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Optimization of screening-level risk assessment and priority selection of emerging pollutants – The case of pharmaceuticals in European surface waters

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ABSTRACT

Pharmaceuticals in surface waters have raised significant concern in recent years for their potential environmental effects. This study identified that at present a total of 477 substances (including 66 metabolites and transformation products) have been analyzed in European surface waters. Around 60% (284) of these compounds belonging to 16 different therapeutic groups were positively detected in one or more of 33 European countries. To conveniently and effectively prioritize potential high-risk compounds, an optimized method that considers the frequency of concentrations above predicted no effects levels was developed on the basis of the traditional method, and it was then used to identify and screen candidate priority pollutants in European surface waters. The results proved the feasibility and advantages of the optimized method. Pharmaceuticals detected in European surface waters were classified into 5 categories (high, moderate, endurable, negligible and safe) depending on their potential environmental effects and the distribution of pharmaceuticals. Circa 9% (45 out of 477) analyzed compounds showed a potential environmental risk to aquatic ecosystems. Among these 45 compounds, 12 compounds were indicated to have high environmental risk in aquatic environments, while 17 and 7 compounds showed moderate and small-scale environmental risks, respectively.

1. Introduction

Pharmaceuticals have gained scientific and public attentions as one of the most important groups of aquatic emerging pollutants, since their occurrence and environmental concentrations have widely been reported in water bodies in Europe and worldwide (e.g., Ashfaq et al., 2017; aus der Beek et al., 2015; Brack et al., 2018; Hughes et al., 2012; Loos et al., 2007, 2009; Munthe et al., 2017; Zhang et al., 2018). Multiple sources contribute to the occurrence of pharmaceuticals in surface waters, such as effluents of wastewater treatment plants (WWTPs) and industries, and agricultural runoff. Pharmaceuticals used in human medicine and not entirely metabolized or incompletely eliminated in WWTPs are released into surface waters. Furthermore, large quantities of pharmaceuticals used in veterinary medicine are excreted as parent compounds and metabolites into the environment without any treatment. Parent compounds and metabolites can undergo structural changes in the environment, resulting in new chemical entities (Michael et al., 2014).

In the last few years, some studies have already compiled, summarized and critically analyzed the measured concentrations of emerging contaminants in surface waters. For example, aus der Beek et al. (2015) and Hughes et al. (2012) analyzed the presence of pharmaceuticals and measured environmental concentrations at the global scale, and Loos et al. (2009) provided the occurrence of 35 organic

Abbreviations: AF, assessment factor; LOECs, lowest-observed effect concentrations; MECs, measured environmental concentrations; NOECs, no-observed effect concentrations; PNEC, predicted no effect concentration; QSAR, quantitative structure activity relationship; RQ, risk quotient; WWTPs, wastewater treatment plants

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compounds in European river waters. Some studies reported that pharmaceuticals could result in adverse effect on non-target organisms at environmentally relevant concentrations (e.g., Oaks et al., 2004; Kidd et al., 2007). However, the occurrence of metabolites and transformation products of pharmaceuticals in the environment was relatively less observed, and the effects of these compounds on non-target aquatic organisms at a large scale have not been fully understood yet.

Measured environmental concentrations (MECs) combined with predicted no effect concentrations (PNECs) as proposed by European commission (2003) are commonly used to screen compounds with potential environmental risks (Desbiolles et al., 2018; Houtman et al., 2014; Mendoza et al., 2014; Palma et al., 2014; Sanderson et al., 2004; Thomaidi et al., 2017; Thomatou et al., 2013; Vazquez-Roig et al., 2012; Vryzas et al., 2011). Burns et al. (2018a) reviewed that 76 pharmaceutical prioritizations were undertaken covering 24 countries. Meanwhile, the limitations of this traditional screening method have been realized and refined methods were proposed to properly identify the priority pollutants that should be regularly monitored in surface waters (e.g., Altenburger et al., 2018; Brack et al., 2017, 2018; Tousova et al., 2017; von der Ohe et al., 2011, 2012). However, to our knowledge there is no study providing a broad screening on the current potential environmental risks, whether assessed by traditional or improved methods, posed by pharmaceuticals to aquatic ecosystems. Therefore, the main objectives of the present study were to: 1) analyze the presence of pharmaceuticals belonging to different therapeutic groups and respective concentrations in European surface waters; 2) develop a reasonable and feasible method that could be used for screening the compounds with potential environmental risks, especially in a wide spatial-scale (e.g., regions, river basins, nations); 3) select the pharmaceuticals that would have priority in risk management and in further analysis of chronic toxicity in aquatic systems.

2. Methodology

2.1. Data collection

The concentration data in surface waters was obtained from peer-reviewed publications and government reports published between 1998 and 2016 by performing searches in Web of Sciences, Scopus and Google Scholar using the keywords “pharmaceutical”, “drug”, “pollutant” or “compound” in combination with the keywords “river”, “lake”, “stream” or “surface water”. The studies developed in European water bodies were then selected for this study. The publications used for data collection are categorized in S1 of the supplementary material. The data was mainly generated from the chemical analysis of samples collected in rivers and streams, followed by lakes and estuaries. Parts of the data for surface waters in Romania, Serbia, Austria, Bulgaria, Hungary, Croatia, Moldova and Ukraine were gained from the SOLUTIONS project (Neale et al., 2015). We considered that the research done in WWTPs did not reflect the dilution and degradation processes of receiving waters, thus data from WWTP effluents was excluded to avoid overestimating the pollution of surface waters. However, concentrations in receiving waters were included to reflect the worst case scenario in freshwater ecosystems. The data collected in this study was presented as the mean and maximum concentration values. The classification of pharmaceuticals was based on the PubChem database (Kim et al., 2015) and previous publications (e.g. aus der Beek et al., 2015; Hughes et al., 2012; Liu and Wong, 2013). In the present study, some compounds that are not pharmaceuticals for therapeutic, preventive, and diagnostic purposes were given due to their high detected frequencies together with pharmaceuticals. These compounds are metabolites and transformation products of pharmaceuticals, natural hormones and triclosan. Some metabolites and transformation products of pharmaceuticals still exhibit bioactivity, natural hormones are endocrine-disrupting compounds, and triclosan is an antimicrobial agent found in a variety of consumer products.

2.2. Risk quotient (RQ)

Based on the concentration data for particular contaminants, a risk quotient (RQ) approach has often been used to screen the compounds with potential environmental risks in surface waters according to the respective EU guidelines (European Commission, 2003). The RQ is based on the consideration that detected environmental concentrations and chronic toxicity of pharmaceuticals to non-target aquatic organisms are crucial for the assessment of environmental risks. Accordingly, in the present study algae (phototrophic level), *Daphnia magna* (invertebrates) and fish (vertebrates) were selected as representative organisms of three different trophic levels in aquatic ecosystems to assess potential ecological effects (European Commission, 2003). Chronic no-observed effect concentrations (NOECs) or chronic lowest-observed effect concentrations (LOECs) values were used for the calculation of PNECs. In the absence of chronic toxicity data, short-term E(L)C50 data was used. Toxicity data was mainly obtained from the United States EPA ECOTOX database (https://cfpub.epa.gov/ecotox/quick_query.htm). When no data was found in the database, short and long-term toxicity data was obtained from published literature by performing searches in Web of Sciences and Google Scholar using the pharmaceutical and the organism names as keywords. Finally, when no experimental toxicity data was available, acute toxicity values of compounds were calculated using the ECOSAR™v. 1.11 and QSAR Toolbox 3.3 by importing chemical name and CAS number. When more than one dataset on toxicity was obtained at the same nutrient level, the one indicating the strongest effect was used. The toxic data that is selected as the toxicological benchmarks for the calculation of the PNECs is shown in Table S1.

The RQ was calculated as a ratio of the MEC (measured environmental concentration) and PNEC (RQ = MEC/PNEC) (Palma et al., 2014). An assessment factor was used to overcome the uncertainty related to the raw toxicity data and to derive the PNEC (Vryzas et al., 2011). According to the EU guidelines (European Commission, 2003): (i) an assessment factor (AF) of 1000 was used in the cases where at least one short-term E(L)C50 from each of the three evaluated trophic levels was available; (ii) an AF of 100 was used when one long-term assay was available for either algae, crustaceans or fish; (iii) an AF of 50 was used in the case of existing two long-term assays in two different trophic levels; and (iv) an AF of 10 was used when three long-term assays in three different trophic levels were available. PNEC values were calculated by dividing the lowest NOEC, LOEC or E(L)C50 values of the most sensitive species by an appropriate AF. To calculate the RQ values under different scenarios, mean and maximum concentrations were used as MECs to reflect general and worst-case scenarios, respectively (Palma et al., 2014; Vryzas et al., 2011). If RQ is < 1, it suggests that the compound is less likely to cause hazardous effects in the aquatic environment. If RQ is higher than or equal to 1, it indicates that the particular substance could pose potential adverse effects.

2.3. Optimized risk quotient (RQ_f)

The current RQ approach as described above characterizes the toxicity of pharmaceuticals under the conditions of measured environmental concentrations, but ignores the possibility of aquatic organisms exposed to potentially unsafe levels. Since certain pharmaceuticals that are the long-term presence in water bodies have a greater impact than those pollutants that are the short-term presence on non-target organisms. That is to say, the risks of pharmaceuticals that were frequently detected and those were occasionally detected should be different. Therefore, it is a tendency to consider frequency during the high-risk compound screening (e.g. Desbiolles et al., 2018; Tousova et al., 2017; von der Ohe et al., 2011, 2012). When screening is given priority to pollutants that are widely distributed and frequently detected, the results could change considerably. Thus, a novel risk quotient (RQ_f) based on the mean RQ value and the frequency of MECs

exceeding PNEC was used to evaluate the potential risks due to detected substances, which is close to the natural scenario and favors the selection of priority pollutants. The RQ_f value was calculated according to the following equations:

$$RQ_f = RQ \times F = \frac{MEC}{PNEC} \times F$$

$$F = \frac{NO_1}{NO_2}$$

RQ_f represents the optimized risk quotient after considering the frequency of MECs exceeding PNEC; RQ represents the ratio of the mean concentration and PNEC; F represents the frequency of MECs exceeding PNEC; NO_1 represents the number of samples with concentrations higher than PNECs; NO_2 represents the total number of samples. RQ_f was classified into 5 groups: if RQ_f is higher than 1 ($RQ_f \geq 1$), high environmental risk is expected (high); if RQ_f lies between 0.1 and 1 ($1 > RQ_f \geq 0.1$), moderate environmental risk is expected (moderate); if RQ_f is between 0.1 and 0.01 ($0.1 > RQ_f \geq 0.01$), small-scale adverse effect is expected (endurable); if RQ_f is below 0.01 ($0.01 > RQ_f > 0$), the effect of this compound was quite limited (negligible); if RQ_f is equal to zero ($RQ_f = 0$), no risk is expected at present (safe).

2.4. Relationships between optimized (RQ_f) and traditional (RQ) risk quotients

According to the equations of RQ_f and RQ, traditional RQ can be regarded as a specific scenario of RQ_f. That is, only one environmental concentration is considered in RQ_f for risk assessment, and is assumed to be a concentration that may cause risks (F = 100%). When only the mean concentration is considered, RQ_f is equal to mean RQ. When only the maximum concentration is considered, RQ_f is equal to maximum RQ. Maximum RQ is likely to overestimate the potential risk of compounds, but the mean RQ does not reflect the natural scenario precisely, since the detected concentrations show great spatial and temporal variation, and the concentrations probably causing the environmental risk do not stably occur.

By considering the variability of concentrations above PNECs the optimized RQ_f favors to screen the pollutants that are widely distributed and frequently detected. Furthermore, this method does not separate general and worst-case scenarios, but includes all possibilities of the detected concentrations above PNECs. Furthermore, RQ_f uses a graded system (high, moderate, endurable, negligible and safe) to categorize the potential risks of chemicals. Thus it is more convenient to select contaminants that should be prioritized in a large-scale water resources management.

3. Results and discussion

3.1. Pharmaceuticals occurrence in European surface waters

3.1.1. Pharmaceuticals therapeutic groups

Fig. 1 shows the analyzed (a) and positively detected (b) therapeutic groups in European surface waters (detailed information is provided in the supplementary materials, Table S2). A total of 477 substances (411 pharmaceuticals and 66 metabolites and transformation products) belonging to 16 therapeutic groups were analyzed in European surface waters. Among these substances, 168 pharmaceuticals and 25 metabolites and transformation products were not present at concentrations above the detection limits of the analytical methods employed in the original publications. The remaining 284 substances (243 pharmaceuticals and 41 metabolites and transformation products) that were positively detected at concentrations above the detection limits belonged to 16 therapeutic groups: fungicides and antibiotics (73), analgesics and anti-inflammatories (30), anxiolytics and anticonvulsants (20), antihypertensives (19), antidepressants (19), opioids and morphine derivatives (18), stimulants (14), steroids and hormones (13), antihistamines (9), lipid-regulating drugs (8), antiviral drugs (7), β-blockers (7), diuretics (5), anaesthetics (3), antidiabetic drugs (3) and others (36). These groups were not only the most frequently detected compounds in Europe, but also were widely detected in other places throughout the world (aus der Beek et al., 2015; Bu et al., 2013; Burns et al., 2018b; Cantwell et al., 2018; Kolpin et al., 2002; Murata et al., 2011).

3.1.2. Detection frequencies and concentrations of pharmaceuticals

Fig. 2 shows the numbers of pharmaceuticals that were analyzed (a) and positively detected (b) in surface waters of each country. In total, there are 33 countries for which pharmaceuticals have been reported in the literature, covering the majority of the European area. Approximately 72% (86 out of 119) of the analyzed pharmaceuticals in the United Kingdom were detected at the concentrations above the limit of detection levels, and circa 55% (182 out of 100) in Germany and 40% in both Sweden and France (51 out of 132 and 61 out of 152, respectively). The most were found in Spain where studies reported circa 67% (153 out of 227) of the analyzed pharmaceuticals and metabolites and transformation products with concentrations over the detection limit. The concentrations and detection frequencies of the top 45 most studied compounds in European surface waters are shown in Table 1. Among these compounds, seven compounds, including 2 non-steroid anti-inflammatory drugs (NSAIDs) (ibuprofen, and diclofenac), 2 lipid-regulating drugs (gemfibrozil and bezafibrate), 1 stimulant (caffeine), 1 anticonvulsant (carbamazepine) as well as 1 antibiotic (sulfamethoxazole), were frequently analyzed in > 28 European countries. Great differences in national-weighted mean and maximum concentrations were observed for these compounds, which may be caused by many factors, including differences in use and release, removal efficiency of the WWTPs, degradation rate, temperature and dilution of receiving waters (Baker and Kasprzyk-Hordern, 2013).

Predominant antibiotic groups, such as macrolide antibiotics (e.g., erythromycin and its metabolite erythromycin–H_2O), fluoroquinolones (e.g., ciprofloxacin, ofloxacin and norfloxacin), and sulfonamides (e.g., sulfadiazine, sulfamethoxazole and its metabolite acetyl-sulfamethoxazole, sulfamethazine and its metabolite N_4-acetyl sulfamethazine), were present in surface waters with high detection frequencies (24 to 84%) and concentrations (up to 19,000 ng/L). The most concerned and studied antibiotic sulfamethoxazole and its metabolite acetyl-sulfamethoxazole were positively detected in over 50% of 892 samples collected in 33 countries, with a mean concentration of 192 ng/L. The concentrations of sulfamethoxazole in European countries were comparable to those in China (up to 940 ng/L) (Bu et al., 2013), and the highest concentration in European surface waters (11,920 ng/L) was higher than the reported maximum concentration in rivers of Australia (2000 ng/L) (Watkinson et al., 2009). Norfloxacin was one of the most reported fluoroquinolones, the concentrations of norfloxacin in surface waters in European countries were similar to those in Australia (Watkinson et al., 2009), but lower than those in China (up to 6800 ng/L) (Bu et al., 2013).

The most ubiquitous anti-inflammatories were ibuprofen and diclofenac. Ibuprofen was detected in 16 out of 31 countries with a concentration higher than 100 ng/L. Especially, diclofenac was found in Spain and Germany with a mean concentration of 514 and 1022 ng/L, respectively. Ibuprofen and diclofenac were frequently detected not only in surface waters, but also in aquatic organisms. It has been reported that the observed concentrations of ibuprofen and diclofenac in the bile of wild fish caught from a lake that received treated municipal wastewater ranged from 15 to 34 ng/mL and 6 to 148 ng/mL, respectively (Brozinski et al., 2012). The metabolites of anti-inflammatories, such as 4-Acetamidoantipyrine and 4-Formylaminoantipyrine, were frequently detected.

Some antidepressants, such as fluoxetine, sertraline, venlafaxine,

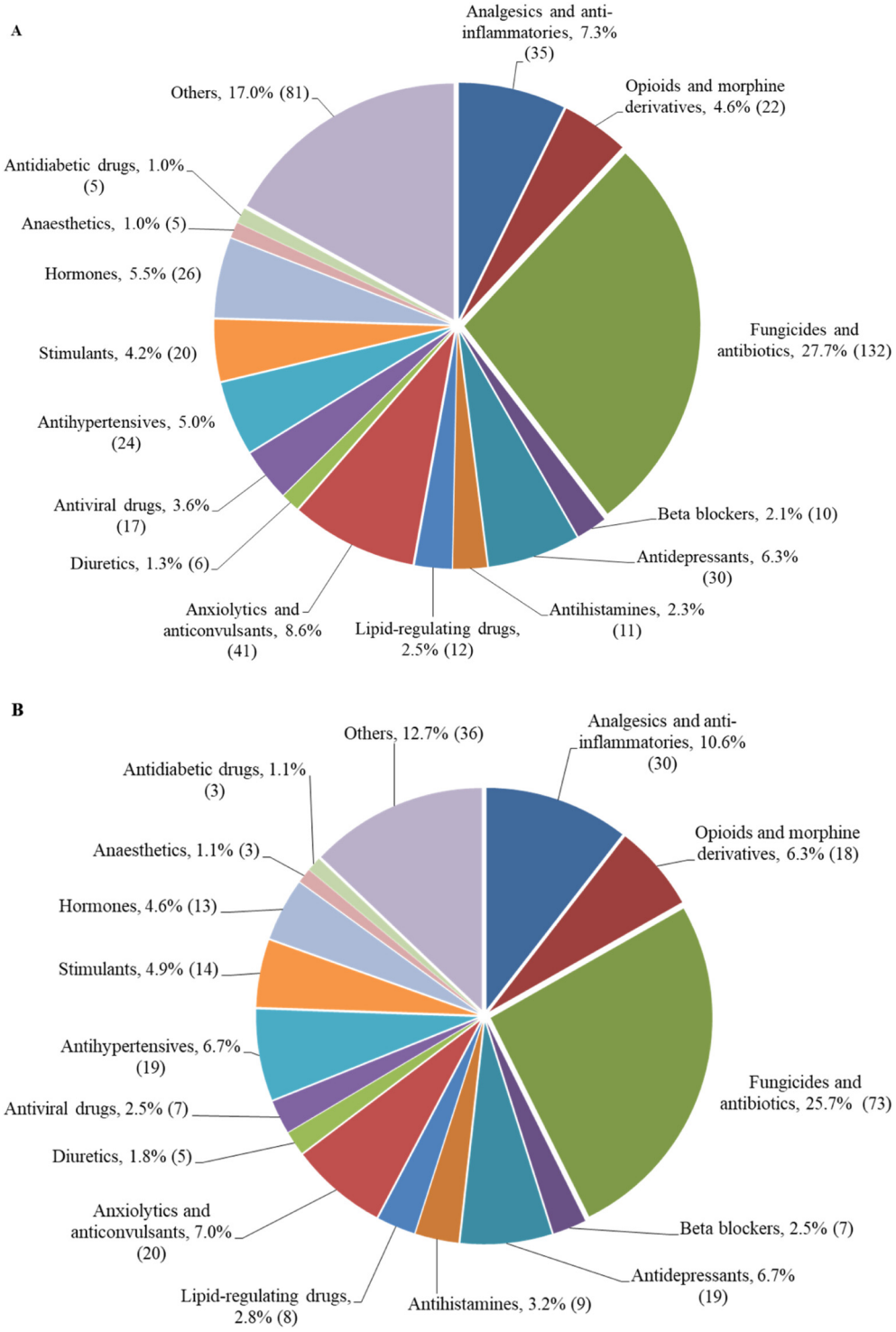

Fig. 1. Therapeutic groups analyzed (A) and positively detected (i.e., conc. > LOD, B) in European surface waters. The number of pharmaceuticals, metabolites and transformation products in each group is expressed as a percentage relative to the total number and the detailed number are given in brackets.

were commonly detected in WWTP effluents and surface waters (Corcoran et al., 2010). Meanwhile, the antidepressants fluoxetine and sertraline and their respective metabolites norfluoxetine and desmethylsertraline were observed in the fillet, liver, muscle and brain of fish caught from effluent-dominated rivers (Brooks et al., 2005; Ramirez et al., 2009; Schultz et al., 2010).

Hormones were frequently detected in European surface waters. Although natural steroid estrogens (e.g., estrone, estradiol and estriol) excreted by humans and animals actually cannot be regarded as pharmaceuticals, these compounds were considered for their potential endocrine disrupting effects. Estriol was found in 20% of the all samples with a concentration range of 0.33–480 ng/L in European surface waters. The most frequently studied synthetic steroid estrogen is ethinylestradiol (EE2) with a concentration range of 0.3–57 ng/L in European surface waters.

The most ubiquitous β-blocker was metoprolol, occurring in 69% of 635 samples analyzed in 20 countries. Another β-blocker sotalol was often present and occurred in the Netherlands, Spain, Sweden,

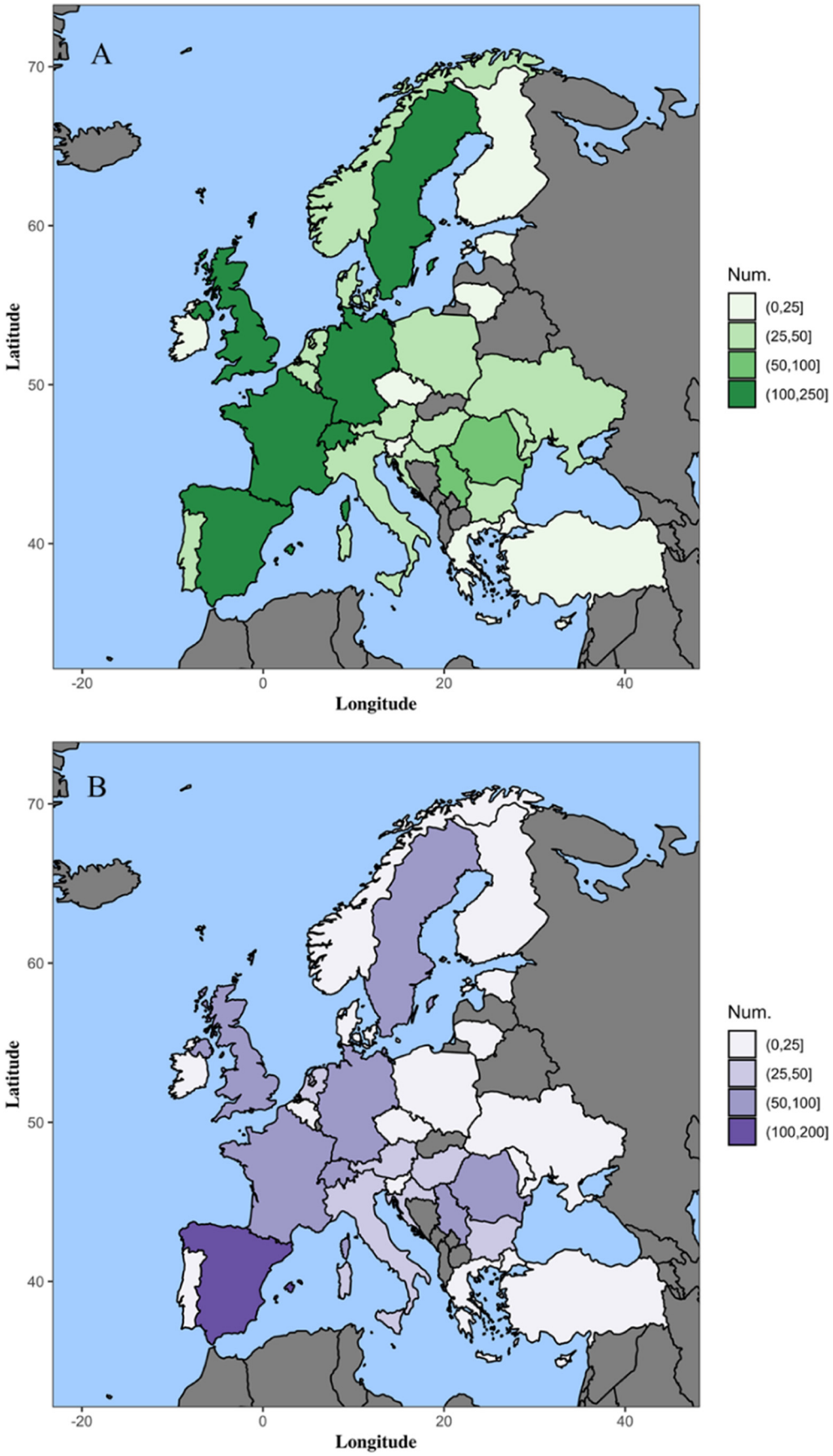

Fig. 2. Total numbers of pharmaceuticals, metabolites and transformation products analyzed (A) and positively detected (i.e., conc. > LOD, B) in European surface waters by country, given as groups.

Table 1
Mean and maximum concentrations, the frequency of measured environmental concentrations (MECs) above the LOD[a], and calculated mean and maximum RQ values for the 45 most frequently analyzed pharmaceuticals in European surface waters. Chemicals were ranked according to maximum RQ values from high to low.

Compounds	CAS	F_1 (%)[a]	Mean concentrations[b] (ng/L)	Maximum concentrations (ng/L)	PNECs (ng/L)	Mean RQ	Maximum RQ[c]
Ethinylestradiol	57-63-6	2	10	57	0.002	4851.00	28,500.00
Diclofenac	15307-86-5	63	247	18,740	1	246.57	18,740.00
Ibuprofen	15687-27-1	59	337	31,323	10	33.71	3132.30
Carbamazepine	298-46-4	68	183	11,561	10	18.32	1156.10
Atorvastatin	134523-00-5	14	26	128	0.26	101.88	492.31
Estriol[d]	50-27-1	20	40	480	1	40.27	480.00
Sulfadiazine	68-35-9	35	952	19,000	135	7.05	140.74
Ciprofloxacin	85721-33-1	35	657	13,567	100	6.57	135.67
Caffeine	58-08-2	90	885	39,813	320	2.76	124.42
Clarithromycin	81103-11-9	51	58	2403	20	2.89	120.15
Paraxanthine[d]	611-59-6	99	355	1412	14	25.38	100.86
Venlafaxine	99300-78-4	62	131	575	91.925	575.00	94.26
Ofloxacin	82419-36-1	37	540	8770	100	5.40	87.70
Atenolol	29122-68-7	n.a.	232	390	5	46.40	78.00
17-β-estradiol[d]	50-28-2	9	9	120	2	5.70	75.00
Bezafibrate	41859-67-0	49	243	15,060	230	1.06	65.48
Erythromycin	114-07-8	53	76	1700	40	1.89	42.50
Ranitidine	66357-35-5	57	34	136	5	6.82	27.69
Dextropropoxyphene	469-62-5	22	152	682	32	4.76	21.31
Amoxicillin	26787-78-0	31	201	622	37	5.44	16.81
Spiramycin	8025-81-8	43	31	74	5	6.19	14.84
Fluoxetine	54910-89-3	15	12	44	3	3.98	14.67
Triclosan[d]	3380-34-5	51	35	223	20	1.74	11.15
Roxithromycin	80214-83-1	26	163	1100	100	1.63	11.00
Zidovudine	30516-87-1	100	57	170	20	2.84	8.50
Tramadol	27203-92-5	77	1127	7731	959	1.17	8.06
Sulfapyridine	144-83-2	84	1222	12,000	1841	0.66	6.52
Citalopram	59729-33-8	60	45	120	20	2.24	6.00
Gemfibrozil	25812-30-0	61	325	7780	1560	0.21	4.99
Sulfamethoxazole	723-46-6	49	200	11,920	2400	0.08	4.97
Paracetamol	103-90-2	77	515	2382	500	1.03	4.76
Estrone[d]	53-16-7	45	6	89	20	0.32	4.45
Telmisartan	144701-48-4	n.a.	110	110	26	4.23	4.23
Propyphenazone	479-92-5	56	1160	1970	571	2.03	3.45
4-Acetamidoantipyrine[d]	83-15-8	90	1684	7239	2530	0.67	2.86
Oxytetracycline	79-57-2	24	101	680	310	0.33	2.19
4-Formylaminoantipyrine[d]	1672-58-8	80	1728	3425	1690	1.02	2.03
Valsartan	137862-53-4	71	1507	7479	3865	0.39	1.94
Sulfamethoxypyridazine	80-35-3	48	379	3704	2085	0.18	1.78
Progesterone	57-83-0	n.a.	23	32	19	1.22	1.72
Propranolol	525-66-6	50	68	590	400	0.17	1.48
Pentoxifylline	6493-05-6	50	30	30	21	1.43	1.43
Tamoxifen	10540-29-1	8	25	71	60	0.42	1.18
Propiconazole	60207-90-1	n.a.	63	100	95	0.67	1.05
Norfloxacin	70458-96-7	78	36	163	160	0.22	1.02

[a] F1 represents the frequency of detected concentrations of compounds above the detection limit (> LOD).
[b] The LODs were different for different methods, only concentrations values above LOD were considered to calculate mean value.
[c] Maximum RQ higher than 1 means that potential environmental risk existed (i.e., $RQ_f > 0$).
[d] Metabolites of pharmaceuticals, natural hormones and triclosan are not pharmaceuticals.

Switzerland and Germany. Although some of β-blockers (e.g. atenolol, bisoprolol and sotalol) were frequently detected in surface waters, they have not been detected in fish tissues in previous studies (Brozinski et al., 2012; Lahti et al., 2012; Ramirez et al., 2009).

For other therapeutic groups, the anxiolytic drug oxazepam was detected in 27% of samples taken from France and 68% in the United Kingdom. The drug metabolite clofibric acid was detected in 32% out of 484 samples collected from European surface waters. Caffeine is the most frequently consumed psychoactive stimulant (Persad, 2011) and is found in foods, beverage and pharmaceuticals. Concentrations of caffeine higher than 100 ng/L were reported in 26 out of 30 countries, and the highest concentration was found in Belgium (39,813 ng/L). The anticonvulsant carbamazepine was detected in mean concentrations up to 572 ng/L in Belgium, up to 771 ng/L in Hungary, and up to 5783 ng/L in Cyprus. It must be mentioned that mean concentrations in some countries (e.g., Greece, Turkey and Cyprus) are based on quite limited numbers of studies, in contrast to other countries such as Spain and Germany in which many measurements are available. Thus a direct comparison between different countries is not expedient.

3.2. Screening-level risk assessment of pharmaceuticals in surface waters

3.2.1. National-scale risk assessment

The number of pharmaceuticals with potential environmental risk in each country is shown in Fig. 3. In these countries, a total of 45 pharmaceuticals yielded an RQ_f above zero. The risk assessment in surface waters of Spain found 26 pharmaceuticals with RQ_f above zero. In France, Germany, the United Kingdom and Sweden, 11, 13, 13 and 16 potentially environmental risk compounds with RQ_f above zero were detected, respectively. The present results reveal high environmental risks in these countries. In contrast, few were detected in Greece, Finland and Ukraine, which does not mean a lower risk in these countries due to the fact that a comprehensive monitoring is often lacking or limited.

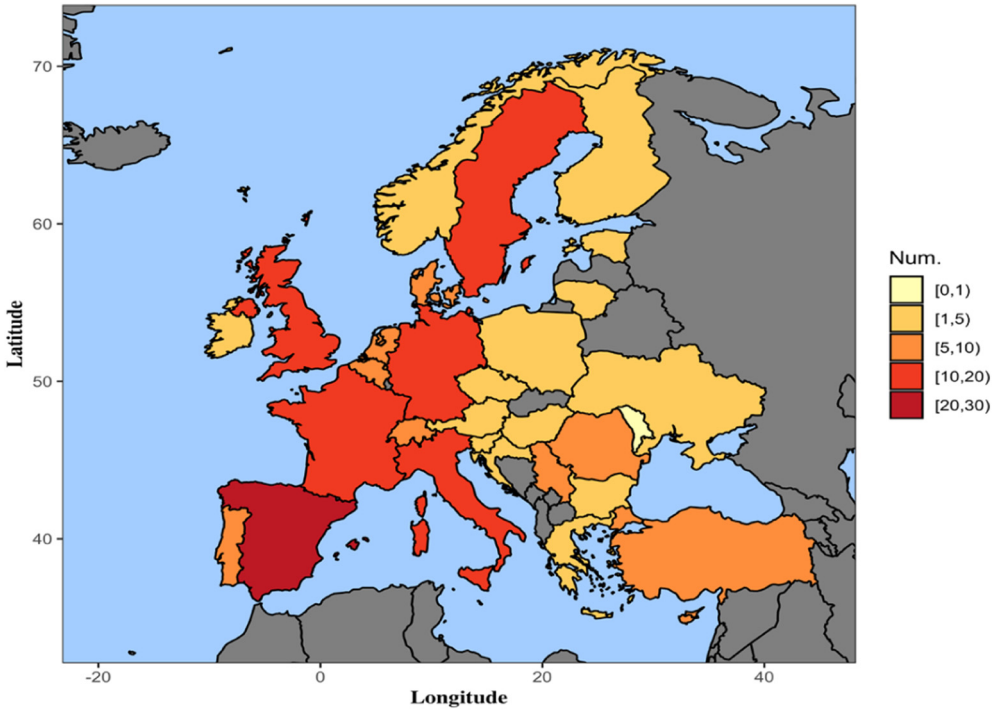

Fig. 3. The total numbers of pharmaceuticals with RQ_f above zero in each country.

For the most frequently detected compounds, concentrations have been measured above PNEC levels for caffeine, ibuprofen, diclofenac and carbamazepine in 16 out of 33, 26 out of 31, 28 out of 33, and 30 out of 32 detected European countries, respectively. Bezafibrate with concentrations higher than PNEC was only detected in Belgium, Cyprus, France, and Spain. For sulfamethoxazole, RQ_f values above zero were only detected in Cyprus and Spain. Other widely detected compounds were paracetamol, triclosan and estradiol with RQ_f values above zero in more than five countries.

3.2.2. Europe-wide ranking system

Table 2 shows prioritized pharmaceuticals according to RQ_f values in descending order. RQ_f ranged from 153.65 for the anti-inflammatory diclofenac to 0.001 for the antibiotic sulfamethoxazole. Compared with the original RQ value, RQ_f showed greater difference in potential environmental risks of the compounds after considering the frequency of MECs exceeding PNECs. For 12 compounds, namely diclofenac, ethinylestradiol, paraxanthine, ibuprofen, atorvastatin, carbamazepine, estriol, venlafaxine, ranitidine, spiramycin, zidovudine and amoxicillin, the RQ_f values were higher than 1.0, meaning high environmental risks in European surface waters according to our proposed approach. For 17 compounds the yielded RQ_f values were between 0.1 and 1.0, which would mean that moderate environmental risk was probable. Among these 29 compounds with high and moderate environmental risks, ethinylestradiol, diclofenac, and 17-β-estradiol have recently been included in the watch list by EU decision 2015/495 (EU, 2015). A previous study suggested that triclosan should be included as a priority pollutant in Europe (von der Ohe et al., 2012). Similarly, a European demonstration program (EDP) for chemical identification and effect-based monitoring of organic pollutants in surface waters prioritized 8 pharmaceuticals on the basis of their frequencies and extent of exceedance of PNECs (Tousova et al., 2017). Seven of them were ranked in our priority list, i.e. diclofenac, triclosan, ibuprofen, caffeine, erythromycin, carbamazepine and clarithromycin.

For 7 compounds the obtained RQ_f values were between 0.1 and 0.01, which we proposed indicated small-scale environmental risks in European surface waters. The RQ_f values of 5 compounds were < 0.01, in terms of the RQ_f indicating quite limited effects to the environment. In general, the selected priority pharmaceuticals were comparable to previous results. Actually, some of pharmaceuticals in our priority list were concerned worldwide. Previous studies suggested the potential ecological risks of erythromycin and oxytetracycline in Asia (Ji et al., 2012; Park and Choi, 2008; Yang et al., 2011). Bu et al. (2013) based on the RQ identified that 6 priority compounds (erythromycin, roxithromycin, diclofenac, ibuprofen, salicylic acid and sulfamethoxazole) posed moderate to high risks to aquatic organisms in surface waters in China. Finally, the RQ_f values of the remaining pharmaceuticals were zero, which would mean that no environmental risk was expected at detected environmental concentrations.

Adverse effects of some high-risk pharmaceuticals on non-target organisms have been observed in the laboratory and field. For example, diclofenac has been shown to bioaccumulate in fish (Lahti et al., 2011) and poses distinct effects in liver, kidney, and gills of fish at environmentally relevant concentrations (Triebskorn et al., 2007). The chronic exposure of fathead minnow (*Pimephales promelas*) to low concentrations (5–6 ng/L) of the potent ethynylestradiol in surface water led to feminization of males (Kidd et al., 2007).

Among these compounds, fungicides and antibiotics appear to be the most toxic in European surface waters. Antibiotics in the environment not only directly influence the health of organisms, but also promote the evolution and spread of antibiotic resistance genes, which can favor the spread of resistant pathogens (Ågerstrand et al., 2015; Pruden et al., 2013). It must be mentioned that propiconazole, progesterone, atenolol and telmisartan were only analyzed in limited sampling sites and the detection frequencies of those compounds were unavailable, thus these 4 chemicals ($RQ_f > 0$) were not in our priority list and further studies should be done.

The environmental fate of pharmaceuticals can be affected by physicochemical properties such as water solubilities, lipophilic characteristics and adsorption coefficients. Therefore partition coefficients such as the octanol–water partition coefficient (Kow) should be considered. Some pharmaceuticals such as caffeine (LogKow = − 0.07) and paracetamol (LogKow = 0.46) are readily biodegradable, but other pharmaceuticals appear to be quite persistent (Stuer-Lauridsen et al.,

Table 2
Prioritized pharmaceuticals according to the RQ_f values in descending order ($RQ_f > 0$).

Name	Therapeutic groups	Log Kow	F (%)	RQ_f
	High risks			
Diclofenac	Anti-inflammatories	4.51	62	153.65
Ethinylestradiol	Hormones	3.67	2	109.89
Paraxanthine[a]	Metabolites	−0.22	92	23.35
Ibuprofen	Anti-inflammatories	3.97	47	15.73
Atorvastatin	Lipid-lowering agent	6.36	14	14.54
Carbamazepine	Anticonvulsants	2.45	55	10.13
Estriol[a]	Hormones	2.45	17	6.75
Venlafaxine	Antidepressants	0.43	44	6.67
Ranitidine	Antihistamines	0.27	42	2.85
Spiramycin	Antibiotics	1.87[b]	40	2.46
Zidovudine	Antiviral drugs	0.05	73	2.07
Amoxicillin	Antibiotics	0.87	31	1.70
Moderate risks				
Citalopram	Antidepressants	3.74	40	0.90
Dextropropoxyphene	Analgesics	4.18	19	0.89
Ciprofloxacin	Antibiotics	0.28	12	0.80
Caffeine	Stimulants	−0.07	28	0.77
Propyphenazone	Analgesics	2.02	6	0.76
Ofloxacin	Antibiotics	−0.39	14	0.74
Pentoxifylline	Peripheral vasodilator	0.29	50	0.71
Fluoxetine	Antidepressants	4.05	14	0.57
Sulfadiazine	Antibiotics	−0.09	7	0.50
Clarithromycin	Antibiotics	3.16	14	0.41
Triclosan[a]	Antibacterial	4.76	21	0.37
Erythromycin	Antibiotics	3.06	18	0.33
Paracetamol	Analgesics	0.46	30	0.31
4-Formylaminoantipyrine[a]	Metabolites	−0.13	30	0.31
Tramadol	Opioids drugs	3.01	25	0.29
17-β-estradiol[a]	Hormones	4.01[b]	9	0.17
4-Acetamidoantipyrine[a]	Metabolites	0.50	20	0.13
Endurable risks				
Sulfapyridine	Antibiotics	0.35	14	0.090
Roxithromycin	Antibiotics	2.75	6	0.090
Bezafibrate	Lipid-regulating drugs	4.25	5	0.051
Valsartan	Antihypertensives	3.65[b]	12	0.046
Norfloxacin	Antibiotics	−1.03	6	0.010
Oxytetracycline	Antibiotics	−0.90	4	0.010
Estrone	Hormones	3.13	3	0.010
Negligible risks				
Sulfamethoxypyridazine	Antibiotics	0.32	5	0.009
Tamoxifen	Anti-estrogen drugs	6.30	1	0.006
Propranolol	β–blockers	3.48	3	0.005
Gemfibrozil	Lipid-regulating drugs	4.77	1	0.003
Sulfamethoxazole	Antibiotics	0.89	1	0.001

[a] Metabolites of pharmaceuticals, natural hormones and triclosan are not pharmaceuticals for therapeutic, preventive, and diagnostic purposes.
[b] LogKow reference from ECOSAR, and other LogKow from SRC (2016).

2000). Compounds with logKow higher than 3.0 show hydrophobic behavior and have a high potential for bioaccumulation (Palma et al., 2014). For example, erythromycin (LogKow = 3.06) can persist in the environment for more than one year. As shown in Table 2, around 40% (12 out of 29) of the highly or moderately hazardous pharmaceuticals have high potentials for bioaccumulation and should be considered as priority at the same risk level.

3.3. Future directions in priority substance selection

The grouping of pharmaceuticals, especially the high-risk compounds, according to therapeutic groups can support the selection of the single compounds that should compose chemical mixtures for further investigations such as by mechanism-specific bioassays. For example, the potential estrogenic effects of pharmaceuticals in surface waters were directly correlated with three compounds (ethinylestradiol, 17-β-estradiol, estrone), rather than other endocrine-disrupting compounds (e.g., 17α-estradiol, testosterone, progesterone, gestoden and bisphenol A) (Kase et al., 2018; Könemann et al., 2018). Studies investigating the toxic potential of chemical mixtures in the laboratory can support the interpretation of results obtained from tests of surface water samples (Di Paolo et al., 2016). By further considering therapeutical groups in mixture design, the involved mechanisms of toxicity can be considered in the risk assessment procedure (Busch et al., 2016; Kienzler et al., 2016). Furthermore, Escher and Fenner (2011) recommended that environmental risk assessment of pharmaceuticals should consider their metabolites and transformation products, since the degradation of pharmaceuticals in the environment may form persistent and toxic transformation products. Although metabolites and transformation products of pharmaceuticals were detected in surface waters, most of their toxicological data could not be acquired. For example, whether the occurrence of several metabolites of carbamazepine (e.g., 10,11-dihydro-10,11-dihydroxy-carbamazepine and 10,11-epoxy-carbamazepine) can pose a threat to aquatic systems is still uncertain.

Traditional pharmaceutical prioritization usually assesses the risk of compounds under general and worst scenarios. A total of 45 chemicals revealed the potential existence of an environmental risk under the worst-scenario (maximum RQ > 1), and 33 chemicals indicated the potential existence of an environmental risk under the general scenario (mean RQ > 1). It is clear that the risk of compounds cannot be precisely reflected by the RQ values no matter based on general or worst scenarios due to the great variations in detected concentrations. For example, potential environmental risk really existed for pentoxifylline (RQ = 1.43) and propranolol (RQ = 1.48), but the possibility of organisms exposed to the unsafe levels were 50% and 3%, respectively. Furthermore, Brack et al. (2017) believed that traditional monitoring and assessment tends to emphasize well known and regulated chemicals and to overlook emerging compounds. They recommended that an integrated strategy for prioritization of contaminants should be used. Tousova et al. (2017) also said that novel tools and approaches are required to monitor micropollutants and their effects in the aquatic environment.

In general, the risks of pharmaceuticals in the aquatic environment should not only rely on the environmental concentrations above PNEC levels, but also correlate with the length of time of aquatic organisms exposed to hazardous compounds, which means that the potential risks of pharmaceuticals in aquatic systems rely on chronic toxicity with long-term exposures rather than acute one with short-time exposures (Brausch and Rand, 2011). The lack of chronic toxicological data and the consequent use of ECOSAR and QSAR estimates often require a high AF, the risk levels of compounds based on acute toxicity data were probably overestimated, leading to a higher priority ranking. Further studies should confirm the risk of pharmaceuticals with RQ_f above zero.

4. Conclusions

Pharmaceuticals are ubiquitous in European surface waters and often detected at the ng/L range, and pose potential threats to aquatic organisms. Thus, in this study an optimized risk assessment method considering the frequency of concentrations above PNECs was recommended for screening-level risk assessment. Results showed that wide-scale water resource management should give priority to high-risk pollutants that are widely distributed and frequently detected. In European surface waters 12 compounds posed high risks to aquatic species and 17 caused moderate risks. Further investigations of the chronic effects of single pharmaceuticals or their mixtures need to be conducted in order to understand potential environmental effects.

Competing financial interests

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

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