Emerging Pharmaceutical Pollutants in Wastewater and Their Effects on Aquatic Organisms

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Abstract
Pharmaceutical pollutants have gained increasing importance as contaminants of concern because they are biologically active substances that are not specifically removed in conventional wastewater treatment plants. Pharmaceuticals are discharged continuously from a range of sources such as municipal wastewater, hospitals, pharmaceutical manufacturing, livestock production, and aquaculture into aquatic ecosystems, where they remain at a range of concentrations from nanograms to micrograms per litre. While concentrations are generally low, pseudo-persistence is set up because of the continuous release, leading to prolonged exposure of aquatic organisms. Many studies have shown that pharmaceuticals can cause changes in fish behaviour, physiology, biochemistry, reproduction, and development in fish, invertebrates, algae, and microbial communities. Antibiotics also help to increase the spread of antimicrobial resistance genes, which have the potential to impact ecosystem functions and human health. This narrative review aims to summarize the key sources, environmental occurrence, fate, and ecotoxicological effects of pharmaceutical pollutants found in wastewater. Special focus is given to their impact on various trophic levels of aquatic ecosystems and the challenges associated with their elimination by traditional wastewater treatment processes. Lack of knowledge about chronic exposure, mixture toxicity, transformation products, and monitoring in developing countries is also pointed out. Therefore, the enhancement of wastewater treatment technologies, better environmental monitoring, and the establishment of comprehensive regulations play a crucial role in reducing pharmaceutical contamination and safeguarding water bodies.

Keywords: Pharmaceutical pollutants, wastewater, aquatic organisms, ecotoxicology, emerging contaminants, antibiotics, wastewater treatment

1. Introduction

The use of pharmaceuticals has proven essential in today's healthcare system because of their role in the prevention, treatment, and management of infectious and chronic diseases. But the higher occurrence and use of these substances have led to their persistent discharge to water, and they are now identified as a significant class of emerging contaminants (Daughton and Ternes, 1999, Patel et al., 2019). Unlike many traditional pollutants, pharmaceuticals are specifically designed to elicit biological responses at low concentrations, and there are concerns about their unwanted effects on non-target aquatic species. Antibiotics, analgesics, anti-inflammatory drugs, antidepressants, antiepileptics, β-blockers, lipid regulators, hormones, and anticancer drugs are some of the pharmaceutical contaminants. The main pathways for these compounds into aquatic ecosystems are municipal wastewaters, effluents from hospitals, pharmaceutical production waste, veterinary medicine, farm animal production, and aquaculture (Kümmerer, 2009, Aus der Beek et al., 2016).
Conventional wastewater treatment plants (WWTPs) were traditionally engineered to remove suspended solids, nutrients, and biodegradable organic matter, but not necessarily trace organic contaminants, which means that many pharmaceuticals are not eliminated and are released to rivers, lakes, estuaries, and coastal waters (Michael et al., 2013, Patel et al., 2019). Pharmaceutical pollutants have one unique characteristic: pseudo-persistence. Many pharmaceutical products are not chemically persistent for long periods of time; however, they are continually released from human and animal activity and therefore have relatively constant concentrations in aquatic systems. Therefore, in aquatic organisms, chronic exposures occur throughout the life cycle even at nanogram to microgram per litre (ng/l, µg/l) levels of pharmaceuticals (Patel et al., 2019, Daughton and Ternes, 1999). Chronic exposure to these low levels has been shown to cause oxidative stress, endocrine disruption, reproductive dysfunction, developmental problems, behavioural effects and immunotoxicity in aquatic organisms (Fabbri and Franzellitti, 2016, Fent et al., 2006).
Among all the pharmaceutical groups, antibiotics have received particular attention due to their role in antimicrobial resistance (AMR). Ongoing input of antibiotics into the wastewater system favors the selection of resistant bacteria and the dissemination of antibiotic resistance genes in the aquatic microbial population. Wastewater treatment plants (WWTPs) are therefore considered significant environmental reservoirs that connect environmental contamination with public health issues within the One Health concept (Grenni et al., 2018, Michael et al., 2013). Advances in analytical techniques, particularly liquid chromatography coupled with tandem mass spectrometry (LC–MS/MS), have greatly improved the detection of pharmaceuticals at environmentally relevant concentrations. Pharmaceutical residues are now reported in surface water, groundwater, sediments, wastewater influents and effluents, drinking water, and even in remote aquatic ecosystems around the world (Wilkinson et al., 2022, Aus der Beek et al., 2016). A

recent global survey detected pharmaceutical pollutants in rivers across more than 100 countries, highlighting that pharmaceutical contamination is a worldwide environmental problem rather than one confined to industrialized regions (Wilkinson et al., 2022)

Despite considerable advancement in the monitoring of pharmaceutical contaminants, there are still large gaps in knowledge about chronic exposure, mixture toxicity, transformation products created during wastewater treatment, and ecological risks in developing countries where monitoring data is still limited (Boxall et al., 2012). Addressing these challenges is essential for effective environmental management strategies and protection of aquatic ecosystems. Therefore, this narrative review provides a summary of the current knowledge on the occurrence, major sources, fate, and ecotoxicological effects of pharmaceutical pollutants in wastewater, while pointing out future research needs and management strategies.

2. Sources and Occurrence of Pharmaceuticals in Wastewater

There are several anthropogenic pathways for the introduction of pharmaceutical residues into aquatic systems. The largest source is municipal wastewater, since the majority of drugs used by humans are poorly metabolized and excreted in urine and faeces as parent and biologically active metabolites. After excretion, they are transported to wastewater treatment plants, where many are not completely removed before being released into rivers, lakes, and coastal waters (Kümmerer, 2009, Aus der Beek et al., 2016).

Another significant source is hospital effluents, as there is a considerable amount of antibiotics, analgesics, antineoplastic drugs, disinfectants, and diagnostic agents discharged by the hospital. Concentrations of pharmaceuticals in hospital wastewaters are often much greater than concentrations in municipal sewage, creating a potential threat of the release of toxic compounds and antimicrobial resistance determinants into aquatic environments. Furthermore, pharmaceutical manufacturing industries might release untreated or incompletely treated wastewater with extremely high concentrations of API in case treatment systems are not available (Michael et al., 2013).

The environmental contamination by pharmaceuticals can also be significant in veterinary medicine and intensive livestock farming. Excretable antibiotics, antiparasitic agents, and growth-promoting agents given to animals are often excreted in the same form as they were initially administered. These compounds then enter the surrounding water bodies via manure application, agricultural runoff, and leaching from the soil. However, aquaculture facilities often add antibiotics to the water to ward off disease outbreaks, which leaves residues of antibiotics in the water and sediments and can also lead to increased antibiotic resistance in the water microbial communities (Grenni et al., 2018)

The presence of pharmaceuticals has been reported in wastewater influents, treated effluents, surface water, ground water, sediments, and drinking water supplies worldwide. Commonly seen drugs include diclofenac, ibuprofen, naproxen, carbamazepine, sulfamethoxazole, ciprofloxacin, erythromycin, fluoxetine, propranolol, and atenolol. The levels in the environment are usually in the range of several nanograms per litre up to a few micrograms per litre, but higher concentrations have been reported in the vicinity of pharmaceutical production sites and hospitals (Ebele et al., 2017).

Pharmaceutical contamination has been found all over Europe, North America, Asia, South America, and Africa, but there are some geographic differences. Monitoring studies have been undertaken mostly in developed countries, while there has been little information collected in many LMICs, despite their growing use of pharmaceuticals and limited wastewater treatment facilities. Thus, the worldwide prevalence of pharmaceutical pollution is probably underreported (Wilkinson et al., 2022). Table 1 summarizes the major pharmaceutical pollutants frequently detected in wastewater

Table 1: Major pharmaceutical pollutants frequently detected in wastewater

Pharmaceutical	Therapeutic Class	Primary Sources	Major Environmental Concern	Reference
Diclofenac	NSAID	Municipal wastewater	Fish toxicity	Fabbri & Franzellitti (2016)
Ibuprofen	NSAID	Domestic wastewater	Oxidative stress	Patel et al. (2019)
Carbamazepine	Antiepileptic	Domestic wastewater	High environmental persistence	Aus der Beek et al. (2016)
Sulfamethoxazole	Antibiotic	Hospitals and households	Antimicrobial resistance development	Grenni, Ancona & Caracciolo (2018)
Ciprofloxacin	Antibiotic	Hospitals and aquaculture activities	Selection of resistant bacteria	Michael et al. (2013)
Fluoxetine	Antidepressant	Municipal wastewater	Behavioural alterations in aquatic organisms	Brodin et al. (2013)

Atenolol	β-blocker	Domestic wastewater	Cardiovascular system disruption in aquatic organisms	Patel et al. (2019)
Erythromycin	Antibiotic	Hospital wastewater	Microbial toxicity and ecological imbalance	Grenni, Ancona & Caracciolo (2018)

3. Fate and Behaviour of Pharmaceuticals in Aquatic Environments

Upon entering water systems, the pharmaceuticals experience physical, chemical, and biological transformations, which dictate the persistence, transport, and impact on the environment. Physicochemical factors influencing environmental behaviour include molecular weight, hydrophobicity, water solubility, ionization potential, degradation potential, and environmental factors (temperature, pH, DOM, and microbial activity) (Patel et al., 2019).

Most pharmaceuticals, however, have been undervalued in terms of their environmental risks because of the inadequate characterization of the transformation products in the environment, as well as the absence of the transformation products in the current environmental risk assessment. Pharmaceuticals are quite recalcitrant in the sense that they are continually affected by WWTPs, and hence their concentrations are relatively constant as compared to a continuous dilution process (Daughton and Ternes, 1999). However, after entering the aquatic environment, pharmaceuticals may undergo several changes – such as photolysis, hydrolysis, microbial degradation, oxidation, and reduction. The metabolites and degradation products of these transformations may be as, or more, environmental toxicants than the original compounds. Most of the pharmaceuticals are, nevertheless, underestimated in terms of their ecological hazards because of the inadequate characterization of transformation products in the environment and because of the absence of transformation products in the existing environmental risk assessment procedures (Ebele et al., 2017).

A significant pathway in the environment is suspended particles and sediments. Sediments are also a source and sink, whereby they release the accumulations of pharmaceutical substances under varying environmental conditions. There is also a likelihood of bioaccumulation with certain pharmaceuticals, particularly in aquatic organisms that are exposed over a long period of time. The bioaccumulation factors are usually lower than those of persistent organic pollutants (POPs), and tissue concentrations of repeated exposures can be measurable, but not always relevant to cause biological effects (Gaw et al., 2014).

The other difficulty with the environmental fate assessment is that instead of being exposed to single pharmaceuticals, aquatic organisms are exposed to complex compounds of pharmaceuticals. The combination, synergistic, or antagonistic toxicity of the mixture might not be predicted based on the toxicity of the drugs tested individually. This is one of the biggest drawbacks of existing ecological risk assessment tools and frameworks (Boxall et al., 2012).

4. Ecotoxicological Effects on Aquatic Organisms

The drug pollutants are capable of affecting the aquatic organisms at all levels, including microorganisms and vertebrates. The environment has relatively low concentrations, although chronic exposure at lower levels can have effects on biochemical pathways common to all species, and their effects can be harmful to physiological and ecological functions (Fent et al., 2006)

4.1 Effects on Fish

One of the most studied species in pharmaceutical ecotoxicology is the fish, as it is a higher trophic level and has more mammalian-like physiological systems. Fluoxetine and other antidepressants have been shown to influence swimming behaviors, predator avoidance, feeding, and social behaviors of fish (Brodin et al., 2013). The application of anti-inflammatory medications, such as diclofenac, in the gill, kidney, and liver tissues, and 0-blockers, which can influence cardiovascular physiology and stress response, has been associated with histological changes (Fabbri and Franzellitti, 2016). Long durations of exposure can also cause negative impacts on reproduction, embryo development, endocrine functions, and the immune system.

4.2 Effects on Aquatic Invertebrates

Daphnia spp., molluscs, and crustaceans are examples of aquatic invertebrates that are highly poisonous to pharmaceutical contaminants. Effects of exposure to different pharmaceutical classes have been reported to include oxidative stress, slowed growth, slowed development, reproductive changes, mobility, and increased mortality impairment (Fent et al., 2006). Their significance in nutrient recycling, food webs, and lower troglo-ecosystems, had they been suppressed by pharmaceuticals, these impacts could percolate up and down the aquatic food web, and even to higher troglo-levels.

4.3 Effects on Algae and Aquatic Plants

Pharmaceuticals (anti-inflammatories and antibiotics) that interfere with photosynthesis and cellular metabolism are especially harmful to primary producers. Exposure may also result in a reduced biomass, photosynthesis inhibition, algal community alterations, and biomass reduction (Grenni et al., 2018). These alterations can decrease primary productivity and can indirectly affect high trophic levels since they cause a decrease in energy flow via the aquatic food web.

4.4 Impacts on Microbial Communities.

The microbial communities are highly vulnerable to the impact of antibiotics due to their continuous exposure to antibiotics. Their antibiotic concentrations in food are often low and can potentially influence the microbial diversity, decrease the growth of beneficial microorganisms, and induce an increase in antibiotic resistance genes and antibiotic-resistant bacteria (Michael et al., 2013). Wastewater Treatment Plants (WWTPs) are nowadays considered a significant environmental reservoir of antimicrobial resistance dissemination to aquatic environments and one of the emerging threats in One Health to environmental, animal, and human health (Richmond et al., 2018, Wilkinson et al., 2022).

5. Wastewater Treatment and Removal Technologies

The conventional wastewater treatment plants (WWTPs) are inadequate since the pharmaceutical residues continue to be released into water bodies. Traditional treatment processes (primary sedimentation and conventional activated sludge systems) are designed such that it eliminates suspended solids, biodegradable organics, and nutrients, but not trace organics. Therefore, a large portion of drugs is present in the receiving waters and will not be eliminated with the help of treatment (Michael et al., 2013).

The removal of various pharmaceuticals is very dependent on the physicochemical properties of the pharmaceuticals, such as molecular weight, hydrophobicity, ionization state, and biodegradability. The majority of easily biodegradable compounds are more efficiently removed, e.g., ibuprofen, and persistent compounds, e.g., carbamazepine and diclofenac, are detected in their native state in WWTPs (Aus der Beek et al., 2016).

Activated sludge is the most common among all biological technologies that are used in the world. The primary removal process is microbiological degradation, and in many cases, not all of the metabolites can be degraded by microorganisms, and can be as toxic or biologically active as the parent compounds (Patel et al., 2019). Even better than a membrane filtration system are membrane bioreactors (MBRs), which integrate a biological degradation process with the filtration. They are also costly to install and run compared to their competitors, more so in the developing nations, and do not contribute to their acceptance.

Nevertheless, high-energy oxidation processes (AOPs) such as ozonation, UV/H2O2 oxidation, Fenton oxidation, and photocatalysis have received a lot of attention because of the generation of a highly reactive hydroxyl radical, which can destroy the recalcitrant pharmaceuticals. In several studies, these technologies have been useful in the efficacy of the removal of different antibiotics, painkillers, and endocrine-disrupting medications. AOPs can also produce transformation products whose environmental toxicity is not well understood, and full-scale toxicity testing is required after treatment (Ebele et al., 2017).

Powdered and granular activated carbon are well known as effective pharmaceutical polishing treatments, which are used through adsorption technologies. Activated carbon is effective at adsorbing hydrophobic and moderately polar pharmaceutical compounds, but the adsorption capacity varies with the pharmaceutical properties and the presence of competition from dissolved organic matter (Patel et al., 2019). High pharmaceutical removal efficiencies are also possible with membrane filtration technologies, such as nanofiltration and reverse osmosis, but the fouling of the membranes, energy consumption, and disposal of the concentrate are challenging issues during the operation of the membrane.

Constructed wetlands, phytoremediation systems, and other NbS are now being identified as environmentally friendly solutions for pharmaceutical removal. These systems are based on the interaction between plants, microorganisms, sediments, and sunlight to promote pharmaceutical degradation and adsorption. Constructed wetlands are cost-effective treatment facilities for small communities and developing areas, although they have different removal efficiencies for different compounds and under varying climatic conditions.

Even though there have been significant technological advances, it is difficult to find a single technology that can remove the diverse pharmaceutical contaminants found in wastewater. Thus, multi-barrier treatment systems are being increasingly recommended, in which the treatment is carried out by using a combination of biological, physical, and chemical processes, to achieve better removal efficiency and reduce environmental risk. Table 2 summarizes common wastewater treatment technologies for pharmaceutical removal.

Table 2: Common wastewater treatment technologies for pharmaceutical removal

Treatment Technology	Removal Mechanism	Advantages	Limitations	Reference
Activated sludge	Biodegradation	Low-cost and widely used in wastewater treatment systems	Ineffective for the removal of persistent pharmaceutical compounds	Michael et al. (2013)
Membrane bioreactor (MBR)	Biological degradation combined with filtration	High removal efficiency for pharmaceutical contaminants	High operational and maintenance costs	Patel et al. (2019)

Ozonation	Advanced oxidation process	Effective removal of many pharmaceutical compounds	Potential formation of transformation products	Patel et al. (2019)
UV/H_2O_2	Hydroxyl radical oxidation	Rapid degradation of pharmaceutical pollutants	High energy requirements	Patel et al. (2019)
Activated Carbon	Adsorption	Effective polishing treatment for residual pharmaceutical removal	Requires adsorbent regeneration or replacement	Patel et al. (2019)
Constructed wetlands	Plant–microbe interactions	Sustainable, economical, and environmentally friendly approach	Variable removal efficiency depending on conditions	Patel et al. (2019)

6. Discussion and Synthesis

Pollution by pharmaceuticals is one of the major environmental issues linked to urbanization, population growth, and rising healthcare needs. Evidence accumulated over the past two decades demonstrates that pharmaceutical residues are now found in aquatic environments around the world, both in surface waters and groundwater, as well as in sediments, wastewater effluents, and even in drinking water sources (Wilkinson et al., 2022, Aus der Beek et al., 2016). Pharmaceuticals are molecules with biological activity, tailored to interact with physiological pathways, as opposed to many other "conventional" pollutants. Thus, adverse effects can be caused by these concentrations even when they are considered environmentally relevant, after a prolonged exposure period (Fent et al., 2006).

The available data indicate that pharmaceutical pollution should not be assessed solely on a species-by-species basis, but rather an ecosystem approach should be used. All of these behavioural changes, reproductive impacts on aquatic invertebrates, growth inhibition of algae, and impacts on the microbial communities have a widespread impact on ecological processes and the cycling of nutrients, interactions with food webs, and the productivity of ecosystems (Richmond et al., 2018, Brodin et al., 2013). The impacts of these ecological consequences can be long-term and result in a loss of biodiversity and ecological resilience.

Antibiotics should be given special attention, since these also have an impact on aquatic organisms and promote the development of antimicrobial resistance. Antibiotics, resistant microorganisms, and antibiotic resistance genes all interact favorably in wastewater treatment plants, which can spread them into natural aquatic environments (Grenni et al., 2018). This environmental aspect of antimicrobial resistance further highlights the need for an integrated approach to One Health, understanding the relationship between environment, human health, and animal health.

Analysis of the pollutants in wastewater and wastewater treatment technologies has improved significantly, but there are also many drawbacks. Most environmental risk assessments are carried out using experiments on individual compounds, while aquatic organisms are exposed to complex pharmaceutical mixtures in which the combination effects of pharmaceuticals are largely unknown (Boxall et al., 2012). Moreover, the transformation products produced during the wastewater treatment process are often overlooked in favour of parent compounds, even when they have been demonstrated to be potentially more toxic than or at least as toxic as the parent compounds.

7. Research Gaps and Future Directions

Though research into pharmaceutical pollution has grown, there are still some major knowledge gaps that hinder the ability to accurately assess the ecological impacts of pharmaceutical pollution (Table 3). First, although many ecotoxicological studies have concentrated on the acute toxic effects, the chronic, multigenerational, and life-cycle (after a prolonged exposure to environmentally realistic pharmaceutical concentrations) effects have received far less attention. Long-term studies are thus crucial in enhancing ecological risk assessments.

Second, exposure of aquatic organisms is to complex mixtures, not to individual pharmaceutical compounds. However, the effects or combination of multiple pharmaceuticals are often synergistic, additive, or antagonistic, and this is largely unexplored, meaning there is a lack of knowledge on which to base an assessment of actual environmental risk from multiple compounds in combination.

Third, the transformation products created in the wastewater treatment process need more research. Degradation products may retain biological activity or be more toxic than the parent compounds in advanced oxidation processes, although these processes are effective at degrading many pharmaceuticals. Therefore, further studies should be conducted with chemical analysis combined with a full-scale ecotoxicological study.

Another significant research gap concerns developing countries, where pharmaceutical consumption is growing, but monitoring of the environment is limited. The knowledge available is largely geographically biased, as most records are from Europe and North America. Therefore, expanding environmental surveillance programs in Asia, Africa, and Latin America should be an international priority.

Finally, the following points need to be included in future management strategies: (1) better drug stewardship, (2) environmentally friendly drug design, (3) enhanced wastewater treatment technologies, (4) more stringent environmental laws and measures, and (5) international monitoring programs. To combat the pollution of pharmaceuticals and the impacts on aquatic ecosystems, there needs to be more collaboration between environmental scientists, engineers, toxicologists, policy makers, health professionals, and the pharmaceutical industry.

Table 3: Major research gaps and future priorities

Research Gap	Current Limitation	Future Recommendation
Chronic exposure	Acute toxicity dominates the literature, with limited understanding of long-term ecological effects.	Conduct long-term ecological studies to evaluate chronic exposure impacts on aquatic organisms and ecosystem functions
Mixture toxicity	Most studies focus on single-compound toxicity rather than real-world contaminant mixtures.	Develop multi-contaminant experiments to assess combined, synergistic, and antagonistic effects of pharmaceutical pollutants
Transformation Products	Limited toxicity information is available for pharmaceutical degradation products and metabolites.	Implement integrated chemical and biological assessments to evaluate the environmental risks of transformation products
Developing Countries	Insufficient monitoring data and limited environmental surveillance capacity	Establish global surveillance programs and strengthen monitoring frameworks in developing regions
Wastewater Treatment	Conventional treatment processes show incomplete removal of pharmaceutical residues.	Develop and implement hybrid advanced treatment technologies for enhanced pharmaceutical removal efficiency
Environmental Regulation	Lack of standardized guidelines and regulatory thresholds for pharmaceutical pollutants	Develop harmonized international policies and standardized environmental quality guidelines.

8. Conclusion

Pharmaceutical pollution is one of the most important groups of environmental contaminants, due to the persistent discharge to aquatic environments and the inadequacy of the removal rates through conventional wastewater treatment systems. They are known to be widely distributed in surface waters, sediments, and wastewater effluents, and have become increasingly of concern due to their potential long-term adverse ecological effects. The evidence currently suggests that pharmaceutical residues can alter the behaviour, physiology, biochemical processes, reproductive function, and microbial community of several different aquatic taxa, and antibiotics also play a role in the spread of antimicrobial resistance (AMR) on a worldwide scale.

While major progress has been achieved in the field of environmental monitoring and wastewater treatment technologies, there are still many issues related to the assessment of chronic exposure, pharmaceutical mixtures, transformation products, and ecosystem-level effects. Current treatment technologies can lower pharmaceutical levels, but are not completely effective, which suggests the need for a combination of treatment technologies and sustainable treatment options.

Long-term ecological research, adoption of standardized monitoring programs, development of better wastewater treatment systems, design of environmentally friendly pharmaceuticals, and better regulatory measures should be emphasized as future initiatives. Therefore, minimizing pharmaceutical pollution and protecting aquatic ecosystems for future generations will require a One Health approach that embraces all disciplines, including environmental science, engineering, toxicology, medicine and public policy.

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References

1. AUS DER BEEK, T., WEBER, F. A., BERGMANN, A., HICKMANN, S., EBERT, I., HEIN, A. & KÜSTER, A. 2016. Pharmaceuticals in the environment—Global occurrences and perspectives. Environmental toxicology and chemistry, 35**,** 823-835.
2. BOXALL, A. B., RUDD, M. A., BROOKS, B. W., CALDWELL, D. J., CHOI, K., HICKMANN, S., INNES, E., OSTAPYK, K., STAVELEY, J. P. & VERSLYCKE, T. 2012. Pharmaceuticals and personal care products in the environment: what are the big questions? Environmental health perspectives, 120**,** 1221.
3. BRODIN, T., FICK, J., JONSSON, M. & KLAMINDER, J. 2013. Dilute concentrations of a psychiatric drug alter the behavior of fish from natural populations. Science, 339**,** 814-815.

4. DAUGHTON, C. G. & TERNES, T. A. 1999. Pharmaceuticals and personal care products in the environment: agents of subtle change? Environmental health perspectives, 107, 907.
5. EBELE, A. J., ABDALLAH, M. A.-E. & HARRAD, S. 2017. Pharmaceuticals and personal care products (PPCPs) in the freshwater aquatic environment. Emerging contaminants, 3, 1-16.
6. FABBRI, E. & FRANZELLITTI, S. 2016. Human pharmaceuticals in the marine environment: focus on exposure and biological effects in animal species. Environmental toxicology and chemistry, 35, 799-812.
7. FENT, K., WESTON, A. A. & CAMINADA, D. 2006. Ecotoxicology of human pharmaceuticals. Aquatic toxicology, 76, 122-159.
8. GAW, S., THOMAS, K. V. & HUTCHINSON, T. H. 2014. Sources, impacts and trends of pharmaceuticals in the marine and coastal environment. Philosophical Transactions of the Royal Society B: Biological Sciences, 369, 20130572.
9. GRENNI, P., ANCONA, V. & CARACCIOLO, A. B. 2018. Ecological effects of antibiotics on natural ecosystems: A review. Microchemical Journal, 136, 25-39.
10. KÜMMERER, K. 2009. The presence of pharmaceuticals in the environment due to human use–present knowledge and future challenges. Journal of environmental management, 90, 2354-2366.
11. MICHAEL, I., RIZZO, L., MCARDELL, C., MANAIA, C., MERLIN, C., SCHWARTZ, T., DAGOT, C. & FATTA-KASSINOS, D. 2013. Urban wastewater treatment plants as hotspots for the release of antibiotics in the environment: a review. Water research, 47, 957-995.
12. PATEL, M., KUMAR, R., KISHOR, K., MLSNA, T., PITTMAN JR, C. U. & MOHAN, D. 2019. Pharmaceuticals of emerging concern in aquatic systems: chemistry, occurrence, effects, and removal methods. Chemical reviews, 119, 3510-3673.
13. RICHMOND, E. K., ROSI, E. J., WALTERS, D. M., FICK, J., HAMILTON, S. K., BRODIN, T., SUNDELIN, A. & GRACE, M. R. 2018. A diverse suite of pharmaceuticals contaminates stream and riparian food webs. Nature Communications, 9, 4491.
14. WILKINSON, J. L., BOXALL, A. B., KOLPIN, D. W., LEUNG, K. M., LAI, R. W., GALBÁN-MALAGÓN, C., ADELL, A. D., MONDON, J., METIAN, M. & MARCHANT, R. A. 2022. Pharmaceutical pollution of the world's rivers. Proceedings of the national academy of sciences, 119, e2113947119.