Journal of Hazardous Materials 453 (2023) 131376

Contents lists available at ScienceDirect

Journal of Hazardous Materials

journal homepage: www.elsevier.com/locate/jhazmat

Research Paper

Hazard screening of contaminants of emerging concern (CECs) in Sweden's three largest lakes and their associated rivers

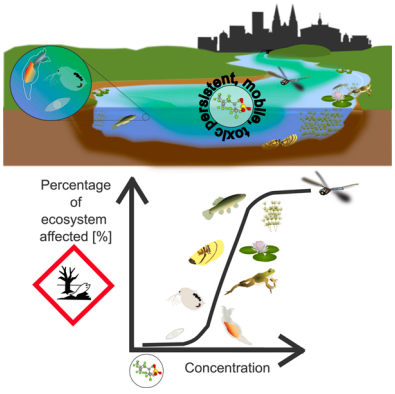
Daniel Malnes [a,*], Sylvia Waara [b], Romain Figuière [c], Lutz Ahrens [a], Karin Wiberg [a], Stephan J. Köhler [a], Oksana Golovko [a]

[a] Department of Aquatic Sciences and Assessment, Swedish University of Agricultural Sciences (SLU), SE-750 07 Uppsala, Sweden
[b] Rydberg Laboratory of Applied Sciences, Department of Environmental and Biosciences, Halmstad University, SE-301 18, Halmstad, Sweden
[c] Department of Environmental Science, Stockholm University (ACES), SE-106 91 Stockholm, Sweden

HIGHLIGHTS

- Contaminants of emerging concern (CECs) were assessed in Swedish surface water.
- Existing and new species sensitivity distributions (SSDs) and RQs were used.
- Potential persistent, mobile and toxic substances were identified.
- Acute and chronic SSDs were derived for studied CECs.
- Furosemide and caffeine exceeded acute toxicity levels in rivers.

GRAPHICAL ABSTRACT



ARTICLE INFO

Editor: Dr. R Teresa

Keywords:
Pharmaceuticals
Industrial chemicals
PFAS
Ionizable substances
Species sensitivity distribution (SSD)

ABSTRACT

Persistent, mobile, and toxic (PMT) substances have recently garnered increased attention by environmental researchers, the water sector and environmental protection agencies. In this study, acute and chronic species sensitivity distributions (SSDs) were retrieved from literature data for previously quantified contaminants of emerging concern (CECs) in Swedish surface waters (n = 92) and risk quotients (RQ) were calculated. To better understand the characteristics of the detected CECs in non-urban lake sites (n = 71), these compounds were checked against established criteria for potentially toxic PMs (PM(T)s) and occurrence in the aquatic environment, respectively. For the CECs with missing SSDs (n = 15 [acute], n = 41 [chronic]), ecotoxicity data were extracted for eight taxonomic groups, and if data were sufficient ($n \geq 3$), SSDs were derived. The retrieved and newly developed SSDs were then used in an environmental hazard assessment (EHA) in the investigated Swedish rivers and lakes. In the rivers, 8 CECs had RQ> 1 in at least one location, and 20 CECs posed a moderate risk ($0.01 < RQ < 1$). In total, 21 of the 71 detected substances had already been identified as PM(T)/vPvM substances. Our study shows the importance of studying field data at large spatial scale to reveal potential environmental hazards far from source areas.

* Corresponding author.
E-mail address: daniel.malnes@slu.se (D. Malnes).

https://doi.org/10.1016/j.jhazmat.2023.131376
Received 6 February 2023; Received in revised form 3 April 2023; Accepted 4 April 2023
Available online 11 April 2023

1. Introduction

Recently, persistent, mobile, and toxic (PMT), as well as very persistent and very mobile (vPvM) substances have garnered attention by environmental researchers, the water sector and environmental protection agencies [5,54]. It has been argued that PMTs pose an equivalent level of concern as the regulated PBT (persistent, bioaccumulative, and toxic) substances [28]. Notably, PMTs could spread on an unknown/uncertain spatial scale, potentially exerting their toxic effects far from the pollution source, and the exposure could be irreversible [28]. These PMT/vPvM substances are mostly associated with substances registered under REACH [3,68], however contaminants of emerging concern (CECs) have also exhibited similar properties of persistence and mobility [39]. In aquatic ecosystems with numerous sources of PMTs, such as lakes with numerous polluted riverine inlets, aquatic fauna far from the polluting source might be affected. Currently, many substances have been labelled potential PMTs/vPvMs [1,29,4,43,45,59], however only a few studies have verified the PM properties by field studies of surface waters (e.g., [29,46]). By tracking potential PMs in field studies predicted PM properties of individual CECs can be tested and in case of (prevalent) occurrence also verified. Earlier investigations of PMTs in surface waters have primarily focused on either the occurrence, the challenges for drinking water producers and/or analytical challenges of PMTs, while, to the best of the authors' knowledge, few studies have examined the hazards posed by PMTs present in European surface water environments. Through assessment of the hazards posed by substances with PM and potentially T (PM(T)) properties present in surface water environments, prioritization of PMT reduction can be done.

One way of assessing the hazard posed by chemical pollution is by component-based methods (CBMs), meaning that a comparison between measured environmental concentrations (MECs) and toxicological endpoints from ecotoxicological studies is made [48]. The CBM approach allows for the derivation of predicted no-effect concentrations (PNECs) [17]. Technical guidance documents define two extrapolation methods for estimating PNECs: assessment factor methods and species sensitivity distribution (SSD) methods (EC-JRC, 2003; [62]). Assessment factor methods are based on both acute (effect concentration for 50% of the population, EC50) and chronic toxicity (no-observed effect concentration, NOEC, or EC10) tests (e.g., [21,33]) and the methods are mostly based on three data-rich standard taxonomic groups: algae, crustaceans and fish. For instance, the toxicity of REACH chemicals are required to be tested using these taxonomic groups; therefore, only a small fraction (12%) of all tests reported within the REACH framework have used other taxonomic groups [31,57]. Recently it has been proposed that these three standard taxonomic groups are insufficient for ensuring a non-toxic environment within the Water Framework Directive (WFD), and that the WFD should include five so-called Biological Quality Elements (BQEs): phytoplankton (algae), macrophytes, phytobenthos, benthic invertebrate fauna (crustaceans) and fish [20,48,9]. However, there are other taxonomic groups relevant for freshwater, e.g., those that have declined in abundance in the past decades [26]. In European freshwater environments, 44% of freshwater molluscs and 23% of amphibians are considered threatened, many of which are endemic to Europe [26]. These threat levels can be compared with the commonly assessed freshwater fish (37%) [26] and the BQE aquatic plants (6.6%) [7]. Not only are there currently knowledge gaps of the ecotoxicity for e.g., amphibians ([2,6]), but these threatened taxonomic groups are currently only considered with the SSD method. The SSD for a specific substance can be derived and the impacts on the species assemblage level can be assessed [48], if it fulfils the data requirement of a minimum of 10 no-observed effect concentrations (NOECs) for at least 8 taxonomic groups [15]. However, no consensus has, so far, been reached on the number of tests needed for the statistical aspects of SSD based methods [12,62]. Posthuma et al. [50] has recently suggested a system for prioritization of potentially hazardous substances in need of additional hazard data and/or for management attention, which relies on available toxicity data combined with uncertainty analysis.

The overall aim of this study was to evaluate the environmental hazards posed by CECs in the aquatic ecosystems of Sweden's three largest lakes. The specific objectives were to (i) collect SSD data and ecotoxicity data for 8 freshwater-relevant taxonomic groups and identify potential data gaps; (ii) generate the most protective PNECs using collected ecotoxicity data, and derive SSDs where possible; (iii) assess potential acute and chronic environmental hazards in aquatic ecosystems; (iv) identify verified and potential PM(T) substances in lake inlets and examine evidence of their PM status (v) check for new PMT substances by studying our occurrence data for CECs in remote areas.

2. Materials and methods

2.1. Target substances and their ecotoxicity data

Target substances were selected based on quantified compounds (n = 91) in surface water from a previous field study [39] (Table S1 in Supporting Information (SI)). The substances comprised pharmaceuticals (n = 63), PFAS (n = 10), industrial chemicals (n = 6), anthropogenic tracers (n = 4), personal care products (n = 3), parabens (n = 3), and pesticides (n = 2) measured in three major Swedish lakes (Lake Mälaren, Lake Vättern and Lake Vänern) and their connecting rivers at a total of 37 sampling sites (n_{river}=24, n_{lake}=13) during four different seasons. Experimental and modelled ecotoxicity data for eight taxonomic groups were collected for all the 91 compounds, and available SSDs (acute and chronic) based on experimental data were collected from Posthuma et al. [50]. Missing SSDs were derived by using the collected experimental and modelled data and each target substance was assigned a four-digit score depending on the quality of (1) SSD fullness, (2) biodiversity coverage, (3) data origin quality, and (4) extrapolation quality as described in Posthuma et al. [50] (Table S2 in SI). Modelled acute toxicity values, within the applicability domain of QSAR, were considered when deriving SSDs, with the exception for the genus *Lemna spp* which was modelled for chronic values only. The SSDs were calculated with ETX 2.3 [65]. SSDs with full SSD parameters (i.e., both μ [population median] and σ [population standard deviation]) were evaluated by the Anderson-Darling and Kolmogorov-Smirnov goodness-of-fit tests for (log)normality at 5% significance level, and estimates for the acutely and hazardous concentrations for 5% of the species assemblage (aHC5 and cHC5, respectively), with a 90% confidence interval around the HC5, were generated by ETX. Where toxicological data were insufficient to derive an SSD, i.e., when only one or two ecotoxicity values were available, the assessment factor methods (i.e., PNECs) were used as recommended [15]. The data collection followed a proposed taxonomic-dependent classification of "acute" and "chronic" toxicity, i.e., both endpoint (e.g., (L)EC50 for "acute" and (L)EC5 to (L)EC25, NOEC, LOEC for "chronic") and duration were considered when classifying exposure to the taxonomic groups [31,57].

Experimental values were collected from WikiPharma Database [42], US EPA ECOTOX (https://cfpub.epa.gov/ecotox/), ETOX database (http://webetox.uba.de/webETOX/index.do), and RIVM's database (https://rvszoeksysteem.rivm.nl/). In this work, focus was on collecting toxicity data from as many taxonomic groups as possible. Therefore, the lowest toxicity values for the following taxonomic groups were included: algae, crustaceans, fish, phytobenthos, macrophytes, molluscs, rotifer, insects, and amphibians. Species within the taxonomic groups were selected based on previous work [31,57]. To ensure toxicity data of high quality, the Klimisch score has been used historically ([32,57]; (Scientific Committee on Health, Environmental and Emerging Risks) [58]). Others have criticized the consistency of the Klimisch score between assessors, proposing the CRED system as more detailed and consistent [32,40,58]. This study has favoured the use of the CRED system. For complementary and/or comparative purposes, PNECs based on experimental data from the "NORMAN Ecotoxicology database of

lowest verified PNECs" (https://www.norman-network.com/nds/ecotox/lowestPnecsIndex.php) for freshwater were collected.

The models ECOSAR and QSARINS [11] were used where experimental data were lacking. QSARINS was preferentially used for pharmaceuticals and personal care products, as QSARINS has been deemed better fitted for these groups of chemicals [27,38,56]. If ECOSAR generated several outputs for the same compound, the most conservative option was selected. The relevance and reliability of experimental studies and QSAR predictions were assessed according to an established workflow [21]. If an experimental study showed the lowest value for a substance, the reliability and relevance of the study were further assessed by following the CRED method [40] using the SciRAP tool [41].

Risk quotients or PAFs were calculated based on measured environmental concentrations (MECs) from Malnes et al. [39], and optimized risk quotients (RQ_f) were calculated as described in Zhou et al. [69] and Eq. 1:

$$RQ_f = RQ \times F = \frac{MEC}{PNEC} \times \frac{NO_1}{NO_2} \quad (1)$$

where MEC: measured environmental concentration [μg/L]; PNEC: predicted no effect value [μg/L]; NO_1: number of samples with concentrations higher than PNECs [unitless]; NO_2: total number of samples [unitless].

Building on the same concept as RQ_f, an SSD-equivalent (PAF_f) was introduced where available. For the calculation of PAF_f, concentrations were transformed into PAFs, according to Eq. 2:

$$PAF - NOEC = \Phi(c_N), c_N = \frac{\log_{10}(c) - \mu}{\sigma} \quad (2)$$

where PAF-NOEC: potentially affected fraction, no observed effect concentration [%]; Φ: standard normal cumulative distribution function; c_N: z-value, standardized (species) sensitivity units; c: concentration [μg/L]; μ: population median [$\log_{10}$ μg/L]; σ: population standard deviation [$\log_{10}$ μg/L] [49].

Thereafter, PAF_f could be calculated by Eq. 3:

$$PAF_f = \frac{MEC}{PAF - NOEC} \times \frac{N_{PAF-NOEC_i>5\%}}{N_{samples}} \quad (3)$$

Where MEC and PAF-NOEC as described above, $N_{PAF\text{-}NOEC,i>5\%}$: number of samples exceeding the 95% protection limit for substance *i* [unitless]; $N_{samples}$: total number of samples [unitless].

Each collected sample, including those collected at same sites but at different occasions, were evaluated as their own entities.

2.2. Persistent, mobile and toxic substance classification

In this study, target substances were also classified in terms of persistence, mobility, and toxicity. A literature search was performed in SCOPUS to identify previously known persistent and mobile organic compounds (PMs). Search terms included "persistent", "mobile", "PMT", "vPvM", "PMOC* " (abbreviation for "persistent and mobile organic compounds"), "surface water", "lake* ", and "river* ". The search results were limited to results after 2017, as that year, the definition criteria of PMs and PMTs were updated by expert authorities [45]. To evaluate potential PM/PM(T) substances for the remaining CECs, their respective properties were examined according to existing criteria detailed below.

2.2.1. Persistence in surface waters

It has been suggested that the persistence assessment should be evaluated through a step-wise approach [15], briefly: "(i) readily biodegradable (OECD 301-tests); (ii) screening information (e.g., enhanced ready biodegradation tests, or specific inherent biodegradation tests); (iii) other information useful in a *Weight-of-Evidence* approach (e.g., abiotic degradation, applicable QSARs, monitoring data, simulation test results etc); and (iv) aerobic biodegradation, if technically feasible (OECD TG 309-tests)". While several environmental degradation processes exist, it is mainly aerobic biodegradation that is considered [14]. However, photodegradation and hydrolysis can be factored into the degradation assessment [14]. An extended discussion regarding environmental persistence is available in SI (Text SI.1).

Aerobic biodegradation data was gathered from literature or models. The combination of the BIOWIN2 and BIOWIN3 [64] model results were used, as suggested by ECHA [14]. Substances modelled with BIOWIN2 and BIOWIN3 models generated outputs not listed as 'non-persistent' (nP), 'persistent' (P), nor 'very persistent' (vP). Some interpretations have been made, however, as to 'convert' the results into the REACH-relevant categories nP, P and vP (i.e., BIOWIN results <'Weeks-Months', 'Months', and 'Recalcitrant' corresponds to 'nP', 'P′, and 'vP', respectively) [25,36]. The same conversions have been made in this study.

As *Weight-of-Evidence*, monitoring, photodegradation, and hydrolysis data were used to make an assessment of the overall persistence of a substance [14]. The *Weight-of-Evidence* and modelled degradation processes were not used to definitively dismiss a substance as persistent, as e.g., monitoring studies may suffer from shortcomings in analytical methods [14].

HYDROWIN [64] was used to model CECs' hydrolysis rate. For the photodegradation studies, preference was given to natural irradiation or with a filtered Xenon lamp (with environmentally relevant wavelengths, i.e., wavelengths > 290 nm) [10]. Some evidence is available that the direct photolysis quantum yield (a property of a compound which can be compared across studies) can be affected, if a pharmaceutical's pK_a is near the pH of the water [10].

2.2.2. Mobility of the CECs in the aquatic environment

The CECs investigated herein are either permanently charged or ionizable within the range of environmental pHs [61]. As such, the CECs' sorption to sediments typically do not follow the established relationship between solid/liquid partition coefficient (K_d) and organic carbon normalized K_d-values (K_{OC}) developed for neutral substances, but rather their sorption, and consequently their mobility, depend to a high degree on local conditions [61]. Therefore, when available, lake-specific K_d values were preferentially used. When not available, the lowest log K_{OC} in the range of environmental pHs (4−9) was used, and was classified as mobile ('M′) if log $K_{OC} < 4$ and very mobile ('vM') if log $K_{OC} < 3$, as done by Neumann and Schliebner [45].

2.2.3. Toxicity

The toxicity evaluation followed the guidance of the ECHA (2017), with some exceptions. If chronic toxicity < 10 μg/L, it was labeled 'T′, while acute toxicity < 100 μg/L indicated 'Potentially T′ [14]. QSAR values were allowed in the assessment if the values were within the applicability domain, however, maximally reaching the status as 'Potentially T′. The (likely) classification of CECs as "toxic to reproduction" was not considered. An extended discussion of the CEC groups herein is available in SI (Text SI.2).

3. Results and Discussions

3.1. Derivation of SSDs and selection of most protective concentrations

Acute and chronic SSDs were extracted from Posthuma et al. [50] for 84% and 55% of the target substances ($n = 91$), respectively (Tables S3 and S4 in SI). Bisoprolol, perfluorobutanesulfonic acid (PFBS), perfluorohexanoic acid (PFHxA), perfluoroheptanoic acid (PFHpA), perfluorodecanoic acid (PFDA), and tolyltriazole were found to lack both acute and chronic SSDs in Posthuma et al. [50]. However, enough experimental ecotoxicity data was available in databases for derivation of an SSD. Additionally, bisoprolol had a modelled value in a relevant QSAR (QSARINS) within the applicability domain, which was added to the derivation of the SSD. Some extrapolation of experimental toxicity

data, e.g., a NOEC to an EC50 within an acute duration period, followed the system of Posthuma et al. [50]. Table 1 contains the acute SSDs parameters for the six substances, while Table 2 contains chronic SSD parameters for five of the substances. For chronic SSDs of bisoprolol, PFBS, and PFHpA, the evaluation stopped at the population median (Table 2, Table S6) due to lack of data to derive the remaining parameters.

Two acute SSDs (perfluorononanoic acid (PFNA) and perfluorooctanoic acid (PFOA)) and four chronic SSDs (atenolol, bezafibrate, PFNA, and PFOA by Posthuma et al. [50]) were replaced with newly derived SSDs, as the SSD scores were deemed to have a higher taxonomic representation (new SSD score: 1311 vs 1123, and 1311 vs 1124, 2411 vs 1223, 1323 vs 1224) (Figs. S1-S2, Tables S5-S6 in SI). After derivation of SSDs from experimental toxicity data, 92% of substances had acute SSDs and 64% had chronic SSDs.

At a significance level of 5%, all derived SSDs were accepted by the Anderson-Darling and Kolmogorov-Smirnov tests in ETX. For PFOA, the substance with most data points in this study, the difference between the upper and lower estimates of the HC5 (UL HC5 and LL HC5, respectively) ranged from 1.5 up to 2.6 $\log_{10}$ concentration units (Tables 1 and 2). The SSDs with fewer data points exhibited a larger spread This is unsurprising, as the uncertainty for HCx values decreases when $n > 4$ [12]. Posthuma et al. [50] argued that some population standard deviations were unrealistic, i.e., a substance has to have $\sigma \in [0.2, 2]$. PFNA's chronic SSD population standard deviation (Table 2) was slightly outside this range ($\sigma = 2.05$), and the HC5 estimate differed with a factor of 14 $\log_{10}$ concentration units between LL HC5 and UL HC5. This difference between the limits of HC5 estimates for PFNA was among the largest of any substance in Tables 1 and 2. Considering the low number of taxonomic representation ($n = 3$), it could be argued that more data points are needed to derive a more stable/representative SSD [12].

Sorgog and Kamo [62] investigated which PNEC derivation method – AF and SSD method – had the lowest failure probability. It was found that the lowest failure probability varied depending on sample size (n) and population standard deviation (σ); for $n = 3$ and $\sigma > 0.9$, and $n = 6$ and $\sigma > 1.1$, the SSD method was recommended [62]. From Table 2, all but tolyltriazole had $\sigma > 1.1$ and $n < 6$, leading to the conclusion that the SSD method yields PNEC values with a lower failure probability in comparison to AF method for most CECs; the generated PNECs from the SSD method should therefore be used in environmental hazard assessment. While Sorgog and Kamo [62] did not consider $\sigma > 1.5$, it is assumed that the results extrapolate for higher σ, which was the case for 4 of the substances in Table 2. For tolyltriazole, however, the AF method was the preferred PNEC derivation method, as "[*t*]*he failure probability is almost negligible for σ lower than roughly 0.4 […] for any* n" [62].

Of the chronic SSDs developed, there were four instances where non-standard taxonomic groups were the most sensitive. Of most concern, PFHxA's most sensitive taxonomic group, rotifers (1000 μg/L), was more than a factor 10 lower than any of the standard taxonomic groups (96000 μg/L) (Table S6 in SI). Thus, with the assessment factor method for the standard taxonomic groups, the risk to the aquatic ecosystem would have been underestimated for PFHxA. The LL HC5 estimate of PFHxA herein (Table 2) were within environmentally relevant concentration ranges in Sweden [22,39].

The median (average) number of collected ecotoxicity studies for any substance was two (two) for acute toxicity and one (two) for chronic toxicity (Fig. S3 in SI). The lacking experimental data coverage of the different taxonomic groups of the collected ecotoxicity data limits the ability to fully assess the environmental hazard of the CECs ([2,6,63]). This could be problematic, as the estimates of the chronic HC5 in Table 2 suggest that the substances could fall within the range of being classified as toxic (i.e., LLHC5 $\leq$ 10 μg/L $\leq$ ULHC5). Furthermore, the experimental bias towards the standard freshwater taxonomic groups (Fig. S4 in SI) could limit the assessment of the WFD's holistic goal of a non-toxic environment by the unknown (potential) effects on the BQEs. While QSARs help to fill important data gaps, the ones included in this study were limited to the taxonomic groups which already were (relatively) data rich (Fig. S4 in SI). If a CEC has been evaluated with the standard taxonomic groups, and there is a possibility of a substance being labelled toxic by the HC5 estimate, it could warrant investigations of further aquatic taxonomic groups to minimize the error margins of the HC5 as "[*t*]*he goal of ecological risk assessment is, of course, not to protect just a single or few species, but entire assemblages of organisms that comprise exposed communities and ecosystems.*" [2].

The most conservative estimates of acute and chronic toxicities were used for all substances (Figs. S5-S7 in SI) to ensure the highest level of protection of the environment. The chronic toxicity relates to current global practices in environmental quality assessment to minimize ecosystem impacts, whereas the acute toxicity relates to current global practices to quantify likely impacts of chemical pollution [50]. The lowest acute toxicity values were derived from Posthuma et al. [50] (51 substances, 56%), lowest effect concentration (EC, 33 substances, 36%), and the newly derived SSDs (7 substances, 8%) (Fig. S5 in SI). The lowest chronic values were obtained from calculated PNECs (39 substances, 43%), NORMAN (14 substances, 15%), Posthuma et al. [50] (9 substances, 10%), and the newly derived SSDs (7 substances, 8%) (Fig. S6 in SI). 22 (24%) substances did not appear in any source for the chronic values, signifying a lack of chronic toxicity data (Fig. S7 in SI). Of these, clindamycin, loperamide and terbutaline had acute toxicity values < 0.1 mg/L, labelling them as 'potentially toxic' [14]. Of the EC substances, 30 (of 33, 91%) of the most sensitive taxonomic groups were from either algae, crustaceans, or fish (Fig. S7A in SI). Of the PNEC substances, 22 (of 39, 56%) had more than one taxonomic group assessed. Algae, crustaceans, fish, and macrophytes were all assessed for more than 10 of the 22 substances, whereas phytobenthos, molluscs, insects, rotifers, and amphibians were assessed for ≤ 5 substances each. Still, molluscs ($n = 2$), insects ($n = 2$) and rotifers ($n = 1$) had instances where they were the determinant of the PNEC (Fig. S7B in SI), thereby accounting for a relatively high degree of the PNEC in relation to how

Table 1
Acute species sensitivity distribution (SSD) parameters for the substances which lacked both acute and chronic SSDs in the literature.

Substance	n	μ	σ	HC5	LL HC5	UL HC5	SSD quality score
Bisoprolol	3	4.68	0.82	3.09	-1.61	4.16	1324
PFBS (perfluorobutanesulfonic acid)	3	5.97	1.02	4.00	-1.83	5.32	1322
PFHxA (perfluorohexanoic acid)	3	5.06	0.22	4.64	3.40	4.92	1224
PFHpA (perfluoroheptanoic acid)	3	5.13	0.24	4.66	3.26	4.98	1322
PFOA (perfluorooctanoic acid)	6	4.73	1.43	2.23	0.27	3.48	1224
PFNA (perfluorononanoic acid)	3	4.29	0.53	3.26	0.22	3.95	1224
PFDA (perfluorodecanoic acid)	4	4.49	0.66	3.29	1.12	4.00	1222
Tolyltriazole	3	4.69	0.68	3.37	-0.30	4.25	1411

n: Number of tested taxonomic groups; μ: log-transformed median population concentration; σ: log-transformed population standard deviation; HC5: log-transformed median estimate of the hazardous concentration for 5% of the species assemblage; LL HC5: log-transformed lower estimate of the HC5; UL HC5: upper estimate of the HC5. Accompanied by an SSD quality score following the scoring system by Posthuma et al. [50] (Table S2 in SI). Empty cells in population standard deviation (σ) signifies a lack of data to derive the variance.

Table 2
Chronic species sensitivity distribution parameters for substances that lacked both acute and chronic SSDs.

Substance	n	μ	σ	HC5	LL HC5	UL HC5	SSD quality score
Atenolol	5	3.77	1.70	0.75	-3.36	2.39	1311
Bezafibrate	4	3.46	1.83	0.11	-5.97	2.10	1311
Bisoprolol	2	4.02	-	-	-	-	1324
PFBS (perfluorobutanesulfonic acid)	2	5.28	-	-	-	-	1224
PFHxA (perfluorohexanoic acid)	4	4.54	1.29	2.17	-2.10	3.57	1311
PFHpA (perfluoroheptanoic acid)	2	4.41	-	-	-	-	1224
PFOA (perfluorooctanoic acid)	8	2.82	1.15	0.85	-0.83	1.73	1224
PFNA (perfluorononanoic acid)	3	3.47	2.05	0.31	-12.2	2.16	1223
PFDA (perfluorodecanoic acid)	3	2.13	1.96	0.021	-12.9	0.87	1224
Tolyltriazole	3	3.00	0.37	2.29	0.20	2.77	1324

n: number of tested taxonomic groups; μ: log-transformed median population concentration; σ: log-transformed population standard deviation; HC5: log-transformed median estimate of the hazardous concentration for 5% of the species assemblage; LL HC5: log-transformed lower estimate of the HC5; UL HC5: upper estimate of the HC5. Accompanied by an SSD quality score following the scoring system by Posthuma et al. [50] (Table S2 in SI). Cells without values signifies a lack of data to derive the parameters.

often these taxonomic groups were tested. Yet, only in one case, the testing of a non-standard taxonomic group potentially serves as a cautionary example; diclofenac was found to have the most sensitive chronic toxicity value for molluscs (0.041 μg/L) followed by macrophytes (3.8 μg/L), both much lower than for the most sensitive standard taxonomic group (fish, 340 μg/L). Both values for molluscs and macrophytes come from the same study [30], the reliability of which has been questioned [34]. Notably, neither molluscs nor macrophytes would have been protected with the assessment factor method, as the application of an assessment factor of 10 would have underestimated the risk to the aquatic ecosystem. This was due to that algae, crustaceans, and fish (the standard taxonomic groups evaluated) all had chronic toxicity values more than 10 times higher than both molluscs and macrophytes.

Using Posthuma et al. [50], NORMAN's verified lowest PNEC, and collected ecotoxicity data, differences in PNECs were expected. The results presented herein demonstrates that using a mix of sources for deriving PNECs could be beneficial, while reliance on one source alone could negatively affect the hazard assessment. This is likely due to the different sources of literature each method relies on, and the frequency of updates to each method/database. It should be pointed out, however, that the different methods/databases use varying levels of certainty: results from the EC and PNEC relies on available expertise for evaluating the reliability of the results through the CRED system, whereas the NORMAN Ecotoxicology database can provide so-called 'verified PNECs', as determined by ecotoxicology experts. The results from Posthuma et al. [50] has not been verified in the same way as the other two sources (i.e. CRED-evaluated ecotoxicity data and NORMAN verified PNECs); however, more often than not, it is data quantity, rather than quality, which limits SSD representativeness [13]. However, especially when deriving an Environmental Quality Standard, the reliance and reliability of the studies should be factored in [34]. A comparison between the acute and chronic estimates from the sources (EC/PNEC, Posthuma, NORMAN, SSDs) are presented in Figs. S5 and S6 in SI, respectively. The median (average) difference between the estimates were $\log_{10}$ 0.37 μg/L (0.39) between the Posthuma and EC, and $\log_{10}$ 1.9 μg/L (1.8) between the maximum and minimum PNEC, for acute and chronic estimates, respectively. Comparing the assessment factor methods to the SSD method in Table 2, the results from the assessment factors were always within the range of the LL-HC5 and UL-HC5. The HC5 estimates ranged between a factor of 0.1 and 3 as compared to the values derived by the assessment factor methods, i.e., the HC5s and the PNECs yielded similar results.

3.2. Evaluation of risks in surface waters

In the Swedish rivers investigated by Malnes et al. [39], 8 CECs had RQ> 1 in at least one spatiotemporal location (Table 3) and 20 CECs posed a moderate risk (0.01 <RQ<1) (Table S7 in SI). Additionally, PAF-NOEC> 5% was exceeded by 2 CECs (Table 3). Fifty CECs identified or suspected as PM(T)s or vPvM were identified across all rivers (Table S8).

With increasing value of either RQ_f or PAF_f, the greater the hazard potential to the environment of the respective substance. Based on the priority list developed by Zhou et al. [69], there are five categories of environmental risk of RQ_f: high ($RQ_f \geq 1$), moderate ($1 > RQ_f \geq 0.1$), small-scale or endurable ($0.1 > RQ_f \geq 0.01$), negligible ($0.01 > RQ_f > 0$), and safe (RQ_f=0). Substances with no exceedance of RQ (i.e., no RQ_f) posed no environmental hazard. Comparing results to studies using the RQ_f-approach [21,69], two previously unmentioned substances (furosemide and PFOS) were found in the endurable to high-risk interval. Additionally, lamotrigine, oxazepam and venlafaxine have previously been identified as likely posing high risk to the environment, while sertraline, desvenlafaxine, and diclofenac have been suggested to pose moderate risk [21]. Recently, the European Commission established an EU-wide monitoring Watch List, including desvenlafaxine and venlafaxine [16]. The ubiquitous distribution of these two substances (detection frequency 100% and 79%, respectively), and their likeliness of posing toxic effects to the environment (11% and 30% (Table 3), respectively) in this study confirm their relevance on the EU Watch List. Furosemide has been modelled to repeatedly exceed acute toxicity levels in Swedish rivers in an earlier study [35]. This was verified in this study, where furosemide exceeded the acutely hazardous concentration for 3% of the species assemblage (aHC3), i.e., the lowest aHC where the toxic pressure on the directly-affected species can cause loss of one or several secondary species within the same food web (resilience towards secondary deletion) [44,70]. This threshold was exceeded at three occasions, twice at the same place (Fig. 1). Caffeine exceeded aHC3 twice, both at the same place (Fig. 1). More intense sampling efforts could be needed to evaluate the temporal extent of the CECs exceedance of acute and chronic toxicity levels. This information should be compared to the exposure scenarios in the toxicity study of the potentially affected taxonomic group(s), as well as the affected taxonomic group's connectance within the food-web [44]. Three of the river samples had no CECs with any risk to the environment, whereas the remaining had at least one CEC with low risk to the environment (Fig. 1). Multiple sites showed co-occurrence of several hazardous CECs, thereby increasing the risk of additional and synergistic effects from different CECs.

Five CECs were identified as hazardous in the lake samples, due to the combination of exposure and available ecotoxicity data: desvenlafaxine ($n = 50$), diclofenac ($n = 14$), lamotrigine ($n = 5$), sulfamethoxazole ($n = 4$), and propylparaben ($n = 3$) (Fig. 2).

The median number was 3 CECs with some risk to the environment, i.e., RQ> 0.01. Urban lake sites for lake Mälaren, i.e., L1, L2, L7, and L8, were the only sites for the lake which had concentrations of CECs which exceeded a chronic RQ of 1 (Fig. 2). Lake Vänern and Lake Vättern had one site, respectively, which exceeded a chronic RQ of 1 (Fig. 2). Thirty-three CECs with identified or suspected PM(T)/vPvM properties were found in the lakes, 30 CECs of which were found in non-urban lake sites (Table S8 in SI).

Table 3
Detection frequency (DF), calculated risk quotient (RQ), optimized RQ (RQ_f), potentially affected fraction (PAF) and optimized PAF (PAF_f) for substances (n = 91) with at least one sampling site exceeding an RQ of 1, i.e., substances posing high risk to the aquatic environment in the rivers investigated by [39].a.

Substance	DF [%]	0.01 <RQ< 1	RQ> 1	Mean RQ	F [%]	RQf
Clarithromycin	55	13	1	9.4E-04	2	2.0E-05
Bicalutamide	98	30	2	2.3E-03	4	9.6E-05
Desvenlafaxine	100	38	5	3.3E-03	11	3.5E-04
Carbamazepine	100	41	4	6.7E-03	9	5.7E-04
Sertraline	26	11	1	5.4E-02	2	1.1E-03
Daidzein[b]	32	12	3	1.1E-01	6	6.9E-03
Oxazepam	87	29	11	4.3E-02	23	1.0E-02
Venlafaxine	79	22	14	4.0E-02	30	1.2E-02
PFOS	64	4	26	1.3E+ 01	55	7.1E+ 00
Substance	**DF [%]**	**1%<PAF< 5%**	**PAF> 5%**	**Mean PAF**	**F [%]**	**PAF_f**
Caffeine	100	1	1	1.5E-03	2.1	3.25E-05
Furosemide	40	4	15	7.0E-02	32	2.24E-02

a RQ< 0.01: unlikely to represent a risk to the environment; 0.01 <RQ< 1: low to moderate risk to the environment; RQ> 1: high risk to the environment; F: frequency of RQ> 1 exceedance; RQ_f: optimized risk quotient; PAF_f: optimized potentially affected fraction. PFOS: perfluorooctanesulfonic acid. [b] Daidzein has, at least a partially, natural origin [51].

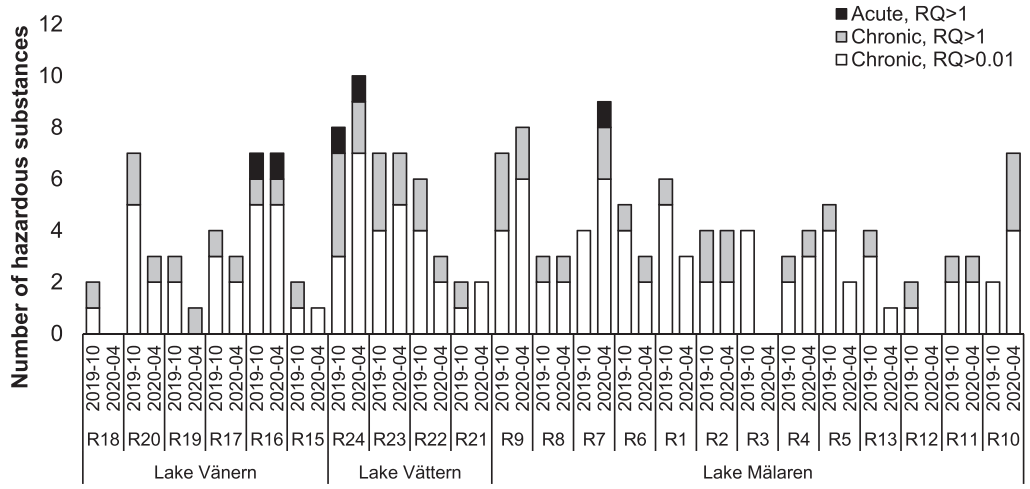


Fig. 1. Number of hazardous substances (out of 91 detected) in river samples entering Lake Vänern, Lake Vättern and Lake Mälaren, Sweden (acute, RQ>1 > chronic, RQ>1 > chronic, RQ>0.01).

While larger bodies of water (e.g., lakes) are thought of as a remediation of pollutants through dilution, the results herein display that the dilution may not be sufficient for some CECs with possible PMT properties as they were exceeding chronic toxicity levels.

3.3. Persistent, mobile, and toxic (PMT) substances

PM substances have the potential of being transported far from their source into the aquatic environment [52]. In the preceding work [39],

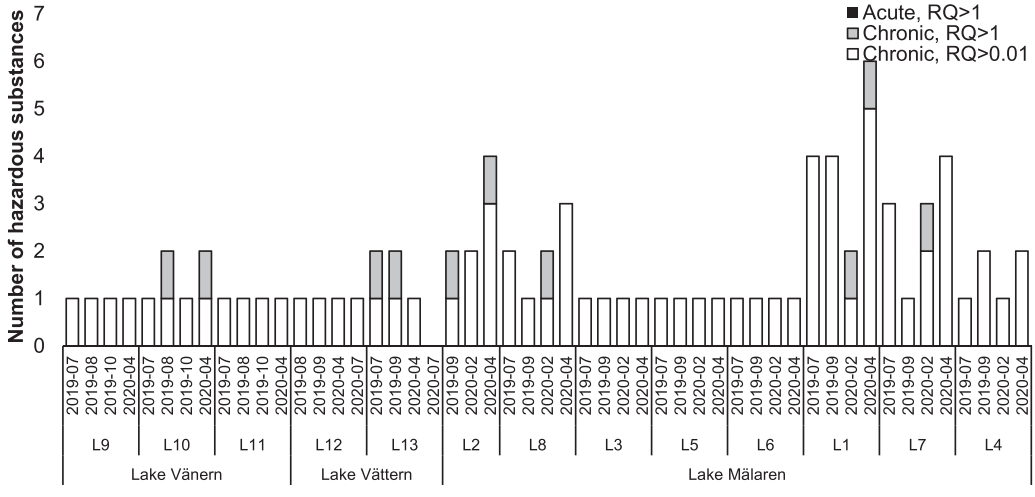


Fig. 2. Number of hazardous substances (out of 71 detected) in Lake Vänern, Lake Vättern and Lake Mälaren, respectively (acute, RQ>1 > chronic, RQ>1 > chronic, RQ>0.01).

some of the 91 detected CECs were argued to be PMs. Twenty of the 91 detected substances had already been identified as PM(T)/vPvM, and an additional 24 have been listed as 'Potential PMT/vPvM' or PM (Table S8 in SI) [1,29,4,43,45,59]. However, three of the suggested PMs (methylparaben, oxybenzone, and sulisobenzone) are listed as readily or inherently biodegradable in their respective ECHA registration dossiers, disqualifying them from the 'P′ criteria [14]. To explore which other CECs could fit the PM(T) criteria, a *Weight-of-Evidence* approach based on detection frequencies (DFs) was applied on monitoring data, accompanied with other available *Weight-of-Evidence* information (Section *2.2.1 Persistence in surface waters*). A subset of sampled lake sites ($n = 9$), namely non-urban sites from Malnes et al. [39], were investigated for potential PM(T)s. This subset of sites was chosen due to their relatively long distance from known point sources, i.e., populated areas, which could indicate environmental persistence [14]. Using a selection criterion of DF $> 0\%$ at the sites, bicalutamide, lamotrigine, nicotine, oxazepam, and tolyltriazole (all DF $\geq 50\%$, PNEC < 10 μg/L) were identified as potential PMT substances (Table 4). Their high occurrence at non-urban lake sites, combined with the *Weight-of-Evidence* presented in Table 4, adds credibility to the potential PM status of these substances.

PFHxS: perfluorohexanesulfonic acid; PFOA: Perfluorooctanoic acid.

While bicalutamide has been identified as 'potential PMT/vPvM' based on modelling results previously (Table S8 in SI) [4], to the best of the authors' knowledge, it is the first time that this strong PMT evidence has been presented for the compound (bicalutamide: P: supplemented with hydrolysis data, aerobic biodegradation based on experimental data rather than modelled data).

Furthermore, the previously identified potential PM substances (Table S8) cetirizine, DEET, PFNA, sucralose, and tramadol were found in DFs$\geq$ 50% at the non-urban sites. These potential PMs' occurrence adds to the credibility of the PM status of these substances. Additionally, fexofenadine and primidone were found in similar DF ranges, which, to the best of the authors' knowledge, was the first time fexofenadine has been identified as a potential PMT candidate. Previously identified PMs with 50%$\geq$DFs$>$ 0% were codeine, FOSA, mirtazapine, and oxycodone. Additionally, carazolol, clindamycin, HCTZ, panthenol, and primidone had 50% $\geq$ DFs $>$ 0%. Additional *Weight-of-Evidence* information of these potential PMs, predicting their environmental fate, can be found in Table S9 in SI. By examining the *Weight-of-Evidence*, some CECs could be disregarded, as their properties do not match the PM(T) profile. Panthenol and HCTZ were predicted to quickly degrade in the aquatic environment. This stresses the need for *Weight-of-Evidence* before conclusions regarding PM status from monitoring data can be drawn. Since no cut-off value for photodegradation persistence currently exists, the analysis for fexofenadine and lamotrigine was not straight-forward. An extended discussion is available in SI (Text SI.3). In essence, it could be argued that fexofenadine might fit the label "transient PM" or "unstable MOC", labels as defined by Arp et al. [3], due to experimental conditions. This discussion also extends to lamotrigine, as it has currently the status of 'potential PMT/vPvM' [4] but has a photodegradation time of 4 days [67].

Primidone has been argued to not have enough data to draw a conclusion of their PMT status [4]. Here, primidone was presented with experimental data for aerobic biodegradation, photodegradation, and monitoring data, as well as modelling results for hydrolysis, mobility and read-across from acute toxicity (Table S9). This combination of data supports the conclusion of primidone as PM, but no definitive conclusion could be reached regarding the 'T′ property. Cetirizine, clindamycin, fexofenadine, mirtazapine, and primidone lacked chronic toxicity tests for all taxonomic groups, only modelled toxicity values were available. Thus, these potential PM substances' chronic ecotoxicity status could be considered unexplored territory.

Currently, PFOS was the only PM(T) substance which had an environmental quality standard (EQS) in surface waters [19]. Proposals for EQSs in surface waters have been suggested for a number of substances: azithromycin, carbamazepine, clarithromycin, diclofenac, erythromycin, ibuprofen, and 24 PFASs [18]. If implemented as proposed, diclofenac would have exceeded the annual EQS in 21% of the river sites, and PFASs would have exceeded the annual EQS in 25% of the investigated lake sites. The most recently established EU-wide Watch List included a number of the previously identified PM(T)s: sulfamethoxazole (potential PMT), trimethoprim (potential PMT), venlafaxine (PMT) and desvenlafaxine (potential PMT), metformin (PM), and BP-3 (PM) [16]. On the same list, the herein identified potential PM(T) substance clindamycin was included. As such, it is expected that more information of the environmental occurrence, and potentially adding more information regarding the environmental persistency and aquatic mobility, of the PM(T)s will be available within the near future. Concentrations of cetirizine and fexofenadine have been found at ng/L levels in one of the lakes studied herein [24,53], concentrations of mirtazapine in other European lakes has been found in pg/L levels [37], while panthenol and primidone were, to the best of the authors' knowledge, unexplored for European lakes. However, both panthenol and primidone has been commonly detected in the low to tens of ng/L levels [23,55] in rivers. Likewise, cetirizine, fexofenadine and panthenol have been detected in WWTP-affected rivers in the hundreds of ng/L levels [23]. While cetirizine, fexofenadine, mirtazapine, panthenol, and primidone have not been included on the upcoming EU-wide Watch List, further studies into the PMT properties of these potential PM substances' could be worthwhile.

Based on their high detection frequency and *Weight-of-Evidence*, cetirizine and fexofenadine should be explored more thoroughly. It has

Table 4
Substances with persistent, mobile, and toxic (PMT) or very persistent and very mobile (vPvM) properties at non-urban lake sites (n = 9). Freshwater persistence as defined in ECHA (2017), mobility as defined by [45].

Substance	Freshwater persistence			Mobility	PNEC (μg/L)
	Aerobic biodegradation	Photo-degradation	Hydrolysis		
Bicalutamide	P[c] vP[d]	NA	5E-03–200 h[a]	log K_d 1.4–1.8[b]	0.092 (T)[e]
Lamotrigine	P[d]	4 d[f]	NA	M-vM[a]	5 (potential T)[†]
Nicotine	nP[d]	NA	NA	vM[a]	1.8 (potential T)[†], 8.8 (potential T)[g]
Tolyltriazole	nP[d]	NA	NA	vM[a]	Potential T (1.58–590)[†]

† HC5/PNEC calculated in this study
[a]US EPA [64]
[b]Golovko et al. [24]
[c]Seller et al. [60]
[d]EPIsuite BIOWIN2&3 models
[e] Panter et al. [47]
[f] Young et al. [67]
[g] Posthuma et al. [50]
nP: not persistent; P: persistent; vP: very persistent nM: not mobile; M: mobile; vM: very mobile NA: not available

been predicted that vertebrates (e.g., fish and amphibians) and metazoa (crustaceans) have drug orthologues for fexofenadine and cetirizine, i.e., that the drug targets have been evolutionary conserved [66]. Since both the antiepileptics carbamazepine and lamotrigine are PMT candidates, the antiepileptic primidone could prove to be harmful.

Cetirizine, clindamycin, fexofenadine, and mirtazapine are all ionisable within the environmentally relevant pH range based on their predicted p*Ka*, meaning that their fate (EC-JRC, 2003; [61]) and toxicity ([8]; EC-JRC, 2003) can drastically alter based on pH. It is the recommendation of the authors that cetirizine, clindamycin, fexofenadine, and mirtazapine should be investigated with regards to their PM criteria under varying pH conditions. Furthermore, if PM criteria are fulfilled for any of the CECs, ecotoxicological studies are recommended for the evaluation of the T criterion.

4. Conclusions

Acute SSDs for bisoprolol, PFBS, PFDA, PFHpA, PFHxA, PFNA, PFOA, and tolyltriazole, as well as chronic SSDs for atenolol, bezafibrate, PFNA, PFDA, PFHxA, and PFOA, were derived. Of the chronic SSDs, all are within the range of being classified as potentially toxic at the HC5-level. Additional ecotoxicity studies are needed to narrow the HC5 estimates. The developed SSDs could be applied in a hazard assessment.

Furosemide and caffeine exceeded acute toxicity levels in some rivers on occasions. Desvenlafaxine, diclofenac, lamotrigine, sulfamethoxazole, and propylparaben were found to exceed no risk to the environment in the lake samples. Of these, lamotrigine, propylparaben, and sulfamethoxazole could be labelled as PMTs. Overall, this study shows the importance of studying field data at large spatial scale to reveal potential environmental hazards in remote areas.

This study contributes to the list of potential PMs and adds credence to the PM status of PM(T)s found at non-urban lake sites. More research is needed to establish the definitive status of the potential PM(T)s, e.g., by examining the PM(T) properties in laboratory studies or in other geographical regions.

Environmental Implication

Recently, persistent, mobile, and toxic (PMT), as well as very persistent and very mobile (vPvM), substances have received increasingly attention. One particular concern for the environment is the spatial distribution and potential toxic effects of PMT substances in remote areas. New species sensitivity distributions (SSDs) were derived for five contaminants of emerging concern (CECs) with potential chronic toxicity (<0.01 mg/L). The exceedance of risk quotients (RQ) in Swedish surface water and the detection of PMT and vPvM compounds at non-urban areas call for source reduction and further monitoring and assessment of CECs in the aquatic environment.

CRediT authorship contribution statement

Daniel Malnes: Writing – original draft, Validation, Methodology. **Sylvia Waara:** Validation, Writing – review & editing. **Romain Figuière:** Methodology, Writing – review & editing· **Lutz Ahrens:** Supervision, Writing – review & editing. **Karin Wiberg:** Supervision, Writing – review & editing. **Stephan J. Köhler:** Supervision, Writing – review & editing. **Oksana Golovko:** 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.

Acknowledgements

Charlie Davey, University of Amsterdam for providing additional ecotoxicological databases. LIFE IP Rich Waters, with support of the EU LIFE programme and Swedish Agency for Marine and Water Management, as well as Mälarens vattenvårdsförbund, Vänerns vattenvårdsförbund, and Vätternvårdsförbundet (funding).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhazmat.2023.131376.

References

[1] Angeles, L.F., Aga, D.S., 2020. Catching the elusive persistent and mobile organic compounds: novel sample preparation and advanced analytical techniques. Trends Environ Anal Chem 25, e00078. https://doi.org/10.1016/j.teac.2019.e00078.
[2] Ankley, G.T., Cureton, P., Hoke, R.A., Houde, M., Kumar, A., Kurias, J., et al., 2021. Assessing the Ecological Risks of Per- and Polyfluoroalkyl Substances: Current State-of-the Science and a Proposed Path Forward. Environ Toxicol Chem 40, 564–605. https://doi.org/10.1002/etc.4869.
[3] Arp, H.P.H., Brown, T.N., Berger, U., Hale, S.E., 2017. Ranking REACH registered neutral, ionizable and ionic organic chemicals based on their aquatic persistency and mobility. Environ Sci: Process Impacts 19, 939–955. https://doi.org/10.1039/C7EM00158D.
[4] Arp, H.P.H., Hale, S.E., 2022. Assessing the persistence and mobility of organic substances to protect freshwater resources. ACS Environ Au 2, 482–509. https://doi.org/10.1021/acsenvironau.2c00024.
[5] Arp, H.P.H., Hale, S.E., 2019. REACH: Improvement of guidance and methods for the identification and assessment of PMT/vPvM substances (No. 126/2019). Umweltbundesamt.
[6] Bean, T.G., Chadwick, E.A., Herrero-Villar, M., Mateo, R., Naidoo, V., Ratter, B., n. d. Do Pharmaceuticals in the Environment Pose a Risk to Wildlife? Environmental Toxicology and Chemistry n/a. https://doi.org/10.1002/etc.5528.
[7] Bilz, M., Kell, S.P., Maxted, N., Lansdown, R.V., 2011. European red list of vascular plants. Publications Office of the European Union, LU.
[8] Boström, M.L., Berglund, O., 2015. Influence of pH-dependent aquatic toxicity of ionizable pharmaceuticals on risk assessments over environmental pH ranges. Water Res, Occur, fate, Remov Assess Emerg Contam Water Water Cycle (Wastewater Drink Water) 72, 154–161. https://doi.org/10.1016/j.watres.2014.08.040.
[9] Brack, W., Escher, B.I., Müller, E., Schmitt-Jansen, M., Schulze, T., Slobodnik, J., et al., 2018. Towards a holistic and solution-oriented monitoring of chemical status of European water bodies: how to support the EU strategy for a non-toxic environment. Environ Sci Eur 30, 33. https://doi.org/10.1186/s12302-018-0161-1.
[10] Challis, J.K., Hanson, M.L., Friesen, K.J., Wong, C.S., 2014. A critical assessment of the photodegradation of pharmaceuticals in aquatic environments: defining our current understanding and identifying knowledge gaps. Environ Sci: Process Impacts 16, 672–696. https://doi.org/10.1039/C3EM00615H.
[11] Chirico, N., Sangion, A., Gramatica, P., Bertato, L., Casartelli, I., Papa, E., 2021. QSARINS-Chem standalone version: a new platform-independent software to profile chemicals for physico-chemical properties, fate, and toxicity. J Comput Chem 42, 1452–1460. https://doi.org/10.1002/jcc.26551.
[12] Del Signore, A., Hendriks, A.J., Lenders, H.J.R., Leuven, R.S.E.W., Breure, A. m, 2016. Development and application of the SSD approach in scientific case studies for ecological risk assessment. Environ Toxicol Chem 35, 2149–2161. https://doi.org/10.1002/etc.3474.
[13] Dowse, R., Tang, D., Palmer, C.G., Kefford, B.J., 2013. Risk assessment using the species sensitivity distribution method: Data quality versus data quantity. Environ Toxicol Chem 32, 1360–1369. https://doi.org/10.1002/etc.2190.
[14] European Chemicals Agency, 2017. Guidance on Information Requirements and Chemical Safety Assessment: Chapter R.11: PBT/vPvB assessment. https://doi.org/10.2823/128621.
[15] European Chemicals Agency, 2008. Guidance on information requirements and chemical safety assessment: Chapter R.10: Characterisation of dose [concentration]-response for environment.
[16] European Commission, 2022. Commission Implementing Decision (EU) 2022/1307 of 22 July 2022 establishing a watch list of substances for Union-wide monitoring in the field of water policy pursuant to Directive 2008/105/EC of the European Parliament and of the Council (notified under document C(2022) 5098) (Text with EEA relevance), OJ L.
[17] European Commission-Joint Research Centre, 2003. Technical Guidance Document on Risk Assessment in support of Commission Directive 03/67/EEC on Risk

Assessment for new notified substances. Commission Regulation (EC) No 1488/94 on Risk Assessment for existing substances. Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market. Part II.
[18] European Parliament and Council of the European Union, 2022. Proposal for a DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL amending Directive 2000/60/EC establishing a framework for Community action in the field of water policy, Directive 2006/118/EC on the protection of groundwater against pollution and deterioration and Directive 2008/105/EC on environmental quality standards in the field of water policy.
[19] European Parliament and Council of the European Union, 2013. Directive 2008/105/EC of the European Parliament and of the Council of 16 December 2008 on environmental quality standards in the field of water policy, amending and subsequently repealing Council Directives 82/176/EEC, 83/513/EEC, 84/156/EEC, 84/491/EEC, 86/280/EEC and amending Directive 2000/60/EC of the European Parliament and of the Council.
[20] European Parliament and Council of the European Union, 2000. Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy, OJ L.
[21] Figuière, R., Waara, S., Ahrens, L., Golovko, O., 2022. Risk-based screening for prioritisation of organic micropollutants in Swedish freshwater. J Hazard Mater 429, 128302. https://doi.org/10.1016/j.jhazmat.2022.128302.
[22] Gobelius, L., Hedlund, J., Dürig, W., Tröger, R., Lilja, K., Wiberg, K., et al., 2018. Per- and polyfluoroalkyl substances in swedish groundwater and surface water: implications for environmental quality standards and drinking water guidelines. Environ Sci Technol 52, 4340–4349. https://doi.org/10.1021/acs.est.7b05718.
[23] Golovko, O., Örn, S., Sörengård, M., Frieberg, K., Nassazzi, W., Lai, F.Y., et al., 2021. Occurrence and removal of chemicals of emerging concern in wastewater treatment plants and their impact on receiving water systems. Sci Total Environ 754, 142122. https://doi.org/10.1016/j.scitotenv.2020.142122.
[24] Golovko, O., Rehrl, A.-L., Köhler, S., Ahrens, L., 2020. Organic micropollutants in water and sediment from Lake Mälaren, Sweden. Chemosphere 258, 127293. https://doi.org/10.1016/j.chemosphere.2020.127293.
[25] Gouin, T., Cousins, I., Mackay, D., 2004. Comparison of two methods for obtaining degradation half-lives. Chemosphere 56, 531–535. https://doi.org/10.1016/j.chemosphere.2004.04.018.
[26] Gozlan, R.E., Karimov, B.K., Zadereev, E., Kuznetsova, D., Brucet, S., 2019. Status, trends, and future dynamics of freshwater ecosystems in Europe and Central Asia. Inland Waters 9, 78–94. https://doi.org/10.1080/20442041.2018.1510271.
[27] Gramatica, P., Cassani, S., Sangion, A., 2016. Aquatic ecotoxicity of personal care products: QSAR models and ranking for prioritization and safer alternatives' design. Green Chem 18, 4393–4406. https://doi.org/10.1039/C5GC02818C.
[28] Hale, S.E., Arp, H.P.H., Schliebner, I., Neumann, M., 2020. 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, 155. https://doi.org/10.1186/s12302-020-00440-4.
[29] Huang, C., Jin, B., Han, M., Yu, Y., Zhang, G., Arp, H.P.H., 2021. The distribution of persistent, mobile and toxic (PMT) pharmaceuticals and personal care products monitored across Chinese water resources. J Hazard Mater Lett 2, 100026. https://doi.org/10.1016/j.hazl.2021.100026.
[30] Joachim, S., Beaudouin, R., Daniele, G., Geffard, A., Bado-Nilles, A., Tebby, C., et al., 2021. Effects of diclofenac on sentinel species and aquatic communities in semi-natural conditions. Ecotoxicol Environ Saf 211, 111812. https://doi.org/10.1016/j.ecoenv.2020.111812.
[31] Saouter, E., Biganzoli, F., Ceriani, L., Versteeg, D., Crenna, E., Zampori, L., et al., 2018. Environmental footprint: Update of Life Cycle Impact Assessment Methods: Ecotoxicity freshwater, human toxicity cancer. In: and non-cancer. Publications Office of the European Union. https://doi.org/10.2760/56750.
[32] Kase, R., Korkaric, M., Werner, I., Ågerstrand, M., 2016. Criteria for Reporting and Evaluating ecotoxicity Data (CRED): comparison and perception of the Klimisch and CRED methods for evaluating reliability and relevance of ecotoxicity studies. Environ Sci Eur 28, 7. https://doi.org/10.1186/s12302-016-0073-x.
[33] Köck-Schulmeyer, M., Ginebreda, A., Petrovic, M., Giulivo, M., Aznar-Alemany, Ò., Eljarrat, E., et al., 2021. Priority and emerging organic microcontaminants in three Mediterranean river basins: occurrence, spatial distribution, and identification of river basin specific pollutants. Sci Total Environ 754, 142344. https://doi.org/10.1016/j.scitotenv.2020.142344.
[34] Leverett, D., Merrington, G., Crane, M., Ryan, J., Wilson, I., 2021. Environmental quality standards for diclofenac derived under the European Water Framework Directive: 1. Aquatic organisms. Environ Sci Eur 33, 133. https://doi.org/10.1186/s12302-021-00574-z.
[35] Lindim, C., de Zwart, D., Cousins, I.T., Kutsarova, S., Kühne, R., Schüürmann, G., 2019. Exposure and ecotoxicological risk assessment of mixtures of top prescribed pharmaceuticals in Swedish freshwaters. Chemosphere 220, 344–352. https://doi.org/10.1016/j.chemosphere.2018.12.118.
[36] Lombardo, A., Manganaro, A., Arning, J., Benfenati, E., 2022. Development of new QSAR models for water, sediment, and soil half-life. Sci Total Environ 838, 156004. https://doi.org/10.1016/j.scitotenv.2022.156004.
[37] Maasz, G., Mayer, M., Zrinyi, Z., Molnar, E., Kuzma, M., Fodor, I., et al., 2019. Spatiotemporal variations of pharmacologically active compounds in surface waters of a summer holiday destination. Sci Total Environ 677, 545–555. https://doi.org/10.1016/j.scitotenv.2019.04.286.
[38] Madden, J.C., Enoch, S.J., Hewitt, M., Cronin, M.T.D., 2009. Pharmaceuticals in the environment: Good practice in predicting acute ecotoxicological effects. Toxicol Lett 185, 85–101. https://doi.org/10.1016/j.toxlet.2008.12.005.
[39] Malnes, D., Ahrens, L., Köhler, S., Forsberg, M., Golovko, O., 2022. Occurrence and mass flows of contaminants of emerging concern (CECs) in Sweden's three largest lakes and associated rivers. Chemosphere 294, 133825. https://doi.org/10.1016/j.chemosphere.2022.133825.
[40] Moermond, C.T.A., Kase, R., Korkaric, M., Ågerstrand, M., 2016. CRED: criteria for reporting and evaluating ecotoxicity data. Environ Toxicol Chem 35, 1297–1309. https://doi.org/10.1002/etc.3259.
[41] Molander, L., Ågerstrand, M., Beronius, A., Hanberg, A., Rudén, C., 2015. Science in risk assessment and policy (SciRAP): an online resource for evaluating and reporting in vivo (eco)toxicity studies. Hum Ecol Risk Assess: Int J 21, 753–762. https://doi.org/10.1080/10807039.2014.928104.
[42] Molander, L., Ågerstrand, M., Rudén, C., 2009. WikiPharma – a freely available, easily accessible, interactive and comprehensive database for environmental effect data for pharmaceuticals. Regul Toxicol Pharmacol 55, 367–371. https://doi.org/10.1016/j.yrtph.2009.08.009.
[43] Montes, R., Aguirre, J., Vidal, X., Rodil, R., Cela, R., Quintana, J.B., 2017. Screening for polar chemicals in water by trifunctional mixed-mode liquid chromatography–high resolution mass spectrometry. Environ Sci Technol 51, 6250–6259. https://doi.org/10.1021/acs.est.6b05135.
[44] Mulder, C., Boit, A., Mori, S., Vonk, J.A., Dyer, S.D., Faggiano, L., et al., 2012. 1 - Distributional (In)Congruence of Biodiversity–Ecosystem Functioning. In: Jacob, U., Woodward, G. (Eds.), Advances in Ecological Research, Global Change in Multispecies Systems Part 1. Academic Press, pp. 1–88. https://doi.org/10.1016/B978-0-12-396992-7.00001-0.
[45] Neumann, M., Schliebner, I., 2019. Protecting the sources of our drinking water: The criteria for identifying persistent, mobile and toxic (PMT) substances and very persistent and very mobile (vPvM) substances under EU Regulation REACH (EC) No 1907/2006 (No. 127/2019). Umweltbundesamt [German Environmental Protection Agency].
[46] Neuwald, I., Muschket, M., Zahn, D., Berger, U., Seiwert, B., Meier, T., et al., 2021. Filling the knowledge gap: A suspect screening study for 1310 potentially persistent and mobile chemicals with SFC- and HILIC-HRMS in two German river systems. Water Res 204, 117645. https://doi.org/10.1016/j.watres.2021.117645.
[47] Panter, G.H., Glennon, Y.C., Robinson, J., Hargreaves, A., Murray-Smith, R., 2012. Effects of the anti-androgen, bicalutamide, in a reduced life-cycle study with the fathead minnow (Pimephales promelas). Aquat Toxicol 114–115, 31–38. https://doi.org/10.1016/j.aquatox.2012.02.002.
[48] Posthuma, L., Altenburger, R., Backhaus, T., Kortenkamp, A., Müller, C., Focks, A., et al., 2019. Improved component-based methods for mixture risk assessment are key to characterize complex chemical pollution in surface waters. Environ Sci Eur 31, 70. https://doi.org/10.1186/s12302-019-0246-5.
[49] Species Sensitivity Distributions in Ecotoxicology. In: Posthuma, L., Suter II, G.W., Traas, T.P. (Eds.), 2002. Environmental and Ecological Risk Assessment. Lewis Publishers.
[50] Posthuma, L., van Gils, J., Zijp, M.C., van de Meent, D., de Zwart, D., 2019. Species sensitivity distributions for use in environmental protection, assessment, and management of aquatic ecosystems for 12 386 chemicals. Environ Toxicol Chem 38, 905–917. https://doi.org/10.1002/etc.4373.
[51] Rearick, D.C., Fleischhacker, N.T., Kelly, M.M., Arnold, W.A., Novak, P.J., Schoenfuss, H.L., 2014. Phytoestrogens in the environment, I: occurrence and exposure effects on fathead minnows. Environ Toxicol Chem 33, 553–559. https://doi.org/10.1002/etc.2461.
[52] Reemtsma, T., Berger, U., Arp, H.P.H., Gallard, H., Knepper, T.P., Neumann, M., et al., 2016. Mind the gap: persistent and mobile organic compounds—water contaminants that slip through. Environ Sci Technol 50, 10308–10315. https://doi.org/10.1021/acs.est.6b03338.
[53] Rehrl, A.-L., Golovko, O., Ahrens, L., Köhler, S., 2020. Spatial and seasonal trends of organic micropollutants in Sweden's most important drinking water reservoir. Chemosphere 249, 126168. https://doi.org/10.1016/j.chemosphere.2020.126168.
[54] Rüdel, H., Körner, W., Letzel, T., Neumann, M., Nödler, K., Reemtsma, T., 2020. Persistent, mobile and toxic substances in the environment: a spotlight on current research and regulatory activities. Environ Sci Eur 32, 5. https://doi.org/10.1186/s12302-019-0286-x.
[55] Ruff, M., Mueller, M.S., Loos, M., Singer, H.P., 2015. Quantitative target and systematic non-target analysis of polar organic micro-pollutants along the river Rhine using high-resolution mass-spectrometry – identification of unknown sources and compounds. Water Res 87, 145–154. https://doi.org/10.1016/j.watres.2015.09.017.
[56] Sangion, A., Gramatica, P., 2016. Hazard of pharmaceuticals for aquatic environment: Prioritization by structural approaches and prediction of ecotoxicity. Environ Int 95, 131–143. https://doi.org/10.1016/j.envint.2016.08.008.
[57] Saouter, E., Biganzoli, F., Pant, R., Sala, S., Versteeg, D., 2019. Using REACH for the EU environmental footprint: building a usable ecotoxicity database, Part I. Integr Environ Assess Manag 15, 783–795. https://doi.org/10.1002/ieam.4168.
[58] SCHEER, 2017. Scientific Advice on Environmental Quality Standards. Publications Office of the European Union, LU.
[59] Scheurer, M., Sandholzer, A., Schnabel, T., Schneider-Werres, S., Schaffer, M., Börnick, H., et al., 2021. Persistent and mobile organic chemicals in water resources: occurrence and removal options for water utilities. Water Supply 22, 1575–1592. https://doi.org/10.2166/ws.2021.336.
[60] Seller, C., Honti, M., Singer, H., Fenner, K., 2020. Biotransformation of chemicals in water–sediment suspensions: influencing factors and implications for persistence assessment. Environ Sci Technol Lett 7, 854–860. https://doi.org/10.1021/acs.estlett.0c00725.
[61] Sigmund, G., Arp, H.P.H., Aumeier, B.M., Bucheli, T.D., Chefetz, B., Chen, W., et al., 2022. Sorption and mobility of charged organic compounds: how to confront

and overcome limitations in their assessment. Environ Sci Technol 56, 4702–4710. https://doi.org/10.1021/acs.est.2c00570.

[62] Sorgog, K., Kamo, M., 2019. Quantifying the precision of ecological risk: conventional assessment factor method vs. species sensitivity distribution method. Ecotoxicol Environ Saf 183, 109494. https://doi.org/10.1016/j.ecoenv.2019.109494.

[63] Sumpter, J.P., Johnson, A.C., Runnalls, T.J., 2022. Pharmaceuticals in the aquatic environment: no answers yet to the major questions. Environ Toxicol Chem N/a. https://doi.org/10.1002/etc.5421.

[64] US EPA, 2022. Estim Prog Interface Suite™ Microsoft® Windows, V 4, 11.

[65] Van Vlaardingen, P., Traas, T., Wintersen, A., Aldenberg, T., 2004. ETX 2.0. A program to calculate hazardous concentrations and fraction affected, based on normally distributed toxicity data (No. 601501028/2004). National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands.

[66] Verbruggen, B., Gunnarsson, L., Kristiansson, E., Österlund, T., Owen, S.F., Snape, J.R., et al., 2018. ECOdrug: a database connecting drugs and conservation of their targets across species. Nucleic Acids Res 46, D930–D936. https://doi.org/10.1093/nar/gkx1024.

[67] Young, R.B., Chefetz, B., Liu, A., Desyaterik, Y., Borch, T., 2014. Direct photodegradation of lamotrigine (an antiepileptic) in simulated sunlight – pH influenced rates and products. Environ Sci: Process Impacts 16, 848–857. https://doi.org/10.1039/C3EM00581J.

[68] Zahn, D., Mucha, P., Zilles, V., Touffet, A., Gallard, H., Knepper, T.P., et al., 2019. Identification of potentially mobile and persistent transformation products of REACH-registered chemicals and their occurrence in surface waters. Water Res 150, 86–96. https://doi.org/10.1016/j.watres.2018.11.042.

[69] Zhou, S., Di Paolo, C., Wu, X., Shao, Y., Seiler, T.-B., Hollert, H., 2019. Optimization of screening-level risk assessment and priority selection of emerging pollutants – the case of pharmaceuticals in European surface waters. Environ Int 128, 1–10. https://doi.org/10.1016/j.envint.2019.04.034.

[70] Zijp, M.C., Posthuma, L., van de Meent, D., 2014. Definition and applications of a versatile chemical pollution footprint methodology. Environ Sci Technol 48, 10588–10597. https://doi.org/10.1021/es500629f.