Environment International 136 (2020) 105454

Contents lists available at ScienceDirect

Environment International

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

Ecological risk assessment of fifty pharmaceuticals and personal care products (PPCPs) in Chinese surface waters: A proposed multiple-level system

Na Liu[a], Xiaowei Jin[b,*], Chenglian Feng[a], Zijian Wang[c], Fengchang Wu[a], Andrew C. Johnson[d], Hongxia Xiao[e], Henner Hollert[e], John P. Giesy[f]

[a] State Key Laboratory of Environmental Criteria and Risk Assessment, Chinese Research Academy of Environmental Sciences, Beijing 100012, China
[b] China National Environmental Monitoring Center, Beijing 100012, China
[c] State Key Laboratory of Environmental Aquatic Chemistry, Research Center for Eco- Environmental Sciences, Chinese Academy of Sciences, Beijing 100085, China
[d] Centre for Ecology and Hydrology, Wallingford, Oxfordshire OX10 8BB, UK
[e] Institute for Environmental Research, RWTH Aachen University, Aachen 52074, Germany
[f] Department of Veterinary Biomedical Sciences and Toxicology Centre, University of Saskatchewan, Saskatoon, Saskatchewan, Canada

ARTICLE INFO

Handling Editor: Adrian Covaci

Keywords:
PPCPs
Occurrence
Prioritization
Risk assessment
Multiple-level

ABSTRACT

Interest in the risks posed by trace concentrations of pharmaceuticals and personal care products (PPCPs) in surface waters is increasing, particularly with regard to potential effects of long-term, low-dose exposures of aquatic organisms. In most cases, the actual studies on PPCPs were risk assessments at screening-level, and accurate estimates were scarce. In this study, exposure and ecotoxicity data of 50 PPCPs were collected based on our previous studies, and a multiple-level environmental risk assessment was performed. The 50 selected PPCPs are likely to be frequently detected in surface waters of China, with concentrations ranging from the ng L^{-1} to the low-g L^{-1}, and the risk quotients based on median concentrations ranged from 2046 for nonylphenol to 0 for phantolide. A semi-probabilistic approach screened 33 PPCPs that posed potential risks to aquatic organisms, among which 15 chemicals (nonylphenol, sulfamethoxazole, di (2-ethylhexyl) phthalate, 17β-ethynyl estradiol, caffeine, tetracycline, 17β-estradiol, estrone, dibutyl phthalate, ibuprofen, carbamazepine, tonalide, galaxolide, triclosan, and bisphenol A) were categorized as priority compounds according to an optimized risk assessment, and then the refined probabilistic risk assessment indicated 12 of them posed low to high risk to aquatic ecosystem, with the maximum risk products ranged from 1.54% to 17.38%. Based on these results, we propose that the optimized risk assessment was appropriate for screening priority contaminants at national scale, and when a more accurate estimation is required, the refined probability risk assessment is useful. The methodology and process might provide reference for other research of chemical evaluation and management for rivers, lakes, and sea waters.

1. Introduction

As one of the most important groups of contaminants of emerging concern, the occurrence of pharmaceuticals and personal care products (PPCPs) in the aquatic environments and their potential detrimental effects on aquatic organisms have given rise to major global concern in recent years. Pharmaceuticals are human and veterinary medicines, including antibiotics, β-blocking drugs, blood lipid regulators, anticonvulsant drugs, X-ray contrast media, and others. Personal care products (PCPs) are chemicals used in soaps, shampoos, conditioners, toothpastes, skin care products, sunscreens, insect repellents, lotions, and fragrances (Yu, 2011). It has been reported that more than 50,000 PPCPs are produced and around thirty million tons are consumed worldwide (Yu, 2011). China exports more than 60% of the total active pharmaceutical ingredients to the global pharmaceutical industry (Rehman et al., 2015) and consumed more than 162,000 tons of antibiotics in 2013 (Zhang et al., 2015). Proportions of the global total of PCPs consumed in China is approximately 6.5%, which is only exceeded by the United States of America (19.1%) and Japan (9.4%) (CIRN, 2012).

While most PPCPs are not persistent, due to their mass production and are used daily for various purposes, they are continually released

* Corresponding author at: China National Environmental Monitoring Center, Anwai Dayangfang No.8, Chaoyang District, Beijing 100012, China.
E-mail address: jinxiaowei07@mails.ucas.ac.cn (X. Jin).

https://doi.org/10.1016/j.envint.2019.105454
Received 26 September 2019; Received in revised form 26 December 2019; Accepted 26 December 2019
Available online 04 February 2020

into the aquatic environments via wastewater treatment plants (WWTPs), agricultural runoff, aquaculture, and PPCP manufacturing sites (Barbara et al., 2008; Larsson et al., 2007; Sim et al., 2011), and are typically considered as "pseudo-persistent" (Santos et al., 2010). The contamination of PPCPs in surface waters has been extensively studied in China and worldwide, with concentration ranging from ng L^{-1} to μg L^{-1} (Ebele et al., 2017; Sun et al., 2015; Bu et al., 2013; Liu et al., 2013; Balakrishna et al., 2017; Kuzmanović et al., 2015; Thomaidi et al., 2015; Carmona et al., 2014; Tewari et al., 2013; Scheurer et al., 2009). Although PPCPs are detected in surface waters at relatively low concentrations, many of them and their metabolites are biologically active and may impact non-target aquatic organisms at a long-term exposure, including endocrine disruption, genotoxicity, carcinogenicity, fetal development (Jin et al., 2014). A major concern raised by the presence of PPCPs in the aquatic environment is their ability to interfere with the endocrine system to produce undesired effects/ disruption of homeostasis (Ebele et al., 2017). It has been reported that more than 20% of PPCPs detected in surface waters were estrogenic chemicals (Kolpin et al., 2002).

Historically, studies on the aquatic risk of PPCPs were most frequently conducted using the simple, deterministic quotient method, which was expressed as the exposure concentration divided by the effect concentration (Donnachie et al., 2016; Wang et al., 2017; Zhang et al., 2017a; Zhang et al., 2017b; Vazquez-Roig et al., 2012). It is inevitable that there may be outliers within both effect and exposure datasets that may lead to bias or misinterpretation of risks. These might include unrepeatable ecotoxicity results, perhaps with ambiguous endpoints or high environmental concentrations reported from one-off measurements at localized, often more contaminated sites (Donnachie et al., 2016). Moreover, these studies were mainly based on acute toxicity data, and cannot adequately reflect the potential for chronic effects of long-term exposure to sub-acute levels (Godoy et al., 2015; Carlsson et al., 2006), particularly with regard to reproductive fitness, which most accurately represents variations between populations and species diversity for modulation of endocrine function in aquatic organisms (Jin et al., 2014; Liu et al., 2016a). Thus, a more accurate evaluation of PPCPs based on chronic effects is urgently needed.

According to the guidelines for ecological risk assessment developed by the US EPA (1998), quantitative risk estimates can be developed on the basis of measured data using one or more of the following techniques: (1) single-point exposure and effects comparisons, (2) comparing an exposure distribution with a point estimate of effects, and (3) comparisons incorporating variability of exposure and effects. Considering the complex effects and the low frequency of detection, risk characterization for PPCPs carried out by one method may be insufficient for the protection of the aquatic environment in China. The objectives of this study were to conduct a comprehensive evaluation of PPCPs in Chinese surface waters using all the three techniques based on chronic effects and concentrations reported during the 12-year period from 2006 to 2017, and to evaluate the protective capacity of this tiered approach, which could provide a more rigorous scientific basis and technical support for risk management options for PPCPs.

2. Materials and methods

2.1. PPCPs selected for this study

The 50 PPCPs (Table 1), on which this China-wide investigation focused, were selected for study based on the results of previous pilot studies (Liu, 2016), in which the risks of 144 PPCPs were assessed based on maximum concentrations in waters and thresholds for the most sensitive endpoints. If based on focused, regional studies, particular PPCPs were deemed to be more likely to cause adverse effects on aquatic environments of China, and most likely to cause more widespread issues. Among the 50 PPCPs, 44 were the prioritization of compounds on the first European Watch List (European Commission, 2015).

Table 1
Relevant information and properties of the selected PPCPs.

Category	Chemical	CAS NO.	Water Solubility at 25 °C(mg L^{-1}) [a]	log Kow [a]
antibiotic	clarithromycin	81103–11-9	0.342	3.16
antibiotic	erythromycin	114–07-8	1.44	3.06
antibiotic	roxithromycin	80214–83-1	0.0189	2.75
antibiotic	tylosin	1401–69-0	5	1.63
antibiotic	trimethoprim	738–70-5	400	0.91
antibiotic	sulfamethazine	57–68-1	1500	0.89
antibiotic	sulfamethoxazole	723–46-6	6.1	0.89
antibiotic	enrofloxacin	93106–60-6	3400	0.7
antibiotic	cephalexin	15686–71-2	1790	0.65
antibiotic	sulfapyridine	144–83-2	268	0.35
antibiotic	sulfamethoxypyridazine	80–32-0	7000	0.31
antibiotic	ciprofloxacin	85721–33-1	30,000	0.28
antibiotic	sulfadiazine	68–35-9	77	−0.09
antibiotic	ofloxacin	82419–36-1	28,300	−0.39
antibiotic	chlorotetracycline	57–62-5	630	−0.62
antibiotic	oxytetracycline	79–57-2	313	−0.9
antibiotic	norfloxacin	70458–96-7	178,000	−1.03
antibiotic	tetracycline	60–54-8	231	−1.3
hormone	diethylstilbestrol	56–53-1	12	5.07
hormone	17β-estradiol	50–28-2	3.6	4.01
hormone	17β-ethynyl estradiol	57–63-6	11.3	3.67
hormone	testosterone	58–22-0	23.4	3.32
hormone	bisphenol A	80–05-7	120	3.32
hormone	estrone	53–16-7	30	3.13
hormone	androstenedione	63–05-8	57.8	2.75
hormone	estriol	50–27-1	441	2.45
others	gemfibrozil	25812–30-0	11	4.77
others	indomethacin	53–86-1	0.937	4.23
others	diclofenac	19367–86-5	2.37	4.02
others	ibuprofen	15687–27-1	21	3.97
others	propranolol	525–66-6	61.7	3.48
others	naproxen	22204–53-1	15.9	3.18
others	clofibric acid	882–09-7	583	2.84
others	salicylic acid	69–72-7	2240	2.26
others	carbamazepine	298–46-4	17.7	2.25
others	caffeine	58–08-2	21,600	−0.07
others	iopromide	73334–07-3	23.8	−2.05
PCP	di-n-octyl phthalate	117–84-0	0.02	8.1
PCP	di(2-ethylhexyl) phthalate	117–81-7	0.27	7.6
PCP	nonylphenol	25154–52-3	6.35	5.99
PCP	galaxolide	1222–05-5	1.75	5.9
PCP	tonalide	1506–02-1	1.25	5.7
PCP	triclocarban	101–20-2	0.00237	4.9
PCP	triclosan	3380–34-5	10	4.76
PCP	dibutyl phthalate	84–74-2	11.2	4.5
PCP	musk ketone	81–14-1	0.387	4.3
PCP	diethyl phthalate	84–66-2	1080	2.42
PCP	dimethyl phthalate	131–11-3	4000	1.6
PCP	traseolide	68140–48-7	NR[b]	NR[b]
PCP	phantolide	15323–35-0	NR[b]	NR[b]

Note: a. Water Solubility and log Kow (octanol–water coefficient) from ChemIDPlus Advanced (http://chem.sis.nlm.nih.gov/chemidplus/) and PubChem (https://pubchem.ncbi.nlm.nih. gov/), U.S. National Library of Medicine. b. NR refers to not reported.

2.2. Evaluation and selection of data

2.2.1. Measured environment concentrations

The concentration data of 50 PPCPs in surface waters were obtained from peer-reviewed publications and government reports published between 2006 and 2017 by performing searches in National Knowledge Infrastructure, Web of Sciences, Scopus and Google Scholar using the keywords "pharmaceutical", "drug", "PCP", "occurrence", "pollutant" or "concentration". The data mainly came from chemical analysis of samples collected in rivers and streams, followed by lakes, reservoirs, and estuaries. In order to reflect the worst and the best case scenario in

freshwater ecosystems, concentrations in receiving waters and drinking water sources were included. Given the number of studies in the literature, the mean concentration for a location was calculated using measured values if greater than the method detection limits (MDL), the 1/2 MDL if < MDL or 0 if not detected. Once the datasets for environmental concentrations at the national scale were considered sufficient, the information was plotted to be evaluated and the 95th, 75th, 50th and 25th centile concentrations were calculated. The purpose of these measures is to describe the upper end of the exposure distribution, allowing researchers to evaluate whether certain locations indicate disproportionate large risks (US EPA, 1996).

2.2.2. Environmental toxicity information

Toxic potencies for the effects of 50 PPCPs on non-target organisms were retrieved from the ECOTOX Knowledgebase (https://cfpub.epa.gov/ecotox/search. cfm) developed by the US EPA, following the principles of accuracy, relevance and reliability according to Klimisch et al. (1997), Durda et al. (2000), Hobbs et al. (2005), US EPA (2011), Moermond et al. (2016). In these five methods or guidelines, there are five evaluate criteria for the quality of ecotoxicity data as follow: (1) test design, including guideline method, experimental process, the validity of the test results and quality controls; (2) the purity of the test substances and other ingredients in formulation; (3) general information and source of test organisms; (4) exposure conditions, including the experimental system appropriate for the test substance, the experimental system appropriate for the test organisms, the reliability of nominal concentration, the spacing between test concentrations, exposure duration, verify concentration and biomass loading; (5) data analysis, including replicate, statistical method, concentration-response curve and raw data (Liu et al., 2016b). Toxicity data were selected using a hierarchical method and chronic toxicity data of no observed effect concentrations (NOECs) or EC_{10} for the most sensitive effect measurements were preferred (EC, 2003). In the absence of NOEC or EC_{10}, the lowest observed effect concentration (LOEC) or the median effect concentration (EC_{50}) was used with assessment factor (AF) of 2 or 10 (EC, 2003; Bu et al., 2013).

2.3. Assessment of risks

The multiple-level ecological risk assessment (MLERA) of PPCPs was conducted according to the Framework for ecotoxicological risk assessment (US EPA, 1998, US EPA, 1992), the Technical Guidance Document on risk assessment (EC, 2003), NORMAN prioritisation framework for emerging substances (NORMAN Association, 2013), and previous studies (Zhou et al., 2019; Desbiolles et al., 2018; Ohe et al., 2011). A brief summary of the method is described in the following sections.

2.3.1. Tier-1 risk quotient (RQ): A screening-level risk assessment.

The ecological risks caused by 50 PPCPs in surface waters of China were assessed by use of deterministic quotient approach. Chronic and sublethal deterministic risk quotients (RQs) were calculated as quotients of the median concentration of individual chemicals in waters divided by the predicted no effect concentration (PNEC) (Eq. (1)). The preliminary risk assessment ranks of PPCPs were classified as insignificant if RQ < 0.1; low risk if 0.1 ≤ RQ < 1; moderate risk if 1 ≤ RQ < 10, and high risk if RQ ≥ 10 (Bu et al., 2013; Ågerstrand, 2010).

$$RQ = \frac{C_m}{PNEC} \tag{1}$$

Where C_m is the median concentration calculated from the collection of values for a single chemical measured at an individual location; *PNEC* is the predicted no effect concentration derived by the most sensitive toxicity data with AFs of 10, 20, or 100 depending on test endpoints of NOEC or EC_{10}, LOEC, EC_{50} (Bu et al., 2013; Tarazona et al., 2010).

2.3.2. Tier-2 frequency of PNEC exceedance: A semi-probabilistic approach.

Using median concentrations as a comparator provides a robust method to compare relative risks from chemicals. However, this relative risk index does not reveal to what degree any of the chemicals might actually be harming aquatic organisms at a national scale. So, a semi-probabilistic risk assessment approach was conducted according to the Framework for ecotoxicological risk assessment (US EPA, 1998, US EPA, 1992). In brief, concentrations of a chemical lower than PNEC are considered as safe, while concentrations exceeding PNEC might pose a risk to aquatic organisms. Measured concentrations of target chemicals at individual sampling sites were compared to PNEC values to determine the frequency of PNEC exceedance. PPCPs were then prioritized by the proportion of concentrations that exceeded the PNEC (Johnson et al., 2018).

$$F = \frac{n}{N} \times 100\% \tag{2}$$

where *F* is the frequency of PNEC exceedance, n is the number of sites with concentrations above PNEC and, *N* is the total number of sampling sites for a chemical. The resulting value indicates the share of sites where potential effects are expected (Ohe et al., 2011).

2.3.3. Tier-3 prioritization indexes: An optimized risk assessment.

Since the current RQ approach based on median concentrations in water could be skewed by the frequency of detection. It is a tendency to consider both concentration and frequency during the high-risk compound screening. Thus, an optimized risk assessment was carried out according to a methodology developed within the NORMAN Network (NORMAN Association, 2013; Zhou et al., 2019; Desbiolles et al., 2018; Tousova et al., 2017). Prioritization index (PI) was calculated, as the result of the RQ value multiplied by the frequency of PNEC exceedance, to highlight the PPCPs of greatest concern in surface waters of China, which are close to the natural scenario and favors the selection of priority pollutants.

$$PI = RQ \times F \tag{3}$$

where *PI* is prioritization index, *RQ* is risk quotient calculated based on median concentration and PNEC, *F* is the frequency of concentrations exceeding PNEC.

2.3.4. Tier-4 Joint probability curves (JPCs): A refined probability risk assessment.

The approaches used in the previous assessments of risk are dependent on the selection of PNECs, which are derived from single-species toxicity tests, and failure to protect diverse ecosystems (Mebane et al., 2010). For chemicals that posed high risk, it would be valuable to characterize their risk for various species at national scale. Thus, JPCs were adopted to identify chemicals that are most likely to have adverse effects on the widest range of species in the widest range of locations/times. In this method, positively detected concentrations in surface waters of China and chronic toxicity data for responses of various species were compiled and transformed to *probits* by fitting appropriate distributions. Linear regressions of the two data sets can then be used to calculate probabilities of concentrations causing adverse effects to a specified proportion (%) of species. Each point on the curve represents both the probability that the chosen proportion of species will be affected (magnitude of effect) and the frequency with which that magnitude of effect would be exceeded in surface waters (exceedance probability). The closer the JPC is to the axes, the less the probability of adverse effects (Solomon et al., 2000). To facilitate communication of the risk outputs, the risk products (risk product = exceedance probability × magnitude of effect) were then used to categorize risk as de minimis, low, intermediate, or high based on the criteria described in

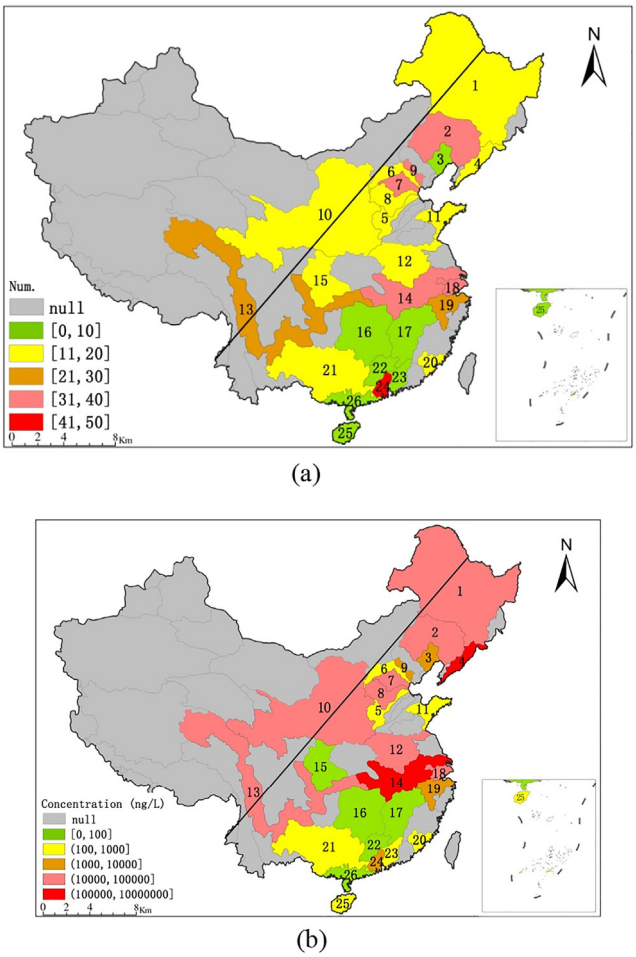

Fig. 1. Total number of PPCPs analyzed (a) and the highest concentration (b) in Chinese surface waters by river system region. The secondary river system regions IDs: 1. Songhua River; 2. Liao River; 3. Daling River; 4. Liaodong Peninsula; 5. Zhangweinan Canal; 6. Yongding River; 7. Daqing River; 8. Ziya River; 9. Chaobai-Beiyun-Jiyun River; 10. Yellow River; 11. Shandong Peninsula; 12. Huai River; 13. Yangtze River Upstream; 14. Yangtze River Downstream; 15. Jialing River; 16. Dongting Lake; 17. Poyang Lake; 18. Taihu Lake; 19. Qiantang River; 20. Mindong-Yuedong; 21. Xijiang River; 22. Beijiang River; 23. Dongjiang River; 24. Pearl River Delta; 25. Hainan; 26. Yueguiqiong. Watersheds IDs: 1–4. Songliao River; 5–9. Hai River; 10. Yellow River; 11–12. Huai River; 13–18. Yangtze River; 19–20. Southeast coast; 21–26. Pearl River.

Moore et al. (2010), Moore et al. (2014), Aslund et al. (2016), and Clemow et al. (2018), in which the risk categories are defined as follows:

If the maximum risk product was < 0.25%, then the risk was categorized as de minimis.
If the maximum risk product was ≥0.25% but < 2%, then the risk was categorized as low.
If the maximum risk product was ≥2% but < 10%, then the risk was categorized as intermediate.
If the maximum risk product was ≥10%, then the risk was categorized as high.

3. Results and discussion

3.1. PPCPs occurrence in Chinese surface waters

In total, 1934 exposure data of 50 target chemicals (Table S1) were collected from 26 secondary river system regions, spread over the sever river watersheds of China (Songliao River, Hai River, Yellow River, Huai River, Yangtze River, Southeast coast, Pearl River) (Fig. 1). The 26 secondary river system regions recovering most of the high population density area that reflected by the famous geographic "Hu Huanyong line" (Zhang et al., 2015), and 20 regions located in eastern coastal China. Pearl River Delta analyzed the most PPCPs (42), followed by Yangtze River downstream (38), Taihu Lake (38), Daqing River (36), Chaobai-Beiyun-Jiyun River (34), and Liao River (33). Liaodong Peninsula (14,718,411 ng L^{-1}) and Yangtze River downstream (731,100 ng L^{-1}) showed the highest concentration, followed by Ziya River (97,434 ng L^{-1}), and Huai River (81,250 ng L^{-1}). The most frequently reported watershed was Yangtze River (ID: 14–18), where 643 samples were reported and approximately 96% (43 out of 45) of the analyzed PPCPs were detected at concentrations above the limit of detection levels. PPCPs were most commonly found in Hai River (ID: 5–9), where 45 chemicals were analyzed and positively detected in 489 samples. Followed by Pearl River (ID: 21–26), where 46 PPCPs was analyzed and 44 of them were positively detected in 352 samples. It should be noted that studies in some watersheds were quite limited, for example, only 52 and 41 samples were reported in Yellow River (ID: 10) and Huai River (ID: 21, 22) respectively, and further studies should be done considering their 100% detection frequency.

Fig. 2 shows measured environmental concentrations of each compound and the frequencies of detection shown as the number of positively detected/all data points. Nationally, except for phantolide, PPCPs were frequently detected in Chinese surface waters (50% to 100%). Among the 50 targeted PPCPs, 23 were found in over 90% of samples. Predominant PCPs groups, such as phthalic acid esters (di-n-octyl phthalate, di (2-ethylhexyl) phthalate, and dibutyl phthalate), were detected frequently (67% to 100%) and at highest concentration levels (up to 14,718,411 ng L^{-1}) (Yao et al., 2011). The antibiotic sulfamethoxazole was the most concerned and investigated chemical, which was positively detected at over 95% of 120 sites collected in 7 watersheds. The highest concentration of sulfamethoxazole (984 ng L^{-1}) was similar to that in India (900 ng L^{-1}) (Balakrishna et al., 2017), but lower than those in Europe (11,920 ng L^{-1}) (Zhou et al., 2019), America (1,500 ng L^{-1}) (Fang et al., 2019) and Australia (2,000 ng L^{-1}) (Watkinson et al., 2009). The most ubiquitous antibiotics were erythromycin and sulfadiazine. Erythromycin was detected in 97% of 65 samples with the highest concentration of 1,418 ng L^{-1} detected in Yangtze River (Yao et al., 2017), similar to those in Europe (1,700 ng L^{-1}) (Zhou et al., 2019). Compared to Europe, sulfadiazine was more frequently detected (97%) in China but with lower exposure concentrations.

Among the seven hormones, the highest concentration was found for estriol in Yangtze River (67 ng L^{-1}) (Zhang et al., 2014), lower than in European surface waters (up to 480 ng L^{-1}), while the frequency of detection (61%) in all the 36 samples was higher than that found in Europe (20%) (Zhou et al., 2019). The most frequently studied hormone was estrone, occurring in 96% of 53 samples in seven watersheds. The concentrations of estrone in China (0.12–57 ng L^{-1}) were comparable to those in European countries (up to 89 ng L^{-1}) (Zhou et al., 2019). Especially, androgens androstenedione and testosterone were less reported globally, but were detected with 100% frequency in three Chinese watersheds with concentrations between 2 and 28 and 0.2–2.5 ng L^{-1}.

For other pharmaceutical groups, the highest concentration was found for iopromide in Yangtze River (26,000 ng L^{-1}) (Zhao et al., 2012). The psychoactive stimulant caffeine was positively detected in all 23 analyzed samples up to a concentration level of 3,712 ng L^{-1} in a river receiving treated wastewater in Beijing (Zhou et al., 2010), five times higher than the reported maximum concentration in Ganges River (743 ng L^{-1}) in India (Sharma et al., 2019), and one order of magnitude lower than those detected in Europe waters (up to 39,813 ng L^{-1}) (Loos et al., 2009), what may be caused by differences in use and release. The most popularity studies were carbamazepine and ibuprofen.

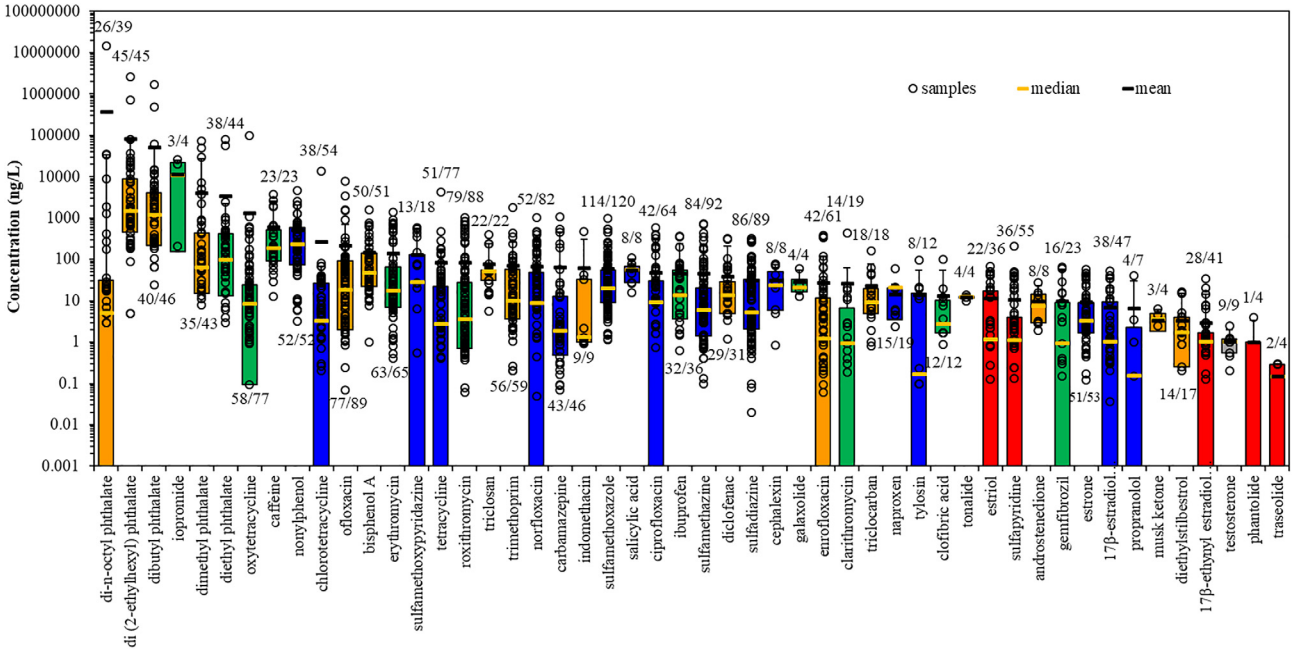

Fig. 2. Box and whisker plots of measured concentrations of 50 target chemicals in 1934 water samples. Concentrations for each sample are shown as individual points. The horizontal lines represent 95th centiles, and the boxes represent 25th and 75th centiles. The color indicates the categorization of compounds: orange: personal care products, green: other pharmaceuticals, blue: antibiotics, red: hormone. Median and mean concentrations are shown as solid horizontal lines. The numbers for each chemical indicate frequencies of detection, shown as the number of positively detected/all data points per data set, for example, di-n-octyl phthalate, ranked 1st, with 26 positively detected samples from 39 samples.

Carbamazepine was found in 93% of 42 samples collected in seven watersheds, with the highest concentration of up to 1,090 ng L^{-1} (Zhou et al., 2011), slightly lower than that reported from Europe (up to 1700 ng L^{-1}) (Fang et al. 2019), and much higher than the concentration range commonly reported in other regions of the world (Vieno et al., 2007; Nakada et al., 2007; Kumar et al., 2010; Sharma et al., 2019). Ibuprofen was detected in 32 out of 36 sites, with the highest concentration of 360 ng L^{-1}, two orders of magnitude lower than that reported in Europe (up to 31,323 ng L^{-1}) (Zhou et al., 2019).

In most cases, the mean concentrations were approximately equal to 75th centiles. While, due to a wide range of concentration in various samples, the distribution of concentrations of residues were skewed to the right (positive skewness). In the present study, 17 mean concentrations were higher than the 75th centile by 2-fold. For example, the mean concentrations of dimethyl phthalate and carbamazepine were higher than the 75th centile values by 9 and 5 times, respectively, with detection frequencies of 81% and 93%. Furthermore, in these 17 compounds, the mean concentrations for six PPCPs, di-n-octyl phthalate, oxytetracycline, chlorotetracycline, diethyl phthalate, dibutyl phthalate, and di (2-ethylhexyl) phthalate, were higher than the 95th centile. This demonstrates how the mean can be skewed by a few higher concentrations, and therefore the results of risk assessment based on median concentrations would be less uncertainty.

3.2. Toxic potencies of PPCPs

For use in this study, available chronic data for aquatic organisms were secured for 50 PPCPs tested (Table 2). The results displayed here possibly represent the most sensitive endpoints yet collated for the 50 PPCPs. All the 50 PPCPs may cause effects on growth, development, or reproduction of aquatic organisms. The data set contained single-species toxicity data for 29 taxa, of which 9 were vertebrates, 11 were invertebrates and 9 were primary producers. The thresholds for chronic toxicity endpoints for vertebrates ranged from 0.03 to 1.2×10^4 ng L^{-1}; for invertebrates, from 0.1 to 1×10^9 ng L^{-1}; and for primary producers, from 1.6×10^3 to 3.2×10^7 ng L^{-1}.

From this collection of 18 antibiotics, 13 of them appear to be more toxic to primary producers, and the other 5 antibiotics were more toxic to aquatic animals. EC_{50} for most antibiotics in lower aquatic organisms (alga and microorganism) were μg L^{-1}-mg L^{-1}, which were 100 to 1000 times more sensitive than higher organisms (Chen et al., 2012; Meng et al., 2015). In comparison, aquatic vertebrates were more sensitive to effects of PCPs, and fishes were more sensitive to hormones and other pharmaceuticals.

3.3. Risk characterization

3.3.1. RQs of 50 PPCPs based on median concentrations

The 50 PPCPs were ranked by RQ values in descending order (Fig. 3). For 9 compounds, the RQ values were higher than 10, meaning high environmental risks in Chinese surface waters according to this approach, among which sulfamethoxazole posed the second highest risk to aquatic organisms, with a RQ of 1955, because of its toxic potency to *Caenorhabditis elegans* (Yu et al., 2011). For 7 compounds the yielded RQ values were between 1 and 10, which would mean that a moderate environmental risk was probable. Among these 16 PPCPs that posted certain risk to aquatic organisms (RQ ≥ 1), PCPs made the largest contribution (8 out of 16), followed by hormones (3 out of 16) and other pharmaceuticals group (3 out of 16). Antibiotics were the most important group in this study, due to their large amount of consumption and extensively reported, but only sulfamethoxazole and tetracycline were identified as high risk in Chinese surface waters. This is expected because the hydrophilicity of antibiotics led to the relatively less toxicity to aquatic organisms. A similar result was achieved by the predicted environmental concentration and ecological effects conducted by Sui et al. (2012), in their study, only 32% of the antibiotics were listed as priority pharmaceuticals.

3.3.2. Characterization of semi-probabilistic risk

While using median concentrations can distort the analysis and therefore be over- cautionary, an alternative is to quantify the probability of concentrations of PPCPs in surface waters exceeding the PNEC

Table 2
Toxic potencies of four categories of PPCPs to aquatic organisms[a].

Category	Chemicals	Species	Class	Effect	Duration (days)	Endpoint	Concentration (ng L^{-1})	AF	PNEC (ng L^{-1})
antibiotic	sulfamethoxazole	*Caenorhabditis elegans*	Worm	Morphology	4	EC10	0.1	10	0.01
antibiotic	tetracycline	*Gambusia holbrooki*	Fish	Biochemical	4	LOEC	5	20	0.25
antibiotic	norfloxacin	*Microcystis aeruginosa*	Alage	Population	6	NOEC	1600	10	160
antibiotic	clarithromycin	*Pseudokirchneriella subcapitata*	Alage	Population	3	NOEC	2000	10	200
antibiotic	erythromycin	*Synechococcus leopoliensis*	Alage	Population	6	NOEC	2000	10	200
antibiotic	ofloxacin	*Microcystis aeruginosa*	Alage	Population	5	EC50	21,000	100	210
antibiotic	sulfapyridine	*Lemna gibba*	Alage	Population	4	NOEC	4600	10	460
antibiotic	roxithromycin	*subcapitata*	Alage	Population	3	LOEC	10,000	20	500
antibiotic	sulfadiazine	*Phaeodactylum tricornutum*	Alage	Population	4	NOEC	10,000	10	1000
antibiotic	trimethoprim	*Brachionus koreanus*	Rotifer	Genetic	1	NOEC	10,000	10	1000
antibiotic	enrofloxacin	*Penaeus monodon*	Crustacean	Growth	4	NR[b]	11,000	10	1100
antibiotic	chlorotetracycline	*Oreochromis niloticus*	Fish	Growth	48	NOEC	12,000	10	1200
antibiotic	oxytetracycline	*Egeria densa -Population*	Plant	Population	42	NOEC	20,000	10	2000
antibiotic	ciprofloxacin	*Lemna gibba*	Plant	Population	7	NOEC	100,000	10	10,000
antibiotic	tylosin	*Lemna gibba*	Plant	Population	7	NOEC	100,000	10	10,000
antibiotic	sulfamethazine	*Lemna gibba*	Plant	Population	7	NOEC	300,000	10	30,000
antibiotic	cephalexin	*Lemna gibba*	Plant	Population	7	NOEC	1,000,000	10	100,000
antibiotic	sulfamethoxypyridazine	*Chlorella fusca* var. *vacuolata*	Alage	Population	1	EC50	32,250,000	100	322,500
hormone	17β-ethynyl estradiol	*Oryzias latipes*	Fish	Morphology	100	NOEC	0.03	10	0.003
hormone	testosterone	*Oncorhynchus kisutch*	Fish	Reproduction	21	LOEC	30	20	1.5
hormone	17β-estradiol	*Oncorhynchus mykiss*	Fish	Reproduction	50	NOEC	0.42	10	0.042
hormone	estrone	*Oncorhynchus mykiss*	Fish	Vitellin	14	NOEC	0.74	10	0.074
hormone	estriol	*Oryzias latipes*	Fish	Hatch	15	NOEC	46.5	10	4.65
hormone	androstenedione	*Poecilia reticulata*	Fish	Morphology	12 ~ 14	NOEC	700	10	70
hormone	diethylstilbestrol	*Nitocra Spinipes*	Copepod	Reproduction	15–18	NOEC	3000	10	300
others	caffeine	*Salmo salar*[c]	Fish	Growth	5	NOEC	10	10	1
others	ibuprofen	*Gammarus pulex*	Crustaceans	Behavior	0.0833	LOEC	10	20	0.5
others	gemfibrozil	*Danio rerio*[c]	Fish	Genetic	7	LOEC	380	20	19
others	diclofenac	*Oncorhynchus mykiss*	Fish	Morphology	21	LOEC	460	20	23
others	carbamazepine	*Gammarus pulex*	Crustaceans	Behavior	0.0833	NOEC	10	10	1
others	indomethacin	*Danio rerio*[c]	Fish	Reproduction	16	NOEC	1000	10	100
others	clofibric acid	*Oncorhynchus mykiss*	Fish	Morphology	28	NOEC	1000	10	100
others	propranolol	*Oryzias latipes*	Fish	Hormone	28	NOEC	1000	10	100
others	naproxen	*Limnodynastes peronii*[d]	Amphibians	Developmental	21	NOEC	10,000	10	1000
others	salicylic acid	*Daphnia longispina*	Crustaceans	Reproduction	21	NOEC	1,000,000	10	100,000
others	iopromide	*Daphnia magna*	Crustaceans	Reproduction	22	NOEC	1,000,000,000	10	100,000,000
PCP	nonylphenol	*Danio rerio*[c]	Fish	Genetic	3	LOEC	2.2	20	0.11
PCP	tonalide	*Dreissena polymorpha*[d]	Molluscs	Physiological	7	NOEC	20.5	10	2.05
PCP	triclocarban	*Americamysis bahia*[c]	Crustaceans	Reproduction	28	NOEC	60	10	6
PCP	galaxolide	*Dreissena polymorpha*[d]	Molluscs	Physiological	4 ~ 21	NOEC	97	10	9.7
PCP	bisphenol A	*Oryzias latipes*	Fish	Reproduction	4	NOEC	100	10	10
PCP	triclosan	*Ruditapes philippinarum*	Molluscs	Reproduction	7	NOEC	300	10	30
PCP	di (2-ethylhexyl) phthalate	*Oryzias latipes*	Fish	Developmental	90	NOEC	1000	10	100
PCP	traseolide	*crucian*	Fish	Physiological	NR	NOEC	1500	10	150
PCP	phantolide	*crucian*	Fish	Physiological	NR	NOEC	1500	10	150
PCP	dibutyl phthalate	*Danio rerio*[c]	Fish	Biochemical	4	LOEC	5000	20	250
PCP	musk ketone	*Danio rerio*[c]	Fish	Physiological	2	NOEC	3300	10	330
PCP	diethyl phthalate	*Danio rerio*[c]	Fish	Genetic	4	NOEC	5000	10	500
PCP	di-n-octyl phthalate	*Haliotis diversicolor*	Molluscs	Developmental	4	NOEC	20,000	10	2000
PCP	dimethyl phthalate	*Haliotis diversicolor*	Molluscs	Developmental	4	NOEC	20,000	10	2000

Note: a. Toxicology data of 50 PPCPs were retrieved from the ECOTOX Knowledgebase (https://cfpub.epa.gov/ecotox/search.cfm). b. NR refers to not reported. c. *Salmo sala*, *Danio rerio*, and *Americamysis bahia were* nonnative species but standard test species. d. *Limnodynastes peronii* and *Dreissena polymorpha were* neither nonnative species nor standard test species.

for aquatic organisms. The percentage of monitoring values which exceed PNEC values can be identified. In this case, 33 PPCPs (Fig. 4) in surface waters of China were predicted with adverse effects on some sensitive species. In this group, the highest likelihood of exceeding PNECs (100% of monitoring values) were nonylphenol, caffeine, tonalide, and galaxolide. Closely followed, with more than 90% of monitoring values exceeding the PNEC were estrone, sulfamethoxazole, bisphenol A, and di (2-ethylhexyl) phthalate. As expected, a possible threat (1–10%) were observed for 6 chemicals (roxithromycin, di-n-octyl phthalate, clarithromycin, trimethoprim, oxytetracycline, chlorotetracycline) that indicated as insignificant risks using the RQ method. The frequencies of PNEC exceedance of the remaining 17 PPCPs were zero, meaning that no ecotoxicological risk to aquatic organisms is to be expected at current environmental concentrations. In a case study performed in Greece by Thomaidi et al. (2015), for 25/25 rivers, 22/25 rivers, and 20/25 rivers, triclosan, caffeine and nonylphenol presented RQ values higher than 1, respectively. Additionally, sulfamethoxazole, bisphenol A, and ofloxacin presented RQ $>$ 1 in two rivers. These results indicated that the distribution of concentrations in surface waters is an important factor to consider when ranking the potential risks of PPCPs.

In order to prioritize chemicals more reasonable, it was essential to compare the results of the semi-probabilistic approach with the frequency of detection. For example, the proportions of 17β-ethynyl estradiol and 17β-estradiol that exceeded their respective PNECs were 68% and 69% respectively, approaching the frequency of detection 68% and 74%. Thus, aquatic organisms could be at risk once such chemicals were detected in waters. According to Burns et al. (2018), risk-based and hazard-based methods identified estrone, 17β-estradiol, 17β-ethynyl estradiol, and testosterone as the highest priority, despite

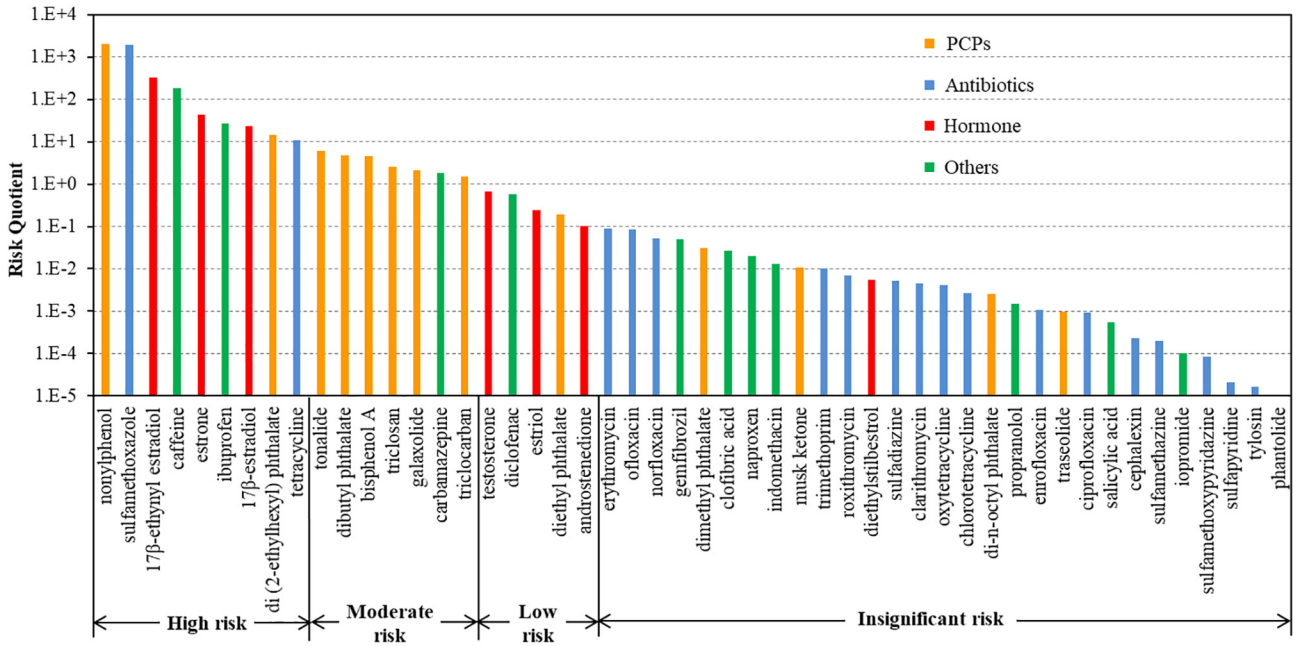

Fig. 3. Risk ranking of 18 antibiotics, 7 hormone, 11 other pharmaceuticals, and 14 PCPs, based on effect concentration for the most sensitive species and the median concentrations in surface waters. Colors refer to the chemical groups.

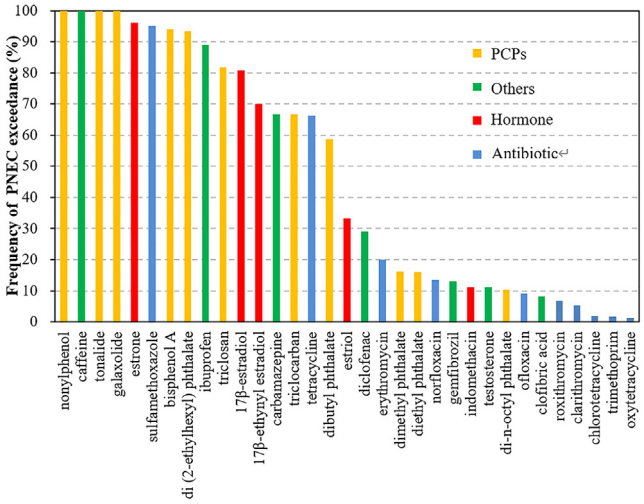

Fig. 4. Proportions (%) of concentrations of 33 PPCPs detected in surface waters of China that exceeded PNEC. Colors refer to the chemical groups.

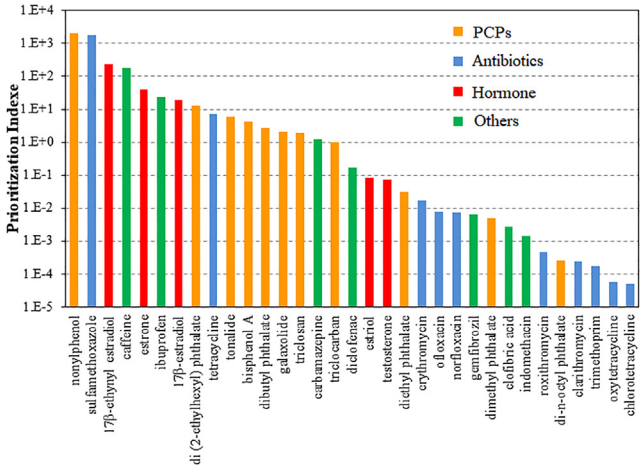

Fig. 5. 33 Prioritized PPCPs according to prioritization indexes in descending order. Colors refer to the chemical groups.

they were not selected in any of the exposure-based exercises, indicating that the perceived risks of these chemicals are more likely a result of toxicity than high exposure. This is expected because they are potent to some species.

3.3.3. *Optimization of screening-level risk assessment for 33 PPCPs.*

Fig. 5 shows 33 prioritized PPCPs according to prioritization indexes in descending order. Prioritization indexes ranged from 2046 for nonylphenol to 4.9×10^{-5} for chlorotetracycline. Compared to the RQ value, prioritization indexes showed a greater difference in the potential environmental risks of the compounds that presented a lower frequency of concentrations exceeding PNECs. For the 15 PPCPs those posed high or moderate risk with the RQ method were still identified as risk due to their great frequency of exceedance (≥59%). For the 3 PPCPs (estriol, testosterone, dimethyl phthalate), however, class of risk were downgraded from a low risk with RQ method to an insignificant risk with prioritization indexes, because they presented a lower frequency of exceedance. Thus, by considering the variability of concentrations above PNECs, the optimized risk assessment method is more convenient to select contaminants that should be prioritized in a large-scale water resources management.

Among these 15 compounds with high or moderate environmental risks, five of them (nonylphenol, caffeine, carbamazepine, ibuprofen, and triclosan) were included in the priority list of the European Demonstration Program (EDP) on the basis of their frequency and extent of exceedance of PNECs (Tousova et al., 2017). Similarly, six compounds, i.e. 17β-ethynyl estradiol, ibuprofen, carbamazepine, caffeine, 17β-estradiol, and triclosan were identified as high or moderate risk in the priority list of pharmaceuticals in European surface waters (Zhou et al., 2019). Galaxolide and nonylphenol was identified as very important and important contaminants in Sava River, Croatia (Smital et al., 2013). Nonylphenol was also found among the ten most important contaminants within a prioritization exercise from Spain carried out by Kuzmanović et al. (2015).

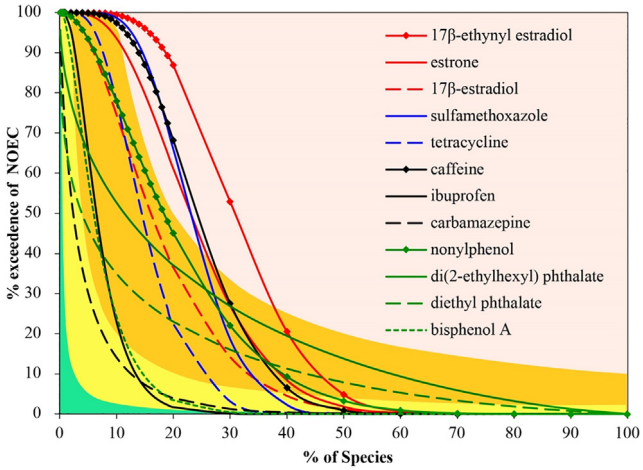

Fig. 6. Joint probability curves for estimated measured environment concentrations (MECs) of 12 PPCPs in surface waters and species sensitivity distributions. The color of risk curves for hormones, antibiotics, other pharmaceuticals, PCPs are shown as red, blue, black, green, respectively. The font color indicates the categorization of risk that identified these compounds: green: *de minimis* risk, yellow: low risk, orange: intermediate risk, pink: high risk.

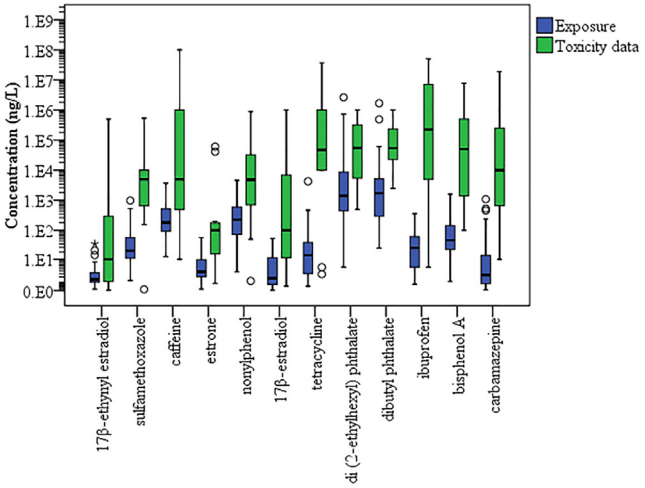

Fig. 7. Comparisons among point-estimates of exposure and effects for 12 PPCPs. The horizontal lines represent 10th and 90th percentiles, and the boxes represent 25th and 75th percentiles. Median concentrations are shown as solid lines. Outliers (< 3 times higher of boxes) and extreme (> 3 times higher of boxes) are shown as "○" and "*", respectively.

3.3.4. Refined risk assessment for twelve PPCPs.

For the 15 PPCPs that posed ecological risks identified by the prioritization indexes, a refined probability risk assessment based on variability in exposure and ecotoxicity data was required. Joint probability curves for each compound, excluding tonalide, galaxolide and triclosan for which less exposure data were available, were derived by integrating the distribution for surface water concentrations with chronic toxicity effects on varies species to indicate the probability of exceeding effects of differing magnitudes (Fig. 6). In the case of JPCs, the measured environment concentrations and toxicity data used are reported in the Supporting Information (Table S1 and S2). Data sets for each chemical were tested for normality by use of the Shapiro-Wilk test ($p < 0.05$) prior to application of parametric statistics (Table S3).

It is not surprising that JPCs of the three hormones were parallel due to their similar modes of action on aquatic species, with a relative rank of risks was as follows: 17β-ethynyl estradiol > estrone > 17β-estradiol. For the same reason, the two antibiotics and the two phthalates are also parallel to each other, with an order of risk at the national scale of: sulfamethoxazole > tetracycline, di (2-ethylhexyl) phthalate > dibutyl phthalate. Based on these results, the twelve PPCPs posed low to high risks to aquatic organisms at the national scale. Chronic risk for 17β-ethynyl estradiol, caffeine, sulfamethoxazole and estrone were categorized as high, with maximum risk product of 17.38%, 13.77%, 13.76%, and 12.39%, respectively. For carbamazepine, the results indicate a low risk of chronic effects in all surface waters of China (maximum risk product of 1.54%). Intermediate risk of chronic effects on aquatic organisms was identified for the other seven PPCPs, with maximum risk products ranged from 3% to 9.21%.

Results from the estimated risk curves can also be used to describe the probability of exceeding percentages of taxa that would be affected. The probability of exceeding 5% adverse effect depended on the most sensitive species, while the shape of the risk curve was related to the ranges and variability of datasets (Fig. 7) that could be described by coefficients of variation (CV). For example, JPCs for ibuprofen and bisphenol A were classified as intermediate risk to 5–10% species, and a low risk to 15–20% species. This is because both chemicals were predicted to exhibit toxicity to a small subgroup, with a large CV for effect data and a small value of exposures (Table S3). Alternatively, the JPCs for di (2-ethylhexyl) phthalate and dibutyl phthalate decreased more slowly, and represented an intermediate risk to a wider range of species (from 5% to > 70%). That was because the CVs for estimates of exposure were much larger than those for relative potencies among species and the maximum exposure data were larger than those for toxic potencies. Because their exposure data were mainly distributed in lower concentrations that were slightly higher than the most sensitive species, with a low CV of exposure and a higher CV of effect, 17β-ethynyl estradiol, sulfamethoxazole, caffeine, and estrone presented high risks to some species, but insignificant risks to 60% of species at the national scale.

3.3.5. Comparing results of risk assessment produced by the four methods

Comparing the results of the risk assessment of the four methods (Table 3), it appears that there is an advantage for the implementation of the multiple-level system. The RQ can be useful in answering whether the relative risks are higher or lower, but a disadvantage of this method is that outliers for estimates of exposure or relative potencies occur. The semi-probabilistic approach provided the possibility of chemicals that posed an ecological risk to aquatic organisms at the national scale. And in the optimized risk assessment, both concentration and frequency were considered, what could make for the utility of the results. For example, the RQ of di-n-octyl phthalate (1 9 0) was similar to that of 17β-estradiol (1 6 3), while the frequency of PNEC exceedance of di-n-octyl phthalate was much lower (10%) than that of 17β-estradiol (81%), so that the results obtained with the optimized method were more reasonable. The risk of trimethoprim was identified as insignificant risk using the RQ method (RQ = 0.07) and the optimized method (PI = 0.001), but it should not be neglected completely because of the 2% frequency of PNEC exceedance in surface waters of China, especially in the water where trimethoprim posed a potential risk to aquatic organisms.

The main disadvantage of the optimized method was that the PNECs were derived from the most sensitive endpoints, which did not take into account the range of species present in the environment. In relative terms, the JPCs method incorporated variability in estimates of both exposure and effects, and then given out a refined result. Take carbamazepine for instance, the frequency of PNEC exceedance was 67% and the prioritization indexes was 43 that presented high risk, but the probability of concentrations causing adverse effects in 5% of species was only 30%, which means it posed a low risk for waters when considering all the aquatic species. While the use of the JPC provides more information, it also requires more information to provide complete results and can thus be severely limited by a lack of information. In addition, due to the log transformation performed, this approach also

Table 3
Information obtained for each level of risk assessment.

Relative ranking	Risk quotient	Frequency of PNEC exceedance (%)	Prioritization index	Maximum risk product (%)
1	sulfamethoxazole (5964)	nonylphenol (1 0 0)	sulfamethoxazole (5666)	17β-ethynyl estradiol (17.38)
2	nonylphenol (4650)	caffeine (1 0 0)	nonylphenol (4651)	caffeine (13.77)
3	17β-ethynyl estradiol (9 8 0)	estrone (95)	di (2-ethylhexyl) phthalate (7 6 2)	sulfamethoxazole (13.76)
4	di (2-ethylhexyl) phthalate (8 1 7)	sulfamethoxazole (94)	17β-ethynyl estradiol (6 8 6)	estrone (12.39)
5	caffeine (6 1 6)	di (2-ethylhexyl) phthalate (93)	caffeine (6 1 6)	nonylphenol (9.21)
6	tetracycline (3 3 6)	bisphenol A (93)	tetracycline (2 2 4)	17β-estradiol (8.12)
7	dibutyl phthalate (2 0 3)	ibuprofen (89)	17β-estradiol (1 3 2)	di (2-ethylhexyl) phthalate (8.06)
8	di-n-octyl phthalate(1 9 0)	tetracycline (70)	estrone (1 2 3)	tetracycline (7.91)
9	17β-estradiol (1 6 3)	17β-estradiol (69)	dibutyl phthalate (1 1 9)	dibutyl phthalate (5)
10	estrone (1 2 7)	17β-ethynyl estradiol (68)	ibuprofen (84)	ibuprofen (3.29)
11	ibuprofen (94)	carbamazepine (67)	carbamazepine (43)	bisphenol A (3)
12	carbamazepine (65)	dibutyl phthalate (59)	di-n-octyl phthalate (19)	carbamazepine (1.54)
13	bisphenol A (15)	di-n-octyl phthalate (10)	bisphenol A (14)	di-n-octyl phthalate (− − −)

had the disadvantage that "0" values are not allowed, which might limit the utility of the method. For example, 17β-ethynyl estradiol presented the greatest risk according to JPCs, but was less detected (68%) than estrone (96%), 17β-estradiol (81%), and caffeine (100%) in surface waters, so it may not be appropriate for identifying 17β-ethynyl estradiol as the first priority chemical.

4. Limitations

Rankings of chemicals carried out in this study were limited by quantities and quality of available data on exposure and effects. There are many examples of measurements of hormones like 17β-ethynyl estradiol, which are problematic due to their low concentrations in aquatic environments (Hannah et al., 2009). Data used to estimate the exposures of chemicals such as musks and iopromide were limited to only 4 samples, and some chemicals were reported mostly for drinking waters, while existing exposure information on heavily polluted surface waters is sparse and limited. In similar cases, toxic potency data for sensitive species are also limited for some chemicals, especially for antibiotics, and potential drug resistance to multiple generations of organisms have been ignored. There were also limitations imposed by chiral chemicals that might have significant differences in biodegradation and toxic potency among enantiomers (Wong, 2006). For example, chronic responses of the fathead minnow (*Pimephales promelas*) to enantiomers of propranolol followed the hypothesis that (S)-propranolol is more toxic than (R)-propranolol (Stanley et al., 2006). The enantioselective biodegradation and ecotoxicity of chiral PPCPs tend to complicate their potential risk (Yin et al., 2016). Therefore, the risks of such chemicals might have been underestimated or overestimated, and this is likely to change drastically as new information becomes available.

Furthermore, the toxicity arising from complex mixtures of PPCPs at low concentrations could lead to additive or synergistic interactions, as demonstrated for similar acting compounds such as antibiotics or estrogens (Ferrari et al., 2004). This means that even though individual PPCPs are present in low concentrations that do not elicit significant toxic effects, PPCP mixtures can still exert considerable ecotoxicity. PPCPs found in the aquatic environment usually occur as mixtures, further research on the toxicity of the target compounds should include not only the individual PPCPs but also mixtures of these compounds (Altenburger et al., 2019; Brack et al., 2019).

In addition, this study was based solely on the measured concentrations and adverse effects, but did not take into account the environmental behavior and bioaccumulation. According to Palma et al. (2014), compounds with logKow higher than 3.0 show hydrophobic behavior and have a high potential for bioaccumulation. For example, the bioconcentration factors measured for ibuprofen and naproxen in rainbow trout (*Oncorhynchus mykiss*) bile were 14,000–49,000 (Brozinski et al., 2013) and 500–2300 (Brozinski et al., 2011) respectively, also Coogan et al. (2007) revealed the accumulation of triclosan and triclocarban in filamentous algae species with the bioaccumulation factor ranged from 900–2100 and 1600–2700 respectively, suggesting a high bioconcentration in aquatic organisms (EU, 2007). In this study, around 46% (23 out of 50) of PPCPs have high potentials for bioaccumulation (Table 1) and should be considered as priority at the same risk level. A more thorough re-analysis of their position following careful bioaccumulation considerations is necessary. Conclusions

The 50 selected PPCPs were frequently detected in surface waters of China, with concentrations ranging from ng L^{-1} to the low-g L^{-1}, which were lower or comparable to those reported worldwide in most cases. The risk quotients of the 50 PPCPs based on median concentrations ranged from 2046 for nonylphenol to 0 for phantolide. When considering all the concentrations analyzed in environment, 33 PPCPs posed risks to the most sensitive aquatic organisms, among which 4 chemicals (caffeine, nonylphenol, tonalide, and galaxolide) posed an ecological risk to 100% surface waters, and 15 chemicals (nonylphenol, sulfamethoxazole, di (2-ethylhexyl) phthalate, 17β-ethynyl estradiol, caffeine, tetracycline, 17β-estradiol, estrone, dibutyl phthalate, ibuprofen, carbamazepine, tonalide, galaxolide, triclosan, and bisphenol A) were identified as high or moderate risk according to prioritization indexes. When considering all the aquatic ecosystems, 17β-ethynyl estradiol, caffeine, estrone, and sulfamethoxazole posed high risks to freshwater species.

The results of this study suggest that researchers should attempt to rank PPCPs using multiple approaches for regulatory goals. In this way, the RQ method may be more useful to prioritize substances at a specific region than on a large scale, while the semi-probabilistic risk approach can be used as initial identification for chemicals that posed an aquatic ecological risk at the national scale. The approach of prioritization indexes incorporated various elements that determine target organism exposure to a chemical would reduce uncertainty and could be considered by risk managers who need to make a decision requiring an incremental quantification of risks. The JPCs method that accounts for variability in exposure and toxicity profiles is appropriate to estimate environmental risk for the whole aquatic ecosystem posed by contaminants.

CRediT authorship contribution statement

Na Liu: Conceptualization, Investigation, Methodology, Software, Visualization, Writing - original draft. **Xiaowei Jin:** Conceptualization, Methodology, Supervision, Writing - review & editing. **Chenglian Feng:** Writing - review & editing. **Zijian Wang:** Methodology, Writing - review & editing. **Fengchang Wu:** Supervision, Writing - review & editing. **Andrew C. Johnson:** Methodology, Writing - review & editing. **Hongxia Xiao:** Writing - review & editing. **Henner Hollert:** Writing -

review & editing. **John P. Giesy:** Methodology, Software, 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.

Acknowledgments

This research was financially supported by the National Natural Science Foundation of China (41807400, 41977364, 41521003, 41630645), Beijing outstanding talent training program.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.105454.

References

Altenburger, R., Brack, W., Burgess, R.M., et al., 2019. Future water quality monitoring: improving the balance between exposure and toxicity assessments of real-world pollutant mixtures. Environ. Sci. Eur. 31, 12.
Aslund, M.W., Breton, R.L., Padilla, L., Reiss, R., Winchell, M., Wooding, K., Moore, D.R.J., 2016. Ecological risk assessment for Pacific salmon exposed to dimethoate in California. Environ Toxicol Chem. 36 (2), 532–543.
Balakrishna, K., Rath, A., Praveenkumarreddy, Y., Guruge, K.S., Subedi, B., 2017. A review of the occurrence of pharmaceuticals and personal care products in Indian water bodies. Ecotoxicol. Environ. Saf. 137, 113–120.
Barbara, K.H., Dinsdale, R.M., Guwy, A.J., 2008. The occurrence of pharmaceuticals, personal care products, endocrine disruptors and illicit drugs in surface water in South Wales. UK. Water Res. 42, 3498–3518.
Brack, W., Aissa, S.A., Backhaus, T., Dulio, V., et al., 2019. Effect-based methods are key. The European collaborative project solutions recommends integrating effect-based methods for diagnosis and monitoring of water quality. Environ. Sci. Eur. 31, 10–15.
Brozinski, J.M., Lahti, M., Oikari, A., Kronberg, L., 2011. Detection of naproxen and its metabolites in fish bile following intraperitoneal and aqueous exposure. Environ. Sci. Pollut. Res. Int. 18, 811–818.
Brozinski, J.M., Lahti, M., Oikari, A., Kronberg, L., 2013. Identification and dose dependency of ibuprofen biliary metabolites in rainbow trout. Chemosphere 93, 1789–1795.
Bu, Q., Wang, B., Huang, J., Deng, S., Yu, G., 2013. Pharmaceuticals and personal care products in the aquatic environment in China: a review. J. Hazard. Mater. 262, 189–211.
Burns, E.E., Carter, L.J., Snape, J., et al., 2018. Application of prioritization approaches to optimize environmental monitoring and testing of pharmaceuticals. J. Toxicol. Environ. Health Part B 21 (3), 115–141.
Carlsson, C., Johansson, A.K., Alvan, G., Bergman, K., Kühler, T., 2006. Are pharmaceuticals potent environmental pollutants? Part I: environmental risk assessments of selected active pharmaceutical ingredients. Sci. Total Environ. 364, 67–87.
Carmona, E., Andreu, V., Picó, Y., 2014. Occurrence of acidic pharmaceuticals and personal care products in Turia River Basin: from waste to drinking water. Sci. Total Environ. 484, 53–63.
Chen, J.Q., Guo, R.X., 2012. Access the toxic effect of the antibiotic cefradine and its UV light degradation products on two freshwater algae. J. Hazard. Mater. 209–210, 520–523.
China Industry Research Net (CIRN), 2012. Personal care product market development analysis. 23-24 (in Chinese).
Clemow, Y.H., Manning, G.E., Breton, R.L., Winchell, M.F., Padilla, L., Rodney, S.I., 2018. A refined ecological risk assessment for california red-legged frog, Delta Smelt, and California tiger salamander exposed to Malathion. Integr. Environ. Assess. Manage. 14, 224–239.
Coogan, M.A., Edziyie, R.E., La Point, T.W., Venables, B.J., 2007. Algal bioaccumulation of triclocarban, triclosan, and methyl-triclosan in a North Texas wastewater treatment plant receiving stream. Chemosphere 67, 1911–1918.
Desbiolles, F., Malleret, L., Tiliacos, C., et al., 2018. Occurrence and ecotoxicological assessment of pharmaceuticals: Is there a risk for the Mediterranean aquatic environment? Sci. Total Environ. 639, 1334–1348.
Donnachie, R.L., Johnson, A.C., Sumpter, J.P., 2016. A rational approach to selecting and ranking some pharmaceuticals of concern for the aquatic environment and their relative importance compared with other chemicals. Environ. Toxicol. Chem. 35, 1021–1027.
Durda, J.L., Preziosi, D.V., 2000. Data quality evaluation of toxicological studies used to derive ecotoxicological benchmarks. Hum. Ecol. Risk Assess. 6 (5), 747–765.
Ebele, A.J., Abdallah, A.E.M., Harrad, S., 2017. Pharmaceuticals and personal care products (ppcps) in the freshwater aquatic environment. Emerging Contaminants. 3, 1–16.
European Commission (EC), 2003. Technical guidance document on risk assessment, Joint Research Centre, Institute for Health and Comsumer Protection, European Chemicals Bureau, Ispra, Italy.
European Union (EU), 2007. Registration, evaluation, authorization and restriction of chemicals. European Parliament and Council, Brussels, Belgium.
Commission, European, 2015. Decision 495/2015/EU of 20 March 2015 establishing a watch list of substances for union-wide monitoring in the field of water policy pursuant to Directive C2008/105/EC of the European Parliament and of the Council. Off. J. Eur. Union. 78, 40–42.
Fang, W.D., Peng, Y., Muir, D., Lin, J., Zhang, X.W., 2019. A critical review of synthetic chemicals in surface waters of the US, the EU and China. Environ. Int. 131, 1–11.
Ferrari, B., Mons, R., Vollat, B., Nicklas, P., Giudice, R.L., Pollio, A., Garric, J., 2004. Environmental risk assessment of six human pharmaceuticals: Are the current environmental risk assessment procedures sufficient for the protection of the aquatic environment? Environ. Toxicol. Chem. 23 (5), 1344–1354.
Godoy, A.A., Kummrow, F., Pamplin, P.A.Z., 2015. Occurrence, ecotoxicological effects and risk assessment of antihypertensive pharmaceutical residues in the aquatic environment - A review. Chemosphere 138, 281–291.
Hannah, R., D'Aco, V.J., Anderson, P.D., Buzby, M.E., Caldwell, D.J., Cunningham, V.L., 2009. Exposure assessment of 17 alpha-ethinylestradiol in surface waters of the United States and Europe. Environ. Toxicol. Chem. 28, 2725–2732.
Hobbs, D.A., Warne, M.S.J., Markich, S.J., 2005. Evaluation of criteria used to assess the quality of aquatic toxicity data. Integr. Environ. Assess. Manage. 1 (3), 174–180.
Jin, X.W., Wang, Y.Y., Jin, W., Rao, K.F., Giesy, J.P., Hollert, H., 2014. Ecological risk of nonylphenol in China surface waters based on reproductive fitness. Environ. Sci. Technol. 48, 1256–1262.
Johnson, A.C., Jürgens, M.D., Su, C., Zhang, M., Zhang, Y., Shi, Y., 2018. Which commonly monitored high risk chemical in the Bohai Region, Yangtze and Pearl Rivers of China poses the greatest threat to aquatic wildlife? Environ. Toxicol. Chem. 37 (4), 1115–1121.
Klimisch, H.J., Tillmann, U., 1997. A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Regulatory Toxicol. Pharmacol. Rtp. 25, 1–5.
Kumar, A., Xagoraraki, I., 2010. Human health risk assessment of pharmaceuticals in water: an uncertainty analysis for meprobamate, carbamazepine, and phenytoin. Regul. Toxicol. Pharm. 57 (2–3), 146–156.
Kuzmanović, M., Ginebreda, A., Petrovič, M., Barceló, D., 2015. Risk assessment based prioritization of 200 organic micropollutants in 4 Iberian rivers. Sci. Total Environ. 503–504, 289–299.
Kolpin, D.W., Furlong, E.T., Meyer, M.T., Thurman, E.M., Zaugg, S.D., Barber, L.B., 2002. Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, 1999–2000: A national reconnaissance. Environ. Sci. Technol. 36, 1202–1211.
Larsson, D.G.J., Pedro, C.D., Paxeus, N., 2007. Effluent from drug manufactures contains extremely high levels of pharmaceuticals. J. Hazard. Mater. 148, 751–755.
Liu, J.L., Wong, M.H., 2013. Pharmaceuticals and personal care products (PPCPs): A review on environmental contamination in China. Environ. Int. 59 (3), 208–224.
Liu, N., 2016. Study for reproductive toxicity effect and ecological risk assessment of typical PPCPs. China University of Geosciences (Beijing), Beijing, China (in Chinese).
Liu, N., Wang, Y.Y., Yang, Q., Lv, Y.B., Jin, X.W., Giesy, J.P., Johnson, A.J., 2016a. a. Probabilistic assessment of risks of diethylhexyl phthalate (DEHP) in surface waters of China on reproduction of fish. Environ. Pollut. 213, 482–488.
Liu, N., Jin, X.W., Wang, Y.Y., Wang, Z.J., 2016b. b. Review of criteria for screening and evaluating ecotoxicity data. Asian J. Ecotoxicol. 11, 1–10 (in Chinese).
Loos, R., Gawlik, B.M., Locoro, G., Rimaviciute, E., Contini, S., Bidoglio, G., 2009. EU-wide survey of polar organic persistent pollutants in European river waters. Environ. Pollut. 157 (2), 561–568.
Ågerstrand, M., Rudén, C., 2010. Evaluation of the accuracy and consistency of the Swedish environmental classification and information system for pharmaceuticals. Sci. Total Environ. 408, 2327–2339.
Mebane, C.A., 2010. Relevance of risk predictions derived from a chronic species sensitivity distribution with cadmium to aquatic populations and ecosystems. Risk Anal. 30 (2), 203–223.
Meng, L., Yang, B., Xue, N.D., Zhang, S.L., Li, F.S., Liu, H.B., 2015. A review on environmental behaviors and ecotoxicology of fluoroquinolone antibiotics. Asian J. Ecotoxicol. 10, 76–88 (in Chinese).
Moermond, C.T.A., Kase, Y.R., Korkaric, Z.M., Muris, Å., 2016. CRED: criteria for reporting and evaluating ecotoxicity data. Environ. Toxicol. Chem. 35 (5), 1297–1309.
Moore, D.R.J., Teed, R.S., Rodney, S.I., Thompson, R.P., Fischer, D.L., 2010. Refined aquatic risk assessment for aldicarb in the United States. Integr Environ Assess Manag. 6 (1), 102–118.
Moore, D.R.J., Teed, R.S., Greer, C.D., Solomon, K.R., Giesy, J.P., 2014. Refined avian risk assessment for chlorpyrifos in the United States. Rev Environ Contam Toxicol. 231, 163–217.
Nakada, N., Komori, K., Suzuki, Y., Konishi, C., Houwa, I., Tanaka, H., 2007. Occurrence of 70 pharmaceutical and personal care products in tone river basin in Japan. Water Sci. Technol. 56 (12), 133–140.
NORMAN Association, 2013. NORMAN Prioritisation framework for emerging substances. ISBN : 978-2-9545254-0-2.
Ohe, P.C.V.D., Dulio, V., Slobodnik, J., Deckere, E.D., Kühne, R., Ebert, R.U., Ginebreda, A., Cooman, W.D., Schüürmann, G., Brack, W., 2011. A new risk assessment approach for the prioritization of 500 classical and emerging organic microcontaminants as potential river basin specific pollutants under the European Water Framework Directive. Sci. Total Environ. 409 (11), 2064–2077.
Palma, P., Köck-Schulmeyer, M., Alvarenga, P., Ledo, L., Barbosa, I.R., López de Alda, M., Barceló, D., 2014. Risk assessment of pesticides detected in surface water of the

Alqueva reservoir (Guadiana basin, southern of Portugal). Sci. Total Environ. 488, 208–219.
Rehman, M.S., Rashid, N., Ashfaq, M., Saif, A., Ahmad, N., Han, J.I., 2015. Global risk of pharmaceutical contamination from highly populated developing countries. Chemosphere 138, 1045–1055.
Santos, L.H., Araújo, A.N., Fachini, A., Pena, A., Deleruematos, C., Montenegro, M.C., 2010. Ecotoxicological aspects related to the presence of pharmaceuticals in the aquatic environment. J. Hazard. Mater. 175 (1), 45–95.
Scheurer, M., Sacher, F., Brauch, H.J., 2009. Occurrence of the antidiabetic drug metformin in sewage and surface waters in Germany. J. Environ. Monit. 11, 1608–1613.
Sharma, B.M., Bečanová, J., Scheringer, M., Sharma, A., Bharat, G.K., Whitehead, P.G., Klánová, J., Nizzetto, L., 2019. Health and ecological risk assessment of emerging contaminants (pharmaceuticals, personal care products, and artificial sweeteners) in surface and groundwater (drinking water) in the Ganges River Basin. India. Sci. Total Environ. 646, 1459–1467.
Sim, W.J., Lee, J.W., Lee, E.S., Shin, S.K., Hwang, S.R., Oh, J.E., 2011. Occurrence and distribution of pharmaceuticals in wastewater from households, livestock farms, hospitals and pharmaceutical manufactures. Chemosphere 82, 179–186.
Smital, T., Terzić, S., Lončar, J., Senta, I., Žaja, R., Popović, M., Mikac, I., Tollefsen, K.-E., Thomas, K.V., Ahel, M., 2013. Prioritisation of organic contaminants in a river basin using chemical analyses and bioassays. Environ. Sci. Pollut. Res. 20, 1384–1395.
Solomon, K., Giesy, J.P., 2000. Probabilistic risk assessment of agrochemicals in the environment. Crop Prot. 19, 649–655.
Stanley, J.K., Ramirez, A.J., Mottaleb, M., Chambliss, C.K., Brooks, B.W., 2006. Enantiospecific toxicity of the beta-blocker propranolol to *Daphnia magna* and *Pimephales promelas*. Environ. Toxicol. Chem. 25, 1780–1786.
Sui, Q., Wang, B., Zhao, W.T., Huang, J., Yu, G., Deng, S.B., Qiu, Z.F., Lu, S.G., 2012. Identification of priority pharmaceuticals in the water environment of China. Chemosphere 89 (3), 280–286.
Sun, J., Luo, Q., Wang, D., Wang, Z., 2015. Occurrences of pharmaceuticals in drinking water sources of major river watersheds. China. Ecotoxicol. Environ. Safety 117, 132–140.
Tarazona, J.V., Escher, B.I., Giltrow, E., Sumpter, J., Knacker, T., 2010. Targeting the environmental risk assessment of pharmaceuticals: facts and fantasies. Integr. Environ. Assess. Manage. 6, 603–613.
Tewari, S., Jindal, R., Kho, Y.L., Eo, S., Choi, K., 2013. Major pharmaceutical residues in wastewater treatment plants and receiving waters in Bangkok, Thailand, and associated ecological risks. Chemosphere 91 (5), 697–704.
Thomaidi, V.S., Stasinakis, A.S., Borova, V.L., Thomaidis, N.S., 2015. Is there a risk for the aquatic environment due to the existence of emerging organic contaminants in treated domestic wastewater? Greece as a case-study. J. Hazard. Mater. 283, 740–747.
Tousova, Z., Oswald, P., Slobodnik, J., Blaha, L., Muz, Me, Hu, M., 2017. European demonstration program on the effect-based and chemical identification and monitoring of organic pollutants in European surface waters. Sci. Total Environ. 601–602, 1849–1868.
US EPA, 1992. Framework for ecotoxicological risk assessment, United States Environmental Protection Agency, Washington, DC.
US EPA, 1996. Guidelines for reproductive toxicity risk assessment, United States Environmental Protection Agency, Washington, DC.
US EPA, 1998. Guidelines for ecological risk assessment., United States Environmental Protection Agency, Washington, DC.
US EPA, 2011. Evaluation guidelines for ecological toxicity data in the open literature. Washington, DC: US EPA.
Vazquez-Roig, P., Andreu, V., Blasco, C., Picó, Y., 2012. Risk assessment on the presence of pharmaceuticals in sediments, soils and waters of the Pego-Oliva Marshlands (Valencia, eastern Spain). Sci. Total Environ. 440 (3), 24–32.
Vieno, N., Tuhkanen, T., Kronberg, L., 2007. Elimination of pharmaceuticals in sewage treatment plants in Finland. Water Res. 41 (5), 1001–1012.
Wang, Z., Du, Y., Yang, C., Liu, X., Zhang, J., Li, E., 2017. Occurrence and ecological hazard assessment of selected antibiotics in the surface waters in and around Lake Honghu. China. Sci. Total Environ. 609, 1423–1432.
Watkinson, A.J., Murby, E.J., Kolpin, D.W., Costanzo, S.D., 2009. The occurrence of antibiotics in an urban watershed: from wastewater to drinking water. Sci. Total Environ. 407, 2711–2723.
Wong, C.S., 2006. Environmental fate processes and biochemical transformations of chiral emerging organic pollutants. Anal. Bioanal. Chem. 386, 544–558.
Yao, H., Li, Q., Zheng, H., Wu, Y., Zhang, W., 2011. Determination and analysis of the five phthalates in environmental water samples in Anshan city. Sciencepaper Online. 6, 692–695.
Yao, L.L., Wang, Y.X., Tong, L., Deng, Y.M., Li, Y.G., Gan, Y.Q., Guo, W., Dong, C.G., Duan, Y.H., Zhao, K., 2017. Occurrence and risk assessment of antibiotics in surface water and groundwater from different depths of aquifers: A case study at Jianghan Plain, central China. Ecotoxicol. Environ. Saf. 135, 236–242.
Yin, L., Wang, B., Ma, R., Yuan, H., Yu, G., 2016. Enantioselective environmental behavior and effect of chiral PPCPs. Prog. Chem. 28 (5), 744–753 (in Chinese).
Yu, Z.Y., Jiang, L., Yin, D.Q., 2011. Behavior toxicity to *Caenorhabditis elegans* transferred to the progeny after exposure to sulfamethoxazole at environmentally relevant concentrations. J. Environ. Sci. 23 (2), 294–300.
Yu, Z.R., 2011. Distribution and purification of pharmaceutical and personal care products (PPCPs) in drinking water. Tsinghua University, Beijing, China (in Chinese).
Zhang, A., Li, Y., Chen, L., 2014. Distribution and seasonal variation of estrogenic endocrine disrupting compounds, N-nitrosodimethylamine, and N- nitrosodimethylamine formation potential in the Huangpu River. China. J. Environ. Sci. 26 (5), 1023–1033.
Zhang, M., Shi, Y., Lu, Y., Johnson, A.C., Sarvajayakesavalu, S., Liu, Z., Su, C., Zhang, Y., Jurgens, M.D., 2017a. a. The relative risk and its distribution of endocrine disrupting chemicals pharmaceuticals and personal care products risk to freshwater organisms in Bohai Rim. China. Sci. Total Environ. 590, 633–642.
Zhang, L., Wei, C., Zhang, H., Song, M., 2017b. b. Criteria for assessing the ecological risk of nonylphenol for aquatic life in Chinese surface fresh water. Chemosphere 184, 569–574.
Zhang, Q.Q., Ying, G.G., Pan, C.G., Liu, Y.S., Zhao, J.L., 2015. A comprehensive evaluation of antibiotics emission and fate in the river basins of China: source analysis, multimedia modeling, and linkage to bacterial resistance. Environ. Sci. Technol. 49, 6772–6782.
Zhao, J., Liu, Y., Mei, S., Tian, X., 2012. Determination of iopromide in water environment by SPE-HPLC. Environ. Sci. Manage. 37 (1), 133–136 (in Chinese).
Zhou, H., Wu, C., Huang, X., Gao, M., Wen, X., Tsuno, H., Tanaka, H., 2010. Occurrence of selected pharmaceuticals and caffeine in sewage treatment plants and receiving rivers in Beijing. China. Water Environ. Res. 82 (11), 2239–2248.
Zhou, X.F., Dai, C.M., Zhang, Y.L., Surampalli, R.Y., Zhang, T.C., 2011. A preliminary study on the occurrence and behavior of carbamazepine (CBZ) in aquatic environment of yangtze river delta. China. Environ. Monitor. Assess. 173, 45–53.
Zhou, S.B., Paolo, C.D., Wu, X.D., Shao, Y., Seiler, T.B., Hollert, H., 2019. Optimization of screening-level risk assessment and priority selection of emerging pollutants - The case of pharmaceuticals in European surface waters. Environ. Int. 128, 1–10.