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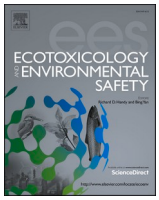

Review

Neurotoxicity of nanoparticles: Insight from studies in zebrafish

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ABSTRACT

Nanoparticles are widely used in industry and personal care, and they inevitably end up in people's bodies and the environment. The widespread use of nanoparticles has raised new concerns about their neurotoxicity, as nanoparticles can enter the nervous system by blood-brain barrier. In neurotoxicity testing, the zebrafish provides powerful tools to overcome the limitations of other models. This paper will provide a comprehensive review of the power of zebrafish in neurotoxicity tests and the neurotoxic effects of nanoparticles, including inorganic, organic, and metal-based nanoparticles, on zebrafish from different perspectives. Such information can be used to predict not only the effects of nanoparticles on other species exposed to the aquatic environment but also the neurotoxicity of nanoparticles in humans.

1. Introduction

Nanoparticles (NPs), ranging in size from 1 to 100 nm, can be classified as inorganic nanoparticles, organic nanoparticles, and metal-based nanoparticles. They exhibit diversely unique chemical, physical and optical properties with their small size and large surface (Spirescu et al., 2021). NPs are widely used in many fields, including tissue engineering, drug delivery, imaging, diagnostics, surface texturing, and bio-interfaces, due to their ease of modification in shape, size, surface, and chemical properties (Chakraborty et al., 2016; Mangematin and Walsh, 2012). For example, Silver (Ag) nanoparticles are used in clothing because of their antibacterial and anti-odor properties (Kulthong et al., 2010); titanium dioxide nanoparticles are widely used in cosmetic sunscreens as a UV protector (Jacobs et al., 2010).

Over 10, 000 tons of waste NPs are released into the environment every year (Pereira et al., 2019), and the accumulation of NPs will be increased significantly in water, sediments, and soils (Giese et al., 2018). Because of the rising demand for nanoparticles and their commercial potential, the toxic effects they have on consumers and the environment should be taken seriously.

Numerous in vitro or in vivo models have been extensively used in the laboratory to conduct toxicity tests. Cell lines are the most frequently used models for in vitro systems because they are inexpensive and allow for large-scale screening. However, they do not adequately mimic in vivo mechanisms. Although rodents including mice and rats are common mammalian systems, they are more expensive and many experiments are restricted due to ethical concerns. The fish embryo toxicity test (FET) (OECD 236) has become standard in the regulatory context of Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) (Busquet et al., 2014). The zebrafish has become the most frequently used species in FET, due to its robust fecundity, in vitro fertilization, and transparent embryos. Additionally, as a vertebrate, zebrafish share similar genetic material as humans (Pereira et al., 2020). As a result, zebrafish provide highly effective approaches for aquatic species and human health tests.

The nervous system is one of the most important systems in animals, as its function is critical for the animals' ability to act, and its dysfunction will result in poor survival. Nanoparticles' neurotoxic effects have only recently come to light, as nanoparticles can cross the blood-brain barrier and enter the brain and other parts of the nervous system, causing new concerns in this field. The advantages of zebrafish in toxicity studies, specifically in neurotoxicity tests, will be discussed in this review, as well as the progress in zebrafish neurotoxicity caused by multiple nanoparticles, including inorganic, metal-based, and organic

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nanoparticles.

1.1. Zebrafish as a powerful model for neurotoxicity studies

Zebrafish are excellent in vivo models for studying developmental neurotoxicity (Garcia et al., 2016; Kalueff et al., 2016; Wiley et al., 2017). Zebrafish have high fecundity external fertilization, resulting in large numbers of embryos available.

Small sizes and abundance of embryos are ideal for high-throughput screening (Horzmann and Freeman, 2018), in which the compounds tested can simply added in the medium of zebrafish, which will passively diffuse (Mathias et al., 2012).

Comparative neurogenetic and neuroanatomical analyses reveal high degrees of conservation between the nervous systems of zebrafish and mammals. Mammalian brain subdivisions, such as the telencephalon, diencephalon, mesencephalon, and rhombencephalon, have zebrafish counterparts (Wullimann and Mueller, 2004; Wullimann, 2009). Additionally, zebrafish and mammals share developmental processes, such as neurogenesis, axon guidance, and relevant genetic signaling (Wullimann and Mueller, 2004; Wullimann, 2009). For example, in all vertebrates the nervous system derive from the ectoderm, which sequentially generate neural plates and neural tubes (Lee and Freeman, 2014). Later, the telencephalon, diencephalon, mesencephalon, and rhombencephalon are visible (Hjorth and Key, 2002; Kimmel et al., 1995). Proneural genes such as neurogenin 1 (neurog1), neurogenic differentiation (neurod), and achaete-scute complex-like 1 (ascl1) are critical for neuron fate determination (Allende and Weinberg, 1994; Korzh and Strahle, 2002). The central nervous system in zebrafish is largely developed within three days of fertilization, making them ideal for rapid neurotoxicity tests.

1.2. Neurotoxicity tests in zebrafish

Damage to the nervous system caused by poisonous chemicals is known as neurotoxicity. Several approaches of using zebrafish in neurotoxicity screening have been developed during the past decade, taking into account the beneficial characteristics of zebrafish. Different neurotoxicity endpoints, including changes in gene expression, neural morphogenesis, and neurobehavioral profiling have been used to assess the effects of substances on zebrafish nervous system (Chueh et al., 2017; Kalueff et al., 2013; Truong et al., 2014).

1.3. Gene expression profiling

Neurotoxicity can be determined by identifying alterations in neural circuits, for which a variety of nervous system genes may be utilized as markers. The transcripts of genes expressed in neural stem cells and/or developing or matured, such as elval3, are among these indicators (Park et al., 2000). A significant obstacle to chemical neurotoxicity is a lack of understanding about the molecular targets of possible neurotoxicants (Crofton et al., 2012). Microarray and high-throughput sequencing technologies have permitted a comprehensive examination of the developing transcriptome's regulation in response to chemical exposure. These approaches allow simultaneous investigation of the transcriptional expression levels of hundreds of thousands of genes in response to chemical exposure using these methods (Rao et al., 2018; Xing et al., 2021). qPCR and in situ hybridization may be employed to validate individual gene alterations, with the latter detecting cell-specific changes in gene expression (Xing et al., 2015).

1.4. Neural morphogenesis analysis

Morphometric endpoints can be investigated using whole-mount immunostaining with neuron-specific antibodies, such as znp-1 and zn-5 antibodies for zebrafish primary and secondary motor neurons, respectively (Zeller et al., 2002). Dye microinjection can also be used to label and visualize in vivo specific neurons and subsets of axonal tracts (D' Amora et al., 2016). Oxidation-induced apoptosis is another technique frequently used to assess the neurotoxicity of various chemicals, in which acridine orange staining has been widely used to detect apoptosis (Parng et al., 2007).

In addition, Zebrafish transgenic lines are an extremely useful tool for determining the neurotoxicity of nanoparticles. Numerous lines have been used as neurotoxicity indicators. Pan neurons can be labeled with *Tg(huc:mcherry)* (Park et al., 2012), whereas motor neurons can be labeled with *Tg(hb9:egfp) (Development 132: 4471–4481)*. Due to the fact that fluorescent proteins are visible during live imaging, they can be used to assess the health of the neurons in which they are expressed.

1.5. Neurobehavioral tests

Locomotor activity is organized at various levels of the nervous system. The neuromuscular junction, muscle, spinal cord, hindbrain, or more rostral levels can all modify locomotor activity (Drapeau et al., 2002; Selderslaghs et al., 2010). A few more specific tests have been developed to assess different neurobehavioral domain, the majority of which are detectable until 5 days after birth. With the capability of a quick rapid video camera, it is possible to monitor more detailed swimming behavior: acceleration, turning angles or frequency, and time spent in various swimming modalities (normal swimming; large movement swimming; small movement swimming; burst swimming, etc.).

In zebrafish, stereotypical sensorimotor responses for vision and audition are detectable by 5 dpf. The light/dark cycle test is frequently used to evaluate vision. As with most mammals, zebrafish are diurnal, with increased activity in light. The optokinetic response test is another vision test. Larvae are immobilized in gels and placed in a circular arena with a rotating striped perimeter, where their saccade movement (following the rotating movement) is measured (Brockerhoff, 2006). To assess auditory responses in larvae and adult zebrafish, a tap-induced startle response has been widely used (Eddins et al., 2010).

Adults exhibit more complex behavior and are larger than larvae, allowing for the visualization of more subtle movement patterns. To evaluate anxiety-like behavior in zebrafish, a novel tank test is performed. Adult zebrafish are placed in a novel tank, and the amount of time spent at the bottom is recorded and correlated with anxiety levels (Egan et al., 2009). Aggression is associated with territorial defense, agonistic intra-social interaction to gain access to a mate or food, prey capture, and predator avoidance behavior. Numerous methods, ranging from mirror tests to dyadic fights and group social interaction, have been used to investigate aggressive-like behavior in laboratory fish (Way et al., 2015). The mirror test is widely used because it detects the majority of aggressive motivation in animals without harming them.

In zebrafish, learning and memory behaviors are also measurable. Habituation is one of the simplest types of learning, defined as the process by which a response (often reflexive) becomes less likely or vigorous following repeated stimulation (Rankin et al., 2009; Thompson and Spencer, 1966). This may be explained by the fact that animals adapt to non-lethal stimuli in order to conserve resources for potentially lethal stimuli. In contrast to habituation, sensitization is a type of non-associative learning in which exposure to an arousing stimulus, most frequently one that is unpleasant or noxious, results in response enhancement (Groves and Thompson, 1970).

Typically, more than one endpoint is used in a neurotoxicity study, depending on the purposes and levels of details to look at. Gene expression changes are good ways to check the basis of neural circuits at the molecular level, and neural morphology analysis is useful for evaluating cellular responses. Adult behavioral testing is robust to decipher the deleterious effects in specific neural circuits, whereas larval locomotor activity is a common and large-scale way to identify changes in neural behavior. The combinations of these neurotoxicity endpoints provide powerful approaches for determining the neurotoxic effects of a substance (Fig. 1).

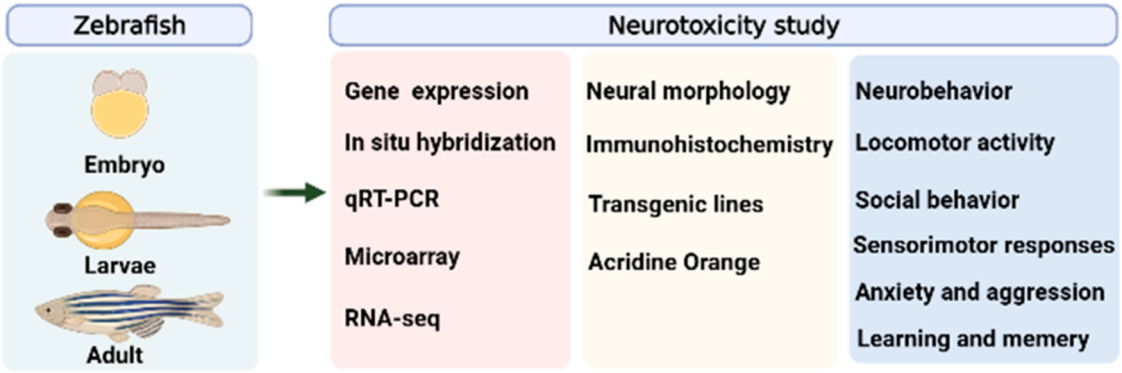

Fig. 1. Schematic illustration of neurotoxicity study in zebrafish from different angles. This figure was generated by BioRender.

2. Neurotoxicity of inorganic nanoparticles

2.1. Silica nanoparticles

Silica NPs and their derivatives with particle sizes less than 100 nm are widely used in diverse biomedical applications and food manufacture that consumed more than 1 million tons every year due to their inert property (Croissant et al., 2018; Li et al., 2020). Specifically, Silica NPs are widely used in drug delivery system due to their large number of empty pores and thus can loaded large amounts of active drugs (Shukur et al., 2022). Biosafety issues of silica-based nanomaterials have received attention, and multiple studies have tested their neurotoxic effects on zebrafish. Interestingly, silica NPs (200 mg/L) do not cause any developmental or organ damage including cardio and hepatotoxicity, but specially lead to neurotoxicity according to locomotor response (LMR) with light/dark cycles and photomotor response (LMR) stimulated by light (Pham et al., 2016). Consistently, silica NPs at environmental relevant concentration (0.05–100 ug/L) does not induce developmental morphological defects but instead disrupts locomotion profiling as show by locomotion response and Light/Dark challenge assay (Li et al., 2021). When treated with silica NPs (12 ng/nl), larvae have an increase of apoptotic cells in the central nervous system, which is accompanied with disturbed neuroactive ligand–receptor interaction signaling pathway (Wei et al., 2020). Whether this accounts for the neural behavior changes in lower concentration still require further investigation.

The neurotoxicity effects of silica NPs are size-dependent. 15 nm NPs have greater neurotoxic effects (rest/wake behavior) than the 50 nm NPs, but 50 nm NPs have greater developmental toxicity (e.g. mortality, lower LC50, malformation) on the zebrafish larvae than the 15 nm NPs (Xue et al., 2013a, 2013b). Smaller size of silica NPs (15 nm vs 50 nm) have greater changes in color preference and more significant decrease in locomoter activity (Parkinson's-like behavior) (Li et al., 2020). The neurotoxic effects of all-size silica NPs are generally concentration-dependent, with higher concentrations having more negative consequences.

2.2. Carbon dots nanoparticle

Carbon nanodots (CDs) with functionalized surfaces group are widely used in drug delivery and bioimaging areas due to their excellent photostability, photoluminescence and water solubility (Sun et al., 2019; Yang et al., 2018). The neurotoxicity of CDs is only beginning to reveal. The toxicity of synthesized CDs with the size around 2.4 nm was assessed on the zebrafish model. Under 150 μg/mL concentration, the CDs showed no embryonic toxicity or apparent teratogenic effects. However, when CDs were exposed to zebrafish embryos at concentrations greater than 150 μg/mL, significant side effects were observed. Notably, CDs exposure can disturb the release of dopamine, which may lead to neuronal damages (Liu et al., 2020a, 2020b).

2.3. Graphene oxide nanoparticle

Graphene oxide (GO) are widely used in many biomedical applications including drug carrier, biosensing, and cancer diagnosis due to their excellent physicochemical properties (Georgakilas et al., 2016; Liu et al., 2013). Carboxyl graphene oxide induces neurotoxicity and Parkinson's disease-like symptoms in zebrafish larvae, which may attribute to an increase of oxidative stress-related genes (Cao et al., 2021). Moreover, Di Mauro revealed that reduced graphene-related materials could affect the nervous system and caused neurotoxicity including impairing swimming performance and breaking synaptic communication by using larval zebrafish in a high-throughput screening of locomotor behavior (Di Mauro et al., 2021).

3. Neurotoxicity of metal-based nanoparticles

3.1. Ag nanoparticles

Because of their large surface area to volume ratio, which allows for better contact with the microorganism, silver nanoparticles (AgNPs) have good antibacterial properties and can fight both Gram-positive and Gram-negative bacteria (Kim et al., 2007; Morones et al., 2005). Therefore, AgNPs are widely used in a variety of products, including everyday consumables like cosmetics and healing creams, as well as laboratory gowns and medical products like surgical gowns and dressings. Therefore, the neurotoxicity effects of AgNP in zebrafish have been studied in multiple studies. After 48 h of exposure to AgNPs and $AgNO_3$, zebrafish embryos develop abnormally in both primary and secondary motor neurons, as well as delayed development, tail malformations, and edema (Muth-Kohne et al., 2013). In general, the toxicity of AgNPs to the environment is proportional to their size (Ferdous and Nemmar, 2020; Kim et al., 2012). AgNPs have a size-dependent neurotoxic effect on zebrafish embryos, with smaller AgNPs accumulating more in the head area and causing more significant changes in head and eye sizes, as well as neuronal developmental genes (Xin et al., 2015).

The effects of AgNPs on neural behavior profiling have also been revealed. The neurotoxicity effects of AgNPs are depending on particle coating and size that different AgNP formulations could produce distinct patterns of developmental neurotoxicity (Powers et al., 2011). When developing zebrafish are exposed to AgNPs at environmentally relevant concentrations (0.3, 1, 3 ppm), they exhibit transient hyperexcitability in their photomotor response (Gonzalez et al., 2018). In adult, a more detailed neural profiling of AgNPS was deciphered. 10 ppb $AgNO_3$ impairs social preference, social recognition, learning, and memory in zebrafish, but has no effect on anxiety, aggressiveness, or shoaling behavior (Fu et al., 2021), implying that specific neural circuits are targeted rather than general toxicity.

3.2. TiO_2 nanoparticle

TiO_2 NPs are widely used in many commercial fields due to their unique electrical and optical properties, such as sunscreen pigments, components of soaps, shampoos, and toothpastes (Noman et al., 2019). Due to their ability to form reactive oxygen species (ROS) on their surface when excited with UV light, TiO_2 NPs as a photo-catalyst are also used in the photodegradation of pollutants, wastewater treatment, and tumor cell destruction (Shi et al., 2013). However, TiO_2 NPs are normally hydrophoic and classified as group 2B carcinogen by the International Agency for Research on Cancer (IARC) (Skocaj et al., 2011).

Until recently, TiO_2's neurotoxicity drew attention. Sheng and co-authors investigated the neurotoxicity of TiO_2 NPs in adult zebrafish and discovered that even low doses of TiO_2 NPs can harm zebrafish by disrupting spatial recognition memory (Sheng et al., 2016). TiO_2 NPs can also reduce swimming speed and clockwise rotation times (Gu et al., 2021). The loss of dopaminergic neurons in zebrafish suggests that TiO_2 NPs exposure can cause neurotoxicity and increase the risk of Parkinson's disease (Jin et al., 2021). TiO_2 NPs could accumulate in the brain of zebrafish larvae, leading to the generation of reactive oxygen species (ROS) and hypothalamus cell death (Hu et al., 2017). Furthermore, TiO_2 NPs inhibit motor neuron axonal growth (Gu et al., 2021), which could partially explain the behavioral change.

Interactions between TiO_2 NPs and other organic toxicants have also been tested. TiO_2 NPs may help zebrafish larvae absorb multiple toxicants, including BDE-209, bisphenol A, and pentachlorophenol (Wang. et al., 2014). Coexposure of nano-TiO_2 with pentachlorophenol or bisphenol A significantly increases thyroid hormone contents, leading to thyroid endocrine disruption and developmental neurotoxicity in zebrafish. In zebrafish larvae, nano-TiO_2 can increase the accumulation of triphenyl phosphate, which causes neuron abnormalities and serotonin system dysfunction, as well as exacerbated abnormal locomotors (Fan et al., 2022).

3.3. Neurotoxicity of other metal-based nanoparticles

Several other metal-based nanoparticles have also been found neurotoxic in zebrafish, including copper oxide nanoparticles (CuO NPs), Gold-based Suvarna Bhasma, and Iron oxide (Biswas et al., 2020; Laurent et al., 2014; Sun et al., 2016). For example, Suvarna Bhasma gold was nontoxic in rat model but has anxiolytic effects in zebrafish behavioral model evidenced by the time spent in the upper zone, and average swimming height (Biswas et al., 2020).

The neurotoxic effects of many metal-based nanoparticles rely on concentration and physicochemical parameters. The effects of IONPs (Iron oxide nanoparticles) and iron ions on neurotoxicity and cardiotoxicity were dependent on the exposure system, including concentration and exposure condition (Pereira et al., 2020). In addition, SPION (Superparamagnetic iron oxide nanoparticles) coated with cross-linked aminated dextran (CLIO-NH2) showed acute brain toxicity due to the inhibition of acetylcholinesterase and induction of apoptosis (de Oliveira et al., 2014). The activity of acetylcholinesterase in embryos affected by nano-Pd is also in a dose-dependent manner (Anila et al., 2021). Magnetic loaded doxorubicin was less toxic than free doxorubicin in terms of cardiotoxicity and neurotoxicity in Zebrafish embryos and larvae, indicating that nanoparticle coating can affect toxicity (Igartúa et al., 2018).

3.4. Neurotoxicity of organic nanoparticles

Because organic nanoparticles, either natural or synthetic, are widely used in a variety of fields, including industry and medicine, their neurotoxicity has gotten a lot of attention. The neurotoxic effects of cellulose nanofibrils (CNFs) and cellulose nanocrystals (CNCs), which are commonly used in tissue engineering scaffolds and filter medium, have been investigated. CNFs and CNCs in concentrations less than 30 mg/mL were found to have no discernible effect on zebrafish embryo toxicity, including malformation and mortality. The motor ability of zebrafish larvae are disrupted when incubated with either CNFs or CNCs. Furthermore, both CNFs and CNCs severely inhibited motor neuron differentiation and morphogenesis, possibly as a result of altered neural gene expression and patterned blood vessels (Liu et al., 2020a, 2020b).

The cytotoxicity and biocompatibility of PAMAM dendrimers of generations 4.5 and 4.0 as drug Carbamazepine (CBZ) carriers have been studied. Igartua found that generation 4.0 PAMAM reduced the survival rate of zebrafish embryos and caused cardiovascular dysfunction, but generation 4.5 PAMAM as CBZ carrier has not shown neurotoxicity, cardiotoxicity, or malformations (Igartua et al., 2018).

Because of their biocompatibility and biodegradability, chitosan nanoparticles are commonly used as brain-targeting carriers (Nagpal et al., 2010). Both chitosan NPs and Tween 80-modified chitosan NPs (TmCS-NPs) inhibited zebrafish development on a dose-dependent basis, resulting in a higher rate of deceased hatching, increased mortality, and increased malformations. In addition, compared to developmental toxicity, zebrafish are more sensitive to neurotoxicity including neurobehavioral, muscle structure, and motor neurons development when they were exposed to both chitosan NPs and TmCS-NPs even at a relatively low concentration (Yuan et al., 2016).

4. Limitations and future prospects

When using zebrafish predicts the potential effects of nanoparticles in mammals, distinctions between zebrafish and mammals, most notably between humans and zebrafish must be considered. To begin, the manner in which chemicals pass through zebrafish and human bodies may differ, as zebrafish embryos do not develop inside a placenta but instead absorb chemicals directly from the cultured medium. Additionally, a small amount of solvent must be used because chemicals that are not water soluble cannot be dispersed easily in the embryo medium, which may affect the physical effects of these chemicals (Maes et al., 2012).

Our knowledge of nanoparticles' potential neurotoxicity is just starting. Systematic investigation of a single nanoparticle throughout many developmental windows in zebrafish and comparison of various nanoparticles, particularly those with comparable characteristics, may give significant information about their neurotoxicity. High-throughput transcriptome analysis will be beneficial in identifying novel nanoparticle targets for neurotoxicity. The incorporation of other omics technologies, such as proteome, metabolome, and methylome investigations, will aid in the assessment of neurotoxicity in nanoparticles. Additionally, other morphologies, such as glia, another key component of the nervous system, may be employed for neurotoxicity investigations. Additionally, given the interaction of nanoparticles with other substances that may coexist in the environment, more combination action should be investigated.

5. Conclusions

Zebrafish have a number of benefits as model organisms and are capable of overcoming the constraints of other systems, which makes them potentially ideal as neurotoxicology models. Applications of zebrafish to assess neurotoxicity of nanoparticles in embryos, larvae, and adults have been reviewed. The degree of neurotoxicity is linked to the nanoparticles' hydrophobicity, size, concentration, and physicochemical parameters. Zebrafish enable the testing of neurotoxicity endpoints by integrating many assays, and thus increased use of zebrafish in chemical testing will expedite this process and aid in the understanding of neurotoxicity processes of nanoparticles (Table 1).

Table 1
The neurotoxicity effects of nanoparticles in zebrafish.

Category	Particles	Size	Stages	Concentration	Neurotoxicity effects	References
Inorganic	silica	19.6 ± 4.5 nm	Adult	100, 300 and 1000 mg/mL	• Perturbation in the expression of parkinsonism-related genes and autophagy-related genes • Impairment in light/dark preference behavior and exploratory behavior; induction of anxiety; and a reduction in memory capability	(Li et al., 2020)
Inorganic	silica	13.9 ± 1.8 nm	Embryo, Larvae	0.05, 0.1,1, 5, 10, 100 μg/L	• Perturbation in the expression of c-fos or gfap • Down-regulation of gap43 • Disturbance of locomotion profiles	(Li et al., 2021)
Inorganic	silica	62 nm	Embryo	3, 6, 12 ng/nL	• Axonal disruption • Downregulation of neural function-related genes (e.g. grm6a, drd1b, etc)	(Wei et al., 2020)
Inorganic	silica	20, 50, 80 nm	Embryo	200 mg/l	• Alteration of photomotor responses in embryos and locomotor responses in larvae	(Pham et al., 2016)
Inorganic	silica	15 nm and 50 nm	Embryo	50, 200, 350, 500, 650, 800, 1000 μg/mL	• Rest/wake behavior is disrupted more by 5 nm NPs than by 50 nm NPs.	(Xue et al., 2013a, 2013b)
Inorganic	silica	15 nm, 50 nm	Adult	300 or 1000 mg/mL	• A decrease in the expression of tyrosine hydroxylase (TH) • A decrease in the locomotive activity • Perturbation in the swimming path patterns and color preference activity	(Li et al., 2014)
Inorganic	Carbon dots (CDs)	2.4 nm	Embryo	50, 100, 150, 200, 250, 300, and 400 μg/mL	• Spinal cord flexure • A reduction in zebrafish larval locomotor activity • A decrease in dopamine levels and TH-positive neurons(CD concentrations >200 μg/mL)	(Liu et al., 2020a, 2020b)
Inorganic	Graphene oxide		Embryo	100 μg/mL	• A decrease in locomotor activity and performance	(Di Mauro et al., 2021)
Inorganic	Graphene-family	50–200 nm	Embryo, larvae	10, 50 and 100 mg/L	• Perturbation in the expression of genes involved in neurodevelopment and neurotransmitter pathway • An increase in the activities of AchE and ATPase and oxidative stress • Neurodevelopmental abnormalities and altered tendency of locomotor	(Cao et al., 2021)
Metal nano-particle	AgNPs	4.99 ± 2.01 nm, 9.35 ± 1.97 nm	Embryo	0.481, 0.963, 1.925, 3.850, 7.700, 11.550, and 23.100 mg/L	• Smaller heads with hypoplastic hindbrain and smaller eyes. • Perturbation in the expression of neural development-related genes (gfap, huC and ngn1), metal-sensitive metal-lothioneins, and ABCC genes, AhR2, and Cyp1A.	(Xin et al., 2015)
Metal nano-particle	AgNPs	1–100 nm	Embryo	0.03, 0.1, 0.3, 1, and 3 ppm (mg/L)	• Transient behavioral changes during development	(Gonzalez et al., 2018)
Metal nano-particle	AgNPs	< 20 nm	Embryo	0.5, 0.66, 0.87, 1.15, 1.5, 4, 8, 16 mg/l,	• Delayed development Abnormalities in both primary and secondary motor neurons	(Muth-Kohne et al., 2013)
Metal nano-particle	AgNPs	10 nm AgNP-C and AgNP-PVP, 50 nm AgNP-PVP	Embryo	0.01–100 μM	• Normal responses in AgNP-C exposed embryos. • Altered light responses in embryos exposed to AgNP-PVPs	(Powers et al., 2011)
Metal nano-particle	$AgNO_3$		Adult	10, 30, 50, 100, and 1000 ppb	• A decrease in neural activity in the medial and dorsal zones of the dorsal telencephalic areas • Impairment in social preference, social recognition, learning, and memory in zebrafish(10 ppb)	(Fu et al., 2021)

(*continued on next page*)

Table 1 (*continued*)

Category	Particles	Size	Stages	Concentration	Neurotoxicity effects	References
Metal nano-particle	TiO_2		Adult	5, 10, 20, and 40 μg/L	• Over proliferation of glial cells, neuron apoptosis levels of norepinephrine, dopamine, and 5-hydroxytryptamine were significantly decreased • NO levels were markedly elevated significantly • Activated expressions of C-fos, C-jun, and BDNF genes, and suppressed expressions of p38, NGF, CREB, NR1, NR2ab, and GluR2 genes • Disrupted spatial recognition memory	(Sheng et al., 2016)
Metal nano-particle	TiO_2	Micro-TiO2:1–2 μm, Nano-TiO2: 20 nm	Embryo	0.01, 0.1, and 1.0 mg/L nano-TiO_2 and 1.0 mg/L micro-TiO_2	• Affected motor neuron axon length in Tg (hb9-GFP) zebrafish • Decreased central nervous system (CNS) neurogenesis in Tg (HuC-GFP) zebrafish • Affected genes related to neurogenesis (nrd and elavl3) and axonal growth (α1-tubulin, mbp, and gap43) • Decreased the body length and weight (1.0 mg/L nano-TiO_2) • Reduced the swimming speed and clockwise rotation times	(Gu et al., 2021)
Metal nano-particle	TiO_2	33.4 ± 1.9 nm.	Embryos	0, 0.1, 1, 10 μg/mL	• Resulting in reactive oxygen species (ROS) generation and cell death of hypothalamus • Increased the pink1, parkin, a-syn and uchl1 gene expression • Causes PD-like behavioral disturbances	(Hu et al., 2017)
Metal nano-particle	TiO_2	21 nm	Embryos	1 mg/L	• Not alter the migration of macrophages into the brain and retina during embryonic development	(Wang et al., 2014)
Metal nano-particle	CuO	50–60 nm	Embryos	50, 25, 12.5, 6.25, or 1 mg/L	• Activated the detoxifying enzymes • Underdeveloped liver • Reduced locomotor capacity	(Sun et al., 2016)
Metal nano-particle	Gold	45 ± 2.8 nm	Adult	3 mg/kg (therapeutic dose, TD) up to 30 mg/kg (10 TD)	• No significant alteration	(Biswas et al., 2020)
Metal nano-particle	Iron oxide	3.97 nm ± 0.85 nm	Embryo	0.3, 0.6, 1.25, 2.5, 5 and 10 mg/L	• Cardiotoxic effects (reduced heartbeat, blood accumulation in the heart and pericardial edema)	(Pereira et al., 2020)
Metal nano-particle	Nano-Pd	5.5 nm	Embryo, Adult	22 and 0.4 ng/L	• Affect apoptosis • Inhibiting the AChE activity in both the concentrations of brain and liver • The antioxidant enzyme activity such as superoxide dismutase (SOD), catalase (CAT), glutathione-S-transferase (GST), glutathione reductase (GR) and lipid peroxidation (LPO), showed a significant change	(Anila et al., 2021)
Metal nano-particle	ZnO	ZnO NPs：54.3 ± 7.3 nm, s-ZnO NRs： D: 251.0 ± 29.0 nm, L: 815.0 ± 92.0 nm, and L-ZnO NRs：D: 159.3 ± 17.9 nm, L: 1.1 ± 0.15 μm	Embryo	0.1, 1, 10, 50, 100 μg/mL L-ZnO NRs	• Considerable numbers of apoptotic cells in the brain areas • Significant decrease in the total distance moved (> 10 μg/mL)	(Jin et al., 2021)
Metal nano-particle	Magnetic	MNPs@FA:453.7 ± 10.61 nm MNPs@FA@DOXO:597.5 ± 34.82 nm	Embryo, larvae	DOXO: 3.12–50.0 μg/mL; MNPs@FA@DOXO: 3.12–50.0 μg/mL of DOXO in 70.75–1132 μg/mL of MNPs@FA，or MNPs@FA:70.75–1132 μg/mL	• Significant embryo-hatching delay and toxicity (>10 μg/mL) • MNPs@FA@DOXO reduced the cardiotoxicity and promoted a more rapid and significant uptake of DOXO	(Igartua et al., 2018)
Metal nano-particle	Superparamagnetic iron oxide	5.5 ± 1.4 nm	Adult	200 mg/kg	• Decreased AChE activity • Significantly higher level of ferric iron in the brains	(de Oliveira et al., 2014)

(*continued on next page*)

Table 1 (*continued*)

Category	Particles	Size	Stages	Concentration	Neurotoxicity effects	References
orgainc	CNFs、CNCs	CNFs:50–70 nm; CNCs:24–35 nm	Embryo	between 30 mg/mL and 0.1 μg/m	• Induction of casp8, casp 9 and jun genes • Reduction in the exploratory performance • The differentiation and the morphogenesis of motor neurons were significantly interrupted • Resulted in compromised motor ability	(Liu et al., 2020a, 2020b)
orgainc	PAMAM dendrimers	DG4.0 : 14,214 g/mol DG4.5 : 236.27 g/mo	Embryo	250 μL of 10-fold-serial dilutions prepared in the E3 medium of CBZ (0.3–30 μM) or D-CBZ complexes (0.012–1.2 μM D and 0.3–30 μM CBZ)	• Reduction of the movement and the heartbeat	(Igartua et al., 2018)
orgainc	Chitosan	CS-NPs: 247 ± 20 nm; TmCS-NPs : 251 ± 15 nm	Embryo	5, 10, 20, 30, 40, and 50 mg/L	• Inhibited axonal development of primary and secondary motor neurons, and affected the muscle structure • Dose-dependent increase in developmental toxicity (decreased hatching rate, increased mortality and incidences of malformation) • Decreased spontaneous movement in TmCS-NP treated • Hyperactive effect in CS-NP treated	(Yuan et al., 2016)

CRediT authorship contribution statement

XL and LT provided ideas and wrote the paper. ZY, YQ, LD, XL were responsible for the retrieval of papers. All authors read the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Consent for Publication

Written informed consent for publication was obtained from all participants.

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