USEtox® – Scientific consensus for human toxicity & ecotoxicity characterization

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USEtox – Main application areas

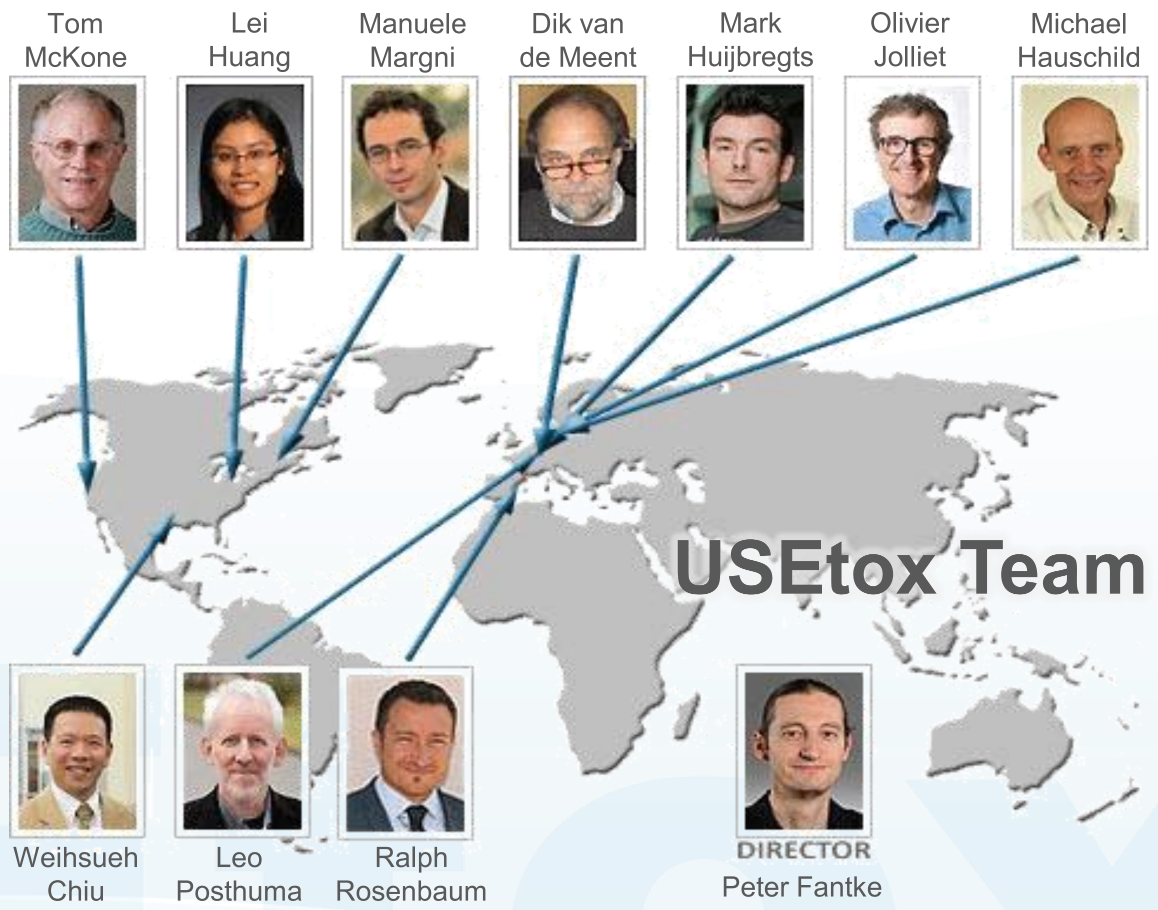
Near-field/far-field USEtox framework is suitable for **comparative evaluation of chemicals** emitted along product life cycles and chemicals in various product applications. Primary application areas are (model already tested):

Application area	Product types already covered in our framework (emissions already directly or indirectly included)
Product life cycle assessment (LCA)	Food contact materials
High-throughput exposure screening	Personal care products; food contact materials
High-throughput risk screening	Children toys; building materials; paints
Chemical exposure and risk prioritization	Household products (cleaning, personal care, and home maintenance products)
Chemical alternatives assessment (CAA) / chemical substitution	Building materials; personal care products; agricultural pesticides

https://doi.org/10.1007/s11367-021-01889-y

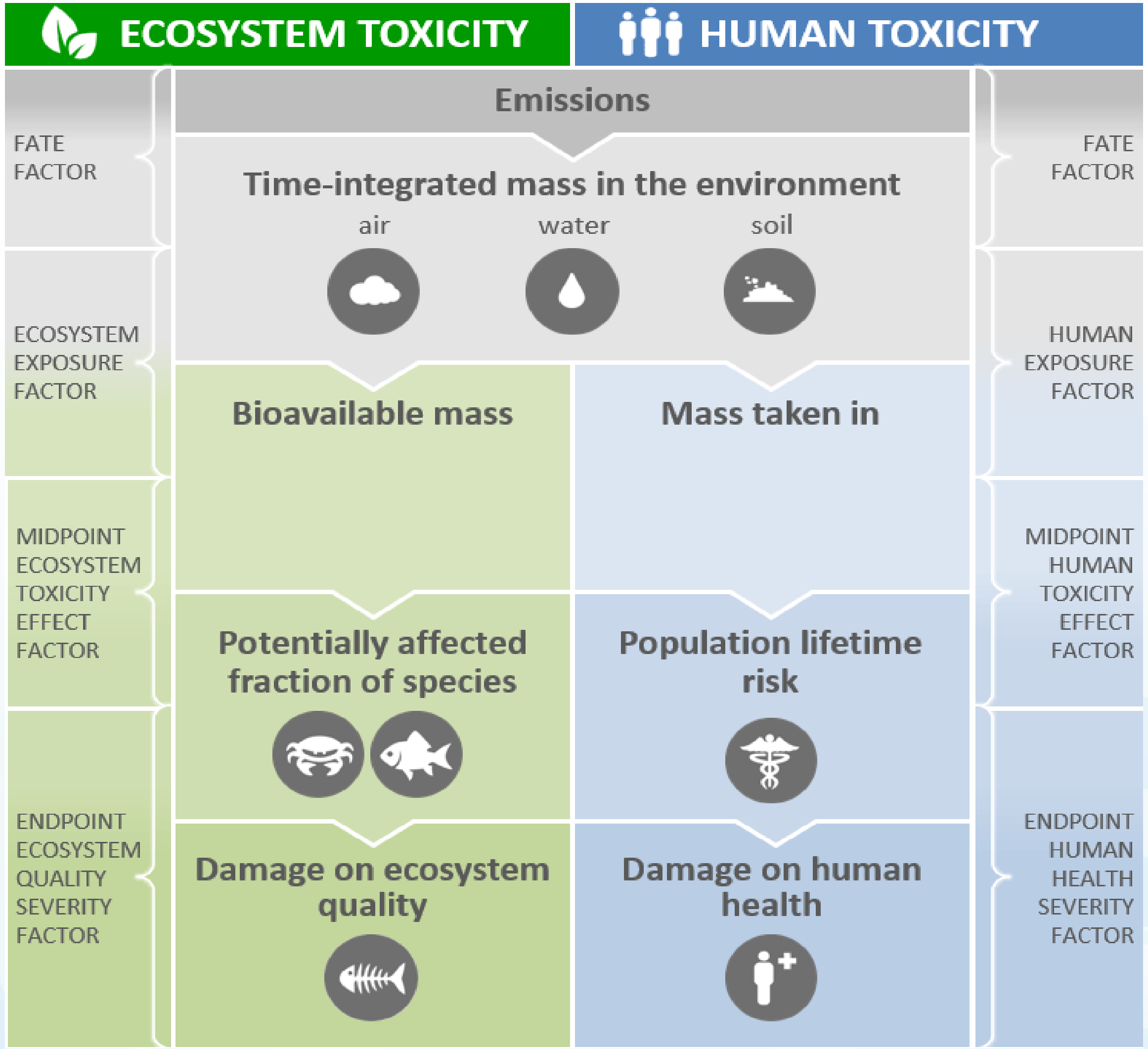
USEtox – Scientific consensus

- ✓ UNEP/SETAC **scientific consensus model**, endorsed by UNEP Life Cycle Initiative since 2015, used by e.g. EC, US-EPA, UNEP, Bayer
- ✓ Implemented in all LCA software
- ✓ Characterizes **human toxicity & ecotoxicity impacts** of organic chemicals & metal ions
- ✓ Considers **emissions over entire life cycle**
- ✓ Provides factors for ~10,000 chemicals emitted or used in ~500 products
- ✓ Applied in **LCA**, exposure/risk screening, chemical substitution, prioritization
- ✓ Continuously further developed (e.g. UNEP GLAM, UNEP SAICM) and striving for scientific consensus
- ✓ **Open/free** to use by all, but training needed



https://usetox.org

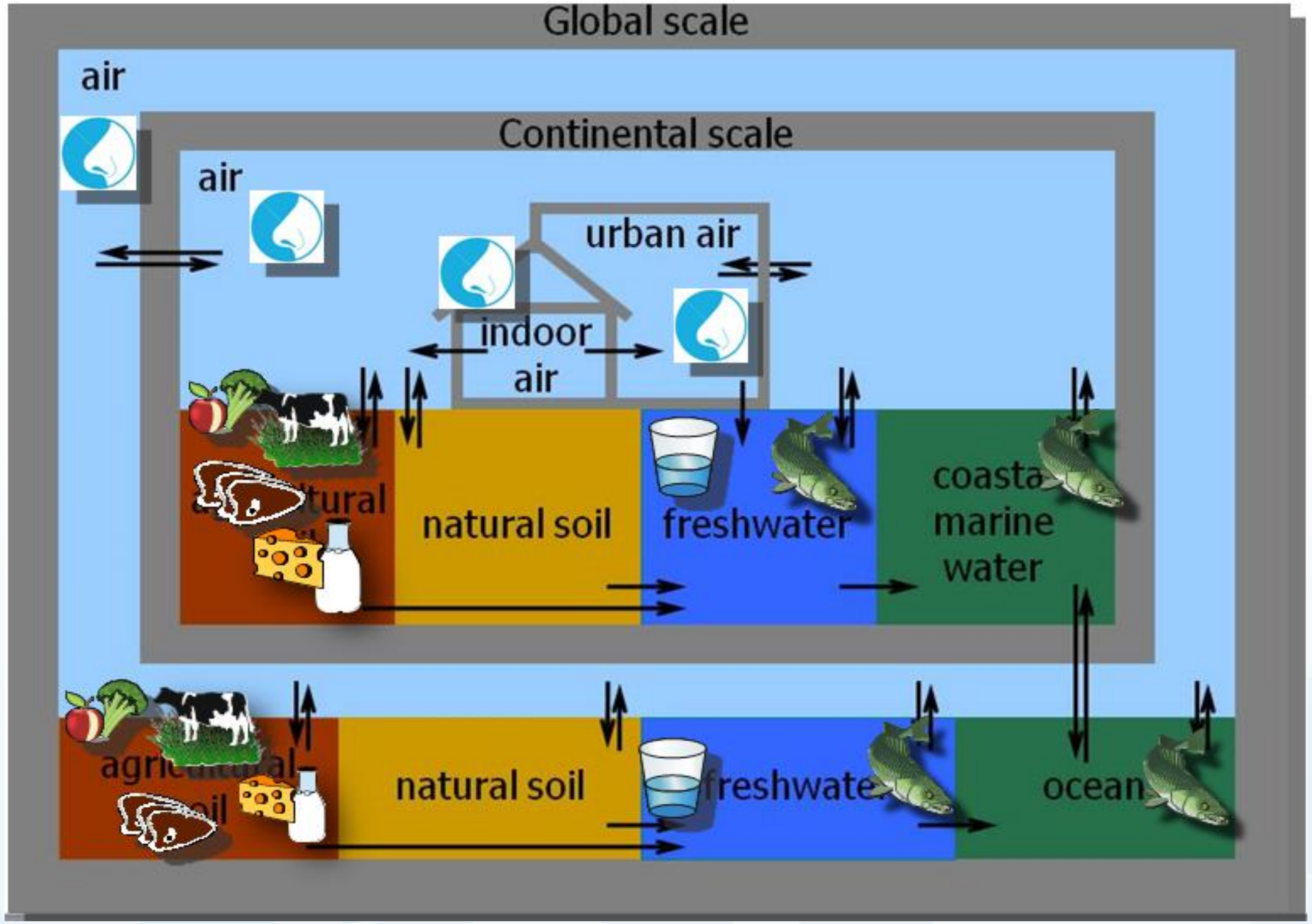
USEtox – Impact pathway framework



https://usetox.org/documentation

- **Scales**
  - Product, indoor, urban, continental, global
  - Steady-state & dynamic solutions
- **Chemical sources**
  - Environ. emissions, chemicals in products
- **Environmental fate processes**
  - Degradation, intermedia transport, phase partitioning
- **Exposures**
  - Human exposure (different routes)
  - Freshwater species exposure
- **Effects**
  - Human toxicity effects (aggregated metrics)
  - Ecotoxicity effects (aggregated metric)

USEtox – Compartments & Pathways



https://usetox.org/documentation

Boxes = compartments
Arrows = fate processes
Icons = exposure pathways

USEtox – Characterization factors

- **Quantitatively** determine the impact score per impact category, in Comparative Toxic Unit (CTU): $CTU_{h\ midpoint}$ = cases or incidences
  $CTU_{h\ damage}$ = DALY – Disability Adjusted Life Years

$$IS = \sum_{i} \sum_{x} CF_{x,i} \times m_{x,i}$$

IS : impact score [CTU/functional unit]=[cases/functional unit]
CF : **characterization factor [CTU/kg]**
m : life cycle emission [kg/functional unit]
x : index for substance
i : index for compartment

- A **characterization factor** is …
- A quantitative representation of the (relative) hazard potential of a specific emission per kg emitted,
- Expressed as absolute metric or relative to a reference substance.

- *Example:* Human toxicity characterization factor of benzene: 5.5E-07 CTU_h/kg (cases per kg emitted to urban air (comparative toxic units = disease 'cases', i.e. population-level incidence risk)

USEtox 3 – In a nutshell

- ✓ USEtox-based **indicators**
  - Human toxicity (cancer, reproduction/developmental, other non-cancer effects)
  - Ecotoxicity (freshwater)
- ✓ Life cycle stages & **pathways**
  - All life cycle stages: chemical mass **emitted** to environmental compartment (impact/kg emitted)
  - Use stage: chemical mass **in product** application (impact/kg in product)
- ✓ **Substance** coverage & input **data** hierarchy
  - ~10,000 chemical substances (organics & metal ions)
  - Combination of measured data sources, combination of best-in-class prediction tools
- ✓ Steady-state & **dynamic** factors (dynamic solution for fate factor)

- ✓ Consistent with risk screening & SSbD metrics/steps
- ✓ USEtox version 3.0 to be released **early 2026**
- ✓ **USEtox^{GEO}** geospatial model & **USEtox^{WEB}** web-based platform currently under development

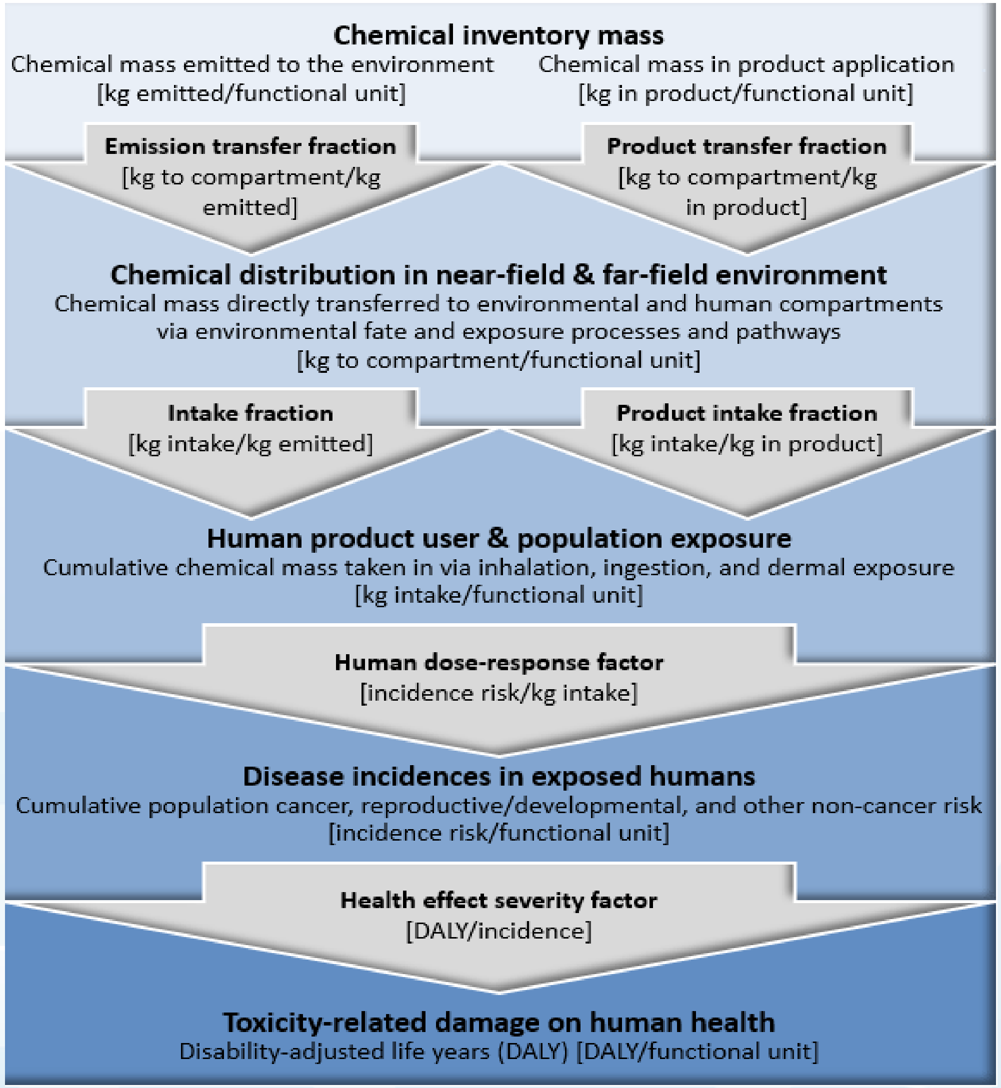
USEtox 3 updates: Near/far-field model

USEtox

- ✓ **Near-field/far-field fate & exposure model**
- ✓ Human toxicity non-cancer effect model
- ✓ Ecotoxicity effect model
- ✓ Input data generation hierarchy

Near-field human exposure pathways

- Inhalation (of indoor or near-person air)
- Dermal intake of gaseous chemicals
- Direct dermal contact
- Dust ingestion (via hand-to-mouth activities)
- Mouthing (via object-to-mouth activities)
- Direct ingestion (of food, pharmaceuticals)



https://doi.org/10.1007/s11367-021-01889-y

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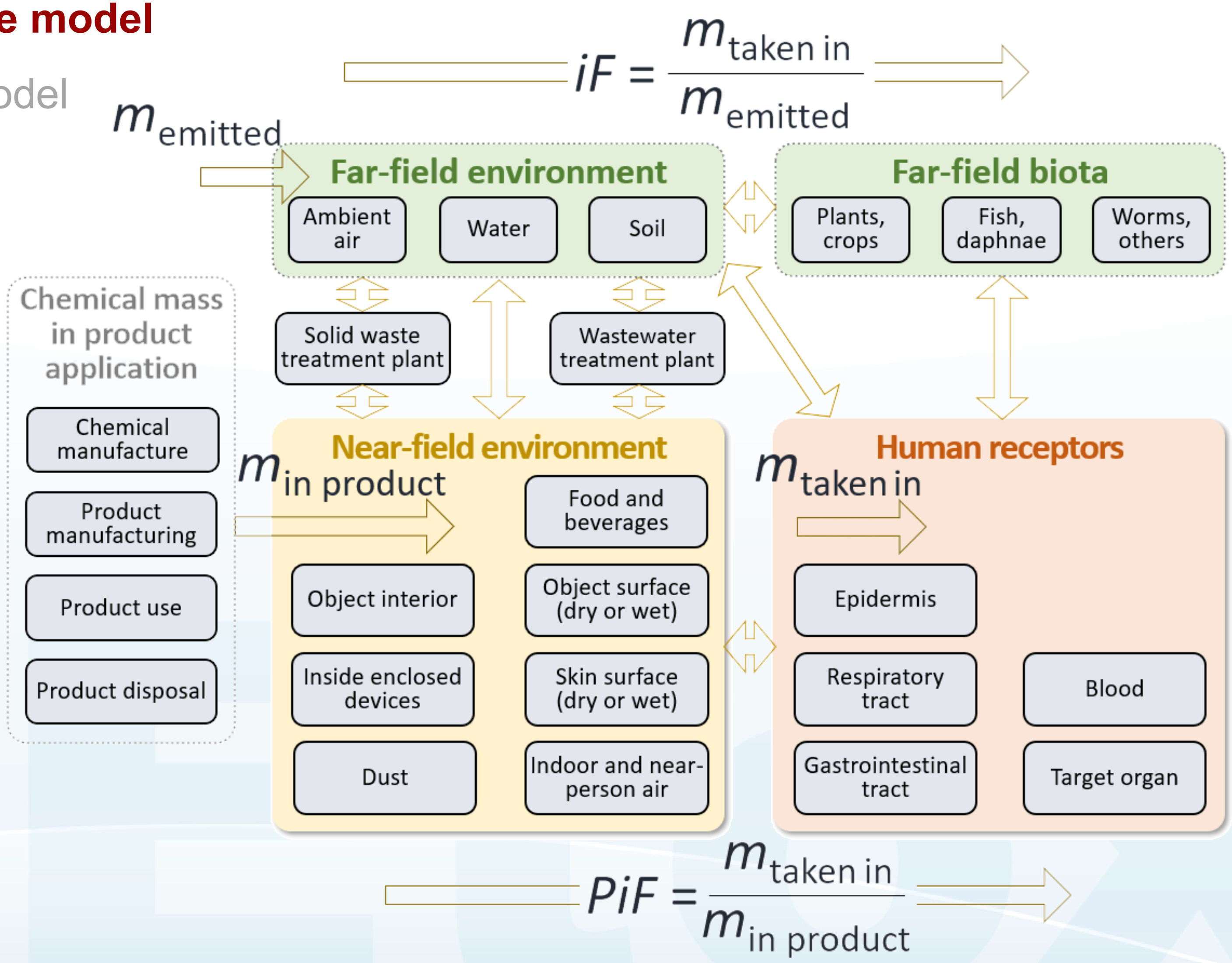

https://doi.org/10.1289/EHP3871

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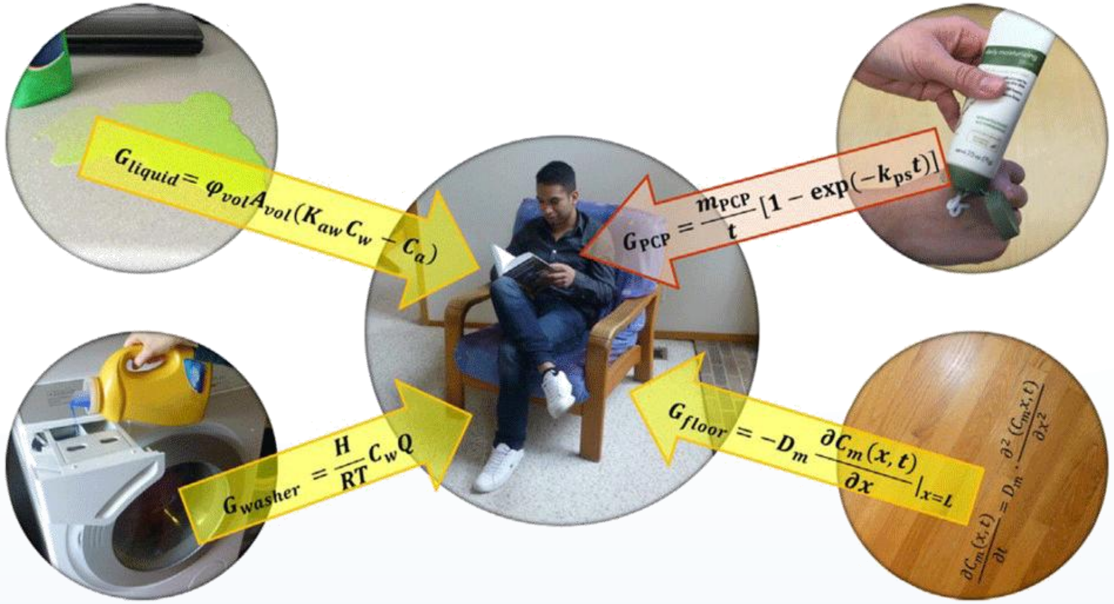


https://doi.org/10.1016/j.scitotenv.2016.06.118

Emission base model + 5 product modules
applied to **~500 customized products**

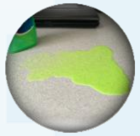
Emission & product source modules

 Indoor/outdoor emissions (base model)

 Skin surfaces (e.g., personal care products)

 Article interiors with indoor sorption (e.g., toys)

 Food contact materials

 Object surfaces (e.g., indoor paints)

 Pesticide residues in food crops

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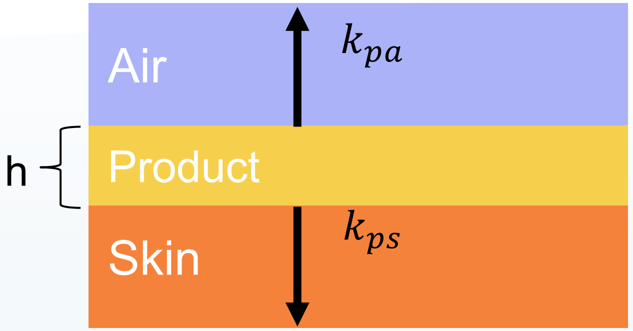
Example: skin surface model

https://doi.org/10.1016/j.envint.2016.03.014



Mass balance equation

Mass in product: $\frac{dm_p(t)}{dt} = -(k_{ps} + k_{pa}) \cdot m_p$

Model solution for direct transfer fraction to skin at time *t*

$$T_{\text{product to epidermis}} = \frac{k_{ps}}{k_{ps} + k_{pa}} \left(1 - e^{-(k_{ps}+k_{pa})\cdot t}\right)$$

$$k_{ps} \cong \frac{K_p}{h} = \frac{1}{h}\left(\frac{1}{K_p} + \frac{1}{\varphi_w}\right)^{-1}$$

$$k_{pa} \cong \frac{P_{aw} \cdot \varphi_a}{h} = \frac{1}{h}\left(\frac{1}{P_{aw} \cdot \varphi_a} + \frac{1}{\varphi_w}\right)^{-1}$$

m_p = mass of chemical in product [kg]
k_{ps} = product-to-skin transfer rate [1/d]
k_{pa} = product-to-air transfer rate [1/d]
K_p = skin permeation coefficient [m/d]
K_{aw} = air water partition coefficient = H/RT
φ_a = air flow at skin surface [$m^3/m^2/d$=m/d]
φ_w = water flow at product interface [m/d]
h = product thickness on skin [m]

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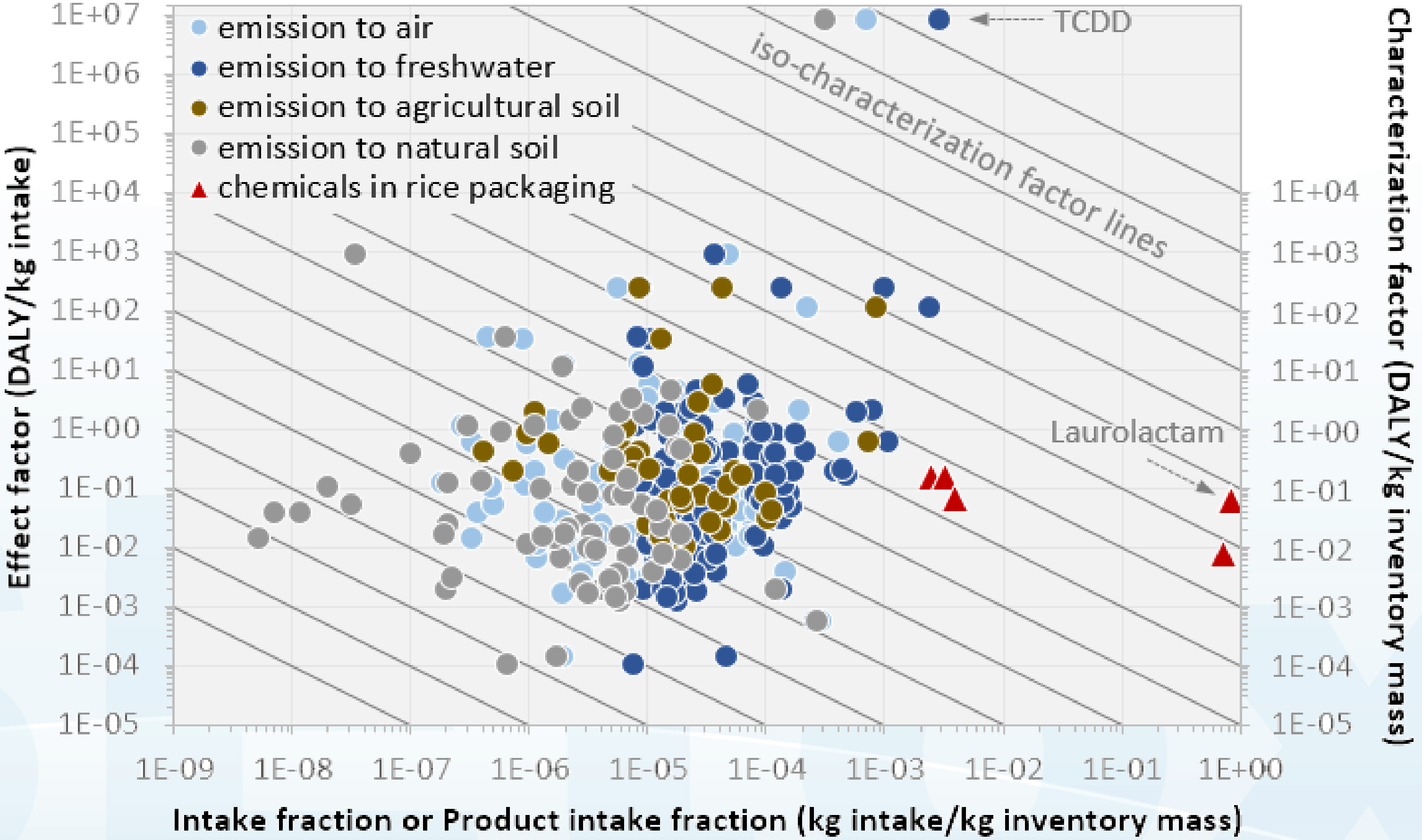

Use-stage exposure of users to chemicals in products often exceeds population exposure to chemicals emitted along entire life cycle

USEtox 3 updates: Near/far-field model

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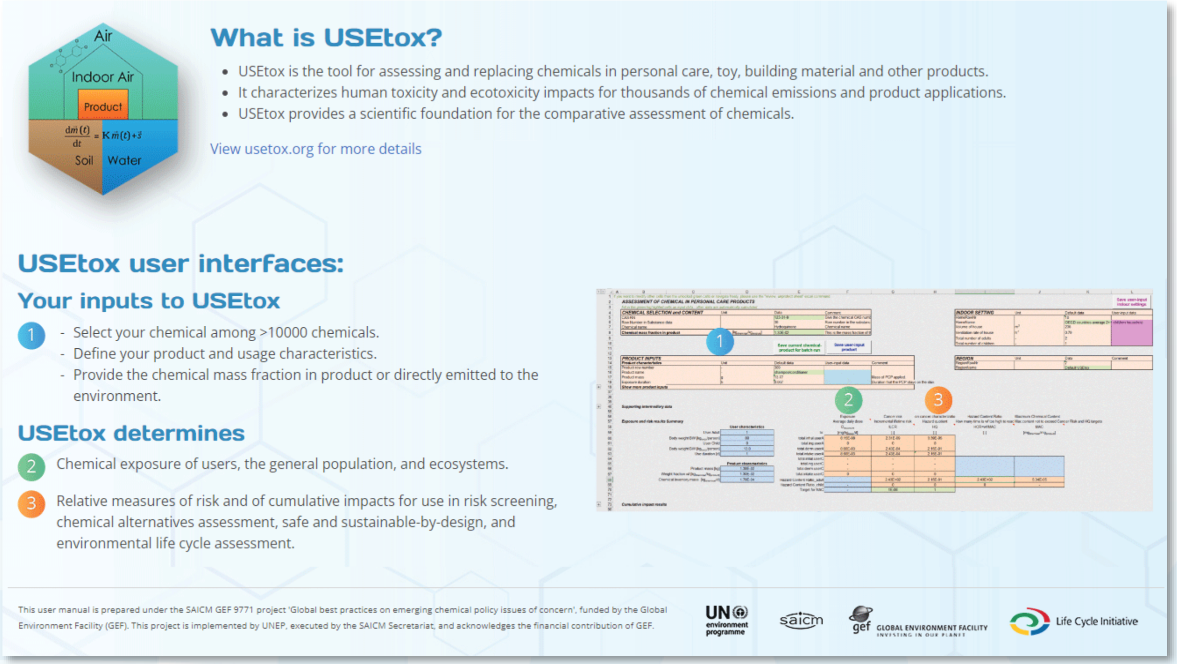
Product use scenario interfaces:

- 11 environmental compartments
- 14 product compartments
- 5000+ substances

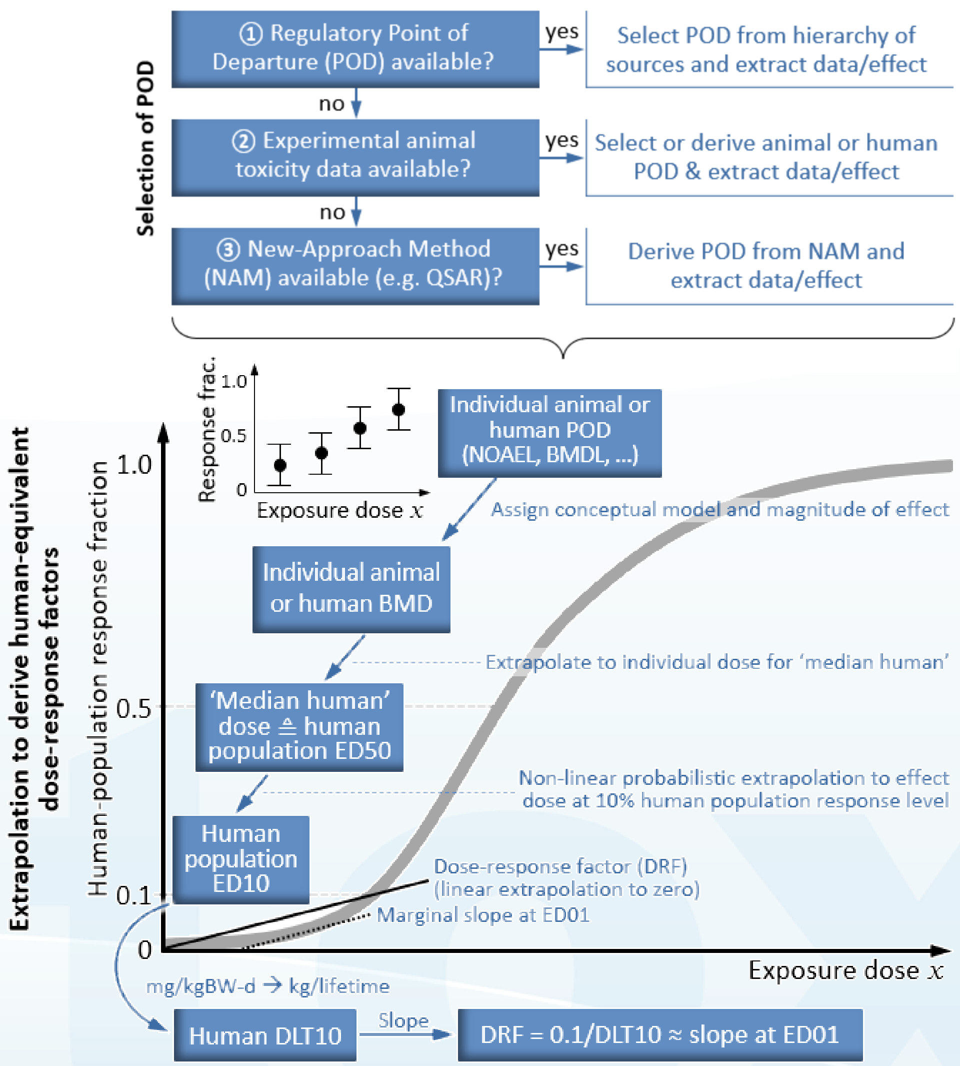


https://manual.usetox.org

USEtox 3 updates: Human toxicity effects

- ✓ Near-field/far-field fate & exposure model
- ✓ **Human toxicity non-cancer effect model**
- ✓ Ecotoxicity effect model
- ✓ Input data generation hierarchy

- Regulatory values when available
- If not, use *in vivo* animal data from US-EPA ToxValDB
  - Derived chronic human equivalent benchmark doses (BMDh)
  - Fitted BMDh by log-normal distribution
  - 25th percentile best predicts regulatory PODs
  - Used 25th percentile as surrogate PODs for chemicals without regulatory data
  - Characterized uncertainties around PODs
- Apply parameterized APROBA model (risk assessment WHO consensus model) to derive population-level human equivalent dose-response factors



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USEtox 3 updates: Human toxicity effects

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- ✓ **Human toxicity non-cancer effect model**
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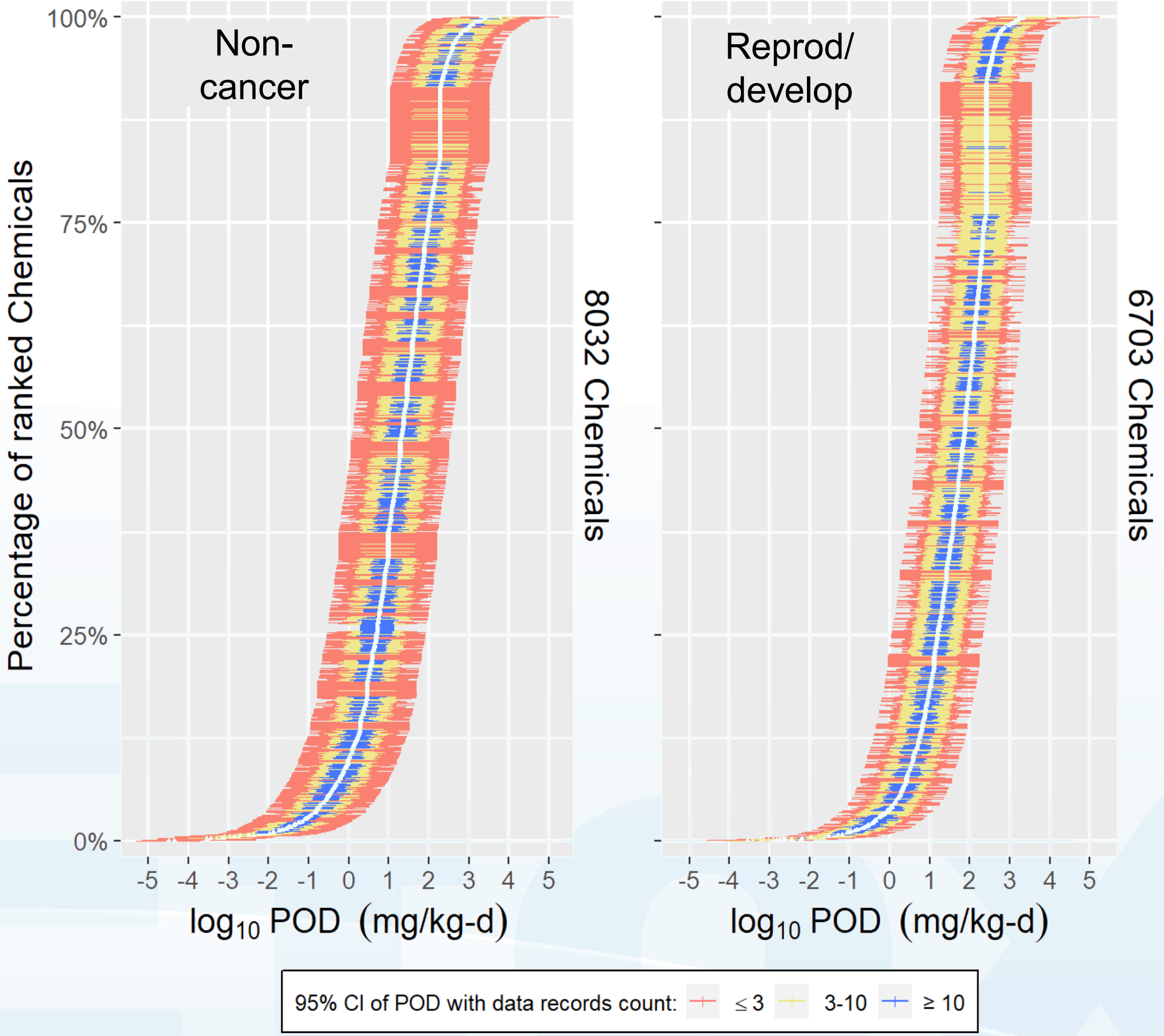
- ✓ Input data generation hierarchy

https://doi.org/10.1289/EHP11524



From PODs → human-equivalent lifetime dose-response factors (population incidence risk/kg_{intake})

Apply severity factors (DALY/incidence) to derive health effect factors (DALY/kg_{intake})

Disease Category	DALY/incidence
Rep/dev effects	44.1
Other non-cancer effects	2.4

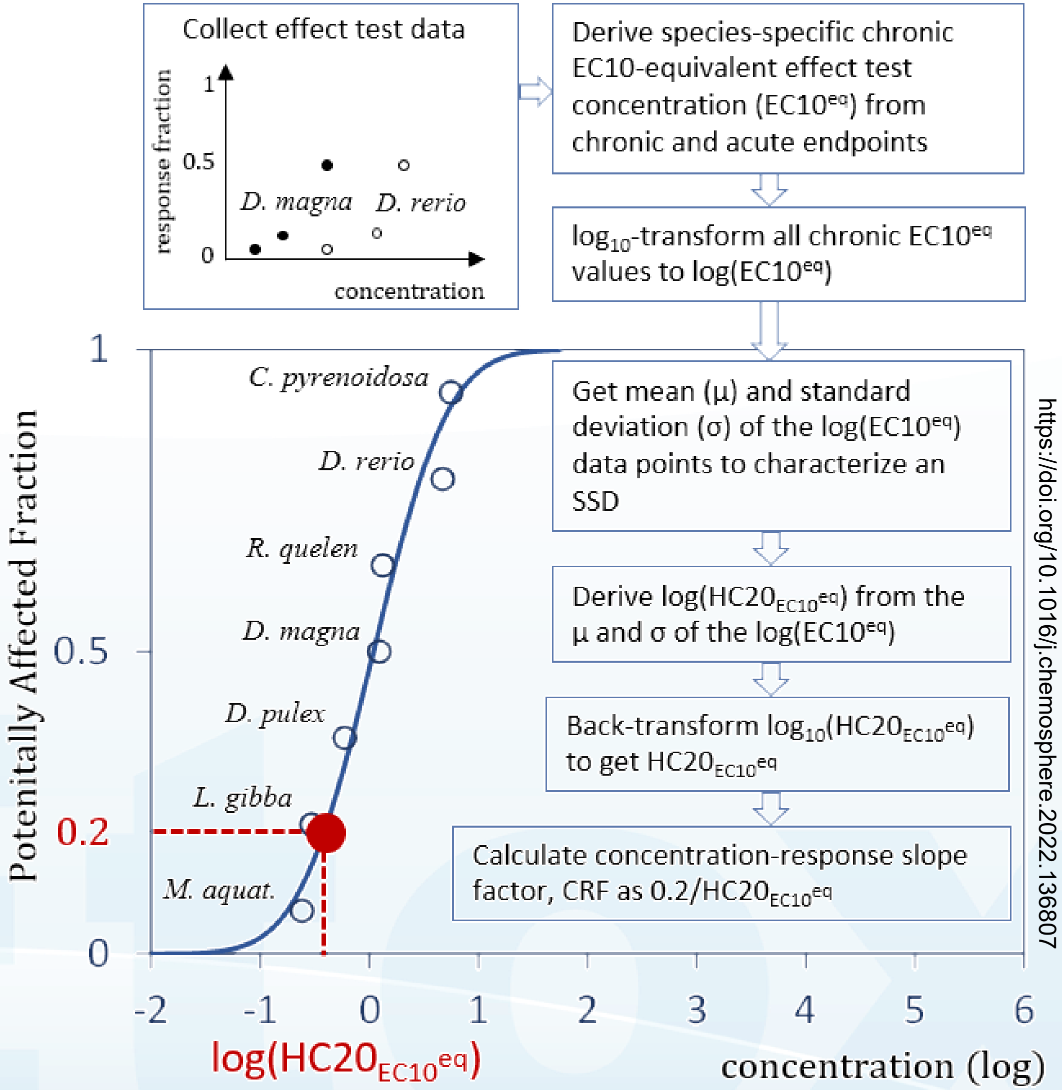
USEtox 3 updates: Ecotoxicity effects

- ✓ Near-field/far-field fate & exposure model
- ✓ Human toxicity non-cancer effect model
- ✓ **Ecotoxicity effect model**
- ✓ Input data generation hierarchy

1. Derive $EC10^{eq}$ from test data (NOEC, L/EC10/50)
2. Log-transform $EC10^{eq}$
3. Generate a species sensitivity distribution (SSD)
4. Get number (n), mean (μ) & standard deviation (σ) of $EC10^{eq}$
5. Define 20^{th} percentile response level across $EC10^{eq}$
6. Derive log HC20 from μ, σ of log $EC10^{eq}$

$$\log HC20_{EC10} = SSD_{\mu \log EC10} + z_{0.2} \cdot SSD_{\sigma \log EC10}$$

7. Back-transform log HC20 to get value in mg/l



USEtox 3 updates: Ecotoxicity effects

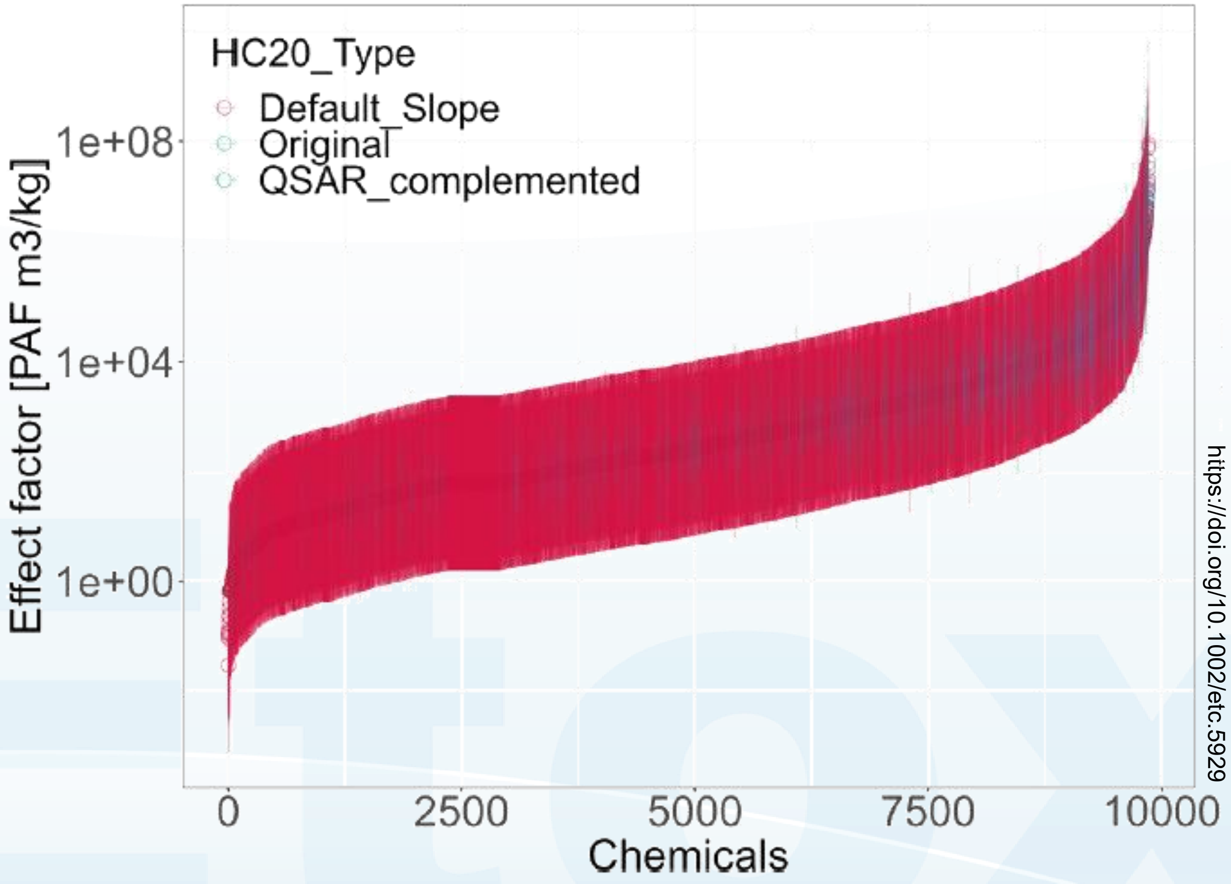
- ✓ Near-field/far-field fate & exposure model
- ✓ Human toxicity non-cancer effect model
- ✓ **Ecotoxicity effect model**
- ✓ Input data generation hierarchy

Data-rich chemicals (min. 3 species from 3 taxa) use SSD and provide average SSD-slope

Data-poor chemicals use average SSD-slope from data-rich chemicals

HC20 for chemicals with no data estimated using different QSARs

PAF:PDF ~ 1:1 ratio based on field monitoring data from The Netherlands

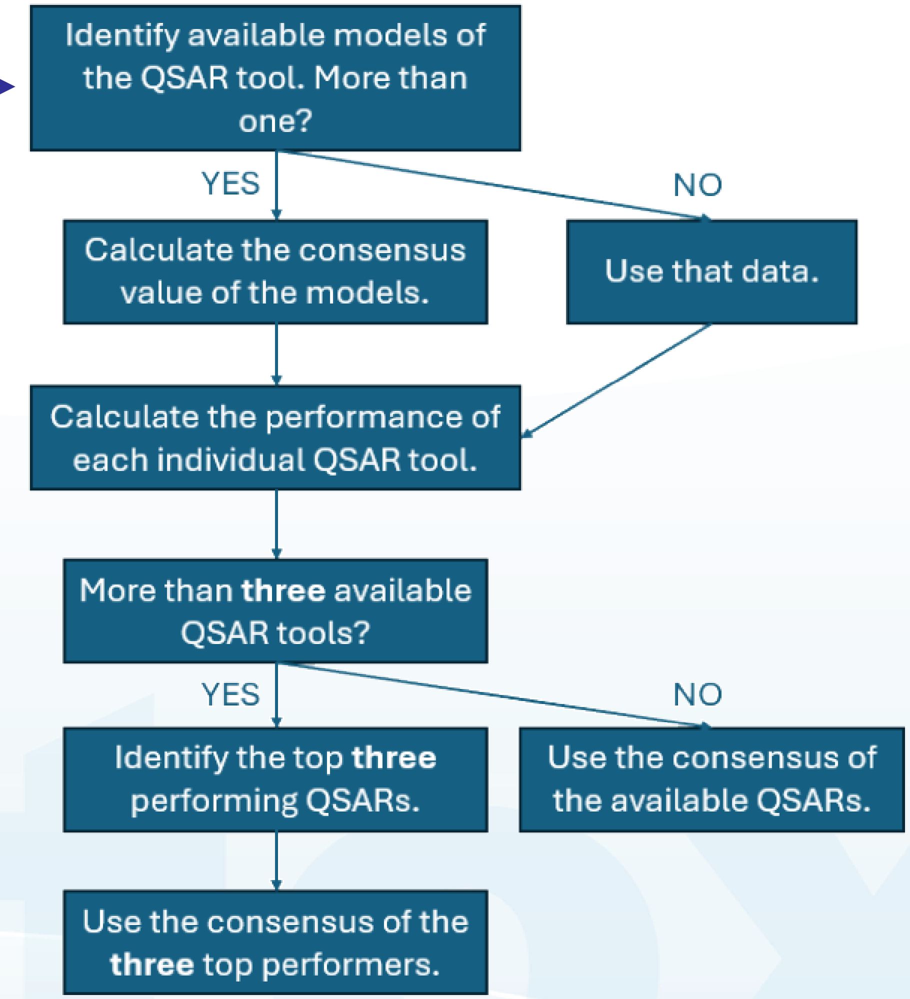


https://doi.org/10.1002/etc.5929

USEtox 3 updates: Input data

- ✓ Near-field/far-field fate & exposure model
- ✓ Human toxicity non-cancer effect model
- ✓ Ecotoxicity effect model
- ✓ **Input data generation hierarchy**

Property	Tools and Models							
	EPI Suite™	*OPERA*	*ACD/Labs*	*QSAR Toolbox*	*IFSQSAR*	*VEGA Hub*	*TEST*	*QSARins*
VP	X	X	X	X	X	X	X	-
WS	X	X	X	X	X	X	X	-
K_{OC}	X	X	-	X	-	X	-	X
K_{OW}	X	X	X	X	X	X	-	-
AOH	X	X	-	X	-		-	-
HL	X	X	-	X	-	X	-	-
Acidic pKa	-	X	X	X	-	-	-	-
Basic pKa	-	X	X	X	-	-	-	-



Akrivou et al. (in preparation)

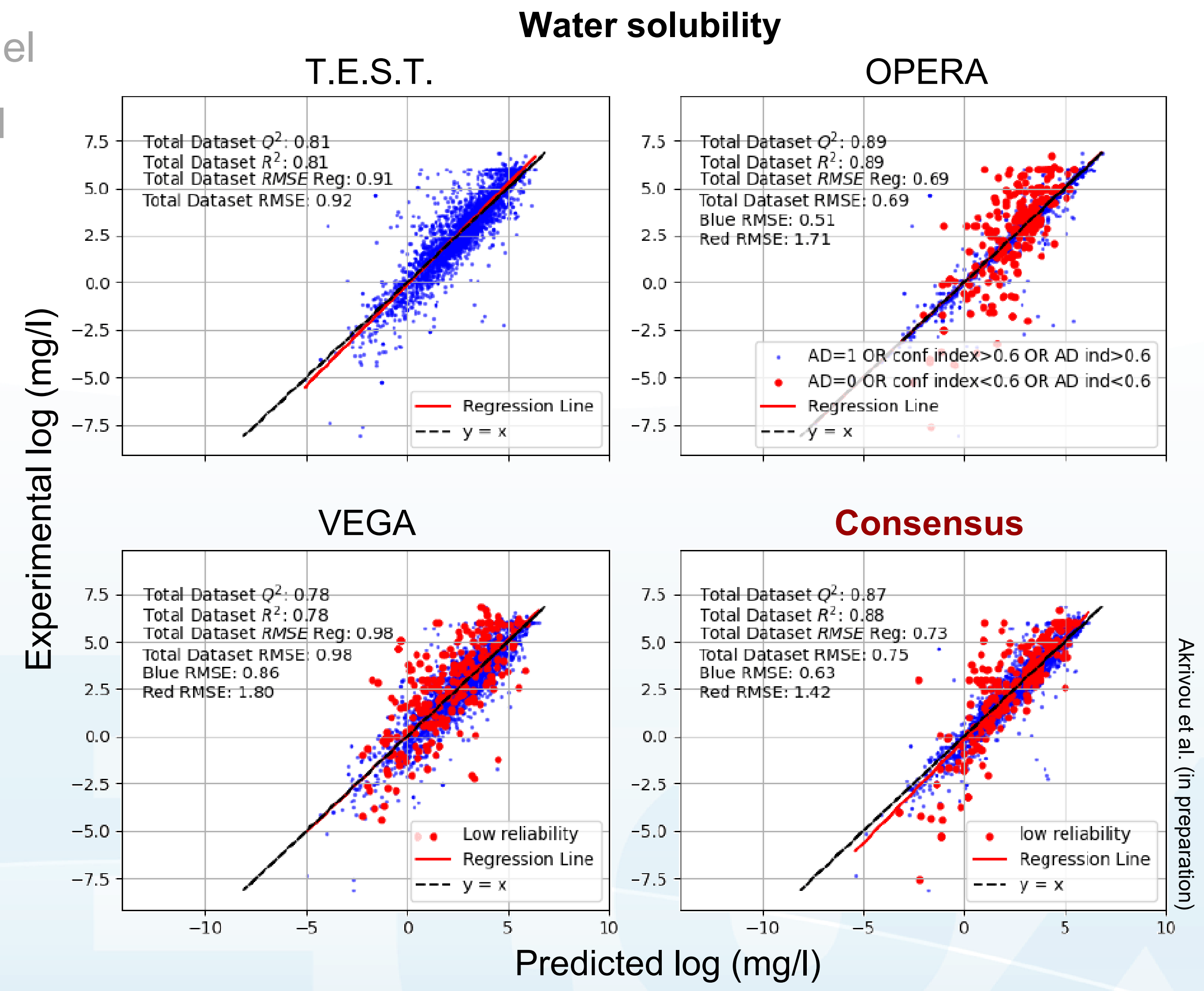
USEtox 3 updates: Input data

- ✓ Near-field/far-field fate & exposure model
- ✓ Human toxicity non-cancer effect model
- ✓ Ecotoxicity effect model
- ✓ **Input data generation hierarchy**

Physicochemical data predicted for most USEtox input parameters (except biodegradation half-life in water)

Highest reliability achieved when combining different prediction models into a “consensus” estimate

USEtox input parameters available for ~10,000 chemicals



UNEP GLAM developments

- ✓ Chemicals in product modules
- ✓ New exposure pathways (e.g. dermal, mouthing)
- ✓ Probabilistic human toxicity effect factors
- ✓ SSD-based freshwater ecotoxicity effect factors
- ✓ Parameter estimation (e.g. diffusion coefficients)
- ✓ Input data/estimation hierarchy

Already in USEtox 3

- ✓ Input data prediction using machine learning (~130,000 substances – global market)
- ✓ Terrestrial soil ecotoxicity indicator
- ✓ Linking PAF to PDF (damage) for ecotoxicity

https://lifecycleinitiative.org/applying-lca/lcia-cf

https://www.lifecycleinitiative.org/activities/life-cycle-assessment-data-and-methods/global-guidance-for-life-cycle-impact-assessment-indicators-and-methods-glam

USEtox – Further reading

USEtox documentation

- ✓ **General USEtox model**: https://doi.org/10.1007/s11367-008-0038-4
- ✓ Consensus building process: https://doi.org/10.1021/es703145t
- ✓ User requirements: https://doi.org/10.1007/s11367-014-0829-8
- ✓ Human toxicity impacts: https://doi.org/10.1007/s11367-021-01889-y
- ✓ Ecotoxicity impacts: https://doi.org/10.1016/j.chemosphere.2022.136807
- ✓ Technical documentation: https://usetox.org/documentation

USEtox 3 documentation

- ✓ **General USEtox 3 model**: *<in preparation>*
- ✓ Input data hierarchy: *<in preparation>*
- ✓ Near-field/far-field metric: https://doi.org/10.1021/acs.est.5b01083
- ✓ Near-field/far-field model: https://doi.org/10.1016/j.envint.2016.06.010
- ✓ Human non-cancer effects: https://doi.org/10.1289/EHP11524
- ✓ **Human toxicity impacts**: https://doi.org/10.1007/s11367-021-01889-y
- ✓ **Ecotoxicity impacts**: https://doi.org/10.1016/j.chemosphere.2022.136807
- ✓ Consensus process for human toxicity: https://doi.org/10.1289/EHP3871
- ✓ Consensus process for ecotoxicity: https://doi.org/10.1002/etc.4261
- ✓ Chemicals in children's toys model: https://doi.org/10.1016/j.envint.2020.106194
- ✓ Chemicals in building materials model: https://doi.org/10.1016/j.jhazmat.2021.127574
- ✓ Chemicals in indoor paints model: https://doi.org/10.1016/j.jhazmat.2023.133145
- ✓ Chemical in food contact materials model: https://doi.org/10.1016/j.fct.2017.09.024
- ✓ Soil ecotoxicity exposure/effects: *<in preparation>*

Thank you! Contact: **Peter Fantke | peter@substitute.dk**