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Effects Of Pharmaceutical Pollutants On Aquatic Life Mechanisms And Mitigation Strategies

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Abstract

The increasing prevalence of pharmaceutical contaminants in aquatic ecosystems poses a profound and multifaceted threat to environmental and ecological health. Originating primarily from domestic wastewater effluents, hospital discharges, pharmaceutical manufacturing, and agricultural runoff, these bioactive compounds—including antibiotics, analgesics, hormones, and antidepressants—are often not fully removed by conventional wastewater treatment processes. As a result, they persist in surface waters, sediments, and even groundwater, leading to chronic exposure of non-target aquatic organisms. This research critically examines the sub-lethal and long-term effects of pharmaceutical pollutants on aquatic life mechanisms, focusing on molecular, cellular, physiological, and population-level impacts. Key mechanisms of toxicity include endocrine system disruption, oxidative stress induction, immunotoxicity, altered reproductive behavior, and antibiotic resistance propagation. Particular attention is given to species-specific responses and the trophic transfer of contaminants within aquatic food webs. The paper also evaluates current mitigation strategies, such as advanced oxidation processes (AOPs), membrane filtration, biochar adsorption, and green chemistry principles in pharmaceutical design. Additionally, it discusses the role of environmental monitoring frameworks, ecopharmacovigilance, and policy-driven interventions in reducing pharmaceutical inputs into aquatic systems. Addressing this complex challenge requires an integrated, transdisciplinary approach that bridges environmental science, toxicology, engineering, and regulatory policy to safeguard aquatic biodiversity and ensure ecosystem resilience in the face of pharmaceutical pollution.

Keywords: *Pharmaceutical contaminants; Aquatic ecotoxicology; Endocrine disruption; Oxidative stress; Wastewater treatment technologies; Antibiotic resistance; Bioaccumulation; Trophic transfer; Ecopharmacovigilance; Environmental risk assessment; Advanced oxidation processes; Aquatic ecosystem resilience*

1. INTRODUCTION

Over the past few decades, the proliferation of pharmaceutical compounds in the environment has emerged as a significant concern in environmental toxicology and aquatic ecology. Pharmaceuticals, by design, are biologically active substances intended to exert specific physiological effects at low concentrations (1). However, their unintended release into natural ecosystems—particularly freshwater and marine environments—has led to growing apprehension regarding their potential to cause harm to non-target organisms. Unlike traditional pollutants such as heavy metals or nutrients, pharmaceuticals often exist in complex mixtures and can persist at trace levels (ng/L to μg/L) in water bodies, yet still exert profound biological effects due to their inherent potency and specificity (2).

The primary routes through which pharmaceuticals enter aquatic systems include municipal and industrial wastewater discharges, effluents from healthcare facilities, aquaculture, and agricultural runoff—especially where veterinary drugs are employed (3). A significant proportion of consumed pharmaceuticals is excreted in unmetabolized or partially metabolized forms, which pass through wastewater treatment plants (WWTPs) that are often not equipped to completely remove these emerging contaminants (4). As a result, compounds such as antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs),

antidepressants, antiepileptics, and synthetic hormones are frequently detected in rivers, lakes, and even drinking water sources globally.

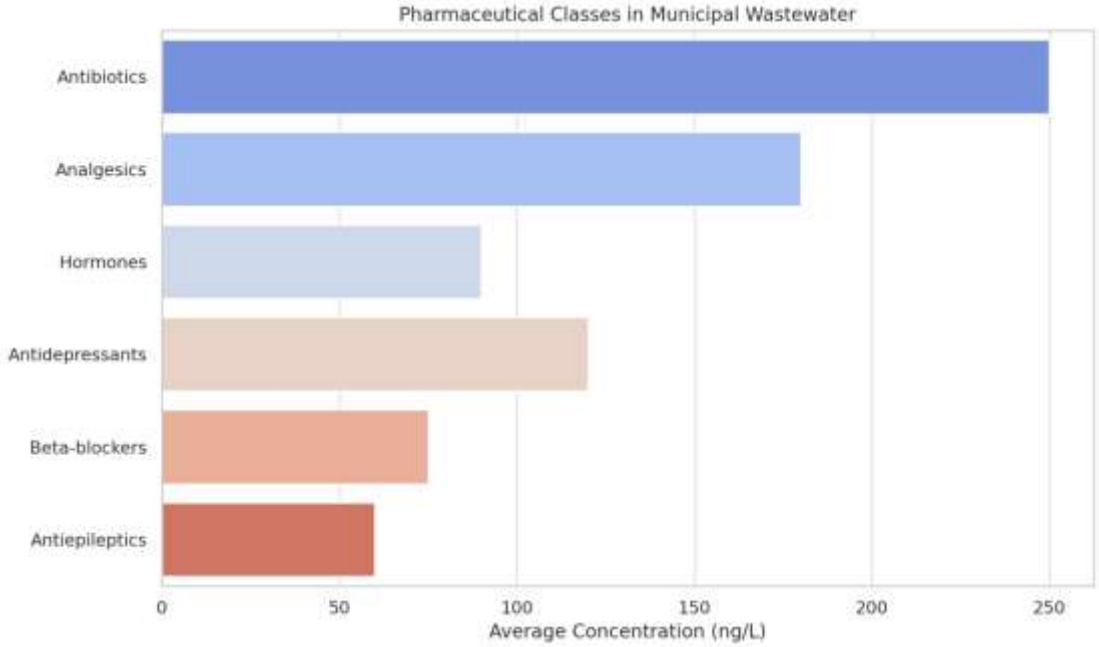

Figure 1 Pharmaceutical concentrations by class in wastewater

The ecological consequences of pharmaceutical contamination are diverse and multifaceted. At the organismal level, exposure to even low concentrations of pharmaceuticals can lead to endocrine disruption, altered reproductive behaviors, developmental anomalies, and impaired immune responses in aquatic species (5). For instance, the feminization of male fish due to exposure to synthetic estrogens such as 17α-ethinylestradiol (EE2) is well-documented and serves as a stark example of the endocrine-disrupting potential of pharmaceutical pollutants (6). At the population and community levels, these sub-lethal effects can cascade into broader ecological disruptions, including population declines, altered species interactions, and trophic imbalances.

Moreover, antibiotics released into aquatic environments contribute to the alarming rise of antibiotic-resistant bacteria and resistance genes, posing not only ecological threats but also significant public health concerns (7). Bioaccumulation and biomagnification of certain pharmaceuticals further exacerbate their impact, particularly in higher trophic organisms such as fish, amphibians, and aquatic birds.

Given the growing recognition of the risks posed by pharmaceutical pollutants, substantial research efforts have been directed toward understanding their environmental behavior, toxicological mechanisms, and potential for mitigation (8). Conventional wastewater treatment methods—while effective for reducing organic load and pathogens—are inadequate for removing many pharmaceutical compounds (9). As a result, there is increasing interest in advanced treatment technologies such as membrane bioreactors, ozonation, advanced oxidation processes (AOPs), and activated carbon filtration. Parallel to technological solutions, the concept of "green pharmacy" encourages the design of biodegradable and environmentally benign drugs. Furthermore, policy frameworks and ecopharmacovigilance systems are being developed to monitor, manage, and mitigate pharmaceutical emissions throughout their life cycle.

This paper aims to provide a comprehensive analysis of the effects of pharmaceutical pollutants on aquatic organisms by elucidating the mechanisms of toxicity at molecular, cellular, physiological, and ecosystem levels. It also evaluates current and emerging strategies for mitigating pharmaceutical pollution and advocates for an integrated, multidisciplinary approach that encompasses scientific innovation, regulatory oversight, and public engagement to address this complex environmental challenge.

2. Sources and Pathways of Pharmaceutical Pollutants

Pharmaceutical pollutants represent a class of emerging contaminants (ECs) characterized by their persistent bioactivity, low environmental concentrations (ng/L to μg/L), and widespread distribution in aquatic systems. Their continuous input into the environment, often via non-point and point sources, leads to pseudo-persistence despite their potentially short half-lives, resulting in chronic exposure

conditions for aquatic biota. A comprehensive understanding of their environmental entry routes is critical for the formulation of accurate exposure models, risk assessments, and regulatory measures.

2.1 Wastewater Effluents

Municipal wastewater treatment plants (WWTPs) are the primary conduits through which human-use pharmaceuticals enter aquatic environments. Following human consumption, pharmaceuticals are often excreted unmetabolized or as pharmacologically active metabolites. These substances, including non-steroidal anti-inflammatory drugs (e.g., diclofenac), β-blockers (e.g., propranolol), antiepileptics (e.g., carbamazepine), and synthetic estrogens (e.g., 17α-ethinylestradiol), are routinely detected in influents and effluents of WWTPs globally.

Conventional WWTPs utilize primary sedimentation, activated sludge, and secondary clarification processes, which are not specifically designed to eliminate micropollutants. Consequently, removal efficiencies vary significantly by compound, physicochemical properties (e.g., hydrophobicity, molecular weight), and operational parameters (e.g., sludge retention time, temperature). Studies have reported effluent concentrations of certain pharmaceuticals in the range of 0.01–1.0 μg/L, with persistence extending through downstream ecosystems. Hospitals and pharmaceutical manufacturing units contribute episodic yet high-intensity discharges, characterized by complex and concentrated pharmaceutical mixtures, further challenging conventional treatment approaches (10).

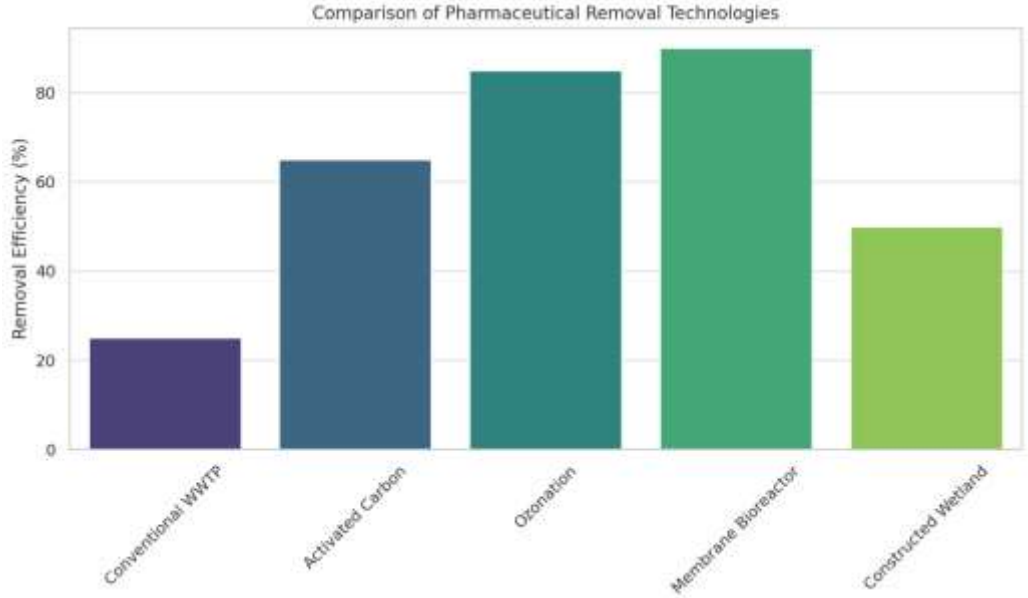

Figure 2 Removal efficiency across treatment technologies

2.2 Agricultural and Veterinary Runoff

Veterinary pharmaceuticals, including antibiotics (e.g., oxytetracycline, sulfamethoxazole), antiparasitics (e.g., ivermectin), and hormone analogs (e.g., trenbolone), are widely used in livestock, aquaculture, and poultry farming. Following administration, a substantial fraction is excreted in active form via feces and urine, entering the environment through manure application, leaching, and surface runoff. These compounds can reach aquatic systems directly during rainfall events or through erosion-driven particulate transport.

In aquaculture, especially intensive fish farming operations, medicated feeds and water treatments directly discharge pharmaceuticals into aquatic environments, leading to highly bioavailable exposure scenarios. Unlike point-source discharges, such as WWTPs, agricultural contributions are characterized by spatial and temporal variability, complicating both detection and management (11). Veterinary antibiotics have been frequently linked to the proliferation of antibiotic resistance genes (ARGs) in aquatic microbial communities, raising ecotoxicological and epidemiological concerns.

2.3 Improper Disposal Practices

The improper disposal of unused or expired medications by consumers and healthcare institutions remains a significant yet often overlooked source of pharmaceutical pollution. Common practices such as flushing medicines into domestic sewage systems or discarding them in household waste can introduce

pharmaceuticals into wastewater streams and landfills. Inadequately engineered landfills lacking leachate containment and treatment systems may facilitate the infiltration of pharmaceuticals into groundwater and surface water bodies.

Studies have identified compounds like acetaminophen, fluoxetine, and metformin in landfill leachates, with environmental concentrations varying seasonally and geographically. The absence of widespread drug take-back programs and limited public awareness exacerbates this issue (12). Moreover, pharmaceuticals in landfills may undergo anaerobic degradation or transformation under acidic and reducing conditions, producing metabolites that retain or exceed the parent compound's toxicity.

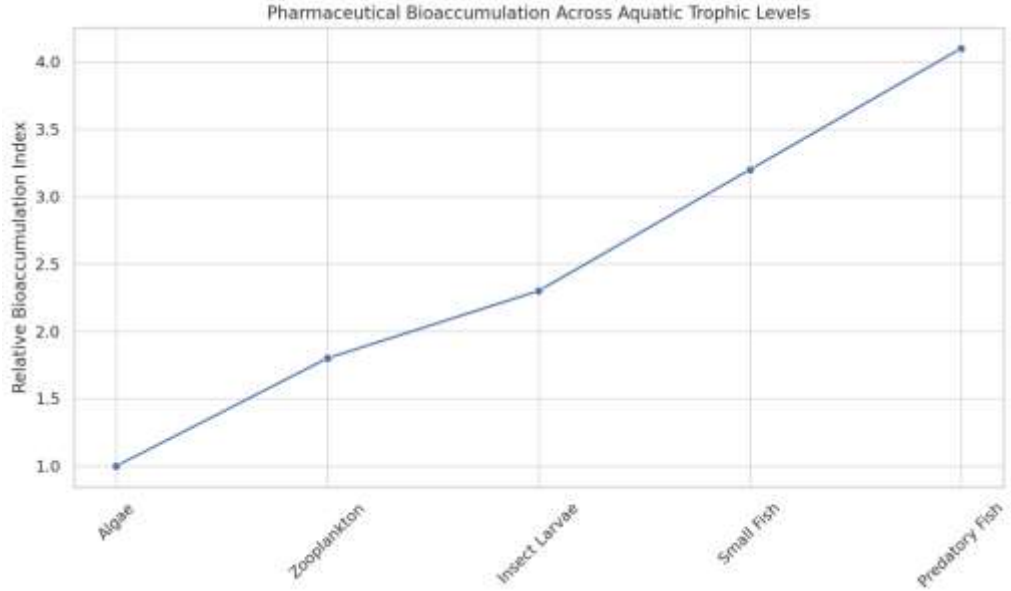

Figure 3 Bioaccumulation trends across aquatic trophic levels

2.4 Environmental Persistence and Transport Mechanisms

Pharmaceutical compounds display diverse environmental fate profiles influenced by intrinsic physicochemical parameters such as water solubility, dissociation constants (pKa), octanol-water partition coefficients (K_ow), and sorption affinity to organic matter (K_oc). Many are structurally stable, with resistance to photolysis, hydrolysis, and microbial degradation, enabling long-term persistence in aquatic matrices.

After entering aquatic systems, pharmaceuticals distribute among water, sediment, and biota compartments. Hydrophilic compounds may remain in the dissolved phase, while lipophilic and ionizable compounds tend to sorb to suspended solids or accumulate in sediments (13). Environmental transformation processes, such as photodegradation (e.g., sulfonamides), microbial metabolism, and chemical hydrolysis, may alter toxicity profiles and bioavailability. However, transformation products (TPs) can be equally or more hazardous, posing an additional layer of environmental risk.

Furthermore, the hydrological transport of pharmaceuticals through riverine flow, stormwater runoff, and groundwater discharge can lead to the contamination of remote or seemingly pristine aquatic environments. Their continuous input creates a pseudo-persistent condition, sustaining chronic, low-dose exposure scenarios that complicate ecotoxicological assessments and mitigation efforts.

3. Mechanisms of Toxicity in Aquatic Organisms

Pharmaceutical pollutants, even at sub-lethal concentrations, can interfere with key physiological, molecular, and behavioral pathways in non-target aquatic organisms. Unlike conventional pollutants, pharmaceuticals are specifically designed to elicit biological activity at low doses, raising concern over their unintended effects on aquatic fauna (14). Toxicity mechanisms vary by compound class and species, and are often cumulative or synergistic in the context of long-term exposure to complex pharmaceutical mixtures. This section elucidates the principal modes of toxic action based on current ecotoxicological research.

3.1 Endocrine Disruption

One of the most studied and well-documented mechanisms of pharmaceutical toxicity in aquatic organisms is endocrine disruption. Endocrine-disrupting compounds (EDCs) interfere with hormone signaling pathways, often by mimicking, blocking, or altering the synthesis, transport, or metabolism of endogenous hormones.

Synthetic estrogens such as 17α-ethinylestradiol (EE2), a common component of oral contraceptives, have been shown to induce feminization in male fish, including intersex conditions (testis-ova), reduced sperm motility, and impaired gonadal development. Chronic exposure at concentrations as low as 1–10 ng/L can result in population-level effects, as demonstrated in long-term field studies involving *Pimephales promelas* (fathead minnow).

Other hormone analogs, including progestins and androgens used in livestock and aquaculture, have been implicated in disrupting reproductive cycles and secondary sexual characteristics. These disruptions interfere with the hypothalamic–pituitary–gonadal (HPG) axis, leading to altered vitellogenin synthesis, skewed sex ratios, and reduced fecundity.

3.2 Oxidative Stress and Cellular Damage

Oxidative stress is a ubiquitous response to a variety of pharmaceutical classes, including antibiotics, NSAIDs, and psychiatric drugs. This mechanism involves the overproduction of reactive oxygen species (ROS) such as superoxide anions (O_2^-), hydroxyl radicals ($\bullet OH$), and hydrogen peroxide (H_2O_2), which can overwhelm antioxidant defense systems (e.g., catalase, superoxide dismutase, glutathione).

The resulting redox imbalance damages cellular macromolecules—lipids (via lipid peroxidation), proteins (via carbonylation), and DNA (via strand breaks and base modifications). For instance, exposure to fluoxetine (an SSRI) and diclofenac has been associated with elevated levels of malondialdehyde (MDA), a key biomarker of lipid peroxidation, in fish liver and gill tissues.

Mitochondrial dysfunction is another downstream effect, impairing ATP production and promoting apoptosis. These cellular impacts compromise organ function, growth, and organismal fitness, particularly under chronic, multi-stressor conditions in the environment.

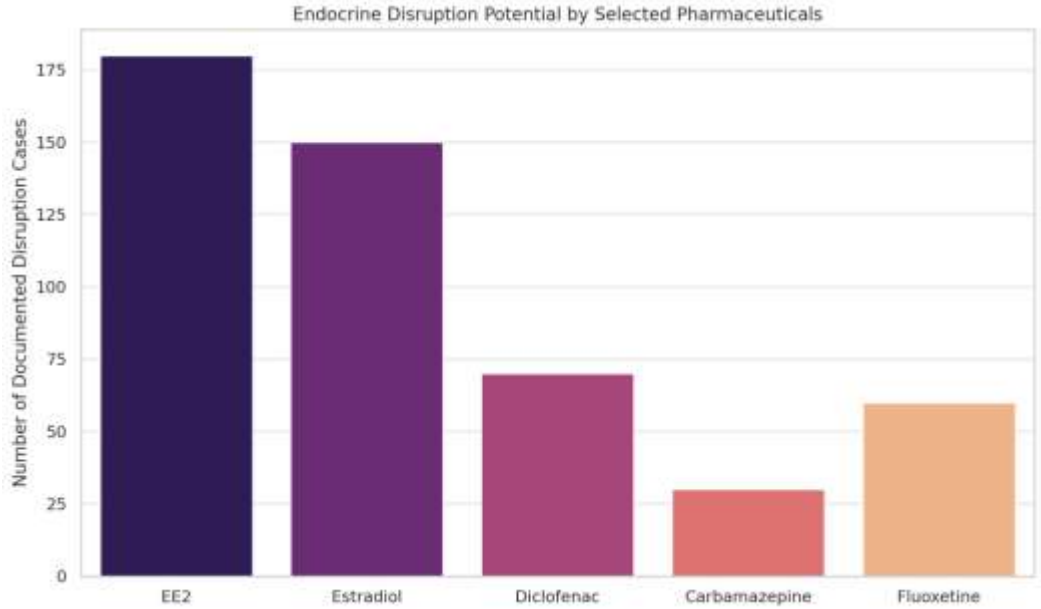

Figure 4 Documented endocrine disruption by compound

3.3 Neurotoxicity and Behavioral Alterations

Many pharmaceuticals target the nervous system in humans and thus pose neurotoxic risks to aquatic organisms, particularly teleost fish and amphibians, which share conserved neurotransmitter pathways (15). Compounds such as antidepressants (e.g., fluoxetine, sertraline), antipsychotics, and anticonvulsants disrupt the regulation of neurotransmitters like serotonin, dopamine, and GABA.

Behavioral endpoints—such as predator avoidance, feeding rate, social interaction, and locomotion—are often more sensitive than lethal endpoints. For instance, fluoxetine exposure has been shown to alter

aggression and boldness in *Oncorhynchus mykiss* (rainbow trout) and reduce mating behaviors in *Danio rerio* (zebrafish), even at environmentally relevant concentrations.

Neurotoxicity is further compounded by potential synergistic effects of pharmaceutical mixtures, which can disrupt neural development and sensory processing during early life stages.

3.4 Reproductive and Developmental Effects

Reproductive and developmental endpoints are especially sensitive to pharmaceutical exposure due to critical hormonal and morphogenetic regulation during gametogenesis, embryogenesis, and larval growth (16). Hormonal modulators (e.g., estrogens, anti-androgens) and teratogenic drugs (e.g., carbamazepine, isotretinoin) interfere with embryonic development, resulting in malformations, delayed hatching, or mortality.

Developmental toxicity has been observed in *Xenopus laevis* embryos exposed to antiepileptics, showing neural tube defects and craniofacial abnormalities. In fish, early-life exposure to hormone disruptors alters gonadal differentiation and delays puberty onset.

Furthermore, chronic exposure to pharmaceutical mixtures can reduce gonadosomatic index (GSI), egg viability, and hatchability, compromising reproductive success and population sustainability over generations.

3.5 Immune System Impairment and Antibiotic Resistance

Pharmaceutical pollutants can suppress or dysregulate immune responses in aquatic species, increasing vulnerability to pathogens. Immunotoxic effects include altered cytokine profiles, reduced leukocyte activity, and suppressed antibody production (17). For example, NSAIDs such as ibuprofen and diclofenac have been shown to reduce phagocytic activity in teleost macrophages.

Perhaps most critically, antibiotics in the aquatic environment select for antimicrobial resistance (AMR) in microbial communities. Sub-inhibitory concentrations facilitate horizontal gene transfer of antibiotic resistance genes (ARGs) via plasmids, transposons, and integrons. This phenomenon has been observed in sediments, biofilms, and aquatic microbiota, where resistant *E. coli*, *Aeromonas spp.*, and other pathogens can proliferate.

The emergence of resistant strains within aquatic environments has significant implications for ecological function, aquaculture health, and human disease transmission through environmental reservoirs of resistance.

4. Ecological and Evolutionary Impacts on Aquatic Ecosystems

Pharmaceutical pollutants exert cascading effects that extend beyond individual organism health to affect population dynamics, community interactions, food web structure, and evolutionary processes (18). Due to their persistent bioactivity, even low-dose, chronic exposure can disrupt ecological stability and drive adaptive responses that may have long-term evolutionary consequences. The indirect and emergent effects of pharmaceuticals often manifest over ecological timescales, complicating risk assessments and regulatory actions.

4.1 Population-Level Changes

At the population level, pharmaceuticals can alter survival rates, reproductive success, and recruitment dynamics, leading to changes in population structure and abundance. For instance, chronic exposure to endocrine-disrupting compounds such as 17α-ethinylestradiol (EE2) has been shown to reduce male fertility, skew sex ratios, and induce intersex conditions in fish, effectively collapsing local populations in mesocosm and field studies.

Sub-lethal effects like impaired reproductive capacity, delayed sexual maturation, and behavioral modifications can reduce reproductive output and disrupt population sustainability (19). Additionally, decreased larval viability or increased embryonic deformities—observed with compounds like carbamazepine and fluoxetine—further reduce recruitment potential, particularly in species with narrow reproductive windows or low fecundity.

Population bottlenecks caused by pharmaceutical exposure may also reduce genetic diversity, increasing susceptibility to stochastic events and reducing adaptive capacity.

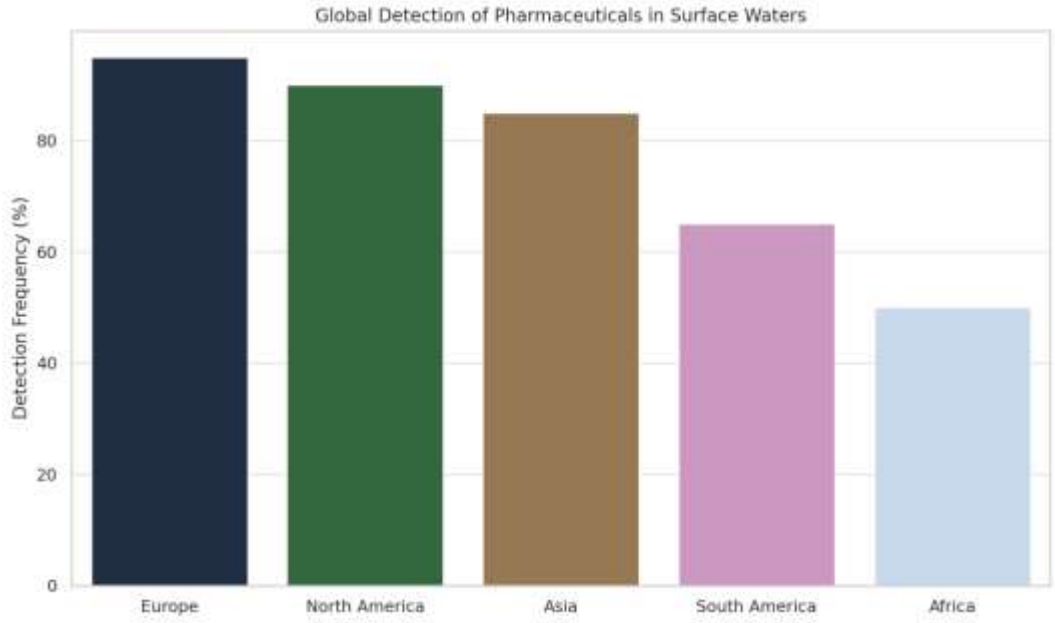

Figure 5 Global detection rates of pharmaceuticals in surface waters

4.2 Community Structure Shifts

Pharmaceutical-induced changes at the species level can cascade into broader shifts in community composition. Selective toxicity can lead to local extinction or dominance of more tolerant species, thereby reducing taxonomic and functional biodiversity. For example, antibiotics and antiparasitics can suppress sensitive microbial taxa, altering microbial community composition in sediments and periphyton, with consequences for nutrient cycling and primary productivity.

Invertebrate assemblages, such as benthic macroinvertebrates and zooplankton, exhibit differential sensitivity to pharmaceuticals. Changes in their abundance can disrupt predator-prey dynamics and detrital processing. In periphyton and phytoplankton communities, exposure to pharmaceutical mixtures can reduce photosynthetic efficiency or shift species dominance, affecting basal resource availability and energy flow through aquatic food webs.

Such community-level disruptions can result in altered ecosystem functions, such as reduced decomposition rates, impaired bioturbation, or increased algal blooms due to the suppression of grazer populations.

4.3 Trophic Transfer and Food Web Disturbances

Pharmaceuticals can bioaccumulate in aquatic organisms and be transferred through trophic interactions, particularly when compounds are lipophilic or persistent. Although many pharmaceuticals are relatively polar, compounds like fluoxetine, diclofenac, and some macrolide antibiotics have been detected in multiple trophic levels, from algae and invertebrates to fish and piscivorous birds.

The trophic transfer of these substances can lead to biomagnification or trophic dilution depending on metabolic capacity and excretion rates of each species. For instance, in aquatic insects that undergo metamorphosis, pharmaceuticals accumulated during larval stages may be transferred to terrestrial systems via emergent adults, representing a cross-ecosystem contamination pathway.

Food web disturbances can result from both direct toxicity and indirect ecological interactions. If primary consumers (e.g., herbivorous zooplankton) are suppressed due to pharmaceutical sensitivity, it can lead to trophic cascades affecting phytoplankton dynamics and higher-order consumers. The disruption of predator-prey behaviors, such as altered foraging or reduced escape responses, also contributes to imbalances in energy distribution and biomass flows.

4.4 Evolutionary Pressures and Resistance Development

Pharmaceuticals can act as environmental stressors that impose strong selective pressures, driving evolutionary changes in exposed populations. The most evident example is the selection for antimicrobial resistance (AMR) in bacterial communities exposed to sub-inhibitory concentrations of antibiotics. This not only alters microbial ecosystem functions but also creates environmental reservoirs of resistance genes (ARGs), which can be horizontally transferred via plasmids, transposons, and integrons across taxa.

Beyond microbial systems, evolutionary pressures in multicellular organisms may manifest as selection for tolerant genotypes. In *Daphnia magna*, for example, exposure to antidepressants has been shown to select for clones with altered metabolic and reproductive profiles. However, such adaptations often carry fitness trade-offs, such as reduced competitive ability or altered life-history traits in uncontaminated environments.

Additionally, persistent pharmaceutical exposure may interfere with natural sexual selection and mate choice, especially in fish and amphibians exposed to endocrine disruptors. This can reduce the efficacy of sexual signals and mating success, potentially altering evolutionary trajectories.

These evolutionary changes, while potentially adaptive in the short term, may compromise long-term ecological resilience, reduce genetic diversity, and limit the ability of populations to respond to new environmental challenges.

5. Detection, Monitoring, and Risk Assessment

Effectively managing the environmental threat posed by pharmaceutical pollutants requires robust detection methods, biologically relevant monitoring tools, and scientifically grounded risk assessment frameworks (20). Given the complex chemical nature, low concentrations, and mixture dynamics of pharmaceuticals in the aquatic environment, detection and risk evaluation pose significant scientific and regulatory challenges. This section outlines current advancements and limitations in analytical methodologies, biological monitoring, and environmental risk assessment paradigms.

5.1 Analytical Techniques for Trace Detection

Detecting pharmaceuticals at environmentally relevant concentrations (typically in the ng/L to low µg/L range) necessitates high-sensitivity, high-specificity analytical methods. The most widely employed techniques include:

- **Liquid Chromatography coupled with Tandem Mass Spectrometry (LC-MS/MS):** This is the gold standard for targeted quantification of pharmaceuticals in water, sediment, and biota due to its excellent sensitivity, selectivity, and ability to detect a broad range of compounds simultaneously.
- **Gas Chromatography-Mass Spectrometry (GC-MS):** Used primarily for volatile or derivatized compounds; less common for polar pharmaceuticals.
- **High-Resolution Mass Spectrometry (HRMS):** Allows for both targeted and non-targeted screening, enabling the identification of unknown transformation products and emerging contaminants.

Pre-concentration techniques such as solid-phase extraction (SPE), solid-phase microextraction (SPME), and QuEChERS (Quick, Easy, Cheap, Effective, Rugged, and Safe) are critical for enhancing detection in complex matrices. Despite technological advancements, challenges remain in the detection of polar metabolites, conjugates, and transformation products, which may evade conventional analytical workflows but still exhibit biological activity.

5.2 Bioindicators and Biomarkers

While chemical analysis quantifies exposure, biological responses provide insight into ecological effects. **Bioindicators** (whole organisms) and **biomarkers** (molecular, biochemical, or physiological responses) are increasingly used to monitor the impact of pharmaceutical pollutants.

- **Bioindicators:** Organisms such as *Daphnia magna*, *Danio rerio* (zebrafish), *Chironomus riparius*, and *Mytilus spp.* (mussels) are widely used due to their ecological relevance, sensitivity, and ease of laboratory and field testing.
- **Biomarkers of Exposure and Effect:**
  - **Vitellogenin (Vtg)** induction in male fish: a hallmark biomarker of estrogenic endocrine disruption.
  - **Cytochrome P450 enzymes (e.g., CYP1A1):** indicators of xenobiotic metabolism and oxidative stress.
  - **Acetylcholinesterase (AChE) activity:** a marker for neurotoxicity.
  - **Comet assay:** to detect genotoxicity via DNA strand breaks.

Biomarker integration into ecological monitoring allows for early detection of sub-lethal effects, providing predictive value before observable population or ecosystem-level damage occurs.

5.3 Environmental Risk Assessment Frameworks

Environmental risk assessment (ERA) of pharmaceuticals typically follows the **PEC/PNEC approach**:

- **Predicted Environmental Concentration (PEC):** Estimated based on pharmaceutical use patterns, excretion rates, and wastewater treatment efficiency.
- **Predicted No Effect Concentration (PNEC):** Derived from ecotoxicological studies, often using uncertainty (assessment) factors on chronic or acute no-observed-effect concentrations (NOECs or EC50s).

Limitations of this approach include its inability to account for:

- Mixture toxicity and synergistic effects.
- Chronic low-dose exposure across multiple generations.
- Transformation products and metabolites.
- Non-target organism sensitivity and real-world environmental variability.

To address these challenges, more holistic approaches such as **species sensitivity distributions (SSDs)**, **ecoTTCs (ecological Thresholds of Toxicological Concern)**, and **Adverse Outcome Pathways (AOPs)** are increasingly recommended to improve ERA resolution.

5.4 Regulatory Thresholds and Monitoring Challenges

Despite the growing evidence of ecological harm, **regulatory frameworks for pharmaceutical pollutants remain limited and fragmented**. Only a few compounds, such as diclofenac, 17α-ethinylestradiol, and 17β-estradiol, are prioritized under monitoring programs like the **EU Water Framework Directive's Watch List**.

Key regulatory challenges include:

- **Lack of universal environmental quality standards (EQS)** for most pharmaceuticals.
- **Geographic variability** in pharmaceutical usage patterns and wastewater infrastructure.
- **Data gaps** in chronic toxicity, mixture effects, and metabolite behavior.
- **Regulatory inertia**, due to the pharmaceutical industry's proprietary data protections and slow policy translation from science to practice.

Additionally, **emerging contaminants** (e.g., new psychoactive substances, biopharmaceuticals) are not yet integrated into most monitoring regimes, creating blind spots in risk governance.

Efforts such as **ecopharmacovigilance (EPV)**, which encourages life-cycle environmental stewardship of pharmaceuticals, and the **One Health approach**, integrating human, animal, and environmental health perspectives, are gaining traction but require broader legislative support.

6. Mitigation Strategies and Technological Solutions

The growing evidence of ecological harm caused by pharmaceutical pollutants has prompted the development of a wide array of mitigation strategies. These strategies can be broadly categorized into end-of-pipe technological interventions, green design of pharmaceutical compounds, source control practices, and policy-level regulatory mechanisms (21). Together, they form a multi-barrier approach essential for minimizing pharmaceutical emissions and reducing ecological risk in aquatic environments.

Advanced wastewater treatment technologies are crucial for enhancing the removal of pharmaceuticals that are resistant to conventional processes. Techniques such as advanced oxidation processes (AOPs), including ozonation, UV/H_2O_2 systems, photocatalysis, and Fenton reactions, have demonstrated high efficiency in degrading a wide range of persistent pharmaceuticals by generating reactive oxygen species like hydroxyl radicals (22). These methods are particularly effective for compounds such as diclofenac and carbamazepine. However, AOPs can produce toxic transformation products if not carefully optimized, and they often involve high operational costs. Membrane bioreactors (MBRs), which combine biological degradation with membrane filtration, offer an alternative with improved pharmaceutical retention and degradation, especially for antibiotics and NSAIDs. Additionally, adsorption techniques using powdered or granular activated carbon can effectively remove hydrophobic compounds, serving as a valuable polishing step in wastewater treatment trains (23). Constructed wetlands and biofilters, while less technologically intensive, leverage natural biogeochemical processes to facilitate degradation and uptake but are often limited in hydraulic loading capacity and are less effective for highly recalcitrant compounds. Given the diversity of pharmaceutical compounds and their environmental behaviors, a multi-stage treatment approach is typically necessary to ensure comprehensive removal.

Beyond treatment technologies, green chemistry and sustainable drug design represent upstream solutions that aim to reduce environmental hazards at the molecular level. The "Benign by Design" (BbD)

concept emphasizes the synthesis of active pharmaceutical ingredients (APIs) that are not only therapeutically effective but also biodegradable, non-bioaccumulative, and environmentally safe (24). This involves tailoring physicochemical properties such as water solubility, partition coefficient, and structural stability to enhance environmental degradability without compromising pharmacological activity. Additionally, predictive toxicology tools and life cycle assessments are increasingly integrated into drug development to evaluate environmental impacts early in the innovation process. However, the practical adoption of green pharmaceuticals is hindered by intellectual property constraints, regulatory inertia, and limited market incentives.

Equally important are source control strategies and pharmaceutical stewardship practices that aim to prevent pharmaceutical pollution at its origin. Public take-back programs and safe disposal initiatives are critical for reducing the improper disposal of unused or expired medications, which often end up in sewage systems or landfills. Educational outreach and pharmacist-led initiatives can improve public awareness and participation. On the clinical side, promoting rational prescribing practices—such as reducing unnecessary prescriptions, tailoring doses, and choosing environmentally benign alternatives—can significantly reduce pharmaceutical loads in wastewater. In the veterinary and agricultural sectors, stricter controls on the prophylactic use of antibiotics and hormones are essential to curb diffuse pharmaceutical inputs (25). Furthermore, eco-labeling of pharmaceutical products, although still nascent, offers a transparent mechanism to inform prescribers and consumers about the environmental footprint of different medications, encouraging more informed choices.

At the policy level, regulatory interventions and monitoring frameworks are vital for enabling and enforcing mitigation strategies. While some progress has been made, such as the inclusion of selected pharmaceuticals (e.g., diclofenac, 17α-ethinylestradiol) in the European Union's Water Framework Directive Watch List, most pharmaceutical compounds remain unregulated with respect to environmental emissions. Ecopharmacovigilance (EPV), a relatively new concept, advocates for post-market surveillance of environmental impacts across the pharmaceutical life cycle. EPV encourages adaptive management based on real-world environmental monitoring data and integrates environmental stewardship into existing pharmacovigilance systems. Moreover, the One Health approach underscores the interconnectedness of human, animal, and environmental health, particularly in managing the spread of antimicrobial resistance through environmental reservoirs. Despite these advances, challenges persist, including data gaps in chronic toxicity, weak enforcement mechanisms, and limited coordination between pharmaceutical regulatory bodies and environmental agencies.

In summary, the mitigation of pharmaceutical pollution in aquatic systems requires a comprehensive and collaborative approach. No single strategy is sufficient on its own; rather, a synergistic combination of advanced treatment technologies, environmentally conscious drug design, responsible usage practices, and robust policy frameworks is essential. Implementing these strategies effectively will necessitate cross-sectoral collaboration among scientists, regulators, industry stakeholders, and the public, grounded in a shared commitment to safeguarding aquatic ecosystems for future generations.

7. CONCLUSION AND FUTURE DIRECTIONS

The pervasive presence of pharmaceutical pollutants in aquatic environments has become a critical global environmental concern, necessitating urgent scientific, technological, and regulatory action. As this review has demonstrated, pharmaceuticals—by virtue of their intrinsic biological activity and environmental persistence—pose unique and complex challenges to aquatic ecosystems. Their sub-lethal, chronic, and often mixture-based exposures can disrupt key biological processes in aquatic organisms, ranging from endocrine and neurological function to immune and reproductive health. These organism-level effects can propagate upward, affecting populations, altering community structure, disturbing food webs, and driving evolutionary adaptations that compromise long-term ecosystem resilience.

The key findings of this review highlight that pharmaceuticals enter aquatic environments through multiple anthropogenic pathways, particularly municipal wastewater effluents, agricultural runoff, and improper disposal practices. Conventional wastewater treatment infrastructure is not fully equipped to address these emerging contaminants, leading to their continuous release and pseudo-persistence in aquatic systems. Mechanistically, pharmaceuticals induce toxicity through a variety of pathways, including

endocrine disruption, oxidative stress, neurotoxicity, reproductive interference, and immune suppression. These effects not only impact individual organisms but also disrupt ecological balance and evolutionary trajectories within aquatic communities. Furthermore, the proliferation of antibiotic resistance genes in aquatic microbiota underscores the interconnectedness of environmental contamination and global public health threats.

Despite growing awareness, there remain significant knowledge gaps that hinder comprehensive risk assessment and effective management. These include limited data on the chronic and transgenerational effects of pharmaceuticals, insufficient understanding of mixture toxicity and transformation products, and underexplored ecological consequences in non-model and benthic species. Analytical challenges persist in detecting trace levels of emerging compounds and their metabolites, particularly in complex environmental matrices. Moreover, current environmental risk assessment frameworks often fail to account for cumulative, sub-lethal, and long-term ecological effects, which limits their predictive utility in real-world scenarios.

To address these deficiencies, future research must adopt interdisciplinary approaches that integrate environmental chemistry, ecotoxicology, molecular biology, and systems ecology. Long-term field studies, mesocosm experiments, and omics-based tools can help unravel subtle biological effects and ecosystem-level consequences. Investment in analytical infrastructure and standardized monitoring protocols will improve detection capabilities and facilitate international data comparability. Research should also explore the fate and behavior of pharmaceutical transformation products, their interactions with other contaminants, and their role in resistance propagation. In parallel, social science research should examine public perceptions, behaviors, and institutional barriers that affect pharmaceutical stewardship and policy implementation.

From a policy and management standpoint, a shift toward proactive, integrated solutions is imperative. Regulatory frameworks must evolve to include environmental risk criteria in the drug approval process, mandate post-market environmental surveillance, and prioritize high-risk compounds for monitoring and mitigation. Source control through pharmaceutical take-back programs, eco-labeling, and responsible prescribing should be widely promoted. The implementation of advanced treatment technologies must be supported through public investment and utility-level incentives. Coordination across sectors—public health, agriculture, wastewater management, and environmental protection—is essential for achieving a cohesive and effective strategy.

Looking ahead, the vision for sustainable aquatic ecosystem protection in the face of pharmaceutical pollution must be built on the principles of **One Health**, **precautionary governance**, and **adaptive management**. This entails recognizing the interdependence of human and environmental health, anticipating emerging risks through early-warning systems, and continuously refining policies based on scientific evidence and environmental feedback. A future where pharmaceuticals are designed, prescribed, and managed with ecological foresight is both a scientific and ethical imperative. By aligning technological innovation, policy reform, and societal engagement, it is possible to safeguard aquatic biodiversity and ensure the resilience of freshwater and marine ecosystems in an increasingly pharmaceutical-laden world.

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