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Nanoplastics and nano-ZnO facilitate Cd accumulation in zebrafish larvae *via* a distinct pathway: Revelation by LA-ICP-MS imaging

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ABSTRACT

The interaction between nanoparticles (NPs) and pollutants affects their bioavailability and toxicity. However, the processes by which NPs and pollutants change *in vivo* have rarely been explored. Here, using laser ablation-inductively coupled plasma-mass spectrometry (LA-ICP–MS), we found that both nanoplastics and ZnO NPs caused more Cd to accumulate in zebrafish larvae, but with distinct pathways. Nanoplastics could adsorb Cd^{2+} and transfer it into the larvae through the "Trojan horse" effect. The coexposure of nanoplastics and Cd^{2+} caused Cd to accumulate in the abdomen where the nanoplastics were located without dissociation, showing a lower toxic effect than Cd^{2+} exposure alone. ZnO NPs weakly adsorbed Cd^{2+}, but they increased the Zn and Cd contents in larvae by enhancing the expression of metal transporters. The coexposure of ZnO and Cd^{2+} evenly distributed Cd in the larvae, revealing a more severe toxic effect than Cd^{2+} exposure alone. Our results demonstrated the changing bioavailability and toxicity of Cd induced by different NPs. This also shows the vital role LA-ICP-MS plays in revealing the relationship between toxicity and bioavailability. In addition, the long-term effect of bioavailability on heavy metal toxicity and nanosafety deserves further investigation.

Nanoparticles (NPs) in the environment inevitably interact with coexisting pollutants, which leads to changes in their bioavailability and subsequent toxic effects [1]. However, the "fate" of these pollutants once they enter the organism, which has a noticeable effect on toxicity, is unknown. For example, Park *et al.* suggested that zebrafish might not be able to utilize 17α-ethinylestradiol (EE2) bound to nC60 because they could not be released, resulting in a diminished toxic effect [2]. Tian *et al.* reported that phenanthrene (Phe) bound by TiO_2 NPs was released due to changes in pH in the mussel gut, causing more severe toxicity [3]. While, these studies tend to infer the interaction of NPs and pollutants through *in vitro* adsorption experiments without *in situ* locations. Since such processes in organisms are very complex and largely unclear, exploring the interaction between NPs and pollutants *in vivo* is essential for linking the biological effects of chemicals to the action site of pollutants. Laser ablation-inductively coupled plasma-mass spectrometry (LA-ICP-MS) is an effective method for obtaining *in situ* elemental images from biological systems [4]. Compared with X-ray fluorescence analysis (XRF) and transmission electron microscopy (TEM), LA-ICP–MS can provide isotope information and high sensitivity. The ability to detect pollutants at ambient concentrations enables LA-ICP–MS to be a promising tool in the elemental imaging of inorganic pollutants [5], NPs [6] and organic pollutants [7].

In the past few decades, white pollution has been caused by the massive use of plastic products. Different types and sizes of plastics can be detected in various types of environments [8,9]. Due to their small size, nanoplastics can be easily absorbed by aquatic organisms and have the ability to adsorb other pollutants [10,11], causing health defects [12]. However, as an emerging environmental pollutant, our understanding of nanoplastics is not as deep as that of other engineered NPs. Zinc oxide NPs (ZnO NPs) as a commonly used engineering NPs has been well studied. Oxidative stress induction, neurotoxicity and genotoxic damages have been found in ZnO NPs exposure fishes [13]. Therefore, ZnO NPs has been used to compare with the toxicity of nanoplastics [14–16]. Their toxicity may be the same or different in different biological models. Exploring the different effects of engineered NPs and

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nanoplastics is of great significance to help us understanding the toxicity mechanism of nanoplastics.

Cadmium (Cd), a heavy metal, is widely used in plastic additives and is often detected in plastic products [17]. Holmes *et al.* observed the adsorption of Cd by microplastics in an aqueous environment [18,19]. Thus, high concentrations of essential elements and trace elements would be adsorbed on microplastics or nanoplastics, making them carriers of metal transportation in ecosystems [20] and affecting their subsequent bioavailability. For example, Lu *et al.* used 5 μm polystyrene (PS) to study the combined effect of microplastics and Cd on adult zebrafish [21]. Co-exposure increased the accumulation of Cd and caused oxidative damage and inflammation in tissues. Zhang *et al.* also used 10 μm PS NPs to evaluate the combined effects of microplastics and Cd on zebrafish embryos [22]. The results showed that coexposure had a negative impact on survival and heart rate. However, nano-sized microplastics have rarely been investigated. The interaction of nanoplastics with Cd^{2+} *in vivo* has not been studied either.

The interaction between NPs and Cd^{2+} after entering the aquatic organisms should be carefully considered for it would affect the bioavailability and the subsequent toxic effects of the two pollutants. Nowadays, the total internal concentration of chemicals in zebrafish embryos is usually determined using their homogenate. In this way, the information on distribution of the pollutants in the different organs of zebrafish embryos was lost. While chemical imaging could provide us with a better understanding of the toxicokinetics because it would show how chemicals are distributed in zebrafish embryos and whether they are enriched in specific areas/organs. Thus, in our work, using LA-ICP–MS, the bioavailability of Cd^{2+} induced by coexposure to PS NPs was investigated and compared with that of ZnO NPs. By linking the elemental images with the biochemical assessment, the effects of PS NPs combined with Cd^{2+} at ambient concentrations on zebrafish larvae were comprehensively explored. For comparative study, both the particle size of ZnO NPs and Eu-PS NPs used were 100 nm (Fig. S1 in Supporting information).

When NPs interact with coexisting pollutants, their bioavailability could be changed, which will lead to a change in toxic effects, such as increased accumulation and toxicity, increased accumulation but no change in toxicity, or even increased accumulation but decreased toxicity. This often has to do with the change and distribution of NPs or coexisting pollutants after they enter the organism. As a powerful elemental imaging method, LA-ICP-MS can help to locate metal contaminants and NPs *in vivo*. Through this direct imaging method, we could clearly obtain the location of pollutants and NPs to understand the interaction between them *in vivo*. The results are shown in Fig. 1. As seen, with the exposure of Cd^{2+}, Cd was uniformly distributed in the larvae except for high fisheye intensity. A higher concentration of Cd^{2+} exposure resulted in a higher Cd signal intensity. When ZnO NPs were coexposed with Cd^{2+}, the distribution of Cd was similar to that obtained under Cd^{2+} exposure alone, and the distribution of Cd in the fish body was relatively uniform. However, with the exposure of Eu-PS NPs, the accumulation of Eu-PS NPs in the heart, head, liver and pancreas of larvae was obvious, which was consistent with a previous report [23]. When Eu-PS NPs and Cd^{2+} were coexposed, the accumulation site of Eu-Ps NPs also showed corresponding accumulation of Cd. Some NPs strongly adsorb pollutants, which makes them carriers for the transmission of pollutants and affects the subsequent bioavailability. This is the so-called "Trojan-horse" effect [24]. It represents the potential carrier function of NPs for chemicals leading to a facilitated uptake of chemicals into organisms and resulting in an increased toxicity [24]. In the *in vitro* interaction study of NPs and Cd, we found that PS NPs could absorb Cd^{2+}, while the adsorption of Cd^{2+} by ZnO NPs was weak (Fig. S1C). It has been reported that PS has a high adsorption capacity

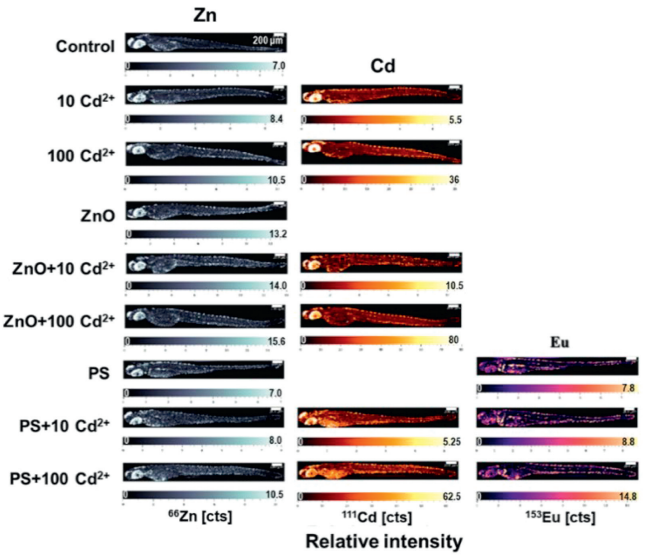

Fig. 1. Elemental image of zebrafish larvae under different exposure conditions. The concentration of NPs was 200 μg/L. And the concentrations of Cd^{2+} were 10 μg/L and 100 μg/L.

for Cd^{2+}, and as time passes, Cd^{2+} will first be rapidly adsorbed on the surface of PS and then diffuse in the pores [25]. Therefore, in the coexposure to PS NPs and Cd^{2+}, Cd entered the larvae through the "Trojan horse" effect. This would also make the distribution of Cd organ specific. Moreover, the Cd^{2+} adsorbed by Eu-PS NPs did not dissociate from Eu-PS NPs during the time span of exposure. Cd remained in the abdomen (including heart, liver and pancreas) where Eu-PS NPs were located but failed to distribute in other organs.

To further investigate the changes in NPs and Cd^{2+} bioavailability caused by coexposure, the Zn, Cd and Eu contents in zebrafish larvae were measured, and the results are shown in Fig. 2. Cd^{2+} exposure significantly increased the Cd and Zn contents in larvae. The increasing Zn content might be related to resistance to the adverse effects of Cd [26,27]. When ZnO NPs were coexposed with Cd^{2+}, the Cd content was significantly increased compared with that obtained by only exposure to Cd^{2+} (1.06 μg/g for ZnO + 10 Cd^{2+} *vs.* 0.67 μg/g for 10 Cd^{2+}, and 5.33 μg/g for ZnO + 100 Cd^{2+} *vs.* 3.43 μg/g for 100 Cd^{2+}). The Zn content also increased compared with ZnO NPs exposure alone (130.1, 144.5 and 163.2 μg/g for ZnO, ZnO + 10 Cd^{2+}, and ZnO + 10 Cd^{2+}, respectively). Eu-PS NPs exposure did not change the Zn content in larvae, and after coexposure to Cd^{2+}, there was still no significant change in Zn content compared with the control group. However, the Cd content was significantly increased after Eu-PS NPs and Cd^{2+} coexposure compared with Cd^{2+} exposure alone. Obviously, the adsorption of Cd^{2+} by Eu-PS NPs would cause more Cd to enter the larvae through the "Trojan horse" effect and accumulate in the abdomen of larvae (Fig. 1). The adsorption of Cd^{2+} by ZnO NPs was much lower than that by Eu-PS NPs; however, the coexposure of ZnO NPs and Cd^{2+} caused more Cd to accumulate in larvae than Eu-PS NPs. Therefore, the "Trojan horse" effect might not be the main reason for the change in Cd bioavailability in the ZnO NPs and Cd^{2+} coexposure groups.

It is worth noting that under exposure to Cd^{2+}, the Zn content changed significantly (Fig. 2). After adding ZnO NPs or Eu-PS NPs for coexposure, the changes in Zn were also different. In mammals, cellular Zn homeostasis is mainly maintained by Zn transporters, in which Zrt-Irt-like protein (ZIP) increases intracellular Zn levels by transporting Zn from the extracellular space to the cytoplasm. The ZIP family has also been found in zebrafish [28,29]. Besides

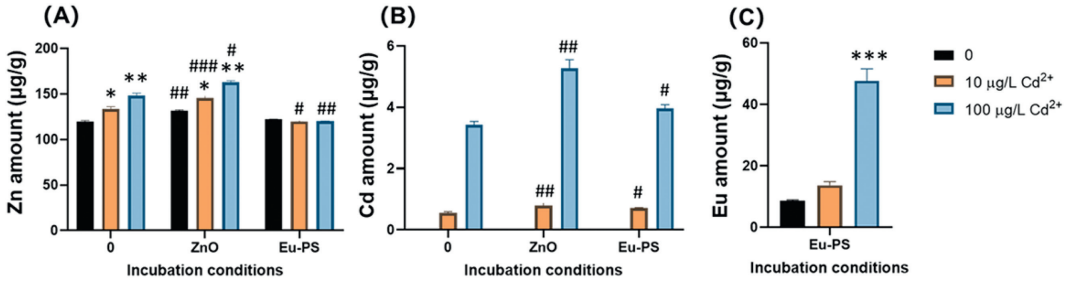

Fig. 2. (A) Zn, (B) Cd and (C) Eu contents in zebrafish larvae exposed to Eu-PS/ZnO NPs and Cd^{2+}. $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$ represent a significant difference within the groups of 0, ZnO, and Eu-PS, and $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, and $^{\#\#\#}P < 0.001$ represent a significant difference between the groups of 0, 10 and 100 μg/L Cd^{2+}.

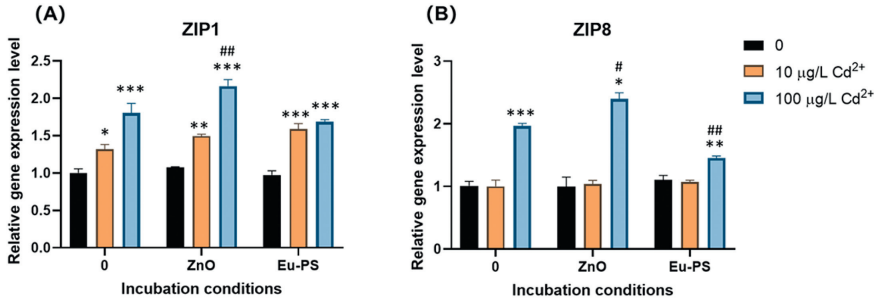

Fig. 3. The gene expression of (A) ZIP1 and (B) ZIP8 in the exposed zebrafish larvae. $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$ represent a significant difference within the groups of 0, ZnO, and Eu-PS, and $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, and $^{\#\#\#}P < 0.001$ represent a significant difference between the groups of 0, 10 and 100 μg/L Cd^{2+}.

the transportation of Zn, the ZIP family could also transport Cd and other heavy metals [30]. Therefore, the gene expression of the transport protein under different exposure conditions was investigated (Fig. 3).

Cd^{2+} exposure significantly increased the gene expression of ZIP1 and ZIP8. Through the increase in transporters, the Cd and Zn contents increased, which resulted in the uniform distribution of Cd and Zn in larvae. In the ZnO NP and Cd^{2+} coexposure group, the expression levels of ZIP1 and ZIP8 also increased, and they were significantly higher than those of ZnO NPs exposed alone. The high ZIP1 and ZIP8 gene expression levels further explained the increase in the Cd and Zn contents in the ZnO NPs- and Cd^{2+}-coexposed group compared to the individual exposures. The Zn and Cd that entered the larvae through the transporter also showed a homogeneous distribution in the larvae, as did Cd^{2+} exposure alone (Fig. 1). In the Eu-PS NP and Cd^{2+} coexposure group, the expression level of ZIP1 was comparable to that of Cd^{2+} exposure alone. When 100 μg/L Cd^{2+} was coexposed to Eu-PS NPs, the expression level of ZIP8 was even lower than that in larvae exposed to Cd^{2+} alone. This indicated that when Eu-PS NPs were coexposed with Cd^{2+}, only a small amount of the Cd might enter the larvae through transporters, while most of the Cd entered the larvae by the "Trojan-horse" effect. Therefore, Cd stayed in the organs where PS NPs accumulated instead of being evenly distributed (Fig. 1).

Since Eu-PS/ZnO NP coexposure with Cd^{2+} could change the bioavailability and distribution of Cd, the adverse effects caused by the coexposure on zebrafish larvae were investigated. Cd can induce oxidative stress and cause toxicity through the production of reactive oxygen species (ROS) [31]. Excessive production of ROS can cause lipid and protein peroxidation, leading to death and pathological damage [32]. Nonetheless, fish also have a suite of defensive mechanisms to cope with increasing oxidative stress. Therefore, we investigated the levels of ROS and antioxidative stress in zebrafish larvae (Fig. 4). From Fig. 4A, the exposure of Cd^{2+} would increase the ROS level significantly. On the contrary, Eu-PS/ZnO NPs exposure would not affect the ROS level. When Eu-PS NPs co-exposed with Cd^{2+}, the ROS level increased with the increase of Cd^{2+} concentration, and the degree was equivalent to that of Cd^{2+} exposed alone. Co-exposure of ZnO NPs and Cd^{2+} would cause the ROS level to rise sharply compared with the exposure of Cd^{2+}. Excessive ROS lead to lipid peroxidation, which can lead to the formation of malondialdehyde (MDA) [33]. Thus, from Fig. 4B, the ZnO NPs and 100 μg/L Cd^{2+} co-exposure group caused the highest MDA content. However, the MDA content barely change for ZnO NPs exposure group, Eu-PS exposure group and the ZnO NPs/Eu-PS + Cd^{2+} co-exposure group with low concentration of Cd^{2+}. Under these exposure conditions, the ROS level might not cause significant lipid peroxidation, therefore, the MDA content did not change. Cd^{2+} exposure could also affect the activity of antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT) in zebrafish [34]. As can be seen from Figs. 4C and D, under the exposure of Cd^{2+} alone, the SOD and CAT activity increased with the increase of Cd^{2+} concentration, indicating that the zebrafish larvae produced an anti-oxidative stress response to resist the ROS. ZnO NPs exposure alone would increase SOD activity. Adult zebrafish exposed to a certain concentration of Zn^{2+} showed increased antioxidant enzyme activity to address the adverse effects of Cd^{2+} [35]. Therefore, when ZnO NPs were exposed with low concentrations of Cd^{2+}, the larvae absorbed more Zn and Cd at the same time (Fig. 2), and the SOD activity was higher than that of ZnO NPs or Cd^{2+} exposure alone. More Zn can alleviate the adverse effects of Cd, which is consistent with the fact that the MDA content does not increase significantly under this exposure condition. When high concentration Cd^{2+} was exposed with ZnO NPs, the SOD and CAT activity was equivalent to that of 100 μg/L Cd^{2+} exposure. Considering that more Cd has been absorbed by larvae than 100 μg/L Cd^{2+}exposure alone at this time, it may not be sufficient for the regulation of oxidative stress, resulting in an increase in ROS and a decrease in survival rate (Fig. S2 in Supporting information). However, for Eu-PS NPs, SOD and CAT activity only increased when coexposed to 100 μg/L Cd^{2+}. Cd remained in the abdomen where Eu-PS NPs were located (Fig. 1), which indicated that the "fixed" Cd failed to attack other systems and did not cause an increase in ROS levels. Both Cd^{2+} and Zn^{2+} exposure could enhance the expression of SOD and CAT through the Nrf2 pathway to resist oxidative stress in fish [36]. The experimental results in

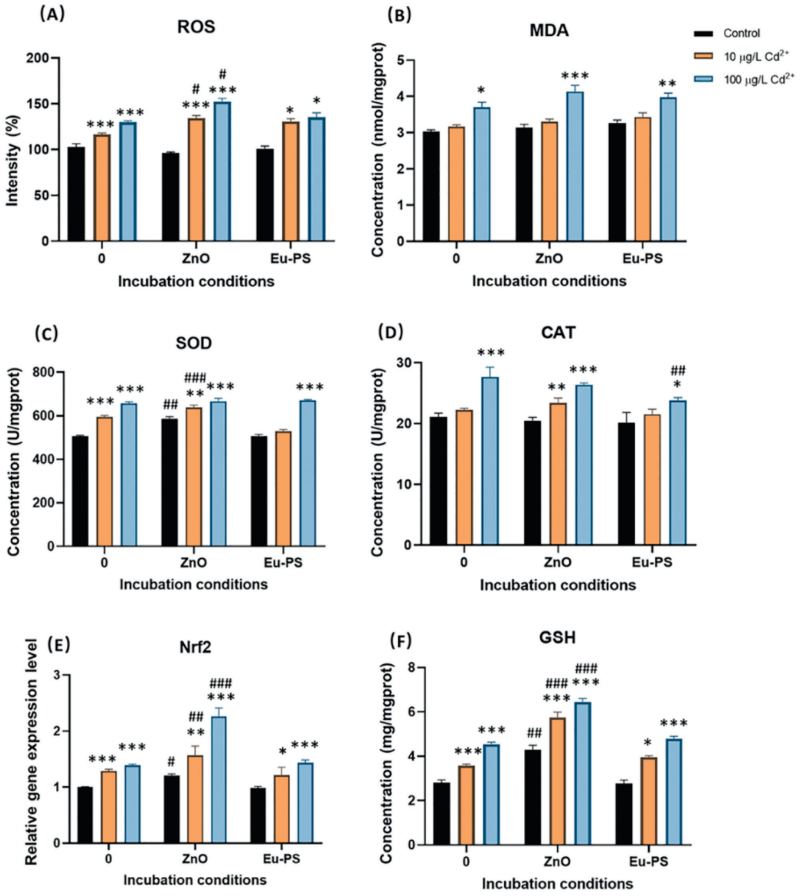

Fig. 4. (A) ROS and (B) MDA levels as well as (C) SOD activities and (D) CAT activities. (E) Nrf2 gene expression level and (F) GSH content in the exposed zebrafish larvae. $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$ represent a significant difference within the groups of 0, ZnO, and Eu-PS, and $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, and $^{\#\#\#}P < 0.001$ represent a significant difference between the groups of 0, 10 and 100 μg/L Cd^{2+}.

Figs. 4E and F showed similar results to changes in antioxidant enzymes. Oxidative stress could also induce immunotoxicity. IL-8 and TNFα have been used as markers to activate the inflammatory response in zebrafish embryos [37]. Similar to the results of oxidative stress, coexposure to ZnO and 100 μg/L Cd^{2+} caused the highest inflammatory response (Fig. S3 in Supporting information).

Cd^{2+} can cause neurotoxicity in aquatic organisms [38]. Therefore, the AChE activity, ATP content and average speed of larvae were investigated to explain the cause of the abnormal behavior of larvae under Cd^{2+} stress (Fig. S4 in Supporting information). Cd^{2+} exposure caused a significant decrease in AchE activity, ATP content and average swimming speed of larvae. Mitochondria are the main site of ROS production and the key intracellular target of Cd stress [39,40]. Dysfunction of mitochondria, which are responsible for the production of ATP, could lead to multisystem failure in energy-demanding organs such as the central nervous system (CNS) [41]. Once the mitochondrial structure is damaged, the ATP level of nerve cells is insufficient, which eventually leads to brain damage and disordered behavior of zebrafish larvae. In the coexposure to ZnO NPs and 100 μg/L Cd^{2+}, the AChE activity and ATP content as well as the average swimming speed of larvae also decreased, which was equivalent to that of Cd^{2+} exposure alone. This might be caused by the excessive Cd in the larvae. Neither Eu-PS NPs exposed alone nor exposed to different concentrations of Cd^{2+} affected the activity of AchE or behavior of fish. In other words, the neurotoxic effect of Eu-PS NP and Cd^{2+} coexposure was lower than that of ZnO NP and Cd^{2+} coexposure.

In general, ZnO NP and Cd^{2+} coexposure caused more serious toxic effects on zebrafish larvae than Eu-PS NP and Cd^{2+} coexposure in terms of oxidative stress, inflammatory response and neurotoxicity. In the ZnO NP and Cd^{2+} coexposure group, Cd was evenly distributed in the larvae through the metal transporter (Fig. 3). The evenly distributed excessive Cd could cause damage to the whole fish body, leading to more dramatic changes in the corresponding toxicity index. In the coexposure of Eu-PS NPs and Cd^{2+}, Cd was absorbed by larvae through the "Trojan horse" effect and remained in the abdomen where Eu-PS NPs were located but failed to attack other systems (Fig. 1). The “fixed” Cd explained why Eu-Ps NP and Cd^{2+} coexposure could make larvae absorb more Cd but cause less toxic effects than Cd^{2+} exposure alone (Fig. 5). This fully demonstrated that the interaction between NPs and metals *in vivo* had a significant impact on bioavailability and subsequent toxicity. This does not mean that coexposure to Eu-Ps NPs and Cd^{2+} is safe. It is unknown whether long-term exposure would lead to

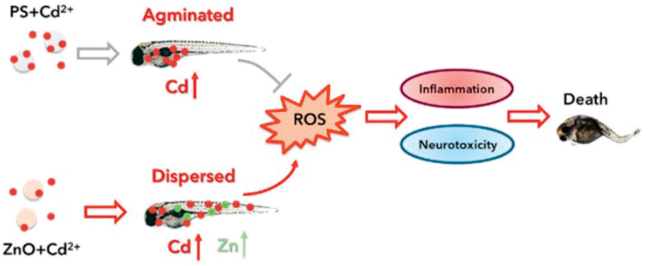

Fig. 5. Possible schematic diagram of the toxic effects caused by bioavailability of Cd on larvae co-exposed to Eu-PS/ZnO NPs and Cd^{2+}.

more dissociation of Cd from PS NPs. Our work reveals that LA-ICP-MS biological imaging combined with toxicity detection can intuitively explain the changes caused by co-exposure, indicating that LA-ICP-MS bioimaging techniques can provide new clues to study the effect of coexposure of nanoparticles with pollutants, showing great promising applications in environmental health.

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.

CRediT authorship contribution statement

Pengyu Chen: Investigation, Methodology, Writing – original draft, Writing – review & editing. **Beibei Chen:** Conceptualization, Methodology, Writing – review & editing. **Man He:** Methodology, Writing – review & editing. **Yuxi Zhou:** Validation. **Lei Lei:** Validation. **Jian Han:** Validation, Writing – review & editing. **Bingsheng Zhou:** Methodology, Writing – review & editing. **Ligang Hu:** Methodology, Writing – review & editing. **Bin Hu:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2024.109908.

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