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Review article

Occurrence and potential risks of pharmaceutical contamination in global Estuaries: A critical review and analysis

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ABSTRACT

Input of pollutants to estuaries is one of the major threats to marine biodiversity and fishery resources, and pharmaceuticals are one of the most important contaminants of emerging concern in aquatic ecosystems. To synthesize pharmaceutical pollution levels in estuaries over the past 20 years from a global perspective, this review identified 3229 individual environmental occurrence data for 239 pharmaceuticals across 91 global estuaries distributed in 26 countries. The highest cumulative weighted average concentration level (*WACL*) of all detected pharmaceuticals in estuarine water was observed in Africa (145,461.86 ng/L), with 30 pharmaceuticals reported. North America (24,316.39 ng/L) was ranked second in terms of *WACL*, followed by South America (20,784.13 ng/L), Asia (5958.38 ng/L), Europe (4691.23 ng/L), and Oceania (2916.32 ng/L). Carbamazepine, diclofenac, and paracetamol were detected in all continents. A total of 41 functional categories of pharmaceuticals were identified, and analgesics, antibiotics, and stimulants were amongst the most ubiquitous groups in estuaries worldwide. Although many pharmaceuticals were observed to present lower than or equal to moderate ecological risk, 34 pharmaceuticals were identified with high or very high ecological risks in at least one continent. Pharmaceutical pollution in estuaries was positively correlated with regional unemployment and poverty ratios, but negatively correlated with life expectancy and GDP per capita. There are some limitations that may affect this synthesis, such as comparability of the sampling and pretreatment methodology, differences in the target pharmaceuticals for monitoring, and potentially limited number and diversity of estuaries covered, which prompt us to standardize methods for monitoring these pharmaceutical contaminants in future global studies.

1. Introduction

Pharmaceuticals are regarded as an important type of contaminants of emerging concern (CECs). Despite pharmaceuticals being used for treatment and prevention of human and animal diseases, and improved quality of life, they are not fully absorbed, utilized, or metabolized during the practice of health care (Khan et al., 2020). An appreciable portion of pharmaceuticals that are used can be excreted in animal feces

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and urine with unchanged composition (Mu et al., 2022). Therefore, the release of residual pharmaceuticals can pose direct and indirect threats to aquatic and terrestrial ecosystem services, biodiversity, and public health (Yang et al., 2022). Over the last two decades, the environmental occurrence, effects and risks of pharmaceuticals have had significant attention globally as a result of their increased demand, consumption, environmental concerns, and ecological impacts (Branchet et al., 2021; Valdez-Carrillo et al., 2020). Pharmaceuticals have been broadly detected in various environmental matrices including but not limited to soil, wastewater treatment plant sludge, sediments, waters (rivers, oceans, and estuaries), and biota (Bavumiragira et al., 2022; Kazakova et al., 2021; Mechelke et al., 2020; Mejías et al., 2021). In particular, studies examining the occurrence of pharmaceuticals in surface waters have been most common (Bexfield et al., 2019; Valdez-Carrillo et al., 2020; Waleng and Nomngongo, 2022). Although the levels of pharmaceutical concentrations in aquatic systems are typically in the ng/L to μg/L levels, hydrophilic and physiologically active pharmaceutical compounds with potential high toxicity can still pose significant risks to aquatic life due to their high potency towards biological targets (Kazakova et al., 2021).

Pharmaceuticals in the environment are originated from multiple sources, such as effluents from wastewater treatment plants (White et al., 2019), pharmaceutical manufacturing industries (Thai et al., 2018), and medical facilities (Low et al., 2020). Numerous studies have reported that the current treatment processes adopted by sewage treatment plants worldwide cannot effectively remove pharmaceuticals (Chen et al., 2022a; Chen et al., 2022b; White et al., 2019). Untreated sewage and partially treated effluent discharges from primary and secondary wastewater treatment facilities, which usually consist of many pharmaceuticals, are therefore discharged to lakes, rivers, estuaries or coastal waters. In addition, contaminant run-off from animal farms and agricultural land, and releases from aquaculture facilities, are also important pathways of entry of pharmaceuticals to aquatic systems (Jaffrezic et al., 2017). Thermal baths have been recently identified as another source of pharmaceutical contamination (Jakab et al., 2020). Pharmaceuticals used in food processing and inconsistent disposal practices for expired drugs via the sewer are also expected sources of pharmaceutical contamination in the environment (Herrero-Villar et al., 2023).

Compared to other aquatic systems, estuaries with diverse habitats such as mud flats, mangroves, marshes, and seagrass beds, are ecological hotspots of biodiversity due to the interface of freshwater and saltwater (Nagarajan et al., 2022). Some estuaries are known as the most productive biological systems in the world (Xu et al., 2022). Estuarine ecosystems are crucial for supporting biodiversity, maintaining the health and functioning of both marine and terrestrial ecosystems (Martinez-Megias and Rico, 2022), and providing food for human populations from coastal fisheries and aquaculture operations. However, estuaries are also potentially very vulnerable, as they are exposed to environmental stressor from both freshwater and marine systems. This characteristic makes estuaries key locations for environmental management, given the dynamic exchange of chemical pollutants and nutrients at the land – sea interface (Martinez-Megias and Rico, 2022). Furthermore, there are usually diverse human activities in urbanized estuaries including aquaculture, water transportation, commerce, tourism, and recreation, making estuaries one of the most impacted waterbodies due to anthropogenic pollution in the world (Xu et al., 2022).

Given the importance of biodiversity and ecosystem services, it is of great importance to strengthen monitoring of contaminants in estuaries. Over the past 20 years, numerous studies have monitored the levels of pharmaceutical residues in estuaries around the world (Korkmaz et al., 2022; Lu et al., 2020; Wu et al., 2022a). However, these have typically focused on estuaries in one location of a region with very few studies attempting to understand the occurrence and risks of pharmaceuticals in estuaries at a global scale (Sanganyado et al., 2021; Tong et al., 2022; Yang et al., 2022), though Gaw et al. (2014) previously examined this space, and several studies have considered occurrence of specific pharmaceuticals in global aquatic matrices, including estuaries and marine systems (Kelly and Brooks, 2018; Kristofco and Brooks, 2017; Mole and Brooks, 2019; Saari et al., 2017; Schafhauser et al., 2018; Wronski and Brooks, 2023). In addition, to our knowledge, no studies have conducted statistical analysis to compare the reported data across different continents, to investigate patterns of different classes of pharmaceutical occurrence in global estuaries, and analyze whether contamination patterns are related to socioeconomic drivers across different countries. A critical review is needed to identify and synthesize the available information, evaluate the contamination status of estuaries globally and develop open questions such as: Have all of the major urbanized estuaries been effectively monitored? Are the categories and types of pollutants sufficiently covered in the monitoring? What are the effect thresholds for the most commonly identified pollutants? Answers to these questions are needed, as a continued increase of studies on CECs in the environment appear in the refereed literature.

Here, we critically reviewed the current status of pharmaceutical pollution in global estuaries over the past 20 years with a *meta*-analysis approach. Initially, we exhaustively collected and summarized available data on the occurrence of various pharmaceuticals in estuaries across the world. These data were then used to understand the variability in levels and patterns of pharmaceutical pollution across different continents. Occurrence data were also combined with ecotoxicological data to perform a screening level assessment of ecological risks resulting from the pharmaceuticals detected in global estuaries. We then explored socio-economic factors that might influence consumption and releases of pharmaceuticals in estuaries. Finally, we identified shortcomings of the current research and directions for future research. This review aimed to consolidate the existing knowledge on the pharmaceutical pollution in global estuaries, diagnose contamination status, identify geographic areas and chemicals of concern, and highlight opportunities for international collaboration and harmonization of the research methodologies.

2. Methods

2.1. Data collection and curation

In order to clearly define the scope of this study and to decrease the possibility of bias, estuaries were defined as the interface between marine and river systems. Web of Science (Science, 2023) and Google Scholar (Scholar, 2023) were used for the literature searching. 72 papers were retrieved with defined and adequate methods across the globe using specific keywords and combinations including “pharmaceutical” AND “contamination” AND “estuary”. Additional searches were performed using alternative keywords. For instance, the keyword “pharmaceutical” was then iteratively replaced for subsequent searches with specific categories such as “antibiotics”, “antiretroviral”, and “NSAIDs”. Similarly, the keyword “contamination” was replaced with “pollution”, “concentration”, and “distribution”, and the keyword “estuary” was also replaced with “estuaries”, “micro-estuary”, “river”, “river mouth”, “marine”, “ocean”, and “sea”. To capture the most recent contamination status of the pharmaceuticals, we set the publication time window from 2003 to 2022 (a recent 20 year period), although no paper was found from 2003 to 2005, and only two records in the database were identified in 2006. The country where the sampling was conducted was used to categorize all publications, and then the literature entries were divided into six continents (i.e., Africa, Asia, Europe, North America, South America, and Oceania). Our review identified 3229 unique concentration data for 239 pharmaceuticals across 91 estuaries around the world. The entries included pharmaceuticals and/ or transformation products measured in rivers and estuaries across 26 countries (Fig. 1). The number of publications in each continent was ranked in descending order as Asia (26), Europe (14), North America (11), South America (9),

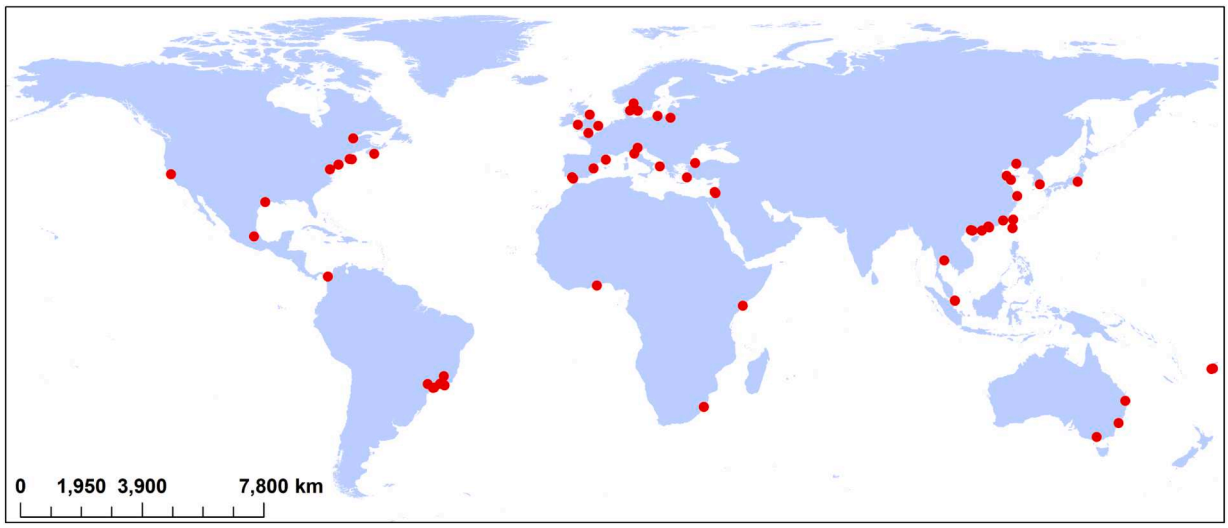

Fig. 1. Ninety-one estuaries in the world with reported pharmaceutical data from 2003 to 2022 used in the current *meta*-analysis. Refer to Table S1 in supplementary information for details of the estuaries.

Africa (7) and Oceania (5).

Due to various summary statistics (such as concentration ranges, mean, median, or maximum and minimum values) being reported, and divergent sample scales and sample times used in different studies, we employed the "weighted average concentration level" (*WACL*, ng/L) to assess the concentration of each compound in a specific region, though, we recognize the limitations of this approach because exposure magnitude, frequency and duration inherent influences the likelihood of adverse outcomes. We also identified the mean *WACL* ($WACL_{mean}$, ng/L) to estimate pharmaceutical concentration levels in specific regions, which could be described as follows:

$$WACL = \frac{\sum_1^{f_x}(C_i \times n_{times,i} \times n_{locations,i})}{\sum_1^{f_x}(n_{times,i} \times n_{locations,i})} \quad (1)$$

$$WACL_{mean} = \frac{\sum_1^{y} WACL}{y} \quad (2)$$

where f_x is the total number of studies reporting that compound x has concentration values, C_i (ng/L) is the concentration of compound x in a specific record i (i ranged from 1 to f_x), $n_{times,i}$ is the number of sampling events (i.e., sampling time) of compound x in a specific record i, $n_{locations,i}$ is the number of sampling locations of compound x in a specific record i, the value of y is equal to the number of compounds reported in a specific region (continent or country) when calculating the $WACL_{mean}$ values.

If the mean value of a specific compound could be obtained from the literature, then the mean values were chosen as C_i, and the $n_{times,i}$ and $n_{locations,i}$ should be accurately recorded. If the mean values are not available, then the median values were collected, and the $n_{times,i}$ and $n_{locations,i}$ were also recorded for further calculation. If neither mean or median values could be obtained, then we collected both the minimum and maximum values, and the $n_{times,i}$ and $n_{locations,i}$ were recorded as one. The concentration data reported as "not detected" or "below detection limits" was arbitrarily converted to zero in this study. This method is similar in principle to the "weighted average HQ (hazard quotient)" calculation reported by Yang et al. (2022) but has been modified so that it was fit for purpose in this study. In all cases, the concentration units published in the literature were converted to ng/L for consistency.

2.2. Socio-economic analysis method

Multiple linear regression and redundancy analyses were carried out to evaluate the potential correlation between contamination levels ($WACL_{mean}$ values) of pharmaceuticals in each region with the socio-economic factors. These included the % population living below the poverty ratio at US$2.15 a day (2017 Purchase Power Parity (PPP)), gross domestic product (GDP) per capita (current US$), life expectancy at birth (years), population size, crude death rate (per 1,000 people), unemployment ratio (% of total labor force) (national estimate), and age dependency ratio for people $<$ 15 years old and $>$ 64 years old (% of working-age population). The socio-economic factor data was obtained from the World Bank Open Data (Data, 2023) and the latest values from 2003 to 2022 were collected. The correlation analysis was performed using a Pearson correlation, and the level of significance was set at $p <$ 0.05 (two-tailed).

2.3. Screening level assessment methodology

Among the 239 identified pharmaceuticals, 209 had chronic toxicity values including no observed effect concentration (*NOEC*) or lowest observed effect concentration (*LOEC*) on aquatic organisms available. Toxicity data from the ECOTOX Knowledgebase (https://cfpub.epa.gov/ecotox/) and the predicted no-effect concentration (PNEC) values from published papers were prioritized for a screening level assessment in this study, followed by the use of predicted toxicity data from the ECOSAR version 2.0 (USEPA, USA). We fully recognize the limitations of this screening level approach, which include Quantitative Structure – Activity Relationship (QSAR) modeling outputs and diverse endpoints, and this may or may not be plausibly linked to molecular initiation events that are evolutionarily conserved for pharmaceuticals and other biologically active compounds (Ankley et al., 2024; Ankley et al., 2007; Gunnarsson et al., 2008; Gunnarsson et al., 2019; Lalone et al., 2013). The lowest toxicity values (*LTV*, mg/L, equation (3) were firstly determined, following Equation (3) (Chen et al., 2020):

$$LTV = \min(ChV_{x,1}, ChV_{x,2}, \cdots, ChV_{x,y}) \quad (3)$$

where $ChV_{x,1}$, $ChV_{x,2}$, and $ChV_{x,y}$ are the chronic toxicity values of a given pharmaceutical (x, mg/L) for several aquatic organisms (y is the number of available organisms).

The *PNEC* (ng/L) was calculated by incorporating the assessment factor (*AF*) (Chen et al., 2020), following Equation (4):

$$PNEC = LTV/AF \times 10^6 \quad (4)$$

where the *AF* value was assigned as 10 in this study.

The hazard quotient (*HQ*) of a specific pharmaceutical (x) was

calculated as follows (Chen et al., 2020):

$$HQ = WACL_x / PNEC_x \quad (5)$$

Here again, we fully recognize the limitations of using a modest *AF* value of 10 for pharmaceuticals and other biologically active compounds. However, for the purpose of this screening level assessment, we have utilized this widely accepted default *AF* value. A *HQ* value less than 0.01, between 0.01 and 0.1, between 0.1 and 1 estimates very low risk, low risk, and moderate risk, respectively, while a *HQ* value greater than 1 usually indicates high ecological risk. A *HQ* value greater than 10 indicates very high ecological risk.

2.4. Statistical analysis

Excel 2021 (Microsoft, USA) and SPSS version 27 (IBM, USA) were used to analyze the data collected for this review. The Geographic spatial distribution maps were prepared using ArcGIS version 10.8 (ESRI, USA). Redundancy analysis was performed using Canoco version 5.0 (Microcomputer Power, USA). The figures were drawn using Origin 2022 (OriginLab, USA).

3. Results and discussion

3.1. Occurrence of pharmaceuticals in global estuaries

This review included nine estuaries in Africa (covering South Africa, Ghana, and Kenya), 31 estuaries in Asia (covering China, Israel, Japan, Korea, and Singapore), 19 estuaries in Europe (covering Denmark, France, Germany, Greece, Turkey, Italy, Poland, Romania, Spain, UK, and Sweden), 11 estuaries in North America (covering USA, Canada, and Mexico), six estuaries in Oceania (covering Fiji and Australia), and 15 estuaries in South America (covering Brazil and Colombia) (Table S1). Data collected from Africa was between 2015 and 2022, as no data from earlier years could be retrieved. In Asia, the earliest research was from Japan in 2008, but the greatest number of studies from 2011 to 2022 came from China. Relatively abundant data was also identified from Europe, with the earliest research appearing in Romania and in the UK in 2006. Data from North America were published between 2007 and 2021, and in Oceania, data from 2009 to 2021 were obtained. In South America, data from 2011 to 2021 were found in Brazil, but only one paper in Colombia was published in 2020. Overall, developed coastal countries had earlier and more data, while developing countries had relatively less data.

On a continental basis, the highest cumulative *WACL* values in estuarine water samples were observed in Africa (145,461.86 ng/L), with 30 pharmaceuticals reported, and a $WACL_{mean}$ value of 4848.73 ng/L (Fig. 2). The cumulative *WACL* values of North America (24,316.39 ng/L with 61 pharmaceuticals reported) and South America (20,784.13 ng/L with 20 pharmaceuticals reported) were ranked as the second and third, and the $WACL_{mean}$ values were 398.63 ng/L and 1039.21 ng/L, respectively (Fig. 2). Asia (5958.38 ng/L with 105 pharmaceuticals reported) and Europe (4691.23 ng/L with 132 pharmaceuticals reported) showed relatively low cumulative *WACL* values, and the $WACL_{mean}$ values were 56.75 ng/L and 35.54 ng/L, respectively (Fig. 2). The lowest cumulative *WACL* value was observed in Oceania (2916.32 ng/L), with 100 pharmaceuticals reported, and the $WACL_{mean}$ value was 29.16 ng/L (Fig. 2). Clearly, *WACL* values did not correlate with the diversity of pharmaceuticals reported.

Among the reported 239 pharmaceuticals, the contaminants with the highest WACL values in estuarine water samples were acetyl salicyclic acid (95,900.00 ng/L) in Africa, caffeine (2296.60 ng/L) in Asia, fenoprofen (640.00 ng/L) in Europe, metformin (17,023.00 ng/L) in North America, norfloxacin (575.02 ng/L) in Oceania, and caffeine (11,761.55 ng/L) in South America (Table S2). Carbamazepine, diclofenac, and paracetamol were constantly detected in estuarine water samples across all six continents. Whereas the *WACL* values of carbamazepine ranged from 8.94 ng/L in North America to 358.04 ng/L in Asia, and *WACL* values for diclofenac ranged from 4.04 ng/L in Oceania to 992.03 ng/L in Africa. In addition, the *WACL* values of paracetamol ranged from 17.50 ng/L in North America to 3085.20 ng/L in South America. Eight pharmaceuticals were detected on five out of the six continents, including atenolol, caffeine, ibuprofen, naproxen, propranolol, salicylic acid, sulfamethoxazole, and trimethoprim.

3.2. Pharmaceutical concentrations in global estuaries

Fig. 3 shows the top 20 pharmaceuticals with the highest *WACL* values in each continent. In Africa, the highest detected *WACLs* were for the analgesics, ranging from 992.03 to 95,900.00 ng/L. Most of the analgesics, also known as non-steroidal anti-inflammatory drugs (NSAIDs), have been extensively found in the environment worldwide, because of high usage and availability over the counter without a prescription (Kawuma et al., 2021). Lamivudine, which is an antiretroviral medication, ranked second among detected pharmaceuticals in estuaries of Africa, especially in Kenya (K'Oreje K et al., 2016). Lamivudine is an effective nucleoside reverse transcriptase inhibitor, and it is usually used to fight against human immunodeficiency virus (HIV) and hepatitis B

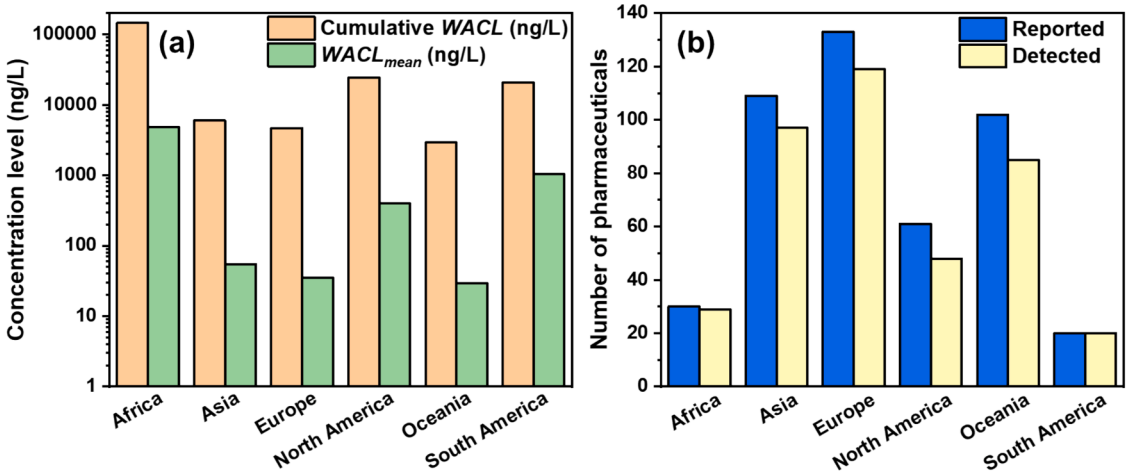

Fig. 2. Pharmaceutical pollution in global estuaries on a continental basis: (a) cumulative and mean values of weighted average concentration level (*WACL*) of all detected pharmaceuticals among studied estuaries in each of the six continents, and (b) the total number of pharmaceuticals (blue bars; Reported) and the total number of pharmaceuticals that were above the detection limit (yellow bars; Detected) among the studied estuaries in each continent.

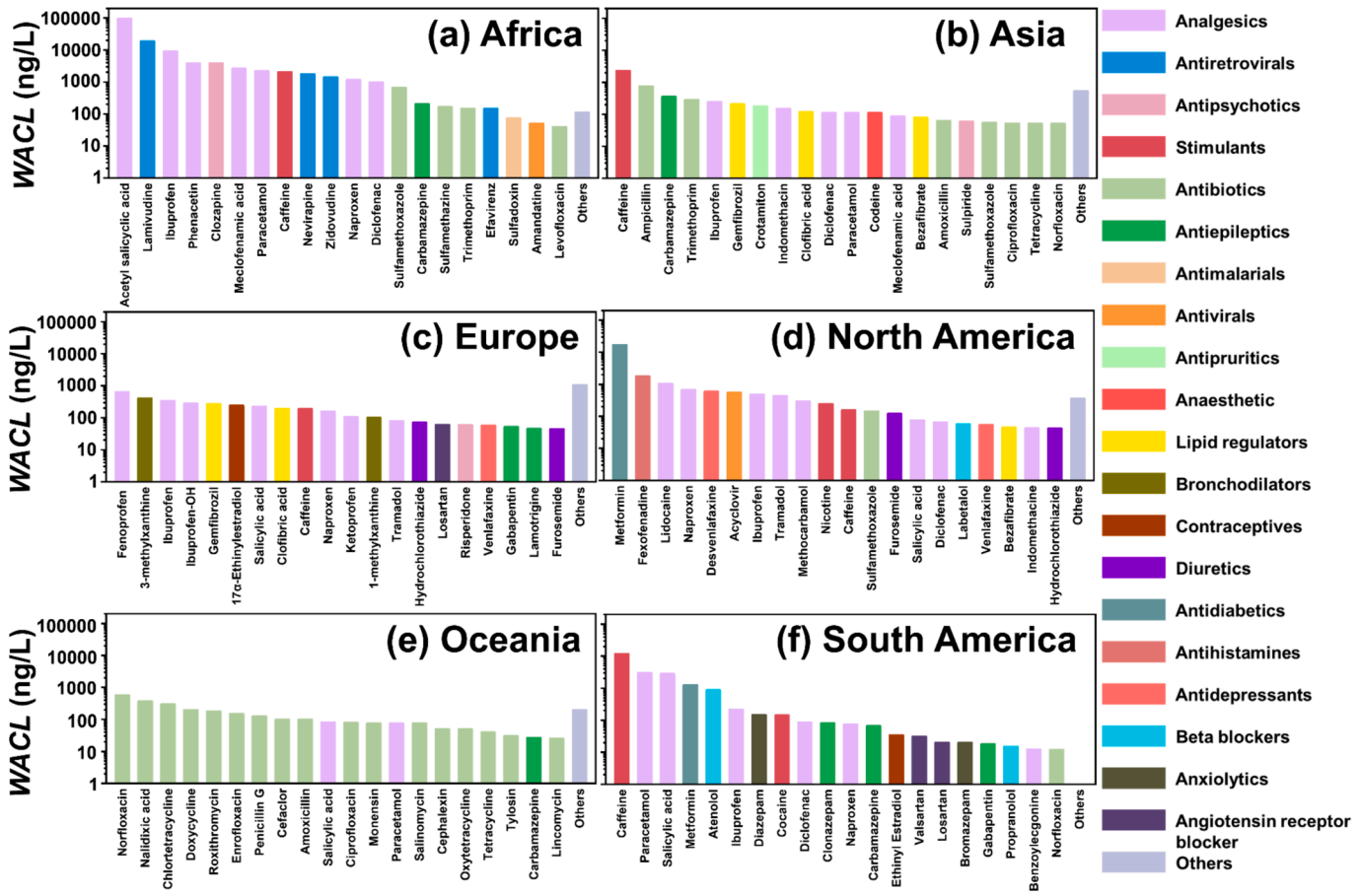

Fig. 3. The top 20 pharmaceuticals with the highest weight average concentration levels (*WACLs*) in each of the six continents.

virus in clinical settings. Nevirapine, zidovudine, and efavirenz, which are also major antiretrovirals, ranked 9th, 10th, and 17th, respectively among the detected pharmaceuticals in Africa. South Africa and Kenya ranked 5th and 12th countries in antiretroviral burdens globally (Gumbi et al., 2017; K'Oreje K et al., 2016; Matongo et al., 2015), but this category of pharmaceuticals has received much less research attention (Gumbi et al., 2019; Ngubane et al., 2019). Additionally, no antiretrovirals were ranked the top 20 in the other five continents. Caffeine, one of the most frequently used stimulants, had the 8th highest *WACL* value (2040.57 ng/L) in African estuaries. Antibiotics including sulfamethoxazole, sulfamethazine, trimethoprim, and levofloxacin ranked within the top 20 in Africa, with *WACL* values ranging from 40.00 to 662.57 ng/L. The widespread use of antibiotics leading to antibiotic resistance is one of the most concerning issues for world health (Fekadu et al., 2019). It has been reported that animal feces and urine have the potential to release up to 90 % of the antibiotic pollution loads in the environment (Mu et al., 2022). In Africa, there are many issues that could increase the discharge of emerging pollutants, including poor sanitation, the widespread use and negligent upkeep of pit latrines, the use of urine-diversion toilets, and inadequate wastewater treatment facilities (Gani et al., 2021; Huff Chester et al., 2022; Madikizela and Chimuka, 2017). The habitual act of dumping wastes into roadways, storm drains, or directly into surface waterways may also cause pollution of estuaries and oceans (Madikizela and Chimuka, 2017).

Pharmaceutical pollution levels in Asian estuaries were lower compared to Africa. Caffeine, which was reported in estuaries of Singapore (Bayen et al., 2013), China (Cui et al., 2019; Fang et al., 2019; Jiang et al., 2015), Korea (Kim et al., 2017), and Israel (Topaz et al., 2020), had the highest *WACL* value of 2296.60 ng/L. Seven of the top 20 are antibiotics, with *WACL* values ranging from 50.97 to 764.50 ng/L. A total of 50 antibiotics were reported in 31 Asian estuaries. Five analgesics, including ibuprofen, indomethacine, diclofenac, paracetamol, and mefenamic acid, presented high levels of pollution, with *WACL* values ranging from 87.00 to 244.37 ng/L. These pharmaceuticals all have a long history of usage (Ooi et al., 2022).

European estuaries had similar pollution levels to Asia, but some differences could be observed in the categories of chemicals reported. Fenoprofen (analgesics) had the highest *WACL* value (640.00 ng/L). Seven analgesics were ranked in the top 20 pharmaceuticals in European estuaries with *WACL* values ranging between 79.14 and 640.00 ng/L. It was noteworthy that tramadol, an opioid analgesic, had a high *WACL* in UK estuaries (Kasprzyk-Hordern et al., 2007), supporting the conclusion reported by LSE (2021) that the UK is the highest per capita consumer of opioids globally (LSE, 2021). Gemfibrozil and clofibric acid, which are lipid regulators, ranked 5th and 8th with *WACLs* of 274.82 and 193.76 ng/L, respectively. Until 2017, the UK, Denmark, Belgium, were reported as the top three country consumers of cholesterol-lowering drugs (Database, 2023; Gonzalez Pena et al., 2021). Caffeine ranked 9th in Europe with a *WACL* of 190.18 ng/L, and this chemical was widely reported in Romania (Moldovan, 2006), Greece, Turkey, Italy, Germany (Nodler et al., 2014), Spain (Camacho-Munoz et al., 2010), Sweden (Malnes et al., 2022), and Denmark (Matamoros et al., 2009). No antibiotic was ranked in the top 20 in Europe, which reflected the relatively strict and effective control of prescription antibiotic usage.

The pharmaceutical with the highest pollution level in North America was metformin (antidiabetics), with a *WACL* value of 17023.00 ng/L, reported from the USA (Elliott et al., 2018). This *WACL* value is the third ranked globally, only lower than acetyl salicyclic acid and lamivudine in Africa. Fexofenadine (antihistamine) ranked 2nd in North American estuaries with a *WACL* value of 1800.00 ng/L, but was

reported as a high-concentration pharmaceutical only in North America. Similar to other continents, analgesics were also one of the most important pharmaceutical categories in North America. A total of 8 analgesics were identified in the top 20 pharmaceuticals, with their *WACL* values ranging from 42.85 to 1050.08 ng/L. Stimulants including nicotine and caffeine were reported with high levels of contamination, both of which are apparently consumed broadly on this continent. Only one antibiotic (sulfamethoxazole) was identified with a *WACL* value of 144.50 ng/L. In addition to the huge consumption (48.9 % of global sales in North America), another factor that may explain the relatively high levels of pharmaceutical residues could be pharmaceutical manufacturing and production (Gonzalez Pena et al., 2021), though very limited research currently has specifically examined estuary contamination by pharmaceutical manufacturing, and further investigation and supplementation in future studies are warranted.

Only three categories of pharmaceuticals (antibiotics, analgesics, and antiepileptics) comprised the top 20 in estuaries of Oceania, with the pollution level being the lowest compared with the other five continents. The *WACL* values of antibiotics ranged from 25.50 to 575.02 ng/L. It was previously reported that antibiotic use in Australia was elevated, and in 2015, through the Pharmaceutical Benefit Scheme, 30 million antibiotic prescriptions had been prescribed by Australian doctors (Australian Government, 2023). The analgesics with relatively high contamination were salicylic acid and paracetamol, with *WACL* values of 82.00 ng/L and 75.60 ng/L, respectively. We only found five publications on pharmaceutical related research in Oceania estuaries (Allinson et al., 2018; Birch et al., 2015; Dehm et al., 2021; Scott et al., 2014; Watkinson et al., 2009); this relatively limited data may affect the robustness of the current analysis. Therefore, we are calling for more global scale research on estuaries, especially in areas with limited data.

A total of 20 pharmaceuticals were reported in South American estuaries in the past 20 years. Among them, two stimulants had relatively high *WACL* values of 11761.55 ng/L (caffeine) and 143.82 ng/L (cocaine). Six analgesics ranked 2nd (paracetamol), 3rd (salicylic acid), 6th (ibuprofen), 9th (diclofenac), 11th (naproxen), and 19th (benzoylecgonine, a primary cocaine metabolite) with *WACL* values of 3085.20 ng/L, 2824 ng/L, 217.06 ng/L, 86.84 ng/L, 74.86 ng/L, and 12.36 ng/L, respectively. Although some analgesics such as diclofenac are prone to experience photodegradation in the natural environment, sustained consumption and input may lead to increased effective exposure duration of these compounds in estuarine waters (Ankley et al., 2007). About 3.7 % of the global pharmaceutical market sales in 2021 came from South America, and Brazil has the largest regional pharmaceutical market (Statista, 2023), where most of the relevant studies in South American estuaries have been carried out.

Of the 41 functional categories of pharmaceuticals recorded in this study (Table S2), 20 categories ranked in the top 20 in global estuaries, indicating relatively high pollution diversity. As indicated in Table S3, three categories, namely analgesics, antibiotics, and stimulants were the most commonly reported contaminants with both widespread distribution (at least five continents having such categories ranked in the top 20) and relatively high pollution levels (cumulative *WACLs* exceeding 5000 ng/L). The cumulative *WACL* values of analgesics, antibiotics, and stimulants reached 127,993.33 ng/L, 5026.51 ng/L, and 16,833.70 ng/L, respectively. The $WACL_{mean}$ values of analgesics and stimulants were 3656.95 ng/L and 2404.81 ng/L, respectively. However, the $WACL_{mean}$ value of antibiotics was 167.55 ng/L, indicating that although antibiotics were widely reported in global estuaries, the detected concentrations were generally low compared with analgesics and stimulants. It is also important to note that this value is lower than minimal selective concentrations and PNECs for antibiotic resistance development (Bengtsson-Palme and Larsson, 2016; Murray et al., 2021). In contrast, antiretrovirals, antidiabetics, antipsychotics, and antihistamines occurred with relative high concentrations at regional scales, with cumulative *WACLs* ranging from 1800.00 ng/L to 22185.00 ng/L.

3.3. Possible factors influencing the environmental occurrence of pharmaceuticals in estuaries

Concentrations of pharmaceuticals in global estuaries could be influenced by many factors, including consumption and usage patterns, waste management, wastewater connectivity and treatment types, and environmental factors. Previous studies have demonstrated the importance of coastal hydrodynamics on the spatial distribution of pharmaceuticals (Wu et al., 2022b). Bayen et al. (2013) concluded that contamination concentrations of pharmaceuticals in surface waters of estuaries and coastal marine systems in Singapore were the highest at locations having the lowest flushing potential and the highest residence time (Bayen et al., 2013). In their study the concentrations of these pharmaceuticals, which were common wastewater contaminants in estuarine water, did not necessarily reflect proximity to sewage treatment plants (Wu et al., 2022b). Specifically, the tides during field sampling can strongly influence reported concentrations of pharmaceuticals and other contaminants in urban estuaries (Scott et al., 2019). Other environmental factors, including loads carried by rivers (Biel-Maeso et al., 2018), stationed maritime vessels (Waleng and Nomngongo, 2022), and industrial or livestock facilities (Husain Khan et al., 2023), can also influence the levels of pharmaceutical residues in estuarine environments. In an earlier study conducted at Guadalete Estuary in Spain (Biel-Maeso et al., 2018), pharmaceuticals were monitored from the river upstream to the estuary, and the results showed that many compounds such as atenolol (mean concentrations in upstream and estuary were 138.90 ng/L and 1.90 ng/L, respectively), caffeine (mean concentrations in upstream and estuary were 320.60 ng/L and 77.60 ng/L, respectively), and ciprofloxacin (mean concentrations in upstream and estuary were 202.90 ng/L and not detected, respectively) consistently had higher concentrations in the river compared to the estuary, indicating input of pollutants from rivers to estuaries and oceans. Such observations are consistent with previous global scanning exercises for pharmaceuticals in aquatic matrices, which consistently identified the highest levels in sewage, followed by effluent discharges, inland water and then estuaries and marine ecosystems (Kelly and Brooks, 2018; Kristofco and Brooks, 2017; Mole and Brooks, 2019; Saari et al., 2017; Schafhauser et al., 2018; Wronski and Brooks, 2023). As a complicated area where humans and marine organisms co-exist, accidental leaks or discharge of the untreated domestic sewage from maritime vessels (Waleng and Nomngongo, 2022), the use of antibiotics or other drugs in aquaculture (Husain Khan et al., 2023), and impacts on chemicals and waste management facilities (e.g., landfills) when disasters (e.g., tsunamis, earthquakes) occur, may also be important non-point sources of pharmaceuticals in estuarine waters.

3.4. Estuarine ecological risks of pharmaceuticals

Concerns have been raised over the ecological health of estuaries influenced by pharmaceuticals, which are intentionally developed to be biologically active. The PNEC values of pharmaceuticals ranged from 2.96×10^{-3} to 8.56×10^{8} ng/L in this study (Table S4). Ethinyl estradiol (contraceptives) and atenolol (beta blockers) showed the lowest PNEC values of 2.96×10^{-3} and 2.66×10^{-2} ng/L, respectively, indicating that aquatic organisms are potentially highly susceptible to these compounds even at low concentrations. The PNEC values of amitriptyline, caffeine, carbamazepine, diclofenac, diltiazem, ibuprofen, sertraline, and tetracycline ranged between 0.1 and 1 ng/L, which were relatively low compared with other pharmaceuticals (Table S4). There were 12 other pharmaceuticals with PNEC values of below 10 ng/L. In addition, there were 21 pharmaceuticals with PNEC values greater than 10 ng/L but below 100 ng/L, and the pollution levels of the above compounds in global estuarine waters should be given special attention, particularly given our reliance on ECOSAR and a common default *AF* of 10 in the current study. Nevertheless, our knowledge about ecological risks is incomplete, as 20 out of the 239 pharmaceuticals reported herein do not

have any toxicity information (Table S4). There is an urgent need to advance estuarine and marine ecotoxicology for these chemicals.

Potential ecological risks of the pharmaceuticals were estimated by comparing the *WACLs* and the available PNECs to derive chemical specific *HQ* values (Fig. 4). Many pharmaceuticals were reported with concentrations lower than the levels we estimated to elicit ecological effects, but there again our results should be taken with caution for potential false negatives resulting from ECOSAR predictions, which were necessary for many compounds given the lack of experimental data plausibly linking endpoints associated with adverse outcomes to evolutionarily conserved molecular initiation events. However, despite this data limitation, in African, Asian, European, North American, Oceanian, and South American estuaries, there were 12, 17, 18, 16, 8, and 10 pharmaceuticals with *HQ* values greater than one, respectively, indicating high ecological risks. It is also important to underscore that the *HQ* values of diclofenac (analgesics) in all six continents, caffeine (stimulants), carbamazepine (antiepileptics), and ibuprofen (analgesics) in five continents, and ethinyl estradiol (contraceptives) and atenolol (beta blockers) in four continents were greater than 10, indicating very high ecological risks. There were also 13 other pharmaceuticals with very high risks in the estuaries of one to three continents (Table S5). Pharmaceuticals with high ecological risks were not entirely consistent with pharmaceuticals having high concentrations or high reporting frequencies, highlighting that multiple factors need to be considered when developing practices and policies for environmental monitoring and risk management. Furthermore, combined effects of coexisting pharmaceuticals may be a concern, particularly for the chemical compounds that share a similar mode of toxic action and exhibit greater than additive or potential synergistic toxicity (Backhaus, 2014; Wilkinson et al., 2022).

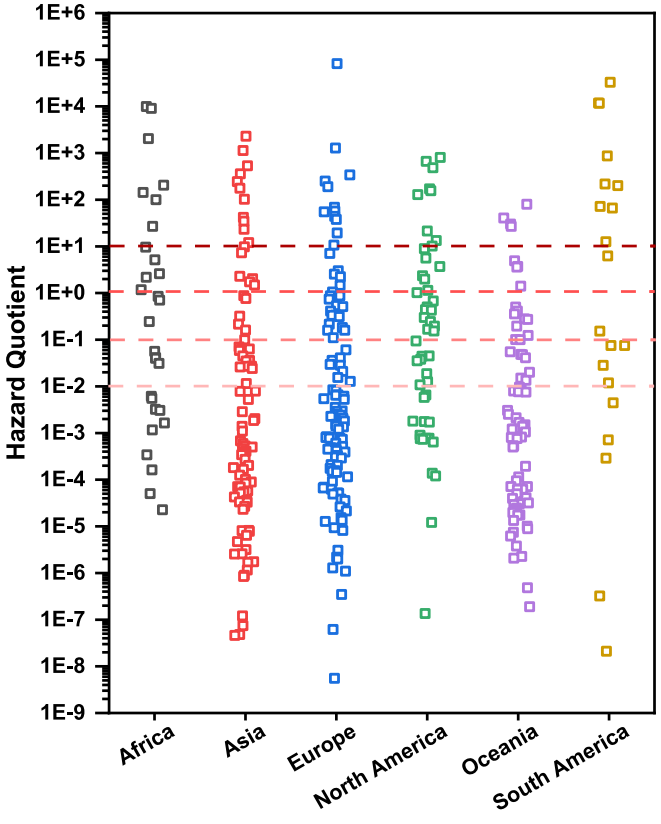

Fig. 4. Hazard quotient of reported pharmaceuticals with available toxicity data in global estuaries.

3.5. Pharmaceutical contamination relationships with socio-economic status

In this study, correlations among seven socio-economic factors and pharmaceutical pollution level ($WACL_{mean}$) in global estuaries were evaluated (Fig. 5a). The multiple regression model was statistically significant with $F_{7,17} = 10.770$ ($p < 0.001$), and adjusted $r^2 = 0.740$. The $WACL_{mean}$ values were positively related with the unemployment ratio ($p < 0.001$) and the poverty ratio ($p = 0.003$), but negatively related to the life expectancy ($p = 0.003$). This is similar to a recent study in global rivers where pharmaceutical pollution was most positively associated with local unemployment and poverty rate, as well as population and median age (Wilkinson et al., 2022). Through the redundancy analysis, we found that the $WACL_{mean}$ value was positively related with the unemployment ratio (*pseudo-F*=27.7; $p = 0.008$), but negatively related with life expectancy (*pseudo-F*=3.7; $p = 0.046$) and GDP per capita (*pseudo-F*=5.2; $p = 0.004$). However, no significant relationships were observed with the other three socio-economic factors (population, death rate, and age dependency ratio) and $WACL_{mean}$ values. As shown in Fig. 5b, although pharmaceutical pollution in estuaries was positively related to the poverty ratio (blue line) and negatively related to GDP per capita (red line) in most regions, some exceptions were also be observed. Ghana is an African country with a very high poverty ratio (25.2 %) and a very low GDP per capita (2363.3 current US$), but the $WACL_{mean}$ value in Gahana was the lowest among all the countries involved in this study. This observation may be attributed to the limited availability and affordability of pharmaceuticals in low-income countries, and relatively low monitoring efforts in these areas (Huff Chester et al., 2022). Other exceptions include South Africa, Australia, and Poland, with the poverty ratios ranging from 0.1 % to 20.5 %, and the GDP per capita ranging from US$7055 to US$60443. However, the $WACL_{mean}$ values in these countries were all relatively high, ranging from 112.39 to 7638.80 ng/L. This could be related to policy settings around regulation of pharmaceutical contaminants, and availability of waste and wastewater treatment facilities. With the increase in pharmaceutical pollution levels in estuaries, life expectancy showed a slight increase at first and then a sharp decreasing trend (Fig. 5c).

There are two primary factors leading to pharmaceutical contamination in estuaries: widespread use of pharmaceuticals (Reis et al., 2019), and insufficient treatment of chemicals and waste (White et al., 2019). Therefore, elevated pharmaceutical residues in estuaries may indicate poor local hygiene and health conditions, which potentially have negative impacts on life expectancy if access to medications are available. Alternatively, lower pharmaceutical residues in estuaries may indicate decreased access to health care and drug consumption. Interestingly, we observed low life expectancies (ranging from 64 to 70 years) as well as low $WACL_{mean}$ values (ranging from 0.39 to 2.75 ng/L) in Ghana, Mexico, and Fiji. Overall, the pharmaceutical pollution levels in estuaries generally increased with the poverty ratio (Fig. 5b) and the unemployment ratio (Fig. 5d). The results imply that low and low-to-middle income countries have inadequate chemicals and waste management infrastructures, leading to greater pollution in their estuaries.

As described above, antibiotics, analgesics, and stimulants were the major categories reported in global estuaries. Therefore, these medicines were also evaluated using correlation analysis with the seven socio-economic factors (Fig. 5a). The distribution characteristics of analgesics in different regions was very similar to the overall distribution characteristics of pharmaceutical pollution levels, and thus this category also showed positive correlations only with the poverty ratio and the unemployment ratio. In addition, only antibiotics had a positive correlation with the age dependency ratio (*pseudo-F*=0.6; $p = 0.574$). It may infer that a larger number of dependents in society (particularly people who are aging or have long-term illness), were often accompanied by greater antibiotic consumption. Stimulants were positively correlated with death rate (*pseudo-F*=0.5; $p = 0.628$), and stimulant pollution levels in estuaries of South Africa, Romania, and Brazil (with $WACL_{mean}$

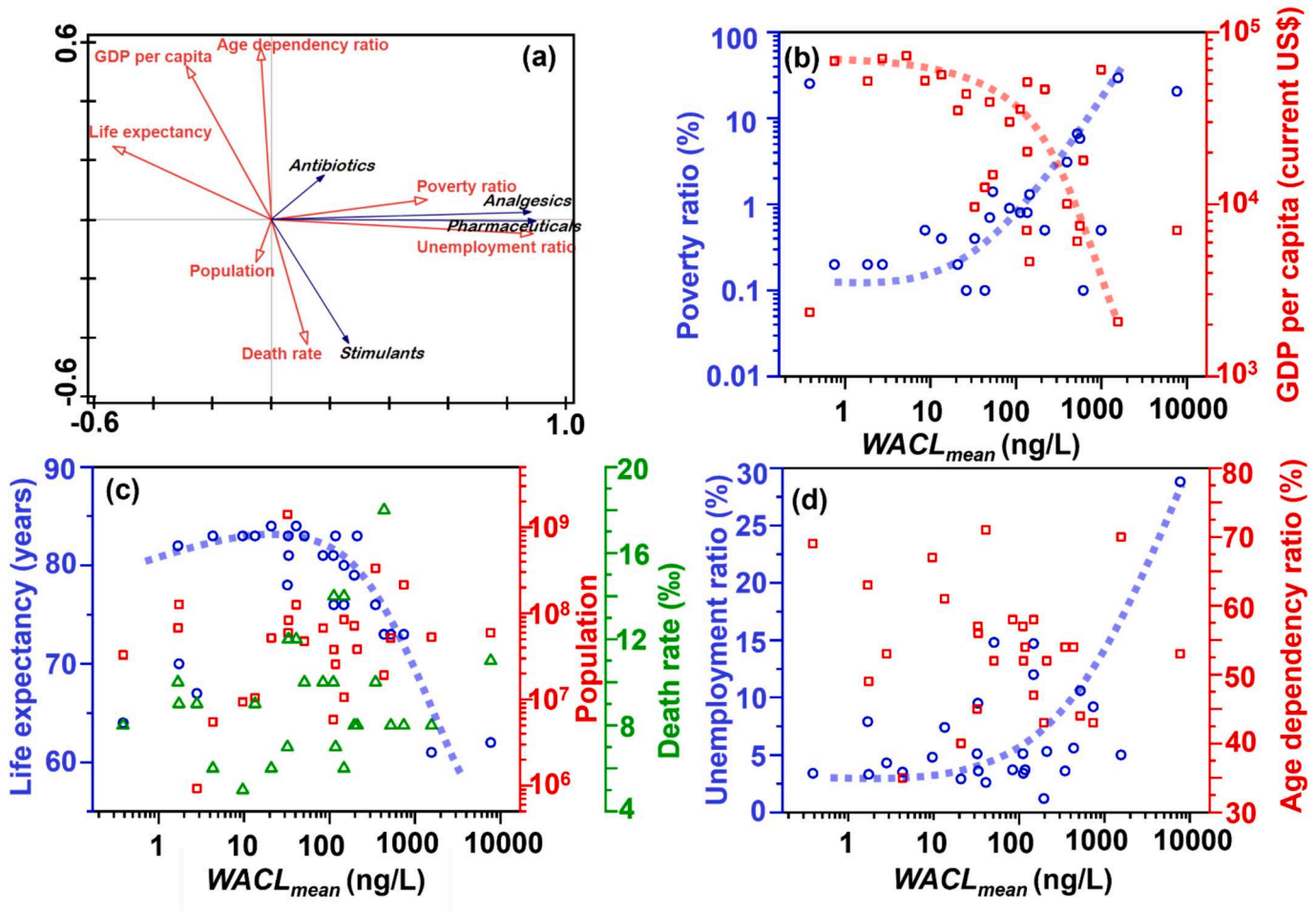

Fig. 5. Correlation and redundancy analysis between pharmaceutical pollution levels ($WACL_{mean}$) in global estuaries and regional socio-economic factors: (a) a vector plot indicating the strength of each factor overlaying with all reported pharmaceuticals and the three key pharmaceutical groups (the longer the vector line the more important it is); the relationships between $WACL_{mean}$ and (b) poverty ratio and GDP; (c) life expectancy, population size, and death rate, and (d) unemployment ratio and age dependency ratio.

ranging from 2040.57 to 5952.69 ng/L) were significantly higher compared with other countries (ranging from 0.00 to 422.21 ng/L). However, the age dependency ratio and the death rate were not the main socio-economic factor affecting the level of pharmaceutical pollution in global estuaries ($p > 0.05$).

3.6. Study limitations and research prospects

The present metadata analysis has some limitations that may affect the results. Firstly, the sample collection, pretreatment, and analysis methods used among different documented studies were inconsistent, and the detection limits of target compounds with different instruments also varied. Although we made every effort to review and include studies with relatively reliable quality assurance and quality control, the issue of data comparability among different studies still deserves attention. From this dataset, we calculated weighted averages, based on data availability, but this did not account for exposure magnitude, frequency or duration. Secondly, there were significant differences in the pharmaceuticals analyzed in different studies. Amongst the huge diversity of pharmaceuticals, some have received more research attention due to their widespread use, while other medications have had more limited attention. Hence, there is an uncertainty that some pharmaceuticals actually exist in estuaries but have yet to be measured and reported. Thirdly, this study collected pharmaceutical pollution data from 91 estuaries distributed in 26 countries worldwide, and there are still many urbanized estuaries in the world for which there is no data. In Africa, Oceania, and South America, less than 10 qualified documents that met the criteria could be found over the past 20 years, indicating that some continents have far better data representation than others. Data from underrepresented regions is needed to garner a more reliable global assessment and a more comprehensive perspective and understanding of the current chemicals and waste situation around the world. Fourthly, as a compromise to the data availability across global estuaries, our study selected a 20-year time window to analyze the spatial distribution characteristics of pharmaceutical pollution in global estuarine waters. However, this may overlook the temporal variations over such a long period of time. Last but not least, the screening level ecological assessment of pharmaceuticals performed here is an important method to evaluate potential hazards to estuarine ecosystems and aquatic life, but not all of the 198 pharmaceutical toxicological data involved in this study were available, or endpoints were not plausibly linked to evolutionarily conserved molecular initiation events, so we had to rely on ECOSAR predictions, which have high uncertainty, particularly for chronic responses to pharmaceuticals and other biologically active chemicals. Therefore, further supplementing and improving mechanistically grounded toxicological data of these chemicals are also essential to assess the hazards of pharmaceutical pollution in estuaries.

Motivated by the aforementioned limitations, the Global Estuaries Monitoring (GEM) Programme (https://www.globalestuaries.org) was proposed to the UNESCO Intergovernmental Oceanographic Commission in 2021 and was among the first group of Ocean Decade Programs endorsed by the United Nations Decade of Ocean Science for Sustainable

Development (2021–2030). The GEM Programme aims to develop standardized methods for sampling, extracting, detecting, and quantifying priority chemical contaminants in environmental samples collected from major urbanized estuaries worldwide. These standardized methods will enable a scientifically sound comparison of contamination profiles across various estuaries. The study focuses on six key aspects, including capacity building, standardization of research methods, promotion of best practices in pollution monitoring and control, data sharing, co-designing research strategies, and revealing the estuary health status. At the moment, a robust method has already been developed and verified to quantify 65 pharmaceuticals in river, estuary, and marine water samples for the GEM Programme, using only a small sample volume (i.e., 20 mL). This allows for economical global transportation of the water samples for standardized chemical analysis. Registrations from more than 160 estuaries across 54 countries have been received, and samples are being collected from these major urbanized estuaries globally. The GEM Programme will contribute to unveiling the global pollution situation and promoting best practices to combat pollution problems, thus achieving cleaner estuaries for a better and greener future.

4. Conclusion

Though estuaries are providing important ecological and economic benefits, increasing reports of pharmaceutical contamination are highlighting the need to better understand the risks presented by these CECs in estuarine ecosystems. In the current critical review, we identified 3229 individual concentration data for 239 pharmaceuticals across 91 global estuaries, involving 26 countries distributed in six continents. We observed that $WACL_{mean}$ levels on a continent basis were ranked as: Africa > South America > North America > Asia > Europe > Oceania. Analgesics, antibiotics, and stimulants are the most commonly reported categories in global estuaries. A total of 19 compounds were identified to present very high ecological risks in at least one continent. Pharmaceutical pollution levels in estuaries appeared to be related to the regional unemployment ratio, poverty ratio, life expectancy, and GDP per capita. Though this critical review provides an initial understanding of pharmaceutical occurrences and contamination in global estuaries over the past 20 years, it also highlights some research limitations and data gaps. The implementation of the GEM Programme addresses key limitation and knowledge gaps and promises to provide a more comprehensive understanding of CECs pollution in the near future.

CRediT authorship contribution statement

Demilade T. Adedipe: Writing – original draft, Investigation, Data curation. **Chong Chen:** Writing – review & editing, Visualization, Validation, Supervision, Software, Methodology, Investigation, Formal analysis. **Racliffe Weng Seng Lai:** Writing – review & editing, Supervision. **Shaopeng Xu:** Visualization, Software. **Qiong Luo:** Investigation, Formal analysis. **Guang-Jie Zhou:** Investigation, Conceptualization. **Alistair Boxall:** Writing – review & editing. **Bryan W. Brooks:** Writing – review & editing. **Martina A. Doblin:** Writing – review & editing. **Xinhong Wang:** Writing – review & editing. **Juying Wang:** Writing – review & editing. **Kenneth Mei Yee Leung:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2024.109031.

References

Allinson, M., Kameda, Y., Kimura, K., Allinson, G., 2018. Occurrence and assessment of the risk of ultraviolet filters and light stabilizers in Victorian estuaries. Environ Sci Pollut Res Int 25 (12), 12022–12033.

Ankley, G.T., Brooks, B.W., Huggett, D.B., Sumpter, J.P., 2007. Repeating history: pharmaceuticals in the environment. Environ Sci Technol 41, 8211–8217.

Ankley, G.T., Berninger, J.P., Maloney, E.M., Olker, J.H., Schaupp, C.M., Villeneuve, D. L., LaLone, C.A., 2024. Linking mechanistic effects of pharmaceuticals and personal care products to ecologically relevant outcomes: A decade of progress. Environ Toxicol Chem 43 (3), 537–548.

Australian Government, AMR and human health in Australia. 2023 https://www.amr.gov.au/about-amr/amr-australia/human-health#:~:text=Antibiotic%20use%20in%20Australia.

Backhaus, T., 2014. Medicines, shaken and stirred: a critical review on the ecotoxicology of pharmaceutical mixtures. Philos Trans R Soc Lond B Biol Sci 369 (1656), 20130585.

Bavumiragira, J.P., Ge, J., Yin, H., 2022. Fate and transport of pharmaceuticals in water systems: A processes review. Sci Total Environ 823, 153635.

Bayen, S., Zhang, H., Desai, M.M., Ooi, S.K., Kelly, B.C., 2013. Occurrence and distribution of pharmaceutically active and endocrine disrupting compounds in Singapore's marine environment: influence of hydrodynamics and physical-chemical properties. Environ Pollut 182, 1–8.

Bengtsson-Palme, J., Larsson, D.G., 2016. Concentrations of antibiotics predicted to select for resistant bacteria: Proposed limits for environmental regulation. Environ Int 86, 140–149.

Bexfield, L.M., Toccalino, P.L., Belitz, K., Foreman, W.T., Furlong, E.T., 2019. Hormones and pharmaceuticals in groundwater used as a source of drinking water across the United States. Environ Sci Technol 53 (6), 2950–2960.

Biel-Maeso, M., Baena-Nogueras, R.M., Corada-Fernandez, C., Lara-Martin, P.A., 2018. Occurrence, distribution and environmental risk of pharmaceutically active compounds (PhACs) in coastal and ocean waters from the Gulf of Cadiz (SW Spain). Sci Total Environ 612, 649–659.

Birch, G.F., Drage, D.S., Thompson, K., Eaglesham, G., Mueller, J.F., 2015. Emerging contaminants (pharmaceuticals, personal care products, a food additive and pesticides) in waters of Sydney estuary. Australia. Mar Pollut Bull 97 (1–2), 56–66.

Branchet, P., Arpin-Pont, L., Piram, A., Boissery, P., Wong-Wah-Chung, P., Doumenq, P., 2021. Pharmaceuticals in the marine environment: What are the present challenges in their monitoring? Sci Total Environ 766, 142644.

Camacho-Munoz, D., Martin, J., Santos, J.L., Aparicio, I., Alonso, E., 2010. Occurrence, temporal evolution and risk assessment of pharmaceutically active compounds in Donana Park (Spain). J Hazard Mater 183 (1–3), 602–608.

Chen, C., Zou, W., Cui, G., Tian, J., Wang, Y., Ma, L., 2020. Ecological risk assessment of current-use pesticides in an aquatic system of Shanghai. China. Chemosphere 257, 127222.

Chen, C., Luo, J., Bu, C., Zhang, W., Ma, L., 2022a. Efficacy of a large-scale integrated constructed wetland for pesticide removal in tail water from a sewage treatment plant. Sci Total Environ 838 (Pt 4), 156568.

Chen, C., Luo, J., Zhang, W., Bu, C., Ma, L., 2022b. Pesticide degradation in an integrated constructed wetland: Insights from compound-specific isotope analysis and 16S rDNA sequencing. Sci Total Environ 841, 156758.

Cui, Y., Wang, Y., Pan, C., Li, R., Xue, R., Guo, J., Zhang, R., 2019. Spatiotemporal distributions, source apportionment and potential risks of 15 pharmaceuticals and personal care products (PPCPs) in Qinzhou Bay, South China. Mar Pollut Bull 141, 104–111.

Drug Bank Database 2023 https://go.drugbank.com/releases/5-1-3.

Dehm, J., Singh, S., Ferreira, M., Piovano, S., Fick, J., 2021. Screening of pharmaceuticals in coastal waters of the southern coast of Viti Levu in Fiji. South Pacific. Chemosphere 276, 130161.
Elliott, S.M., Brigham, M.E., Kiesling, R.L., Schoenfuss, H.L., Jorgenson, Z.G., 2018. Environmentally relevant chemical mixtures of concern in waters of United States tributaries to the Great Lakes. Integr Environ Assess Manag 14 (4), 509–518.
Fang, T.H., Lin, C.W., Kao, C.H., 2019. Occurrence and distribution of pharmaceutical compounds in the Danshuei River Estuary and the Northern Taiwan Strait. Mar Pollut Bull 146, 509–520.
Fekadu, S., Alemayehu, E., Dewil, R., Van der Bruggen, B., 2019. Pharmaceuticals in freshwater aquatic environments: A comparison of the African and European challenge. Sci Total Environ 654, 324–337.
Gani, K.M., Hlongwa, N., Abunama, T., Kumari, S., Bux, F., 2021. Emerging contaminants in South African water environment- a critical review of their occurrence, sources and ecotoxicological risks. Chemosphere 269, 128737.
Gaw, S., Thomas, K.V., Hutchinson, T.H., 2014. Sources, impacts and trends of pharmaceuticals in the marine and coastal environment. Philos Trans R Soc Lond B Biol Sci 369 (1656), 20130572.
Gonzalez Pena, O.I., Lopez Zavala, M.A., Cabral Ruelas, H., 2021. Pharmaceuticals market, consumption trends and disease incidence are not driving the pharmaceutical research on water and wastewater. Int J Environ Res Public Health 18 (5), 2532.
Gumbi, B.P., Moodley, B., Birungi, G., Ndungu, P.G., 2017. Detection and quantification of acidic drug residues in South African surface water using gas chromatography-mass spectrometry. Chemosphere 168, 1042–1050.
Gumbi, B.P., Moodley, B., Birungi, G., Ndungu, P.G., 2019. Target, suspect and non-target screening of silylated derivatives of polar compounds based on single ion monitoring GC-MS. Int J Environ Res Public Health 16 (20), 4022.
Gunnarsson, L., Jauhiainen, A., Kristiansson, E., Nerman, O., Larsson, D.G.J., 2008. Evolutionary conservation of human drug targets in organisms used for environmental risk assessments. Environ Sci Technol 42, 5807–5813.
Gunnarsson, L., Snape, J.R., Verbruggen, B., Owen, S.F., Kristiansson, E., Margiotta-Casaluci, L., Osterlund, T., Hutchinson, K., Leverett, D., Marks, B., Tyler, C.R., 2019. Pharmacology beyond the patient - The environmental risks of human drugs. Environ Int 129, 320–332.
Herrero-Villar, M., Taggart, M.A., Mateo, R., 2023. Medicated livestock carcasses and landfill sites: Sources of highly toxic veterinary pharmaceuticals and caffeine for avian scavengers. J Hazard Mater 459, 132195.
Huff Chester, A., Gordon, C., Hartmann, H.A., Bartell, S.E., Ansah, E., Yan, T., Li, B., Dampha, N.K., Edmiston, P.L., Novak, P.J., Schoenfuss, H.L., 2022. Contaminants of emerging concern in the Lower Volta River, Ghana, West Africa: The agriculture, aquaculture, and urban development nexus. Environ Toxicol Chem 41 (2), 369–381.
Husain Khan, A., Abdul Aziz, H., Palaniandy, P., Naushad, M., Cevik, E., Zahmatkesh, S., 2023. Pharmaceutical residues in the ecosystem: Antibiotic resistance, health impacts, and removal techniques. Chemosphere 339, 139647.
Jaffrezic, A., Jarde, E., Soulier, A., Carrera, L., Marengue, E., Cailleau, A., Le Bot, B., 2017. Veterinary pharmaceutical contamination in mixed land use watersheds: from agricultural headwater to water monitoring watershed. Sci Total Environ 609, 992–1000.
Jakab, G., Szalai, Z., Michalko, G., Ringer, M., Filep, T., Szabo, L., Maasz, G., Pirger, Z., Ferincz, A., Staszny, A., Dobosy, P., Kondor, A.C., 2020. Thermal baths as sources of pharmaceutical and illicit drug contamination. Environ Sci Pollut Res Int 27 (1), 399–410.
Jiang, J.J., Lee, C.L., Fang, M.D., Boyd, K.G., Gibb, S.W., 2015. Source apportionment and risk assessment of emerging contaminants: an approach of pharmaco-signature in water systems. PLoS One 10 (4), e0122813.
Kasprzyk-Hordern, B., Dinsdale, R.M., Guwy, A.J., 2007. Multi-residue method for the determination of basic/neutral pharmaceuticals and illicit drugs in surface water by solid-phase extraction and ultra performance liquid chromatography-positive electrospray ionisation tandem mass spectrometry. J Chromatogr A 1161 (1–2), 132–145.
Kawuma, R., Chimukuche, R.S., Francis, S.C., Seeley, J., Weiss, H.A., 2021. Knowledge, use (misuse) and perceptions of over-the-counter analgesics in sub-Saharan Africa: a scoping review. Glob Health Action 14 (1), 1955476.
Kazakova, J., Villar-Navarro, M., Ramos-Payan, M., Aranda-Merino, N., Roman-Hidalgo, C., Bello-Lopez, M.A., Fernandez-Torres, R., 2021. Monitoring of pharmaceuticals in aquatic biota (Procambarus clarkii) of the Donana National Park (Spain). J Environ Manage 297, 113314.
Kelly, K.R., Brooks, B.W., 2018. Chapter Three - Global aquatic hazard assessment of ciprofloxacin: Exceedances of antibiotic resistance development and ecotoxicological thresholds. Prog Mol Bio Transl Sci 159, 59–77.
Khan, H.K., Rehman, M.Y.A., Malik, R.N., 2020. Fate and toxicity of pharmaceuticals in water environment: An insight on their occurrence in South Asia. J Environ Manage 271, 111030.
Kim, H.Y., Lee, I.S., Oh, J.E., 2017. Human and veterinary pharmaceuticals in the marine environment including fish farms in Korea. Sci Total Environ 579, 940–949.
K'Oreje, K., O., Vergeynst, L., Ombaka, D., De Wispelaere, P., Okoth, M., Van Langenhove, H. and Demeestere, K, 2016. Occurrence patterns of pharmaceutical residues in wastewater, surface water and groundwater of Nairobi and Kisumu city, Kenya. Chemosphere 149, 238–244.
Korkmaz, N.E., Caglar, N.B., Aksu, A., 2022. Presence and distribution of selected pharmaceutical compounds in water and surface sediment of the Golden Horn Estuary, Sea of Marmara. Turkey. Reg Stud Mar Sci 51, 102221.
Kristofco, L.A., Brooks, B.W., 2017. Global scanning of antihistamines in the environment: Analysis of occurrence and hazards in aquatic systems. Sci Total Environ 592, 477–487.
Lalone, C.A., Villeneuve, D.L., Burgoon, L.D., Russom, C.L., Helgen, H.W., Berninger, J. P., Tietge, J.E., Severson, M.N., Cavallin, J.E., Ankley, G.T., 2013. Molecular target sequence similarity as a basis for species extrapolation to assess the ecological risk of chemicals with known modes of action. Aquat Toxicol 144–145, 141–154.
Low, K., Chai, L., Lee, C., Zhang, G., Zhang, R., Vahab, V., Bong, C., 2020. Prevalence and risk assessment of antibiotics in riverine estuarine waters of Larut and Sangga Besar River. Perak. J Oceanol Limnol 39 (1), 122–134.
LSE, the London School of Economics and Political Science 2021 https://www.lse.ac.uk/News/Latest-news-from-LSE/2021/l-december-21/UK-highest-consumer-of-opioids-globally.
Lu, S., Lin, C., Lei, K., Wang, B., Xin, M., Gu, X., Cao, Y., Liu, X., Ouyang, W., He, M., 2020. Occurrence, spatiotemporal variation, and ecological risk of antibiotics in the water of the semi-enclosed urbanized Jiaozhou Bay in eastern China. Water Res 184, 116187.
Madikizela, L.M., Chimuka, L., 2017. Occurrence of naproxen, ibuprofen, and diclofenac residues in wastewater and river water of KwaZulu-Natal Province in South Africa. Environ Monit Assess 189 (7), 348.
Malnes, D., Ahrens, L., Kohler, S., Forsberg, M., Golovko, O., 2022. Occurrence and mass flows of contaminants of emerging concern (CECs) in Sweden's three largest lakes and associated rivers. Chemosphere 294, 133825.
Martinez-Megias, C., Rico, A., 2022. Biodiversity impacts by multiple anthropogenic stressors in Mediterranean coastal wetlands. Sci Total Environ 818, 151712.
Matamoros, V., Arias, C., Brix, H., Bayona, J.M., 2009. Preliminary screening of small-scale domestic wastewater treatment systems for removal of pharmaceutical and personal care products. Water Res 43 (1), 55–62.
Matongo, S., Birungi, G., Moodley, B., Ndungu, P., 2015. Occurrence of selected pharmaceuticals in water and sediment of Umgeni River, KwaZulu-Natal, South Africa. Environ Sci Pollut Res Int 22 (13), 10298–10308.
Mechelke, J., Rust, D., Jaeger, A., Hollender, J., 2020. Enantiomeric fractionation during biotransformation of chiral pharmaceuticals in recirculating water-sediment test flumes. Environ Sci Technol 54 (12), 7291–7301.
Mejías, C., Martín, J., Santos, J.L., Aparicio, I., Alonso, E., 2021. Occurrence of pharmaceuticals and their metabolites in sewage sludge and soil: A review on their distribution and environmental risk assessment. Trends Environ Anal Chem 30, e00125.
Moldovan, Z., 2006. Occurrences of pharmaceutical and personal care products as micropollutants in rivers from Romania. Chemosphere 64 (11), 1808–1817.
Mole, R.A., Brooks, B.W., 2019. Global scanning of selective serotonin reuptake inhibitors: occurrence, wastewater treatment and hazards in aquatic systems. Environ Pollut 250, 1019–1031.
Mu, K., Jiang, K., Wang, Y., Zhao, Z., Cang, S., Bi, K., Li, Q., Liu, R., 2022. The biological fate of pharmaceutical excipient beta-cyclodextrin: Pharmacokinetics, tissue distribution, excretion, and metabolism of beta-cyclodextrin in rats. Molecules 27 (3), 1138.
Murray, A.K., Stanton, I., Gaze, W.H., Snape, J., 2021. Dawning of a new ERA: Environmental Risk Assessment of antibiotics and their potential to select for antimicrobial resistance. Water Res 200, 117233.
Nagarajan, R.P., Bedwell, M., Holmes, A.E., Sanches, T., Acuña, S., Baerwald, M., Barnes, M.A., Blankenship, S., Connon, R.E., Deiner, K., Gille, D., Goldberg, C.S., Hunter, M.E., Jerde, C.L., Luikart, G., Meyer, R.S., Watts, A., Schreier, A., 2022. Environmental DNA Methods for Ecological Monitoring and Biodiversity Assessment in Estuaries. Estuar Coast 45 (7), 2254–2273.
Ngubane, N.P., Naicker, D., Ncube, S., Chimuka, L., Madikizela, L.M., 2019. Determination of naproxen, diclofenac and ibuprofen in Umgeni estuary and seawater: A case of northern Durban in KwaZulu–Natal Province of South Africa. Reg Stud Mar Sci 29, 100675.
Nodler, K., Voutsa, D., Licha, T., 2014. Polar organic micropollutants in the coastal environment of different marine systems. Mar Pollut Bull 85 (1), 50–59.
Ooi, E.E., Dhar, A., Petruschke, R., Locht, C., Buchy, P., Low, J.G.H., 2022. Use of analgesics/antipyretics in the management of symptoms associated with COVID-19 vaccination. NPJ Vaccines 7 (1), 31.
Reis, E.O., Foureaux, A.F.S., Rodrigues, J.S., Moreira, V.R., Lebron, Y.A.R., Santos, L.V.S., Amaral, M.C.S., Lange, L.C., 2019. Occurrence, removal and seasonal variation of pharmaceuticals in Brasilian drinking water treatment plants. Environ Pollut 250, 773–781.
Saari, G.N., Scott, W.C., Brooks, B.W., 2017. Global scanning assessment of calcium channel blockers in the environment: Review and analysis of occurrence, ecotoxicology and hazards in aquatic systems. Chemosphere 189, 466–478.
Sanganyado, E., Chingono, K.E., Gwenzi, W., Chaukura, N., Liu, W., 2021. Organic pollutants in deep sea: Occurrence, fate, and ecological implications. Water Res 205, 117658.
Schafhauser, B.H., Kristofco, L.A., de Oliveira, C.M.R., Brooks, B.W., 2018. Global review and analysis of erythromycin in the environment: Occurrence, bioaccumulation and antibiotic resistance hazards. Environ Pollut 238, 440–451.
Google Scholar 2023 https://scholar.google.com.hk/.
Scott, P.D., Bartkow, M., Blockwell, S.J., Coleman, H.M., Khan, S.J., Lim, R., McDonald, J.A., Nice, H., Nugegoda, D., Pettigrove, V., Tremblay, L.A., Warne, M.S., Leusch, F.D., 2014. A national survey of trace organic contaminants in Australian rivers. J Environ Qual 43 (5), 1702–1712.
Scott, W.C., Breed, C.S., Haddad, S.P., Burket, S.R., Saari, G.N., Pearce, P.J., Chambliss, C.K., Brooks, B.W., 2019. Spatial and temporal influence of onsite wastewater treatment systems, centralized effluent discharge, and tides on aquatic hazards of nutrients, indicator bacteria, and pharmaceuticals in a coastal bayou. Sci Total Environ 650 (Pt 1), 354–364.

Statista, Market value of pharmaceuticals in selected countries and regions in Latin America in 2021. 2023 https://www.statista.com/statistics/418021/revenue-from-pharmaceutical-industry-in-latin-america-by-major-country/.
Thai, P.K., Ky, L.X., Binh, V.N., Nhung, P.H., Nhan, P.T., Hieu, N.Q., Dang, N.T.T., Tam, N.K.B., Anh, N.T.K., 2018. Occurrence of antibiotic residues and antibiotic-resistant bacteria in effluents of pharmaceutical manufacturers and other sources around Hanoi. Vietnam. Sci Total Environ 645, 393–400.
Tong, X., Mohapatra, S., Zhang, J., Tran, N.H., You, L., He, Y., Gin, K.Y., 2022. Source, fate, transport and modelling of selected emerging contaminants in the aquatic environment: Current status and future perspectives. Water Res 217, 118418.
Topaz, T., Boxall, A., Suari, Y., Egozi, R., Sade, T., Chefetz, B., 2020. Ecological Risk Dynamics of Pharmaceuticals in Micro-Estuary Environments. Environ Sci Technol 54 (18), 11182–11190.
Valdez-Carrillo, M., Abrell, L., Ramirez-Hernandez, J., Reyes-Lopez, J.A., Carreon-Diazconti, C., 2020. Pharmaceuticals as emerging contaminants in the aquatic environment of Latin America: a review. Environ Sci Pollut Res Int 27 (36), 44863–44891.
Waleng, N.J., Nomngongo, P.N., 2022. Occurrence of pharmaceuticals in the environmental waters: African and Asian perspectives. Environ Chem Ecotox 4, 50–66.
Watkinson, A.J., Murby, E.J., Kolpin, D.W., Costanzo, S.D., 2009. The occurrence of antibiotics in an urban watershed: from wastewater to drinking water. Sci Total Environ 407 (8), 2711–2723.
Web of Science 2023 https://www.webofscience.com/.
White, D., Lapworth, D.J., Civil, W., Williams, P., 2019. Tracking changes in the occurrence and source of pharmaceuticals within the River Thames, UK; from source to sea. Environ Pollut 249, 257–266.
Wilkinson, J.L., Boxall, A.B.A., Kolpin, D.W., Leung, K.M.Y., Lai, R.W.S., Teta, C., 2022. Pharmaceutical pollution of the world's rivers. PNAS 119 (8), e2113947119.
World Bank Open Data 2023 https://data.worldbank.org/.
Wronski, A.R., Brooks, B.W., 2023. Global occurrence and aquatic hazards of antipsychotics in sewage influents, effluent discharges and surface waters. Environ Pollut 320, 121042.
Wu, R., Ruan, Y., Huang, G., Li, J., Lao, J.Y., Lin, H., Liu, Y., Cui, Y., Zhang, K., Wang, Q., Yan, M., Wu, J., Huang, B., Lam, P.K.S., 2022b. Source Apportionment, Hydrodynamic Influence, and Environmental Stress of Pharmaceuticals in a Microtidal Estuary with Multiple Outlets in South China. Environ Sci Technol 56 (16), 11374–11386.
Wu, Q., Xiao, S.K., Pan, C.G., Yin, C., Wang, Y.H., Yu, K.F., 2022a. Occurrence, source apportionment and risk assessment of antibiotics in water and sediment from the subtropical Beibu Gulf. South China. Sci Total Environ 806 (Pt 2), 150439.
Xu, H., Liu, K., Ning, T., Huang, G., Zhang, Q., Li, Y., Wang, M., Fan, Y., an, W., Ji, L., Guo, Q. and Ren, H, 2022. Environmental remediation promotes the restoration of biodiversity in the Shenzhen Bay Estuary. South China. Ecosyst Health Sustain 8 (1), 2026250.
Yang, Y., Zhang, X., Jiang, J., Han, J., Li, W., Li, X., Yee Leung, K.M., Snyder, S.A., Alvarez, P.J.J., 2022. Which micropollutants in water environments deserve more attention globally? Environ Sci Technol 56 (1), 13–29.