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A Review on Ecotoxicological Effects of Pharmaceutical Residues on Non–Target Organisms

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ABSTRACT

Pharmaceutical residues represent a growing class of environmental contaminants, entering aquatic and terrestrial ecosystems through wastewater treatment plant effluents, agricultural runoff, and improper disposal. Unlike conventional industrial pollutants, pharmaceuticals are designed to elicit biological responses at extremely low concentrations, posing a unique threat to non-target wildlife. Bioaccumulation of active pharmaceutical ingredients specifically endocrine-disrupting compounds, non-steroidal anti-inflammatory drugs, and psychiatric medications alters physiology, behavior, and reproductive success in diverse organisms. Endocrine disruptors trigger feminization and reproductive failure in fish populations, while anti-inflammatory agents cause systemic organ failure in avian scavengers and aquatic vertebrates. Neurological therapeutics modify crucial behaviors such as predator avoidance, foraging efficiency, and social interaction, leading to population-level declines and the destabilization of trophic webs. The ubiquitous presence of sub-lethal antibiotic concentrations in soil and aquatic environments accelerates the selection and horizontal transfer of antibiotic resistance genes, disrupting microbial community dynamics and essential nutrient cycles. Mitigating these ecological threats requires the integration of ecopharmacovigilance into drug development, environmental risk assessment, and wastewater reclamation technologies. Advancing active surveillance methodologies and establishing ecologically relevant toxicity thresholds remain paramount to preserving global biodiversity and maintaining ecosystem resilience against chronic pharmaceutical contamination.

Keywords: *Ecopharmacovigilance, Pharmaceutical pollutants, Endocrine disruption, Trophic cascades, Biodiversity conservation.*

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1. Introduction

Active pharmaceutical ingredients (APIs) are synthetic or natural compounds engineered to induce specific physiological changes in human and veterinary medicine [1]. Over the past several decades, global pharmaceutical consumption has escalated dramatically, driven by demographic shifts, expanding healthcare access, and intensive agricultural practices [2]. Consequently, these chemically active substances continuously enter the biosphere, transforming pristine habitats into sinks for complex chemical mixtures. Unlike legacy industrial contaminants such as polychlorinated biphenyls or heavy metals, APIs are termed "pseudo-persistent" pollutants [3]. Although many pharmaceuticals possess relatively short environmental half-lives, their continuous discharge into natural systems ensures a constant, uninterrupted exposure profile for resident biota, mimicking the exposure dynamics of truly persistent compounds. This perpetual contamination has driven the emergence of ecopharmacovigilance (EPV), a scientific discipline defined as the science and activities concerning the detection, assessment, comprehension, and prevention of adverse effects related to the presence of pharmaceuticals in the environment [4]. The foundational framework of EPV parallels clinical pharmacovigilance but shifts the analytical endpoint from human patient safety to the preservation of ecosystem structure and function. Historically, environmental toxicology focused primarily on acute lethality metrics, such as median lethal concentration (LC50) values. However, APIs are designed to interact with highly specific biological targets at therapeutic doses that are often orders of magnitude lower than lethal levels.

Thus, the primary hazard of environmental pharmaceutical contamination lies in chronic, sublethal toxicity, which alters subtle behavioral, physiological, and reproductive parameters in non-target wildlife [5].

A prominent historical precedent illustrating this vulnerability occurred in the early 2000s with the near-extinction of *Gyps* vulture populations across the Indian subcontinent [6]. The widespread veterinary administration of the non-steroidal anti-inflammatory drug (NSAID) diclofenac to cattle led to secondary exposure in avian scavengers feeding on carcasses. Because vultures lack the specific metabolic pathway to detoxify diclofenac, ingestion led to severe renal failure, visceral gout, and rapid mortality, resulting in a population collapse exceeding ninety-nine percent. This ecological disaster indicated that highly targeted, clinically safe veterinary pharmaceuticals can exhibit unexpected, catastrophic toxicity when introduced to non-target taxa.

Similarly, the aquatic environment serves as the primary receptacle for human pharmaceutical waste. Research has shown that exposure to picogram-per-liter concentrations of 17α-ethinylestradiol (EE2), a synthetic estrogen widely used in oral contraceptives, causes the complete feminization of male fathead minnows (*Pimephales promelas*), culminating in population collapse [7]. These case studies highlight the critical necessity of integrating pharmacology with ecology to assess how low-level pharmaceutical exposure propagates through biological hierarchies, from molecular interactions to ecosystem-scale alterations. Establishing a robust pharmacotherapeutic baseline for environmental contaminants is critical for predicting ecological risks and safeguarding global biodiversity.

2. Environmental Pathways and Environmental Fate of Pharmaceuticals

2.1 Sources and Entry Routes

The introduction of pharmaceuticals into environmental matrices occurs through several distinct vectors, divided primarily into human, veterinary, and industrial sources [8]. Municipal wastewater treatment plants (WWTPs) represent the dominant pathway for human-use pharmaceuticals. Following clinical administration, APIs undergo varying degrees of hepatic metabolism, resulting in the excretion of both parent compounds and polar metabolites via urine and feces [9]. These substances travel through sewage systems to treatment facilities, which are historically designed to remove suspended solids, biodegradable organic carbon, and excess nutrients, rather than complex trace organic contaminants.

Veterinary pharmaceuticals present a distinct environmental entry profile, bypass municipal treatment infrastructures entirely, and directly contaminate terrestrial and agricultural aquatic systems [10]. Intensive livestock operations and aquaculture utilize significant quantities of antibiotics, antiparasitics, and growth promoters. These compounds are excreted by animals onto pastures or stored in manure lagoons, which are subsequently applied to agricultural fields as fertilizer. Rainfall events facilitate the transport of these veterinary residues from agricultural soil into surface waters via surface runoff and macropore flow, leading to widespread contamination of headwater streams and adjacent wetlands [11].

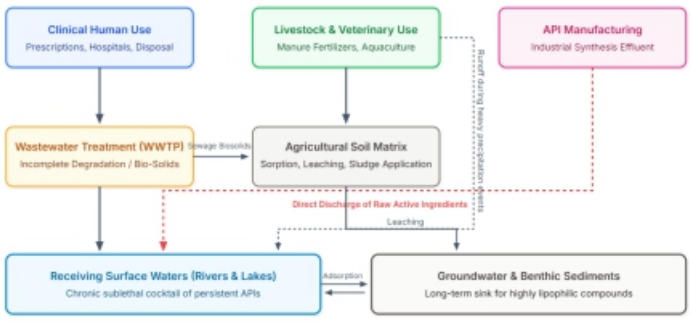

Figure 1: Environmental Fate of Active Pharmaceutical Ingredients

2.1.1 Wastewater Treatment Limitations

Conventional wastewater treatment facilities employ primary physical separation and secondary biological treatment, typically utilizing activated sludge processes. The efficiency of pharmaceutical removal within these facilities is highly variable and compound-specific, depending on the operational parameters of the plant, such as hydraulic retention time and solid retention time [12]. Hydrophobic compounds partition into primary and secondary sludges, while polar, hydrophilic pharmaceuticals remain in the aqueous phase, escaping into receiving water bodies. Advanced tertiary treatments, including ozonation, membrane bioreactors, and activated carbon adsorption, offer significantly higher removal rates for recalcitrant compounds [13]. However, the high capital costs and energy demand of these advanced technologies limit their implementation, particularly in developing nations, ensuring that receiving rivers, estuaries, and coastal zones remain chronically exposed to untreated or partially treated chemical effluents.

2.2 Environmental Persistence and Bioavailability

Once discharged into aquatic or terrestrial systems, the environmental persistence and subsequent bioavailability of a pharmaceutical are governed by its physicochemical properties and prevailing environmental conditions [14]. The octanol-water partition coefficient (log $K_{o/w}$) serves as a primary predictor of a compound's environmental partitioning. Compounds with low log $K_{o/w}$ values remain highly mobile in the water column, whereas highly lipophilic compounds (log $K_{o/w}$ > 4) exhibit a strong affinity for organic matter, sorbing to sediments and suspended particles where they become bioavailable to benthic organisms [15].

Abiotic degradation pathways, primarily photolysis and hydrolysis, play a key role in reducing the concentration of active parent compounds in surface waters. Many pharmaceuticals contain chromophores that absorb solar radiation, leading to direct photolytic cleavage or indirect degradation via reactive oxygen species generated in the water column [16]. Biotic degradation by microbial communities in soil and sediment also contributes to attenuation. However, both biotic and abiotic degradation processes often yield stable transformation products that retain the biological activity of the parent drug, sometimes exhibiting higher toxicity or environmental persistence than the original compound [17].

Table 1: Physicochemical and Degradation Parameters of Model APIs

Active Pharmaceutical Ingredient (API)	Therapeutic Class	Octanol-Water Partition Coefficient (log $K_{o/w}$)	Dominant Environmental Entry Vector	Primary Degradation Mechanism	Est. Surface Water Half-Life ($t_{1/2}$)	References
Diclofenac	Non-Steroidal Anti-Inflammatory	4.51	Municipal Wastewater Effluents	Direct Photolysis / Photodegradation	1 to 8 Days	[1, 8]
17α-Ethinylestradiol (EE2)	Synthetic Estrogen	3.67 - 4.15	Sewage Treatment Discharges	Sediment Adsorption / Biodegradation	2 to 10 Days	[7]
Fluoxetine	Psychiatric (SSRI)	4.05	Wastewater Effluents	Sedimentary Partitioning / Photolysis	30 to 120 Days	[9]
Carbamazepine	Antiepileptic	2.45	Municipal Effluents	Highly Recalcitrant (Minimal Abiotic/Biotic Decay)	>100 Days	[5, 12]
Sulfamethoxazole	Sulfonamide Antibiotic	0.89	Agricultural Runoff / WWTP Outfalls	Indirect Photolysis / Microbial Biodegradation	2 to 20 Days	[11, 16]

3. Pharmacological Mechanisms of Toxicity in Non-Target Species

3.1 Target Receptor Conservation Across Taxa

The fundamental premise of ecopharmacology rests on the evolutionary conservation of drug targets across diverse taxonomic groups [18]. During drug discovery, target receptors, enzymes, and signaling pathways are identified based on mammalian physiology. Because many of these biochemical targets emerged early in evolutionary history, they are shared across broad phylogenetic lineages, including fish, amphibians, birds, and invertebrates [19]. This conservation means that non-target organisms possessing orthologous receptors are vulnerable to the same pharmacodynamic pathways that the drugs are designed to modulate in human patients.

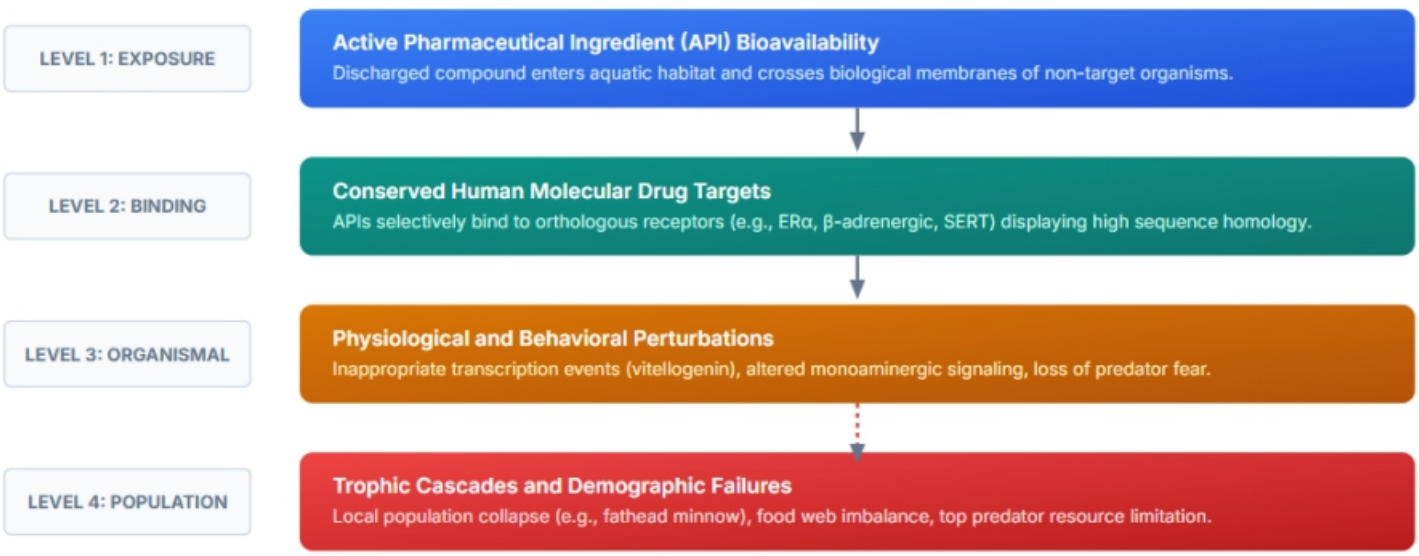

Figure 2: Evolutionary Receptor Conservation and Sublethal Ecotoxicological Cascade

Phylogenetic sequence analysis has revealed that while mammals and teleost fish diverged hundreds of millions of years ago, the ligand-binding domains of many critical receptors such as beta-adrenergic receptors, glucocorticoid receptors, and peroxisome proliferator-activated receptors show high structural homology [20]. Consequently, human pharmaceuticals can bind to these conserved receptors in aquatic wildlife with similar affinity. This receptor conservation explains why therapeutic human plasma concentrations often correspond directly to the concentrations that elicit physiological effects in wild aquatic species, transforming low-level environmental exposures into significant physiological perturbations.

Table 2: Evolutionary Conservation and Target Homology Across Non-Target Taxa

Drug Class / Representative API	Primary Human Molecular Target	Vulnerable Non-Target Organism	Sequence Homology of Binding Domain (%)	Chronic Sublethal Physiological Consequence	References
Beta-Blockers (e.g., Propranolol)	β-Adrenergic Receptor	*Danio rerio* (Zebrafish)	>85%	Diminished heart rate, reduced spawning viability, altered energy allocation	[18, 19]
SSRIs (e.g., Fluoxetine)	Serotonin Transporter (SERT)	*Daphnia magna* (Water flea)	>70%	Altered swimming kinetics, accelerated reproductive cycle, increased metabolic expenditure	[18]
NSAIDs (e.g., Diclofenac)	Cyclooxygenase-1/2 (COX-1/COX-2)	*Gyps* Vulture Genus	>80%	Severe renal proximal tubule necrosis, hyperuricemia (visceral gout), acute mortality	[6, 18]
Synthetic Estrogens (e.g., EE2)	Estrogen Receptor Alpha (ERα)	*Pimephales promelas* (Fathead minnow)	>90%	Inappropriate hepatic vitellogenin synthesis, intersex gonadogenesis (testicular oocytes)	[20]

3.2 Endocrine Disruption and Reproductive Impairment

Endocrine-disrupting compounds (EDCs) represent one of the most thoroughly documented classes of pharmaceutical pollutants, interfering with the synthesis, transport, binding, and elimination of natural hormones [21]. Natural estrogens, such as 17β-estradiol (E2) and estrone, alongside synthetic formulations like 17α-ethinylestradiol (EE2), possess high affinity for estrogen receptors (ERα and ERβ) in non-target vertebrates. In teleost fish, the binding of these estrogens to hepatic receptors initiates the transcription of vitellogenin, a phospholipoprotein precursor to egg yolk [22]. Under normal physiological conditions, vitellogenin synthesis is restricted to mature females during oogenesis. Exposure of juvenile and adult male fish to environmental concentrations of estrogens triggers high levels of vitellogenin production, leading to renal damage, testicular oocytes (intersex development), and reduced sperm quality [23].

Beyond the estrogenic pathways, pharmaceuticals disrupt the hypothalamic-pituitary-thyroid (HPT) and hypothalamic-pituitary-adrenal (HPA) axes in wildlife. For example, thyroid hormone synthesis and regulation are critical for amphibian metamorphosis and early development. Exposure to anti-thyroid drugs, beta-blockers, and certain lipid-regulating agents can inhibit key enzymes like thyroid peroxidase or displace thyroid hormones from transport proteins, delaying or permanently arresting development in larval amphibians [24]. Similarly, psychiatric pharmaceuticals, such as selective serotonin reuptake inhibitors (SSRIs), modify systemic hormone levels by altering central monoaminergic signaling, which regulates both stress responses and reproductive behaviors in aquatic vertebrates and invertebrates [25].

4. Behavioral Ecotoxicology and Neuro-active Drug Exposure

4.1 Neuro-active Drugs in Aquatic Systems

The widespread detection of neuro-active pharmaceuticals, including selective serotonin reuptake inhibitors (SSRIs), benzodiazepines, and antiepileptic drugs, in municipal effluents has generated concern regarding their impact on aquatic organisms [26]. These compounds are designed to alter neurotransmission in human patients by modulating neurotransporter proteins, ligand-gated ion channels, and G-protein coupled receptors. Because the biochemical architecture of the central nervous system is highly conserved across vertebrate lineages, fish and amphibians exposed to trace concentrations of psychiatric medications exhibit distinct neurochemical and physiological alterations [27].

Unlike acute toxicological endpoints, neuro-active contaminant exposure manifests primarily as subtle alterations in ecologically critical behaviors, which can occur at concentrations several orders of magnitude below lethal thresholds.

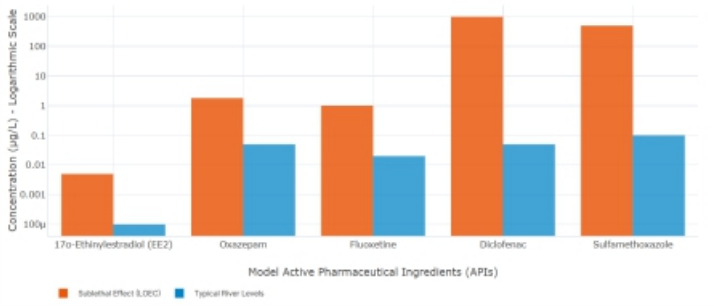

Figure 3: Exposure-Response and Sublethal Toxicity Thresholds

4.1.1 Altered Predator Avoidance and Boldness

Among the most ecologically damaging behavioral modifications is the disruption of predator avoidance mechanisms and the elevation of baseline boldness in prey species. Exposure to low environmental concentrations of benzodiazepines, such as oxazepam, acts on conserved γ-aminobutyric acid type A (GABAA) receptors, facilitating chloride ion influx and inducing anxiolytic effects in fish [28]. In wild populations, anxiety serves as a vital survival mechanism, keeping organisms hidden from predators and limiting risk-taking activities. Under the influence of benzodiazepines, exposed teleosts exhibit increased boldness, elevated activity levels, and a higher propensity to venture into open, high-risk zones.

Similarly, SSRIs like fluoxetine and sertraline increase synaptic serotonin concentrations by inhibiting the serotonin transporter (SERT) protein [29]. Chronic exposure to these compounds disrupts the highly regulated serotonergic pathways that govern schooling behavior, shelter-seeking, and startle responses in prey species. Exposed individuals frequently display a diminished response to alarm cues, such as the chemical distress signals released by injured conspecifics. When prey organisms exhibit reduced sensitivity to environmental threats and increased exploratory behavior in dangerous zones, their susceptibility to predation increases exponentially, threatening the demographic stability of the local population.

Table 3: Behavioral Alterations and Ecotoxicological Endpoints of Neuro-Active and Endocrine-Disrupting Drugs

Compound	Target Model Organism	Exposure Concentration Range	Observed Behavioral or Physiological Alteration	Ecological Consequence	References
Oxazepam	*Perca fluviatilis* (European perch)	1.8 µg/L	Elevation of boldness, diminished schooling drive, enhanced independent foraging	Higher vulnerability to predation, disruption of population age structure	[26, 28]
Fluoxetine	*Pimephales promelas* (Fathead minnow)	1.0 µg/L	Suppression of predator startle response, loss of seeking refuge	Increased susceptibility to wild piscivorous predators	[29, 30]
17alpha-Ethinylestradiol (EE2)	*Pimephales promelas* (Fathead minnow)	5.0 - 10.0 ng/L	Upregulation of female mating behaviors in males, reduced courtship vocalizations	Direct reproductive failure, localized population collapse	[23]
Sertraline	*Daphnia magna* (Water flea)	10.0 µg/L	Inversion of phototactic behavior, loss of vertical migration control	Elevated predation by planktivorous fish, structural zooplankton community drift	[25]

4.1.2 Impacts on Foraging Success and Migration

Beyond predator-prey dynamics, neuro-active contaminants impair foraging efficiency and migratory behaviors. Aquatic predators, such as predatory fish and macroinvertebrates, rely on highly coordinated sensory-motor systems to detect, track, and capture prey. Exposure to carbamazepine, a widely prescribed sodium channel blocker used as an antiepileptic, has been shown to reduce prey-capture efficiency by slowing reaction times and degrading spatial orientation [30]. This decline in foraging success directly reduces energy assimilation, compromising growth rates, physical conditioning, and long-term reproductive fitness.

Migratory behaviors, which require precise physiological adaptations and navigation cues, are also vulnerable to neuro-active drug exposure. Many salmonid species rely on olfactory cues and endocrine-driven developmental shifts, such as smoltification, to navigate between freshwater spawning grounds and marine feeding areas. SSRIs and other neuro-active agents interfere with the olfactory bulb signaling pathways, disrupting the sensory processing needed for migration [31]. Consequently, exposed fish show reduced migratory drive and compromised directional navigation, which can disrupt the genetic connectivity and population replenishment of migratory fish stocks.

5. Trophic Cascades and Ecological Consequences

5.1 Primary Producer and Decomposer Disruptions

The ecological consequences of pharmaceutical contamination extend beyond direct taxonomic toxicity to affect the foundational trophic levels of ecosystems. Primary producers, such as freshwater algae, macrophytes, and marine phytoplankton, form the base of aquatic food webs and drive primary productivity. Many therapeutic classes, particularly antibiotics and herbicides, exhibit high toxicity toward these photosynthetic organisms. Sulfonamides, tetracyclines, and fluoroquinolones target conserved bacterial pathways, but because plastids like chloroplasts share evolutionary origins with cyanobacteria, these drugs also inhibit algal growth and disrupt photosynthetic efficiency [32]. A reduction in primary producer biomass limits the availability of organic carbon for primary consumers, destabilizing the energy balance of the entire ecosystem.

Similarly, decomposers, including aquatic fungi and heterotrophic bacteria, are critical for leaf litter decomposition and nutrient cycling in lotic ecosystems. Antifungal agents and broad-spectrum antibiotics released from wastewater systems alter the community structure of these micro-decomposers, reducing the rate of organic matter breakdown [33].

When decomposer communities are suppressed, the cycling of essential nutrients like nitrogen and phosphorus is delayed, leading to nutrient-limiting conditions that affect both primary productivity and higher trophic levels.

5.2 Secondary and Tertiary Consumer Population Declines

As sublethal pharmaceutical toxicity reduces the survival and reproductive output of primary and secondary consumers, these effects propagate upward through food webs, triggering trophic cascades. A decline in herbivorous zooplankton populations, such as *Daphnia* species, caused by chronic pharmaceutical mixtures, can release phytoplankton from grazing pressure, leading to localized algal blooms and subsequent eutrophication [34]. Conversely, if primary consumers decline, carnivorous macroinvertebrates and small fish face acute food shortages, forcing them to alter their diet or suffer population declines.

At the highest trophic levels, tertiary consumers and apex predators are vulnerable to both bottom-up resource limitation and top-down demographic alterations. If key forage fish populations experience reproductive failure due to endocrine-disrupting compounds, predatory piscivorous fish, birds, and mammals experience reduced carrying capacities [35]. These cascading dynamics show that even when a pharmaceutical exhibits low toxicity to a specific high-trophic-level species, that species can still suffer severe population declines due to food web disruption.

5.2.1 Bioaccumulation and Biomagnification in Food Webs

The ecological threat to top predators is amplified by the bioaccumulation and biomagnification of certain lipophilic pharmaceuticals through terrestrial and aquatic trophic chains. Hydrophobic compounds, characterized by high octanol-water partition coefficients (log $K_{o/w} > 4$), can readily cross biological membranes and accumulate within the lipid reserves of aquatic organisms [36]. Although many vertebrates possess metabolic pathways to biotransform and excrete these substances, continuous exposure through contaminated food sources can overwhelm these detoxification mechanisms.

In complex food webs, bioaccumulation at lower trophic levels can lead to biomagnification, where the concentration of a contaminant increases progressively with each trophic step. For example, synthetic progestins, lipid-regulating drugs like gemfibrozil, and psychiatric drugs have been detected at significantly higher tissue concentrations in piscivorous fish and predatory birds than in the surrounding water or prey organisms [37].

This biomagnification process exposes long-lived apex predators to chronic, elevated concentrations of multiple pharmacologically active agents, increasing the risk of organ damage, reproductive failure, and systemic physiological dysfunction.

6. Antibiotic Resistance (AMR) in Environmental Reservoirs

6.1 Environmental Selection Pressures

The presence of antibiotics in soil, sediment, and water bodies has emerged as a major global environmental health hazard, driving the proliferation of antimicrobial resistance (AMR). Wastewater treatment plant effluents, aquaculture facilities, and agricultural runoff release sub-therapeutic concentrations of antibiotics into aquatic and soil systems, creating persistent selective gradients [38]. Unlike clinical environments where high antibiotic concentrations aim to eliminate pathogen populations, natural habitats are often characterized by sub-lethal, sub-inhibitory concentrations of these compounds.

At these sub-inhibitory levels, antibiotics act as environmental selection pressures rather than lethal agents. Instead of killing environmental bacteria, low concentrations of antibiotics stimulate adaptive stress responses, such as the SOS response, which increases mutation rates and facilitates genetic adaptation [39]. This selective pressure favors the survival and proliferation of resistant bacterial strains possessing specific mutational adaptations or resistance genes, transforming natural aquatic and terrestrial environments into breeding grounds for drug-resistant pathogens.

Table 4: Resistance Genes and Selective Pressures in Environmental Compartments

Antibiotic Class	Representative Residues	Est. Minimum Selective Concentration (MSC)	Selected Resistance Genes (ARGs)	Associated Mobile Genetic Elements (MGEs)	Primary Impacted Ecological Compartment	References
Tetracyclines	Oxytetracycline, Chlortetracycline	0.1 - 1.0 µg/L	*tet*(A), *tet*(B), *tet*(M)	Plasmids (IncP-1), Conjugative Transposons (Tn916)	Agricultural soils, manure-amended sediments	[40, 41]
Sulfonamides	Sulfamethoxazole	0.5 - 2.0 µg/L	*sul1*, *sul2*, *sul3*	Class 1 Integrons (*intI1*), Insertion Sequences	Aquatic receiving waters, sewage sludge basins	[40, 41, 42]
Fluoroquinolones	Ciprofloxacin, Ofloxacin	0.05 - 0.5 µg/L	*qnrA*, *qnrB*, *qnrS*	Multidrug resistance plasmids, Integrons	Riverine benthic biofilms downstream of WWTP outfalls	[4, 41]
Macrolides	Erythromycin, Clarithromycin	0.1 - 1.5 µg/L	*erm*(B), *erm*(F), *mef*(A)	Integrative Conjugative Elements (ICEs)	Estuarine sediments, freshwater microbial biofilms	[38, 41, 42, 43]

6.1.1 Horizontal Gene Transfer (HGT) Dynamics

The dissemination of resistance traits within environmental bacterial communities is mediated primarily by horizontal gene transfer (HGT), a process that allows the exchange of genetic material across diverse taxonomic boundaries. HGT occurs via three primary pathways: conjugation, transduction, and transformation [40]. Conjugation, involving direct cell-to-cell contact and the transfer of plasmids or integrative conjugative elements, is highly active in environments with high bacterial densities and sub-lethal antibiotic selective pressures, such as WWTP activated sludge basins.

Antibiotic resistance genes (ARGs) are frequently localized on mobile genetic elements, such as plasmids, transposons, and integrons, which facilitate their rapid movement between different bacterial species [41]. Sub-lethal concentrations of antibiotics, particularly aminoglycosides and fluoroquinolones, have been shown to upregulate the expression of integrase genes, accelerating the capture and integration of novel resistance cassettes. This continuous genetic exchange allows non-pathogenic environmental bacteria to transfer resistance genes to human and veterinary pathogens, compromising the efficacy of clinical antimicrobial therapies.

6.2 Impact on Soil and Aquatic Microbial Ecology

The accumulation of antibiotic residues and the subsequent spread of AMR significantly disrupt the composition and function of environmental microbial communities. Microorganisms drive critical biogeochemical cycles, including nitrogen fixation, nitrification, denitrification, carbon mineralization, and sulfur oxidation. Exposure to environmental antibiotic mixtures selectively suppresses sensitive bacterial taxa while favoring resistant groups, altering the functional capacity of these microbial networks [42].

In agricultural soils, contamination from veterinary antibiotics like tetracyclines and sulfonamides reduces the abundance of nitrogen-fixing bacteria (*Rhizobium* and *Bradyrhizobium* species) and inhibits the activity of ammonia-oxidizing archaea and bacteria [43]. This disruption impairs the conversion of organic nitrogen into forms accessible to plants, reducing soil fertility and agricultural productivity. Similarly, in aquatic sediments, altered microbial community profiles can lead to reduced denitrification rates, causing excess nitrogen buildup and contributing to the degradation of aquatic habitats.

7. Environmental Risk Assessment

7.1 Current Regulatory Guidelines

Regulatory frameworks established by international environmental and drug administration agencies play a key role in controlling the entry of active pharmaceutical ingredients (APIs) into ecological systems [44]. In both the European Union and the United States, ecological risk evaluations are legally mandated before a novel human or veterinary medicinal product can be granted marketing authorization. These regulatory policies seek to balance the clinical necessity of pharmaceuticals with the preservation of natural ecosystems, establishing standardized protocols to estimate potential environmental exposures and ecological hazards.

7.1.1 Tiered Assessment

The Environmental Risk Assessment (ERA) protocols established by the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) utilize structured, tiered assessment strategies [45,46]. The initial phase, designated as Phase I, serves as an exposure-based screening mechanism.

Under EMA guidelines, a Phase I assessment calculates the Predicted Environmental Concentration in surface water (PECwater). If this value is less than the action threshold of 0.01 µg/L, and there are no specific spatial or chemical indicators of high eco-toxicity, the compound is deemed unlikely to pose an environmental risk, and no further testing is required. The FDA operates under a similar exposure threshold, utilizing an action trigger of 1 µg/L for the active moiety in receiving waters.

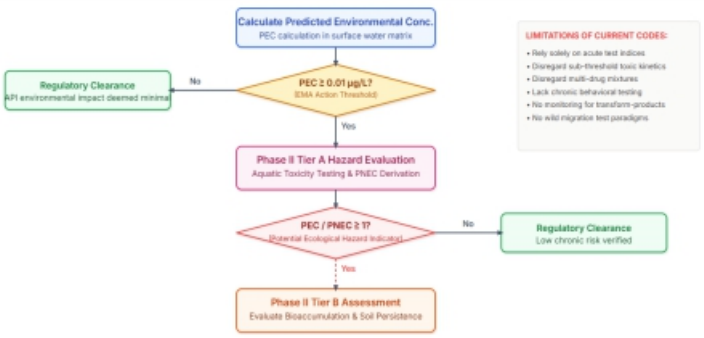

Figure 4: Phased Regulatory Environmental Risk Assessment (ERA)

If the calculated PECwater exceeds the designated threshold, the assessment advances to Phase II, which represents a hazard-based evaluation [47]. Phase II is divided into Tier A and Tier B. Tier A evaluates the physical, chemical, and ecotoxicological properties of the substance. This phase requires standard aquatic toxicity assays to determine the concentration at which no adverse effects are observed. Regulatory scientists use these values to calculate the Predicted No-Effect Concentration (PNEC) for aquatic organisms. Standard testing regimes evaluate the effects of the compound on three trophic levels: primary producers (algae), primary consumers (crustaceans), and secondary consumers (fish). To account for uncertainties in translating laboratory data to wild populations, assessment factors are applied to the laboratory endpoints to derive a conservative PNEC. If the resulting PEC/PNEC ratio is equal to or greater than 1, a potential risk is identified, initiating Tier B testing, which evaluates chronic toxicity, bioaccumulation potential, and environmental fate in soil and sediment compartments [48,49].

7.2 Limitations of Existing Guidelines

Despite the structured nature of current regulatory assessments, substantial limitations exist that can compromise the protective capacity of these frameworks. The reliance on acute, single-species laboratory assays often fails to capture the chronic, low-level exposure profiles that characterize real-world aquatic and terrestrial habitats. Consequently, current regulatory guidelines may underestimate the long-term ecological risks posed by pseudo-persistent contaminants.

7.2.1 The Focus on Acute vs. Chronic Toxicity

A primary limitation of existing ERA guidelines is their historical reliance on acute toxicity metrics, such as median lethal concentration (LC50) or median effect concentration (EC50) values derived from short-term laboratory exposures [50]. APIs are designed to alter specific biological pathways at low therapeutic doses, meaning their primary ecological hazards are chronic, sublethal alterations rather than acute lethality. Chronic exposure to sub-lethal concentrations can lead to reproductive impairment, developmental delays, and behavioral modifications that are not captured in standard 48-hour or 96-hour acute survival assays [51]. Although Phase II evaluations require chronic toxicity data for compounds that exceed the initial exposure trigger, the high thresholds of Phase I screening can allow highly toxic compounds with low discharge volumes to escape chronic evaluation entirely.

7.2.2 Neglect of Mixture Toxicity and Synergistic Effects

Standard regulatory risk assessments evaluate environmental safety on a single-substance basis, overlooking the ecological reality that aquatic and terrestrial habitats are chronically exposed to complex chemical mixtures [52]. In municipal effluents and receiving waters, organisms encounter hundreds of distinct pharmaceutical residues, metabolites, and transformation products simultaneously. These co-occurring compounds can interact through additive or synergistic mechanisms, generating significant biological responses even when each individual pharmaceutical is present at concentrations well below its respective PNEC [53]. Current regulatory frameworks can underestimate the cumulative ecological hazards of environmental pharmaceutical pollution by neglecting these mixture dynamics, highlighting the need for mixture-based risk assessment models in ecopharmacovigilance.

8. Mitigation Measures

8.1 Advanced Wastewater Reclamation

Reducing the input of pharmaceutical residues into aquatic ecosystems requires upgrading wastewater treatment infrastructure to target trace organic contaminants [54]. Because conventional wastewater plants are not designed to remove complex polar molecules, integrating advanced tertiary treatment technologies is necessary to protect downstream habitats.

8.1.1 Tertiary Treatment Engineering

Advanced Oxidation Processes (AOPs) and physical adsorption technologies represent the primary engineering strategies for removing recalcitrant APIs from municipal wastewater [55]. AOPs utilize highly reactive chemical species, primarily hydroxyl radicals (OH), to non-selectively oxidize organic micropollutants into simpler, less toxic compounds or fully mineralize them into carbon dioxide and water. Technologies such as ozonation (O_3), UV-irradiation combined with hydrogen peroxide (UV/H_2O_2), and photocatalytic systems have showed high removal efficiencies for persistent pharmaceuticals, including carbamazepine and diclofenac.

In addition to chemical oxidation, physical adsorption using powdered activated carbon (PAC) or granular activated carbon (GAC) is highly effective for removing hydrophobic and moderately hydrophilic pharmaceuticals [56]. Activated carbon possesses a high surface area and a porous structure, allowing it to adsorb a wide range of organic compounds from the liquid phase. Membrane filtration technologies, including nanofiltration and reverse osmosis, also offer high removal rates by physically separating APIs based on molecular weight and charge. However, the wider adoption of these advanced technologies remains limited by their high energy requirements, operational costs, and the need to manage concentrated waste streams or toxic transformation products generated during chemical oxidation.

Table 5: Engineering Performance and Sustainable "Green Pharmacy" Alternatives

Treatment or Prevention Strategy	Operational Mechanism for API Control	Removal / Biodegradation Efficiency Range (%)	Prominent Operational or Technical Limitation	Preventive Sustainable Alternative (Green Pharmacy)	Reference
Ozonation (O_3)	Hydroxyl radical (•OH) mediated non-selective chemical oxidation	80% - 95%	Synthesis of bromate and toxic transformation intermediates; high operational costs	Molecular structural revision incorporating photolytically cleavable ester groups	[54, 55]
Activated Carbon (PAC / GAC)	Physical adsorption onto highly porous carbon structures	75% - 90%	Poor affinity for polar compounds; energy-intensive thermal regeneration of spent carbon	Modification of parent pharmacophores to enhance native biodegradation	[56, 57, 58]
Membrane Filtration (NF / RO)	Size exclusion and charge-based electrostatic repulsion	90% - >99%	Generation of highly concentrated waste brine streams; rapid membrane fouling	Substitution of persistent chemical entities with easily mineralized alternatives	[56, 59]

8.2 Green Pharmacy and Benign by Design Concept

While end-of-pipe wastewater treatment technologies are critical, addressing pharmaceutical pollution at the source through the principles of sustainable chemistry offers a preventative strategy [57]. The concept of "Green Pharmacy" aims to design, manufacture, and utilize medicinal products in a manner that minimizes their environmental footprint throughout their life cycle, from molecular design to clinical disposal.

The core principle of Green Pharmacy involves "benign by design" molecular engineering, where environmental biodegradability is integrated into the drug discovery process alongside pharmacological efficacy [58]. Historically, drug candidates have been optimized solely for metabolic stability, high target affinity, and oral bioavailability in human patients, which often results in highly persistent molecules that resist environmental degradation. Benign by design methodologies seek to introduce chemically vulnerable linkages, such as ester groups, or specific molecular configurations that remain stable within the human body but undergo rapid biodegradation when exposed to environmental microbial communities or solar radiation.

Figure 5: Conventional vs. Sustainable Green Pharmacy Design

Medicinal chemists can identify modifications that enhance environmental degradation without reducing clinical efficacy by utilizing computational toxicology models and structural-biodegradability relationship analyses [59]. Promoting the clinical adoption of rapidly biodegradable alternatives could reduce the environmental persistence of active pharmaceuticals, minimizing chronic exposure for non-target wildlife and reducing the burden on municipal wastewater treatment systems.

9. Conclusion

The chronic contamination of global ecosystems by active pharmaceutical ingredients represents a complex challenge at the intersection of human medicine, environmental toxicology, and conservation biology.

These biologically active compounds bypass conventional wastewater treatment infrastructure, entering aquatic and terrestrial systems where they can alter the physiology, reproduction, and behavior of non-target organisms. The conservation of pharmacological drug targets across diverse taxa ensures that low-level, sublethal exposure can trigger significant physiological perturbations. These perturbations propagate through trophic webs, leading to behavioral alterations in wildlife, food web disruptions, and the selection of antimicrobial resistance in environmental microbial reservoirs. Addressing the ecological threats of pharmaceutical residues requires a multidisciplinary approach that integrates ecopharmacovigilance into the life cycle of medicinal products. Upgrading municipal wastewater reclamation facilities with advanced tertiary treatment engineering remains critical to reducing current contaminant loads. Concurrently, adopting green chemistry principles to design more biodegradable pharmaceuticals offers a preventative solution for the future. Strengthening environmental risk assessment frameworks by incorporating chronic exposure metrics, behavior-based endpoints, and mixture toxicity profiles is essential to protect non-target species. Enhancing global monitoring networks and establishing ecologically relevant toxicity standards will be key to preserving biodiversity, maintaining ecosystem resilience, and securing the long-term health of our biosphere.

References

1. Daughton CG, Ternes TA. Pharmaceuticals in the environment: sources, fate, effects, and risks. *Environ Health Perspect*. 1999 Dec;107(Suppl 6):907-938.
2. Boxall AB, Rudd MA, Brooks BW, Caldwell DJ, Choi K, Christensen JR, et al. Pharmaceuticals and personal care products in the environment: what are the big questions? *Environ Health Perspect*. 2012 Sep;120(9):1221-1229.
3. Kümmerer K. Pharmaceuticals in the environment: a review. *Annu Rev Environ Resour*. 2009 Nov;34:113-145.
4. Larsson DG. Pollution from drug manufacturing: review and perspectives. *Philos Trans R Soc Lond B Biol Sci*. 2014 Nov;369(1656):20130571.
5. Ternes TA, Joss A, Siegrist H. Scrutinizing pharmaceuticals and personal care products in wastewater treatment. *Environ Sci Technol*. 2004 Oct;38(20):392A-399A.
6. Bound JP, Voulvoulis N. Household disposal of pharmaceuticals as a pathway for entry into the environment in the United Kingdom. *Drug Saf*. 2005 Oct;28(10):843-857.
7. Richardson SD, Ternes TA. Water analysis: emerging contaminants and current issues. *Anal Chem*. 2018 Jan;90(1):398-428.
8. Fent K, Weston AA, Caminada D. Ecotoxicology of human pharmaceuticals. *Aquat Toxicol*. 2006 Feb;76(2):122-159.
9. Brooks BW, Foran CM, Richards SM, Weston J, Turner PK, Stanley JK, et al. Aquatic ecotoxicology of fluoxetine. *Toxicol Lett*. 2003 Apr;142(3):169-183.

10. Boxall AB. The environmental side of pharmaceuticals. *EMBO Rep*. 2004 Dec;5(12):1110-1116.
11. Boxall AB, Blackwell PA, Cavallo R, Boucard P, Lewis TH, Everett CJ, et al. The sorption and transport of a suite of veterinary pharmaceuticals in the soil environment. *Toxicol Lett*. 2003 Apr;142(3):165-174.
12. Clara M, Kreuzinger N, Strenn B, Gans O, Kroiss H. The elimination of pharmaceutical residues and organic xenobiotics in municipal wastewater treatment plants a comparison with sensitive parameters. *Water Res*. 2005 Dec;39(20):4797-4807.
13. Oller I, Malato S, Sánchez-Pérez JA. Combination of Advanced Oxidation Processes and biological treatments for wastewater decontamination a review. *Sci Total Environ*. 2011 Oct;409(20):4141-4166.
14. Schwarzenbach RP, Escher BI, Fenner K, Hofstetter TB, Johnson CA, von Gunten U, et al. The challenge of micropollutants in aquatic systems. *Science*. 2006 Aug;313(5790):1072-1077.
15. Tolls J. Sorption of veterinary pharmaceuticals in soils: a review. *Environ Sci Technol*. 2001 Sep;35(17):3397-3406.
16. Boreen AL, Arnold WA, McNeill K. Photodegradation of pharmaceuticals in the aquatic environment: a review. *Aquat Sci*. 2003 Dec;65(4):320-341.
17. Celiz MD, Tuan-Wood FD, Aga DS. Pharmaceutical metabolites in the environment: analytical challenges and ecological risks. *Environ Toxicol Chem*. 2009 Dec;28(12):2473-2484.
18. Gunnarsson L, Jauhiainen A, Kristiansson E, Nerman O, Larsson DG. Evolutionary conservation of human drug targets in organisms used for environmental risk assessments. *Environ Sci Technol*. 2008 Aug;42(15):5807-5813.
19. Huggett DB, Cook JC, Ericson JF, Williams RT. A theoretical model for utilizing mammalian pharmacology data to prioritize and assess the potential effects of human pharmaceuticals to fish. *Hum Ecol Risk Assess*. 2003 Dec;9(7):1789-1799.
20. Rand-Weaver M, Margiotta-Casaluci L, Patel A, Panter GH, Owen SF, Sumpter JP. The receptor-mediated model of pharmaceutical hazard in the environment. *Environ Sci Technol*. 2013 Nov;47(22):12601-12602.
21. Jobling S, Nolan M, Tyler CR, Brighty G, Sumpter JP. Widespread sexual disruption in wild fish. *Environ Sci Technol*. 1998 Sep;32(17):2498-2506.
22. Sumpter JP, Jobling S. Vitellogenin: a biomarker for estrogenic contamination of the aquatic environment. *Environ Health Perspect*. 1995 Sep;103(Suppl 7):173-178.
23. Palace VP, Wautier KG, Evans RE, Blazer PJ, Duchesne S, O'Shaughnessy B, et al. Effects of 17α-ethynylestradiol on vitellogenin expression and development of male fathead minnows (*Pimephales promelas*) during a whole-lake study. *Environ Toxicol Chem*. 2006 Apr;25(4):1110-1116.
24. Kloas W, Lutz I, Einspanier R. Amphibians as a model to study endocrine disruptors on thyroid system. *Chemosphere*. 2009 Mar;75(1):1-10.
25. Valenti TW, Perez-Hurtado P, Chambliss CK, Brooks BW. Aquatic toxicity of sertraline to daphnids and fish. *Environ Toxicol Chem*. 2009 Dec;28(12):2685-2694.
26. Brodin T, Fick J, Jonsson M, Klaminder J. Dilute concentrations of a psychiatric drug alter behavior of fish in the wild. *Science*. 2013 Feb;339(6121):814-815.
27. Jonsson M, Fick J, Klaminder J, Brodin T. Behavioral ecotoxicology of psychiatric pharmaceuticals in fish: a review. *Environ Sci Technol*. 2014 Jun;48(11):5800-5807.
28. Jonsson M, Fick J, Klaminder J, Brodin T. Environmental concentration of an anxiolytic drug (oxazepam) alters behavior of fish. *Sci Rep*. 2015 May;5:10522.
29. Schultz MM, Furlong ET, Kolpin DW, Werner SL, Schoenfuss HL, Barber LB, et al. Antidepressant pharmaceuticals in two U.S. effluent-impacted streams: occurrence and fate in water and sediment, and selective uptake in fish neural tissue. *Environ Sci Technol*. 2010 Mar;44(6):1918-1925.
30. Painter MM, Buerkley MA, Julius ML, Vajda AM, Norris DO, Barber LB, et al. Antidepressants at environmentally relevant concentrations affect predator avoidance behavior of larval fathead minnows (*Pimephales promelas*). *Environ Toxicol Chem*. 2009 Dec;28(12):2677-2684.
31. Tierney KB, Sampson AL, Ross PS, Sekela MA, Kennedy CJ. Olfactory toxicity in fishes: a review. *Aquat Toxicol*. 2010 Jan;96(1):2-26.
32. Brain RA, Johnson DJ, Richards SM, Hanson ML, Sanderson H, Lam MW, et al. Microcosm evaluation of the effects of an eight-pharmaceutical mixture, along with tylosin, on lemon duckweed (*Lemna gibba*). *Environ Toxicol Chem*. 2004 Feb;23(2):370-376.
33. Bundschuh M, Zubrod JP, Schulz R. The fungicide tebuconazole, even at low concentrations, alters the decomposer community and organic matter decomposition in streams. *Environ Toxicol Chem*. 2011 Apr;30(4):940-947.
34. Flaherty CM, Dodson SI. Effects of pharmaceuticals on *Daphnia magna* life-history parameters. *Chemosphere*. 2005 Oct;61(2):225-232.
35. Kidd KA, Blanchfield PJ, Paterson MJ, Shearer DL, Podemski CL, Findlay DL, et al. Collapse of a fish population after exposure to a synthetic estrogen. *Proc Natl Acad Sci U S A*. 2007 May;104(21):8897-8901.
36. Ramirez AJ, Brain RA, Usenko S, Mottaleb MA, O'Donnell JG, Stahl LL, et al. Occurrence of pharmaceuticals and personal care products in fish: results of a national pilot study in the United States. *Environ Sci Technol*. 2009 Feb;43(3):861-867.
37. Brooks BW, Chambliss CK, Stanley JK, Ramirez A, Banks KE, Johnson RD, et al. Determination of select antidepressants in fish from an effluent-dominated stream. *Environ Toxicol Chem*. 2005 Feb;24(2):464-469.
38. Kümmerer K. Resistance in the environment. *J Antimicrob Chemother*. 2004 Aug;54(2):311-320.
39. Beaber JW, Novick RP, Waldor MK. SOS response promotes horizontal transfer of antibiotic resistance genes. *Nature*. 2004 Jan;427(6969):72-74.
40. Aminov RI. A brief history of the antibiotic era: lessons learned and challenges for the future. *Front Microbiol*. 2010 Dec;1:134.
41. Martinez JL. Environmental pollution by antibiotics and antibiotic resistance genes. *Environ Pollut*. 2009 Nov;157(11):2893-2902.
42. Roose-Amsaleg C, Laverman AM. Do antibiotics have environmental effects on aquatic microbes? A systematic review. *Trends Biotechnol*. 2016 Jan;34(1):33-44.
43. Liu F, Ying GG, Tao R, Zhao JL, Yang JF, Zhao LF. Effects of nine veterinary antibiotics on agricultural soil microbial community. *J Environ Sci Health B*. 2009 Dec;44(8):810-817.
44. Straub JO. An environmental risk assessment for diclofenac in cosmetic applications. *Toxicol Lett*. 2002 May;131(1-2):117-137.
45. European Medicines Agency (EMA). Guideline on the environmental risk assessment of medicinal products for human use. London, UK: EMA; 2006. Report No.: EMEA/CHMP/SWP/4447/00.
46. Food and Drug Administration (FDA). Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications. Rockville, MD: FDA; 1998.
47. Ågerstrand M, Westerberg H, Rudén C. Evaluating the environmental risk assessment of human pharmaceuticals in the European Union. *Regul Toxicol Pharmacol*. 2015 Feb;71(1):111-120.

48. Organisation for Economic Co-operation and Development (OECD). Test No. 301: Ready Biodegradability. Paris, France: OECD Publishing; 1992.
49. Organisation for Economic Co-operation and Development (OECD). Test No. 305: Bioaccumulation in Fish: Aqueous and Dietary Exposure. Paris, France: OECD Publishing; 2012.
50. Backhaus T. Medicines in the environment: mixture toxicity of pharmaceuticals. *Philos Trans R Soc Lond B Biol Sci*. 2014 Nov;369(1656):20130584.
51. Crane M, Watts C, Boucard T. Chronic aquatic toxicity of human pharmaceuticals. *Environ Int*. 2006 Aug;32(6):793-799.
52. Cleuvers M. Mixture toxicity of the anti-inflammatory drugs diclofenac, ibuprofen, naproxen, and acetylsalicylic acid. *Ecotoxicol Environ Saf*. 2004 Oct;59(3):309-315.
53. Parrott JL, Bennie DT. Life-cycle exposure of fathead minnows to a mixture of six common pharmaceuticals and personal care products at environmentally relevant concentrations. *Environ Toxicol*. 2009 Jun;24(3):213-222.
54. Verlicchi P, Al Aukidy M, Zambello E. What occurs to pharmaceuticals and personal care products in hospital wastewaters? A review on occurrence, removal and environmental risk. *Sci Total Environ*. 2012 Mar;420:1-45.
55. Kanakaraju D, Glass BD, Oelgemöller M. Advanced oxidation processes for pharmaceutical destruction: a review. *Environ Chem Lett*. 2018 Mar;16(1):137-174.
56. Kovalova L, Siegrist H, Singer H, Wittmer A, McArdell CS. Elimination of micropollutants during tertiary treatment of hospital wastewater with powdered activated carbon, ozone, and membrane bioreactor. *Environ Sci Technol*. 2013 Mar;47(14):7899-7908.
57. Kümmerer K. Green chemistry, sustainable chemistry, and pharmaceuticals: an overview. *Green Chem*. 2007 Aug;9(8):899-907.
58. Rastogi T, Leder C, Kümmerer K. Re-design of the persistent beta-blocker metoprolol to highly biodegradable alternatives. *Environ Sci Technol*. 2015 Aug;49(15):9156-9164.
59. Sanderson H, Johnson DJ, Reitsma T, Brain RA, Wilson CJ, Solomon KR. Ranking and prioritization of environmental risks of pharmaceuticals in North America. *Environ Sci Technol*. 2004 Nov;38(22):5942-5953.