

Contaminants of Emerging Concern in Swedish Freshwater Environments: Sources, Occurrence, and Impacts

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Cover: Organisms in a river polluted by a pulse of persistent, mobile and organic pollutant
(photo: D. Malnes)

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Abstract

Contaminants of emerging concern (CECs) is one of several reasons for the deterioration of surface water quality globally, even though the CECs occur in trace concentrations. This thesis produced new CEC data through a one-year field study for substances which occur in Sweden's three largest lakes and their associated rivers. The purpose was to investigate mass flows and seasonal variations of CECs, as well as estimate the potential ecotoxicological hazard posed by the CECs' occurrence. It was found that numerous CECs occurred in all examined rivers, and that a continuous influx of CECs with suspected hazardous properties into the lakes occurred. Total mass loads of the investigated CECs were estimated from 0.51 to 5.6 kg/day in the influx to the lakes, and from 0.12 to 4.3 kg/day in the outflux from the lakes. Seasonal variations were observed in the aquatic environment for both individual and groups of CECs. This could be due to variations in consumption and environmental conditions. Some of the seasonal variations were being reported for the first time in the academic literature. Many of the CECs were suspected to have the combination of the hazardous properties of persistency, mobility, and toxicity (PMT). Of the 71 CECs detected far from any suspected input into the lakes, 20 had previously been suspected of having PMT properties. Within the remaining 51 CECs, multiple others also had suspected PMT properties. The thesis suggests that CECs with suspected PMT properties should be analysed closer with respect to these properties.

Keywords: environmental contaminants, persistent mobile and toxic (PMT) substances, pharmaceuticals, per- and polyfluoroalkyl substances, seasonal variations

Miljöföroreningar som orsakar oro i svenska sötvattensmiljöer: Källor, förekomst och påverkan

Sammanfattning

Miljöföroreningar som orsakar oro ('Contaminants of emerging concern'; CEC) är en av flera anledningar till försämrad vattenkvalitet för ytvatten globalt, trots att de förekommer i spårkoncentrationer. Denna avhandling har producerat nya CEC data genom en fältstudie som varade under ett år för substanser som förekommer i Sveriges tre största sjöar och deras angränsade vattendrag. Syftet var att undersöka massflöden och säsongsvariationer av CEC samt att uppskatta eventuell ekotoxikologisk påverkan i vattenmiljön relaterad till förekomsten. Det visade sig att ett stort antal substanser var närvarande i alla undersökta vattendrag, och att ett flöde av CEC med misstänkt miljöfarliga egenskaper kontinuerligt sker in i sjöarna. Massflödena för totalhalten av de analyserade ämnena uppskattades variera från 0,51 till 5,6 kg/dag in i sjöarna och variationen i utflödet från sjöarna var 0,12 - 4,3 kg/dag. Säsongsvariationer observerades i vattenmiljön för både individuella samt grupper av CEC. Detta skulle kunna bero på variationer i konsumtion och miljöförhållanden. Några av de observerade säsongsvariationerna rapporterades för första gången i den akademiska litteraturen. Många av de CEC som förekommer i sötvattensmiljön misstänks ha en kombination av icke önskvärda egenskaper: persistens, mobilitet och toxicitet (PMT). Av de 71 CEC som detekterades långt från misstänkta källområden i sjöarna hade 20 av dessa misstänkta PMT egenskaper sedan tidigare. Bland de resterande 51 fanns ytterligare substanser med misstänkta PMT egenskaper. Avhandlingen föreslår att CEC med misstänkta PMT egenskaper bör analyseras närmare med avseende på dessa egenskaper.

Nyckelord: miljöföroreningar, persistenta, mobila och toxiska (PMT) ämnen, läkemedelsrester, per- och polyfluorerade alkylsubstanser, säsongsvariationer

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List of publications

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- I. **Daniel Malnes**, Lutz Ahrens*, Stephan Köhler, Malin Forsberg, Oksana Golovko* (2022). Occurrence and mass flows of contaminants of emerging concern (CECs) in Sweden's three largest lakes and associated rivers. *Chemosphere*, 294, 133825.
- II. **Daniel Malnes***, Sylvia Waara, Romain Figuière, Lutz Ahrens, Karin Wiberg, Stephan Köhler, Oksana Golovko (2023). Hazard screening of contaminants of emerging concern (CECs) in Sweden's three largest lakes and their associated rivers. *Journal of Hazardous Materials*, vol 453, 131376.

Papers I and II are published under open access license (CC BY 4.0).

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The contribution of Daniel Malnes to the papers included in this thesis was as follows:

- I. Main responsibility for sample collection, laboratory experiments, data analysing, interpretations, writing.
- II. Planned the study together with the co-authors. Main responsibility for methodology, data handling, validation, interpretations, writing and submission.

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Abbreviations

AD	Applicability domain
ATBC	Tributyl citrate acetate (acetyl tributyl citrate)
CECs	Contaminants of emerging concern
CRED	Criteria for reporting and evaluating ecotoxicity data
DEET	Diethyltoluamide
EFSA	European Food Safety Agency
EU	European Union
HCTZ	Hydrochlorothiazide
HC _x	Hazardous concentration for x% of species
HLB	Hydrophilic lipophilic balance
ISs	Internal standards
JRC-EC	Joint Research Centre (European Commission)
LOQ	Limit of quantification
MEC	Measured environmental concentration
MEC95	Measured environmental concentration in the 95 th percentile
MS/MS	Tandem mass spectrometry
NOEC	No-observed effect concentration

NSs	Native Standards
PE	Personal equivalents
PFAS	Per- and polyfluorinated alkyl substances
PFNA	Perfluorononanoic acid
PFOA	Perfluorooctanoic acid
PM	Persistent and mobile compound
PMT	Persistent, mobile, and toxic compound
PNEC	Predicted no effect concentration
QSAR	Quantitative structure-activity relationship
RQ	Risk quotient
SPE	Solid-phase extraction
SSD	Species sensitivity distribution
TBEP	Tris(2-butoxyethyl) phosphate
UPLC	Ultraperformance liquid chromatograph
WFD	Water Framework Directive
WWTP	Wastewater treatment plant

1. Introduction

1.1 Contaminants of emerging concern (CECs)

Contaminants of emerging concern (CECs, also called: ‘emerging contaminants’, ‘emerging pollutants’, ‘organic micropollutants’, etc.) are a collection of anthropogenic chemicals with widely different application areas for human use (Richardson and Kimura, 2020; Richardson and Ternes, 2022; Tousova et al., 2017). While lacking a proper definition (Nilsen et al., 2019), CECs have come to be associated with some specific types of contaminants (Sima et al., 2014); Examples of CECs include pharmaceuticals and personal care products, per- and polyfluoroalkyl substances (PFAS), industrial chemicals, and CEC transformation products (Mueller et al., 2023; Richardson and Kimura, 2020; Richardson and Ternes, 2022). CECs can be detected in various environmental matrices in trace concentrations, for instance in water, sediments, soil and biota (aus der Beek et al., 2016; Fu et al., 2022; Luo et al., 2019; Shen et al., 2023; Wei et al., 2021). Furthermore, the fate and transport processes are complex, and can depend on numerous factors (Escher et al., 2020; Sigmund et al., 2022).

It has been acknowledged that CECs have likely been spread across the environment over the past several decades (Pan et al., 2020; Vestel et al., 2016), however multiresidue methods for the CECs’ detection in freshwater only became widespread from the year 2000 (e.g., Chen et al., 2002; Laganà et al., 2004). Since then, there has been an ever-growing body of evidence of CECs contaminating the world’s aquatic environments (e.g., Cousins et al., 2022; Wei et al., 2021; Wilkinson et al., 2022; Yang et al., 2022). The occurrence of CECs in aquatic environments have sparked increasing interest

with respect to the potential effects of CECs. Thus far, it has been demonstrated that CECs can:

- (i) transfer between trophic levels in the freshwater food web (Fu et al., 2022);
- (ii) transfer from freshwater to terrestrial food webs (Koch et al., 2020; Previšić et al., 2021; Richmond et al., 2018);
- (iii) cause human toxicity (Fenton et al., 2021);
- (iv) spread antibiotic-resistant genes in sewer systems, which could spread into the freshwater environment (Bengtsson-Palme and Larsson, 2016; Hutinel et al., 2021);

This in an addition to the still insufficient (Ankley et al., 2021; Sumpter et al., 2022) but emerging evidence of effects that CECs have on aquatic organisms. The occurrence of CECs constitutes an additional concern for the aquatic environment, as:

- (i) CECs are not regularly monitored, however they have increasingly started to be included through the Watch list-mechanism ([JRC-EC] Joint Research Centre (European Commission) et al., 2022, 2020, 2018, 2015);
- (ii) the apical effects of CECs on aquatic species and aquatic ecology are currently understudied (e.g., Ankley et al., 2021; Bernhardt et al., 2017; Kümmerer et al., 2019; Sumpter et al., 2022);
- (iii) emerging evidence suggests that some of the effects of the CECs are not covered in current legislation (e.g., Bertram et al., 2022; Ford et al., 2021); and
- (iv) there is a general trend for anthropogenic chemicals to be designed for increased stability, thereby also affecting their environmental persistency (Kümmerer et al., 2019) .

1.2 Sources of CECs

CEC pollution is a global scale problem (Cousins et al., 2022; Wei et al., 2021; Wilkinson et al., 2022). Once released into the environment, CECs can have direct biological effects (European Environment Agency, 2013), or undergo transformations leading to transformation products (e.g., Bonnot et al., 2023) which could lead to unintended and undesirable effects (Maculewicz et al., 2022; Podder et al., 2021).

There are multiple different ways for CECs to enter the environment; in general, one can classify these as point and diffuse sources (Naidu et al., 2016). Point sources are single locations that are clearly distinguishable from other pollution sources, whereas diffuse sources are rather elusive and are characteristically across broad geographical scales (Naidu et al., 2016).

Urban wastewater treatment plants (WWTPs) are one example of a point source. WWTPs receive wastewater from a range of sources – e.g., the general public, the health sector, and industry – which can affect the composition of the influent wastewater (e.g., Kümmerer et al., 2019; Söregård et al., 2019). Most WWTPs in Sweden had tertiary treatment technologies in 2018 (Åkerblom et al., 2020), however these have proven insufficient to reduce CECs to the effluent wastewater (Golovko et al., 2021). Thus, WWTPs has been important funnels of CECs into the aquatic environment (Finckh et al., 2022; Gollong et al., 2022; Lenka et al., 2021; Tran et al., 2018). It has been suspected that the CECs have affected downstream aquatic environments, due to the CECs' occurrence in effluent wastewater, by e.g., shaping aquatic communities (Bernhardt et al., 2017; McCallum et al., 2019). Implementation of quaternary treatment has been suggested to reduce CECs in certain WWTPs by the end of 2040 (European Commission, 2022). Currently, a major point of discussion is which quaternary treatment could be implemented for the removal of CECs at the affected WWTPs (e.g., European Commission, 2022; Neth et al., 2023; Rizzo et al., 2019).

1.3 Persistency and fate of CECs

Once entered into the aquatic environment, the concentration of CECs is expected to decrease with increasing distance from the point of discharge due to dilution and natural attenuation processes. Significant attenuation processes are typically sorption (Golovko et al., 2020b) and biodegradation (Jaeger et al., 2019), and in some cases photodegradation can transform CECs into less harmful compounds (Carena and Vione, 2020; OECD, 2023; Schmitt et al., 2021). The rate of photodegradation relies on *in situ* light conditions (i.e., strength of solar irradiation) (Schmitt et al., 2021) and on the presence of photosensitizers (Carena and Vione, 2020). While natural attenuation processes decrease CECs concentrations overall, spatiotemporal differences and physicochemical properties of CECs affect their occurrence in downstream aquatic environments.

In recent years a subset of CECs has been suspected to have the combined hazardous properties of environmental persistency, aquatic mobility, and toxicity (PMT), due to their physicochemical properties. The PMT properties entail that CECs: (1) resist typical environmental attenuation processes (e.g., sorption, biodegradation, and photodegradation) due to persistency, (2) can be spatially distributed on an unknown scale due to the mobility, (3) have PM properties that risk increasing the concentration levels to toxic levels (Hale et al., 2020). PMTs have thus garnered increased attention from environmental researchers, the water sector and environmental protection agencies (European Commission, 2020; Rüdél et al., 2020). The continuous input of PMTs into aquatic environments, while being oblivious to their hazardous properties, could lead to a future scenario where it becomes difficult to reverse the environmental exposure when the toxic effects become known (Hale et al., 2020; MacLeod et al., 2014). Similar historical and emerging examples of difficult-to-reverse environmental issues are known (European Environment Agency, 2013); a famous historical example is the rampant use of DDT (Dichlorodiphenyltrichloroethane) without prior awareness of its harmful side effects to non-target organisms (European Environment Agency, 2013). However, it might become even more challenging in the future as the trend for chemical use is trending towards increased volume, diversity, and chemical stability (and thus persistency), resulting in more potential environmental contaminants (Kümmerer et al., 2019; Persson et al., 2022). With the diversity of potential environmental

contaminants, it is of utmost importance to examine available evidence, with regards to their hazardous properties, for CECs found in the environment.

A challenge for assessing a significant fraction of CECs for PMT properties is that CECs are ionisable within the freshwater-relevant pH range in Europe (Escher et al., 2020; Sigmund et al., 2022). This may affect both the environmental fate (e.g., the sorption and photodegradation) and the ecotoxicity (Escher et al., 2020; Sigmund et al., 2022; Young et al., 2014). In a European context, Swedish rivers have a comparatively acidic pH with median pH at 7.0 and a standard deviation of ± 1 pH unit (Boström and Berglund, 2015).

1.4 Hazard assessment of CECs

When evaluating whether a chemical contaminant could be hazardous, a meta-analysis has to be performed with available evidence (EFSA Scientific Committee et al., 2017; Suter and Cormier, 2011). In essence, two main aspects are considered:

- (i) the reliability, relevance, and consistency of the available evidence, in order to answer the overarching question of whether an environmental hazard exists (EFSA Scientific Committee et al., 2017); and
- (ii) if there are uncertainties due to data gaps, how these uncertainties influence the overall hazard assessment (EFSA Scientific Committee et al., 2017).

The importance of these considerations has been reflected in e.g., the academic science-policy literature through encouraging the assessment of the reliability and relevance of ecotoxicity tests (e.g., Kase et al., 2016; Klimisch et al., 1997); increasing consistency in how environmentally hazardous properties are evaluated through the harmonising of existing legislature (European Commission, 2020; van Dijk et al., 2021); and increasing consistency through a harmonised approach to chemical risk assessment of CECs (Dulio et al., 2020).

If hazardous properties have been identified or are strongly suspected for a freshwater contaminant, the European Commission has the Watch list-mechanism at their disposal for the collection of Union-wide environmental monitoring data for unregulated contaminants (JRC-EC 2022, 2020, 2018, 2015). Thus, it can be assessed whether the freshwater contaminant poses a Europe-wide risk. If a freshwater contaminant has been found to pose a hazard to the European water environment, the contaminant could be subjected to future regulation within the EU.

1.5 Regulation of CECs

As a member of the European Union (EU), Sweden implements strategic plans in collaboration with other member states and adheres to directives mandated by the EU.

Among the strategies which are currently in effect, and of importance for this thesis, are the Biodiversity strategy (Directorate-General for Environment (European Commission), 2021), to restore EU biosphere integrity by addressing the main drivers of biodiversity loss e.g., pollution; the Strategic Approach to Pharmaceuticals in the Environment (Deloitte et al., 2019; Directorate-General for Environment (European Commission), 2020), to maintain the societal benefits and simultaneously minimise the environmental impact of pharmaceuticals; and the Zero Pollution Strategy (European Commission, 2020), which aims to use various tools to reduce the occurrence of hazardous substances in circulation within the EU, thus reducing the risk of their spread into the environment.

Among the directives are common-market rules (European Parliament and Council of the European Union, 2022) affecting which (chemical) products can be used; water management policies (European Parliament and Council of the European Union, 2000); and urban wastewater treatment (European Council, 1991) affecting which type of treatments should be used in WWTPs.

In an increasing number of documents and articles, many of the challenges addressed in EU strategies and directives have been acknowledged to be interconnected, e.g., (organic) micropollutants (e.g., CECs), chemical regulation, WWTPs, and biodiversity (European Commission, 2022, 2020; Fantke et al., 2022).

The above-mentioned combination of common Directives and Strategies thus make comparisons of CECs' occurrence, concentrations, and hazards with other EU countries the most relevant.

2. Aims of the thesis

The overall aim of the thesis was to improve the understanding of sources and processes affecting the occurrence and fate of CECs in the Swedish lakes Vänern, Vättern, and Mälaren, as well as their associated rivers. Additionally, the aim was to conduct hazard screening to prioritize detected CECs in terms of ecotoxicological risk and to detect spatial trends.

All three lakes have multiple important values, and it was therefore of high importance to assess occurrence as well as contaminant hazards.

The thesis encompassed the following research questions and hypotheses:

- 1) Can spatial and seasonal trends of CECs in the three Swedish lakes Lake Mälaren, Lake Vänern, Lake Vättern be detected? If so, what factors are important in causing these trends? An important pathway of CECs into the aquatic environment is through wastewater treatment plant effluents. It was hypothesized that CECs' variable consumption pattern and annual variations in environmental attenuation processes cause observable seasonal variations of CECs in wastewater effluent-impacted rivers and lake sites. Furthermore, it was hypothesized that persistent CECs affected lake sites far from the polluting source.
- 2) Can detected CECs pose hazards to aquatic life? It was hypothesized that organisms in river and lake systems can be negatively affected by the occurrence of CECs.



3. Materials and methods

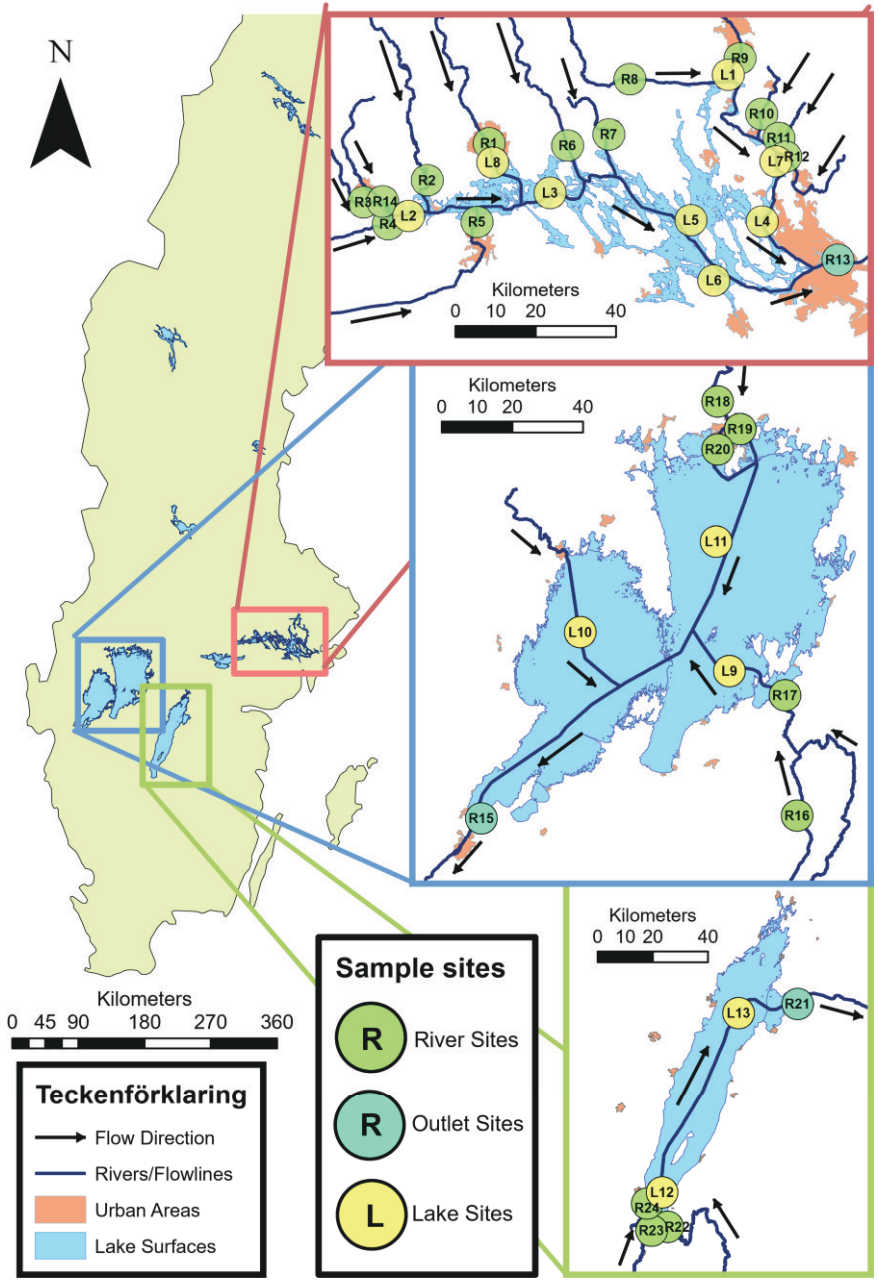
The following sections describes the study designs and provides rationales for the selected methods used.

3.1 Sampling sites and sampling

With a volume of 153, 73.5, and 14.3 km³ for Lake Vänern, Lake Vättern, and Lake Mälaren, respectively (Eklund et al., 2018), the studied lakes represent some of Europe's largest lakes . Major river inlets, identified by median flow, of the studied lakes were also sampled (**Paper I**, Figure 1). The sampled rivers accounted for 16%, 37%, and 79% of the total median water flux to Lake Vänern, Lake Vättern, and Lake Mälaren, respectively (**Paper I**).

Sweden has an overall low population density in comparison to many regions in Europe, albeit with some regional variation (Eurostat - GISCO, 2019). Lakeshore areas of Lake Vänern, Lake Vättern, and Lake Mälaren had a population of 0.3, 0.2, and 3 million, respectively (Eklund et al., 2018). For this thesis, the sampling points of lakes and rivers were mostly performed in the vicinity of populated areas (*viz.* Figure 1) affected by urban WWTP effluents of varying size (WWTPs with personal equivalents [PE] ranging between 3 400 – 180 000, or reference sites with potentially some smaller [$<2\ 000$ PE] on-site sewage facilities) (**Paper I**).

With the above information, it could be expected that the concentrations of CECs in the studied lakes would be at the lower end in a European context.



The sampling sites ($n = 37$) within this project had pH values ranging from 6.5 to 9 with a median of 7.6 ± 0.42 during the studied time. Within the studied sites, the rivers tended to be more acidic (median pH: 7.47 ± 0.36) than the lakes (median pH: 7.8 ± 0.40) (Miljödata-MVM, 2023). However, the pH of assessed rivers were more alkaline than the previously reported for Swedish rivers (median pH: 7.0 ± 1.0) (Boström and Berglund, 2015).

3.2 Standards, reagents, and chemicals

Reference standards were purchased from Sigma-Aldrich (Sweden). Isotopically labelled internal standards were purchased from Wellington laboratories (Canada), Teknolab AB (Kungsbacka, Sweden), Sigma-Aldrich and Toronto Research Chemicals (Toronto, Canada). All analytical standards were of high analytical grade (>95%).

Based on earlier studies of CECs in aquatic environments, a total of 105 target CECs were selected for analysis (Golovko et al., 2021, 2020a, 2020b; Örn et al., 2019; Rehrl et al., 2020). Detailed information regarding purchased substances can be found in Rostvall et al. (2018) and in the Supplementary Information in **Paper I**. These CECs comprise of 71 pharmaceuticals, 13 PFAS, eight industrial chemicals, four PCPs, three parabens, two pesticides, and four others, mostly anthropogenic tracers.

The quantified CECs in **Paper I** ($n = 91$) were subsequently used in **Paper II**.

3.3 Chemical analysis and quality control

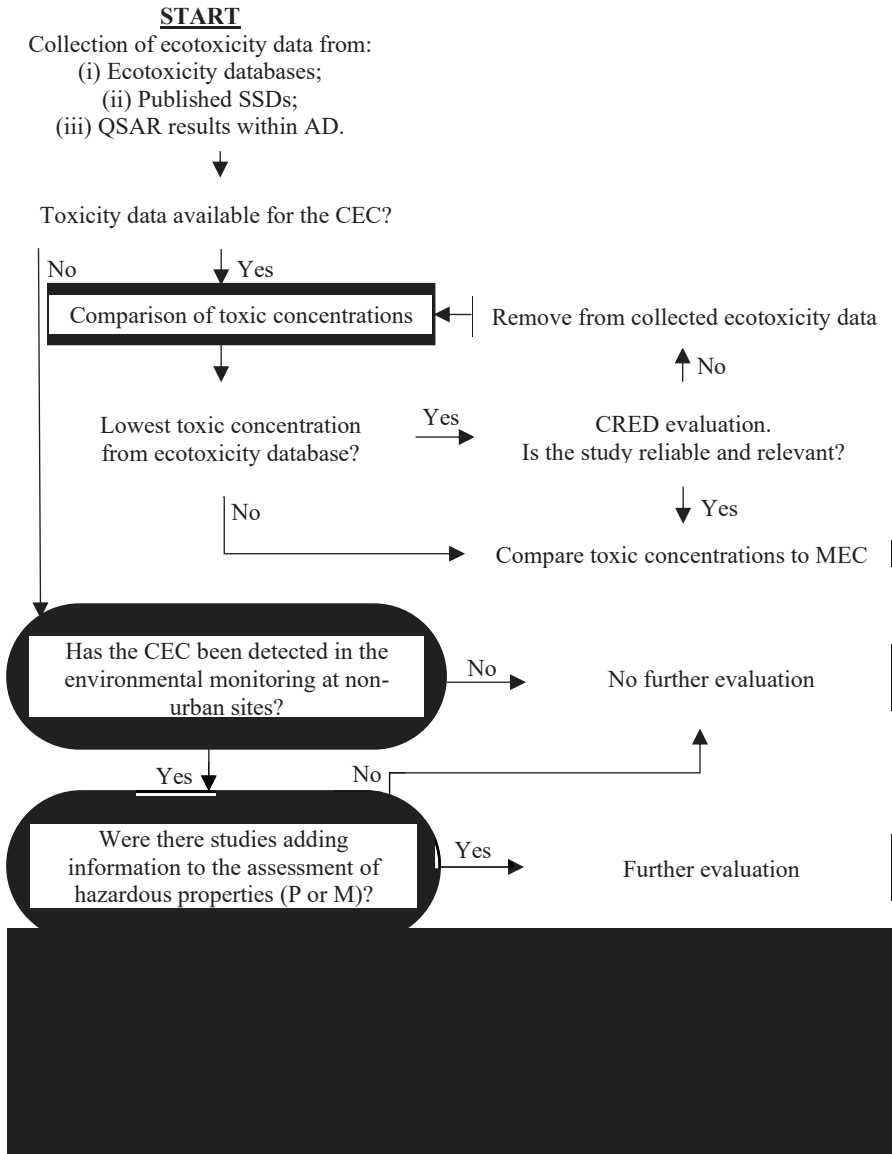
Water samples (500 mL) from rivers ($n = 47$) and lakes ($n = 51$) were extracted by solid-phase extraction (SPE) using Oasis HLB-cartridges (6 mL, 200 mg, 30 μm) following the procedure described by Sörengård et al. (2019). Samples were analysed using a DIONEX UltiMate 3000 ultraperformance liquid chromatograph (UPLC) system (Thermo Scientific, Waltham, MA, USA) coupled to a triple quadrupole mass spectrometer (MS/MS) (TSQ Quantiva, Thermo Fischer Scientific, Waltham, MA, USA). The data were evaluated with Tracefinder 4.1 (Thermo Fischer Scientific, MA, USA). Detailed information on instrument configuration and analysis

is described in the following publications (Golovko et al., 2021; Rehrl et al., 2020; Söregård et al., 2019).

Duplicate samples ($n = 13$) were prepared for every tenth sample. Fortified samples were prepared by spiking samples with internal and native standards (ISs and NSs respectively) before extraction and were prepared for at least one lake sample and one river sample per season (in total $n = 22$). The calibration curves for individual substances (0.05-250 ng/L) generally had R-values >0.99 . The blanks consisted of Milli-Q water ($n = 9$) and were prepared and extracted in the same way as the samples and no target analytes were detected in method blanks. The limit of quantification (LOQ) was calculated as one half of the lowest calibration point in the calibration curve where the relative standard deviation of the average response factor was $<30\%$. For all studied CECs, LOQs were in the range of 0.007 to 30 ng/L. The recoveries were on average 93% for the lake samples and 84% for the river samples. Matrix-matched standards were used to assess the matrix effect and were prepared from sample extract spiked with ISs and NSs at concentration levels equivalent to 20 ng/L and 100 ng/L, respectively. Matrix-matching samples were prepared for at least one lake sample and one river sample per season (in total $n = 13$).

3.4 Hazard assessment

The hazard assessment evaluated the environmentally hazardous properties of persistency, aquatic mobility, and toxicity according to established criteria (European Chemicals Agency, 2017; Neumann and Schliebner, 2019; Saouter et al., 2019). The workflow is briefly presented below (Figure 2), and with more detail in **Paper II**.



3.5 Statistical analysis

A Friedman test followed by a Tukey-Kramer post hoc test was performed to discern seasonal variations for groups of chemicals. After these tests, a visual inspection, now also including statistical uncertainties based on standard deviations, was used. If large overlaps of the statistical uncertainty were detected, then the seasonal variation for the compound (group) was excluded from further assessment.

Relationships between \sum CECs concentrations and various environmental and technical parameters were investigated through use of Pearson correlation tests. The investigated parameters were recipient flow (a proxy of the dilution coefficient), distance from the nearest known WWTP, and the number of PE connected to the nearest WWTP. As the investigated parameters tend to sometimes span several orders of magnitude, a Spearman rho's test was used to investigate the ranked relationships as well.

3.6 Collection of ecotoxicity data

Ecotoxicity data was collected from various sources, including published SSDs (i.e., Posthuma et al., 2019), ecotoxicological databases (WikiPharma (Molander et al., 2009), ECOTOX, and ETOX), and from models (ECOSAR (US EPA, 2022) and QSARINS (Chirico et al., 2021)).

The selection of species within each taxa was based on similar work for REACH chemicals (Saouter et al., 2019), in the direction of legislation-harmonised way to derive a protective concentration (van Dijk et al., 2021) for the wide range of surface waters and aquatic communities which can occur within Europe (European Commission, 2018). This enabled a selection of the most conservative predicted no-effect concentration (PNEC) for any one substance, as well as comparisons of PNECs between the literature ecotoxicity values and the collected ecotoxicity data.

4. Results and discussion

Selected results from Papers I-II are presented and discussed in the following sections.

4.1 Occurrence, mass flows, and seasonal variations of CECs (Paper I)

4.1.1 Occurrence

The concentrations of CECs in the rivers were mostly higher than in the lakes. In the rivers, the \sum CECs concentrations ranged between 31 ng/L and 5 200 ng/L, whereas in the lakes the \sum CECs concentrations ranged between 36 ng/L and 900 ng/L (Figure 3).

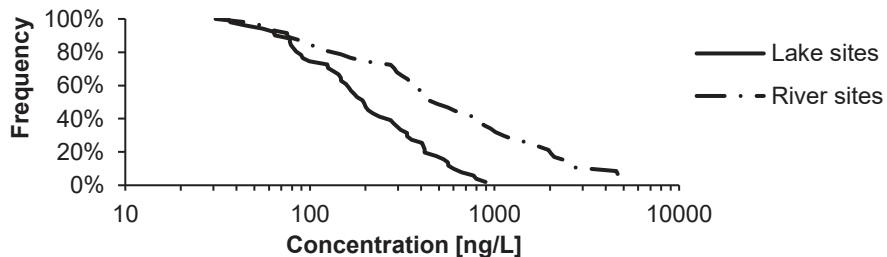


Figure 3. Concentration ranges of \sum CECs in the lake ($n = 51$) and river ($n = 47$) samples. Figure adjusted from Paper I.

Multiple CECs were ubiquitous in the river and lake samples. In the river samples, the following CECs were quantified in every sample: desvenlafaxine, fexofenadine, tributyl citrate acetate (ATBC), carbamazepine, caffeine, tris(2-butoxyethyl) phosphate (TBEP), nicotine,

and diethyltoluamide (DEET). In the lake samples, the following CECs were quantified in every sample: lamotrigine, ATBC, carbamazepine, desvenlafaxine, bicalutamide, DEET, fexofenadine, perfluorooctanoic acid (PFOA), metoprolol, and trisopropanolamine. The results above show a large overlap in the substances present in the rivers and in the lakes, suggesting the flux of CECs from rivers into lakes. In the case of ubiquitous persistent and mobile chemicals (PMs), the accumulation into freshwater lakes is concerning, as the contamination and its associated effects could be long-lasting (Hale et al., 2020; MacLeod et al., 2014). Of particular concern is that these significant inlets were contributing PMs into freshwater lakes with multiple important values – e.g., drinking water production, fishing, and unique ecosystems (Eklund et al., 2018)) – as the effects of the occurrence of PMs were not fully understood or was unknown in many cases.

Some CECs exhibited particularly high concentrations in rivers, e.g., sucralose, caffeine, tolyltriazole, TBEP, losartan, sulisobenzone, metoprolol, and hydrochlorothiazide (HCTZ). At lake sites, the following CECs exhibited high concentrations: sucralose, lamotrigine, laurilsulfate, caffeine, tramadol, sulisobenzone, HCTZ, and lidocaine. Similar maximum concentration levels of these CECs in rivers and lakes have previously been reported in Sweden and in Europe, as further detailed in **Paper I**.

Table 1. Concentrations (ng/L) of contaminants of emerging concern along with the highest concentrations (ng/L) found in the study. Concentrations are given in ng/L. MEC95: measured environmental concentration in the 95th percentile.

Contaminant	River		Lake	
	MEC95	Max	MEC95	Max
Caffeine	18	880	60	91
Hydrochlorothiazide (HCTZ)	220	400	37	54
Lamotrigine	190	230	84	150
Laurilsulfate	220	420	120	40
Lidocaine	54	67	36	50
Losartan	340	460	22	29
Metoprolol	220	400	16	24
Sulisobenzone (benzophenone-4)	200	420	32	59
Sucralose	770	1100	330	370
Tolyltriazole	150	750	18	20
Tris(2-butoxyethyl)phosphate	81	570	11	13
Tramadol	150	290	24	59

The concentration ranges of CECs, and the 95th percentile concentration, provide important information for subsequent hazard assessments, where the concentrations can be compared against predicted no-effect concentrations (Sousa et al., 2018; Touseva et al., 2017).

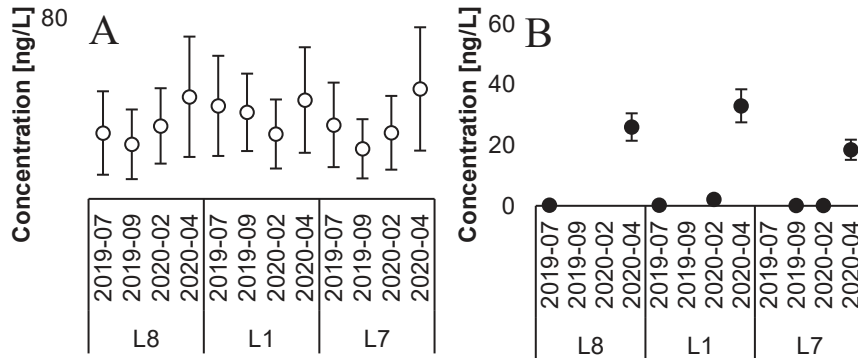
4.1.2 Seasonal variation of CECs

The assessment of seasonal variations was based on mass loads in rivers, to account for the variations of flow and its effects on quantifiable loads throughout the year. In lakes, the assessment of seasonal variations was based on concentrations, as no information could be found for seasonal variations in lake or subbasin volume. Therefore, the calculations proceeded as if the change in lake and subbasin volumes were negligible in relation to the total lake or subbasin volume. Additionally, the seasonal variations in \sum CECs concentration were most pronounced at lake sites close to urban settlements, hereafter referred to as “urban lake sites”, motivating the assessment focus on these sites.

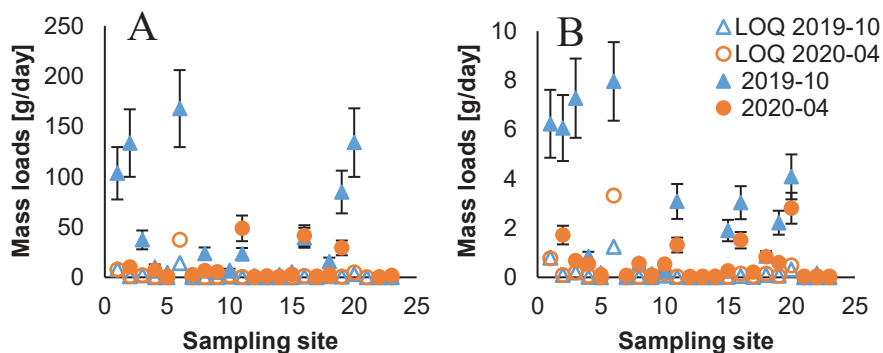
While the presented results could be indicative of seasonal trends, the current refers to it as the more conservative “seasonal variation” due to two important reasons:

- (i) the relatively short time period of monitoring (one year), as previous works have indicated that twelve years could be needed to separate human-induced trends from natural between-year variability for water chemistry parameters (Fölster et al., 2014), and
- (ii) the limitations of the grab sample methodology (Ort et al., 2010).

The Friedman and Tukey-Kramer tests indicated seasonal variations for eight compound groups in the urban lake samples. However, an *ad hoc* investigation of the measurement uncertainties (e.g., sample standard deviation, matrix effects etc.) revealed that the overlaps of compound group ‘industrial chemicals’ were too large to conclude seasonal variations (Figure 4).



For the river samples, a compound-oriented approach was applied, investigating seasonal variation compound-by-compound. The highest detected seasonal variation was for the UV-filter sulisobenzone (benzophenone-4), with loads up to 170 g/day at single river sites during October 2019 compared with the highest load of 50 g/day in April 2020 (Figure 5A). Other relatively consistent across-site seasonal detected include the industrial chemical di-(2-ethylhexyl)phosphoric acid (Figure 5B), with more examples in the SI of **Paper I**.



The seasonal variations of CECs demonstrate that the aquatic environment was exposed to varying compositions and concentrations of CECs throughout the examined period. Different explanations have previously been suggested for seasonal variations of CECs (i) increased use of a product containing a CEC (e.g., Golovko et al., 2014; Moreno-González et al., 2014), e.g., UV-filters in sunscreens during summer; or (ii) variations in environmental degradation processes, e.g., reduced photolysis or aerobic (microbial) degradation (Baena-Nogueras et al., 2017). Indeed, the base-setting conditions for photodegradation of CECs varied throughout the sampling period, as indicated by Figure 6.

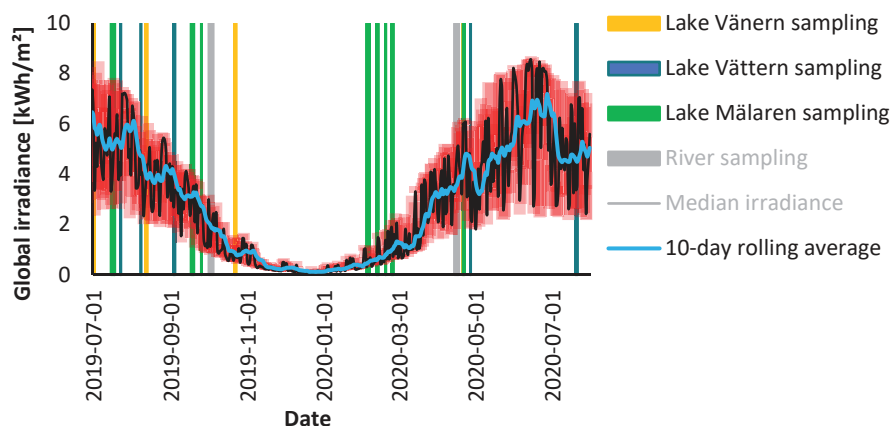


Figure 6. Modelled variations of direct and diffuse sunlight (global [normal] irradiance) reaching the surface of the studied sampling locations. Red bars represent the maximum and the minimum global irradiance modelled for the sampling locations. Data collected from <https://strang.smhi.se/extraction/index.php> (CC BY-SA 4.0, STRÅNG SMHI Open data, without warranties), accessed 2021-12-06. Adjustments made by converting data points into a graphical format as well as conversion of units.

The variations in global irradiance, and thus the base conditions for photolysis, can be described as the summer months having a higher average (generally $>4 \text{ kWh/m}^2$) and larger variations, contrasted by the low average (generally $<0.5 \text{ kWh/m}^2$) and smaller variations during the winter months of the sampling period. No formal analysis was performed to investigate the relationship between photolysis, biodegradation, and CEC concentrations in the freshwater samples to discern whether the seasonal variations were driven by environmental conditions or variations in use/consumption. Thus, Figure 6 is presented as the basic indicator for photodegradation potential at the studied sites, however the importance of the environmental conditions for individual CECs was discussed in more detail in **Paper I**.

4.2 Hazards of CECs (**Paper II**)

Paper II consists of numerous subparts for the environmental hazard assessment, to maximize the utility of the data set from **Paper I**: (1) Collection of ecotoxicity data for the CECs quantified in **Paper I** and, in cases where it was possible and such information was missing from literature, the derivation of species sensitivity distributions; (2) Comparisons of ecotoxicological data from different sources, and an assessment of the quality of the collected ecotoxicity data; (3) A hazard assessment based on the available ecotoxicological data; and (4) An evaluation of potentially hazardous CECs, based on the *weight-of-evidence* approach. In this work, focus will be on (1), (3), and (4), while (2) is elaborated on in **Paper II** main text and SI.

4.2.1 Derivation of Species Sensitivity Distributions (SSDs)

Based on the substance with most taxa tested (perfluorooctanoic acid, PFOA), the lowest and highest estimate of the hazardous concentration for 5% of species (HC5) varied at best 2.6 \log_{10} concentration units. This would mean that the 90% confidence interval for the HC5 ranged between 0.15 and 54 $\mu\text{g/L}$ for PFOA specifically. The largest variance in HC5 confidence interval was found for perfluorononanoic acid's (PFNA) chronic SSD. The HC5 estimates ranged from 0.126 ag/L and 144 $\mu\text{g/L}$. As argued in **Paper II**, in alignment with the European Commission (2018), more taxa (and species) need to be evaluated to resolve uncertainties in the HC5 estimates.

When the HC5s from the SSD methods were used, the median estimate of the HC5 was used, which was in accordance with standard practice for the derivation of environmental quality standards (European Commission, 2018).

4.2.2 Hazards in surface waters

The distribution of available ecotoxicity data for the detected CECs, within the taxonomic group which have previously been considered in European environmental hazard assessments (Saouter et al., 2019), are presented in Figure 7.

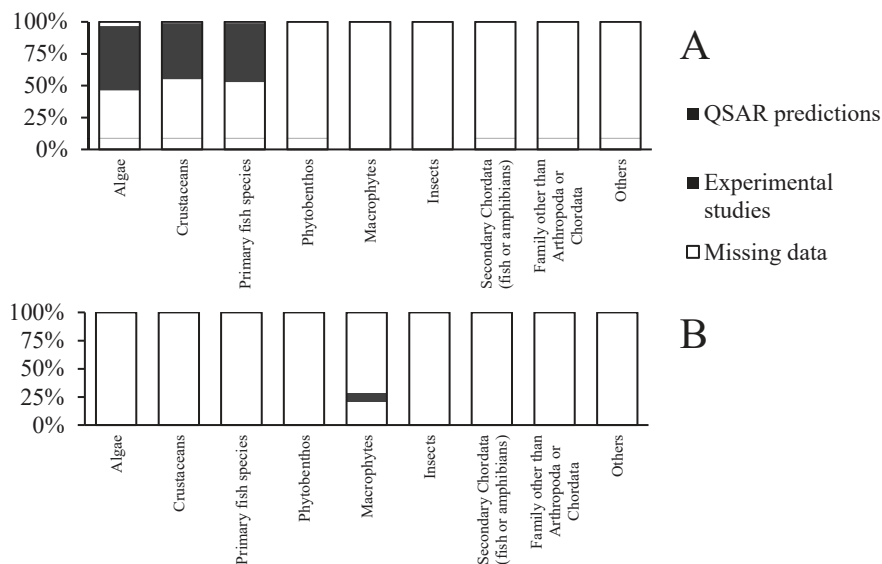
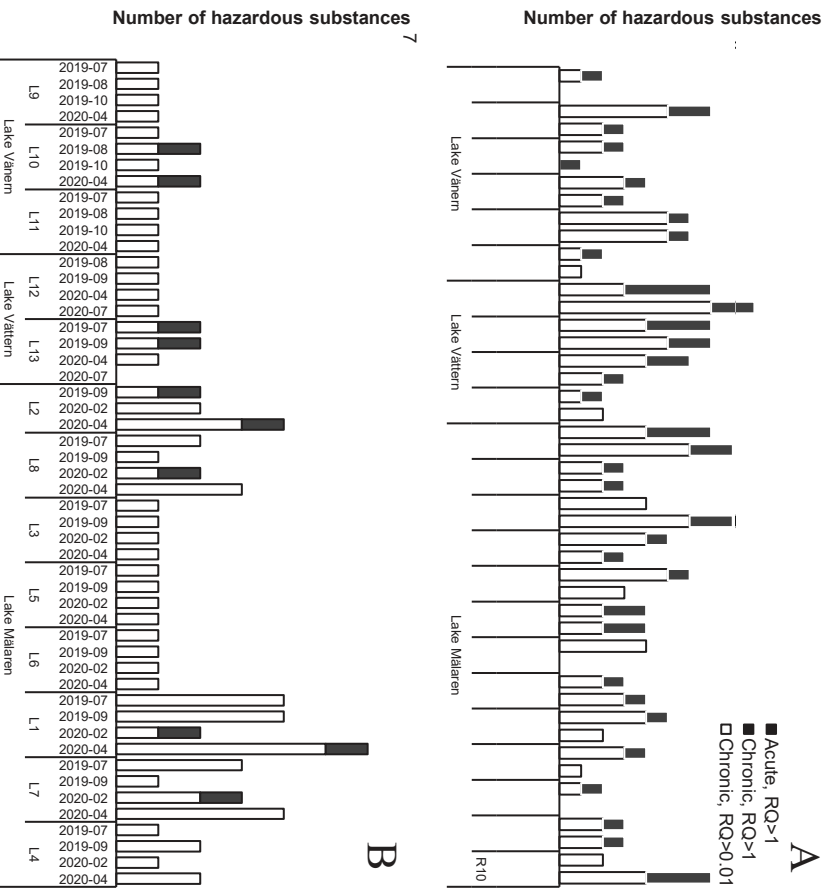


Figure 7. Availability of (A) acute and (B) chronic ecotoxicity data for the substances found in the Swedish freshwater environment, divided into the taxonomic groups considered in European environmental hazard assessment.

Data for acutely toxic effects of the CECs detected in **Paper I** were mostly complete for the basic set of taxonomic classes (i.e., algae, crustaceans, and fish). However, other taxonomic groups lacked such coverage for acute toxicity (Figure 7A), and no taxonomic group had full coverage for chronic toxicity (Figure 7B). Typically, the toxicity property is investigated as the last hazardous property, after other combined hazardous properties of concern (herein, PM properties) have been confirmed (European Chemicals Agency, 2017). The various aspects of environmental hazards posed by CECs were investigated in two separate parts below.

Hazard due to toxicity

The number of hazardous CECs due to toxicity found at the freshwater sites are presented in Figure 8.



Two CECs were acutely hazardous in the rivers, whereas another nine were chronically hazardous. Five CECs were hazardous in lake samples. In the rivers and the lakes, 50 and 33 CECs of the detected CECs respectively had suspected PMT properties.

Hazard due to PM properties

Several CECs were found in the non-urban lake sites – e.g., fexofenadine, hydrochlorothiazide, and primidone – which had thus demonstrated suspected PM properties. Additional persistence studies suggested that primidone was of particular concern. Fexofenadine had studies suggesting transient persistence due to photodegradation, however this information went against the ubiquity of fexofenadine in **Paper I**. Photodegradation was determined to be the major important attenuation process for fexofenadine (Blum et al., 2017). Recently, standardized guidelines were established for the evaluation of direct photolysis as a degradation process (OECD, 2023), thus affecting the discussion of this attenuation process in **Paper II**. The above-mentioned CECs' acute ecotoxicity values were based on either read across or QSAR predictions. Also, none of these CECs had chronic ecotoxicity data. These CECs additionally occurred in concentrations levels which could be considered relatively high in a CEC context, $MEC95_{lakes} > 10$ ng/L and $MEC95_{rivers} > 50$ ng/L. With regards to the CECs' suspected PM properties, the lack of experimental ecotoxicity data, and the relatively high concentrations in freshwaters, these CECs could be suitable candidates for prioritized research into the PMT properties.

The hazard assessment based on this *weight-of-evidence* approach proposed CECs for which further studies could be conducted. However, conclusive evidence for their PM properties could not be reached. This is primarily because (i) Swedish freshwaters are comparatively acidic in a European context (Boström and Berglund, 2015), thus any ionisable CEC's environmental fate could be altered (Escher et al., 2020; Sigmund et al., 2022), and (ii) the CECs were studied on a latitude where solar irradiation varies more than in continental European countries. It was therefore suggested to investigate the hazardous PMT properties in more detail for the CECs identified as 'potential PMTs'.

4.3 General discussion

The results from **Paper I** identified varying occurrence and concentrations of CECs, primarily in the rivers but also at some lake sites. While these seasonal variations were consistent throughout sites, no seasonal hazards were identified in **Paper II**. This could however be due to the lack of ecotoxicity data.

Paper I reinforces the importance of WWTPs as an important funnel of CECs into the aquatic environment. Spatial differences were found throughout both rivers and lakes. In rivers, high concentrations were associated with a low river flow, acting as a proxy for wastewater effluent dilution. It was further reinforced that seasonal variations could be observed in rivers, and it was demonstrated that lake sites close to urban areas were also affected by seasonal variations. The occurrence of suspected PMTs in rivers was demonstrated, with many of the same suspected PMTs also occurring in the lakes.

The results from **Paper II** identified some key knowledge gap areas for the environmental hazard assessment of the studied CECs:

- (i) many of the studied CECs lacked the base set of freshwater ecotoxicological data (i.e., algae, crustaceans, and fish); however, for some CECs, it was deemed not necessary to perform ecotoxicity tests for fish, in an effort to reduce vertebrate toxicity tests (European Parliament and Council of the European Union, 2010);
- (ii) for compliance with the WFD, ecotoxicological data was largely missing for another two taxa, namely phytobenthos and macrophytes. Together with the base set, these five taxonomic groups would constitute the biological quality elements in the studied context;
- (iii) pH-dependent ecotoxicity and environmental fate for ionisable substances were lacking in the literature. While recognised at least more than a decade ago (Franco et al., 2010), this issue has only started to gain momentum again relatively recently (e.g., Escher et al., 2020; Sigmund et al., 2022)

(iv) while the *Weight-of-Evidence* indicated environmental persistence of CECs, experimental biodegradation data and other environmental persistence data were scarce.

These knowledge gap areas impeded a comprehensive hazard assessment.

To address the knowledge gaps, a prioritisation of the CECs which should be evaluated in more detail should be made. The main criterium for the prioritisation was the detection frequency of the CECs in the so-called non-urban lake sites – i.e., sites with no direct anthropogenic input from e.g., WWTPs – and additional persistence data. The occurrence of CECs at these sites could thus indicate environmental persistence and aquatic mobility. Therefore, these CECs have to be prioritized to investigate whether the CECs are at concentration levels that cause harm.

The suggested ‘potential PMT’ primidone was highlighted on the hypothesized basis that its toxic properties could be similar to that of pharmaceuticals of the same class (antiepileptics/anticonvulsants), which have proven hazardous in environmentally-relevant concentrations (e.g., Zhou et al., 2019).

5. Conclusions

The overall aim of this thesis was to improve the understanding of sources and processes affecting the occurrence and fate of CECs in the Swedish lakes, to investigate whether seasonal trends could affect the occurrence of CECs, and to conduct a hazard screening to prioritize CECs in terms of hazardous properties.

Paper I investigated spatial and seasonal variations of CECs in both lakes and river. Spatial variations of CECs' occurrence could be found in both the river and lake sites, which were largely affected by the flow in the recipient (rivers, $r = -0.43$, $p < 0.05$) and distance from urban areas (lakes, not statistically investigated). The investigated time series was not long enough to assess seasonal trends, however seasonal variations were detected. For example, parabens had significant differences between autumn and spring concentrations in lake samples, while the industrial chemical di-(2-ethylhexyl)phosphoric acid had significant mass load differences in the river samples.

Paper II investigated the hazards posed by the CECs in the rivers and lakes. Two substances were acutely hazardous in river sites and another nine were chronically hazardous. Five CECs were identified as hazardous in the lake samples. The study identified several knowledge gaps including a lack of availability of ecotoxicity studies for the CECs investigated. While toxicity is typically the last hazardous property to investigate, a number of other combined hazard criteria were suspected or verified.

The investigated Swedish freshwater environment was exposed to varying concentrations of CECs throughout the investigated year. While seasonal hazards could not be identified, it is acknowledged that ecotoxicity data is still missing.

6. Outlook

The increasing body of evidence of CECs' occurrence in rivers and other water bodies worldwide puts the CECs at the forefront of further investigation into their hazardous properties. Comparisons of occurrences of PMs and PMTs between EU countries could help establish their PM status, particularly between countries with varying freshwater pHs.

While many of the EU's strategies and proposed new directives are yet to materialise, it has been herein shown that the species sensitivity distribution method can help identify areas of improvement for ecotoxicity studies, i.e., in cases where there are large variances in the confidence interval for the chronic HC5.

It has been demonstrated that the *weight-of-evidence* approach is a useful tool for the prioritization of CECs for further research. While the approach was not used to its full potential herein not incorporating information indicative of toxicity beyond the level of a full organism, and not performing uncertainty analysis of missing hazard properties – the evaluation of reliance, relevancy, and consistency of the existing hazard data can help to guide the prioritization process.

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Popular science summary

In recent times, some anthropogenic chemicals used in everyday products – for example pharmaceuticals, Teflon frying pans, dishwasher detergents, cosmetics – have been shown to be harmful to organisms in the aquatic environment. In this thesis, unwanted chemicals which are being flushed away with wastewater have been studied. Wastewater treatment plants often have difficulties removing all hazardous chemicals. Harmful chemicals can thus spread to contaminate rivers and lakes. The thesis has studied:

- (i) Which of these chemicals could be measures as environmental contaminants in surface waters and in which concentrations.
- (ii) How many grams per day of the environmental contaminants are transported with the rivers to and from Sweden's largest lakes.
- (iii) Whether the environmental contaminants had a season variation due to varying consumption or degradation processes.
- (iv) If the concentrations of the environmental contaminants were harmful for organisms in the aquatic environment.
- (v) Which environmental contaminants should be recommended for further research.

The thesis found that:

- (i) Many potentially harmful environmental contaminants were found in the rivers which transported the contaminants to the lakes. Many of the same contaminants could also be found in the lakes.

- (ii) In total 0.51 and 5.6 kg/day of the studied contaminants were added to the lakes via the rivers, and between 0.12 and 4.3 kg/day flowed out from the lakes.
- (iii) Seasonal variations did occur for some contaminants in both rivers and lakes, some of which were new findings and thus not known before.
- (iv) Some contaminants occurred in concentrations which were suspected to be harmful to organisms in the aquatic environment. Some of them were suspected harmful in the long term; while others were suspected harmful also in the short term. For many of the studied environmental contaminants there was not enough information to say whether the concentration levels were harmful or not.
- (v) Among the studied environmental contaminants, some were concluded to be prioritised for further research, among these were active ingredients in pharmaceuticals and chemicals which are contained in dishwasher detergents etc.

Populärvetenskaplig sammanfattning

På senare år har vissa kemiska ämnen som ingår i varor och produkter som används i vardagen – exempelvis läkemedel, teflonpannor, diskmaskinstabletter och kosmetika – visat sig vara skadliga för organismer i vattenmiljön. I denna avhandling har oönskade kemiska ämnen som spolats ned med avloppsvattnet studerats. Avloppsreningsverk har ofta svårt att avlägsna alla farliga ämnen. Skadliga ämnen kan därmed spridas vidare och förorena vattendrag och sjöar. Avhandlingen har studerat:

- (i) vilka av dessa kemiska ämnen som kunde uppmätas som miljöföroreningar i ytvatten och i vilka halter.
- (ii) hur många gram per dag av miljöföroreningarna som transporterades med vattendragen till och från Sveriges största sjöar.
- (iii) om miljöföroreningarna hade ett säsonsberoende som skulle kunna bero på variation i konsumtion eller nedbrytningsprocesser.
- (iv) om halterna av miljöföroreningarna kan vara skadliga för organismer i vattenmiljön.
- (v) vilka miljöföroreningar som bör rekommenderas för vidare forskning.

Avhandlingen fann att:

- (i) många potentiellt skadliga miljöföroreningar återfanns i vattendragen som transporterade dessa ämnen till sjöarna. Många av ämnena detekterades även i sjöarna.
- (ii) totalt tillfördes mellan 0,51 och 5,6 kg per dag av de studerade miljöföroreningarna till sjöarna via vattendragen, och mellan 0,12 och 4,3 kg per dag rann ut från sjöarna.

- (iii) säsongsvariationer förekom för vissa miljöföreningar i både sjöar och vattendrag, varav vissa variationer var nya upptäckter och alltså inte kända sedan tidigare.
- (iv) vissa miljöföreningar uppmättes i halter som misstänks vara skadliga för organismer i vattenmiljön. För en del av dem kan skada ske på lång sikt, medan andra misstänks orsaka skada även på kort sikt. För många av de studerade miljöföreningarna saknades dock underlag för att kunna bedöma om halterna är skadliga eller inte.
- (v) bland de undersökta miljöföreningarna bedömdes några som prioriterade för vidare forskning, bland annat vissa aktiva ämnen i läkemedel och kemiska ämnen som ingår i diskmaskintabletter med mera.

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Occurrence and mass flows of contaminants of emerging concern (CECs) in Sweden's three largest lakes and associated rivers

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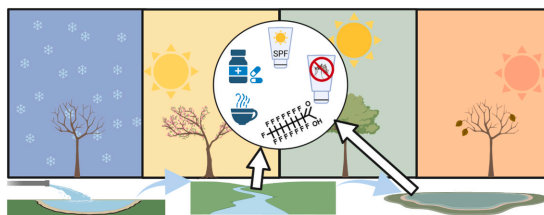
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HIGHLIGHTS

- Trace levels of CECs were found at all drinking water source area sites.
- Many CECs showed seasonal changes in concentrations.
- Riverine CEC concentrations were correlated to distance or discharge of WWTPs.
- Rarely investigated CECs were detected with potential PMT properties.

GRAPHICAL ABSTRACT



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ABSTRACT

Contaminants of emerging concern (CECs) are a concern in aquatic environments due to possible adverse effects on the environment and humans. This study assessed the occurrence and mass flows of CECs in Sweden's three largest lakes and 24 associated rivers. The occurrence and distribution of 105 CECs was investigated, comprising 71 pharmaceuticals, 13 perfluoroalkyl substances (PFASs), eight industrial chemicals, four personal care products (PCPs), three parabens, two pesticides, and four other CECs (mostly anthropogenic markers). This is the first systematic study of CECs in Sweden's main lakes and one of the first to report environmental concentrations of the industrial chemicals tributyl citrate acetate and 2,2'-dimorpholinyl-diethyl-ether. The Σ CEC concentration was generally higher in river water (31–5200 ng/L; median 440 ng/L) than in lake water (36–900 ng/L; median 190 ng/L). At urban lake sites, seasonal variations were observed for PCPs and parabens, and also for antihistamines, antidiabetics, antineoplastic agents, antibiotics, and fungicides. The median mass CEC load in river water was 180 g/day (range 4.0–4300 g/day), with a total mass load of 5000 g/day to Lake Vänern, 510 g/day to Lake Vättern, and 5600 g/day to Lake Mälaren. All three lakes are used as drinking water reservoirs, so further investigations of the impact of CECs on the ecosystem and human health are needed.

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1. Introduction

Contaminants of emerging concern (CECs) constitute a large and diverse group of chemicals, including pharmaceuticals, personal care products (PCPs), and perfluoroalkyl substances (PFASs) (Naidu et al., 2016; Naidu and Wong, 2013). CECs are widely used in industrial and consumer products, and can be released to the aquatic environment from various polluting sources such as wastewater treatment plants (WWTPs) (Ibáñez et al., 2017; Keller et al., 2014; Lindberg et al., 2010; Rostvall et al., 2018; Söregård et al., 2019), on-site sewage treatment facilities (OSSFs) (Blum et al., 2018), landfill leachate (Gobelius et al., 2018), and other sources (Ahrens et al., 2015). Thus, CECs are continuously released into the aquatic environment (Brausch and Rand, 2011; Chen and Ying, 2015; Godoy et al., 2015; Haman et al., 2015; Li, 2014; Meffe and de Bustamante, 2014; Merel and Snyder, 2016; Wilkinson et al., 2017), where they can have long-term adverse effects (Nilsen et al., 2019). Moreover, CECs in aquatic resources used as drinking water sources (Castiglioni et al., 2020) can affect drinking water quality (Karki et al., 2020; Valcárcel et al., 2011).

Earlier research has shown that seasonal variations occur in WWTP influent and effluent (Golovko et al., 2014), rivers (Daneshvar et al., 2010; Gago-Ferrero et al., 2017; Müller et al., 2020), and lakes (Maasz et al., 2019; Rehr et al., 2020). Seasonal variations in WWTP influent might be attributable to consumption patterns (Golovko et al., 2014), but variations in aquatic systems are more complex (Kunkel and Radke, 2011; Li et al., 2016). Once CECs are released into the aquatic environment, their geochemical cycling can be affected by various processes (Rehr et al., 2020). Seasonal variations in the environment can depend on physical (e.g., varying flow patterns and stratification), chemical (photolysis) (Batchu et al., 2014; Blum et al., 2017; Dodson et al., 2011; Trawiński and Skibiński, 2019) and biological (biodegradation) (Baena-Nogueras et al., 2017) factors. In lake systems, temporal variations can occur due to e.g., recreational activities and usage patterns of certain CECs (Mao et al., 2019), or to variations in photodegradation between seasons (Bonvin et al., 2011; Lindholm-Lehto et al., 2016). Spatial variations in lake systems can occur depending on proximity to large-scale WWTPs (Rehr et al., 2020) and WWTP treatment efficiency (Golovko et al., 2021), or other pollution sources, e.g., landfill leachate (Gobelius et al., 2018). Spatiotemporal variations can occur due to fluxes of people, e.g., summer or winter tourism (Maasz et al., 2019; Mandarić et al., 2017). However, more research is needed to better understand the seasonal cycling of CECs in the aquatic environment.

The overall aim of this study was to assess the occurrence and mass flows of CECs in Sweden's three largest lakes and associated rivers. Specific objectives were to (i) evaluate the occurrence of CECs in lake and river waters, (ii) determine the variation between seasons, (iii) estimate the loads of CECs from rivers to the lakes, and (iv) assess the environmental impact of CEC loads. This was the first systematic study of CECs in the three largest lakes in Sweden.

2. Materials and methods

2.1. Standards, reagents, and chemicals

Standards, reagents and chemicals: Reference standards were purchased from Sigma-Aldrich (Sweden). Isotopically labelled internal standards were purchased from Wellington laboratories (Canada), Teknolab AB (Kungsbacka, Sweden), Sigma-Aldrich and Toronto Research Chemicals (Toronto, Canada). All analytical standards were of high analytical grade (>95%).

A total of 105 target CECs were selected for analysis, based on occurrence and distribution in the aquatic environment, and production and consumption patterns (Golovko et al., 2020a, 2020b, 2021; Örn et al., 2019; Rehr et al., 2020). Detailed information about the target contaminants can be found in Table S1A and S1B in Supporting Information (SI) and detailed information about purchased standards,

reagents, and chemicals can be found in text in SI.

2.2. Study sites and sample collection

Lake Vänern, Lake Vättern, and Lake Mälaren are the three largest lakes in Sweden, with a respective area of 5450, 1890, and 1070 km² and a respective volume of 153, 73.5, and 14.3 km³ (Eklund et al., 2018). They are also among the largest lakes in Europe (European Environment Agency, 2018). Lakeshore areas of Lake Vänern, Vättern, and Mälaren have a population of 0.3, 0.2, and 3 million, respectively (Eklund et al., 2018). The water residence time is nine years, 60 years, and three years, respectively (Eklund et al., 2018). All three lakes are vital drinking water reservoirs (Eklund et al., 2018).

Rivers were selected for sampling based on their water flux to the lakes and expected high impact of urbanization or industry (Sonesten et al., 2013) (Table S2 in SI). The selected rivers for Lake Vänern were: Göta älv (R15 in Fig. 1), Ösan (R16), Tidan (R17), and Klarälven (R18-R20). Those for Lake Vättern were: Motala ström (R21), Huskvarnaån (R22), the outlet from Munksjön (R23), and Lillån (R24), and those for Lake Mälaren were Svartån (R1), Kolbäckån (R2), Hedströmmen (R3), Arbogaån (R4), Eskilstunaån (R5), Sagån (R6), Enköpingsån (R7), Örsundaån (R8), Fyrisån (R9), Lövsån (R10), Märstaån (R11), Oxundaån (R12), Norrström (R13), and Köpingsån (R14) (Fig. 1).

Grab samples were collected in polypropylene (PP) or polyethylene bottles. Grab sampling was performed for two sampling events for rivers

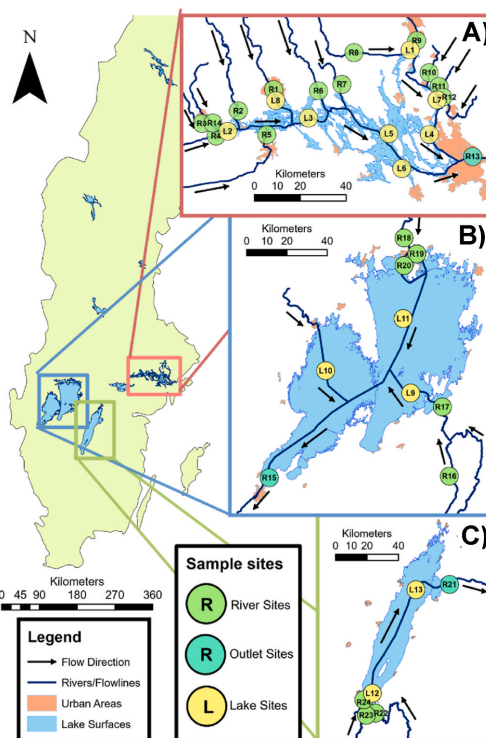


Fig. 1. Map showing surface water sampling locations in rivers (R) and lakes (L) (Lake Vänern (B), Lake Vättern (C), Lake Mälaren (A)) in Sweden.

(October 2019 and April 2020) (in total $n = 47$) and four sampling events for the lakes (Lake Vänern: July 2019, August 2019, October 2019, and April 2020; Lake Vättern: July 2019, September 2019, April 2020, and July 2020; Lake Mälaren: July 2019, September 2019, February 2020, and April 2020) (in total $n = 51$). The lake samples were collected at 0.5 m depth. Detailed information on sampling can be found in Figure S1 in SI. After collection, the samples were stored frozen ($-20\text{ }^{\circ}\text{C}$) in darkness until extraction.

2.3. Sample preparation and UPLC-MS/MS analysis

Water samples (500 mL) from rivers ($n = 47$) and lakes ($n = 51$) were extracted by solid-phase extraction (SPE) using Oasis HLB-cartridges (6 mL, 200 mg, 30 μm) following the procedure described by Söregård et al. (2019). Samples were analyzed using a DIONEX UltiMate 3000 ultraperformance liquid chromatograph (UPLC) system (Thermo Scientific, Waltham, MA, USA) coupled to a triple quadrupole mass spectrometer (MS/MS) (TSQ Quantiva, Thermo Fischer Scientific, Waltham, MA, USA). The data were evaluated with Tracefinder 4.1 (Thermo Fischer Scientific, MA, USA). Detailed information regarding instrument configuration and analysis is described elsewhere (Golovko et al., 2020a, 2020b, 2021; Rehl et al., 2020).

2.4. Quality assurance and quality control

Method performance was evaluated with respect to blanks, precision, relative recovery, matrix effects, limit of quantification (LOQ), and linearity of the calibration curve (Table S1 in SI).

Duplicate samples ($n = 13$) were prepared for every tenth sample. Fortified samples were prepared by spiking samples with internal and native standards (ISs and NSs respectively) before extraction. Fortified samples were prepared for minimum one lake sample and one river sample per season (in total $n = 22$). The calibration curves for individual substances (0.05–250 ng/L) generally had R-values >0.99 . The blanks consisted of Milli-Q water ($n = 9$) and were prepared and extracted in the same way as the samples and no target analytes were detected in method blanks. LOQ was calculated as one half of the lowest calibration point in the calibration curve where the relative standard deviation of the average response factor was $<30\%$. For all studied CECs, LOQs were in the range of 0.007–30 ng/L. The recoveries were on average 93% for the lake samples and 84% for the river samples. Matrix-matched standards were used to assess the matrix effect and were prepared from sample extract spiked with ISs and NSs at concentration levels equivalent to 20 ng/L and 100 ng/L, respectively. Matrix-matching samples were prepared for minimum one lake sample and one river sample per season (in total $n = 13$).

2.5. Statistical analysis

A Friedman test followed by a Tukey-Kramer post hoc test was performed, due to non-normal distribution of the data. Pearson correlation test was used to analyze the relationship between concentration and various parameters.

Data for total CEC concentration, flow, personal equivalents (PE) and distance were ranked from low to high numerical values. The corresponding ranks were then plotted pairwise. Spearman's rho was used to identify which pair of values had the highest observed rho when predicting the ranking of observed total concentration.

2.6. Data analysis

Mass flows of CECs were calculated for all rivers sampled, based on concentration and flow rate (Söregård et al., 2019), using the following equation:

$$m_{CECs,river} = \left(\sum_{i=1}^n C_{analyte(i)} (1 \pm \sigma) \right) \times Q_{river} (1 \pm (1 - NSE)) \times 8.64 \times 10^6$$

where $m_{CECs,river}$ [g/day] is the mass of quantified contaminants in sampled river, $C_{analyte}$ is the concentration of analyte in sample [g/L], σ is the standard deviation of analyte in chemical analysis, is the modeled river flow rate [m^3/s], NSE is the Nash Sutcliffe Efficiency coefficient, and the numerical values are conversion factors [$\text{L s m}^{-3} \text{day}^{-1}$].

3. Results and discussion

3.1. Occurrence of CECs in river water

The \sum CEC concentrations in river water ranged between 31 and 5200 ng/L (mean 1100 ng/L, median 440 ng/L) (Fig. 2, Figure S2 in SI). Of the 105 target contaminants, 92 were detected at least once and 60 were detected in $>50\%$ of all samples (Table S3 in SI). Numerous compounds were detected in all river samples analyzed, including desvenlafaxine (median concentration 11 ng/L; maximum concentration 150 ng/L), fexofenadine (7.8 ng/L; 200 ng/L), tributyl citrate acetate (ATBC) (5.4 ng/L; 29 ng/L), carbamazepine (5.0 ng/L; 91 ng/L), caffeine (4.3 ng/L; 880 ng/L), tris(2-butoxyethyl) phosphate (TBEP) (4.1 ng/L; 570 ng/L), nicotine (3.6 ng/L; 36 ng/L), and diethyltoluamide (DEET) (1.2 ng/L; 32 ng/L) (Table S3 in SI). The highest concentrations were found for sucralose (1100 ng/L), caffeine (880 ng/L), tolyltriazole (750 ng/L), TBEP (570 ng/L), losartan (460 ng/L), sulisobenzone (BP-4) (420 ng/L), metoprolol (400 ng/L), and hydrochlorothiazide (HCTZ) (400 ng/L). On average, pharmaceuticals accounted for approximately 60% of \sum CEC concentrations, followed by other contaminants (20%), industrial chemicals (9%), PCPs (5%), pesticides (3%), PFASs (2%), and parabens (0.5%). The high percentage contribution by the group 'other contaminants' was due to high concentrations of the artificial sweetener sucralose (median concentration 74 ng/L; maximum concentration 1100 ng/L).

Some of the pharmaceuticals found in high concentrations, such as metoprolol and HCTZ, have been detected previously in river waters (e.g., Celić et al., 2019; Maszkowska et al., 2014). Carbamazepine has been detected in numerous studies (e.g., Loos et al., 2009; Tousova et al., 2017), in median concentrations up to 15-fold higher than seen in this study. Ruff et al. (2015) analyzed three antiepileptic drugs in water from the river Rhine and reported a similar combined concentration as seen in the present study (median 64 ng/L; maximum concentration 244 ng/L). High detection frequency and high median concentration of beta-blockers in river water have been reported globally (Maszkowska et al., 2014), with concentrations in surface waters being highest for e.g., metoprolol (Godoy et al., 2015).

For industrial chemicals, except for tolyltriazole (median 15 ng/L), the concentrations were low compared with those reported in other European studies. Wolschke et al. (2011) compared concentrations in rivers in central Europe, where tolyltriazole was typically present in median concentration >100 ng/L and maximum concentration 470 ng/L. TBEP was found ubiquitously in the present study (median 4.1 ng/L), contradicting earlier findings in Sweden (Gustavsson et al., 2018), which could be due to lower LOQ in this study (0.072 ng/L) compared with the previous study (150 ng/L). ATBC was detected in low concentrations in this study (median 5.4 ng/L), whereas seven-fold higher concentrations have been found in Swedish rivers impacted by wastewater (Golovko et al., 2021). To the best of our knowledge, only three other studies have examined ATBC in freshwater environments (Bolívar-Subirats et al., 2021; Golovko et al., 2021; Nagorka and Koschorreck, 2020).

Among PCPs, BP-4 had a detection frequency (DF) of 83% in the present study (median 27 ng/L), whereas the other UV-filter products 3-(4-methylbenzylidene) camphor (4MBC) was not detected and oxybenzone (BP-3) had low DF (38%). The high DF for BP-4 supports previous findings of DF 93% in wastewater-impacted Swedish rivers (Golovko et al., 2021). Non-detection of 4MBC in this study is in contrast to findings in other studies in Sweden (DF 73%; median concentration

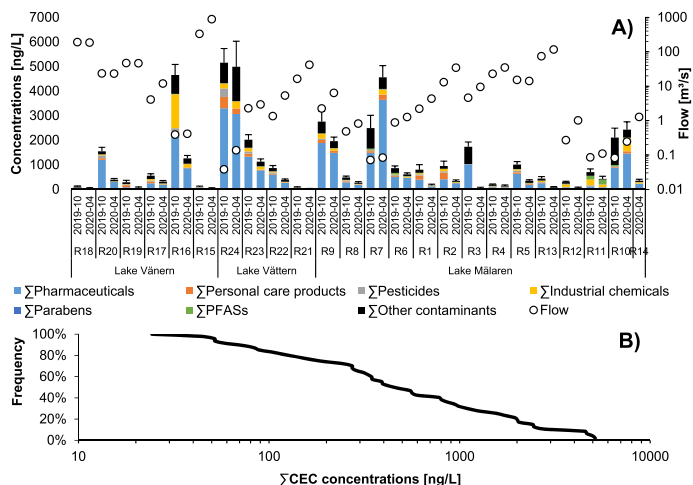


Fig. 2. Σ CEC concentrations in river water samples ($n = 47$). A) Σ CEC concentration and river flow rate; and B) reverse cumulative distribution as a function of Σ CEC concentration.

9.5 ng/L (Golovko et al., 2021), and internationally (DF 86%; median concentration 10 ng/L) (reviewed by Brausch and Rand, 2011).

Among the target pesticides, DEET had DF of 100%, which is similar to the level reported in other studies (e.g., DF 87% in Golovko et al., 2021; DF 94% in Tousova et al., 2017). However, both median and maximum concentration were lower in the present study (1.2 and 32 ng/L, respectively) than in the two earlier studies (23 and 180 ng/L; 17 and 490 ng/L, respectively).

The Σ PFASs concentration (median 8.2 ng/L) was slightly higher than observed by Nguyen et al. (2017) for sites R13, R15, and R21 (median 4.0 ng/L), but site R9 (11 ng/L) had only one-third of the Σ PFASs concentration detected by Nguyen et al. (2017) (33 ng/L). These differences could be due to seasonal variations and decreasing concentrations over time due to introduction of new regulations on PFASs (Gobelius et al., 2018), since samples for this study were collected more recently (2019–2020) than those analyzed by Nguyen et al. (2017) (collected 2013). In addition, C₈-based PFASs have been banned, which has resulted in decreasing concentrations in the environment (Gobelius et al., 2018). This can, for example, explain the low concentrations of PFOA (0.78 ng/L and 1.4 ng/L) and PFOS (1.6 ng/L and 3.1 ng/L) in this study (2019–2020) compared to a previous study on PFOA and PFOS (4.2 ng/L and 5.3 ng/L, respectively, 2013) (Nguyen et al., 2017) at site R9. Other contaminants were detected in similar concentrations to those reported previously, such as caffeine (median 4.3 ng/L) (e.g., 72 ng/L in Loos et al., 2009) and nicotine (median 3.6 ng/L) (e.g., 530 ng/L in Valcárcel et al., 2011). Sucralose was detected at higher concentrations in this study (median 100 ng/L, maximum 1100 ng/L) than in water from the river Rhine (range 20–170 ng/L in Ruff et al., 2015) and from major German rivers (range 60–80 ng/L) (Scheurer et al., 2009).

3.2. Factors impacting CEC concentrations in river water

Higher Σ CEC concentrations (range 1300–5200 ng/L) were found in wastewater-impacted rivers with low discharge ($<0.5 \text{ m}^3/\text{s}$) ($n = 8$) than in rivers with high discharge (typically $>40 \text{ m}^3/\text{s}$) (range 31–440 ng/L; $n = 10$). This indicates that low-discharge rivers are more impacted by point sources such as WWTP effluent (i.e., less dilution) than rivers with high discharge (higher dilution), which is in agreement with previous findings (Castiglioni et al., 2018; Golovko et al., 2021). A Pearson

correlation test was performed for wastewater-impacted rivers ($n = 14$ of 24 river sites), covering Σ CEC concentrations (ng/L) versus flow rate (m^3/s), PE of upstream WWTPs, and distance (m) between the sampling point and upstream WWTP effluent (Table S2 and Figure S3 in SI). The Σ CEC concentrations were significantly negatively correlated with discharge ($r = -0.43$, $p = 0.0093$) (Figure S3A in SI), and with distance between the sampling point and WWTP ($r = -0.36$, $p = 0.036$) (Figure S3C in SI). River discharge determines the ratio between river water and effluent wastewater, resulting in a dilution factor (Li et al., 2016). The estimated dilution factor in Sweden is typically between 100 and 1000 (Keller et al., 2014). Decreasing concentrations with increasing distance from the polluting source have been reported previously (e.g., Kunkel and Radke, 2011). There was no correlation between Σ CEC concentration and PE ($r = -0.04$, $p = 0.85$; Figure S3B in SI). This could be explained by the strong impact of water flow, which resulted in dilution of Σ CEC concentrations independently of number of PE served by upstream WWTPs. When comparing all three factors (flow rate, PE, and distance between the sampling point and the upstream WWTP) against the Σ CEC concentrations, a significant correlation was found ($r = 0.49$, $p = 0.002$) (Fig. 3), but with two outliers (R7, both sampling seasons).

Without the outliers, the correlation was even higher ($r = 0.65$, $p = 0.00001$). Uncertainties relating to the modeled flow rate could not explain the outliers. The outlier location R7 could be due to potential underestimation of the distance between the sampling point and the upstream wastewater effluent, or the nonlinear relationship between Σ CEC concentrations and river discharge (Figure S3A in SI). Contrary to our expectations, neither distance to point nor PE equivalents showed significant correlations with CEC concentrations ($p > 0.05$). Water flow on the other hand revealed to have a rho of 0.71 ($p > 0.05$). This indicates that water flow is an important driver when sampling for CECs and changes of water flow needs to be taken into account when evaluating the risks of CECs to the environment. Mass fluxes, on the other hand, should rely on representative flow conditions instead of unrepresentative low flow events.

3.3. Occurrence of CECs in lake water

The cumulative concentration in lake water varied between 36 and

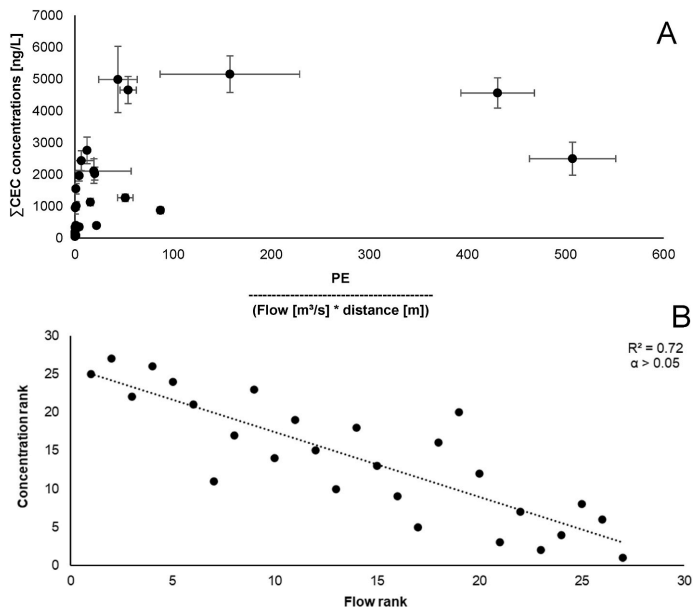


Fig. 3. A) Evaluation of Σ CEC concentrations vs PE and the inverse of flow and distance to WWTP. Vertical error bars: standard deviation of Σ CEC concentrations, horizontal error bars: model uncertainties of river discharge. B) Evaluation of Σ CEC concentrations vs riverine flow using ranked data.

900 ng/L, with a median value of 190 ng/L (Fig. 4, Figure S4 in SI). Of the 105 target CECs analyzed, 75 contaminants were detected at least once, 33 contaminants in >50% the samples, and 11 contaminants in all samples (Table S4 in SI). On average, the category 'other contaminants' accounted for approximately 47% of the Σ CEC concentration, followed by pharmaceuticals (35%), industrial chemicals (7%), PCPs (3%),

pesticides (2%), PFASs (2%), and parabens (2%). Σ_1 artificial sweetener (other contaminants) was the group with the highest median concentration (72 ng/L; maximum concentration 370 ng/L), followed by Σ_2 stimulants (other contaminants; 21 ng/L; 91 ng/L), Σ_8 industrial chemicals (17 ng/L; 49 ng/L), Σ_4 antiepileptics (pharmaceuticals; 16 ng/L; 190 ng/L), Σ_8 antidepressants (pharmaceuticals; 4 ng/L; 65 ng/L)

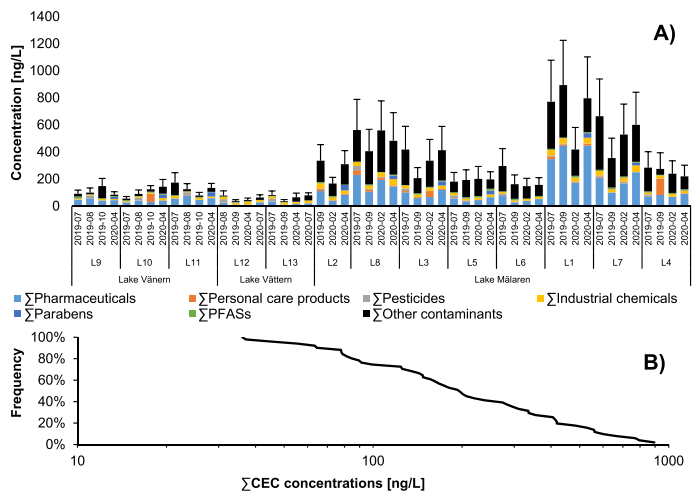


Fig. 4. Σ CEC concentrations in lake water samples ($n = 51$). A) Σ CEC concentration in samples L1-L8 from Lake Mälaren, samples L9-L11 from Lake Vänern, and samples L12-L13 from Lake Vättern; and B) reverse cumulative distribution as a function of Σ CEC concentration.

L), \sum_1 anesthetic (pharmaceuticals; 3.2 ng/L; 50 ng/L), and \sum_2 pesticides (2.9 ng/L; 31 ng/L).

Contaminants detected in all samples were caffeine (median concentration 20 ng/L; maximum concentration 91 ng/L), lamotrigine (9.6 ng/L; 150 ng/L), ATBC (8.3 ng/L; 32 ng/L), carbamazepine (5.0 ng/L; 37 ng/L), desvenlafaxine (3.9 ng/L; 19 ng/L), bicalutamide (2.4 ng/L; 19 ng/L), DEET (2.1 ng/L; 6.5 ng/L), fexofenadine (1.6 ng/L; 32 ng/L), PFOA (1.5 ng/L; 4.5 ng/L), metoprolol (1.2 ng/L; 24 ng/L), and trisopropanolamine (0.87 ng/L; 4.4 ng/L) (Table S4 in SI). The highest concentrations were found for sucralose (370 ng/L), lamotrigine (150 ng/L), laurilsulfate (120 ng/L), caffeine (91 ng/L), tramadol (59 ng/L), sulisobenzone (59 ng/L), HCTZ (54 ng/L), and lidocaine (50 ng/L). Lake Mälaren had higher median (340 ng/L) and maximum \sum CEC concentration (900 ng/L) than Lake Vänern (110 ng/L and 170 ng/L, respectively) and Lake Vättern (64 ng/L and 81 ng/L, respectively).

The dominant CECs detected in this study (i.e., lamotrigine, carbamazepine, bicalutamide, fexofenadine, metoprolol, tramadol, lidocaine, and DEET) showed similar patterns to those reported in previous studies (Golovko et al., 2020b; Maasz et al., 2019; Moschet et al., 2013; Rehr et al., 2020). HCTZ was not detected in lake water in a previous analysis (Moschet et al., 2013), but sampling in that study was performed during sun-intensive months (May–October 2009). HCTZ degradation is strongly dependent on photolysis (Baena-Nogueras et al., 2017), which could explain why the highest DF in this study was seen in April 2020 (33%, 50% and 63% in Lake Vänern, Vättern, and Mälaren, respectively, 54% overall), and the lowest in July 2019 (67%, 0%, and 29% in Lake Vänern, Vättern, and Mälaren respectively, 33% overall). Similar caffeine concentrations and DF values have been reported previously for Swedish surface waters (Rehr et al., 2020). However, higher concentrations of caffeine have been found lake water in other countries, e.g., in Lake Batalon, Hungary (Maasz et al., 2019). ATBC and trisopropanolamine were ubiquitously detected in lake waters in this study, but few previous studies have examined these chemicals. PFOA has previously been investigated in Swedish lakes in remote areas (Gobelius et al., 2018), with concentrations in the range <0.40–0.90 ng/L (DF 50%, $n = 10$), which is slightly lower than in this study (median 1.5 ng/L, DF 100%).

The largest variation in \sum CEC concentrations between seasons was observed for Lake Mälaren in July 2019 and February 2020 or April 2020 (Fig. 4A). These differences in \sum CEC concentrations (range 160–480 ng/L between seasons) were observed at sites L1–L3 and L7–L8, i.e., mostly urban lake sites. A Friedman test followed by a Tukey–Kramer post hoc test was performed for sites L1, L7, and L8 to evaluate seasonal variations at sites close to urban areas (viz. Fig. 1), using data for four seasons (Fig. 4). Of the major CEC groups, PCPs ($Q = 15.50$, $p = 0.00043$) and parabens ($Q = 15.50$, $p = 0.00043$) showed seasonal variations (Figure S5 in SI), the results for industrial chemicals ($Q = 17.00$, $p = 0.00020$) were inconclusive (Figure S5 in SI), and no variation was observed for the other major groups. PCPs showed seasonal variations between July 2019 and April 2020, and parabens showed seasonal variations between September 2019 and April 2020. Several pharmaceutical groups exhibited seasonal variations (Figure S5 in SI), including: antihistamines ($Q = 16.50$, $p = 0.00026$) between July 2019 and February 2020, antidiabetics ($Q = 15.88$, $p = 0.00036$) between July 2019 and April 2020, antineoplastic agents ($Q = 18.50$, $p = 0.00010$) between all seasons except February and April 2020, antibiotics ($Q = 18.50$, $p = 0.00010$) between all seasons except September 2019 and February 2020, and fungicides ($Q = 17.00$, $p = 0.00020$) between July 2019 and February 2020, and between July 2019 and April 2020.

Seasonal variations have been reported previously for PCPs (UV-filters) (reviewed by Mao et al., 2019), parabens (reviewed by Haman et al., 2015), antihistamines (Rehr et al., 2020), and antibiotics (Moreno-González et al., 2014). To our knowledge, seasonal variations have not been reported previously for antidiabetics and antineoplastics. The results for antidiabetics could be a result of reduced biodegradation

(Straub et al., 2019). The results for antineoplastics are in contrast to Rehr et al. (2020), who reported that bicalutamide concentrations in lake water showed little annual fluctuation. The elevated concentrations of fungicides in lake water in July 2019 could possibly be due to increased use, as photolysis degrades fluconazole (Chen and Ying, 2015) and it undergoes negligible removal in WWTPs (Lindberg et al., 2010). Concentrations of the pesticides DEET and 2,6-dichlorobenzamide (BAM) did not show clear variations at the lake water sampling sites. The use of BAM's parent compound has been banned since 1990 (Ulén et al., 2002) and it is therefore suspected that leaching occurs independent of season. DEET is primarily used as an insect repellent during spring and summer (Merel and Snyder, 2016), however, DEET showed no temporal trends in surface waters in this study, which is supported by earlier studies (reviewed by Merel and Snyder, 2016).

3.4. Mass flows and seasonal variations in CEC concentrations in river water

The total mass of \sum CECs ($n = 105$) in the studied rivers ($n = 24$) had a median value of 180 g/day and a mean value of 610 ± 320 g/day (Fig. 5). The inlets corresponded to an estimated 16% (Table S5), 37% (Table S6), and 79% (Sonesten et al., 2013) of the total median river discharge into Lake Vänern, Lake Vättern, and Lake Mälaren, respectively. The average total mass load of CECs into the lakes was 5000 g/day (Lake Vänern, $n = 10$), 510 g/day (Lake Vättern, $n = 6$), and 5600 g/day (Lake Mälaren, $n = 24$). The outlets generally had high loads, Göta älv (Lake Vänern, R15, 3100 ± 2300 and 4300 ± 2700 g/day) Norrström (Lake Mälaren, R13, 2800 ± 1400 g/day), and Motala ström (Lake Vättern, R21, 120 ± 82 g/day).

The highest median loads in all rivers came from \sum_8 industrial chemicals, followed by \sum_1 artificial sweeteners (14 g/day), \sum_4 antiepileptics and \sum_3 antidepressants (both 11 g/day), \sum_6 beta blockers (9.3 g/day), \sum_2 analgesics (8.9 g/day), \sum_6 antihypertensives (8.1 g/day), \sum_2 diuretics (7.9 g/day), and \sum_6 NSAIDs (non-steroidal anti-inflammatory drugs) (6.1 ng/day) (Table S7). The top 10 substances with detection frequency >50% and with the highest median load were sucralose (40 g/day), BAM (8.9 g/day), acetaminophen (8.8 g/day), lamotrigine (8.4 g/day), venlafaxine (8.4 g/day), HCTZ (8.3 g/day), metoprolol (6.6 g/day), losartan (6.2 g/day), tolyltriazole (5.7 g/day), and sulisobenzone (5.5 g/day). High loads of anthropogenic markers, industrial chemicals, and pharmaceuticals in recipient waters have been reported in other studies (e.g., Castiglioni et al., 2018; Meffe and Bustamante, 2014).

Variations in mass loads between seasons were observed for some compounds (Figure S6 in SI). During autumn, the antibiotic metronidazole, the UV-filters BP-3 and BP-4, the antipsychotic clozapine, the industrial chemical di-(2-ethylhexyl)phosphoric acid, the anti-asthmatic albuterol, the Alzheimer medicine memantine, and the anti-depressant amitriptyline were typically found in higher loads at the sampled sites. During spring, the antibiotic erythromycin was typically found in higher loads.

Seasonal variations in concentrations of benzophenone-type UV-filters in river water are known, and their lower mass loads in spring could be due to their use in other PCPs (Mao et al., 2019). Clozapine degrades under direct photolysis (Trawiński and Skibiński, 2019). Seasonal variations in industrial chemicals were most likely due to their specific usages, as some such as motor vehicle antifreeze are used seasonally (Janna et al., 2011). While albuterol is expected to slowly photodegrade at environmentally-relevant pH (Dodson et al., 2011), its use in treating chronic-type diseases and its limited variations in the present study (Figure S6F in SI) make seasonal variation unlikely. Memantine is not affected by photolysis (Blum et al., 2017), and few reasons for seasonal use are expected (Golovko et al., 2014; Ibáñez et al., 2017). The increased loads of amitriptyline during autumn likely reflected an increase in use, as amitriptyline degrades by photolysis (Blum et al., 2017). In Greece, metronidazole was detected only in spring-time

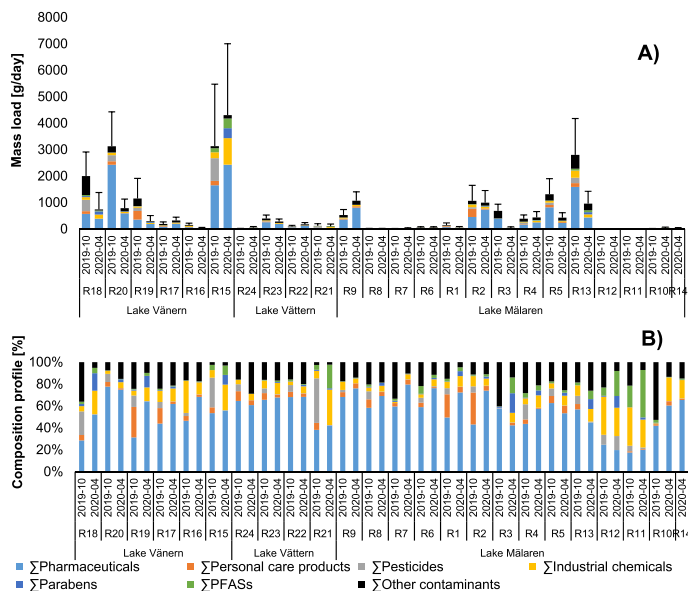


Fig. 5. Mass loads of target CECs in sampled rivers ($n = 47$). A) Overview of total mass load in all sampled rivers; and B) composition profile of sampled rivers.

(Papageorgiou et al., 2016), but in the present study metronidazole was detected in both autumn and spring (Figure S6A). In contrast with Papageorgiou et al. (2016), the highest mass loads were found in autumn. Data for erythromycin were not publicly available, but group-level data for macrolide antibiotics (category J01FA) show stable consumption throughout the year (Folkhälsomyndigheten, 2021). Macrolides have been shown to require days to photodegrade in environmental waters (Batchu et al., 2014).

3.5. Impact on the aquatic environment

The target CECs were detected in lake waters far from their point of emission. Thus the CECs showed high mobility and were transported via rivers and diffuse sources to the main Swedish lakes. The detected CECs also appeared to be persistent to degradation processes in the aquatic environment. Examples of persistent and mobile organic compounds (PMOCs) (Reemtsma et al., 2016) have been observed previously, e.g., metoprolol (reviewed by Godoy et al., 2015), or suspected, e.g., 2, 2'-dimorpholinyl-diethyl-ether (Schulze et al., 2018). This highlights the need for environmental monitoring of PMOCs, which are currently understudied (Reemtsma et al., 2016). It has been predicted that PMOC concentrations in (semi)enclosed water systems will increase over time as a result of their continued use in society (Hale et al., 2020). As the turnover time for Lake Vänern, Lake Vättern, and Lake Mälaren is nine years, 60 years, and three years, respectively, the CEC concentrations could persist or even increase over time. This is not only problematic for the environment (Galus et al., 2013; Kortenkamp et al., 2019), but possibly also for drinking water producers (Arp et al., 2017; Reemtsma et al., 2016), since the three Swedish lakes are all used as drinking water reservoirs. If PMOCs are also toxic (persistent, mobile, and toxic, PMT) (Schrenk et al., 2020; Vossen et al., 2020; Sangion and Gramatica, 2016), there are risks of long-lasting effects for humans and environment on an equivalent level of concern (ELoC) as reported for PBT substances (Hale et al., 2020; Richmond et al., 2018). Some CECs have been proven to be toxic at environmentally relevant concentrations (e.

g., Aguirre-Martínez et al., 2015), but mixtures of CECs are of most concern (Dravvik et al., 2020). A recent review of 10 years of experimental studies on CEC mixtures concluded that the default assumption should be of concentration addition for chemicals which produce a common toxic effect (Martin et al., 2021). Using the information on CEC composition in surface water provided in this study, CEC mixtures and concentrations can be assessed in hazard screening (Posthuma et al., 2019). The findings on seasonal variation in CECs provide additional information on the level of hazard, which might not be chronic but could be recurrent (Beckers et al., 2018; Nilsen et al., 2019).

4. Conclusions

The highest \sum CEC concentrations were found in wastewater-impacted Swedish rivers with low water flows. Of the parameters studied, river discharge was the best predictor of \sum CEC concentrations, followed by distance between the sampling point and upstream WWTP effluent in river water samples. The highest \sum CEC concentrations in lake water samples were found for Lake Mälaren. Three CEC groups, i.e., other contaminants, pharmaceuticals, and industrial chemicals, dominated the composition profiles in both lakes and rivers. Rivers were the main source of CECs in the lakes, supplying a median mass load of 180 g/day and a total mass load of 5600, 5000, and 510 g/day to Lake Mälaren, Lake Vänern, and Lake Vättern, respectively.

In river water samples, most CECs exhibiting seasonal variations had their highest load during autumn, whereas urban lake sites exhibited higher concentrations in winter and spring than in summer and autumn. In lake water samples, PCPs had their highest concentrations in summer and paracetamols in spring. The pharmaceutical groups fungicides, antihistamines, and antineoplastic agents exhibited their highest concentrations in summer, while antibiotic concentrations were highest in spring and summer. This shows that aquatic environments in Sweden are exposed to varying mixtures of CECs during the year.

A large number of CECs were detected and quantified in this study, some of which have scarcely been reported previously. It was shown that

some CECs were transported far from their point source in the fresh-water environment. Non-urban lake sites exhibited relatively stable concentrations between sampling occasions, showing persistence of some CECs. More studies are needed to estimate the hazard posed by CECs to the aquatic ecosystem.

Credit statement

Daniel Malnes: Formal analysis, Writing – Original & Draft, Sampling **Oksana Golovko:** Writing – Reviewing & Editing, Supervision, Methodology, Formal analysis, Data handling **Lutz Ahrens:** Writing – Reviewing & Editing, Supervision, Project administration **Stephan Köhler:** Sampling design, Supervision **Malin Forsberg:** Formal analysis, Sampling.

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.

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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.2022.133825>.

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Research Paper



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

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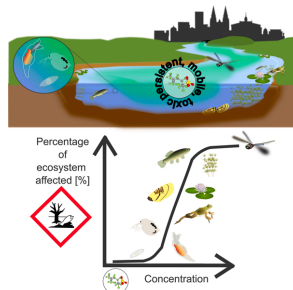
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HIGHLIGHTS

- 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



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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.

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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, bio-accumulative, 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, phyto-benthos, 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 [12,6], 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 ($n_{\text{river}}=24$, $n_{\text{lake}}=13$) 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 *Lemma 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://rvszoekstysteem.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, phyto-benthos, 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 [132,57]; (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_i) were calculated as described in Zhou et al. [69] and Eq. 1:

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

where MEC: measured environmental concentration [$\mu\text{g/L}$]; PNEC: predicted no effect value [$\mu\text{g/L}$]; NO₁: number of samples with concentrations higher than PNECs [unitless]; NO₂: total number of samples [unitless].

Building on the same concept as RQ_i, an SSD-equivalent (PAF_i) was introduced where available. For the calculation of PAF_i, 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 [$\mu\text{g/L}$]; μ : population median [$\log_{10} \mu\text{g/L}$]; σ : population standard deviation [$\log_{10} \mu\text{g/L}$] [49].

Thereafter, PAF_i could be calculated by Eq. 3:

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

Where MEC and PAF-NOEC as described above, N_{PAF-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 SL1).

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 $\mu\text{g/L}$, it was labeled ‘T’, while acute toxicity < 100 $\mu\text{g/L}$ 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 SL2).

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 $\mu\text{g/L}$), was more than a factor 10 lower than any of the standard taxonomic groups

(96000 $\mu\text{g/L}$) (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., $\text{LLHC5} \leq 10 \mu\text{g/L} \leq \text{ULHC5}$). 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 $< 0.1 \text{ mg/L}$, 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 phyto-benthos, 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
Tolytriazole	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 $\mu\text{g/L}$) followed by macrophytes (3.8 $\mu\text{g/L}$), both much lower than for the most sensitive standard taxonomic group (fish, 340 $\mu\text{g/L}$). 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 $\mu\text{g/L}$ (0.39) between the Posthuma and EC, and \log_{10} 1.9 $\mu\text{g/L}$ (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 $\text{RQ} > 1$ in at least one spatiotemporal location (Table 3) and 20 CECs posed a moderate risk ($0.01 < \text{RQ} < 1$) (Table S7 in SI). Additionally, $\text{PAF-NOEC} > 5\%$ was exceeded by 2 CECs (Table 3). Fifty CECs identified

or suspected as PM(T)s or vPM 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 ($\text{RQ}_f \geq 1$), moderate ($1 > \text{RQ}_f \geq 0.1$), small-scale or endurable ($0.1 > \text{RQ}_f \geq 0.01$), negligible ($0.01 > \text{RQ}_f > 0$), and safe ($\text{RQ}_f = 0$). 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., $\text{RQ} > 0.01$. 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)/vPM 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_o), potentially affected fraction (PAF) and optimized PAF (PAF_o) 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_o: optimized risk quotient; PAF_f: optimized potentially affected fraction. PFOS: perfluorooctanesulfonic acid. ^b Daidzein has, at least a partially, natural origin [51].

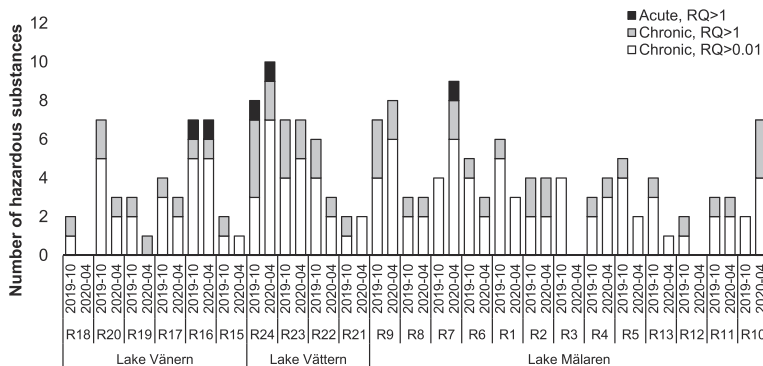


Fig. 1. Number of hazardous substances (out of 91 detected) in river samples entering Lake Vänern, Lake Vättern and Lake Mälaren, Sweden (acute, RQ>1 > chronic, RQ>1 > chronic, RQ>0.01).

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],

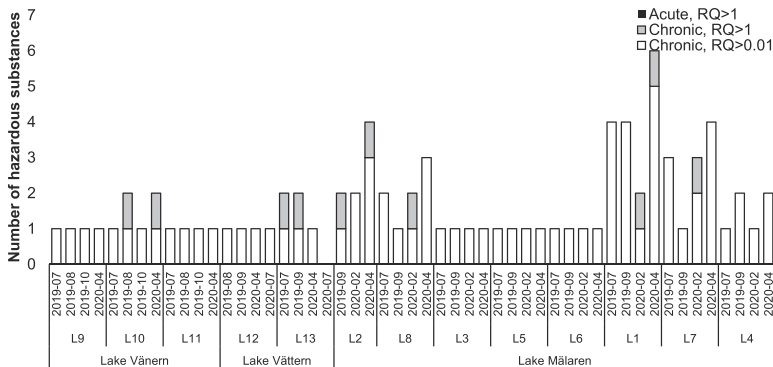


Fig. 2. Number of hazardous substances (out of 71 detected) in Lake Vänern, Lake Vättern and Lake Mälaren, respectively (acute, RQ>1 > chronic, RQ>1 > chronic, RQ>0.01).

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 sulisobenzon) 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 $DF \geq 50\%$, $PNEC < 10 \mu\text{g/L}$) 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 ($\mu\text{g/L}$)
	Aerobic biodegradation	Photo-degradation	Hydrolysis			
Bicalutamide	p ^c vp ^d	NA	5E-03–200 h ^a	$\log K_{ow}$ 1.4–1.8 ^b	0.092 (T) ^e	
Lamotrigine	p ^d	4 d ^f	NA	M-vM ^g	5 (potential T) ⁱ	
Nicotine	nP ^d	NA	NA	vM ^g	1.8 (potential T) ^j , 8.8 (potential T) ^k	
Tolyltriazole	nP ^d	NA	NA	vM ^g	Potential T (1.58–590) ^l	

[†] HCS/PNEC calculated in this study

^aUS EPA [64]

^bGolovko et al. [24]

^cSeller et al. [60]

^dEPIsuite BIOWIN2&3 models

^ePanter et al. [47]

^fYoung et al. [67]

^gPosthuma 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 evolutionarily 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 pK_a , 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 Figure:** 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.

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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.

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