Environmental Sciences Europe

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Occurrence and multiple-level ecological risk assessment of pharmaceuticals and personal care products (PPCPs) in two shallow lakes of China

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Abstract

Background: Management of pharmaceuticals and personal care products (PPCPs) in the environment has become a social issue. In the present study, concentrations of 140 PPCPs at 20 sites in Baiyangdian Lake and Tai Lake from 2016 to 2017 were analyzed by ultra performance liquid chromatography mass spectrometer (UPLC–MS). Risk quotients (RQ) were calculated for each detected chemical at all sites and prioritization indices (PI), based on maximum RQ, were calculated. To assess the risk of chemicals that identified high priority (PI > 1), a more accurate method of joint probability curves (JPCs) was applied.

Results: A total of 42 PPCPs were identified and quantified detected in the two lakes, with maximum concentrations ranging from 0.04 to 889 ng/L. Among these, seven PPCPs were identified as high or moderate-risk pollutants for at least one site, 3 in Tai Lake and 5 in Baiyangdian Lake. Carbamazepine posed significant ecological risk at all 20 sites, such that more attention should be paid to that drug. Based on results of the JPCs, sulfamethoxazole, caffeine, diethyltoluamide, and carbamazepine were categorized as high or intermediate risks.

Conclusion: Occurrences and distributions of PPCPs were different in the two lakes. Multiple-level risk assessment from simple to more complex was appropriate in chemical risk management.

Keywords: PPCPs, Concentration, Multiple-level, Risk assessment, China, Tai Lake, Baiyangdian Lake, Probabilistic, Asia

Background

Pharmaceuticals are defined as prescription, over the counter and veterinary therapeutic drugs that are used to prevent or treat diseases in humans and animals, while personal care products (PCPs) are used mainly to improve grooming during daily life [1]. Total usage of antibiotics in China for 2013 was estimated to be approximately 162,000 tons, which means that China consumed 9 times more antibiotics than the USA (17,900 tons) and 150 times more than the UK (1060 tons) [2]. The proportion of the global total of PCPs consumed in China is approximately 6.5%, which is exceeded only by the United States of America (19.1%) and Japan (9.4%) [3]. A growing body of literature demonstrates that pharmaceuticals and personal care products (PPCPs) are present in surface waters of China, particularly in those receiving effluents from wastewater treatment plants (WWTPs). Although PPCPs are detected in surface waters at relatively small concentrations, they and their metabolites are biologically active and can, during long-term exposure, affect non-target aquatic organisms including endocrine disruption, genotoxicity, carcinogenicity, fetal development [4, 5]. Data on occurrences of PPCPs in aquatic environments

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in China revealed that concentration of these PPCPs in waters occurred at concentrations of μg/L-ng/L [6, 7]. Diclofenac and ibuprofen were identified as priority PPCPs based on previous screening-level risk assessments. Presence and concentrations of pharmaceuticals in European surface waters were surveyed [8] and based on the results of an optimization of screening-level risk assessment, 29 compounds were indicated to present significant risks to aquatic environments.

Based on the region and scale of assessment, due to differences in density of human population, development level of the regional economy, and hydrology in different environmental compartments, several sets of priority compounds were expected. In most cases, hot spots for pollution by PPCPs were waters affected by megacities with greater densities of population [6]. For example, East China consumed 38,800 tons of antibiotics in 2013, while Northwest China consumed only 2360 tons [2]. Relationships between catchment-specific sociodemographic parameters and biomarkers in wastewater generated for respective catchments were explored [9]. Results showed that biomarkers of caffeine had positive correlations with indices of relative socioeconomic advantage and disadvantage (IRSAD), concentrations of pregabalin were negatively correlated with IRSAD, while concentrations of carbamazepine, cotinine, ibuprofen, and sulfamethoxazole exhibited insignificant correlations with IRSAD. Therefore, so that effective management measures could be implemented, it was deemed necessary to identify PPCPs most likely to pose risks in various regions.

Lake Tai (Ch: *Taihu*) is the largest shallow freshwater lake in China [10], with mean depth of 1.94 m, surface area of 2338 km^2 and volume of 4.4 billion m^3 [11], is located in the Yangtze Delta in Eastern China, which is one of the most heavily urbanized and industrialized areas of China [12]. In addition to being a popular recreational and tourist attraction, it serves as an important source of water for drinking, irrigation of agriculture and use by industries [13]. Baiyangdian Lake is the largest lake and most hydrologically strategic freshwater lake on the North China Plain and is an important ecological function zone of the Xiong'an New Area [14]. Baiyangdian Lake is a nearly closed, inter-locking lake which collects rainwater, floodwater and runoff from over 20% of the plain [15, 16]. In addition to providing direct water supply for domestic, agricultural and industrial use, the lake is a source of livelihood, via fishing, tourism, transportation and reed/lotus farming, for more than 200,000 inhabitants around its shore [17, 18]. Because of the invaluable socio-ecological functions and services of the lake, it is vital to develop a sustainable management strategy to preserve its environment, ecology and hydrology.

In the last few years, risks posed by PPCPs to ecological parameters have been assessed in Lakes Tai [10, 12, 19, 20] and Baiyangdian [21, 22]. However, because assessments were based solely on screening-level risk quotients (RQ), occurrences and environmental risks of PPCPs in the two lakes were not well described and their sources were not understood, Thus, more detailed and accurate understandings of occurrences and risks posed by PPCPs in these two large lake systems were needed. The objectives of this study were to: 1. determine presence and concentrations of PPCPs in Tai and Baiyangdian Lakes, which represented lakes in two regions with different hydrology, climate conditions and social-economic structures; 2. ranking PPCPs that have potential risk for aquatic organisms; 3. conduct accurate ecological risk assessment based on multiple species for priority chemicals.

Materials and methods

Target chemicals and sample collection

Based on reported uses of PPCPs in livestock farms, WWTPs, and environment media in China, 140 frequently detected PPCPs (Additional file 1: Table S1) were selected as target chemicals. Two sampling campaigns were conducted in June 2016 for Tai Lake and June 2017 for Baiyangdian Lake. Ten water samples from 10 locations were collected from each study area (Fig. 1). Two liters of surface water were collected from each location into brown glass bottles that had been pre-cleaned with methanol and deionized water, then rinsed with water from the sampling site before collection. All samples were kept at 4 °C, and target PPCPs were extracted from water samples within 4 days of collection [22].

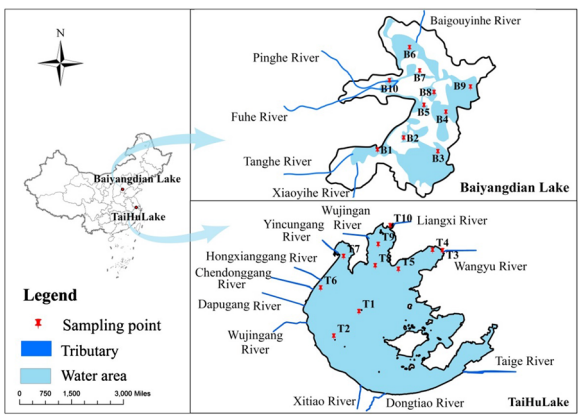

Fig. 1 Map of the sampling locations for surface water in Lakes Tai and Baiyangdian

Preparation and instrumental analysis

Before extraction, samples were filtered through 0.45 μm GHP membrane filters, to which 0.2 g Na_2EDTA was added, and spiked with 20 ng each of surrogate standards. Filtered water was extracted by solid-phase extraction (SPE) with tandem cartridges: Oasis WAX (150 mg; 6 mL) weak anion exchange mixed-mode cartridge coupled with Oasis HLB (500 mg; 6 mL) hydrophilic–lipophilic balance cartridges. Cartridges were activated and conditioned with 6 mL methanol and 6 mL ultrapure water. Samples of water were passed through the tandem cartridges at a flow rate of 1 mL/min. After extraction, the columns were separated, rinsed with 6 mL water, and dried for 30 min. Elution was performed sequentially by use of 6–8 mL 1% (v/v) ammonia in methanol (WAX cartridge) or 2% (v/v) formic acid in methanol (HLB cartridge), 6–8 mL methanol–MTBE (1/9, v/v) and 6-8 mL methanol–dichloromethane (2/8, v/v) for both WAX and HLB cartridges. Elution fractions from WAX and HLB cartridges were mixed and dried under a gentle nitrogen stream, then redissolved in 1 mL of ultrapure water [23–25].

Extracts were analyzed by UPLC–MS (LC-Agilent Technologies 1290 Infinity, MS-ABI Triple Quadrupole 6495; CA). Chromatographic separation of analytes was performed by use of an Agilent ZORBAX Eclipse Plus C18 (2.1 × 100 mm, 1.8 μm). For the positive electrospray ionization mode (ESI), the mobile phase A contained 0.02% acetic acid in water, while mobile phase B was acetonitrile. During negative ESI, the mobile phase A contained water, while mobile phase B was acetonitrile. A binary gradient with a flow rate of 0.3 mL/min was used. Injection volume was 10 μL. To avoid analytical interference and/or cross-contamination, equipment and containers were rinsed with methanol and water before use. Field blanks and procedural blanks were analyzed with extraction to control travel contamination and laboratory contamination [21]. Linearity of calibration curves was confirmed ($r^2 > 0.99$) with the concentration of standards ranged from 0.005 to 100 μg/L, and mean relative recoveries of three replicates spiked at 50 ng/L varied from 75.2 to 121.0%. Limit of detections (LOD) or limits of quantification (LOQ) were defined as the concentration at which the signal-to-noise ratios (S/N) were greater than 3 or 10, respectively.

Characterization of risks

Environmental toxicity information

Toxic potencies of PPCPs to non-target organisms were mainly obtained from the ECOTOX Knowledgebase (https://cfpub.epa.gov/ecotox/search.cfm) developed by the US EPA, following principles of accuracy, relevance and reliability [26–29]. Because the habitat and geographical distribution of species do not have a significant influence on the assessment of hazard [30, 31], data for non-native species were used in this study. In this study, data on toxic potencies were selected by use of hierarchical methods [32] and data on chronic toxic potencies expressed as no observed effect concentrations (NOECs) or 10% effect concentration (EC_{10}) for the most sensitive endpoints. If an NOEC or EC_{10} was not available, a lowest observed effect concentration (LOEC) or median effect concentration (EC_{50}) was used with assessment factors (AFs) of 2 or 10 [6, 32].

Assessment of risks

Ecological risks of PPCPs in surface waters were assessed by use of a methodology developed within the NORMAN Association [33] and previous studies [8, 33–36]. Chronic, sublethal, risk quotients (RQ) were calculated by dividing measured concentration of individual chemicals in waters by the predicted no effect concentration (PNEC; Eq. 1). Preliminary assessment ranks for risks posed by PPCPs was developed by classifying PPCPs posing di minimis ($RQ < 0.1$), lesser ($0.1 \leq RQ < 1$), moderate ($1 \leq RQ < 10$) and greater ($RQ \geq 10$) risks [6, 37]. Furthermore, to identify PPCPs of greatest concern in the two lakes a prioritization index (PI; Eq. 2) was calculated, as the result of RQ_{max}, calculated for the maximum concentration, multiplied by the frequency of PNEC exceedance (Eq. 3). This index allows to smooth out the impact of compounds with high RQ but rarely detected [34]:

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

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

$$PI = RQ_{max} \times F, \tag{3}$$

where C_m is the measured concentration for a single chemical measured at a sample; *PNEC* is the predicted no effect concentration derived from the most sensitive toxicity data with assessment factor of 10, 20, or 100 depending on test endpoints of NOEC or EC_{10}, LOEC, EC_{50} [6, 32]; 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; PI is prioritization index; RQ_{max} is risk quotient calculated based on maximum concentration.

PNECs introduce an element of subjectivity and are driven by a few reports of effects reported to occur at small concentrations, which might not be repeatable. Thus, it is desirable to corroborate risks predicted by use

of joint probability curves (JPCs). In this method, measured concentrations and chronic toxicity data on various species to PPCPs were compiled and transformed to *probits* by fitting appropriate distributions. Linear regression of the two data sets can then be used to calculate probabilities of concentrations causing adverse effects to a specified proportion (%) of species [38]. 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). JPCs were developed by use of the Probabilistic Risk Assessment Tool (PRAT) [39]. In this assessment, the area under the risk curve (AUC) was estimated for each combination of focal species and exposure scenario, and then used to categorize risks as either *de minimis*, lesser, intermediate or greater by risk products (Eq. 4) for 0.25%, 2%, and 10% [40]:

$$\text{Risk product} = \text{exceedance probability} \times \text{magnitude of effect.} \quad (4)$$

Statistical analysis

During the analysis, concentrations were set to 0 if less than LOD, and one half of the LOQ if less than LOQ. Frequency of detection and mean concentrations of PPCPs were calculated using Microsoft Excel 2010 (Microsoft China, Beijing). Figures for exposure distributions were developed by use of Origin Pro 9.1 (Northampton, MA, USA). Prior to correlation analyses, tests of normality were carried out by use of SPSS Statistics V20.0 (IBM, Armonk, NY, USA). Normality for each concentration was confirmed by use of the Shapiro–Wilk test and homogeneity of variance was confirmed by use of Levine's test.

Results and discussion

Occurrence and spatial variations

Of the 140 target PPCPs, 42 were detected in the two lakes at one or more sampling sites. Among these compounds, five PPCPs, carbamazepine, diethyltoluamide, lidocaine, cotinine, chlorpheniramine, and triadimefon were found in both lakes. Approximately 11.5% (16 out of 140) of the analyzed PPCPs in Tai Lake were detected at the concentrations above the limit of detection levels, and circa 22.3% (31 out of 140) in Baiyangdian Lake. Concentrations of PPCPs in surface waters from Tai and Baiyangdian Lakes are summarized in Fig. 2. There were differences in the number, types and concentrations of PPCPs detected in waters of the two lakes. This result might be caused by several factors, including differences

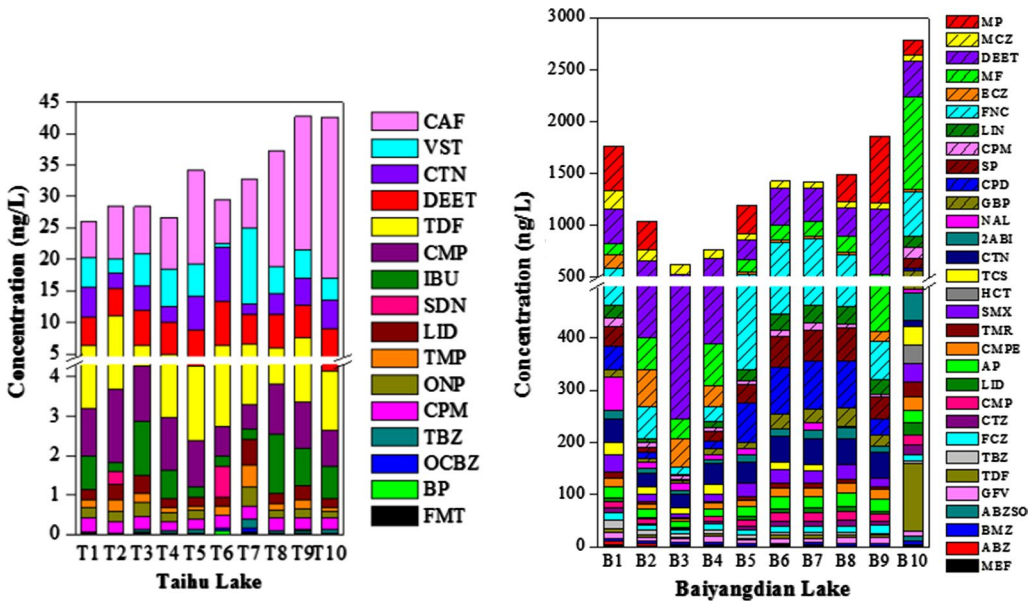

Fig. 2 Relative compositions of PPCPs in water of Tai and Baiyangdian Lakes. *CAF* caffeine, *VST* valsartan, *CTN* cotinine, *DEET* diethyltoluamide, *TDF* triadimefon, *CMP* carbamazepine, *IBU* Ibuprofen, *SDN* sildenafil, *LID* lidocaine, *TMP* trimethoprim, *ONP* oxidized nifedipine, *CPM* chlorpheniramine, *TBZ* thiabendazole, *OCBZ* oxcarbazepine, *BP* butylparaben, *FMT* famotidine, *MP* methylparaben, *MCZ* miconazole, *MF* metformin; *ECZ* econazole, *FNC* florfenicol, *LIN* lincomycin, *SP* sulpiride, *CPD* clopidol, GBP gabapentin, *NAL* nalidixic acid, *2ABI* 2-aminobenzimidazole, *TCS* triclosan, *HCT* hydrochlorothiazide, *SMX* sulfamethoxazole, *TMR* triamterene, *CMPE* carbamazepine epoxide, AP antipyrine, *CTZ* cetirizine, *FCZ* fluconazole *TBZ* triclabendazole, *GFV* griseofulvin, *ABZSO* albendazole–sulfoxide, *BMZ* benzimidazole, *ABZ* albendazole, *MEF* mefenamic acid

in use and release, removal efficiency of the WWTPs, degradation rate, temperature and dilution of receiving waters [8, 41]. Compared with Baiyangdian Lake, Tai Lake possesses richer water resources and higher temperature that could result in PPCPs being diluted and more quickly being degraded. Consumption of caffeine is associated with aspects of financial capability [9], so it was more frequently detected in Tai Lake, which located in the eastern developed area of China. The bactericide, triadimefon and insect repellent, diethyltoluamide were consumed more in agricultural regions, near Baiyangdian Lake. Maximum concentrations of antibiotics sulfamethoxazole, griseofulvin, and lincomycin reported in Baiyangdian Lake were 34.5, 12.2, and 113.4 ng/L, while the antibiotic trimethoprim was 0.6 ng/L observed in Tai Lake. These results were consistent with amounts of antibiotics used in the two regions [2].

Total concentrations of the 16 PPCPs detected at ten sites in Tai Lake, ranged from 26.02 to 42.72 ng/L, with a median concentration of 31.11 ng/L. Maximum concentrations of individual chemicals ranged from 0.04 ng/L for famotidine to 25.77 ng/L for caffeine, and detection of frequencies of 10%–100%. Nine chemicals, caffeine, valsartan, diethyltoluamide, cotinine, carbamazepine, chlorpheniramine, trimethoprim, and triadimefon, were positively detected in all 10 samples. Concentrations of carbamazepine, ranging from 0.63 to 1.86 ng/L, were similar to concentrations previously reported for Tai Lake, which ranged from 0.24 to 8.74 ng/L [19]. However, the maximum concentration of ibuprofen was found to be 1.48 ng/L, which was less than those mean concentrations reported previously for Tai Lake (65.3 ng/L) [19], Liao River (246 ng/L) [23] and the Peal River (1417 ng/L) [42]. Diclofenac, propranolol and erythromycin were not detectable in all water samples during this study, have been previously reported to occur at relatively great concentrations [19].

In Tai Lake, coefficients of variation (CV; CV = mean concentration/standard deviation) for concentrations of individual PPCPs ranged from 12% to 258%. This result indicated spatial variations and large differences among chemicals. Spatial variation might result from a combination of distances of sampling sites from sources of emissions and variations in volumes of discharges [43]. For example, the predominant pollutant, caffeine, was present at relatively great concentrations (up to 25.77 ng/L) at Meiliang Bay (T5, T8, T9, T10) near a densely populated and scenic spot [44] and a relatively stable, thermal stratification that had been established for some days [45]. Eight PPCPs occurred at the greatest concentrations at T7, because the Yincungang River receives domestic wastewater from a densely populated and urbanized area [46]. These results were in general agreement with previous observations in sediments [20], where caffeine was the dominant pollutant near the Yincungang River estuary, and PPCPs in the west of Tai Lake exhibited greater concentrations than those other locations sites.

Analyzed occurrence of 31 PPCPs detected in Baiyangdian Lake, total concentrations at ten sites ranged from 622 to 2781 ng/L, with a median of 1421 ng/L. Although most individual compounds occurred at lesser concentrations, total concentrations of PPCPs exceeded 1 μg/L at eight locations. Mean concentrations of individual chemicals ranged from 0.79 to 329.18 ng/L. Concentrations of diethyltoluamide (329.18 ng/L), methylparaben (201.47 ng/L), florfenicol (196.74 ng/L), metformin (183.14 ng/L) were greatest among PPCPs. Frequencies of detection for the 31 PPCPs were 10%–100%, among which 24 chemicals were detected at all the ten locations. Concentrations ranged from 0.94 to 113.40 ng/L. These results are consistent with those of previous studies where 22 antibiotics were observed in waters of Baiyangdian Lake and tributaries [21]. In that previous study, antibiotics occurred widely in waters samples, with sulfamethoxazole occurring at the greatest concentrations, with a maximum concentration of 940 ng/L, which was much greater than that of 34.54 ng/L, observed in this study.

All 31 PPCPs were found at B10, and the total concentration of combined PPCPs was 2780 ng/L. The most likely reason for this is that location B10 is located near the lakeshore, at a frequently visited, scenic spot, and near the estuary of Fuhe River that receives huge amount of wastewater from Baoding City. Results of previous studies indicated that sewage discharged from Baoding City with over one million residents is likely to be the main source of PPCPs to Baiyangdian Lake [47, 48]. In addition, relatively great concentrations of PPCPs were found at B9 (1856.9 ng/L) and B1 (1751.7 ng/L). As expected, least concentrations of PPCPs (622-1190 ng/L) in water samples were observed in the middle of the lake (B2, B3, B4, B5), where there was little direct influence by human being activities. These studies demonstrated that human activities played a key role in distributions of PPCPs in Baiyangdian Lake.

Screening-level risk assessment

Chronic toxicity data for detected compounds were collected and PNEC values were calculated by use of a conservative AF (Additional file 1: Table S2), excepted for valsartan, miconazole, triamterene, clopidol, nalidixic acid, triclabendazole, and cetirizine, since ecotoxicological data were not available. The 16 PPCPs in Tai Lake and 28 PPCPs in Baiyangdian Lake were ranked, in descending order, by RQ values (Fig. 3). In the two lakes, a total of 7 PPCPs yielded PI values greater than zero, including carbamazepine in both lakes (Table 1).

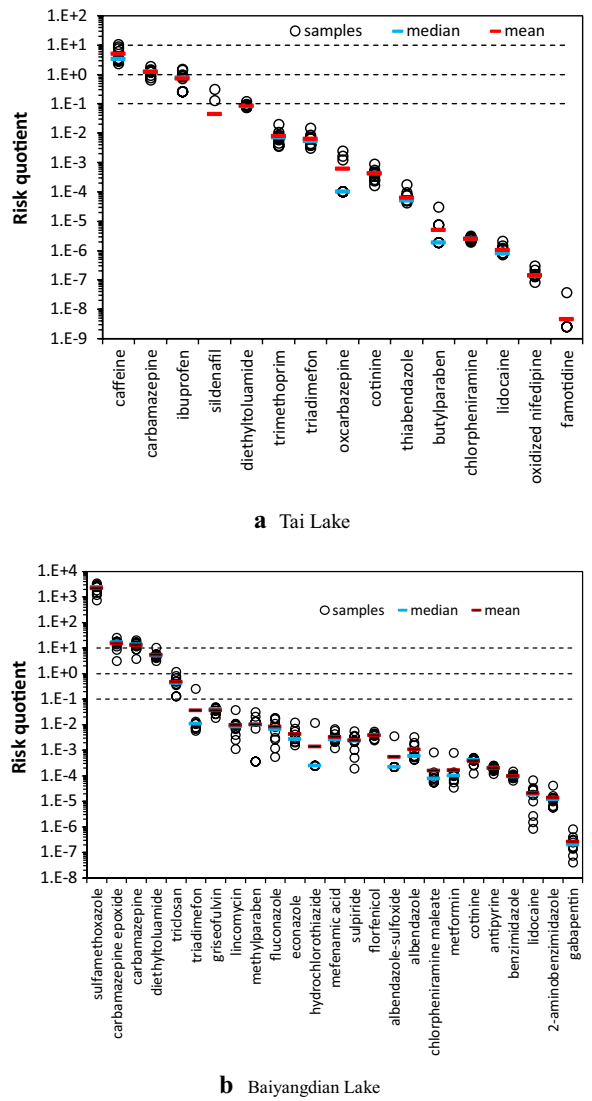

Fig. 3 Risk quotients of PPCPs in Tai and Baiyangdian Lakes of China. **a** Tai Lake **b** Baiyangdian Lake. Concentrations of chemicals in each sample are shown as circles. Median and mean concentrations for each chemical are shown as blue and red lines, respectively

Table 1 Prioritization of target compounds based on PI values (PI > 0)

Rank	Chemical	CAS	RQ_{max}	F (%)	PI
Tai Lake					
1	Caffeine	58-08-2	10.3	100	10.3
2	Carbamazepine	298-46-4	1.9	70	1.3
3	Ibuprofen	15,687-27-1	1.5	20	0.3
Baiyangdian Lake					
1	Sulfamethoxazole	723-46-6	1128.6	100	1128.6
2	Carbamazepine epoxide	36,507-30-9	25.6	100	25.6
3	Carbamazepine	298-46-4	20.5	100	20.5
4	Diethyltoluamide	134-62-3	10.5	100	10.5
5	Triclosan	3380-34-5	1.2	10	0.12

RQ_{max} reference risk quotient based on the maximum measured concentration, *F* reference frequency of PNEC exceedance, *PI* reference prioritization index

In Tai Lake, three pharmaceuticals, caffeine, carbamazepine, and ibuprofen, posed risk to aquatic organisms, with PI values of 10.3, 1.3, and 0.3, respectively. The maximum RQ value for caffeine was 10.3, and the frequency of PNEC exceedance was 100%, which would mean that a great or moderate environmental risk at all 10 locations was probable. RQ values of carbamazepine and ibuprofen ranged from 0.63 to 1.86, 0.25 to 1.48, and frequencies of exceeding the PNECs were 70% and 20%, respectively, which indicated environmental risks in Tai Lake. Frequencies of exceedances for the remaining 12 PPCPs were zero, while that of sildenafil and diethyltoluamide presented least risk ($0.1 < RQ < 1$), indicated potential risk to aquatic organisms and should be paid more attention in the future.

In Baiyangdian Lake, five compounds were determined to pose measurable environmental risks, sulfamethoxazole, carbamazepine epoxide, carbamazepine, diethyltoluamide, and triclosan with PI values of 3454, 25.6, 20.5, 10.5, and 1.1, respectively. Sulfamethoxazole exhibited greater risks to non-target organisms in Baiyangdian Lake for 100% of samples, with RQs ranged from 758 to 3454, because of its toxic potency to *Caenorhabditis elegans*. Carbamazepine epoxide, carbamazepine, and diethyltoluamide represented great or moderate risks at all 10 sites, with RQs ranging from 3.2 to 25.6, 3.8 to 20.5, and 3.2 to 10.5, respectively. Triclosan exhibits a moderate risk ($RQ = 1.2$) in only 10% of samples, with concentrations greater than PNECs observed only at B10. Amongst target compounds, 22 PPCPs presented $RQ < 0.1$ for all studied samples, indicating di minimis risks to aquatic ecosystems in Baiyangdian.

The PPCPs priority list partially overlaps with compounds prioritized in earlier studies. Eighteen PPCPs were selected and RQ values of sulfamethoxazole and carbamazepine were less than 0.01 in Baiyangdian Lake [22]. That result can be attributed to the relatively great values for PNECs of those two chemicals. In a case study performed in Europe, 42 compounds were prioritized and 5 of them can also be found in this priority

list, i.e., caffeine, ibuprofen, triclosan, sulfamethoxazole, and carbamazepine [8].

Probabilistic analysis of risk

In the present study, based on prioritization indexes, caffeine, carbamazepine, diethyltoluamide, carbamazepine epoxide, and sulfamethoxazole were identified as posing great or moderate risk in Baiyangdian Lake or in Tai Lake. Therefore, they were assessed by a higher-tier assessment based on variability in exposure and ecotoxicity data. Toxicity data used were reported in Additional file 1: Table S3, and data sets were tested for log-normal distribution by use of the Shapiro–Wilk test ($p < 0.05$) prior to application of parametric statistics (Table 2). Joint probability curves for each compound, excluding carbamazepine epoxide, for which too few toxicity data were available to provide sufficient meaningful resolution, 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. 4). Three reference lines were used to categorize risk as *de minimis*, lesser, intermediate or greater [38, 39]. Each point on the curve represents both the probability that the chosen proportion of species will be affected and the frequency with which that magnitude of effect would be exceeded in surface waters.

Based on these results, the four PPCPs in the two lakes posed lesser to greater risks to aquatic organisms. Risk, based on chronic toxicity data, for sulfamethoxazole in Baiyangdian Lake was categorized as greater, with a maximum risk product of 16.62%. For caffeine in Tai Lake, diethyltoluamide and carbamazepine in Baiyangdian Lake, concentrations represent intermediate risk of chronic effects with maximum risk products of 7.25%, 6.68%, and 2.76%, respectively. Lesser risk of chronic effects on aquatic organisms was identified for carbamazepine in Tai Lake, with maximum risk products of 0.82%. Results from the estimated risk curves can also be used to describe the probability of exceeding various percentages of effects. The probability of exceeding 5% adverse effect depended on the most sensitive species, while the shape of the risk curve was related to ranges and variability of datasets (Fig. 5). For example, JPCs for sulfamethoxazole were classified as greater risk to more than 20% of species, but slightly above the reference line for lesser risk to 30% of species. This is because concentrations of sulfamethoxazole were only slightly greater than thresholds for adverse effects on the most sensitive species, and

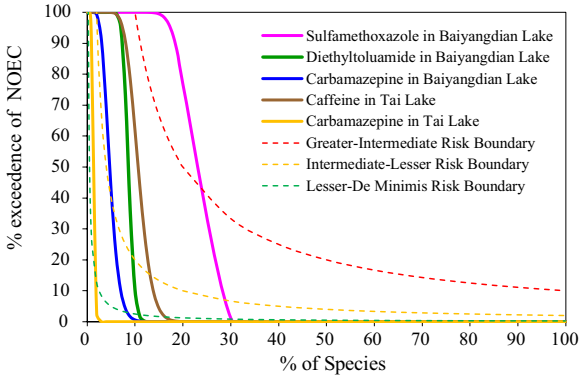

Fig. 4 Joint probability curves for estimated measured environment concentrations of high prioritized PPCPs in Tai and Baiyangdian Lakes. Three reference lines were used to categorize risk as *de minimis*, lesser, intermediate or greater

Table 2 Parameters of joint probability curves (JPCs) for screened PPCPs

Chemical	N	Mean (ng/L)	SD	CV	Shapiro–Wilk test for log-normal distribution
Exposure data set					
Caffeine	10	12.51	7.08	0.57	0.140
Carbamazepine (Tai Lake)	10	1.18	0.35	0.30	0.471
Carbamazepine (Baiyangdian Lake)	10	13.26	4.93	0.37	0.056
Diethyltoluamide	10	329.18	117.48	0.36	0.062
Sulfamethoxazole	10	1.18	0.35	0.30	0.194
Toxicity data set					
Caffeine	17	6,949,090	23,411,509	3.37	0.355
Carbamazepine	24	1,051,828	3,858,902	3.67	0.879
Diethyltoluamide	7	14,724,975	19,980,915	136	0.066
Sulfamethoxazole	9	68,611	165,164	2.41	0.272

N refers to number of data; *SD* refers to standard deviation; *CV* refers to coefficient of variation

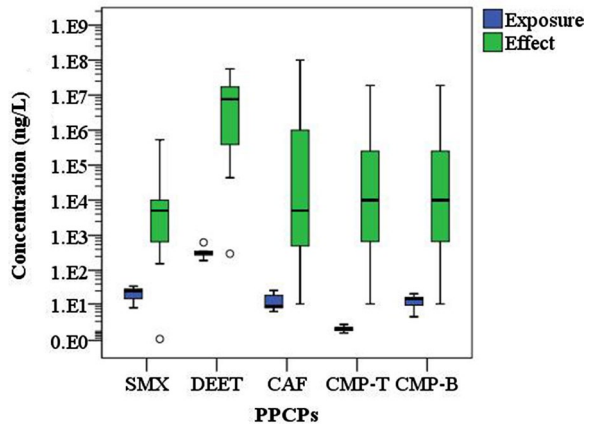

Fig. 5 Comparisons among point-estimates of exposure and effects for the four high prioritized PPCPs. *SMX* sulfamethoxazole, *DEET* diethyltoluamide, *CAF* caffeine, *CMP-T* carbamazepine in Tai Lake, *CMP-B* carbamazepine in Baiyangdian Lake

CVs for estimates of exposure were much less than those for relative potencies among species. In other words, ecological risk would not occur if the most sensitive species was not native species or not important for the local aquatic ecosystem. Therefore, PNEC derived by the most sensitive species and risk assessment according to RQ is likely to be over protective of aquatic ecosystems, and ecological risk assessment based on multiple species is necessary.

Uncertainty analysis

Due to the limited measured surface water concentrations and the lack of data, for toxic potencies of some of the PPCPs to aquatic organisms, some uncertainty in conclusions reached was unavoidable. To more accurately describe exposure and ecological risks, measured concentrations of PPCPs at various temporal scales in waters are required. For seven chemicals, no conclusion can be drawn because ecotoxicological data were not available. However, environmental risks of some drugs are of concern, and due to their great frequency of detection, especially for valsartan in Tai Lake, clopidol and triclabendazole in Baiyangdian Lake. Furthermore, toxicity arising from complex mixtures of PPCPs, each of which occurred at small concentrations that would result in di minimis risks, could lead to additive or synergistic interactions, as demonstrated for similar acting compounds such as antibiotics [49]. This means that even though individual PPCPs are present in relatively small concentrations that do not elicit significant toxic effects, PPCPs mixtures can still exert considerable ecotoxicity. Further research on the risk of these detected compounds should be considered based on combined toxic. At another level, the risk that PPCPs might pose to aquatic species is not only directly related to toxicity of dissolved substances but also to possible bioaccumulation through the food web [50, 51]. For example, bioconcentration factors measured for ibuprofen in rainbow trout (*Oncorhynchus mykiss*) bile were 14,000~49,000 [52], also Coogan et al. [53] revealed accumulation of triclosan in filamentous algae species with the bioaccumulation factor ranged from 900 ~ 2100, suggesting a high bioconcentration in aquatic organisms [54].

There were also limitations imposed by chiral chemicals that might exhibit significant differences in biodegradation and toxic potency among enantiomers [55]. The enantioselective biodegradation and ecotoxicity of chiral PPCPs tend to complicate their potential risk [56]. For example, when waters from several lakes and rivers in Switzerland were investigated, enantiomeric ratios (ER) of ibuprofen ranged from 0.7 to 4.2 [57]. There appears to be a trend toward lesser ERs (closer to racemic) during the warmer season, and greater ERs in winter, with concentration of S-ibuprofen higher than R-ibuprofen. Results of previous studies have shown that inhibition of prostaglandins by R-ibuprofen was 100 times than that of S-ibuprofen [58]. On the contrary, inhibition of cyclooxygenase by R-ibuprofen was 1.4 times less than that of S-ibuprofen [59]. In this study, enantioselectivity of the three chiral pharmaceuticals, caffeine, carbamazepine and ibuprofen that have potential risk in surface waters were not analyzed. Therefore, the risks of such chemicals might have been underestimated or overestimated, and this is likely to change drastically as new information becomes available. Further considerations on ecotoxicity effect of chiral pharmaceuticals in the aquatic environment are possibly needed, which could provide scientific basis and technical support to improve the accuracy of ecological risk assessment.

Conclusions

Forty-two PPCPs were positively detected in Tai and Baiyangdian Lakes, including carbamazepine, diethyltoluamide, cotinine, chlorpheniramine, and triadimefon, which were found in all the 20 sites. Concentrations were generally small and rarely exceeded PNECs, and only three chemicals, caffeine, carbamazepine, and ibuprofen, in Tai Lake and four chemicals, sulfamethoxazole, carbamazepine epoxide, carbamazepine, diethyltoluamide, and triclosan, in Baiyangdian Lake represent concentrations that could be hazardous to non-target organisms, with RQ_{max} values > 1 and PI values > 0. Based on results of the JPCs, caffeine in Tai Lake, diethyltoluamide, sulfamethoxazole, and carbamazepine in Baiyangdian Lake were categorized as greater or intermediate risk. In order to

prevent over protection, it would be valuable to conduct accurate ecological risk assessment based on multiple species for screened chemicals.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12302-020-00346-1.

Additional file 1: Table S1. List of the 140 selected pharmaceuticals and personal care products (PPCPs): chemical .name and CAS. **Table S2.** Toxicity potencies for target PPCPs in aquatic organisms **Table S3.** Toxicity values for caffeine, carbamazepine, diethyltoluamide, and sulfamethoxazole in aquatic organisms.

Abbreviations

PPCPs: Personal care products; UPLC–MS: Ultra performance liquid chromatography–mass spectrometer; RQ: Risk quotients; PI: Prioritization index; JPCs: Joint probability curves; PCPs: Personal care products; WWTPs: Wastewater treatment plants; IRSAD: Index of relative socioeconomic advantage and disadvantage; SPE: Solid-phase extraction; ESI: Electrospray ionization mode; LOD: Limit of detections; LOQ: Limits of quantification; S/N: Signal-to-noise ratios; NOECs: No observed effect concentrations; EC_{10}: 10% Effect concentration; LOEC: Lowest observed effect concentration; EC_{50}: Median effect concentration; AFs: Assessment factors; PRAT: Probabilistic risk assessment tool; AUC: Area under the risk curve; CV: Coefficients of variation; ER: Enantiomeric ratios.

Acknowledgements

This research was financially supported by the National Natural Science Foundation of China (41807400, 41977364, 41521003, 41630645), Beijing outstanding talent training program, National Major S&T Program for Water Pollution Control and Treatment (2017ZX07301-005). Prof Giesy was supported by the Canada Research Chairs Program of the Natural Science and Engineering Research Council of Canada (NSERC).

Authors' contributions

NL was the major contributor in experiments, data analysis and manuscript writing. NL and XJ designed the study. ZY and YL helped with the sample collection and instrumental analysis. CF, ZF and ZT contributed to data collection, evaluation and manuscript writing. FW and JPG contributed to improvements of the manuscript. All authors read and approved the final manuscript.

Funding

This research was financially supported by the National Natural Science Foundation of China (41807400, 41977364, 41521003, 41630645), Beijing outstanding talent training program, National Major S&T Program for Water Pollution Control and Treatment (2017ZX07301-005). Prof Giesy was supported by the Canada Research Chairs Program of the Natural Science and Engineering Research Council of Canada (NSERC).

Availability of data and materials

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

Not applicable.

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Received: 10 February 2020 Accepted: 24 April 2020
Published online: 06 May 2020

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Publisher's Note

Additional file 1

Occurrence and multiple-level ecological risk assessment of pharmaceuticals and personal care products (PPCPs) in two lakes of China

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Table S1 List of the 140 selected pharmaceuticals and personal care products (PPCPs): chemical name and CAS.

2-aminobenzimidazole, 934-32-7; 4-hydroxydiclofenac, 64118-84-9; 6-acetylmorphine, 2784-73-8; acebutolol, 37517-30-9; acetaminophen, 103-90-2; albendazole, 54965-21-8; albendazole-sulfoxide, 51767-39-6; amfebutamone, 34911-55-2; amitriptyline, 50-48-6; amphetamine, 300-62-9; antipyrine, 60-80-0; aripiprazole, 129722-12-9; atenolol, 60966-51-0; atorvastatin, 110862-48-1; bentazon, 25057-89-0; benzimidazole, 51-17-2; benzoylecgonine, 1130667-83-2; bezafibrate, 41859-67-0; buprenorphine, 52485-79-7; butylparaben, 94-26-8; caffeine, 58-08-2; carbamazepine, 298-46-4; carbamazepine epoxide, 36507-30-9; carisoprodol, 78-44-4; cetirizine, 83881-51-0; chloramphenicol, 56-75-7; chlorpheniramine maleate, 113-92-8; clenbuterol, 37148-27-9; clindamycin, 18323-44-9; clopidogrel carboxylic acid, 144457-28-3; clopidol, 2971-90-6; cocaine, 7058-74-4; codeine, 76-57-3; cotinine, 486-56-6; dapsone, 80-08-0; dehydro aripiprazole, 129722-25-4; desvenlafaxine, 93413-62-8; dextromethorphan, 125-71-3; diclofenac, 644-62-2; diethyltoluamide, 134-62-3; diltiazem, 42399-41-7; diphenhydramine, 58-73-1; disopyramide, 3737-9-5; doluxitine, 116539-60-7; donepezil, 110119-84-1; econazole, 27220-47-9; erythromycin, 114-07-8; erythromycin-H_2O, 23893-13-2; escitalopram, 128196-01-0; eslicarbazepine, 104746-04-5; famotidine, 76824-35-6; fentanyl, 437-38-7; florfenicol, 73231-34-2; fluconazole, 86386-73-4; fluoxetine, 54910-89-3; fluticasone propionate, 80474-14-2; frusemide, 54-31-9; gabapentin, 60142-96-3; gemfibrozil, 25812-30-0; griseofulvin, 126-07-8; griseofulvin, 126-07-8; hydrochlorothiazide, 58-93-5; hydroxybupropione, 92264-81-8; ibuprofen, 15687-27-1; ketoprofen, 22071-15-4; lamotrigine, 84057-84-1; lidocaine, 137-58-6; lincomycin, 154-21-2; loratadine, 79794-75-5; lorazepam, 846-49-1; mefenamic acid, 61-68-7; meprobamate, 57-53-4; metformin, 657-24-9; methadone, 297-88-1; methotrexate, 1959-5-2; methylamphetamine, 537-46-2; methylparaben, 99-76-3; metoprolol, 51384-51-1; metronidazole-hydroxy, 4812-40-2; mevastatin, 73573-88-3; miconazole, 22916-47-8; modafinil, 68693-11-8; modafinil, 68693-11-8; morphine, 57-27-2; morpholine, 134-49-6; nalidixic acid, 51940-44-4; nifedipine, 21829-25-4; norfentanyl, 1609-66-1; norfluoxetine hydrochloride, 83891-03-6; omeprazole, 73950-58-6; oxazepam, 604-75-1; oxcarbazepine, 28721-07-5; oxidized nifedipine, 67035-22-7; oxycodone, 76-42-6; oxymorphone, 76-41-5; paracetamol, 103-90-2;

paroxetine, 61869-08-7; pethidine, 57-42-1; phenobarbital, 1950-6-6; phentermine, 122-09-8; phenylpropanolamine, 14838-15-4; phenytion, 630-93-3; pioglitazone, 146062-45-5; pravastatin, 81093-37-0; pregabalin, 148553-50-8; primidone, 125-33-7; propranolol, 318-98-9; pseudoephedrine, 90-82-4; quetiapine, 111974-69-7; ronidazole, 7681-76-7; salbutamol, 18559-94-9; sertraline, 79617-96-2; sildenafil, 139755-83-2; simvastatin, 79902-63-9; sotalol, 3930-20-9; sulfadiazine, 68-35-9; sulfadimethoxine, 122-11-2; sulfafurazole, 127-69-5; sulfameter, 651-06-9; sulfamethoxazole, 723-46-6; sulfamonomethoxine, 1220-83-3; sulfamoxole, 729-99-7; sulpiride, 15676-16-1; sumatriptan succinate, 103628-48-4; tadalafil, 171596-29-5; temazepam, 846-50-4; thiabendazole, 148-79-8; tramadol, 27203-92-5; trazodone, 19794-93-5; triadimefon, 43121-43-3; triamterene, 396-01-0; triclabendazole, 68786-66-3; triclocarban, 101-20-2; triclosan, 3380-34-5; trimethoprim, 738-70-5; tylosin, 1401-69-0; valsartan, 137862-53-4; venlafaxine, 99300-78-4; verapamil, 52-53-9; warfarin, 81-81-2.

Table S2 Toxicity potencies for target PPCPs in aquatic organisms

Chemicals	Species Group	Species	Effect Measurement	Duration (Days)	Endpoint	Concentration (ng/L)	Assessment Factor	PNEC (ng/L)
2-aminobenzimidazole	Worms	*Tetrahymena pyriformis*	Population	2.5	IC50	120660000	100	1206600
albendazole	Fish	*Danio rerio*	Development	2	NOEC	22000	10	2200
albendazole-sulfoxide	Fish	*Danio rerio*	Development	2	NOEC	22000	10	2200
antipyrine	Fish	*Oncorhynchus kisutch*	Morphology	1	NR	10000000	100	100000
benzimidazole	Fish	*Oncorhynchus mykissh*	/	1	NR	5000000	100	50000
butylparaben	Fish	*Salmo trutta*	Biochemistry	10	EC10	27000	10	2700
caffeine	Amphibians	*Xenopus laevis*	Growth	4	LOEC	50	20	2.5
carbamazepine	Crustaceans	*Gammarus pulex*	Behavior	0.0833	NOEC	10	10	1
carbamazepine epoxide	Crustaceans	*Daphnia magna*	Reproduction	6	NOEC	10	10	1
chlorphenamine	Worms	*Dugesia japonica*	Mortality	4	LC50	12200000	100	122000
cotinine	Plant	*Lemna gibba*	Reproduction	7	NOEC	1000000	10	100000
diethyltoluamide	Fish	*Pimephales promelas*	Growth	2	NOEC	600	10	60
econazole	Arthropoda	*Penaeus monodon*	Morphology	1	NR	1000000	100	10000

Chemicals	Species Group	Species	Effect Measurement	Duration (Days)	Endpoint	Concentration (ng/L)	Assessment Factor	PNEC (ng/L)
famotidine	Fish	*Oryzias latipes*	Mortality	4	LC50	100000000	100	1000000
florfenicol	Algae	*Pseudokirchneriella subcapitata*	Population	2	EC50	2300000	100	23000
fluconazole	Fish	*Danio rerio*	Development	5	NOEL	30600	10	3060
gabapentin	Fish	*Danio rerio*	Genetics	2	NOEC	8550000000	10	855000000
griseofulvin	Molluscs	*Mercenaria mercenaria*	Growth	14	EC50	25000	100	250
hydrochlorothiazide	Fish	*Danio rerio*	Development	5	NOEL	29800	10	2980
ibuprofen	Fish	*Oryzias latipes*	Hatch	NR	NOEC	10	10	1
lidocaine	Algae	*Chlorella fusca var. vacuolata*	Population	1	ER50	32003000	100	320030
lincomycin	Plant	*Lemna gibba*	Population	7	NOEC	30000	10	3000
mefenamic acid	Fish	*Danio rerio*	Development	6	NOEC	5000	10	500
metformin	Plant	*Lemna minor*	Population	7	EC50	110000000	100	1100000
methylparaben	Crustaceans	*Daphnia magna*	Behavior	2	NR	2000000	100	20000

Chemicals	Species Group	Species	Effect Measurement	Duration (Days)	Endpoint	Concentration (ng/L)	Assessment Factor	PNEC (ng/L)
oxcarbazepine	Crustaceans	*Daphnia magna*	Reproduction	6	NOEC	10	10	1
oxidized nifedipine	Fish	*Lepomis macrochirus*	Reproduction	0.042	LOEC	34600000	20	1730000
sildenafil	Fish	*Danio rerio*	Genetics	35	NOEC	26.25	10	2.625
sulfamethoxazole	Worms	*Caenorhabditis elegans*	Growth	4	EC10	0.1	10	0.01
sulpiride	Worms	*Dugesia gonocephala*	Behavior	0.0208	NR	1705000	100	17050
thiabendazole	Fish	*Oncorhynchus mykissh*	No Effect	21	NOEC	12000	10	1200
triadimefon	Fish	*Oryzias latipes*	Population	28	NOEC	5000	10	500
triclosan	Algae	*Pseudokirchneriella subcapitata*	Population	3	NOEC	200	10	20
trimethoprim	Molluscs	*Dreissena polymorpha*	Genetics	4	NOEC	290	10	29

Table S3 Toxicity values for caffeine, carbamazepine, diethyltoluamide, and sulfamethoxazole in aquatic organisms

Chemicals	Species Group	Species	Effect Measurement	Duration (days)	Endpoint	Concentration (ng/L)	Assessment Factor
caffeine	Amphibians	*Xenopus laevis*	Growth	4	LOEC	50	2
caffeine	Molluscs	*Corbicula manilensis*	Enzyme	21	NOEC	100	1
caffeine	Molluscs	*Ruditapes philippinarum*	Physiology	21	NOEC	100	1
caffeine	Worms	*Diopatra neapolitana*	Growth	25	NOEC	500	1
caffeine	Amphibian	*Lithobates pipiens*	Growth	28	NOEC	600	1
caffeine	Fish	*Carassius auratus*	Enzyme	7	NOEC	3200	1
caffeine	Algae	*Cyanophyceae*	Population	56	NOEC	5000	1
caffeine	Molluscs	*Carcinus maenas*	Physiology	28	NOEC	5000	1
caffeine	Worms	*Animalia*	Population	56	NR	5000	1
caffeine	Worms	*Protozoa*	Population	56	NR	5000	1
caffeine	Crustaceans	*Daphnia magna*	Population	21	LOEC	120000	2
caffeine	Insects	*Chironomus tentans*	Behavior	2	NOEC	1000000	1
caffeine	Plant	*Lemna gibba*	Injury	7	NOEC	1000000	1
caffeine	Fish	*Danio rerio*	Enzyme	4	NOEC	6050000	1
caffeine	Fish	*Pimephales promelas*	Growth	5	LOEC	20000000	2

Chemicals	Species Group	Species	Effect Measurement	Duration (days)	Endpoint	Concentration (ng/L)	Assessment Factor
caffeine	Rotifera	*Plationus patulus*	Population	6	NOEC	100000000	1
carbamazepine	Molluscs	*Dreissena polymorpha*	Genetics	7	LOEC	55.5241785	2
carbamazepine	Insects	*Stenonema sp.*	Development	9	NOEC	200	1
carbamazepine	Molluscs	*Corbicula manilensis*	Enzyme(s)	30	LOEC	450	2
carbamazepine	Crustaceans	*Daphnia magna*	Reproduction	6	LOEC	500	2
carbamazepine	Fish	*Cyprinus carpio*	Histology	28	LOEC	1000	2
carbamazepine	Fish	*Oncorhynchus mykiss*	Enzyme(s)	42	NOEC	890	1
carbamazepine	Fish	*Salmo salar*	Genetics	5	LOEC	7850	2
carbamazepine	Algae	*Neochloris pseudoalveolaris*	Biochemistry	3	LOEC	10000	2
carbamazepine	Algae	*Parachlorella kessleri*	Biochemistry	3	LOEC	10000	2
carbamazepine	Algae	*Monera*	Population	56	LOEC	10000	2
carbamazepine	Algae	*Algae*	Population	56	NOEC	10000	1
carbamazepine	Amphibians	*Limnodynastes peronii*	Growth	NR	NOEC	10000	1
carbamazepine	Fish	*Danio rerio*	Reproduction	NR	NOEC	10000	1
carbamazepine	Fish	*Pimephales promelas*	Behavior	14	LOEC	100000	2
carbamazepine	Fish	*Lepomis gibbosus*	Enzyme(s)	4	NOEC	125000	1

Chemicals	Species Group	Species	Effect Measurement	Duration (days)	Endpoint	Concentration (ng/L)	Assessment Factor
carbamazepine	Insects	*Chironomus riparius*	Development	28	NOEC	164000	1
carbamazepine	Plant	*Typha sp.*	Enzyme(s)	14	LOEC	500000	2
carbamazepine	Molluscs	*Potamopyrgus antipodarum*	Reproduction	21	NOEC	250000	1
carbamazepine	Invertebrates	*Brachionus calyciflorus*	Mortality	2	NOEC	377000	1
carbamazepine	Plant	*Lemna gibba*	Injury	7	NOEC	1000000	1
carbamazepine	Invertebrates	*Hydra vulgaris*	Morphology	4	NOEC	1000000	1
carbamazepine	Fish	*Oryzias latipes*	Behavior	8	LOEC	6150000	2
carbamazepine	Molluscs	*Elliptio complanata*	Biochemistry	2	NOEC	18901848	1
diethyltoluamide	Fish	*Pimephales promelas*	Morphology	2	LOEC	600	2
diethyltoluamide	Crustaceans	*Daphnia magna*	Reproduction	21	NOEC	43600	1
diethyltoluamide	Insects	*Chironomus riparius*	Enzyme	2	LOEC	6900000	2
diethyltoluamide	Fish	*Danio rerio*	Multiple	5	NR	15301848	2
diethyltoluamide	Worms	*Dugesia japonica*	Mortality	4	LC50	124300000	10
diethyltoluamide	Fish	*Gambusia affinis*	Mortality	2	LC50	235000000	10
diethyltoluamide	Fish	*Oncorhynchus mykiss*	Mortality	4	NOEL	56000000	1
sulfamethoxazole	Worm	*Caenorhabditis elegans*	Behavior	4	EC10	0.1	1

Chemicals	Species Group	Species	Effect Measurement	Duration (days)	Endpoint	Concentration (ng/L)	Assessment Factor
sulfamethoxazole	Plant	*Lemna gibba*	Biochemical	7	EC10	655	1
sulfamethoxazole	Algae	*vacuolata*	Population	1	EC50	1540	10
sulfamethoxazole	Worm	*Hydra*	/	4	NOEC	5000	1
sulfamethoxazole	Rotifera	*Brachionus calyciflorus*	Reproduction	2	EC50	6930	10
sulfamethoxazole	Amphibians	*Limnodynastes peronii*	Growth	21	NOEC	10000	1
sulfamethoxazole	fish	*Carassius auratus*	Enzyme	1	LOEC	16000	2
sulfamethoxazole	Crustaceans	*Daphnia magna*	Reproduction	21	LEOC	120000	2
sulfamethoxazole	Fish	*Danio rerio*	Reproduction	21	NOEC	533000	1