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Effects of Cadmium and Nickel on Embryonic Development of Fish: A Review

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Abstract

In fish embryos, a variety of abnormalities have been found, including stunted growth, a reduced survival rate, and aberrant development. One plausible explanation is that early embryonic stages are more sensitive. Embryonic studies provide additional information regarding the various impacts of heavy metals on fish, but information on larval abnormalities caused by waterborne metals is lacking. It is found that cadmium (Cd) causes a decrease in thyroid hormone levels as well as a disruption in fish growth hormone expression. Similarly, negative health effects have been documented as a result of nickel (Ni) exposure. Some toxic effects on organs, skin irritation, skin itches or blisters and allergic reactions may occur as a result of Ni exposure. This review study focuses on the impacts of Cd and Ni, on the embryonic development of different fish species. The evidence on abnormalities in fish larvae caused by Cd and Ni was also provided in text.

Balıkların Embriyonik Gelişimi Üzerinde Kadmiyum ve Nikelin Etkileri: Bir Derleme

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Öz

Balık embriyolarında, büyümenin engellenmesi, düşük yaşama oranı ve anormal gelişmenin de dahil olduğu çeşitli anormallikler bulunmuştur. Bunun makul bir açıklaması ise, erken embriyonik aşamaların daha hassas olması olabilir. Embriyonik çalışmalar, ağır metallerin balıklar üzerindeki çeşitli etkileri hakkında bilgi sağlamaktadır, ancak suda taşınan metallerin neden olduğu larva anormallikleri hakkında bilgiler eksik kalmıştır. Kadmiyumun (Cd) balık büyüme hormonu ekspresyonunda bozulmaya ek olarak tiroid hormon düzeylerinde azalmaya neden olduğu tespit edilmiştir. Benzer şekilde, nikele (Ni) maruz kalmanın bir sonucu olarak olumsuz sağlık etkileri de belgelenmiştir. Ni'ye maruz kalmanın bir sonucu olarak organlar üzerinde, cilt tahrişi, cilt kaşıntıları veya kabarcıkları ile alerjik reaksiyonlar gibi bazı toksik etkiler meydana gelebilmektedir. Bu derleme çalışması, Cd ve Ni'nin farklı balık türlerinin embriyonik gelişimi üzerindeki etkilerine odaklanmaktadır. Cd ve Ni'nin neden olduğu balık larvalarındaki anormalliklere ilişkin kanıtlar da

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INTRODUCTION

Contamination of fresh and salt water due to various heavy metals such as mercury (Hg), lead (Pb), cadmium (Cd), and nickel (Ni) is a rising concern, posing a serious hazard to the aquatic ecosystem even in miserable concentrations (Aldavood et al. 2020). Many toxicants cause more harm during embryonic development than they do in adulthood. Such hazardous substances (Cd, Ni, and other heavy metals) are exposed to fish in aquaculture during the culture period. Excessive use of feed, pesticides, fertilizers, and medicines, as well as the discharge of effluents containing inorganic components like Cd and copper (Cu) that can build in the sediment, are serious issues for farming systems (Pinto et al. 2021). Metals from skin and/or gills diffuse into tissues after being taken up by diet, interfering with both traditional primary targets like kidney and liver and unconventional ones including muscles, retina, and the lateral line (Motta et al. 2021).

Cadmium and chromium (Cr) are the major environmental pollutants that pose substantial health hazards (Jin et al. 2015). Cadmium is a non-essential trace element having no role in human metabolism, but is slowly released in the body and is easily stored in internal organ owing to 10-30 years half-life (Kumar and Sharma 2019). Long term Cd exposure via water, soil, air and contaminated foods can affect urinary and reproductive system, central and peripheral nervous systems, liver, respiratory and cardiovascular system, causing serious cancers (Puangprasert and Prueksasit 2019). Owing to negative effects on both organisms and environment, the International Agency for Research on Cancer (IARC) has declared Cd as a carcinogenic metal for human consumption. Recent studies indicated that Cd concentration in water can reach 0.1–0.3 μg L^{-1}, and can also reach 30 μg L^{-1} in the wastewater discharge of numerous factories (Ahmed and Mokhtar 2020). In ecotoxicology, sensitive warnings are important to monitor aquatic ecosystems (Hani et al., 2018).

Although most aquatic organisms need Ni as a necessary trace element (Bielmyer et al. 2013), large amounts can be hazardous to fish, amphibians, and invertebrates (Eisler 1998; Brix et al. 2017). So many parameters like environmental Ni concentrations, physico-chemical characteristics of water (e.g., pH, dissolved organic carbon, water hardness), and biological / physiological functions, influence Ni bioavailability and toxicity in freshwater (FW) species (Bielmyer et al. 2013; Custer et al. 2016). Human industrial activities can cause Ni quantities in the environment to increase (Alsop et al. 2014). Natural processes and human actions, such as rock weathering, industrial effluent discharge, and resource extraction, can also introduce Ni into aquatic ecosystems. To measure the chemical's toxicity, embryonic morphological, physiological, and behavioural endpoints of various fishes are frequently used (Liu et al. 2021). In aquatic toxicology, zebrafish have great value as they exhibit a short-term reproductive cycle and strong progeny breeding ability, drug treatments, and toxin-induced phenotypic changes can be easily observed (Tian et al. 2020). Scheil et al. (2010) found that Ni exposure hindered zebrafish embryo hatching. Exposure to Ni with vanadium (V) caused heart developmental damage in exposed zebrafish embryos, according to Kim et al (2019).

Fish embryos are increasingly being used in aquatic toxicity testing, as indicated by the approval of the fish embryo acute toxicity (FET) test by the Organization for Economic Cooperation and Development (Krzykwa et al. 2019). There is a pressing need for impressive methodologies to assess the neurotoxic potential of contaminants being in the environment in ecotoxicology (Zindler et al. 2019).

Aquatic sediments are regarded as a long-term source of contamination for aquatic species due to their great potential to absorb toxins such as persistent organic pollutants and heavy metals (Barjhoux et al. 2012). Low-level metal pollution is a common problem with often-unknown health and environmental implications (Sonnack et al. 2015). Multiple contaminants coexist and interact in the ecosystem, usually at low levels. However, most of the published research either looked at single toxicant exposures rather than combinations, or looked at many toxicant combinations, making it difficult to deduce the underlying individual mechanisms of action. To assess the possible ecological risk, it is necessary to assess the toxicity of combinations of coexisting substances (Ku et al. 2015). This review focussed on the effects of some metals on developments in the embryonic stages of different fish species.

MATERIAL and METHOD

Fish embryos are increasingly being used in aquatic toxicity testing, as indicated by the approval of the fish embryo acute toxicity (FET) test by the Organization for Economic Cooperation and Development. Embryos were checked daily for standard signs of death (coagulation, lack of tail separation, lack of so mite development, and lack of heartbeat) until the test was completed at 120 hours (Krzykwa et al. 2019).

Present study was designed to review the studies from 2000-2020, based on the embryonic developmental alterations in fish due to the impact of Cd and/or Ni. Effect of Cd and Ni on larval and embryonic development of fish was reviewed from different research papers. It was used a number of keywords such as heavy metals, deformities, survival rate, fish growth, embryonic development, toxic effects in reference to both Ni and Cd. All the articles studied were further explored by using their references for more detailed information. This search work was completed by October 10, 2021.

A study design was prepared to select a limited number of articles to be included in this paper. The searching process was started from reading titles and abstracts of potentially relevant research articles, then irrelevant articles were removed from the list. The remaining articles were scrutinized further for their relevance to Cd and Ni having adverse effect to the focused subjects. After that, the remaining articles were studied in detail (Table 1 and 2). However, some of these articles were not included in this paper for providing repeated or less valuable information regarding studied heavy metals.

Table 1. Different studies reviewed on the effects of Nickel on embryonic development of different fish species

Study No.	Heavy metals	Fish species	Concentration	Duration	Stages	Effect	References
1	Ni	*Pimephales promelas*	13.87 mg g^{-1}	21 days after hatching	24 hpf*	Decreased hatching time and elevated CCO* and NDPK* activity	Lapointe and Couture (2010)
2	Ni /graphene nanocomposites	*Danio rerio*	0-1000 µg L^{-1}	96 h	3 hpf	Reduced locomotion	Almeida et al. (2019)
3	$NiSO_4$	*Danio rerio*	5-100 mg L^{-1}	24 h	24 hpf	Increased mortality with Synergetic toxicity	Ku et al. (2015)
4	$NiCl_2$	*Danio rerio*	Acute 7.5-15 mg L^{-1}	2 h	5-days old larvae	Decreased locomotory activity	Kienle et al. (2008)
			Sub chronic ≥10 mg L^{-1}	After fertilization to 11 days	11 days old	Delayed hatching at 96h, decreased locomotory and increased mortality at age of 5 and 11 days, respectively.	
5	$NiCl_2$	*Danio rerio*	0.5 – 15 mg L^{-1}	From fertilization to 168 h	168 hpf	Reduced hatching success, increased Hsp70* levels in larvae when exposed to 1 mg$L^{-1}$of Ni, Strong histopathological effect on different organs (gut, liver, pancreas, kidney, skin) including necrosis, caryolysis, hypertrophy.	Scheil et al. (2010)
6	Ni	*Danio rerio*	100 ppm	Until 96 hpf	6 hpf	Increased mortality, delayed development of yolk sac, pericardial oedema, reduced heart rate, negative effects on heart chamber and reduced regulation of *amhc* and *nppa* genes	Kimáková et al. (2018)
7	$NiCl_2$	*Pimephales promelas*	0-2 mg L^{-1}	120 h	≤2 hpf to 120 hpf	Coagulation, lack of tail detachment, lack of somite development, absence of heart beat, and non-significant effect on weight	Krzykwa et al. (2019)
8	NOM* (Ni)	*Pimephales promelas*	1.5-3 mg L^{-1}	21 days	Breeding pairs	Decreased egg production and tissue specific accumulation in gonads and gills.	Ouellet et al. (2013)
9	Ni	*Danio rerio*	3.7 mg L^{-1}	144 h	0.5 hpf	Egg coagulation, Lack of somite development, no tail detachment, Lack of heart beat and blood circulation, Gross morphological malformation, oedema, Growth retardation, and decreased pigmentation	Bartzke et al. (2010)
10	Ni	*Danio rerio*	116 µg g^{-1}	82 days	0.2 -0.3g of fish weight	Significant decrease in egg production, decreased growth of male fish, and increased mortality	Alsop et al. (2014)
11	Ni- Cr alloy	*Danio rerio*	33.65% of alloy	4-7 week	4-144 hpf	Decreased heart-beat rate and altered swimming behaviour, decreased body length of larvae, eye	Zhao et al. (2018)

						deformation, pericardial oedema, spine flexion, tail deformity, and yolk sac oedema	
12	Ni	*Danio rerio*	7.7-240 µM	0-78 hpf	0-78 hpf	Observed effects on Epigenetic	Bouwmeester et al. (2016)
13	Ni	*Oryzias melastigma*	0.13–65.80 mg L^{-1}	3–4 hpf	Newly hatched larvae (1-day post-hatch)	Changed the egg size and heart rate of the embryos, lowered the hatchability, increased the deformity rate, and shortened the total body length of newly hatched larvae	Liu et al., 2021
14	Ni	*Danio rerio*	5.2, 6.2, 7.4, 8.9, and 10.7 mg L^{-1}	4 hpf	4 h (late blastula stage)	Impact on alterations of mortality, hatching rate, malformation rate, body length, heartbeat rates, and gene expressions	Yang et al., 2021
15	Ni	*Danio rerio*	0.4, 2.1, 10.5, and 21.0 µM	2 hpf	48,72 hpf	Decreased spontaneous movement and myosin expression	Aldavood et al., 2020

*** hpf =** Hours post fertilization, **CCO**= Cytochrome C oxidase, **NDPK**= Nucleoside diphosphate kinase, **Hsp70**= Heat shock protein 70, **NOM**= Natural organic matter

Table 2. Different studies reviewed on the effects of Cadmium on embryonic development of different fish species

Study No.	Fish species	Concentration	Duration	Stages	Effect	References
1	*Danio rerio*	0.032-32.4 mgL^{-1}	24 hpf	Late pharyngula stage	Increased the frequency of tail coiling and delayed embryonic development	Zindler et al. (2019)
2	*Pagrus major*	9.8,6.6 mgL^{-1}	96 hpf	3 hpf	Reduced hatchability, delayed hatching time, increased mortality, reduced length in embryo and larvae, inhibited heart beat and yolk absorption	Cao et al. (2009)
3	*Alopias vulpinus*	0.006 μgg^{-1} BDL*	-	Embryo FL* (73 cm)	No significant effects	Dutton and Venuti (2019)
4	*Oryzias latipes*	5g d. w	10 days	Pre- blastula stage	Spinal and cardiovascular deformities, tachycardia, Significant increase in DNA damage	Barjhoux et al. (2012)
5	*Danio rerio*	2-34.8 mg L^{-1}	72 h	72 hpf	Neuromast damage, coagulated egg, increased mortality rate	Sonnack et al. (2015)
6	*Danio rerio*	10 µM	96 h	96 hpf	Oxidative stress, increased MDA* level, decreased GSH* level	Jin et al. (2015)
7	*Danio rerio*	1.0 µM	30 days	Embryo	Affects gene expression level, hepatotoxicity, altered liver size, abnormal expression of gene	Duan et al. (2017)
8	*Pimephales promelas*	0-100 µg L^{-1}	-	Embryo/ larvae	Alteration in length, reduced eye size, significant decreased in snout- vent length, increased pericardial area	Krzykwa et al. (2019)
9	*Danio rerio*	0-5 µg L-1	15 Weeks	24 hpf – sexual maturity	Declined NO* level in liver and spleen, m RNA level sharply increased and decreased immunity	Guo et al. (2017)
10	*Danio rerio*	-	72 h	3-days old embryo	Decreased regulation of gene expression	Chouchene et al. (2016)
11	*Danio rerio*	0-5 µg L-1	15 Weeks	Embryo	Reduced GSH, no significant changes in cellular organelles	Zhu et al. (2018)
12	*Danio rerio*	9 µM	24 h	-	Increased apoptotic event and induced cell death in brain of embryo	Monaco et al. (2017)
13	*Gobiocypris rarus*	0.1-100 µg L-1	24 h	Newly hatched larvae	Increased mortality of the embryo	Zhu et al. (2011)
14	*Leuciscus idus*	100 µg L-1	21 Days	Embryonic and larval	Reduced embryonic survival, increased frequency of malformation and delayed hatching	Witeska et al. (2014)
15	*Danio rerio*	0-10 µM	24-96 hpf	Embryonic and larval	Increased heart beat rate of larvae and decreased brain size	Wold et al. (2017)
16	*Leuciscus idus L.*	0.1 mg dm3	2 h	Embryos and newly hatched larvae	Reduced egg swelling, slowed the rate of development (especially body movements), and delayed hatching	Ługowska and Kondera, 2020

17	*Odontesthes bonariensis*	0.25 ugL-1	10 Days	Advanced stage embryos and recently hatched larvae	Decreased hatching rate and the survival of embryo and larvae	Gárriz and Miranda, 2020
18	*Trematomus bernacchii*	0.890 Mm ($CdCl_2$)	10 days	Adult stage	Reduce fecundity by increasing degeneration among previtellogenic oocytes. Induces changes in the localization of progesterone and beta-estrogen receptors. Alter carbohydrates composition of chorion and cytosol and the alveolar content.	Motta et al., 2021
19	Zebrafish	0.01-1 μmol L^{-1} ($CdCl_2$)	48, 60 and 72 hpf	Sexually mature	Reduced egg production and fertilization rates. Increased occurrence of various malformations and organ toxicity effects and developmental toxicity in the thyroid endocrine system.	Tian et al., 2020
20	Zebrafish	0.01-1 μmol L^{-1} ($CdCl_2$)	14-h/10-h	Sexually-mature	Reduced swimming speed and levels of neurotransmitters such as dopamine, serotonin, and AChE in offspring; disrupted neurotransmitter metabolism; and deregulated the expression of genes related to neuronal development, thereby inducing developmental neurotoxicity in off springs	Tian et al., 2021
21	Zebrafish	0.0089, 0.089, and 0.89 μM	24 hours post-fertilizatio n	8-cell stage	Cadmium caused up-regulation and downregulation in the DNA methylation levels and DNA methylation reflects the carcinogenicity of Cd through the regulation of proliferation, differentiation, apoptosis, and transcriptional protein expression.	Bian and Gao,2021
22	*Gobiocypris rarus*	-	3hpf	3-h post-fertilization (hpf)	Antagonistic and synergistic responses were detected	Li et al., 2020
24	*Danio rerio*	0.07, 0.7, 3.1, and 6.6 μM	2 hpf	48,72 hpf	Increased yolk sac area, an index of metabolic rate	Aldavood et al., 2020

EFFECTS OF CADMIUM ON FISH EMBRYO

The frequency of tail coiling predominantly increased by Cd at late pharyngeal stage. Dichlorvos played an effective role in delaying embryonic development, causing convulsive movements of tail, which in turn extends the duration of tail coils. At 24 h post-fertilization period (hpf), embryos showed absence of spontaneous tail movements, when exposed to citalopram and fluoxetine teratogenic concentrations. In 10 to 50 % of embryos during development, hindrance along with incomplete detachment of tail (≥5.93 mgL^{-1} concentration) and set back of coiling activity (≥5.93 mgL^{-1}; visual assessment) at 24 hpf was observed respectively. From 72 hpf, developmental slows down as reduced growth in 20% of embryos at concentration value ≥5.93 mgL^{-1} (Zinder et al. 2019).

In a study reported by Cao et al. (2009), it was found that LC_{50} values of Cd at 24 and 48 h were 9.8 and 6.6 mgL^{-1} while LC_{50} values at 24, 48, 72, and 96 h were 18.9, 16.2, 8.0, and 5.6 mgL^{-1} for red sea bream (*Pagrus major*) embryo and larvae, respectively showing larvae are less susceptible to Cd toxicity than embryos. Cadmium concentration at 0.8 mgL^{-1} led to many changes including abnormalities in morphology (42–100% vs. 1–10%), highest mortality rate (38–100% vs. 1–10%), reduced hatchability (0–90% in 0.8 mgL^{-1} solutions vs. 97–100% in lower ones), slow down hatching time and major reduction in length (3.55–3.60 vs. 3.71–3.72 mm) in both larvae and embryos. They were considered an important endpoint of biological significance helpful in assessment of Cd risk factor for aquatic organisms. Moreover, yolk absorption and heart beat rate somehow inhibited at higher concentrations, but not serve as much sensitive endpoints to Cd exposure.

Heavy metals have predominant role in aquatic environment species throughout their developmental period. Medaka (*Oryzias latipes*) embryos in their pre-blastula stage and 10th day of their development were exposed to 2 heavy metals namely Cu and Cd via static sediments contact. By keeping deadly toxicity and phenotypic restraints in consideration, some outcomes as lethal and sub-lethal were monitored in embryos and larvae for post fertilization of 20 days (dpf).

Above mentioned metals incite significantly spinal and cardiovascular distortion as well as increase in DNA damage at all tested concentrations (Barjhoux et al. 2012).

Out of heavy metals, Cr and Cd are considered major environmental contaminants posing noxious risks for healthy life. Cadmium-exposed embryos having excessive conc. 34.8 mgL^{-1}(309 µM) showed maximum mortality (90%) mainly caused by concentration-dependent rise in coagulated eggs in zebra fish. Similarly, hatchability reduced remarkably, when 10 µM Cd was given during 60 and 96 hpf. Sonnack et al. (2015) demonstrated that if Cd was exposed as $CdCl_2$ leads to some changes in neuromast cells showing more sensitivity towards metal exposure than motor neuron damaging and tactile stimulation effect.

Reactive oxygen species and oxidative stress levels significantly affect metabolism and organs functioning of aquatic organism, and rise in toxicity levels. Cadmium and Cr induced the changes in oxidative stress zebrafish in its larval stage. The exposure of both these metals for 96 hpf rise MDA levels which in turn decreased GSH contents (Jin et al. 2015). In a reported study, transgenic zebrafish (*Danio rerio*) and wild-type were selected to investigate acute toxicity together with single and joint hepatotoxicity of Cd and 1-H-benzotriazole (1H-BTR). The exposure of 5.0 µM of 1H-BTR in transgenic zebra fish for a period of one month elevated liver- specific fatty acid binding protein expression while acute toxicity was significantly low. Apart from, co-exposure to 1H-BTR diminished not only acute toxic outcomes but also highlighted Cd-induced atrophy in liver of transgenic fish. Correspondingly, how combined exposure to 1H-BTR effects Cd-induced expressions of various genes related signalling pathways, glutathione-s-transferase proteins and SOD were also studied (Duan et al. 2017).

Following method of OECD TG 236 (OECD Guidelines for Testing of Chemicals, Test No.236: Fish Embryo Acute Toxicity Test), 5.0 µM of 1H-BTR and 1.0 mM Cd concentrations both singly or jointly using 24 well multi plates were exposed to wide-type developing embryo. This exposure influence expressing level of gene, up-regulating expression of TNF and SERP mRNA dramatically reduced ($p<0.01$). Even though, 1H-BTR acute toxicity was verified to be low. Hepatotoxicity comprising variations in liver size due to abnormal genes and enzymes functioning was observed in zebrafish (Duan et al. 2017).

Procedures incorporating fathead minnows were performed with Texas Christian University (TCU) IACUC-approved methods (Protocol 14/05). Different exposures were carried out over course of one and half year. For, proper maintenance of reproductive activity of breeding colonies numerous cohorts look after larvae/embryos utilized in each set of exposures. Cadmium exposure (ANOVA, $p<0.01$) results in a remarkable increase in pericardial area. There was a significant decrease in snout-vent length in Cd treated embryos as well as in all other Cd groups confirmed by performing ANOVA at $p<0.01$. However, there was a threshold response with no significant variations among Cd groups. It was investigated in a report that sub lethal endpoints showed variations only during Cd exposure. Embryos/eleuthero embryos when treated with heavy metal Cd present changes in length, pericardial area and eye size if observed at five-fold less concentrations than estimated LC50 value, demonstrating that for Cd the incorporation of above sublethal endpoints may helpful in improving sensitivity offish embryo acute toxicity(FET) test (Krzykwa et al. 2019).

The immune responses in organs of zebrafish (i.e., spleen and liver) was investigated at environmental levels of Cd (0, 2.5 and 5 μgL^{-1}) for 15 weeks from embryos to their sexually maturity period. When liver and spleen were exposed to5 μgL^{-1} Cd the NO and iNOS activities lessened showing immune suppressive effect. In spleen, an increase in levels of mRNA of these cytokines was seen (Guo et al. 2017). By using Real-Time Quantitative PCR (RT-qPCR) experimental techniques, mRNA levels of CYP19A1B gene were assessed in zebrafish embryos after given treatment of Cd, E2 and/or Zn. In this case, remarkable effect of Zn or Cd alone was not prominent. However, E2 revitalize CYP19A1B gene expression, results in 38 times more fold

induction on comparison with control condition (EtOH). In addition to that, E2 and Cd co-treatment caused inhibition of E2-induced CYP19A1B mRNA levels. Surprisingly, Zn alone represent zero effect confirmed by (Chouchene et al. 2016).

Examined after effects of waterborne Cd was also evaluated at (0, 2.5, and 5 mgL^{-1}) concentrations in zebrafish female for various responses such as histology, survival chances, metal homeostasis plus antioxidant effects (Zhu et al. 2018). This study was carried out with the help of cytochemical staining. Six hours post fertilization embryos of zebrafish were given treatment of 9 μM Cd for one day followed by Acridine orange stain in whole mount for brain apoptosis detection which showed an elevation in apoptotic events. This gives a clear cut idea that Cd even at its sub-lethal concentration induces cell death in brain of zebrafish embryos and adults (Monaco et al. 2017).

Copper, Zn, and Cd acute toxicity levels were evaluated both singly and in mixtures on Chinese rare minnow (*Gobio cyprisrarus*) in larvae and embryos during their early developmental stages. Mainly 3 hpf larvae (newly hatched) and normal embryos were selected for this purpose. Metal solution exposure were given to embryos which lasts for 24h and studied up to different developing stages including detachment of tail (25 h 10 min), so mite formation (15h), heart-beat (34 h 10 min), hatching (75h) and appearance of pectoral fin bud (47 h 40 min) respectively. Single toxicity tests confirmed that with increasing exposure duration, the mortality rate of embryos also increases (Zhu et al. 2011). Hatching time, size of larvae newly hatched and embryos survival were checked when the embryonic period was ended. The outcomes revealed the significant decrease in embryonic survival, larvae death and delay in hatching time. In addition, body malformations became more as reported by a study confirmed by Witeska et al. (2014).

We check out that what would be the longitudinal effects (long lasting) from Cd exposure in early stages of development (between 24 and 96 hpf) having a range in which larvae might experience living a top typical Cd containing surface sediments (0, 0.01, 0.1, 1.0, and 10 μM $CdCl_2$: 1.124, 11.24, 112.4, and 1124 μg CdL^{-1}). The aim was to target cardiovascular development, secondary neurogenesis and monoaminergic differentiation without affecting initial patterning activities. Major development based abnormalities in central nervous system morphology along with body size increased with concentration, but significantly at highest concentration (10 μM). Furthermore, Cd reduces brain size and elevates acridine orange-positive (AO +) cell number in forebrain of treated larvae. Telencephalic area showed a significant reduction in given 10 μM $CdCl_2$ (Wold et al. 2017).

NICKEL METAL EFFECTS ON FISH EMBRYO

Early-life fathead minnows were subjected to environmentally relevant quantities of aqueous and dietary Ni and thallium (Tl), and metal build up was tracked from the embryo to 21 days after hatching. Aqueous Ni exposure shortened the time to hatch and boosted aerobic and biosynthetic capacity (as demonstrated by higher cytochrome C oxidase (CCO) and Nucleoside-diphosphate kinase (NDPK) activity, respectively), implying that aqueous Ni stimulates metabolism in fathead minnows in their early life stages (Lapointe and Couture 2010).

Zebrafish embryos were given various doses of the two nanocomposites: 0, 0.024, 0.12, 0.6, 3.0, and 15.0 mg L^{-1} of G/Ni1 and 0, 0.016, 0.08, 0.4, 2.0, and 10.0 mg L^{-1} of G/Ni2. GO was also analyzed at concentrations of 0.016, 0.08, 0.4, 2.0, and 10.0 mg L^{-1}, as well as Ni at values of 0, 1.4, 4.1, 12.3, 37, 11.1, 333.3, and 1000.0 g L^{-1} (nickel sulfate hexahydrate was used as a source of the Ni ions). The purpose of this study was to determine the toxicity of two nickel/graphene nanocomposites (G/Ni1 and G/Ni2) to *Danio rerio* embryos, that differed in size and shape. Both nanocomposites, however, had behavioural impacts, reducing swimming distances. The G/Ni1 nanocomposite, on the other hand, showed this action at lower concentrations. Only the G/Ni1 nanocomposite interfered with the observed parameters at the biochemical level, raising the activities of ChE, CAT, and GST (Almeida et al. 2019).

The combined effects of the heavy metal Ni($NiSO_4$) and the insect growth regulator buprofezin on zebrafish embryo toxicity were investigated in this study. We randomly subjected normally developed embryos to Ni at 10.0, 20.0, 40.0, 80.0, 200.0, 300.0, 400.0, 500.0, and 600.0 mg L^{-1} or buprofezin at 2.5, 10.0, 40.0, 200.0, 300.0, 400.0, 500.0, and 600.0 mg L^{-1} respectively at 24 h postfertilization (hpf). 294.0 mg L^{-1} $CaCl_2 \cdot 2H_2O$, 123.3 mg L^{-1} $MgSO_4 \cdot 7H_2O$, 63.0 mg L^{-1} $NaHCO_3$, and 5.5 mg L^{-1} KCl, were present in exposure solutions. Ni- and buprofezin levels were 5.0, 10.0, 20.0, 40.0, 80.0, and 100.0 mgL^{-1} in co-exposure treatment, that combined exposure to Ni and buprofezin at low doses generates synergistic toxicity that would not have generated detectable effects from such levels of both chemicals alone, and that their coexistence in various habitats poses an ecological and health danger (Ku et. al. 2015).

The effects of $NiCl_2.6H_2O$ on zebrafish (*Danio rerio*) both of embryos and larvae were studied in both acute (2 h exposure of 5-day-old larvae) and sub-chronic (exposure from fertilization to age of 11 days) conditions, both alone and in conjunction with oxygen deprivation. In the sub-chronic examination exposure to 10.0 mg NiL^{-1} resulted in delayed hatching at 96 h, locomotive activity decreased at 5 days and mortality increased at 11 days of age (LC20 1⁄4 9.5 mg NiL^{-1}) (Kienle et al. 2008).

Another study used a multilevel strategy to examine two separate groups of chemicals: $NiCl_2$ as a heavy metal representative and chlorpyrifos, a pesticide. The effects of single chemicals and mixtures of them on embryonic development, histological changes, and the stress protein (Hsp70) response in the zebrafish, *Danio rerio* were studied. Depending on the endpoint studied, fishes were exposed from egg fertilization to a maximum of 168 hours after fertilization. When larvae are exposed to 1.0 mgL^{-1} of Ni, they have a lower hatching success and have higher hsp70 levels. Strong histopathological effects include necrosis, caryolysis, and hypertrophy in several organs (gut, liver, pancreas, kidney, skin) (Scheil et al. 2010).

The developmental toxicity of water-soluble carbon black wastes (CBW) extract (1:5, w/v) in zebrafish embryos (*D. rerio*) was investigated in this work. The OECD guideline 236 for acute embryonic toxicity was followed. ICP-OES analysis found that nickel (Ni) and V were the most abundant elements in CBW. CBW-exposed embryos showed developmental delays as well as pericardial and yolk sac edemas. CBW-exposed embryos had malformed heart chambers, and significantly lower heart rates were obtained for post-fertilization of 48 h (hpf). Two cardiac forming-related genes, AMHC and NPPA, which are important for atrial cardiac myofibril assembly and cardiac muscle cell proliferation, were up-regulated after 96 hpf, according to RT-qPCR research. An increasing mortality rate and more slowly yolk-sac development ontained to be linked to a pH drop to around 5.5 caused by CBW. Individual Ni and V treatments did not have the same harmful effects as CBW. Vanadium had a pH of about 5.5 at 100 ppm, which caused developmental delays and pericardial edema in zebrafish embryos. At the same pH, combined Ni and V caused morphological abnormalities and decreased heart rates in embryos that had been exposed to CBW (Kimáková et al. 2018)

The fish teratogenicity index (FTI), a new evaluation scheme that allows for sediment classifications into quality classes of ecologic fields consistent with the WFD, was created for the ecotoxicological researches (toxicity test for fish embryo with *Danio rerio*). Viable eggs were individually picked using an inverted microscope 30 minutes after fertilization and then put into the sediment-containing cavities of the 24-well plates. Each experiment included ten duplicates per sediment sample. At a final test concentration of 3.7 mgL^{-1}, 3,4-dichloraniline solution was used as a positive control. Negative controls were reconstituted water (standard water according to DIN 38415-6) and native reference sediment from the Elbrighäuserbach. An inverse microscope was used to examine embryos after 24, 48, 72, and 144 hours. Egg coagulation, absence of so mite development, no tail separation, lack of heartbeat and blood circulation, gross morphological deformities, edema, growth retardation, and diminished or missing pigmentation were all observed during the inspections (Bartzke et al. 2010).

In a study on zebrafish, they were fed with two different concentrations of Ni (control and exposure including 116 g Ni/g feed). At 80 days, males fish exposure to Ni were considerably smaller (26%) than controls. Furthermore, by 75–78 days of the trial, reduced overall egg productions were observed in the Ni exposure group (65%). Zebrafish *(Danio rerio*; 0.2 to 0.3 g) were acquired from a commercial supplier and housed in six 40-L tanks, each holding 40 fish (3 control and 3 Ni-exposed). The absorption rates of waterborne Ni in the two treatments were compared after 82 days of exposure. After 80 days of exposure to Ni, growth of male zebrafish was slowed. These include population-level consequences including reproductive capacity, male growth, and physiological changes in progeny (Alsop et al. 2014).

The leach solution was collected and used to treat zebrafish embryos at 4–144 h PFM. Gold palladium (Au-Pd), silver palladium (Ag-Pd), nickel chromium (Ni-Cr), cobalt chromium (Co-Cr), and titanium (Ti) alloy porcelain crowns were immersed in artificial saliva for 1, 4, and 7 weeks. For 4- and 7-week leachates, the Ni-Cr alloy group had higher rates of death and malformation, but spontaneous movement, heart rate, and swimming behaviour were lower. In comparison to the control group (3.61 mm), the body length of larvae in the 7-week Ti alloy (3.193 mm), Ag-Pd alloy (3.164 mm), Co-Cr alloy (3.193 mm), and Ni-Cr alloy (2.878 mm) leach solution treatment groups was reduced (Zhao et al. 2018).

The zebrafish embryo's suitability as a screening model for DNA methylation alterations is enough. Bisphenol-A (BPA), diethylstilbestrol, 17α-ethynylestradiol, Ni, Cd, tributyltin, arsenite, perfluoroctanoic acid, valproic acid, flusilazole, and 5-azacytidine (5AC) were given to embryos in subtoxic quantities from 0 to 72 hours post fertilization (hpf). Epigenetic effects have been observed (Bouwmeester et al. 2016).

CONCLUSION

We concluded that Cd and Ni are among the most toxic metals at different developmental stages of fish species including embryonic and larval. Exposure to these metals even at very low concentration can cause severe deformities and abnormal growth and development of fish embryo and larvae. The effect of heavy metal exposure at these developmental stages is also reflected at later stages of fish. Furthermore, fish embryo and larvae are among excellent bio indicators to study level of pollutant in any aquatic ecosystem.

STATEMENTS AND DECLERATIONS

Declaration of Competing Interest

The authors declare that there is no conflict of interest among authors of this manuscript.

Ethics Approval and Consent to Participate

This manuscript is a review and contains any animal experiments. So, it isn't need an ethics approval.

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Authors' Contributions

SN had the initial idea for the manuscript and was involved in the literature search, data analysis, and writing and development of the article, as well as the final proof stage. AMMC and DD were involved in the writing and development of the article, and also in the final proof stage. In addition, DD assumed the responsibility of the corresponding author. All authors have read and approved the final manuscript.

Data Availability Statement

All data used in the manuscript was given in the text of manuscript. There were no additional data sources.

Statement of Human Rights

For this type of study, formal consent is not required.

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