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Review Article

Environmental Concerns and Toxicogenetic Endpoints of Priority Substances (PSs) and Contaminants of Emerging Concerns (CECs): A Comprehensive Review

[1,2*]Yi Liu, [1,2*]Muhammad Junaid, [1,2]Naima Hamid, [1]Chun-Di Chen and [1]De-Sheng Pei

[1]*Key Laboratory of Reservoir Aquatic Environment, Chongqing Institute of Green and Intelligent Technology, Chinese Academy of Sciences, Chongqing 400714, China*
[2]*University of Chinese Academy of Sciences, Beijing 100049, China*

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Corresponding Author:
De-Sheng Pei
Key Laboratory of Reservoir Aquatic Environment, Chongqing Institute of Green and Intelligent Technology, Chinese Academy of Sciences, Chongqing 400714, China
Emails: peids@cigit.ac.cn
deshengpei@gmail.com

*These authors contributed equally to this work.

Abstract: Priority Substance (PSs) and Contaminant of Emerging Concerns (CECs) exhibited a wide range of environmental and public health concerns worldwide. This review summarized the documented studies related to the current surface water occurrence, spatial distribution, ecological risks and toxicity of selected PSs, such as polycyclic aromatic hydrocarbons (PAHs) and CECs, such as Di(2-Ethylhexyl) Phthalate (DEHP) and Pharmaceuticals and Personal Care Products (PPCPs). The spatial distribution analysis revealed alarming levels of PAHs in the surface waters of Asian counties, *e.g*., 84210 ng L^{-1} in Gomti River, India, 29325 ng L^{-1} in Daya Bay, China and 1287 ng L^{-1} in Chenab River, Pakistan. As for DEHP, the highest concentrations of 13050 µg L^{-1} in Liao River, China, and 2306 µg L^{-1} in Rivers of Eastern Cape, South Africa were reported. These environmental levels of PAHs and DEHP were many folds higher than the surface water permissible levels devised by WHO and USEPA. Contrarily, the emerging PPCPs were reported in relatively lower levels in the surface waters globally, compared to that of PAHs and DEHP. Consistent with the environmental levels, PAHs and DEHP revealed alarming ecological risks in the surface water sources, compared to that of PPCPs. Regarding to the sources of PSs and CECs, PAHs emissions were mostly linked to the incomplete combustion of petroleum products, DEHP contamination was associated to its applications in consumption and production of plastic appliances and PPCPs emissions were largely related to the domestic and industrial effluents. As for toxic endpoints of PAHs, DEHP and PPCPs, all of these were reported to cause DNA damage, genotoxicity, reproductive toxicity, developmental toxicity and immunotoxicity, as revealed in reviewed *in vitro*/*vivo* studies. In addition, the current review also highlighted the existing environmental regulations to control the emissions of these pollutants to the environmental matrices. Taken together, this review concluded that despite the existing environmental regulations, the current levels of organic pollutants are still on rising, especially in Asian countries. Therefore, the strict implementation of the existing regulations is highly necessary to control these pollutants to ensure public health and ecological integrity.

Keywords: PAHs, DEHP, PPCPs, Environmental Occurrence, Ecological Risks, Toxicity

Background Information

Recent population growth and rapid economic development have imposed immense pressures on environmental resources, including the deteriorated water quality, worldwide (Han *et al*., 2016). Despite the serious threat to the freshwater resources, the water quality grading system still largely depends on the concentrations of basic organic pollution indicators, such as Biological Oxygen Demand (BOD) and Chemical

Oxygen Demand (COD) and inorganic contaminants such as ammonia (NH_4), phosphate (PO_4 and heavy metals (Han and Currell, 2016). Generally, baseline data are still elusive on the specific classes of organic pollutants, despite the fact that the past-half century has been capitalized by scientists all over the world to investigate environmental hazards of Persistent Organic Pollutants (POPs) (Loganathan and Lam, 2012), especially after the Stockholm Convention (UNEP, 2009) and Aarhus Protocol on POPs (UNECE, 1998). Water pollution decreases the availability of freshwater resources, which in return increases the pressure on demand, especially in the countries that have limited sources of fresh water, such as China. China has about one-fifth of the world's population, but only retains 5% (2.73×10^{12} m^3) of world's freshwater resources (MWR, 2015). This situation is not limited to China, many other countries are also facing serious challenges to control water pollution and overcome the water scarcity (Gleick, 2009). Di(2-Ethylhexyl) Phthalate (DEHP), Polycyclic Aromatic Hydrocarbons (PAHs) and Pharmaceuticals and Personal Care Products (PPCPs) are known as Priority Substances (PSs)/contaminants of emerging concerns (CECs), usually present in ng/L to µg/L concentrations in the aquatic environment. They have shown alarming ecotoxicological concerns in recent years (Sousa *et al*., 2017; Tijani *et al*., 2016). These ubiquitous compounds have pseudo-persistent behavior and also have potentials to trigger adverse toxicological effects due to their continuous introduction into the water resources (Wilkinson *et al*., 2017).

Existing Regulations for Priority Substances (PSs) and Contaminants of Emerging Concerns (CECs)

Based on the presence or absence of regulations, the organic pollutants are classified as PSs or CECs (Gorito *et al*., 2017; Sousa *et al*., 2017). A European environmental legislative body Water Framework Directive (WFD) defines PSs as "presenting a significant risk to or via the aquatic environment" and includes compounds, such as PAHs, Polychlorinated Biphenyls (PCBs) and *etc*. CECs comprise several types of compounds, such as PPCPs, phthalates and *etc*. (WFD, 2000). Previously, it wasn't pre-requisite to perform chemical analysis of PSs and CECs in the water bodies for environmental regulation (Tiedeken *et al*., 2017). However, increasing environmental concerns of these contaminants in the aquatic resources have greatly acknowledged their qualitative and quantitative analysis for the regulatory purpose to improve water quality and WFD has recommended continuous monitoring of these organic pollutants for all of the EU countries (WFD, 2015). The environmental regulation of PSs in the surface waters dated back to the year 2000, when WFD (2000/60/EC) launched a water policy framework to identify some chemicals that need to monitor in the environment to provide necessary mitigation measures (WFD, 2000). In the same year, The Stockholm Convention on POPs was first signed in 2001 (2455/2001/EC) that later adopted to EU legislation in 2004 (850/2004) and also ratified by 180 countries (UNEP, 2009). Five years later, the first list of Environmental Quality Standards (EQS) was published by WFD (2008/105/EC) for basic water quality parameters and that list was later revised in 2013 for PSs (2013/39/EU) (WFD, 2013). The PSs, *e.g.,* PAHs, pharmaceuticals and pesticides have been added to Annex A by WFD in 2013 and monitoring of these PSs declared compulsory in surface waters and article 16(4) of this legislation bounded the EU member states to revise the list of these PSs and their levels shall not exceed the threshold values (WFD 2013).

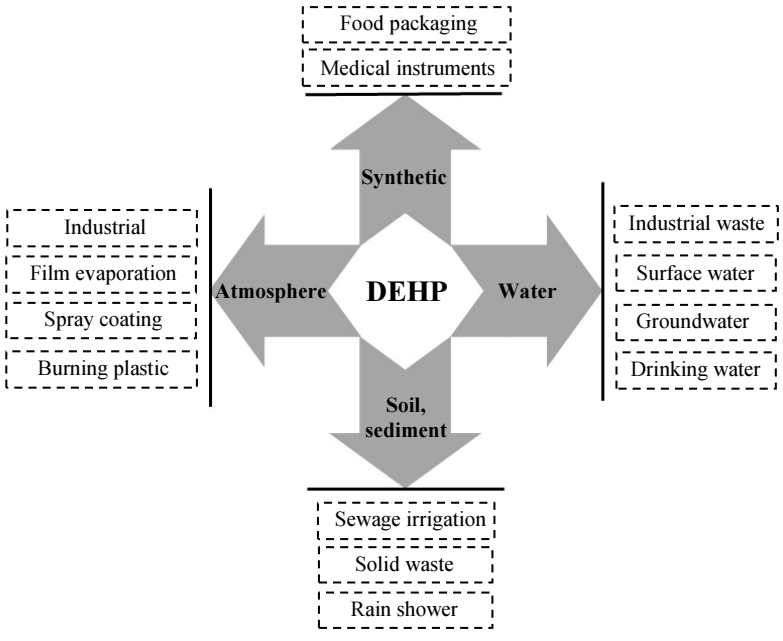
United States Environmental Protection Agency (USEPA) classified DEHP as a top-priority environmental pollutant and also listed it as B2 class compound (probable human carcinogen) (USEPA, 2000). Further, Agency for Toxic Substances and Disease Registry (ATSDR) also categorized DEHP as an epigenetic toxicant and an endocrine disruptor (ATSDR, 2002). EU also banned the use of six phthalates including DEHP in plastics in 2005 (EU, 2008). In the U.S., similar kinds of efforts were made in 2008 to ban phthalates (Magdouli *et al*., 2013). In 2000, the Ministry of Health and Welfare of Japan also restricted the use of DEHP in plastics (Suzuki *et al*., 2001; Tsumura *et al*., 2003). WFD categorized DEHP as PSs (WFD, 2013) due to the various factors, such as high detection frequency and persistence in environmental compartments (Luo *et al*., 2014) and augmented toxicity and bioaccumulation in aquatic species (Sousa *et al*., 2017). PAHs were also declared as PSs by ATSDR and WFD a long-time ago (ATDSR, 1995; WFD, 2000) and PAHs exhibited fused aromatic ring structure with mutagenic and carcinogenic properties, long-half lives and potential to generate heteroaromatic hydrocarbons after chemical reactions (Kafilzadeh, 2015; Nagy *et al*., 2013).

U.S. Food and Drug Administration (FDA) implemented the ecological risk assessment (ERA) for pharmaceuticals under the National Environmental Policy Act (NEPA) (FDA, 1969) and later Center for Drug Evaluation and Research (CDER) established the guidelines for a tiered risk assessment method (CDER, 1998). In the same year, USEPA enacted regulations for pharmaceutical industry to control their both air emissions and effluent discharges (USEPA, 1998). In 2006, European Medicine Agency (EMA) devised the first guidelines for ERA for human pharmaceuticals (EMA, 2006). Similarly, Australian Therapeutic Goods Administration (ATGA) devised the regulations and ERA for newly registered PPCPs (TGA, 2008). China

promulgated the Environmental Management Methods (EMMs) for newly produced chemicals in 2010 and recently in 2013. Recently, another similar regulation, "Environmental Management and Registration Method for Hazardous Chemicals" (MEP's order 22), was also formulated (MEP, 2010; 2012). The ingredients of drugs (including that of NSAIDs) and personal care products (PCPs) have been regulated under these laws. The livestock wastes comprising veterinary drugs and effluents have been also regulated by Ministry of Environment Protection (MEP), China (MEP, 2001). Further, the wastewater discharge containing 16 different types of pharmaceuticals, such as Ibuprofen (IBU), Sulfadiazine (SDZ) and Caffeine (CAF), have been regulated in China (MEP, 2008). Recently, WFD recommended to establish water treatment strategies and monitor 54 PSs including 49 organic pollutants and 4 metals (WFD, 2015). For CECs, no definite EQS are existed, however, the previous studies have suggested a prioritization system based on two indicators, the extent of exceedance and the frequency of exceedance of predicted no effect concentrations (PNECs) (Ohe and Dulio, 2013; Tiedeken *et al*., 2017). Recently, WFD has listed 17 CECs to their Watch List (Decision 2015/495/EU), including five pharmaceuticals, such as erythromycin (ERY) and Diclofenac (DIC), *etc.* (WFD, 2015). DIC belongs to non-steroidal anti-inflammatory (NSAIDs), which is of great concern due both to the largest over-the-counter drugs and their wide administration as pain relievers, worldwide (Shanmugam *et al*., 2014). Altogether, this section clearly listed the major global and local regulations to control the emissions of PSs and CECs.

Sources of DEHP, PAHs and PPCPs

The major sources of DEHP, PAHs and PPCPs are illustrated in Fig. 1. To track the diverse sources of organic pollutants is of immense importance to implement control measures and source base regulations (Ribeiro *et al*., 2016). Different industrial processes, such as raw material processing, manufacturing and distribution, are the possible sources of organic pollutants (Barbosa *et al*., 2016a). Multiple sources of DEHP have been reported in the literature based on its widespread applications and detection across different environmental compartments (Fig. 1A). DEHP releases into the environment through dissolution and volatilization processes during transportation, storage and production (Magdouli *et al*., 2013; Sirivithayapakorn and Limtrakul, 2008). The potential release of DEHP may attributes to its applications in PPCPs, paints, medical devices and laboratory equipment (Chen *et al*., 2008; Franco *et al*., 2011; Koniecki *et al*., 2011). Its intensive applications as plasticizer have been also reported in non-polyvinyl chloride materials, such as natural and synthetic, rubber, polyvinyl butyral, chlorinated rubber, ethyl cellulose and nitrocellulose (NTP, 2011; SPMP, 2001; Teil *et al*., 2007). Globally, the annual production of DEHP is reported as more than 2 million tons (Chan *et al*., 2007; Koch *et al*., 2003b). For example, EU produces approximately 1 million tons of phthalates each year, with 50% DEHP as a dominant compound (Lin *et al*., 2009). Similarly, 60% phthalates production with the annual potential of 250, 000 tons is attributed to DEHP in Germany and 100,000 tons of DEHP-laden waste is released into the environment (Koch *et al*., 2003a; 2003b).



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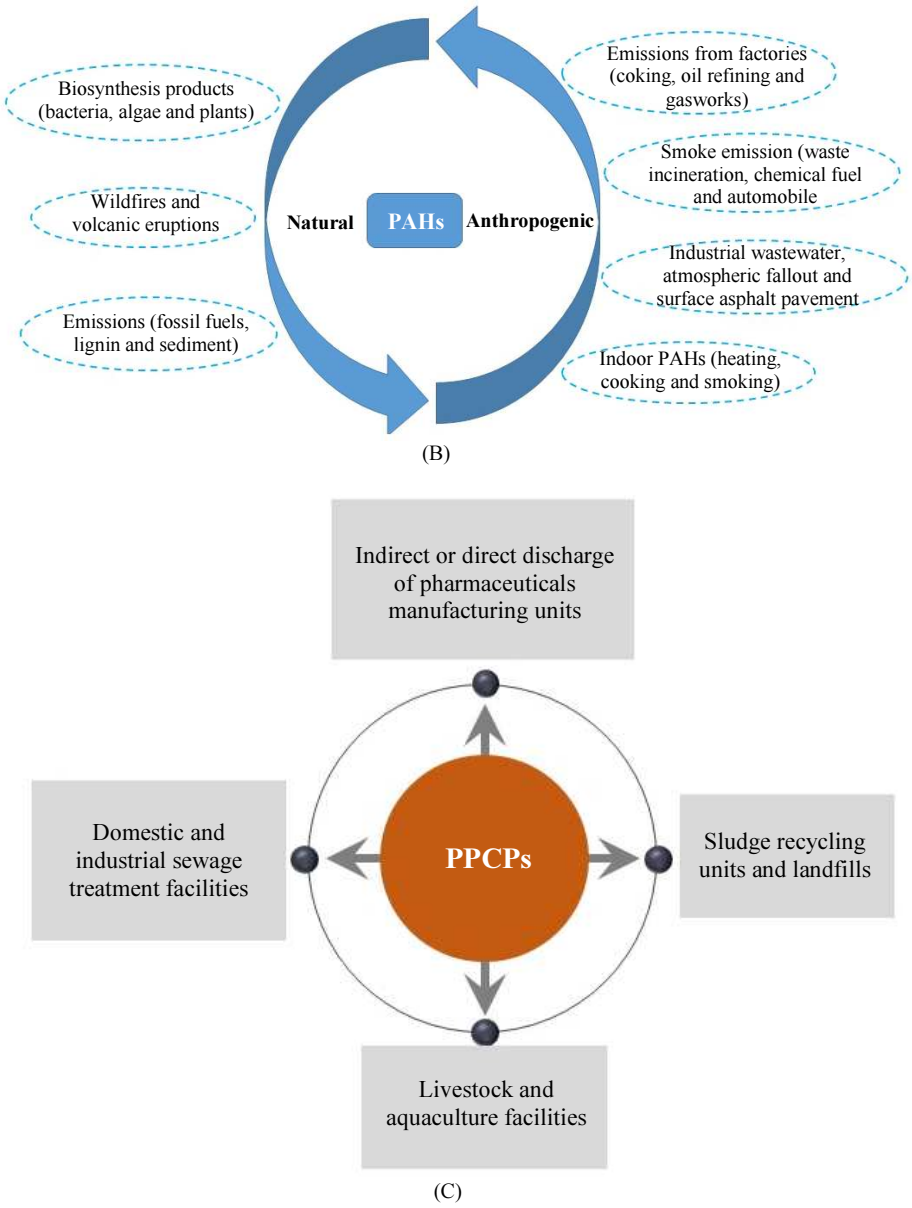


Fig. 1: Potential sources of DEHP (A), PAHs (B) and PPCPs (C)

PAHs comprise of both the natural and anthropogenic sources (Fig. 1B). The natural sources of PAHs include carbonization, hydrothermal process, forest fire and volcanic eruption and anthropogenic sources comprise incomplete combustion of fossil fuels, pyrolysis of hydrocarbon materials, the release of oil and petroleum products (Lee *et al*. 1981; Ravindra *et al*., 2008). The anthropogenic sources of PAHs are further classified as pyrogenic (combustion) and petrogenic (non-combustion). PAHs have unique characteristics, such as ubiquitous nature, resistance to degradation and long-range transportations through environmental media (Turner *et al*., 2014; Yunker *et al*., 2002). The surface water contamination of PAHs is usually linked to the industrial emissions through atmospheric deposition and industrial effluents (Han and Currell, 2016).

Regarding the sources of PPCPs, domestic wastewater and hospital effluents are the significant contributing sources for their presence in surface waters (Fig. 1C). Pharmaceuticals are not fully metabolized in the human body, therefore, the parent compound and associated metabolites excrete and make their way to Wastewater Treatment Plants (WWTPs) (Ribeiro *et al*., 2016). Agriculture run-off is also reported as a significant source of organic pollutants (Moore *et al*., 2002). Further, the farming of livestock has been also

reported to produce wastewater containing veterinary drugs that are excreted by animals (Moore *et al*., 2002). Sewage treatment facilities and leaching of dumping sites and environmental disaster are also the other possible sources PPCPs (Ribeiro *et al*., 2015). Although many of the basic water pollutants efficiently remove *via* WWTPs, the removal of organic pollutants especially pharmaceutical is still a dilemma that has attracted the significant attention of the scientific community, recently (Fattakassinos *et al*., 2015; Luo *et al*., 2014). The conventional WWTPs are not usually designed to remove organic pollutants, therefore, the introduction of such pollutants to waterways is inevitable and a serious threat for ecological and human health (Barbosa *et al*., 2016b). Tracking the point and non-point sources of organic pollutants is of immense importance to control the emissions at the source level, albeit the studies are still scarce related to specific source inventories for emerging organic contaminants.

Occurrence and Spatial Distribution of DEHP, PAHs and PPCPs in the Surface Water

DEHP

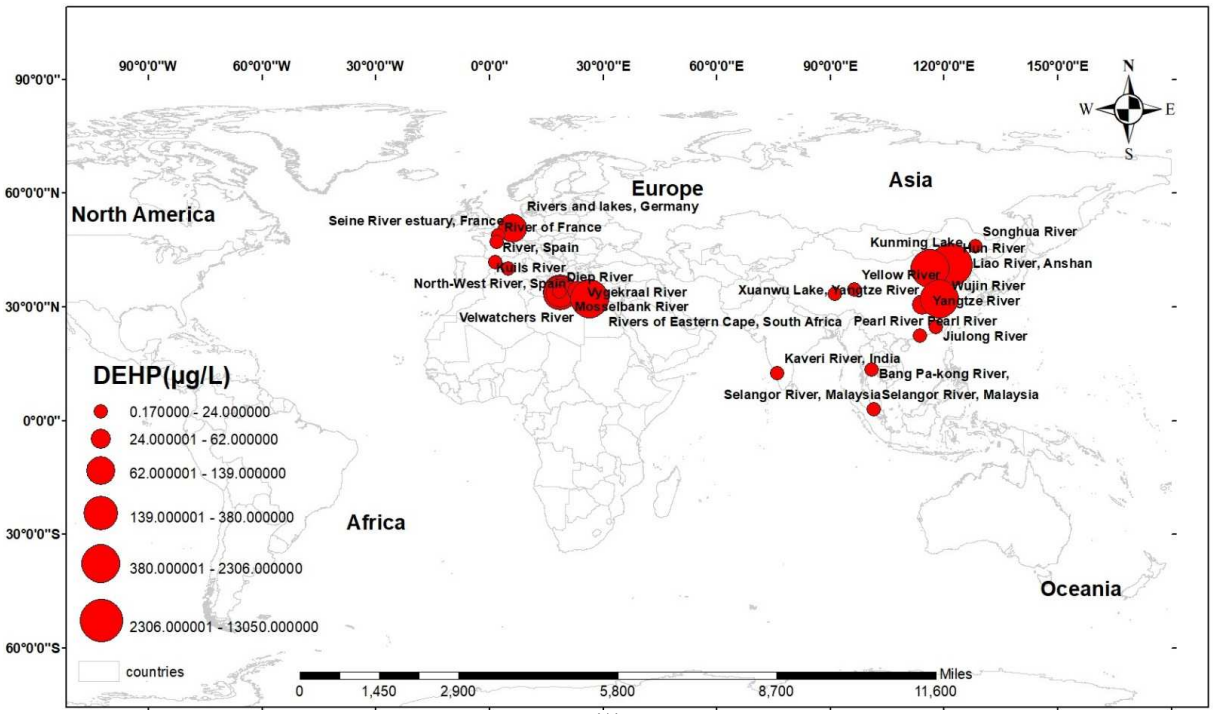
Due to the ubiquitous nature of organic pollutants, they have been detected in most of the waterways worldwide. The compositional pattern of organic compounds greatly varies according to different spatial and temporal scenarios, albeit their occurrence in the surface waters has been reported substantially higher than that of groundwater and drinking water and only a few contaminants are regulated till now (Benotti and Brownawell, 2009; Caliman and Gavrilescu, 2009; NACWA, 2012). In 2007, the European WFD has devised the permissible limit of DEHP in the surface water as 1.3 μg L^{-1} (Magdouli *et al*., 2013). Previously, alarming levels of DEHP as high as 13050 μg L^{-1} in the Liao River (China), 2306 μg L^{-1} in the Eastern Cape River (South Africa), 1390 μg L^{-1} in Kunming Lake (China), 1299 μg L^{-1} in the Xuanwu Lake (China), 380 μg L^{-1} in the Kulis River (South Africa) and 97.87 μg L^{-1} in Furu River (Japan), have been reported in different freshwater systems (An and Jin, 2000; Fatoki and Noma, 2002; Fromme *et al*., 2002; Olujimi *et al*., 2012; Shen *et al*., 2010; Yu *et al*., 2011a) (Table S1). Further, the elevated but relatively lower levels of DEHP have been also reported in other riverine systems in China, such as 54.73 μg L^{-1} in the Wuhan section, Yangtze River, 34.20 μg L^{-1} in the Hun River and 24 μg L^{-1} in the Yellow River (Li *et al*., 2015a; Sha *et al*., 2006; Wang *et al*., 2008). However, DEHP level was less in the rivers of EU countries, *e.g.*, 6.44 μg L^{-1} in the Seine River estuary (France), 1.70 μg L^{-1} in the River of France and <0.44 μg L^{-1} in North-West River (Spain) (Dargnat *et al*., 2009; Regueiro *et al*., 2008; Tran *et al*., 2015). Similarly, the lower DEHP levels have been reported at <1.10 μg L^{-1} in the Bang Pa-kong and other River (Thailand), 1.4 μg L^{-1} in the Kaveri River (India), 0.38 μg L^{-1} in the Selangor River (Malaysia) (Santhi and Mustafa, 2013; Selvaraj *et al*., 2015; Sirivithayapakorn and Thuyviang, 2010).

The main sources of DEHP in the water bodies can be attributed to the discharge of the untreated industrial wastewater, cosmetics, lubricants and adhesive wastes containing traces of plastics (Chen *et al*., 2012). The spatial distribution of DEHP levels (μg/L) in surface waters worldwide revealed elevated levels in Asian and African regions (Fig. 2A). For instance, the levels of DEHP (μg/L) were reported highest in China; Liao River, Anshan (13050 μg L^{-1}) followed by Kunming Lake (1390 μg L^{-1}) and Yangtze river (1299 μg L^{-1}) (Yu *et al*., 2011a; He *et al*., 2011a; An and Jin, 2000). Overall, the DEHP levels from the world indicated the highest loads in Asia followed by Africa, Europe and North America (Fatoki and Noma, 2002; Dargnat *et al*., 2009; Fromme *et al*., 2002; Yu *et al*., 2011a). Perhaps the main reason behind the rapid industrialization in the Asian region, especially in China. It is reported that in China, over one million tons of phthalates (including DEHP) is consumed per year, accounting for one-fifth of the global consumption (Liu *et al*., 2014).

PAHs

Regarding the environmental occurrence of PAHs, the elevated levels have been reported in the rivers those stretch through densely populated regions in China, such as Yangtze River (Chongqing and Shanghai sections), Haihe River (Tianjin), Taihu Lake (Beijing), Tonghui River (Beijing) (Han and Currell 2016). Some of the previous studies are summarized in Table S2. The maximum values of PAHs were reported as high as 43,226 ng L^{-1} in the Lanzhou section of the Yellow River (Li *et al*., 2006), 35,210 ng L^{-1} in the Tianjin section of the Haihe River (Cao *et al*., 2005), 96,210 ng L^{-1} in the Hangzhou River (Zhu *et al*., 2004), 26,920 ng L^{-1} in the Jiulong River Estuary (Maskaoui *et al*., 2002), 34,000 ng L^{-1} in the Taihu Lake (Guo and Fang, 2012), 474,000 ng L^{-1} in the Minjiang River Estuary (Zhang *et al*., 2004) and 34,338 ng L^{-1} in Humen section of the Pearl River (Yang *et al*., 2004). These reported values in different riverine systems of China are substantially higher than that of PAHs permissible values of 100 ng L^{-1} (WFD 98/83/EC) and 200 ng L^{-1}, respectively devised by WFD and USEPA (Han and Currell, 2016). Similarly, the alarming levels of PAHs have been reported in the Gomti, River, India (60-84,210 ng L^{-1}) (Malik *et al*., 2011). These high levels of PAHs can induce alarming ecological risk and acute toxicity to aquatic species. In comparison, the rivers from USA, Europe and Australia have been reported with lower PAHs levels than those in Asia, as reviewed previously (Han and Currell 2016). For example, PAHs concentrations

were detected at 12.4 to 2321 ng L^{-1} in the Sarno River, Italy (Montuori and Triassi 2012), 4-36 ng L^{-1} in the Seine River, France (Fernandes *et al*. 1997), 5.1-12 ng L^{-1} in the Brisbane River, Australia (Shaw *et al*., 2004) and 12-434 ng L^{-1} in the lower Mississippi River, USA (Mitra and Bianchi 2003).



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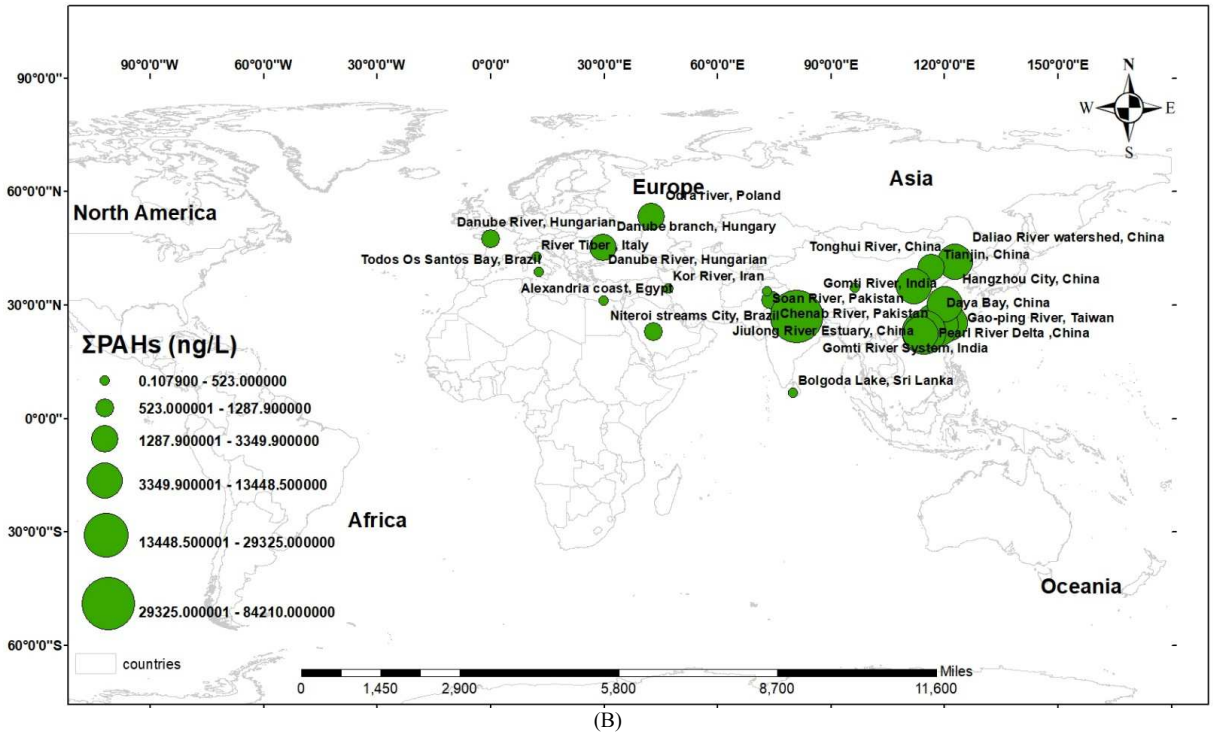


(B)

Fig. 2: Spatial distribution of DEHP (μg/L)(A) and Σ PAHs (ng/L)(B) in the surface waters

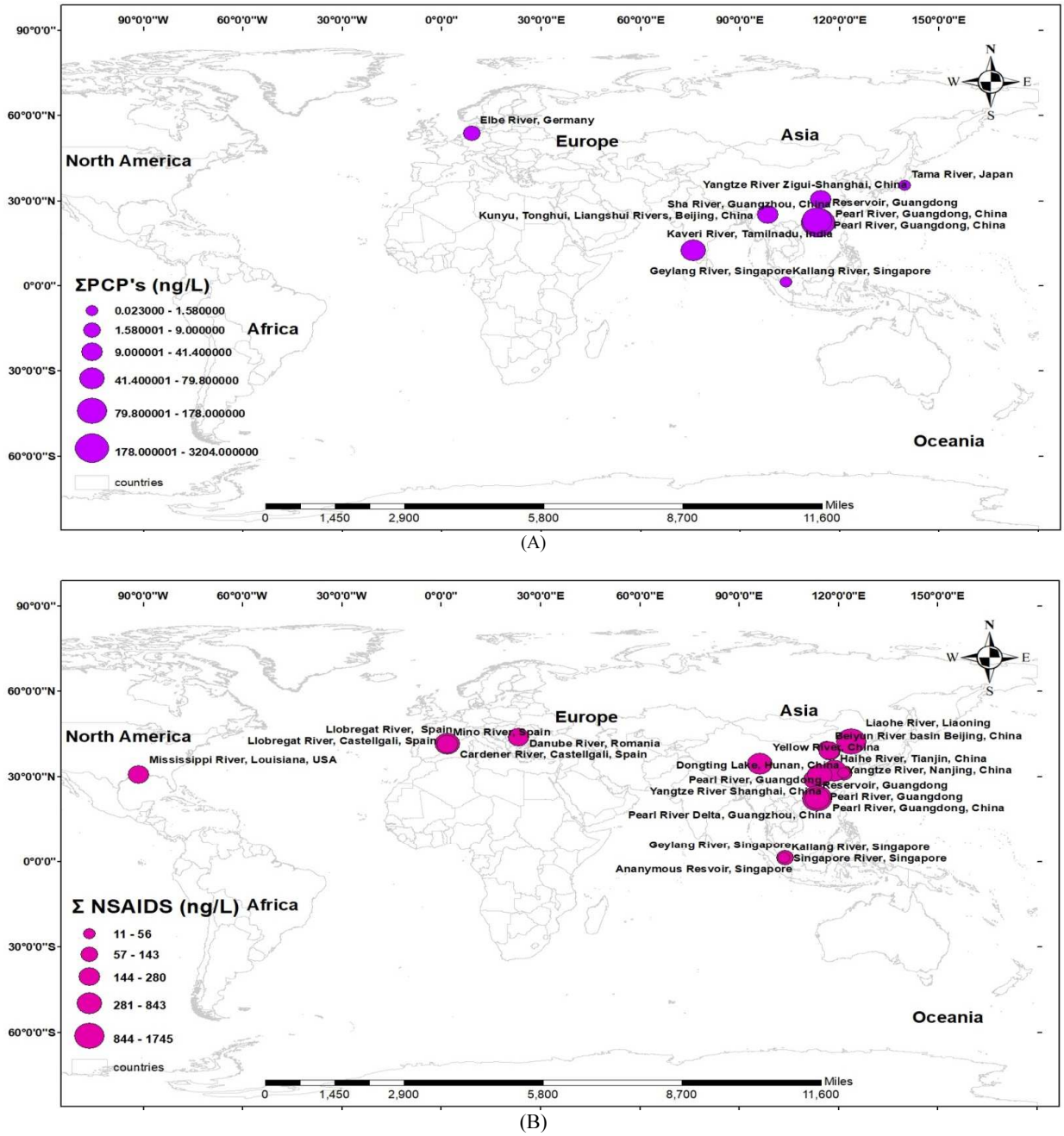
The major route of PAHs entering in the water bodies is the direct release of the untreated domestic waste water, industrial discharges, petroleum spills and through atmospheric deposition (Hamid *et al*., 2016). Due to the hydrophobic nature of PAHs, in the aquatic environment it rapidly tends to become associated with the particulate matter and deposited in the sediments (Srinivasa *et al*., 2005). Globally, a comparative spatial distribution analysis revealed that the environmental levels of PAHs in surface water were in the following order: India> China> Poland> Taiwan> Pakistan (Fig. 2B). ∑PAHs concentration levels ranged between 0.10 ng L^{-1} (Todos os Santos Bay, Brazil) and 75570 ng L^{-1} (Gomti river system, India) (Jose celino *et al*., 2012). Industrialization and urbanization have escalated rapidly during the last few decades in India. The massive biomass burning to meet fuel requirements aggravates the situation (Malik *et al*., 2004). In contrast with, China is considered to the 3rd major PAHs emitter country because of large coal production (Zhang and Tao, 2009). Worldwide, the PAHs pollution was in the order of Asia>Africa> Europe respectively.

PPCPs

Wastewater from domestic and industrial WWTPs is mainly responsible for the occurrence of PPCPs in the aquatic environment due to the poor removal efficiency of conventional treatment plants for PPCPs (Deblonde *et al*., 2011; Ke *et al*., 2015). Further, improper dumping of unused and expired pharmaceuticals also directly contribute to the abundance of pharmaceuticals' in the waterways, which are basically originated from toilet sinks or solid waste (Aydin and Talinli, 2013; Barbosa *et al*., 2016a; Gorito *et al*., 2017). Aquatic environment has been reported with the contamination of more than 80 PPCPs and several metabolites (Heberer, 2002; Jelic *et al*., 2011). The basic reasons behind the wide existence of PPCPs are the ease of excess and product proliferation, which significantly contribute to the invasion of these xenobiotics to the natural and built environments (NACWA, 2012). However, the detection of PPCPs in the aquatic environment is not new, as they have gained considerable attention during last decade due to their alarming levels, diverse and growing ecotoxicological risks in the environment (Wilkinson *et al*., 2017). For instance, Jones *et al.* (2002) modelled the concentrations of the frequently used 25 pharmaceuticals including antiepileptic and analgesic drugs in the aquatic environment of the U.K and conservative estimates revealed the concentration was exceeding 1 ng L^{-1} for most of the pharmaceuticals. Pharmaceuticals used for the treatment of different disease, such as antidepressant, asthma, central nervous system stimulus and cholesterol-regulating medication are also detected in the surface waters of U.S. (CDC, 2010). In 2000, U.S. Geological Survey conducted a comprehensive study on 95 most common PPCPs in 136 different streams and rivers running through the urban centers of U.S. The findings of this survey generally revealed low levels of PPCPs in surface waters and even lower than that of drinking water quality standards. However, the detection frequency of PPCPs was as high as 82 out of 95 total PPCPs (Buxton and Kolpin, 2005; Kolpin *et al*., 2002). Further, the physiologically active compounds were also found in the surface waters that were known to be endocrine disruptors. In addition, the median number for PPCPs mixture found in an individual river was 7 and the maximum number was 38, implying the combined or co-existence of these compounds (Kolpin *et al*., 2002). PPCPs can be further classified into several categories and this review included two of them, *i.e.* PCPs and NSAIDs. The comparative highest environmental levels of NSAIDs and PCPs are listed in Table S3 and S4. NSAIDs, *e.g.* IBU, NAP and DIC are easily accessible, commonly prescribed and highly consumed drugs, worldwide. Recently, the environmental concentration of NSAIDs has been reported to be constant over the years in specific regions. The median levels of IBU and NAP have been measured at 200 and 550 ng L^{-1} in the surface water samples from canals of Canada and New Jersey, respectively (Li, 2014). Further, the concentration of PCPs, such as synthetic musks, *e.g.,* musk xylene (MX) and musk ketone (MK), typically ranged between 150-16700 ng L^{-1} and these PCPs have widely used in cosmetics, lotions, perfumes, soaps and deodorants (Lee *et al*., 2010; Roosens *et al*., 2007).

In China, the pharmaceutical fraction of PPCPs revealed wide occurrence in the major riverine systems, such as Yangtze River (Zhou *et al*., 2011), Pearl River (Peng *et al*., 2008), Hai River, Liao River and Yellow River (Wang *et al*., 2010). Due to the dilution effect of rainfall, the median concentrations and detection frequency were reported to be lower during the high flow seasons than that of low flow seasons (Peng *et al*., 2008). Further, the sampling sites near metropolis appeared more contaminated with pharmaceuticals because of the direct disposal of pharmaceuticals to the surface waters *via* untreated wastewater from WWTPs and domestic sources (Wang *et al*., 2010; Yu *et al*., 2011b). Similarly, the elevated levels of pharmaceuticals were reported in the Rivers from Brazil (Stumpf *et al*. 1999), Japan (Nakada *et al*., 2008), Korea (Kim *et al*., 2007), U.S. (Kolpin *et al*., 2004) and U.K. (Thomas and Hilton, 2004). Comparatively, the Vantaa River in Finland appeared with low concentrations of pharmaceuticals (Vieno *et al*., 2007). For PCPs, the elevated

concentration was reported in the urban rivers of Pearl Delta region, Guangzhou. PCPs, such as Methylparaben (MP) and Propylparaben (PP), Triclosan (TCS) and Triclocarban (TCC) were detected with high frequency (Liu and Wong 2013; Peng *et al*., 2008; Zhao *et al*., 2009). Similarly, TCS and TCC were also reported in the Liao River, Hai River, Yellow River, Pearl River and Dongjiang River in China (Zhao *et al*., 2013). The Shanghai section of the Yangtze River was also reported with elevated concentrations and detection frequency of synthetic musks (Zhang *et al*., 2008). The extremely high concentration of TCS was reported in the Tamiraparani River, Kaveri River and Vellar River in India (Ramaswamy *et al*., 2011).



(A)

(B)

Fig. 3: Spatial distribution of ΣPPCPs levels (ng/L) in terms of Personal Care Products (PCPs) (A) and Non-Steroid Anti-Inflammatory Drugs (NSAIDs) (B) inthe surface waters worldwide. The maximal reported concentrations of DEHP in the surface waters of different riverine systems are used to develop this map. Σ PCPs included Methylparaben (MP), Propylparaben (PP) and Musk Xylene (MX) and Σ NSAIDs included Naproxen (NAP), Ibuprofen (IBU) and Diclofenac (DIC)

There are few limited studies reported in surface water of PCPs, worldwide. The spatial distribution analysis of the reported PCPs in the surface waters clearly showed that the rivers in Asia are appeared to be more polluted with PCP's than the rivers in Europe and Africa (Fig. 3A). In China, the Liaohe River, Liaoning was found the maximum levels reported (123.875 ng L^{-1}), followed by the Huangpu River, Shanghai (121.5 ng L^{-1}) and the Yangtze River, Nanjing section, (118.73 ng L^{-1}) (Liu *et al*., 2015a; Gao *et al*., 2016; Yang *et al*., 2011). NSAIDs enter in the aquatic environment is through the untreated waste-water coming from the pharmaceutical industries. However, the residues contain trace levels of NSAIDs. The spatial distribution of NSAIDs showed that the highest concentration was found in the Liaohe River, Liaoning (1003.7 ng L^{-1}) followed by Pearl River, Guangdong (1475 ng L^{-1}) and Cardener River, Castellgali, Spain (484 ng L^{-1}). (Liu *et al*., 2015a; 2015b; Chitescu *et al*., 2015) (Fig. 3B). Limited studies are available for NSAIDS creates a gap and difficult to define the global distribution pattern. Therefore, comprehensive quantification evaluation is required to assess the toxicity in the aquatic environment.

Ecological risks of PAHs, DEHP and PPCPs

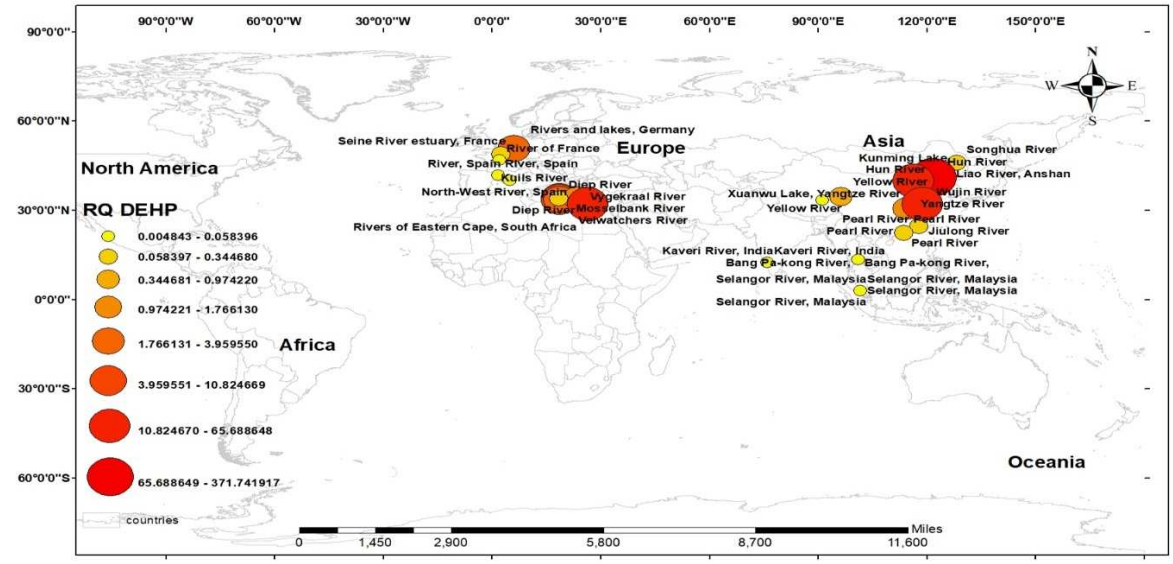
The presence of pollutants in the aquatic environment has been reported to cause ecotoxicological risks, which is yet elusive for several organic contaminants in many surface waters resources and hotspot locations, worldwide (Gorito *et al*., 2017). The lower concentration of organic pollutants may not capable of inducing the acute toxic effects, albeit chronic exposure can cause adverse impacts that are more difficult to investigate (Tijani *et al*., 2016). Contrarily, previous studies revealed that even the low concentrations of organic pollutants have potentials to impair biological functions in aquatic species. In addition, the bioaccumulation of organic pollutants in the aquatic species can also cause adverse impacts by disturbing immune system and endocrine disruption, which can lead to the neurological, reproductive and developmental abnormalities (UNESCO, 2015).

Several methods have been devised till now to quantify the ecological risks of organic pollutants to the aquatic species. The most common method is to calculate Risk Quotients (RQs) based on spatial exposure by using Measured Environmental Concentrations (MECs) and compared them with the Predicted No-Effect Concentrations (PNECs) for acute exposure or chronic exposures (Slobodnik *et al*., 2012; Tousova *et al*., 2017). The RQs were calculated as the ratio between the maximum MECs (95%) and the lowest PNECs, which actually highlight the levels ecological risks associated to a specific class of pollutants (Pc *et al*., 2011). Further, the ecological risks are also calculated by using the guidelines devised by EMA. In which the RQs are extracted as the ratio between Predicted Environmental Concentrations (PECs) and PNECs (EMA, 2006). For a better understanding, the ecological risks are usually classified on the basis of RQs, such as the values < 0.1 indicating the low-level risk, 0.1-1 meaning the medium-level risks and the values >1 indicating the high-level risks (Hernando *et al*., 2006; Paiga *et al*., 2016).

The lack of ecological risk inventory for acute and chronic adverse effects of organic pollutants in the aquatic environment demands precautionary measures (Deblonde *et al*., 2011; Gavrilescu *et al*., 2015). Ecological risk/hazard assessment is to investigate the changes in aquatic species as result of exposure to environmental stressors, such as organic contaminants (Ogbeide *et al*., 2015). The tracking of ecological risks of organic pollutants is of critical importance to regulate the PSs and CECs and the adverse effects may accumulate continuously to cause irreversible molecular damages to the aquatic ecosystems (Jjemba, 2006). Another alarming concern related to ecological risk is the synergistic interactions of organic pollutants that can cause unexpected adverse impacts on the aquatic species (Aydin and Talinli, 2013; Dai *et al*., 2015).

We also calculated the ecological risks of DEHP, PAHs and PPCPs in terms of RQs using MECs and PNECs reported in the surface waters, worldwide. The spatial distribution of RQs for DEHP indicated that the highest risks were observed in terms of RQs in the rivers of China, such as Liao River, Anshan (371.7) followed by Kunming Lake (39.5) and Yangtze River (37) than the river present in South Africa (65.6) (Fig 4a). DEHP is the most ubiquitous chemical phthalate in the aquatic environment with the ability to pose high level risks in the ecological environment. Based on the calculated high level risks found in China's surface water, necessary mitigation actions should be taken by the government agencies to overcome the associated effects (Chen *et al*., 2012). Globally, for the estimation of the ecological risk caused by PAH's in surface waters, the results of spatial distribution showed that RQs order was in accordance with the PAHs levels *i.e.* India (311) > China (110) > Poland>(38.5) Taiwan (17.5) > Pakistan (5.3) respectively. While lower level risk reported inthe rivers of Brazil, Italy and Europe (Fig 4b).

In comparison with the risk calculated for PAHs and DEHP, PCP's showed relatively low levels. The low-level RQs range (0.001-0.2) were extracted for PCPs reported in the surface waters of different rivers worldwide (Liu and Wong, 2013; Yu *et al*., 2011b) (Fig 5a). Likewise, for NSAIDs, the calculated RQs showed negligible risk (0.001-0.2) (Fig 5b). Contrarily, some of the previous studies revealed alarming ecological risks in the surface water resources associated to NSAIDs and other pharmaceuticals (Nie *et al*., 2015; Xu *et al*., 2013).



(A)

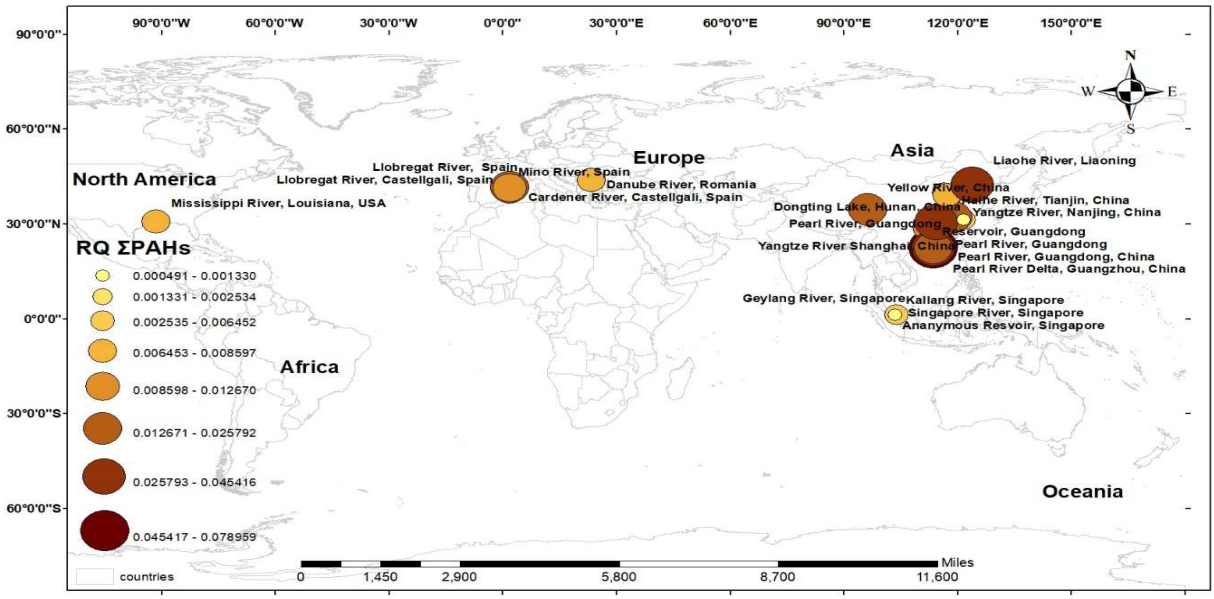


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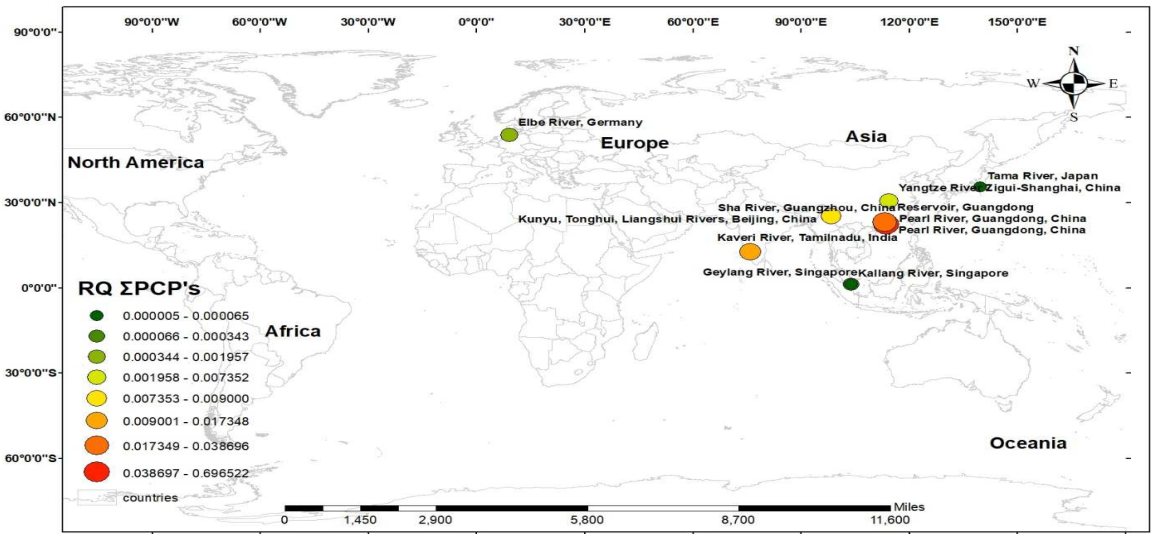
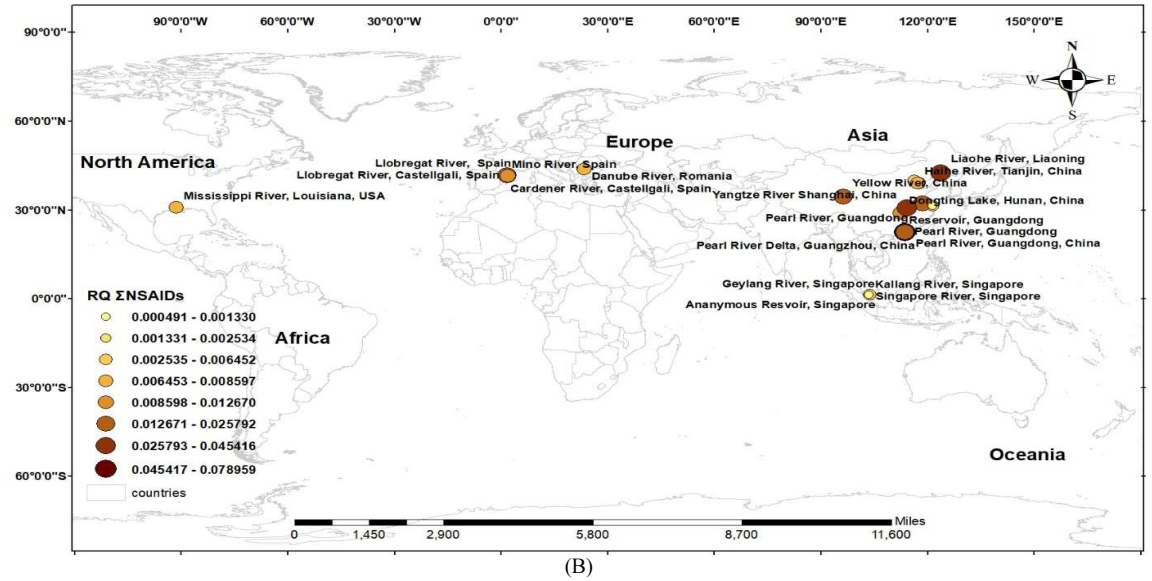
Fig. 4: Spatial distribution of ecological risks in terms of risk quotients (RQ) of DEHP (A) and ΣPAHs (B) observed in the surface waters worldwide. RQs were calculated as a ratio of Measured Environmental Concentrations (MECs) and Predicted no Effect Concentrations (PNECs) of DEHP and PAHs reported previously. MECs used in this study for ecological risk assessment of DEHP and PAHs are given in Table S1 and S2. PNECs for DEHP and PAHs were respectively extracted from Liu *et al*. (2016 and Cao *et al*., 2005)

Liu *et al.* (2016) performed ERA of DEHP in surface waters of China and found that DEHP caused elevated risks to the reproduction and other biochemical functions in aquatic species. Yan *et al.* reported that 3-ring and 4-ring PAHs induced higher ecological risk than 2-ring, 5-ring and 6-ring PAHs based on their corresponding environmental levels in Hai River basin China (Jia *et al*., 2016). A study from Denmark evaluated the ecological risk of 25 commonly used pharmaceuticals in the aquatic environment and RQs higher than 1 were reported for IBU, paracetamol and acetylsalicylic acid (Stuerlauridsen *et al*., 2000). Similarly, the RQs of mefenamic acid, oxytetracycline and amoxicillin in the Rivers of U.K. were also higher than 1 (Jones *et al*.,

2002). Another comprehensive study from France investigated 120 pharmaceuticals and their metabolites in the aquatic environment and 49 pharmaceuticals and 14 metabolites needed immediate control on the basis of their bio-chemical properties and PECs (Besse and Garric, 2008). A prioritization approach based study on 200 drugs was conducted in the U.S. that highlighted montelukast sodium and levothyroxine with the highest scores (Dong *et al*., 2013). Similarly, a ranking based study was performed on 39 pharmaceuticals in China, which revealed DIC and IBU with elevated concerns among investigated pharmaceuticals (Sui *et al*., 2012). Further, NSAIDs and lipid-lowering drugs were respectively revealed 100% and 71% as priority drugs, while for antibiotics it was only 32%. This study concluded that NSAIDs posed the highest ecological risks in aquatic systems in China (Sui *et al*., 2012). Similarly, the pharmaceuticals, such as amoxicillin, sulfasalazine, trimethoprim, oxytetracycline and erythromycin, also showed elevated ecological risks (RQs values > 1) in different aquatic environments in China (Chen *et al*., 2015).



(A)



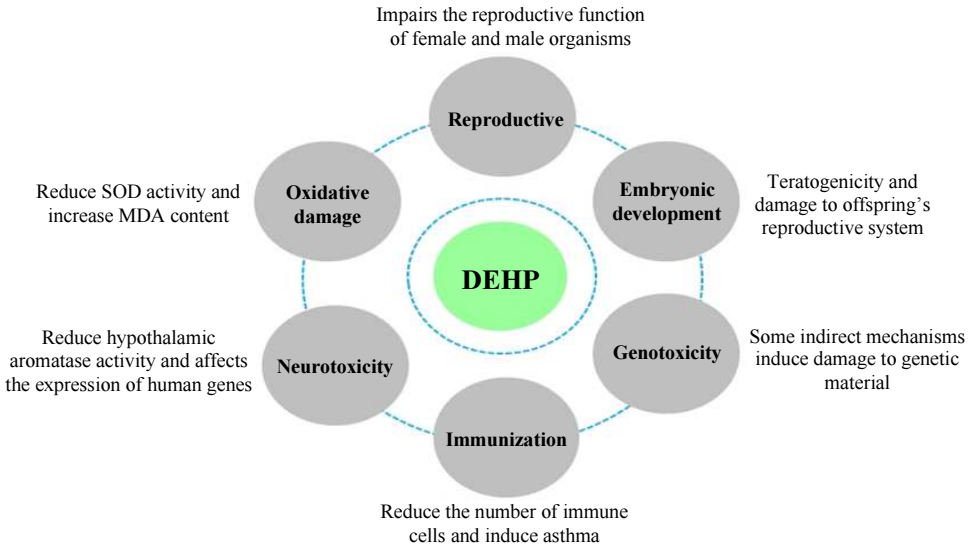
(B)

Fig. 5: Spatial distribution of ecological risks in terms of Risk Quotients (RQ) of ΣPCPs (A) and ΣNSAIDs (B) observed in the surface waters worldwide. RQs were calculated as a ratio of Measured Environmental Concentrations (MECs) and Predicted no Effect Concentrations (PNECs) of ΣPCPs and ΣNSAIDs reported previously. MECs used in this study for ecological risk assessment of ΣPCPs and ΣNSAIDs are given in Table S1 and S2. PNECs for PCPPs were extracted by Barbosa *et al*. (2016a). ΣPCPs included Methylparaben (MP), Propylparaben (PP) and Musk Xylene (MX) and ΣNSAIDs included Naproxen (NAP), Ibuprofen (IBU) and Diclofenac (DIC)

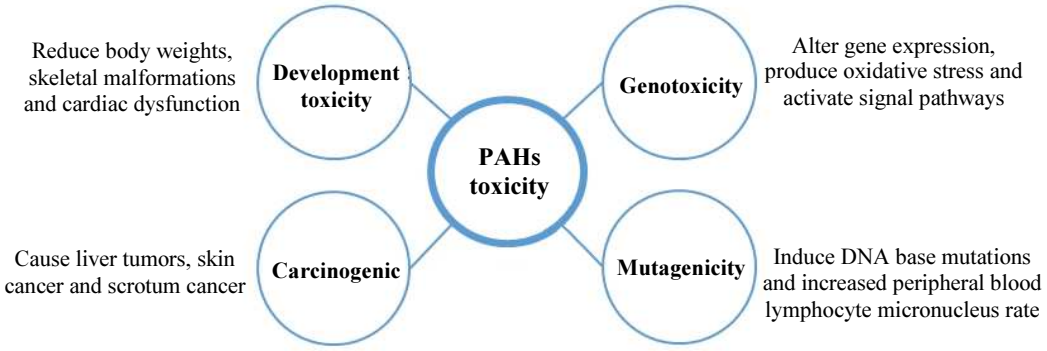
Potential Toxicity of DEHP, PAHs and PPCPs in Vitro/Vivo

DEHP contamination and associated toxicity caught a considerable amount of attention of the scientific community because of its ubiquitous presence in different environmental compartments (Caldwell, 2012). Although a significant number of previous studies have revealed the potential toxicity of DEHP, the researchers recommended for further in-depth studies to understand conclusive toxic hazards of DEHP after acute and chronic exposures (Magdouli *et al*., 2013). The general toxicological concerns of DEHP exposure are illustrated in Fig. 6A. DEHP is well known as an endocrine disruptor. It can alter the regulation of reproductive hormones in rat, cause hyperplasia in the Leydig cells, and disturb the systematic physiology (Akingbemi *et al*., 2004; Sharpe 2001). Further, the speculation exists that the acute toxicity of DEHP is relatively low, whereas chronic exposure can induce drastic effects both *in vitro/vivo* (Shea, 2003). Further, the inevitable evidence also showed the genotoxicity caused by DEHP through different signaling pathways, such as Peroxisome Proliferator-Activated Receptor (PPAR) and pregnane X receptor (PXR) (Desvergne *et al*., 2009; Hurst and Waxman, 2004). The PPAR regulates the energy homeostasis and is also responsible for the regulation of hormones involved in the metabolism of lipid, carbohydrates and xenobiotics (Singh and Li, 2011). As a result of PPAR activation after DEHP exposure, other nuclear receptors, such as the Vascular Endothelial Growth Factor A (VEGFA), Estrogen Receptor 1 (ESR1) and Retinoid X Receptor (RXR), are also activated, which play critical roles in hepatocarcinogenesis and atherosclerosis (Botelho *et al*., 2009; Feige *et al*., 2010). Further, DEHP promoted the lipid accumulation in HepG2 cells *via* activating the SREBP-1c and PPAR α-signaling pathways (Wang *et al*., 2016). DEHP can cause apoptosis and down regulate lactotransferrin in MCF-7 and MDA-MB-231 cell lines (Tanay *et al*., 2014) and induce hepatocellular adenomas in mice (Takashima *et al*., 2008). Previous studies also showed that DEHP exhibited potential to induce developmental toxicity and disturb the balance of Thyroid Hormones (THs) through activation of HPT axis pathway in zebrafish at Environmentally Relevant Concentrations (ERCs) (Gao *et al*., 2016; Ma *et al*., 2017).

The general view of PAHs mediated toxicity is highlighted in Fig. 6B. The toxic impacts of PAHs exposure have been immensely investigated because of their known genotoxic, carcinogenic and mutagenic nature (Kim *et al*., 2013). Some of PAHs congeners are not classified as the carcinogen, albeit they may induce synergistic toxic impacts (Staal *et al*., 2007). PAH binary mixtures revealed synergistic effects on cell cycle blockage and apoptosis in HepG2 cells (Staal *et al*., 2007). The dermal exposure of rats to petroleum products containing high molecular weight (HMW) PAHs can induce developmental toxicity, such as reduced body weights, skeletal malformations and other teratogenic effects (Mackerer 1996). Another study highlighted that the exposure to individual PAHs: naphthalene (Nap), phenanthrene (Phe), Benzo(a)Anthracene (BaA) and benzo(a)pyrene (BaP) altered the molecular markers in the whole blood of rat and these molecular alterations can be used for discriminating different PAHs congeners (Jung *et al*., 2011).



(A)



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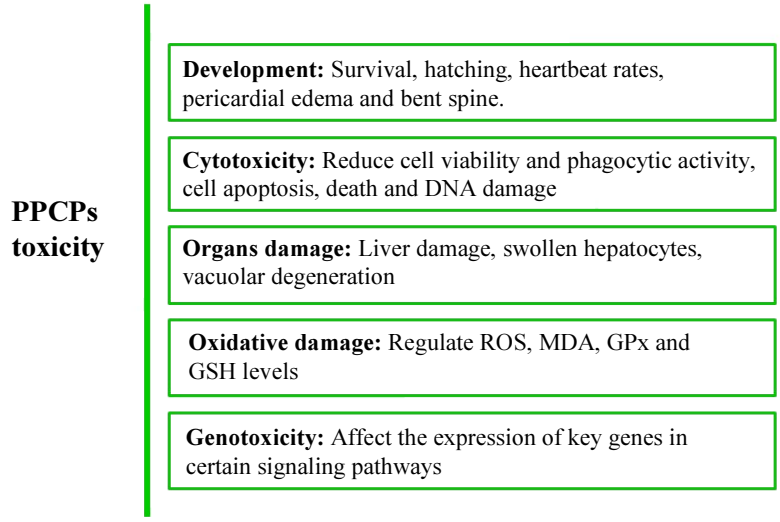

(C)

Fig. 6: Toxicological concerns of DEHP (A), PAHs (B) and PPCPs (C) revealed in different *in vitro*

Hook *et al*. (2010) reported that the PAHs exposure altered the genetic expression of *cyp1a3* in the liver of trout fish. Further, the enzymes involved in xenobiotic metabolism and immune systems, such as GSTs, were also significantly altered, which might be an indicator of oxidative stress, PAHs congeners induced genetic toxicity through activation of PPAR and Mitogen-Activated Protein Kinase (MAPK) signaling pathways in liver tissues of exposed rats (Jung *et al*., 2013). PAHs with similar structures induced comparable levels of genetic alterations, which was ascribed to the same metabolic pathway, such as cytochromes P450 (CYP450) associated oxidation. Structural variations in PAHs can induce diversified developmental abnormalities and skeleton malformations in fish (Huang *et al*., 2013; Zhang *et al*., 2012). A transcriptome analysis based study revealed that exposure to BaA altered the genetic expressions *hox* and *fox* in zebrafish and these genes control the skeletal development in zebrafish. The genetic expression of *hox* was also altered by other PAHs congeners, such as pyrene (Pyr) and benzo[b]fluoracene (BbF) (Goodale *et al*., 2013; Hawliczek *et al*., 2012). The *pax6* gene that is responsible for the morphogenesis of eye was also found with abnormal expressions after exposure to Phe (Huang *et al*., 2013). Further, exposure to BaP (a model carcinogen) can induce negative effects on the Sonic Hedgehog (SHH) signaling pathway in rockfish, which also play a crucial role in skeleton development (He *et al*., 2011a).

PAHs commonly plays an important role through Aryl hydrocarbon Receptor (AhR) pathway and alters the expression levels of CYP450 family enzymes (Staal *et al*., 2006; Xie *et al*., 2017). However, the Low Molecular Weight (LMW) PAHs (3- and 4-ring), such as Fluorene (Flu), Acenaphthene (Ace), Acenaphthylene (Acp) and Phe, showed no affinity to AhR (Xu *et al*., 2015). Although 3-

ring Phe revealed no AhR activity, its exposure at elevated doses can cause developmental effects on cardiac dysfunction in zebrafish. These studies suggested that AhR pathway may not be the only mode of action associated with PAHs toxic impacts (Incardona *et al*., 2004). In addition, the exposure to BaA, BbF and BaP also caused AhR mediated cardiac toxicity in fish. Whereas, Benzo[k]Fluoranthene (BkF) and Pyr were reported to induce cardiac malformations *via* the signaling pathways other than AhR (Huang *et al*., 2012; Incardona *et al*., 2011). Estrogen receptor (ER) pathway is also activated after exposure to BaP through the upregulation of *cyp19* aromatase, which might increase ER activity and ultimately induced the developmental toxicity in zebrafish (Hoffmann and Oris, 2006).

Exposure to the elevated levels of PPCPs may lead to the subtle effects (Fig. 6C). The continuous introduction of PPCPs to the environment and their accumulation in animals can induce irreversible toxic effect, *e.g.* DIC caused a substantial decline in the population of white-necked vultures in Pakistan (Brausch and Rand, 2011; Oaks *et al*., 2004). Certain pharmaceuticals act as endocrine disruptors and cause reproductive and developmental toxicity through the induction of vitellogenesis in males (the generation of vitellogenin in plasma), intersex phenomenon, feminization of males and infertility (Lai *et al*., 2002). Among PCPs, UV filters and parabens also act as endocrine disrupting chemicals (Gomez *et al*., 2005). Further, the pharmaceuticals: TCS, TCC, GEM, CAF also exhibit potentials to disturb the endocrine system in different fish and other aquatic species (Foran *et al*., 2000; Kudrjashov *et al*., 2010; Rosal *et al*., 2010). In addition, the reduced hatching rates were observed in Japanese medaka after exposure to propranolol (Huggett *et al*., 2002). The exposure to synthetic musks and Carbamazepine (CBZ) induced oxidative stress in rainbow trout and goldfish (Fang *et al*., 2012; Li *et al*., 2010). Further, DIC induced gill disruptions and renal lesions in rainbow trout (Schwaiger *et al*., 2004). In addition, the mixture toxicity of CBZ, DIC and IBU on *Daphnia magna* revealed synergistic effects that were significantly higher than that of the individual pharmaceuticals (Cleuvers, 2003). Bioaccumulation of PPCPs is also responsible for their innate toxicity. Synthetic musks, disinfectants and UV filters are reported to accumulate in biological systems and caused adverse impacts *via* bio-magnification (Brausch and Rand, 2011).

Concluding Remarks and Recommendations

In summary, this review revealed the jolting environmental concentrations of DEHP and PAHs in the surface water resources of Asian counties, albeit the levels of emerging PPCPs were relatively low. The spatial distribution analysis of environmental levels and associated ecological risk of DEHP, PAHs and PPCPs further highlighted that the riverine systems of Asian countries especially that of China and India were expressed that alarming situation and need immediate rehabilitation measures. Comparatively, the riverine systems in Europe were relatively less contaminated and pose fewer risks to the ecological resources. Although considerable environmental regulations are existing to control legacy organic pollutants, the strict implementation of those regulations in Asian counties is specifically needed. In case of emerging environmental pollutants, such as PPCPs, the studies are still scarce and the environmental regulations are also not available. Therefore, more studies are recommended to unveil the current environmental occurrence, spatial distribution, sources and occurrence especially in South Asian countries. The petroleum products and incomplete combustion of fossil fuels were mentioned as the primary sources of PAHs in the environment, while DEHP is solely produced from plastic laden consumed products and medical appliances. Regarding the sources of PPCPs, the effluents from households, hospitals and PPCPs manufacturing units were listed as principal sources of PCPs and NSAIDs in the environment. PAHs were reported to cause the elicited toxicological concerns in terms of carcinogenicity, mutagenicity, developmental toxicity, and genotoxicity, while DEHP exhibited specific toxicity for reproductive, immune and nervous systems. PPCPs-appeared with least toxic concerns, such as developmental abnormalities, DNA damage, and genotoxicity. In a nutshell, this review unveiled the current alarming environmental levels of emerging and legacy organic pollutants and their toxicological impacts. On the basis of these findings, the strict implementation of environmental regulations is recommended to avoid future worst scenarios and ensure the ecological integrity and environmental safety.

Acknowledgment

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Table S1: Comparative levels of DEHP reported in the surface waters worldwide

Locations	DEHP levels (μg/L)	References
Wuhan section, Yangtze River, China	54.73	(Wang *et al*., 2008)
Hun River, China	34.2	(Li *et al*., 2015b)
Yellow River, China	24	(Sha *et al*., 2006)
Songhua River, China	11.55	(Gao *et al*., 2014)
Pearl River Estuary, China	12.1	(Li, 2016)
Jiulong River, China	10.9	(Li *et al*., 2016)
Wujin River, China	8.89	(Zhang *et al*., 2011)
Pearl River Delta, China	8.84	(Li, 2015)
Jiangsu section, Yangtze River, China	2.05	(He *et al*., 2011b)
Liao River, Anshan, China	13050	(Yu *et al*., 2011a)
Kunming Lake, China	1390	(An and Jin, 2000)
Xuanwu Lake, Yangtze River, China	1299	(Shen *et al*., 2010)
Kuils River	380	(Olujimi *et al*., 2012)
Velwatchers River	280	
Mosselbank River	139	
Vygekraal River	62	
Diep River	7	
Kuils River, South Africa	ND	
Rivers of Eastern Cape, South Africa	2306	(Fatoki and Noma, 2002)
Rivers and lakes, Germany	98	(Fromme *et al*., 2002)
Seine River estuary,France	6.44	(Dargnat *et al*., 2009)
River of France	1.7	(Tran *et al*., 2015)
Bang Pa-kong River, Chao Phraya River, Tha-chin River, Mae-klong River,Thailand	<1.10	(Sirivithayapakorn, 2010)
Kaveri River, India	1.4	(Selvaraj *et al*., 2015)
Selangor River, Malaysia	0.97	(Veerasingam, 2013)
Selangor River,Malaysia	0.38	(Santhi and Mustafa, 2013)
Manzanares River and Jarama River,Spain	ND	(Dominguez *et al*., 2014)
North-West River, Spain	<0.44	(Regueiro *et al*., 2008)
River, Spain	0.17	(Sanchez *et al*., 2011)

The values listed here are the high-end (max.) reported concentrations

Table S2: Comparative levels of ΣPAHs reported in the surface waters of China and worldwide

Locations	Concentration of ΣPAHs (ng/L)	References
Gao-ping River, Taiwan	9400	(Doong and Lin, 2004)
Yellow River Delta, China	334	(Wang *et al*., 2009)
Jiulong River Estuary, China	26920	(Maskaoui *et al*., 2002)
Alexandria coast, Egypt	523	(El-Nemr and Abd-Allah, 2003)
Tianjin, China	1272	(Shi *et al*., 2005)
Kor River, Iran	375	(Kafilzadeh *et al*., 2011)
Gomti River System, India	75570	(Malik *et al*., 2004)
Daliao River watershed, China	13448.5	(Guo *et al*., 2007)
Hangzhou City, China	9663	(Chen *et al*., 2004)
Danube River, Hungarian	357	(Nagy *et al*., 2012)
Bolgoda Lake, Sri Lanka	127	(Pathiratne *et al*., 2007)
Tonghui River, China	2651	(Zhang *et al*., 2004)
River Tiber, Italy	72	(Patrolecco *et al*., 2010)
Chenab River, Pakistan	436.66-1287.9	(Farooq *et al*., 2011)
Odra river,Poland	0.0-3349.9	(Wolska *et al*., 2003)
Todos Os Santos Bay, Brazil	0.0029-0.1079	(Jose Celino *et al*., 2012)
Danube branch, Hungary	6.7-3026	(Nagy *et al*., 2007)
Danube River, Hungarian	25-1208	(Nagy *et al*., 2013)
Daya Bay, China	4228-29325	(Zhoua and Maskaouib, 2003)
Gomti River, India	60-84210	(Farooq *et al*., 2011)
Pearl River Delta, China	944-6654	(Luo *et al*., 2004)
Niteroi streams City, Brazil	4-870	(Ribeiro *et al*., 2012)
Hai River Basin estuary, China	232.12-7596.56	(Yan *et al*., 2016)
Soan River, Pakistan	61-207	(Aziz *et al*., 2014)

The values listed here are the high-end (max.) reported concentrations

Table S3: Comparative levels (ng/L) of PPCPs reported in the surface waters of China and worldwide

River name and location	ΣPCP's	Reference
Kunyu, Tonghui, Liangshui Rivers, Beijing, China	41.400	(Li *et al*., 2016)
Pearl River, Guangdong, China	152.100	(Yu *et al*., 2011b)
Pearl River, Guangdong, China	3204.000	(Peng *et al*., 2008)
Yangtze River Zigui-Shanghai, China	26.000	(Liu *et al*., 2015b)
	33.820	(Zhang *et al*., 2015)
Sha River, Guangzhou, China	19.650	
	65.700	(Ramaswamy *et al*., 2011)
Kaveri River, Tamilnadu, India	79.800	
Reservoir, Guangdong, China	178.000	(Peng *et al*., 2014)
Geylang River, Singapore	0.370	(Xu *et al*., 2011; Wang and Kelly, 2016)
	1.580	(Yamagishi *et al*., 1983)
Kallang River, Singapore	0.300	
Tama River, Japan	0.023	
Elbe River, Germany	9.000	(Gatermann *et al*., 1998)

The values listed here are the high-end (max.) reported concentrations. PCPs included methylparaben (MP), propylparaben (PP) and musk xylene (MX)

Table S4: Comparative levels (ng/L) of ΣNSAIDs reported in the surface waters of China and worldwide.

Location	ΣNSAIDs	Reference
Pearl River, Guangdong, China	1745.00	(Peng *et al*., 2008)
Kaveri River, Tamilnadu, India	0.00	(Ramaswamy *et al*., 2011)
Reservoir, Guangdong	40.50	(Peng *et al*., 2014)
Geylang River, Singapore	91.00	(Xu *et al*., 2011; Wang and Kelly, 2016)
Kallang River, Singapore	56.00	(Xu *et al*., 2011; Wang and Kelly, 2016)
Beiyun River basin Beijing, China	121.60	(Ma *et al*., 2017)
Danube River, Romania	188.00	(Chitescu *et al*., 2015)
Mino River, Spain	46.00	(Iglesias *et al*., 2014)
Dongting Lake, Hunan, China	249.80	(Barbosa *et al*., 2016b)
Haihe River System, Beijing and Tianjin	190.00	(Heeb *et al*., 2012)
Centeral and lower Yangtze River, China	99.30	(Wu *et al*., 2014)
Mississippi River, Louisiana, USA	169.00	(Zhang *et al*., 2007)
Huangpu River, Shanghai, China	142.60	(Gao *et al*., 2014)
Yangtze River, Nanjing, China	442.00	(Liu *et al*., 2015a)
Llobregat River, Castellgali, Spain	226.00	(Farre *et al*., 2012)
Cardener River, Castellgali, Spain	484.00	(Farre *et al*., 2012)
Singapore River, Singapore	110.00	(Xu *et al*., 2011)
Ananymous Resvoir, Singapore	10.85	(You *et al*., 2015)
Tributaries	22.05	(You *et al*., 2015)
Pearl River, Guangdong	755.00	(Zhao *et al*., 2009)
Pearl River, Guangdong	960.00	(Zhao *et al*., 2011)
Pearl River Delta, Guangzhou, China	442.00	(Huang *et al*., 2011)
Yangtze River Shanghai, China	843.00	(Yang *et al*., 2011)
Haihe River, Tianjin, China	152.20	(Li *et al*., 2010)
	46.40	(Li *et al*., 2010)
Liaohe River, Liaoning	155.00	(Li *et al*., 2010)
	963.00	(Li *et al*., 2010)
Yellow River, China	74.20	(Li *et al*., 2010)
	552.00	(Li *et al*., 2010)
Zhangweinanyunhe River, Northern China	29.40	(Cao *et al*., 2010)
Llobregat River, Spain	280.00	(Aldekoa *et al*., 2013)

The values listed here are the high-end (max.) reported concentrations. ΣNSAIDs included naproxen (NAP), ibuprofen (IBU) and diclofenac (DIC)

Author's Contributions

Yi Liu and Muhammad Junaid: Contributed equally to the manuscript. Extracted and analyzed the data and wrote the first draft.

Chun-Di Chen Naima Hamid: Develop illustration, analyze and revise the paper.

De-Sheng Pei: Conceived and designed this review, wrote the paper and revised the paper.

Conflict of Interest

The authors declare no conflict of interest.

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