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Freshwater ecotoxicity characterization factors for PMT/vPvM substances

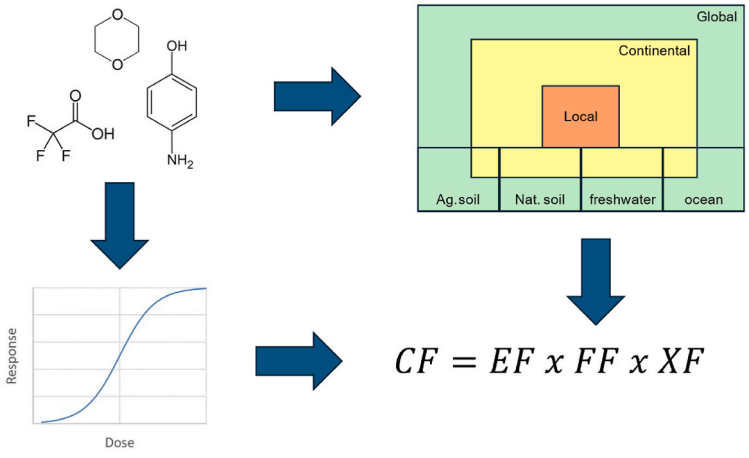
Rahul Aggarwal *, Gregory Peters

Environmental Systems Analysis, Chalmers University of Technology, Vera Sandbergs Allé 8, 41296, Gothenburg, Sweden

HIGHLIGHTS

- Freshwater ecotoxicological characterization factors (CFs) computed for 244 PMT/vPvM substances.
- New freshwater ecotoxicological characterization factors (CFs) for 137 PMT/vPvM substances.
- Discrepancies in CF values were identified for 107 substances that overlapped with those in the USEtox database.
- Characterization factors (CFs) for substances are dynamic entities that necessitate regular updates.

GRAPHICAL ABSTRACT



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ABSTRACT

This study addresses the gap in freshwater ecotoxicological characterization factors (CFs) for Persistent, Mobile, and Toxic (PMT) and Very Persistent and Very Mobile (vPvM) substances. These CFs are vital for integrating the ecotoxicity impacts of these chemicals into life cycle assessments. Our goals are twofold: first, to calculate experimental freshwater CFs for PMT/vPvM substances listed by the German Environment Agency (UBA); second, to compare these CFs with those from the USEtox database. The expanded UBA list includes 343 PMT/vPvM substances, each representing a unique chemical structure, and linked to 474 REACH-registered substances. This study successfully computed CFs for 244 substances, with 107 overlapping the USEtox database and 137 being new. However, ecotoxicity data limitations prevented CF determination for 97 substances. This research enhances our understanding of freshwater CFs for PMT/vPvM substances, covering 72% of UBA's 343 PMT/vPvM substances. Data scarcity remains a significant challenge, which invariably impedes CF calculations. Notably, the disparities observed between CF values in the USEtox database and those derived in this research largely stem from variations in ecotoxicity data. Consequently, this research underscores the dynamic nature of CFs for substances, emphasizing the need for regular updates to ensure their accuracy and relevance.

* Corresponding author.
E-mail address: rahula@chalmers.se (R. Aggarwal).

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1. Introduction

Chemicals classified as PMT (Persistent, Mobile, and Toxic) and vPvM (Very Persistent and Very Mobile) have raised significant concerns particularly due to their potential for environmental accumulation. These chemicals include chlorinated solvents (e.g. trichloroethylene); chlorinated organophosphate flame retardants (e.g. tris(2-chloroisopropyl)phosphate); guanidines (e.g. 1,3-diphenylguanidine); PFAS-substances (e.g. trifluoroacetic acid); phenyleneamines (e.g. 1,2-phenylenediamine) and others. Literature including Arp and Hale (2019); Hale et al. (2020a); Neumann and Schliebner (2017) have emphasized that the REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals EC, 1907/2006) registration process should recognize the risks posed by PMT/vPvM substances, equating them to persistent, bioaccumulative and toxic or very persistent and very bioaccumulative (PBT/vPvB) substances. PBT, vPvB, PMT, and vPvM classes are defined in detail by ECHA (2023a) under European Union (EU) hazard statements. Under REACH, substances meeting the PBT/vPvB criteria can be designated as Substances of Very High Concern (SVHC), leading to rigorous evaluations and potential restrictions (Hale et al., 2020b). In 2020, the European Commission, in its Chemical Strategy for Sustainability, resolved to categorize PMT/vPvM as SVHC under REACH by 2022 (EU, 2020). By 2023, the Commission introduced a delegated regulation updating the CLP regulation, which introduced new hazard classifications, including PMT and vPvM (ECHA, 2023a). This move clarifies the hazardous nature of these chemicals, mandating their new classifications by 2026.

A significant concern regarding PMT/vPvM chemicals is their ability to bypass wastewater and drinking water treatment systems, including in some cases advanced granular activated carbon filtration, ultrafiltration, advanced oxidation processes and even reverse osmosis (Sjerps et al., 2021; Stackelberg et al., 2007; Van Der Hoek et al., 2014). Hale et al. (2022) conducted an extensive study identifying gaps in managing PMT/vPvM substances, highlighting gaps in areas like chemical legislation, analytical methods, risk assessment tools, data on mobility, persistency, water treatment infrastructure, toxicity, safe substitutes, monitoring, and knowledge on substance mixtures and transformation products.

Amid safety concerns to our drinking water sources, governments and stakeholders, particularly in developed countries, are working to ensure the safe lifecycle management of chemicals through established regulatory frameworks (ECHA, 2012, 2023a; REACH, 2020; Wang et al., 2020). With rising awareness, there is an intensified push to eliminate hazardous chemicals from consumer products, driven by growing concerns over their impacts on public health, worker safety, and ecosystems among scientists, industries, and regulators (Bălan et al., 2023; Jacobs et al., 2016). Frameworks for chemical management and assessment, encompassing tools such as life cycle impact assessment (LCIA), chemical alternatives assessment (CAA), comparative risk screening, and risk assessment, are designed to evaluate the toxicological impacts of chemical exposures (Fantke et al., 2018, 2020, 2021; McCarty et al., 2018), nonetheless, these frameworks vary significantly in their objectives and foundational assumptions. Driven by NGO initiatives, civil activism, and the "Right-to-Know" ethos, there is a growing demand for transparency about hazardous chemicals in products, pushing providers to rigorously evaluate and disclose their products' toxicity implications. Consequently, Life Cycle Assessment (LCA), compliant with standards like ISO 14040, is gaining traction as it can in principle quantify potential toxicity impacts throughout a product's life cycle (Jacobs et al., 2016; Rosenbaum, 2015; Tickner et al., 2021).

Using readily available LCA methods and tools, it is possible to theoretically assess the potential toxicity impacts of products and processes containing PMT/vPvM substances. However, the actual inclusion of these chemical emissions in toxicity impact quantification hinges on the presence of characterization factors (CFs) for every associated chemical emission. CFs, in general, are factors derived from a characterisation model to convert life cycle inventory results into impact category indicator (ISO, 2006). USEtox database (version 2.01) stands as one of the largest databases, with CFs for 3104 substances (3077 organic and 27 inorganic) (Fantke et al., 2017). These CFs bridge the gap between chemical emissions and potential environmental impacts in an LCA. Without them, a chemical's emissions cannot be linked to potential environmental impacts, leading to gaps in the final impact assessment (Pennington et al., 2004). Despite these chemicals posing potential risks to water systems, only a fraction have been characterized for life cycle assessment (LCA), for instance, the USEtox database (version 2.01) has a coverage rate of 32% [n = 109/343] out of the 343 chemicals identified as PMT/vPvM by the German Environment Agency (UBA), leading to potential inaccuracies and gaps in assessments (Arp et al., 2023; Fantke et al., 2017; Rosenbaum et al., 2017). Thus, there is a gap in availability in CFs related to PMT/vPvM substances that hinders their inclusion in LCA. As an initial step towards addressing this issue, Aggarwal et al. (2024) calculated the CFs for 67 persistent and mobile chemicals, which comprised 24 perfluoroalkyl and polyfluoroalkyl substances (PFAS), 17 triazines, 23 triazoles, and 3 transformation products, with an overlap of 12 chemicals with this study.

The USEtox database (version 2.01) currently provides freshwater ecotoxicity CFs for only 2499 organic substances, leaving a vast number of commercially used chemicals uncharacterized (Fantke et al., 2017). This shortfall primarily stems from the limited availability of underlying EC50 chronic data. Fortunately, the proliferation of online experimental databases now makes it feasible to access ecotoxicity data for tens of thousands of chemical substances. Among these, REACH and CompTox are prominent, serving as comprehensive and current reservoirs of experimental ecotoxicity information. These databases are widely acknowledged in both regulatory and academic spheres. However, before this data can be effectively utilized, it requires meticulous curation to ensure harmonization across variables such as test species, units, endpoints, and exposure durations (Aurisano et al., 2019). While the growing accessibility of these databases is promising, harmonization challenges need to be addressed that vary from database to database as identified by Aggarwal et al. (2024).

This study tackles the lack of freshwater ecotoxicological characterization factors (CFs) for PMT/vPvM substances from the UBA list, all of which are chemical entities registered in the REACH database. The research sets out with two main objectives: (1) To provide a set of experimental aquatic freshwater characterization factors for the PMT/vPvM substances listed in UBA as per data availability, and (2) To contrast the characterization factors derived from USEtox with those computed in our research.

2. Materials and methods

2.1. PMT/vPvM substance selection

This research began by examining a set of PMT/vPvM chemicals, previously identified as potential contaminants to European drinking water sources (Hale et al., 2022). With the assessment criteria for PMT/vPvM rapidly evolving and nearing consensus, especially after the introduction of new hazard classifications by the European Chemicals Agency (ECHA, 2023a), the study's foundation was built upon existing literature on PMT/vPvM chemicals. Rather than classifying chemicals into PMT or vPvM categories, the study's primary aim was to provide CFs for a list of chemicals already recognized as PMT/vPvM. Consequently, the emphasis was on sourcing this list from reliable, openly accessible resources with clear and transparent classification criteria. An initial literature review highlighted the German Environment Agency (UBA) as a potential source with a comprehensive list of PMT/vPvM substances. The foundation for this study was the UBA's 2019 report, which assessed all substances registered under REACH (up to 2017) and identified 260 PMT/vPvM substances (Arp et al., 2023). This list was later updated by UBA in September 2019, resulting in 343 distinct

chemical structures (Arp et al., 2023). However, when considering the PMT/vPvM criteria proposed by the European Commission (EC) in 2021, only 259 of these chemicals met the criteria (Arp et al., 2023; ECHA, 2023b). For comprehensiveness, this research utilized the updated UBA list with 343 chemicals. Within the UBA's categorization of the 343 substances, 68, 130, and 145 chemicals were PMT, vPvM, and both vPvM and PMT, respectively. However, due to the absence of CAS numbers for 8 chemicals, which posed challenges in data collection, only 335 chemicals were considered for subsequent data collection phases. Detailed information about all the PMT/vPvM chemicals included in the analysis is given in the supplementary information in Table S1.

2.2. Characterization factor calculation tool

To assess a chemical's ecotoxicity impacts, understanding its environmental fate, exposure, and ecotoxicological effects is crucial (Jolliet et al., 2006). The USEtox model (version 2.13) offers a structured approach to compute freshwater ecotoxicity characterization factors (CFs) for various chemicals (Fantke et al., 2017; Rosenbaum et al., 2008). In USEtox, the CF is determined by integrating three separate factors in a matrix system: fate factors (FF), exposure factors (XF), and ecotoxicological effect factors (EF), as illustrated by the formula: CF=FF × XF × EF. The official USEtox documentation by Fantke et al. (2017) provides detailed explanations of all equations, abbreviations and input data used to calculate USEtox CFs. This research employs USEtox to determine aquatic CFs for the identified PMT/vPvM chemicals.

Owsianiak et al. (2023) introduced recommendations for ecotoxicity characterization factor calculation in USEtox, developed through collaborative work by the Ecotoxicity Task Force and the SETAC Pellston Workshop. These suggestions advocate for an $HC20_{EC10eq}$ based approach utilizing EC10 equivalents instead of the traditional $HC50_{E\text{-}C50eq}$ based approach using EC50 values, which are employed in the original USEtox framework. The recommended methodology is explained in detail in Owsianiak et al. (2023). However, it is important to note that these recommendations have not yet been incorporated into USEtox but implemented in product environmental footprint (PEF) methodology in the calculation of the CFs for the freshwater ecotoxicity related impact in the EU environmental footprint (EF) version 3.0 (Sala et al., 2022). Consequently, this study employs USEtox (version 2.13) in accordance with its established methodologies.

2.3. Data collection for PMT/vPvM substances

For the calculation of ecotoxicity CFs in the freshwater compartment using USEtox, data collection encompasses two types as shown in Table 1: (1) physicochemical properties related data, and (2) data on ecotoxicological effect data for aquatic organisms (Fantke et al., 2017). Details regarding the input data required to calculate CFs are thoroughly described in the USEtox documentation, and the input data collected in this study from various sources are elaborated in Table S9 of the supplementary information. In summary, to establish a robust dataset for aquatic ecotoxicity, data was sourced from the REACH and CompTox databases (REACH, 2020; Williams et al., 2017). The data from REACH, obtained through another research project, was retrieved in August 2020, while data from the CompTox database were sourced in July 2023 for this study. The accessed REACH database contained 4840 toxicity datapoints across 270 chemicals identified by their CAS numbers. The CompTox database includes 29,481 ecotoxicity data points for 167 chemicals. Physicochemical data for this study was collected from three primary sources: CompTox, EPI Suite v4.11, and USEPA TEST (U.S.EPA, 2020; 2023; Williams et al., 2017). Data was also extracted from the OPERA Model Prediction through the CompTox chemical dashboard.

Table 1
Overview of the data collection strategy for PMT/vPvM substances using different databases and type of data collection.

USEtox data requirements	Databases Used	Type of data collected	Data harmonization and prioritization
Physicochemical properties data	CompTox database OPERA Model Prediction EPI Suite v4.11 USEPA TEST	Both experimental and estimated	Harmonized experimental data, if not available then harmonized estimated data
Ecotoxicological effect data for aquatic organisms	REACH database (datapoints: 4840, chemicals: 270) CompTox database (datapoints: 29,481, chemicals: 167)	Experimental data only	Harmonized experimental data

To harmonize the physical-chemical dataset, duplicate entries were identified and removed, while averages were taken to combine multiple datapoints. Subsequently, the data was categorized into experimental and estimated sets. All units were standardized in line with USEtox specifications. For parameters like pKaChemClass, pKa.gain, and pKa.loss, priority was given to data from USEtox if there was an overlap with the chemicals. In cases where USEtox data was unavailable, the sequence followed was: experimental data and then estimated data. In the absence of any data on pKa, chemicals were assumed to be neutral, which means pKa.gain is assumed to be 0 and pKa.loss is assumed to be 14. For USEtox physical-chemical data inputs, experimental data was the primary choice, but in its absence, estimated data was utilized. Input data values used in this research for PMT/vPvM chemicals is provided in the supplementary information in Table S4.

2.4. Harmonization of ecotoxicity data

To ensure the integrity and consistency of the experimental ecotoxicological effect data, a data harmonization process was implemented. Aggarwal et al. (2024) outlined a detailed ecotoxicological effect data harmonization strategy comprising 19 steps. In this study, the overarching goal was to develop an effective but applicable harmonization process based on Aggarwal et al. (2024) to streamline and standardize the collected ecotoxicity data, facilitating uniform comparisons across parameters such as test species, endpoint type, exposure duration, and ecotoxicity concentration metrics. Chemical entities with incomplete or ambiguous information, as delineated by our selection criteria, were systematically omitted. This harmonization process was structured into four phases: chemical identification, data quality assessment, data harmonization, and consistency verification.

The first phase of the framework, "Chemical Identification," was dedicated to associating each data point with its respective chemical, using the CAS number, supplemented by DTXSID (DSSTox substance identifier) used in the CompTox Dashboard. The data quality control phase was pivotal in ensuring the integrity of the data. For the ECHA dataset, the Klimisch score was the benchmark for reliability (Klimisch et al., 1997). Only data points with scores of 1 (reliable without restriction) or 2 (reliable with restrictions) were retained. For the CompTox dataset, the QC Status determined the reliability. Entries marked with a "pass" in QC Status flag were kept. In the "Data Harmonization" phase as shown in Fig. 1, the emphasis was on refining the data to ensure uniformity across various parameters. It includes five steps, starting with numeric qualifiers, tested species naming and classification, Exposure duration classification, endpoint classification, and effect concentration unit standardization to milligrams per liter (mg/L). These steps are described in detail in Aggarwal et al. (2024). In the concluding consistency check phase, the emphasis was on ensuring the authenticity and completeness of the data. The goal was to confirm that the data from REACH and CompTox was purely experimental along with ensuring the

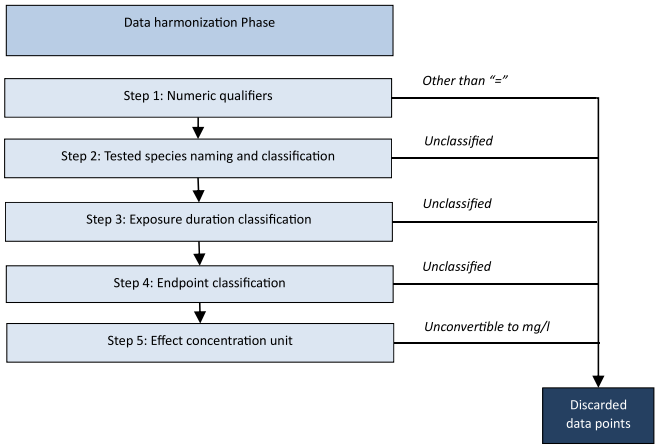

Fig. 1. Steps involved in the experimental ecotoxicity data harmonization phase.

absence of data gaps and duplicate entries. After this phase, the REACH and CompTox datasets were combined. A subsequent duplicate verification was carried out on this consolidated dataset to remove duplicates.

2.5. Ecotoxicity effect factors calculation strategy

Aquatic ecotoxicity effect factors (EFs) are essential for determining freshwater ecotoxicity characterization factors (CFs). These are based on the HC50 [kg m^{-3}], calculated as EF = 0.5/HC50 [PAF m^3 kg^{-1}]. The HC50 represents the hazardous concentration at which half of the species in a freshwater ecosystem are exposed above their EC50 value. This is determined by taking the geometric mean of chronic EC50s for freshwater species (Fantke et al., 2017). For the results given in USEtox database to be classified as "recommended", the effect factor must be grounded in data from at least three trophic levels, which is typically data for algae, crustacean, and fish (Fantke et al., 2017). Within USEtox, chemical-specific HC50s are presented on a logarithmic scale, derived from the geometric means of individual species EC50 test data.

In this study, log HC50 was determined through a three-step process using precautionary approach, and harmonized data from earlier stages. Each data point was categorized by its chemical CAS number, unique species name, species group, exposure class, and endpoint classification. The first step involved aggregating the input data at the species level using the geometric mean, yielding a consolidated effect concentration for each chemical. This was defined by its endpoint, exposure class, species group, and species name. In the subsequent step, this aggregated data was further consolidated at the species group level, again using the geometric mean. This produced a consolidated effect concentration for each chemical, defined by its endpoint, exposure class, and species group. If necessary, this data was then extrapolated to chronic EC50 using species group-specific extrapolation factors as given by Aurisano et al. (2019). In the final step, the chronic EC50 data from the previous stage was aggregated once more, this time using the average of their logarithmic values, resulting in the logHC50 for each chemical. This refined data was then input into USEtox to calculate the EF for each chemical.

In this study, to understand the influence of extrapolation on the EFs and CFs, three different data combinations are used. Firstly, all the experimental ecotoxicity data, with extrapolation to EC50 Chronic if needed, is used, to calculate EFs and CFs and denoted by "All." Secondly, only the EC50 chronic data, excluding all other endpoints, is used, denoted as "EC50 chronic." This combination is important for assessing the influence of extrapolation factors on the EFs and CFs calculations. Lastly, data related to EC50 endpoints only are used, which includes both EC50 chronic data and extrapolated EC50 acute data, excluding all other endpoints, and is denoted as "EC50." This combination is crucial for examining the extrapolation from acute to chronic exposure within the same endpoint but excluding extrapolation between different endpoints to EC50 chronic.

2.6. Comparing ecotoxicity effect factors and characterization factors

The derived effect factors form the basis for subsequent comparisons. For analysis, all effect factors were subjected to a log10 transformation. Pairwise correlations were then employed to assess the linear relationship between these transformed effect factors, with the correlation coefficient, r, indicating the strength and direction of this relationship. Further, regression analyses were conducted to gauge the correlation's intensity, as represented by the coefficients of determination (R^2). These analyses were carried out between paired effect factors. Initially, a comparison was made between the effect factors for the freshwater ecosystem, as determined in this study using all experimental data, and the pre-established USEtox EFs from the USEtox organic substances database (version 2.01). Subsequently, two additional comparisons were conducted, contrasting the experimental EFs derived in this study with EFs obtained using different combinations of EC50 endpoint data, both with and without extrapolations against USEtox EFs. The same process was applied to compare characterization factors.

3. Results and discussion

3.1. Ecotoxicity data selection and harmonization results

Following the data harmonization process as described in section 2.4, the REACH dataset was distilled down to 2025 datapoints for 217 chemicals, and the CompTox dataset had 21,966 datapoints for 163 chemicals. The harmonized datasets were then combined, followed by the removal of duplicates, yielding a unified dataset with 23,658 data points spanning 254 distinct chemicals. The distribution of the endpoints is shown in Table 2. Every data point in this consolidated dataset is distinctly identified by its CAS, species name, species group, exposure classification, and endpoint classification.

3.2. Ecotoxicity effect factors results

In this research, following the calculation strategy as detailed in section 2.5, effect factors were derived from a combination of experimental EC50 chronic data and, where necessary, extrapolated endpoints to EC50 chronic, yielding effect factors for 254 chemicals. While USEtox recommends the exclusive use of EC50 chronic data to minimize uncertainty, this study also presents effect factors based solely on EC50 chronic data for 170 chemicals. Additionally, effect factors using only EC50 endpoints, both chronic and extrapolated acute, are provided for 224 chemicals. There is an overlap of 108 PMT/vPvM chemicals that were already present in the USEtox database. The summary statistics of EFs are given in the supplementary information in Table S2, including data on EFs along with the number of ecotoxicity data points and the associated number of species groups used in the calculations. In terms of the species groups, the final overall harmonized dataset includes an average of more than three species groups per chemical, with an average of about two species groups with EC50 chronic datapoints, and an average of more than three species groups with EC50 (both chronic and extrapolated acute EC50 datapoints).

3.3. Comparison of ecotoxicity effect factors

In this research, EFs for 108 PMT/vPvM chemicals already listed in the USEtox database were calculated using experimental ecotoxicity data harmonized in this study. A comparison of these calculated EFs for the freshwater ecosystem with the original EFs from the USEtox organic substances database (version 2.01) is illustrated in Fig. 2. The regression analysis showed an R^2 value of 0.78, suggesting a moderate correlation.

Table 2
Overview of the distribution of harmonized ecotoxicity datapoints across different endpoints.

Type	EC10 acute	EC10 chronic	EC50 acute	EC50 chronic	NOEC acute	NOEC chronic	Grand Total
Datapoints	2355	3158	7817	2858	2977	4493	23,658
Chemicals	100	139	207	170	178	175	254

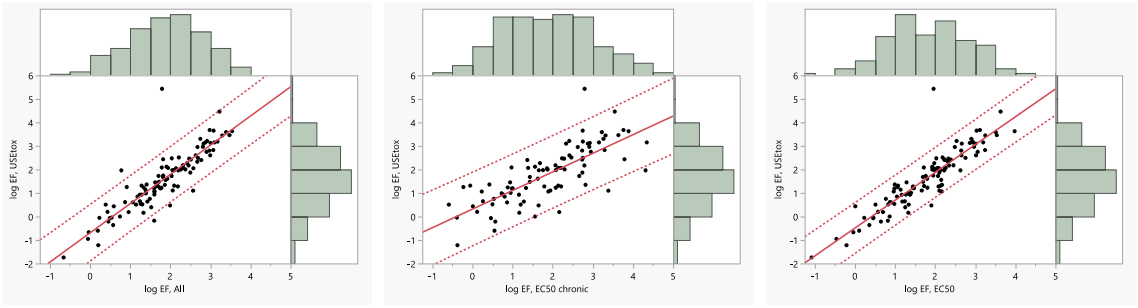

Fig. 2. Regression analysis of pre-calculated log transformed USEtox database EFs [PAF m^3 kg-1] in freshwater ecosystem versus log transformed EFs [PAF m^3. kg^{-1}] calculated in this study with experimental ecotoxicity data: all (left), EC50 chronic (middle), and EC50 (combined chronic EC50 and extrapolated acute EC50) (right), with correlation: moderate (n = 108, R^2 = 0.78, r = 0.88), low (n = 89, R^2 = 0.58, r = 0.76), and high (n = 108, R^2 = 0.82, r = 0.91) respectively.

Following the USEtox guideline to prioritize EC50 chronic data, a distinct analysis was conducted comparing EFs calculated using only experimental EC50 chronic data with USEtox EFs. This yielded an R^2 value of 0.58, pointing to a weaker correlation. The weak correlation is mainly because in USEtox the data is both EC50 chronic and if not available then extrapolated EC50 acute with an extrapolation factor of 2. Therefore, when effect factors derived from combining both chronic EC50 and extrapolated acute EC50 were compared against USEtox EFs, the R^2 value rose to 0.82, signifying a strong correlation that aligns more closely with USEtox values. The increase in the R^2 value with the inclusion of more data points suggests that incorporating extrapolated data enhances data coverage and species group representation. The high correlation between calculated EFs as compared to USEtox implies that the derived values for chemicals not available in USEtox database probably align with USEtox calculation criteria. This provides a degree of confidence in the EFs calculated for chemicals that are absent from the USEtox database are consistent with the norms of USEtox 2.13. Table 3 provides summary statistics of the regression analysis of log transformed EFs calculated in this study versus pre-calculated log transformed USEtox 2.13 database EFs.

In this study, data from REACH and CompTox were harmonized using a structured framework to ensure the integrity of the dataset for EF calculations. This rigorous process resulted in a 30% reduction in data points. However, the study faced limitations stemming from harmonization process. For example, there is no globally recognized standard for species naming and categorization that is easily applicable without the need for renaming the species based on their scientific and common names. Discrepancies also arise in exposure classifications. In algae tests, there is no clear distinction between acute and chronic effects, with a typical exposure duration of 72 h. Given algae's fast reproduction rate, such tests tend to lean towards chronic assessments (Hahn et al., 2014). The seven-day exposure threshold for fish could be considered short, especially when compared to the standard 14-day test used in risk assessments, which is not considered chronic (OECD, 2013). The classification of endpoints is further complicated by uncertainties, particularly in the lower spectrum of species sensitivity distributions, making it difficult to differentiate between NOEC, LOEC, and EC 1–10 values (Iwasaki et al., 2015). Another hurdle was the inconsistency in units across different endpoints. Moreover, the type of effect being studied posed a significant challenge during the harmonization phase. For a specific endpoint, species, and exposure type, tests can span a wide range of effects such as reproduction, mortality, etc. The varying sensitivities to these effects can lead to discrepancies in exposure concentrations, making harmonization a complex task given the data limitations. There may also other influencing factors, both identified and unidentified, that were not accounted for when determining the effect factors. These elements can substantially impact ecotoxicity test results and, consequently, the effect factors derived in this study. Given these challenges, the study aimed to provide a close approximation of the situation rather than an exact representation.

3.4. Ecotoxicity characterization factor results

This study assessed the representation of specific PMT/vPvM chemicals within the USEtox organic substances database (version 2.01). Out of the 343 PMT/vPvM chemicals selected, only 109 were found in the USEtox database, translating to a coverage rate of 32% [n = 109/343]. This underscores a significant gap in the availability of CFs for PMT/vPvM substances. When breaking down the UBA's categorization of the 343 substances into PMT, vPvM, and both vPvM & PMT, the coverage rates stand at 30% [n = 21/68], 17% [n = 22/130], and 46% [n = 66/145], respectively.

In this study, characterization factors were computed using all experimental ecotoxicity data. This approach resulted in CFs for 244 chemicals. While relying solely on EC50 chronic data resulted in CFs for 166 chemicals. Furthermore, relying on EC50 endpoints, combining both chronic EC50 and extrapolated EC50 acute data, resulted in CFs for 215 chemicals. Summary statistics of the calculated CFs in the freshwater compartment are provided in the supplementary information in Table S3. Additionally, Table S5 in the supplementary information

Table 3
Overview of the regression analysis of calculated log transformed EFs versus pre-calculated log transformed USEtox 2.13 database EFs [PAF m^3.kg^{-1}].

Variable	by Variable	Correlation (r)	Rsquare (R^2)	Root Mean Square Error	Covariance	Count	Lower 95%	Upper 95%
log EF, USEtox	log EF, All	0.88	0.78	0.59	0.97	108	0.83	0.92
log EF, USEtox	log EF, EC50 chronic	0.76	0.58	0.77	1.05	89	0.66	0.84
log EF, USEtox	log EF, EC50	0.91	0.82	0.53	1.08	108	0.86	0.93

presents the complete USEtox output table calculated using all experimental data. Table S6 details the USEtox output table calculated using only EC50 chronic experimental data, while Table S7 displays the USEtox output table calculated using only EC50 endpoint-related experimental data. Furthermore, Table S8 lists values available in USEtox for 107 chemicals that overlap with the USEtox database. It should be noted that these CFs are primarily for preliminary assessments and should be treated as indicative values. While they offer valuable preliminary insights, any application of these CFs beyond initial screenings should be accompanied by rigorous validation and verification. Also, there are limitations of the USEtox model for the assessment of PMT/vPvM substances, which have been discussed previously by Aggarwal et al. (2024) and Holmquist et al. (2020). Analyzing the coverage of the 244 chemicals against the UBA's classification of the 343 substances into PMT, vPvM, and both vPvM & PMT categories, the representation is 69% [n = 47/68], 65% [n = 85/130], and 77% [n = 112/145], respectively. It is worth mentioning that while EFs are available for an additional 10 chemicals, CFs are absent due to the unavailability of the requisite physical-chemical data to determine the fate and exposure of these substances.

The freshwater compartment's midpoint CFs span between six to seven orders of magnitude, as illustrated in Fig. 3 and elaborated in the supplementary information in Table S3 with values available per chemical. To showcase this variation, Fig. 3 presents box plots that display the range of CFs based on the UBA's categorization of the 343 substances into PMT, vPvM, and both vPvM & PMT. These plots visually capture the distribution of CFs, emphasizing the wide spectrum of values observed within each category. As may be expected, the figure reveals that the median toxicity of the PMT chemical group surpasses that of the vPvM & PMT group, which in turn exceeds the vPvM group. The plots underscore the significance of evaluating individual chemical attributes and unique molecular structures when determining its CF in the freshwater compartment. It suggests a more case-by-case approach rather than a blanket categorization based on PMT/vPvM classifications. This is because there is no conclusive evidence that one category consistently exhibits higher toxicity than another, and the toxicity can vary considerably within a range. Nonetheless, the box plots distinctly show that the PMT chemical group generally exhibits higher CFs compared to the vPvM & PMT group, which in turn has marginally elevated CFs relative to the vPvM group.

In our research, CFs for 107 PMT/vPvM chemicals, already cataloged in the USEtox database, were calculated using experimental data collected in this study. These calculated CFs were then compared with the pre-existing CFs from the USEtox organic substances database (version 2.01), as shown in Fig. 4. Regression analysis yielded an R^2 value of 0.80, signifying a substantial correlation between the datasets. The USEtox guidelines emphasize the importance of EC50 chronic data, so a distinct analysis was undertaken. When the recalibrated CFs, based solely on this chronic data, were compared to the USEtox CFs, the correlation was found to be moderate, reflected by an R^2 value of 0.63. However, the correlation became more pronounced, with an R^2 value of 0.81, when both chronic EC50 and extrapolated acute EC50 data were considered. The increase in the R^2 value upon the inclusion of additional data points underscores the value of incorporating extrapolated data, as it enriches the data coverage and offers a holistic representation of species groups. This comprehensive approach yields values that resonate more with the USEtox values. The pronounced correlation between our recalibrated CFs and the USEtox CFs implies that the CFs we derived for chemicals absent from USEtox probably align with the established USEtox computation methodologies. This gives confidence in our CFs for chemicals not included in the USEtox database. Table 4 provides summary statistics of the regression analysis of log transformed CFs calculated in this study versus pre-calculated log transformed USEtox 2.13 database CFs.

4. Conclusions

This study bridges the gap in the lack of CFs for UBA-identified PMT/vPvM substances by providing CFs based on experimental aquatic data for an additional 137 PMT/vPvM substances, beyond the 109 available in the USEtox database (version 2.01), thereby enhancing their representation in LCA evaluations. Together with the existing USEtox CFs, our research now encompasses 72% of the UBA's list of 343 PMT/vPvM chemicals. In total, we calculated 244 CFs, with 107 overlapping with the USEtox database. A prominent challenge faced during this research was the limited availability of data, which hindered the CF calculation and the full integration of these chemicals' impacts into LCA. As a result, CFs for 97 substances remain undetermined. The observed

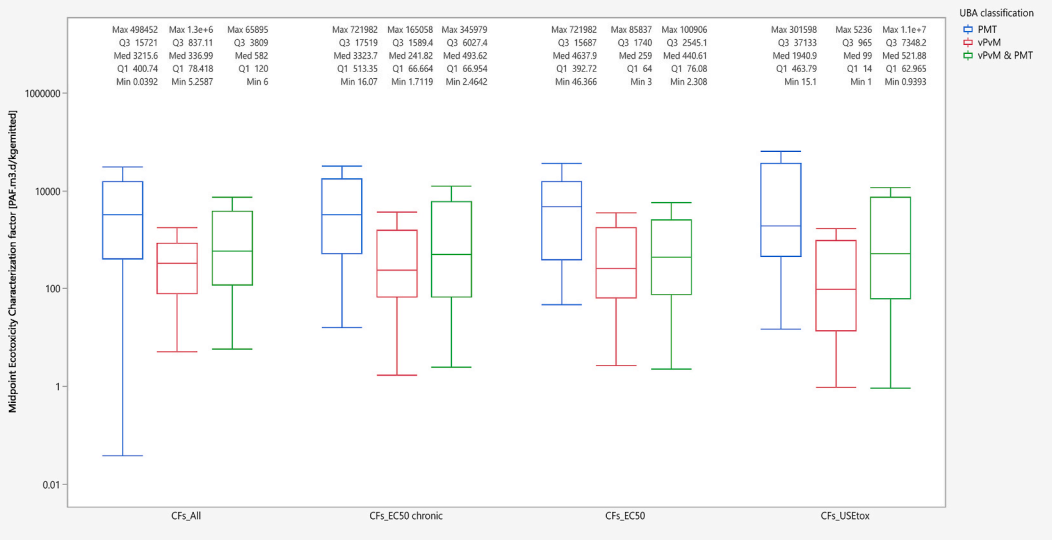

Fig. 3. Box plots of calculated mid-point CFs [PAF.m^3. d/kg emitted] derived from experimental data for three ecotoxicity data combinations in the freshwater compartment along with available USEtox CFs for 107 overlapping chemicals. These combinations include all experimental data, denoted as "All"; only EC50 chronic data, denoted as "EC50 chronic"; and only EC50 endpoint data, which includes both acute and chronic EC50 data, denoted as "EC50". Within each combination, the plots categorize different PMT/vPvM chemicals according to UBA classification.. (Note that these classifications groups are treated exclusively, that is the box for PMT substances does not include any in the vPvM & PMT box.)

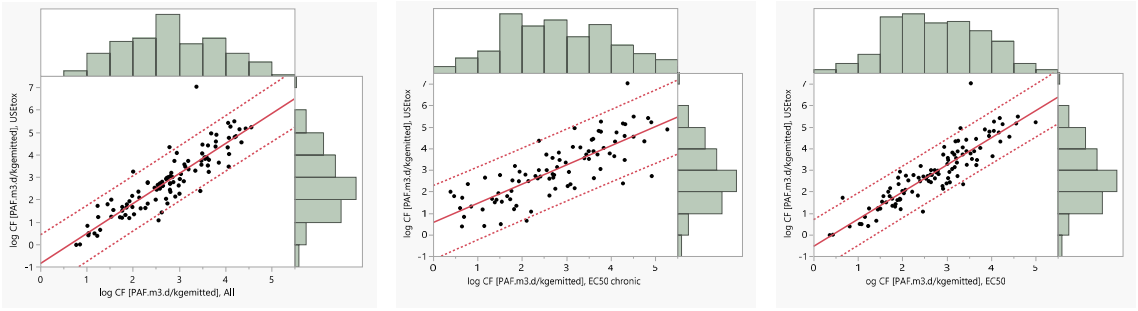

Fig. 4. Regression analysis of log transformed pre-calculated USEtox 2.13 database CFs in freshwater ecosystem versus log transformed CFs calculated in this study with experimental ecotoxicity data: all (left), EC50 chronic (middle), and EC50 (right), with correlation: moderate (n = 107, R^2 = 0.80, r = 0.90, low (n = 88, R^2 = 0.63, r = 0.79, and high (n = 107, R^2 = 0.81, r = 0.90) respectively.

Table 4
Overview of the regression analysis of calculated log transformed CFs versus pre-calculated log transformed USEtox 2.13 database CFs [PAF.m^3.d/kg emitted].

Variable	by Variable	Correlation	Rsquare (R^2)	Root Mean Square Error	Covariance	Count	Lower 95%	Upper 95%
log CF, USEtox	log CF, All	0.90	0.80	0.62	1.14	107	0.85	0.93
log CF, USEtox	log CF, EC50 chronic	0.79	0.63	0.84	1.33	88	0.70	0.86
log CF, USEtox	log CF, EC50	0.90	0.81	0.60	1.22	107	0.86	0.93

discrepancies, marked by a low correlation between the USEtox CF values and those derived in this study using EC50 chronic values, can be attributed to differences in the ecotoxicity data. However, the correlation strengthened when both chronic and extrapolated EC50 data were incorporated. The enhanced R^2 value, upon including more data points, highlights the importance of using extrapolated data to achieve a more comprehensive data set and a broader representation of species groups. Furthermore, the CFs of chemicals are contingent on the evolving chemical data landscape. As data improves and becomes more available, there is potential for further refinement. Hence, CFs should be viewed as evolving metrics that need periodic updates to reflect the latest data. In conclusion, it is essential to recognize that CFs are dynamic and should be updated regularly to ensure they remain relevant and accurate.

Conflict of interest statement

There are no conflicts of interest to declare.

Disclosure statement

During the preparation of this work the author(s) used ChatGPT 3.5 in order to improve grammar. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

CRediT authorship contribution statement

Rahul Aggarwal: Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Gregory Peters:** Funding acquisition, Methodology, Supervision, Writing – review & editing.

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

Supplementary data to this article can be found online at https://doi.org/10.1016/j.chemosphere.2024.142391.

References

Aggarwal, R., Holmquist, H., Arvidsson, R., Reppas-Chrysovitsinos, E., Peters, G., 2024. Influence of data selection on aquatic ecotoxicity characterization factors for selected persistent and mobile substances. Int. J. Life Cycle Assess. 29 (2), 344–354. https://doi.org/10.1007/s11367-023-02263-w.

Arp, H.P.H., Hale, S.E., 2019. REACH: Improvement of guidance methods for the identification and evaluation of PM/PMT substances. UBA TEXTE 126/2019. German Environment Agency (UBA), Dessau-Roßlau, Germany 130.

Arp, H.P.H., Hale, S.E., Schliebner, I., Neumann, M., 2023. Prioritised PMT/vPvM substances in the REACH registration database. Ukr. Bioorg. Acta 4804. https://www.umweltbundesamt.de/publikationen/prioritised-pmtvpvm-substances-in-the-reach.

Aurisano, N., Albizzati, P.F., Hauschild, M., Fantke, P., 2019. Extrapolation factors for characterizing freshwater ecotoxicity effects. Environ. Toxicol. Chem. 38 (11), 2568–2582. https://doi.org/10.1002/etc.4564 [Article].

Bălan, S.A., Andrews, D.Q., Blum, A., Diamond, M.L., Fernández, S.R., Harriman, E., Lindstrom, A.B., Reade, A., Richter, L., Sutton, R., Wang, Z., Kwiatkowski, C.F., 2023. Optimizing chemicals management in the United States and Canada through the essential-use approach. Environ. Sci. Technol. 57 (4), 1568–1575. https://doi.org/10.1021/acs.est.2c05932 [Review].

ECHA, 2012. *Guidance On Information Requirements and Chemical Safety Assessment Chapter R.8: Characterisation Of Dose [concentration]-Response for Human Health* (ECHA-2010-G-19-EN). E. C. Agency. https://echa.europa.eu/documents/10162/17224/information_requirements_r8_en.pdf.

ECHA, 2023a. New hazard classes 2023 - ECHA. https://echa.europa.eu/new-hazard-classes-2023.

ECHA, 2023b. Pre-registered substances - ECHA. Retrieved March from. https://echa.europa.eu/information-on-chemicals/pre-registered-substances.

EU, 2020. The EU's chemicals strategy for sustainability towards a toxic-free environment. https://environment.ec.europa.eu/strategy/chemicals-strategy_en.

Fantke, P., Aurisano, N., Bare, J., Backhaus, T., Bulle, C., Chapman, P.M., De Zwart, D., Dwyer, R., Ernstoff, A., Golsteijn, L., Holmquist, H., Jolliet, O., McKone, T.E., Owsianiak, M., Peijnenburg, W., Posthuma, L., Roos, S., Saouter, E., Schowanek, D., Hauschild, M., 2018. Toward harmonizing ecotoxicity characterization in life cycle

impact assessment. Environ. Toxicol. Chem. 37 (12), 2955–2971. https://doi.org/10.1002/etc.4261.
Fantke, P., Bijster, M., Guignard, C., Hauschild, M., Huijbregts, M., Jolliet, O., Kounina, A., Magaud, V., Margni, M., McKone, T.E., Posthuma, L., Rosenbaum, R., Van de meent, D., Zelm, R., 2017. USEtox 2.0 : documentation (version 1). https://usetox.org/.
Fantke, P., Chiu, W.A., Aylward, L., Judson, R., Huang, L., Jang, S., Gouin, T., Rhomberg, L., Aurisano, N., McKone, T., Jolliet, O., 2021. Exposure and toxicity characterization of chemical emissions and chemicals in products: global recommendations and implementation in USEtox. Int. J. Life Cycle Assess. 26 (5), 899–915. https://doi.org/10.1007/s11367-021-01889-y.
Fantke, P., Huang, L., Overcash, M., Griffing, E., Jolliet, O., 2020. Life cycle based alternatives assessment (LCAA) for chemical substitution. Green Chem. 22 (18), 6008–6024. https://doi.org/10.1039/d0gc01544j.
Hahn, T., Diamond, J., Dobson, S., Howe, P., Kielhorn, J., Koennecker, G., Lee-Steere, C., Mangelsdorf, I., Schneider, U., Sugaya, Y., Taylor, K., Dam, R.V., Stauber, J.L., 2014. Predicted no effect concentration derivation as a significant source of variability in environmental hazard assessments of chemicals in aquatic systems: an international analysis. Integrated Environ. Assess. Manag. 10 (1), 30–36. https://doi.org/10.1002/ieam.1473.
Hale, S.E., Arp, H.P.H., Schliebner, I., Neumann, M., 2020a. Persistent, mobile and toxic (PMT) and very persistent and very mobile (vPvM) substances pose an equivalent level of concern to persistent, bioaccumulative and toxic (PBT) and very persistent and very bioaccumulative (vPvB) substances under REACH. Environ. Sci. Eur. 32 (1), 155. https://doi.org/10.1186/s12302-020-00440-4.
Hale, S.E., Arp, H.P.H., Schliebner, I., Neumann, M., 2020b. What's in a name: persistent, mobile, and toxic (PMT) and very persistent and very mobile (vPvM) substances. Environ. Sci. Technol. 54 (23), 14790–14792. https://doi.org/10.1021/acs.est.0c05257.
Hale, S.E., Kalantzi, O.I., Arp, H.P.H., 2022a. Introducing the EU project ZeroPM: zero pollution of persistent, mobile substances [Editorial]. Environ. Sci. Eur. 34 (1) https://doi.org/10.1186/s12302-022-00681-5. Article 108.
Hale, S.E., Neumann, M., Schliebner, I., Schulze, J., Averbeck, F.S., Castell-Exner, C., Collard, M., Drmač, D., Hartmann, J., Hofman-Caris, R., Hollender, J., de Jonge, M., Kullick, T., Lennquist, A., Letzel, T., Nödler, K., Pawlowski, S., Reineke, N., Rorije, E., Arp, H.P.H., 2022b. Getting in control of persistent, mobile and toxic (PMT) and very persistent and very mobile (vPvM) substances to protect water resources: strategies from diverse perspectives [Article] Environ. Sci. Eur. 34 (1). https://doi.org/10.1186/s12302-022-00604-4. Article 22.
Holmquist, H., Fantke, P., Cousins, I.T., Owsianiak, M., Liagkouridis, I., Peters, G.M., 2020. An (eco) toxicity life cycle impact assessment framework for per-and polyfluoroalkyl substances. Environ. Sci. Technol. 54 (10), 6224–6234.
ISO, 2006. ISO14040:2006. Environmental Management - Life Cycle Assessment - Requirements and Guidelines. *Environmental Management - Life Cycle Assessment - Requirements And Guidelines*.
Iwasaki, Y., Kotani, K., Kashiwada, S., Masunaga, S., 2015. Does the choice of NOEC or EC10 affect the hazardous concentration for 5% of the species? Environ. Sci. Technol. 49 (15), 9326–9330. https://doi.org/10.1021/acs.est.5b02069.
Jacobs, M.M., Malloy, T.F., Tickner, J.A., Edwards, S., 2016. Alternatives assessment frameworks: research needs for the informed substitution of hazardous chemicals. Environ. Health Perspect. 124 (3), 265–280.
Jolliet, O., Rosenbaum, R., Chapman, P.M., McKone, T., Margni, M., Scheringer, M., Van Straalen, N., Wania, F., 2006. Establishing a framework for life cycle toxicity assessment: findings of the Lausanne review workshop. Int. J. Life Cycle Assess. 11 (3), 209–212. https://doi.org/10.1065/lca2006.03.002.
Klimisch, H.J., Andreae, M., Tillmann, U., 1997. A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25 (1), 1–5. https://doi.org/10.1006/rtph.1996.1076.
McCarty, L.S., Borgert, C.J., Posthuma, L., 2018. The regulatory challenge of chemicals in the environment: toxicity testing, risk assessment, and decision-making models. Regul. Toxicol. Pharmacol. 99, 289–295. https://doi.org/10.1016/j.yrtph.2018.10.001.
Neumann, M., Schliebner, I., 2017. Protecting the sources of our drinking water. A revised proposal for implementing criteria and an assessment procedure to identify persistent, mobile and toxic (PMT) and very persistent, very mobile (vPvM) substances registered under REACH. Protecting the Sources of Our Drinking Water.
OECD, 2013. OECD Guidelines for the Testing of Chemicals Section 2: Effects on Biotic Systems Test No 236: Fish Embryo Acute Toxicity (FET) Test. Organization for Economic Cooperation and Development, Paris, France.
Owsianiak, M., Hauschild, M.Z., Posthuma, L., Saouter, E., Vijver, M.G., Backhaus, T., Douziech, M., Schlekat, T., Fantke, P., 2023. Ecotoxicity characterization of chemicals: global recommendations and implementation in USEtox. Chemosphere 310, 136807. https://doi.org/10.1016/j.chemosphere.2022.136807.
Pennington, D.W., Potting, J., Finnveden, G., Lindeijer, E., Jolliet, O., Rydberg, T., Rebitzer, G., 2004. Life cycle assessment Part 2: current impact assessment practice. Environ. Int. 30 (5), 721–739. https://doi.org/10.1016/j.envint.2003.12.009.
REACH, 2020. REACH Dossier Database. Retrieved August from. https://echa.europa.eu/fr/search-for-chemicals.
Rosenbaum, R.K., 2015. Ecotoxicity. In: Hauschild, M.Z., Huijbregts, M.A.J. (Eds.), Life Cycle Impact Assessment. Springer, Netherlands, pp. 139–162. https://doi.org/10.1007/978-94-017-9744-3_8.
Rosenbaum, R.K., Bachmann, T.M., Gold, L.S., Huijbregts, M.A., Jolliet, O., Juraske, R., Koehler, A., Larsen, H.F., MacLeod, M., Margni, M., 2008. USEtox—the UNEP-SETAC toxicity model: recommended characterisation factors for human toxicity and freshwater ecotoxicity in life cycle impact assessment. Int. J. Life Cycle Assess. 13, 532.
Rosenbaum, R.K., Hauschild, M.Z., Boulay, A.M., Fantke, P., Laurent, A., Núñez, M., Vieira, M., 2017. Life cycle impact assessment. Life Cycle Assessment: Theory and Practice 167–270. https://doi.org/10.1007/978-3-319-56475-3_10.
Sala, S., Biganzoli, F., Mengual, E.S., Saouter, E., 2022. Toxicity impacts in the environmental footprint method: calculation principles. Int. J. Life Cycle Assess. 27 (4), 587–602.
Sjerps, R.M.A., Brunner, A.M., Fujita, Y., Bajema, B., de Jonge, M., Bäuerlein, P.S., de Munk, J., Schriks, M., van Wezel, A., 2021. Clustering and prioritization to design a risk-based monitoring program in groundwater sources for drinking water. Environ. Sci. Eur. 33 (1) https://doi.org/10.1186/s12302-021-00470-6. Article 32.
Stackelberg, P.E., Gibs, J., Furlong, E.T., Meyer, M.T., Zaugg, S.D., Lippincott, R.L., 2007. Efficiency of conventional drinking-water-treatment processes in removal of pharmaceuticals and other organic compounds. Sci. Total Environ. 377 (2–3), 255–272.
Tickner, J.A., Simon, R.V., Jacobs, M., Pollard, L.D., van Bergen, S.K., 2021. The nexus between alternatives assessment and green chemistry: supporting the development and adoption of safer chemicals. Green Chem. Lett. Rev. 14 (1), 23–44. https://doi.org/10.1080/17518253.2020.1856427.
U.S.EPA, 2020. User's guide for T.E.S.T. Progr. Estim. Toxic. Mol. Struct.: [Data and Tools]. https://www.epa.gov/chemical-research/toxicity-estimation-software-tool-test.
U.S.EPA, 2023. Estimation Programs Interface Suite™ for Microsoft® Windows 4.11. Retrieved March from. https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface.
Van Der Hoek, J.P., Bertelkamp, C., Verliefde Bertelkamp, A.R.D., Singhal, N., 2014. Drinking water treatment technologies in Europe: state of the art - challenges - Research needs. J. Water Supply Res. Technol. - Aqua 63 (2), 124–130. https://doi.org/10.2166/aqua.2013.007.
Wang, Z., Walker, G.W., Muir, D.C.G., Nagatani-Yoshida, K., 2020. Toward a global understanding of chemical pollution: a first comprehensive analysis of national and regional chemical inventories. Environ. Sci. Technol. 54 (5), 2575–2584. https://doi.org/10.1021/acs.est.9b06379.
Williams, A.J., Grulke, C.M., Edwards, J., McEachran, A.D., Mansouri, K., Baker, N.C., Patlewicz, G., Shah, I., Wambaugh, J.F., Judson, R.S., Richard, A.M., 2017. The CompTox Chemistry Dashboard: a community data resource for environmental chemistry. J. Cheminf. 9 (1), 61. https://doi.org/10.1186/s13321-017-0247-6.