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USEtox human exposure and toxicity factors for comparative assessment of toxic emissions in life cycle analysis: sensitivity to key chemical properties

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Abstract
Purpose The aim of this paper is to provide science-based consensus and guidance for health effects modelling in comparative assessments based on human exposure and toxicity. This aim is achieved by (a) describing the USEtox™ exposure and toxicity models representing consensus and recommended modelling practice, (b) identifying key mechanisms influencing human exposure and toxicity effects of chemical emissions, (c) extending substance coverage.
Methods The methods section of this paper contains a detailed documentation of both the human exposure and toxic effects models of USEtox™, to determine impacts on human health per kilogram substance emitted in different compartments. These are considered as scientific consensus and therefore recommended practice for comparative toxic impact assessment. The framework of the exposure model is described in details including the modelling of each exposure pathway considered (i.e. inhalation through air, ingestion through (a) drinking water, (b) agricultural produce, (c) meat and milk, and (d) fish). The calculation of human health effect factors for cancer and non-cancer effects via ingestion and inhalation exposure respectively is described. This section also includes discussions regarding parameterisation and estimation of input data needed, including route-to-route and acute-to-chronic extrapolations.
Results and discussion For most chemicals in USEtox™, inhalation, above-ground agricultural produce, and fish are the important exposure pathways with key driving factors being

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the compartment and place of emission, partitioning, degradation, bioaccumulation and bioconcentration, and dietary habits of the population. For inhalation, the population density is the key factor driving the intake, thus the importance to differentiate emissions in urban areas, except for very persistent and mobile chemicals that are taken in by the global population independently from their place of emission. The analysis of carcinogenic potency (TD_{50}) when volatile chemicals are administrated to rats and mice by both inhalation and an oral route suggests that results by one route can reasonably be used to represent another route. However, we first identify and mark as interim chemicals for which observed tumours are directly related to a given exposure route (e.g. for nasal or lung, or gastrointestinal cancers) or for which absorbed fraction by inhalation and by oral route differ greatly.

Conclusions A documentation of the human exposure and toxicity models of USEtox™ is provided, and key factors driving the human health characterisation factor are identified. Approaches are proposed to derive human toxic effect factors and expand the number of chemicals in USEtox™, primarily by extrapolating from an oral route to exposure in air (and optionally acute-to-chronic). Some exposure pathways (e.g. indoor inhalation, pesticide residues, dermal exposure) will be included in a later stage. USEtox™ is applicable in various comparative toxicity impact assessments and not limited to LCA.

Keywords Consensus · Human exposure · Human health · LCIA · Life cycle impact assessment · Toxicity · USEtox

1 Introduction

Sustainable technologies require assessment and control of impacts at local to global scales. Identification and quantification of impacts on human health linked to the use and emissions of toxic substances are thus of central importance to the development of sustainable technology. Life cycle assessment (LCA) provides indicators of toxicological effects based on the relative risk and associated consequences of chemicals that are released into the environment (Pennington et al. 2004; Udo de Haes et al. 2002; Assies 1997; Hogan et al. 1996). In LCIA, the mass of each chemical emitted is multiplied by a characterisation factor (CF) to provide the impact indicators (ISO 2006; Pennington et al. 2004; Udo de Haes et al. 2002). CFs are obtained with characterisation models that represent the mechanism of a cause–effect chain starting from an emission followed by environmental fate, human exposure, and the resulting effect on the exposed population (Udo de Haes et al. 2002; Jolliet et al. 2004; Rosenbaum et al. 2008). Thus, human exposure modelling is an important element that quantitatively links emissions to impacts.

Several published characterisation models have been used to report human toxicity indicators. All these are based on mechanistic methodologies accounting for fate, exposure and toxic effects providing cardinal impact measures. Among these methods are IMPACT 2002 (Pennington et al. 2005; Jolliet et al. 2003), USES-LCA (Huijbregts et al. 2000; van Zelm et al. 2009), Eco-Indicator 99 (Goedkoop et al. 1998) and human toxicity potentials provided by Hertwich et al. (2001) and McKone (2001) using the CalTOX model (McKone et al. 2001). Aiming to consolidate the differences in results when applying these models in LCA (Dreyer et al. 2003; Pant et al. 2004), a scientific consensus model called USEtox™ was developed through an harmonization process based on (1) comparison of the existing models (Rosenbaum et al. 2008; Hauschild et al. 2008), (2) recommendations from a series of workshops (Jolliet et al. 2006; McKone et al. 2006; Ligthart et al. 2004), and (3) experiences from the OMNIITOX project (Molander et al. 2004; Guinée et al. 2004). All these methods adopt environmental multimedia, multi-pathway models to account for the full extent of intermedia-transfer and multi-pathways exposure processes. A measure of toxicity is added to capture the key potential health effects (cancer and non-cancer) from an environmental release.

The early metrics of toxic impacts in LCA were based on regulatory standards such as reference doses (RfD) or acceptable daily intake based on the assumption that these standards reflect similar levels of hazard. But such standards can actually incorporate different levels of safety factors, (Pennington et al. 2006). The above-mentioned UNEP-SETAC workshops provided several recommendations for life cycle indicators of toxicological effects based on comparative measures of risk: benchmark measures of effect should be used as a means of scaling relative toxicity, rather than a no observed adverse effect level (NOEL), lowest observed adverse effect level or RfD (Jolliet et al. 2006; McKone et al. 2006). Benchmark measures include TD_{50}s—tumourigenic dose-rate for 50% of animals in a chronic, lifetime cancer test and the derived—adjusted for human effect—ED_{10} and the ED_{50}, the effect (or toxic) doses that result in a toxic effect to 10% and 50% of the exposed population for a lifetime exposure. Other recommendations of these workshops addressed the complexity of multi-chemical comparisons, low-dose extrapolations and relationship between potency and severity. In parallel with these recommendations, Crettaz et al. (2002) and Pennington et al. (2002) proposed a method using the ED_{10} as a point of departure for cancer and non-cancer effects, ED_{10} being

mostly derived from the positive tests of the Carcinogenic Potency Database (CPDB: http://potency.berkeley.edu), Gold (2011). For LCA applications, Crettaz et al. (2002) made a linear assumption on the dose–response for low-dose extrapolation. Huijbregts et al. (2005) used the ED_{50} as a point of departure and further elaborated this approach proposing a lognormal dose–response. In the development of USEtox™, several knowledge gaps need to receive particular attention in order to extend the results of the above-described approaches:

- In most reported tests, chemicals are administered orally. This means that missing exposure routes need to be characterised using basic hypotheses, e.g. for human inhalation exposures from cancer tests by oral gavage. In practice, there are different ways to handle missing information on various exposure routes: Crettaz et al. (2002) only retained positive tests for the measured exposure route, implying that exposure through another route is disregarded. On the other hand, Huijbregts et al. (2000) assumed equal TD_{50} values independent of the exposure route. Further information is therefore required on how to develop a procedure to estimate effects from inhalation using data from ingestion studies for several hundreds of substances.
- So far in the LCA use of the Carcinogenic Potency Database, information on chemicals that do not have positive results have not been considered, and those chemicals have been treated as if data were entirely missing.
- Chronic carcinogenicity data are only available for about 1,600 substances. To expand the number of chemicals for toxic effects in USEtox™, a reassessment is needed of the possibility of acute-to-chronic extrapolation when only acute (primarily LD_{50}) data are available.

The aim of this paper is to provide science-based consensus and guidance for health effects modelling in comparative assessments based on human exposure and toxicological information. This aim is achieved by (a) describing the USEtox™ exposure and toxicity models representing consensus and recommended modelling practice, (b) identifying key mechanisms influencing human exposure and toxicological effects of chemical emissions, (c) extending the number of chemicals in USEtox™ by including, where feasible, route-to-route and acute-to-chronic extrapolation methods based on available animal data for both ingestion and inhalation.

This paper describes both the human exposure model and the human toxic effects model of USEtox™ and presents the related recommendations for human toxicity impacts modelling in comparative assessments, such as LCA. These results are the outcome of a harmonization effort carried out[1] by a Task Force of the UNEP-SETAC Life Cycle Initiative and aimed at building consensus for human exposure characterisation modelling in comparative assessments (Rosenbaum et al. 2008; Hauschild et al. 2008). This paper is one of a series of papers presenting the USEtox™ model components and recommended inputs along with its characterisation factors for human toxicity and freshwater ecotoxicity in LCA (Rosenbaum et al. 2008), and its fate and aquatic ecotoxicity model (Henderson et al. 2011).

As discussed by Rosenbaum et al. (2008) and Hauschild et al. (2008), USEtox™ is the result of an extensive model comparison process aiming to identify those modelling elements that are common to all compared models and hence consensus among modellers focusing on comparing toxic impacts of substances. It is therefore an intrinsic property of the USEtox™ model that it is not spearheading the scientific development in the field, but rather representing the common ground among all relevant characterisation models that were included in the comparison. It is intended by its developers as an interface between those models that do contain the latest developments (but which are not yet scientific consensus) and the need for stability, transparency, parsimony, and consensus in practice when applying comparative methods such as LCA and interpreting its results.

2 Materials and methods

2.1 Fate and human exposure

General framework The general framework is illustrated in Fig. 1. Human exposure to a chemical emitted into the environment is based on a cause–effect chain assessment linking the mass emitted ($\vec{S}$ in kilograms) first to the time-integrated mass in the environmental compartments ($\int \vec{M}dt$ in kilograms day), and then to the substance intake by the total population ($\vec{I}$ in kilograms). It should be noted that the relationship between the steady-state solution for a continuous emission and the time-integrated solution for a

[1] The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the United Nations Environment Programme concerning the legal status of any country, territory, city or area or of its authorities, or concerning delimitation of its frontiers or boundaries. Moreover, the views expressed do not necessarily represent the decision or the stated policy of the United Nations Environment Programme or any participants such as members of the International Life Cycle Board, nor does citing of trade names or commercial processes constitute endorsement. Information contained herein does not necessarily reflect the policy or views of the Society of Environmental Toxicology and Chemistry (SETAC). Mention of commercial or noncommercial products and services does not imply endorsement or affiliation by SETAC.

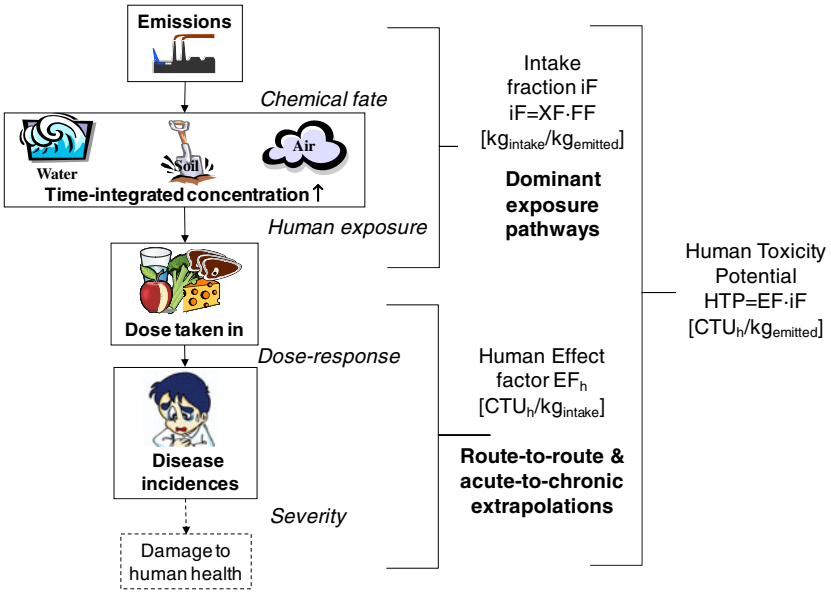

Fig. 1 The USEtox™ framework for human exposure and health impact, with points of focus of the present analysis

pulse emission of mass into the environment, as applied in LCA and shown below, has been demonstrated by several authors (Guinée and Heijungs 1993; Heijungs 1995; Mackay and Seth 1999). This can be modelled as a matrix product (Rosenbaum et al. 2007; for the equation for emission pulses we refer the reader to that paper): [2]

$$\vec{I} = \overline{\mathrm{XF}} \cdot \overline{\mathrm{FF}} \cdot \vec{S} = \overline{\mathrm{XF}} \cdot \int \vec{\mathrm{M}}\mathrm{dt} = \overline{\mathrm{iF}} \cdot \vec{S} \qquad (1)$$

where the fate factor $\overline{\mathrm{FF}}$ [day] links the substance release into the environment to the chemical mass increase in a given compartment and is the main result of the fate model (for further details on the USEtox™ fate model see Henderson et al. 2011). The exposure factor $\overline{\mathrm{XF}}$ [per day] relates the chemical mass in a given environmental compartment to the chemical intake by humans. It represents the equivalent rate of ingestion of the environmental medium by humans. Finally, the intake fraction $\overline{\mathrm{iF}} = \overline{\mathrm{XF}} \cdot \overline{\mathrm{FF}}$ [dimensionless, $\mathrm{kilogram}_{\mathrm{intake}}$ per $\mathrm{kilogram}_{\mathrm{emitted}}$] expresses the fraction of a pollutant emission that is eventually taken in by the human population via various exposure pathways (Bennett et al. 2002b). The iF is the product of fate and exposure factors and hence covers both parts of the cause–effect chain (Rosenbaum et al. 2007). Due to the difficulty of linking a specific substance molecule (found in a population sample) to a specific emission source, iF is difficult to measure or monitor, but well-calibrated fate and exposure models can be used to calculate iF for a broad range of exposure pathways (e.g. inhalation of air, ingestion of water or food). It is then straightforward to sum up an exposure route specific (e.g. inhalation, ingestion) or total iF (Bennett et al. 2002a). Based on the recommendation of an independent expert panel this matrix algebra framework was adopted for USEtox™ and the underlying model comparison (Jolliet et al. 2006), making the fate factor, exposure factor, and resulting intake fraction the key intermediary parameters compared among different models.

Human exposure factors corresponding to specific pathways can be distinguished into direct (e.g. direct consumption of an environmental compartment such as drinking water, or inhalation of air) and indirect (e.g. meat, dairy produce, vegetables, and fish) exposure factors, respectively, expressed as (Rosenbaum et al. 2007):

$$\mathrm{XF}_{\mathrm{xp},i}^{\mathrm{direct}} = \frac{\mathrm{IR}_{\mathrm{xp},i} \cdot P}{\rho_i \cdot V_i} \qquad (2)$$

$$\mathrm{XF}_{\mathrm{xp},i}^{\mathrm{indirect}} = \frac{\mathrm{BAF}_{\mathrm{xp},i} \cdot \mathrm{IR}_{\mathrm{xp}} \cdot P}{\rho_i \cdot V_i} \qquad (3)$$

Where $\mathrm{IR}_{\mathrm{xp},i}$ [kilograms per day] symbolizes the direct intake rate of an environmental medium i, polluted at a certain level, by the overall population via an exposure pathway xp, ρ_i is the bulk density of medium i [$\mathrm{kilograms}_i$ per m_i^3], and V_i [m_i^3] is the volume of medium i linked to the exposure pathway xp. $\mathrm{IR}_{\mathrm{xp}}$ [kilograms per day] is the individual ingestion rate of a food substrate corresponding to exposure pathway xp, P is the population head count, and $\mathrm{BAF}_{\mathrm{xp},i} = C_{\mathrm{xp}}/C_i$ [$\mathrm{kilograms}_{\mathrm{xp}}/\mathrm{kilograms}_i$] is the bioaccumulation factor (steady-state concentration ratio between food substrate corresponding to exposure pathway xp—such as meat or milk—and a specific compartment i).

[2] Note that to easily distinguish each matrix term, and to indicate that the same calculation also applies to single values, dot products are used here to indicate multiplications between matrices and vectors. Matrices are topped by bars, and vectors are topped by arrows.

The inverse of $XF^{direct}_{xp,i}$ represents the equivalent time required by the population to inhale or ingest the whole chemical mass in the medium. $XF^{indirect}_{xp,i}$ can be interpreted as the equivalent intake rate of the polluted medium *i* via the food substrate corresponding to exposure pathway xp. Each exposure factor represents the increase in human exposure via pathway xp due to an increase in concentration in compartment/medium *i*.

Each exposure pathway represents a contaminant transport mechanism from an environmental compartment into the human population. For indirect exposures, a food substrate can be contaminated from various environmental compartments. For example, a cow breathes air, drinks water, and eats forage (plants) and soil, any of which might contain a contaminant that can be subsequently transferred to the milk or meat obtained from that cow. Similar to fate factors in $\overline{FF}$ that quantify the transfer from one environmental compartment to another, the exposure factors in $\overline{XF}$ quantify the contaminant transfer from an environmental compartment into the human population via each exposure pathway.

Key assumptions and landscape parameters Similar to any predictive model used to inform decisions, USEtox™ is based on a set of necessary assumptions to address factors that are difficult to measure or that involve decision variables. There are a large number of assumptions deployed in USEtox™, but only a small number that are over-arching and important for interpreting model results. Listed below are key assumptions in USEtox™ that must be considered when interpreting the characterisation factors generated by this model:

- Population densities are assumed to be $2\times10^6/240$ km^2= 8,333 persons/km^2 (Humbert et al. 2011) for the urban scale, $9.98\times10^8/9013369.37$ km^2=111 persons/km^2 for the continental, and $6\times10^9/1.41E10^8$ km^2=43 persons/km^2 for the global scale.
- For the inhalation pathway, urban exposure is considered separately from rural exposure to better estimate the higher iF for emissions in areas with higher population densities.
- No distinction is made between sub-populations (e.g. age groups or gender), with averaging applied over the entire population.
- The BAF for direct exposure to environmental media is equal to one (and therefore not present in Eq. 1) as the medium is directly taken in and hence no transfer modelling between medium and food substrate is meaningful.
- For exposure pathways that relate to concentrations in fresh or marine water (e.g. drinking water and fish), only the dissolved fraction is considered (relevant) instead of total concentration.
- Modelled and measured input data are assumed to represent steady-state values.
- We consider a production-based intake scenario where the contaminant levels in food and drinking water are associated with where food is produced (and contaminated) and not necessarily the location of where the population lives. This differs from a subsistence scenario, which is more often adopted in chemical screening and reflects exposure for an individual who eats, drinks, and lives within the region of an emission (Pennington et al. 2005).
- Exposure pathways that are only relevant for a small fraction of the population (e.g. breast milk) or that have been demonstrated as negligible contributors to total exposure (e.g. eggs) for most contaminants have been neglected following the USEtox™ development principle of parsimony (Hauschild et al. 2008).

The specific parameters and assumptions used to calculate XF in USEtox™ depend on the respective exposure pathway and are discussed below:

Inhalation through air (direct) depends on the individual's breathing rate ($IR_{inhalation,air}$), which is averaged over the entire population and assumed to be 13 m^3/day on an individual level (USEPA 1997).

Ingestion through drinking water (direct) is assumed to be 1.4 l/day of purified (particle filtered) surface water per person ($IR_{drinking\ water,freshwater}$; USEPA 1997). The amount and source of ground water use for drinking are currently under research and thus not used as drinking water in the current version of USEtox™.

Ingestion through agricultural produce (indirect) for organic chemicals is estimated using a simple vegetation equilibrium model for plant-uptake that addresses both the soil–plant and air–plant transfer of chemicals. It has been developed to consolidate the significant differences in vegetation uptake algorithms used in multimedia fate/exposure models for toxic characterisation in LCA as revealed during the USEtox™ model comparison (Rosenbaum et al. 2008). The model includes both below-ground and above-ground plant components. The below-ground plant parts concentration (in moles per cubic meter) is calculated as:

$$C_{plant-bgpp} = C_{sw} \times RCF \times 0.8 \quad (4)$$

where C_{sw} is the concentration of contaminant in soil solution (in moles per cubic meter), and RCF is the root concentration factor truncated to Min [200, $0.82+0.0303\ (K_{ow})^{0.77}$] (moles per kilogram per moles per litres). The above-ground plant parts concentration (in moles per cubic meter) is the sum of the respective concentrations due to transfer from soil $C^{sw}_{plant-agpp}$, from air gas phase $C^{air}_{plant-agpp}$, and from particulate matter in air $C^{ap}_{plant-agpp}$ to

above-ground plant tissues, which are calculated according to:

$$C^{sw}_{plant-agpp} = \frac{\left\{C_{sw} \times 0.784 \times \exp\left[-\frac{(\log K_{ow}-1.78)^2}{2.44}\right] \times Q_{trans}\right\}}{\left[\frac{MTC \times 2 \times LAI}{\left(0.3+\frac{0.65}{K_{aw}}+0.015\frac{K_{ow}}{K_{aw}}\right)} + \left(\lambda_g + \lambda_t\right)V_{plant}\right]}$$

$$C^{ap}_{plant-agpp} = \frac{C_{ap} v_d}{\left[\frac{MTC \times 2 \times LAI}{\left(0.3+\frac{0.65}{K_{aw}}+0.015\frac{K_{ow}}{K_{aw}}\right)} + \left(\lambda_g + \lambda_t\right)V_{plant}\right]}$$

$$C^{air}_{plant-agpp} = \frac{C_{air} \times MTC \times 2 \times LAI}{\left[\frac{MTC \times 2 \times LAI}{\left(0.3+\frac{0.65}{K_{aw}}+0.015\frac{K_{ow}}{K_{aw}}\right)} + \left\{\left(\lambda_g + \lambda_t\right)V_{plant}\right\}\right]} \quad (5)$$

where C_{sw} is the concentration of contaminant in soil solution (in moles per cubic meter); C_{air} the concentration of contaminant in gas phase of the air (in moles per cubic meter); C_{ap} the chemical concentration in air attached to particles (in moles per cubic meter); K_{ow} the octanol–water partition coefficient; K_{aw} the air-water partition coefficient (H/RT); Q_{trans} the area equivalent transpiration flow from soil through stems ($m^3_{transpiration}/m^2_{land\ area}$; default=0.001); MTC, the mass transfer coefficient at the air–leaf interface (m/d; default=86); LAI the leaf area index, the one-sided area of plant leaf surfaces per unit land area, ($m^2_{leaf\ surface}/m^2_{land\ area}$; default=4); λ_g the growth dilution rate constant (1/d; default=0.035); λ_t the rate constant for elimination by chemical transformation (i.e. metabolism) within above-ground plant tissues (1/d; assumed to be a factor 10 lower than soil half-lives of chemicals based on Juraske et al. 2008); V_{plant} the area equivalent volume of above-ground plant tissues ($m^3_{tissues}/m^2_{land\ area}$), assumed to be the sum of cuticle and leaf volumes (default=0.0125); and v_d the deposition ratio accounting for both wet and dry particle deposition of particles from air to plant surfaces (mol/(m^2 d) per mol/m^3 or m/d; default=500). More details including a complete description of the model can be found in section S1 of supporting information. For inorganic chemicals, notably metals, only measured data are used. The BAF, as the steady-state ratio of the concentrations in the respective plant part and the respective contact compartment, can then be calculated for all four transfer pathways mentioned above. All BAF referring to above-ground plant parts are used as BAF for exposed produce (i.e. grain, fruit, leafy vegetables, etc.), while the BAF for below-ground plant parts represents the BAF for unexposed produce (i.e. root vegetables).

Ingestion through meat and milk (indirect) is estimated using the Travis and Arms (1988) biotransfer factor models for cows (BTF=$C_{substrate}/I_{chemical}$ [in days per $kilogram_{substrate}$] the steady-state ratio between the concentration in meat or milk respectively and the intake of a chemical by the animal) which were truncated to the corresponding constant value above the log value of 6.5 of the octanol–water partition coefficient (K_{ow}) and below log K_{ow} 3 following recommendations of the Technical Guidance Document on Risk Assessment (EC 2003), as these would otherwise overestimate chemical transfer into biota (Rosenbaum et al. 2009; Bennett et al. 2002a). The BAF for meat and milk exposure is then the product of the respective BTF and the direct intake of the animal of the respective environmental medium (air, water, vegetation, soil). It should be noted that improved biotransfer models with significantly reduced uncertainties have been recently published (Rosenbaum et al. 2009; Hendriks et al. 2007; Birak et al. 2001; Dowdy et al. 1996), but scientific consensus has not yet been established. Biotransfer of chemicals into meat and milk has to be modelled due to availability of measured values that is limited to 42 and 73 organic substances respectively (Rosenbaum et al. 2009) plus a few dissociating organics and some metals. These measured BTF data are all included in the USEtox™ substance database and used instead of the model for the respective chemicals. Different types of meat have different contamination levels due to variation in fat content and feedstock intake rates of the respective animals. In USEtox™, this is accounted for by a correction of the (cow-based) BTF_{meat} for both fat content of meat types and respective animal intake rates log BTF_{meat}=log K_{ow}−7.6+log (average meat fat content/average cattle vegetation intake)=log K_{ow}−5.8 (Margni 2003). The average meat fat content is calculated as an average fat content of meat producing cattle weighted by the respective share of each meat type in the human population's meat diet. The assumed fat contents were: beef=25%, pork=23%, poultry=6%, goat/sheep=14% (supporting information of Pennington et al. 2005). The composition of the population's meat diet (which varies significantly between continents and even countries) was assumed as: pork=39%, beef=24%, poultry=30%, goat and sheep=5%, and other meat=2% (fractions corresponding to world average meat production taken from FAO 2002). The resulting weighted average meat fat content is then 17.8%. The specific intake rates of vegetation, air, water, and soil for meat producing cattle were calculated similarly as an average weighted by the respective share of each meat type in the human population's meat diet. The vegetation, air, water, and soil intake rates of beef, pork, poultry, and goat/sheep meat producing farm animals (supporting information of Pennington et al. 2005) can be found in the exposure model of the USEtox™ model. For inorganic chemicals, notably metals, only measured data are used. The BAF for human milk and meat consumption is then the product of the respective BTF and the intake rates of

vegetation, air, water, and soil for dairy and meat producing cattle respectively.

Ingestion through fish (indirect) is represented by measured bioaccumulation factors when these measurements are available in literature. Otherwise, the Arnot and Gobas (2003) model in EPI Suite™ for the upper trophic level is used to estimate directly the steady-state BAF (l/kg) for non-dissociating chemicals and chemicals with log K_{ow}<9. This model includes mechanistic processes for bioconcentration and bioaccumulation such as chemical uptake from the water at the gill surface and the dietary inputs, and chemical elimination at the gill surface, faecal egestion, growth dilution and metabolic biotransformation. Input parameters to predict BAF values are the K_{ow} of the chemical and the estimated whole-body metabolic biotransformation rate constant (1/day). The BAF values for fish calculated by the Arnot–Gobas model refer to the total concentration in water, while BAF values related to the dissolved phase are required in USEtox™. We therefore recalculated the Arnot–Gobas BAF values for fish by dividing them by the fraction dissolved following the default settings in EPI Suite™: $1/(1+0.08\times DOC\times K_{ow}+0.35\times POC\times K_{ow})$, where DOC is the dissolved organic carbon concentration and POC the particulate organic carbon concentration that both equal 5.10–7 kg/l in EPI Suite™. In case the chemical is indicated as dissociating or has a log K_{ow} larger than 9, the Arnot–Gobas model is not recommended. Instead, we applied the log K_{ow}-based bioconcentration factor (BCF; in litres per kilogram) estimation routine in EPI suite™ for these chemicals. Here, we assume that the BCF refers to the dissolved fraction of the chemical in water. Generally, whenever available, BAF values have been used in priority and may be significantly higher than BCF.

2.2 Human health effect and human toxicity impact

General framework As illustrated in Fig. 1, the subsequent step after human exposure occurred in the emission-to-impact cause–effect chain is a potential toxic effect, extending Eq. 1 by an effect factor EF (Rosenbaum et al. 2007):

$$\vec{N} = \overline{\mathrm{EF}} \cdot \overline{\mathrm{iF}} \cdot \vec{S} = \overline{\mathrm{EF}} \cdot \vec{I} = \overline{\mathrm{HTP}} \cdot \vec{S} \qquad (6)$$

Where $\vec{N}$ is the population-based human health impact (disease cases), $\overline{\mathrm{EF}}$ the human health Effect Factor (disease cases per kilogram$_{intake}$), and $\overline{\mathrm{HTP}}$ the Human Toxicity Potential (disease cases per kilogram$_{emitted}$ or comparative toxic units (CTU_h) as discussed by Rosenbaum et al. 2008), the midpoint characterisation factor for human toxicity impacts. The USEtox™ characterisation factors are not normalised to a reference substance.

Building on the recommendations of an expert workshop held within the UNEP-SETAC Life Cycle Initiative (McKone et al. 2006) and on several additional sources (Pennington et al. 2006; Huijbregts et al. 2005; Crettaz et al. 2002) the HTP can be expressed as a combination of the ratios of intake fractions to ED_{50}s, keeping inhalation and ingestion route separate and differentiating between the contributions of cancer and non-cancer impacts:

$$\begin{aligned}\mathrm{HTP} &= \mathrm{HTP}_{\mathrm{cancer}} + \mathrm{HTP}_{\mathrm{non\ cancer}} \\ &= \mathrm{iF}^{\mathrm{inh}}\left(\frac{\alpha}{\mathrm{ED}^{\mathrm{inh}}_{\mathrm{50h\ cancer}}} + \frac{\alpha}{\mathrm{ED}^{\mathrm{inh}}_{\mathrm{50h\ non\ cancer}}}\right) \\ &\quad + \mathrm{iF}^{\mathrm{oral}}\left(\frac{\alpha}{\mathrm{ED}^{\mathrm{ing}}_{\mathrm{50h\ cancer}}} + \frac{\alpha}{\mathrm{ED}^{\mathrm{ing}}_{\mathrm{50h\ non\ cancer}}}\right)\end{aligned} \qquad (7)$$

where $\mathrm{ED}^{\mathrm{route}}_{\mathrm{50h}}$ is the estimated lifetime dose for humans related to inhalation or oral exposure that causes an increase in disease probability of 50% (in kilograms per person per lifetime). This lifetime ED_{50} is calculated either in priority from human based data for a few substances for which such data are available or nearly always derived from animal cancer tests from the TD_{50} (tumourigenic dose-rate in milligrams per kilogram per day for 50% of the animals over background in a standard lifetime), as shown in Eq. S18 and the example of Eq. S19 in section S.3.3 of the supporting information. α is the slope factor that relates the inverse of the ED_{50} to a potential probability of getting a cancer. For example, a default value of α=0.5 assumes a linear effect with 50% additional chance to get cancer while ingesting a quantity equal to the ED_{50} over lifetime.

For calculations of carcinogenicity effect factors, the following order of preference in toxicity data has been used in the USEtox™ calculations (see additional details in section S3.3 of supporting information):

1. In the few cases for which data from human studies were available from the IRIS database (USEPA 2011), the 50% effect dose (ED_{50}) was estimated from the low-dose slope factor (q_1*) in humans (N=9).
2. For carcinogenic potency values from animal cancer tests, ED_{50}s were derived from TD_{50} values in the CPDB (Gold 2011: N=584).
3. In case no quantitative effect information was available from the CPDB, the carcinogenic ED_{50} has been estimated from the animal-based low-dose slope factor (q_1*) from the IRIS database (USEPA 2011) using a $1/q_1$*-to-ED_{50} conversion factor of 0.8 (N=10).
4. Chemicals with all negative carcinogenic effect data in the CPDB were also included as true zero carcinogenic effect factors and thus distinguished from missing data (N=417).

For effects other than cancer, insufficient data were available for most substances to recalculate an ED_{50} with dose–response models. For chemicals with no evidence of carcinogenicity, the ED_{50} has been estimated from NOEL by a NOEL-to-ED_{50} conversion factor of 9. In case only a LOEL was available, a LOEL-to-ED_{50} conversion factor of 2.25 has been applied. NOELs and LOELs were derived from the IRIS database (USEPA 2011) and from the World Health Organisation (WHO; JMPR 2004; Lu 1995) with priority for data from the WHO.

Several knowledge gaps deserved particular attention in order to determine an extended list of ED_{50}s: (a) most of the available toxicity tests have been carried out for oral intake. This means that missing exposure routes need to be characterised using basic hypotheses. Thus, the route-to-route and interspecies extrapolations need to be further analysed based on available bioassays and on theoretical pharmacokinetics knowledge in order to propose a recommendation for the extrapolation. (b) Only chronic carcinogenicity data are presently used in USEtox™ and these are only available for about 1,600 chemicals. To expand the number of chemicals in the future, there is a need to reassess the possibility of acute-to-chronic extrapolation. Methods developed to address and analyse these two main points are described below.

Approach for comparing positivity and carcinogenic potency by route To empirically test for route-to-route extrapolation, cancer potencies are compared by route using results in the CPDB of Gold et al. (http://potency.berkeley.edu), which includes 6,540 experiments on 1,547 chemicals tested in rats, mice, hamsters, dogs, and non-human primates. We identified 106 chemicals as having an experiment where the route of administration was inhalation (99 chemicals in rats, 79 in mice, and 12 in hamsters). Only 31% (33/106) of these also have an experiment in the CPDB in which the chemical was administered to the same species by an oral route, usually by gavage, and less frequently by water or diet. Nearly all are tested in rats by both routes (32), and only 18 in mice. In our analysis, if there is one positive cancer test by either an oral or inhalation route in a species, then the result is considered positive regardless of whether other inhalation tests or other oral tests are negative. These 33 chemicals have been tested more often than usual in the CPDB. Overall, 85% (28/33) are carcinogenic in at least one experiment, which compares to 52% in the CPDB overall.

The experimental comparison between inhalation and oral routes is carried out by comparing positivity by the two routes and by plotting the harmonic mean of TD_{50} for one route against the other. The results of the route comparison may reflect variation in factors other than route for each chemical, thus making conclusions difficult for this small number of chemicals, e.g. the power to detect a carcinogenic effect is greater when there are more experiments or when more strains are tested, or more animals are used in an experiment.

In our route analysis, harmonic means of TD_{50} in each species are calculated separately for positive experiments by the inhalation and oral routes of administration. In USEtox™, for each exposure route, the lower (more potent) harmonic mean of TD_{50} in rats or mice is retained after application of an interspecies allometric factor (see Table S3 supporting information). The CPDB reports the harmonic mean to summarize potency values from different experiments because it uses all of the experimental data and is more similar to the most potent site than other averaging measures (Gold et al. 1989). The use of harmonic mean is also consistent with the use of ED_{50} (as derived from the TD_{50}) in the denominator of Eq. 7 (*).

Complementary to the experimental approach, special attention is given to the few outliers in the potency comparison of routes by accounting for the following exclusion criteria: first, one can expect important variations in sensitivity if observed tumours are related to toxic effects at the site of application for a given route, e.g. for nasal or lung tumours by inhalation or stomach tumours by gavage. Second, inhalation and oral doses in bioassays are based on maximum tolerated doses, which may differ by oral vs inhalation routes due to differences in absorption between the two routes. Physico-chemical properties may influence the absorbed fraction by each route of intake. These properties, especially the different partition coefficients, may also affect the subsequent distribution of the dose to the target organs. Therefore, chemicals for which absorbed fraction by inhalation and by oral route differ greatly may also show important variations between TD_{50}s by different routes of exposure.

The calculation of these two absorption fractions are presented in supporting information S3: Building on the Physiology Based Pharmacokinetic model proposed by Chiu and White (2006), f_{abs}^{inh} was determined as a function of the blood–air partition coefficient K_{ba} (Price et al. 2003; Poulin and Krishnan 1996). For the oral route, Moser and McLachlan (2002) and Rosenbaum et al. (2009) show that the transfer from the gastrointestinal tract to blood f_{abs}^{oral} mostly depends on the octanol–water partition coefficient, with a peak around log K_{ow}=7 and a decrease in absorption at low and high K_{ow}. According to Eq. S15 in supporting information, large differences between routes of exposure and therefore outliers can be identified by calculating the ratio of the two absorption coefficients of equations respectively for inhalation and oral routes.

Acute-to-chronic extrapolation At present, USEtox™ is based only on chronic data, which limits the number of substances covered. Extrapolation of chronic results from

acute toxicity data have been carried out and discussed by Zeise et al. (1984) and Crettaz et al. (2002). However, these previous extrapolations were often based on a limited number of chemicals and a limited range of toxicity values. We have used an alternative, approach to extend the chemical coverage: In order to cover the broadest range possible in cancer values, all positive chemicals with a cancer ED_{50} were selected in the USEtox™ database, excluding those that also have a NOEL or a non-cancer ED_{50} available in order to keep the analysis of cancer and non-cancer effects separate. We then checked if corresponding acute animal data (LD_{50} in mg/kg) were available in the HSDB database (NLM 2011). The calculated ED_{50}s were then plotted against the lowest mouse or rat acute data from the HSDB database to study their correlation (N=106). A similar approach was tested for the non-cancer data from the USEtox™ database against HSDB LD_{50}s, using all the human adjusted non-cancer ED_{50} in the USEtox™ database as derived from NOEL and LOEL, for which HSDB data are also available (N=207). Chemicals that also had positive carcinogenic effect data in USEtox™ were excluded to keep the analysis of cancer and non-cancer effects separate. The few substances for which non-cancer ED_{50}s are directly calculated from bioassays and are not extrapolated from NOELs or LOELs were all kept in the analysis since they provide a more accurate estimate of the ED_{50} (N=10). A regression and variance analysis was performed to test the adequacy of a fixed extrapolation ratio between chronic ED_{50} and acute LD_{50}.

Based on earlier work by Bernstein et al. (1985a, b), for statistical reasons one expects to find that TD_{50} and LD_{50} are correlated, assuming that doses tested in acute and chronic experiments are related: measured effects in bioassays are restricted to a narrow range around the maximum dose tested, whereas the doses tested for individual chemicals vary greatly and span a very wide range.

Creation of a full set of ED_{50} for use in USEtox™ Finally, applying the above-described approach, a full set of ED_{50}s was derived on the basis of the full CPDB database. Resulting factors are differentiated between recommended and interim factors for which uncertainty is high.

3 Results and discussion

3.1 Human exposure

The dominant routes of exposure have traditionally been analysed using a K_{ow}–K_{aw} representation (e.g. Bennett et al. 2002a). This representation provides a useful starting point (Figs. S2 and S3, supporting information). However, in this paper, we further analyse the mechanisms and parameters that drive not only the dominant pathway but also the absolute values of intake fraction, effect factors, and thus HTP, looking at intake and human health impact per kilogram substance emitted in different compartments. Throughout the presentation and discussion of results, a set of six chemicals (Table 1) is identified in the figures. These substances have been selected as representing a variety of human exposures and toxicities.

3.1.1 Inhalation intake fractions for emissions to air

For inhalation of an emission to continental rural air, the fate factor and inhalation intake fraction are linked by the multiplicative factor of the exposure, i.e. the population intake. Because for inhalation, exposure does not vary from substance to substance, variation of iF among chemicals depends on the fate factor (persistence in air). Persistence in air is a function of degradation, partitioning to the air phase, and affinity to organic matter (lipophilicity). In the USEtox™ model, airborne substances that are adsorbed to particulate matter (i.e. with a low fraction in the gas phase) are assumed not to undergo degradation in the air.

Figure 2 shows that the inhalation iF for an emission to air increases proportionally to the half-life of the chemical in air, while being influenced by two other main parameters: (a) at high half-life in air (>10 days), chemicals with K_{aw} values lower than 7×10^{-3} tend to partition to other media in the model (e.g. PCB-77), decreasing their iF by up to two orders of magnitude. (b) At low half-life in air (<1 day), substances with high octanol–air partition coefficient K_{oa} (e.g. azocyclotin) adsorb to particulate matter and are therefore not degraded in air, increasing

Table 1 Properties of selected chemicals

Name	Abbrev.	CAS	K_{ow}	K_{aw}	K_{oa}	K_{pa}	$t_{1/2}$ air (d)	λ_t (1/d)	EF_{ing}	EF_{inh}
Azocyclotin	Azocyc.	41083-11-8	2.0E+05	9.2E−11	2.2E+15	3.3E+13	9.8E−02	5.8E−04	1.8E−01	1.8E−01
Glyphosphate	Glyphos.	1071-83-6	4.0E−04	8.9E−11	4.4E+06	7.3E+09	1.4E−01	2.3E−03	4.1E−03	4.1E−03
Chlorodifluoro-methane	HCFC-22	75-45-6	1.2E+01	1.7E+00	6.9E+00	7.8E−01	2.3E+03	2.3E−03	3.2E−05	3.2E−05
PCB-77 (3,3′,4,4′-tetrachloro-biphenyl)	PCB-77	32598-13-3	4.3E+06	4.0E−04	1.1E+10	1.6E+08	6.3E+01	1.9E−04	4.9E+00	4.9E+00
2,3,7,8-tetracdd	TCDD	1746-01-6	6.3E+06	2.1E−03	3.0E+09	4.4E+07	8.3E+00	1.9E−04	4.9E+04	4.9E+04
Toluene	Toluene	108-88-3	5.4E+02	2.8E−01	1.9E+03	3.1E+01	1.8E+00	2.3E−03	1.5E−03	3.6E−03

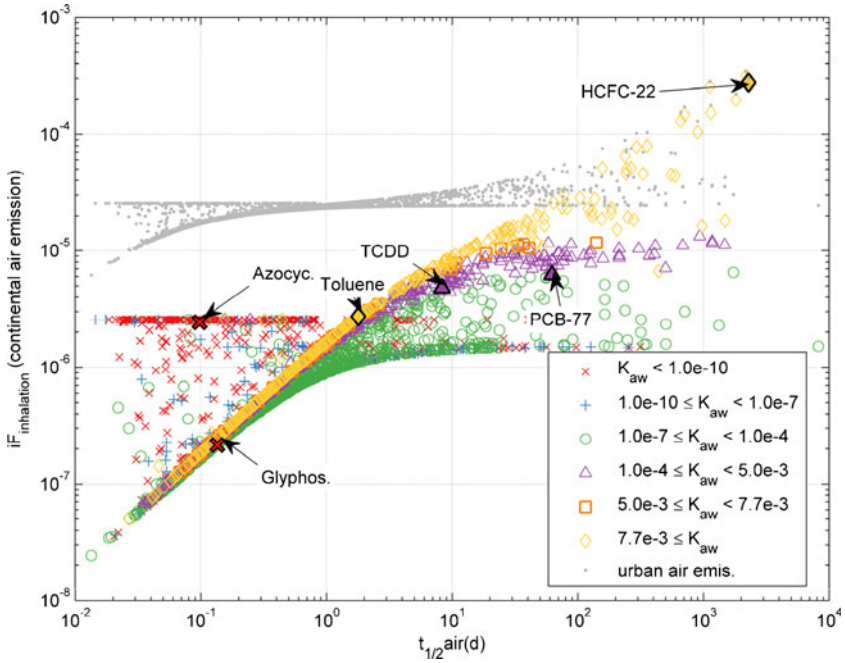

Fig. 2 Intake fraction [dimensionless, $kilogram_{intake}$/$kilogram_{emitted}$] for an emission to continental and urban air as a function of the half-life in air, differentiated for various K_{aw}

their persistence and resulting in an increased inhalation iF (see Fig. S4).

Note that the emission to urban air (see Fig. 2, in grey) mimics the behaviour of the emission to continental air; the urban iF by inhalation is usually at least an order of magnitude higher than the continental iF (iF_{inh} urban 10^{-4}> iF_{inh} rural 10^{-5} to 10^{-7} for most chemicals). Therefore, it is important to differentiate between emissions to urban and rural areas. The difference in iF is due to the higher population density in urban area and lower dilution volume, leading to a higher population intake. The urban iF is relatively constant for all substances, since it mainly depends on the residence time of air in the urban area.

Substances with high half-life and high K_{aw} may achieve inhalation intake fractions >10^{-4} (e.g. HCFC-22). This high iF is a result of high persistence and eventual transfer to the global air compartment, such that the iF by the continental population and the global population may be of the same order of magnitude.

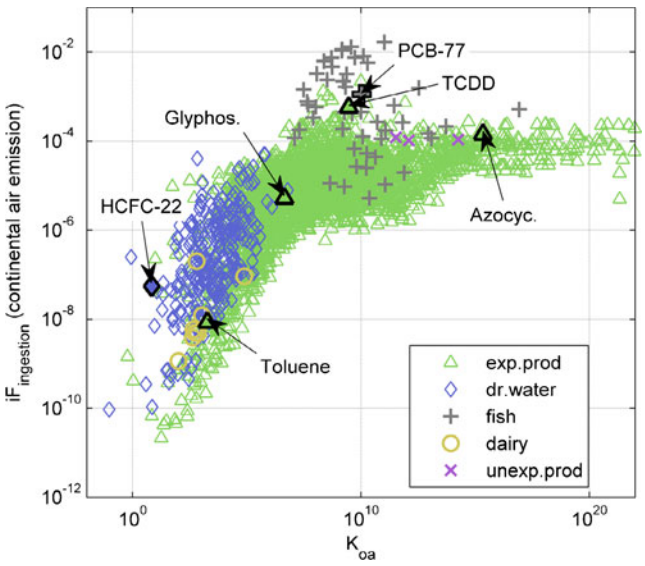

Fig. 3 Ingestion intake fraction [dimensionless, $kilogram_{intake}$/$kilogram_{emitted}$] for emission to continental air vs. K_{oa}, showing the dominant ingestion pathway

3.1.2 Inhalation intake fractions for emissions to freshwater

The inhalation iF for emissions to freshwater is mainly influenced by substance K_{aw}, increasing linearly with K_{aw} with a limited influence of the half-life in air. Only in the case of volatile chemicals (K_{aw}>10^{-4}) with long half-lives (>100 day), the inhalation iF may reach 10^{-5}, which can be comparable to or greater than the ingestion route for other chemicals emitted to freshwater (Fig. S5, supporting information).

3.1.3 Ingestion intake fractions for emissions to air

Total ingestion In the USEtox™ model, the ingestion intake fraction is a function of a variety of mechanisms, including fate in the freshwater, sorption to and bioaccumulation in plant material, and bioconcentration in fish, meat, and dairy products. See Henderson et al. (2011) for a discussion of fate and multimedia transfer.

Figure 3 presents the total ingestion iF versus the substance K_{oa}, with dominant ingestion routes identified. In general, ingestion iF increases with K_{oa}; for most chemicals, above-ground produce is the dominant route. Intake via the fish ingestion route can lead to the highest iF (e.g. PCB-77),

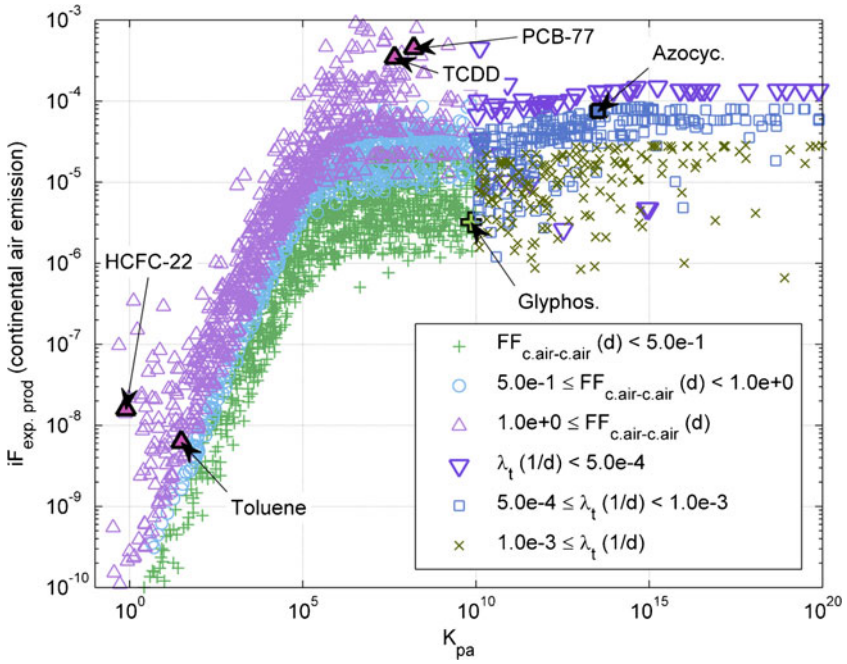

Fig. 4 Intake fraction [dimensionless: kilogram$_{intake}$/kilogram$_{emitted}$] by ingestion of above-ground produce vs. K_{pa}, for various fate factors in air

occurring at mid-range K_{oa} values (~1×10^{7} to 1×10^{12}), where substances are still somewhat lipophilic, and do not have very high K_{aw} values (Fig. S6, supporting information) allowing them to partition into the water compartment and bioconcentrate in fish. Drinking water is dominant at low K_{oa} (e.g. HCFC-22); however, iF values associated with this route tend to be low (10×10^{-10} to 1×10^{-5}), and the dominant pathway may be inhalation. Therefore, we focus on above-ground produce and fish as the important ingestion pathways.

Ingestion through above-ground produce Intake fraction by ingestion of above-ground produce is the product of bioaccumulation in that compartment, the mass in the air compartment, and the population intake of this produce. The bioaccumulation factor (BAF) is determined by diffusion and deposition from the air to the plant surface as well as uptake from the soil. The latter term is, at most, about 1/100th of the value of the sum of the deposition and diffusion terms, with a median of 1×10^{-5} and 90th percentile of 5×10^{-10}. Therefore, it is transfer from the air to the plant that is the route of concern. The BAF air–plant is primarily dependent on the plant–air partition coefficient, K_{pa}, increasing linearly until $K_{pa}=10^{6}$, after which BAF saturates between 300 and 3,000 and is controlled by λ_t, the degradation rate in the plant (Fig. S7, supporting information).

Figure 4 shows that the ingestion iF is therefore also largely a function of K_{pa}: for $K_{pa}<10^{8}$, the ingestion iF increases up to 10^{-3} as K_{pa} increases. For K_{pa} less than approximately 10^{10}, iF varies by three orders of magnitude, depending on the fate factor in continental air for an emission to continental air ($FF_{c.air–c.air}$), as shown by PCB-77 and glyphosate. $FF_{c.air–c.air}$ determines the mass in the air compartment and is a function of K_{aw}, degradation in air, and lipophilicity, as discussed with respect to inhalation. At high K_{pa}, iF varies as a function of degradation in the plant (λ_t), over approximately two orders of magnitude.

Ingestion via fish is determined by the transferred fraction from air to water (discussed as a function of K_{aw}, the freshwater surface area, and indirect transfer from air to soil to water; Henderson et al. 2011) and the ingestion via fish for an emission to freshwater (discussed below).

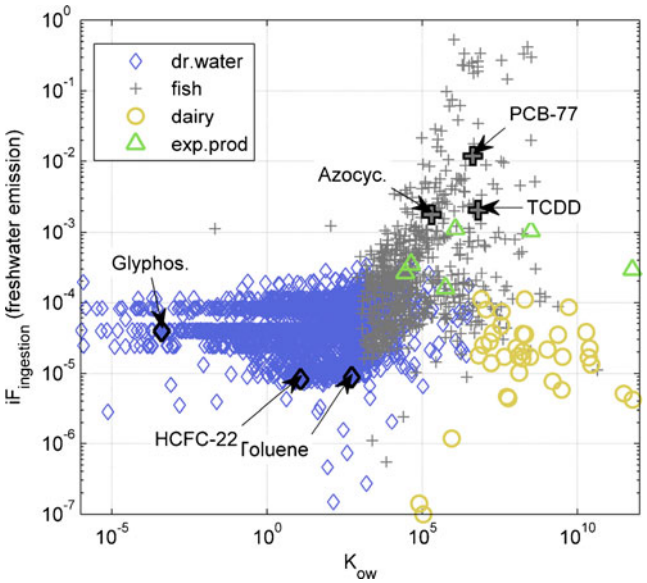

Fig. 5 Total ingestion intake fraction for emission to freshwater [dimensionless, kilogram$_{intake}$/kilogram$_{emitted}$] vs. K_{ow}, showing the dominant ingestion pathway

3.1.4 Ingestion intake fractions for emission to freshwater

Total ingestion In the case of an emission to freshwater, ingestion is strongly controlled by the K_{ow} (Fig. 5). Chemicals at low K_{ow} ($<10^3$, such as toluene, HCFC-22, or glyphosate) tend to have freshwater as the dominant ingestion pathway, leading to an iF between 10^{-4} and 10^{-5}. These chemicals remain in the water column, rather than bioconcentrating and their intake fraction is limited by the water and substance residence time in water as illustrated by Henderson et al. (2011; Fig. 2). At K_{ow} between 10^3 and 10^9, the fish intake pathway dominates (e.g. azocyclotin, PCB-77, or TCDD). In this range, the ingestion fraction increases with increasing K_{ow}, peaking at $K_{ow} \sim 10^7$ and decreasing thereafter (note that iF$>10^{-2}$ should be interpreted with care (Bennett et al. 2002a; Bennett et al. 2002b). At high K_{ow}, there is a set of chemicals for which the dominant ingestion pathway is dairy products, due to consumption of water and bioconcentration of the substance by dairy cows. These ingestion iF tend to be restricted to less than 1×10^{-4}.

The relative importance of ingestion and inhalation can be viewed as a function of K_{oa}. Above $K_{oa} \sim 10^6$, ingestion is the dominant route; below this K_{oa} value, substances with $K_{aw}>3\times10^{-4}$ have a higher inhalation intake fraction (Fig. S8, supporting information).

Ingestion through fish The peak of iF via fish ingestion observed around $K_{ow}=10^{-7}$ in Fig. 5 is directly linked to a peak in the BAF_{fish} (Arnot and Gobas 2003) and the fate factor in freshwater (Fig. S9, supporting information). Since bioaccumulation provides a more comprehensive representation of the food web, BAF values have been used in priority and may be significantly higher than the BCF. Care must also be taken when absolute values of the intake fraction exceeds 10^{-2}, the relative values between chemical being more reliable than the absolute value in that range, linked to uncertainties on the BAF.

3.2 Human health effect factors

3.2.1 Route-to-route extrapolation

Potency comparison Figure 6 shows the inhalation TD_{50} against the oral TD_{50} in rats and mice for the 19 chemicals that are positive by both routes in each species. Most observations are aligned along the $x=y$ line, but for three outliers that are tested and positive in rats by both routes, the TD_{50} by inhalation is more than 100-fold more potent than the TD_{50} by an oral route (formaldehyde, hydrazine and cadmium chloride), i.e. the dose to induce tumours is far lower by inhalation. These three chemicals have the most potent TD_{50} values by inhalation in the dataset. As the intercept was not significantly different from zero, we considered statistics with and without the intercept set equal to zero (leading to R^2, respectively, of 0.21 and 0.20). As expected, the correlation is higher when the outliers are excluded (R^2=0.49 with free intercept and R^2=0.43, s.e. on

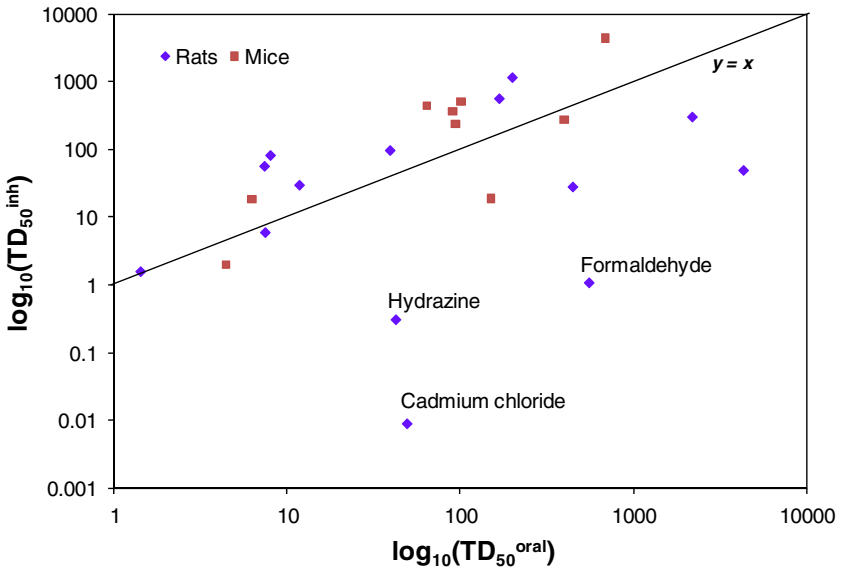

Fig. 6 Harmonic mean of the inhalation $\log_{10}$ (TD_{50}) [log milligrams/(kilogram day)] as a function of the oral $\log_{10}$ (TD_{50}) [log milligrams/(kilogram day)] for rats and mice (free intercept all data: R^2=0.21, standard error on $\log_{10}$=1.25, intercept −0.32 (95% confidence interval (CI) −0.8 to 1.4), slope=0.65 (95% CI 0.1 to 1.2). For a fixed intercept regression applied to all 23 observations: R^2=0.20, standard error on $\log_{10}$=1.23, slope=0.79 (95% CI 0.5 to 1.1). If cadmium chloride, hydrazine and formaldehyde are excluded, statistics with a free intercept: R^2=0.49, standard error on $\log_{10}$=0.78, intercept 0.52 (95% CI −0.2 to 1.2), slope=0.74 (95% CI 0.4 to 1.1). The regression with fixed intercept yields: R^2=0.43, standard error on $\log_{10}$=0.81 (95% CI of a factor $10^{2.086\ 0.81}$=49≅50), slope=0.97, (95% CI 0.8 to 1.2))

Log=0.8, slope on Log=0.96 for a fixed intercept; see detailed statistics in the legend of Fig. 6). As the slope does not differ significantly from 1, setting the inhalation TD_{50} equal to the ingestion TD_{50} could be taken as a first approximation. However, these outliers need to be identified a priori in order to first be given special treatment when extrapolating potency from one route to another. Applying two exclusion criteria described in the method section enables identification of these three outliers: formaldehyde is carcinogenic by inhalation at the highest doses tested in rats, only at the site of administration, the nasal cavity, which meets an exclusion criterion linked to tumours that are directly related to a given exposure route. This is not the case for oral administration. For cadmium chloride and hydrazine, the estimated absorbed fractions show large differences by route due to their partitioning properties: the fraction absorbed by inhalation is far greater than by oral route (Table S2, supporting information). The standard error on the $\log_{10}$=0.81 means that the 95% confidence interval associated with this route-to-route extrapolation amounts to a factor of 50, which compares to a wide range in TD_{50} values of seven orders of magnitude across chemicals. This confidence interval may be higher for chemicals that meet the above-described exclusion criteria and are flagged as interim.

Methods and further results of the route analysis for each chemical in each species are detailed in section S3 of supporting information.

3.2.2 Acute-to-chronic extrapolation

Although this approach is not incorporated into the current version of USEtox™, new developments for extrapolation of chronic data from acute data are presented hereafter in order to provide the user with the option to further increase substance coverage. The present version of USEtox™ uses only chronic data. To expand chemical coverage in the future, we analysed the correlation between chronic and acute toxicity data, notwithstanding the limitation of the approach due to the difference in mode of action between acute and chronic effects.

Carcinogens Since LD_{50}s in HSDB are for acute rather than carcinogenic effects, a judgment on the likelihood that the chemical is carcinogenic is first required; this judgment is based on either information in the acute database or on the lists of carcinogenic substances in the different classifications (IARC, USEPA, etc.). The correlation presented below only applies to substances that are, at a minimum, explicitly mentioned as possible carcinogens. Figure 7 shows the base 10 logarithm of the cancer ED_{50} from the USEtox™ database—as derived from the positive chronic TD_{50} from the CPDB—against the lowest acute cancer LD_{50} between mice and rats from the HSDB database. Compared to previous correlations based on randomly selected points (e.g. Crettaz et al. 2002), this approach covers a wider range of chronic data, enabling a better correlation and slightly higher R^2 (0.32). When the extreme low value of TCDD is excluded, the correlation coefficient is reduced (R^2=0.21), without significantly affecting the parameter estimates for the slope and the intercept. The standard error on the $\log_{10}$ of SE=1.01 means that the 95% confidence interval (CI) associated with this acute-to-chronic extrapolation amounts for individual prediction to a factor $10^{1.98\ 1.01}$=101, that is ±2orders of

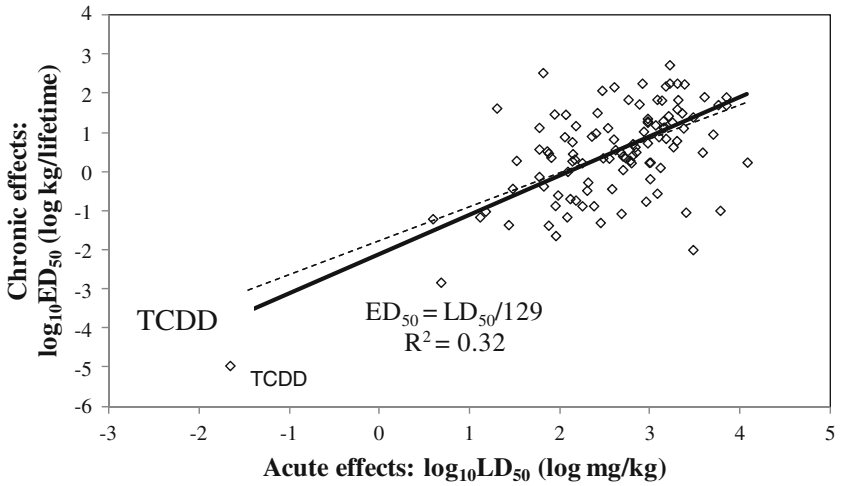

Fig. 7 Chronic cancer log value of ingestion human ED_{50} from USEtox™ as a function of the minimum acute LD_{50} from HSDB between rats and mice. *Plain line* $ED_{50}=LD_{50}/129$, 107 observations, R^2=0.32, standard error on $\log_{10}$=1.02 (95% CI of a factor 104), $1/10^{intercept}$=129, slope=1. *Dashed line* $ED_{50}=LD_{50}{}^{0.87}/60$, 107 observations, R^2=0.33, standard error on $\log_{10}$=1.01 (95% CI of a factor 101), $1/10^{intercept}$=60 (95% CI=13 to 267), slope=0.87 (95% CI=0.63 to 1.11). If TCDD is excluded: $ED_{50}=LD_{50}{}^{0.72}/24$, 106 observations, R^2=0.21, standard error on $\log_{10}$=0.99 (95% CI of a factor 94), $1/10^{intercept}$=24 (95% CI=4.2 to 132), slope=0.72 (95% CI 0.45 to 1.0)

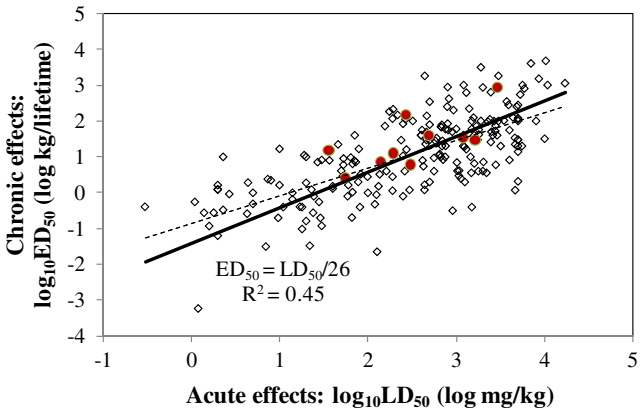

Fig. 8 Chronic non-cancer $\log_{10}$ value of ingestion human ED_{50} from USEtox™ as a function of the $\log_{10}$ of the minimum acute LD_{50} from HSDB between rats and mice. *Plain line* $ED_{50}=LD_{50}/26$, 207 observations, $R^2=0.45$, standard error on $\log_{10}=0.84$ (95% CI of a factor 46), $1/10^{intercept}=26$, slope=1. *Dashed line* $ED_{50}=LD_{50}^{0.77}/7.1$, 207 observations, $R^2=0.49$, standard error on $\log_{10}=0.81$ (95% CI of a factor 39), $1/10^{intercept}=7.1$ (95% confidence interval CI 3.6 to 13.7), slope=0.77 (95% CI 0.66 to 0.88). *Red circles* data for which ED_{50} are directly determined without NOEL-to-ED_{50} extrapolation: $ED_{50}=LD_{50}/10$, 10 observations, $R^2=0.54$, standard error on $\log_{10}=0.52$ (95% CI of a factor 16)

magnitude, out of a total variation in the ED_{50} of six (without TCDD) to eight orders of magnitude. Since the slope factor is not significantly different from unity, a simpler correlation can be tested by setting the slope equal to 1, i.e. assuming a fixed ratio between the ED_{50} and the LD_{50} and calculating its geometric mean over all available data. This correlation yields an average ratio of $ED_{50}=LD_{50}/129$ with a typical 95% lognormal CI of a factor 104. These results are consistent with the correlations between TD_{50}s and LD_{50}s obtained by Zeise et al. (1984) and by Cox and Ricci (1990).

Non-cancer effects Figure 8 shows a similar correlation for non-cancer data, presenting two sets of data. First are the 207 available data that have only a non-cancer endpoint and are based on a NOEL-to-ED_{50} extrapolation (with diamonds). For these points, the correlation is $ED_{50}=LD_{50}^{0.77}/7.1$, with a correlation coefficient of $R^2=0.49$ and a standard error on log of 0.81 (95% CI of a factor 40). The slope is significantly different from 1; however for the sake of parsimony, the case of a slope equal to 1 was tested, leading to a fixed ratio extrapolation of $ED_{50}=LD_{50}/26$ and a typical 95% CI of a factor 46. The latter approach only leads to a restricted decrease in R^2 (from 0.49 to 0.45) and a modest increase in the standard error on log=0.84. Furthermore, since the underlying correlation from NOEL to ED_{50} is itself based on a fixed ratio (Huijbregts et al. 2005), we propose to use this ratio of 26 as the default extrapolation value, with its lognormal 95% CI of a factor 46. The solid red circles of Fig. 8 correspond to the few data for which ED_{50} values are directly available, confirming this correlation approach, since these data fall within the range of the larger set and since the extrapolation ratio of 15 is not significantly different from 26. This ratio of $LD_{50}/ED_{50}=26$ differs by less than a factor 3 from the value of 68 obtained by combining the $LD_{50\ acute}/NOAEL_{chronic}$ ratio of 267 from Kramer et al. (1996) with an allometric factor for rat to human of 4.1 and the $NOEL/ED_{50}$ lifetime ratio of 9× 1.79 from Huijbregts et al. (2005). Note that for the non-cancer human endpoint, chemicals with high toxicity often correspond to effects on the central nervous system and developmental/reproductive effects, while the less toxic ones are more often associated to irritation and vomiting (Table S4, supporting information).

Although not used in the present version of USEtox™, this correlation is of interest for future expansion of the chemical coverage especially for non-cancer effects, since HSDB provides data on more than 5,000 chemicals. This correlation may also be valid for use in conjunction with other databases. The list of chemicals and raw data used for the cancer and non-cancer extrapolations are presented in Table S4 and S5 of supporting information.

3.3 Human health impact

In USEtox™, the HTP is the final output used as a characterisation factor for human health impacts per kilogram substance emitted. As discussed in Section 2, HTP is the product of effect factor (EF) and intake fraction (iF). We analyse here the respective influence of these two factors, looking at the main exposure pathways.

Figure 9 presents HTP for over 900 chemicals as a function of EF. Figure 9a is for an emission to continental air, and shows (1) $HTP_{inhalation}$ against $EF_{inhalation}$ for those compounds with inhalation as the dominant exposure route; (2) $HTP_{ingestion}$ against $EF_{inhalation}$ for compounds with ingestion as the dominant exposure route (for an emission to rural air, only above-ground produce, fish, and drinking water are dominant); and (3) superimposed on this are $HTP_{inhalation}$ against $EF_{inhalation}$ for an emission to urban air. Figure 9b is for an emission to freshwater (therefore, an emission to urban air is not included), and shows the same distinction between inhalation and ingestion.

Figure 9 shows that the Effect Factors for the substances covered by the USEtox™ database vary up to ten orders of magnitude (eight orders when excluding TCDD). The variation in EF therefore explains a large part of the variation in HTP among the substances.

For an emission to rural air (see Fig. 9a), the variation in iF is responsible for a variation of up to five orders of magnitude in the HTP for a given EF. For those compounds for which inhalation is the dominant route, the $HTP_{inhalation}$ tends to be about two orders of magnitude lower than the

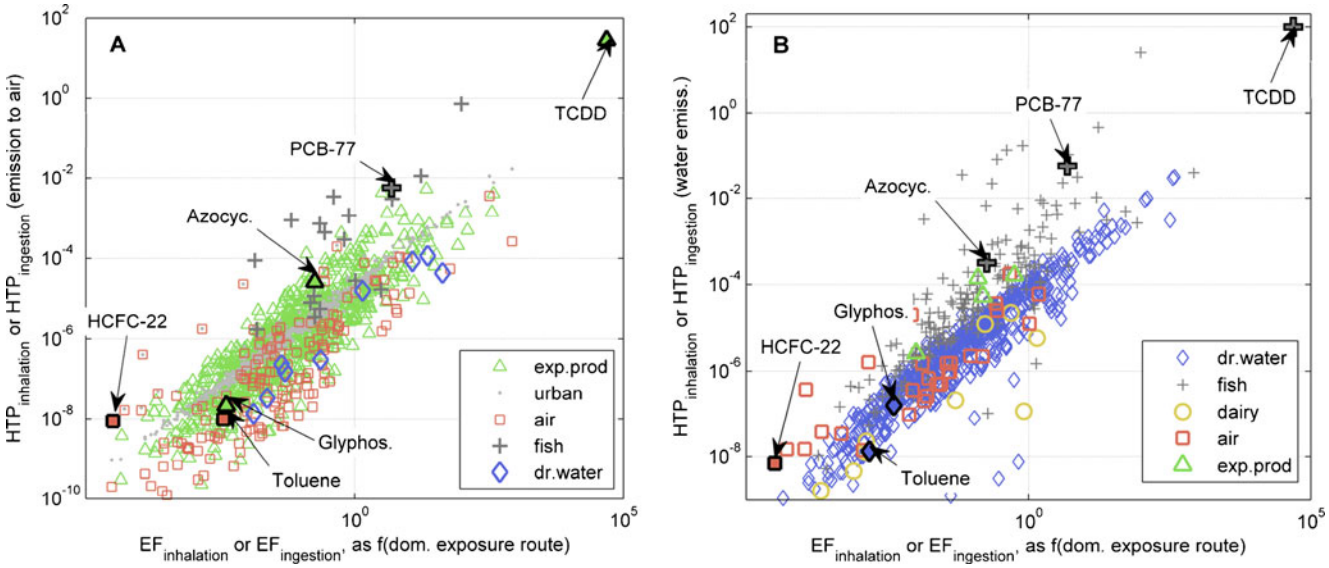

Fig. 9 Human toxicity potentials [CTU_h per $kilogram_{emitted}$] vs. effect factors [CTU_h per $kilograms_{intake}$] for **A** rural continental and urban air emission and **B** freshwater emissions, differentiating between dominant routes of exposure

range of $HTP_{ingestion}$, for a given EF. This is largely due to the variation in iF for the inhalation route vs. ingestion routes, reflecting the relatively high iF for ingestion, as discussed above. There are a handful of chemicals (e.g., HCFC-22) that have very high $HTP_{inhalation}$, relative to other compounds with a similar EF; this is a result of their persistence and corresponding high iF. In the case of an urban air emission, iF does not vary significantly for the majority of chemicals for inhalation. Therefore, the urban emission inhalation dataset is a strong linear function of the EF.

In the case of an emission to freshwater (see Fig. 9b), the variation in iF is smaller, except for those compounds for which fish is the dominant pathway. This variation creates a variation in HTP of approximately two orders of magnitude for pathways excluding fish and a few outliers with low iF. When the fish pathway is included, this variation in HTP increases to five orders of magnitude. The majority of compounds have drinking water as the dominant exposure pathway. Two sets of iF create the two lines of data visible in the centre of the figure. Compounds for which the dominant exposure route is fish have high $HTP_{ingestion}$ (e.g. PCB-77, TCDD), because bioconcentration can drive iF to high levels. Those compounds for which the main exposure route for an emission to freshwater is inhalation are very volatile and persistent substances with high inhalation iF, leading to HTPs for inhalation that are comparable to drinking water ingestion.

4 Conclusions

To increase transparency of human toxicity characterisation factors, a detailed documentation of the human exposure and toxicity models as applied in USEtox™ was provided. In particular, the component accounting for exposure through agricultural produce plays an important role due to above-ground produce being the dominant exposure pathway for most chemicals emitted to air. Milk and meat are rarely the dominant exposure pathways here, in contrast to results for the North American based iFs in Bennett et al. (2002a). One reason is that the US produces two to four times more meat and milk per capita than the global average, and future continental-specific parameterizations can further examine this discrepancy. For inhalation, the population density is the key factor driving the intake, except for very persistent and mobile chemicals that are taken in by the global population independently from their place of emission. For most chemicals in USEtox™, inhalation, above-ground produce, and fish are the important exposure pathways with key driving factors being the (1) compartment and place of emission, (2) partitioning, (3) degradation, (4) bioaccumulation and bioconcentration, and (5) dietary habits of the population (in no particular order and to various degrees depending on the respective dominating exposure pathway).

In order to model toxicity for those chemicals where measured data are only available for one specific exposure route (either ingestion or inhalation), we have explored a route-to-route extrapolation model attempting to increase substance coverage and leading to the following recommendations: In all cases, it is useful to give separate factors for oral and inhalation routes when available. In case no data were available for a specific exposure route, an analysis of route-to-route extrapolation has been carried out, assuming equal potency or slope factor between inhalation and ingestion route, but flagging chemicals as

interim that meet one of the following criteria: (a) the primary target site is specifically related to the route of entry (e.g. the case of formaldehyde linked to nasal cancer); (b) the expected fraction absorbed via inhalation is much higher than the fraction absorbed via ingestion (factor>500), that are chemicals with $K_{ow}<2.5\times10^{-2}$ or $K_{ow}>10^{10}$. In these cases, the interim characterisation factor can underestimate the potential impact by inhalation. A proposal for further increase of substance coverage using acute-to-chronic extrapolation has been made available to the user, but is not part of the present USEtox™ recommendations.

It should be noted that several potentially important exposure pathways are excluded in USEtox™ due to lack of scientific consensus indicating further research needs. These are notably breast milk, indoor inhalation, exposure to directly applied pesticide residues, or increased exposure due to proximity to the source (e.g. workers handling chemicals), and dermal exposure. They can be a dominant exposure pathway for specific sub-populations (e.g. babies, children, workers, consumers, etc.). The impact of neglecting important exposure pathways has been discussed by Franco et al. (2007). For chemicals with an important fish intake pathway, bioaccumulation modelling is an area of improvement, better considering the role of organisms in the food web living in sediments.

Another notable limitation is that the majority of the exposure equations are based on empirical regressions instead of mechanistic insight such as published by Czub and McLachlan (2004) for example. The problematic of empirical vs. mechanistic exposure modelling has been discussed by Rosenbaum et al. (2009) who also demonstrated how empirical regressions may be used in conjunction with a mechanistic model to increase understanding of the underlying processes. However, as shown by Smitkova et al. (2005) mechanistic bioaccumulation models for fish may produce approximately the same result as an empirical regression. This type of work can be used to further underpin or adapt the use of other empirical regressions in human exposure models, such as USEtox™.

The USEtox™ exposure model is best suited to model non-dissociating and non-amphiphilic organic substances. However, meaningful value choices for important parameters enable the model to also cover chemicals with a more complex behaviour, like metals, dissociating organics, or detergents. These are then flagged as interim characterisation factors and their impact scores need to be interpreted cautiously as explained by Rosenbaum et al. (2008).

As the model was developed with comparative assertions regarding the variation of potential toxic impacts within a large range of potential impact among thousands of chemicals in mind, USEtox™ is applicable in any comparative toxicity impact assessment (e.g. comparative risk/hazard assessment, ranking of chemicals according to their potential impact–comparative toxic benchmarking, or prioritisation of chemicals in a policy context) and not limited to be used in the context of life cycle assessment only. Comparative assessments aim to estimate the impact of a chemical relative to other substances establishing rankings that can be used as the basis for decisions, e.g. regarding choices of chemicals as product compounds with the least toxic impact, or in the context of chemical policy identifying priority substances for regulation, etc. Important assumptions commonly made in comparative models are for example (Barnthouse et al. 1997; Olsen et al. 2001; Udo de Haes et al. 2002; Owens 1997; Pennington et al. 2006): (1) use of best estimates instead of conservative choices (i.e. often mean or median instead of lowest/highest parameter value); (2) consideration of large sets of chemical emissions instead of one substance at a time; (3) consideration of impacts integrated over time and space (global in the case of USEtox™) at the population level instead of, e.g. peak exposures of individuals or sub-populations at a specific site and point in time.

5 Recommendations and perspectives

Recommendations regarding exposure modelling for comparative assessments are discussed extensively in section 2.1 and therefore not reiterated here

The parameterisation of USEtox™ represents global averages. The impact of adapting these to continental or even regional conditions can be important and will be explored by the developers in the future. In the same manner as such spatial or temporal variability remains to be quantified, the quantification of uncertainty and identification of its main sources are future focal points. Extension of USEtox™ to further exposure pathways, most notably indoor inhalation exposure in industrial and home settings, is currently under development. There is also a need to adapt USEtox™ for the treatment of ionisable chemicals, building on Franco and Trapp (2010) and Trapp et al. (2010).

Both error corrections and updates to USEtox™ will be published in a new version of the model via the developer team's homepage www.usetox.org. Also, the latest versions of characterisation factors, model, substance databases, and handbooks can always be found on this website. These replace any versions published earlier, independently through which medium (including characterisation factors published in Rosenbaum et al. 2008). The authors would also like to stress that the so-called "interim" USEtox™ characterisation factors should always be used together with the "recommended" factors, as otherwise the substances concerned would be characterised with zero impact as no characterisation factor is applied to their emissions.

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