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Ecotoxicity characterization of chemicals: Global recommendations and implementation in USEtox

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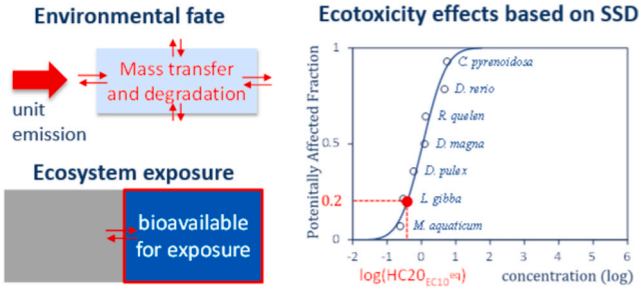
HIGHLIGHTS

- Global recommendation for ecotoxicity characterization of chemicals.
- Matching mathematical framework for calculating effect and exposure factors.
- New characterization factors derived for a set of chemicals from a case study.
- Advancing current approaches for life cycle impact assessment of chemicals.

GRAPHICAL ABSTRACT



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ABSTRACT

Chemicals emitted to the environment affect ecosystem health from local to global scale, and reducing chemical impacts has become an important element of European and global sustainability efforts. The present work advances ecotoxicity characterization of chemicals in life cycle impact assessment by proposing recommendations resulting from international expert workshops and work conducted under the umbrella of the UNEP-SETAC Life Cycle Initiative in the GLAM project (Global guidance on environmental life cycle impact assessment indicators). We include specific recommendations for broadening the assessment scope through proposing to introduce additional environmental compartments beyond freshwater and related ecotoxicity indicators, as well as for adapting the ecotoxicity effect modelling approach to better reflect environmentally relevant exposure levels and including to a larger extent chronic test data. As result, we (1) propose a consistent mathematical framework for

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calculating freshwater ecotoxicity characterization factors and their underlying fate, exposure and effect parameters; (2) implement the framework into the USEtox scientific consensus model; (3) calculate characterization factors for chemicals reported in an inventory of a life cycle assessment case study on rice production and consumption; and (4) investigate the influence of effect data selection criteria on resulting indicator scores. Our results highlight the need for careful interpretation of life cycle assessment impact scores in light of robustness of underlying species sensitivity distributions. Next steps are to apply the recommended characterization framework in additional case studies, and to adapt it to soil, sediment and the marine environment. Our framework is applicable for evaluating chemicals in life cycle assessment, chemical and environmental footprinting, chemical substitution, risk screening, chemical prioritization, and comparison with environmental sustainability targets.

1. Introduction

Ecotoxicological stress from chemical emissions is one of the drivers of biodiversity loss on local and regional scales and a recognized threat on a planetary scale (Alpizar et al., 2019; Kosnik et al., 2022; Lemm et al., 2021; Persson et al., 2022; Posthuma et al., 2020). Several tens of thousands of chemicals can contribute to ecosystem damage, but only a limited fraction of all potentially harmful chemicals has been characterized for use in life cycle assessment (LCA) or environmental footprinting (EF) (Rosenbaum et al., 2018). The ecotoxicological characterization of all relevant chemicals requires approaches which are consistent, transparent and reflect the level of maturity of the science today. Such an approach, developed as a result of an international expert workshop and consultations, is presented in the following manuscript.

Characterizing the ecotoxicological profile of a chemical requires modelling of environmental fate and exposure, as well as the resulting ecotoxicological effects (Jolliet et al., 2006). The ecotoxicological effect factor (EF) in life cycle impact assessment (LCIA) represents the chronic ecotoxicity of an emitted substance in an exposed ecosystem (Fantke et al., 2017), such that an array of chemicals can be represented by an array of EFs, with increasing values indicating increased ecotoxicity. In current LCIA practice, this effect factor is derived as the 50th percentile of a species sensitivity distribution (SSD), constructed using measured or extrapolated chronic EC50 values (i.e., the concentration that causes a 50%-reduction of a vital trait, such as growth or reproduction, after chronic exposure) (Henderson et al., 2011; Huijbregts et al., 2002; Larsen and Hauschild, 2007; Pennington et al., 2004). It has been shown that this so-called $HC50_{EC50}$ (i.e., hazardous concentration affecting 50% of the exposed species at their chronic EC50 level) is statistically robust, thereby facilitating the comparison between substances (Henderson et al., 2011; Pennington et al., 2004). However, because EC50 effect data are usually well above environmentally relevant concentrations, it has been argued that comparison between chemicals is biased when based on $HC50_{EC50}$ estimates (Rorije et al., 2022). Further, as the majority of EC50 data is derived from acute tests and $HC50_{EC50}$ values are thus based on a mostly extrapolated data, it would be more appropriate to use actual chronic test data (e.g. chronic no-observed effect concentrations, NOECs) when calculating effect factors, in order to better reflect long-term ecotoxicological effects of a chemical (Saouter et al. 2017a, 2019). Using chronic NOEC directly to derive SSD and model ecotoxicological effects of chemicals is not straightforward, since no-effect oriented metrics are not suitable to indicate and compare effects and related species loss (Fantke et al., 2018a, 2018b). However, NOEC can be used as input to derive effect-oriented metrics, since variability in ecotoxicological effects across chemicals (which spans over several orders of magnitude) is significantly larger than the related uncertainty in the estimation of the effect-oriented metrics (Aurisano et al., 2019; Hiki and Iwasaki, 2020; Iwasaki et al., 2015).

Ecotoxicological effect factors are derived for each chemical using the sensitivity data from a set of tested species and a selected SSD model, with >1 million test data points available globally (Olker et al., 2022). Dependent on scientific and practical goals, the available databases can be tapped with various, goal-dependent data extraction and curation criteria (Fantke et al., 2020a; Müller et al., 2017; Spilsbury et al., 2020). For example, the global preference for environmental chemical safety assessments is to use chronic NOEC data for a minimum number of species and trophic groups, which differs across jurisdictions. Over time, the global available test data grows, and furthermore that automated protocols can be employed for updates (see e.g., Scharmüller et al., 2020). Some data portals present data from a variety of data owners, such that new data can be added and other data removed (see e.g. https://echa.europa.eu/legal-notice). Such undocumented changes in the content of primary data sources hamper transparency and reproducibility of ecotoxicity characterization factors. Recently, these matters have been subject of a consensus-building process on updating ecotoxicity characterization, held under the umbrella of the UNEP-SETAC Life Cycle Initiative in the GLAM project (Frischknecht et al., 2016; Jolliet et al., 2017, 2014).

2. Consensus-building process

The GLAM project aims to provide contemporary global guidance on LCIA indicators for several life cycle impact categories (Frischknecht and Jolliet, 2019, 2016). For ecotoxicity, consensual recommendations for refining and expanding the current LCIA characterization framework, and for implementing these recommendations into USEtox, were developed within two main activities: (1) the Ecotoxicity Task Force; and (2) the SETAC Pellston workshop held in 2018 in Valencia, Spain. The Ecotoxicity Task Force identified key scientific questions to improve ecotoxicity characterization, reviewed existing models and data, drafted preliminary recommendations, and proposed further action for harmonization. Details of these activities are presented in Fantke et al. (2018a, 2018b). The preliminary recommendations were presented and discussed further by a wider range of experts at a dedicated SETAC Pellston workshop, resulting in a set of recommendations (Frischknecht and Jolliet, 2019). The recommendations go beyond modelling ecotoxicity effect factors and additionally address aspects related to: (1) The general assessment framework; (2) Additional non-aquatic compartments, exposed representative organisms, and impact pathways; (3) Metrics for ecotoxicity characterization; (4) Ecotoxicity modelling of metals; and (5) Result interpretation. All 19 recommendations are presented in Table 1. Recommendations for environmental fate are the same for characterization modelling of ecotoxicity and human toxicity and are presented elsewhere (Fantke et al., 2021). Yet, we summarize the main features of the fate modelling-related recommendations in the present paper as they influence the interpretation of characterization factors and resulting impact scores.

The present paper focuses on the specific recommendations that concern changes in the mathematical framework for calculating characterization factors. The first recommendation (no. 8 in Table 1) is to "base effect modelling on a concentration domain of the SSD curve that is close to the domain of environmental (ambient) concentrations", which deviates from the currently prevailing approach of using the 50th percentile across chronic EC50 values that are mostly extrapolated from acute data. More specifically, it has been recommended to use SSDs based on measured or extrapolated chronic EC10-equivalents ($EC10^{eq}$), derived from chronic or acute NOEC, EC10, or EC50, and to utilize the 20th percentile (P20) as the working point on the SSD curve. In the

Table 1
Recommendations of the Ecotoxicity Task Force and the Pellston workshop that was held in 2018 in Valencia, Spain. Modified from Table 7.2 in Owsianiak et al. (2019).

Recommendation	Implementation status	Recommendation level [a]
General assessment framework		
1 "Build upon the current framework in LCIA for assessing ecosystem damages from emissions of toxic chemicals" (Fantke et al., 2018a, 2018b)	Implemented (USEtox v.2.1) (Fantke et al., 2017)	Strongly recommended
2 "Sum up impact scores across chemicals as a first approximation for handling mixture toxicity under the typical situation of unknown chemical emission location and time along product life cycles" (Fantke et al., 2018a, 2018b)	Implemented (USEtox v.2.1) (Fantke et al., 2017)	Strongly recommended
Additional compartments, exposed organisms, and impact pathways		
3 "Include ecotoxicological effects of chemical substances on organisms living in freshwater sediment, soil, and coastal seawaters in LCIA" (Owsianiak et al., 2019)	Partly implemented, as effect factors are not yet available for all relevant compartments (Fantke et al., 2017).	Recommended
4 "Consider specific characteristics of chemicals, organisms, and compartments in the calculation of effect factors". This is particularly relevant if effect concentrations are derived from effect data representing organisms living in other compartments, such as deriving soil terrestrial effect factors based on freshwater organism test data (Owsianiak et al., 2019).	Not implemented; part of ongoing activities within Ecosystem Quality Task Force	Strongly recommended
5 "Develop methods to address pollinator exposure and related impacts in LCIA due to the importance of this impact pathway" (Fantke et al., 2018a, 2018b)	Not implemented; part of ongoing activities in dedicated collaboration with industry, based on initial pollinator framework for LCA (Crenna et al., 2020)	Strongly recommended
6 "Disregard bioaccumulation as removal mechanisms in all compartments when calculating exposure factors" (Owsianiak et al., 2019)	Implemented (this work)	Strongly recommended
Metrics for ecotoxicity characterization in LCIA		
7 "Use data that has a traceable origin" (Owsianiak et al., 2019)	Not implemented; part of ongoing activities within Ecosystem Quality Task Force; considered in this work for 31 chemicals	Strongly recommended
8 "Base effect modelling on a concentration domain of the SSD curve that is close to the domain of environmental (ambient) concentrations. Use the 20th percentile as the working point on the SSD curve. Derive the SSD curve using chronic EC10-equivalents as underlying effect data to estimate the potentially affected fraction of species (PAF)" (Owsianiak et al., 2019)	Implemented (this work), and building on initial EC10-based approach (López i Losada et al., 2020)	Recommended
9 "Base damage on potentially disappeared fraction of species. However, the link between fraction affected and fraction lost must be established." (Owsianiak et al., 2019)	Not implemented; part of ongoing activities within Ecosystem Quality Task Force	Strongly recommended
Ecotoxicity modelling of metals		
10 "Use free ion activity models to calculate effect factors for metals" (Owsianiak et al., 2019)	Partly implemented, as liquid phase speciation is considered for 15 metals in freshwater (Fantke et al., 2017)	Strongly recommended
11 "Consider liquid phase speciation on metals in the calculation of exposure factor in freshwater, coastal seawater, soil, and freshwater sediment" (Owsianiak et al., 2019)	Partly implemented, as liquid phase speciation is considered for 15 metals in freshwater (Fantke et al., 2017)	Strongly recommended
12 "Consider solid phase speciation (accessibility) in the calculation of exposure factor for metals in soil" (Owsianiak et al., 2019)	Not implemented; considered in the LC-Impact version of USEtox (Verones et al., 2020)	Strongly recommended
13 "Consider solid phase speciation (accessibility) in the calculation of exposure factor for metals in freshwater sediment" (Owsianiak et al., 2019)	Not implemented; part of ongoing activities within Ecosystem Quality Task Force	Interim recommended
14 "Essentiality is recognized but of low relevance for LCIA ecotoxicity characterization, since ecotoxicological effects on some (sensitive) species can always be characterized independently of 'fertilizing' effects on other species at the same concentration range" (Fantke et al., 2018a, 2018b)	Implemented (Fantke et al., 2017)	Strongly recommended
Meaning and interpretation of results		
15 "Where appropriate (i.e. where results span over more than 1 order of magnitude), present impact scores on a $\log_{10}$-scale" (Owsianiak et al., 2019)	Implementation depends on LCA modelling software and/or LCA practitioner	Strongly recommended
16 "Present impact scores separately for organic and inorganic substances" (Owsianiak et al., 2019; Fantke et al., 2018a, 2018b)	Implementation depends on LCA modelling software and/or LCA practitioner	Strongly recommended
17 "Present impact scores separately for different time horizons" (Owsianiak et al., 2019)	Not implemented; part of ongoing activities to test dynamic version of USEtox initially developed for USEtox 2 (Fantke et al., 2015) and implemented in LC-Impact (Verones et al., 2020)	Interim recommended
18 "Stress when interpreting results that impact scores represent time- and space-integrated impact *potential* and (not actual) ecotoxicological impact on receiving ecosystems" (Owsianiak et al., 2019)	Implementation depends on LCA modelling software and/or LCA practitioner	Strongly recommended
19 "Use comparative toxic units for ecotoxicity (CTUe) as unit of impact score" (Owsianiak et al., 2019)	Not implemented; to be included in the next release of USEtox	Recommended

[a] Strength of recommendations ranges from interim recommended, through recommended, to strongly recommended (Owsianiak et al., 2019). No recommendation was classified to be at the lowest level (suggested/advisable). As explained in Frischknecht and Jolliet (2019), the levels of recommendations are based on the maturity of methods, assessed using the following criteria: i) environmental relevance and scientific robustness, ii) availability of data and extrapolation approaches within domain of applicability, iii) completeness, iv) parsimony, v) documentation and transparency, vi) testing, vii) stakeholder acceptance and comprehensibility, and vii) improvement relative to existing approaches.

present study, we detail the rationale for these recommendations and show how to calculate the resulting metric, the $HC20_{EC10^{eq}}$ using analytical methods. These recommendations have already been adopted by Sala et al. (2022), based on earlier discussions (Fantke et al., 2018a, 2018b; Owsianiak et al., 2019), while the full mathematical framework underlying these recommendations is provided in the present study. The second recommendation (no. 6 in Table 1) is to "disregard bioaccumulation as a removal mechanism in all compartments when calculating exposure factors". It was proposed to bring more consistency between exposure calculations, where bioaccumulation is modelled at steady-state, and conditions in ecotoxicological experiments where steady-state is not always reached (Saouter et al., 2017b). Implementing this recommendation requires a modification for calculating exposure factors.

Here, we provide the governing equations and apply them for characterizing chemicals that are listed in the inventories of an illustrative LCA case study. Recommendations that are relevant for metals (no. 10–14 in Table 1), which address speciation in fate, exposure and effect modelling, are not further discussed in the present paper as they can be implemented by combining the new calculation procedures presented below with methods presented elsewhere (Dong et al., 2016; Owsianiak et al., 2013, 2015; Plouffe et al., 2016; Sydow et al., 2020). Exclusion of metals in this paper makes recommendations related to no. 15–17 less relevant to consider here. Recommendations about the inclusion of additional compartments relevant for ecosystem exposure and effect modelling (no. 3–5 in Table 1) require additional research efforts before they can be included in the consensus modelling framework of USEtox. These additional efforts include the collection, curation and analysis of effect data for terrestrial and marine organisms and a mathematical framework that consistently links fate, exposure and effect results in these compartments.

3. Proposed methodological assessment framework

3.1. General characterization framework

Chemicals emitted into the environment reach various compartments in different ecosystems. Impact scores *IS* for a given ecosystem type (e.g. freshwater ecosystems) represent ecotoxicity-related damages on that ecosystem, and are expressed as Potentially Disappeared Fraction (PDF) of species per functional unit [PDF m^3 d/functional unit]. Such impact scores are derived from the product of chemical inventory mass, m_c [$kg_{inventory}$/functional unit] and corresponding endpoint ecotoxicity characterization factors, CF_c [PDF m^3 d/$kg_{inventory}$], aggregated over environmental compartments *c*:

$$IS = \sum_c (m_c \times CF_c) \quad (1)$$

The calculation of characterization factors builds upon a generic framework for the evaluation of environmental fate, ecosystem exposure, and ecotoxicological effects (Jolliet et al., 2006; Rosenbaum et al. 2007, 2008). Some alignments were necessary to make these steps consistent with the recommended approach for characterizing human toxicity impacts in LCIA under GLAM (Fantke et al., 2018a, 2018b, 2021).

Ecotoxicity characterization factors CF_c are derived from cumulative chemical mass transfer fractions from emission compartment *c* to the receiving compartment (i.e., the compartment in which the ecotoxicological effects are evaluated), TF_c^{cum} [$kg_{to\ compartment}$/$kg_{inventory}$]. Cumulative transfer fractions are multiplied with the first-order residence time in the receiving exposure compartment, which is the inverse of the direct overall removal rate constant of chemical mass from that compartment, k^{loss} [($kg_{loss\ from\ compartment}$/d)/$kg_{to\ compartment}$]. This product is finally combined with the ecosystem exposure factor, *XF* [$kg_{bioavailable}$/$kg_{to\ compartment}$], representing the bioavailable mass fraction in the compartment of exposed ecosystems, and with the ecotoxicological effect factor, *EF* [PDF m^3/$kg_{bioavailable}$]. EF is derived from the product of a concentration-response slope factor for the ecosystem of interest, *CRF* [PAF m^3/$kg_{bioavailable}$] (details see below), and a related severity factor, *SF* [PDF/PAF], which translates 'affected' into 'disappeared' fractions of exposed species. With that, ecotoxicity characterization factors at the level of damaged species, are derived as:

$$CF_c = TF_c^{cum} \times \frac{1}{k^{loss}} \times XF \times \overbrace{CRF \times SF}^{EF} \quad (2)$$

Ecotoxicity indicator may be chosen at any point in the impact pathway between emissions and damage to the functioning of ecosystems (Hauschild and Huijbregts, 2015). Equation (2) represents characterization at the level of damaged species (in LCIA also known as endpoint modelling). In this paper, however, we compute characterization factors at the level of affected species (in LCIA known as midpoint modelling), applying the *CRF* only without using severity factors, since further effort is required to arrive at global recommendations for ecotoxicological effects severity. Note that in current LCIA practice (based on $HC50_{EC50}$ calculations), this *CRF* is often directly referred to as effect factor. Fig. 1 presents the main steps of the proposed assessment framework to calculate ecotoxicity characterization factors at midpoint.

3.2. Environmental fate

The product of TF_c^{cum} and the inverse of k^{loss} represents the environmental fate of a compound. Since relevant multimedia transfer processes are already considered in TF_c^{cum}, we do not use the diagonal elements of the fate factors matrix as in earlier versions of USEtox (Henderson et al., 2011). Instead, we use the first-order chemical residence time (i.e. the inverse of k^{loss}), to avoid double counting of feedback into the original emission compartment. Further details of the underlying framework to derive chemical mass transfer fractions are provided elsewhere (Fantke et al., 2021, 2016).

The product of TF_c^{cum} and the inverse of k^{loss} has the unit $kg_{to\ compartment}$/($kg_{inventory}$/d) and represents the change in steady-state substance amount in the final receiving compartment that results from a unit change in the emission mass flow rate into the same or any other compartment that is reported in the inventory. This emission flow rate is used as an interface to LCIA multimedia models for calculating impact scores. Note, that because multimedia fate models applied in LCIA use constant coefficients, the steady-state concentration is a linear function of the emission flow rate. Hence, a change in steady-state substance amount in the water column that results from a unit change in the emission flow rate is mathematically equivalent to the overall cumulative amount from a pulse emission, accounting for the environmental residence time of the substance (Heijungs, 1995). This makes multimedia fate models appropriate for characterization of emissions reported in life cycle inventories of product systems assessed in LCA. Given the integrative nature of the fate component as part of the characterization factor, both short-term and long-term impacts are considered, since an infinite time horizon is applied for calculating CF_c that integrates over the entire relevant time frame.

3.3. Ecosystem exposure

The ecosystem exposure factor, *XF* [$kg_{bioavailable}$/$kg_{to\ compartment}$], represents the bioavailable mass fraction in the compartment of exposed ecosystems (Fantke et al., 2017). It considers important processes which lower chemical concentration. For organic chemicals in freshwater, these processes are sorption to suspended solids and sorption to dissolved organic carbon. These processes are respectively controlled by the suspended solids/water partition coefficient, K_{susp} [L/kg], and the dissolved (colloidal) organic carbon/water partition coefficient, K_{DOC} [L/kg], which depend on concentrations of suspended matter, C_{susp}

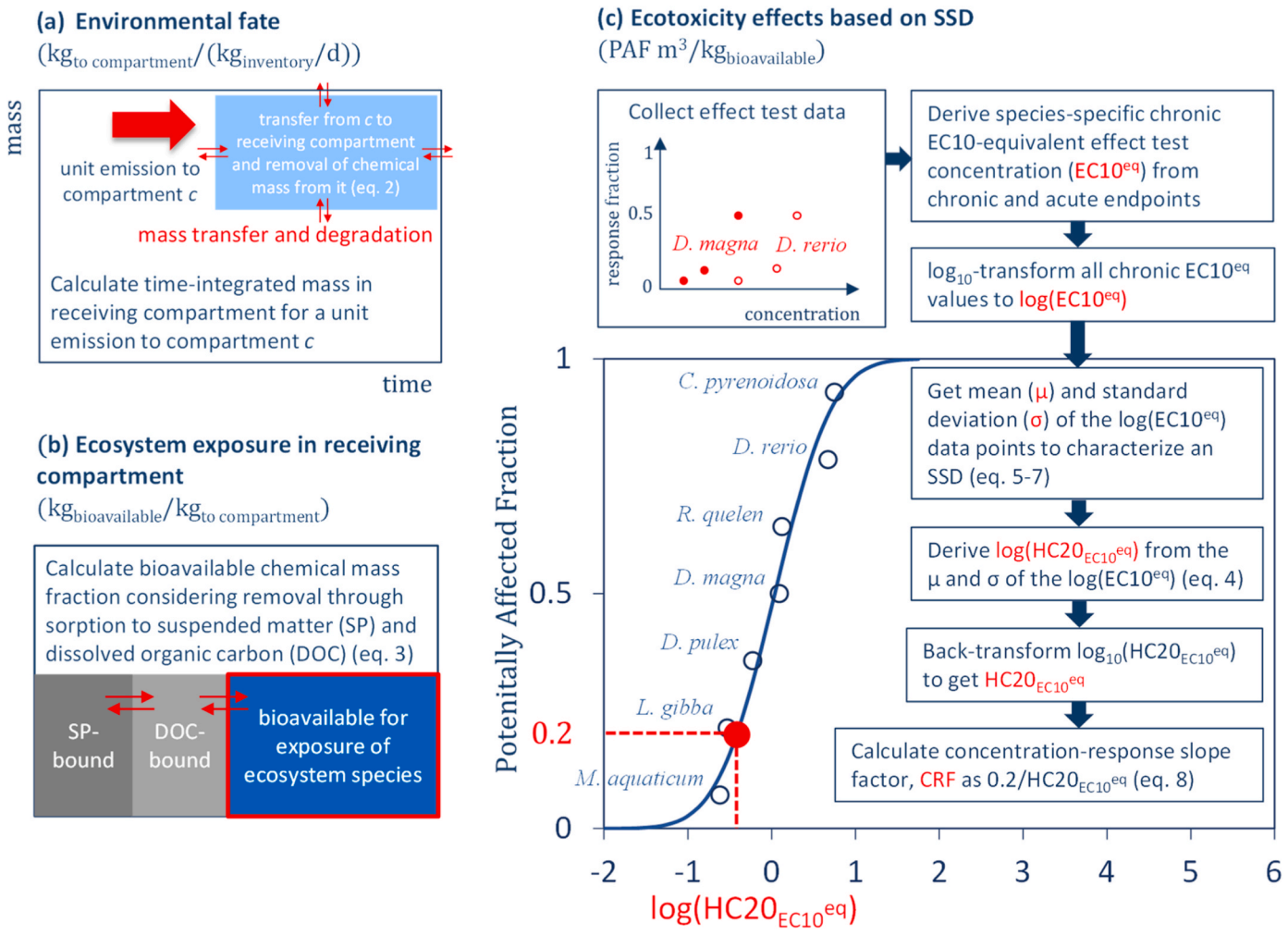


Fig. 1. Recommended approach for deriving ecotoxicity characterization factors at midpoint, as a product of: **(a)** environmental fate (that is, cumulative chemical mass transfer fractions from emission compartment *c* to the receiving compartment multiplied with the inverse of the direct overall removal rate constant of chemical mass from the receiving compartment, which is equal to the time-integrated mass in the receiving compartment for a unit emission to compartment *c*); **(b)** ecosystem exposure, considering removal mechanisms through sorption to suspended matter and dissolved organic carbon and, for metals, speciation within the dissolved phase (not shown); and **(c)** ecotoxicological effects based on species sensitivity distributions (SSD). Abbreviations: SP = suspended matter, DOC = dissolved organic carbon, PAF = potentially affected fraction, SSD = species sensitivity distribution, HC = hazardous concentration, CRF = concentration-response slope factor.

[kg/L], and dissolved (colloidal) organic carbon, C_{DOC} [kg/L]. Consistent with recommendation no. 6 (Table 1), bioaccumulation is not considered as an additional removal mechanism. With that, ecosystem exposure factors in freshwater are now derived as:

$$XF = \frac{1}{(1 + K_{susp} \times C_{susp} + K_{DOC} \times C_{DOC})} \quad (3)$$

Note that because uptake of a chemical into biota influences the residence time of that chemical in all other relevant compartments, bioaccumulation is not to be disregarded when assessing environmental fate.

3.4. Concentration-response slope factor based on species sensitivity distributions

The equations below detail the procedure for calculating $HC20_{EC10^{eq}}$ values and the resulting concentration-response slope factors. Because ecotoxicity data are generally log-normally distributed (Posthuma et al., 2019), it follows that:

$$\log HC20_{EC10^{eq}} = SSD\mu_{\log EC10^{eq}} + z_{0.2} \times SSD\sigma_{\log EC10^{eq}} \quad (4)$$

with

$$SSD\mu_{\log EC10^{eq}} = \frac{1}{n} \times \sum_{i=1}^{n} (\log EC10_i^{eq}) \quad (5)$$

$$SSD\sigma_{\log EC10^{eq}} = \sqrt{\frac{1}{n} \times \sum_{i=1}^{n} \left(\log EC10_i^{eq} - SSD\mu_{\log EC10^{eq}}\right)^2} \quad (6)$$

$$z_{0.2} = \sqrt{2} \times \mathrm{erf}^{-1}(2 \times P_{0.2} - 1) \quad (7)$$

where μ and σ are respectively the arithmetic mean and standard deviation of the normal distribution of the underlying log-transformed $EC10^{eq}$ data; $z_{0.2}$ is the inverse of the standard normal distribution at the 0.2 probability level, i.e. − 0.842, and erf is the error function.

The $\log EC10_i^{eq}$ refers to the arithmetic mean across $\log_{10}$-transformed chronic $EC10_i^{eq}$ data points per species *i*, if more than 1 data point per species is available. Alternative approaches might be discussed in the future of how to average multiple available data points per species (e.g. based on how many chronic data are considered sufficient vs. including also acute data, or how to best combine different effects). The concentration-response slope factor is derived from taking the slope on the SSD at the $HC20_{EC10^{eq}}$ (eq (8)). It represents an incremental change in the potentially affected fraction of species due to an incremental exposure to the bioavailable concentration of a chemical at the HC20 level.

$$CRF = \frac{0.2}{10^{\log\ HC20_{EC10^{eq}}}} = \frac{0.2}{HC20_{EC10^{eq}}} \quad (8)$$

Recommendations presented in Table 1 do not prescribe which database to use for extracting effect data or which methods should be used to estimate chronic $EC10^{eq}$ from other effect data such as acute EC50 values, if empirical EC10 data from chronic tests are missing. Also, the minimum number of data points, species and taxonomic groups required to construct a robust SSD are not prescribed. In the present study, for statistical reasons, chronic $EC10^{eq}$ were derived from SSDs using at least 5 different species, from at least 3 distinct trophic levels (primary producers, primary consumers, secondary consumers or decomposers). With a minimum of 5 species, at least 1 data point on the SSD falls into the range below the 20th percentile of an SSD, so that the final HC20-estimate is not based on an extrapolation beyond the actual dataset. In the present work, we applied the approaches presented by Aurisano et al. (2019) to estimate chronic $EC10^{eq}$ values from either chronic NOEC, chronic LOEC (i.e., lowest observed effect concentration), or chronic EC50 values. These extrapolation methods were chosen because they: (1) were developed using a curated set of effect data; (2) were developed using a set of chemicals representing a relatively large chemical space (e.g., log-transformed octanol–water partitioning coefficient, log K_{OW} ranging from 0 to 6); and (3) have acceptable goodness of fit ($R^2 \geq 0.84$ for extrapolations across chronic endpoints). Only for those chemicals for which the number of species with chronic $EC10^{eq}$ derived from chronic effect data was less than 5, species-specific chronic $EC10^{eq}$ were extrapolated from all available chronic and acute (i.e., acute NOEC, acute EC10 and acute EC50) effect data.

Raw data on effects from lab-based ecotoxicity studies for deriving $HC20_{EC10^{eq}}$ were extracted from the SOLUTIONS database (Posthuma et al., 2019). This database was used, because (1) it comprises curated data points for >12,000 chemicals compiled from different sources; and (2) it includes a subset of data traceable in the peer-reviewed literature, next to data entries obtained for research from the data portal from the European Chemicals Agency (ECHA) that presents regulatory dossier data for chemical safety assessments. To make the choice of data consistent with recommendation no. 7 (Table 1), for the present paper, the subset of data traceable in the peer-reviewed literature only was used. We note that with increasing numbers of observations, the SSDs of compounds based on peer reviewed data and those exclusively based on ECHA-portal data resembled each other more than with lower data numbers (unpublished observation of RIVM). Other ecotoxicity data collection and curation efforts (e.g., JRC's ecotox explorer, Envirotox database, US-EPA's ToxValDB) could be considered as potential alternative or complementary data sources for deriving ecotoxicity effect factors.

To illustrate the workflow and make use of the formulated recommendations, a case study on chemicals used in rice production and consumption is implemented. Characterization factors derived for the rice case study chemicals, however, are only calculated for demonstration purposes and are not official USEtox characterization factors, which are only formally included in official USEtox release versions. Case study SSDs were characterized based on the number of available data points and coverage of taxonomic groups, and SSD-quality earmarks were assigned following the recommendation of Posthuma et al. (2019), considering four aspects; (1) SSD fullness; (2) biodiversity coverage; (3) data origin quality; and (4) extrapolation quality. The earmarks can range from 1111, representing highest possible scores across all four criteria, to 2437, representing lowest possible scores across criteria. Note, that the lowest possible score 2 for the SSD fullness (1st digit in the quality earmark) and the lowest possible score 3 for data origin quality (3rd digit in the earmark) were not used in this work as any chemical for which an insufficient number of empirical data points was available was excluded from the analysis (see above). Further, quality scores for extrapolation quality are not directly comparable with those of Posthuma et al. (2019) because different extrapolation approaches were used. Details of the quality earmarks and extrapolations schemes for our case study are presented in the SI, Tables S1 and S2.

4. Case study on rice production and consumption

The presented approach for advancing ecotoxicity characterization via $HC20^{eq}_{EC10}$ was evaluated in an illustrative case study on rice production and consumption across three scenarios, for a functional unit (FU) of 1 kg cooked, white rice. This case study was chosen as it allows for a comparison of ecotoxicity results with other impact categories, for which consensual recommendations have been developed and tested earlier in GLAM (Frischknecht et al., 2016; Verones et al., 2017). In the first scenario, rice is produced (i.e. agricultural production and processing) in rural areas and prepared (i.e. distribution and cooking) in urban areas of China (CN). In the second scenario, rice is produced and prepared in rural areas of India (IN). In the third scenario, rice is produced in rural areas of the U.S. and prepared in urban areas of Switzerland (US/CH). Details of the case study, including goal and scope definition and life cycle inventories of unit processes, are presented in the Electronic Supplementary Material of Frischknecht et al. (2016), while the inventory of chemical emissions relevant for ecotoxicity impacts is presented in Fantke et al. (2021).

4.1. Freshwater ecotoxicity characterization factors

For ecotoxicity characterization, we considered all 115 organic chemicals reported in rice case study inventories, for which we could determine non-zero emissions along the rice production and preparation life cycle for at least one of the three considered scenarios (Fantke et al., 2021). CAS registry numbers were used to extract effect data (EC10s, EC50s, and NOECs) from the SOLUTIONS database. Confidential data and data points for genera with unspecified species names were excluded. For 7 chemicals, concentration-response slope factors could be computed based solely on empirical chronic effect data (i.e. without acute-to-chronic extrapolations). Additionally, a set of 24 chemicals was covered by combining chronic and acute effect data in order to reach the minimum requirement of at least 5 species from at least 3 trophic levels. That is, only 31 of 115 chemicals could be characterized using the present framework. This small coverage is mainly due to the demand of having representatives of at least three distinct trophic levels included in an SSD. This reduces number of chemicals which meet the criterion because two dominant species groups (i.e., crustaceans and fish) often belong to the same trophic level (i.e., secondary consumers).

For all 31 case study chemicals, concentration-response slope factors were calculated using Eq. 8. For these chemicals, we also computed ecosystem exposure factors, adapted to disregard bioaccumulation as removal mechanism, as well as environmental fate factors from the product of TF_c^{cum} and the inverse of k^{loss}, using USEtox version 2.12 (Fantke et al., 2017).

Across the 31 characterized chemicals, concentration-response slope factors ranged from 2.4 to 4.3×10^7 PAF $m^3/kg_{bioavailable}$. Quality earmarks of underlying SSDs across these chemicals ranged from 1123 (1 chemical) through 1126 (3 chemicals), 1223 (5 chemicals), 1226 (17 chemicals), 1323 (1 chemical), to 1326 (4 chemicals). These earmarks suggest that for most (but not all) chemicals, the underlying SSDs are relatively robust in terms of taxa coverage (for 25 out of 31 chemicals, the number of taxa evaluated is > 5). However, for most (but not all) chemicals, the underlying SSDs are less robust in terms of extrapolation quality (for 24 out of 31 chemicals, because extrapolation to chronic $EC10^{eq}$ had to be done from acute EC50, see SI, Table S1). The largest concentration-response slope factors (CRF) were calculated for the pesticides λ-cyhalothrin, cypermethrin, and parathion (4.3×10^7, 1.2×10^7, and 4.7×10^6 PAF $m^3/kg_{bioavailable}$, respectively). Quality earmarks of the respective underlying SSDs are 1226, 1226 and 1223.

Across chemicals, the numerical values of the new CRFs were on

average 6.4 times higher when compared to earlier effect factors based on $HC50_{EC50}$, as implemented in USEtox 2.12 (note, however, that for damage assessment the severity factor for the $HC20_{EC10^{eq}}$ will have the opposite trend). This numerical increase is mainly because SSD curve is constructed using log_{10}-transformed $EC10^{eq}$ data, resulting in a large decrease of the hazardous concentration when the species response level changes from the 50th to the 20th percentile. Exposure factors ranged from 0.121 to 1 kg/kg, but none of all 31 chemicals showed noticeable (>1%) increase in the exposure factor when bioaccumulation was disregarded as removal process. The product of TF_c^{cum} and k^{loss} were equal to the fate factors of USEtox 2.12, which confirms their mathematical equivalence, while being now adapted fully with the characterization framework for human toxicity (Fantke et al., 2021).

Across all chemicals and emission compartments, CRFs of the different chemicals spanned over 7 orders of magnitude. That is, the relative differences in ecotoxicity profiles of the compounds show larger variability and consequently had larger influence on the variability of characterization factors than related exposure or fate parameters. Indeed, freshwater characterization factors were highest for those substances with highest CRF values, and were equal to 4.1×10^8, 2.1×10^8, and 1.7×10^8 PAF m^3 d/$kg_{inventory}$ for λ-cyhalothrin, cypermethrin and parathion, respectively, highlighting the influence of the higher variability in CRFs of 8 orders of magnitude across the 31 considered chemicals as compared to the variability of around a factor of five across related exposure factors and a factor of 23 across related fate factors.

5. Freshwater ecotoxicity impact scores

Inventory results spanned over 10 orders of magnitude, with varying contributions of emission compartments across chemicals and case study scenarios (Fig. 2). Freshwater ecotoxicity impact scores were equal to 24, 24 and 6.6 PAF m^3 d/functional unit (1 kg of cooked white rice) for the China, India and U.S/Switzerland scenarios, respectively. Across all three scenarios, impact scores were driven mainly by soil-borne emissions of the pesticide parathion which has relatively high characterization factor across chemicals (contribution to total impact score equal to 94% for all three scenarios), followed by phenol which is less toxic than parathion and its emissions are significantly smaller (resulting in ~1% contribution to the total ecotoxicity impact score for all three scenarios). Although emitted masses of some toxic chemicals differed between the scenarios by up to ~2 orders of magnitude (e.g., toluene, formaldehyde, ethylbenzene, acetaldehyde), these differences did not propagate to differences in total impact scores because total impact scores were dominated by the contribution of parathion, with its relatively high emitted mass and high characterization factor. For China and India, parathion emissions were identical (~46 mg/functional unit), which explains why there are no significant differences in the impact scores of both scenarios. Parathion emissions were ~3.5 times smaller for the U.S./Switzerland scenario, and the impact scores for U.S./Switzerland were therefore lower (Fig. 2).

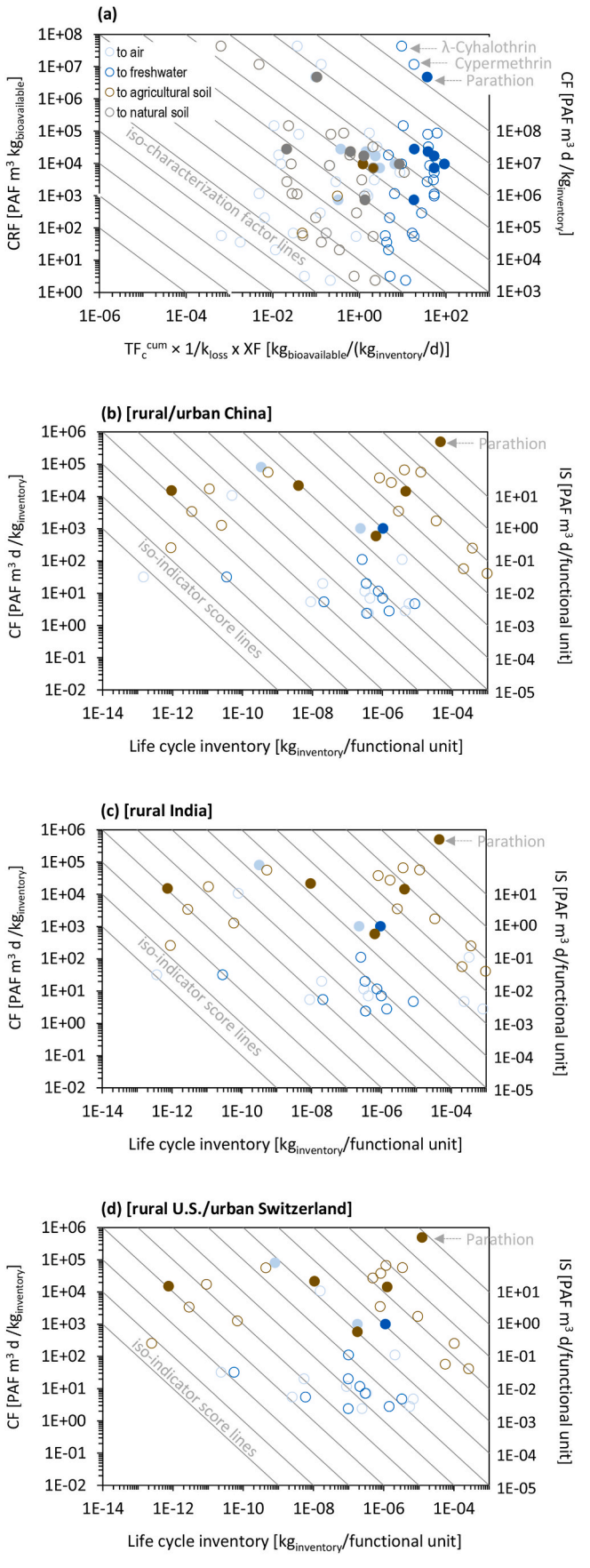
5.1. Sensitivity analysis

We tested the significance of two methodological choices made on substance coverage and resulting impact scores, with emphasis on evaluating SSD and $HC20_{EC10^{eq}}$ robustness, whereby robustness for $HC20_{EC10eq}$ and impact scores is present if the estimate is insensitive to changes in input data sets, and for product comparisons where the rank order and position of the impact scores across chemicals used for a product scenario provide the same information on relative importance of chemicals. Generally, it can be expected that robustness of HC20 values is low if the number of test data used to generate the SSD is low, which can result in a misestimation of the SSD slope. That robustness is also low if included data contains high proportion of relatively sensitive (or relatively insensitive) species, which may misestimate $HC20_{EC10^{eq}}$, particularly so for those chemicals which target specific groups of organisms according to their toxic mode of action. In turn, these matters influence the robustness of across-chemicals impact scores.

First, we tested the implications of excluding a significant portion of the available effect data because full species names were not provided. This was done by assigning genus and/or species names to unspecified algae, daphnids and fish based on the statistical distribution of species used in ecotoxicological experiments in the SOLUTIONS database for 31 chemicals from the case study. For example, 90% and 7% of tests on daphnids were performed using *Daphnia magna* and *Daphnia pulex*, respectively, with contributions <1% for 8 other daphnia species, and this statistic was used to assign all those possible names to unspecified daphnids. Results showed that assigning names to unspecified algae, daphnids and fish increased the number of characterized substances from 31 to 33 (Table 2). Quality earmarks increased for a total of 4 substances (from 1226 to 1126), reflecting increasing number of taxa evaluated for these 4 substances. These increases in substance and biodiversity coverage had very small influence on impact scores, which increased by ~1% across the three scenarios. Thus, benefits from increasing species coverage by assigning names based on statistical occurrence of the most dominant groups of organisms used in ecotoxicological tests were modest in the rice case study.

Second, we tested the implication of the decision to set the required number of species from at least 3 different trophic levels to 5. Here, comparisons were made with a stricter requirement where the minimum number of species is set equal to 9, with at least 3 species from each of a minimum of 3 trophic levels. Again, unknown genera and/or species were assigned names based on their relative occurrence in ecotoxicological tests for the case study chemicals. Note, that for some chemicals this approach resulted in an increasing number of data points in the SSD, because the stricter requirement led to the use of acute effect data which are more abundant as compared to chronic test data. Overall, this had a substantial effect on substance coverage (which decreased from, 31 to 16 compounds characterized) and total impact scores, which decreased by ~95% across the three scenarios. Four factors can explain this decrease: (1) exclusion of substances which have relatively large contribution to total impact scores; (2) higher proportion of species with relatively low sensitivity when more abundant acute effect data are used to construct SSDs, which is mainly related to (3) bias towards relatively more data from species of taxonomic groups that are in fact not targeted by a chemical's toxic mode of action; and (4) uncertainty in the extrapolation to chronic $EC10^{eq}$. The first factor was less relevant in this case study (although the number of characterized substances dropped by half compared to the original criterion), since the contribution of the excluded substances to total impact score was only ~5%. The second and related third factors were, however, far more important. When stricter criteria were used for data selection, none of the chemicals could be characterized based solely on chronic effect data (which is reflected in reduced extrapolation quality score from 2 to 5). This increased species coverage for the top contributing substance, parathion (which is reflected in increased biodiversity coverage score from 2 to 1), increasing the proportion of relatively less sensitive vertebrate species. Fig. 3 shows that this more balanced representation of species groups reduced CF of parathion by about one order of magnitude. Extrapolations from EC50s to chronic $EC10^{eq}$ further contributed to the decrease in the CF for parathion of about half an order of magnitude, indicating that the applied extrapolation factors may be too low for parathion. Aurisano et al. (2019) already showed that while their extrapolation factors were generally representing a relatively large chemical space, there is a substantial variability in factors across chemicals.

Altoghether, these aspects suggest that there is a tradeoff between quality of effect data (which decreases with increasing number of extrapolation steps toward chronic $EC10^{eq}$) and robustness of SSDs (which increases when more species and taxa are used to construct the SSD curve; however, also introducing potential additional bias). This calls for careful interpretation of impact scores in light of robustness of



(caption on next column)

Fig. 2. Freshwater ecotoxicity characterization factors at midpoint level (**a**) and indicator scores (**b–d**) for the rice case study. Characterization factors (right-side *y*-axis in **a**) are plotted as product of the combination of exposure factor, the cumulative chemical mass transfer fraction and the inverse of the direct overall removal rate constant (*x*-axis) and corresponding freshwater ecotoxicity-related concentration-response slope factors (left-side *y*-axis). Indicator scores (right-side *y*-axis in **b-d**) are plotted as product of life cycle inventory mass (*x*-axis) and midpoint characterization factors (left-side *y*-axis). Industrial chemicals are emitted to continental rural air, freshwater, and natural soil, and pesticides are emitted to agricultural soil. Inventory data, characterization factors and their underlying factors for all case study chemicals, and impact scores for all 3 scenarios are provided in the SI, Table S3. Filled circles represent values calculated using chronic effect data only. Empty circles represent values calculated using chronic and acute data.

SSD curves and for careful selection of extrapolation approaches for higher-order extrapolations (e.g., from acute EC50 to chronic $EC10^{eq}$). Our rice case study highlights the added value of using chronic NOEC to estimate $EC10^{eq}$. If NOEC data were excluded from extrapolation to chronic $EC10^{eq}$, none of the substances reported in the life cycle inventory of rice, including the top contributor parathion, could be characterized using the criterion of minimum 5 species from at least 3 different trophic levels. Including NOEC in the extrapolation to $EC10^{eq}$ increases the substance coverage and allows to capture orders of magnitude difference in characterization factors and resulting impact scores across rice case study chemicals. For data-rich chemicals it is likely that NOEC closely relates to $EC10^{eq}$ values (Hiki and Iwasaki, 2020; Iwasaki et al., 2015), whilst use of NOEC to estimate $EC10^{eq}$ for data poor compounds would most likely show non-robustness of hazardous concentration estimates.

5.2. *Applicability*

The proposed framework is directly applicable to all those groups of chemical substances, which are at characterized using official USEtox release versions, namely neutral and dissociating organic compounds that can be characterized based on partitioning and degradation, and metal ions for which speciation patterns can be obtained. Although characterization of metals was not done in the present case study, the proposed approaches can be applied by adopting earlier approaches, which consider metals' speciation in environmental fate, exposure, and effects (Dong et al., 2014; Gandhi and Diamond, 2018; Owsianiak et al., 2015; Plouffe et al., 2016; Sydow et al., 2020). The proposed framework and the general underlying USEtox model that was applied are not applicable without further adaptation to inorganic anions, reactive gases, nanoparticles, and ionic liquids and per- and polyfluoroalkyl substances. Table 3 presents aspects to consider when adopting the presented framework to these groups of substances.

6. Conclusions and next steps

We propose a mathematical framework for deriving ecotoxicity effect factors together with adaptations of ecosystem exposure factors based on recommendations from a global expert taskforce. This advances earlier ecotoxicity characterization frameworks for life cycle impact assessment and is consistent with the approach implemented in the scientific consensus model USEtox. We include specific recommendations for broadening the assessment scope through proposing to introduce additional environmental compartments next to freshwater and related ecotoxicity indicators, as well as for adapting the ecotoxicity effect modelling approach to better reflect environmentally relevant exposure levels and including to a larger extent chronic test data. These adaptations will enable future assessments to (a) expand their scope beyond freshwater ecotoxicity by also considering marine and soil terrestrial ecotoxicity impacts, (b) follow a systematic data selection and curation approach for deriving a consistent set of $EC10^{eq}$ values for each

Table 2
Total impact scores expressed in PAF m^3 d/$kg_{inventory}$ calculated for 3 scenarios (China, India, and U.S./Switzerland) using 3 different approaches to extract and include effect data in calculation of CRF values.

Rice case study scenario	Total impact score [PAF m^3 d/$kg_{inventory}$]		
	Minimum 5 species from at least 3 trophic levels [a)]	Minimum 5 species from at least 3 trophic levels, including "unknown" fish and algae [b)]	Minimum 9 species from at least 3 trophic levels (minimum 3 species from each trophic level), including "unknown" fish and algae [b)]
China (total impact)	**19.5**	**19.8**	**1.78**
chronic effect test data	18	18	0.052
chronic and acute effect test data	1.46	1.83	1.73
India (total impact)	**19.5**	**19.9**	**1.81**
chronic effect test data	18	18	0.052
chronic and acute effect test data	1.48	1.86	1.76
U·S./ Switzerland (total impact)	**5.3**	**5.4**	**0.52**
chronic effect test data	4.9	4.9	0.014
chronic and acute effect test data	0.42	0.53	0.5

[a] "Unknown" species (e.g. "algae", "daphnia" and "fish") not used to calculate concentration-response slope factors (CRF).
[b] ("algae", "daphnia" and "fish" assigned names based on statistical distribution of species in ecotoxicological tests and used to calculate CRFs.

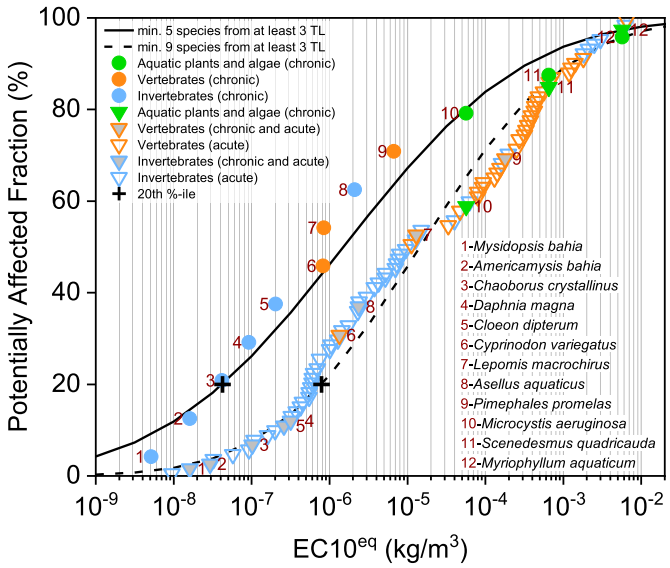


Fig. 3. Influence of data selection criteria on species sensitivity distributions (SSD) for parathion as top-contributing substance to freshwater ecotoxicity impacts in the rice case study. Filled circles represent chronic (log-transformed) $EC10^{eq}$ derived from chronic NOEC, and black continuous line represents the related SSD, with data selected based on the following criterion: minimum 5 species from at least 3 different trophic levels (TL). Triangles represent chronic (log-transformed) $EC10^{eq}$ derived from acute NOEC and acute EC10, and dashed black line represents the related SSD, with data selected based on the following criterion: minimum 9 species from at least 3 different trophic levels (minimum 3 species from each trophic level), including "unknown" fish and algae. Filled triangles represent values calculated using chronic effect data only. Triangles filled with gray represent data calculated using chronic and acute effect data, while empty triangles represent data calculated using acute effect data only. Black crosses represent (log-transformed) $HC20_{EC10^{eq}}$, showing high sensitivity to data selection criteria.

considered chemical, (c) improve the reliability of ecotoxicity effect factors by constructing non-linear distributions from sensitivities across ecological species from different trophic levels or taxonomic groups, and (d) propose concentration-response slope factors at chemical concentration levels that are more environmentally relevant, and (e) enhance consistency in ranking of chemicals according to their ecotoxicity impact scores with their ranking using hazard characterization in regulatory risk assessment (Saouter et al., 2017a). With that, the presented methodological improvements for ecotoxicity characterization address several limitations of existing frameworks. Using effect factors based on $EC10^{eq}$ values we hence deal with ecological impacts at environmentally-relevant exposure levels.

Practical implementation of the proposed framework revealed remaining challenges for a wider implementation. The ecotoxicity of 84 out of 115 emitted organic chemicals could not be characterized, although 51 of these chemicals have a characterization factor in USEtox 2.11, and additional 26 chemicals have a characterization factor that is flagged 'indicative' (indicating higher uncertainty due to the fact that the criterion for an effect factor to be based on effect data representing algae, crustacean and fish, was not fulfilled). Since USEtox 2.12, the effect data selection criterion was adapted to be applied at the level of taxonomic or species groups, rather than true trophic levels. Operating at the level of trophic level significantly reduces the number of chemicals which can be characterized using the presented approach. To increase substance coverage further, future efforts should focus on (1) comparing different criteria for inclusion of effect data and determining resulting tradeoffs between number of data points and representatives (in terms of representation of relevant species) and robustness (in terms of statistical uncertainty) of resulting SSDs; (2) exploring the use of predictive tools, such as quantitative structure-activity relationships (QSAR) and interspecies correlation estimation (ICE) models, which may become useful to increase number of data points for developing SSD curves; (3) deriving SSD slope parameters for data-poor chemicals based on high-quality effect test data for data-rich chemicals; and (4) developing higher-level predictive approaches for estimation of SSD parameters from physicochemical properties and potentially species and effect characteristics.

To improve the presented framework the next steps are to propose a systematic set of extrapolation approaches to derive underlying SSD effect data as input for obtaining $HC20_{EC10^{eq}}$ and related effect factors, to address remaining research gaps with respect to missing effect data for different environments (e.g. soil or sediment-dwelling organisms), to translate $HC20_{EC10^{eq}}$ based ecotoxicity impacts into affected or potential disappearing genetic diversity (i.e. species loss) and functional diversity, to report statistical uncertainty of characterization factors; and to test the recommended characterization framework in additional case studies. With these advances, our proposed ecotoxicity characterization framework is designed for evaluating chemical emissions in LCIA, but is also applicable for use in chemical and environmental footprinting (Saouter et al. 2017a, 2017b; Jolliet et al., 2020), chemical substitution (Fantke et al., 2016, 2020b; Steingrímsdóttir et al., 2018), risk screening and chemical prioritization (Posthuma et al., 2019; Wender et al., 2018), and comparison with sustainability targets (Fantke and Illner, 2019; Posthuma et al., 2014). While freshwater ecotoxicity effect factors and related characterization factors can now be calculated for several thousands of chemicals based on available, curated effect data, additional extrapolation approaches and predictive techniques are needed to (a) cover the wider range of ~100,000 globally marketed chemicals, and (b) derive effect factors for additional environments for which test data

Table 3
Main challenges for characterization of chemical substances classified as inorganic anions and oxoanions, reactive gases, nanoparticles, ionic liquids, and per- and polyfluoroalkyl substances.

Substance group	Examples	Challenges for implementation of the proposed framework
Inorganic anions and related salts	fluoride (F^-), potassium fluoride (KF)	Characterization of inorganic anions and related salts must consider environmental chemistry parameters (like pH, hardness or content of amorphous phases) and related complex reaction kinetics and dynamics as they influence environmental fate, exposure and ecotoxic effects (Elphick et al., 2011; Goldberg and Kabengi, 2010; Kirchhübel and Fantke, 2019)
Inorganic oxoanions and related salts	bromate (BrO_3^-), potassium bromate ($KBrO_3$)	Oxoanions and related salts can have strong oxidizing properties, and their ecotoxicity characterization must therefore consider kinetics of reduction to simpler forms (e.g. bromate reduced to bromide) (He et al., 2019; Van Ginkel et al., 2005; Vanwijk and Hutchinson, 1995).
Reactive gases	chlorine (Cl_2), hydrogen cyanide (HCN)	Characterization of reactive gases should consider the complex reaction mechanisms and kinetics of degradation to resulting products (like chloride salts and chlorinated organic chemicals resulting from reaction of chlorine gas with inorganic and organic substances in the respective compartments or phases) (McNamara et al., 2019; Westerhoff et al., 2004).
Nanoparticles	nano titanium dioxide (nano-TiO_2), nano copper (nano-Cu)	Characterization of nanoparticles should consider aggregation and potential differences in bioavailability of free and aggregated particles) on environmental fate, exposure and effects. Characterization of some metallic nanoparticles should furthermore consider speciation, as influenced by ambient chemistry parameters (Meesters et al., 2014; Qiu and Smolders, 2017).
Ionic liquids	1-butyl-3-methylimidazolium bromide ($C_8H_{15}BrN_2$)	Characterization of ionic liquids should consider their ionic nature and potential for dissociation in the environment, which may require separate characterization of cations and anions forming the ionic liquid (Thuy Pham et al., 2010; Wilms et al., 2020).
Per- and polyfluoroalkyl substances (PFASs)	perfluorobutane sulfonate (PFBS)	Characterization of PFAS compounds should consider degradation to potentially toxic degradation products and their unique chemical character (like the combination of lipophobic and hydrophobic properties, to which the conventional Kow-based partitioning as applied for other organic substances does not apply) (Holmquist et al., 2020).

are much more limited.

Credit author statement

M.O.: Conceptualization, Methodology, Software, Investigation, Visualization, Writing – original draft preparation. M.H: Conceptualization, Methodology, Writing- Reviewing and Editing, Supervision. L.P.: Conceptualization, Methodology, Validation, Data curation, Writing-Reviewing and Editing. E.S., M.V., T.B., T.S.: Conceptualization, Writing- Reviewing and Editing. M.D.: Software, Writing- Reviewing and Editing. P.F.: Conceptualization, Methodology, Writing – original draft preparation, Supervision, Project administration; Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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