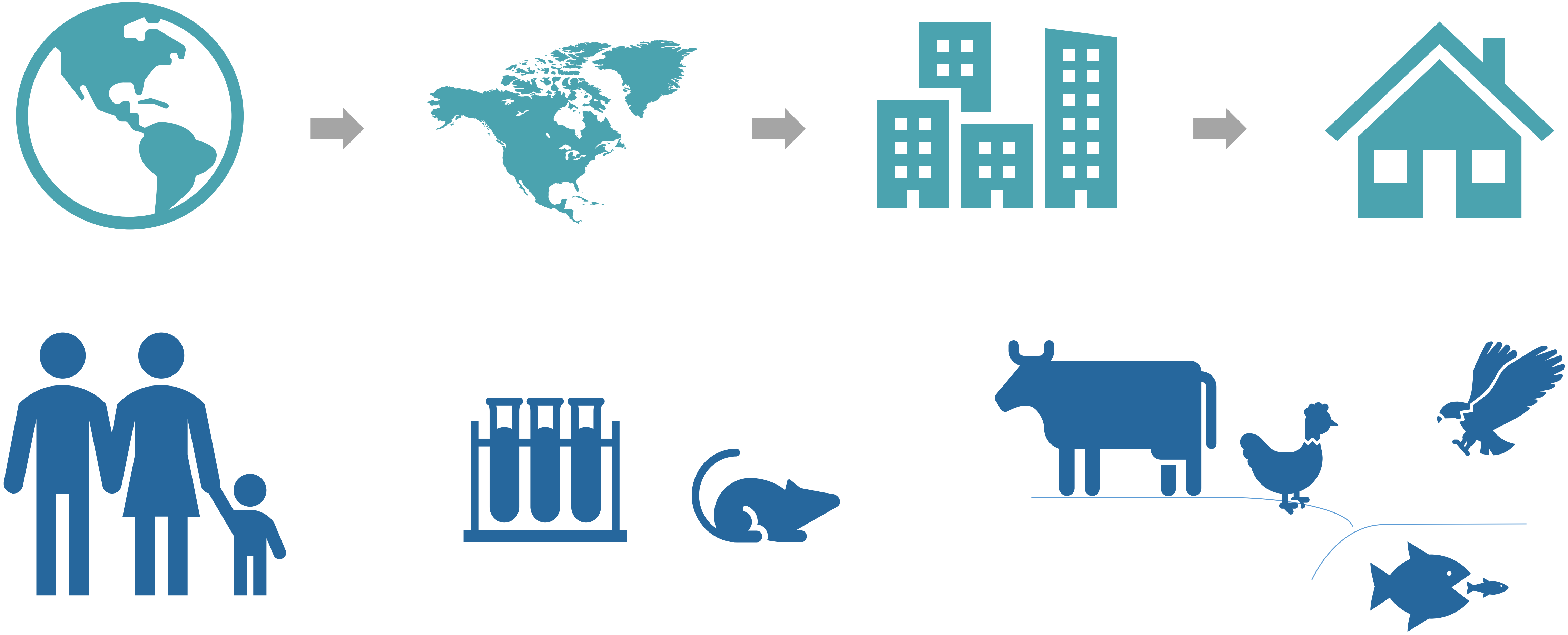
- Generic schematic of a multimedia mass balance chemical fate model for a natural environment (system)
- Chemicals move in and out of the system
- Chemicals react (degrade) in compartments (media) and move between compartments
- Common input parameter requirements, i.e., emission rates, phys-chem properties, degradation rates (half-lives)



<u>Concept of parsimony:</u>

- Balance between model complexity and the answers required; don't make models more complex than they need to be, also need to consider the availability of chemical information required to use ("parameterize") the model!

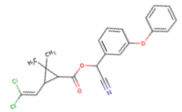
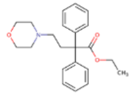
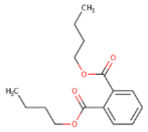
Different Systems and Scales*



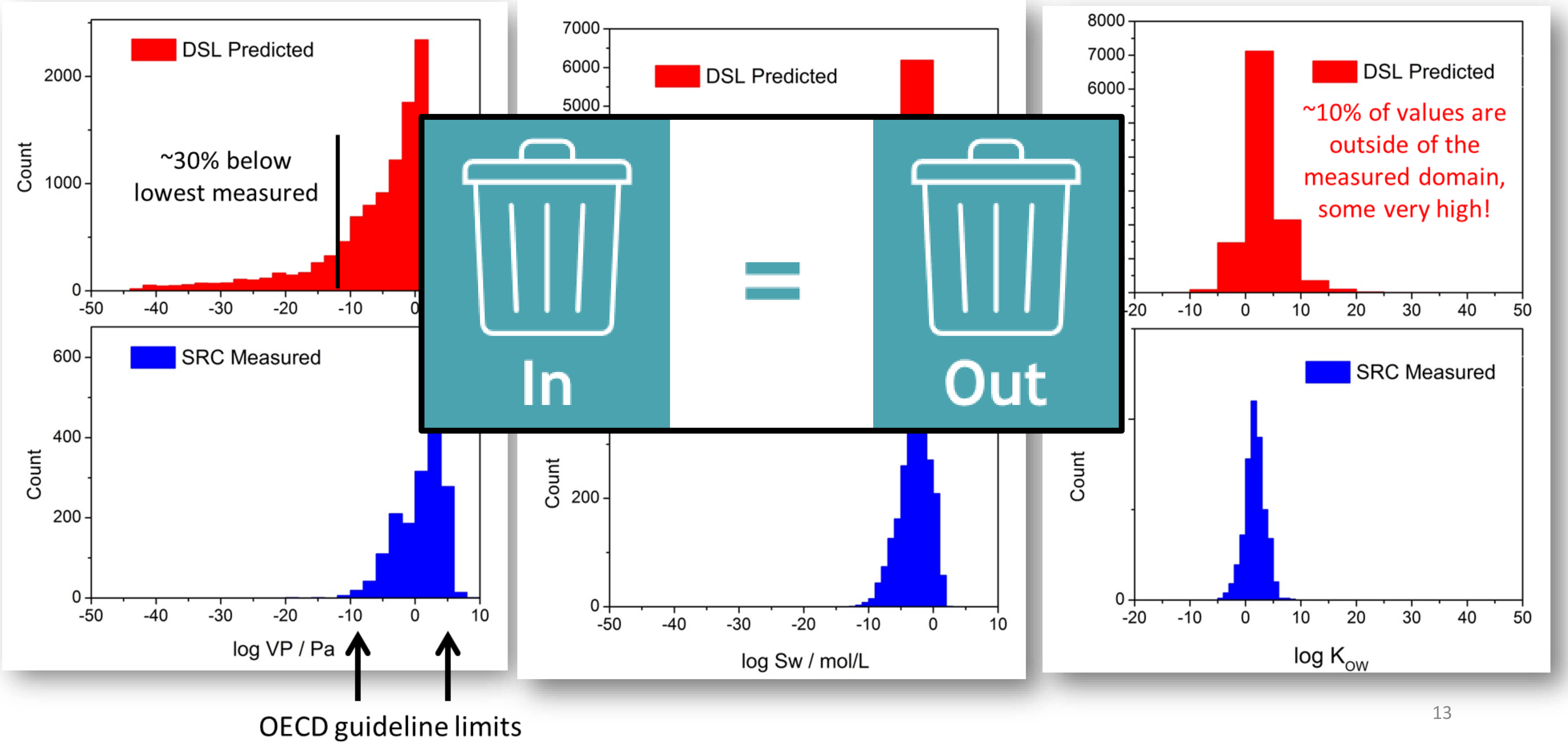
*Spatial and temporal

Chemical Information -> Model Input Parameters

- Chemical use (emission, application, release) rates – how much?
- Mode-of-entry (release) information – how is it used/released?
- Physical-chemical properties, e.g.,:
  - Molar mass (MW; g/mol)
  - Water solubility (S_W; mmol/L)
  - Dissociation constants (pK_a)
  - Vapor pressure (P; P_a)
  - Partition coefficients: Henry's law constant (H; Pa·m^3/mol), K_{OW} or K_{OA} or K_{AW}
- Reaction rate constants (or half-lives) in air, water, soil, and sediment
- Biotransformation rate constants (or half-lives) in biota
- Etc….

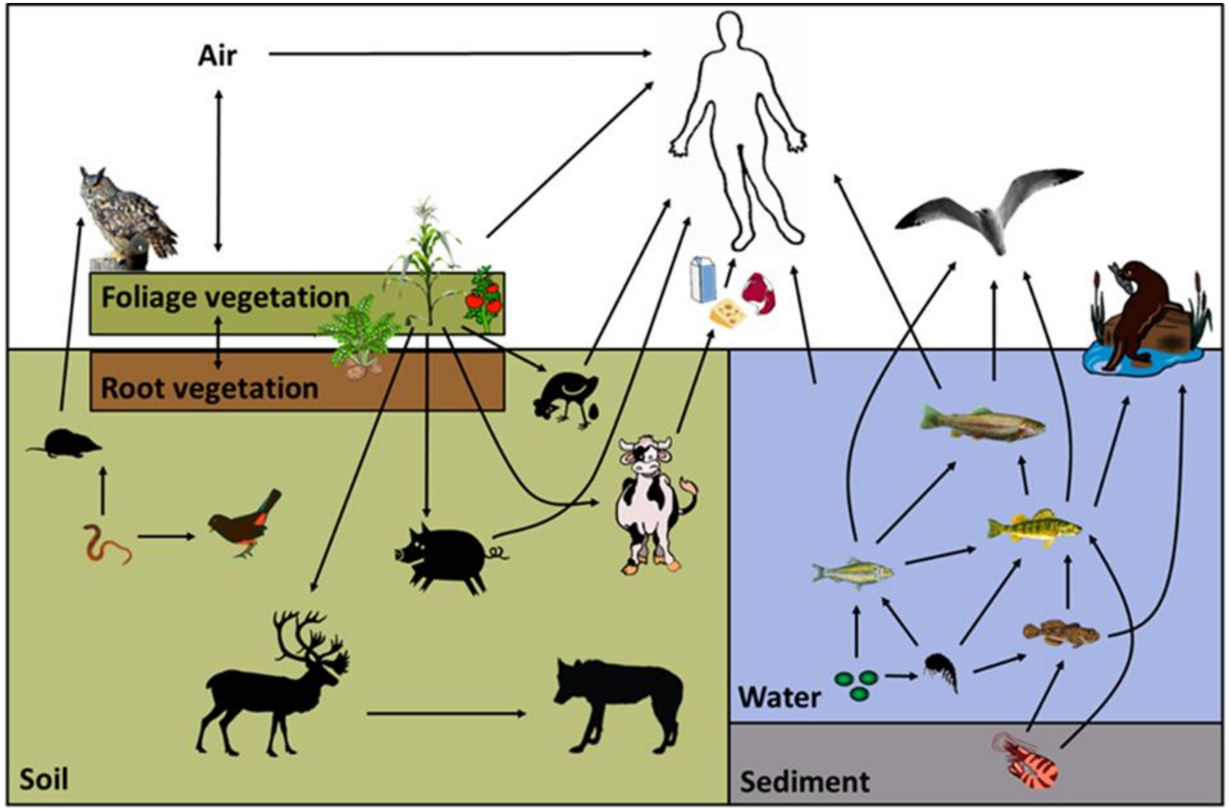




Broad Range of Chemical Properties (& Predictions)



Risk Assessment Identification And Ranking (RAIDAR): Conceptual Overview

Combined mass balance **fate and bioaccumulation models** to link chemical emissions to exposure (ADD hazard data for risk/safety assessment)

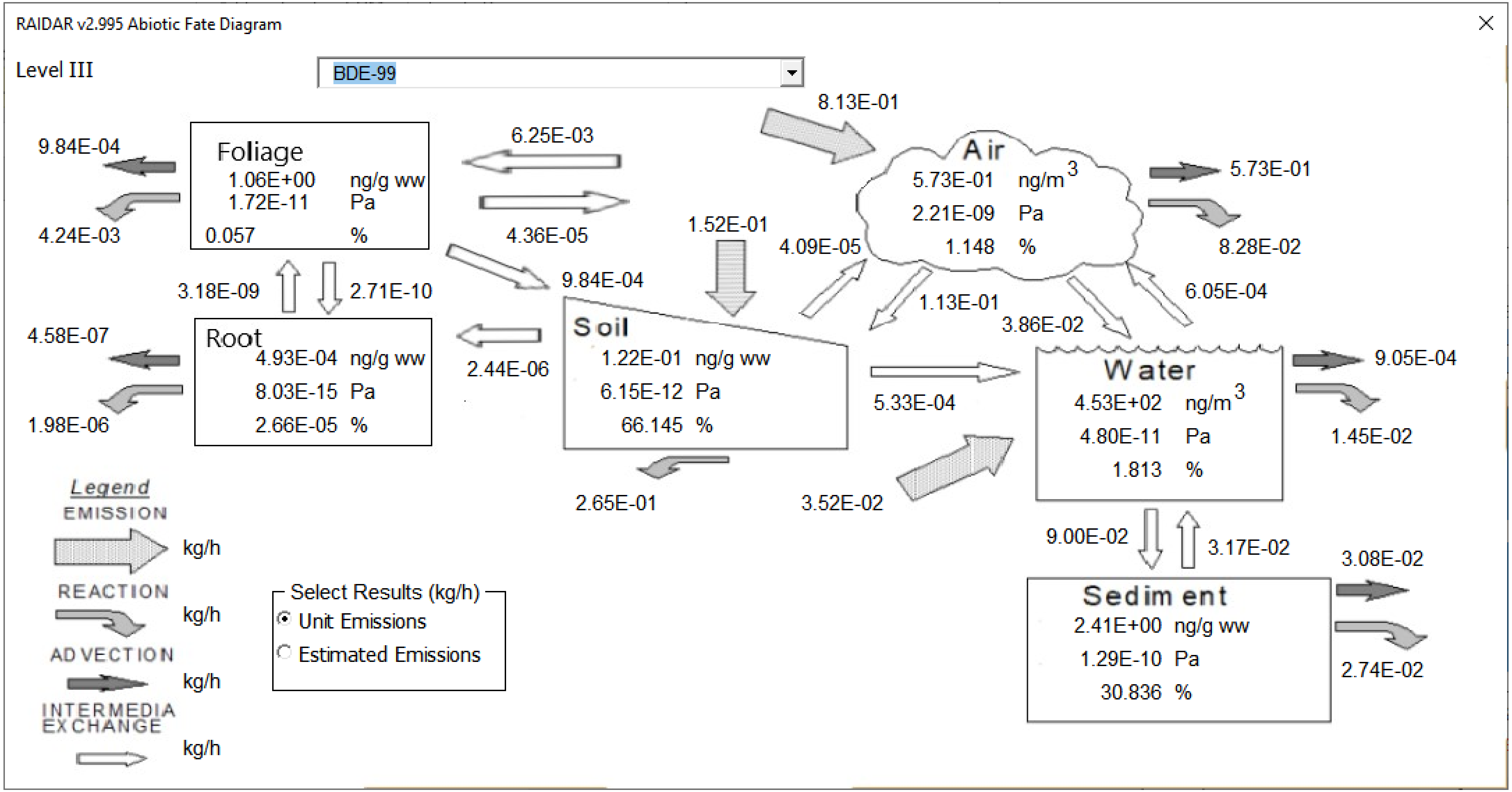


- Evolution of the EQuilibrium Criterion (EQC) fate model (Mackay et al., 1996)
- Broad range of representative ecological receptors and far-field human exposure pathways (diet, water, outdoor air)
- Regional scale 100,000 km^2: default conditions typical of temperate North America
- Neutral and ionizable organic chemicals

Arnot et al., ES&T 2006

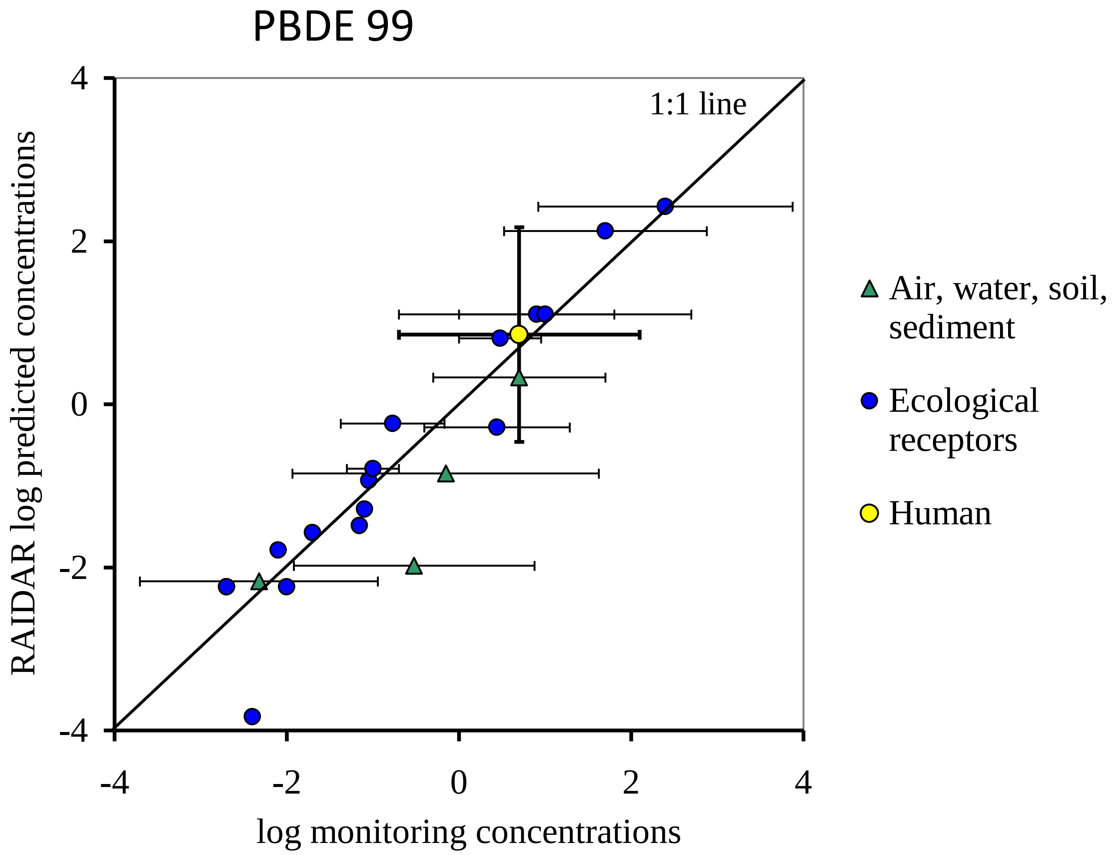
Arnot and Mackay, ES&T 2008

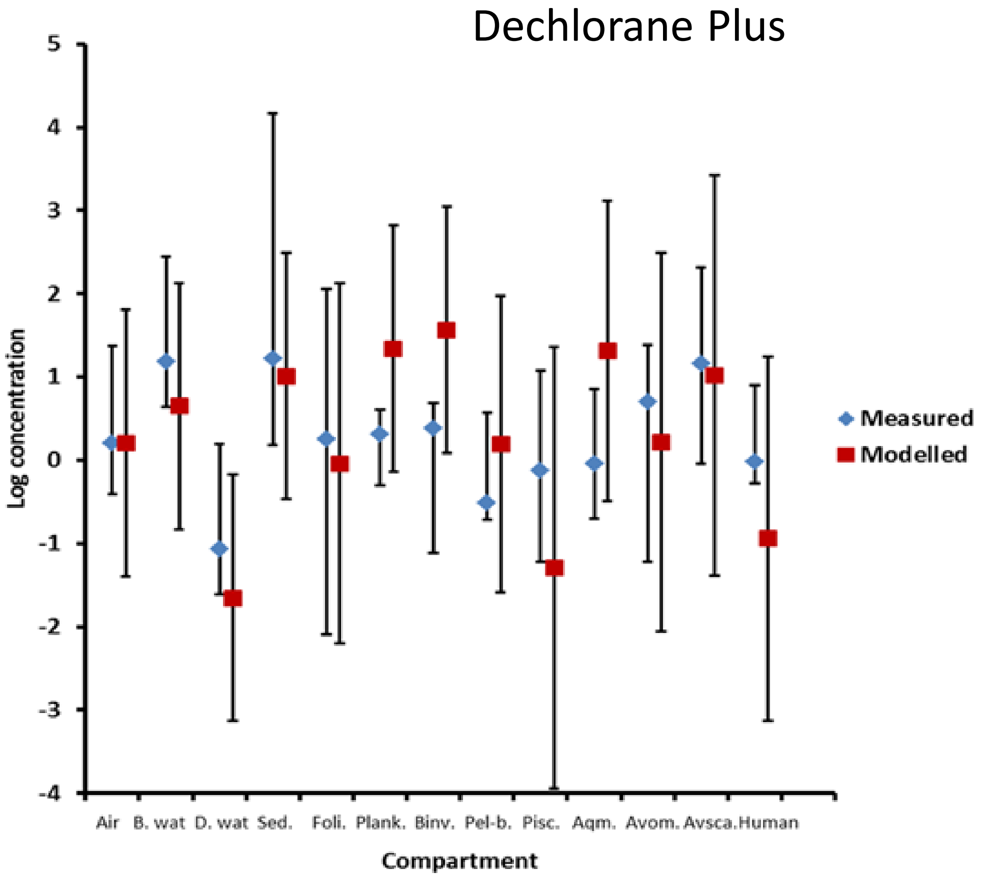
RAIDAR, e.g., chemical fate & transport calculations



RAIDAR: e.g., model evaluations

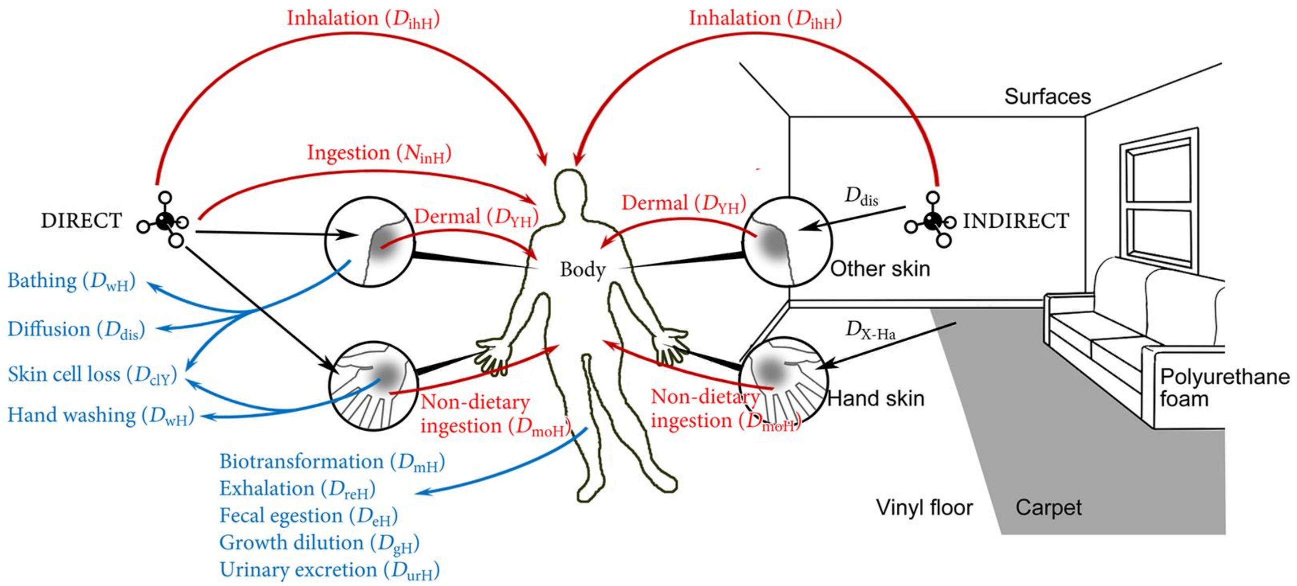
"Ground-truthing the source-to-dose continuum"

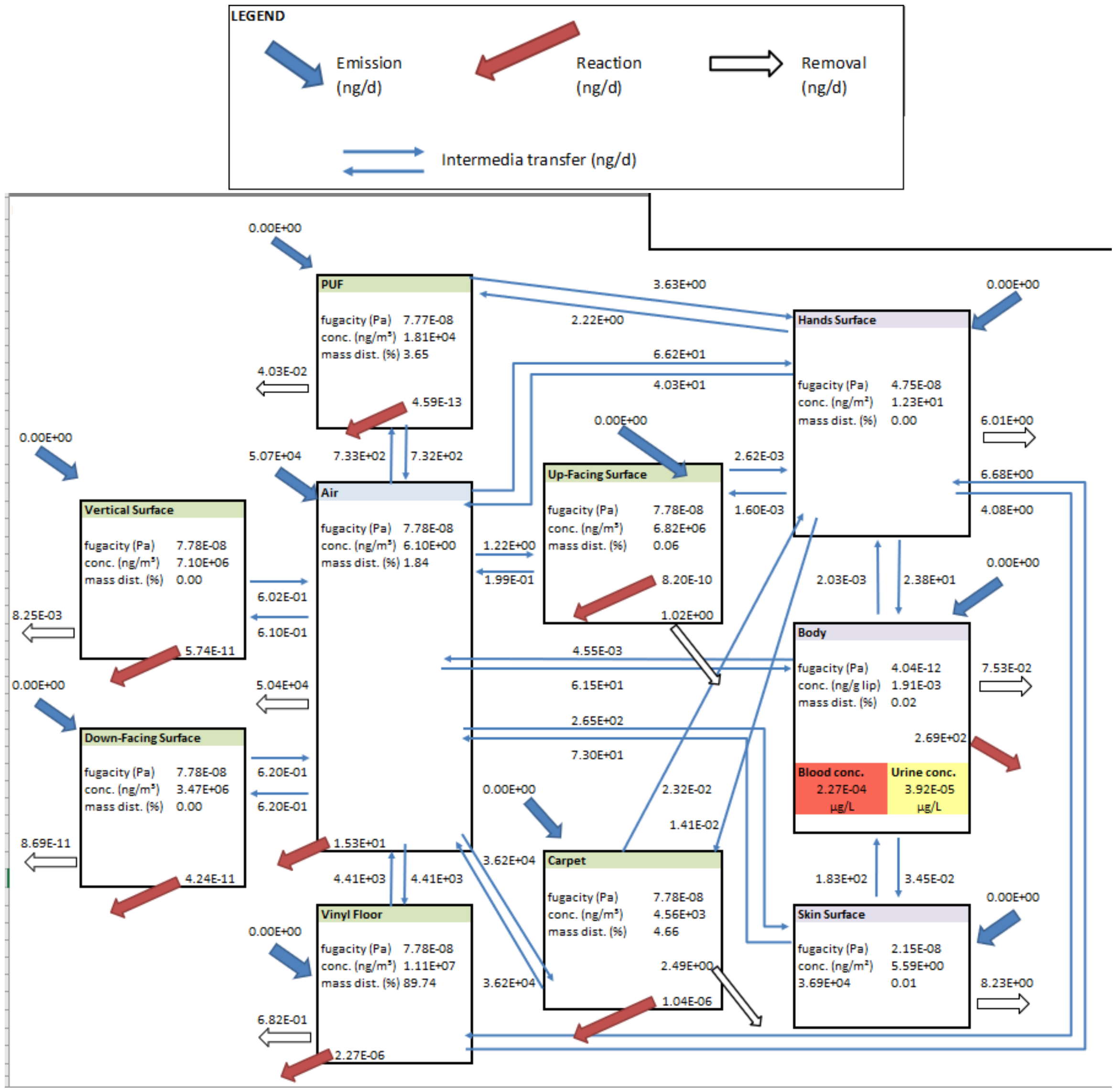




Based on Cowan et al. *IEAM* 2009

RAIDAR – Indoor and Consumer Exposure (ICE) model





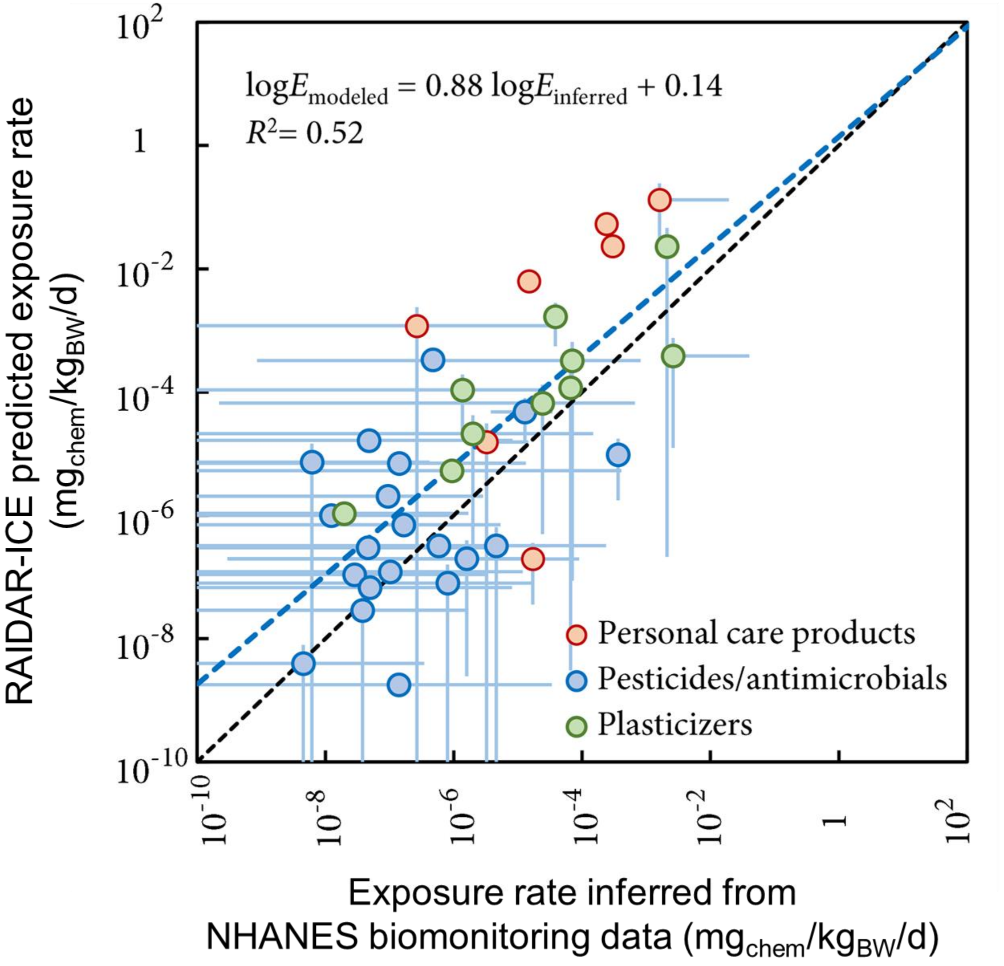
Combines indoor fate and toxicokinetic mass balance models to simulate human exposure from chemicals used indoors and/or direct applications (e.g., dermal)

Route-specific intake rates, total intake rates, as well as steady-state **blood** and **urine** concentrations

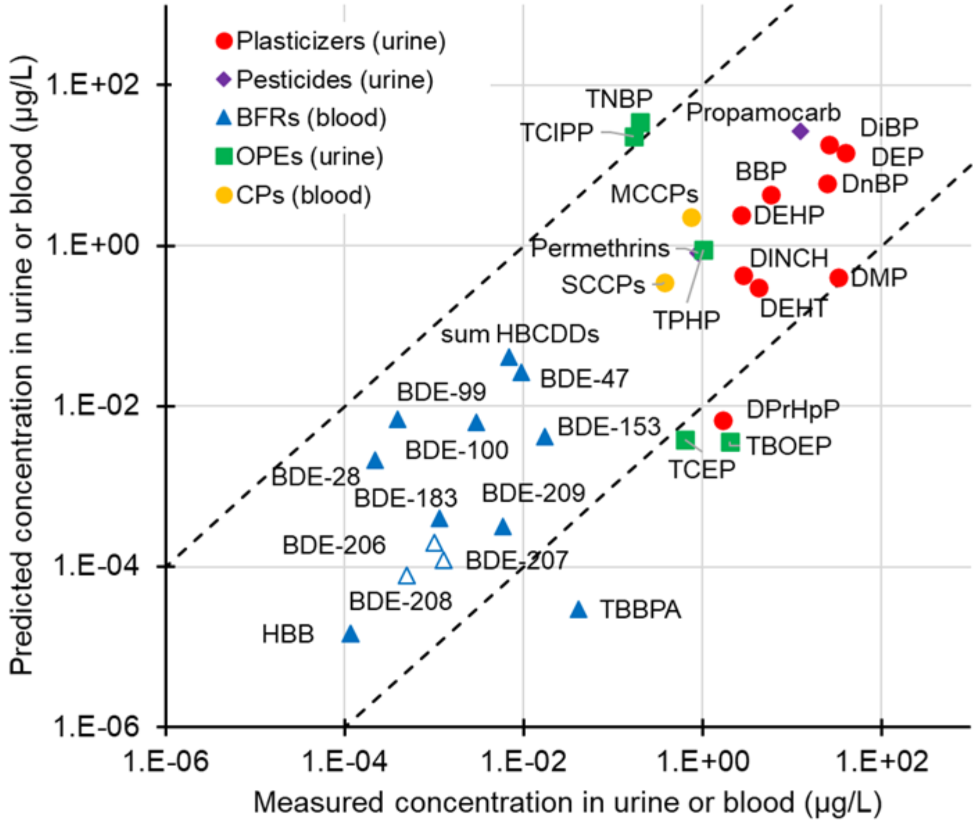
Li et al., ES&T 2018

RAIDAR-ICE: e.g., model evaluations

United States



Europe

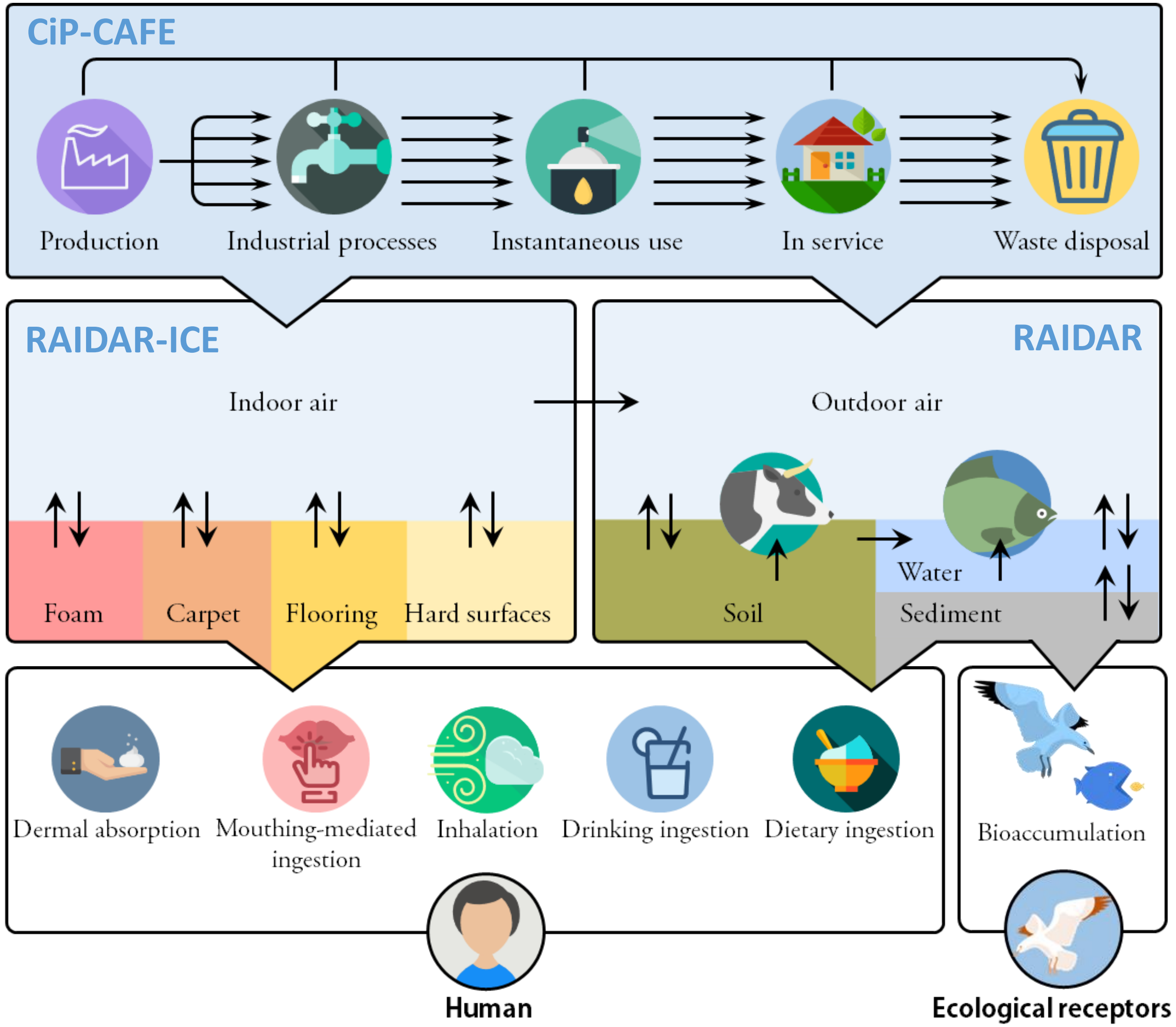


Li et al., ES&T 2018

Arnot et al., in prep

PROduction-To-EXposure High Throughput (PROTEX-HT) model: Conceptual Overview

- Holistic
- Mechanistic
- Consolidated modules
- **Steady-state**
- *Automated in EAS-E Suite*



<u>THREE input parameters</u>:

1. SMILES
2. Production Volume
3. Functional Use Category

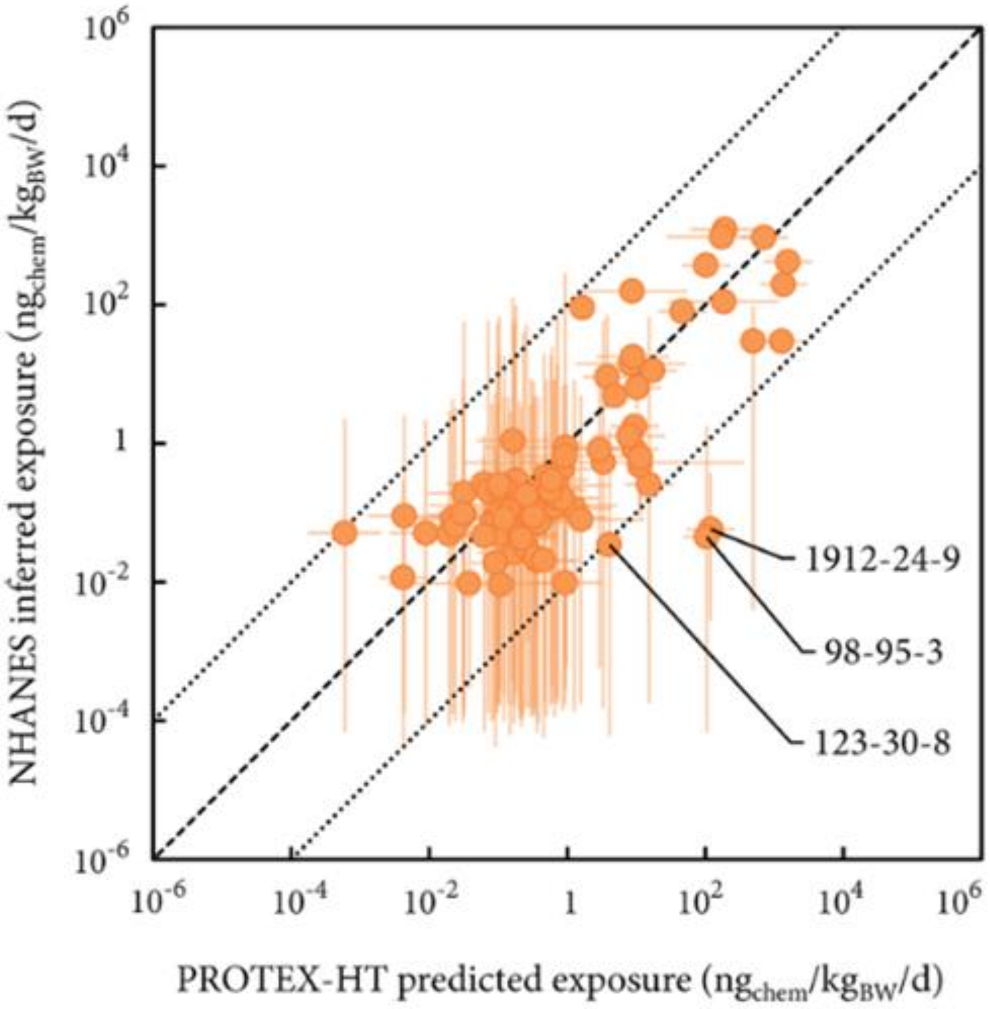
A LOT OF INFORMATION!

Li et al., EHP 2021

PROTEX-HT: e.g., human exposure model evaluation

- Evaluated as a case study using 95 chemicals with human exposure estimates inferred from biomonitoring data in the US population (NHANES data)

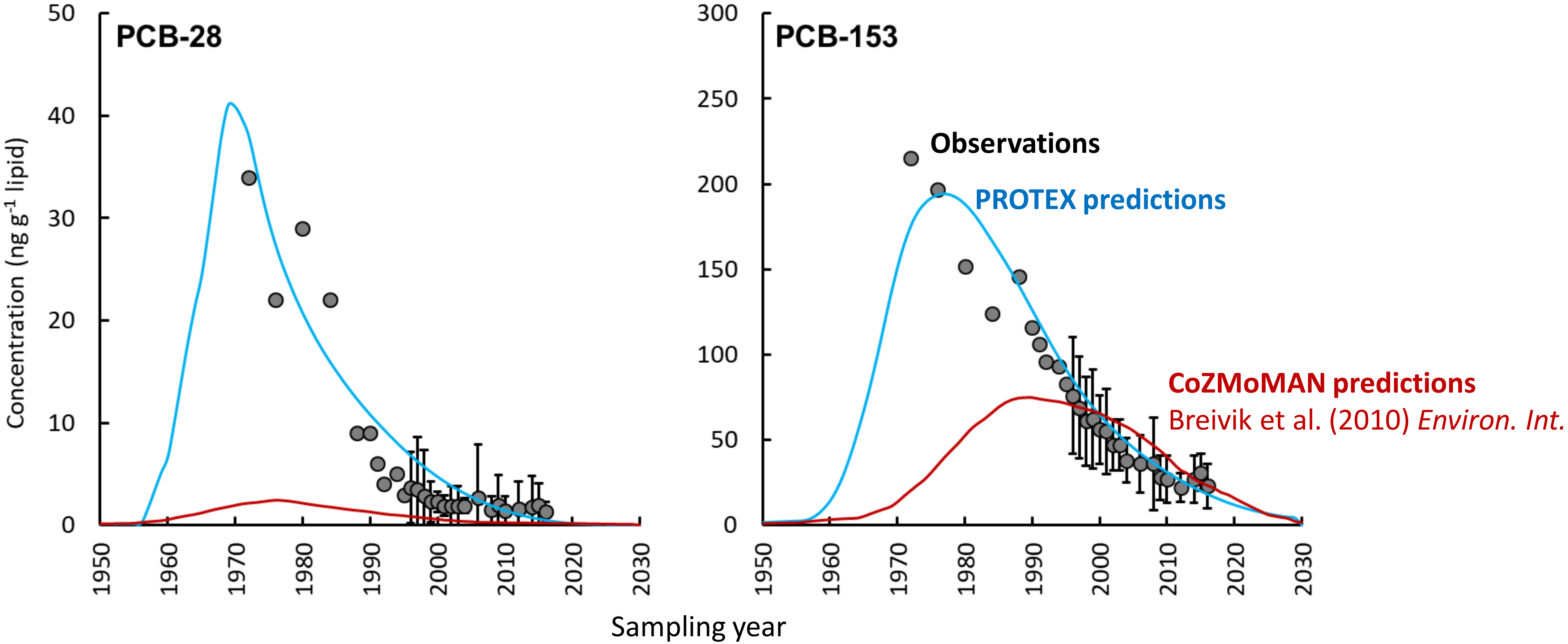
- **79%** and **97%** of the human exposure predictions are within **one** and **two** orders of magnitude, respectively, of the independent observations



Li et al., EHP 2021

PROTEX: e.g., human exposure model evaluation

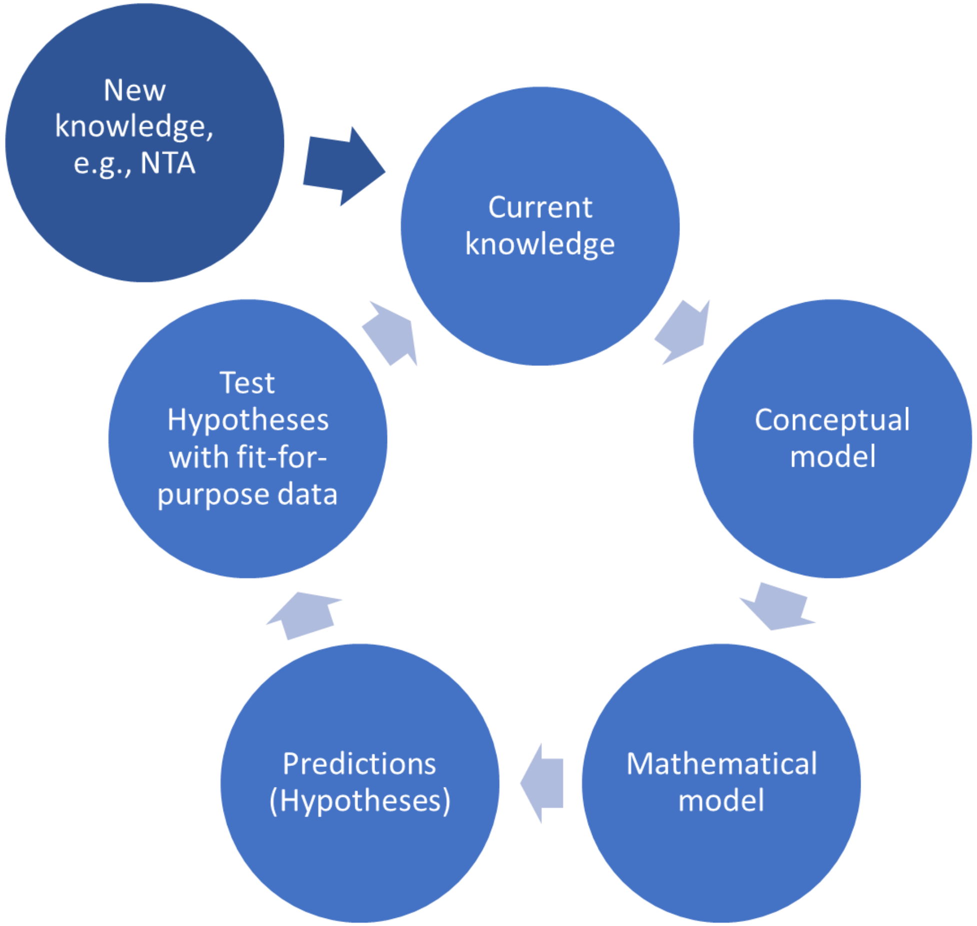
Reproducing PCB contamination in milk of Swedish mothers collected between 1972 and 2016



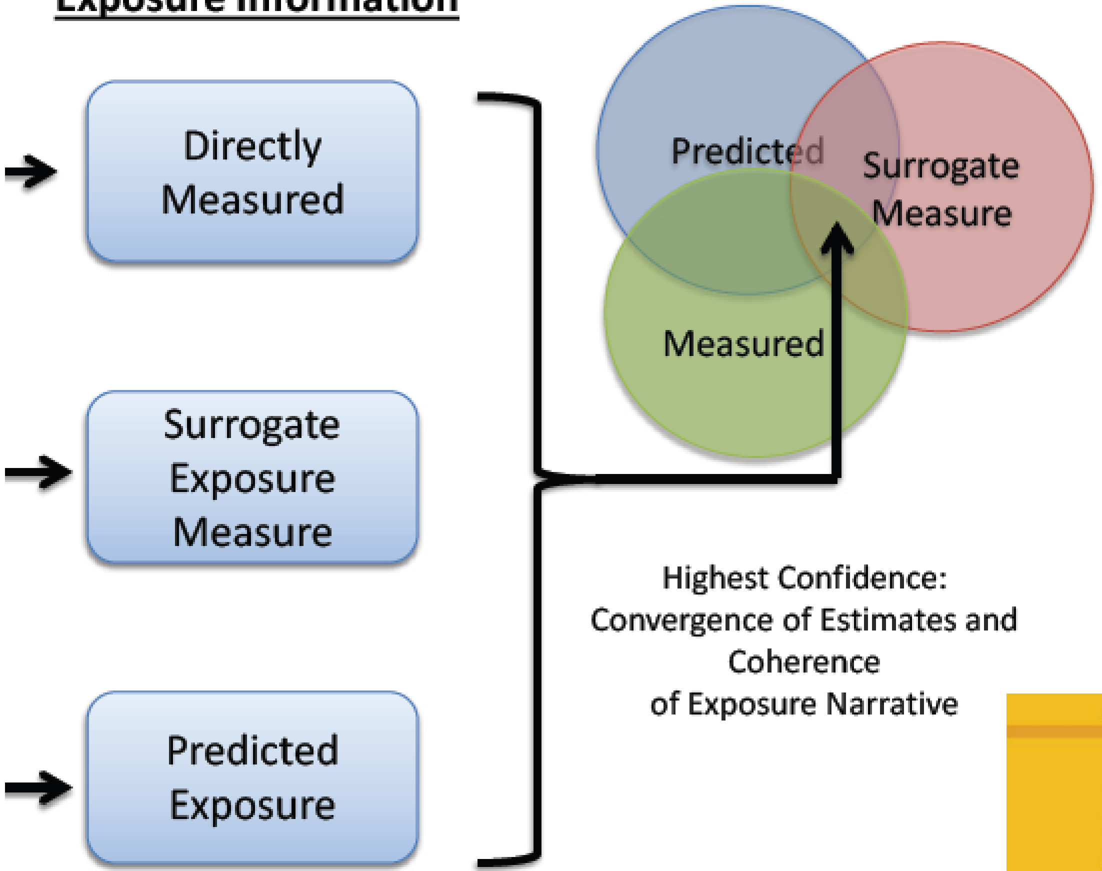
Li et al., ES&T 2018

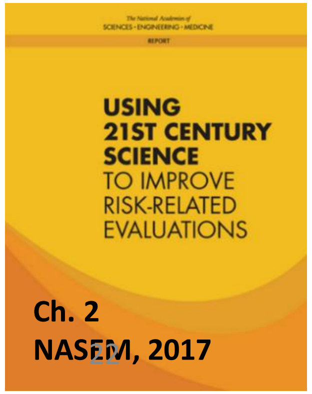
Fostering Confidence in Exposure Assessment

The Scientific Method



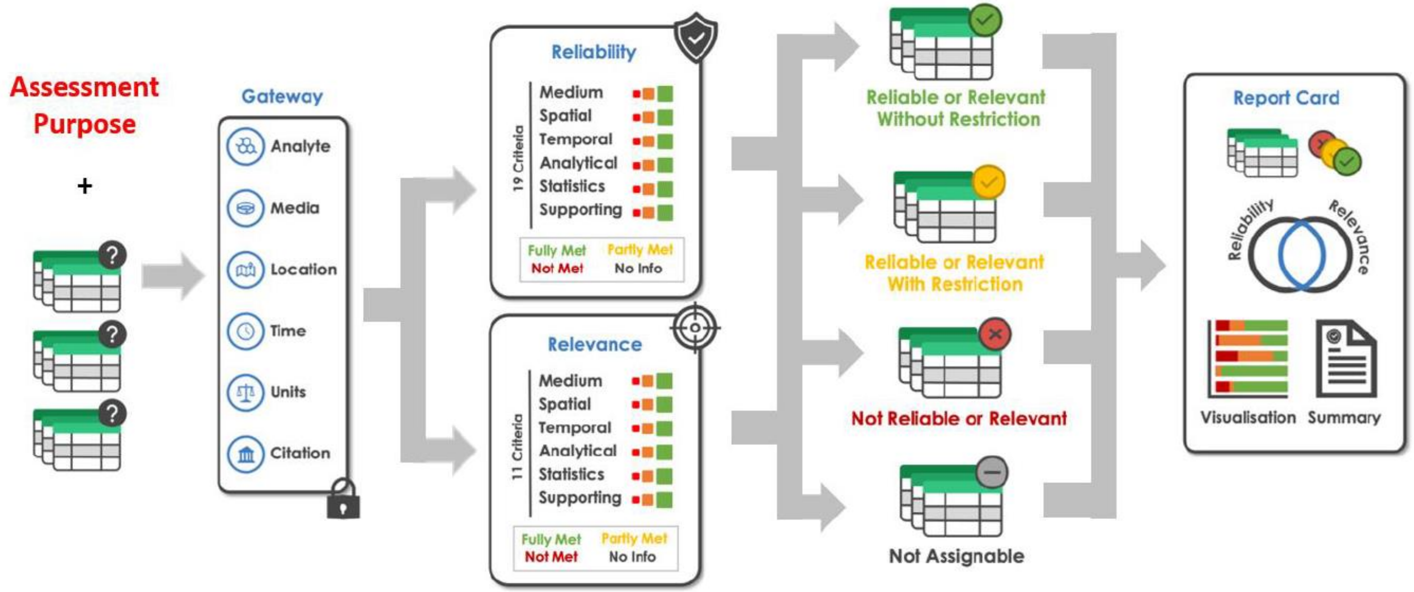
<u>Coherence in Exposure Information</u>





Criteria for Reporting and Evaluation of Exposure Data (CREED)

- Society of Environmental Toxicology & Chemistry (SETAC) workshop
- Supports a transparent approach towards evaluating reliability and relevance of measured exposure data
  - Strengthens the application of monitoring data towards 'ground-truthing' model performance
  - Supports iterative process and scientific method using reliable and relevant (**fit-for-purpose**) monitoring data
  - Papers in development; will be very helpful globally to improve use of monitoring data



https://globe.setac.org/latest-developments-in-data-quality-assessment-for-risk-assessment/

Some Challenges in Exposure Assessment:

- Reliable measured data and models are required to evaluate thousands of chemicals
- Exposure data are a vital part of risk-based decision-making; **50% of the equation!**

However:

- Reliable measured exposure data are difficult and resource-intensive to obtain
- Inappropriate & outdated models & tools are often used for exposure & risk estimation
- Stakeholders have **limited time and training** to apply new and existing data and tools
- Compiling required **model input parameters** can be time consuming and challenging
- Pace of scientific advancements > integration into decision-making = **Challenge**

SCIENCE

Traditional and New Approach Methods

Measurements & Models

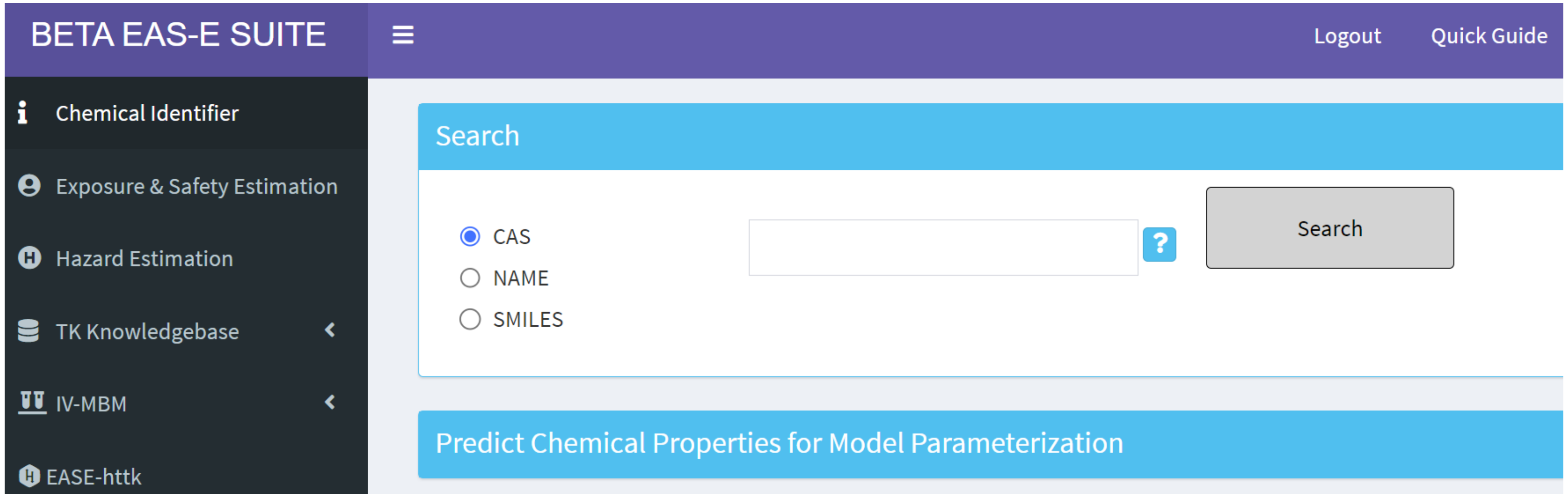
NEED TO "BRIDGE THE GAP"

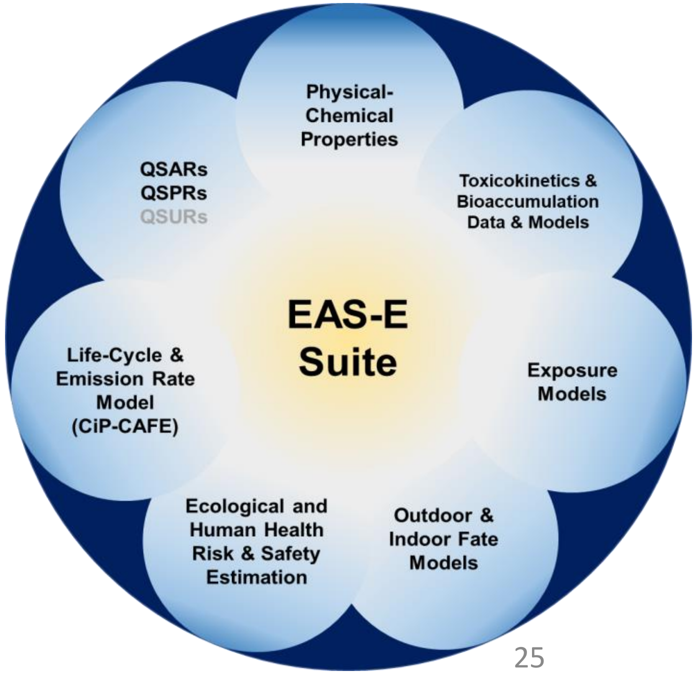
APPLICATION & DECISION-MAKING

Regulatory = safety
Business = sustainability

Exposure And Safety Estimation (EAS-E) Suite

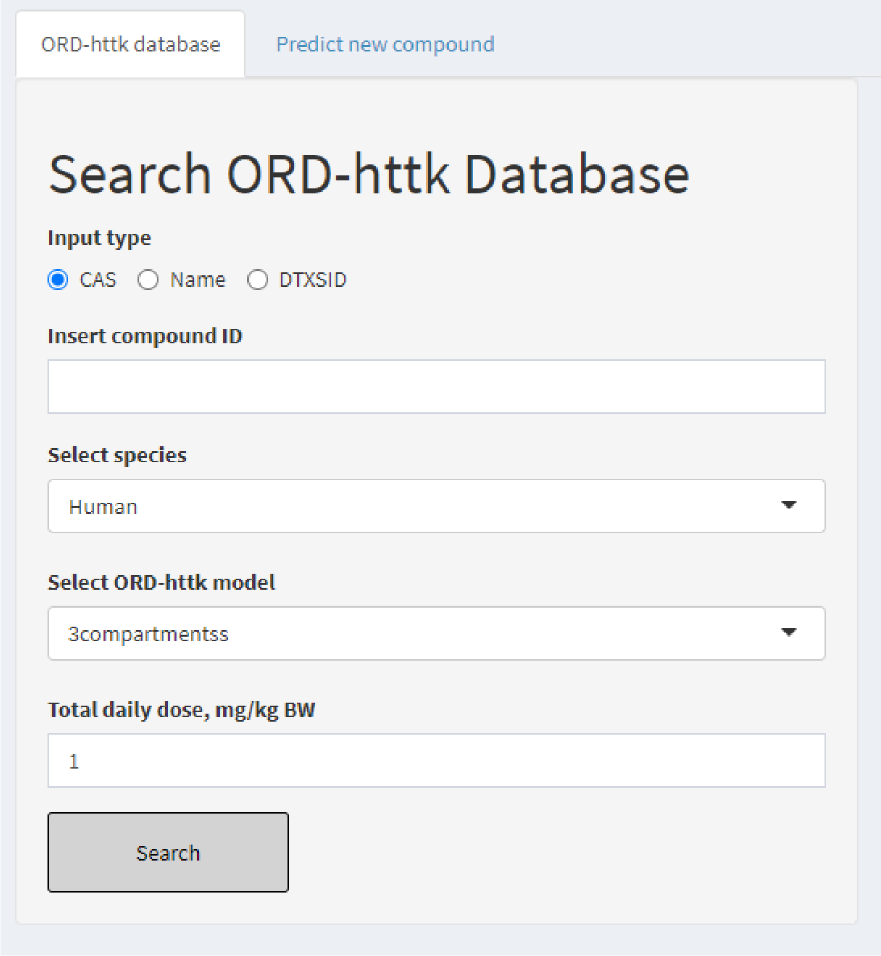
- Provides free, user-friendly access to new and existing data and tools: www.eas-e-suite.com
- Integrates curated databases, OECD validated QSARs, and environmental fate (P/LRTP/M), B/TK, and exposure models to aid chemical assessments for **ecological and human health** & **chemical safety and sustainability**
- **Modular** components can be used individually (e.g., properties, environmental fate, various dermal models, etc) **or consolidated** for aggregate and holistic exposure estimates (i.e., PROTEX-HT)
- Includes internal Threshold of Toxicological Concern (iTTC); Effect (or no effect) data can be entered
- Facilitates model parameterization and data queries based on **CAS, SMILES or chemical name entry**
- Options for user-preferred input information to replace "defaults" (**Tiered**)



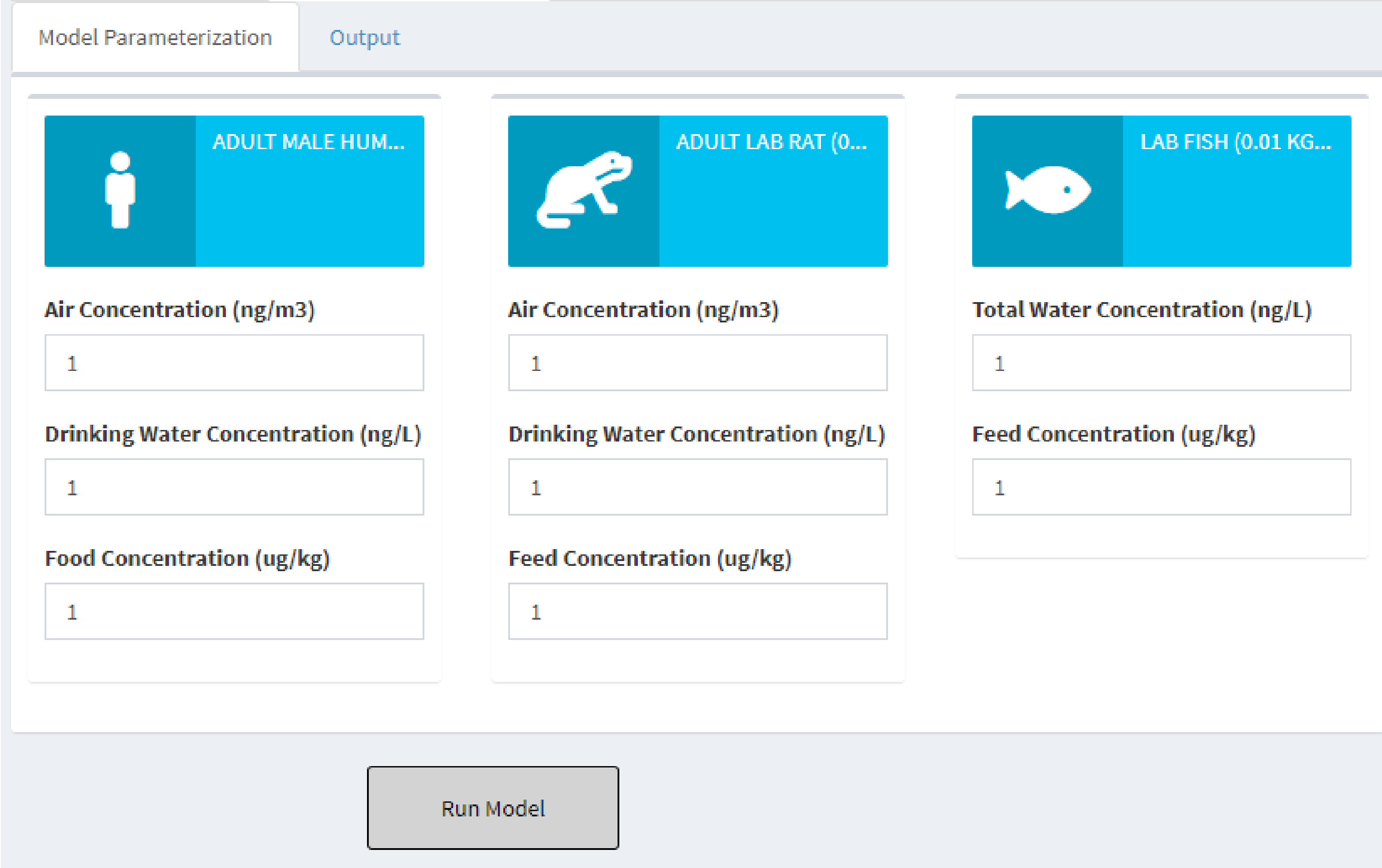


High Throughput Toxicokinetic (HTTK) Models

EPA-ORD HTTK models (R package)



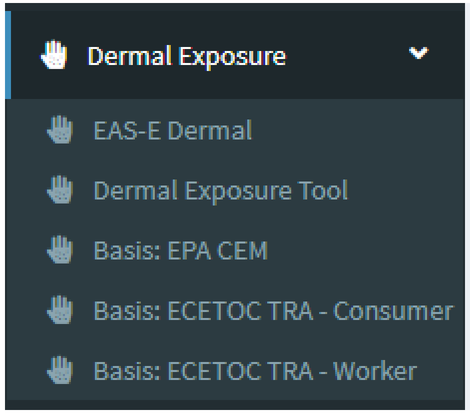
EAS-E HTTK models

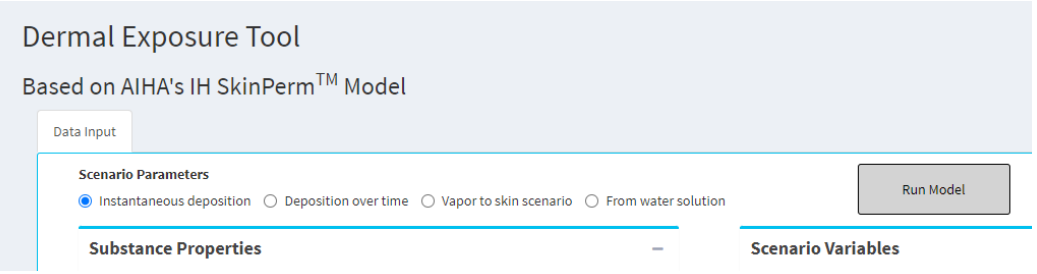


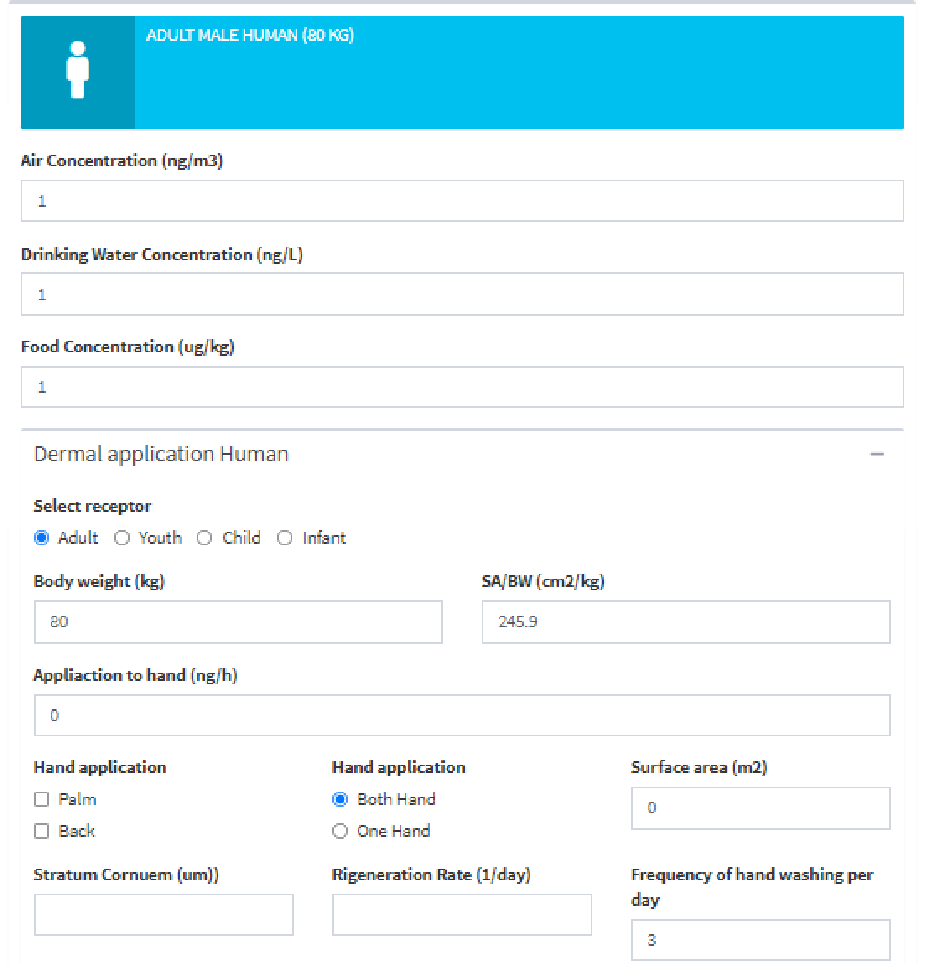
www.eas-e-suite.com

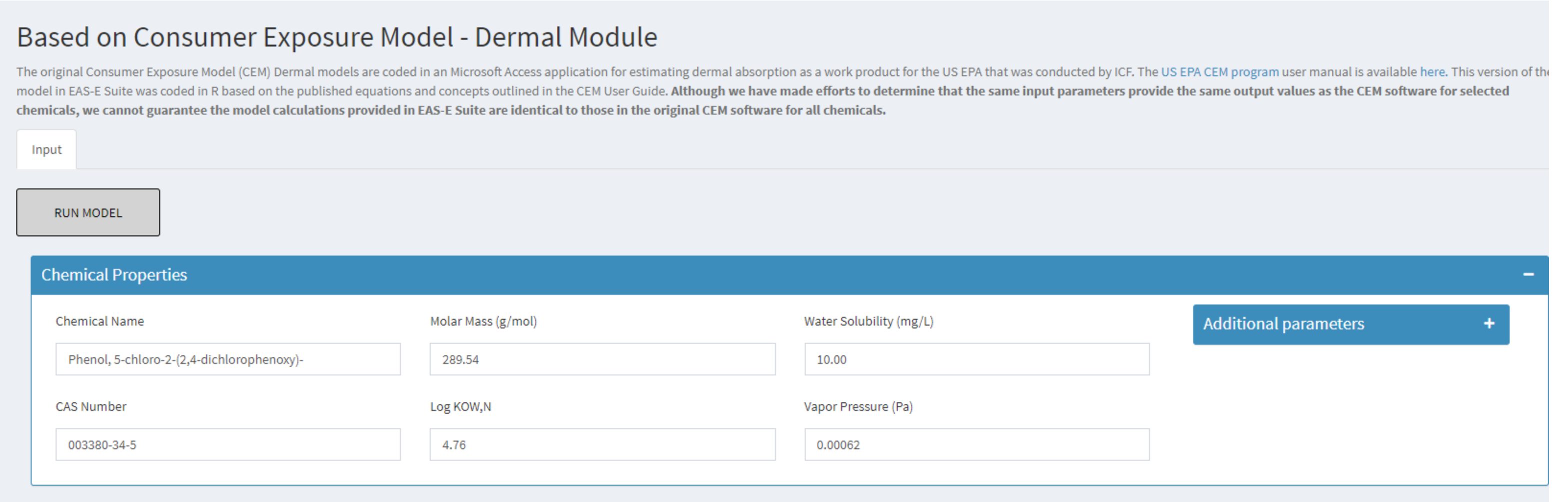
Dermal Exposure Models

Suite of different dermal exposure models for human exposure assessment







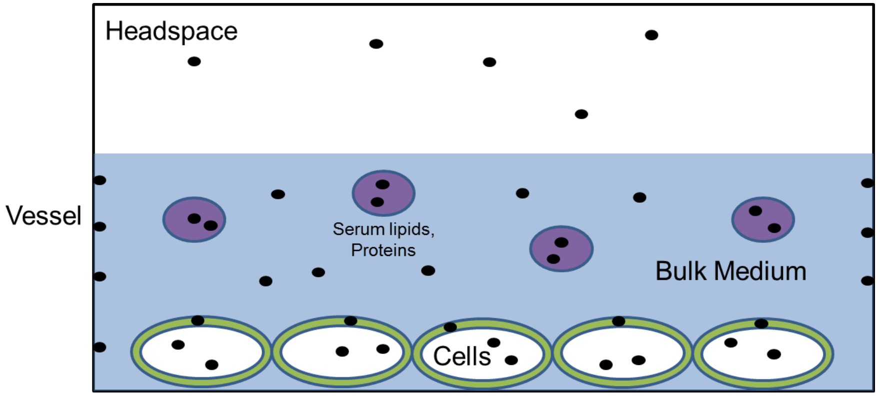


www.eas-e-suite.com

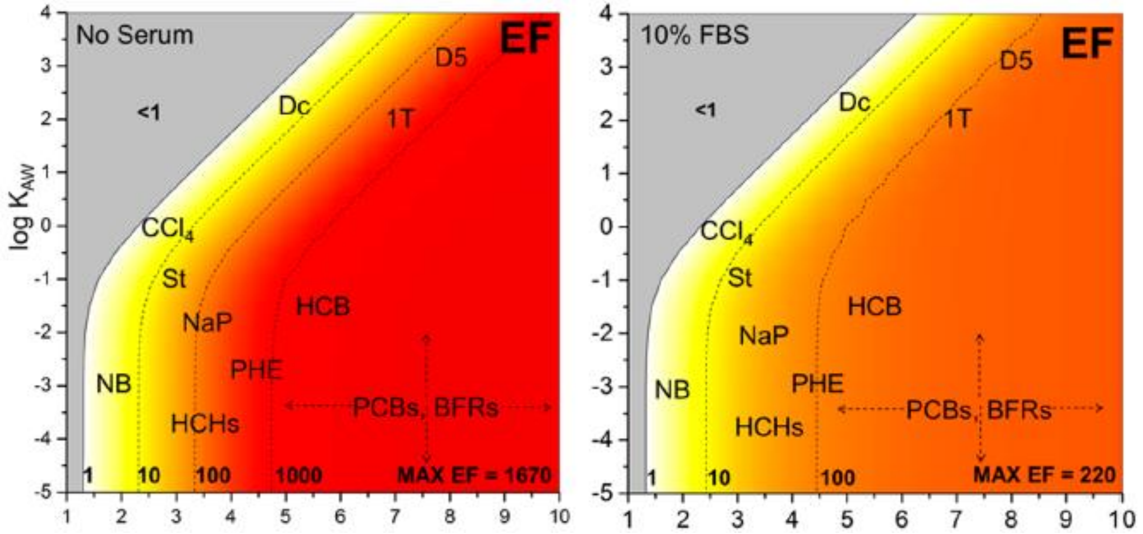
In Vitro Mass Balance Models

Interpreting and applying in vitro (NAMs) data for hazard and risk

- Chemical is added to bulk medium
- Final in vitro disposition (distribution) can vary greatly and is a function of:
  i. test system properties
  ii. chemical properties, i.e., partitioning



$$\textbf{EF} = \frac{\text{Cell Concentration}}{\text{Initial Nominal Medium}}$$



Armitage et al., ES&T 2014

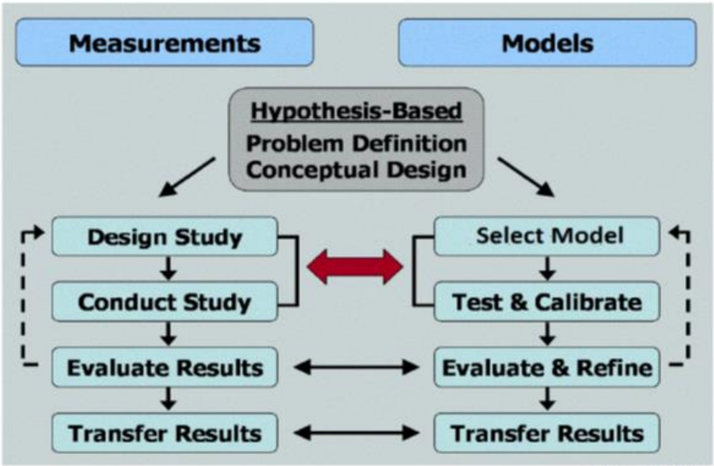
Armitage et al., Toxics 2021

www.eas-e-suite.com

Summary

- If there is no exposure; there is no risk -> **Quantifying exposure is important**
- Measurements are gold, *but very limited* -> **Exposure models are required**

Iterative Use of Measurements and Models



Ozkaynak 2009

- **<u>Merging measurements and models to:</u>**
  - Integrate data and develop the exposure narrative
  - Identify sources and pathways for mitigation when necessary
  - Systematically address data gaps and test hypotheses
  - Systematically address uncertainty

- Continue advancing complementary exposure estimation methods such as suspect screening & non-targeted analysis to identify “unknowns”

Data and tools for PBT, exposure and risk assessment

www.eas-e-suite.com

www.arnotresearch.com

jon@arnotresearch.com