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IMPROVING SUBSTANCE INFORMATION IN USETOX®, PART 1: DISCUSSION ON DATA AND APPROACHES FOR ESTIMATING FRESHWATER ECOTOXICITY EFFECT FACTORS

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Abstract: The scientific consensus model USEtox® is recommended by the European Commission as the reference model to characterize life cycle chemical emissions in terms of their potential human toxicity and freshwater aquatic ecotoxicity impacts in the context of the International Reference Life Cycle Data System Handbook and the Environmental Footprint pilot phase looking at products (PEF) and organizations (OEF). Consequently, this model has been systematically used within the PEF/OEF pilot phase by 25 European Union industry sectors, which manufacture a wide variety of consumer products. This testing phase has raised some questions regarding the derivation of and the data used for the chemical-specific freshwater ecotoxicity effect factor in USEtox. For calculating the potential freshwater aquatic ecotoxicity impacts, USEtox bases the effect factor on the chronic hazard concentration (HC50) value for a chemical calculated as the arithmetic mean of all logarithmized geometric means of species-specific chronic median lethal (or effect) concentrations (L[E]C50). We investigated the dependency of the USEtox effect factor on the selection of ecotoxicological data source and toxicological endpoints, and we found that both influence the ecotoxicity ranking of chemicals and may hence influence the conclusions of a PEF/OEF study. We furthermore compared the average measure (HC50) with other types of ecotoxicity effect indicators, such as the lowest species EC50 or no-observable-effect concentration, frequently used in regulatory risk assessment, and demonstrated how they may also influence the ecotoxicity ranking of chemicals. We acknowledge that these indicators represent different aspects of a chemical's ecotoxicity potential and discuss their pros and cons for a comparative chemical assessment as performed in life cycle assessment and in particular within the PEF/OEF context. *Environ Toxicol Chem* 2017;36:3450–3462. © 2017 The Authors. Environmental Toxicology and Chemistry published by Wiley Periodicals, Inc. on behalf of SETAC

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INTRODUCTION

The main goal of life cycle assessment (LCA) is to quantify and compare the potential impacts on the environment, including ecosystem quality, human health, and natural resources, occurring along the life cycle of products and services (from extraction of raw materials to end-of-life treatment). Potential impacts are thus associated with the consumption of natural resources and emissions of chemical substances into air, soil, and aquatic environments. Originally, the LCA methodology developed in the late 1960s focused mainly on the accounting of resources and energy flows (and related greenhouse gas emissions into air). New impact categories have been steadily added to LCA, including depletion of stratospheric ozone, acidification and eutrophication of terrestrial and aquatic ecosystems, abiotic resources depletion, ecotoxicity and human toxicity, and impacts resulting from land and water use. Each impact category indicator covers a different impact pathway and relies on models that describe these impact pathways by linking the resources used or chemical emissions into the environment as quantified in the life cycle inventory phase to impact along a cause–effect chain as quantified in the life cycle impact assessment phase. For the characterization of each type of impact, different models are usually available [1–3].

Over the years, several models for characterizing freshwater ecotoxicity impacts have been developed that are based on different assumptions and algorithms and can lead to results that differ by several orders of magnitude [4]. To overcome intrinsic differences between models and capitalize on available knowledge, the scientific consensus model USEtox® has been used since 2003 under the auspices of the United Nations Environment Programme–Society of Environmental Toxicology and Chemistry (UNEP–SETAC) Life Cycle Initiative [4–6]. The USEtox model aims to characterize the toxicity-related impacts of chemical emissions on freshwater ecosystems and on humans by combining multimedia environmental fate modeling to estimate chemical distributions in various environmental compartments with exposure and effect assessment. After a review of several models performed by the European Commission–Joint Research Centre (EC-JRC) [1,2], USEtox has been retained as reference model for human toxicity and freshwater ecotoxicity impact characterization. Indeed, USEtox is the reference model in the International Reference Life Cycle Data System recommendations [2] and is consequently also applied in the context of the European Commission's Product and Organization Environmental Footprint (PEF/OEF) pilot phase [7,8]. The USEtox model is a screening-level model that aims to help identify, out of hundreds of chemicals emitted

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along product life cycles, those emissions with the greatest contribution to potential aquatic ecotoxicity and human toxicity profiles [9]. A chemical will be further evaluated if the outcome of the USEtox calculation helps with the identification of the chemical of concern in the context of the PEF/OEF and with the identification of environmentally preferable products, as far as potential toxicity is concerned.

To assess the overall potential human toxicity and freshwater ecotoxicity impacts of a product, the mass of each chemical emitted along the product's life cycle into particular environmental compartments is multiplied by its corresponding characterization factors, representing the potency of chemicals toward causing human toxicity and/or freshwater ecotoxicity impacts. In a product life cycle, thousands of different chemicals can be emitted to air, water, and soil. Version 1.01 of USEtox already provides 2498 characterization factors for freshwater ecotoxicity. For each substance emitted to compartment i, ecotoxicity characterization factors (CFs) are calculated from the combination of matrices containing fate factors (FF), exposure factors related to freshwater compartment w (XF), and ecotoxicity effect factors (EFs), with $CF_i = FF_{i,w} \times XF_w \times EF_w$. Since its first release in 2008, USEtox has been widely used but only recently systematically applied and evaluated across industry sectors for the purpose of product comparison and communication in the PEF/OEF pilot phase (2013–2017). In 2015, the European Commission organized a workshop with the PEF/OEF pilots, which have been using USEtox Ver 1.01 in their screening studies. The main conclusions from this workshop were that using USEtox in PEF/OEF might lead to results that are difficult to understand and interpret. Moreover, USEtox substance-related input data, including physicochemical properties, chemical half-lives, and freshwater ecotoxicity data, should be aligned with the most recent data sources, such as the IUCLID database of the European Chemical Agency, which is used for the Registration, Evaluation, Authorisation, and Restriction of Chemicals (REACH) in the European Union [10]. After this workshop, the EC-JRC conducted a re-evaluation of USEtox in the light of the newly performed PEF/OEF screening studies, with the aim of increasing the acceptability of toxicity and ecotoxicity characterization factors. The results of this evaluation related to the calculation of ecotoxicity effect factors are summarized in the present study and apply to both Ver 1.01 and Ver 2.0 of USEtox, as the underlying approach and the related input data are identical except for some substances, regarding the latter.

The rationale behind the USEtox methodology has been published [3,11–16], and is also the result of a series of scientific consensus workshops between LCA and environmental risk assessment (ERA) experts. Furthermore, USEtox has the endorsement of the UNEP–SETAC Life Cycle Initiative [17]. Via the present study, we examine some of the consequences of the current approach as an input to the scientific developments around USEtox; in addition, by presenting 2 case studies, we illustrate the potential issues encountered while applying the recommended model.

Our analysis is divided into 4 main blocks. First we present a critical discussion on the methodology and assumptions applied by USEtox to derive freshwater ecotoxicity effect factors to be used in the European Union context with the PEF/OEF activities. This topic has been (and still is) debated within the LCA and the risk assessment communities for both the ecological and human health–related impacts. Because of the collaborative nature of the present study (some authors are risk assessment experts, some are LCA experts and have actively participated in the development of USEtox, and others have double expertise in LCA and ERA), no final recommendation is provided on how effect factors should be calculated; instead, 5 possible options to calculate effect factor in the context of the PEF/OEF are presented. The present study does not provide case studies where all the different options are tested and compared. This will be done in future work.

Our analysis is further developed by, second, a comparison between USEtox effect factors and how ecotoxicity is dealt with in European chemicals regulation; third, an illustrative case study to highlight the implications of the original methodological choices in the PEF/OEF context; and fourth, a comparison of USEtox median hazard concentration (HC50) values with metrics used in regulatory chemical ERA.

MATERIALS AND METHODS

As basis for critically discussing the approach that USEtox follows for deriving the freshwater ecotoxicity effect factor, we reviewed the user manuals for Ver 1.01 [11], the official model publications [12–15], and 2 related book chapters [3,16]. Furthermore, 2 case studies were designed to analyze the influence of input data source on effect factor results and to compare official USEtox effect factors with ecotoxicity effect indicators used in the context of the European chemicals regulation, respectively. The USEtox model aims to quantify potential ecotoxicity impacts from any studied product system and to help identify the 10 to 20 most contributing chemicals out of the potentially thousands of chemicals emitted to air, water, and soil from a product life cycle inventory. The analysis of a dozen recent food, housing, and mobility LCAs has shown that in most cases few metals and a few organic chemicals (often pesticides) are identified as the most contributing chemicals [18,19]. Because the USEtox model is specifically suited for organic chemicals, we have selected chemicals that are organic and for which the input data to run the model are easily retrievable and of high quality. By high quality we mean that all the data have been peer-reviewed and supposedly validated by a competent authority (e.g., the European Food Safety Authority [EFSA]) for use in an ERA. The EFSA produces scientific opinions and advice for policy support on food and feed safety, nutrition, animal health and welfare, plant protection, and plant health. In this context, the EFSA performs risk assessments of pesticides and thorough assessments of all data needed for ERAs including physicochemical substance properties, and data relevant for environmental fate and ecotoxicity. Related EFSA reports are available on the authority's website (http://efsa.europa.eu/efsajournal). Draft assessment reports are prepared by the reporting Member States, which are then peer-reviewed by the EFSA, resulting in the Conclusions on Pesticides. The observations we present on pesticides should be equally applicable to a wider range of organic chemicals, although the risk assessment procedure differs between industrial chemicals and pesticides.

We therefore defined 2 sets of chemical substances—all being active ingredients of plant protection products currently used on the European market—because pesticide active ingredients are designed to be toxic to certain target organisms, pesticides are widely applied in European Union food production and hence represent important chemical flows toward ecosystems to be considered in an LCA or PEF/OEF study, and peer-reviewed risk assessment reports from the EFSA are publicly available for many pesticides.

However, the observations described in the present study also apply to organic substances in general. A first set of the 15 most recently approved pesticides was compiled from the European Union Pesticides Database [20]. From this list, 6 pesticides were kept for further analysis because they had an available EFSA Conclusions on Pesticides, were included in the USEtox organic substances database, and had a complete inventory of physicochemical and ecotoxicity data in the EFSA reports. For the 6 pesticides, EFSA Conclusions on Pesticides data were extracted and compared with corresponding data in the USEtox organic substances database. To strengthen the observations made on this set of 6 pesticides, a second set of 34 pesticides was compiled from the European Union Pesticide Database using the following search criteria: 1) approved for the European Union market; 2) classified as *aquatic chronic 1* [21] (i.e., nonrapidly degradable with chronic no-observable-effect concentration [NOEC] ≤ 0.1 mg/L, or rapidly biodegradable and with chronic NOEC ≤ 0.01 mg/L); and 3) fulfilling either persistent or bioaccumulative criteria.

Of these 34 pesticides, 26 were present in USEtox and hence allowed a comparison of ecotoxicity effect factors, expressed as HC50, based on applying different underlying substance input data sources, namely: the USEtox organic substances databases 1.01 containing EFs calculated with USEtox (http://usetox.org/current-version); the EFSA database reports compilation on ecotoxicological properties of active substances and plant protection products (http://efsa.europa.eu/supporting/pub/364e; this database, hereafter referred to as the EFSA database, contains reports with data on aquatic and terrestrial ecotoxicity representing the agreed endpoints to be used for pesticide ERAs in the European Union); the Pesticide Properties Database (PPDB; http://sitem.herts.ac.uk/aeru/iupac/), which among data from various sources of different quality and reliability includes data originating from the EFSA Conclusions on Pesticides [22]; and the Aquatic Impact Indicator Database (AiiDA), which provides precalculated HC50 values that could potentially be used as input for deriving effect factors, but that would need to be extracted manually for each considered chemical (http://aiida.tools4env.com) [23].

RESULTS AND DISCUSSION

USEtox effect factor: Description of the approach and critical discussion

The freshwater ecotoxicity effect factor in USEtox represents the potential toxicity of individual chemical substances to freshwater aquatic ecosystems. The equation to calculate substance-specific effect factors in USEtox is EF = 0.5/HC50, where HC50 is the hazardous concentration at which 50% of the species tested are exposed above their chronic median lethal (or effect) concentration (L[E]C50). In USEtox, log HC50 is derived from first taking the geometric mean across $i \in$ available chronic L(E)C50 data points per species and then taking the arithmetic mean of the logarithmic values for all $j \in \{1, \ldots, n\}$ species-specific chronic L(E)C50 geometric mean values as in Equation 1 (L stands for lethal effect; E for other type of effect, both affecting 50% of the tested organisms)

$$log_{10}\mathrm{HC50} = \frac{1}{n}\sum_{j=1}^{n} log_{10}\left[\left(\prod_{i=1}^{m}\mathrm{L(E)C50}_{i,j}\right)^{\frac{1}{m}}\right] = \frac{1}{n}\sum_{j=1}^{n}\frac{1}{m}\sum_{i=1}^{m} log_{10}\mathrm{L(E)C50}_{i,j} \quad (1)$$

In a concentration–effect graph with the concentration along the *x*-axis and the effect on the *y*-axis, the effect factor corresponds to the slope of a straight line connecting the point (HC50, 0.5) with the origin (0, 0) [16]. This approach corresponds to assuming linearity between the concentration and the response (percentage of affected species). The slope is, therefore, used as an indicator of a chemical's ecotoxicity potency; that is, the more ecotoxic the chemical, the steeper the slope and hence the higher effect factor. Assuming linearity between concentration and effect is a straightforward way to attribute an ecotoxicity score to the emitted mass of a chemical, which is the only information available in a life cycle inventory. This assumption thereby accommodates the facts that little is typically known about the shape of all the chemical- and species-specific concentration–effect curves at very low concentrations that are relevant for environmental exposure, and that in LCA we normally have no information about the background concentration of chemicals in the environmental compartments that receive the emission from the product system along its life cycle.

The HC50 is chemical specific and based on all available aquatic ecotoxicity data. Chronic L(E)C50 data are preferred over acute L(E)C50 data, but an extrapolation factor of 2 is suggested to convert acute data to chronic data for chemicals for which insufficient or no chronic aquatic ecotoxicity data are available. This factor is based on an analysis of 92 compounds (18 organics, 22 inorganics, 54 pesticides) [24]. For chemicals not already included in USEtox and for which the user has to calculate a HC50 value, guidance is provided on page 17 of the USEtox Ver 1.01 user manual [11]. For calculating effect factors, USEtox has so far relied on 2 ecotoxicological data sources providing the underlying acute and chronic L(E)C50 data. The first source contains acute L(E)C50 from the RIVM e-toxBase [25], and the second source contains mainly acute and chronic data compiled by Payet [26] for the Assessment of the Mean Impact (AMI) method. The rationale for using in USEtox the arithmetic mean of all species-specific geometric means of the log of L(E)C50 values to derive the HC50 as well as the linear relationship between concentration and response has been documented [3,11–16] and relies on several key points.

In the following sections, we discuss the justifications provided by USEtox for choosing this approach to derive chemical effect factors. Paragraphs within quotation marks refer to text copied from USEtox publications and manuals.

> "A HC50 based on L(E)C50 values represents a best estimate, while using a metric like the risk assessment related PNEC [predicted no-effect concentration] would introduce significant levels of conservatism due to the use of the NOEC and introducing assessment factors by regulatory agencies to set PNECs" [9,12,14,16].

The HC50 is not by definition a best estimate for comparing chemical ecotoxicity, but represents an average ecotoxicity-related pressure on the entire exposed ecosystem. It is the least sensitive value regarding inclusion of additional data above or below the HC50; that is, the HC50 is the value on a species sensitivity distribution (SSD) curve at which statistical variability is minimized. Variability is also minimized in regulatory approaches based on establishing the PNEC (and hence representing conservative rather than average estimates), which includes safety factors applied to the lowest valid ecotoxicity values (EC50 or NOEC), by taking into account the number of species and trophic levels tested, and the type of tests (acute or chronic) [27,28]. However, the NOEC or LOEC values

do not carry any conservatism (they are the actual outcomes of an experimental test even if the underlying statistic to derive the NOEC/LOEC is questionable), and these values could be used to present another way to derive the effect factor in PEF/OEF.

> "The HC50 is more robust as (a) it is derived from all available data and hence less sensitive to new data points than risk assessment metrics (i.e. PNECs) that only use the lowest available and validated ecotoxicity value [9,14], and (b) it is the point on the concentration-response curve associated with the less statistical uncertainty than other toxicity-based estimates like the HC5 or the predicted no effect concentration (PNEC), where this uncertainty can be estimated and used in calculations of the uncertainty accompanying the overall freshwater ecotoxicity characterization factor" [12,14,15].

The HC50 is indeed more robust and less affected by the introduction of new ecotoxicity data than other effect indicators such as the lowest chronic test result, PNEC, or HC5. However, the availability of new or additional data might potentially suggest that one or more ecosystem taxa are more sensitive to a particular substance. Such values impact the lower extreme of the species sensitivity relationship more than a central value like HC50. Such new information may be ecologically important, because in cases where it might indicate that not just the tested species but the whole trophic level is impacted, it is the full ecosystem structure and functioning that is impacted.

In risk assessment decisions, all data are also used. The fact that the lowest value is chosen on which to base future decisions does not mean the other data do not contribute to the decision and provide support for that value. The lowest value can, however, potentially change a great deal as new data are developed, and this usually increases ecological relevance and protection. Thus, using the lowest available toxicity value will only change when a more sensitive species is tested. In regulatory assessment, in this context, it is not the actual lowest value of a set of toxicological data that is used, but the lowest *validated* data, meeting strict data quality criteria covering relevance, reliability, and adequacy. Finally, as new data are generated, HC50 values might also change (to a lesser extent though, as the effect will be moderated by the bulk of the data) [29,30].

> "LCA commonly uses averages or best estimates and assumes linear relationships between inventory flows (reported in mass) and environmental responses to estimate impacts of processes on human health, ecosystem quality, and resources [3], and additivity of ecotoxicity can readily be incorporated into LCA with a linear concentration-response model" [9].

This assumption (linearity) ignores the possible existence of a threshold below which the chemical has no potential ecotoxicity effects on aquatic ecosystems and ascribes an ecotoxicity effect to any amount of chemical emitted to the environment proportional to the mass emitted. In reality, the concentration–response is usually not linear, and threshold concentrations below which no effects are observed for individual species or species groups can be established for different chemicals [31–33]. The assumption is, however, needed for 2 reasons. First, the life cycle inventory reports emissions in mass related to the functional unit (i.e., function on which product systems are ultimately compared) and brings no information about the total emission over time from each process to the receiving environments (e.g., small or large river, sea, or soil), permitting one to calculate an exposure expressed in concentration, which would be needed to judge whether a potential low threshold is exceeded or not. Second, the exceedance of thresholds also depends on the background concentration of the chemical in the exposed environments, and this information is usually not possible to attain for all processes involved in a considered product life cycle. The use of a linear concentration–response curve corresponds to the assumption of toxicity additivity, meaning that even if thresholds exist for individual chemicals, and they are not exceeded for any chemical in a concrete exposure situation, with the presence of a multitude of chemicals at the same time in the same compartment, toxicity additivity may still lead to an effect (cocktail or combined toxicity effect). Inherent in the linearity assumption is that any quantity of a chemical emitted will contribute to a potential ecotoxicity impact. This linearity assumption, however, clearly overestimates toxicity in the lower part of the S-curve and underestimates the toxicity in the upper part; but because HC50 is based on the slope between 0 and 50% effect, this under- or overestimation is of little consequence.

Assuming additivity of ecotoxicity effects in LCA is a pragmatic solution to allow the calculation of one single score for a full product LCA in which hundreds of chemicals may be emitted. The reality is of course more complex; and while chemicals present at the same time in the same exposure medium can exert combined effects in an additive way, synergistic or antagonistic effects are also possible [34–36]. Additive combined effects are mainly elicited by coexposure to chemicals acting with a similar toxic mode of action (TMoA), as chemicals with different TMoAs are theoretically not believed to contribute to the combined effect, if they are present below their individual threshold concentrations [35]. There are thus large numbers of chemicals that may not contribute to combined toxicity, although in ERA, combination effects cannot be ruled out [37]. On the other hand, the life cycle emissions from a product system interact not just with other emissions from the same product system but also with other chemicals that are present in the environment and that originate from other human activities with no relation to the studied life cycle. It is therefore difficult to know the nature of all occurring chemical interactions, and ecotoxicity additivity has been assumed as a straightforward proxy solution [27,28].

Comparison of ecotoxicity effect approaches in LCA and in chemical risk assessment

The USEtox approach to characterize potential freshwater ecotoxicity of chemicals—like other methods of ecotoxicity characterization in LCA—differs from approaches used in European chemical safety assessments and regulatory schemes (REACH, Classification and Labelling, Plant Protection Products regulation) [10,22,38]. General differences and similarities between LCA and risk assessment have been addressed elsewhere [39–43]. In short, regulatory ERA for industrial chemicals is performed one chemical at a time, and requires the estimation of a predicted environmental concentration in a specific compartment (river water, sediment, or soil) using actual usage of the substance (tonnage, emission scenario) and the estimation of a PNEC (using standard ecotoxicological tests). If the predicted exposure concentration/PNEC ratio is below 1, the conclusion can be drawn that the chemical is of low or no concern. For pesticides, the procedure is slightly different. A standard set of ecotoxicity tests is provided according to the legal data requirements. Based on these, a so-called regulatory acceptable concentration (RAC) is derived for different

organism groups. The lowest RAC is then used for the risk assessment, putting it into context with the predicted exposure, and usually modeled using FOCUS scenarios. If the ratio of predicted concentration/RAC is less than 1, there is low concern. If the ratio is close to or greater than 1, then more refined higher-tier testing is an option. For pesticides, it has to be decided whether slight population effects followed by recovery are considered acceptable or not [44]. Pharmaceuticals and biocides also have their specificities, but all are assessed using the same principle of exposure estimate over toxicity indicator. For all categories of chemicals, the toxicity indicator is established to protect the most sensitive species/trophic level.

The present study, in contrast, focuses on differences in characterizing chemical ecotoxicity in the context of PEF/OEF. Table 1 summarizes the main differences between the general LCA (e.g., USEtox) approach and the general approach used in European Union chemical regulation for characterizing chemical ecotoxicity (presenting succinctly the approach for industrial chemicals and pesticides).

Although USEtox relies on all available L(E)C50 data, as explained, ecotoxicological endpoints including EC10, NOEC, and LOEC, which are used to report chronic toxicity test results, are presently not considered. In contrast, in risk assessment or labeling approaches, all data available for selected endpoints for a chemical are used to understand the impacts of short-term and long-term exposures in support of any final conclusion. For long-term environmental exposures, there is a focus on the most sensitive species from at least 3 trophic levels representative of essential ecosystem functions to be protected. These trophic levels refer to producers (photosynthetic organisms like algae and plants), primary consumers (herbivores like *Daphnia* species), and secondary consumers (predators like carnivorous fish species). If one of these trophic levels disappears from the ecological food web, the ecosystem might collapse. Usually, the lowest ecotoxicity value from these trophic levels is used per chemical to represent its ecotoxicity and to protect the entire ecosystem. Alternatively, when ecotoxicity values are available for more than 10 exposed species, a cumulative SSD can be used to derive the specific endpoint, often HC5 in ERA, where the median HC5 is the concentration that with 50% certainty is below other ecotoxicity values (e.g., EC50s) for 95% of the species tested [32,33]. In regulatory risk assessment and depending on the type of data available (acute, chronic, controlled mesocosm studies), safety factors are added. The lowest validated endpoint is also used to assess hazard criteria (persistence, bioaccumulation, and toxicity [PBT]) for priority setting and for deriving the classification and labeling of chemicals. The exact procedure used to classify chemicals is complex, as all tests considered must be scrutinized to ensure their reliability, accuracy, and adequacy. There are also important subtleties on how to deal with ecotoxicity data used for ERA and classification and labeling, which will not be further discussed in the context of the present study. In summary, USEtox uses an average of all species-specific, aggregated EC50 values, whereas chemical risk assessment, PBT assessment, priority setting, and classification and labeling use one of the lowest validated endpoints (e.g., EC50, NOEC, HC5).

Results of applying the USEtox approach in the PEF/OEF context

Following the USEtox recommended steps for deriving HC50 (see Equation 1), we calculated the HC50 and effect

Table 1. Different approaches to derive an effect indicator for chemicals' ecotoxicity in EU chemical regulation (REACH and Plant Protection Products) and USEtox

USEtox	European Union chemical regulation: REACH	European Union chemical regulation: PPP
Principle: Average toxicity from all toxicity tests	Principle: Lowest (valid and relevant) most sensitive trophic level	Principle: Lowest (valid and relevant) most sensitive trophic level
Gather existing experimental EC50 data for the chemical of interest; EC10, EC20, NOEC, and LOEC are not used.	Collect all data and assign a Klimisch score (K1: reliable without restriction; K2: reliable with restriction; K3: unreliable. . .) according to guidelines.	Ecotoxicity data for a predefined set of aquatic organisms are provided by the applicant according to the legal data requirements and available guidance. This includes EC50, EC10, or NOEC values.
Specify for every EC50 value whether it is chronic or acute. If acute, extrapolate to chronic by dividing by 2.	Use only K1 and K2 and select the lowest for each trophic leve (i.e., algae, invertebrate, fish, etc.).	At tier 1, for each trophic level (i.e., algae/plants, invertebrates [e.g., crustaceans/insects), vertebrates [fish, amphibians]), the RAC is calculated using the lowest endpoint (EC50 for acute, EC10/NOEC for chronic) and an SF. In tier 1 an SF of 100 is applied to acute data and of 10 to chronic data.
Calculate the geometric mean EC50 (mg/L) of the data available for each individualspecies.	Take the lowest of the 3 trophic levels. In some circumstances, it is possible to calculate the geometric mean of multiple comparable toxicity values for the same species and the same endpoint.	For higher-tier risk assessment, geometric means within a taxonomic group (arthropods, vertebrates, algae, etc..) are calculated if more data than from standard data requirements are available. Then the lowest geometric mean is used for the risk assessment with the same SF.
Take the log of the geometric means = log EC50 (mg/L). Calculate the arithmetic average of the log values.		
The effect factor is then calculated by dividing 0.5 by the inverse of the avlog EC50.	Apply SF to count for intra- and interspecies variability, and laboratory to field extrapolation (i.e., SF of 1000 if acute tests, 10 if chronic tests with different species) representing 3 trophic levels.	In data-rich situations, species sensitivity distribution HC5 values can be calculated and used to derive the RAC applying lower SFs.
This final result gives the effect factor that characterizes chemical toxicity.	The result gives the predicted no-effect concentration used in ERA.	The lowest derived RAC is used in the ERA that is protective for all organism groups.

REACH = Registration, Evaluation, Authorisation, and Restriction of Chemicals; PPP = plant protection product; EC50 = median effective concentration; EC10 = 10% effective concentration; EC20 = 20% effective concentration; NOEC = no-observed-effect concentration; LOEC lowest-observed-effect concentration; RAC = regulatory acceptable concentration; SF = safety factor; ERA = environmental risk assessment.

Table 2. The USEtox approach applied to the ecotoxicological endpoints of the pesticide clomazone (CAS 81777-89-1) available in the EFSA Conclusions on Pesticides report[a]

Group	Species	Test No.	Timescale	Acute or Chronic	Endpoint	Material tested	Toxicity (mg/L)	Present in other pesticide DB	Reason for not selecting for HC50 calculation	Extrap. fact	Toxicity Extrapolation (mg/l)	Geometric mean of individual species (mg/l)	Log of geometric means (mg/l)	Average of log values = logHC50 (mg/l)	HC50 (mg/l)
Fish															
	Oncorhynchus mykiss	1	96 h (static)	Acute	LC50	Active substance	15.5	In PPDB, EFSA lowest	→	2	7.750	7.750	0.889	0.413	2.59
					NOEC		1		NOEC value						
		2	96 h (static)	Acute	LC50	Formulation (exp. as a.s)	187.9		Formulation						
					NOEC		142.8								
		3	96 h (static)	Acute	NOEC	Metabolite 1 (exp. as a.s)	20		Metabolite						
		4	96 h (static)	Acute	NOEC	Metabolite 2 (exp. as a.s)	20		Metabolite						
		5	21 d (flow-through)	Chronic	NOEC (sublethal)	Active substance	2.3	In PPDB, EFSA lowest	NOEC value						
Invertebrates (arthropode, mollusca)															
	Crassostrea virginica	6	96 h (flow-through)	Acute	EC50 (reduction in shell deposition)	Active substance	5.3		Marine species						
					NOEC (reduction in shell deposition)		2.75								
	Daphnia magna	7	48 h (static)	Acute	EC50 (immobility)	Active substance	12.7	In PPDB	→	2	6.350	6.350	0.803		
		8	21 d (flow-through)	Sub-chronic	NOEC (immobility)	Active substance	4.38		NOEC value						
		9	21 d (flow-through)	Sub-chronic	NOEC (reproduction)	Active substance	2.2	In PPDB, EFSA lowest	NOEC value						
		10	48 h (static)	Acute	NOEC (immobility)	Metabolite 1 (exp. as a.s)	5		Metabolite						
		11	48 h (static)	Acute	NOEC (immobility)	Metabolite 2 (exp. as a.s)	5		Metabolite						
		12	48 h (static)	Acute	EC50 (immobility)	Formulation (exp. as a.s)	155.7		Formulation						
					NOEC (immobility)		79.3								
	Mysidopsis bahia	13	96 h (flow-through)	Acute	EC50 (immobility)	Active substance	0.57	in PPDB, marine	Marine species						
Algae															
	Navicula pelliculosa	14	120 h (static)	Acute	EbC50	Active substance	0.136	In PPDB, EFSA lowest	→	2	0.068	0.068	–1.167		
					ErC50		> 0.185		Preferably ErC50,						
					NOEC		0.05	in PPDB	but ErC50 is >						
	Pseudokirchneriella subcapitata (= selenatrum capri)	15	72 h (static)	Acute	EbC50	Active substance	2		Preferably ErC50						
					ErC50		4.1		→	2	2.050	2.050	0.312		
					NOEC		0.5								
		16	72 h (static)	chronic	NOEC	Metabolite 1 (exp. as a.s)	3		Metabolite						
		17	72 h (static)	chronic	NOEC	Metabolite 2	3		Metabolite						

(*continued*)

Table 2. (*Continued*)

Group	Species	Test No.	Timescale	Acute or Chronic	Endpoint	Material tested	Toxicity (mg/L)	Present in other pesticide DB	Reason for not selecting for HC50 calculation	Extrap. fact	Toxicity Extrapolation (mg/l)	Geometric mean of individual species (mg/l)	Log of geometric means (mg/l)	Average of log values = logHC50 (mg/l)	HC50 (mg/l)
						(exp. as a.s)									
	Pseudokirchneriella subcapitata (= selenatrum capri)	18	72 h (static)	Acute	EbC50	Formulation (exp. as a.s)	53.3		Formulation						
					ErC50		116.1								
					NOEC		29.8								
Macrophyte															
	Lemna gibba	19	7 d (static)	Acute	EC50, growth	Active substance	34	In PPDB	→	2	17.000	17.000	1.230		
		20	7 d (static)	Acute	ErC50	Formulation (exp. as a.s)	357		Formulation						
				Acute	EbC50		138								
				Acute	NOEC		106								
	Lemna minor	21	7 d (static)	Acute	EbC50	Formulation (exp. as a.s)	435		Formulation						
				Acute	ErC50		1127								
				Acute	EC50, biomass fronds		333								

[a]The equivalent table for the remaining 5 pesticides can be found in the Supplemental Data (Table S2).

DB = database; Extrap Fact = extrapolation factor; HC50 = hazard concentration; LC50 = median lethal concentration; NOEC = no-observable-effect concentration; EC50 = median effect concentration; EbC50 = median effect concentration, biomass; ErC50 = median effect concentration, growth rate; exp as a.s. = expressed as active substance; PPDB = Pesticide Properties Database [17]; European Food Safety Authority (EFSA) lowest = agreed endpoint to be used in environmental risk assessment (http://www.efsa.europa.eu/en/supporting/pub/364e).

factor values for the 6 selected pesticides using ecotoxicological test results for algae, aquatic plants, invertebrates, and fish as reported in the EFSA database. Table 2 summarizes the results of the calculation for the pesticide clomazone (CAS 81777-89-1), while details for the other 5 pesticides (namely, fludioxonil [CAS 131341-86-1], halosulfuron methyl [CAS 100784-20-1], prosulfocarb [CAS 52888-80-9]; teflubenzuron [CAS 83121-18-0], and fenbutatin oxide [CAS 13356-08-6]) as well as a link to the corresponding EFSA Conclusions on Pesticides are available in the Supplemental Data (Table S1). From Table 2 (and Supplemental Data, Table S1), we made the following 5 observations.

First, of 21 ecotoxicological endpoints for 9 species available in the EFSA conclusion on clomazone, 11 tests are excluded from the analysis, because they were performed either on a formulation containing clomazone or on metabolites and, hence, these data do not represent the ecotoxicity of clomazone. Furthermore, 2 tests on marine species are excluded, as the effect factor refers to freshwater ecosystems.

Second, 3 chronic tests on 2 organisms (one fish species and one *Daphnia* species) are excluded, because values are expressed as NOEC, whereas USEtox currently only uses L(E)C50 data. In acute ecotoxicity tests, L(E)C50 values are the most commonly reported endpoints; however, for chronic ecotoxicity tests, typically EC10, NOEC, or LOEC values are reported. This results in disregarding potentially valuable chronic data for chemical ecotoxicity characterization when only considering L(E)C50. As a consequence, only 5 acute L(E)C50 values can be used for the final calculation of the HC50 in USEtox for our clomazone case study.

Third, clear rules on selecting and interpreting ecotoxicological tests are lacking within the current USEtox HC50 calculation procedure. For example, is a 7-d exposure duration for a macrophyte (e.g., *Lemna gibba*) an acute or a chronic exposure? Should biomass or growth rate data be used on macrophytes (analogous to algae or in contrast)? Should an EC50 value from an algae test be considered as acute, knowing that the cells divide every 20 to 30 min and thus go through a multicycle reproduction process during the 72 h of the test? Depending on the answer, within USEtox, a factor of 2 will be used to extrapolate from acute to chronic. A response to these questions can be found in the literature, but this requires effort, relevant ecotoxicological expertise, and consensus by experts to ensure that similar endpoints are handled consistently for all materials going forward [31,45–47]. A compiled overview of acute and chronic exposure durations for approximately 550 aquatic ecosystem species, including their trophic level information, is given in Table S2 of Müller et al. [48]; but this list should be extended and included in any upcoming USEtox documentation along with additional guidance on how to properly process any related ecotoxicity test data.

Fourth, the selection of correct input data for ecotoxicity effect factors is also problematic for the average LCA or PEF/OEF practitioner. Within USEtox, detailed guidance is currently lacking but will be included in the upcoming official documentation (http://usetox.org/documentation) on how to select the appropriate data from the literature to derive HC50 values. Without extensive guidance combined with ecotoxicological background knowledge, a practitioner may use all available data, including those that should potentially be rejected as not being reliable and/or as toxicologically invalid (e.g., high mortality in the control, test item concentration not measured or not appropriately maintained). The reason for building criteria that may exclude results of a test are numerous, and specific guidance is provided in the relevant European

Table 3. Comparison of the HC50 values from the USEtox, the AiiDA, and the present study for 6 pesticides[a]

Name	Database	HC50 (mg/L) chronic	Total tests	Total no. of tests on active substance	No. of tests that can be used according to USEtox	Number of tests extrapolated (Acute to chronic)	Total no. species tested	Number trophic levels	Total phylum
Clomazone	USEtox	2.5	ns	ns	ns	ns	ns	ns	ns
	EFSA DB	2.6	21	10	5	5	9	5	ns
	AiiDA	4.7	41	ns	ns	29	20	ns	9
Fludioxonil	USEtox	0.26	ns	ns	ns	ns	ns	ns	ns
	EFSA DB	0.16	25	8	3	3	10	5	ns
	AiiDA	0.88	37	ns	ns	30	16	ns	6
Halosulfuron methyl	USEtox	0.17	ns	ns	ns	ns	ns	ns	ns
	EFSA DB	0.0008	29	14	3	3	14	5	ns
	AiiDA	0.42	29	ns	ns	24	14	ns	7
Prosulfocarb	USEtox	0.55	ns	ns	ns	ns	11	3	ns
	EFSA DB	0.27	11	8	5	5	6	5	ns
	AiiDA	0.32	6	ns	ns	3	4	ns	4
Teflubenzuron	USEtox	4E-02	ns	ns	ns	ns	3	2	ns
	EFSA DB	1E-03	15	7	1	1	6	4	ns
	AiiDA	7E-03	7	ns	ns	6	4	ns	1
Fenbutatin	USEtox	9E-03	ns	ns	ns	ns	11	3	ns
	EFSA DB	2E-03	17	11	3	3	8	4	ns
	AiiDA	2E-01	56	ns	ns	45	27	ns	7

[a]Numbers of ecotoxicological tests, species, and phylum used for the calculation of the effect factor are reported when available.
HC50 = hazard concentration; AiiDA = Aquatic Impact Indicator Database; EFSA DB = European Food Safety Authority database; ns = not specified.

Union chemicals regulation guidelines to avoid the possibility of assessing chemical substances with invalid endpoints. In principle, each test should be assessed for its relevance, reliability, and adequacy. For substances currently included in USEtox, effect factors have been derived from a database on which a first level of scrutiny was applied; however, not all available endpoints might be fit-for-purpose. The current lack of specific guidance may lead to inconsistency in the selection of ecotoxicity data and thereby affect the calculation of effect factors.

Fifth, although for our case study all data were extracted from the EFSA database, to which a high level of review and scrutiny has already been applied, the interpretation and selection of the correct endpoint for the derivation of the HC50 was nevertheless complex and time consuming. Applying this approach to thousands of chemicals, as usually reported in PEF/OEF studies, not only is a difficult task, but will likely lead to varying HC50 estimations depending on the level of expertise of the practitioner performing the work. Table 3 shows that the compiled HC50 for the 6 case study pesticides can vary by up to 3 orders of magnitude as a function of which underlying data source is applied (i.e., HC50 reported in USEtox, precompiled HC50 from the AiiDA database, or HC50 based on EFSA data). It can also be seen that each estimation method has used a different number of tests, species, and trophic levels. Information on individual ecotoxicological tests are either not available (USEtox) or not specified (AiiDA), making it currently impossible for users to verify which data points were taken into account in the calculation of the final HC50. Hence, this information should be made available in USEtox for any chemical included in the future to provide maximum transparency and reproducibility of ecotoxicity effect factors for PEF/OEF and LCA practitioners.

Comparison of USEtox HC50 with values used for risk assessment

The initial investigation on 6 pesticides has been complemented with the additional selection of 26 pesticides (being also very toxic, persistent, and/or bioaccumulative). The USEtox HC50 values are also compared for the additional set of pesticides with the lowest validated chronic toxicity value for

Table 4. Comparison of the USEtox average toxicity (HC50; mg/L) and the lowest agreed toxicity value for aquatic toxicity for algae, fish, invertebrate, and aquatic plants retained by the European Food Safety Authority for performing aquatic environmental risk assessment[a]

			Chronic validated endpoints (mg/L)				
Name	CAS	USEtox_avEC50 (mg/L)	NOEC fish[b]	NOEC Daphnia[b]	LC50 algae[1]	Plant EC50	Ratio: HC50 USEtox/Lowest chronic (rounded number)
Etofenprox	80844-07-1	2.70	0.0032	0.000054	>0.15	na	50 074
Pirimicarb	23103-98-2	16.28	<18	0.0009	140	na	18 093
Halosulfuron methyl	100784-20-1	0.17	34	>6.9	0.0053	0.0005	845
Teflubenzuron	83121-18-0	0.04	0.0186	0.000062	0.02	na	720
Imazamox	114311-32-9	5.37	>122	137	0.011	0.014	488
Bifenthrin	82657-04-3	0.00036	0.000012	0.00000095	8	na	381
Chlorotoluron	15545-48-9	7.24	0.4	16.7	0.024	0.041	302
Tri-allate	2303-17-5	0.60	0.038	0.013	0.0022	2.6	274
Flufenacet	142459-58-3	0.26	0.2	3.26	0.00204	0.005	130
Metribuzin	21087-64-9	2.07	5.6	0.32	0.02	0.011	103
Cyprodinil	121552-61-2	0.67	0.083	0.0088	2.6	7.74	76
Triasulfuron	82097-50-5	2.40	36.6	10	0.035	0.000071	69
Metsulfuron-methyl	74223-64-6	1.26	68	150	NOEC 0.02	0.00039	63
Cyproconazole	94361-06-5	5.76	0.65	0.29	0.099	0.062	58
Fludioxonil	131341-86-1	0.26	0.04	0.005	0.024	0.95	52
Lenacil	2164-08-1	0.33	2.3	0.48	0.0077	0.022	47
Oxadiazon	19666-30-9	0.04	0.00088	0.03	0.004	0.060	43
Tebuconazole	107534-96-3	0.38	0.012	0.01	1.96	0.147	32
Prosulfuron	94125-34-5	0.25	5.8	148	0.0089	0.00129	28
Clomazone	81777-89-1	2.49	2.3	2.2	0.136	37	18
Propiconazole	60207-90-1	1.15	0.068	0.31	0.093	4.12	17
Esfenvalerate	66230-04-4	0.0008	0.00025	0.000052	0.0065	na	15
Isoproturon	34123-59-6	0.17	1	0.12	0.013	0.034	13
Prosulfocarb	52888-80-9	0.55	0.31	0.045	0.049	0.72	12
Pendimethalin	40487-42-1	0.05	0.006	0.0145	0.004	0.025	11
Diquat (dibromide)	2764-72-9	0.12	0.12	0.125	0.011	na	11
Aclonifen	74070-46-5	0.04	0.005	0.016	0.47	0.009	8
Fenbutatin oxide	13356-08-6	0.01	0.00127	0.016	>0.0036	na	7
Ziram	137-30-4	0.06	0.189	0.01	0.066	na	6
Prochloraz	67747-09-5	0.11	0.049	EC50 4.3	>0.0055	0.174	2
Flumetralin	62924-70-3	0.02	EC50 0.023	EC50 >0.16	0.85	0.18	1
lambda-Cyhalothrin	91465-08-6	0.00003	0.00025	0.3	>0.3	na	0.1

[a]Data were extracted from the Pesticide Properties Database (PPDB).
EC50 = median effective concentration; NOEC = no-observed-effect concentration; LC50 = median lethal concentration; na = not available; 1 = unless otherwise specified.

algae, aquatic plants, *Daphnia*, and fish extracted from the PPDB (Table 4; Supplemental Data, Table S2). Ratios between the HC50 based on USEtox and the lowest available value from the PPDB ranged from 0.14 to >50 000, thus differing by up to 4 orders of magnitude. For 26 of the total set of 32 case study pesticides, the ratio between the values from the 2 sources is greater than 10. Note that in most cases NOEC or LOEC values represent the lowest endpoints from a risk assessment perspective, while USEtox HC50 values are based mainly on (estimated) chronic values extrapolated from acute EC50 (with a factor of 2), leading to some expected inherent difference. This extrapolation factor of 2 appears to be low relative to similar factors published in the peer-reviewed literature [49,50], and it is questionable to apply it in the same way to thousands of

Table 5. Comparison of several options for deriving the effect factor to be used in assessing the toxic impact of chemical in life cycle assessment (LCA) via the USEtox model

	Pros	Cons	Feasibility
HC50[a]	Statistically more robust Less influenced by extreme values Recommended indicator from USEtox consensus workshop Lends itself to damage modeling	Chemical toxicity ranking different from other schemes (CLP/GHS) used internationally Some chemicals classified very toxic according to worldwide regulatory schemes may be considered less toxic Because of absence of reported EC50 for chronic toxicity (usually expressed as NOEC or LOEC), the majority of chronic toxicity data are not used to derived the HC50	Difficult: All toxicity data need to be collected, interpreted correctly, and finally processed to calculate the HC50 Requires considerable ecotoxicology expertise
HC5	Statistical measure that takes into account all available data Better accounts for more sensitive species than HC50 Lends itself to damage modeling	Higher variability The result depends on the number of underlying data points and the model chosen to calculate the HC5	Difficult: All toxicity data need to be collected, interpreted correctly, and finally processed to calculate the HC5 Requires considerable ecotoxicology expertise
PNEC[b]	Used in most worldwide regulatory schemes to assess chemical safety Available for > thousands of chemicals in REACH and other chemical databases Extrapolation factors are used to compensate lack of ecotoxicological data	PNEC can be derived from NOEC, which is a statistically weak toxicity endpoint (values influenced by the test design) Data-rich chemicals are penalized (the more a chemical is tested, the more likely a lower value will be found)	Easy to extract or to calculate from existing databases (e.g., REACH) or Pesticide Properties Database Only limited expertise required (value often already calculated by experts)
Lowest validated endpoint (lowest EC50 or NOEC, or EC10) across at least 3 trophic levels[c]	Represent the toxicity of concern of a chemical (to which trophic level the chemical is truly toxic) In line with chemical toxicity classification schemes (CLP/GHS) that used the lowest validated endpoint Toxicity ranking in LCA is similar to toxicity ranking in regulatory schemes	Data-rich chemicals are penalized (the more a chemical is tested, more likely a lower value will be found) If based on NOEC or LOEC, statistically weak toxicity endpoint (values influenced by the test design)	Easy to extract or to calculate from existing databases (e.g., REACH) or Pesticides Properties Database Only limited expertise required (value often already calculated by experts)
Weighted average of lowest toxicity for 3 trophic levels[d]	All the substances are assessed on the same set of species, avoiding a situation in which the substances are in some cases evaluated with a wide number of data points and in others with few data points Ensuring the 3 basic aquatic trophic levels are covered Accounting for differences in the recovery capability of the different trophic levels, giving a different weight to fast recovering (such as algae) and slow recovering (such as fish)	Weighting set to be tested and further validated Most sensitive species not accounted for Never applied in LCA before	Easy to extract or to calculate from existing databases (e.g., REACH) or Pesticides Properties Database Only limited expertise required (value often already calculated by experts)

[a]Hauschild et al. [4]; Rosenbaum et al. [5].
[b]European Commission [10]; European Commission [38]; European Food Safety Authority [44].
[c]European Commission [21].
[d]Finizio et al. [53].
HC50 = hazard concentration; CLP/GHS = Classification, Labeling, and Packaging/Globally Harmonized Systems; REACH = Registration, Evaluation, Authorization, and Restriction of Chemicals; PNEC = predicted-no-effect concentration; NOEC = no-observable-effect concentration; EC50 = median effective concentration.

chemicals disregarding their different properties and modes of action.

Moving from the USEtox average approach to an approach based on the lowest chronic toxicity as a potential alternative for PEF/OEF might have a large influence on the EF and might potentially also affect any substance ranking in terms of ecotoxicity. Not only does the ecotoxicity ranking of the selected pesticides change depending on the method used to derive the effect factor, but the absolute ratio between the values for some of those pesticides might also change.

In an LCA context, chemicals are compared with each other as practitioners seek to confront impacts of different sets of chemicals associated with a product system life cycle and ideally identify those chemicals (or products) with a lower impact on the environment. In other words, when comparing 2 agricultural products that include the use of pesticides for their production in terms of their overall ecotoxicity profiles, the use of average toxicity could lead to a small difference between the product systems, while using the lowest agreed toxicity value from risk assessment might show that one farm is using a much more toxic pesticide than another. It should be recalled that in the USEtox characterization factor applied in LCA, differences in the ecotoxicity of pesticides can be mitigated by differences in their fate and exposure factors, leading to a potentially different contribution in the freshwater ecotoxicity impact category.

CONCLUSIONS AND OUTLOOK

The main conclusion to be drawn from the present study is that the USEtox model to estimate the chemical effect value has a clear impact on the conclusion to be drawn from a PEF/OEF study. In the case of pesticides, the shift from basing the effect factor on average endpoint to lowest endpoint can lead to opposite conclusions on the question of which product is the environmentally preferable option. It is expected that the same observations can be made for a wide range of industrial chemicals, as previously demonstrated by Larsen and Hauschild [14]. We also demonstrated that the selection of the underlying data needs clear guidelines and that the use of all ecotoxicological end points (EC50 but also NOEC and LOEC) will be helpful to strengthen the comparison of chemical toxicity, as most chronic experimental data do not report EC50 values. As a consequence, USEtox presently does not make use of all toxicity information that may be seen as relevant when the potential toxicity effects of chemicals are compared.

Comparing chemical ecotoxicity with freshwater ecosystems on a fair basis for use in LCA in general and for use in PEF/OEF in particular is a major challenge. The ecotoxicity of a chemical can vary between species and within the same species depending on life stage, exposure duration, endpoint assessed (mortality, reproduction, etc.), and test conditions (water hardness, pH, temperature, dissolved matters, etc.). Some chemicals are difficult to dissolve in water, and others volatilize or (bio)degrade quickly. Many ecotoxicological tests failed because the test conditions were not maintained, but the results of these tests still end up in a database, because they may bring some information to those that are able to interpret them. The amount of information on ecotoxicity also varies between substances, with several hundred experimental data for some and only few data points for others. In this context, comparing ecotoxicity of chemicals is not a straightforward task. Because of this complexity, we recommend that the data selection procedure is being harmonized and clearly described and made available to users to avoid personal interpretation of the data that may lead to different estimation of effect values used in LCA and PEF/OEF.

More specifically, some substances cause effects in a narrow concentration range to different organisms (i.e., different organisms have similar ecotoxicological sensitivity), whereas others (especially pesticides and pharmaceuticals) may cause ecotoxicity effects to different species across a wide range of concentrations. Averaging ecotoxicity data puts generally less weight on particularly sensitive species than applying data for the most sensitive species only. In USEtox, the toxicity of chemicals is assessed based on an arithmetic mean of the logarithm of all species-specific geometric mean L(E)C50 values. A geometric-based HC50 was chosen because it puts more weight on the lower values and hence on the more sensitive species while maintaining the statistical robustness that lies in being based on an average of effect data and offering an empirically based quantitative link to ecosystem damage in the form of disappearance of species. However, the use of average condition ignores biological variability. It remains to be further investigated which of the 2 approaches (average vs most sensitive species) can be ecologically more relevant in an LCA or PEF/OEF context [51,52]. To derive an ecotoxicity effect factor to be used in LCA, different options would have to be considered in such an investigation.

First, the average HC50 takes into account all species data but tones down the influence of very sensitive species and ignores interspecies variability. Second, the use of HC5 considers the whole range of ecotoxicity data but puts more emphasis on the more sensitive species than a HC50. The use of SSD-based solutions such as HC50 and HC5 has the advantage that the whole range of values across all tested species is considered. Disadvantages of using HC5 are the higher uncertainty that accompanies it and the more cumbersome way of calculating it, compared with calculations needed for determining the HC50 or selecting the lowest toxicity value. Third, the use of PNEC is another alternative and has the advantage of being readily available for chemicals that have been risk assessed, thanks to the REACH regulation, although the quantity of available PNEC data is probably limited. Fourth, the use of the most sensitive species value takes into account stronger specific effects but also introduces a stronger dependence on the selection of species assessed. Finally, the use of the weighted average of lowest toxicity for 3 trophic levels might be another alternative, but has not yet been tested in the context of LCA [53]. This approach builds largely on consistently using the same species, while weights for different species need to be further explored and validated.

Table 5 summarizes the pros and cons of these 5 possible alternatives to derive an effect factor to be potentially used in a PEF/OEF context. Because the effect factor is one of the factors that control the freshwater ecotoxicity characterization factor [15], the possible methods used to derive this parameter deserve further analysis for their ability to identify substances of concern. These alternatives would need to be tested on a larger set of substances, and the results would need to be compared with current ecotoxicity classification of chemicals (Classification, Labeling, and Packaging/Globally Harmonized Systems) to evaluate whether what is already classified as ecotoxic in European Union and global chemical legislation is also considered toxic in a PEF/OEF context, and if not, what the reasons for this are.

Supplemental Data—The Supplemental Data are available on the Wiley Online Library at 10.1002/etc.3889.

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Data availability—All data and models are freely downloadable from public internet websites. The urls are provided in the text.

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