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A review on oxidative stress, DNA damage, and biochemical changes in fish due to Ibuprofen exposure

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Abstract
The occurrence of pharmaceutical compounds, especially non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen, in aquatic ecosystems has emerged as a major environmental issue. Ibuprofen is commonly found in water bodies and presents potential risks to aquatic organisms, particularly fish, by inducing biochemical disturbances and genetic damage. This review compiles existing knowledge on the effects of ibuprofen exposure in fish, with emphasis on oxidative stress, hepatic and renal dysfunction, metabolic alterations, endocrine disruption, and genotoxic impacts. Exposure to ibuprofen leads to elevated production of reactive oxygen species (ROS), disruption of antioxidant defense systems, and impairment of vital organs such as the liver and kidneys. Additionally, endocrine-related effects include hormonal imbalances and compromised reproductive functions. Growing evidence also indicates the genotoxic nature of ibuprofen, demonstrated through DNA damage, micronuclei formation, and chromosomal abnormalities. The prolonged and sub-lethal effects of these changes may significantly influence fish health, population stability, and overall aquatic ecosystem integrity. Therefore, improving wastewater treatment processes and enforcing stricter environmental regulations are essential to reduce the impact of ibuprofen and related contaminants in aquatic environments.

Keywords: Biochemical alterations, DNA damage, genotoxicity, Ibuprofen, oxidative stress

Introduction

The presence of pharmaceutical contaminants, particularly non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen, has become a significant ecological issue due to their frequent detection in aquatic ecosystems. These drugs often enter water bodies from untreated or partially treated wastewater, creating risks for non-target species like fish (Buser *et al.*, 1998; Tixier *et al.*, 2003) [2, 16]. While NSAIDs are designed to act on specific biological pathways in humans and terrestrial animals, they can unintentionally interfere with the physiology of aquatic organisms, causing various adverse effects. Recent reviews (Kummerer *et al.*, 2022; Maldonado *et al.*, 2023) [9, 10] emphasize the urgency of addressing these effects to better understand and mitigate long-term ecological impacts. This review consolidates existing research on ibuprofen's effects on fish, emphasizing its biochemical, endocrine, and genotoxic impacts to support informed environmental management and regulatory actions.

Ibuprofen, as one of the most widely used NSAIDs, is consistently detected at concerning levels in both freshwater and marine environments. Its persistence and resistance to conventional wastewater treatments make it a common contaminant in surface waters, where it induces oxidative stress, liver and kidney dysfunction, and hormonal disruption in fish (Hoeger *et al.*, 2005) [5]. These impacts harm individual health and could pose broader ecological threats with potential long-term consequences for fish populations and aquatic ecosystem health.

A substantial body of research highlights the environmental risks posed by NSAIDs like ibuprofen. (Hoeger *et al.*, 2005) [5] Showed that fish exposed to ibuprofen produce elevated levels of reactive oxygen species (ROS), resulting in oxidative stress that overwhelms their antioxidant defenses, causing cellular and organ damage, particularly in the liver and kidneys. (Islas-Flores *et al.*, 2013) [6] They similarly observed liver and kidney dysfunction in ibuprofen-exposed fish, attributing it to oxidative stress and altered enzyme activity.

Endocrine disruption is another major concern associated with ibuprofen exposure. (Schwaiger *et al.*, 2004) [15] Observed hormonal imbalances in fish, including reproductive impairments such as reduced fertility and changes in sex hormone levels. (Fent *et al.*, 2006) [3] Highlighted the genotoxic effects of ibuprofen, finding DNA damage, micronucleus formation, and chromosomal changes in exposed fish, raising concerns over possible genetic impacts on fish populations.

Recent studies have reinforced these findings. (Gonzalez-Rey and Bebianno, 2014) [4] Observed that chronic exposure to low ibuprofen levels can lead to oxidative damage and significant gene expression changes in marine species. (Santos *et al.*, 2018) [13] Reported that ibuprofen alters lipid metabolism in fish, which exacerbates oxidative stress and leads to further organ damage. Additionally, (Sanchez-Marin *et al.*, 2020) [11] documented increased DNA fragmentation in fish exposed to environmentally relevant concentrations of ibuprofen, further highlighting its genotoxic risks.

Overall, the literature indicates that even low concentrations of ibuprofen can lead to serious ecological risks through its biochemical, endocrine, and genotoxic effects on aquatic life. The ongoing presence of ibuprofen and other pharmaceuticals in aquatic environments underscores the

need for improved wastewater treatment processes and stricter regulatory measures to reduce contamination. Recent reviews (Kummerer *et al.,* 2022; Maldonado *et al.,* 2023) [9, 10] have highlighted innovative treatment technologies and policy interventions as critical components in mitigating pharmaceutical pollution and protecting aquatic organisms. Additional research remains essential to fully understand the long-term, population-level effects and develop effective strategies to manage pharmaceutical pollution in aquatic ecosystems.

Pathways of Ibuprofen in Aquatic Environments

Ibuprofen primarily enters aquatic environments through wastewater, although urban runoff also plays a role in its presence. Research conducted by (Buser *et al. (*1998) and Tixier *et al.,* 2003) [2, 16] has demonstrated that conventional wastewater treatment methods are often ineffective at completely removing ibuprofen, allowing it to remain in water bodies. The detection of ibuprofen in these ecosystems raises significant concerns, as evidence suggests it can accumulate and adversely affect aquatic organisms due to its chemical stability. Recent literature reviews stress the importance of enhancing wastewater management practices and point out the potential risks of pharmaceutical pollution in aquatic ecosystems (Kummerer *et al.,* 2022; Maldonado *et al.,* 2023; Jindal *et al.,* 2023) [8, 9, 10].

Behavioral Changes in Fish Due to Ibuprofen Exposure

Research has increasingly highlighted the diverse behavioral changes in fish resulting from ibuprofen exposure, even at low, environmentally relevant concentrations. Behavioral alterations are crucial indicators of sub-lethal stress, reflecting underlying physiological and neurological disruptions in aquatic organisms caused by contaminants.

Reduced Activity and Altered Swimming Patterns

Studies have shown that ibuprofen exposure leads to reduced activity levels and abnormal swimming behavior. For instance, (Ji *et al.*, 2022) reported that Ibuprofen-exposed fish exhibited lethargy, slower swimming speeds, and erratic movements. These changes likely result from oxidative stress and neurotoxicity that compromise the central nervous system, impairing coordination and energy balance.

Feeding Behavior Changes

Ibuprofen also disrupts feeding behaviors in fish. (Abbas *et al.,* 2023) [1] Fish exposed to chronic ibuprofen levels showed decreased motivation to feed, likely due to the energetic and metabolic toll of oxidative stress, organ dysfunction, and neuroendocrine disruptions. Reduced food intake could impair growth and energy reserves, potentially impacting populations.

Social Interactions and Aggressiveness

The drug's impact on social behaviors, such as increased aggression or social withdrawal, has also been documented. (Santos *et al.,* 2018) [13] Found that Ibuprofen-exposed fish exhibited altered social dynamics, including signs of social isolation and modified social hierarchies. These changes may stem from Ibuprofen's interference with neurotransmitter pathways, which could affect reproductive success and social cohesion, ultimately influencing population dynamics.

Risk-Taking and Predator Avoidance

Ibuprofen exposure appears to impair predator avoidance in fish, making them more vulnerable. (Ji *et al.,* 2022) observed that fish exposed to ibuprofen were slower to react to predator cues, indicating impaired neurological function and risk perception. This reduced response could increase predation rates in natural settings, potentially destabilizing populations and impacting ecosystem stability.

Exploration and Anxiety-Like Behaviors

Ibuprofen exposure has been shown to reduce exploratory behavior and increase anxiety-like responses. (Maldonado *et al.,* 2023) [10] Suggests that these behaviors arise from the drug's effects on neurotransmitter pathways, particularly those involving serotonin, which regulates stress and behavior. Reduced exploration can limit a fish's ability to adapt to environmental changes and find resources.

Impaired Reproductive and Parental Behaviors

(Kummerer *et al.,* 2022) [9] Reviewed evidence that ibuprofen and other pharmaceuticals disrupt endocrine function, altering courtship and mating behaviors through hormonal imbalances. Such shifts may not only affect immediate reproductive success but could have long-term consequences if they impact parental care.

Learning and Memory Deficits

Chronic ibuprofen exposure has been associated with cognitive impairments in fish, including learning and memory deficits. (Jindal *et al.,* 2023) [8] Found that fish exposed to NSAIDs like Ibuprofen were less able to recognize threats or remember locations of resources, potentially reducing their survival ability and adaptability in the wild.

Sensory Responses

Ibuprofen exposure also affects sensory processing. (Gonzalez-Rey and Bebianno 2014) [4] Documented disruptions in normal sensory responses, potentially impacting predator-prey interactions. This could reduce foraging efficiency and increase vulnerability to predation, with potential consequences at both individual and population levels.

Developmental and Juvenile Behavior Effects

Ibuprofen impacts extend beyond adult fish, affecting juvenile behavior and development. (Abbas *et al.,* 2023) [1] Observed that juvenile fish exposed to ibuprofen showed a delayed response to stimuli and disrupted schooling behavior, which can impact survival, growth, and adaptability, with broader implications for population and ecosystem stability.

Biochemical Effects of Ibuprofen on Fish

Oxidative Stress and Antioxidant Response

The presence of ibuprofen in water bodies is linked to increased oxidative stress in fish. Research by (Hoeger *et al.,* 2005) [5] shows that exposure to ibuprofen increases reactive oxygen species (ROS) production, impairing antioxidant defenses and causing cellular damage. Further studies, such as those by (Islas-Flores *et al.,* 2013) [6], indicate that ibuprofen disrupts antioxidant enzyme activity, affecting key enzymes like catalase, superoxide dismutase, and glutathione peroxidase, which contribute to oxidative

damage in the liver and other organs. Recent reviews (Kummerer *et al.*, 2022; Maldonado *et al.*, 2023) [9, 10] reinforce these findings, highlighting oxidative stress as a key mechanism through which NSAIDs, including ibuprofen, affect aquatic organisms.

Liver and Kidney Dysfunction

Ibuprofen exposure leads to liver and kidney dysfunction in fish, organs essential for detoxification and waste processing. (Islas-Flores *et al.*,2013) [6] Observed liver damage in fish exposed to ibuprofen, noting necrosis and altered enzyme function, which impairs detoxification capabilities. Similarly, kidney function is compromised, disrupting osmoregulation and causing water retention issues. Studies by (Santos *et al.*,2018) [13] further support these findings, indicating that ibuprofen affects lipid metabolism, thereby increasing oxidative stress and contributing to both hepatic and renal impairment. Recent analyses (Jindal *et al.*, 2023) [8] highlight the critical nature of these organ-level disruptions in overall fish health and resilience.

Metabolic Disturbances

Exposure to ibuprofen also causes metabolic disruptions in fish. (Santos *et al.*, 2018) [13] Noted altered lipid and carbohydrate metabolism, likely resulting from oxidative stress and organ damage, which affect energy balance and reduce physiological resilience. These metabolic changes, particularly lipid metabolism disruptions, underscore how prolonged ibuprofen exposure affects cellular and systemic health in fish. Recent reviews (Kummerer *et al.*, 2022; Jindal *et al.*, 2023) [8, 9] provide additional evidence of NSAID-induced metabolic alterations, highlighting the implications for aquatic life.

Endocrine Disruption and Reproductive Impacts

Research indicates that ibuprofen disrupts hormonal regulation in fish, affecting reproductive and thyroid hormone levels. (Schwaiger *et al.*, 2004) [15] Observed changes in reproductive hormones that led to reduced fertility and sex ratio imbalances in fish exposed to ibuprofen. Similarly, (Gonzalez-Rey and Bebianno, 2014) [4] reported hormonal disturbances that compromised reproductive health, which could lead to population-level declines over time. Recent reviews (Maldonado *et al.*, 2023; Kummerer *et al.*, 2022) [9, 10] reinforce these findings, discussing the broader impacts of NSAIDs on endocrine function and reproductive health in fish.

Additionally, ibuprofen's effects extend to thyroid function, which is crucial for growth and development in fish. Its endocrine-disrupting properties may lead to lasting reproductive impairments. (Fent *et al.*, 2006) [3] Reported significant reproductive issues in fish exposed to NSAIDs, including decreased offspring viability and altered reproductive morphology. Recent studies underscore these risks, with (Jindal *et al.*, 2023) [8] highlighting how NSAIDs, including ibuprofen, pose substantial reproductive and developmental risks to aquatic species.

Genotoxic and Neurotoxic Effects of Ibuprofen on Fish

The risk of genotoxicity from ibuprofen exposure in aquatic environments extends beyond individual fish to affect entire populations. (Fent *et al.*, 2006) [3] Demonstrated that ibuprofen has significant genotoxic potential, resulting in DNA damage, micronucleus formation, and chromosomal abnormalities in fish exposed to levels commonly found in the environment. These genetic disruptions pose serious threats to the health of individual organisms and reproductive success, potentially diminishing population resilience.

Building on these findings, (Sanchez-Marin *et al.*, 2020) [11] found that ibuprofen exposure increases DNA fragmentation and structural damage, with risks for lasting genetic harm. If this DNA damage is not repaired, it can lead to persistent mutations that may be passed down through generations, compromising the genetic integrity and adaptability of fish populations. Recent studies by (Maldonado *et al.*, 2023 and Jindal *et al.*, 2023) [8, 10] also examined the wider implications of genotoxicity from pharmaceuticals, noting that ibuprofen and other NSAIDs disrupt DNA replication and repair processes, leading to chromosomal abnormalities and micronuclei formation. These indicators suggest cellular instability that can affect overall genetic health.

Recent literature emphasizes that prolonged ibuprofen exposure could reduce genetic diversity in fish populations, which is crucial for resilience to environmental changes. Genetic diversity is vital for survival, especially with growing stressors like climate change, pollution, and habitat loss. Decreased genetic diversity from genotoxic effects risks population stability by reducing adaptability and increasing vulnerability to disease. This genetic instability not only affects fish populations but may also disrupt aquatic food webs and ecosystems. As genetic damage accumulates, it can cascade through food chains, impacting predator species dependent on fish, and ultimately leading to instability in aquatic ecosystems.

Neurotoxic Effects of Ibuprofen on Fish

In addition to genotoxic risks, ibuprofen has neurotoxic effects on fish, impacting behaviors, sensory functions, and cognitive processes essential for survival. Studies by (Ji *et al.*, 2022 and Abbas *et al.*, 2023) [1] suggest that ibuprofen interferes with fish's central nervous systems, altering levels of neurotransmitters like dopamine and acetylcholine, which are critical for motor control, learning, and memory.

Ibuprofen exposure has been linked to impaired predator-prey interactions, social behaviors, and feeding efficiency, as it affects the brain areas responsible for sensory processing and response. (Ji *et al.*, 2022) observed that chronic exposure to ibuprofen increases neuroinflammatory markers, indicating ongoing neural tissue damage. Such neurotoxic impacts can reduce a fish's ability to adapt to its environment, locate food, evade predators, and reproduce, ultimately threatening the sustainability of fish populations.

The neurotoxic effects of ibuprofen raise additional ecological concerns, as changes in fish behavior and cognition can disrupt aquatic ecosystem dynamics. Alterations in fish behaviors can impact predator-prey relationships and competition for resources, potentially leading to imbalances within the food web. Chronic neurotoxicity also raises concerns about the cumulative effects of low-dose pharmaceutical pollutants, as continued exposure, even at low levels, could gradually compromise fish health and population resilience.

Mechanisms of Ibuprofen-Induced Alterations in Fish

This section examines the cellular and molecular pathways through which ibuprofen induces oxidative stress, disrupts hormone pathways, and causes DNA damage in fish.

Oxidative Stress Pathways

Ibuprofen exposure is linked to increased production of reactive oxygen species (ROS), which can overwhelm antioxidant defenses and result in oxidative damage to cellular structures. Gonzalez-(Rey and Bebianno 2014) [4] demonstrated that ibuprofen exposure induces oxidative stress by elevating ROS, leading to lipid peroxidation, protein oxidation, and damage to cellular membranes in marine organisms. Recent studies (Kummerer *et al.,* 2022; Jindal *et al.,* 2023) [8, 9] highlight that NSAIDs like ibuprofen increase oxidative stress through interactions with mitochondrial pathways, affecting energy production and resulting in cellular apoptosis. The accumulation of ROS disrupts the balance of enzymatic antioxidants, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), making fish more susceptible to oxidative damage and cellular dysfunction.

Hormone Pathway Disruption

Ibuprofen has been shown to interfere with the endocrine system in fish, specifically affecting the hypothalamic-pituitary-gonadal (HPG) axis and provides evidence that ibuprofen exposure disrupts the HPG axis, altering sex hormone levels and impairing reproductive processes. Research by (Maldonado *et al.,* 2023) [10] suggests that ibuprofen and other NSAIDs can act as endocrine-disrupting chemicals (EDCs), interfering with receptors and signaling pathways involved in hormone production and regulation. These disruptions in hormone pathways can lead to decreased fertility, altered sex ratios, and developmental delays in fish. Additionally, hormonal imbalances from ibuprofen exposure can result in thyroid hormone alterations, which are essential for metabolic processes, growth, and development in fish species.

Genotoxic Mechanisms

Ibuprofen exposure is associated with genotoxic effects, including chromosomal abnormalities and DNA damage in fish. (Fent *et al.,* 2006 and Sanchez-Marin *et al.,* 2020) [3, 11] Documented that ibuprofen induces DNA strand breaks, leading to micronuclei formation and chromosomal alterations. Recent literature (Jindal *et al.,* 2023) [8] has also discussed the genotoxicity of NSAIDs, indicating that ibuprofen's interaction with DNA and chromosomal structures results in genetic mutations that could be transmitted to future generations, potentially affecting genetic diversity and resilience in fish populations. These genotoxic mechanisms not only contribute to immediate cellular damage but may also pose long-term risks to population health and stability due to compromised genetic integrity.

Implications for Aquatic Ecosystems

The presence of ibuprofen in aquatic systems is increasingly recognized as a substantial risk to biodiversity and ecosystem stability. Studies have shown that ibuprofen exposure can lead to reduced fish populations due to its biochemical, endocrine, and genotoxic effects, with broader implications for food web dynamics and ecosystem functions. (Fent *et al.,* 2006) [3] Suggested that the chronic effects of ibuprofen exposure, including DNA damage and endocrine disruption, could diminish fish population resilience, ultimately impacting biodiversity. The resulting declines in fish populations, especially in sensitive species, can disrupt predator-prey relationships and alter nutrient cycling within ecosystems.

More recent studies reinforce these concerns. (Jindal *et al.,* 2023 and Maldonado *et al.,* 2023) [8, 10] Discuss how pharmaceutical pollutants like ibuprofen can have cascading effects on aquatic food webs. Reduced fish populations not only threaten biodiversity but also affect higher trophic levels, such as bird and mammal populations that rely on fish as a food source. (Kummerer *et al.,* 2022) [9] Highlight the potential for bioaccumulation of NSAIDs in aquatic species, which could exacerbate these ecological impacts by extending the effects up the food chain and possibly impacting organisms that are further removed from direct exposure to contaminated water.

In addition, studies by (Santos *et al.,* 2018) [13] and recent findings by (Sanchez-Marin *et al.,* 2020) [11] emphasize that organ dysfunction and hormonal imbalances in fish exposed to ibuprofen could reduce reproductive success and disrupt seasonal breeding patterns, leading to population declines. The potential reduction in genetic diversity due to the genotoxic effects of ibuprofen further threatens population stability, as genetic variability is critical for adaptation to changing environmental conditions.

The loss of fish populations and the resulting imbalance in aquatic ecosystems could have profound impacts on ecosystem services, including water quality regulation, nutrient cycling, and habitat provision. (Maldonado *et al.,* 2023 and Kummerer *et al.,* 2022) [9, 10] Call for improved water treatment processes and stricter environmental regulations to limit ibuprofen contamination and protect ecosystem health.

Strategies for Mitigation

Reducing ibuprofen contamination in aquatic environments requires a multi-faceted approach, including enhanced wastewater treatment technologies, regulatory reforms, and public awareness initiatives. Traditional wastewater treatment methods are often insufficient for removing ibuprofen and other pharmaceuticals, as shown by (Tixier *et al.,* 2003) [16], highlighting the need for advanced filtration and oxidation techniques to effectively reduce pharmaceutical loads in treated water. Recent studies support this, with (Kummerer *et al.,* 2022 and Jindal *et al.,* 2023) [8, 9] discussing advanced oxidation processes (AOPs), membrane bioreactors (MBRs), and activated carbon adsorption as promising technologies to remove ibuprofen and similar contaminants from wastewater.

In addition to technological advancements, regulatory measures are essential for managing pharmaceutical pollution. (Gonzalez-Rey and Bebianno, 2014) [4] Underscored the need for stricter guidelines on pharmaceutical discharge, especially from manufacturing sites and healthcare facilities. (Maldonado *et al.,* 2023) [10] Echoing this need, setting limits on permissible pharmaceutical concentrations in wastewater discharge could significantly mitigate the impact of ibuprofen and other NSAIDs on aquatic ecosystems.

Public awareness and education about proper disposal of pharmaceuticals are also crucial to reducing ibuprofen pollution. Programs that educate the public on the environmental consequences of improper disposal and encourage the use of designated drug take-back programs can reduce the amount of ibuprofen entering wastewater systems. (Kummerer *et al.,* 2022) [9] Emphasized the role of

public awareness campaigns in preventing unused pharmaceuticals from being flushed down drains or discarded inappropriately. Additionally, (Jindal *et al.*, 2023) [8] noted that integrating these initiatives with municipal waste management practices could further improve outcomes.

A holistic approach that combines advanced treatment technologies, regulatory frameworks, and public education has the potential to significantly reduce ibuprofen contamination in aquatic environments and protect ecosystem health.

Conclusion

In conclusion, ibuprofen contamination in aquatic systems poses a significant ecological risk, particularly to fish and other sensitive aquatic organisms. Extensive research has demonstrated that ibuprofen exposure leads to biochemical alterations such as oxidative stress, enzyme inhibition, hormonal disruption, and metabolic impairments, which can compromise fish health and reduce reproductive success. Genotoxic effects, including DNA fragmentation and chromosomal anomalies, raise concerns about long-term genetic damage, threatening not only individual organisms but also entire populations and the genetic diversity critical for resilience in changing environments.

The accumulation of ibuprofen in aquatic ecosystems highlights urgent gaps in wastewater treatment efficacy and the need for advanced technologies to better capture and degrade pharmaceutical contaminants before they reach natural water bodies. Studies suggest that enhanced treatment approaches such as advanced oxidation processes, membrane bioreactors, and activated carbon filtration can improve removal rates, but these technologies require broader adoption and standardization to have a widespread impact. Stricter environmental regulations targeting pharmaceutical discharge from both industrial and domestic sources are essential, as well as regulatory policies that establish maximum allowable concentrations for pharmaceuticals in wastewater.

Moreover, addressing ibuprofen pollution necessitates public education and awareness about the environmental impacts of improper pharmaceutical disposal. Increasing the availability of drug take-back programs and raising awareness about safe disposal methods can reduce the influx of unused medications into water systems. Collaborative efforts between policymakers, wastewater treatment facilities, healthcare providers, and communities are essential to developing sustainable solutions.

Given the rising detection of pharmaceuticals in aquatic ecosystems, comprehensive strategies are needed to mitigate ibuprofen pollution and safeguard ecosystem health. By combining advanced treatment methods, effective regulatory policies, and public education, it is possible to protect aquatic biodiversity, stabilize food webs, and ensure healthier water systems. As research continues, understanding the cumulative and synergistic effects of multiple pharmaceuticals in aquatic environments will further inform conservation efforts and strengthen regulatory frameworks aimed at reducing pharmaceutical pollution on a global scale.

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