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PHARMACEUTICAL WASTE IN FRESHWATER SYSTEMS: RE-ENTRY CYCLES, ECOTOXICOLOGICAL TIPPING POINTS, AND PUBLIC HEALTH RISKS

RESÍDUOS FARMACÊUTICOS EM ECOSSISTEMAS DE ÁGUA DOCE: CICLOS DE REENTRADA, PONTOS DE RUPTURA ECOTOXICOLÓGICOS E RISCOS À SAÚDE PÚBLICA

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ABSTRACT

The widespread use of pharmaceuticals has introduced a persistent and largely unregulated source of contamination in freshwater systems, raising critical concerns about ecological integrity and public health. The central problem lies in the re-entry cycle, in which antidepressants and hormones are inadequately removed during wastewater treatment and subsequently reintroduced into aquatic environments, where they accumulate and potentially return to humans through water and food consumption. This study aimed to analyze how the inefficiency of wastewater treatment systems contributes to bioaccumulation processes and to identify critical thresholds at which pharmaceutical residues pose ecological and public health risks. An integrative literature review was conducted based on a structured search strategy in major scientific databases, followed by systematic screening and evidence synthesis. The analysis revealed that pharmaceutical residues are globally distributed in freshwater systems at concentrations ranging from ng/L to µg/L, with documented effects including endocrine disruption, behavioral alterations, and population-level impacts in aquatic organisms. The findings also highlighted the occurrence of mixture effects and the inability of conventional treatment systems to effectively remove complex bioactive compounds. The discussion emphasized the existence of non-linear toxicity patterns and the emergence of ecotoxicological tipping points, beyond which ecosystem stability may be compromised. The results further indicated significant gaps in long-term monitoring and regulatory frameworks. In conclusion, pharmaceutical contamination represents a systemic challenge requiring the integration of advanced treatment technologies, environmental pharmacovigilance, and a One Health approach to mitigate long-term ecological and public health risks.

Keywords: Bioaccumulation. Ecotoxicology. Endocrine disruption. Wastewater treatment. One Health

RESUMO

O uso disseminado de fármacos tem introduzido uma fonte persistente e amplamente não regulamentada de contaminação em sistemas de água doce, levantando preocupações críticas quanto à integridade ecológica e à saúde pública. O problema central reside no ciclo de reentrada, no qual antidepressivos e hormônios não são completamente removidos nos processos convencionais de tratamento de esgoto, sendo reintroduzidos no ambiente aquático, onde podem se acumular e retornar à população por meio da água e da cadeia alimentar. Este estudo teve como objetivo analisar como a ineficiência dos sistemas de tratamento contribui para processos de bioacumulação e identificar limiares críticos nos quais resíduos farmacêuticos passam a representar riscos ecológicos e à saúde. Foi realizada uma revisão integrativa da literatura com base em estratégia estruturada de busca em bases científicas, seguida de triagem sistemática e síntese das evidências. Os resultados demonstraram que resíduos farmacêuticos estão amplamente distribuídos em sistemas de água doce em concentrações variando de ng/L a µg/L, com efeitos documentados como desregulação endócrina, alterações comportamentais e impactos populacionais em organismos aquáticos. Evidenciou-se também a ocorrência de efeitos combinados e a limitação dos sistemas convencionais de tratamento na remoção desses compostos. A discussão destacou padrões de toxicidade não linear e a emergência de pontos de ruptura ecotoxicológicos, capazes de comprometer a estabilidade dos ecossistemas. Os achados também indicaram lacunas importantes em monitoramento e regulação. Conclui-se que a contaminação por fármacos representa um desafio sistêmico,

exigindo tecnologias avançadas de tratamento, farmacovigilância ambiental e integração da abordagem One Health.

Palavras-chave: Bioacumulação. Ecotoxicologia. Desregulação endócrina. Tratamento de esgoto. One Health

1. INTRODUCTION

The expansion of modern pharmacology represents one of the most significant achievements in public health, contributing to increased life expectancy, improved mental health outcomes, and enhanced quality of life worldwide. However, this therapeutic success has simultaneously generated an unintended and largely unregulated environmental consequence: the continuous release of bioactive pharmaceutical compounds into aquatic ecosystems. This phenomenon establishes a critical paradox in which substances designed to restore physiological balance in humans become persistent disruptors of ecological homeostasis (Boxall et al., 2012; Schwarzenbach et al., 2006).

Pharmaceutical residues, including antidepressants and synthetic hormones, are increasingly detected in freshwater systems across the globe, often at concentrations capable of inducing biological effects in non-target organisms. Large-scale monitoring studies have demonstrated that these compounds are not confined to isolated regions but are ubiquitously distributed across rivers, lakes, and effluent-receiving environments, reflecting the global scale of pharmaceutical consumption and disposal (Kolpin et al., 2002; Wilkinson et al., 2022). This widespread occurrence highlights the emergence of what can be conceptualized as “invisible contamination”, a form of pollution characterized not by acute

toxicity, but by chronic, low-dose exposure to biologically active molecules.

Unlike conventional pollutants, pharmaceutical compounds are specifically engineered to interact with biological pathways at very low concentrations, raising concerns about their ecological effects even at nanogram-per-liter levels. Their physicochemical stability and partial resistance to degradation further contribute to environmental persistence, allowing them to accumulate and interact within complex aquatic systems (Aus der Beek et al., 2016). Despite growing recognition of this issue, current environmental policies and wastewater treatment infrastructures remain insufficiently adapted to address the scale and complexity of pharmaceutical contamination, reinforcing a systemic gap between therapeutic innovation and environmental protection (OECD, 2019).

The concept of the exposome, originally developed to describe the totality of human environmental exposures throughout life, provides a powerful framework for understanding pharmaceutical contamination in aquatic ecosystems. When applied to freshwater environments, the exposome encompasses the continuous and cumulative exposure of aquatic organisms, and indirectly humans, to a dynamic mixture of chemical stressors, including pharmaceuticals, metabolites, and transformation products (Richardson; Ternes, 2014).

In this context, exposure is not episodic but chronic, occurring at low concentrations over extended periods. Such exposure patterns challenge traditional toxicological paradigms, which are largely based on acute, high-dose assessments. Pharmaceuticals such as selective serotonin reuptake inhibitors (SSRIs) and endocrine-

disrupting hormones can exert subtle yet significant biological effects, including behavioral alterations, reproductive disruption, and metabolic changes, even at environmentally relevant concentrations (Li, 2014). These effects are particularly concerning because they may not produce immediate mortality but can impair population dynamics and ecosystem resilience over time.

Furthermore, the freshwater exposome is directly linked to human health through multiple pathways. Drinking water abstraction, irrigation, and especially the consumption of aquatic organisms represent key routes through which pharmaceutical residues re-enter the human body. This interconnected exposure network underscores the inadequacy of compartmentalized risk assessments and highlights the need for integrative approaches that consider environmental and human health as part of a unified system.

A critical yet underexplored dimension of pharmaceutical pollution is the re-entry cycle, a feedback loop in which compounds consumed by humans are excreted, inadequately removed during wastewater treatment, and subsequently reintroduced into natural water bodies. From these environments, they can bioaccumulate in aquatic organisms and eventually return to humans through the food chain or water consumption, completing a cycle of exposure that blurs the boundaries between source and receptor (Ebele et al., 2017).

Wastewater treatment plants (WWTPs), designed primarily to remove organic matter and nutrients, are not equipped to fully eliminate complex pharmaceutical molecules. As a result, treated effluents become a continuous source of contamination, introducing a diverse mixture of bioactive compounds into receiving

ecosystems. Once in the environment, these substances can undergo transformation, partition into sediments, or accumulate in biota, further complicating their ecological and toxicological profiles.

This cyclical process aligns closely with the One Health framework, which recognizes the interdependence of human, animal, and environmental health. Within this perspective, pharmaceutical contamination is not merely an environmental issue but a systemic challenge that reflects the interconnected consequences of human activity. The persistence of pharmaceutical residues in aquatic systems thus represents both an ecological disturbance and a potential public health concern, particularly in regions where water reuse and fish consumption are significant.

Given the increasing evidence of pharmaceutical persistence, bioactivity, and ecological impact, there is a pressing need to synthesize current knowledge through an integrative and critical approach. This study aims to examine how the inefficiency of conventional wastewater treatment systems in removing antidepressants and hormones contributes to their accumulation in freshwater ecosystems and to identify the conditions under which these substances pose a significant risk to environmental and human health.

Guided by the PICo strategy, this review addresses the following research question: How does the inefficiency of wastewater treatment systems in removing pharmaceutical residues, specifically antidepressants and hormones, establish a cycle of bioaccumulation in freshwater ecosystems, and what are the critical thresholds at which these contaminants transition from therapeutic benefit to ecotoxicological risk within a One Health perspective?

To address this question, the study focuses on three interrelated dimensions: (i) the environmental persistence and bioaccumulation of pharmaceutical compounds, (ii) the technological limitations of current treatment systems, and (iii) the identification of potential ecological tipping points, where cumulative exposure leads to irreversible biological and ecological effects. This integrative perspective seeks not only to consolidate existing evidence but also to challenge prevailing assumptions regarding the safety and sustainability of pharmaceutical use in a globalized and interconnected environment.

2. METHODOLOGY

2.1. Study Design

This study was conducted as an integrative literature review, a method selected because it allowed the synthesis of empirical, analytical, and review-based evidence within a single interpretive framework. This approach was considered the most appropriate for the present investigation because the research problem was not limited to a single disciplinary field or to a single type of evidence. The environmental persistence of antidepressants and hormones, the technological limitations of wastewater treatment systems, the ecotoxicological effects observed in freshwater organisms, and the implications for public health required an analytical structure capable of integrating heterogeneous studies without reducing the complexity of the phenomenon under examination (Whittemore; Knafl, 2005; Torraco, 2005; Souza; Silva; Carvalho, 2010).

The review design was structured according to the methodological assumptions proposed for integrative reviews, especially the stages

related to problem identification, literature search, data evaluation, data analysis, and presentation of the synthesis. The adoption of this framework was justified by its flexibility and epistemological adequacy for multidisciplinary topics in environmental health, where experimental, monitoring, and review studies often contribute complementary forms of evidence rather than strictly comparable results. In this sense, the integrative review did not aim merely to summarize findings, but to critically interpret patterns, identify conceptual gaps, and organize evidence capable of supporting a more comprehensive understanding of pharmaceutical contamination in freshwater systems and its implications for the One Health perspective (Whittemore; Knafl, 2005; Torraco, 2005).

This methodological choice was also aligned with the analytical objective of the article. Since the study sought to discuss not only the occurrence of pharmaceutical residues, but also the logic of environmental re-entry, the synergistic effects of mixed contaminants, and the hypothesis of ecological tipping points, a narrowly restrictive review model would not have been sufficient. The integrative design made it possible to combine quantitative information, such as detected concentrations and occurrence patterns, with qualitative interpretations related to ecological risk, technological failure, and public health relevance. It also supported the development of a critical synthesis rather than a purely descriptive inventory of prior publications (Souza; Silva; Carvalho, 2010).

2.2. Research Question (pico Strategy)

The review question was structured using the PICo strategy in order to ensure conceptual clarity and alignment between the research

objective, the search process, and the analytical scope of the study. This approach was selected because the investigation focused on an environmental exposure phenomenon rather than on a clinical intervention, which made PICo more appropriate than traditional frameworks designed for intervention-based studies.

The components of the PICo strategy were defined as follows:

- P (Population / Phenomenon): Persistent pharmaceutical residues in aquatic environments, with emphasis on antidepressants and hormones;

- I (Interest): Bioaccumulation, ecotoxicological effects, and the inefficiency of wastewater treatment systems;

- Co (Context): Freshwater ecosystems and associated public health risks within the One Health framework.

Based on this structure, the guiding research question was formulated as follows: How did the inefficiency of wastewater treatment systems in removing antidepressants and hormones contribute to a cycle of bioaccumulation in freshwater ecosystems, and what critical thresholds of environmental and public health risk could be identified within a One Health perspective?

This formulation ensured consistency between the theoretical foundation of the study and the empirical evidence targeted during the search and selection process, allowing for a structured and integrative interpretation of the environmental and health implications of pharmaceutical contamination.

2.3. Search Strategy And Databases

The bibliographic search was carried out between October 2025 and February 2026 in three international databases selected for their broad coverage of environmental sciences, toxicology, public health, and interdisciplinary research: PubMed, Scopus, and Web of Science. These databases were chosen because they index high-impact literature relevant to pharmaceutical residues, aquatic contamination, endocrine disruption, ecotoxicology, and environmental exposure, while also allowing advanced Boolean combinations and controlled search refinement.

The search strategy was developed from descriptors associated with three major conceptual domains: contaminants, environmental context, and biological or public health effects. The descriptors were organized on the basis of terminological convergence between environmental and health sciences, with attention to terms recurrent in the literature on pharmaceutical pollution and freshwater ecotoxicology. The final search logic aimed to balance sensitivity and specificity. It needed to be broad enough to retrieve studies addressing pharmaceutical residues in aquatic systems, but sufficiently focused to avoid excessive dispersion into unrelated industrial, veterinary, or strictly pharmaceutical synthesis literature.

The search strings combined terms related to pharmaceutical residues and specific pharmacological groups with descriptors associated with freshwater environments and ecological or health outcomes. The search strategy included, among others, the following Boolean structure: ("Pharmaceutical residues" OR "Antidepressive Agents" OR "Hormones" OR "Endocrine Disruptors" OR "Emerging Contaminants") AND ("Freshwater" OR "Rivers" OR "Aquatic Ecosystems" OR "Water Supply" OR "Effluent Treatment") AND ("Bioaccumulation" OR "Ecotoxicology" OR "Public Health Risk"

OR "One Health" OR "Toxicity" OR "Environmental Exposure") NOT ("Veterinary Medicine")

To improve retrieval consistency across databases, equivalent controlled vocabulary and indexed terms were adapted when necessary according to the search architecture of each platform. Additional manual screening of titles, abstracts, and keywords was conducted to ensure thematic coherence with the guiding question. The initial search yielded 189 records, which constituted the primary screening universe for the review.

Table 1 summarizes the operational structure of the literature search and selection process adopted in this integrative review. It systematizes the key methodological components, including database selection, descriptor construction, Boolean strategy, and eligibility criteria, as well as the sequential screening stages applied to the initial dataset. This organization reflects the effort to ensure transparency, reproducibility, and alignment between the research question and the evidence included in the analytical corpus.

Table 1. Search strategy, descriptors, and selection criteria (PRISMA-based)

Component	Description	Operationalization	Purpose in the Review	Outcome

Databases	Scientific indexing platforms selected for literature retrieval	PubMed, Scopus, Web of Science	Ensure broad and multidisciplinary coverage of environmental health and ecotoxicology studies	189 records identified
Search Terms (Descriptors)	Controlled and free terms related to contaminants, environment, and effects	"Pharmaceutical residues", "Antidepressive Agents", "Hormones", "Freshwater", "Rivers", "Bioaccumulation", "Ecotoxicology", "Public Health Risk", "One Health"	Capture studies addressing pharmaceutical contamination and ecological/public health implications	High sensitivity retrieval
Boolean Strategy	Logical combination of descriptors	(Pharmaceutical residues OR Antidepressive Agents OR Hormones) AND (Freshwater OR Rivers) AND (Bioaccumulation OR Ecotoxicology OR Public Health Risk) AND NOT (Veterinary Medicine)	Increase specificity and exclude irrelevant domains	Refined dataset for screening

Inclusion Criteria	Eligibility parameters aligned with research objective	Environmental relevance, focus on antidepressants/hormones, mixture effects, recent publications, full-text availability	Ensure analytical coherence and relevance to the research question	Final corpus defined after screening
Exclusion Criteria	Removal of non-relevant or low-impact studies	Veterinary focus, industrial contaminants, purely chemical studies, gray literature, duplicates	Reduce bias and eliminate non-aligned evidence	Dataset reduced for synthesis
Screening Process	Sequential filtering of studies	Title and abstract screening followed by full-text assessment	Identify studies consistent with PICo framework	Progressive refinement of corpus

Source: Own authorship.

The configuration presented in Table 1 reveals a deliberate balance between sensitivity and specificity in the search strategy. The combination of broad descriptors related to pharmaceutical contamination with targeted environmental and health-related terms enabled the retrieval of a comprehensive initial dataset while maintaining thematic coherence with the study objective. The application of Boolean operators played a central role in refining the results, particularly by excluding veterinary-related studies that

could introduce conceptual noise. In parallel, the inclusion and exclusion criteria strengthened the analytical rigor by prioritizing studies with direct environmental relevance and focus on mixture effects and treatment inefficiency, preventing fragmentation of the evidence base and ensuring meaningful contributions to the analysis of bioaccumulation and ecotoxicological risks.

The sequential screening process, progressing from title and abstract evaluation to full-text analysis, allowed a structured reduction of the initial 189 records into a coherent corpus aligned with the PICo framework. At the same time, the table highlights a methodological limitation inherent to integrative reviews, since the need to balance breadth and depth required selective decisions that may have excluded less directly aligned studies. This constraint, however, was necessary to preserve conceptual focus and to support a robust synthesis capable of addressing the hypothesis of ecological tipping points and systemic failure in wastewater treatment systems.

2.4. Inclusion And Exclusion Criteria

Eligibility criteria were defined before the screening process in order to preserve analytical consistency and reduce selection bias. These criteria were directly aligned with the review question and with the conceptual emphasis of the study on environmental persistence, mixture effects, treatment inefficiency, freshwater exposure, and public health implications.

Inclusion criteria:

- Original articles and high-quality review studies addressing pharmaceutical residues in freshwater ecosystems;

- Studies focusing on antidepressants, hormones, endocrine-disrupting compounds, or related pharmaceutical contaminants with clear environmental relevance;

- Investigations examining occurrence, distribution, persistence, bioaccumulation, trophic transfer, ecotoxicological effects, or wastewater treatment inefficiency;

- Studies addressing contaminant mixtures or providing evidence relevant to the cocktail effect;

- Publications issued within a recent time horizon considered adequate to capture current scientific and regulatory discussions, while allowing the inclusion of seminal studies essential to the topic;

- Articles available in full text and presenting sufficient methodological and analytical detail for extraction.

Exclusion criteria:

- Studies focused exclusively on veterinary pharmaceuticals or non-pharmaceutical industrial contaminants;

- Publications restricted to laboratory synthesis, analytical method development, or pharmaceutical formulation without environmental application;

- Case reports, editorials, conference abstracts, monographs, and other forms of gray literature not indexed in the selected databases;

- Experimental studies with no environmental correlation or no relevance to freshwater contamination pathways;

- Records with insufficient information in title, abstract, or full text to support analytical extraction;

- Duplicate records retrieved from more than one database.

After the search stage, the 189 identified records underwent title and abstract screening. Duplicate studies were removed first. The remaining records were then evaluated for thematic adherence to the review question, with special attention to four dimensions: relevance to freshwater systems, focus on antidepressants and hormones or comparable pharmaceutical residues, evidence of treatment limitations or environmental persistence, and analytical contribution to ecological or public health interpretation. Full-text reading was subsequently performed for the studies retained after preliminary screening. This step supported the final selection of the corpus used in the integrative synthesis.

2.5. Data Extraction And Synthesis

Data extraction was conducted systematically through an evidence matrix designed to organize heterogeneous findings into comparable analytical categories. This matrix served as the central instrument of synthesis and was structured to preserve both the quantitative and interpretive dimensions of the selected literature. The extracted information included authorship, year of publication, study design, country or region, pharmaceutical class investigated, environmental matrix analyzed, concentration ranges, type of biological effect observed, evidence of bioaccumulation or trophic

transfer, treatment-related findings, and implications for public health or environmental regulation.

The matrix also included interpretive fields specifically created for the objectives of this article, such as indicators of cocktail effect, evidence related to ecological destabilization, re-entry pathways into human exposure, and unresolved knowledge gaps. This organization made it possible to compare studies not only by substance class, but also by ecological consequence and analytical relevance. Particular attention was given to concentration patterns expressed in ng/L or µg/L, because these values were essential for supporting the discussion on critical exposure thresholds and the tipping point hypothesis.

The synthesis process was performed through thematic categorization and critical integration. Rather than aggregating results mechanically, the analysis sought to identify recurrent patterns, convergences, inconsistencies, and absences in the literature. Studies were interpreted in relation to three major analytical axes: persistence and occurrence of pharmaceutical residues in freshwater systems, biological and ecological effects associated with antidepressants and hormones, and technological failure of conventional wastewater treatment as a structural driver of environmental recirculation. This procedure supported a synthesis capable of linking environmental contamination to broader public health concerns, while preserving the complexity of the evidence and the interdisciplinary character of the review.

The final analytical corpus was then used to support the interpretive sections of the article, especially the discussion of mixture toxicity,

ecological tipping points, and the One Health implications of chronic pharmaceutical exposure in freshwater environments.

3. RESULTS

3.1. Occurrence And Distribution Of Pharmaceuticals In Freshwater

The occurrence of pharmaceutical residues in freshwater systems has been consistently documented across multiple geographic regions, revealing a pattern of global dispersion that reflects both consumption intensity and infrastructural limitations in wastewater management. Early large-scale monitoring studies demonstrated that a wide range of pharmaceuticals, including hormones and psychoactive compounds, were already present in surface waters at the beginning of the 21st century, with detection frequencies exceeding 80% for certain classes of contaminants (Kolpin et al., 2002). Concentrations reported in these systems typically ranged from low nanogram per liter levels to several micrograms per liter, depending on proximity to urban discharge points and hydrological conditions.

More recent global assessments have reinforced the ubiquity and scale of this contamination. A worldwide survey of river systems indicated that pharmaceutical pollution is not restricted to highly industrialized regions, but also affects low- and middle-income countries, often at higher concentrations due to limited treatment infrastructure (Wilkinson et al., 2022). In some cases, concentrations of active pharmaceutical ingredients exceeded 1 µg/L, particularly downstream of wastewater discharge zones. This reinforces the idea

that freshwater contamination is not a localized anomaly but a systemic environmental condition.

Regional monitoring programs have further demonstrated the persistence and widespread distribution of pharmaceuticals across European aquatic systems. An extensive survey of wastewater treatment plant effluents detected multiple emerging contaminants in the majority of sampled sites, confirming the continuous release of these substances into receiving water bodies (Loos et al., 2013). Similarly, comprehensive reviews have highlighted that pharmaceuticals are now considered a dominant class of emerging contaminants, frequently detected in rivers, lakes, and groundwater systems worldwide, with concentrations commonly reported in the ng/L to µg/L range (Gogoi et al., 2018).

This pattern of occurrence challenges conventional assumptions about dilution as a mitigating factor. As noted by Kolpin et al., “pharmaceuticals and other organic wastewater contaminants were frequently detected in streams” (Kolpin et al., 2002, p. 1205), indicating that environmental dispersion does not necessarily translate into ecological safety. Instead, the widespread distribution of low-dose contaminants establishes a persistent exposure scenario that may be more relevant for chronic ecological effects than sporadic high-concentration events.

3.2. Persistence And Inefficiency Of Wastewater Treatment Systems

The persistence of pharmaceutical residues in freshwater systems is closely linked to the limitations of conventional wastewater treatment technologies, particularly those based on activated

sludge processes. These systems were originally designed to remove organic matter and nutrients, not structurally complex and biologically active molecules such as antidepressants and synthetic hormones. As a result, removal efficiencies for many pharmaceutical compounds remain partial and inconsistent.

Empirical evidence has shown that several pharmaceuticals pass through treatment systems with minimal degradation. Studies evaluating sewage treatment processes have demonstrated that removal rates vary widely depending on the compound, with some substances showing negligible reduction during treatment (Carballa et al., 2004). This variability is associated with physicochemical properties such as solubility, molecular stability, and resistance to microbial degradation. In this context, pharmaceutical compounds often exhibit behavior that differs fundamentally from traditional pollutants.

A critical review of wastewater treatment performance highlighted that “conventional systems are not fully effective in removing pharmaceuticals and endocrine disruptors” (Aquino; Brandt; Chernicharo, 2013, p. 190), emphasizing the structural inadequacy of existing infrastructure. This inefficiency is further compounded by transformation processes that may generate metabolites with unknown or even enhanced biological activity. Advanced oxidation processes have been proposed as potential solutions, yet their implementation remains limited due to economic and operational constraints (Melo et al., 2009).

The persistence of pharmaceuticals in treated effluents therefore represents not merely a technical limitation, but a systemic failure in aligning environmental protection strategies with contemporary

patterns of chemical consumption. The continuous discharge of partially treated wastewater establishes a chronic input of contaminants into aquatic systems, reinforcing the re-entry cycle and sustaining long-term ecological exposure.

3.3. Bioaccumulation And Trophic Transfer

Once introduced into aquatic environments, pharmaceutical compounds can be taken up by organisms and transferred across trophic levels, establishing a pathway for bioaccumulation and potential biomagnification. The extent of accumulation depends on factors such as lipophilicity, ionization, and environmental persistence, as well as species-specific metabolic capacities.

Pharmaceutical residues have been detected in various aquatic organisms, including fish, invertebrates, and algae, indicating that uptake occurs across multiple biological compartments. The accumulation of these substances in tissues raises concerns about long-term exposure and physiological disruption. As highlighted in the literature, “pharmaceuticals can accumulate in aquatic organisms and potentially enter the food chain” (Li, 2014, p. 196), reinforcing the connection between environmental contamination and human exposure.

The process of trophic transfer amplifies this concern. Compounds present in water can be absorbed by primary producers and subsequently transferred to higher trophic levels through feeding interactions. Reviews have emphasized that the continuous input of pharmaceuticals into aquatic systems creates conditions for sustained exposure, even when individual concentrations remain relatively low (Ebele et al., 2017). This dynamic challenges the

traditional assumption that low environmental concentrations correspond to negligible biological risk.

From a mechanistic perspective, the potential for bioaccumulation is not limited to hydrophobic compounds. Several pharmaceuticals with moderate polarity have also been shown to accumulate in organisms due to continuous exposure and incomplete elimination. This reinforces the need to consider exposure duration and environmental persistence alongside concentration levels when assessing ecological risk (Patel et al., 2019).

3.4. Ecotoxicological Effects On Aquatic Organisms

One of the most well-documented consequences of pharmaceutical contamination in aquatic environments is endocrine disruption, particularly associated with synthetic hormones. Experimental and field studies have demonstrated that even low concentrations of estrogenic compounds can induce profound alterations in reproductive physiology.

A landmark whole-ecosystem experiment revealed that exposure to synthetic estrogen resulted in the collapse of a fish population due to reproductive failure (Kidd et al., 2007). The study reported that “fathead minnows were nearly eliminated from the lake” following chronic exposure (Kidd et al., 2007, p. 8900), providing direct evidence of ecological destabilization at environmentally relevant concentrations. Observed effects included feminization of male fish, reduced fertility, and disruption of normal reproductive cycles.

These findings indicate that endocrine-disrupting pharmaceuticals can act as potent ecological stressors, capable of altering population dynamics and ecosystem structure. The sensitivity of reproductive

processes to hormonal interference suggests that even subtle changes in environmental concentrations may have disproportionate biological consequences.

In addition to endocrine disruption, antidepressants have been shown to affect neurological and behavioral functions in aquatic organisms. These compounds are designed to modulate neurotransmitter systems, which are evolutionarily conserved across species. As a result, their presence in aquatic environments can interfere with normal behavioral patterns in non-target organisms.

Experimental studies have reported alterations in feeding behavior, predator avoidance, and social interactions following exposure to selective serotonin reuptake inhibitors. For example, it has been observed that exposure to fluoxetine can lead to increased risk-taking behavior and reduced predator response in fish (Correia et al., 2023). Similarly, antidepressants have been associated with changes in growth, survival, and behavioral regulation in aquatic species (Słoczyńska et al., 2023).

Recent analyses have emphasized that these effects may occur at environmentally relevant concentrations, raising concerns about the ecological implications of chronic exposure. As noted in the literature, antidepressants can “induce behavioral and physiological alterations even at low concentrations” (Liu et al., 2025, p. 1203), suggesting that their impact may be underestimated when assessed solely through traditional toxicological endpoints.

Table 2 synthesizes the empirical and analytical evidence identified in the selected studies, organizing key variables related to pharmaceutical contamination in freshwater systems. The matrix

integrates information on pharmaceutical classes, detected environmental concentrations, observed biological effects, affected organisms, and associated pathways of re-entry or knowledge gaps. This structured approach enables the comparison of heterogeneous studies and supports the identification of patterns that are not immediately evident in isolated analyses.

Table 2. Evidence matrix of pharmaceutical classes, concentrations, and biological effects

Pharmaceutical class	Detected concentration	Biological effect	Affected species / system	Re-entry pathway / knowledge gap
Synthetic estrogens (e.g., EE2)	5–50 ng/L	Feminization, reproductive failure, population collapse	Fish (fathead minnow)	Bioaccumulation in fish; unclear threshold for ecosystem collapse
SSRIs (e.g., fluoxetine)	10–500 ng/L	Altered behavior, reduced predator avoidance, feeding disruption	Fish, invertebrates	Chronic low-dose exposure; insufficient mixture studies
Antidepressants (general)	1–1000 ng/L	Neurobehavioral changes, altered growth and survival	Aquatic organisms	Long-term ecological consequences not fully established

Mixed pharmaceuticals (cocktail effect)	ng/L–µg/L range (combined)	Synergistic toxicity, non-linear biological responses	Multi-species systems	Lack of regulatory thresholds for mixtures
Endocrine disruptors (hormonal class)	<1–100 ng/L	Hormonal imbalance, reproductive disruption	Fish, amphibians	Limited understanding of multigenerational effects
Pharmaceuticals in WWTP effluents	up to µg/L	Continuous exposure, ecological stress	Freshwater ecosystems	Inefficient removal; transformation products unknown
Persistent pharmaceuticals in sediments	Variable (bioaccumulated)	Chronic exposure, trophic transfer	Benthic organisms	Sediment role underexplored in risk assessment
Emerging contaminants (global scale)	ng/L–µg/L	Ecosystem-level impacts, biodiversity risk	Rivers worldwide	Geographic disparities in monitoring and regulation

Source: Own authorship.

The evidence matrix reveals a consistent pattern in which biologically active pharmaceutical compounds exert measurable effects at concentrations far below those traditionally considered hazardous. Substances such as synthetic estrogens and antidepressants demonstrate that ecological disruption does not require high-dose exposure, but rather sustained presence at low concentrations. The case of endocrine disruption is particularly

illustrative, where concentrations in the order of a few nanograms per liter were sufficient to induce reproductive failure and population decline. This finding challenges conventional toxicological thresholds and suggests that current environmental safety parameters may underestimate real-world risks.

Another critical aspect emerging from the table is the role of mixture exposure. The presence of multiple pharmaceutical compounds in the same aquatic system introduces the possibility of synergistic or non-linear effects that cannot be predicted based on single-compound studies. Despite this, most available data remain focused on individual substances, revealing a significant gap in the literature.

At the same time, the persistence of pharmaceuticals in wastewater effluents and sediments indicates that exposure is continuous and multifaceted, involving both waterborne and trophic pathways. These observations reinforce the need for integrated assessment models that consider cumulative exposure, ecological interactions, and feedback mechanisms associated with the re-entry cycle.

4. DISCUSSION

4.1. The Cocktail Effect: Synergistic Toxicity In Aquatic Systems

The results indicate that pharmaceutical contamination in freshwater systems cannot be adequately understood through single-compound analysis. The coexistence of antidepressants, hormones, and other bioactive substances creates conditions for mixture toxicity, in which combined effects differ qualitatively and quantitatively from individual exposures. This phenomenon, commonly referred to as the cocktail effect, introduces a layer of

complexity that challenges traditional ecotoxicological assessment models.

Evidence suggests that interactions between selective serotonin reuptake inhibitors and endocrine-disrupting compounds may produce non-linear and potentially amplified biological responses, even when each compound is present at low concentrations. Backhaus and Karlsson emphasized that “mixture toxicity may occur even when individual substances are below their effect thresholds” (Backhaus; Karlsson, 2014, p. 159), indicating that risk cannot be inferred from isolated concentration values. This finding directly contradicts regulatory approaches that rely on single-substance safety limits.

From a global perspective, the presence of multiple pharmaceutical residues in aquatic environments has been consistently reported. As highlighted by Aus der Beek et al., pharmaceuticals are “ubiquitously present in the environment” (Aus der Beek et al., 2016, p. 824), which implies that mixture exposure is not an exception but a baseline condition. The interaction between compounds with different modes of action, such as neuroactive antidepressants and hormonally active substances, may result in overlapping or synergistic disruptions in physiological systems. This raises a fundamental question regarding the adequacy of current risk assessment frameworks, which rarely incorporate multi-compound dynamics into regulatory thresholds.

4.2. The Failure Of Current Wastewater Technologies

The persistence of pharmaceutical residues observed in the results reflects a structural limitation in wastewater treatment technologies.

Conventional systems based on activated sludge processes were not designed to remove micropollutants with high chemical stability and biological activity at low concentrations. As a consequence, many pharmaceuticals are only partially degraded or remain unchanged during treatment, leading to continuous environmental discharge.

The limitations of current treatment processes are not solely operational but are rooted in the chemical nature of pharmaceutical compounds. These substances are often resistant to biodegradation and may undergo transformation into metabolites that retain biological activity. According to Gavrilescu et al., emerging contaminants “are not completely removed by conventional wastewater treatment processes” (Gavrilescu et al., 2015, p. 149), reinforcing the systemic inadequacy of existing infrastructure.

This technological gap has been recognized at the policy level, yet implementation of advanced treatment solutions remains limited. The OECD has noted that wastewater systems were not originally designed to address pharmaceutical contamination, which results in “continuous release of these substances into aquatic environments” (OECD, 2019). The persistence of this scenario suggests that the problem extends beyond technical inefficiency and reflects a broader misalignment between environmental management systems and contemporary patterns of chemical use. Without significant adaptation, wastewater treatment plants will continue to function as pathways of redistribution rather than barriers to contamination.

4.3. Defining The Ecological Tipping Point

One of the central questions emerging from this analysis concerns the identification of ecological tipping points, defined as thresholds beyond which environmental systems undergo irreversible change. The evidence suggests that pharmaceutical contamination may reach such thresholds at concentrations lower than traditionally assumed, particularly when exposure is chronic and involves multiple compounds.

The experimental collapse of fish populations exposed to synthetic estrogen provides a critical empirical reference for this discussion. In a whole-ecosystem study, Kidd et al. reported that sustained exposure to low concentrations of estrogen led to reproductive failure and near elimination of a fish population, demonstrating that “fathead minnows were nearly eliminated from the lake” (Kidd et al., 2007, p. 8900). This case illustrates that tipping points are not theoretical constructs but observable outcomes under environmentally realistic conditions.

At a broader scale, global monitoring data indicate that pharmaceutical concentrations in rivers frequently approach or exceed levels associated with biological effects. Wilkinson et al. highlighted that pharmaceutical pollution is widespread and that some sites present concentrations above predicted no-effect levels, suggesting that ecological thresholds may already be exceeded in certain regions (Wilkinson et al., 2022). These findings challenge the assumption that environmental systems possess sufficient resilience to absorb continuous low-dose contamination. Instead, they point to the possibility of cumulative effects leading to systemic instability.

4.4. Human Health Implications Within The One Health Framework

The environmental persistence and bioaccumulation of pharmaceutical residues have direct implications for human health, particularly when considered within the One Health framework. This perspective emphasizes the interconnectedness of environmental, animal, and human health, highlighting that contamination in one domain inevitably affects the others.

Pharmaceutical residues present in freshwater systems can enter the human body through multiple pathways, including drinking water and the consumption of contaminated aquatic organisms. Analytical studies have demonstrated that trace levels of pharmaceuticals are detectable in water sources, raising concerns about chronic exposure. Richardson and Ternes noted that “emerging contaminants are increasingly detected in water supplies” (Richardson; Ternes, 2014, p. 2815), indicating that exposure is not limited to ecological receptors.

The long-term health implications of such exposure remain uncertain. While concentrations are typically low, the chronic nature of exposure and the presence of mixtures complicate risk assessment. The OECD has emphasized that endocrine-disrupting chemicals in freshwater systems may have subtle but significant effects on both wildlife and humans, particularly through cumulative exposure pathways (OECD, 2022). This uncertainty introduces a critical gap in current public health frameworks, which are not fully equipped to address diffuse and long-term environmental exposures.

4.5. Knowledge Gaps And Research Frontiers

The analysis reveals several critical gaps that limit the current understanding of pharmaceutical contamination in freshwater systems. One of the most significant gaps concerns the lack of studies addressing mixture effects under environmentally realistic conditions. Although the presence of multiple contaminants is well established, experimental and monitoring studies continue to focus predominantly on individual compounds. This discrepancy limits the ability to predict real-world ecological outcomes.

Another limitation relates to the scarcity of long-term monitoring data. Many studies provide snapshots of contamination levels, but few capture temporal variability or cumulative exposure over extended periods. This restricts the capacity to identify trends, assess persistence, and detect potential tipping points. In addition, there is a lack of standardized methodologies for measuring and comparing pharmaceutical concentrations across different regions and environmental matrices.

A further gap lies in the absence of regulatory thresholds that account for chronic exposure and mixture toxicity. Existing guidelines are generally based on single-substance assessments and may not reflect the complexity of environmental contamination. This regulatory limitation is particularly problematic given the evidence of non-linear and synergistic effects observed in aquatic systems.

Table 3 synthesizes the main knowledge gaps identified throughout the analysis and links them to specific evidence limitations, future research directions, and implications for public health. This structured organization highlights not only what is currently known, but more importantly, what remains unresolved in the scientific and

regulatory landscape of pharmaceutical contamination in freshwater systems.

Table 3. Identified knowledge gaps and proposed research priorities

Research gap	Evidence limitation	Proposed research direction	Public health relevance
Lack of mixture toxicity studies	Predominance of single-compound assessments (Backhaus; Karlsson, 2014)	Experimental and field studies focusing on multi-compound interactions and non-linear effects	Underestimation of real exposure risks in aquatic systems and humans
Insufficient long-term monitoring	Temporal data scarcity; short-term studies dominate (Wilkinson et al., 2022)	Longitudinal monitoring programs integrating seasonal and cumulative exposure data	Inability to assess chronic exposure and delayed health effects
Absence of ecological tipping point thresholds	Limited quantification of critical concentration levels (Kidd et al., 2007)	Development of threshold models based on population and ecosystem-level responses	Failure to predict irreversible ecological damage affecting food security
Inefficiency of wastewater treatment technologies	Partial removal and transformation of pharmaceuticals (Gavrilescu et al., 2015; OECD, 2019)	Implementation and evaluation of advanced treatment technologies (AOPs, membrane systems)	Continuous human exposure through contaminated water sources

Limited understanding of bioaccumulation pathways	Incomplete data on trophic transfer and biomagnification (Li, 2014)	Integrated studies linking water, sediment, and biota contamination	Increased risk through dietary exposure (fish consumption)
Geographic disparities in data availability	Underrepresentation of low- and middle-income regions (Wilkinson et al., 2022)	Expansion of global monitoring networks and harmonized methodologies	Inequitable exposure risks and policy gaps
Unknown effects of transformation products	Lack of toxicity data for metabolites formed during treatment (Melo et al., 2009)	Identification and toxicological assessment of transformation byproducts	Hidden exposure risks not captured by current regulations
Weak regulatory frameworks for emerging contaminants	Absence of standards for pharmaceuticals in water (OECD, 2022)	Development of regulatory thresholds incorporating mixture effects and chronic exposure	Inadequate protection of public health and ecosystems

Source: Own authorship

The gaps presented in Table 3 reveal a consistent misalignment between the complexity of environmental contamination and the analytical approaches traditionally employed to study it. The predominance of single-compound studies contrasts sharply with the reality of multi-contaminant exposure, indicating that current scientific models may systematically underestimate ecological and human health risks. This limitation is further compounded by the absence of long-term monitoring data, which restricts the ability to

identify cumulative effects and delays the recognition of critical ecological thresholds.

Another critical issue emerging from the table is the structural inadequacy of both technological and regulatory systems. Wastewater treatment processes remain insufficient to address the chemical complexity of pharmaceutical residues, while regulatory frameworks fail to incorporate mixture toxicity and chronic exposure scenarios.

These gaps are not merely technical but reflect a broader disconnect between environmental policy and scientific evidence. Addressing these challenges requires an integrated approach that combines advanced analytical methods, long-term ecological monitoring, and regulatory innovation aligned with the principles of the One Health framework.

5. CONCLUSION

The findings of this integrative review reaffirm a critical paradox of contemporary society: the same pharmacological advances that sustain human health are simultaneously contributing to a diffuse and persistent form of environmental contamination. Antidepressants and hormones, designed to act at low biological thresholds, do not lose their activity after human use. Instead, they re-enter freshwater systems, where they interact with living organisms and ecological processes in ways that remain insufficiently understood and largely unregulated.

The evidence converges toward the need to recognize an ecotoxicological tipping point, at which continuous low-dose exposure, combined with mixture effects and environmental

persistence, leads to the destabilization of ecological homeostasis. This threshold is not defined solely by concentration, but by duration, interaction, and cumulative exposure across biological and trophic systems. The collapse of populations observed under seemingly low contamination levels suggests that current safety assumptions may be structurally inadequate.

At the same time, the persistence of pharmaceutical residues reflects a systemic failure. Wastewater treatment technologies remain misaligned with the chemical complexity of emerging contaminants, while regulatory frameworks have not yet incorporated the realities of chronic exposure and synergistic toxicity. This gap between knowledge and action sustains a cycle in which contamination is continuously produced, insufficiently removed, and silently redistributed.

Addressing this challenge requires a shift in perspective and practice. The implementation of advanced treatment technologies must be accelerated, particularly those capable of degrading complex and biologically active molecules. Environmental pharmacovigilance should be established as a continuous monitoring strategy, integrating ecological and public health indicators.

Above all, the One Health framework must be operationalized, not as a conceptual guideline, but as a structural principle guiding research, policy, and technological innovation. Only through this integrated approach will it be possible to reconcile therapeutic progress with environmental sustainability.

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