Journal of Hazardous Materials 429 (2022) 128302

Contents lists available at ScienceDirect

Journal of Hazardous Materials

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

Research Paper

Risk-based screening for prioritisation of organic micropollutants in Swedish freshwater

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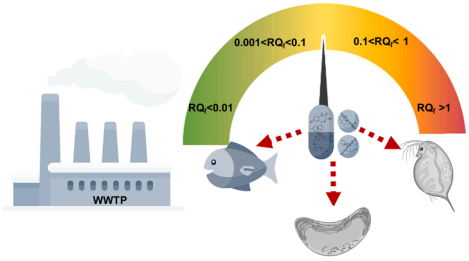
HIGHLIGHTS

- The risk posed by OMPs to aquatic ecosystems in Swedish freshwaters was evaluated.
- Less than 10% of the substances investigated pose a risk to the aquatic ecosystem.
- The influence of WWTPs on the risk posed by OMPs is substance and site specific.
- A noval optimised assessment approach was used.
- The reliability of the assessment depends on the quality of the data available.

GRAPHICAL ABSTRACT



ARTICLE INFO

Editor: Dr. B. Lee

Keywords:
Risk assessment
Pharmaceuticals
Aquatic environment
Ecotoxicology
Environmental monitoring

ABSTRACT

Concerns about environmental contamination by organic micropollutants (OMPs) are increasing, due to their potential bioaccumulative and toxic properties. This study evaluated the risk posed by OMPs to aquatic ecosystems in Swedish freshwaters. The assessment was based on measured environmental concentrations (MEC) of OMPs in surface waters upstream and downstream of Swedish wastewater treatment plants (WWTPs). A novel optimised risk quotient (RQ_f) was used to identify potential high-risk substances in the aquatic environment. A secondary objective was to assess the impact of WWTP effluent on aquatic ecosystems using a novel impact factor (I) based on the risk quotient (RQ). Among the 126 substances investigated, four compounds (metformin, N,N-dimethyltetradecylamine, oxazepam, and venlafaxine) were identified as likely to pose a risk to aquatic ecosystems in Swedish surface waters (RQ_f>1), and five compounds (clindamycin, gemfibrozil, sertraline, o-desmethylvenlafaxine, and diclofenac) were identified as posing a moderate risk to aquatic ecosystems (0.1 <RQ_f<1). WWTP effluent appeared to pose an environmental risk for all recipient sites, but the impact of calculated RQ was site-specific. These results can be used by authorities to prioritise OMPs and contaminated hotspots, in order to decrease negative impacts on aquatic ecosystems.

Synopsis: A novel optimised risk assessment approach for identification of high-concern organic micropollutants in aquatic environments.

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https://doi.org/10.1016/j.jhazmat.2022.128302
Received 19 October 2021; Received in revised form 15 December 2021; Accepted 16 January 2022
Available online 20 January 2022

1. Introduction

Organic micropollutants (OMPs) is a general definition given to a group of compounds that are not covered by existing water quality regulations due to their low concentrations (ng/L to μg/L) (Arslan et al., 2017; La Farre et al., 2008). The group includes several classes of chemicals, such as pharmaceuticals, personal care products, pesticides, per- and polyfluoroalkyl substances (PFAS) and endocrine disruptive chemicals (EDC) (Arslan et al., 2017). Contamination of the aquatic environment by OMPs has recently raised concerns, due to their potential bioaccumulative and toxic properties (Arslan et al., 2017; La Farre et al., 2008; Golovko et al., 2021; Petrie et al., 2015; Sörengård et al., 2019). Moreover, the widespread and increasing uses of OMPs are responsible for continuous release of these compounds to the aquatic environment (Golovko et al., 2021; Petrie et al., 2015).

Wastewater treatment plants (WWTPs) have been shown to be one of the main sources of emissions of OMPs to the aquatic environment (Golovko et al., 2021; Sörengård et al., 2019). Previous studies have demonstrated that removal of OMPs during wastewater treatment is incomplete, resulting in significant concentrations of these compounds in WWTP effluent (Golovko et al., 2021, 2020; Sörengård et al., 2019) Thus effluent water discharged into the environment has high impacts on the occurrence of OMPs in recipient water bodies (Golovko et al., 2021; Wallberg et al., 2016).

Measured environmental concentrations (MEC), together with predicted no-effects concentrations (PNEC), are commonly used to assess the risk posed by chemicals to aquatic ecosystems, as recommended in environmental risk assessment (ERA) guidelines (ECHA, 2008; EMA, 2006; European Commission, 2003). Multiple studies have used this method to screen OMPs posing potential environmental risks (Villain et al., 2016; Schwarz et al., 2021; Załęska-Radziwiłł et al., 2011; Zhou et al., 2019) However, most of these screening studies have focused on a limited number of pharmaceuticals and rarely assess the quality of the data used for PNEC derivation. It is therefore difficult to assess the reliability and relevance of the data, which impedes authorities from using the derived PNEC values for managing the identified risk. There is presently two methods available for evaluating data quality when establishing environmental quality standards (EQS) in the EU (European Commission, 2018); the Klimisch method (Klimisch et al., 1997) and the CRED method (Moermond et al., 2016) and the advantage with the latter is that both reliability and relevance can be assessed (Kase et al., 2016). In this study we therefore use the CRED method to evaluate data quality and so far data quality assessment of derived PNEC values is rarely presented in the open scientific literature (Godoy et al., 2018).

The aim of this study was to improve current risk estimation for OMPs in aquatic ecosystems and to identify the most concerning compounds, using MEC in recipient surface waters impacted by WWTPs in Sweden. Specific objectives were to i) estimate the effect concentrations and quality assess the derived PNEC for 126 OMPs; ii) identify OMPs posing the highest risks to aquatic ecosystems, using a novel optimised risk quotient (RQ_f) approach; and iii) assess the impact of WWTPs on the aquatic environment.

2. Materials and methods

2.1. Measured environmental concentrations of compounds of interest

The water samples analysed were collected as part of a large-scale monitoring study, which is described in detail elsewhere (Golovko et al., 2021, 2020). All information concerning the sampling campaign and analysis of water samples is provided in Golovko et al. (2020). In the present study, the focus was only on samples from recipient surface waters upstream (RU) and downstream (RD) of WWTPs ($n = 37$). The investigated WWTPs were selected based on a report by the Swedish Environmental Protection Agency (SEPA), which identified WWTPs with potentially large impacts on the receiving water body (Wallberg et al., 2016). Of the 225 OMPs of interest analysed, 178 compounds were detected and quantified in at least one sample (Golovko et al., 2020). This paper focuses on substances which were detected in at least 10% of samples ($n = 126$). Sampling locations and a list of the 126 compounds of interest and their physicochemical properties are presented in Tables S1–1 and S1–2, and Fig. S1–1 in Supplementary Information (SI).

2.2. Calculation of risk quotient

2.2.1. Data collection

The potential toxicological risks posed by OMPs to aquatic ecosystems were assessed following technical guidance from the European Commission (EC) (European Commission, 2003) and the ERA Guidelines from the European Medicines Agency (EMA)(EMA, 2006). In brief, the risk posed by a chemical substance to aquatic ecosystems was assessed by calculating the risk quotient (RQ), determined by comparing the MEC of a certain substance with its PNEC.

The EC defines PNEC as the concentration below which an unacceptable effect will most likely not occur (European Commission, 2003) (10). In assessment of effects on the aquatic compartment, PNEC is derived based on laboratory data from standardised tests, if available, on organisms from three major trophic levels of aquatic ecosystems: primary producers, primary consumers and secondary consumers. In this study, microalgae (primary producers), invertebrates (primary consumers) and fish (secondary consumers) were used as representative organisms of each trophic level.

The following data sources were used to gather experimental ecotoxicological data: i) Reports from national and international regulatory authorities (e.g. Environmental Quality Standards (EQS), Watch List (WL) under the Water Framework Directive (WFD) reports); ii) WikiPharma database for pharmaceuticals (WikiPharma Database); iii) the pesticides properties database (PPDB) (Lewis et al., 2016); iv) the US EPA ECOTOX database (ECOTOX Database); v) the Organisation for Economic Co-operation and Development (OECD) Existing Chemicals Database (OECD Existing Chemicals Database); and vi) the European Chemicals Agency (ECHA) registration dossiers database (ECHA website). If no laboratory studies were available, quantitative structure-activity relationship (QSAR) models were used to predict short-term toxicity for each species using: i) the QSARINS-Chem standalone version software developed by Gramatica et al. (2013); Gramatica et al. (2014); Chirico et al. (2021); QSARINS-Chem) and ii) the Ecological Structure Activity Relationship (ECOSAR) predictive model developed by the United States Environmental Protection Agency (US EPA) (ECOSAR).

The key toxicological data used for PNEC calculation were assessed following the CRED method (Moermond et al., 2016). A study was scored 1 for reliability if the experiment was well-designed and well-performed; it was scored 2 if the experiment was generally well-designed with some minor flaws in the documentation of the data and/or the experiment set-up; it was scored 3 if there were clear flaws in experiment design and/or how it was performed; and it was scored 4 if the authors did not provide enough information to make a thorough assessment. Similarly, the relevance of a study was scored 1 if the data were relevant and 2 if the data were of limited relevance for the purpose for which they were evaluated; it was scored 3 if the data were not relevant; and it was scored 4 if not enough information was provided to make a proper assessment. Any data found in reports from regulatory authorities were automatically scored 1 for both reliability and relevance, as it was assumed that these data had been assessed by the regulatory bodies.

The reliability of the predictions obtained with QSAR models cannot be assessed with the CRED method and they were assessed following the OECD guideline on validation of (Q)SAR models (OECD, 2014) and (Gramatica, 2020). The QSARINS and ECOSAR models both fulfilled all the requirements listed in the OECD validation. However, based on the molecular descriptors of each model, it was considered that predictions

from QSARINS were more reliable than predictions from ECOSAR for pharmaceutical substances. Therefore, as long as the compound was included in the applicability domain (AD) of the models, all predictions from QSARINS were scored 1 for their reliability and all predictions from ECOSAR were scored 2. If a substance was not in the AD, the reliability of the prediction was scored 3.

To ensure consistency, the ecotoxicological data were selected following the same decision tree, as illustrated in Fig. 1. Section 2 in SI provides a detailed description of how ecotoxicological data were selected and how the reliability of model predictions was assessed.

2.2.2. PNEC calculation

As recommended in the technical guidance for deriving EQS, the quality of all data used for PNEC calculation was assessed following the CRED method (European Commission, 2018; Moermond et al., 2016). An assessment factor (AF) was applied in the PNEC calculation in order to address uncertainties related to intra- and inter-laboratory variation in toxicity data, intra- and inter-species variations, short-term to long-term toxicity extrapolation, and laboratory data to field impact extrapolation. Therefore, the value of AF depended on the number, type and quality of the toxicological studies available in the dataset (10). If long-term no observed effect concentration (NOEC) data were available for each of three taxonomic groups, AF was set equal to 10; if long-term NOEC data were available for one and two different taxonomic group(s), a value of 100 and 50, respectively, was selected as AF; if only short-term L(E)50 (i.e. lethal (effect) concentration 50%) data were available, a value of 1000 was selected as AF. If PNEC was calculated based on lowest observed effect concentration (LOEC) instead of NOEC, an additional AF of 2 was used to compensate for the additional uncertainty. PNEC was calculated as:

$$PNEC_i = \frac{\min\left(NOEC_{algae,i},\ NOEC_{invertebrate,i},\ NOEC_{fish,i},\ EC_{50,\ algae,i},\ EC_{50,\ invertebrate,i},\ EC_{50,\ fish,i}\right)}{AF} \quad (1)$$

2. Determination of RQ

The RQ of substance i at sampling location j was calculated as:

$$RQ_{i,j} = \frac{MEC_{i,j}}{PNEC_i} \quad (2)$$

As a precautionary principle, if MEC was lower than the limit of quantification (LOQ) of the analytical instrument, the RQ of substance i at sampling location j was calculated by making the assumption that $MEC_{i,j} = LOQ_i$. The environmental risk of substance i at sampling location j was then determined according to the value of RQ: if $RQ_i < 0.01$, substance i is unlikely to represent a risk to the environment; if $0.01 < RQ_i < 0.1$, substance i represents a low risk to the environment; if $0.1 < RQ_i < 1$, substance i represents a moderate risk to the environment; and if $RQ_i > 1$, substance i represents a high risk to the environment (Zhou et al., 2019; Pereira et al., 2020; Cunha et al., 2019). It is important to note here that for some substances, the LOQ can be of the same order of magnitude or even lower than the PNEC, which could result in overestimation of the risk.

In order to make a distinction between pollutants for which RQ was frequently greater than 1 and those for which RQ was greater than 1 only in a limited number of locations, a novel optimised risk quotient (RQ_f), as defined by Zhou et al. (2019), was determined. In brief, $RQ_{f,i}$ was calculated based on the mean RQ of substance i and the frequency of MEC_i exceeding $PNEC_i$:

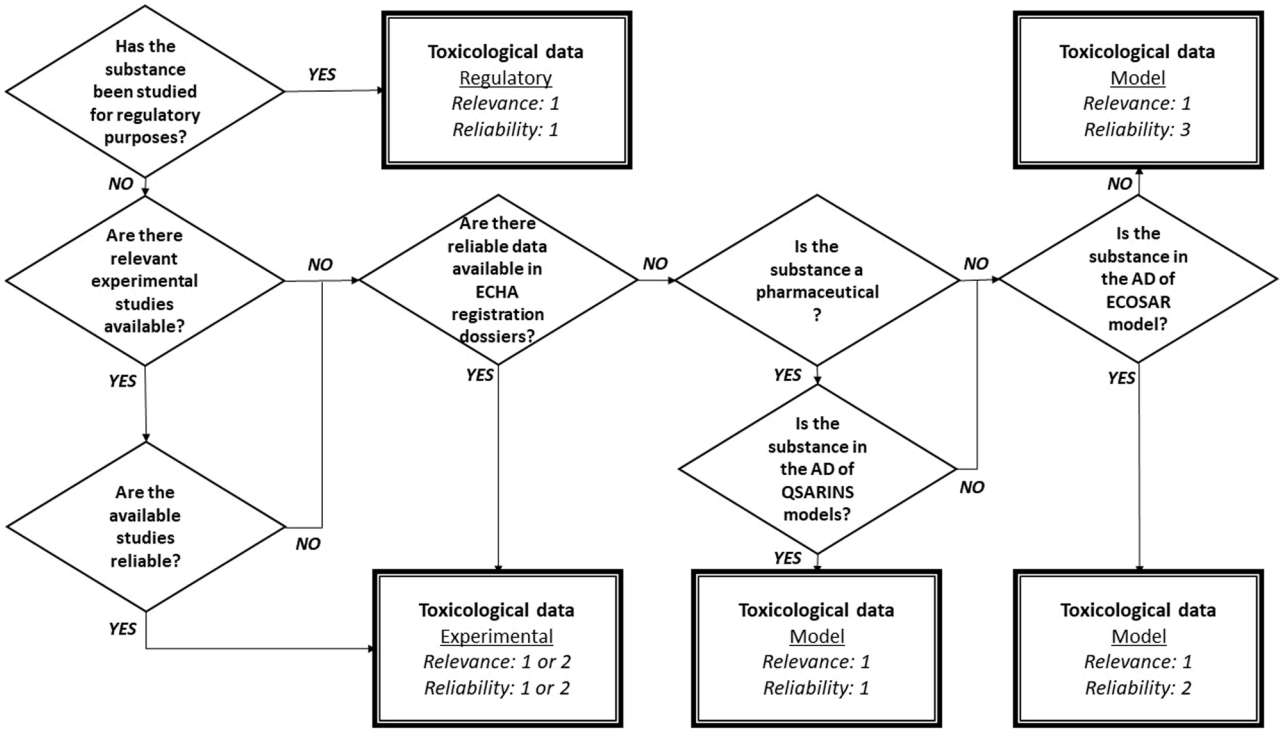

Fig. 1. Decision tree for selecting ecotoxicological data (AD = applicability domain). The flowchart is starting on the top left corner. The possible outcomes of the decision process are shown in the squares, along with the type of toxicological data, and the corresponding "relevance" and "reliability" scores.

$$RQ_{f,i} = \frac{MEC_{average,i}}{PNEC_i} * \frac{\text{Number of samples } \textit{where } MEC_{i,j} > PNEC_i}{\text{Total number of } \textit{samples} \ (n = 37)} \quad (3)$$

$RQ_{f,i}$ allows identification of pollutants of most concern over a wide range of sampling sites.

2.3. Impacts of WWTPs on RQ

RQs for a specific substance in recipient surface waters downstream (RQ_{RD}) and upstream (RQ_{RU}) of a WWTP were compared by introducing an impact factor I for substance *i* at location *j*, defined as:

$$I_{i,j} = \frac{RQ_{RD,i,j} - RQ_{RU,i,j}}{RQ_{RD,i,j}} \quad (4)$$

If $I_{i,j}$ is greater than 0, it can be assumed that at location *j* the WWTP is contributing to the value of $RQ_{i,j}$ downstream of the WWTP, i.e. it is possible that the WWTP is partly responsible for the assessed risk to the local aquatic ecosystem. The closer the impact factor $I_{i,j}$ of substance *i* at location *j* is to 1, the higher the influence of the WWTP at location *j* on the $RQ_{i,j}$ value.

3. Results and discussion

3.1. Estimation and validation of effect concentrations and PNEC for individual OMPs

Tables S3–1, S3–2 and S3–3 in SI list the ecotoxicological data used in the PNEC calculation for each substance for algae, invertebrates and fishes, respectively. They show the type of substance the compounds belong to, the effect concentration (in μg/L), the origin of the data (i.e. QSAR model predictions, experimental studies or regulatory activities), the exposure duration, the critical effect, the toxicological endpoint, the test species and the source of the data. Among the 126 substances investigated in this study, there were 89 pharmaceuticals, 16 pesticides, 8 industrial chemicals, 3 personal care products, 3 PFAS, 2 parabens, 2 stimulants, 2 vitamins and 1 isoflavone. The environmental risk were already assessed for 13 compounds as part of regulatory activities, among them 12 were pesticides (as indicated in Tables S3–1, S3–2 and S3–3 in SI). An EQS has already been derived for 3 of these substances, namely atrazine, diuron, and sulfamethoxazole. Experimental studies on all taxonomic groups (i.e. algae, invertebrates and fish) were available for 39 additional compounds. For 46 substances, no experimental studies could be found, thus their PNEC was calculated based on QSAR predictions.

Tables S4–1 in SI shows the calculated PNEC for all substances of interest, along with effect concentrations for each taxonomic group, the related AF, a reference to the key study and the scores for data reliability and relevance. Only studies on the most sensitive taxonomic group were assessed for their reliability, adding uncertainty to the AF value and, by extension, to the PNEC. Tables S4–1 in SI also indicates the origin of the toxicological data (i.e. experimental study, QSAR predictions or regulatory activities).

For the vast majority of the substances of interest, PNEC was calculated based on ecotoxicological data judged to be reliable and relevant, or reliable/relevant with restrictions. There were only two substances (di-(2-ethylhexyl)phosphoric acid and perfluoroundecanoate (PFUnDA)) for which PNEC was calculated based on ecotoxicological data that were judged not to be reliable. For eight substances (atorvastatin, azithromycin, benzophenone, cyanazine, diltiazem, mefenamic acid, methotrexate and metoprolol), the key experimental studies providing the effect concentrations were lacking information concerning the experimental set-up. These studies stated that they followed OECD guidelines, but did not provide further information (Vestel et al., 2016; Harada et al., 2008; Registration dossier of benzophenone; Fairchild et al., 1997; Kim et al., 2007; Henschel et al., 1997; Czech et al., 2014). Therefore, it was not possible to make a thorough assessment of the reliability of these studies.

For six substances (dichlorobenzamide, losartan, oxazepam, propamocarb, sulfamethoxazole and tetracycline), PNEC was calculated based on experimental data on non-standard species. However, data for dichlorobenzamide and propamocarb were found in the PPDB and these data are reported to be verified and used for regulatory purposes (Lewis et al., 2016). The effect concentration for Losartan was from a test on *Lemna minor*, which is strongly recommended in international guidelines for the purpose of ecotoxicity screening (Alkimin et al., 2019). The effect concentration for oxazepam was from a ecotoxicity test on a fish species commonly found in Swedish freshwaters (Brodin et al., 2013). The ecotoxicological data for sulfamethoxazole were from Gomez Cortes et al. Cortes et al. (2020), as the substance has been selected for the third WL under the WFD. The effect concentration for tetracycline was from an experiment using mesocosms in a natural stream (Quinlan et al., 2011). For all the reasons stated above, the relevance was scored 1 even though the ecotoxicological data were from tests on non-standard species. However, the PNEC for terbutryn was calculated based on results from an ecotoxicity test on *Chlorella vulgaris* (Rioboo et al., 2009), an algal species unlikely to be found in Swedish freshwater, and hence its relevance was scored 2.

For N,N-dimethyltetradecylamine, PNEC was calculated based on data from the registration dossier under the REACH regulation (Registration dossier of Dimethyltetradecylamine), as these were the only experimental data available. The registration dossier gathers ecotoxicological data on several dimethyl alkyl amines (DMA) of different carbon chain length. For the purpose of this study, PNEC was determined based on ecotoxicological data for the compound C16 DMA, as it is the most toxic substance according to the information in the registration dossier. It is important to note that the experimental studies supplying the ecotoxicological data were performed using natural water from “Innerste” in Lower Saxony, Germany (Registration dossier of Dimethyltetradecylamine), which may have different physico-chemical properties than Swedish freshwaters. For that reason, both the reliability and the relevance of the data were scored 2.

Table 1 lists the substances for which PNEC was ≤ 1 μg/L, which were considered the most toxic compounds in this assessment. Among the 52 substances listed in Table 1, only three (namely, diuron, isoproturon, and atrazine) were already investigated as part of regulatory activities. This highlight the emergency for authorities to take actions to better regulate the most hazardous chemicals to better protect the aquatic ecosystem. Furthermore, experimental studies are publicly available on at least one taxonomic group for 41 of these compounds, which should encourage further investigations on the risk that these substances may pose to the aquatic environment.

Although the guidelines advise choosing relevant key studies and a correct value of the AF to avoid variability in PNEC calculations (EMA, 2006, 2018; European Commission, 2003), the selection of effect concentrations relies mainly on expert judgement. Therefore, the PNEC values, and the resulting RQs, may differ between risk assessments. For instance, the PNEC for sertraline determined in the present study was seven-fold lower than the value calculated by Zhou et al. Zhou et al. (2019), who calculated PNEC based on estimations from ECOSAR. In the present study, PNEC was calculated based on effect concentrations from experimental studies on each taxonomic group, which were lower than the predictions from the QSAR model. This highlight the importance to always specify the original source of the toxicological data for future studies to verify and quality assess the results, which makes it more reliable for further regulatory actions.

For two substances (sertraline and oxazepam), PNEC was lower than 10 ng/L, which is the trigger value for further investigation according to the EMA guidelines (9). This action limit has recently been assessed as protective enough by Schwarz et al. (2021), based on evaluation of aquatic effect data on approximately 300 active pharmaceutical ingredients (Schwarz et al., 2021). Therefore, it is possible that the toxicity of these compounds was overestimated in this study. It is important to

Table 1
List of substances with predicted no-effects concentration (PNEC) ≤ 1 μg/L, which is believed to be a relevant cut-off value to identify the most toxic compounds to aquatic organisms. Underlined values are predictions from QSAR models, values in bold are from chronic experimental studies, values in italics are from experimental studies on non-standard species. Colour code of listed substances: Blue: The environmental risk posed by the substance has been investigated as part of regulatory activities; Green: Experimental studies were available for all taxonomic groups; Orange: Experimental studies were available for only one or two taxonomic groups; Red: No experimental studies available and thus the PNEC has been calculated only based on QSAR predictions (Brooks et al., 2003; Crago and Klaper, 2018; EC. Water, 2005b; EC. Water, 2005c; EC. Water, 2005a; Ferrari et al., 2004; Galus et al., 2013; Iesce et al., 2019; Isidori et al., 2005; Isidori et al., 2007; Kim et al., 2014; Kusk et al., 2018; Lamichhane et al., 2014; Lu et al., 2015; Memmert et al., 2013; Oh et al., 2006; Overturf et al., 2012; Panter et al., 2012; Savino and Tanabe, 1989; Wenzel et al., 2001; Yang et al., 2008; Yang et al., 2014; Brodin et al., 2013; Villain et al., 2016; Quinlan et al., 2011; Registration dossier of Dimethyl(tetradecyl)amine; Rioboo et al., 2009; Chirico et al., 2021; QSARINS-Chem; Fairchild et al., 1997; Harada et al., 2008; ECOSAR; Lewis et al., 2016).

Substance name	CAS Number	Category	Algae		Invertebrates		Fish		PNEC (μg/L)	Assessment factor	Reliability	Relevance	Source
			Effect conc. (μg/L)	Toxicological endpoint	Effect conc. (μg/L)	Toxicological endpoint	Effect conc. (μg/L)	Toxicological endpoint					
Sertraline	79617-96-2	Pharmaceutical	12	IC50	**0.47**	NOEC	380	LC50	**0.0047**	100	1	1	(50)
Oxazepam	604-75-1	Pharmaceutical	1300	EC50	21000	EC50	***1.8***	LOEC	***0.009***	200	2	1	(42)
Clindamycin	18323-44-9	Pharmaceutical	10	EC50	100000	EC50	11000	LC50	**0.01**	1000	2	1	(11)
Tetracycline	60-54-8	Pharmaceutical	***0.96***	NOEC	**100**	LOEC	22000	LC50	***0.019***	50	1	1	(44)
Gemfibrozil	25812-30-0	Pharmaceutical	***3100***	NOEC	**78**	NOEC	**0.39**	LOEC	**0.019**	20	1	1	(51)
Erythromycin	114-07-8	Pharmaceutical	20	EC50	220	EC50	*410000*	LC50	**0.02**	1000	2	1	(52)
N,N-dimethyltetradecylamine	112-75-4	Industrial chemical	**2.6**	EC10	67	LC50	260	LC50	**0.026**	100	2	2	(46)
Venlafaxine	93413-69-5	Pharmaceutical	48000	EC50	14000	EC50	**5.2**	LOEC	**0.026**	200	2	1	(51)
Loratadine	79794-75-5	Pharmaceutical	2200	EC50	28	EC50	260	LC50	**0.028**	1000	1	1	(53)
Terbutryn	886-50-0	Pesticide	***3***	NOEC	*20000*	LC50	820	LC50	***0.03***	100	2	2	(45)
Telmisartan	144701-48-4	Pharmaceutical	28	EC50	46	LC50	37	LC50	**0.037**	1000	1	1	(27; 28)
Clarithromycin	81103-11-9	Pharmaceutical	2	EC50	**4600**	NOEC	**680000**	NOEC	**0.04**	50	2	1	(52)
Genistein	446-72-0	Pharmaceutical	2600	EC50	6100	EC50	**4.2**	NOEC	**0.042**	100	1	1	(54)
Cyanazine	21725-46-2	Pesticide	**9**	NOEC	*2000*	LC50	3500	LC50	**0.09**	100	4	1	(37)
Bicalutamide	90357-06-5	Pharmaceutical	9500	EC50	66000	LC50	**9.2**	NOEC	**0.092**	100	1	1	(55)
Azithromycin	83905-01-5	Pharmaceutical	**5.2**	NOEC	100000	EC50	**4600**	NOEC	**0.1**	50	4	1	(35)
Diclofenac	15307-86-5	Pharmaceutical	**10000**	NOEC	**45000**	NOEC	**1**	NOEC	**0.1**	10	1	1	(56)
Roxithromycin	80214-83-1	Pharmaceutical	**10**	NOEC	7100	EC50	290000	LC50	**0.1**	100	2	1	(57)
Oxybenzone	131-57-7	Personal care product	670	EC50	1900	EC50	**11**	NOEC	**0.11**	100	1	1	(58)
Fenbendazole	43210-67-9	Pharmaceutical	2000	EC50	**6.3**	NOEC	**200**	NOEC	**0.13**	50	2	1	(59)
Irbesartan	138402-11-6	Pharmaceutical	130	EC50	5600	EC50	5300	LC50	**0.13**	1000	2	1	(29)
Propylparaben	94-13-3	Paraben	170	EC50	3500	LC50	5200	LC50	**0.17**	1000	1	1	(60)
Clozapine	5786-21-0	Pharmaceutical	2200	EC50	6100	EC50	**18**	NOEC	**0.18**	100	1	1	(61)
Norfluoxetine	83891-03-6	Pharmaceutical	4100	EC50	5900	EC50	180	LC50	**0.18**	1000	1	1	(27; 28)
PFUnDA	2058-94-8	PFAS	900	EC50	190	LC50	220	LC50	**0.19**	1000	3	1	(29)
Diuron	330-54-1	Pesticide	**2**	NOEC	**96**	NOEC	**410**	NOEC	**0.2**	10	1	1	(62)
Iopromide	73334-07-3	Pharmaceutical	20	EC50	**1000000**	NOEC	10000000	LC50	**0.2**	100	1	1	(27; 28)
Triticonazole	131983-72-7	Pesticide	1000	EC50	**92**	NOEC	**10**	NOEC	**0.2**	50	1	1	(21)
Loperamide	53179-11-6	Pharmaceutical	5000	EC50	7700	EC50	240	LC50	**0.24**	1000	1	1	(27; 28)
Isoproturon	34123-59-6	Pesticide	**3.2**	NOEC	**120**	NOEC	**1000**	NOEC	**0.32**	10	1	1	(63)
Desethyl atrazine	6190-65-4	Pesticide	340	EC50	2200	LC50	28000	LC50	**0.34**	1000	2	1	(29)
Memantine	19982-08-2	Pharmaceutical	390	EC50	12000	EC50	40000	LC50	**0.39**	1000	2	1	(29)
Ethylparaben	120-47-8	Paraben	400	EC50	5700	LC50	11000	LC50	**0.4**	1000	1	1	(60)
Metformin	657-24-9	Pharmaceutical	*110000*	EC50	14000	EC50	**40**	NOEC	**0.4**	100	1	1	(64)
Fexofenadine	83799-24-0	Pharmaceutical	450	EC50	34000	EC50	2600	LC50	**0.45**	1000	1	1	(27; 28)
Lamotrigine	84057-84-1	Pharmaceutical	470	EC50	5100	EC50	5900	LC50	**0.47**	1000	1	1	(27; 28)
Fluoxetine	54910-89-3	Pharmaceutical	24	EC50	**56**	NOEC	**51**	NOEC	**0.48**	50	1	1	(65)
Norsertraline	87857-41-8	Pharmaceutical	1600	EC50	1900	EC50	510	LC50	**0.51**	1000	1	1	(27; 28)
N-Desmethylcitalopram	62498-67-3	Pharmaceutical	6300	EC50	11000	EC50	530	LC50	**0.53**	1000	1	1	(27; 28)
Sulfamethoxazole	723-46-6	Pharmaceutical	***5.9***	NOEC	**5.9**	NOEC	**10**	NOEC	***0.59***	10	2	1	(66)
Chloroquine	50-63-5	Pharmaceutical	*16000*	EC50	610	EC50	590	LC50	**0.59**	1000	1	1	(27; 28)
Atrazine	1912-24-9	Pesticide	NA	NA	NA	NA	NA	NA	**0.6**	5	1	1	(67)
Cetirizine	83881-51-0	Pharmaceutical	660	EC50	84000	EC50	17000	LC50	**0.66**	1000	1	1	(27; 28)
Fenofibrate	49562-28-9	Pharmaceutical	**3100**	NOEC	**39**	NOEC	*3200*	EC50	**0.78**	50	2	1	(68)
PFNA	375-95-1	PFAS	**460000**	LOEC	**8**	NOEC	**300**	LOEC	**0.8**	10	2	1	(69)
Codeine	76-57-3	Pharmaceutical	820	EC50	19000	LC50	1300	LC50	**0.82**	1000	2	1	(29)
Clopidogrel	113665-84-2	Pharmaceutical	9500	EC50	8400	EC50	820	LC50	**0.82**	1000	1	1	(27; 28)
Azoxystrobin	131860-33-8	Pesticide	360	EC50	**44**	NOEC	**150**	NOEC	**0.88**	50	1	1	(21)
Nicotine	54-11-5	Stimulant	16000	EC50	**180**	LOEC	4000	LC50	**0.9**	200	1	1	(70)
Propranolol	525-66-6	Pharmaceutical	**160**	NOEC	**9**	NOEC	**130**	LOEC	**0.9**	10	2	1	(66)
Mirtazapine	85650-52-8	Pharmaceutical	970	EC50	8700	EC50	3600	LC50	**0.97**	1000	1	1	(27; 28)
Amitriptyline	50-48-6	Pharmaceutical	720	EC50	220	EC50	**100**	NOEC	**1**	100	1	1	(71)

note that Schwarz et al. (2021) used ecotoxicological information which is not publicly available because of property rights (Schwarz et al., 2021). It was therefore not possible to use their data for PNEC derivation in this study. This highlights the issue of transparency when it comes to ERA for pharmaceuticals produced by private companies. National and international authorities should ask companies to provide public ecotoxicological information on any substance they wish to place on the market. Similar requirements already exist under other regulations on chemicals. For instance under the REACH regulation, any company wishing to manufacture or import a new substance into the European Union in an amount exceeding one tonne per year must provide a registration dossier including physicochemical, toxicological and ecotoxicological information on the substance (ECHA, 2017). All registration dossiers are made public and are accessible via the ECHA website (ECHA website).

Following the ERA guidelines, it was assumed that effect concentrations from long-term toxicity tests on algae, invertebrates and fish standard species (EMA, 2006, 2018; European Commission, 2003) are sufficient to determine PNEC for the whole aquatic ecosystem. However, it is possible that another taxonomic group may be more sensitive to a certain substance than algae, invertebrates and fishes. Therefore, a more thorough assessment based on sensitive species distribution (SSD) would consider larger ecotoxicity datasets, including other taxonomic groups based on the substance's mode of action. Such an approach would enable use of probabilistic methods to determine PNEC and would ensure that the most sensitive species are covered. According to Belanger et al. (2017), this method is better aligned with the principle of risk assessment as a probabilistic science, in contrast to the deterministic approach based on AF used in this study. Although guidelines on SSD exist (ECHA, 2008), the method requires a considerable amount of ecotoxicity data to ensure reliability, which makes it difficult to use for overview studies such as this. As highlighted by Belanger et al. (2017), the highest priority is to develop guidance on best practices in order to harmonise the SSD methodology. Regulatory authorities should develop such guidance to encourage companies to evaluate the hazard of their substances using the SSD approach. This would facilitate the work of risk assessors seeking to identify chemical substances of most concern globally.

Table 2
List of compounds for which optimised risk quotient (RQf) was > 0. These compounds are suspected to be the most concerning to aquatic ecosystems in Sweden and should be prioritized for further work. PNEC = predicted no-effects concentration, LOQ = limit of quantification.

Substance	CAS Number	Category	PNEC (µg/L)	Reliability	Relevance	LOQ (ng/L)[1]	LOQ:PNEC ratio	No risk (RQ<0.01)	Low risk (0.01 <RQ<0.1)	Moderate risk (0.1 <RQ<1)	High risk (RQ>1)	Mean RQ	F[2]	RQf
Metformin	657–24–9	Pharmaceutical	0.4	1	1	3.5	0.0088	0	1	8	28	8.3	76	6.2
N,N-Dimethyltetradecylamine	112–75–4	Industrial chemical	0.026	2	2	50	1.9	0	0	0	37	4.3	100	4.3
Oxazepam	604–75–1	Pharmaceutical	0.009	2	1	5	0.56	0	0	18	19	6.4	51	3.6
Venlafaxine	93,413–69–5	Pharmaceutical	0.026	2	1	3.7	0.14	0	0	23	14	3.6	38	1.4
Clindamycin	18,323–44–9	Pharmaceutical	0.01	2	1	1.3	0.13	0	0	26	11	1.5	30	0.45
Gemfibrozil	25,812–30–0	Pharmaceutical	0.019	1	1	4.8	0.25	0	0	29	8	0.68	22	0.15
Sertraline	79,617–96–2	Pharmaceutical	0.0047	1	1	0.72	0.15	0	0	30	7	0.74	19	0.14
O-Desmethylvenlafaxine	93,413–62–8	Pharmaceutical	2.3	1	1	5.5	0.0024	3	12	16	6	0.84	16	0.14
Diclofenac	15,307–86–5	Pharmaceutical	0.1	1	1	1.8	0.018	0	23	8	6	0.61	16	0.1
Bicalutamide	90,357–06–5	Pharmaceutical	0.092	1	1	1.6	0.017	0	19	11	7	0.51	19	0.097
Erythromycin	114–07–8	Pharmaceutical	0.02	2	1	1.1	0.055	0	23	9	5	0.47	14	0.064
Lamotrigine	84,057–84–1	Pharmaceutical	0.47	1	1	1.1	0.0023	8	13	14	2	0.31	5	0.017
Caffeine	58–08–2	Stimulant	1.2	1	1	7	0.0058	3	19	12	2	0.26	5	0.014
Telmisartan	144,701–48–4	Pharmaceutical	0.037	1	1	0.99	0.026	0	19	17	1	0.29	3	0.0078
Fexofenadine	83,799–24–0	Pharmaceutical	0.45	1	1	1.4	0.0031	9	14	13	1	0.21	3	0.0057
Irbesartan	138,402–11–6	Pharmaceutical	0.13	2	1	1.1	0.0086	8	15	13	1	0.18	3	0.0048
Clarithromycin	81,103–11–9	Pharmaceutical	0.04	2	1	0.6	0.015	0	28	8	1	0.16	3	0.0043
Ranitidine	66,357–35–5	Pharmaceutical	2.1	2	1	4.2	0.002	20	11	5	1	0.13	3	0.0036

[1]LOQ from (Golovko et al., 2020; Golovko et al., 2020). [2]Percentage of sampling sites for which RQ> 1.

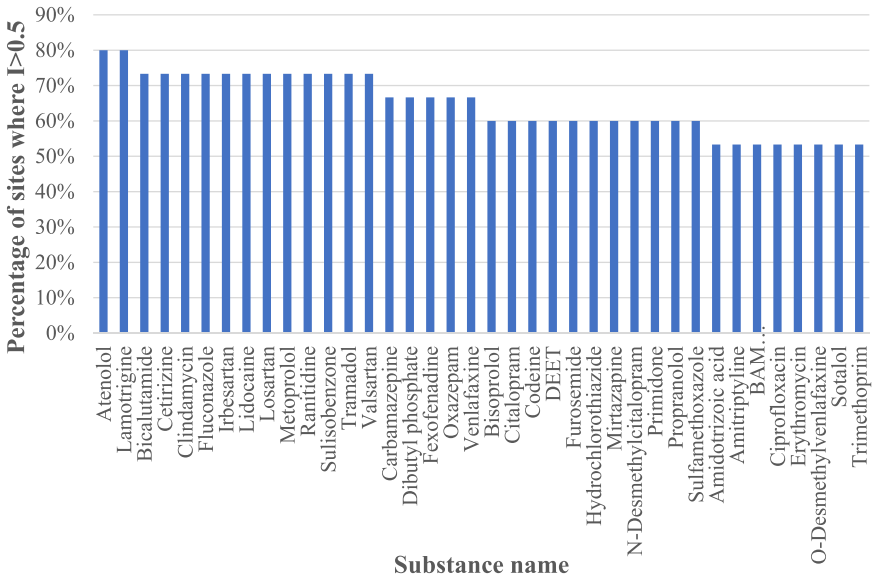

Fig. 2. List of compounds for which the factor $I_{i,j}$ (see Eq. 4) was greater than 0.5 in at least 50% of sampling locations. If $I_{i,j}$ is greater than 0.5, it can be assumed that the WWTP is the major contributor to the risk to the aquatic ecosystems.

3.2. *Identification of OMPs posing the highest risks to aquatic ecosystems*

Tables S5–1, S5–2 and S5–3 in SI present the RQ values calculated for all substances and for each sampling site, while Tables S6–1 in SI summarises the information contained in those tables. It also presents the number of sampling sites showing no, low, moderate, and high risk to aquatic ecosystems, mean RQ and RQ_f, LOQ for each compound (according to (Golovko et al., 2020)), LOQ to PNEC ratio, and percentage of sampling sites with MEC of a particular substance lower than its LOQ.

Table 2 lists the 18 compounds with $RQ_f > 0$ (for details, see Tables S6–1 in SI). For four compounds (namely, metformin, N,N-dimethyltetradecylamine, oxazepam, and venlafaxine), the RQ_f value was greater than 1, indicating a high risk to aquatic ecosystems in Swedish freshwaters. As the reliability and relevance of the key data used for PNEC calculation was scored 1 or 2, it can be assumed these substances represent a high risk to aquatic ecosystems in Swedish freshwaters, and should be prioritised for further actions. This is in agreement with conclusions in previous international studies (Zhou et al., 2019; Briones et al., 2016; Franquet-Griell et al., 2017). The RQ_f value for clindamycin, gemfibrozil, sertraline, o-desmethylvenlafaxine and diclofenac was between 0.1 and 1, indicating that these compounds may pose a moderate risk to aquatic ecosystems in Swedish freshwaters. These compounds should be monitored to ensure that their concentrations in surface waters are not increasing. For bicalutamide, erythromycin, caffeine, and lamotigrine, RQ_f values were lower than 0.1, which indicates that these compounds represent a low risk to aquatic ecosystems in Swedish freshwaters. The reliability and relevance of the key data used for PNEC calculation was scored 1 or 2, so the PNEC values of these compounds can be considered reliable.

It is important to note that $RQ_{f,i}$ value for a specific compound depends on the frequency of sites where $RQ_i > 1$, as indicated in Eq. 3. Thus, a low $RQ_{f,i}$ does not necessarily mean that a substance does not represent a risk for aquatic ecosystems. As shown in Table 2, RQ is greater than 1 in seven, five, and two different sampling locations for bicalutamide, erythromycin, lamotigrine, and caffeine, respectively. These findings indicate that, although these substances do not represent a high risk to Swedish freshwater ecosystems at the national scale, they may pose a risk to aquatic ecosystems locally. Similarly, $RQ_{f,i} < 0.01$ for

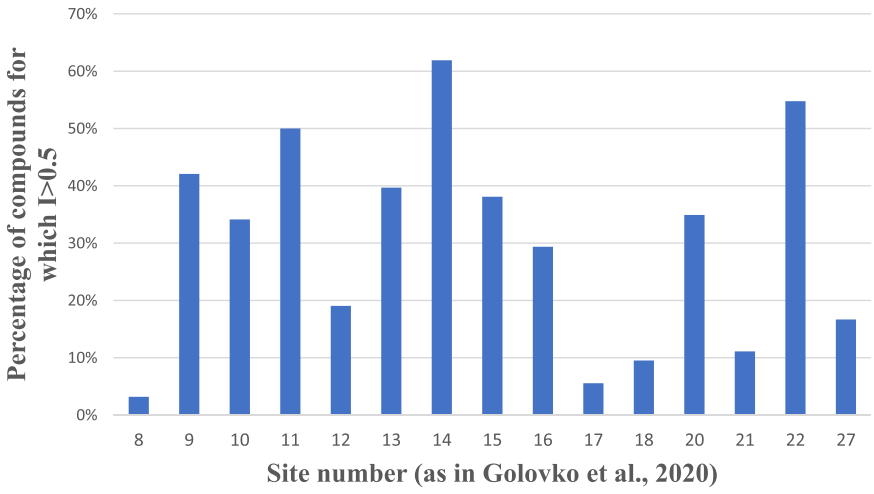

Fig. 3. Percentage of compounds for which the factor I_i was greater than 0.5 for each sampling sites. A high percentage indicates that the WWTP at the site j is the major contributor to the risk to the aquatic ecosystem for most of the investigated compounds. The information about site number can be found in Golovko et al., 2020a, 2020b).

telmisartan, fexofenadine, irbesartan, clarithromycin and ranitidine which indicates that these compounds pose a negligible risk to aquatic ecosystems in Swedish freshwaters. However, for these five substances, RQ was greater than 1 in one sampling location. Further investigations on the use of these substances should be carried out in these particular locations where RQ> 1 to identify the source of releases in order to decrease the potential risk they represent. As shown in Tables S6–1 in SI, the other substances investigated in this study were found to pose a negligible risk to aquatic ecosystems in Swedish freshwaters (i.e. $RQ_{f,i}$ =0). Nevertheless, 0.1 <RQ< 1 in a limited number of sampling locations for 21 compounds which indicates that these substances may pose a moderate risk to aquatic ecosystems locally. Further monitoring should be performed in these particular locations to ensure that the concentrations of these compounds are not increasing.

As mentioned previously, in cases where $MEC_{i,j}$ was lower than LOQ_i for substance *i* at location *j*, $RQ_{i,j}$ was calculated using LOQ_i. Hence, the resulting $RQ_{i,j}$ corresponds to a "worst case scenario", but it is unlikely to be representative of the actual risk posed by substance *i* to aquatic ecosystems. Subsequently, for clindamycin, gemfibrozil, N,N-dimethyltetradecylamine, norsertraline, oxazepam, sertraline, tetracycline and venlafaxine, LOQ:PNEC ratio was greater than 0.1 which would lead to the conclusion that these compounds represent a moderate risk to the aquatic environment as soon as they are detected. Thus, the risk that these substances may represent to the aquatic ecosystem could be overestimated. Further research on analytical methods for these compounds is needed to improve their quantification in environmental samples in order to get a better estimation of the risk that they may represent to aquatic ecosystems.

Additionally, further investigations are needed on substances for which PNEC was determined based on data with a reliability score of 3 or 4 (atorvastatin, azithromycin, benzophenone, cyanazine, di-(2-ethylhexyl)phosphoric acid, diltiazem, mefenamic acid, methotrexate, metoprolol and PFUnDA), to ensure that the risks that these compounds may pose were not underestimated.

As previously explained o-desmethylvenlafaxine, a transformation product of venlafaxine, has been identified as posing a moderate risk to aquatic ecosystems. Another study on the ecotoxicity of the two main photoderivatives of ranitidine showed that the half-life of ranitidine in freshwater is rather short, but that one of these photoderivatives has a NOEC of 2 ng/L for reproduction of *Ceriodaphnia dubia* (Isidori et al., 2009). This highlight the importance to also consider the risk posed by transformation products when performing an ERA.

By basing calculation of $RQ_{i,j}$ on $MEC_{i,j}$, this study obtained an assessment of the risk at a certain point in time. Previous studies have shown that the removal efficiency of WWTPs is likely to be lower during winter months, due to the lower temperatures (Golovko et al., 2020a, 2014; Gago-Ferrero et al., 2017; Fernández et al., 2014). Therefore, it is possible that releases of chemical substances from WWTPs into the environment are higher in winter, which would result in higher risk to aquatic ecosystems. Furthermore, the concentrations of pharmaceuticals in WWTP influent change according to the season, which is likely to impact the concentrations emitted to the environment (Golovko et al., 2014). It is also likely that degradation of chemicals in surface waters (e.g. via photolysis) is lower during winter, so their concentrations are likely to be higher then than during summer months, which would result in a higher risk to aquatic ecosystems (Rehrl et al., 2020). As this study was based on results from a sampling campaign performed in June 2018, it is possible that during the winter months, the risk posed by the compounds investigated is higher than reported here. According to the Swedish Meteorological and Hydrological Institute, summer 2018 was particularly warm (SMHI, 2018), which may have accentuated the difference in identified risk compared with winter months. Unfortunately, data on MEC during winter months were not available at the time of study to test this hypothesis.

Under the current guidelines, the risks of specific substances to aquatic ecosystems are assessed individually. However, as shown by the MEC values in Golovko et al. (2020a), aquatic organisms are exposed to a complex mixture of chemicals. Therefore, the actual risk to aquatic organisms might be higher since they are exposed to a mixture of OMPs (Backhaus and Faust, 2012; Backhaus, 2016). In order to assess the risk posed by mixtures of OMPs, it would be necessary to determine which chemicals have a similar mode of action and differentiate those which have a different mode of action. As such an analysis is very time-consuming, no assessment of potential mixture effects was performed in this study.

3.3. Impacts of WWTPs on aquatic ecosystems

Tables S7–1 in SI presents the impact factors of WWTPs for all substances in each sampling location where RQ_{RD} and RQ_{RU} were available ($n = 15$). Fig. 2 shows the compounds for which the factor $I_{i,j}$ was greater than 0.5 in more than 50% of the sampling locations. It can be assumed that for the 38 compounds listed in Fig. 2, WWTPs could be an important factor explaining the risk to aquatic ecosystems in the majority of sampling locations investigated. Interestingly, 34 of these compounds are pharmaceuticals, which correlates with previous findings of poor removal efficiency of pharmaceuticals by WWTPs (Golovko et al., 2020a). The present study supports the assumption that poor removal of pharmaceuticals during wastewater treatment is partly responsible for an increasing risk of these compounds to aquatic ecosystems. It is also important to note that two of these compounds (oxazepam and venlafaxine) had RQ_f greater than 1. These findings further support the assumption that the observed risks posed by these substances are partly explained by the presence of WWTPs at a majority of the sampling sites.

For metformin and N,N-dimethyltetradecylamine, the RQ_f value was greater than 1, but I was not greater than 0.5 for a majority of the sampling sites, so it could be assumed that WWTPs do not have an influence on these RQ values. This is probably the case for N,N-dimethyltetradecylamine as I was greater than 0.5 in only one location and lower than 0 in the majority of the sampling locations, indicating that the risk posed by this substance is greater upstream of WWTPs than downstream. Therefore, the source of the risk posed by this substance appears not to be the WWTPs investigated in this study. Based on information available on the ECHA website, N,N-dimethyltetradecylamine is used "in articles, by professional workers, in formulation or re-packaging, at industrial sites and in manufacturing" (Brief profile of Dimethyl(tetradecyl)amine). Hence, releases to the environment are likely to occur during industrial use, which supports the hypothesis that WWTPs are not the source of the risk posed by this compound to aquatic ecosystems.

Another possible explanation is that WWTPs influence RQ values in only a limited number of locations. This is probably the case for metformin, for which I was greater than 0.5 in five locations. Thus, the influence of WWTPs on RQ values seems to also depend on the location. To test this hypothesis, the percentage of each substance for which $I_{i,j}$ was greater than 0.5 was determined for each sampling site, illustrated in Fig. 3. At six locations, WWTPs influenced the RQ value of less than 20% of compounds investigated, while at three other locations WWTPs influenced the identified risk for more than half the substances. Therefore, the influence of WWTPs on the calculated RQs was location-specific.

A preliminary assumption could be that the influence of a WWTP depends on the population density in the area. However, there was no linear relationship between the population equivalent indicator and the percentage of substance for which I was greater than 0.5 ($R^2 = 0.08$). Hence, the influence of WWTPs on the RQ values of the substances investigated is not likely to be linearly related to population density. This agrees with previous findings that the concentration in receiving waters does not depend on the size of the WWTP, but rather on the amount of compound released and water circulation in the receiving waters (Wallberg et al., 2016).

There are at least four alternative explanations for the observed differences in the impact of WWTPs on RQ values. First, the influent wastewater to the WWTPs may come from different sources, which would affect the concentration of substances present, e.g. influents coming from industries and/or hospitals may differ from influents coming from municipal wastewater in terms of the substances they contain. Second, the WWTPs may not have the same type of treatments installed, e.g. some WWTPs may use more advanced techniques than others to ensure better treatment of the wastewater, which would influence the concentrations of substances in the effluent. Third, as explained previously, by calculating RQ based on MEC, the assessed risk can be influenced by the dilution of the substance. So low RQ_{RD} might be due to high volume of recipient surface water, which would tend to underestimate the impact of WWTPs. For instance, the RQ_{RD} of diclofenac was estimated to be 4.3, 0.038 and 0.018 at sites 2, 20 and 21, respectively (Tables S5–1 and S5–3 in SI). However, as indicated in Golovko et al. (2020b), the concentration of diclofenac in effluents of the WWTP in site 2 was 570 ng/L, and 910 ng/L in sites 20 and 21 (Golovko et al., 2020b). Thus, a lower concentration of diclofenac in WWTP effluents resulted in a higher risk for the local aquatic ecosystem, which is probably due to a difference in water flow of the recipient. Due to lack of information, it was not possible to test that hypothesis for this study.

Lastly, there could be other sources such as agricultural activities, surface runoffs, or industrial plants which can have a negative impact on the ecosystem in the recipient water. However, due to lack of information, a proper assessment of the influence of other sources on the identified risk was not possible in this study.

3.4. Environmental relevance and recommendations

In this study, a transparent assessment was performed of the toxicity of 126 OMPs to aquatic organisms. Calculation of the RQ values was linked to environmental monitoring data, which allowed identification of hotspots of contamination for aquatic ecosystems in Swedish freshwaters. This information could be used to identify substances of major concern for aquatic ecosystems. More reliable experimental data are needed for calculation of PNEC values and more monitoring data are needed for OMPs. The data presented here could be used for assessing the effects of OMP mixtures in aquatic ecosystems, and ultimately by local and international authorities to prioritise OMPs and contaminated hotspots, in order to decrease the risk posed by these compounds.

CRediT authorship contribution statement

Romain Figuière: Methodology, Investigation, Writing – original draft. **Oksana Golovko:** Supervision, Writing – review & editing. **Lutz Ahrens**: Supervision, Writing – review & editing. **Sylvia Waara**: Validation, 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.

Acknowledgement

We acknowledge Professor Paola Gramatica, University of Insubria, Varese, Italy, and her research team for letting us using the QSARINS software standalone version freely. The study was financially supported by Swedish Environmental Protection Agency (NV-09085-20) and Rydberg Laboratory for Applied Sciences at Halmstad University, Halmstad, Sweden.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhazmat.2022.128302.

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