Environment International 131 (2019) 104994

Contents lists available at ScienceDirect

Environment International

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

Review article

A critical review of synthetic chemicals in surface waters of the US, the EU and China

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ARTICLE INFO

Handling editor: Adrian Covaci

Keywords:
Chemical pollution
Risk assessment
Pesticide
Industry
Pharmaceutical and personal care products
Land use

ABSTRACT

There is a wide concern that emerging organic pollutants (EOPs) in surface water could adversely affect human health and wildlife. However, the geographic distribution, exposure pattern and ecological risk of emerging organic pollutants are poorly understood at a global scale. This paper provides a comprehensive survey on the exposure level of EOPs in China, the US and the EU based on the published literature. The hazard level of three categories of EOPs, namely pharmaceuticals and personal care products (PPCPs), pesticides and industrial chemicals was further evaluated by adopting a novel Aquatic HazPi index that jointly accounts for the persistence, bioaccumulation, toxicity and bioactivity. Furthermore, a correlation analysis of land use with the surface water exposure status regarding the synthetic chemicals was conducted. According to the published data reported between 2010 and 2016, the concentration of pesticides in the US was higher than in the EU and China. The concentration of PPCPs in the EU was generally lower than in both the US and China, while the concentration of industrial chemicals in China was higher than in the EU and the US. Among the chemicals whose median concentration in surface water was > 10 ng/L, the antiretroviral Efavirenz, the pesticide Fipronil, and octocrylene, an industrial chemical and cosmetic ingredient, were found with the highest aquatic HazPi value. Lastly, the spatial distribution and concentration of hazardous EOPs was shown to depend on local landscape and land usages. Our study provides the first broad overview on the geographic distribution, exposure pattern of hazardous EOPs in the three major economic entities: China, the US and the EU.

1. Introduction

The security of global surface water has been increasingly threatened by emerging organic pollutants (EOPs) (Schwarzenbach et al., 2006; Stehle and Schulz, 2015). One of the United Nations global sustainability goals is to achieve the environmentally sound management of chemicals and all wastes throughout their life cycle to minimize their adverse impacts on human health and the environment (United Nation, 2018). Unfortunately the release of synthetic chemicals to the environment is accelerating, largely due to the increasing scale of global trade, urbanization, agriculture and medical applications, resulting in a large number of EOPs detected in surface water, that threatens natural ecosystems and environmental safety (Schwarzenbach et al., 2006; Stehle and Schulz, 2015). In the past 50 years, the production and diversification of synthetic chemicals has increased much faster than other byproducts of economic expansion, such as carbon dioxide emissions and phosphorus fertilizer (Bernhardt et al., 2017). A large number of the EOPs detected in the surface water environment are potentially toxic to aquatic organisms (Cho et al., 2012; Kamel, 2013; Kinch et al., 2015), and may lead to the loss of biodiversity globally (Beketov et al., 2013; Malaj et al., 2014; Voeroesmarty et al., 2010). Furthermore, there is a wide concern that persistent pollution by synthetic chemicals threatens human health since surface water plays an important role in the ecosystem such as providing water sources for drinking, crop irrigation, and commercial or indigenous fisheries. Therefore, the current status on the geographic distribution, exposure pattern and ecological risk of emerging organic pollutants (EOPs) in global surface water needs to be studied comprehensively (Rockstrom et al., 2009; Steffen et al., 2015).

It is important to focus on the distribution and risk of chemical pollution in China, the US and the EU, since they are the three largest importers and exporters of chemicals (WTO, 2018). But these three

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https://doi.org/10.1016/j.envint.2019.104994
Received 24 March 2019; Received in revised form 11 June 2019; Accepted 3 July 2019
Available online 11 July 2019

economic entities exhibit different patterns and severities of chemical pollution because of their distinctive industrial structures and different stages of development. China, as an emerging economy, has undergone a sharp rise in the production and use of synthetic chemicals in the past two decades (National Bureau of Statistics of China, 2018), unlike the EU and the US. The three economies also have different regulations for chemical regulation and management, further contributing to their differences in chemical pollution. China is now at the stage in the process of developing suitable laws to regulate the production and usage of chemicals (Ministry of Ecology and Environment, 2019). While, the EU and the US have already established comprehensive chemicals management regulation, e.g. the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (European Commission, 2016) and the Toxic Substances Control Act (TSCA) (Environmental Protection Agency, 2019). It has been hypothesized that China may have a very similar or more serious pattern of surface water pollution by EOPs compared with the US and the EU due to its large scale of chemical industry and lack of strict chemicals law (Tang et al., 2015; Wang et al., 2018). However, this area is largely unexplored.

As is well known, the enforcement of chemical management and waste water regulations is essential for controlling surface water pollution. One of the major challenges for effective chemical regulation and management is how to identify the chemicals that are the primary cause of adverse effects in the environment. Hazard quotients (HQ), an index that divides an effect concentration (EC) by the measured environmental concentration, are useful for evaluating the ecological risk of EOPs in aquatic environment (Brack et al., 2018; Busch et al., 2016). Exposure and environmental risk assessment for human health are often conducted by calculating the potential level of carcinogenic risk from exposure (Environmental Protection Agency, 2005). But the above assessment methods largely depend on detected concentrations, and acute or chronic toxicity information on the chemicals, while persistence and bioaccumulation are often assessed separately. In this study, we propose to evaluate the hazard of EOPs in surface waters by use of the Aquatic HazPi, a modified index following Tilley et al. (Tilley et al., 2017), which jointly accounts for the persistence, bioaccumulation, bioactivities and toxicity of each chemical to derive its hazard level.

To assess the state of pollution of aquatic environments by EOPs on a global scale, we conducted this study with the following goals: 1) to survey the literature on the aquatic monitoring data for EOPs around the world since 2010, and compare EOPs in China and developed areas (the US and the EU) under the categories of PPCPs, pesticides and industrial chemicals; 2) to profile the hazard potential of the detected EOPs using Aquatic HazPi tool; 3) to evaluate the main source of hazardous EOPs in the US, the EU and China by performing a correlation analysis between the EOPs categorization and the land utilization near the aquatic monitoring study sites.

2. Materials and methods

2.1. Extraction and compilation of surface water monitoring data

The workflow of data extraction and compilation is shown in Fig. 1. Firstly, research papers published after 2010 and the reported concentrations of EOPs in global surface waters were reviewed and related papers were tabulated (Table S1), as the number of papers and citations about EOPs has increased exponentially since 2010. The distribution of the sites and the number of chemicals analyzed in these studies are summarized in Fig. 2. Then, the chemical information and concentration data for China (7 provinces, located in east, southeast or northeast parts where highly urbanized and industrialized area), the US (25 states) and the EU (14 countries) were extracted. The EOPs were classified as “PPCPs”, “pesticides” and “industrial chemicals” by a modified classification method (Meffe and de Bustamante, 2014). One of our major considerations was that the selected data must have compounds that could be clearly identified with at least a CAS number and SMILES formula, therefore structures without unambiguous identification were excluded in this study. The concentration units of all data were converted into ng/L (Table S2).

2.2. Persistence & Bioaccumulation analysis

All the detected chemicals in the surface water from China, the EU and the US were individually examined to determine if they were persistent (P) and bioaccumulative (B) according to the thresholds of half-life and bioconcentration factor (BCF) defined in the US EPA TSCA New Chemicals Program for Policy for PBT Chemical Substances (Environmental Protection Agency, 1999). In particular, the half-life for degradation of a chemical in water, soil, and sediment at 25 °C was used to estimate the environmental persistence of a chemical; and the BCF was used to estimate its potential ability for bioaccumulation. The half-life and BCF were gathered for each chemical by using the CASRN and SMILES formula with the PBT profiler (http://www.pbtprofiler.net/notice.asp). The ultimate biodegradation expert survey module of the BIOWIN estimation program was used to determine the half-life of a chemical in water, soil, and sediment (Boethling et al., 1994). BCF was estimated using the USEPA EPI Suite BCFWIN estimation program, which is based on a chemical's octanol/water partition coefficient (Meylan et al., 1999). The criteria for P and B substances were modified according to Sangion and Gramatica (Sangion and Gramatica, 2016) as shown in Fig. S1; all the P and B substances were over class 16.

2.3. Acute toxicity data extraction and compilation

To protect the biodiversity at different levels of food web in aquatic ecosystem, chemical toxicity is determined on organisms representing the three trophic levels, i.e. vertebrates (fish), invertebrates (crustaceans as Daphnia) and plants (algae). Here, acute effect concentrations (EC) for each of three groups of aquatic organisms (fish, crustaceans, and algae) were derived according to the workflow from Busch et al. (2016). If data for a chemical was unavailable in the Busch's paper, the US EPA ECOTOX database (http://www.epa.gov/ecotox) was used to search for acute ECs. We adopted the 5th percentile of the reported ECs or a single EC if only one value was available. Alternatively, the acute toxicity was predicted by the USEPA ECOSAR software tool (https://www.epa.gov/tsca-screening-tools/ecological-structure-activity-relationships-ecosar-predictive-model). ECOSAR software uses physiochemical properties (Kow, melting point, water solubility, and molecular weight) to calculate the ECs for acute toxicity in fish, crustaceans, and algae. All the toxicity values are listed in the Supporting Information (Table S3).

2.4. ToxCast and Tox21 assay data extraction and compilation

To further assess the toxicity level of each chemical, high-throughput assay data from the ToxCast Dashboard were used to inform chemical safety properties. All the test data in ToxCast project were downloaded (https://www.epa.gov/chemical-research/toxicity-forecaster-toxcasttm-data) and the EC data of each activity bioassay for EOPs in surface water were extracted using the CASRN number by a program written in R (https://www.r-project.org/). If detected EOPs were not available in the Tox21 testing program, we first tried to find alternative chemicals that have the same parent as the original EOPs using PubChem identifier Exchange Service (https://pubchem.ncbi.nlm.nih.gov/idexchange/idexchange.cgi). If there was no alternative with tested bioactivity result, the bioactivity of that particular EOP was listed as not available (NA).

2.5. Aquatic HazPi analysis

To comprehensively assess the hazard level of the EOPs in surface

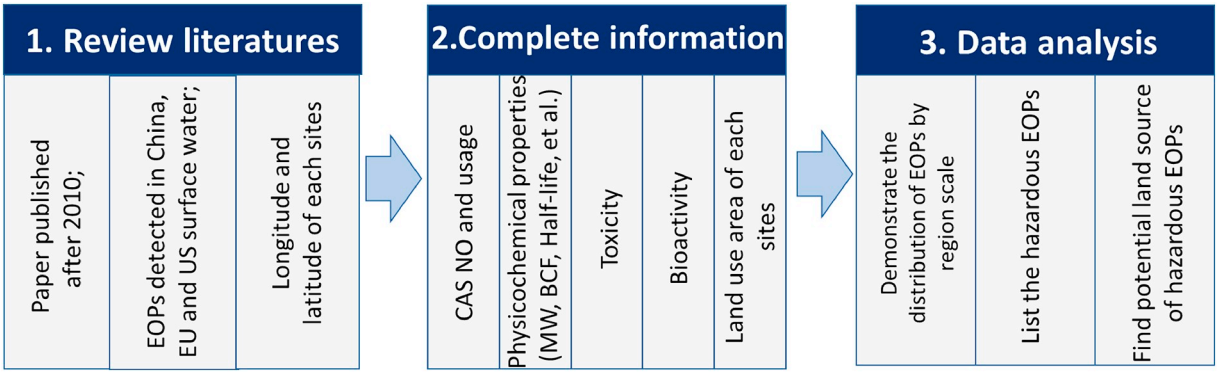

Fig. 1. Workflow of literature review, data collection and analysis.

waters, four categories of chemical properties, i.e., persistence, bioaccumulation, aquatic ecotoxicity and human health, were evaluated using a ToxPi GUI (Toxicological Priority Index graphical user interface) software (http://www.comptox.us/toxpi.php). A total of 733 chemicals (excluding PCBs, DDT and its metabolites) were evaluated by Aquatic ToxPi. Each category was assigned equal weight of the ToxPi (25% per category). Persistence was equally weighted by the half-life for degradation of each chemical in water, soil, and sediment. The half-life and bioaccumulation values were scored in ToxPi using the built-in sqrt(x) normalization scheme. The category of aquatic ecotoxicity was comprised of the ECs of acute and chronic toxicity in fish, crustaceans, and algae with equal weights. All EC data were scored using the –log10(x) + log10(max(x)) scheme in ToxPi, as higher EC values corresponded to smaller ToxPi radii. For bioactivity, only the assay data in Tox21 testing program were used. We chose 12 kinds of molecular targets for this category (NFE2L2, AR, AHR, ESR1, ATF6, NR1H4, NR3C1, HSF1, NFKB1, PPARD, CYP24A1 and TP53; see Supporting Info for details), which had been tested with at least three different assays. The assay values were scored in ToxPi using the built-in –log10(x) + 6 normalization scheme. All missing data values in dataset were entered as "NA". Finally, the ranking of Aquatic HazPi score of all EOPs was set up by inputting the completed data file into ToxPi GUI software. Since most of the previously reported B and P substances were in the top 20% of the Aquatic Hazpi value ranking list, the 20th percentile was used as

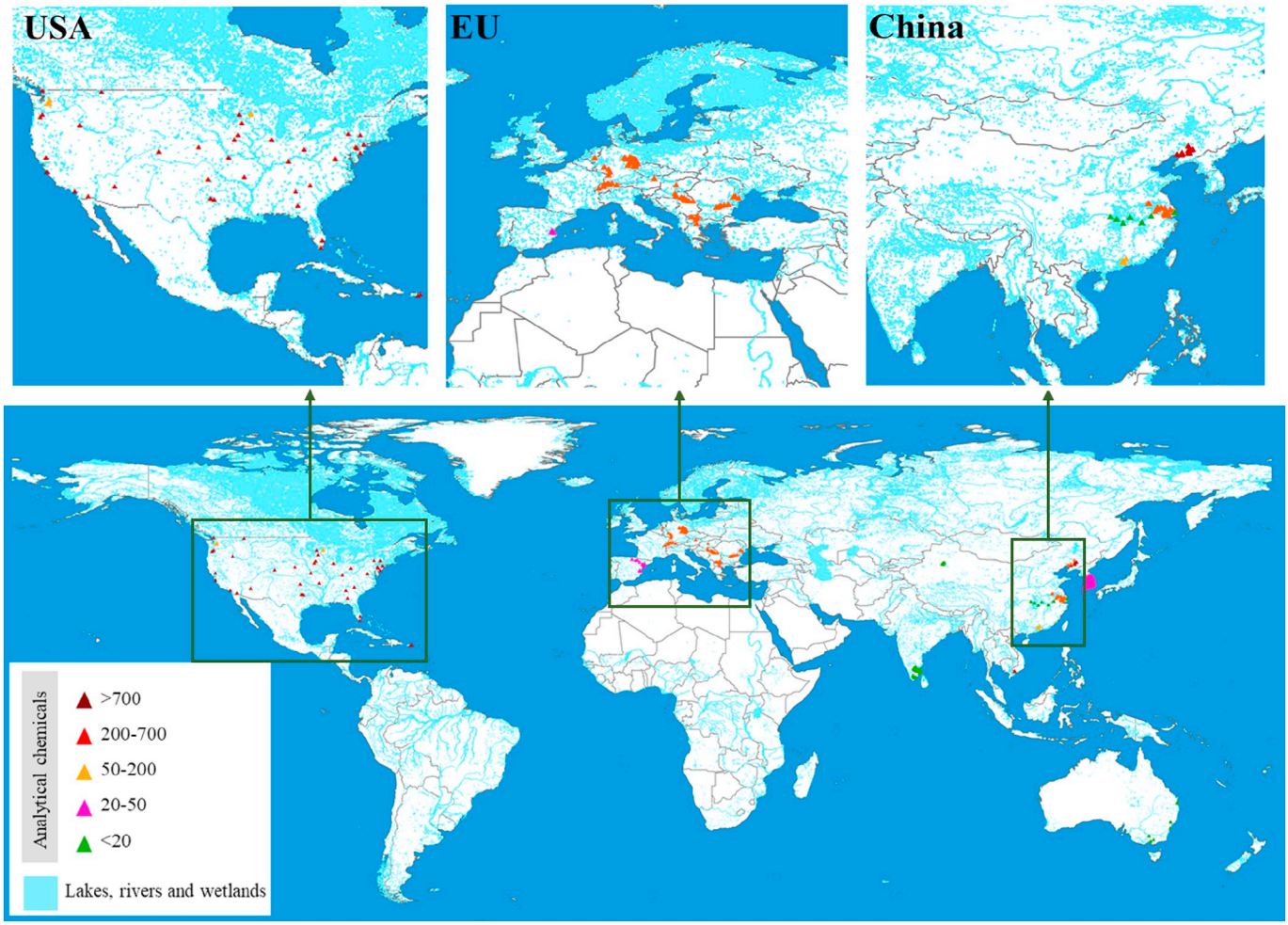

Fig. 2. Distribution of sampling sites we used for in US, EU and China.

the threshold for categorizing hazardous and less hazardous chemicals.

2.6. EOPs categorization and land utilization analysis

The correlation between land use and EOPs was estimated to help identify the source of pollutants in the sampling area. The association between the concentration of EOPs and the land of each sampling site was investigated by Pearson correlation analyses. The land category was classified according to the UN Land Cover Classification System (UN-LCCS) legend (Table S4). Then, based on the statistical correlation ($P < 0.05$, over 80% detection accompanied with the type of specific land usage and the number of detected sites > 4), we identified the EOPs which were correlated to the area of the land category.

2.7. Statistical analysis

Statistical analyses were performed using SPSS Statistics and GraphPad Prism 5 (GraphPad Software Inc.). *t*-Kruskal Wallis test ($P \leq 0.05$) was used to determine differences in chemical concentrations reported between China, the EU or the US.

3. Results and discussion

3.1. The basic information of global EOPs

Our literature search revealed that 2638 chemicals have been analyzed and reported in surface waters over the period 2010 to 2016 (Table S5). Of these, 819 were detected in more than one location around world (Table S6) and 78 were substances with persistent and bioaccumulative properties over class 16 (Figure S1, Table S7). All these detected EOPs were separated to 3 main and 84 specific categories based on different usage (Table S8), with the main categories being PPCPs, pesticides and industrial chemicals. More than 90% of the detected chemicals were from Europe, North America and Asia with a heterogeneous geographical distribution (Fig. 2). Data from China, the US and the EU, the three regions which detected the largest number of emerging chemicals, and represent different stages of urban and industrial development, were selected for further analysis.

3.2. Comparing the exposure level of EOPs in China, the EU and the US

744 organic pollutants were detected in surface waters of China, the US and the EU, including 238 PPCPs, 284 pesticides and 222 industrial chemicals (Table S2). Of these, 130 PPCPs were detected in the US, followed by 113 in Europe and 81 in China. Meanwhile, 201 pesticides were detected in Europe, followed by106 and 89 in the US and China, respectively. In addition, 109 industrial chemicals were detected in China, followed by 104 in the US, and 56 in Europe. Finally, 14 PPCPs, 29 pesticides and 2 industrial chemicals were co-detected in all three regions (Fig. S3).

China, the EU and the US also demonstrated different patterns of pollution intensity for PPCPs, pesticides and industrial chemicals based on the concentration of chemicals co-detected in all three regions (Fig. S2). The concentration of PPCPs was higher in the US than in the EU ($P < 0.01$). Among the 14 PPCPs concurrently detected in China, the EU and the US (Fig. S3, Table 1), gemfibrozil, an antilipemic (lipid reducing) drug, had the highest median concentration in China (Peng et al., 2018) and the US (Meador et al., 2016). In addition, gemfibrozil was detected at all the tested sites in the EU (Carmona et al., 2014; Stipanicev et al., 2017). Furthermore, 14, 7 and 3 PPCPs from the US, the EU, and China, respectively, ranked in the top 15% of all detected chemicals in the three regions (based on high concentrations and high detection frequency (> 30%)). In the US, most of the PPCPs were antilipemics (gemfibrozil (Meador et al., 2016)), hormones (cholesterol (Bradley et al., 2017), muscle relaxants (methocarbamol (Bradley et al., 2017)) and antibiotics (ciprofloxacin (Bradley et al., 2017; Meador et al., 2016)) (Fig. 4, Table S9). In the EU, the prominent PPCPs were mainly anti-inflammatory drugs and central nervous-stimulators (Fig. 4, Table S9), such as ketoprofen (Hug et al., 2015; Neale et al., 2015; Ruff et al., 2015), diclofenac (Hug et al., 2015; Neale et al., 2015; Ruff et al., 2015) and caffeine (Hug et al., 2015; Neale et al., 2015; Stipanicev et al., 2017). While in China, the top PPCP pollutants were antiviral drugs, antibiotics and contrast medium chemicals (Fig. 4, Table S9), including amantadine (Peng et al., 2018), lincomycin (Peng et al., 2018; Yang et al., 2017) and iopromide (Yang et al., 2017).

Pesticide concentrations in surface water of the US were higher than that of the EU ($P < 0.01$) and China ($P < 0.05$), while the levels in China were indistinguishable from those in the EU, based on the 29 pesticides detected from all three regions (Fig. 3, Fig. S3). These pesticides included 15 herbicides and their metabolites, 7 insecticides and 10 fungicides (Table 1). Atrazine and its metabolites were the most ubiquitous herbicides. Although the EU banned the use of atrazine in 2004, it was still detected in European surface water with the median concentration of 3.3 ng/L (Hug et al., 2015; Moschet et al., 2014; Neale et al., 2015; Ruff et al., 2015; Stipanicev et al., 2017), which was about 1/25 of the median concentration in China (Bu et al., 2015; Peng et al., 2018), and about 1/10 in the United States (Bradley et al., 2017). Furthermore, most atrazine metabolites co-occurred with the parent chemical in surface water with higher concentrations. In the EU and the US, the median concentrations of desisopropylatrazine reached 25.0 ng/L (Hug et al., 2015; Stipanicev et al., 2017) and 81.9 ng/L (Bradley et al., 2017) respectively; and in China, the median concentration of 2-hydroxyatrazine was 92.9 ng/L (Peng et al., 2018). The insect repellent, DEET was present with highest median concentration in China and the EU, which were 46.5 ng/L (Peng et al., 2018; Yang et al., 2017) and 19.6 ng/L (Hug et al., 2015; Moschet et al., 2014; Neale et al., 2015; Stipanicev et al., 2017), respectively. In the US, although the median concentration of DEET was not as high, it still reached 23 ng/L (Bradley et al., 2017; Meador et al., 2016). Dimethoate had the highest median concentrations of insecticides in the US surface waters, reaching 185 ng/L (Bradley et al., 2017), which was 51-fold and 18-fold higher than median concentration in the EU (Stipanicev et al., 2017) and China (Peng et al., 2018), respectively. The fungicide, tebuconazole had the highest median concentration in China, reaching 35.3 ng/L (Peng et al., 2018), which is 4-fold and 1.4-fold higher than the median concentration in Europe (Hug et al., 2015; Moschet et al., 2014; Neale et al., 2015; Ruff et al., 2015; Stipanicev et al., 2017) and the US (Bradley et al., 2017). Previous studies reported that tebuconazole may be an endocrine disruptor, as well as affect the nervous system and induce genotoxicity (Castro et al., 2018; Moser et al., 2001; Taxvig et al., 2007). Myclobutanil had the highest concentration of fungicides in the US with median concentration of 161 ng/L and a detection rate of 5.3% (Bradley et al., 2017). In Europe, the fungicide azoxystrobin had the highest median concentration (45 ng/L, (Moschet et al., 2014)), which was 4.5-fold and 1.6-fold higher than median concentration in China (Peng et al., 2018) or the US (Bradley et al., 2017).

Furthermore, among the EOPs ranked in the top 15% of all detected chemicals in the three regions (and with detection rate > 30%), 11 pesticides from the EU, 3 from the US, and 3 from China, respectively, were considered the most prominent pollutants based on their median concentrations in surface water. More than 60% of them were herbicides and their degradation products. In the EU, S-Metolachlor had the highest median concentration reaching 430 ng/L (Moschet et al., 2014).

Table 1
Chemicals were co-detected in surface water from China, the EU and the US.

Usage	Chemical name	CASRN	China (ng/L)			EU (ng/L)			US (ng/L)		
			Con. range	Median con.	Cumulative detection	Con. rage	Median con.	Cumulative detection	Con. rage	Median con.	Cumulative detection
Industrial chemical	Triethylcitrate	77-93-0	135.4–1834.7	830.0	29(100%)	1.8–644.8	80.0	32(60.4%)	26.6–694.0	110.0	15(39.5%)
	4-/5-Methyl-Benzotriazole	136-85-6	4.0–1465.1	66.1	42(80.8%)	11.1–4412.7	132.6	48(77.4%)	228.0–921.0	494.0	12(31.6%)
PPCPs	Genistein	446-72-0	1.9–58.8	12.3	15(51.7%)	2.5–44.9	4.8	12(54.5%)	3.0–42.0	7.7	14(36.8%)
	Daidzein	486-66-8	4.8–87.6	17.1	26(89.7%)	2.1–8.3	4.0	9(40.9%)	0.7–46.0	8.1	19(50%)
	Acetaminophen	103-90-2	21.0–338.0	41.3	13(30.2%)	1.1–3000.0	80.1	13(28.3%)	1.9–244.0	10.8	15(36.6%)
	Trimethoprim	738-70-5	0.8–46.3	5.0	39(92.9%)	1.4–185.8	9.2	46(67.6%)	5.5–198.8	52.4	14(34.1%)
	Carbamazepine	298-46-4	1.1–146.0	7.9	35(83.3%)	2.6–1711.0	34.9	66(97.1%)	0.9–382.7	70.7	22(53.7%)
	Lidocaine	137-58-6	1.0–58.1	2.9	24(82.8%)	1.5–204.3	15.0	49(72.1%)	0.9–408.8	84.1	21(55.3%)
	Caffeine	58-08-2	24.6–1370.0	215.0	13(24.5%)	13.9–4873.1	249.6	48(81.4%)	6.9–1275.9	84.6	29(70.7%)
	Ciprofloxacin	85721-33-1	5.4–91.8	8.3	10(23.3%)	10.4–448.1	14.2	5(33.3%)	6.0–400.0	135.0	12(29.3%)
	Tramadol	27203-92-5	0.224–11.091	1.0	22(75.9%)	1.9–2082.7	53.9	58(85.3%)	1.1–1311.3	152.2	18(47.4%)
	Ibuprofen	15687-27-1	9.31–128	44.9	13(30.2%)	5.0–16,482.0	93.8	25(67.6%)	129.0–1620.0	488.0	9(22%)
	Sulfamethoxazole	723-46-6	1.8–138.0	10.1	41(97.6%)	1.6–676.7	56.6	45(66.2%)	5.0–1500.0	115.0	20(48.8%)
	Gemfibrozil	25812-30-0	223.4–1419.3	269.4	5(11.9%)	1.8–934.0	11.1	28(100%)	3.4–1360.0	681.7	2(66.7%)
	Triclocarban	101-20-2	1.1–239.0	2.6	60(68.2%)	10.0–57.0	21.0	3(13.6%)	14.0	14.0	1(33.3%)
	Triclosan	3380-34-5	2.5–241.0	14.7	61(62.2%)	3.0–16.0	5.1	22(24.4%)	1.5–534.0	14.6	25(61%)
Pesticide	Boscalid (Nicobifen)	188425-85-6	2.9–10.8	3.9	17(43.6%)	0.9–55.0	6.5	4(36.4%)	5.2–678.1	9.0	11(28.9%)
	Terbuthylazine	5915-41-3	1.1–75.2	3.8	19(48.7%)	1.0–630.0	13.6	38(52.1%)	10.4	10.4	1(2.6%)
	Thiabendazole	148-79-8	0.9–8.4	1.6	28(28.6%)	3.3–7.5	5.4	11(29.7%)	4.0–42.2	11.7	12(29.3%)
	Pyrimethanil	53112-28-0	112.6–112.6	112.6	1(10.0%)	0.9–89.0	1.0	8(40%)	2.5–28.1	15.3	2(5.3%)
	Prometryn	7287-19-6	2.3–18.0	7.7	4(40.0%)	3.8–30.9	6.1	30(50.8%)	3.2–28.6	15.9	2(5.3%)
	Thiamethoxam_DP	153719-23-4	3.0–90.8	9.3	28(96.6%)	1.6–47.0	6.4	6(54.5%)	1.9–190.4	16.1	8(21.1%)
	Atrazine-desethyl	6190-65-4	2.6–65.4	10.4	25(64.1%)	1.1–34.0	2.8	15(45.5%)	4.7–851.0	17.9	26(68.4%)
	Simazine	122-34-9	2.8–488.8	54.7	27(69.2%)	0.2–29.0	9.9	33(45.2%)	6.1–401.0	17.9	17(44.7%)
	Metribuzin	21087-64-9	1.6–163.4	8.4	3(7.7%)	0.9–120.0	26.3	6(30%)	15.9–541.0	18.4	3(7.9%)
	Bentazone	25057-89-0	18.0–1415.2	54.8	27(69.2%)	1.0–537.0	3.0	65(89%)	11.6–88.0	18.7	5(13.2%)
	Bromoxynil	1689-84-5	2.4–2.4	2.4	2(5.1%)	4.0–23.0	4.1	3(21.4%)	12.8–118.5	19.4	4(10.5%)
	N,N-Diethyl-m-toluamide	134-62-3	3.8–574.7	46.5	42(80.8%)	1.1–520.0	19.6	61(95.3%)	2.4–119.0	23.0	25(61%)
	Fipronil	120068-37-3	1.0–5.6	1.8	4(10.3%)	0.7–14.0	3.1	11(21.6%)	6.6–153.0	23.8	17(44.7%)
	Tebuconazole	107534-96-3	3.6–133.4	35.3	27(69.2%)	2.6–86.0	8.6	33(45.2%)	17.3–42.1	25.5	7(18.4%)
	Diuron	330-54-1	1.7–107.3	15.0	27(69.2%)	1.4–667.5	12.5	34(46.6%)	2.4–1362.0	25.6	20(52.6%)
	Imidacloprid	138261-41-3	10.9–1886.9	38.6	28(96.6%)	5.9–9.2	7.4	4(20%)	3.6–142.8	27.5	14(36.8%)
	Azoxystrobin	131860-33-8	2.1–45.2	10.0	28(71.8%)	14.0–120.0	45.0	9(45%)	5.0–279.5	28.1	9(23.7%)
	Diazinon	333-41-5	0.6–8.5	0.9	12(30.8%)	1.6–43.0	10.1	16(38.1%)	21.2–276.0	34.2	3(7.9%)
	2-Hydroxyatrazine	2163-68-0	0.8–2680.4	92.9	29(100%)	10.0–28.0	15.0	5(100%)	5.5–542.8	34.4	19(50%)
	Atrazine	1912-24-9	1.3–1726.1	75.2	39(100%)	0.9–345.0	3.3	45(61.6%)	6.3–5170.0	34.9	26(68.4%)
	Aacetamiprid	135410-20-7	1.9–58.5	17.8	29(74.4%)	0.6–1.1	0.8	2(7.1%)	39.5	39.5	1(2.6%)
	Metolachlor	51218-45-2	9.4–316.7	32.5	28(71.8%)	0.8–17.6	2.0	45(66.2%)	20.0–660.0	40.0	16(42.1%)
	MCPA	94-74-6	17.3–1470.1	108.7	26(89.7%)	1.3–270.0	3.0	29(43.3%)	21.7–105.7	42.7	4(10.5%)
	Propiconazole-I	60207-90-1	1.8–810.4	30.2	29(74.4%)	2.7–165.0	5.6	27(52.9%)	20.2–404.5	64.4	6(15.8%)
	2,4-Dichlorophenoxyacetic acid	94-75-7	9.6–6440.5	30.2	25(86.2%)	1.4–555.4	1.6	28(43.8%)	38.5–411.4	77.2	14(36.8%)
	Desisopropylatrazine	1007-28-9	9.9–39.3	12.7	3(10.3%)	1.2–429.7	25.0	20(54.1%)	36.0–286.6	81.9	5(13.2%)
	Myclobutanil	88671-89-0	3.4–12.5	6.0	11(28.2%)	2.1–15.0	10.5	4(36.4%)	49.7–273.0	161.4	2(5.3%)
	Dimethoate	60-51-5	2.1–57.9	10.4	28(71.8%)	1.8–21.0	3.6	9(81.8%)	133.0–236.0	184.5	2(5.3%)
	Clomazone	81777-89-1	1.0–11.3	1.7	19(48.7%)	2.6–17.5	3.5	5(9.8%)	6.4–927.1	466.8	2(5.3%)

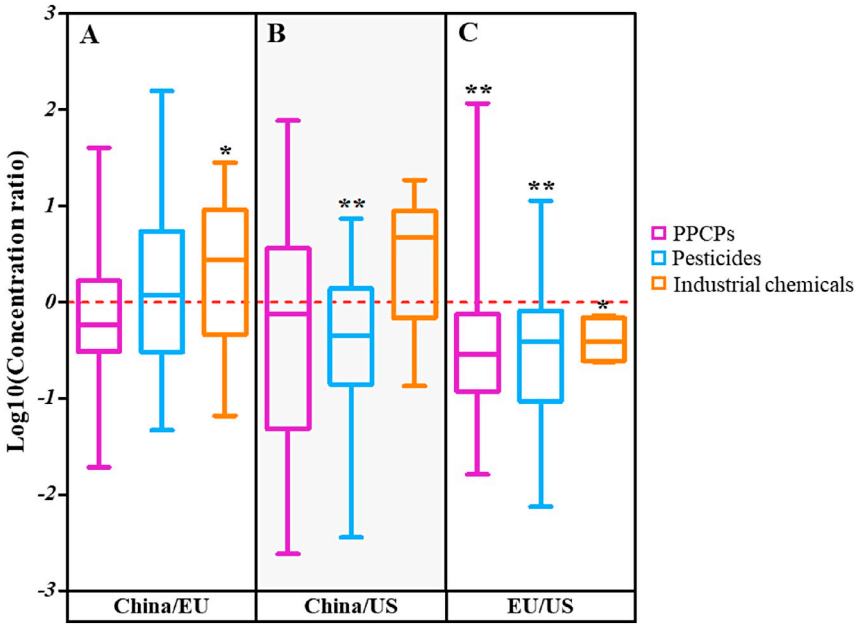

Fig. 3. Concentration ratios of synthetic chemicals (PPCPs, pesticides and industrial chemicals) between two regions, (A) Ratios of chemical concentrations between China and the EU, (B) Ratios of chemical concentrations between China and US, (C) Ratios of chemical concentrations between the EU and the US, $*P < 0.05$ and $**P < 0.01$ indicates significant differences between each group of Log10 (concentration ratio) and 0.

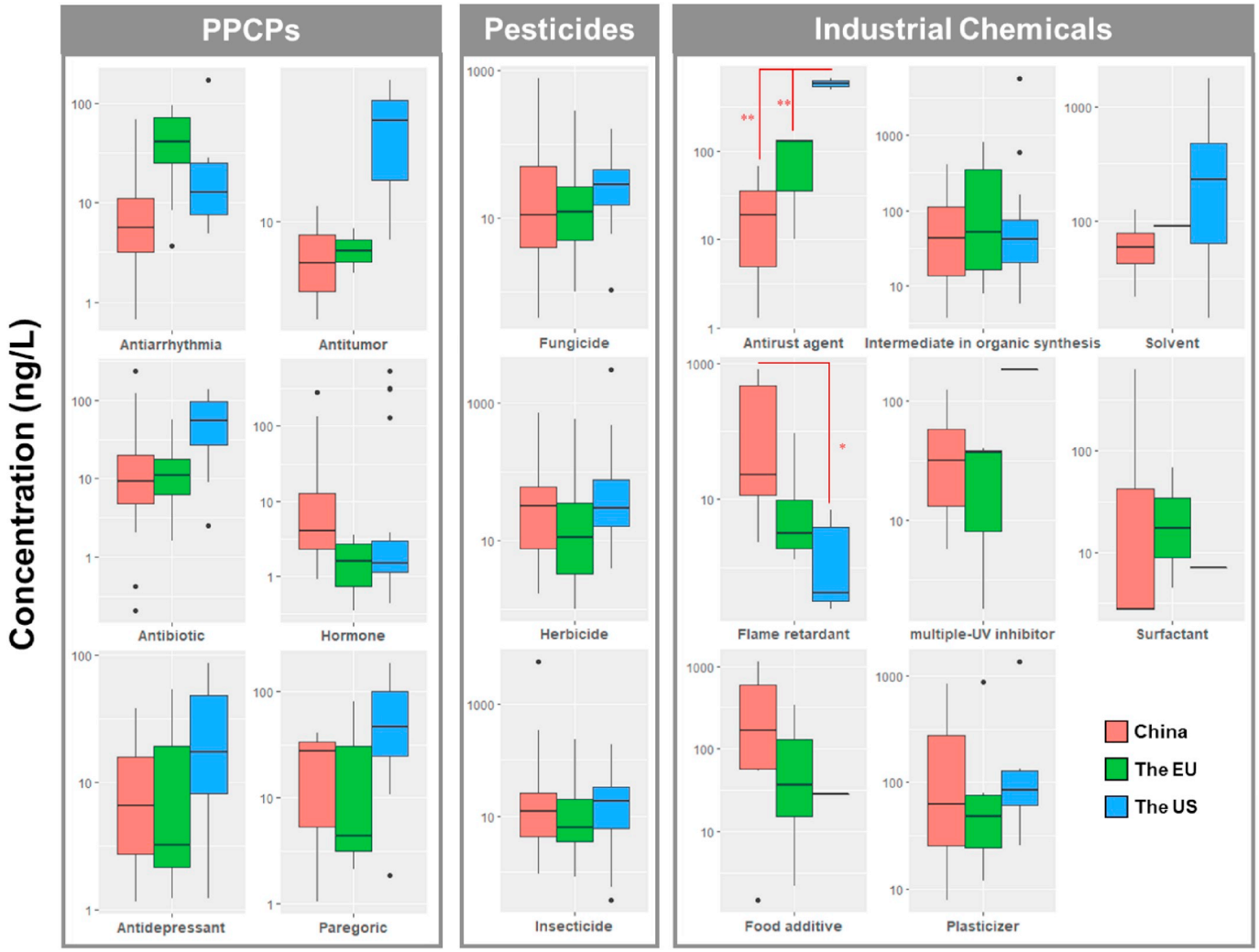

Fig. 4. Box plot representation of the median concentration of PPCPs, pesticides and industrial chemicals in China, the EU and the US. PPCPs are subdivided into antiarrhythmia, antitumor, antibiotic, hormone, antidepressant and paregoric; pesticides category contained herbicide, insecticide and fungicide; and antirust agent, intermediate in organic synthesis, solvent, flame retardant, multiple-UV inhibitor, surfactant, food additive as well as plasticizer are classified as industrial chemical. $*P < 0.05$ and $**P < 0.01$.

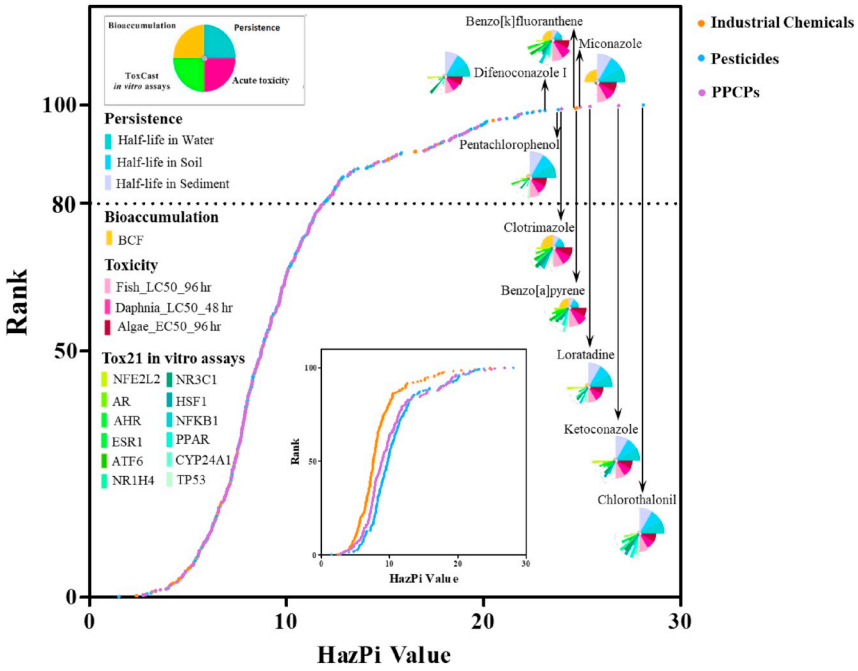

Fig. 5. Distribution curves of Aquatic HazPi score of EOPs detected in the surface water. Aquatic HazPi index jointly accounts for the persistence, bioaccumulation, toxicity and bioactivity. Orange dots are industrial chemicals; blue dots are pesticides; and purple dots are PPCPs. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

In the US, the top pollutant was AMPA (aminomethylphosphonic acid, a metabolite of glyphosate) with median concentration of 295 ng/L (Bradley et al., 2017). Finally the top pesticide pollutant in China was terbucarb with a median concentration of 699 ng/L (Bu et al., 2015).

Concentrations of industrial chemicals in surface waters in China were higher than in the EU ($P < 0.05$), based on concentrations of two co-detected analytes, triethylcitrate and 4-/5-methyl-benzotriazole (Table 1, Fig. 3, Fig. S3). Triethylcitrate, which is used as a plasticizer, had the highest median concentration in China, reaching 830 ng/L (Peng et al., 2018), which was 7.5-fold (Bradley et al., 2017) and 10.4-fold (Neale et al., 2015; Ruff et al., 2015) higher than in the US and in the EU, respectively. While the median concentration of 4-/5-Methyl-Benzotriazole, a corrosion inhibitor, was the highest in the US, reaching 494 ng/L (Bradley et al., 2017), which was 7.5-fold (Peng et al., 2018; Yang et al., 2017) and 3.7-fold (Neale et al., 2015; Ruff et al., 2015) higher compared with China and the EU. Furthermore, among the industrial chemicals ranked in the top 15% detected in the three regions, 21, 12 and 7 were detected respectively in China, the US and the EU. In China, most of the high-concentration and high-frequency industrial chemicals were used as food additives, flame retardant and plasticizers (Fig. 4, Table S9), such as sucralose (Yang et al., 2017), acesulfame (Yang et al., 2017), saccharin sodium hydrate (Yang et al., 2017), triethylcitrate (Peng et al., 2018), triethylphosphate (Bu et al., 2015; Peng et al., 2018) tris(2-chloroethyl) phosphate (Peng et al., 2018) and tris(1,3-dichloro-2-propyl) phosphate (Peng et al., 2018). In the US, they were mainly chemicals used as organic solvents and anticorrosion agents (Fig. 4, Table S9), including acetone (Bradley et al., 2017), methyl-1H-benzotriazole (Bradley et al., 2017) and 4-/5-methyl-benzotriazole (Bradley et al., 2017). Finally in the EU, food additives (acesulfame K (Neale et al., 2015; Ruff et al., 2015), sucralose (Hug et al., 2015; Neale et al., 2015; Ruff et al., 2015)) and anticorrosion and antioxidants chemicals (such as, 4-/5-methyl-benzotriazole (Hug et al., 2015; Neale et al., 2015) and methylparaben (Carmona et al., 2014)) were widely detected (Fig. 4, Table S9).

3.3. Substances with potential P and B properties detected in China, the EU and the US

About half of 45 chemicals with P and B properties had been previously reported to be vPvB (very persistent and very bioaccumulative) substances, including 2 PPCPs, 7 pesticides and 13 industrial chemicals (Table S10). Among them, 2 polycyclic aromatic hydrocarbons (chrysene and benzo[a]pyrene) have been on the Candidate List of substances of very high concern in European Chemicals Agency (ECHA) due to persistence, bioaccumulation and toxicity (European Chemicals Agency, 2018). Another 10 were well known vPvBs (PCB and PBDE congeners, DDT-related compounds and dieldrin). In addition, 10 substances had predicted vPvB properties in previous reports. They are miconazole (Gramatica et al., 2015; Scheringer et al., 2012; Strempel et al., 2012), cyhalothrin (Gramatica et al., 2015; Rorije et al., 2011), pentachlorophenol (Gramatica et al., 2015; Howard and Muir, 2010), fenpropidin (Strempel et al., 2012), clotrimazole (Scheringer et al., 2012; Strempel et al., 2012), benzo[k]fluoranthene (Gramatica et al., 2015; Strempel et al., 2012), hexahydrohexamethyl cyclopentabenzopyran (Howard and Muir, 2010; Strempel et al., 2012), phenanthrene (Gramatica et al., 2015), fluoranthene (Gramatica et al., 2015), 4-tert-octylphenol (Brooke et al., 2005; Howard and Muir, 2010).

A significant number of chemicals (23 with potential B and P substances are in red in Table S10) were difficult to classify or lacked the necessary data on persistence and bioaccumulation. For example, bis(2-ethylhexyl)phthalate (DEHP) was reported to have an aqueous hydrolysis half-life is 2000 years, parent BCF for Chlorella is 5400 mL/g wet^{-1} (Staples et al., 1997), and it is correlated with endocrine activity (Axelsson et al., 2015) and cardiotoxicity (Gillum et al., 2009); but in natural waters, the half-life of DEHP can decrease to 78 d (Staples et al., 1997) because of biodegradation. Also it has been reported to have a trophic magnification factor of < 1(Mackintosh et al., 2004). Most of the P and B substances detected in this study lacked experimental data on persistence and bioaccumulation. For example, previous research showed that cannabicyclohexanol can cause DNA damage and inflammation in directly exposed human cells in vitro (Bileck et al., 2016), but it lacks data for P and B properties. Furthermore, the herbicide terbucarb is recognized as a potential P and B substance, with highest median concentration (698 ng/L) in the Liaohe River in China, but little is known about its aquatic toxicity, persistence or bioaccumulation potential.

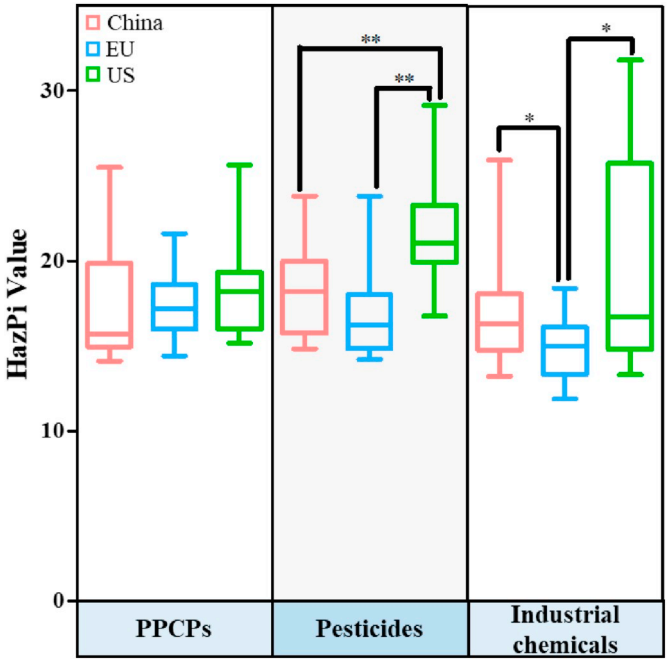

Fig. 6. Comparison of the top 20% HazPi value of detected EOPs of different usage in China, the EU and the US. *$P < 0.05$ and **$P < 0.01$.

3.4. Aquatic HazPi used in hazard assessment

A total of 148 EOPs ranked in the top 20% of HazPi value (Fig. 5), including 29 industrial chemicals, 62 pesticides, and 57 PPCPs. The Aquatic HazPi scores of chemicals in each usage category were uniformly distributed on the curve. In the case of industrial chemicals, one third of the high HazPi EOPs were flame retardants. For PPCPs, high HazPi chemicals were mostly antibiotics and hormones (23.1% and 21.2% respectively). For pesticides, high HazPi chemicals were largely fungicides, followed by insecticides, and lastly herbicides.

Furthermore, the distribution of the highly ranked chemicals in the US, the EU and China differed. For PPCPs, there were no significant differences across China, the EU and the US according to the HazPi values of EOPs ranking of the top 20% in each region (Fig. 6), but the types of the most hazardous EOPs were different. In the US, the anti-allergic, loratadine had the highest HazPi value among PPCPs due to its long half-life (180 d) in water and activation of the bio-targets of ESR1, NFE2L2, TP53 (Table S11). The hazard statements of Globally Harmonized System of Classification and Labelling of Chemicals (GHS) also shows that loratadine is considered very toxic to aquatic life with long lasting effects (H400, H410). In the EU, cannabinol had the highest HazPi value because of bioaccumulation (BCF = 10,000) and activation of the bio-targets of AR, ESR1, NR3C1, TP53, PPARG and AHR (Table S11). GSH hazard statements report that cannabinol is suspected to cause reproductive toxicity (H361). In China, the chemical with the highest HazPi value among PPCPs was clotrimazole (Table S11), which had relatively high bioaccumulation potential (BCF = 6300) and activated the bio-targets of AR, ESR1, NR3C1, HSF1, NFKB1, NFE2L2, NR1H4, TP53. The GSH information also identifies that clotrimazole is toxic to aquatic organisms with long term exposure (H400, H410), and suspected to induce reproductive toxicity (H361).

After comparing the HazPi value of the top 20% EOPs in each region ($P < 0.01$) (Fig. 6), it is suggested that pesticides concentrations in the US were a greater threat to aquatic systems than in China and in the EU. Despite having been banned for over 40 years in the US and the EU, the insecticide p,p'-DDT, was detected with a median concentration of 4.7 ng/L (Bradley et al., 2017) exceeding the US EPA guideline (1 ng/L) (Environmental Protection Agency, 1980). Also in the US, chlorothalonil and pentachlorophenol were ranked as the most hazardous EOPs in the fungicide usage category. The Aquatic HazPi score shows that chlorothalonil can be persistent in surface water and activate the gene of ESR, AR, TP53, NR1H4, PPARG. McMahon et al. (2011) reported that at water concentrations of chlorothalonil between 0.0164 and 16.4 μg/L, the liver tissues, immune cell and corticosterone level of the amphibians will be adversely affected. Meanwhile, pentachlorophenol has been banned under the Stockholm Convention (in May 2015), but remains a concern due to its persistence and adverse effects on ecosystem and human health. It continues to have limited use in the US as a wood preservative (Environmental Protection Agency, 2000). In China and the EU, the most hazardous pesticide detected was difenoconazol I (Table S12). Difenoconazol I is used as a fungicide and can be persistent in water (predicted half-life in water is 180 d). It is reported to decrease the heart rate in zebrafish larvae over 24 h at 0.5 mg/L (Mu et al., 2013). The highest HazPi insecticide in China and the EU was fipronil whose calculated half-life in water is 180 d. Gunasekara and Troung (2007) also reported that fipronil, which hydrolysis half-life is over 100 d at pH 7, is persistent in water. Fipronil has been found to be toxic to many birds and most fish, exerting sublethal effects, which range from genotoxic and cytotoxic effects, and impaired immune function, to reduced growth and reproductive success (Gibbons et al., 2015). Lastly, the highest HazPi herbicides in China and the EU were diflufenican and flufenacet, respectively. The hazards of diflufenican and flufenacet were mostly due to their persistence in water.

The hazard for the industrial chemicals in surface waters in the EU was lower than that in the US ($P < 0.01$) and China ($P < 0.05$) based on the comparison of the HazPi values of the top 20% EOPs in each region (Fig. 6). In the EU, the most hazardous industrial chemical was the flame-retardant tris (1,3-dichloro-2-propyl) phosphate (TDCPP) whose median concentration reached 93.4 ng/L (Table S13). The high HazPi value of TCDCPP was due to its persistence in water and to bioaccumulation. The calculated half-life of TCDCPP in water is 180 d, and its BCF reaches 1600. Furthermore, TCDCPP may threaten aquatic organisms and human health by inducing reproductive toxicity and neurotoxicity after prolonged exposure (Wang et al., 2015a; Wang et al., 2015b). In China, benzo(k)fluoranthene was ranked as the most hazardous industrial chemical, due to a predicted BCF of 5000, and activation of the aryl hydrocarbon receptor (AHR) pathway. With the exception of PAHs, octocrylene, a UV inhibitor in cosmetics and other products, ranked as the most hazardous industrial chemical because of its bioaccumulation. Previous studies reported that concentrations of octocrylene can reach 7000 ng/g dry weight (Bachelot et al., 2012) and 2400 ng/g lipid weight (Buser et al., 2006) in fish tissues. In the US, the industrial chemicals with the highest HazPi were all flame retardants, including legacy contaminants such as PCBs and PBDEs, with concentrations ranging from 0.1 to 7.9 ng/L. But in addition to flame retardants and PAHs, 4-tert-octylphenol, a plasticizer and antioxidant, had a high HazPi score among the industrial chemicals in the US surface water. The predicted BCF value for 4-tert-octylphenol of 1400 shows the potential to be bioaccumulative. Also, 4-tert-octylphenol may be genotoxic as well as estrogenic in *Oryzias latipes* at the concentration ranging from 20 to 230 μg/L for 21 days (Gronen et al., 1999).

3.5. The differential of distribution EOPs caused by land use

The sources of EOPs related to land use were found to differ in China (Table S14), the EU (Table S15) and the US (Table S16). In China, concentrations of 24 organic pollutants were linearly related to the area of mosaic cropland, which suggests that areas of mixed cropland, forest, and human settlements adjacent to the sampling sites for EOPs were the main source of EOPs. In the EU, cropland was correlated with the surface concentrations of 23 chemicals. Finally, urban area in the US was related to 18 organic pollutants, suggesting that it is the main source of these EOPs (Fig. 7).

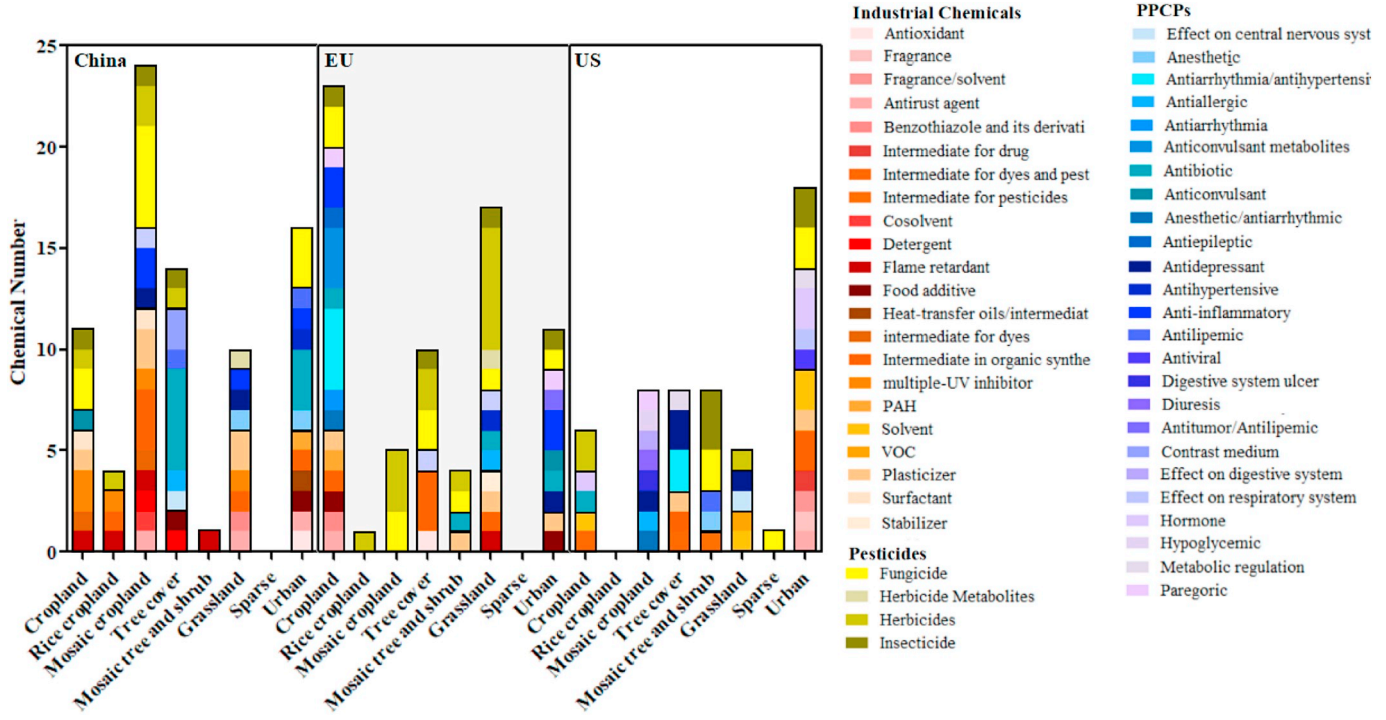

Fig. 7. Number of EOPs correlated to the area of corresponding land use ($P < 0.05$, over 80% detection accompanied with the type of specific land use usage type and the number of detected sites is > 4) in China, the EU and US. The EOPs according their usage were classified as "PPCPs", "pesticides" and "industrial chemicals" by a modified classification method (Meffe and de Bustamante, 2014).

The spatial distribution and concentration of hazardous EOPs is shown to depend on local landscape and land usages. In China, tree cover area was always correlated to most hazardous antibiotics, such as anhydroerythromycin, roxithromycin, clarithromycin, which probably resulted from the focused distribution of livestock and poultry farming in these area. Furthermore, mosiac cropland, an area of transition between city and farmland, had a significant positive correlation with high HazPi industrial chemicals, such as octocrylene, perfluorohexanoic acid, etc. While in the US, hormones like cholesterol, coprostanol and industrial chemicals (e.g., hexahydrohexamethyl), were all correlated with urban areas.

In addition, triclosan was significantly correlated to urban area in both China and the US, which suggested that the main source was likely from urban waste waters. A large number of EOPs with high HazPi values could not be related to their main source based on land use analysis since they are generated from other applications or due to insufficient monitoring data.

4. Conclusions and implications

This study investigated the levels of aquatic exposure, hazard ranking, and land use sources of EOPs in China, the US and the EU based on the literature published during 2010–2016. The aquatic HazPi index was applied to evaluate the hazard level of individual EOPs on a global scale by jointly accounting for the persistence, bioaccumulation, bioactivities and toxicity. The results show that pesticides in the US had higher water concentrations and hazard ranking compared with China and the EU, while industrial chemicals like surfactants, flame retardants, plasticizers and food additives were more prominent in China's surface water. The total EOP exposure level in the EU was lower than China or the US. The above results help us understand the distribution of pollution by EOPs; future assessments of organic pollutants could be improved by addressing the following questions: 1) since all possible pollutants in surface water cannot be entirely known, bioassays could be used to assess the hazard levels from unknown EOPs; 2) currently the data for pollutants in the surface waters is limited by detection limits, analytical methodology, and the extent of measurements over spatial and temporal scales; it would be desirable to set up a world network to monitor and assess EOPs; 3) there is a lack of experimental data on toxicity, BCF and biodegradation half-life required for hazard evaluation, an integrated data set for risk assessment should be created; 5) with a more powerful global dataset on EOPs, we would be able to evaluate how differences in chemical policies, use patterns and efforts to reduce releases, affect the EOPs in surface water.

Acknowledgements

For support, we thank National Key Research and Development Program of China (2016YFC0801701), Environmental Protection Fund of Jiangsu Province (2016017), and Nature Science Foundation of Jiangsu Province (BK20160650). X. Zhang. was supported by the Fundamental Research Funds for the Central Universities and the Collaborative Innovation Center of Regional Environmental Quality. D.C.G. Muir acknowledges financial support by the Pearl River Scholar Program of the province of Guangdong.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.104994.

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