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REVIEW ARTICLE

The Impact of Bioaccumulation of Nano-pharmaceuticals in the Aquatic Ecosystems

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Abstract: Nano-pharmaceuticals consists of various therapeutic agents produced at the nanoscale, which have higher drug delivery and better therapeutic efficacy. Their unique physicochemical properties, such as high surface-area-to-volume ratios and tunable surface functionalities, enable targeted therapies andS improved bioavailability compared to their conventional counterparts. However, the increasing production and use of these agents raise substantial concerns about their environmental fate and potential ecotoxicological impacts following their inevitable release into aquatic ecosystems. Once in the environment, nano-pharmaceuticals can persist, interact with natural organic matter, and undergo transformations that alter their bioavailability and toxicity. Evidence indicates that these nanoparticles can induce adverse effects across various trophic levels, from microorganisms and algae to invertebrates and fish, through mechanisms including oxidative stress, membrane disruption, and genotoxicity. The potential for nano-pharmaceuticals to bioaccumulate in aquatic organisms and undergo trophic transfer presents a plausible, yet poorly quantified, pathway for chronic human exposure through the consumption of contaminated water and seafood. This review discusses about the current evidence on the environmental pathways, ecotoxicological effects, and potential human health risks associated with nano-pharmaceuticals.

Keywords: Nanomedicine; Contaminants; Ecotoxicology; Aquatic Pollution; Bioaccumulation; Environmental Risk

1. Introduction

The rapid development of nanotechnology has led to a paradigm shift across numerous scientific and industrial sectors, with particularly transformative effects observed in medicine and pharmacology [1]. This has led to the development of nano-pharmaceuticals—medicinal products in which the active pharmaceutical ingredient (API) or a carrier vehicle is produced at the nanoscale, typically within a size range of 1 to 100 nanometers [2]. The reduction in particle size provides better physicochemical properties, including an exceptionally high surface-area-to-volume ratio, quantum effects, and unique surface reactivities, which are not apparent in the bulk material [3].

These characteristics are harnessed to overcome many limitations of conventional drug formulations. For instance, nano-pharmaceuticals can enhance the solubility and bioavailability of poorly water-soluble drugs, extend circulation half-life, and facilitate passage across biological barriers [4]. Moreover, their surfaces can be functionalized with targeting ligands to enable precise delivery to specific cells or tissues, thereby maximizing therapeutic efficacy while minimizing off-target side effects, a strategy that has shown considerable promise in fields such as oncology [5, 6].

Despite their clear therapeutic benefits, the proliferation of nano-pharmaceuticals in clinical and commercial applications has created a new and complex environmental challenge [7]. Following administration, these agents and their metabolites are excreted and enter municipal wastewater streams. Compounded by discharges from manufacturing facilities and improper disposal of unused medications, this creates direct pathways for their entry into aquatic ecosystems [8].

Conventional wastewater treatment plants (WWTPs) are not specifically designed to remove or degrade these complex nanoparticles, leading to their release into surface waters or their partitioning into sewage sludge, which may subsequently be applied to land as fertilizer [9]. The unique properties that make nano-pharmaceuticals effective *in vivo*—such as stability, mobility, and biological reactivity—also govern their behavior and potential toxicity in the environment, making them a distinct class of emerging contaminants [10]. This review discusses about the fate, ecotoxicological impact, and potential human health risks of nano-pharmaceuticals in the aquatic environment.

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2. Classification of Nano-Pharmaceuticals

The difference between nano-pharmaceuticals and conventional drugs lies particularly in their physicochemical characteristics, which dictate their biological interactions, therapeutic efficacy, and environmental behavior [11].

Table 1. Classification and Characteristics of Common Nano-pharmaceutical Carriers

Nanocarrier Type	Typical Size Range (nm)	Composition	Characteristics	Therapeutic Applications
Liposomes	80–300	Phospholipid bilayers	Biocompatible; can encapsulate both hydrophilic and hydrophobic drugs; surface can be modified (e.g., PEGylation) to increase circulation time.	Cancer therapy (e.g., Doxil®), antifungal agents, vaccines.
Solid Lipid Nanoparticles (SLNs)	50–1000	Solid lipids (e.g., triglycerides) stabilized by surfactants	High drug stability; controlled release; good biocompatibility; avoids organic solvents in production.	Oral drug delivery, topical applications, parenteral administration.
Polymeric Micelles	10–100	Amphiphilic block copolymers	Self-assemble in aqueous solution; hydrophobic core for drug encapsulation; hydrophilic shell provides stability and stealth properties.	Delivery of poorly soluble anticancer drugs.
Dendrimers	1–15	Highly branched, synthetic polymers	Well-defined, monodisperse structure; high density of surface functional groups for targeting and solubility enhancement.	Drug delivery, gene therapy, diagnostic imaging.
Gold Nanoparticles (AuNPs)	2–100	Elemental gold	Unique optical properties (surface plasmon resonance); easily functionalized surface; high stability.	Photothermal therapy, diagnostic assays, targeted drug delivery.
Silver Nanoparticles (AgNPs)	10–100	Elemental silver	Strong antimicrobial and antiviral properties; high surface area-to-volume ratio.	Antimicrobial coatings on medical devices, wound dressings.
Iron Oxide Nanoparticles (IONPs)	5–200	Magnetite (Fe_3O_4) or Maghemite (γ-Fe_2O_3)	Superparamagnetic properties; biocompatible; can be guided by external magnetic fields.	Magnetic Resonance Imaging (MRI) contrast agents, hyperthermia cancer treatment, cell separation.

2.1. Physicochemical Properties

The primary determinant of a nano-pharmaceutical's behavior is its size. The nanoscale dimensions result in a dramatic increase in the surface-area-to-volume ratio, which enhances dissolution rates and provides a larger interface for biological interactions [12]. Surface charge, often quantified as the zeta potential, is another critical parameter that influences particle stability in suspension and interactions with biological membranes. A high absolute zeta potential value generally corresponds to greater colloidal stability due to electrostatic repulsion, preventing aggregation [13]. Moreover, the surface of a nanoparticle can be deliberately modified or "functionalized" with various molecules (e.g., polymers like polyethylene glycol [PEG]) to improve stability, evade the immune system, and attach targeting ligands [14]. These engineered properties, while beneficial for therapeutic purposes, also profoundly influence how the nanoparticles interact with environmental matrices.

2.2. Major Classes of Nano-Pharmaceuticals

Nano-pharmaceuticals consists of a wide variety of materials, which can be broadly categorized based on their core composition.

2.2.1. Lipid-Based Nanocarriers

This class includes liposomes and solid lipid nanoparticles (SLNs). Liposomes are spherical vesicles composed of one or more lipid bilayers enclosing an aqueous core, making them suitable for encapsulating both hydrophilic and lipophilic drugs [15]. Their structural similarity to cell membranes imparts high biocompatibility and biodegradability. SLNs are similar but possess a solid lipid

core matrix, offering improved stability and controlled release capabilities [16]. The successful deployment of lipid nanoparticles as delivery vehicles for mRNA in COVID-19 vaccines has prominently highlighted the clinical significance of this class [17].

2.2.2. Polymeric Nanoparticles

Polymeric nanoparticles are formed from natural or synthetic polymers, which self-assemble into various structures such as nanospheres, nanocapsules, micelles, and dendrimers. Polymeric micelles are core-shell structures that are particularly effective for solubilizing hydrophobic drugs [18]. Dendrimers are highly branched, tree-like macromolecules with a well-defined architecture that allows for the precise attachment of multiple drug molecules and targeting agents on their surface [19]. The versatility and tunability of polymers enable the design of stimuli-responsive systems that release their payload in response to specific environmental triggers like pH or temperature changes, which is highly advantageous for targeted cancer therapy [20].

2.2.3. Inorganic Nanoparticles

This category includes nanoparticles derived from metals (e.g., gold, silver) and metal oxides (e.g., titanium dioxide, zinc oxide, iron oxides). Gold nanoparticles are widely investigated for their applications in diagnostics and photothermal therapy due to their unique optical properties (surface plasmon resonance) [21]. Silver nanoparticles are incorporated into medical devices and wound dressings for their potent antimicrobial activity [22]. Superparamagnetic iron oxide nanoparticles (SPIONs) serve as contrast agents in magnetic resonance imaging (MRI) and can be guided by external magnetic fields for targeted drug delivery [23]. While highly effective, the environmental persistence and potential toxicity of inorganic nanoparticles, particularly those containing silver or other heavy metals, are significant areas of concern.

3. Environmental Pathways, Fate, and Transport of Nano-Pharmaceuticals

The journey of a nano-pharmaceutical from its point of use to its ultimate environmental sink is complex and influenced by both the nanoparticle's intrinsic properties and the characteristics of the receiving environment.

3.1. Environmental Transformations in Aquatic Systems

Once nano-pharmaceuticals enter the dynamic and chemically complex aquatic environment, they rarely remain in their pristine, engineered state. They undergo a series of transformations that collectively determine their fate, transport, and bioavailability. A key process is heteroaggregation, where nanoparticles interact and clump together with other suspended particles, such as clays, minerals, and organic detritus [24].

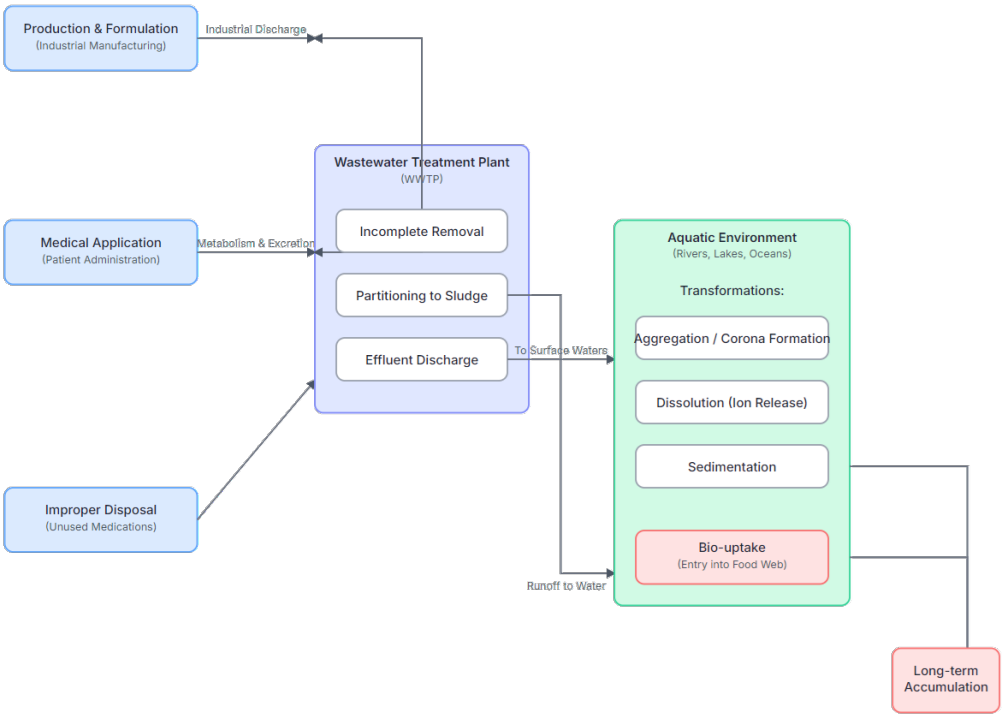

Figure 1. Life Cycle and Environmental Pathways of Nano-pharmaceuticals

Simultaneously, molecules present in the water, particularly natural organic matter (NOM) like humic and fulvic acids, rapidly adsorb to the nanoparticle surface. This process forms an "eco-corona," which alters the particle's surface charge, stability, and reactivity [25]. The formation of an eco-corona can either stabilize the nanoparticles, keeping them suspended in the water column for longer periods, or promote their aggregation and subsequent sedimentation [26]. The pH, ionic strength, and temperature of the water significantly mediate these aggregation and corona formation processes. For instance, in high-salinity environments such as estuaries, charge screening effects can accelerate nanoparticle aggregation and removal from the water column [27].

3.2. Transport and Persistence

The transport of nano-pharmaceuticals is dictated by their stability in the water column. Small, well-dispersed nanoparticles can be transported over long distances by water currents. Conversely, larger aggregates or particles that have adsorbed to suspended sediments are more likely to be deposited in benthic zones [28]. This partitioning between the water column and sediment is a critical factor in determining exposure routes for different aquatic organisms. Benthic organisms may be exposed to high concentrations through sediment ingestion, while pelagic organisms are more likely to be exposed to waterborne nanoparticles. The persistence of these materials varies greatly. Biocompatible lipid- and polymer-based nanoparticles may be susceptible to biodegradation over time, whereas inorganic nanoparticles are non-biodegradable and can persist indefinitely, potentially accumulating in sediments that act as long-term environmental sinks [29, 30].

Table 2. Physicochemical Properties of Nanoparticles and Their Influence on Environment

Physicochemical Property	Description	Influence on Environmental Behavior	Reference
Size and Surface Area	Core diameter and the total surface area per unit mass.	Smaller size increases diffusion and potential to cross biological membranes. High surface area increases reactivity and dissolution rates.	[7, 12]
Surface Charge (Zeta Potential)	The electrical potential at the nanoparticle-fluid interface.	Governs colloidal stability. Highly positive or negative zeta potentials lead to electrostatic repulsion, preventing aggregation (homoaggregation). Neutral or near-neutral charges promote aggregation.	[13, 26]
Composition	The core material of the nanoparticle (e.g., metal, lipid, polymer).	Determines intrinsic properties like solubility, density, and reactivity. For example, AgNPs can release toxic Ag^+ ions through dissolution.	[28]
Surface Coating/Functionalization	Molecules attached to the nanoparticle surface (e.g., PEG, citrate, specific ligands).	Modifies surface charge and hydrophilicity. Can either stabilize particles against aggregation or promote interaction with natural organic matter (heteroaggregation).	[14, 25]
Crystallinity	The degree of structural order in a solid material.	Affects dissolution rates and surface reactivity. For example, anatase TiO_2 is generally more photo-catalytically active and toxic than rutile TiO_2.	[28]

4. Ecotoxicological Impacts of Nano-Pharmaceuticals

The entry of nano-pharmaceuticals into aquatic ecosystems raises significant ecotoxicological concerns due to their potential to interact with and harm non-target organisms. Their biological activity is governed by a combination of their physical form (the nanoparticle itself) and their chemical composition (the core material, surface coatings, and any encapsulated drug) [31].

4.1. Mechanisms of Nanotoxicity in Aquatic Organisms

Several mechanisms have been identified through which nano-pharmaceuticals can exert toxicity.

4.1.1. Oxidative Stress

One of the most commonly reported mechanisms of nanotoxicity is the generation of reactive oxygen species (ROS) [32]. The high surface reactivity of many nanoparticles can catalyze the formation of ROS (e.g., superoxide anion, hydroxyl radical) in excess of the organism's antioxidant capacity, leading to oxidative stress. This, in turn, can cause damage to vital cellular components, including lipids, proteins, and DNA [33].

4.1.2. Physical and Mechanical Damage

Nanoparticles can cause direct physical harm to cells and tissues. For instance, they can adsorb to the external surfaces of organisms, such as the gills of fish or the carapaces of crustaceans, leading to abrasion, irritation, and impaired physiological functions like respiration [34]. Ingestion can lead to damage to the gut epithelium.

4.1.3. Dissolution and Ion Release

For metallic and metal oxide nanoparticles (e.g., AgNPs, ZnO-NPs), a significant component of their toxicity arises from the release of dissolved metal ions (e.g., Ag+, Zn2+). These ions are often highly toxic and can disrupt essential enzymatic processes and ion regulation within the organism [35]. This makes it challenging to disentangle particle-specific effects from the effects of dissolved ions.

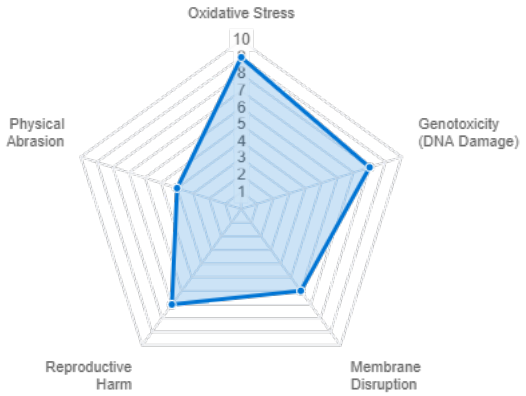

Figure 2. Mechanisms of Nanotoxicity on Organisms

4.1.4. Genotoxicity

Some nano-pharmaceuticals have been shown to be genotoxic, capable of causing damage to an organism's genetic material. This can occur directly through nanoparticle interaction with DNA or indirectly through oxidative stress. Such damage can lead to mutations, developmental abnormalities, and cancer [36].

Table 3. Ecotoxicological Effects of Nanoparticles on Aquatic Organisms

Trophic Level	Organism Type	Type of Nanoparticle Studied	Observed Ecotoxicological Effects	References
Producers	Algae (e.g., *Pseudokirchneriella subcapitata*)	AgNPs, TiO_2, ZnO NPs	Inhibition of photosynthesis; induction of oxidative stress (ROS production); physical aggregation and cell membrane damage; reduced growth rate.	[10, 38]
Primary Consumers	Invertebrates (e.g., *Daphnia magna*)	AgNPs, Carbon Nanotubes (CNTs), TiO_2	Acute toxicity (mortality); reproductive impairment (reduced offspring); developmental abnormalities; accumulation in the gut.	[35, 39]
Secondary/Tertiary Consumers	Fish (e.g., Zebrafish, Rainbow Trout)	AgNPs, AuNPs, TiO_2, CuO NPs	Gill damage and respiratory distress; oxidative stress and inflammation in liver and brain; genotoxicity (DNA damage); bioaccumulation in various organs; altered swimming behavior.	[41, 42, 53]
Benthic Organisms	Bivalves, Amphipods	AgNPs, CuNPs	Accumulation from sediment; reduced feeding rates; immune system modulation; mortality at high concentrations.	[40]

4.2. Effects Across Aquatic Trophic Levels

The impact of nano-pharmaceuticals has been observed across a wide range of aquatic organisms, from the base of the food web to higher-order predators.

4.2.1. Microorganisms and Algae

Since the foundation of most aquatic food webs, impacts on bacteria and algae can have cascading ecosystem-level effects. Silver nanoparticles, valued for their antimicrobial properties, can disrupt essential microbial processes like nutrient cycling [37]. For photosynthetic organisms like algae, nanoparticles can reduce light penetration, physically abrade cell walls, and induce oxidative stress, ultimately inhibiting growth and photosynthesis [38].

4.2.2. Invertebrates

Zooplankton, such as the water flea *Daphnia magna*, are standard models in aquatic toxicology and have shown high sensitivity to nano-pharmaceuticals. Exposure can lead to reduced mobility, impaired reproduction, and increased mortality, even at low concentrations [39]. Benthic invertebrates can be exposed to high concentrations of nanoparticles that accumulate in sediments, leading to developmental and reproductive toxicity [40].

4.2.3. Fish

As vertebrate predators, fish can be exposed to nano-pharmaceuticals directly from the water via their gills and skin, or through their diet. Studies using model organisms like zebrafish (*Danio rerio*) have documented a range of adverse effects, including developmental malformations, neurotoxicity, gill pathology, and altered behavior [41, 42]. The ability of some nanoparticles to cross the blood-brain barrier in fish is a particular concern, raising questions about potential neurological impacts [43].

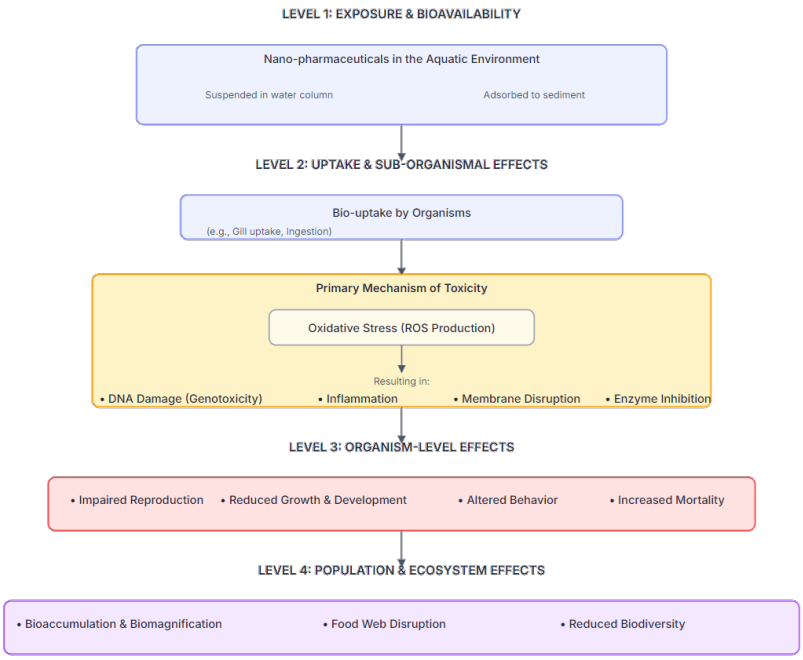

Figure 3. Ecotoxicological Effects of Nano-pharmaceuticals in Aquatic Systems

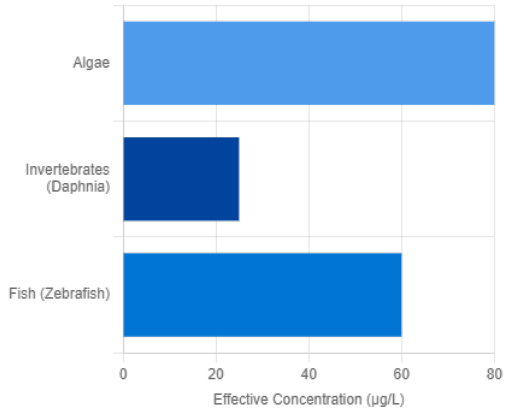

Figure 4. Relative Sensitivity of Aquatic Life

5. Bioaccumulation and Human Health Risks

A critical aspect of the environmental risk of nano-pharmaceuticals is their potential to enter the food chain, accumulate in organisms, and ultimately reach human consumers.

5.1. Bioaccumulation and Trophic Transfer

Bioaccumulation occurs when an organism absorbs a substance at a rate faster than that at which the substance is lost by catabolism and excretion. Nano-pharmaceuticals can be taken up by aquatic organisms through various routes, including passive diffusion across membranes, endocytosis, and dietary ingestion [44]. Once inside the organism, they can translocate to various tissues and organs, where they may persist and accumulate over time.

The subsequent transfer of these accumulated nanoparticles through the food web is known as trophic transfer or biomagnification. While the biomagnification of classic persistent pollutants like mercury and PCBs is well-established, the trophic transfer potential of nanoparticles is a more complex and emergent area of research [45]. Some studies have demonstrated the transfer of nanoparticles from algae to zooplankton and subsequently to fish [46]. However, the extent of transfer and whether concentrations are magnified at each trophic step appears to depend heavily on the specific nanoparticle, the food chain structure, and the feeding dynamics of the ecosystem. The formation of the eco-corona and particle aggregation can significantly influence bioavailability and thus the potential for uptake and transfer [47].

5.2. Potential Pathways for Human Exposure

The primary pathway for human exposure to environmentally dispersed nano-pharmaceuticals is through the consumption of contaminated seafood and drinking water. While the concentrations in environmental media are currently predicted to be low, the potential for chronic, low-dose exposure over a lifetime is a public health concern [48].

Direct evidence of human health effects from the environmental exposure to nano-pharmaceuticals is currently lacking. However, risks can be inferred from toxicological studies on mammals and data from occupational exposures. Inhaled or ingested nanoparticles can induce inflammatory responses, oxidative stress, and cellular damage in various organs [49]. A key concern is the ability of very small nanoparticles to cross biological barriers, such as the intestinal wall, the blood-brain barrier, and the placental barrier, allowing them to reach sensitive organs like the brain or a developing fetus [50]. Therefore, while the therapeutic application of nano-pharmaceuticals is highly targeted and controlled, their uncontrolled and chronic exposure through environmental routes could pose unforeseen health risks which requires careful control and regulation.

Table 4. Potential Human Exposure Pathways and Associated Health Risks of Nano-pharmaceuticals

Exposure Pathway	Source/Mechanism	Potential Target Organs	Reported or Hypothesized Health Risks	Reference
Oral Ingestion	Consumption of contaminated drinking water; consumption of seafood or crops that have bioaccumulated nanoparticles.	Gastrointestinal (GI) tract, Liver, Spleen, Kidneys	Direct translocation across the intestinal wall (persorption); accumulation in reticuloendothelial system organs; induction of inflammation and oxidative stress.	[48, 50]
Inhalation	Aerosolization of nanoparticles from water bodies or sludge application (less direct for nano-pharmaceuticals but possible).	Lungs, Cardiovascular System, Brain	Pulmonary inflammation; potential translocation from lungs into systemic circulation; potential for crossing the blood-brain barrier via the olfactory nerve.	[49]
Dermal Contact	Recreational water activities; use of consumer products containing nanoparticles (e.g., sunscreens).	Skin, Systemic Circulation (if skin is compromised)	Limited penetration through intact skin, but potential for absorption through damaged skin or hair follicles; local inflammatory responses.	[49]

6. Conclusion

Nano-pharmaceuticals are important drug delivery systems that help in diagnosis and treatment of a wide range of diseases with precision and efficacy. However, this therapeutic promise is accompanied by valid concerns regarding their environmental impact. Once released into aquatic systems, these novel entities can persist, interact with biota in complex ways, and induce a spectrum of toxicological effects across multiple trophic levels. The potential for bioaccumulation and trophic transfer raises further questions about long-term risks to both ecosystem integrity and human health. Currently, significant knowledge gaps exist regarding the

chronic effects of nano-pharmaceuticals at environmentally relevant concentrations and their behavior in complex ecosystems. The existing regulatory paradigms are ill-equipped to address the unique challenges posed by nanomaterials. A proactive and precautionary approach is essential. This requires a collaborative effort from the scientific community to close critical research gaps, coupled with the development of adaptive, nano-specific policies. It will be possible to fully utilize their profound medical benefits while diligently safeguarding the health of our aquatic environments by embedding principles of environmental stewardship and "Safe-by-Design" into the lifecycle of nano-pharmaceuticals.

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