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Review

Cadmium as an Endocrine Disruptor That Hinders the Reproductive and Developmental Pathways in Freshwater Fish: A Review

Kaakarlu Shivakumar Vinanthi Rajalakshmi [1,†], Wen-Chao Liu [2,†], Balasubramanian Balamuralikrishnan [3,†], Arun Meyyazhagan [1], Govindharajan Sattanathan [4], Manikantan Pappuswamy [1], Kadanthottu Sebastian Joseph [1], Kuppusamy Alagesan Paari [1,*] and Jang-Won Lee [5,*]

1 Department of Life Sciences, School of Sciences, Christ University, Bangalore 560029, Karnataka, India; vinanthi.rajalakshmi@res.christuniversity.in (K.S.V.R.); joseph.ks@christuniversity.in (K.S.J.)
2 Department of Animal Science, College of Coastal Agricultural Sciences, Guangdong Ocean University, Zhanjiang 524088, China
3 Department of Food Science and Biotechnology, College of Life Science, Sejong University, Seoul 05006, Republic of Korea; bala.m.k@sejong.ac.kr
4 Department of Zoology, St. Joseph University, Chumukedima 797115, Nagaland, India; sattanathanphd@gmail.com
5 Department of Integrative Biological Sciences and Industry, Sejong University, Seoul 05006, Republic of Korea
* Correspondence: paari.ka@christuniversity.in (K.A.P.); wintrelove@sejong.ac.kr (J.-W.L.)
† These authors contributed equally to this work.

Abstract: Cadmium (Cd) is a non-essential element with sub-lethal effects even at low concentrations. The persistent nature of Cd and its tendency to bioaccumulate eventually create harmful effects on water biota, including fish. Cd affects various aspects of hormonal action in fish since it bioaccumulates in the endocrine system and hinders the synthesis, secretion, and metabolic activity of hormones, causing severe damage along the hypothalamus–pituitary–gonadal axis. Linking reproductive and developmental impairments in fish with ecologically relevant concentrations of individual metals can be challenging due to the complexity of aquatic ecosystems. This review deliberated the significant and novel trends of toxicological difficulties and approaches, including elucidating environmental sources' bioavailability and Cd-induced toxic effects in freshwater fish. Both acute and chronic exposure to Cd can cause a range of adverse effects, such as growth inhibition, impaired reproductive capacity, endocrine disruption, and developmental abnormalities in freshwater fish, as evidenced by the present review. These investigations support the concept of Cd as a naturally available pollutant that causes irreversible damage in fish. These findings will help to understand the etiology of environmental circumstances that pose substantial dangers to fish health and are also crucial for preventing and treating exposure-related reproductive disturbances in freshwater fish due to environmental pollution.

Keywords: cadmium; endocrine disruptor; freshwater fish; metallothionein; HPG axis; reproductive and developmental impairments

Key Contribution: Cadmium has been found to cause cellular-to-organ-level damage in fish. This review examines the toxicity of cadmium exposure along the hypothalamus–pituitary–gonadal–liver axis, focusing on the reproductive and developmental alterations in freshwater fish.

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1. Introduction

The contamination of the freshwater environment with trace elements discharged from anthropogenic activities and natural resources has become an eco-environmental concern over the past few decades [1]. Trace elements refer to any metallic elements that occur in nature, possess a relatively high density (3.5 to 7 g cm^{-3}), and are toxic even at ppb

levels [2,3]. Some metals, Cu, Fe, Mn, Co, Zn, and Ni, are essential micro-nutrients required for various biochemical and physiological functions in biological systems [4,5]. In comparison, non-essential metals such as cadmium (Cd), Pb, and Hg with no established biological processes are known to induce multiple organ damages even at trace concentrations and are hence considered a burden when they enter the host [5,6]. However, each metal is recognized to have distinct physicochemical characteristics that bestow toxicological modes of action [7].

Among the trace elements, Cd is considered one of the most ubiquitous and toxic chemicals that adversely affect the permanence of freshwater biota [8]. Cadmium occurs in water or environmental matrices (such as sediment, aerosols, etc.) and accumulates in aquatic organisms such as mollusks, crustaceans, and fish [9,10]. Fish are the central community that reflects the quality of aquatic systems by accumulating large amounts of toxic metals, as they are one of the topmost consumers in the aquatic food chain [11]. Freshwater fish have also become the primary route for transporting Cd along the food chain due to their significant contribution to the diet of their higher trophic levels and rural communities [12,13]. The bioaccumulation of freshwater fish organs with Cd led to an impairment in their feral populations by altering their reproductive and physiological functions [12]. Once absorbed, the Cd is moved by circulation to either a storage location (bones, liver) or carried further to other organs such as the kidneys, gills, muscles, and gonads [14]. The chronic exposure of fish to Cd can disrupt the natural system and may endanger the affected fish species. Therefore, hazardous metals in freshwater aquatic systems are currently a major issue for the sustainability of the ecosystem and living things. Since Cd is known to have many harmful impacts, such as neurotoxic, genotoxic, and endocrinological effects on fish, it is essential to monitor its bioaccumulation patterns [15,16].

The exposure of freshwater biota to endocrine-disrupting metals like Cd can have significant implications for the population dynamics of affected fish species. Reduced fertility, skewed sex ratios, and altered reproductive behavior can lead to decreased population size and genetic diversity, which can have long-term effects on the survival and viability of a species [17]. Due to the crucial involvement of the endocrine system in regulating homeostasis and other physiological processes, the study of the effects of such a disruption may be significant. The stimulation of the endocrine system via the hypothalamicpituitary–gonadal (HPG) axis has been the center of outstanding research on how animals react to stressors [18]. In response to a wide range of stressors, including endocrine-disrupting metals, the hypothalamus pumps releasing factors along this axis, stimulating the production of hormones. Emerging research suggests that fish can be a potent biological model for assessing the hormonal status and viability of aquatic environments. They can be a powerful species model for examining endocrine signaling pathways related to testicular function, spermatogenesis, and their interaction with reproductive behavior.

The impact of Cd on the endocrine disruption of freshwater fish is a multifaceted study dealing with the abnormalities caused by inducing alterations in the normal functioning of the endocrine system. However, decades-long research dealing with fish health related to environmental conditions impacted by Cd has revealed an increasing testimonial of altered developmental effects on the reproductive health of fish along the HPG axis. Surprisingly, only a few works from the literature address the action and biological consequences of Cd as an endocrine disruptor in freshwater fish. Hence, this review aimed to accumulate the significant hormonal changes caused by the bioaccumulation of Cd in the bodies of freshwater fish from different perspectives. It also elucidates the mechanism of action by which Cd affects the circuits of the HPG axis in controlling reproductive and developmental pathways in freshwater fish.

2. Sources of Cadmium Contamination in Aquatic Systems

Cadmium is relatively minor in the Earth's crust, with concentrations ranging from 0.1 to 0.5 ppm, but it can be found in small amounts in zinc, lead, and copper ores [19,20]. Natural Cd emissions to the aquatic biota can result from volcanic eruptions (60%), for-

est fires, sea salt aerosol formation, the weathering of rocks, or other biological factors (Figure 1). Refined Cd is being used in the manufacturing of electrodes in batteries (83%), the production of Cd-containing pigments (8%), electroplating and coatings (7%), plastic stabilizers (1.2%), nonferrous alloys, solar devices, and other applications (0.8%) [21,22]. With historical and current activities, water systems near these Cd-emitting industries have revealed a significant increase in Cd levels in the water (<1.0 to 77 µg/L), sediment, and aquatic organisms [19]. The aquaculture project for fish farming installed in part of a disused mining pool showed the accumulation of Cd in the tissues of the freshwater species *Barbonymus schwanenfeldii*, *Cyclocheilicthys apogon*, *Hampala microlepidota*, *Hemibagrus nemurus*, *Mystacoleucus marginatus*, and *Oreochromis niloticus* [23,24].

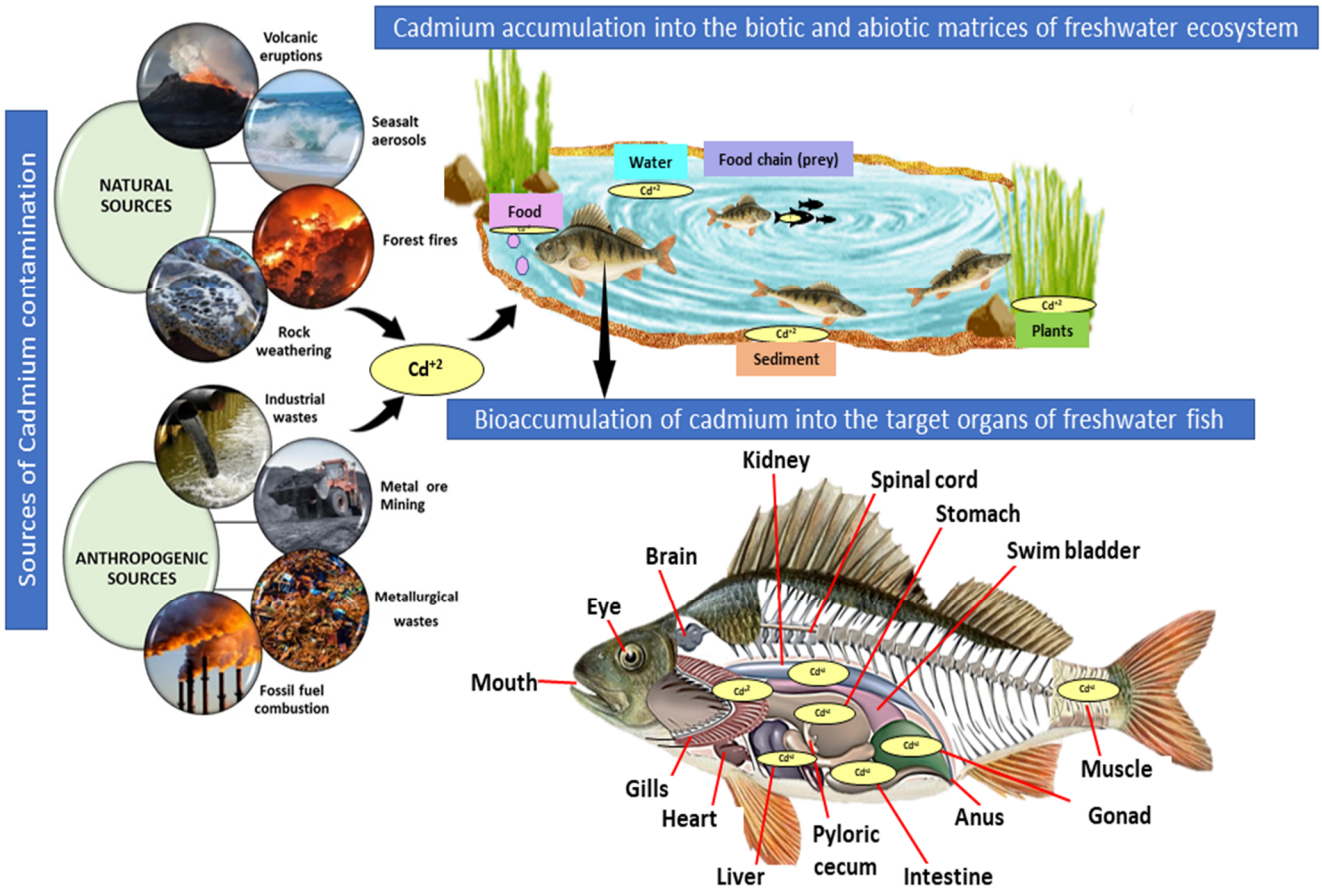

Figure 1. Sources of Cd contamination and accumulation in the freshwater ecosystem.

In freshwater ecosystems, Cd can exist as a hydrated ion or as ionic compounds with other inorganic or organic substances [25]; while soluble forms (sulfate and chloride salts of Cd) may migrate in water [26], Cd is relatively immobile in insoluble complexes [27]. Cd is a serious global environmental pollutant and has the potential to alter higher trophic levels for centuries. Freshwater fish could be susceptible to Cd exposure and subsequent toxicity through dietary and waterborne exposure [28–30]. The negative impact of chronic Cd exposure (3 to 6 months) was reported in channel catfish, *Ictalurus punctatus*, with a reduced survival rate and altered growth patterns [30]. Similarly, another study using rainbow trout, *Oncorhynchus mykiss*, showed that prolonged exposure to Cd reduced the accumulation rate of Ca in gills, which is possibly a result of a blockage of Ca channels by cytosolic Cd [31]. The WHO recommended levels of Cd in environmental matrixes range from 0.01 to 1 mg/kg in soil and 3 µg/L in water, so partitioning the accumulation of Cd between the sediment and water is a key element in determining its availability to aquatic organisms. The pathways of Cd uptake and accumulation can vary depending on the

species present and their feeding habits. For example, predatory fish feed on smaller fish that have accumulated higher levels of Cd in their tissues than herbivorous fish that do not consume other fish [32]. Cadmium concentrations in benthic macroinvertebrates and fish tissues were highly linked, indicating metal transfer via a feeding mechanism (Figure 1). As a result, fish that live in contaminated waters collect Cd in their tissues [33].

3. Bioaccumulation of Cadmium in Freshwater Fish

The tendency of trace elements to enter and alter a biological system is referred to as bioavailability [34]. Even though bioaccumulation and bioavailability are distinctly discussed in direct and indirect exposures, both processes are interdependent in natural systems [35]. Fish bioaccumulate essential nutrients regularly, including proteins, lipids, fats, amino acids, trace vitamins, and minerals [36]. Many harmful trace elements accumulate in freshwater biota through bioconcentration, which can eventually threaten freshwater fish and those who consume them [37].

As a hazardous metal, Cd may serve as a stress inducer in fish, which may impart toxicity to the aquatic ecosystem even at a very low concentration [38]. Fish absorb Cd through direct contact with a polluted medium or through the intake of food contaminated with Cd (Figure 1). Different fish species living in the same habitat may acquire varying quantities of Cd in their tissues due to differences in their living and dietary patterns. According to studies, *Serranochromis thumbergi*, a predatory fish, has shown the least accumulation of Cd in their tissues, which can be due to the inverse correlation of metal concentration with the trophic level. Since fish gills are constantly exposed to Cd ions in their aquatic environment, their metal intake significantly differs from that of terrestrial species [39]. Gills are considered the primary entrance site for the penetration of dissolved Cd metals into the body of freshwater fish. Generally, Cd uptake could occur through passive transport, the process by which metal ions enter a fish's body through diffusion. Cd can also enter through carrier-mediated transport, which involves the binding of metal ions to specific proteins on the surface of chloride cells in the gills.

In contrast, the Cd ions linked to any chemical compounds are devoured by intestinal endocytosis [40]. Cadmium that is absorbed across the gills or intestinal walls is circulated, attached to the transport proteins, and transported to various tissues throughout the body [41]. A few immunochemical studies revealed that the dietary uptake of Cd by rainbow trout via the gut could accumulate in the chloride cells of the gills via calcium channels, thereby stimulating metallothionein (MT) expression [42]. The gastrointestinal tract facilitates Cd absorption in fish, and a modest proportion of Cd available in a dissolved form may be assimilated directly through contact with the skin [43]. Dietary Cd intake had a considerable influence on gastrointestinal Cd absorption and disposal in the gut (particularly pyloric caeca) and non-gut tissues (liver, gills, and kidney) of fish [44].

Fish adsorb dissolved Cd in its free ionic form, which is indirectly attained via diet when Cd is ingested into organisms of lower trophic positions [20,45]. Distinct Cd forms influence the effect of Cd on aquatic organisms, each with a toxicity range and bio-concentration factors. The free divalent ion (Cd^{2+}) will be the dominant and most bio-available toxic form in well-aerated freshwater bodies containing low carbon contents (Figure 2) [12]. Exposure to this form stimulates the production of a small, cysteine-rich, low-molecular-weight metal-binding protein MT in the liver that binds to metals such as Cd [46]. It reduces toxicity by limiting its availability to cells and tissues [47,48]. Long-term exposure to Cd causes chronic toxicity and may result in larval mortality and pathophysiological effects in fish such as *Heteropneustes fossilis* [49], such as stunted and decreased developmental rates in juvenile channel catfish [30]. Temporary growth reduction, reproductive endocrine disruption, and incomplete embryo development have been observed in juvenile *Colossoma macropomum* and *Oreochromis mossambicus* [50,51].

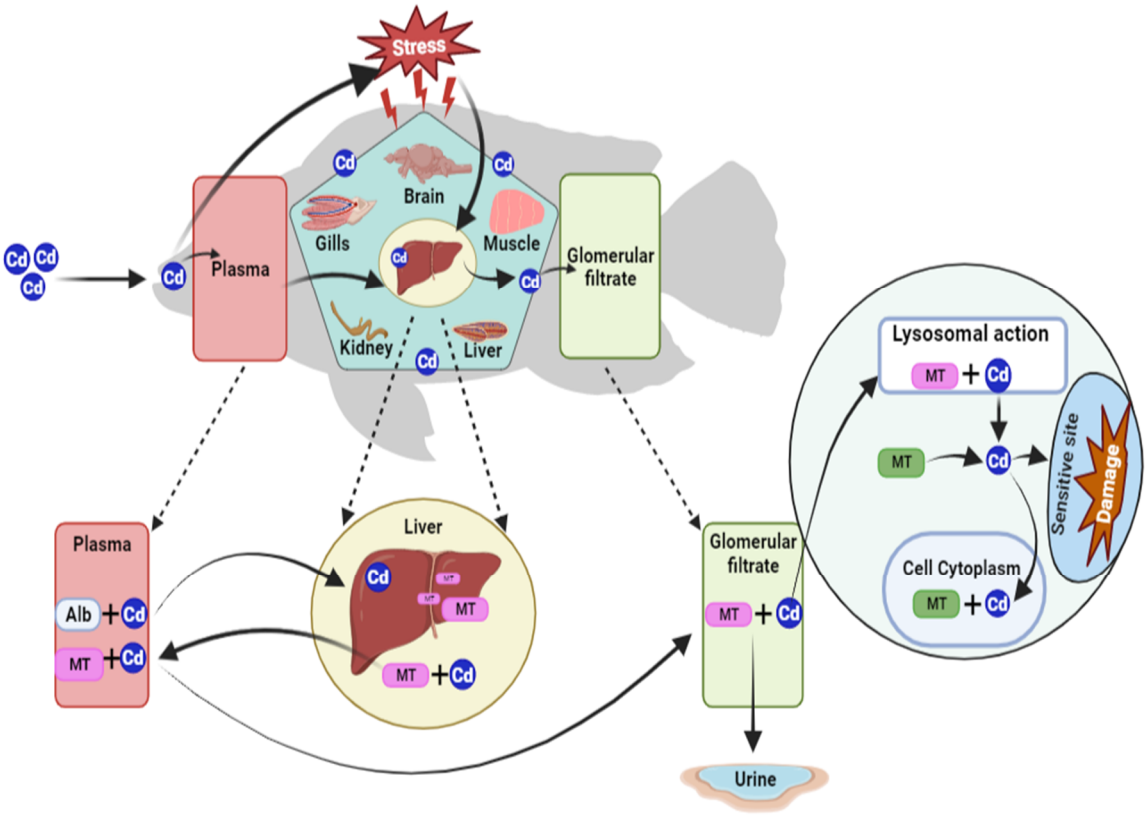

Figure 2. Mechanism of cadmium uptake, transportation, detoxification, and glomerular filtration in freshwater fish.

4. Metallothionein as a Cadmium Detoxifier

The production of MT is a well-known metabolic detoxification mechanism for trace elements, and it has been well documented that exposure to Cd can induce the expression of MT [52]. A study demonstrated a positive correlation between Cd accumulation and MT induction in the tissues (liver > kidney > gills > brain) of freshwater catfish, *Clarias gariepinus*, exposed to waterborne Cd [53]. The toxic effects are partially a function of the amount of free Cd^{2+} relative to MT-bound Cd (MT-Cd), which is available to interact with cellular components such as enzymes. Because Cd exposure causes MT induction, MT levels can be employed as a biomarker for acute waterborne Cd contamination. MT induction was reported in various tissues of juvenile rainbow trout, with the liver showing the highest levels, followed by the kidney and gills. Negligible amounts were found in the brain and muscles (Figure 2) [54]. Another study showed higher concentrations of MT in the posterior kidney of *Oncorhynchus kisutch*, suggesting its association with excretory functions [55].

MT plays a crucial role in the liver's dealing with elevated levels of Cd. Following absorption, Cd detoxification occurs so that Cd is bound to albumin and transported to the liver, where it binds to MT [56]. The MT-Cd complex is then transported to lysosomes, where Cd is released, and free ions are excreted into the tubular fluid before eventually being eliminated in the urine (Figure 2). This process is essential for protecting the liver from Cd's toxic effects and preventing Cd accumulation in the body [57]. Cadmium binds to MT, which serves as a protective mechanism against the harmful effects of Cd by sequestering the metal and preventing it from interacting with other proteins like enzymes, resulting in cellular protection. Metallothionein is also important in regulating the levels of zinc and copper, which are essential for normal cellular function. A few studies indicated that Cd may compete with other metals (Zn and Cu) for binding sites on MT and non-MT proteins in the tissues of rainbow trout that were exposed to Cd and a mixture (Cd + Zn + Cu) through water and food sources. Despite Cd levels remaining lower than the MT binding

capacity in both exposure groups, the metallic mixture exceeded the MT binding capacity in all tissues of Cd-exposed fish [54,58].

5. Cadmium as an Endocrine Disruptor in Freshwater Fish

Fish with a high concentration of Cd in their tissues may exhibit modest endocrine changes that impede reproduction [51]. In toxicity studies, several reproductive and developmental biomarkers have been employed, including:

1. Enzymatic activity: Changes in the activity of certain enzymes can indicate the presence of toxic substances in the fish body. For example, Cd burden in fish can affect the activity of enzymes involved in steroid hormone synthesis or detoxification.
2. Pituitary gonadotropins: alterations in gonadotropin levels can indicate a disruption of the HPG axis, leading to downstream effects on reproductive development and function.
3. Steroid hormones: changes in hormone levels can lead to developmental abnormalities, reproductive dysfunction, or other adverse effects.
4. Growth abnormalities: exposure to toxic substances can impair normal growth and development in fish, causing deformities or other abnormalities that can have adverse effects on survival and reproductive success (Table 1) [59].
5. Vitellogenin: This yolk precursor protein, produced by the liver in response to estrogen stimulation, shows elevated levels of vitellogenin in male fish exposed to estrogenic compounds. This can indicate feminizing effects and a disruption in reproductive function (Figure 3) (Table 2).
6. Gonadal structures: an examination of gonadal tissues can reveal abnormalities such as atrophy, hypertrophy, or intersex characteristics, indicating possible exposure to endocrine-disrupting compounds.

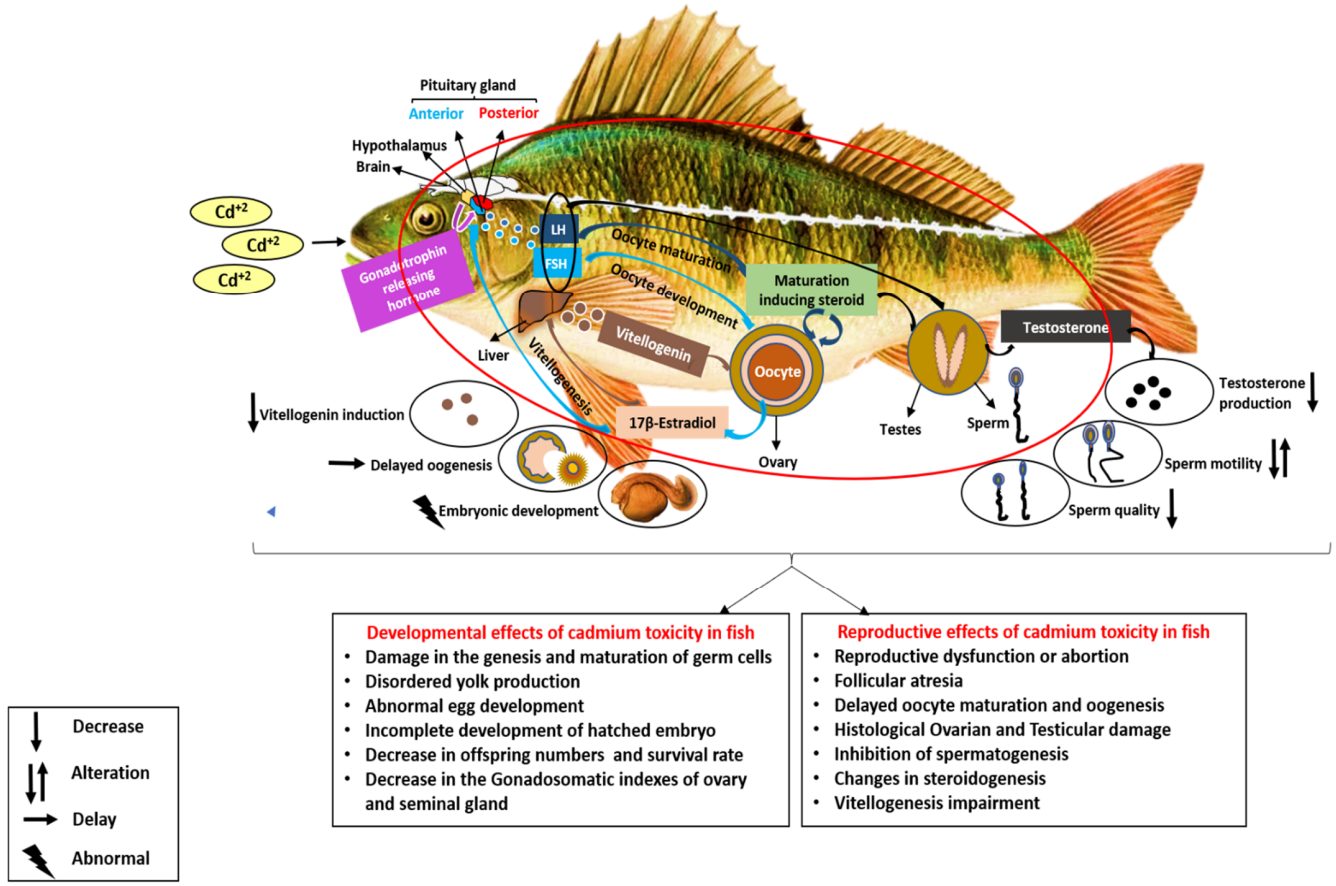

Figure 3. Representation of cadmium effects on development and reproduction in freshwater fish.

Cadmium can cause premature and delayed hatching, deformed larval development, and mortality in newly hatched larvae (Figure 3). Indeed, these developmental alterations during the embryonic stage decrease the number and quality of progeny [60,61]. However, these factors, evaluated over a specific period, provide insights into the reproductive damage that can be affected by environmentally relevant concentrations during reproductive phases. So, the analysis of biomarkers must be assessed to determine the potential impacts of environmental contaminants on fish populations and ecosystems.

The involvement of various endocrine pathways in reproduction and development during Cd exposure in fish has been studied [62,63]. However, the mechanisms underlying these effects are not fully understood. Previous studies indicate that Cd can impact gene transcription and interfere with the normal functioning of fish hormones, such as estrogen, testosterone, and thyroid hormones [64]. The exposure of fish to Cd triggered biological responses involving oxidative damage in intracellular molecules by generating ROS in cells (Figure 4) [65–67]. Cadmium has been shown to interfere with gonadal development and steroidogenesis. This interference can be caused by the release of cell membrane receptors, triggered by the activation of the protein kinase C signal pathway. In vitro experimental studies on Cd toxicity show that it impedes LH and FSH binding to receptors and alters steroid production in ovarian cells [68]. The regulation of steroidogenic acute regulatory protein production through activating the xenoestrogen receptor in the ovary of the largemouth bass, *Micropterus salmoides*, was also reported [69]. However, further studies are needed to comprehend how transcriptional factors interact with Cd^{2+} to regulate the activity of steroidogenic genes. The regulatory action of FSH on gonadal steroid hormone synthesis has been altered when the Cd interferes with calcium ions (Ca^{+2}). Cadmium can directly influence gene transcription by substituting zinc (Zn^{2+}) in the DNA-binding zinc-finger domain. It particularly changes the P_{450} side-chain cleavage (P_{450} scc) gene activity by turning on a cis-acting element in the promoter (regulatory) region [70]. The receptor of estrogen, which serves as a transcription factor and is ligand-dependent, typically mediates the impact of estrogens. The expression of the estrogen receptor gene in the liver of rainbow trout can be increased by estrogens [71]. It has been reported that Cd reduces the transcription factor's binding with DNA, suppressing the estrogen receptor's biological activity in rainbow trout [72].

The combined effect of Cd coupled with estradiol (E2) on the expression of multiple genes involved in juvenile rainbow trout fish reproduction was assessed using a relative reverse transcription PCR methodology. Cadmium decreased vitellogenin and both rtERα isoforms' (rtERαS, rtERαL) mRNA levels in the liver in response to E2 in a dose-dependent manner. However, in fish brain tissue, the treatments with Cd alone reduced the expression of rtERαL and showed a significant enhancement in the expression of salmon GnRH genes [62]. These outcomes support the notion that Cd acts as an endocrine disruptor by inhibiting estrogen-stimulated genes in the liver and having a central impact on GnRH in the brain. Cadmium has been found to suppress gonadal development during the pre-reproductive season and impair protein synthesis in adult fish ovaries [73]. In vitro and in vivo experiments linked to Cd^{2+}-induced developmental defects, early hatching, growth retardation, increased mortality, and testicular hormone imbalance in the embryos of various fish species, including *Rhamdia quelen* [74], Ide, *Leuciscus idus* [75], and rainbow trout [76,77]. During the exposure of the eggs and larvae of Medaka, *Oryzias latipes*, to 0.1–1 ppm of Cd, the eggs showed more accumulation than the larvae [78].

Cadmium in larvae is readily transported into different organs or tissues. In contrast, most of the Cd in eggs is found in the chorion and is rarely carried into the embryos due to its resistance to Cd. However, their hatchability and survival rate decreased, and noticeable changes in their behavior, such as erratic swimming and a loss of equilibrium, were observed. However, the Japanese medaka raised from eggs exposed to 0–10 mg/L of Cd for two weeks and re-exposed to Cd at the adult stage did not exhibit significant changes in their reproductive capacity, except for some alterations in male steroid and vitellogenin levels [78]. Similarly, there were no changes in gonadosomatic indexes, estrogen

receptors, or vitellogenin. At the same time, steroid hormone secretion was considerably decreased in both sexes of Japanese medaka subjected to Cd (0–10 ppb) for an exposure period of 7 weeks [79]. With findings from multiple experimental examinations, it can be postulated that the impacts of Cd toxicity on reproductive and developmental outcomes (Tables 1 and 2) are more pronounced in the hypothalamic–hypophyseal–gonadal axis.

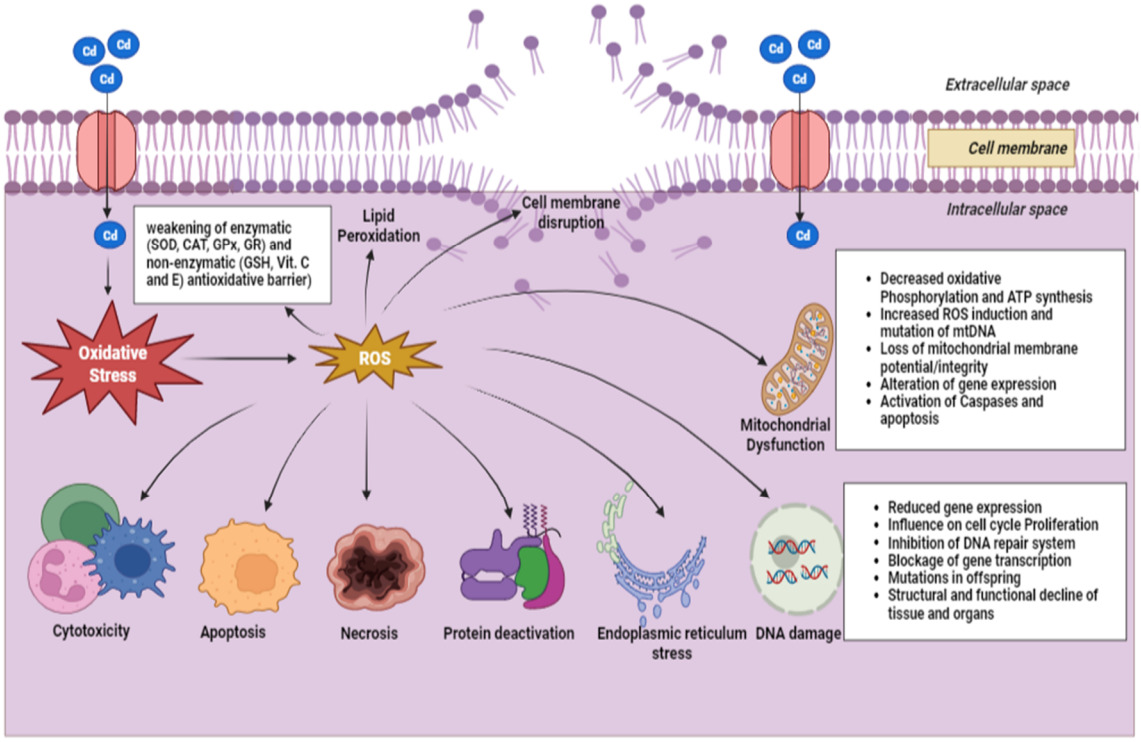

Figure 4. Cadmium-induced oxidative stress damages inside the cell.

5.1. Reproductive Effects of Cadmium in Freshwater Fish

The reproductive toxicity of trace elements frequently depends on the degree, duration, and mode of exposure, the distribution and accumulation patterns in tissues, and the rate of depuration. The toxicokinetics of Cd in fish are additionally influenced by biological parameters, such as nutritional conditions, age, species, and sex [80]. Cadmium is known as an endocrine disruptor and is regarded as a metallo-estrogen due to its various effects on the hormones and enzymes involved in reproduction. This endocrine disruptor activity can be studied through the HPG axis due to its importance and control over the reproduction of fish. The bioaccumulation of Cd in fish disrupts endocrine mechanisms in producing hormones' active synthesis, discharge, and metabolism. Acute exposure to sublethal Cd concentrations influences alterations in endocrine status and carbohydrate metabolism in *O. niloticus* [81]. Research on in vitro and in vivo studies investigating the impact of Cd toxicity on freshwater fish has observed that salmonids are more sensitive to Cd [82]. Several studies suggest that even modest levels of Cd exposure disrupt the action of sex hormones in both the male and female reproductive systems of fish. Cd interferes with the biogenesis of androgens, estrogens, and progesterone in both in vivo and in vitro tests, which is associated with impaired sex differentiation and gametogenesis [83].

On the other hand, it can potentially bind both the estrogen and androgen receptors. Different frameworks of the HPG axis can be used as biomarkers to evaluate the level and operation of the disruption caused [84]. The survival efficacy of the offspring produced is also affected due to the consequences of Cd toxicity on sex hormones. A study on rainbow trout suggested that Cd acts as an endocrine disruptor, directly impacting estrogen receptor activity and further affecting several estrogens signaling pathways, causing deformities in

egg development in gonads and disordered yolk formation [85]. In *O. niloticus*, exposure to 143.78 and 161.15 g/L Cd concentrations for 30 and 60 days reportedly deteriorated the amount of spermatocyte, thus forming immature spermatids [86]. A study evaluated 1 mg/g of Cd with several testicular irregularities in the Sertoli and Leydig cells of red tilapia, eliciting abnormal offspring [73].

The administration of Cd in the male *Juvenile tilapia*'s diet led to the percolation of blood, decreased sperm motility, and fibrosis in the lobular walls [73]. Chronic Cd exposure through dissolved Cd and food intake induced testicular damage in *O. niloticus* [86]. An experiment conducted on pejerrey fish, *Odontesthes bonariensis*, by exposing them to Cd for about 14 days resulted in morphological damage to the gonadal organs, i.e., a truncation of spermatic lobules, fibrotic testis–ovarian structures, and pyknotic cells [87]. The probability of Cd exposure can cause toxic effects by intensifying sperm quality due to decreased cell motility and larval mortality in *Prochilodus magdalenae* [63]. It can also affect sperm maturation in the common snook, *Centropomus undecimalis* [88]. An in vitro study conducted with sperm cells of zebrafish, *Danio rerio*, showed substantial alterations in the motility rate, the curvilinear motion of sperm, and DNA integrity (Figure 4) when exposed to different Cd concentrations [89]. A similar disruption resulted from pejerrey fish being exposed to 0.25 µg/L of $CdCl_2$, adversely affecting sperm quality, fertilization rate, hatching probability, and mortality percentage [90].

The fish common carp, *Cyprinus carpio*, collected from Cd-polluted zones showed significantly lower testosterone production than in unpolluted riverine zones [91]. In vitro studies on rainbow trout exposed to $CdCl_2$ toxicity showed that it induced a testicular steroidogenic imbalance [92]. In contrast, sub-chronic Cd exposure showed decreased gonadal hormonal secretion in male Medaka [79]. A Cd concentration of even 5 and 10 µg/L was proven to be harmful to zebrafish sperm cells. Lower spermatozoa movement affects these species' fertility rate, lowering their longevity. The mentioned concentrations of Cd, 5 and 10 µg/L, led to a decrease in the plasma membrane integrity. This is essential in maintaining the membrane's selective permeability, thereby affecting the metabolism of the spermatozoa [89]. Increased DNA damage may also lead to an increased chance of mutation among offspring (Figure 4). The accumulation and influence of Cd also affect the gonadal structure and, thereby, the reproductive function [93]. A 1 mg/g Cd dosage fed to red *tilapia* caused structural degradation of the spermatogenic elements and decreased sperm number and motility [73]. An earlier study showed that *Puntius sarana* was susceptible to a 20 mg/L Cd dose. This experiment was conducted over 30 days, and the after-effects concluded testicular injury [94]. Males of *Pimephales promelas* exposed to a concentration of 50 mg/L showed a decreased rate of spawning and fertility [95]. Variations in the male secondary sexual characteristics, including fewer nuptial tubercles, were also detected in the study at a concentration of 25 mg/L. Research also observed testicular changes in *Gymnotus carapo*, with the appearance of necrotic areas and germ cell reduction at a dosage of 5 M. A dosage of 20 M induced a further decrease in the germ cell number and was followed by the complete absence of the cells at a dosage of 40 M. This dosage of 40 M might also be capable of causing irreparable damage to the testes due to the cellular changes brought about by the Cd toxicity. Furthermore, germ cell genesis and maturation are affected by Cd vulnerability. Spermatocyte alteration at dosages of 20 and 30 M was also detected in the study [96].

Cadmium may collectively have disruptive effects on the production of gonadal steroids by modulating either the hypothalamus–pituitary axis or the gonadal cells' capacity to stimulate androgen production [64]. A higher Cd exposure induces dysfunctional ovarian growth, spawning errors, and the detachment of the follicular membrane from the underlying ooplasm. In comparison, exposure to a low dosage of Cd minimizes the breeding egg count and hatchability percentages and increases fry abnormalities. Juveniles of red *tilapia* fed with different doses of Cd were found to have altered gonadal structure, ovarian maturation, reproduction, and developmental parameters (Figure 3). A Cd dosage of 1 mg/g changed the assembly of the ovaries by bringing about the deformity in the

ova. The follicle walls were dissociated from the ova along with a greater vacuole count, eventually risking the offspring growth rate of red *Tilapia* [71]. A study analyzed the destructive effects of minimal concentrations of Cd exposure, specifically 0.1, 1, 10, and 100 µg/L, on the HPG axis in *R. quelen* females. It found no considerable changes in the plasma levels of testosterone, estradiol, hepatic, and gonadosomatic indexes after exposure, as reported in reference [84]. The accumulation of Cd in the ovaries induces the stimulation of estrogen receptors. However, the expression of vitellogenin was markedly reduced in *O. niloticus* when exposed to Cd at concentrations of 70.32 and 143.78 µg/L for 30 days and at 143.78 µg/L for 60 days, respectively [86]. Varying effects on sex-related gene expression in gonads were observed, along with ovarian injuries and down-regulated vitellogenin expression in the ovaries. On further examination of the maternal transfer of the Cd metal, the results revealed the passing of the accumulated metal onto the eggs but not the fry.

Cadmium toxicity could also alter different parameters related to the reproductive axis. *Tilapia zillii* exhibited deterioration in the oocyte's granulosa, restricting oocyte maturation and enhancing ovarian atresia due to Cd toxicity [97]. In goldfish, a Cd dose of 10 mg/g ceased ovarian development at the vacuolization stage, resulting in the termination of the ovulation process in the females [29]. Similar results were observed in an experiment executed for a female *Prussian carp*, *Carassius gibelio*, with a 4.0 mg/L dose of Cd [98]. Another study reported an alteration in the ovaries when subjected to concentrations of 50, 100, and 200 µg/L for 60 days (the dosages were higher than the environmentally relevant concentration of 5 µg/L of Cd) [84]. Several experimental data indicated that Cd's negative impact on gonadal development might be due to fluctuations in steroid hormonal production and expressions of sex-related genes (Tables 1 and 2).

Table 1. Reported reproductive effects of cadmium in freshwater fish.

Fish Species	Features of Fish			Cadmium Concentration	Time of Exposure	Effects	References
	Stage	Length	Weight				
Carassius auratus	Sperm and egg	NA	NA	10 mg/g	NS	Discontinuation of ovulation	[29]
Danio rerio	Reproductive phase	NS	NS	5–10 µg/L	10 min	Sperm motility affected and disintegration of the plasma membrane	[89]
Gymnotus carapo	Sexually matured	NS	NS	5–40 M	24–96	Reduced germ cells	[96]
Oreochromis niloticus	2-month-old	12.38 ± 0.92 cm	58.80 ± 13.84 g	70.32–143.78 µg/L	30 and 60 days	Altered effects on sex-related gene expression and deformed follicle	[86]
Pimephales promelas	Sexually matured	NS	NS	50 mg/L	21 days	Reduced fertility and spawning	[95]
Oreochromis sp. (Red tilapia)	Sexually matured	8.2 ± 2.5 cm	38.3 ± 2.5 g	1 mg/g	NS	Decreased sperm motility and deformed ova	[73]
Rhamdia quelen	Adult	20.0 ± 4.4 cm	70.5 ± 38.0 g	>100 µg/L	NS	Increased hepatic vitellogenin expression	[84]

Table 1. *Cont.*

Fish Species	Features of Fish			Cadmium Concentration	Time of Exposure	Effects	References
	Stage	Length	Weight				
Carassius auratus	fingerlings	NS	6 ± 1.2 g	0.5 g	14 days	Pronounced release of AST, ALT, Cortisol, and glucose concentrations	[17]
Danio rerio	7 weeks old	NS	NS	20 µg/L	48 days	Reduced gonadosomatic index and 17 β-estradiol and vitellogenin concentrations in plasma	[18]
Siganus rivulatus	8–14 months	19.8 ± 1.9 cm	NS	NS	NS	Alterations in the levels of testosterone, β-estradiol, and progesterone hormones	[83]
Colossoma macropomum	NS	NS	NS	0.6, 1.2 and 1.8 mg/L	NS	Increased SOD enzyme activity and LPO levels in sperm cells. Impairment of fertilization and hatching rate of the oocytes.	[50]
Odontesthes bonariensis	Adult	14.82 ± 0.56 cm	41.17 ± 6.51 g	0.25 µg/L	14 days	Decreased follicle-stimulating hormone transcript levels and showed structural damages in spermatic lobules, fibrosis, testis, and ova	[87]
Tilapia zilli	Adult	11.5–22.8 cm	32–235.4 g	0.57 ± 0.11 µg/g wet wt.	Annual	Increased atresia, degenerative and necrotic changes in the oocytes, and conversion of ovarian to testicular cells.	[97]
Carassius gibelio B.	Adult	23.25 ± 0.49 cm	204.65 ± 12.58 g	0.4 or 4.0 mg/L	3–5 months	Decreased GSI, impaired LH secretion during exposure, and stimulation of spawning	[98]

Table 1. *Cont.*

Fish Species	Features of Fish			Cadmium Concentration	Time of Exposure	Effects	References
	Stage	Length	Weight				
Danio rerio	Embryo	NS	NS	NS	72 h	Inhibition of Estradiol induction of Aromatase-B in radial glial cells	[99]
Pimephales promelas	12 months old	NS	NS	5 µg/L	21 days	Impaired gametogenesis, reduced steroid levels and vitellogenesis, and delayed oogenesis.	[100]

Note: NA—not applicable; NS—not specified.

Table 2. Reported developmental effects of cadmium in freshwater fish.

Fish Species	Features of Fish			Cadmium Concentration	Time of Exposure	Effects	References
	Stage	Length	Weight				
Danio rerio	6 days post-fertilization larvae	NS	NS	10 µg/L	3 days	Deformed larvae	[101]
Danio rerio	Embryo	NA	NA	Environmentally relevant concentration	24 to 72 h post fertilization	Alterations in optomotor responses in the treated larvae of all ages	[8]
Gymnotus carapo	Sexually matured	36.8 ± 6.0 cm	205.8 ± 59.9 g	5–40 M	24–96 h	Damaged germ cell genesis	[96]
Odontesthes bonariensis	Sexually matured	NS	NS	0.25–2.5 µg/L	NS	Reduced hatching, embryo, and larvae survival	[90]
Oreochromis niloticus	2-month-old	12.38 ± 0.92 cm	58.80 ± 13.84 g	143.78–161.15 g/L	30 and 60 days	Premature spermatid	[86]
Prochilodus magdalenae	Two-year-old	NS	282.3 ± 40.8 g	0.0025–2.5 ppm	NS	Low fertility and decreased egg production	[63]
Oplegnathus fasciatus	Fingerlings	NS	5.5 ± 0.06 g	162 mg/kg	NS	Reduced growth rate	[14]
Carassius auratus	Fingerlings	NS	6 ± 1.2 g	0.5 g	14 days	Dilation in sinusoids and unusual Kupffer cells occurs	[17]
Ictalurus punctatus	Fertilization to 6-month-old fingerlings	NS	NS	NS	3 months	Increased metallothionein gene expression in heat-shock proteins in the liver	[30]

Table 2. *Cont.*

Fish Species	Features of Fish			Cadmium Concentration	Time of Exposure	Effects	References
	Stage	Length	Weight				
Trematomus hansoni	Adult	21.2–24.6 cm	130–159 g	0.89 µM	5 days	Increased metallothionein gene transcription	[52]
Ide Leuciscus idus	21 days post-hatching	NS	NS	100 µg/L	NS	Reduced embryonic survival	[75]
Oncorhynchus mykiss	Embryos and larvae	NA	NS	0.5–8.0 µg/L	96 h	Induced geno–cytotoxicity disturbs cardio-respiratory system activity and negatively impacts fish development at early life stages.	[77]
Danio rerio	Embryo	NA	NA	30 µM	1–3 days post fertilization	Increased mortality rate and delayed hatching	[102]
Gasterosteus aculeatus	Adult	40.40 ± 0.49 mm	955.80 ± 55.13 mg	1 ppb	15, 60, and 120 days	Reduced germ cell quality, decreased hatching rate, and increased mortality rate.	[103]
Oryzias javanicus	Newly spawned eggs	NS	NS	0.01–0.10 ppm	NS	Failure in embryo development	[104]
Cyprinus carpio L.	Adult	NS	768.50 g	0.5 mg/L	NS	Reduced body weight gain	[64]
Danio rerio	Adult (120 days post fertilization)	NS	NS	1 µmol/L	NS	Malformations in the produced offspring	[105]
Channa marulius and *Hepteroneustes fossillis*	Juveniles and smaller adults	NS	NS	0–10 mg/L	96 h	Respiratory strategy and adaptation to low-ionic-strength environments	[82]

Note: NA—not applicable; NS—not specified.

5.2. Developmental Effects of Cadmium on Freshwater Fish

Freshwater fish exposed to Cd have exhibited significant impairment in reproductive capacity as well as retardation in overall growth and development. The fundamental consequence is due to the structural and functional failure of the fish gonads, in addition to the annihilation of the reproductive development system [51,61,86]. According to reports, Cd negatively affects fish in two ways: either it directly inhibits the gene expression and secretion of the endocrine hormone concerning the HPG axis, or it may affect sex hormone synthesis, thereby reducing the survival efficacy of the offspring produced [99,100]. The exposure of *Silurus soldatovi* to a dosage of 10 µg/L of Cd reportedly reduced the larval survival rate, thereby supporting the concept of Cd as an environmental pollutant that causes embryotoxicity in fish [106]. A study suggested a disordered yolk production

abnormality in egg development in rainbow trout gonads because Cd exposure results in the suppression of estrogen receptor gene expression [85]. Cadmium exposure into the reproductive tissue interferes with gonadal differentiation [107].

A study on their growth rate, survival rate, locomotor activity, and sensory activities indicated that zebrafish embryos exposed to Cd exhibited delayed hatching and a higher mortality rate [102]. Another toxicity assessment analysis of zebrafish showed abnormalities in embryonic development, producing offspring with varying extents of deformity (Table 1) [18,105,108]. Embryonic abnormalities account for impairments in the olfactory placode and defects in the head where the subdivisions of the brain are not well defined, therefore ultimately targeting neurogenesis [109,110]. Further, in the case of *Gasterosteus aculeatus*, exposure to 1 ppb of Cd for about 15, 60, and 120 days reduced both the egg and the sperm quality [103]. A review of *G. carapo* revealed varying outcomes concerning varying administered Cd dosages. A treatment with a Cd concentration of 20 M for 24 h led to a reduction in male germ cells. A concentration of 40 M of Cd treatment leads to a complete lack of germ cells. After 96 h of exposure at all Cd concentrations, the germ cells had a critical impairment [96]. Advanced-stage embryos of *O. bonariensis* were studied, where an analysis with 0.25 and 2.5 µg/L of Cd showed a decrease in the hatching rate by 20%, and the mortality rate in both the embryonic and larval stages was increased (Tables 1 and 2) [90]. Under 4–10 mg/L Cd conditions, the observed germ cells were disrupted at a post-meiotic stage in *Labeo bata* [111].

Cadmium has been proven to be a potent agent responsible for reproductive and developmental abnormalities in fish. However, the effects may vary from species to species regarding their susceptibility and acquired Cd dosage. There are impacts on both females and their offspring. For females, a reduced fecundity rate has been reported, whereas offspring have shown a decreased rate of gamete development [112]. A study on *P. magdalenae* eggs resulted in a lower fertility rate and deceased eggs with 0.0025 and 2.5 ppm of $CdCl_2$, respectively [63]. The authors studied multiple parameters of *Oryzias javanicus*, such as premature hatching, life span of the juvenile, and embryonic development [104], where the tropical fish were exposed to Cd. At a 0.01–0.10 ppm exposure, embryonic development was restrained with a 10–37.5% mortality rate. However, at a 0.01–0.05 ppm exposure, premature hatching decreased by up to 20%. Another study on red sea bream, *Pagrus major*, again observed a lower hatchability rate at more than a 0.8 mg/L concentration. The mortality rate was greater, and unusual morphological changes were observed at more than a 0.4 mg/L concentration [113]. Several in vitro and in vivo studies have shown Cd-induced alterations in the steroidogenesis, oocyte maturation, growth retardation, increased mortality rate, premature hatching, and abnormal embryonic development in fish like common carp. An incubation with Cd minimized the swellings of common carp eggs at a 5–50 mg/dm^3 concentration [114], and in some cases, craniofacial anomalies and yolk sac deformities were observed [60]. Ide embryos were considered and subjected to Cd, which gave numerous results. The hatching process was retarded compared to the control groups, wherein the larvae body size significantly dropped and induced a mortality rate of up to 50% [75]. In zebrafish, defective embryos were reported at increasing concentrations, i.e., 3.3, 6.7, and 13.3 µM. The same experiment also calculated the hatching period, which showed no or delayed hatching [115]. Similarly, 6 days post fertilization, zebrafish exposed to 25 and 125 µg/L of Cd showed detrimental effects, with reduced opercular bone growth and skeletal malformation during larval development [101].

6. Research Gaps and Future Research Directions

The complexity of aquatic ecosystems can make our understanding of the biogeochemistry of pollutants such as Cd more challenging [116]. Furthermore, due to the fluctuation in the levels and types of pollutants over time, the consequences of Cd accumulation and its biomagnification on each trophic level have become more diverse and complex [117]. Although numerous studies have focused on understanding the bioaccumulation patterns of Cd and its toxicity as an oxidative stressor in various tissues of freshwater fish

species [118–122], there is limited information available on its impacts on endocrine disruption. As Cd is highly bioavailable to aquatic animals in freshwater, including fish, it readily accumulates in various tissues, including those related to reproduction and endocrine functions [123]. To substantiate the hypothesis that Cd in aquatic habitats harms fish's reproductive and developmental health, the current review has compiled data from recent research investigations. Most of the literature has focused on various networks of endocrine disruption caused by Cd at the gonad level, as well as the assessment of chromosomal structural abnormalities and modifications in the gonadsomatic index (GSI), gametogenesis, steroidogenesis, and vitellogenesis (Table 2) [68,69,86].

A few investigations have strongly evidenced the role of the HPG axis in the reproductive impairments in fish brought on by Cd exposure. The release of pituitary LH or hypothalamic GnRH may be affected by Cd through altering brain neurotransmission [64]. Trace elements found in the aquatic biota can synergistically or antagonistically impact fish reproduction and development [124]. The studies involving the wild fish population attempt to distinguish the interactive roles of multiple trace elements and the effect of different concentrations of an individual trace element on the endocrine system [10,59,105]. Therefore, future environmental toxicology studies should employ holistic in vitro and in vivo analyses of fish health related to multiple trace elements. Studies evidencing Cd exposure at low-level and environmentally relevant concentrations are limited. Thus, the toxic effects of ecologically relevant doses of Cd on fish reproductive-endocrine systems and their mechanism of action on multiple sites along the reproductive axis should be the primary concern of researchers. Emerging studies will thoroughly explore the control of neuroendocrine function during metal-induced disruption of reproductive activities in fish. Therefore, broad research is needed to understand the mechanisms behind Cd's actions as an endocrine disruptor.

However, the correlation of reproductive abnormalities in wild fish with an ecologically pertinent amount of Cd is challenging to show. Some trace elements, like Cd, are found to be available in natural water systems, which in turn cause a noxious impact on wild fish populations [125]. The concentration of Cd absorption and its accumulation into tissues/organs depend on the fish's physiological, ecological, chemical, and physical conditions [126]. So, thorough investigations are needed, particularly on commercially important and threatened freshwater fish under various contaminated circumstances. Merely comprehending the interdependence between water quality parameters and Cd concentration in fish, along with the presence of other metals and their synergistic effects with Cd, is inadequate to bridge the knowledge gaps between Cd accumulation in fish and its potential ecological consequences. Likewise, an in-depth comprehension of the species-level seasonal shifts of Cd absorption by fish living in their native habitats aids in safeguarding them from impending threats. The present review contains strong evidence that demonstrates the serious implications caused by the chronic exposure of Cd on the development and reproduction of fish.

7. Conclusions

The present review examined reports concerned with the endocrine-disrupting activity of Cd, which impacts various signaling pathways crucial to the development and reproduction of freshwater fish. This comprehensive analysis of Cd exposure's endocrine effects has revealed a greater research gap to fill. Since Cd has evolved to be a vital part of our ecosystem and livelihood, stopping its production or utilization in the decades ahead is impossible. Due to increased industrialization, the widespread dispersal of Cd and its destructive effects pose serious issues for higher tropic levels, as there will be more possibilities for accidental or incidental exposure of Cd to freshwater living beings. So, there is a need for more research investigations that characterize the mechanisms of reproductive endocrine disruption, its mode of action, and alterations caused at different levels of Cd exposure in fish to interpret toxicological solutions referring to fish health and diseases.

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