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Endocrine disrupting chemicals and their harmful effects in fish: A comprehensive review

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Abstract
Endocrine disrupting chemicals (EDCs) are a major hazard to fish populations, with significant implications for aquatic environments and the well-being of humans. This comprehensive review investigates the adverse impacts of EDCs exposure on fish, concentrating on alterations in reproductive. Endocrine systems, intersex development, modifications to gamete efficacy, gonadosomatic index (GSI) variations, and possible consequences for populations of fish. The review synthesizes findings from laboratory and field studies to elucidate the mechanisms through which EDCs disrupt sexual behaviors in fish and discusses the implications for aquatic ecosystems.This review emphasizes the intricate relationship between EDCs and fish reproductive behaviors, underscoring the need for further investigation and legislative initiatives to limit the adverse effects of EDCs on fish reproduction and population structure.

Keywords: Endocrine disrupting chemicals, fish, reproduction, intersex development, gamete quality, gonadosomatic index, aquatic ecosystems

Introduction

Endocrine disruptors pose an insidious threat to aquatic ecosystems around the world, raising significant concern for the health and well-being of fish populations. Fish serve as sentinel species in aquatic environments, providing valuable insights into the impacts of endocrine disruptors (Soffker & Tyler, 2012) [40]. They act as indicators of ecosystem health, while also raising serious concerns about potential consequences for both aquatic biodiversity and human welfare. Endocrine disruptors, a diverse group of synthetic and natural substances, possess the ability to interfere with hormonal signaling pathways in fish, causing an array of physiological and behavioral changes. These disruptions have been linked to adverse effects on fish reproduction, development, and growth, raising concerns about population sustainability and the ecological repercussions within aquatic ecosystems (Delbes *et al.*, 2022) [10].

Fish, being constantly exposed to pollutants present in water, are particularly vulnerable to the effects of EDCs that can enter their bodies through multiple routes such as gills, skin, and diet (Geyer *et al.*, 2000) [16]. Although fish may not possess an inherent susceptibility to EDCs in comparison to other fauna, specific components of their endocrine physiology, including smoltification in salmonids and the determination of sex, may increase their vulnerability to these compounds (Zhou *et al.*, 2019) [35]. Despite the well-documented individual-level impacts of EDCs on fish, demonstrating population-level consequences remains a challenge. However, studies have linked declines in fish populations to EDC exposure, highlighting the potential broader implications of these contaminants on aquatic ecosystems. For instance, roach exposed to treated sewage effluent exhibited reduced reproductive capacity, underscoring the need for further research and regulatory measures to address the effects of EDCs on wild fish populations. Evaluating the spatial spread of endocrine disruption in freshwater fish is crucial for understanding its impact on ecosystems and human health. Access to reliable data concerning the population dynamics of freshwater fish and the repercussions of endocrine-disrupting chemicals (EDCs) on different life history traits is fundamental for conducting thorough ecological risk evaluations and devising successful mitigation approaches. High-quality data on the population biology of freshwater fish and the effects of EDCs on various life history characteristics are essential for comprehensive ecological risk assessments and the development of effective mitigation strategies (Fan *et al.*, 2019) [12]. By investigating the mechanisms through which EDCs disrupt wild fish populations, researchers can inform conservation efforts and safeguard vulnerable species from the consequences of chemical contamination. This critical review examines the existing data on the detrimental impacts of endocrine-disrupting chemicals (EDCs) on fish, encompassing aspects such as physiology, reproduction, population dynamics, and behavior. The available evidence suggests that exposure to EDCs can have long-term effects on fish reproduction and subsequent population development, emphasizing the importance of understanding the influence of these chemicals on various life history characteristicsThis review critically analyses the available data on the adverse effects of endocrine-disrupting chemicals (EDCs) on fish, including their physiology, reproduction, population, and behaviour.

The Sources of EDCs in Aquatic Environments

Endocrine disruptors can enter aquatic environments through various sources, including industrial waste, agricultural effluent, urban drainage, wastewater discharge, and atmospheric emissions. EDCs comprise pesticides, industrial chemicals, medicines, plasticizers, and personal care products. Flame retardants, bisphenols, and phthalates are common EDCs found in consumer products such as electronics and textiles (Flaws *et al.*, 2020) [13]. Beauty products and personal care products may also contain EDCs such as DBP, parabens, phthalates, and triclosan. Food contact items, such as food packaged in plastic packages, infant bottles, and food wrappers, may contain bisphenols and perfluorooctanoic acid (PFOA). Chemicals from industry such as bisphenol A and PCBs are also sources of EDCs in aquatic ecosystems. Metals including lead, cadmium, and mercury can also function as EDCs. Pesticides like chlorpyrifos and herbicides like atrazine and vinclozolin can introduce EDCs into sources of water. Pharmaceuticals for humans and livestock, such as trenbolone acetate and synthetic estrogens, can also cause EDCs in aquatic systems. These different sources contribute to the prevalence of EDCs in water bodies, which damage aquatic animals and ecosystems (Gore *et al.*, 2015; Kabir, Rahman and Rahman, 2015; Kassotis *et al.*, 2020; Metcalfe *et al.*, 2022) [17, 23, 24, 31]. Once released into water bodies, these compounds can persist and accumulate, creating a complex milieu of potential threats to aquatic organisms. Environmental migration plays a crucial role in transporting EDCs from one ecosystem to another through atmospheric currents, river flows, ocean currents, and fish spawning. It can be transported from land-based activities to marine environments via rivers, highlighting the interconnected nature of contamination pathways. Fish can take up EDCs through their gills or by ingesting contaminated food sources, leading to bioaccumulation within their tissues. Trophic transfer through the food web allows EDCs to accumulate in higher trophic levels, increasing exposure risks for predators. Different sources of EDCs in aquatic environment were summarized in table 1.

Table 1: Summary of different sources of EDCs in aquatic environment

Sources	Examples	References
Surface Water Bodies	Pharmaceuticals, plastics, toys	Jordan *et al.*, 2010 [22]
Groundwater Bodies	N, N-diethyl-meta-toluamide (DEET), Di(2-ethylhexyl) phthalate (DEHP), dimethyl phthalate (DMP)	Thacharodi *et al.*, 2023 [42]
Drinking Water	Estradiol, estriol, estrone, ethinylestradiol	Thacharodi *et al.*, 2023 [42]
Marine Environment	Galaxolide, gemfibrozil, ibuprofen, naproxen	Cunha *et al.*, 2022 [9]
Aquatic Organisms	Nonylphenol, octylphenol, salicylic acid	Fan *et al.*, 2019 [12]
Urban Water Cycle	Tonalide, triclosan	Pena-Guzmán *et al.*, 2019 [38]
Agriculture and Aquaculture	Treated sewage sludge, pesticides, poultry and fish feed	Ismail *et al.*, 2017 [20]
Industrial Production	Combustion by-products, metals, plasticizers	Jordan *et al.*, 2010 [22]
Transportation	Fossil fuel combustion emissions, ship discharges	Thacharodi *et al.*, 2023 [42]
Point Sources	Waste water treatment plants	Jordan *et al.*, 2010 [22]
Diffuse Sources	Agricultural runoff, urban runoff, industrial outfalls, waste disposal	Muller *et al.*, 2020 [33]

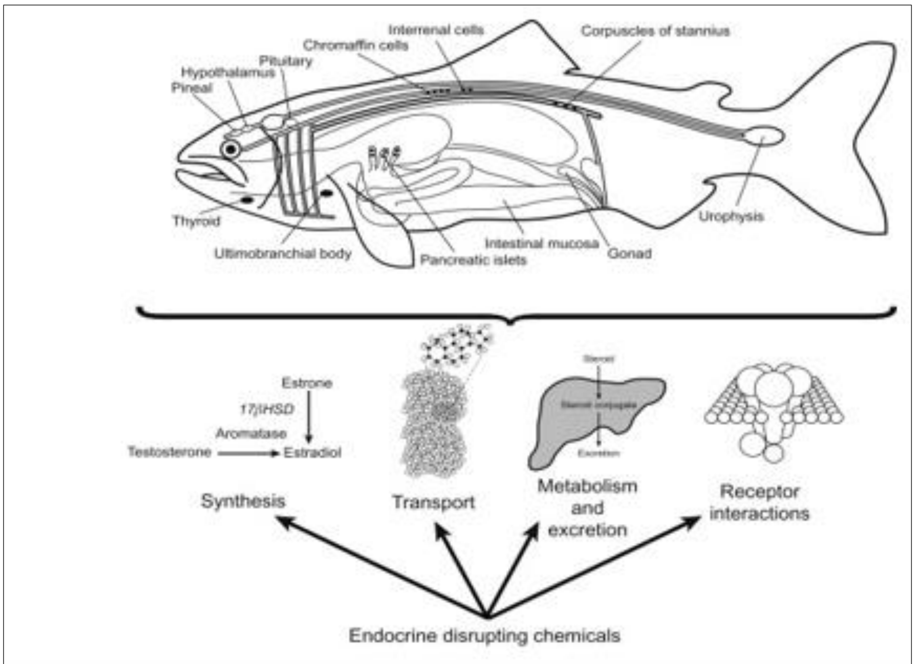
Mode of Action (MOA$_s$) of Endocrine Disruption in Fish:
The endocrine system in fish, as in other vertebrates, plays a crucial role in regulating various physiological processes. The modes of action of EDCs consist of affecting binding to receptors, hormone production, or hormone transmission. Several studies are focused on investigating the stimulation or disruption of estrogen, testosterone, and thyroid receptor signaling and its consequences on steroidogenesis (Amir *et al.*, 2021) [1]. EDCs can disrupt this delicate balance by mimicking or blocking hormonal signals. For example, compounds with estrogenic or anti-androgenic properties can interfere with reproductive processes in fish, leading to issues such as altered sex ratios, impaired reproductive success, and skewed development of sexual organs. Endocrine disrupting chemicals (EDCs) can interfere with normal metabolic functions by binding to nuclear receptor superfamily elements like liver X receptors, intrinsic androstane receptors, and peroxisome proliferator–activated receptors (PPARs). Nuclear receptors play a crucial role in various biological processes including growth, reproduction, the immune response, and metabolic processes (Delfosse *et al.*, 2015) [11].

The mechanisms of action of endocrine disrupting chemicals (EDCs) in fish, providing specific examples, the corresponding fish species are mentioned in Table 2.

Table 2: Mechanisms of action of endocrine disrupting chemicals (EDCs) in fish species

Mechanism of Action	Examples	Fish Species	References
Steroid Homeostasis	Alterations in sexual development	Rainbow Trout (Oncorhynchus mykiss)	Delbes *et al*., 2022 [10]
Hormone Receptor Activation	Disruption of gonad development	Zebrafish (Danio rerio)	Jobling and Tyler, 2003 [21]
Estrogenic Effects	Impaired reproductive performance	Fathead Minnow (*Pimephales promelas*)	Zhou *et al*. 2019 [35]
Androgenic Effects	Altered gene expression related to liver function and immune response	Zebrafish (*Danio rerio*)	Fan *et al*., 2019 [12]

EDCs can impact fish through various mechanisms, as highlighted in the following research findings. The MOAs of EDCs are highly conserved among vertebrates, indicating that compounds acting as estrogen receptor ligands in mammals can also bind to fish receptors with comparable affinities. Although Endocrine Disrupting Chemicals (EDCs) may have similar molecular actions across species, they can elicit a wide range of physiological and biological reactions, resulting in diverse outcomes (Robitaille *et al*., 2022) [39]. Understanding the (MOAs) of EDCs requires collecting information on biomarker responses in fish, including secondary sexual characteristics, gonadosomatic index, plasma steroids, vitellogenin (VTG), and gonad histology (Hutchinson *et al*., 2006) [19]. To evaluate harmful effects and biomarker responses which are indicative of particular mechanisms of action (MOAs), fish assays designed for EDC testing incorporate an array of outcomes at various biological levels. Omics technologies, such as DNA microarrays, offer insights into how EDCs interact with fish at the molecular level and mediate their effects. These technologies provide a platform for unraveling complex pathways affected by EDCs exposure and understanding the underlying molecular mechanisms driving adverse effects in fish (Oliveira *et al*., 2016) [37]. There is a growing focus on pharmaceutical waste as endocrine-disrupting chemicals. Synthetic substances used for medical purposes have been observed in the environment as a result of the direct elimination of household waste. For example, the synthetic progestin norethindrone (NET) is a sex steroid present in surface water. Exposing zebrafish to NET during early life stages led to changes in phototransduction and development of the eye. Moreover, it impacted glycerolipid /steroid metabolic processes and different protein utilization pathways (Bridges *et al*., 2019) [6].



Mode of action of EDC in fish (Kennedy et al., 2013)

Impact of EDCs on Fish Reproduction and Development

Studies have shown that EDCs can interfere with the reproductive endocrine systems of fish, leading to disruptions in sexual behaviors, intersex development, alterations in gamete quality, and gonadal abnormalities. These disruptions not only affect individual fish but can also have cascading effects on population dynamics and ecosystem health (Arcand-Hoy and Benson, 1998) [3].

Extensive research has been conducted on endocrine disrupting chemicals (EDCs), which interrupt the action of sex steroid hormones and have implications for sexual development and reproduction.

Sex hormones such as steroids play essential roles in various aspects of reproduction including differentiation of sex, gonadal development, and reproductive behaviors. Among the most potent sex steroid EDCs are receptor agonists like the synthetic estrogen 17α-ethinylestradiol (EE2) used in fertilization therapy and the growth-promoting androgen trenbolone (TB) utilized in livestock production (Lintelmann *et al*., 2003) [29]. There are over 900 compounds that have been reported as potential endocrine disruptors. Among these chemicals, more than 100 were considered to be of high or medium exposure concern (The Endocrine Disruption Exchange, 2011) [43].

Furthermore, over 200 of these chemicals have been found to have estrogenic actions. Evidence of exposure to EDCs can often be deduced from the observation of intersex and other modifications to gonadal growth in numerous populations of fish found in the wild. GSI refers to the ratio of total gonad weight to total body weight, serving as an indicator of gonad maturity and reproductive condition in fish. Prolonged exposure to EDCs, even at low concentrations, can lead to GSI alterations, which may negatively impact fish population. Various studies have documented GSI alterations in fish exposed to EDCs. For example, rainbow trout (*Oncorhynchus mykiss*) exposed to polycyclic aromatic hydrocarbons (PAHs) displayed decreased GSI values, indicating compromised gonad development. Similarly, zebrafish (*Danio rerio*) exposed to bisphenol A (BPA) experienced GSI reductions, reflecting impaired gonad development (Celino-Brady *et al.*, 2021) [8]. Table 3 represents some of the studies on the effects of EDCs on various fish species.

Table 3: The effect of EDCs on various fish species

Species	Effect	Reference
Medaka (Oryzias latipes)	Abnormalities in growth and reproductive development due to exposure to EDCs	Celino-Brady *et al.*, 2021 [8]
Roach (Rutilus rutilus)	Reduced reproductive capacity when exposed to treated sewage effluent	Jobling and Tyler, 2003 [21]
Roach (Rutilus rutilus)	Vtg and er1 expression are elevated in both sexes.Decrease in the quantity of type B spermatogonia in the testis	Kroupova *et al.*, (2014) [27]
Atlantic salmon (*Salmo salar*)	Susceptibility to EDCs during sex determination and smoltification processes	Jobling and Tyler, 2003 [21]
Fathead Minnow (*Pimephales promelas*)	Impaired reproductive performance due to EDC exposure	Armstrong *et al.*, 2016 [4]
Zebrafish (*Danio rerio*)	Altered gene expression related to liver function and immune response from EDC exposure	Thacharodi, *et al.*, 2023 [42]
Rainbow Trout (*Oncorhynchus mykiss*)	Disruption of gonad development leading to intersex characteristics	Jobling and Tyler, 2003 [21]
European Eel (*Anguilla anguilla*)	Feminization of male fish due to EDC exposure	Thacharodi, *et al.*, 2023 [42]
Common Carp (*Cyprinus carpio*)	Altered reproductive behavior and reduced fertility from EDC exposure	Thacharodi, *et al.*, 2023 [42]
Casper mutant transparent zebrafish (*Danio rerio*)	Delay between male and female adolescence	Lessman and Brantley (2020) [28]
Wild type and cyp19 a1a and nER mutant zebrafish (*Danio rerio*)	An increase in the quantity of male fish and a larger proportion of intersex fish	Song *et al.*, (2020) [41]
White suckers (*Catostomus commersoni*)	Both sexes experience delayed puberty and lowered testosterone, 17a,20b-dihydroxyprogesterone.	McMaster *et al.*, (1991) [30]; Munkittrick *et al.* (1992) [34]

Consequences for Fish Populations

The impact of endocrine disruptors on fish populations extends beyond reproductive challenges. Behavioral changes, compromised immune function, and altered metabolism are among the cascading effects observed in fish exposed to these contaminants. Additionally, the potential for EDCs to induce epigenetic changes raises concerns about long-term population resilience and adaptability. Epigenomic changes resulting from EDC exposure can lead to transgenerational effects in fish populations, influencing traits and behaviors across generations. Long-term exposure to EDCs over multiple generations can result in significant effects on fish populations, highlighting the need for comprehensive assessments of transgenerational impacts.

The examples of endocrine disrupting chemicals (EDCs) causing consequences for fish populations include Kraft mill effluents (BKME), Exposure to BKME has been linked to altered reproductive success in lake trout (*Salvelinus namaycush*). Roach (*Rutilus rutilus*): Treated sewage effluent exposure led to reduced reproductive capacity in roach. (Jobling, and Tyler 2003) [21]. Zebrafish (*Danio rerio*): Behavioral changes in zebrafish populations enhanced adverse effects of EDC exposure (Windsor *et al.*, 2018) [45]. Perch (*Perca fluviatilis*), Increased feeding rate in response to oxazepam exposure led to increased transfer and bioaccumulation of oxazepam (Heynen *et al.*, 2016) [18].

Bioaccumulation and Transgenerational Effects

EDCs have the potential to bioaccumulate in fish tissues, posing risks to human consumers who rely on fish as a food source. Moreover, research has revealed transgenerational impacts of EDC exposure, where fish offspring inherit health issues such as reproductive problems and reduced survival rates. This highlights the long-lasting consequences of EDCs on fish populations and the need for comprehensive regulatory measures (Windsor *et al.*, 2018) [45]. Polybrominated diphenyl ethers (PBDEs) have been found to bioaccumulate in fatty tissues of fish, with concentrations increasing as you move up the food chain (Hutchinson *et al.*, 2006) [19]. Polychlorinated biphenyls (PCBs) are persistent organic. Pollutants that bioaccumulate in fish especially in predatory species (Zhou *et al*. 2019) [35]. Exposure of fathead minnows (*Pimephales promelas*) to the synthetic estrogen diethylstilbestrol (DES) resulted in transgenerational effects, with third-generation offspring exhibiting impaired reproductive performance. Zebrafish (*Danio rerio*) exposed to bisphenol A (BPA) showed transgenerational effects, with fourth-generation offspring displaying altered gene expression related to liver function and immune response (Celino-Brady *et al.*, 2021) [8].

Evidencing Endocrine Disruption in Natural Fish Populations

There is substantial evidence of endocrine disruption in both wild and captive fish populations, resulting in feminized responses such as male fish producing vitellogenin (VTG) and producing oocytes in their testicles.Studies conducted in the United States have found that female mosquitofish (*Gambusia holbrooki*) treated with bleached kraft mill effluents and male fathead minnows (*Pimephales promelas*) exposed to cattle feedlot discharges containing the growth inducer trenbolone exhibited androgenic responses. This resulted in the female mosquitofish developing more masculine secondary sex traits (Ankley *et al*., 2009) [2].

Environmental Concerns and Regulatory Challenges

Fish, as integral components of aquatic food webs, serve as bioindicators of environmental health. Disruptions in fish populations due to endocrine disruptors can have cascading effects on entire ecosystems. Changes in fish abundance and behavior may influence predator-prey dynamics, nutrient cycling, and the overall balance of aquatic communities (OECD, 2023) [35-36].

The presence of EDCs in aquatic environments raises concerns about the broader ecological implications of these contaminants. Understanding the complex interactions between EDCs and fish physiology is crucial for developing effective strategies to mitigate their harmful effects on aquatic biodiversity. Mitigating EDC pollution in water proves challenging due to the numerous sources and intricate mechanisms through which these chemicals get into aquatic ecosystems. Adopting a singular, universal treatment strategy is impractical, necessitating a blend of end-of-pipe, source-directed, and use-oriented approaches to effectively address this complex environmental issue. Research efforts should prioritize the improved detection approaches including the exploration of bioassays and non-targeted investigations. These innovative approaches aim to enhance our ability to comprehensively assess the consequences of EDCs in water, supplementing conventional chemical analysis techniques (Gaw, *et al*., 2019) [15].

It is crucial to implement policy instruments that effectively manage the lifecycle of EDCs, encompassing their journey from source to end-of-pipe. The design of tools and regulations should be strategic, capable of addressing the adverse effects of endocrine disruption, even in situations where the specific chemical causing the disruption is unknown (Cunha *et al*., 2022) [9].

Risks to Human Health

As humans rely on fish as a significant source of nutrition, the presence of endocrine disruptors in fish raises questions about potential risks to human health. Bioaccumulation of these contaminants in fish tissues can lead to human exposure through the consumption of contaminated seafood, with potential implications for reproductive health, developmental disorders, behavior, and other health outcomes. Studies have shown that EDCs in fish can lead to a range of adverse effects, including reproductive problems, deformities, reduced survival rates, and altered DNA methylation. These harmful effects can be passed on to future generations, impacting not only the exposed fish but also their offspring and subsequent generations. Exposure to EDCs like pesticides, synthetic hormones, and steroids found in waterways can result in altered gene expression, deformities, decreased egg production, reduced hatching success, and changes in survival rates across multiple generation. Populations that are particularly at risk for EDC exposure include people with high fish consumption, the elderly, pregnant women and their fetuses, and people living near hazardous waste site (Caballero-Gallardo *et al*., 2017) [7]. The presence of EDCs in seafood raises concerns about the potential risks to human health, emphasizing the need for continued monitoring and regulation to mitigate these health hazards. Overall, consuming fish exposed to EDCs can lead to various health issues due to the disruptive effects of these chemicals on fish populations and the potential transfer of these effects to humans through the food chain.

Studies have shown associations between fish consumption and human risks attributable to EDCs such as triclosan, organochlorine pesticides, and bisphenol A (BPA) (Gallardo *et al*., 2017). Exposure to EDCs can lead to abnormalities in growth, reproduction, and behavior, with implications for population sustainability. Populations that are particularly at risk for EDC exposure include people with high fish consumption, the elderly, pregnant women and their fetuses, and people living near hazardous waste sites (OECD, 2023) [35-36]. Adverse effects associated with EDC exposure include birth defects, neurodevelopment conditions, reproductive health impacts, obesity, and metabolic diseases.

Future Directions and Research Needs

Moving forward, it is essential to expand research efforts to encompass a wider range of fish species and habitats to fully grasp the extent of EDC impacts on aquatic ecosystems. The identification of EDCs in complex mixtures remains a challenge, demanding the development of novel analytical techniques capable of adequately detecting and quantifying these compounds (Barra *et al*., 2021) [5]. Future research should focus on improving analytical tools to better understand the prevalence and impacts of EDCs in aquatic ecosystems. Mechanistic investigations are critical for determining the correlation between EDC exposure and identified consequences in fish populations. Understanding the mechanisms by which EDCs exert their impact may assist to locate the causes of contamination and execute remedial efforts (Mills and Chichester, 2005) [322]. Given the biological differences between species, it is important to consider how each species will respond to exposure to EDCs. EDCs may have varying impacts on different species. Therefore, it is necessary to use specific investigation techniques to accurately assess their ecotoxicological effects (Ankley *et al*., 2009; Knacker *et al*., 2010) [2, 26]. It is essential to enhance the monitoring of water quality initiatives, especially in the context of rivers and aquatic ecosystems, to efficiently track the concentrations and distribution of endocrine-disrupting chemicals (EDCs). Expanding the range of parameters analyzed and incorporating standardized techniques can contribute to a more comprehensive evaluation of water conditions and EDC exposure (Robitaille *et al*., 2022) [39]. Additionally, regulatory frameworks must be strengthened to address the risks posed by EDCs and safeguard both fish populations and human health.

Conclusion

The comprehensive review sheds light on the alarming prevalence and detrimental impact of endocrine-disrupting chemicals (EDCs) on fish populations. The evidence presented underscores the urgency of addressing this pervasive environmental issue. From disruptions in reproductive and developmental processes to alterations in behavior and immune functions, the adverse effects of EDCs on fish pose a significant threat to aquatic ecosystems. The harmful effects of EDCs in fish underscore the urgent need for proactive measures to mitigate their impact on aquatic environments. By raising awareness about the detrimental consequences of EDC exposure in fish, this review aims to catalyze further research, policy development, and conservation efforts to protect vulnerable aquatic species and preserve the integrity of our waterways

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