UNEP/SETAC scientific consensus model for characterizing human toxicological and ecotoxicological impacts of chemical emissions in life cycle assessment

USEtox® 2.0

USER MANUAL

(Version 2)

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USEtox® 2.0 User Manual (Version 2)

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PREFACE

This document represents the official **user manual of USEtox**, the United Nations Environment Programme (UNEP) / Society of Environmental Toxicology and Chemistry (SETAC) scientific consensus model for characterizing human and ecotoxicological impacts of chemical emissions in life cycle assessment. Main output of USEtox is a database of **«recommended» and «indicative» characterization factors** for human toxicity and freshwater ecotoxicity, based on modelling of environmental fate, exposure, and effect parameters for the substances. Due to deficiencies in the model or the available substance data, the «indicative» factors are accompanied by a higher uncertainty than the «recommended» factors, and this should be considered when applying the factors and interpreting the results.

USEtox is officially endorsed by the UNEP/SETAC Life Cycle Initiative, and recommended as assessment method by the European Commission (EC) in the Recommendations on the Use of Common Methods to Measure and Communicate the Life Cycle Environmental Performance of Products and Organisations, 2013/179/EU, by the European Commission's Joint Research Centre – Institute for Environment and Sustainability (JRC-IES) in the International Reference Life Cycle Data System (ILCD) Handbook – Recommendations for Life Cycle Impact Assessment in the European context, EUR 24571 EN, by the World Business Council for Sustainable Development (WBCSD) in the Life Cycle Metrics for Chemical Products – A Guideline by the Chemical Sector to Assess and Report on the Environmental Footprint of Products, Based on Life Cycle Assessment, and by the United States Environmental Protection Agency in the Tool for the Reduction and Assessment of Chemical and other Environmental Impacts (TRACI) User's Manual, S-10637-OP-1-0.

The latest release version of USEtox is available at http://usetox.org.

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1. INTRODUCTION

This user manual provides basic information needed to understand and apply the USEtox model and to calculate midpoint and endpoint characterization factors for human toxicity and freshwater ecotoxicity.

The USEtox model is an environmental model for characterization of human toxicological and ecotoxicological impacts in life cycle assessment. It has been developed by a team of researchers from the Task Force on Toxic Impacts under the UNEP-SETAC Life Cycle Initiative (Hauschild et al. 2008, Rosenbaum et al. 2008). The mission of USEtox is to improve understanding and management of chemicals in the global environment by further developing, evaluating, applying and disseminating the model USEtox that describes the fate, exposure and effects of chemicals (Westh et al. 2015).

The USEtox model has been implemented in Microsoft® Excel® and applied to calculate characterization factors for human toxicity and freshwater aquatic ecotoxicity for organic and inorganic substances. The original USEtox model is further described in Rosenbaum et al. (2008) and USEtox 2.0 as current release version is described in detail in the official USEtox Documentation (Fantke et al. 2015) available at http://usetox.org. It should be stressed that the characterization factors are useful for a first tier assessment. In case a substance appears to dominantly contribute to the impact scores for toxicity, it is recommended to verify the reliability of the chemical-specific input data for this substance and to improve the data whenever possible.

Life cycle impact assessment

Life cycle impact assessment (LCIA) aims to improve the understanding of the relative importance of the individual emissions in life-cycle inventories. This is done using a weighted summation of the releases of substances of a product system with help of characterization factors:

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

where *IS* is the impact score for e.g. human toxicity (disease cases at midpoint level or disability-adjusted life years, DALY, at endpoint level); $CF_{x,i}$ the characterization factor of substance *x* emitted to compartment *i* (disease cases/kg at midpoint level or DALY/kg at endpoint level) and $m_{x,i}$ is the emitted mass of substance *x* to compartment *i* (kg). The summation holds for substances and emission compartments for the same impact category (in case of USEtox either human toxicity or freshwater ecosystem toxicity).

For human toxicity, the USEtox model calculates characterization factors for carcinogenic impacts, non-carcinogenic impacts, and total impacts (carcinogenic and non-carcinogenic aggregated assuming equal weighting at midpoint level or impact-specific weighting at endpoint level, where in the latter carcinogenic and non-carcinogenic impacts are weighted differently) for substance emissions to household indoor air, occupational indoor air, urban air, continental rural air, continental freshwater, continental (coastal) sea water, continental agricultural soil and/or continental natural soil. The unit of the characterization factor for freshwater ecosystem toxicity is potentially affected fraction of species (PAF) at midpoint level and potentially disappeared fraction of species (PDF) at endpoint level integrated over the freshwater volume (m³) and the duration of 1 day (d) per kg emission, PAF.m³.d/kg

(midpoint level) and PDF.m^3.d/kg (endpoint level). The unit of USEtox characterization factors and for human toxicity is number of disease cases at midpoint level and number of DALY at endpoint level per kg emission, cases/kg (midpoint level) and DALY/kg (endpoint level). Thereby, USEtox characterization factors are summarized as **Comparative Toxic Units (CTU)** at midpoint level and **Comparative Damage Unit (CDU)** at endpoint level to stress the comparative nature of the characterization factors.

USEtox calculates characterization factors for human toxicity and freshwater aquatic ecosystem toxicity as shown in Figure 1.
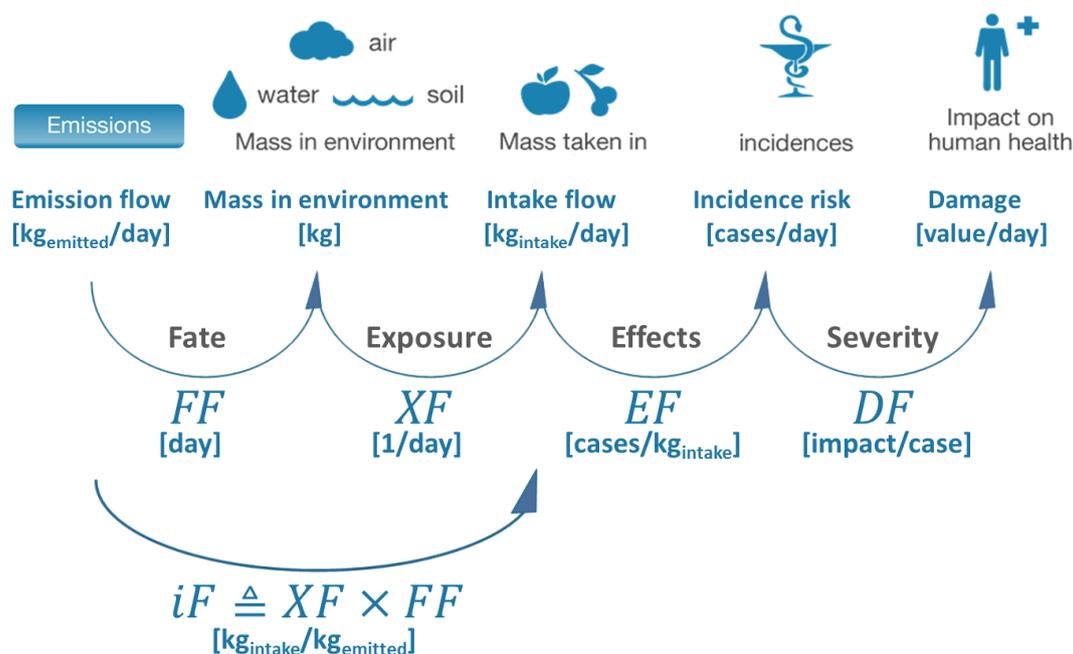

Figure 1. Framework for characterizing human toxicity and freshwater ecotoxicity impacts in USEtox 2.0.

Human toxicity

In USEtox, substances that have a potential to increase human disease have a human toxicity characterization factor that is derived from the product of three matrices including fate factors (FF), human exposure factors (XF), and human toxicological effect factors (EF):

CF = EF XF FF

The product of the fate factor matrix **FF** and the human exposure factor matrix **XF** results in the matrix containing human intake fractions (iF). The intake fraction represents the fraction of the mass emitted into a specific compartment that is taken in by the human population:

iF = XF FF

In USEtox, intake through inhalation and ingestion routes are considered in iF calculations.

The fate factors (FF) link the quantity released into the environment to the chemical masses (or concentrations) in a given compartment and are the same for ecotoxicity and human toxicity. Fate factors are described in the next section. A human exposure model is put on top of this to describe the transport from environmental compartments to the human via

inhalation and ingestion (XF). Apart from the fate factors and exposure factors, effect factors are also required in the calculation of human-toxicological characterization factors. The effect factor (EF) reflects the change in life time disease probability due to change in life time intake of a pollutant (cases/kg). USEtox determines effect factors for carcinogenic and non-carcinogenic chemicals separately. Data for effects after inhalation and oral (ingestion) exposure are also determined separately. To arrive at endpoint level, the midpoint characterization factors for human toxicity are multiplied with a severity factor (DALY/case) separately for cancer and non-cancer cases.

Ecotoxicity

In USEtox, an ecotoxicological characterization factor for freshwater ecosystems is derived from the product of three matrices including fate factors (FF), freshwater ecosystem exposure factors (XF), and freshwater aquatic ecosystem toxicity effect factors (EF):

$$\mathbf{CF = EF\ XF\ FF}$$

Multimedia fate models are commonly used for predicting environmental fate factors (FF) and ecosystem exposure factors (XF) for a substance of concern. In this type of model the study area is represented by a number of homogeneously mixed compartments, each representing a specific part of the environment (i.e. atmosphere, water, soil). The fate factor of a substance in a certain compartment can be calculated by solving a set of mass balance equations that describe processes such as degradation and inter-compartment transfer. The fate factor represents the increase of chemical mass in an environmental compartment (for freshwater ecotoxicity this is freshwater) due to an emission in a given compartment. It can be interpreted as the product of the fraction of an emission that reaches freshwater (dimensionless) times its persistence in freshwater (e.g. in days). The exposure factor represents the bioavailability of a substance, i.e. the fraction of the chemical dissolved in freshwater. Which processes are the most important for a certain compound depends on the physical-chemical properties of the compound. Also the environmental conditions (temperature, rain intensity etc.) influence the model predictions.

Apart from the fate factors and exposure factors, freshwater aquatic ecotoxicity effect factors (EF) are also required in the calculation of ecotoxicological characterization factors. The ecotoxicological effect factor reflects the change in the potentially affected fraction (PAF) of species at midpoint level and the change in the potentially disappeared fraction (PDF) of species at endpoint level due to change in substance concentration in freshwater, integrated over the freshwater volume (m^3) per substance mass emitted to freshwater (kg), PAF.m^3/kg (midpoint level) and PDF.m^3/kg (endpoint level).

Characterization factors for freshwater aquatic ecotoxicity are reported for emissions to household indoor air, occupational indoor air, urban air, continental rural air, continental freshwater, and/or continental agricultural soil. To arrive at endpoint level, the midpoint characterization factors for freshwater aquatic ecosystem toxicity are multiplied with a severity factor (PDF/PAF).

2. RUNNING USEtox

2.1 Installing USEtox

The latest release version of USEtox can be downloaded as archive file in ZIP format from the official website http://usetox.org. After download, the ZIP archive needs to be saved on a local computer and extracted in a user-defined directory. After extraction, the user will find the main directory «USEtox_<*version no*>» hat contains the main USEtox model file, a readme file in TXT format explaining the folder structure and the following 4 sub-folders:

- Documentation – contains the main USEtox documentation and manual files
- InputData – contains the USEtox organic and inorganic substances database files
- Results – contain the USEtox results files for organic and inorganic substances
- Templates – contains the USEtox read-only template files used by the USEtox user interface wizard to create new or customize existing substances, to enter new toxicological effect data and to export user-defined scenario results and factors

To use USEtox, open the USEtox main model file «USEtox2.0.xlsm». This file is implemented as a Microsoft® Excel® workbook in XLSM file format (32 bit) containing multiple worksheets and macros written in Visual Basic for Applications (VBA). Note that macros need to be activated to run USEtox, whereas no macros are required to use the USEtox substances database files, results files or any other model-related files. After opening the main USEtox model file, you need to carefully read and agree to the USEtox® LICENSE AGREEMENT and then USEtox is ready to run.
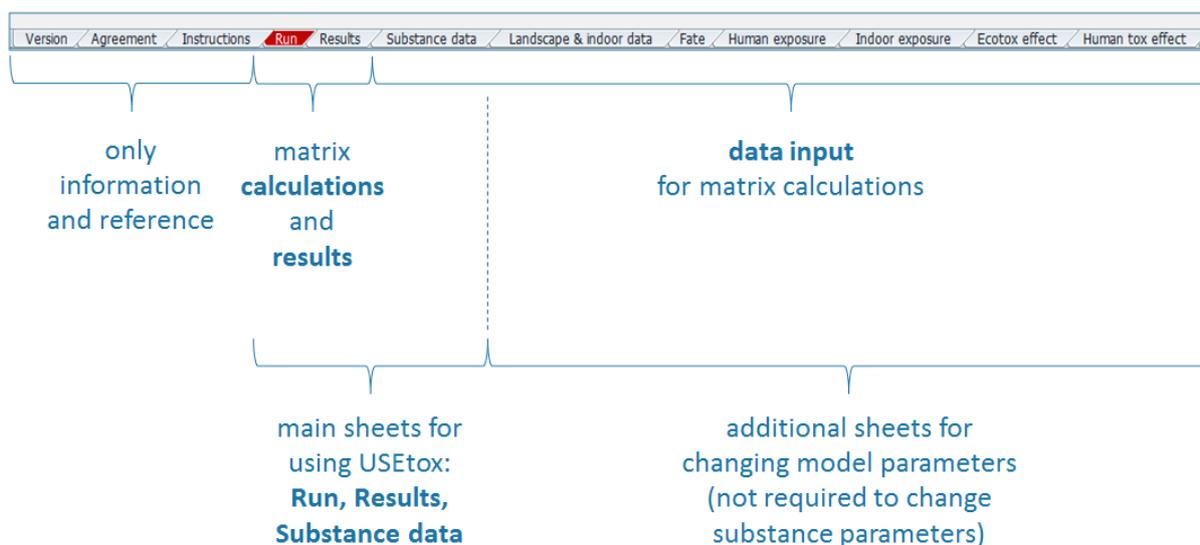
2.2 Worksheet structure

Figure 2. Worksheet structure of the USEtox 2.0 model file implemented in Microsoft Excel.

The USEtox model file contains a number of interlinked worksheets. An overview over all worksheets is given in Figure 2 and a brief explanation of the content of each worksheet is provided in Table 1.

Table 1. Explanation of the content of USEtox model file worksheets.

Worksheet	Explanation	Remarks
Version	Background information on the USEtox model and its developers	Only for reference
Agreement	Text of the license agreement for using USEtox model, data, factors, and documentation	Only for reference
Instructions	Instructions how to perform single substance calculations and series calculation for a list of substances	Only for reference
Run	Specification of the model runs and calculation routines for fate factors, exposure factors, intake fractions, effect factors and characterization factors for human toxicity and freshwater aquatic ecotoxicity	Full matrix calculation framework and results for currently selected substance
Results	Presentation of the relevant outcomes of USEtox	Results for all substances run in series
Substance data	Substance-specific information required to calculate characterization factors with USEtox.	User input for editing existing/new substances
Landscape & indoor data	Default landscape data applied in USEtox, regionalized landscape data for sensitivity study of default data, and indoor settings data	Background data sheet
Fate	Background data and equations required for the calculation of fate factors and aquatic ecosystem exposure factors	Background data sheet
Human exposure	Background data and equations required for the calculation of human exposure factors	Background data sheet
Indoor exposure	Background data and equations required for the calculation of indoor air exposure	Background data sheet
Ecotox effect	Background data and equations required for the calculation of ecotoxicological effect factors	Background data sheet
Human tox effect	Background data and equations required for the calculation of human toxicological effect factors (carcinogenic and non-carcinogenic)	Background data sheet
avlogEC50	Data input via the USEtox user interface wizard for ecotoxicological effect data	Only relevant when using the USEtox user interface wizard
Human tox ED50	Data input via the USEtox user interface wizard for human toxicological effect data	Only relevant when using the USEtox user interface wizard
Conversion table	Conversion factors for internal use in equations	Hidden worksheet
Lists	Lists that are used in the forms of the USEtox user interface wizard	Hidden worksheet; only relevant when using the USEtox user interface wizard

Worksheet	Explanation	Remarks
Code inputs	Text inputs that are used in the forms of the USEtox user interface wizard	Hidden worksheet; only relevant when using the USEtox user interface wizard

To work with the USEtox model in practice, substance-specific information for the chemical(s) under consideration need to be gathered and stored in the sheet «Substance data». The sheet «Run» contains the user interface to define the substances and scenarios for which characterization factors should be calculated (Figure 3). Substances and scenarios can also be defined via the USEtox user interface wizard that can be started by clicking on the button «Launch the USEtox user interface» in sheet «Version». The sheet «Results» provides the characterization factors, fate factors, intake fractions and effect factors for the chemical(s) considered.

Figure 3. USEtox user interface in sheet «Run» for defining substances and scenarios to run.

More detailed information on the USEtox model results can be found in the sheet «Run». Both the human and ecotoxicity characterization factors are calculated using standard matrix algebra. This means that each of the above mentioned factors (e.g. fate, exposure, and effect factors) are represented in matrices which are multiplied to obtain a characterization factor matrix, as the final result. This optimizes calculation efficiency (i.e. only one model run for all emission scenarios per substance), transparency, and interpretability of results.

On the left side (top to bottom) of the worksheet «Run» the main matrices with fate, exposure, intake fraction and effect factors, followed by the characterization factor matrices can be found. In detail, matrices containing the following factors representing the respective intermediate/final results are given:

- Loss processes rate constants – k (d^{-1})
- Transfer rate constants – k (d^{-1})
- Fate factors – FF (d)
- Available fraction (fraction in dissolved/gaseous phase) – XF_{eco} (-)
- Human exposure factors – XF_{hum} (d^{-1})
- Human intake fractions – iF ($kg_{intake}/kg_{emitted}$)
- Human health effect factors – EF_{hum} ($cases/kg_{intake}$)
- Midpoint characterization factors: human toxicity potentials expressed as comparative toxic units – CTU_h ($cases/kg_{emitted}$)
- Endpoint characterization factors: human health impact potentials expressed as comparative damage units – CDU_h ($DALY/kg_{emitted}$)
- Ecotoxicity effect factors – EF_{eco} ($PAF \times m^3/kg$)
- Midpoint characterization factors: ecotoxicity potentials expressed as comparative toxic units – CTU_e ($PAF \times m^3 \times d/kg_{emitted}$)
- Endpoint characterization factors: ecosystem impact potentials expressed as comparative damage units – CTU_e ($PDF \times m^3 \times d/kg_{emitted}$)

On the right side (top to bottom) of the «Run» worksheet, the following additional interpretations of these intermediate results can be found:

- Direct removal pathways – the contribution of each removal pathway (i.e. diffusion/advection to another compartment, advection to another spatial scale, or degradation within the same compartment – diagonal element) to the total removal from each emission compartment (column)
- Feedback fraction – the fraction of an emission that returns to the medium of release after transfer to other media providing a measure of the level of coupling between media
- Residence time in the environment (d) – effective residence time in the compartments
- Mass fraction in the receiving environment for an emission to the column
- Overall transferred fractions from emission (columns) to receiving (row) compartment – the transferred fractions already include the sum of all possible transfer pathways through a third media
- Fraction of ingestion per intake pathway – contribution of each exposure pathway (row) to overall exposure via ingestion for an emission to the respective compartment (row)

More in-depth explanations and the basis for this matrix-algebra framework can be found in Rosenbaum et al. (2007).

In the middle (top to bottom on the right side of the main matrices) and on the far right (top to bottom on the right of the matrices for the additional interpretation) of the «Run» worksheet, the following additional interpretation plots can be found with an example plot shown in :

- Direct removal from emission to receiving compartments (% removal)
- Fate factors (d)
- Human intake fractions (kg$_{intake}$/kg$_{emitted}$ and % contribution to intake fractions)
- Midpoint characterization factors: human toxicity potentials (cases/kg$_{emitted}$)
- Midpoint characterization factors: ecotoxicity potentials (PAF×m^3×d/kg$_{emitted}$)
- Residence times in the environment (d)
- Overall transferred fractions from emission to receiving compartments (% transferred)
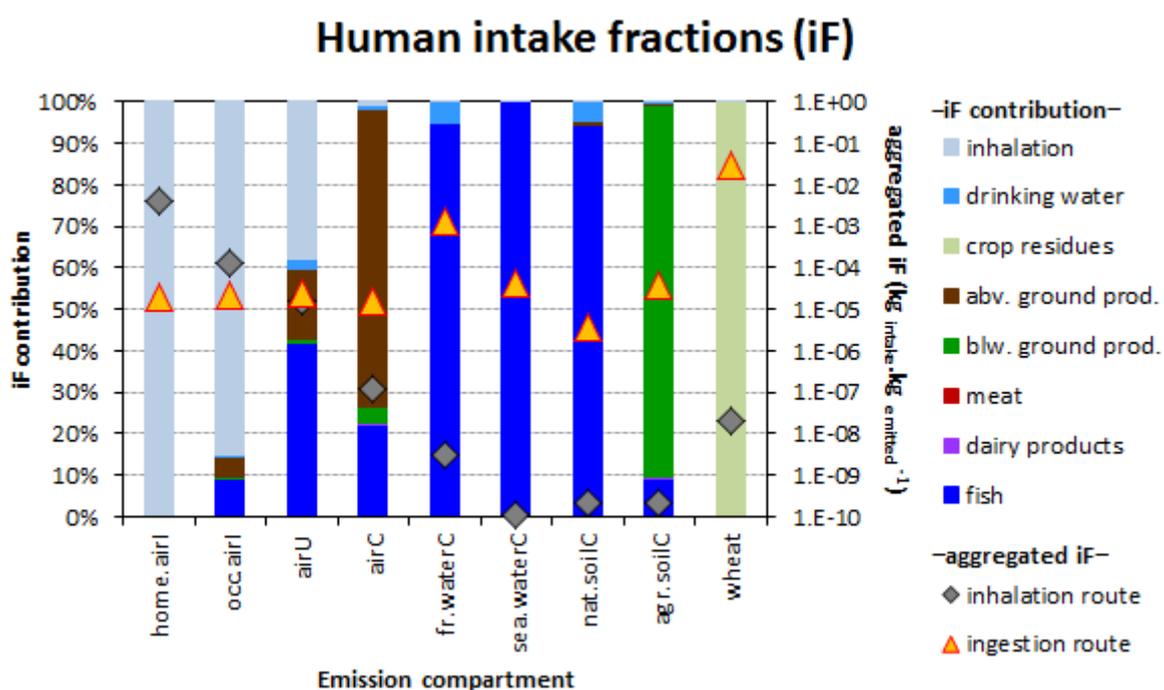
Figure 4. Example interpretation plot of the results matrices in the «Run» model sheet.

2.3 User interface wizard

In USEtox, it is possible to create or import substances, update existing substances, implement new toxicological effect data, and perform calculations for either up to 10 substances with user-defined emission scenarios or for all substances via the USEtox user interface wizard (new in USEtox 2.0). The interface wizard can be opened by clicking in the USEtox model file in sheet «Version» on the button «Launch the USEtox user interface». Then, click in the interface wizard start page (see Figure 5) on the available buttons «Create or customize substance data» or «Set up calculations with USEtox. More information on how to use the USEtox user interface wizard can be found in the «Manual: User Interface Wizard» that can be found on http//usetox.org.

Figure 5. USEtox user interface wizard start screen.

3. FATE FACTOR

In USEtox, different nested scales are specified:

- The indoor environment scale for household settings (parameterized for non-OECD countries average (non-airtight building), non-OECD countries average (airtight building), OECD countries average, Europe (EU-27) average, and North America) and occupational settings (parameterized for Industry, OECD, Office, OECD, Industry, non-OECD, Office, and non-OECD regions);
- The urban scale with the urban air compartment;
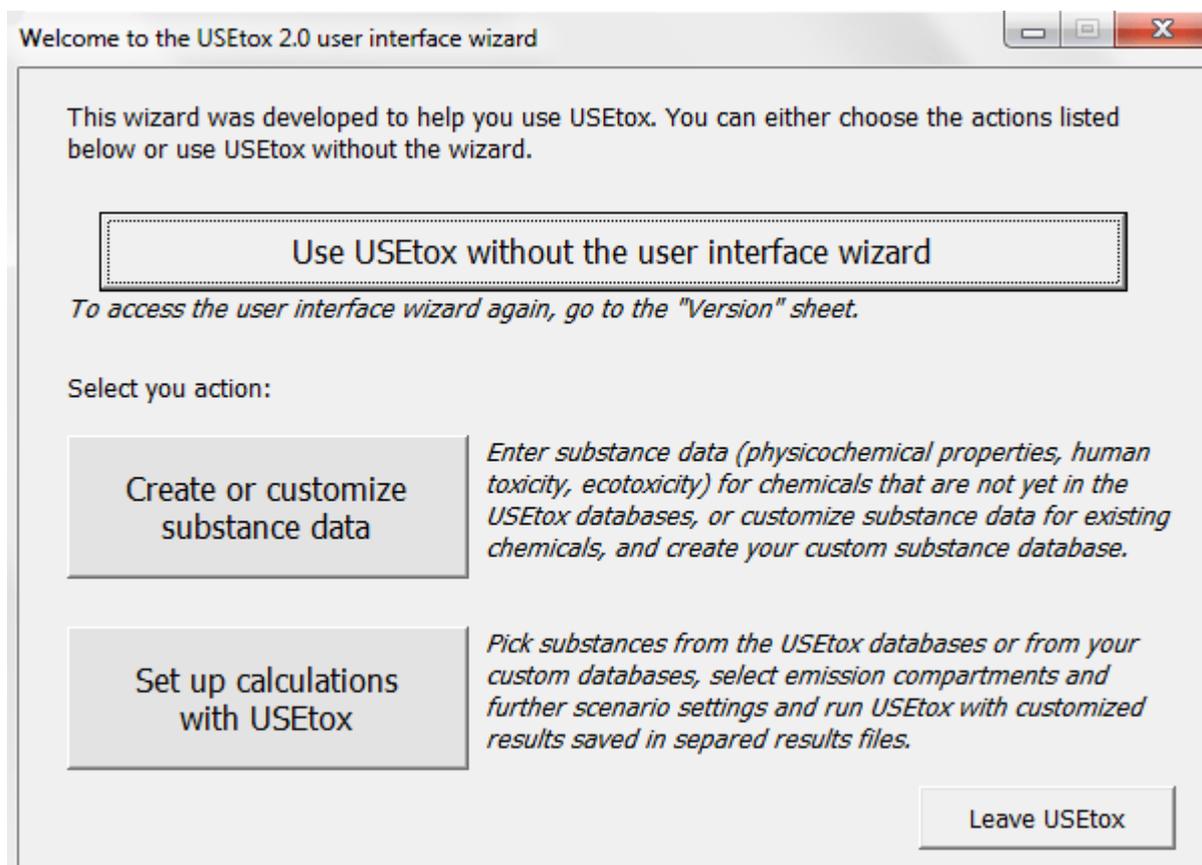- The continental scale with the following compartments: air, freshwater, coastal sea, natural soil and agricultural soil;
- The global scale with the following compartments, air, freshwater, ocean water, natural soil and agricultural soil.

The indoor environment scale and urban scale are nested in the continental scale and the continental scale is nested in the global scale (see Figure 6).
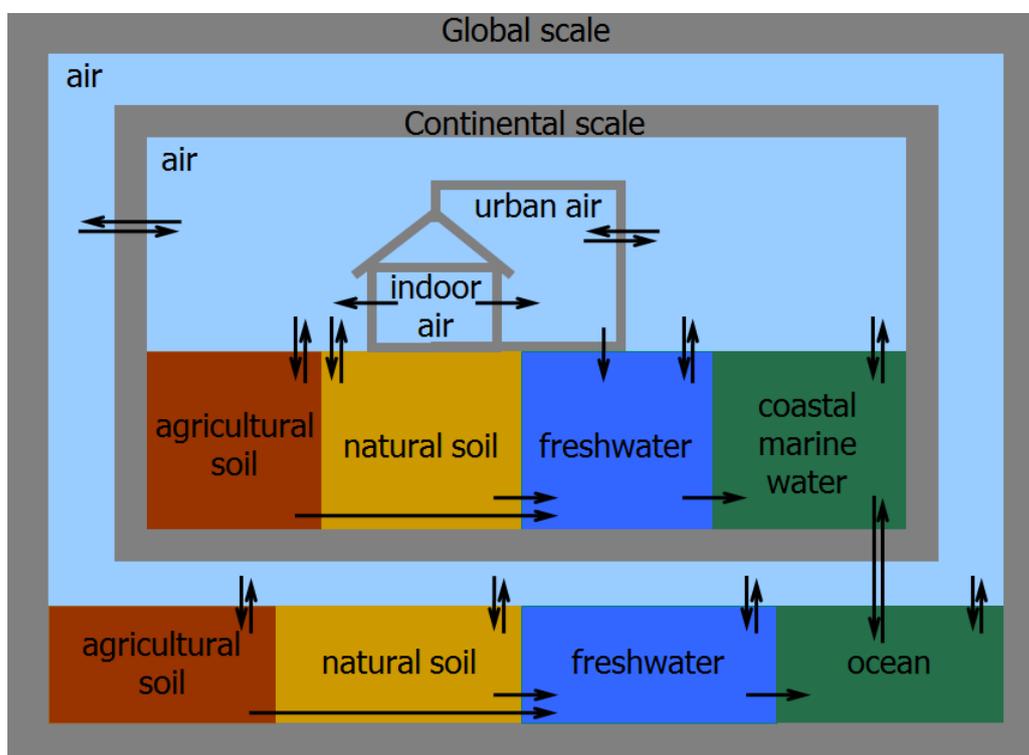
Figure 6. USEtox nested compartment structure and transfer processes.

The main diagonal elements of the fate factor matrix (see main model file, sheet «Run») represents the compartment-specific residence time (in days) of a substance. The longer the residence time the longer the persistence of a substance in the considered environmental compartment. Off-diagonal elements of the fate factor matrix represent the fraction of a substance emitted into a given compartment (column) reaching the any receiving compartment (raw) that is not the same as the emission compartment multiplied by the residence time of the receiving compartment (main diagonal element). Within the USEtox model, the fate factor of a chemical depends on (i) the properties of the chemical and (ii) the landscape properties of the emitting and receiving compartment. For instance, USEtox

calculates a fate factor from continental air to agricultural soil for dioxin (2,3,7,8-TetraCDD) of 2.88×10^3 days. It represents the product of the fraction of dioxin transferred from continental air to agricultural soil (0.079, see matrix of «Overall rate constant for transferred fractions from emission to receiving compartment» in sheet «Run») multiplied by the residence time in continental agricultural soil (3.61×10^4 days, see fate factor matrix in the same sheet).

The fate module of USEtox accounts for removal processes and intermedia transport processes of substances in the environment. Examples of removal processes are (bio-) degradation by micro-organisms, burial into the sediment, leaching to the groundwater and escape to the stratosphere. Intermedia transport processes account for substance transfer from one compartment to the other within the same scale or across different scales. Two types of intermedia transport processes exist: advective and diffusive transport. In the case of advective transport, a substance moves with an environmental medium from one compartment to the other (one-way transport). For example, rivers transport a substance from freshwater to seawater and rain transports a substance from air to the earth's surface. Diffusive transport between two compartments, on the other hand, is passive two-way transport, i.e. a substance can move from one compartment to another and back. Diffusive transport from air to water is called gas absorption, while diffusive transport from water to air is called volatilization.

Intermedia transfer rates and removal rates depend on substance properties. To give a few examples:

- Substances that are easily transformed by micro-organisms have high degradation rates in soil, water and sediment;
- Substances that tend to bind strongly to particles (hydrophobic chemicals) have a relative high removal rate from water to sediment via sedimentation of suspended particles;
- Substances with a high vapor pressure (and low solubility) will have a relatively high tendency to volatilize from water to air.

The fate module of USEtox considers all environmental processes within a system of mass balance equations. The system is solved with the help of linear algebra calculation rules assuming steady state conditions. Steady state means that substance masses (or concentrations) in environmental compartments do not change over time by a constant emission rate. To run the USEtox fate module for organic or inorganic (currently limited to cationic metals) substances, a set of substance-specific input parameters must be provided in the worksheet «Substance data» of the main model file (Table 2). We recommend giving preference to experimental data over estimated data. Inputs shall exactly match the units specified in Table 2 (and the «Substance data» worksheet in the main model file).

Table 2. Chemical-specific substance data in USEtox for calculating fate factors

Parameter	Symbol	Unit	Required[a]	Remarks
Molar mass	MW	g/mol	yes	-
pKa chemical class	pKaChemClass	-	yes	New in USEtox 2.0
pKa base reaction	pKa.gain	-	yes	New in USEtox 2.0
pKa acid reaction	pKa.loss	-	yes	New in USEtox 2.0
Partitioning coefficient	K_{OW}	L/L	yes (for organic	-

Parameter	Symbol	Unit	Required[a]	Remarks
between *n*-octanol and water			substances)	
Partitioning coefficient between organic carbon and water	K_{OC}	L/kg	no (for organic substances)	-
Henry's law constant (at 25°C)	K_{H25C}	Pa·m^3/mol	no (set to 1×10^{-20} for inorganic substances)	-
Vapor pressure (at 25°C)	P_{vap25}	Pa	yes (for organic substances)	-
Solubility (at 25°C)	Sol_{25}	mg/L	yes (for organic substances)	-
Partitioning coefficient between dissolved organic carbon and water	K_{DOC}	L/kg	no (for organic substances); yes (for inorganic substances)	-
Partitioning coefficient between suspended solids and water	Kp_{SS}	L/kg	yes (for inorganic substances)	Updated in USEtox 2.0
Partitioning coefficient between sediment particles and water	Kp_{Sd}	L/kg	yes (for inorganic substances)	Updated in USEtox 2.0
Partitioning coefficient between soil particles and water	Kp_{Sl}	L/kg	yes (for inorganic substances)	Updated in USEtox 2.0
Rate constant degradation in air	k_{degA}	1/s	yes (for organic substances); no (set to 1×10^{-20} for inorganic substances)	-
Rate constant degradation in water	k_{degW}	1/s	yes (for organic substances); no (set to 1×10^{-20} for inorganic substances)	-
Rate constant degradation in sediment	k_{degSd}	1/s	yes (for organic substances); no (set to 1×10^{-20} for inorganic substances)	-
Rate constant degradation in soil	k_{degSl}	1/s	yes (for organic substances); no (set to 1×10^{-20} for inorganic substances)	Updated in USEtox 2.0

[a]In cases where no experimental data are available, default QSAR models implemented in USEtox are applied to estimate input parameters.

The fate factor results (in days) can be found in columns BV:FC of the «Results» worksheet of the main model file and the USEtox results files. Explanation of the abbreviations used in these columns is given in Table 3.

Table 3. Explanation of the abbreviations used in the fate factor results of USEtox

Abbreviation	Explanation
home.airI	Household indoor air at the indoor scale
ind.airI	Occupational indoor air at the indoor scale
airU	Urban air at the urban scale
airC	Rural air at the continental scale
fr.waterC	Freshwater at the continental scale
seawaterC	Coastal sea water at the continental scale
nat.soilC	Natural soil at the continental scale
agr.soilC	Agricultural soil at the continental scale
airG	Rural air at the global scale
fr.waterG	Freshwater at the global scale
oceanG	Ocean at the global scale
nat.soilG	Natural soil at the global scale
agr.soilG	Agricultural soil at the global scale

All equations involved in the calculation of USEtox fate factors are detailed in the official USEtox documentation (Fantke et al. 2015) available at http://usetox.org.

4. EXPOSURE FACTOR

4.1 Freshwater aquatic ecosystem exposure

In USEtox, the freshwater aquatic ecosystem exposure factor is defined as the fraction of a substance dissolved in freshwater.

The chemical-specific substance data required for calculating the freshwater aquatic ecosystem exposure factor is already gathered for the fate factor calculation (see previous chapter). No additional chemical-specific data are required.

The freshwater aquatic ecosystem exposure factor results, i.e. the dissolved fraction of a substance in freshwater (dimensionless) can be found in column HT of the «Results» worksheet of the main model file and the USEtox results files.

All equations involved in the calculation of USEtox freshwater aquatic ecosystem exposure factors are detailed in the official USEtox documentation (Fantke et al. 2015) available at http://usetox.org.

4.2 Human exposure

Human exposure factors reflect the rate at which a pollutant is able to transfer from a receiving compartment into the human population through a series of exposure pathways. In USEtox the following human exposure pathways are modelled:

- Inhalation (of air);
- Drinking water (ingestion);
- (Ingestion of) above-ground produce (leaf crops, including fruit and cereals);
- (Ingestion of) below-ground produce (root and tuber crops);
- (Ingestion of) meat;
- (Ingestion of) dairy products;
- (Ingestion of) fish;
- (Ingestion of) crop residues (from application of agricultural pesticides).

The human exposure factor of a substance depends on (i) the properties of the substance, (ii) the selected receiving compartment (e.g. fresh water at the continental scale) and (iii) the exposure pathway (e.g. ingestion of drinking water).

In USEtox, also the application of pesticides to agricultural crops leading to exposure to the respective pesticide residues in crop harvest are included as exposure pathway based on the approach followed by Fantke and Jolliet (2015). For this exposure pathway, additional information is required on pesticide target (e.g. herbicide) and chemical (e.g. carbamate) class, and dissipation rates (see Table 4) in the covered crop archetypes wheat (representing cereals), paddy rice (paddy crops), tomato (herbaceous crops), apply (fruit trees), lettuce (leaf crops) and potato (root and tuber crops). When experimental dissipation rates representing specific application scenarios are not available, they are estimated for organic pesticides from substance properties, crop characteristics and temperature (Fantke et al. 2014).

Substance-specific bioaccumulation factors (BAF) are required in the human exposure factor calculation for all exposure pathways except crop residues (Table 4). For most substances, experimental data are lacking for the BAF. In these cases, Quantitative Structure Activity Relationships (QSARs) can be applied to estimate the BAF on chemical properties that are

well-known. In USEtox, most BAFs for organic substances are estimated on the basis of the Kow. Additionally, for the BAF of crops, the vapor pressure and solubility of a substance play a role.

Table 4. Chemical-specific substance data in USEtox for calculating human exposure factors

Parameter	Symbol	Unit	Required[a]	Remarks
Target class for pesticides	PesticideTargetClass	-	yes (for organic pesticides)	New in USEtox 2.0
Chemical class for pesticides	PesticideChemClass	-	yes (for organic pesticides)	New in USEtox 2.0
Rate constant dissipation in above-ground plant tissues	k_{dissP}	1/s	no (for organic substances)	Updated in USEtox 2.0
Rate constant dissipation in wheat	$k_{dissWheat}$	1/s	no (for organic pesticides)	New in USEtox 2.0
Rate constant dissipation in rice	$k_{dissRice}$	1/s	no (for organic pesticides)	New in USEtox 2.0
Rate constant dissipation in tomato	$k_{dissTomato}$	1/s	no (for organic pesticides)	New in USEtox 2.0
Rate constant dissipation in apple	$k_{dissApple}$	1/s	no (for organic pesticides)	New in USEtox 2.0
Rate constant dissipation in lettuce	$k_{dissLettuce}$	1/s	no (for organic pesticides)	New in USEtox 2.0
Rate constant dissipation in potato	$k_{dissPotato}$	1/s	no (for organic pesticides)	New in USEtox 2.0
Bioaccumulation factor in plant roots	BAF_{root}	kg_{veg}/kg_{soil}	no	-
Bioaccumulation factor in plant leaves	BAF_{leaf}	kg_{veg}/kg_{soil}	no	-
Biotransfer factor in meat	BTF_{meat}	d/kg_{meat}	no	-
Biotransfer factor in milk	BTF_{milk}	d/kg_{milk}	no	-
Bioaccumulation factor in fish	BAF_{fish}	L/kg_{fish}	no	-

[a]In cases where no experimental data are available, default QSAR models implemented in USEtox are applied to estimate input parameters.

The combined fate factor and human exposure factor results, i.e. the human intake fractions of a substance can be found in the columns FD:HO of the «Results» worksheet of the main model file and the USEtox results files.

All equations involved in the calculation of USEtox human exposure factors are detailed in the official USEtox documentation (Fantke et al. 2015) available at http://usetox.org.

5. TOXICOLOGICAL EFFECT FACTOR

5.1 Human toxicity

The human toxicological effect factor (EF) reflects the change in life time disease probability due to change in life time intake of a pollutant (cases/kg_{intake}). In USEtox, separate effect factors are derived for carcinogenic effects and non-carcinogenic effects based on Huijbregts et al. (2005). Furthermore, for each aggregated effect type (carcinogenic and non-carcinogenic), exposure routes (currently considered: inhalation and ingestion) are addressed separately. The human toxicological effect factor is calculated under the assumption of linearity in concentration–response up to the point of at which the life time disease probability is 0.5 (Figure 7).
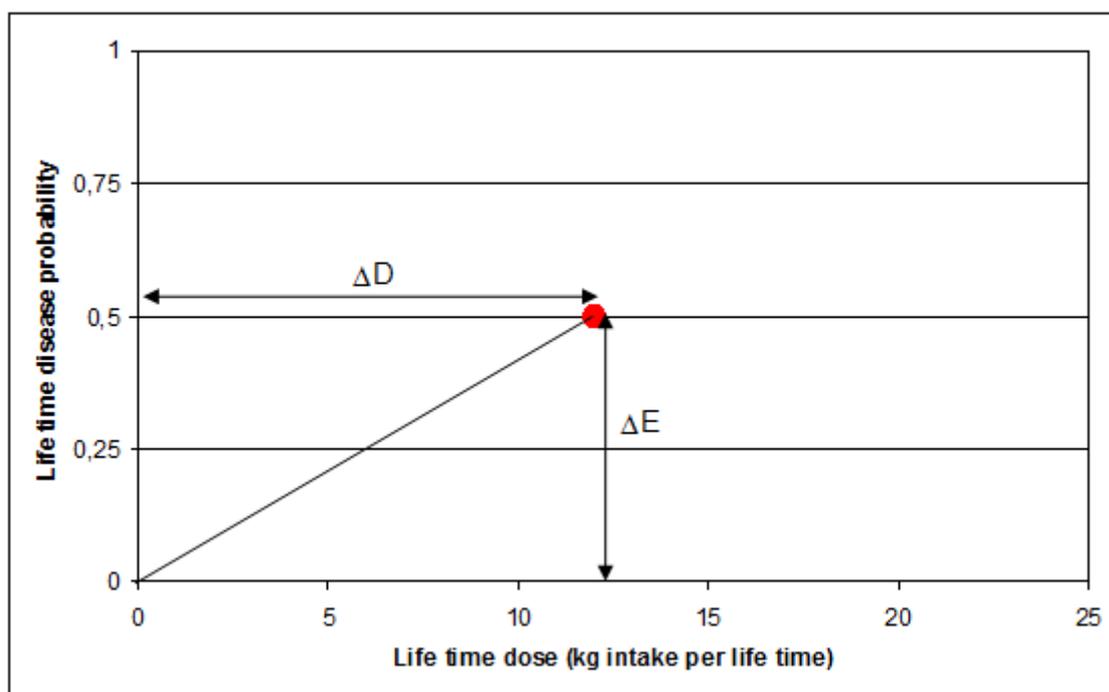

Figure 7. Visualisation of the extrapolation procedure for the human toxicological effect factor in USEtox.

For carcinogenic and non-carcinogenic effects, the effective dose affecting 50% of exposed individuals (ED_{50}) for a defined health endpoint for humans related to inhalation or oral (ingestion) exposure (kg/person/lifetime) is calculated from the daily dose for animal a (e.g. rat) and exposure duration (e.g. subchronic) per kg body weight that causes a disease probability of 50% for a specific exposure route (mg/kg/d), an extrapolation factor for interspecies differences (see Table 5), an extrapolation factor for differences in time of exposure, i.e. a factor of 2 for subchronic to chronic exposure and a factor of 5 for subacute to chronic exposure (Huijbregts et al. 2005), an average body weight of humans (70 kg), an average lifetime of humans (70 years), and the number of days per year (365 d/yr). Note that the extrapolation factor for interspecies differences is by default 1 if the ED_{50} is given as concentration in the air. Metabolic activity and inhalation rate are assumed to have the same ratio for all species.

For carcinogenic effects, the ED_{50} can also be estimated from the carcinogenic low-dose slope factor (q*) by a $1/q*$-to-ED_{50} conversion factor of 0.8, based on animal data, where q* is the carcinogenic, low-dose, slope factor for animal a (e.g. rat) and exposure duration (e.g. chronic) for a specific exposure route (kg.day/mg or m^3/mg) (Huijbregts et al. 2005).

In the case of effects other than cancer, for most of the organic substances insufficient data were available to recalculate an ED_{50} with dose–response models. In those cases the ED_{50} has been estimated from no-observed effect level (NOEL) by a NOEL-to-ED_{50} conversion factor of 9 (Huijbregts et al. 2005). In case only a LOEL was available, a LOEL-to-ED_{50} conversion factor of 2.25 has been applied (Huijbregts et al. 2005). NOELs and LOELs were derived from the IRIS database (http://www.epa.gov/iris/) and from the World Health Organisation (WHO) with priority for data from the WHO (Rosenbaum et al. 2011). If relevant, conversion factors to extrapolate from sub-chronic to chronic exposure were applied as well (see Huijbregts et al. (2005) for further details). Also for non-carcinogenic effects, the units were converted to kg/person/lifetime, using a default lifetime of 70 years and a default body weight of 70 kg for ingestion and a default inhalation rate of 13 m^3/day and a default lifetime of 70 years for inhalation, all per person. An allometric interspecies conversion factor proportional to body weight to the power of 0.25 has been applied to the ED_{50} for ingestion (see Table 5). As for non-cancer effects for inhalation, the critical effect concentration is defined as the concentration in the air, the interspecies extrapolation factor for inhalation is in principle 1, assuming that inhalation rates between species scale proportionally to metabolic rates. For some toxicity data after inhalation, however, substance-specific interspecies differences were derived by the US-EPA via pharmacokinetic modelling. In these specific cases, the interspecies conversion factors reported by the US-EPA were applied. As for carcinogenic effects, in case no data is available for a specific exposure route, a route-to-route extrapolation has been carried out, assuming equal ED_{50} between inhalation and ingestion route.

Table 5. Interspecies conversion factors (CF) to humans for various animal species.

Type	CF interspecies (-)	Average body weight (kg)
human	1.0	70
pig	1.1	48
dog	1.5	15
monkey	1.9	5
cat	1.9	5
rabbit	2.4	2
mink	2.9	1
guinea pig	3.1	0.750
rat	4.1	0.250
hamster	4.9	0.125
gerbil	5.5	0.075
mouse	7.3	0.025

In summary, the following calculation steps of the human-equivalent ED_{50} for organic and inorganic substances are identified:

1. Gather experimental (i) carcinogenic oral (ingestion exposure) ED_{50} data, (ii) carcinogenic inhalation exposure ED_{50} data, (iii) non-carcinogenic oral (ingestion exposure) ED_{50} data, and (iv) non-carcinogenic inhalation exposure ED_{50} data;
2. Specify for every ED_{50} value whether it is chronic, subchronic or subacute exposure;
3. In case of subchronic or subacute ED_{50} data, derive the chronic-equivalent ED_{50} by respectively dividing by a factor of 2 and a factor of 5 (subchronic-to-chronic extrapolation factor and subacute-to-chronic extrapolation factor);
4. In case of non-human ED_{50} data, derive the human-equivalent ED_{50} by dividing by an extrapolation factor for interspecies differences (see Table 5);
5. In case only carcinogenic, low-dose, slope factors are available, derive the carcinogenic ED_{50} via multiplication of $1/q*$ with the extrapolation factor for $1/q*$ to ED_{50}, which is a factor of 0.8;
6. In case only NOAEL-data or NOAEC-data are available, derive the non-carcinogenic ED_{50} via multiplication with the extrapolation factor for NOAEL to ED_{50}, which is a factor of 9;
7. In case only LOAEL-data or LOAEC-data are available, derive the non-carcinogenic ED_{50} via division by the extrapolation factor for LOAEL to NOAEL, which is a factor of 4, and multiply with the extrapolation factor for NOAEL to ED_{50}, which is a factor of 9;
8. Implement the human-equivalent ED_{50} values (maximum 4 values) in columns AE:AH of the sheet «Substance data» of USEtox model file or of the USEtox substances database files.
9. Always be careful with the units!

All equations involved in the calculation of USEtox human toxicity effect factors are detailed in the official USEtox documentation (Fantke et al. 2015) available at http://usetox.org.

5.2 Freshwater aquatic ecosystem toxicity

In USEtox, the ecotoxicological effect factor is calculated by determining the linear slope along the concentration–response relationship of the HC_{50} (the hazardous concentration of chemical at which 50% of the species are exposed above their EC_{50}) up to the point where the fraction of effected species is 0.5 (Figure 8).

HC_{50} is based on species-specific EC_{50} data. The EC_{50} is the water concentration at which 50% of an exposed ecosystem species population displays an effect (e.g. mortality). Aquatic ecotoxicological effect factors have the dimension m^3/kg.
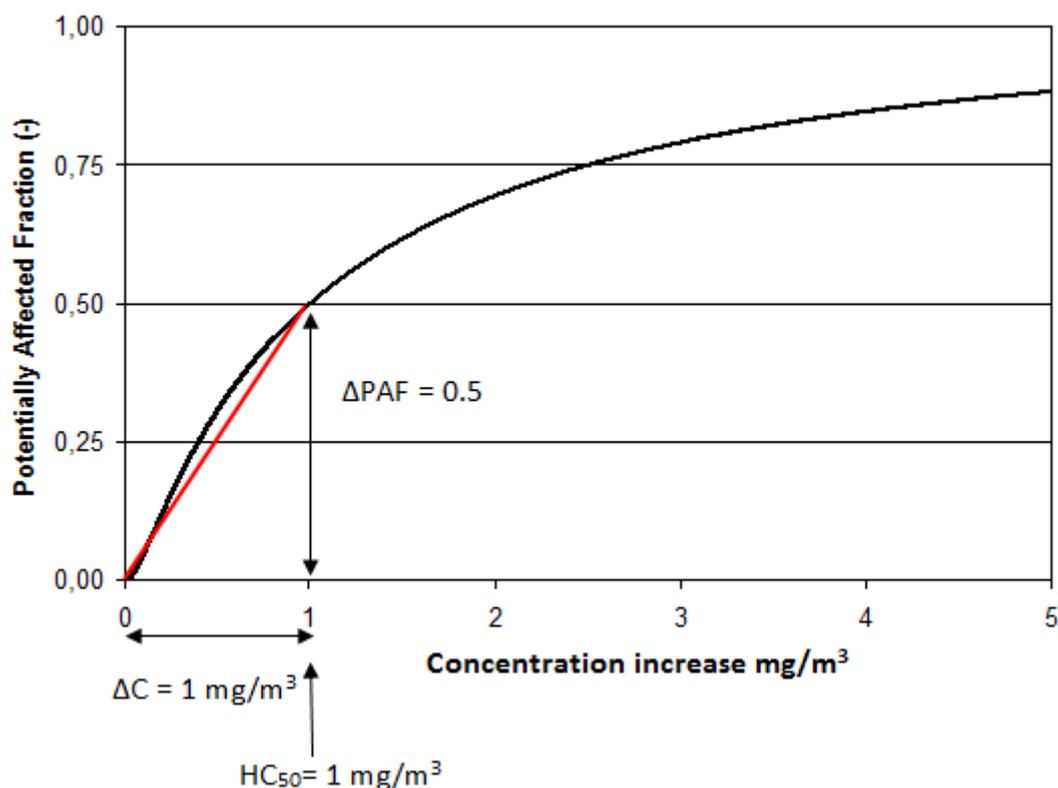
Figure 8. Example visualisation of the extrapolation procedure for the ecotoxicological effect factor in USEtox.

In USEtox, we calculate aquatic ecotoxicological effect factors based on geometric means of single species EC_{50} tests data. Chronic values have priority as long as they represent measured EC_{50} values. Note that chronic EC_{50} values are rarely reported. Second-order priority is given to acute data, applying an acute-to-chronic extrapolation factor that is set to a default factor of 2 based on Payet (2004) for organic substances (Rosenbaum et al. 2011), and to a factor of 10 (crustaceans) and 20 (fishes) and their average of 15 (all other trophic levels) for inorganic substances (cationic metals) according to Dong et al. (2014).

The following calculation steps of the HC_{50} for organic and inorganic substances are identified:
1. Gather experimental or estimated EC_{50} data for the chemical of interest;
2. Specify for every EC_{50}-value whether it is based on chronic or acute exposure;
3. For acute EC_{50}-data, derive the chronic-equivalent EC_{50} per species by dividing by a chronic-to-acute ratio (ACR). For organic substances, ACR is set to 2 (Payet 2004). For cationic metals as specific inorganic substances group, ACR depends on the trophic level, that is 10 for crustacean and 20 for fish (Dong et al. 2014). For all other trophic levels, we recommend to apply an ACR of 15 as average between crustaceans and fishes;
4. Calculate the geometric mean of EC_{50} (mg/L) for every individual species (this can e.g. be done with the function =GEOMEAN() in Excel);
5. Take the log of the geometric mean EC_{50} per species and calculate the average of the log-values. This average equals the $logHC_{50}$ (log mg/L);
6. Implement this value in column AD of the sheet «Substance data» of USEtox model file or of the USEtox organic substances database file.
7. Always be careful with the units!

All equations involved in the calculation of USEtox freshwater aquatic ecosystem toxicity effect factors are detailed in the official USEtox documentation (Fantke et al. 2015) available at http://usetox.org.

6. CHARACTERIZATION FACTORS

An outcome of the work in the USEtox team, apart from the USEtox model itself, is the calculation of **midpoint and endpoint characterization factors** for several thousand substances applied in life cycle assessment, product environmental footprinting or other comparative screening-level assessments. The provided characterization factors have been classified as «recommended» or «indicative». Recommended factors are given for substances where the USEtox model is considered fully appropriate and the underlying substance data are of sufficient quality to support a recommendation based on scientific consensus in line with Hauschild et al. (2008). In cases where relatively high uncertainty in addressing fate, exposure and/or effects of a substance is expected, the related characterization factors are labeled as «indicative». In practice, we give this recommendation in cases where the substance is a metal or an inorganic chemical, an organometallic chemical, an amphiphilic chemical (e.g. detergents) or when information on dissociation under environmental conditions could not be determined. We also recommend that freshwater aquatic ecotoxicological characterization factors be specified as «indicative», if effect factors are based on species toxicity data covering less than three different trophic levels. This is to ensure a minimum variability of biological responses.

For human toxicological effects, we recommend that characterization factors be specified as «indicative», if effect factors are based on sub-acute data. Furthermore, if route-to-route extrapolation is applied to obtain ingestion or inhalation-related effect factors, a subdivision should be made between recommended and «indicative» characterization factors. First, human toxicity characterization factors based on route-to-route extrapolation should be considered «indicative» when the primary target site is specifically related to the route of entry. In addition, characterization factors based on extrapolation from the ingestion to inhalation route of entry should be considered «indicative» if the expected fraction absorbed via inhalation is much higher than the fraction absorbed via ingestion, e.g. a factor of 1,000. This factor of 1,000 is rare but indicates that exposure by inhalation may be far more toxic than by ingestion. With the Kow-based QSARs applied to calculate the expected fraction absorbed via inhalation, it appears that this factor of 1,000 applies for substances with Kow smaller than 2.5×10^{-2} or Kow larger than 4.5×10^{9}. In these cases, the «indicative» characterization factors can underestimate the potential impact by inhalation.

6.1 Calculation of characterization factors

Single substance calculation

1. Worksheet «Substance data»
   - Create input row by filling out columns B to AX for the substance of interest. Do NOT use row 5 for this purpose, but always row 6 or further below.
2. Worksheet «Run»
   - Select a substance by entering the substance row number in cell C5 in which this substance appears in sheet «Substance data»
   - Select a region by entering the region row nr in cell F10 in which this region appears in sheet «Landscape & indoor data». **«Default USEtox» is recommended; all other regions are for sensitivity study only.**
   - Specify indoor exposure settings in cells H10 and H11 corresponding to the settings specified in sheet «Landscape & indoor data»

- Specify food crop residue exposure settings in cell K10 by selecting the crop of interest. This is only relevant for pesticides applied to food crops.
- Read midpoint characterization factors for human toxicity (cancer and non-cancer effects per emission compartment) from the matrix in range D135:Q137.
- Read endpoint characterization factors for human toxicity (cancer and non-cancer effects and aggregated cancer/non-cancer effects per emission compartment) from the matrix in range D142:Q144.
- Read midpoint characterization factors for freshwater aquatic ecotoxicity from the matrix in range D154:P154.
- Read midpoint characterization factors for freshwater aquatic ecotoxicity from the matrix in range D159:P159.
3. Worksheet «Results»
   - Read characterization factors for human toxicity (cancer and non-cancer effects and aggregated cancer/non-cancer effects per emission compartment) from columns D:BE.
   - Read characterization factors for freshwater aquatic ecotoxicity from columns BF:BU.
   - Read additional factors (fate factors, intake fractions, eco-exposure factors, human and ecosystem toxicity effect factors) from columns BV:HU.

Series calculation

1. Worksheet «Substance data»
   - Create input row by filling out columns B to AX, one row per substance. Do NOT use row 5 for this purpose, but always row 6 or further below.
2. Worksheet «Run»
   - Fill in the number of the start row and the end row of your substance dataset in cells C5 and F5, respectively.
   - Run series calculation by clicking the button «Run Series»
3. Worksheet «Results»
   - Read characterization factors for human toxicity (cancer and non-cancer effects and aggregated cancer/non-cancer effects per emission compartment) from columns D:BE.
   - Read characterization factors for freshwater aquatic ecotoxicity from columns BF:BU.
   - Read additional factors (fate factors, intake fractions, eco-exposure factors, human and ecosystem toxicity effect factors) from columns BV:HU.

6.2 Use of characterization factors

An emission compartment-specific toxicity impact score is calculated by multiplying the mass of a substance emitted in a given compartment with the corresponding toxicity midpoint or endpoint characterization factor. For example, benzene emitted with a mass of 0.1 kg to rural air and with a mass of 0.2 kg to continental freshwater would be characterized at midpoint level with a human toxicity impact score (aggregated over cancer and non-cancer effects assuming equal weighting at midpoint level) in comparative toxic units (CTU_h) of:

$$IS_{\text{human tox}} = CF_{h, \text{benzene, rural air}} \times m_{\text{benzene, rural air}} + CF_{h, \text{benzene, freshwater}} \times m_{\text{benzene, freshwater}}$$

$$= 1.1 \cdot 10^{-7} \tfrac{CTU_h}{kg} \times 0.1 \, kg + 1.7 \cdot 10^{-7} \tfrac{CTU_h}{kg} \times 0.2 \, kg$$

$$= 4.4 \cdot 10^{-8} CTU_h$$

As described by Rosenbaum et al. (2008), the characterization factors must be used in a way that reflects the large variation, often orders of magnitude, between substance characterization factors as well as the three orders of magnitude uncertainty on the individual factors. This means that contributions of 1%, 5%, or 90% to the total human toxicity score

are essentially equal but significantly larger than those of a substance contributing to less than one per thousand or less than one per million of the total score. Disregarding this fact has been a major cause of complaints about the variability of these factors across impact assessment methods, whereas the most important substances were often the same within a factor 1,000 across methods. In practice, this means that for practitioners, these toxicity factors are very useful to identify the 10 or 20 most important toxic substances pertinent for their applications. The life cycle toxicity scores thus enable the identification of all substances contributing more than, e.g. one thousandth to the total score. In most applications this will allow the practitioner to identify 10 to 30 substances to look at in priority and, perhaps more importantly, to disregard 400 other substances whose impacts are not significant for the considered application. Once these most important substances have been identified further analysis can be carried out on the life cycle phase, application components responsible for these emissions, and the respective importance of fate, exposure and effect in determining the impacts of this substance.

Due to its simple and transparent matrix-based calculation structure, USEtox will also allow identification of the main exposure pathways, (e.g. inhalation, drinking water ingestion, ingestion of various food items including direct residues of pesticides in agricultural crops) as well as the relative importance of potential carcinogenic and non-carcinogenic effects in the overall score. The inclusion of indoor air environments for household and occupational settings as well as an urban area as a sub-compartment and emission scenario implies that the life cycle inventory should accommodate a distinction between air emissions in high- and low- population density areas. When air emissions are undifferentiated, a possible assumption is that emissions take place proportionally to population living in each area, leading to e.g. 50% emitted in urban air and 50% in rural air at world level.

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