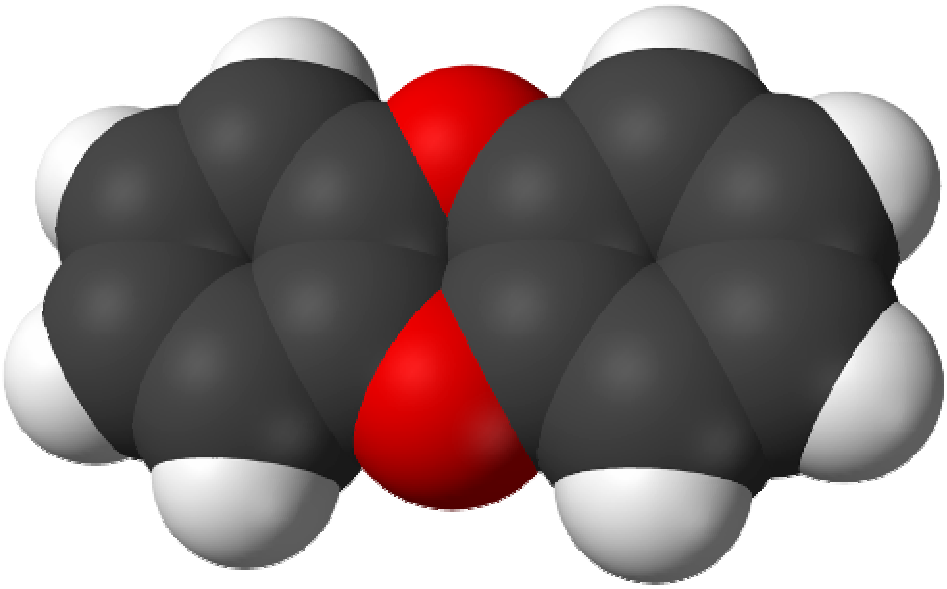
USEtox™

- Chemical database: organics -



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Colophon

Title: USEtox™ Chemical-specific database: organics

Written by: Mark Huijbregts, Manuele Margni, Dik van de Meent, Olivier Jolliet, Ralph K. Rosenbaum, Tom McKone, Michael Hauschild

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Content

1. Background

The USEtox™ model is an environmental model for characterisation of human and ecotoxicological impacts in Life Cycle Impact Assessment (LCIA) and Comparative Risk Assessment (CRA) of chemicals. It has been developed by a team of researchers from the Task Force on Toxic Impacts under the UNEP-SETAC Life Cycle Initiative. USEtox™ is designed to describe the fate, exposure and effects of chemicals. The UNEP-SETAC Initiative supports the development, evaluation, application, and dissemination of USEtox™ to improve understanding and management of chemicals in the global environment.

The USEtox™ model has been implemented in Microsoft Excel® and applied for 3000+ organic chemicals and 20+ metal species to calculate characterisation factors for human toxicity and freshwater aquatic ecotoxicity. The chemical-specific data selection for the calculations of the organic chemicals is described in this report. It should be stressed that the characterisation factors are useful for a first tier assessment only. In case a chemical 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 chemical and improve the data whenever possible.

A database of chemical properties was set up with data aiming to (a) have a consistent set of data (b) of a certain minimum quality (c) for as many chemicals as possible for which characterisation factors can be computed. This includes three types of datasets: (1) physico-chemical properties, (2) toxicological effect data on laboratory animals as a surrogate to humans and (3) ecotoxicological effect data for freshwater organisms. We focused our effort on identifying and collecting existing reviewed databases for which scientific judgement was already made in selecting and recommending values from a large range of values collected from the literature. For each of the three types of datasets, we (1) identified the existing databases, (2) defined a selection scheme and criteria for data gathering and (3) compiled the database for all the chemicals for which effect data were found.

In USEtox™, characterisation factors can be specified as 'interim', reflecting the level of reliability of the calculations in a qualitative way. Due to the relatively high uncertainty of addressing fate and human exposure, the following substance groups were classified as interim:

- Dissociating substances: Bases with pKa larger than physiological pH (7.4), Acids with pKa smaller than physiological pH (7.4) and salts are classified as interim. A pKa cut off value of pKa of 7.4 implies that the chemical is 50% or less in the neutral phase at physiological pH of 7.4. Empirical pKa values were taken from the EPI Suite™ database. If empirical values were not available, pKa-values were estimated with the software program SPARC (http://ibmlc2.chem.uga.edu/sparc/). In case a pKa value of a chemical was not available and could not be estimated, the chemical was kept as recommended.
- Amphiphilics: a list of marketed detergents received from Procter & Gamble has been used to specify these chemicals in the database as interim (Pant 2008, personal communication).
- Organo-metallic chemicals.

Aquatic ecotoxicological characterisation factors are also specified as interim, 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 health effects, characterisation factors are specified as interim if effect factors are based on sub-acute data. Furthermore, if route-to-route extrapolation is applied to obtain ingestion or inhalation human health effect factors, a subdivision should be made between

recommended and interim characterisation factors. First, human health characterisation factors based on route-to-route extrapolation should be considered interim when the primary target site is specifically related to the route of entry. In addition, characterisation factors based on extrapolation from the ingestion to inhalation route of entry should be considered interim 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 interim characterisation factor can underestimate the potential impact by inhalation.

2. Fate and exposure data

The EPI Suite™ chemical estimation programme version 4.0 has been selected as the default database for the derivation of physico-chemical properties for the USEtox™ fate calculations (http://www.epa.gov/oppt/exposure/pubs/episuite.htm). The EPI (Estimation Programs Interface) Suite™ is a Windows®-based suite of physical/chemical property and environmental fate estimation programs developed by the EPA's Office of Pollution Prevention Toxics and Syracuse Research Corporation (SRC). EPI Suite™ requires only a single input, a representation of the chemical structure in SMILES notation. SMILES means "Simplified Molecular Information and Line Entry System." Experimental data are also provided in EPI Suite™, and as a general rule, these experimental data were favoured over estimated data.

Physico-chemical properties
If experimental data were not available, the following estimation routines in EPI Suite™ were applied:

1. Molecular weight (MW in g/mol): no estimation routine required;
2. Octanol-water partitioning coefficient (Kow): A "fragment constant" methodology to predict log Kow has been applied. In a "fragment constant" method, a structure is divided into fragments (atoms or larger functional groups).
3. Organic carbon-water partitioning coefficient (Koc in l/kg): Regression equations developed with the molecular connectivity index (MCI) were used.
4. Vapour pressure ($P_{vap}25$ in Pa): For solids, the modified Grain estimate is the suggested VP. For liquids and gases, the suggested VP is the average of the Antoine and the modified Grain estimates. Both methods use the boiling point to estimate vapour pressure.
5. Solubility (Sol25 in mg/l): The water solubility is estimated with regression equations using the octanol-water partition coefficient (Kow) and the melting point of a chemical.

In case experimental information is lacking for the Henry coefficient (K_H25C in Pa.m^3/mol), the K_H25C is calculated by $P_{vap}25$*MW/ Sol25.

For the partitioning coefficient between dissolved and organic carbon (Kdoc) no experimental data were implemented in the database and no estimation routine in EPI Suite™ was available. In USEtox™, the Kdoc was estimated by Kdoc = 0.08 * Kow in the log Kow range up to 7.5 (based on Burkhard, 2000).

Degradation in the environment
Degradation rates in air, water, soil and sediment are required for the USEtox™ calculations. For air degradation rates, experimental values for the k_{OH} (the hydroxyl radical rate constant in units of cm^3/molecule-sec) are for some chemicals available in EPI Suite™. To derive the degradation rate in air ($k_{deg}A$ in 1/s), the k_{OH} is multiplied with the [OH] (the hydroxyl radical concentration in units of molecules (or radicals) per cm^3),. The default [OH] is set at 1.5×10^6 molecules (radicals)/cm^3 per 12h of daylight. Furthermore, experimental degradation data in air, water, soil and sediments were taken from Sinkkonen and Paasivirta (2000) for dioxins and PCBs

If experimental data were not available, the following estimation routines in EPI Suite™ were applied:

1. Degradation in air ($k_{deg}A$ in 1/s): The estimation methods for k_{OH} are based upon structure-activity relationship (SAR) methods using "fragment constants".
2. Degradation in water, soil and sediment ($k_{deg}W$, $k_{deg}Sl$, $k_{deg}Sd$ in 1/s): specifically for estimating biodegradation half lifes with EPI Suite™, the Biowin3 model is used for USEtox™ input to convert the ultimate biodegradation probability in half-lives for all chemicals in the database (Table 1).

Table 1: Relation between BIOWIN3 output and default biodegradation half-lives and biodegradation rates

BIOWIN3 Output	Assigned Half-Life (days)	Biodegradation rate (1/s)
Hours	0.17	$4.7.10^{-5}$
Hours to Days	1.25	$6.4.10^{-6}$
Days	2.33	$3.4.10^{-6}$
Days to Weeks	8.67	$9.3.10^{-7}$
Weeks	15	$5.3.10^{-7}$
Weeks to Months	37.5	$2.1.10^{-7}$
Months	60	$1.3.10^{-7}$
Recalcitrant	180	$4.5.10^{-8}$

In addition, division factors of 1:2:9 are used to extrapolate biodegradation rates for water, soil and sediment compartments respectively, as suggested in EPI Suite™. Other degradation mechanisms, such as direct photolysis and hydrolysis, were not included in the chemical database of USEtox™. The user could of course adjust the specific degradation rates in any environmental compartment considering that $k_{degradation,total} = k_{biodegradation} + k_{hydrolysis} + k_{photolysis}$, etc.

Human exposure

Experimental data for the bioaccumulation in fish are provided in EPI Suite™ which were favoured over estimated data. For biotransfer factors for milk and meat, experimental data was collected by Rosenbaum et al. (2009) and implemented in the USEtox™ database.

If experimental data were not available, the following estimation routines were applied:

1. Bioaccumulation factors for fish: the Arnot-Gobas model for the upper trophic level in EPI Suite™ is selected to estimate steady-state bioaccumulation factors (BAF; L/kg) for non-dissociating chemicals and chemicals with log Kow < 9. The model includes mechanistic processes for bioconcentration and bioaccumulation such as chemical uptake from the water at the gill surface and the diet, and chemical elimination at the gill surface, faecal egestion, growth dilution and metabolic biotransformation. The model requires the octanol-water partition coefficient (Kow) of the chemical and the estimated whole-body metabolic biotransformation rate constant (1/day) as input parameters to predict BAF values. In case the chemical is indicated as dissociating or the chemical has a log Kow larger than 9, the Arnot-Gobas model is not recommended. Instead we applied the log Kow-based Bioconcentration factor (BCF; l/kg) estimation routine in EPI suite™ for these chemicals.
2. Biotransfer factors (BTF) for milk and meat are estimated based on the Travis & Arms (1988) model, truncated at the maximum and minimum Kow used in the underlying data. This results in a constant BTF outside the Kow range of their training set, as recommended in the Technical Guidance Document (TGD) on Risk Assessment (EC, 2003).
3. For bioaccumulation in roots and leaves, no experimental data are implemented in the USEtox™ database for organic chemicals. QSARs readily implemented in USEtox™ are applied for this purpose.
4. For degradation in plants, chemical-specific information is hardly available. Based on Juraske et al. (2008), USEtox™ assumes that plant half lives are a factor of 10 lower compared to soil half lives of chemicals.

3. Toxicity

Ecotoxicity

Two databases with ecotoxicity effect data on average EC50 values (i.e. HC50s) were available, covering, respectively, 3,498 (Van Zelm et al. 2007, 2009) and 1,408 chemicals (Payet 2004), the first one being based on acute EC50 values from the RIVM e-toxBase (www.e-toxbase.com) and the second one on chronic and acute EC50-data mainly from ECOTOX (http://www.epa.gov/ecotox) and IUCLID (2000). We prioritise chronic values from Payet (2004) as long as they represent measured EC50 values. Second priority is given to acute data from Payet (2004), applying a best estimate extrapolation factor as an acute-to-chronic ratio (ACR), e.g. 1.9 for organic substances and 2.2 for pesticides. In case Payet (2004) does not provide ecotoxicity information for a chemical, acute toxicity data from the RIVM e-toxBase was used, applying an acute-to-chronic ratio (ACR) of 2.

Human carcinogenic toxicity

The following order of preference in toxicity data has been used in the USEtox^{TM} calculations of carcinogenic effect factors:

1. The carcinogenic effect factor takes as a point of departure the effect dose 50% (ED50) which is preferably estimated from the low-dose, slope factor (q*), based on human data. The slope factors for 1,3-butadiene, acrylonitrile, benzene and benzidine for humans after inhalation were available via the IRIS database (http://www.epa.gov/iris/). Low-dose, slope factors for inhalation are reported in units of $m^3/\mu g$. The ED50 is derived by 0.8/q* where 0.8 is a 1/q*-to-ED50 conversion factor. After that, the unit was converted from $\mu g/m^3$ to kg/person/lifetime, using a lifetime of 70 years and an inhalation rate of 13 m^3/day.
2. In case no quantitative effect information on humans was available from the IRIS database, ED50s from the carcinogenic potency database were taken (CPDB; http://potency.berkeley.edu/). ED50s for ingestion and inhalation are reported in units of mg/kg/day and converted to kg/person/lifetime, using a lifetime of 70 years and a body weight of 70 kg. For cancer, the harmonic mean of all positive ED50s in the CPDB is retained for the most sensitive species of animal cancer tests after application of an allometric interspecies conversion factor proportional to bodyweight to the power of 0.25. Table 2 provides an overview of interspecies conversion factors applied in constructing the USEtox^{TM} chemical database (Huijbregts et al., 2005). Experimental data in the CPDB are available for rats, mice, hamsters, dogs, monkeys.
3. In case no quantitative effect information was available from the CPDB, the carcinogenic ED50 has been estimated from the low-dose, slope factor (q*) by a 1/q*-to-ED50 conversion factor of 0.8, based on animal data. The slope factors were again taken from the IRIS database (http://www.epa.gov/iris/).
4. In case no data was available for a specific exposure route, a route-to-route extrapolation has been carried out, assuming equal ED50 or slope factor between inhalation and ingestion route. Chemicals with all negative carcinogenic effect data were also included as true zero carcinogenic effect factors and distinguished from missing data.

Non-cancer human toxicity

In the case of effects other than cancer, for most of the substances, insufficient data were available to recalculate an ED50 with dose–response models. For chemicals with no evidence of carcinogenicity, the ED50 has been estimated from no-observed effect level (NOEL) by a NOEL-to-ED50 conversion factor of 9. In case only a LOEL was available, a LOEL-to-ED50 conversion factor of 2.25 has been applied. NOELs and LOELs were derived from the IRIS database and from the World Health Organisation (WHO) with priority for data from the WHO. If relevant, conversion factors to extrapolate from sub-chronic to chronic exposure and sub-acute 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 lifetime of 70 years and a body weight of 70 kg for ingestion and an inhalation rate of 13 m^3/day

and a lifetime of 70 years for inhalation. An allometric interspecies conversion factor proportional to bodyweight to the power of 0.25 has been applied to the ED50 for ingestion (Table 2). 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 pharmaco-kinetic 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 ED50 between inhalation and ingestion route.

Table 2: Interspecies conversion factors to humans for various species

Type	***CF interspecies (-)***	***Average bodyweight (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

4. Database import into USEtox™

The substance database, which can be downloaded from www.usetox.org, will be independently updated from USEtox™ itself. To ensure a proper connection between database and USEtox™, we provide a step-by-step procedure to import a new version of the substance database into the model below. The proposed procedure assures that the new substance database will be fully and correctly functional and readable by USEtox™:

1. Open both the USEtox™ model ("USEtox.xls") and the database file for the organics ("Database_organics.xls").
2. Select the worksheet named "Substance data" in the "USEtox.xls" file.
3. Click on the button 'Import Database Organics' located in cel C3.

You have now successfully imported the new substance database into your USEtox™ model which is ready to calculate new updated characterisation factors. See the User Manual for further information on the calculation procedure.

5. Literature

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