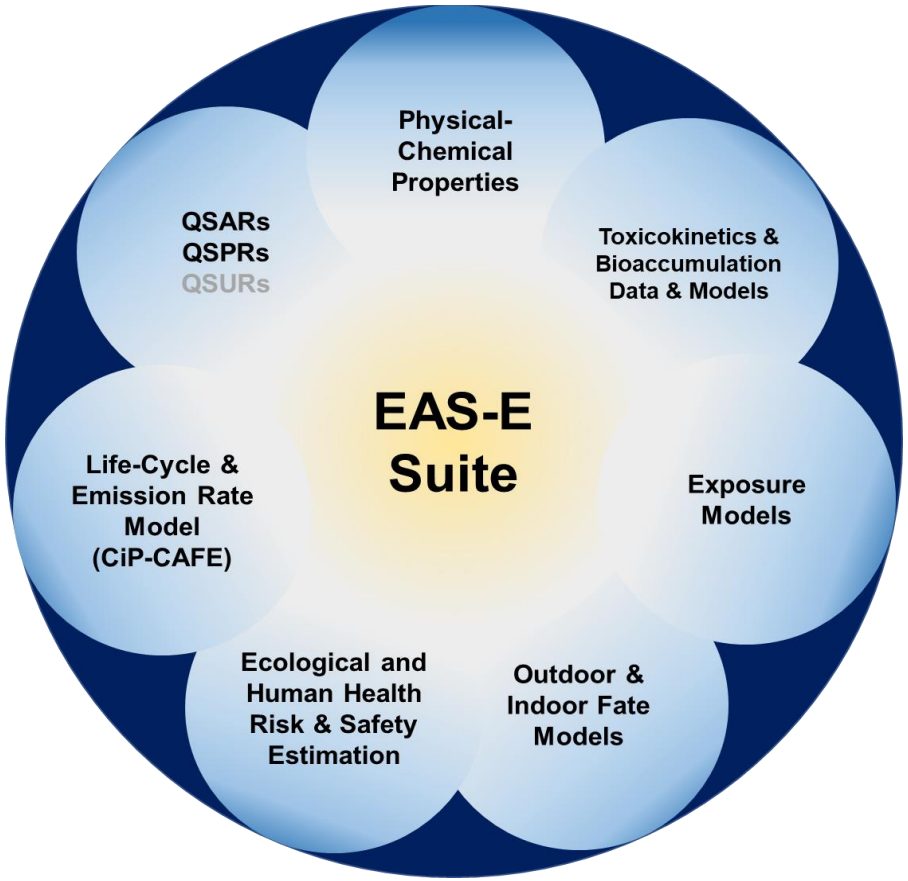
Introductory User Guidance for EAS-E Suite Ver.0.95

June 2022

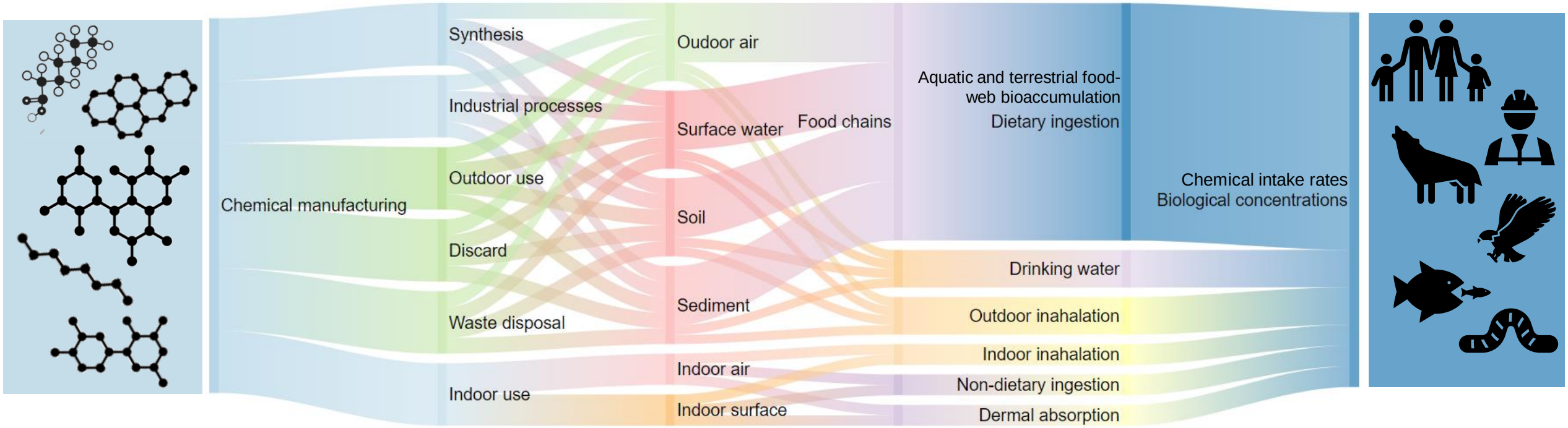


Arnot Research & Consulting

www.eas-e-suite.com

Arnot Research & Consulting

The Scope of Exposure Science: Production to Exposure



Chemical properties, production volumes & use information

Physiologically-based BioKinetic (PBK) models for various receptors

Life Cycle Assessment (LCA), emission rates

Food-web bioaccumulation models

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

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

General Overview

- Free, user-friendly online platform of new and existing data and tools: **www.eas-e-suite.com**
- Integrates curated databases, OECD validated QSARs, and environmental fate (P/LRTP), B/TK and exposure models to aid **chemical assessments for ecological and human health** & **chemical safety and sustainability**
- Facilitates model parameterization and data queries based on CAS, SMILES or chemical name entry using built-in databases (~70K chemicals); options for user-preferred input information to replace "defaults"

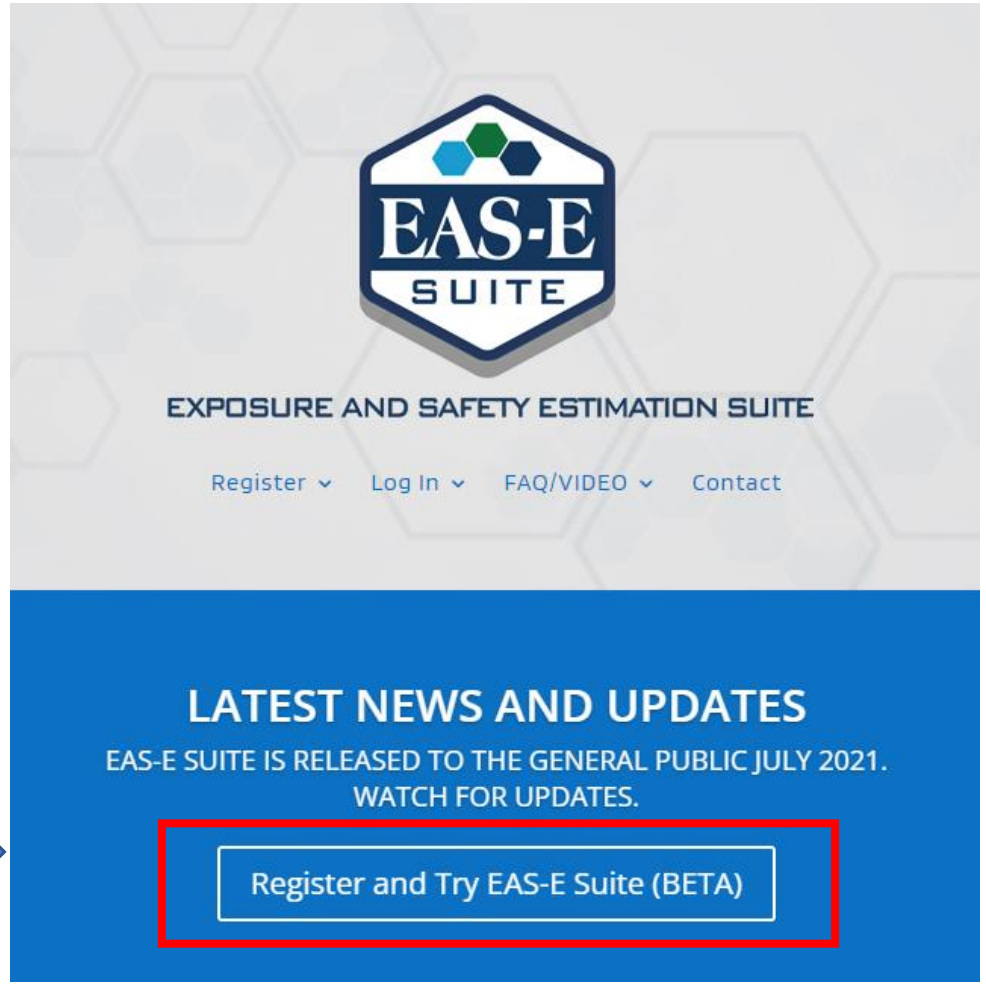
Ver.0.9 Publicly Released July 2021; Ver.0.95 Publicly Released February 2022

Chemical properties & $t_{1/2}$s for >70K organic chemicals	**RAIDAR:** mass balance for environmental fate, exposure & risk; far-field human exposure & risk	**PROTEX-HT:** aggregate human exposure & risk (CiP-CAFÉ+RAIDAR+RAIDAR-ICE)
IFSQSAR and ppLFER models for chemical properties and $t_{1/2}$s	**RAIDAR-ICE:** mass balance for indoor fate and near-field human exposure & risk	**Dermal exposure** models (ES, "IH-SkinPerm", **EPA CEM**, ECETOC TRA consumer & worker)
EPA OPERA QSAR models for chemical properties and $t_{1/2}$s	**POINT SOURCE:** mass balance (**RAIDAR-PS**) & dilution models for eco & human exposure & risk	**EAS-E Suite HTTK** models (incl. rTK & IVIVE) for fish, humans, rat; **EPA ORD httk**
QSARINS for biotransformation and total elimination $t_{1/2}$s (fish & humans)	**F-PEST**: environmental fate & distribution, persistence, long-range transport, mobility	**IV-MBM Ver.2.0**: mass balance model for chemical fate & disposition in in vitro assays
CiP-CAFE: mass flow model to predict emission rate & release throughout life-cycle	**BET**: bioaccumulation estimation tool: lab & field, aquatic & air-breathing organisms	**In vitro and in vivo TK data**: 1,000s of critically evaluated values for fish, rodents, humans

How to register for free access to EAS-E Suite

Pronounced "Easy Suite"

GO TO **www.eas-e-suite.com**



PRESS TO REGISTER

You will fill out a registration form asking for your name and e-mail address. The "Consent *" button must be activated to receive your password!

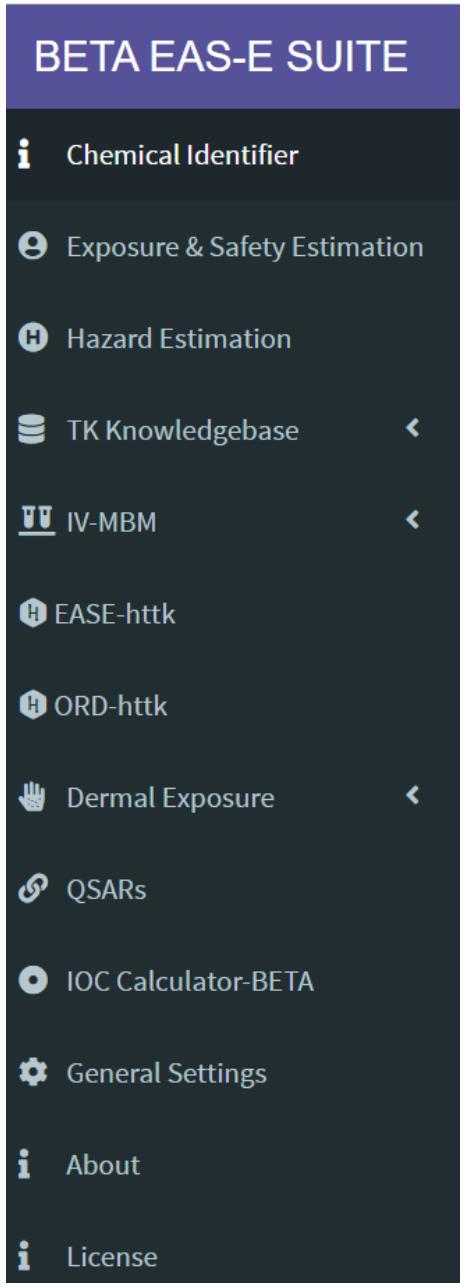
After you submit the on-line form you will receive a password to the e-mail address provided.

You can keep the default password that is e-mailed to you or make your own.

We only keep user name and e-mail addresses to inform users of key updates.

Access and log in to EAS-E Suite using your web browser

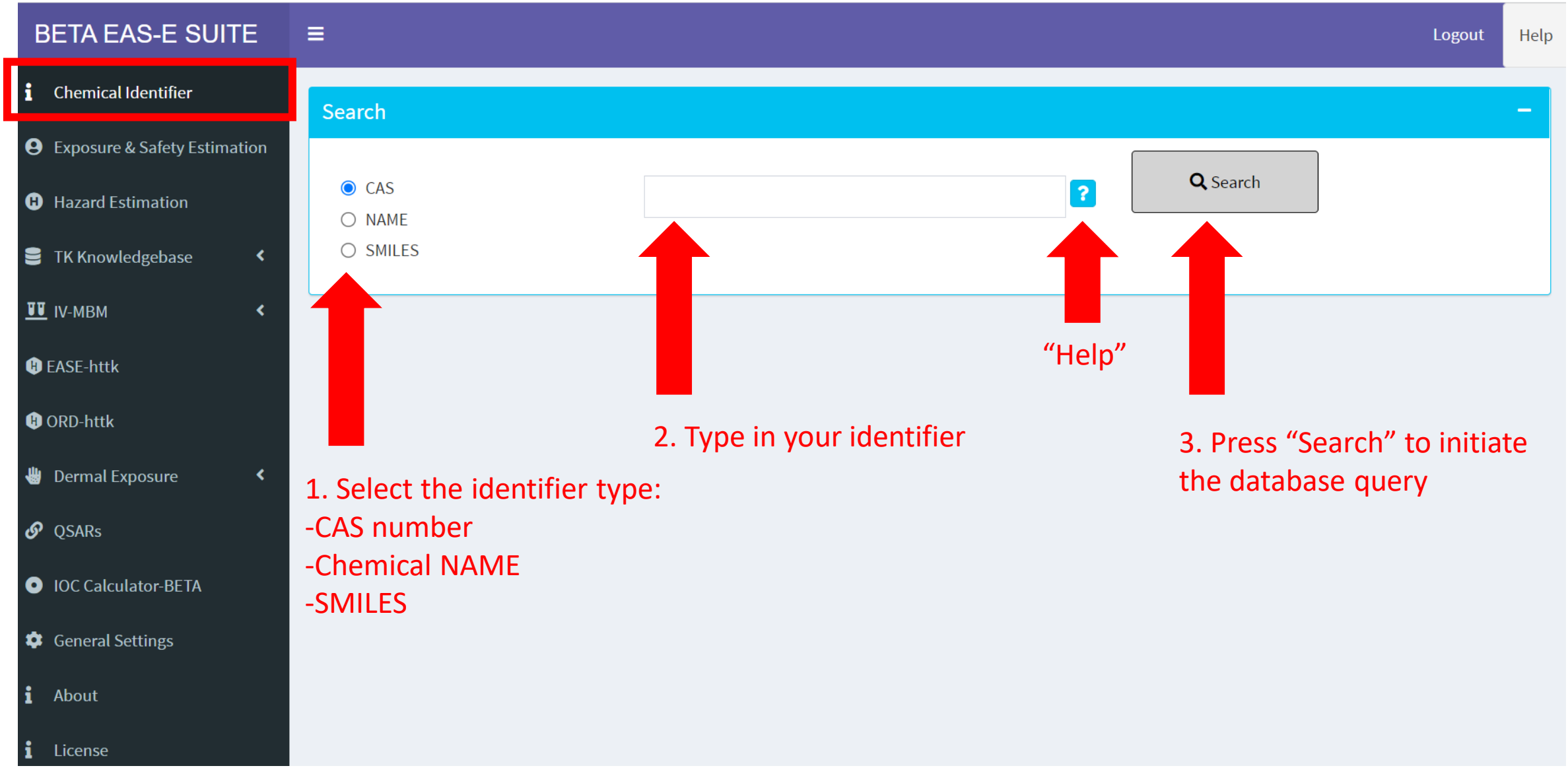
Navigating EAS-E Suite



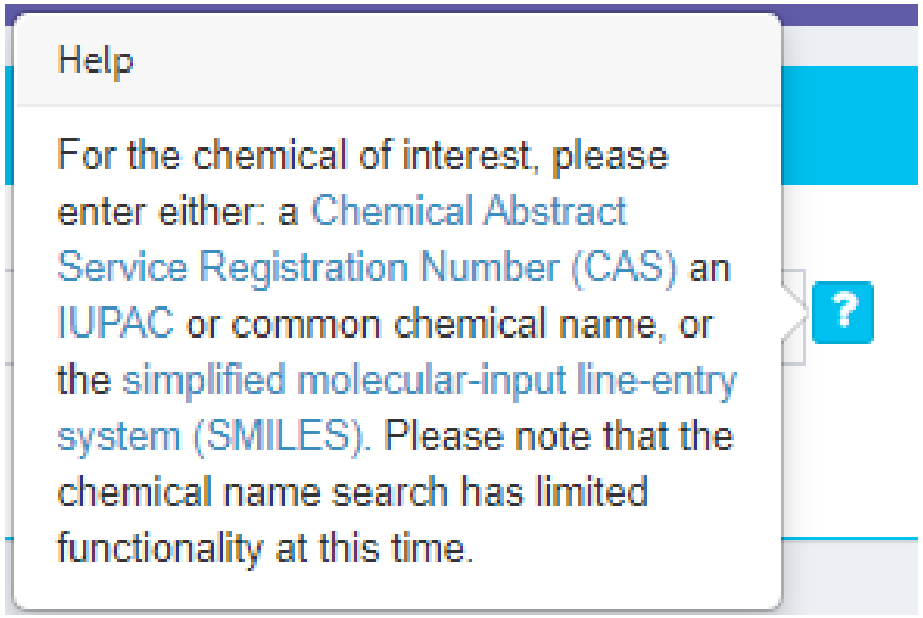
- The menu on the left guides users to tools and databases.
- The first step is to query the built-in database to determine if the chemical of interest is in the current system. If the chemical is in the system, EAS-E Suite will parameterize all models*.
- **The initial chemical parameters provided by the system to facilitate model applications can easily be changed by the users**.
- If the chemical is NOT currently in the system, the user will have to use the built-in QSARs (or other databases and QSARs to obtain the required input parameters to run the models in EAS-E Suite).

*** For Ionizable Organic Chemicals (IOCs, i.e., Acids, Bases) users are required to obtain pKa for the major base or major acid and enter these data into EAS-E Suite**

How to query the system for a chemical of interest



Identifier Help



CAS Number,
is a unique numerical identifier assigned by the Chemical Abstracts Service (CAS) to every chemical substance described in the open scientific literature.

XXXXXX-YY-N
50-29-3
58-89-9
3380-34-5
000080-05-7

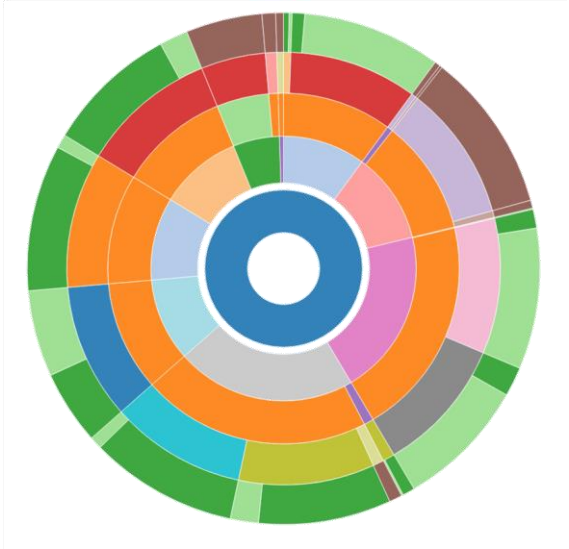
Chemical NAME,
Must be exact match in the database.

DDT
Lindane
Triclosan
Bisphenol A

SMILES,
(Simplified Molecular Input Line Entry System) is a chemical notation that allows a user to represent a chemical structure in a way that can be used by the computer.

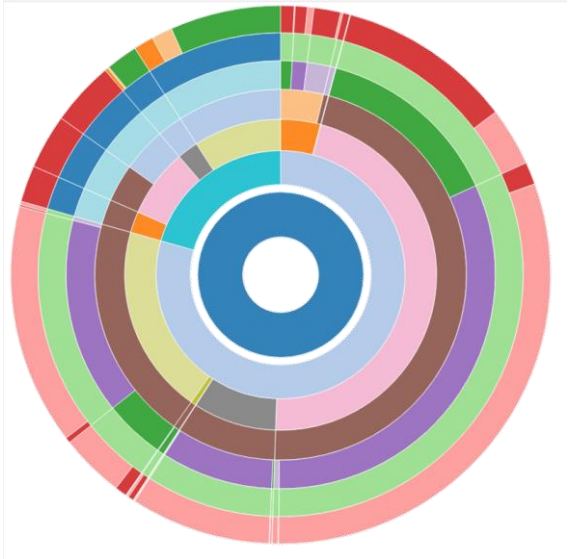
ClC(C(c1ccc(cc1)Cl)c1ccc(cc1)Cl)(Cl)Cl
Cl[C@@H]1[C@H](Cl)[C@@H](Cl)[C@@H]([C@@H]([C@H]1Cl)Cl)Cl
Clc1ccc(c(c1)O)Oc1ccc(cc1Cl)Cl
CC(c1ccc(cc1)O)(c1ccc(cc1)O)C

Physical-chemical properties



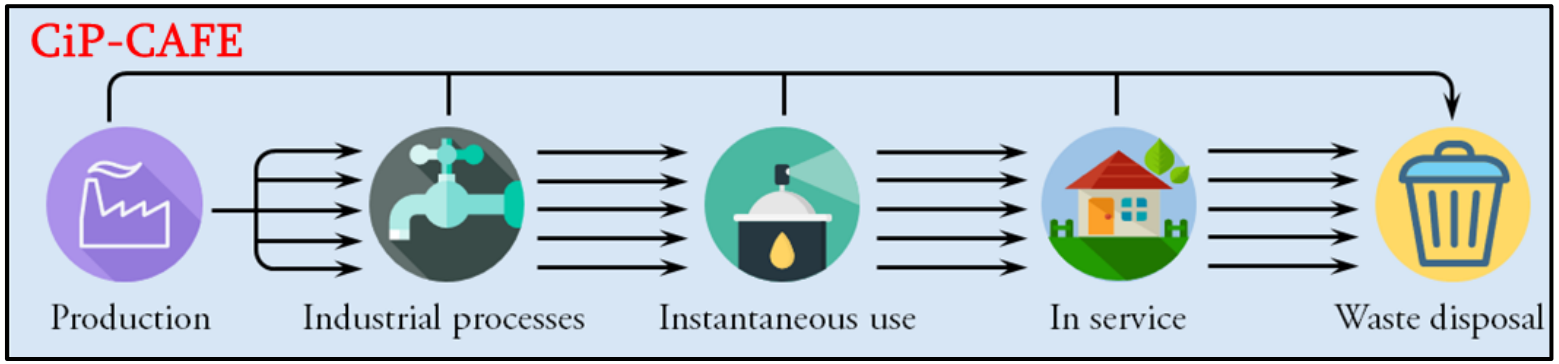
- Currently >200,000 data for ~50,000 compounds
- **Information available:**
  - Various phys-chem (e.g., K_{OW}, K_{OA}, melting point, etc)
  - Experimental and predicted
  - References
  - Applicability Domain for predicted properties (including for EPI Suite predictions*)

Toxicokinetics data



- Currently >28,000 curated data for >10,000 compounds
- **Information available:**
  - Level of the test (i.e., in vitro or in vivo)
  - Species (i.e., fish, rat, mouse, human)
  - Tissue/Assay medium
  - Data type
  - References
  - Data consistency (reliability) score

Chemicals in Products - Comprehensive Anthropospheric Fate Estimation (CiP-CAFE)



- **Emission rates are required input parameters for most fate and exposure models**
- Steady-state version of CiP-CAFÉ can estimate mode-of-entry and emission rates estimated over the life-cycle from chemical structure, production volume and functional use category

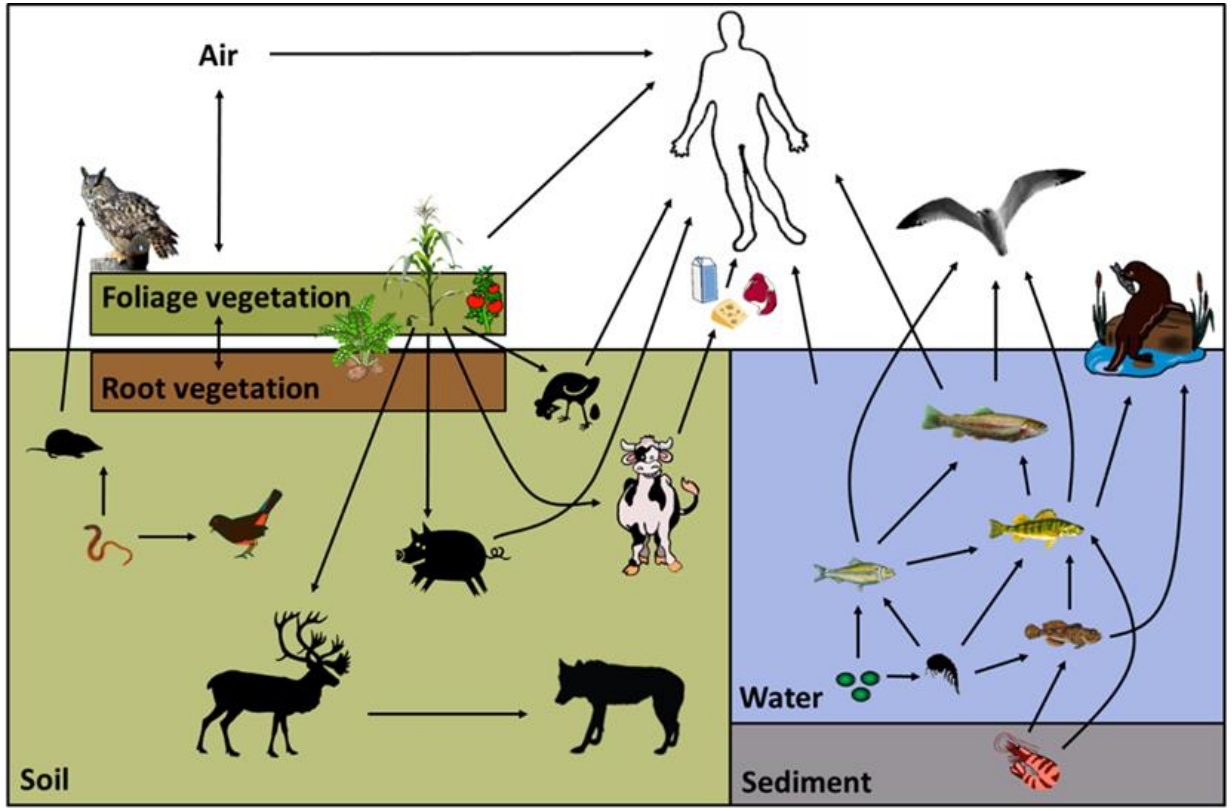
EASE Suite

- **Provides user-friendly access to the model**
- **Autoparameterizes** CiP-CAFÉ and estimation of emission/application/release rates to environmental compartments and direct human exposure (i.e., to skin)

Li et al. 2016, 2018, 2020, 2021

Risk Assessment IDentification And Ranking (RAIDAR)

- Combined mass balance fate and bioaccumulation models to link chemical emissions to exposure
- Used extensively at Environment Canada since 2007, part of PROTEX-HT & US EPA's SEEM3



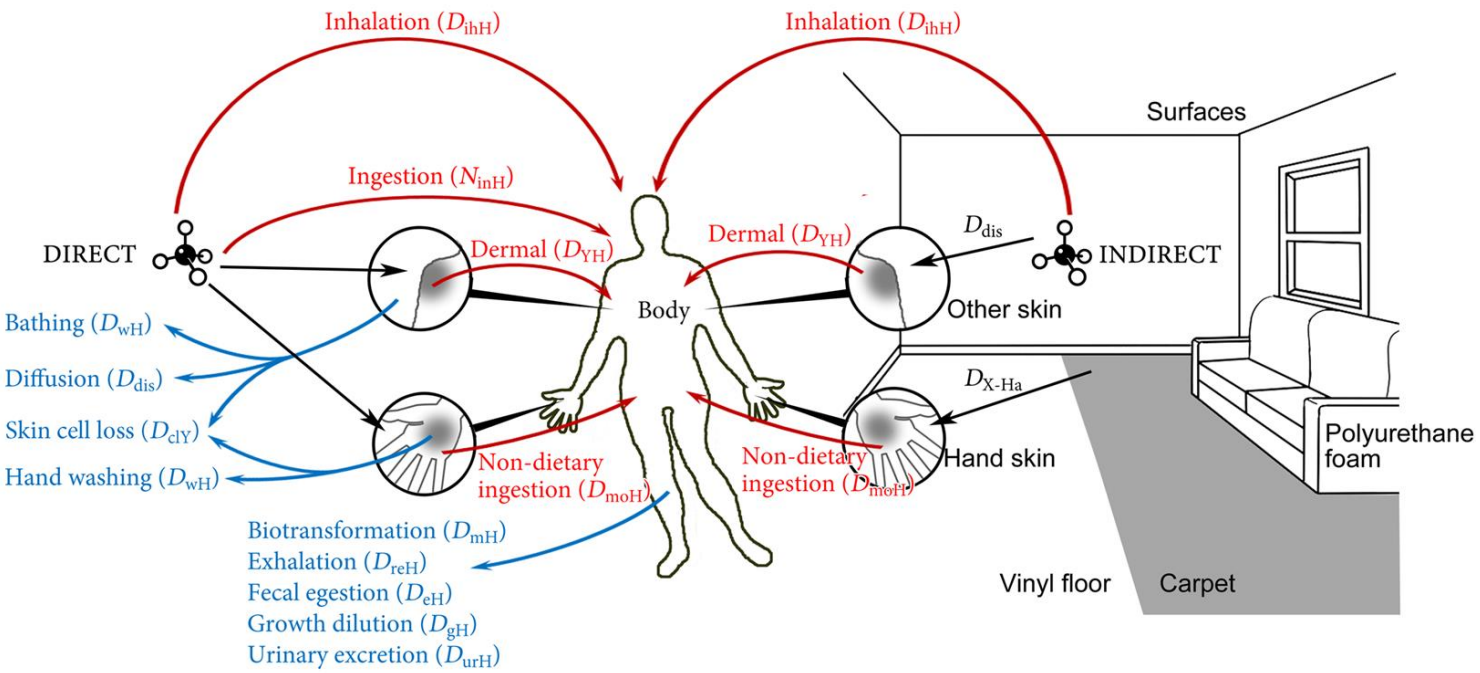
- Evolution of the EQuilibrium Criterion (EQC) fate model (Mackay et al., 1996)
- Broad range of ecological receptors and far-field human exposure pathways (diet, water, outdoor air)
- Regional scale: default conditions typical of temperate North America
- Neutral and ionizable organic chemicals
- Steady-state (Level II or Level III)

EAS-E Suite

- **Provides user-friendly access to the model**
- **Autoparameterizes** RAIDAR to estimate environmental fate, exposure and risk

Arnot et al. 2006, 2008, 2012; Li et al., 2021

RAIDAR – Indoor and Consumer Exposure (ICE)



- Combines indoor fate and toxicokinetic mass balance models to simulate human exposure from chemicals used indoors and/or direct applications (e.g., dermal)
- Part of PROTEX-HT & US EPA's SEEM3
- Far-field exposures can be entered by the user or obtained from RAIDAR

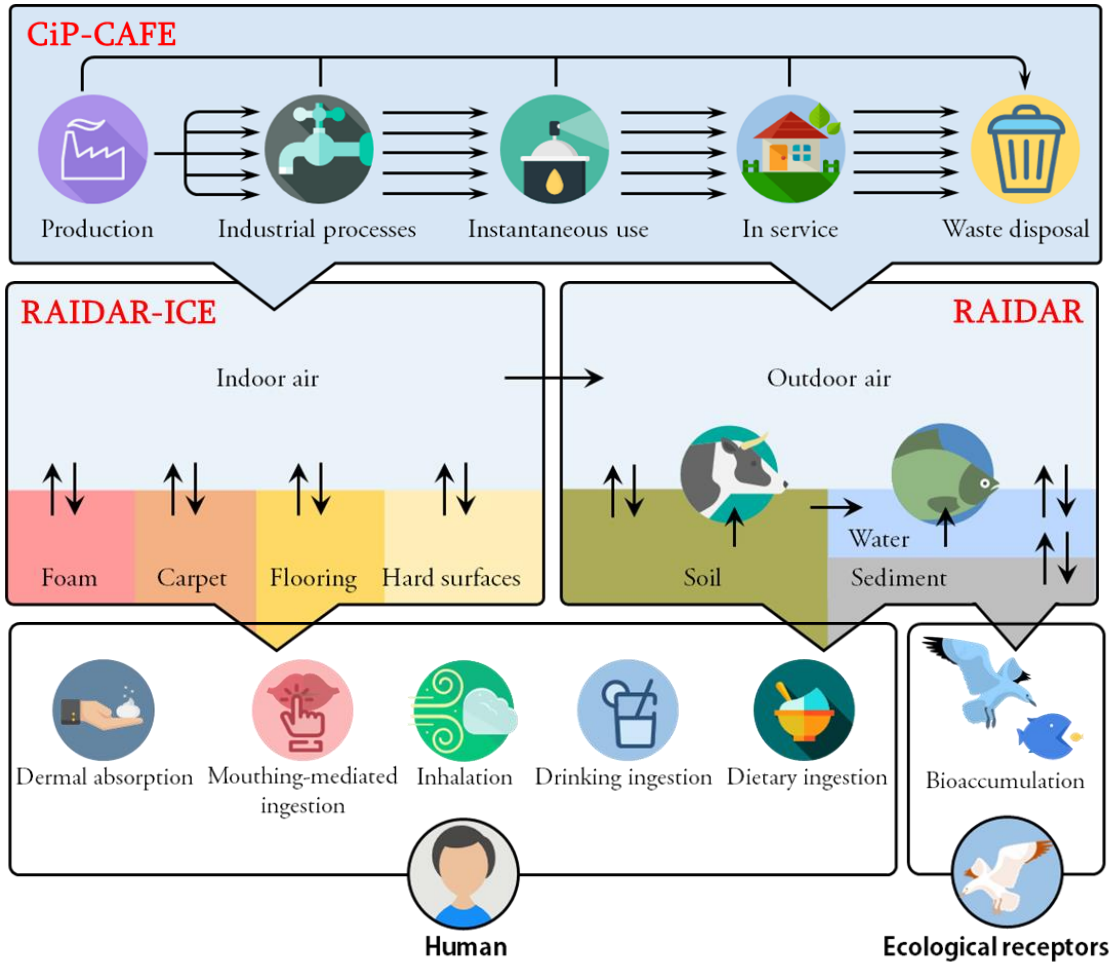
EAS-E Suite

- **Provides user-friendly access to the model**
- **Autoparameterizes** RAIDAR-ICE to estimate indoor fate, exposure and route-specific and **aggregate intake rates** as well as whole body, blood and urine concentrations

Li et al. 2019

PROduction-To-EXposure High-Throughput (PROTEX-HT)

Simulating aggregate human exposure and ecological exposure – a "One Health" approach



- Holistic & mechanistic (**process-driven**)
- Consolidation of some new modules and some that have evolved for decades
- Only user input data required are:
  1) chemical structure,
  2) production volume
  3) functional use category

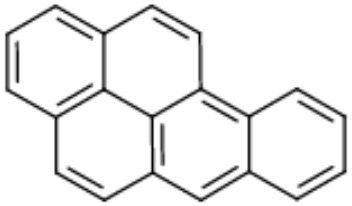
EAS-E Suite

- Provides user-friendly access to the model
- **Autoparameterizes** and runs sequentially CiP-CAFE, RAIDAR and RAIDAR-ICE to estimate **the external and internal exposures of humans and diverse range of ecological and agricultural receptors**

Li et al., *Environ Health Perspect* 2021

Screening-level aggregate exposure estimation is now as “EAS-E” as 1-2-3

- The **PROTEX-HT** model requires **only 2 input parameters** to simulate aggregate human and ecological exposures and associated risks:
  1. Chemical structure, i.e., SMILES notation
  2. Chemical production volume



→ QSA(P)Rs – predict physical-chemical properties, half-lives, toxicity

→ QSURs – predict functional use categories

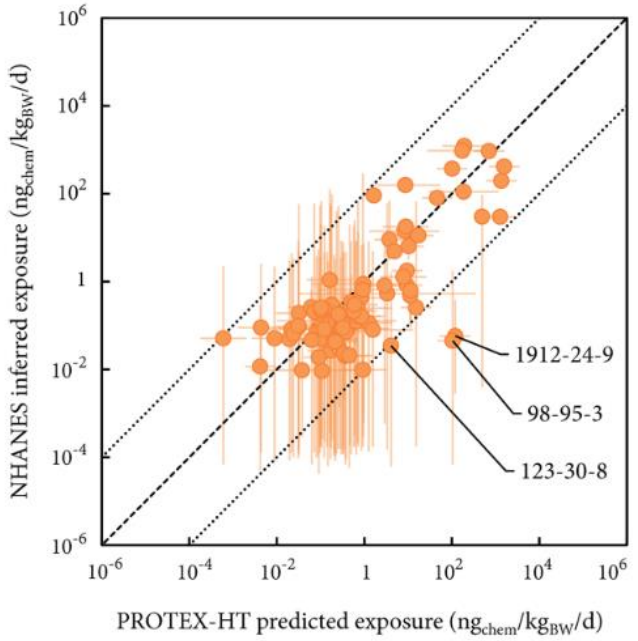
Research

A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP9372.

Development and Evaluation of a Holistic and Mechanistic Modeling Framework for Chemical Emissions, Fate, Exposure, and Risk

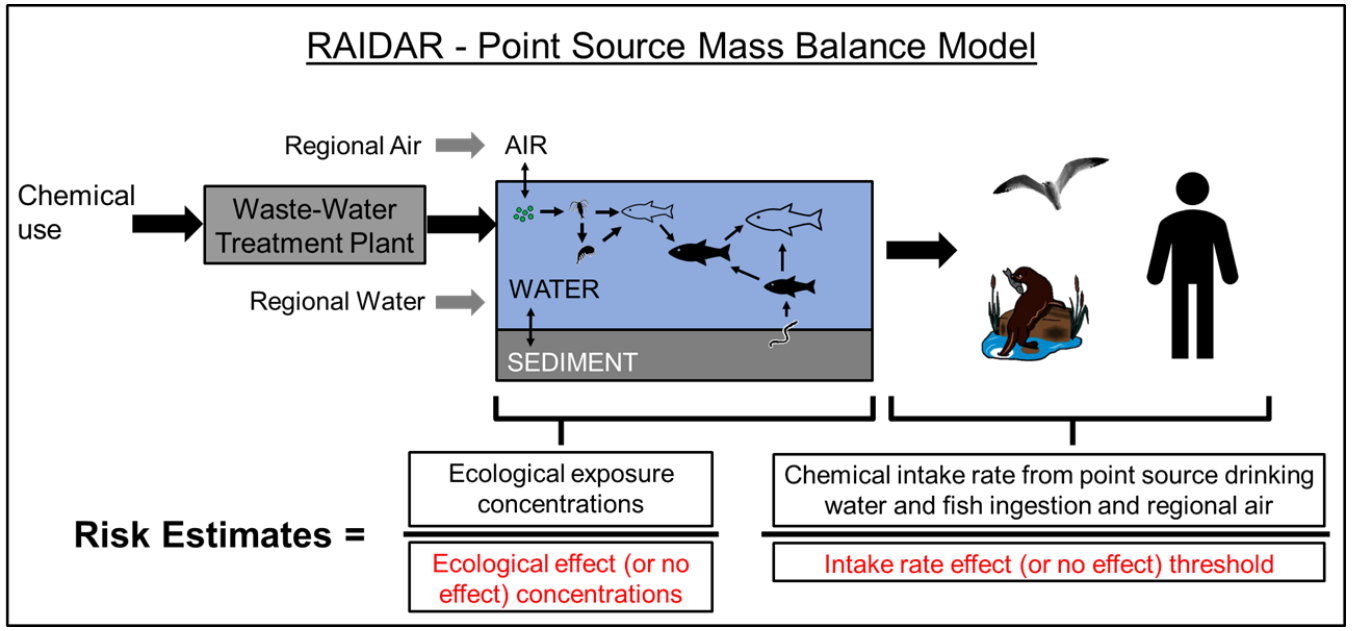
Li Li,[1,2] Alessandro Sangion,[2,3] Frank Wania,[2] James M. Armitage,[4] Liisa Toose,[3] Lauren Hughes,[3] and Jon A. Arnot[2,3,5]

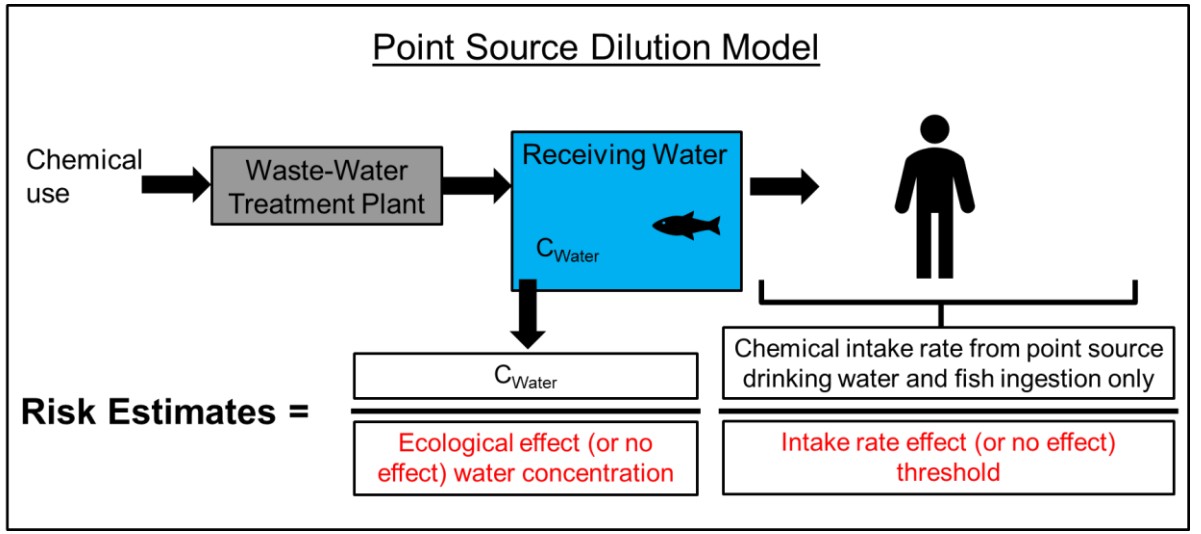
Environmental Health Perspectives, December 2021



Li et al., EHP 2021

Point Source Fate and Exposure Models



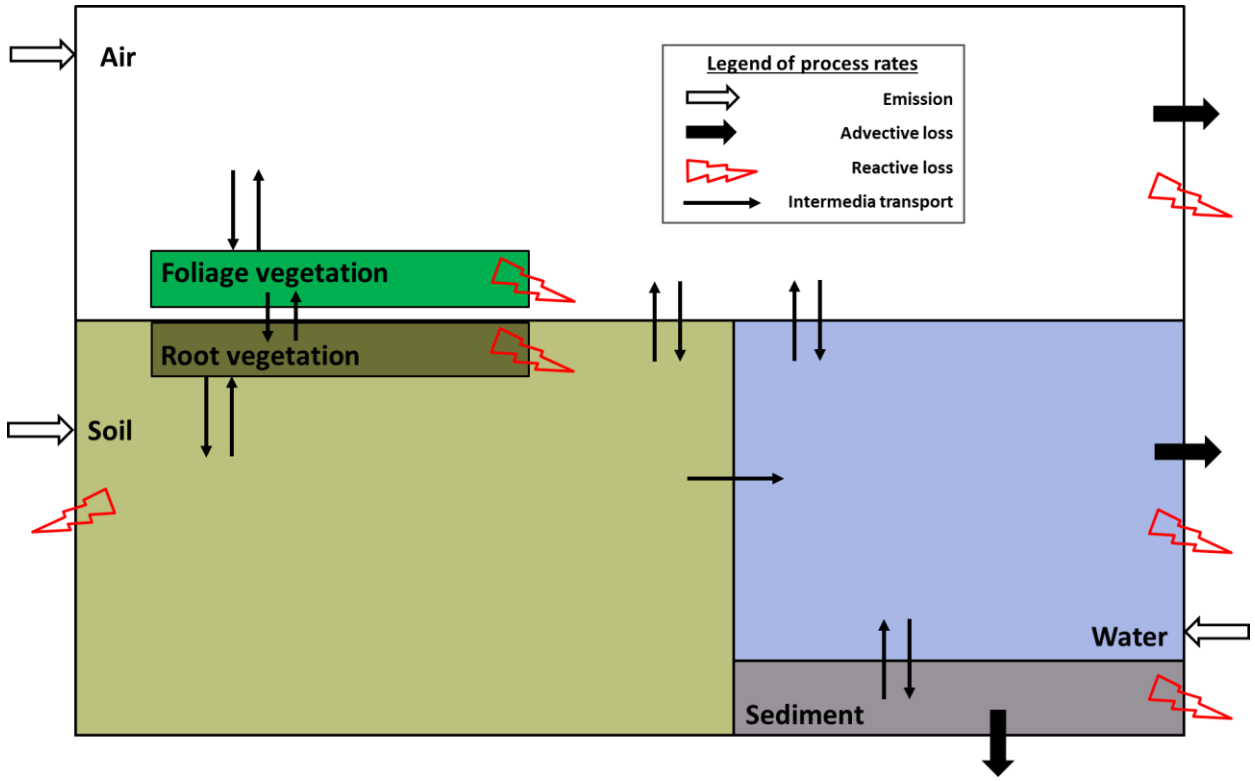


- Mass balance for air, water, and sediment
- Food web bioaccumulation models
- Readily parameterized to different receiving environments
- Neutral and ionizable organic chemicals…
- Linkages with regional-scale fate and transport (RAIDAR)

- Simple dilution model (like many currently used in regulatory agencies, HC, ECCC, EPA, etc)
- Not multimedia, no degradation
- Neutrals only
- No food webs

Fate - Persistence Estimation & Simulation Tool (F-PEST) – Phase 1

- The environmental fate model is similar in many aspects to the EQuilibrium Criterion (EQC) model (1996), **but with significant updates outlined in the RAIDAR publications**.
- **Autoparameterized in EAS-E Suite**
- Neutrals and IOCs
- Constant or intermittent rain options
- Level II or Level III fate & mass distribution
- Overall Persistence (P_{OV})
- Characteristic Travel Distance (CTD) in air and water
- The default environment is the same default fate model used in RAIDAR and PROTEX-HT



Bioaccumulation Estimation Tool (BET) – Phase 1

The **Bioaccumulation Assessment Tool (BAT) & RAIDAR Bioaccumulation** models:

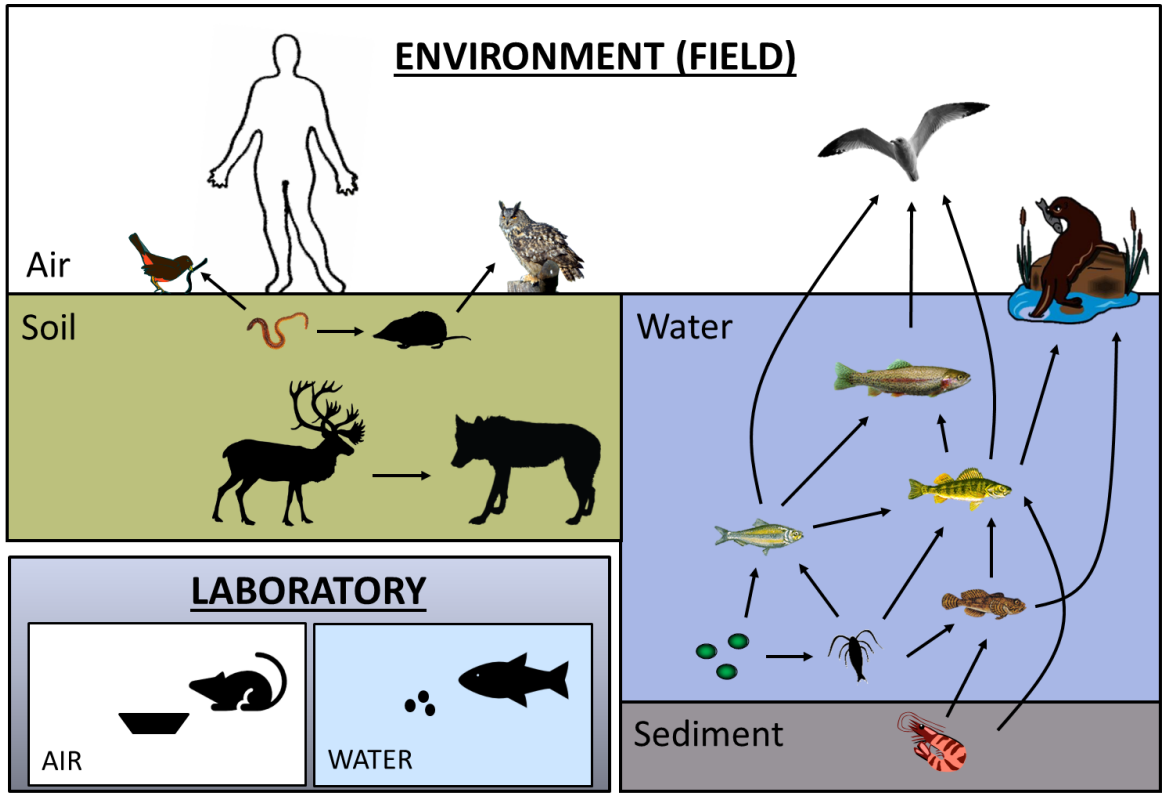
- **Autoparameterized in EAS-E Suite**

- Lab BCFs for fish and invertebrates
- Lab BMFs and HL_T for rodents

- Field BAFs and BMFs for fish and invertebrates
- Field BMFs for air-breathing organisms

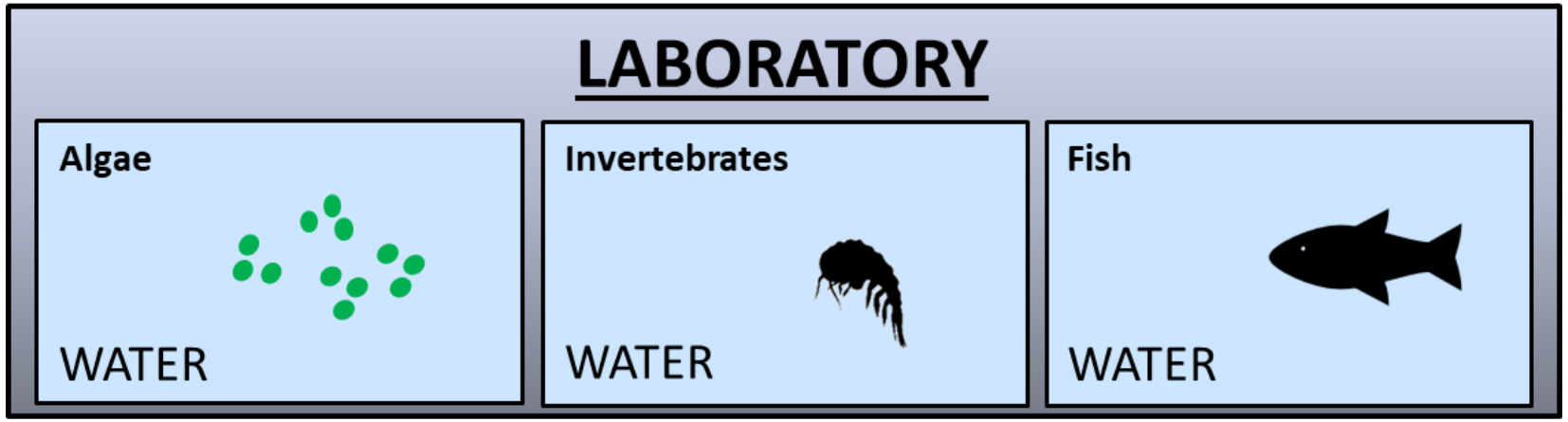
- Ionizable and Neutral Organics

- **The IVIVE model in EAS-E Suite can also be used to convert in vitro biotransformation rate data into HL_B data as BET model input for fish and mammals**

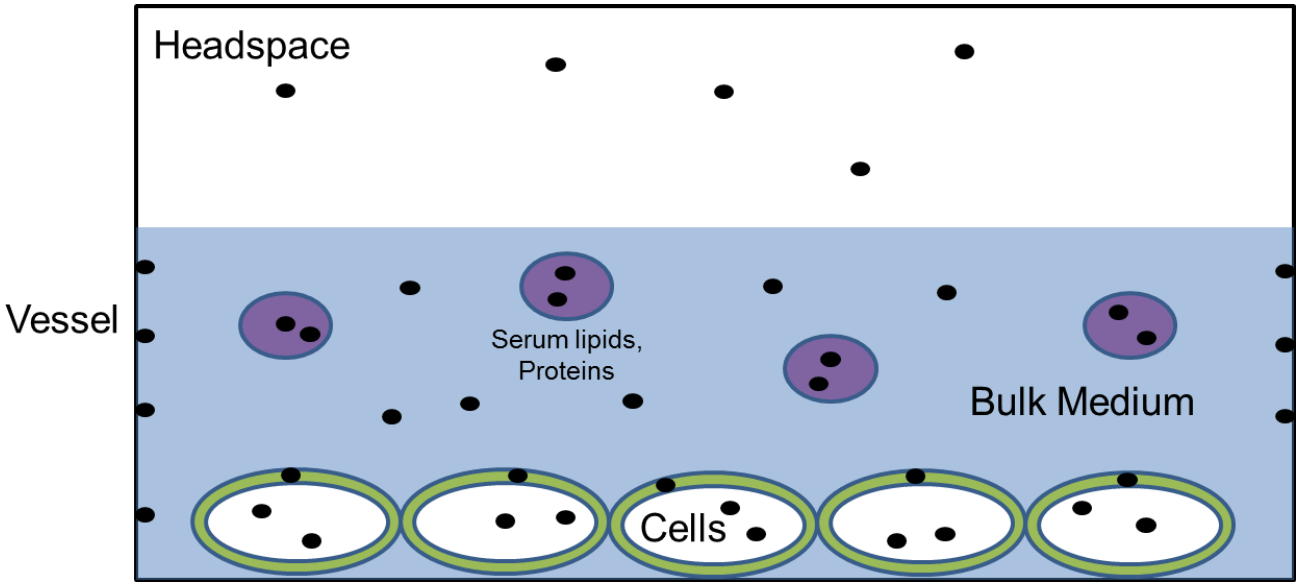


Toxicity Estimation & Simulation Tool (TEST) – Phase 1

- Same TK models used in RAIDAR & BET but parameterized to laboratory toxicity testing conditions
- Autoparameterized in EAS-E Suite
- Converting external effect (or no-effect) concentrations to internal effect (or no-effect) concentrations
- Ionizable and Neutral Organics
- The IVIVE model in EAS-E Suite can also be used to convert in vitro biotransformation rate data into HL_B data as TEST model input for fish



In Vitro Mass Balance Model (IV-MBM v2.0)



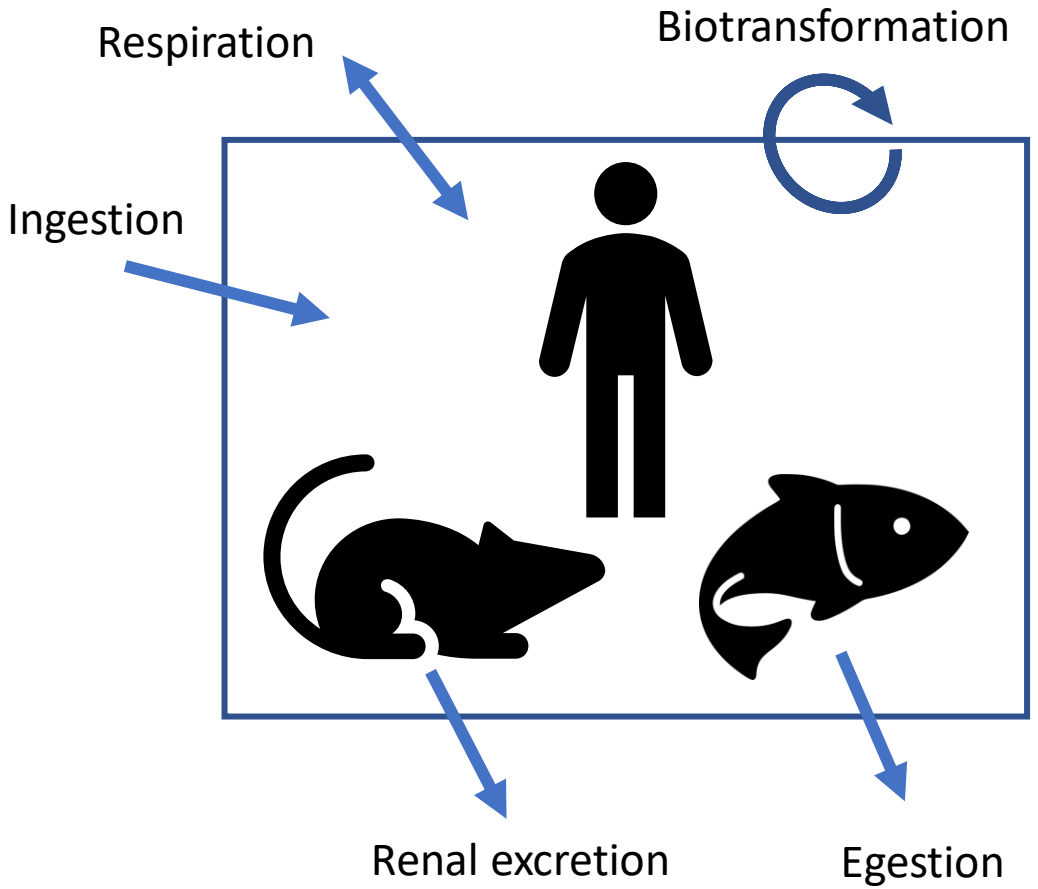
- Simulates the equilibrium distribution of organic chemicals in in vitro test systems based on partitioning data and system properties
- Applicable to neutral and ionizable organic chemicals (IOCs)

EAS-E Suite

- **Provides user-friendly access to the model**
- **Autoparameterizes** the model and the test systems to estimate concentrations in bulk medium, freely-dissolved phase, cells, cell membranes and amount sorbed to vessel wall (plastic) and volatilized into the air

Armitage et al. *Toxics* 2021

Generic 1-CoPBTK models and supporting databases and QSARs

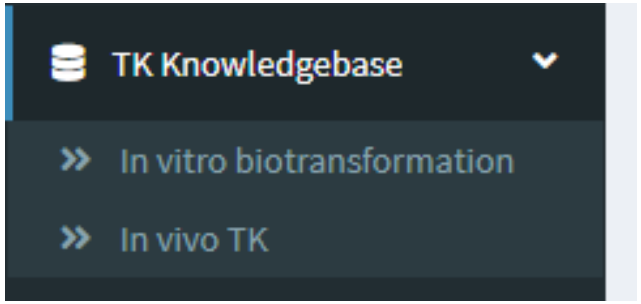


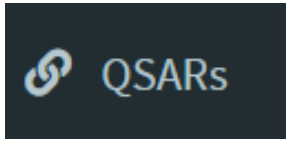
- General PBTK model parameterized for different species for neutral organics & IOCs
- Same models used in other modules (PROTEX-HT, etc)

EAS-E Suite

- **Provides user-friendly access to the models**
- **Autoparameterizes** the HTTK models and estimate uptake and elimination rate constants, whole body, blood and urine concentrations, total (terminal) elimination half-life (HL_T), etc

- **EPA ORD-httk models also included in EAS-E Suite**





EAS-E HTTK: 1Co-PBTK models

- Chemical Identifier
- Exposure & Safety Estimation
- Hazard Estimation
- Phys-Chem Knowledgebase
- TK Knowledgebase
- IV-MBM
- EASE-HTTK
- ORD-httk
- Dermal Exposure
- QSARs
- Aquaculture Model
- Point Source
- IOC Calculator-BETA
- General Settings
- About
- License
- How to cite
- Help & Feedback

Chemical Input Data | 1Co-PBPK Steady State | IVIVE - BIOTRANSFORMATION | IVIVE - REVERSE TOXICOKINETICS (rTK)

Model Parameterization

Model Description - EAS-E HTTK Ver.0.9

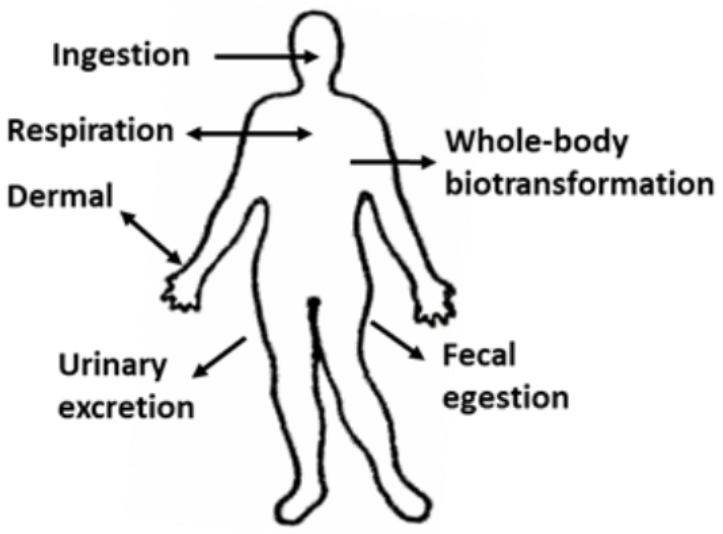
The HTTK models are one-compartment physiologically-based toxicokinetic (1-CoPBTK) models. The mass balance models calculate toxicokinetic processes for chemical uptake and elimination in a representative adult human male, adult male rat, and a fish. The figure on the right provides a conceptual overview of the processes considered by the models. By default, chemicals are assumed to be neutral organics. For IOCs, the user is required to obtain and enter the pka for acids or bases and select the 'IOC type'. Quaternary (permanently charged) chemicals can also be simulated by selecting 'Quats' in the IOC type dropdown menu; however, these chemicals do not have pka, so none is required. Default scaling factors for estimating the partitioning properties of the charged form are in the 'General Settings' Tab and can be modified by the user. The mass balance solutions are for steady-state conditions, i.e., there are no changes to chemical concentrations as a function of time.

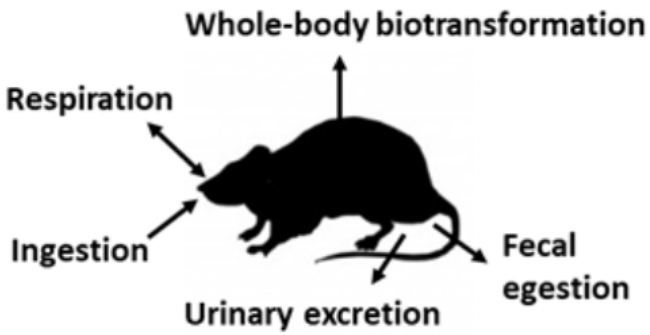
The biological parameters for the representative organisms are summarized below. The user can select exposure media concentrations in the boxes below. If empirical dietary absorption efficiency data are available, the user can enter those values in the boxes provided below. The dietary absorption efficiency parameter quantifies the chemical transfer efficiency from the lumen of the gastrointestinal tract to the blood (hepatic portal vein) and is therefore different from oral bioavailability. The user can select different model assumptions for renal clearance for the human and rodent simulations.

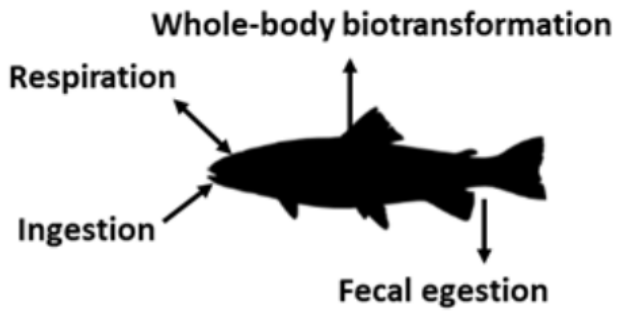
The human TK model is incorporated within the RAIDAR, RAIDAR-ICE and PROTEX-HT exposure and risk estimation models. However, the exposure conditions of the human TK model in the HTTK module are different than the exposure conditions in the other models. In the HTTK module the user can select concentrations in the exposure media of air, water & food, and dermal applications. When a chemical is eliminated from the body in the HTTK models, it is lost from the mass balance. For example, chemical mass transfer from the skin to the air is not considered for inhalation exposure. If the user is interested in an estimate of aggregate human exposure, please run the RAIDAR-ICE or PROTEX-HT models. The human 1-CoPBTK model has been compared with multi-compartment PBTK models (see Armitage et al., 2021 for details).

The general rodent TK model is also used in the Bioaccumulation Estimation Tool (BET) and the Bioaccumulation Assessment Tool (BAT; Arnot et al., 2022) ; however, the exposure conditions in those models are not necessarily the same as the default exposure conditions in the HTTK module.

The general fish TK model is also used in the Bioaccumulation Estimation Tool (BET), Bioaccumulation Assessment Tool (BAT), RAIDAR and PROTEX-HT and in the Toxicity Estimation & Simulation Tool (TEST) ; however, the exposure conditions in those modules are not necessarily the same as the default exposure conditions in the HTTK module.







EAS-E HTTK: IVIVE - Biotransformation

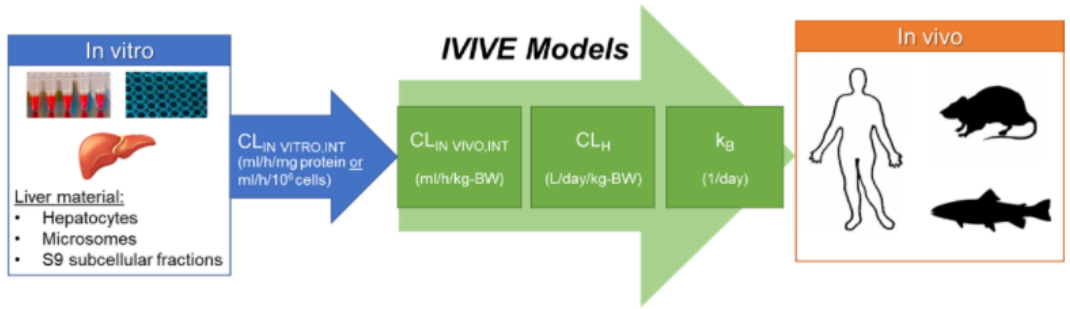
- Chemical Identifier
- Exposure & Safety Estimation
- Hazard Estimation
- Phys-Chem Knowledgebase
- TK Knowledgebase
- IV-MBM
- EASE-HTTK
- ORD-httk
- Dermal Exposure
- QSARs
- Aquaculture Model
- Point Source
- IOC Calculator-BETA
- General Settings
- About
- License
- How to cite
- Help & Feedback

Chemical Input Data | 1Co-PBPK Steady State | IVIVE - BIOTRANSFORMATION | IVIVE - REVERSE TOXICOKINETICS (rTK)

Model Description - IVIVE - BIOTRANSFORMATION Ver.0.09

The **In Vitro-In Vivo Extrapolation (IVIVE) - Biotransformation model** can be used to scale in vitro biotransformation rates from liver tissue assays to hepatic clearance and whole body biotransformation rate constants and half-lives (HLB). The IVIVE model can be used for assays derived from liver S9, liver microsomes and hepatocytes for humans, rodents, and fish. The figure on the right provides a conceptual overview of the IVIVE - Biotransformation models. In vitro biotransformation rate data that have already been critically evaluated for reliability using the methods published in the Bioaccumulation Assessment Tool (BAT; Arnot et al., 2022) are available in the EAS-E Suite TK knowledgebase. For unevaluated in vitro biotransformation rate data, the user is encouraged to consider the methods for assessing in vitro biotransformation rate data quality that are provided in the Bioaccumulation Assessment Tool (BAT). The default experimental bioassay and biological parameters for the representative organisms are summarized below. Users are encouraged to parameterize the model with the reported study-specific values. **The user must also enter the in vitro intrinsic clearance value in the appropriate units in the box below.** The HLB output from the IVIVE - Biotransformation model can be used in various other modules within the EAS-E Suite platform (e.g., HTTK, BET, RAIDAR, PROTEX-HT, POINT SOURCE) by copying the results from this module and pasting in the appropriate input parameter boxes.

By default, chemicals are assumed to be neutral organics. For IOCs, the user is required to obtain and enter the pka for acids or bases and select the 'IOC type'. Quaternary (permanently charged) chemicals can also be simulated by selecting 'Quats' in the IOC type dropdown menu; however, these chemicals do not have a pka, so none is required. Default scaling factors for estimating the partitioning properties of the charged form are in the 'General Settings' Tab and can be modified by the user.



Calculate IVIVE

In Vitro Assay Parameterization

Organism: Human

In vitro cell or protein concentration (10^6Cell/mL assay or mg protein/mL assay): 1

In vitro assay pH: 7.4

Assay:: Hepatocyte

Membrane Lipid:Protein ratio (S9 and Microsome assays only): 0.35

In vitro assay Temperature (DegC): 37

In vitro intrinsic Clearance (mL/h/10^6Cell or mg protein)

Can be used to parameterize other models too!

EAS-E HTTK: IVIVE - rTK

- Chemical Identifier
- Exposure & Safety Estimation
- Hazard Estimation
- Phys-Chem Knowledgebase
- TK Knowledgebase
- IV-MBM
- EASE-HTTK
- ORD-httk
- Dermal Exposure
- QSARs
- Aquaculture Model
- Point Source
- IOC Calculator-BETA
- General Settings
- About
- License
- How to cite
- Help & Feedback

Chemical Input Data | 1Co-PBPK Steady State | IVIVE - BIOTRANSFORMATION | IVIVE - REVERSE TOXICOKINETICS (rTK)

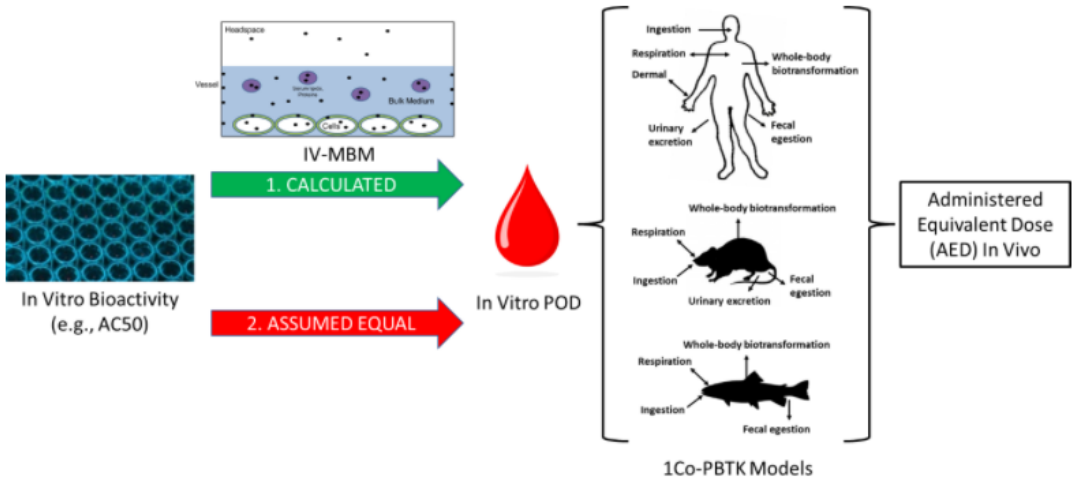
Model Parameterization

Model Description - EAS-E REVERSE TOXICOKINETICS (rTK) Ver.0.9

The **In Vitro-In Vivo Extrapolation (IVIVE) - Reverse Toxicokinetics (rTK) model** can be used to scale in vitro experimental bioactivity or toxicity concentration data to corresponding in vivo exposure intake rates and concentrations, e.g., the Oral Equivalent Dose (OED) or Administered Equivalent Dose (AED). The steady state one compartment physiologically-based toxicokinetic (1Co-PBTK) models included in this EAS-E HTTK module are used to perform the calculations. An initial and completely arbitrary value of 1 umol/L is included in the input parameter boxes below to run the model. **To obtain meaningful results, the user must enter an assumed or calculated in vitro point of departure (POD) corresponding to the reported study-specific in vitro value.**

The figure at the right provides a conceptual overview of the workflow for using the IVIVE - rTK model. It is often assumed that nominal administered in vitro concentration is equivalent to the steady-state blood concentration (e.g., Rotroff et al., 2010; Wetmore et al., 2012); however, several studies (e.g., Armitage et al., 2014; Groothuis et al ., 2015; Proenca et al., 2021; Armitage et al., 2021) have shown that the assumed, nominal administered concentration in an in vitro assay does not correspond to the effective concentration associated with the response (or no-response). **Users are encouraged to first use the In Vitro Mass Balance Model (IV-MBM Ver.2.0) to CALCULATE in vitro POD corresponding to the steady state blood concentration to parameterize the IVIVE - rTK model.** After parameterizing the IV-MBM tool with appropriate assay data, the calculated in vitro POD corresponding to a steady state blood concentration can be transferred to the IVIVE - rTK model by pressing the button under the 'IVIVE' results in the IV-MBM module.

By default, chemicals are assumed to be neutral organics. For IOCs, the user is required to obtain and enter the pka for acids or bases and select the 'IOC type'. Quaternary (permanently charged) chemicals can also be simulated by selecting 'Quats' in the IOC type dropdown menu; however, these chemicals do not have a pka, so none is required. Default scaling factors for estimating the partitioning properties of the charged form are in the 'General Settings' Tab and can be modified by the user.



Run Models

ADULT MALE HUMAN (80 KG)

*In vitro Point of Departure (POD) (umol/L)

1

ADULT LAB RAT (0.25 KG)

*In vitro Point of Departure (POD) (umol/L)

1

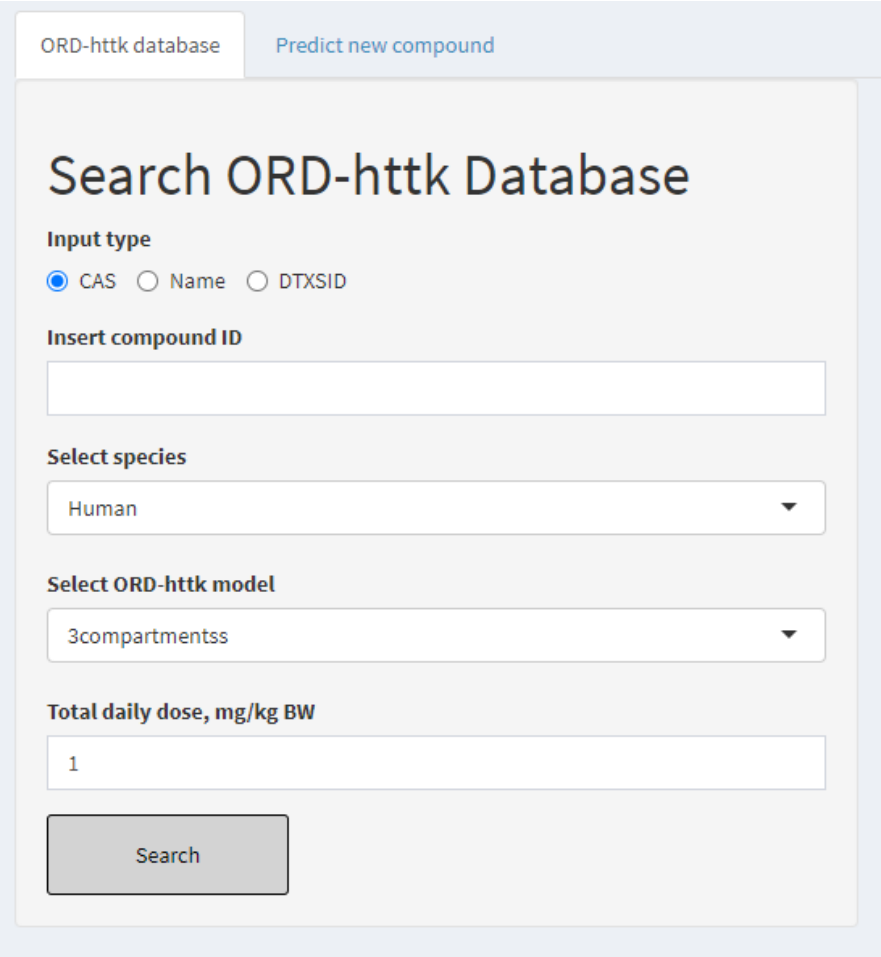
LAB FISH (0.01 KG AT 10 C)

*In vitro Point of Departure (POD) (umol/L)

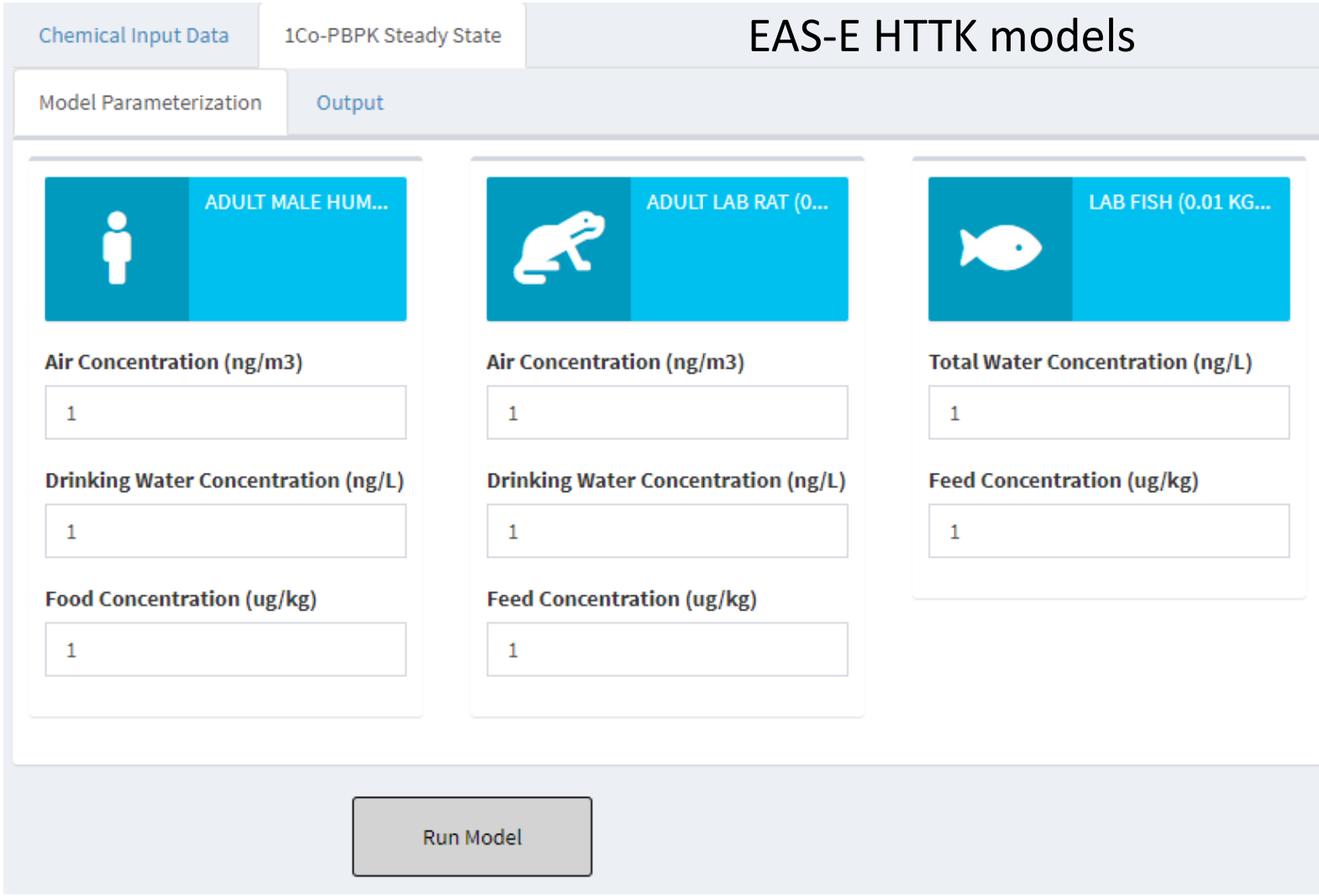
1

EPA/ORD HTTK and EAS-E HTTK

ORD HTTK models (R package)

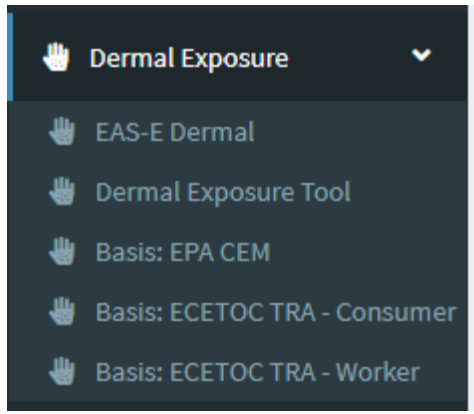


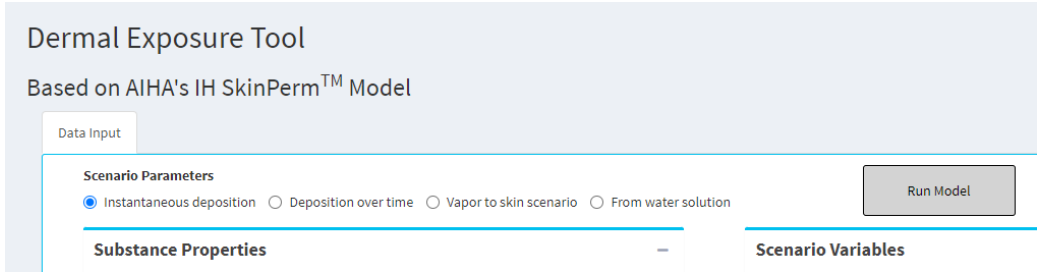
EAS-E HTTK models

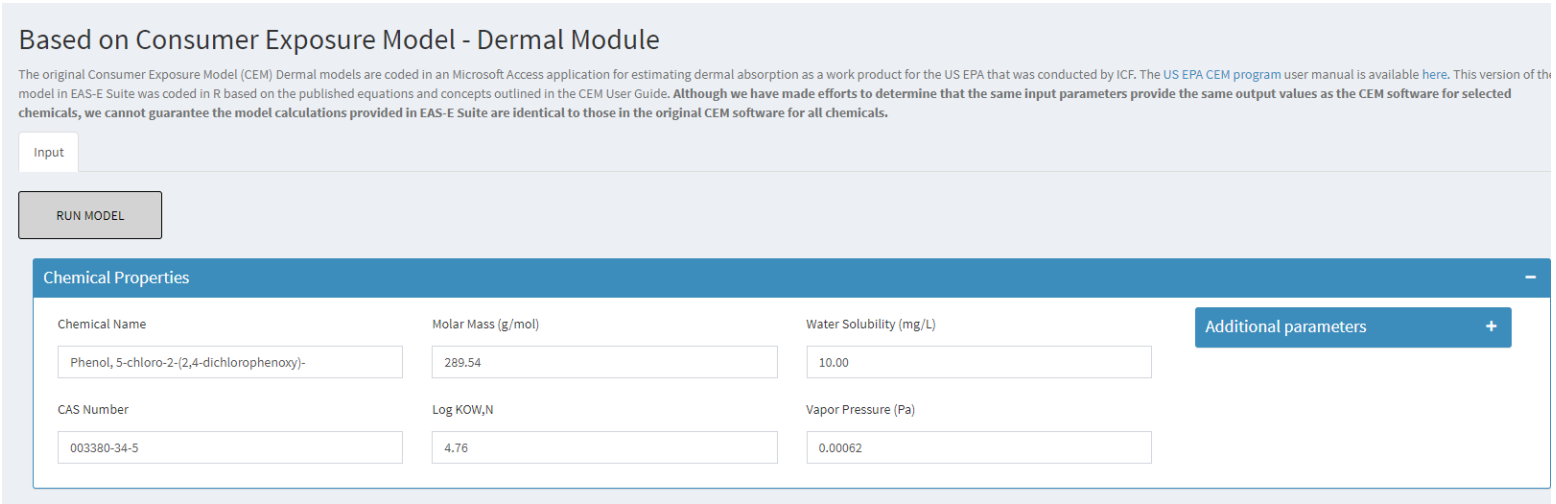


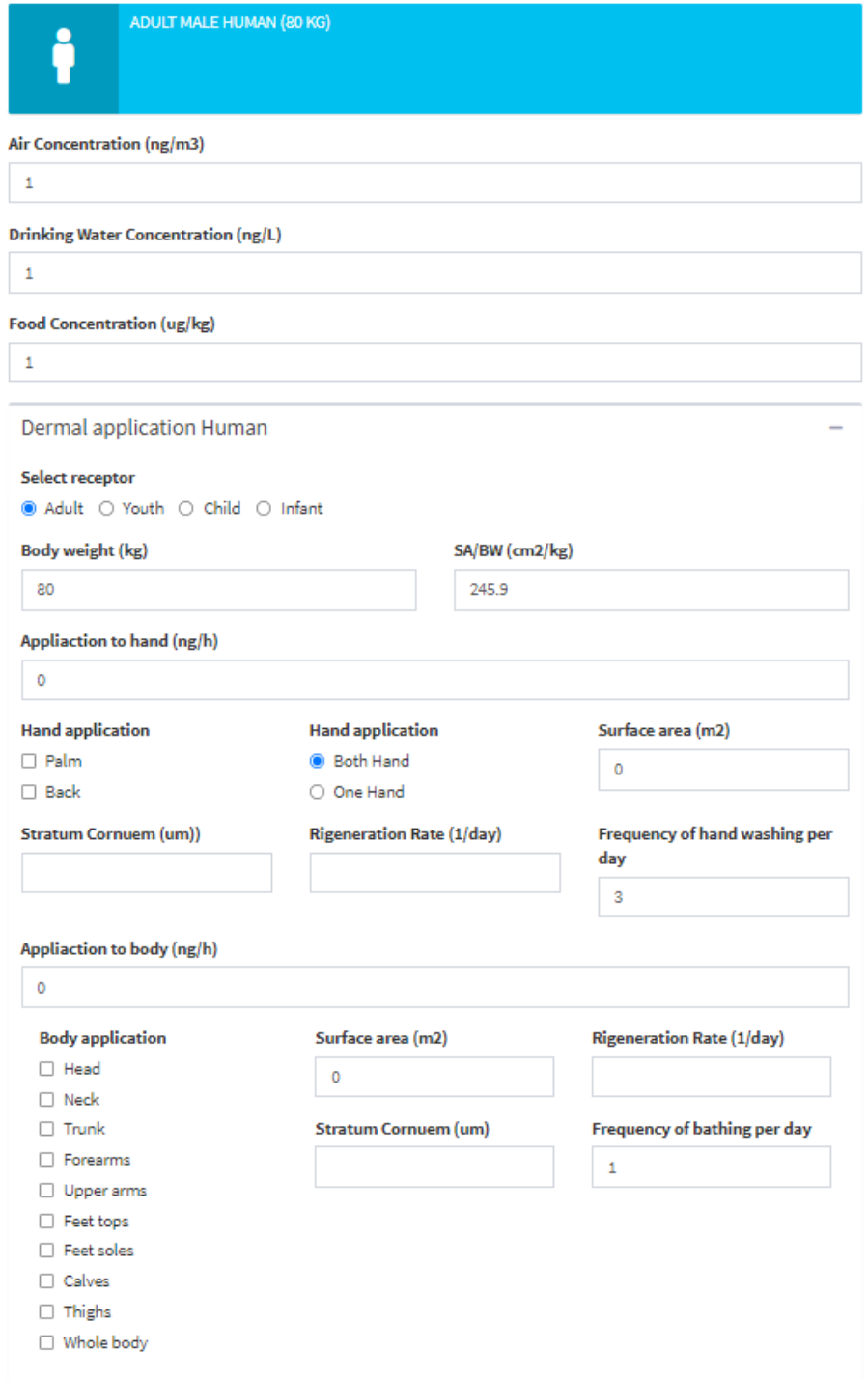
Dermal Exposure Models

Suite of different dermal exposure models for human exposure assessment









QSA(P)Rs

- QSA(P)R models for estimating partitioning and biotransformation half-lives in human and fish
- OECD QSAR guidance for applications in regulatory decision-making; Applicability Domain (AD) information, etc

QSARINS (University of Insubria, Ester Papa)

Multiple Linear Regression models based on PaDEL molecular descriptors selected by Genetic Algorithm

- Whole-body biotransformation half-life in fish and human
- Whole-body total (terminal) elimination half-life in human

IFSQSAR

Statistical models based on Iterative Fragment Selection procedures (Trevor N. Brown)

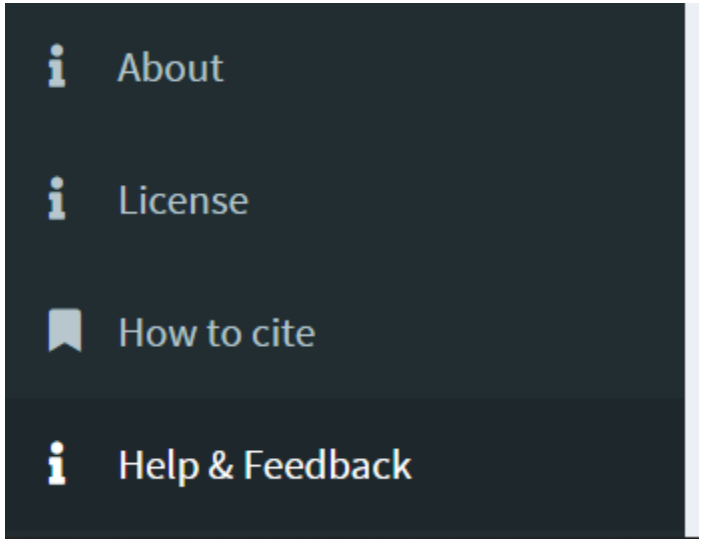
- Whole-body biotransformation half-life in fish and human
- Whole-body total (terminal) elimination half-life in human
- Common phys-chem properties (e.g., K_{OW}, K_{OA}, Henry's Law constant, melting point, **& MUCH more!**)
- Biodegradation half-lives in water for organic chemicals

OPERA

Model based on KNN and PaDEL molecular descriptors by EPA (Mansouri et al., 2018)

- Phys-Chem properties (e.g., K_{OW}, K_{OA}, melting point)
- Biodegradation half-lives in water for hydrocarbons
- OH reaction rate constants
- Whole-body biotransformation half-life in fish

Some additional details…



www.arnotresearch.com

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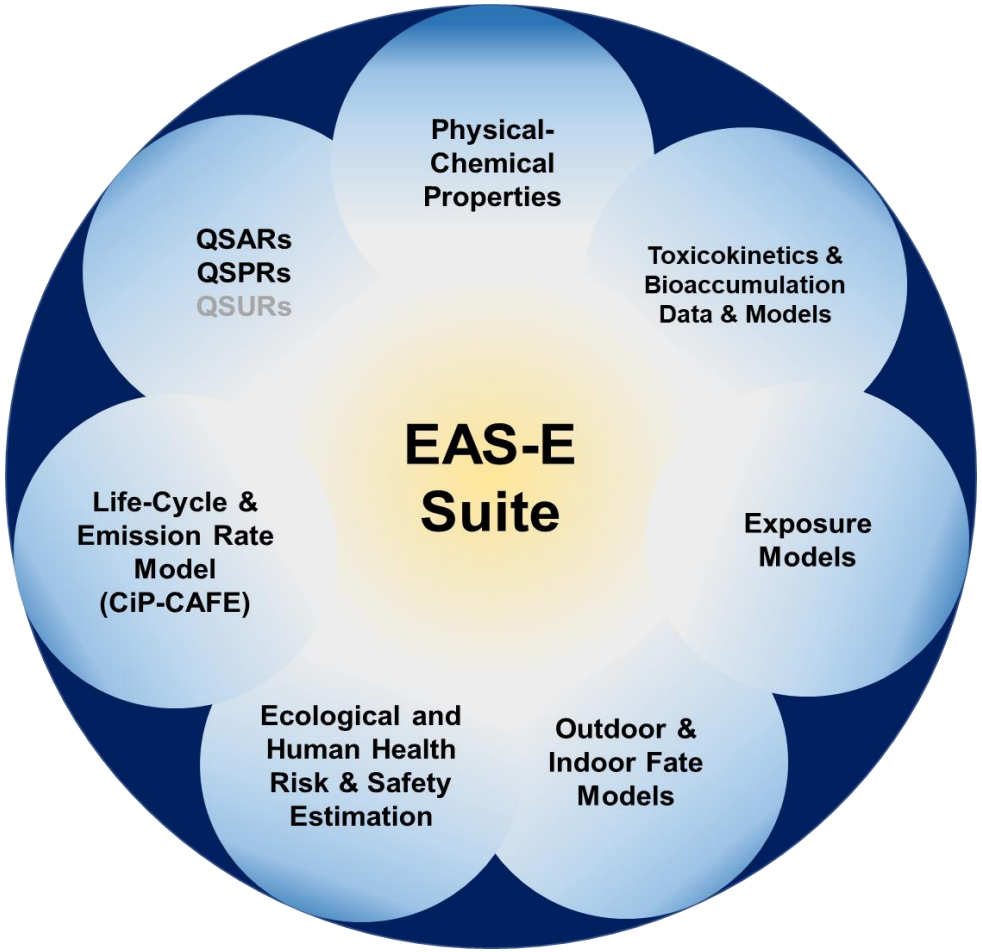
EAS-E Suite funding acknowledgements:



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General Objectives (What we do)

1. **Research**: Develop, evaluate and apply empirical databases, models and QSARs for **exposure, hazard and risk assessment**
2. **Collaboration:** Colleagues in academia, industry and government
3. **Knowledge transfer:** Stakeholder engagement, training

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