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Pharmaceutical Micropollutants: Ecotoxicity, Risk Assessment and Detection Methods.

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ABSTRACT

Pharmaceutical micropollutants (PMPs) represent a significant environmental concern due to their persistence and potential ecotoxicological effects. This review provides a comprehensive analysis of PMPs, focusing on their sources, detection methods, and impacts on aquatic ecosystems. PMPs originate from various sources, including domestic sewage, hospital effluents, pharmaceutical manufacturing, and agricultural runoff. Detection methods such as high-performance liquid chromatography (HPLC), gas chromatography (GC), and mass spectrometry (MS) are discussed, highlighting the challenges in detecting low concentrations in complex matrices. The review also addresses the ecotoxicological effects of PMPs, including the promotion of antibiotic-resistant bacteria and endocrine disruption in aquatic organisms. The need for improved risk assessment frameworks that incorporate chronic toxicity and bioaccumulation is emphasized. This review concludes with recommendations for future research directions and policy measures to mitigate the environmental impacts of PMPs.

Keywords: Pharmaceutical micropollutants, Ecotoxicity, Risk assessment, Detection methods, Antibiotic resistance, Environmental impact, Aquatic ecosystems.

I. INTRODUCTION

Pharmaceutical micropollutants (PMPs) have become a major environmental issue, largely due to their persistent occurrence and the potential ecological risks they pose. [1-3]. These substances encompass a wide variety of pharmaceuticals, agricultural chemicals, and personal care products, and have been found in soils, groundwater, and river bodies. [1, 4-7]. Their ubiquity is attributed to the widespread use of pharmaceuticals in agricultural practices, veterinary and humanmedicine, and industrial applications [6]. The continual discharge of these compounds, coupled with the limitations of conventional wastewater treatment processes, has resulted to their accumulation in the environment, threatening the health of humans (Figure 1).

The detection and quantification of PMPs in environmental samples are challenging due to their typically low concentrations and the complex nature of environmental matrices [6, 8-10]. Gas chromatography (GC), mass spectrometry (MS), and High-performance liquid chromatography (HPLC) are among the advanced analytical techniques employed to identify and measure these contaminants [11-13]. Despite these technological advancements, there remain significant challenges in accurately detecting and quantifying PMPs due to matrix interferences and the need for extensive sample preparation [13-15].

Ecotoxicologically, PMPs can exert adverse effects even at trace concentrations, affecting aquatic organisms and disrupting ecological processes [1, 2, 16-18]. The presence of antibiotics in the environment, for instance, has been linked to the proliferation of antibiotic-resistant bacteria, posing a public health threat [16, 18]. Additionally, pharmaceuticals like hormones and analgesics can interfere with the endocrine systems of wildlife, causing developmental and reproductive problems. [18-22]. These impacts highlight the urgent need for comprehensive risk assessment frameworks that consider both the exposure and hazard potential of PMPs [4, 22].

Given the pressing nature of these concerns, this review paper aims to provide a comprehensive synthesis of the current knowledge on pharmaceutical micropollutants, focusing on their detection methods, risk assessment, and ecotoxicity. The specific objectives are to review the ecotoxicological impacts of PMPs on various environmental matrices and biological systems, evaluate existing risk assessment frameworks and identify gaps in current methodologies, discuss advanced analytical methods for identifying and measuring PMPs, and highlight research gaps while proposing future research directions and policy strategies for the efficient management of PMPs in the environment. By addressing these objectives, the review seeks to enhance the understanding of the health and environmental risks associated with PMPs and to aid the development of improved monitoring, regulatory, and remediation strategies.

Figure 1: Some sources of PMPs

II. SOURCES AND OCCURRENCE OF PHARMACEUTICAL MICROPOLLUTANTS

PMPs originate from diverse sources and are prevalent across various environmental matrices, presenting significant ecological and health concerns. A major source of PMPs is the effluent discharged from wastewater treatment plants (WWTP), which contain a complex mixture of pharmaceuticals, pesticides, and industrial chemicals [1, 3, 6, 20]. These substances enter WWTPs through a variety of sources, including household sewage, industrial discharges, and wastewater from hospital [6, 19]. Although various treatment methods are employed, a significant number of pharmaceuticals are not completely eliminated and are therefore released into surface waters. [4, 23, 24].A study in China screened 216 micropollutants from 46 WWTPs and highlighted the presence of pharmaceuticals like perfluorooctanoic acid and bisphenol A, highlighting the limited effectiveness of traditional wastewater treatment methods in removing these pollutants [2]. Some PMPs like blood lipid regulators and synthetic musks are known for their persistence due to their stable physicochemical properties [16, 25]. Although PMPs are present at minimal levels, ranging from micrograms per liter (µg/L) to nanograms per liter (ng/L), their prolonged exposure and potential for synergistic effects can lead to significant ecological impacts [26, 28].

Environmental monitoring has revealed different pharmaceuticals in many water bodies. Ibuprofen levels in surface waters have been found to be between 450 ng/L to 4500 ng/L, while carbamazepine has been seen at levels up to 15,780 ng/L [11]. Other frequently detected PMPs include sulfamethoxazole, ofloxacin, and triclosan, which are common in both surface waters and WWTP effluents [29-32]. A study in Germany has detected carbamazepine and bezafibrate in river waters at concentrations of 6.3 µg/L and 3.5 µg/L, respectively, while ibuprofen has been found at 3.5 µg/L [33]. Also, the United Kingdom rivers such as the Belfast Lough, Tees, Thames, Tyne, and Mersey have shown the presence of clotrimazole at 22 ng/L [33].

In the USA, naproxen, triclosan, bisphenolA, acetaminophen, carbamazepine, ibuprofen, and caffeine were major contaminants in the Mississippi River. Sulfamethoxazole and carbamazepine were detected in groundwater near Cape Cod, Massachusetts, at levels of 113 ng/L and 72 ng/L, respectively [34].

In addition to WWTPs, agricultural activities significantly contribute to the presence of PMPs in the environment. The use of veterinary drugs, pesticides, and herbicides leads to the contamination of soils and water bodies. Substances such as nonylphenol, di-(2-ethylhexyl)phthalate, and various pesticides are prevalent in agricultural fields [35, 36]. Numerous researchhave shown the ubiquitous presence of macrolides, sulfonamides, and trimethoprim in tropical aquatic environments, highlighting the widespread contamination from agricultural sources [37-39]. In Germany, antibiotics such as erythromycin, sulfamethoxazole, and roxithromycin were identified at 6 µg/L in waters [33, 40]. A study conducted in Brazil found that surface water intended for drinking contained diclofenac, clofibric acid, and naproxen at concentrations ranging from 0.01 to 0.06 µg/L. [41]. A study conducted across more than 100 rivers in 27 European countries revealed that carbamazepine, benzotriazole, and caffeine were present in nearly every water body tested. [33]. These pollutants infiltrate the ecosystem through the use of contaminated water for irrigation, the application of biosolids, and runoff from agricultural land [42-44]. Once in the soil, they can remain for extended periods, affecting soil quality and microbial diversity, and ultimately making their way into the food chain, thereby posing threats to the environment and human health[42, 43].

In the same vein, pharmaceuticals and personal care products (PPCPs) used in cosmetics, medicines, and other consumer products, have been identified in soil, groundwater, and surface water [45-47]. PPCPs enter the environment viavarious pathways, including household waste, incorrect disposal of unused medications, and agricultural runoff [47]. Their ubiquitous presence raises concerns about their ecotoxicological effects, as they can bioaccumulate in organisms and disrupt biological processes even at low concentrations [45, 48]. The difficulty in detecting and removing PPCPs from the environment exacerbates their impact, making them a growing area of concern for ecotoxicologists [49, 50]. Pharmaceutical manufacturing processes generate substantial quantities of wastewater containing active pharmaceutical ingredients (APIs) and various by-products [51, 52]. These effluents are often discharged with minimal treatment, adding to the environmental load of pharmaceuticals [51]. In Mexico's Tula Valley, wastewater samples revealed elevated levels of diclofenac (4824 ng/L), naproxen (13,589 ng/L), and ibuprofen (1406 ng/L) [33, 41]. Comparative studies in the River Tamagawa, Vietnam, and Mekong Delta, Japan, further emphasize the global nature of pharmaceutical contamination [53].

Hospitals and healthcare facilities are major contributors to pharmaceutical pollution due to the high volume of medications used and disposed of [54]. Wastewater from these facilities often contains unmetabolized drugs, which are challenging for conventional WWTPs to remove [3-5, 54-57].Drugs such as ciprofloxacin and sulfamethoxazole have been detected in significant quantities in the effluents from healthcare facilities, which then mix with domestic sewage and enter WWTPs [29, 38, 58, 59].

Households contribute to pharmaceutical pollution through the excretion of unmetabolized drugs and the improper disposal of unused medications [60, 61]. Disposing of medications by flushing them down the toilet or sink leads to their direct entry into the sewage system, which complicates the process of removing them as wastewater is treated [61]. The widespread use of analgesics, antibiotics, hormones, anti-inflammatories, and antidepressants means these substances are commonly detected in various concentrations in groundwater, treated effluents, and surface water, reflecting their persistence and widespread use [60, 62].

Various studies have documented the presence of pharmaceutical residues in water bodies worldwide, with concentrations varying based on environmental conditions, wastewater treatment efficiency, and local usage patterns(Table 1).

Table 1: Global Occurrence and Concentrations of Pharmaceuticals in Aquatic Environments

Location	PMPs Detected	Concentrations (ng/L - µg/L)	References
Germany	Carbamazepine, Bezafibrate, Ibuprofen	Carbamazepine: 6.3 µg/L; Bezafibrate: 3.5 µg/L; Ibuprofen: 3.5 µg/L	[33]
United Kingdom	Clotrimazole	Clotrimazole: 22 ng/L	[33]
Brazil	Clofibric Acid, Naproxen, Diclofenac	0.01-0.06 µg/L	[63]
USA	Acetaminophen, Naproxen, Bisphenol A, Carbamazepine, Triclosan, Caffeine, Ibuprofen	Mississippi River: Major contaminants; Cape Cod: Sulfamethoxazole: 113 ng/L; Carbamazepine: 72 ng/L	[34]
Mexico	Diclofenac, Ibuprofen, Naproxen	Naproxen: 13,589 ng/L; Diclofenac: 4824 ng/L; Ibuprofen: 1406 ng/L	[33,41]
Vietnam, Japan	Various Pharmaceuticals	Wide distribution in Mekong Delta and River Tamagawa	[53]

III. ECOTOXICITY AND ENVIRONMENTAL IMPACT

PMPs pose significant ecotoxicological risks to aquatic ecosystems, disrupting biological processes in non-target organisms and leading to adverse health and population impacts [64, 65]. Antibiotics such as erythromycin, ciprofloxacin, and sulfamethoxazole are particularly concerning [58, 59, 66-68]. These antibiotics impair the photosynthetic apparatus in aquatic plants like Selenastrumcapricornutum, resulting in reduced growth and vitality [69]. The detection of these antibiotics in surface waters and WWTP effluents further highlights the potential for promoting antibiotic resistance [70].

Emerging studies have provided more precise ecotoxicity data for these substances. SigurnjakBureš et al. [71] assessed the impact of 5-fluorouracil, ciprofloxacin, and 17α-ethinylestradiolon microbial communities using enzymatic and growth tests. Ciprofloxacin exhibited extreme toxicity to nine species, high toxicity to three species, and no toxicity to activated sludge microorganisms [71]. The EC50 values for ciprofloxacin ranged from 0.0137 µg/L for Vibrio fischeri to 5,057 µg/L for Brevundimonasdiminuta[71]. Non-steroidal anti-inflammatory drugs (NSAIDs) such as diclofenac and ibuprofen have been linked to toxicity in fish and other aquatic organisms [72-74]. Diclofenac, detected at high concentrations, can cause significant organ damage in fish [75,76]. Similarly, ibuprofen has been observed to negatively impact fish health, contributing to broader ecological imbalances [77]. Pharmaceuticals such as gemfibrozil can bioaccumulate in fish tissues, with bioconcentration factors reaching 113, indicating significant ecological risks [78-81].

Algae, which are crucial for aquatic ecosystems, are also negatively impacted by PMPs. Sulfamethoxazole disrupts algal photosynthesis, reducing energy production and nutrient cycling in aquatic environments [82]. Antibiotic contamination is particularly concerning as it promotes the growth of antibiotic-resistant bacteria, which presents considerable dangers to both human and environmental health. [83]. Ciprofloxacin, in particular, has shown extreme toxicity to multiple species, with EC50 values as low as 0.175 µg/L for Pseudomonas fluorescens [5], further emphasizing its potential to disrupt microbial communities and ecological balance. Understanding these impacts is essential for developing effective mitigation strategies. Research indicates that prolonged exposure to low concentrations of PMPs can impact the developmental and reproductive processes of aquatic species, resulting in decreased populations and disturbances to ecosystems [84-86].

A comprehensive study by Erdélyi et al., [87] revealed that ibuprofen, carbamazepine, and diclofenacwere frequently found in river water, highlighting the persistent presence and potential ecotoxicity of these compounds [88,89]. Another study demonstrated that PMPs could cause oxidative stress and enzymatic activity changes in fish, indicating physiological stress and potential long-term impacts on fish populations [90].

Several research have shown the bioaccumulation of PMPs in aquatic organisms, resulting in significant ecological impacts. According to Mimeault et al., [91], goldfish exposed to gemfibrozil, a common blood lipid regulator, exhibited a bioconcentration factor of 113 over 14 days. Similarly, Vernouillet et al. [92]observed that carbamazepine accumulates in algae and crustaceans, highlighting the potential for long-term ecological consequences. Załęska-Radziwiłł et al. [5] found that 5-fluorouracil exhibited high toxicity across seven species and very high toxicity across five species, with EC50 values for microbial tests ranging from 37.3 µg/L to 695.6 µg/L.This suggests a significant potential for bioaccumulation and chronic toxicity in aquatic life.

Fish are especially at risk of contamination from micropollutants because they are continuously exposed to polluted water. Chronic exposure to PMPs can impair survival and reproductive success in fish [81, 84]. Diclofenac, a commonly used anti-inflammatory medication, has been documented to cause significant organ damage in fish [93]. Additionally, algae, which are essential for managing energy and nutrient cycles in aquatic environments, are also affected. A study by Khalidi-Idrissi et al., [94] revealed that carbamazepine and diclofenac damage algal chloroplasts, disrupting photosynthesis and overall algal health.An assessment by Załęska-Radziwiłł et al. [5] of 17α-ethinylestradioldemonstrated extreme toxicity to five species, toxicity to another five species, and harmful effects on an additional five species, with significant impacts on microbial community health and function, which can further disrupt aquatic ecosystems.

The development of antibiotic resistance among bacteria has become a critical issue related to PMP contamination. Even low levels of antibiotics in the environment can promote antibiotic tolerance in naturally occurring bacteria [95,96]. This correlation has been observed with various antibiotics, including ciprofloxacin, which is toxic to green algae [95,97]. The occurrence of antibiotics in aquatic environments can contribute to the emergence of antibiotic-resistant bacterial strains, which poses considerable risks to public health [98,99].

Hormones and hormone-like substances in PMPs can disrupt endocrine systems, leading to physiological changes in non-target organisms. These disruptions can cause significant reproductive and developmental issues [100]. Also, prolonged contact with environmental hormones can cause male fish to develop female characteristics, disrupting population dynamics and ecosystem stability [101-103].

3.1 Global Occurrence and Impact

Several studies highlight the widespread occurrence and impact of PMPs globally. In Taiwan, traces of pharmaceutical substances were found in the discharge from major sewage treatment facilities as well as in coastal waters, indicating significant contamination [104]. High levels of ciprofloxacin (up to 31 mg/L) were reported in the effluent from a wastewater treatment facility located in Patancheru, India, influenced by a nearby drug manufacturing facility [105-107]. These cases illustrate the diverse and far-reaching impacts of PMPs on various environmental matrices and organisms.

Pharmaceuticals can disrupt microbial populations in aquatic systems, altering their composition and functionality in essential ecosystems [16,32,60,67,108,109]. This disruption affects nutrient cycling, decomposition processes, and the overall health of the ecosystem [108,109]. Persistent pharmaceuticals can bioaccumulate in the tissues of aquatic organisms and biomagnify up the food web, posing risks to predators, including humans. This accumulation can lead to higher concentrations of contaminants in top predators, with potential health implications [110-115].

Pharmaceutical residues in drinking water can pose health risks to humans, including endocrine disruption, developmental issues, and the promotion of antibiotic-resistant infections. These risks highlight the need for improved water treatment and stricter regulatory controls [116-119]. The environmental presence of antibiotics can foster the emergence and proliferation of antibiotic-resistant bacteria, creating a serious public health concern. [117]. This risk necessitates urgent action to control pharmaceutical pollution and manage antibiotic use effectively [118].

The ecotoxicity and environmental impact of PMPs are substantial and multifaceted, affecting a wide range of aquatic organisms and ecosystems [115-117,119]. Theirbioaccumulation, persistence, and potential for chronic toxicity stress the need for improved wastewater treatment processes and stricter regulations to mitigate their adverse effects [120,121]. To gain a comprehensive understanding of the long-term effects of PMPs and to create effective management and removal strategies, additional research is crucial.

IV. RISK ASSESSMENT FRAMEWORKS

Developing effective risk assessment frameworks for PMPs requires several key steps, such as identifying hazards, evaluating dose-response relationships, assessing exposure, and characterizing risk. [122-125]. These frameworks must accommodate the complex nature of PMPs, taking into account factors such as chronic toxicity, bioaccumulation, and the potential for synergistic effects among multiple contaminants [123,124]. Several frameworks and methodologies have been developed to assess the human health and ecological risks linked to PMPs.

4.1 Risk Quotient (RQ) Method

The Risk Quotient (RQ) method is a widely used approach in ecological risk assessment [126-128]. It involves calculating the ratio of the predicted environmental concentration (PEC) of a pharmaceutical to its predicted no-effect concentration (PNEC). If the RQ exceeds 1, it indicates a potential ecological risk. Research has shown that carbamazepine, a common pharmaceutical, often has an RQ greater than 1 in various water bodies, indicating a potential risk to aquatic life [129].While being a cornerstone in ecological risk assessments for PMPs, RQ method is primarily limited by its static nature, as it does not consider the temporal dynamics of contaminants in the environment [130]. This limitation can be significant because due to factors like varying environmental conditions, degradation, and seasonal changes, the concentrations of PMPs frequently fluctuate [130]. Additionally, the RQ method does not fully address the potential for bioaccumulation, where contaminants can accumulate in organisms over time, leading to long-term ecological effects even if short-term concentrations appear harmless [130,131]. To overcome these challenges, more dynamic and comprehensive risk assessment frameworks are needed. Probabilistic risk assessment (PRA) offers one such solution by incorporating variability and uncertainty into the assessment process. PRA can model the distribution of exposure and effect levels rather than relying on single-point estimates, providing a more nuanced understanding of potential risks.

Furthermore, the integration of multi-criteria decision analysis (MCDA) into risk assessment frameworks can enhance decision-making by considering multiple factors simultaneously, including the trade-offs between different risk management options. MCDA allows for a more holistic approach to risk management, taking into account not only the human health and ecological risks but also socio-economic factors, regulatory requirements, and public perceptions [130,132].

4.2 Quantitative Risk-Based Ranking

This approach integrates production estimates, degradation rates, and toxicity thresholds to rank pharmaceuticals in light of their potential human health and ecological impacts [133,134]. It is particularly useful for prioritizing pharmaceuticals for further study and regulatory action. For instance, anti-inflammatory drugs like diclofenac have been ranked highly because of their toxicity and persistence in fish and other marine organisms [133-136]. This methodology not only aids in prioritizing pharmaceuticals for further investigation but also informs the development of regulatory frameworks and mitigation strategies [133]. Pharmaceuticals like antibiotics and antidepressants are increasingly recognized for their potential to cause significant ecological disruptions [101]. Their persistence in the environment, coupled with their potential for bioaccumulate, makes them a priority for risk management [101,133].

Antibiotics represent a dual threat. Not only do they directly harm non-target organisms, but their persistence in aquatic systems also fosters the growth of antibiotic-resistant bacteria, which poses a significant threat to the health of both humans and animals. [133,136]. This highlights the importance of integrating assessments of antimicrobial resistance (AMR) into the ranking process, further refining the prioritization of pharmaceuticals that require stringent regulatory control [133]. Also, the integration of toxicity thresholds and degradation rates into the ranking process allows for a more nuanced understanding of the long-term impacts of PMPs [133,134]. Chronic exposure to low concentrations of PMPs, which might not cause immediate harm, could lead to sub-lethal effects over time, such as altered reproductive patterns in aquatic life or disrupted endocrine systems [136].

To address these concerns, the risk-based ranking should consider both acute and chronic toxicity data, along with bioaccumulation factors and potential for synergistic effects between multiple PMPs [133]. This comprehensive approach ensures that not only are the most harmful pharmaceuticals identified, but also those that, in combination with other contaminants, could lead to unforeseen environmental and health impacts [133-135].Incorporating stakeholder input and socio-economic factors into the risk-based ranking is also essential for ensuring that the resulting regulatory actions are both effective and equitable. This could involve collaborating with pharmaceutical companies to phase out particularly harmful substances, or investing in advanced water treatment technologies that can better remove PMPs from wastewater [133].

4.3 Spatially Explicit Ranking

This method evaluates risks based on specific geographic locations, considering local environmental conditions and pharmaceutical usage patterns. Regions with high population densities and extensive use of pharmaceuticals, such as urban areas, are often identified as high-risk zones [137,138]. In addition to high-risk zones identified in urban areas due to population density and pharmaceutical usage, spatially explicit ranking models can further refine risk assessments by incorporating environmental elements like the proximity of water treatment facilities, water flow patterns, and the natural degradation rates of pharmaceuticals [137]. These models enable a more detailed comprehension of the distribution and concentration of micropollutants, helping to prioritize areas for intervention [138]. Areas downstream of pharmaceutical manufacturing sites or hospitals often exhibit higher concentrations of specific pollutants, necessitating targeted monitoring and mitigation strategies [137,138]. In such locations, sophisticated treatment technologies like activated carbon filtration or ozonationmay be more urgently required to reduce the levels of hazardous compounds.Furthermore, these models also take into account the variability in local aquatic ecosystems' sensitivity to pollutants, which can differ significantly across regions [138]. This approach ensures that the ecological and human health risks are assessed more accurately, leading to better-informed decisions regarding environmental management and public health policies [137,138].

4.4 Quantitative Structure–Activity Relationship (QSAR) Models

QSAR models estimate the ecotoxicological risks associated with pharmaceuticals by analyzing their chemical structures. These models are especially valuable for evaluating the risks posed by new or less-studied pharmaceuticals [139,140]. QSAR models have been employed to estimate the bioaccumulation potential and ecological hazards of various pharmaceuticals, including beta-blockers and antiepileptics [141-143].A comprehensive study conducted in Spain utilized multiple assessment methods, including Microtox acute ecotoxicity tests and the US EPA's ECOSARTM QSAR program, to evaluate the risks of 26 PPCPs [144]. The research revealed that 65% of these substances were classified as "highly toxic" or "detrimental to aquatic life," highlighting the significant ecological risks posed by PMPs such as triclosan and propylparaben [144].

V. HAZARD IDENTIFICATION AND CHARACTERIZATION

This involves understanding the chemical properties of these substances, including their bioaccumulation potential, persistence in the environment, and toxicity [145,146]. The persistence and bioaccumulation of pharmaceuticals like anti-inflammatory drugs and antibiotics have been documented, demonstrating their ability to persist in the environment for extended durations and accumulate in biological tissues [48,78,81].Exposure assessment quantifies the degree of exposure that organisms and humans have to PMPs [72,100,119]. This includes measuring their concentrations in various environmental elementslikesediment, biota, and water [100]. Advanced analytical techniques, likeMS and chromatography, are employed to detect PMPs at trace levels [147]. A study on the Mankyung River in South Korea identified various PMPs, indicating significant exposure levels in that area [148].Effect assessment involves evaluating the adverse effects of PMPs on individual species, populations, and entire ecosystems. This is achieved through laboratory and field studies that determine the toxicity of these substances [138]. Erythromycin, ciprofloxacin, and sulfamethoxazole have been shown to significantly impact photosynthetic organisms by affecting their photosynthetic processes [149]. Additionally, research involving aquatic species like fish, have demonstrated that PMPs have the potential to disrupt endocrine systems and cause reproductive harm [4,100].

5.1 Risk Characterization

This combines data from hazard identification, exposure assessment, and effect assessment to provide a comprehensive risk estimate. This process often involves using probabilistic models and risk quotients to quantify the risk levels [1,4,25]. Assessing the environmental risks associated with antibiotics in wastewater treatment facilities involves combining data on antibiotic concentrations with toxicity thresholds to assess potential risks to aquatic life [150,151]. Based on the findings from risk characterization, regulatory and management strategies are developed to mitigate identified risks. These strategies may include setting permissible limits for PMP concentrations in environmental matrices and enhancing wastewater treatment processes [151]. For instance, advanced treatment technologies likebiological activated carbon filtration and ozonationhave been recommended to effectively remove PMPs from wastewater [8,86]. Additionally, encouraging the appropriate disposal of drugs and fostering the creation of eco-friendly alternatives are crucial components of these strategies [22].

Continuous monitoring and reassessment are essential to ensure the effectiveness of the risk assessment frameworks. Monitoring programs track the concentrations of PMPs in the environment over time, allowing for adjustments to management strategies as needed [27]. A comprehensive survey across the EU on persistent polar organic pollutants in river waters reveals valuable data for ongoing risk assessments [152]. This continuous assessment guarantees that risk management strategies stay effective in protecting both environmental and human health.

5.2 Implementation of Risk Management Strategies

Effective risk management requires the development and enforcement of regulatory standards and guidelines to control pharmaceutical pollution [133,146]. These regulations should set permissible limits for pharmaceutical residues in water bodies, ensuring that they do not exceed safe levels for environmental and human health [10,19,22]. Additionally, improving wastewater treatment technologies is essential for removing PMPs from effluents before they are discharged into the environment [25]. Promoting the safe disposal of unused medications, encouraging the advancement of eco-friendly pharmaceuticals, and implementing best practices in the production and use of pharmaceuticals are essential steps to reduce the environmental effect of PMPs [22,60].

International collaboration and the standardization of risk assessment protocols are crucial for tackling the worldwide issue of pharmaceutical contamination [153]. Developed countries have made significant progress in understanding PMP pathways and impacts, but developing countries also need to prioritize regular monitoring and adopt standardized risk assessment frameworks [87, 153]. Sharing data, methodologies, and best practices across borders can enhance the collective ability to manage pharmaceutical contamination effectively [153]. Collaborative efforts can result in the creation of international standards and policies that safeguard ecosystems and public health from negative impacts of PMPs.

Comprehensive risk assessment frameworks for PMPs require a multi-faceted approach that includes hazard identification, exposure and effect assessments, risk characterization, and the development of regulatory strategies [145,148]. The continuous monitoring and reassessment of these frameworks are critical to adapting to new data and emerging risks, ultimately safeguarding human health and ecosystems from the adverse impacts of PMPs [109]. Effective risk management strategies, supported by international collaboration and standardized protocols, are essential for addressing the persistent issue of pharmaceutical pollution and ensuring a sustainable and healthy environment for future generations [27,64,66].

VI. DETECTION AND QUANTIFICATION METHODS

Identifying and measuring PMPs in samples from the environment necessitate sophisticated analytical techniques due to the intricate nature of environmental matrices and the typically low concentrations of these contaminants (Figure 2) [1,8, 63]. Several techniques have been created and enhanced to ensure precise detection and measurement of PMPs.

6.1 High-Performance Liquid Chromatography

HPLC, often associated with MS, is widely utilized for detecting PMPs [1,154,155]. This technique demonstrates a high level of sensitivity and specificity, enabling the separation, identification, and measurement of numerous pharmaceutical compounds in complex samples from the environment[154,155]. HPLC-MS/MS has been used successfully to analyze compounds likediclofenac, ibuprofen, andcarbamazepine in wastewater samples, demonstrating identification limits in the low range ofng/L [156]. The detection limits for compounds like ciprofloxacin and 17α-ethinylestradiol using HPLC-MS/MS were as low as 0.1 ng/L [6].

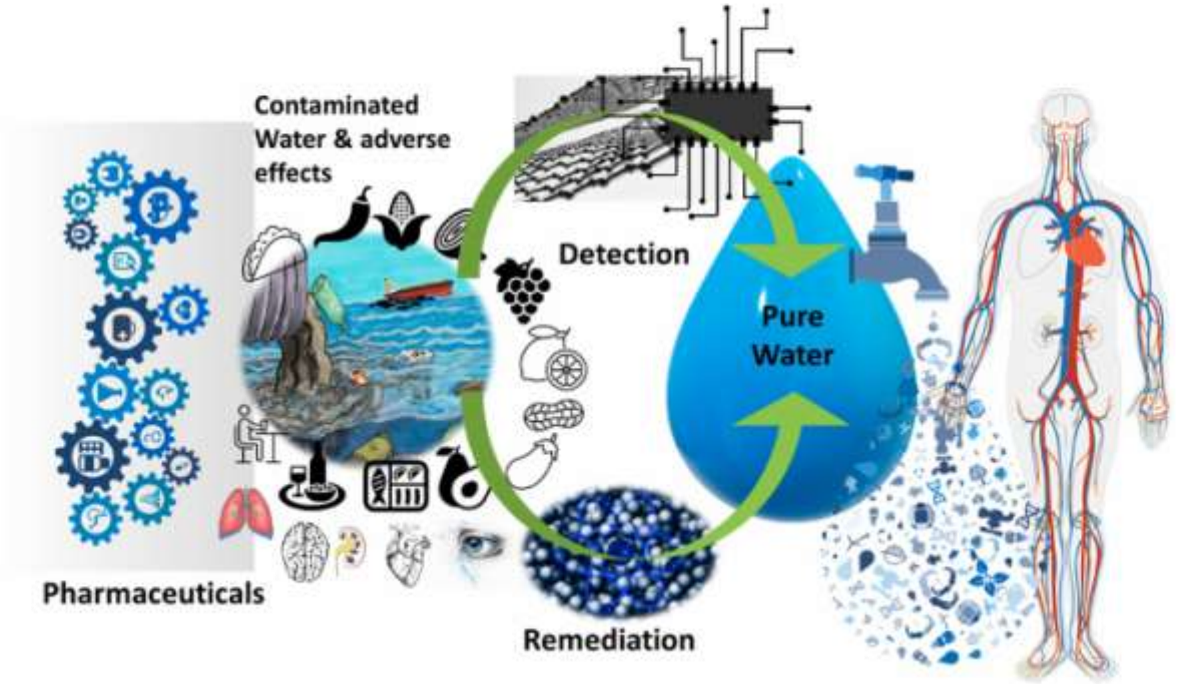

Figure 2: Systems for trapping, eradicating, and detecting PMPs reproduced with permission from Letsoalo et al., [155]

6.2 Gas Chromatography-Mass Spectrometry (GC-MS)

GC-MS is particularly effective for volatile and semi-volatile compounds [157,158]. This method has been extensively applied for analyzing PMPs in various environmental media. GC-MS's sensitivity, combined with its ability to manage complex mixtures, makes it an ideal choice for detecting compounds like caffeine, triclosan, and several synthetic musk fragrances [6,159].Hermes et al. [6] noted that GC-MS achieved detection limits of 0.2 ng/L for triclosan and 0.5 ng/L for synthetic musks, highlighting its efficacy in analyzing environmental samples.

6.3 Solid-Phase Extraction (SPE)

Before chromatographic analysis, environmental samples often require pre-concentration and cleanup, for which SPE is widely utilized. SPE techniques enhance PMP detection by concentrating analytes from large water volumes and reducing matrix interferences [160]. Studies have demonstrated that using SPE followed by HPLC-MS/MS can significantly improve recovery rates and detection limits of various pharmaceuticals in water samples [1,6,160].Hermes et al. [6] indicated recovery rates of over 90% for antibiotics like ciprofloxacin and sulfamethoxazole when using SPE, illustrating the method's efficiency.

6.4 Enzyme-Linked Immunosorbent Assay(ELISA)

ELISA is a biochemical method used to identify specific molecules, including PMPs, based on antigen-antibody interactions [161-163]. While not as widely used as chromatographic methods, ELISA offers a relatively simple and cost-effective alternative for screening pharmaceuticals, especially in large-scale monitoring programs [162]. ELISA has been applied successfully to identify antibiotics like sulfamethoxazole and tetracycline in water samples [164]. The ELISA method detected in limits as low as 0.01 ng/L for sulfamethoxazole, demonstrating its potential for high-sensitivity applications [6].

6.5 Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)

LC-MS/MS is widely used for its high sensitivity and specificity. It can detect PMPs at very low concentrations (ng/L to µg/L) and is capable of identifying multiple compounds simultaneously [165]. However, this method is expensive, requires extensive sample preparation, and is limited by matrix effects which can affect accuracy and precision [154,165]. A study by Hermes et al. [6] found that LC-MS/MS was able to quantify ciprofloxacin at concentrations as low as 0.05 ng/L, showcasing its powerful analytical capabilities.

6.6 Bioanalytical Methods and Biosensors

Bioanalytical methods, such as immunoassays, offer rapid and cost-effective detection of PMPs. Immunoassays utilize antibodies to specifically bind target pharmaceuticals, allowing for their detection and quantification [6,166]. Although these methods are less specific and sensitive compared to chromatographic techniques, they are valuable for initial screening and large-scale monitoring programs [166]. Immunoassays have been effectively used to detect antibiotics and hormones in water samples [6].

Biosensors represent an emerging technology for the detection of PMPs. These devices incorporate biological recognition components, like antibodies or enzymes, to identify specific contaminants [167,169]. They offer the advantage of continuous monitoring, enhanced sensitivity, and the possibility for downsizing and on-site analysis [167]. Biosensors have been engineered to identify hormones, antibiotics, and various other pharmaceuticals in environmental samples [168,169]. Hermes et al. [6] highlighted the development of biosensors with detection limits as low as 0.05 ng/L for hormones like 17α-ethinylestradiol, emphasizing their potential for on-site environmental monitoring.

6.7 Nanotechnology-Based Approaches

Nanotechnology-based approaches enhance the sensitivity and selectivity of detection methods for PMPs. Nanomaterials, such as nanoparticles and nanotubes, are used to improve the performance of analytical techniques, enabling the detection of pharmaceuticals at ultra-trace levels [21,170]. Gold nanoparticles have been employed in colorimetric assays for the detection of antibiotics, providing a simple and rapid means of identifying contaminants in water samples [170].

VII. CHALLENGES AND LIMITATIONS IN THE DETECTION OF PMPS

The identification and quantification of PMPs in samples from the environment play a vital role in evaluatingtheir occurrence, spread, and possible effects. While advanced analytical methods like HPLC-MS/MS, GC-MS, and ELISA offer robust solutions for this purpose, they are not without challenges.Environmental samples, such as wastewater and surface water, contain a myriad of organic and inorganic substances that can interfere with the detection of PMPs [171]. These matrix effects complicate the analytical process, necessitating extensive sample preparation and cleanup procedures to achieve accurate results. Humic substances in natural waters can interfere with the detection of PMPs, requiring additional purification steps [171,172].PMPs are often present at very low concentrations, typically in the range of ng/L to µg/L. Detecting these trace levels requires highly sensitive and selective methods [1,6,161]. Techniques like GC-MS and HPLC-MS/MS offer the necessary sensitivity, but the instrumentation and operational costs are substantial, limiting their accessibility for routine monitoring [154,155]. Moreover, the detection limits need to be constantly improved to keep up with emerging contaminants.

Protocols for detecting and quantifying PMPs are also not standardized across different laboratories and studies. This variability can lead to inconsistencies in reported concentrations and hinder the comparability of data. Furthermore, the validation of analytical methods is crucial to ensure reliability, which requires comprehensive calibration, quality control, and proficiency testing.Pharmaceuticals can undergo various transformation processes occurring in the environment, leading to the creation of metabolites and breakdown products that can represent up to 40% of the total pharmaceutical residues in some samples [159,173]. These transformation products may exhibit distinct toxicological properties and analytical characteristics relative to the original compounds [159]. Detecting and quantifying these products adds another layer of complexity to the analysis, requiring tailored analytical approaches and additional reference standards.

High-end analytical techniques like GC-MS and HPLC-MS/MS are expensive, both in terms of initial investment and operational costs [154]. They require skilled personnel and extensive maintenance, which can be a barrier for many laboratories, especially in developing regions. This cost factor limits the frequency and scope of monitoring programs, potentially leading to an underestimation of environmental contamination levels.

VIII. FUTURE PERSPECTIVES AND RESEARCH DIRECTIONS

Addressing the global concern of PMPs in the environment necessitates advancements in several critical areas, starting with comprehensive prioritization and monitoring. Developing systematic prioritization frameworks based on exposure and hazard potential will help identify high-risk PMPs and inform regulatory measures [4,25]. Expanding these schemes globally and incorporating a wider range of micropollutants from various sources will provide a more comprehensive understanding of PMPs in diverse environmental contexts [27,66].

Improving detection and quantification techniques is vital because of the intricate nature of environmental matrices and low PMP concentrations. While existing methods like GC-MS and HPLC-MS/MS have proven effective, there is a need for more sensitive and selective techniques [154,155]. Future studies should aim to create more sophisticated nanotechnology-based approaches and biosensors for real-time monitoring. Integrating these advanced techniques with existing methods will enhance detection capabilities and provide more accurate data on PMP concentrations across various environmental samples.

Understanding the ecotoxicological impacts of PMPs, even at minute concentrations, is crucial for assessing risks to ecosystems. Future studies should aim to identify comprehensively the extended impacts of various PMPs, including their byproducts and transformation derivatives [139]. This requires a multidisciplinary approach combining ecotoxicology, microbiology, and environmental chemistry. Concurrently, optimizing alternative treatment methods like photolysis, reverse osmosis, UV-degradation, biodegradation, and nanofiltration is essential. Integrating these methods and making them more cost-effective and scalable can enhance removal efficiencies and reduce environmental footprints.

Socio-economic and regulatory considerations are also critical in addressing pharmaceutical pollution. Research into the socio-economic impacts of pharmaceutical pollution, including healthcare costs and water treatment, is needed alongside public awareness campaigns promoting responsible disposal practices. Evolving regulatory frameworks to address emerging contaminants and enforce stricter discharge limits for pharmaceuticals in wastewater is essential. Additionally, bridging data gaps with standardized protocols for PMP analysis will ensure consistency and reliability in monitoring programs [9,87]. Exploring innovative approaches such as phagotherapy, vaccines, and green chemistry principles can offer sustainable solutions, protecting environmental and human health for future generations.

IX. CONCLUSION

This review has elucidated the pervasive and persistent nature of PMPs in the environment, emphasizing their diverse sources and significant ecotoxicological impacts. PMPs enter aquatic ecosystems through domestic sewage, hospital effluents, pharmaceutical manufacturing, and agricultural runoff. Advanced detection methods such as HPLC, GC, and MS are crucial for identifying these pollutants, although difficulties remain because of their low concentrations and the complex nature of environmental matrices. PMPs, even at trace levels, can disrupt ecological processes and harm marine organisms. They facilitate the spread of antibiotic-resistant bacteria and disrupt wildlife endocrine systems, causing problems with reproduction and development. Current risk assessment frameworks are inadequate, as they often fail to account for the cumulative and synergistic effects of multiple contaminants. Comprehensive models that integrate chronic toxicity, bioaccumulation, and complex interactions are necessary to address these risks effectively.

There are still gaps in research regarding the long-term impacts of PMPs and their metabolites on aquatic ecosystems. Future studies should adopt a multidisciplinary approach, combining ecotoxicology, microbiology, and environmental chemistry to address these gaps. There is an urgent need to create detection methods that are both more sensitive and cost-efficient to better monitor PMP concentrations in various environmental matrices. Effective management of PMPs requires robust regulatory standards, enhanced wastewater treatment technologies, and international collaboration to standardize risk assessment protocols. By addressing these objectives, this review supports the enhancement of monitoring, regulatory, and remediation approaches to address and reduce the public health and environmental risks associated with PMPs.

Declaration of competing interest

The authors declare that they have no known competing financial interests.

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