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Review

Toxicology of Nanomaterials on Zebrafish

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Abstract: Increases in the use and the progressive manufacture of new Engineered Nanomaterials (ENMs) lead to inquire about their impact on the environment. Due to the small size, high reactivity inside organisms and the unusual physicochemical properties of the ENMs, the predictions of toxicity are very complex. The zebrafish (*Danio rerio*) has been granted as a practical alternative to study the toxicity of ENMs. In this article the toxic effects of silver nanoparticles, titanium oxide nanoparticles, zinc oxide nanoparticles, carbon nanotubes, copper nanoparticles, gold nanoparticles, cadmium nanoparticles and nano plastics were reviewed trough the most recent literature available. Every ENMs should be studied in depth independently, considering co-exposures, environmental matrices, the effects of variations in size and concentrations, the potential effects of prolonged exposure, the coverage of ENMs, specific organism and targeted organs. This information will help to identify deficiencies in research trends and reinforce the safest ways to use ENMs.

Keywords: Zebrafish, Toxicity, Nanomaterial, Copper, Gold, Silver, Titanium Oxide, Zinc Oxide, Carbon Nanotubes, Cadmium, Nanoplastics, Environmental Impact

Introduction

The Engineered Nanomaterials (ENMs) are very innovative products that have a wide field of utilities, so they can easily access the environment. The properties of ENMs are as different as their composition, doing predictions of destination and risk assessment very complex. The physicochemical properties of nanomaterials are not enough to estimate organisms risks; it is necessary to consider other aspects including matrix, ions, impurities, physical and chemical parameters and the entire ecosystem as a whole. The aquatic environment is one of the matrices with more probability to be affected by ENMS and it is also very difficult challenge to predict. Aquatic systems can interact with nanomaterials and transform them by dissolution, aggregation, sedimentation and photoreactions, among others (Vale *et al*., 2016). The reactions between ENMs and environmental pollutants are also a cause for concern. In cell-free systems the most usual interaction between ENMs and pollutants is the adsorption, based on hydrophobic effects, hydrogen bonds, ion exchange and pi-pi bonding and covalent and electrical interaction (Liu *et al*., 2018). Under cellular and molecular approach, ENMs within the organism can modify bioaccumulation and affect the biodistribution and metabolism of pollutants (Liu *et al*., 2018). Some interactions may produce mitigations of toxic mechanisms in specifics organisms. Dissolved natural organic matter, humic substance, carbohydrates and proteins can play an important role in reducing the adverse effects of ENMs released in aquatic environments (Kteeba *et al*., 2017).

The ENMs are increasing their environmental applications in different processes, such as water and waste water treatment, due to their properties of high surface area, energy cost and energy efficiency, ease of regeneration and chemical activity, among others (Gautam *et al*., 2019). The efficiency of ENMs in certain processes, for example remediation of contaminated water, is clearly established, although the uses in the free environment are subjects of great concern. Fate predictions of ENMs, especially on aquatic systems, are quite difficult and, until now, modeling is restricted to the processes of aggregation and dissolution (Williams *et al*., 2019). Each nanomaterial has specifics properties that can change according to the conditions and, even more, the same ENM can vary its effects by size and concentrations.

Biological Models and "Nanotoxicology"

Studies have been underway for a number of years to determine the potential toxicity of specific nanomaterials and, until now, the researchers conclude with the need to generate new assessment and strategies of evaluation. Approaches as *in silico* technics emerge as essentials methods for risk assessments that undoubtedly have their advantages. Nanotoxicity studies, developed using computational methods, have the potential to be rapid and inexpensive screening tests, allowing the categorization of materials by toxic levels (Oksel *et al*., 2015). ENMs toxicological modeling faces some crucial issues, i.e., experimental data deficiency, lacks of common metrics, the need for standardized toxicological protocols and validated methods, instability of small particles that produce bulk materials by agglomeration and the complexity of creating a complete database of attributes to predict toxicity across the great diversity of ENMs (Oksel *et al*., 2015). Most of the research concludes on the need to develop research that contributes with quality data to the characterization of the toxic effect of ENMs. The use of biological models is presented as a useful method to investigate the behavior of ENMs, providing empirical information to improve modeling, methodologies and materials manufacturing. The *in vivo* toxicity models commonly applied to evaluate nanomaterials include Daphnia magna, zebrafish, rats, C. elegans, Drosophila and artemia, among others.

Zebrafish as Biological Model

Danio rerio, or zebrafish, is a well-known model organism studied since 1960's (Kalueff *et al*., 2014). This organism has several characteristics that make it suitable for environmental toxicology research, starting with the economic feasibility, in comparison with others biologicals models of vertebrates. As shown in Fig. 1, due to the relatively small size of the adult fish, studies with a large number of samples are feasible. The external fertilization and transparency during development are useful characteristics to toxicological studies. More important is that D. *rerio* is very homologue to humans; they have chambers and rhythmically pump oxygen-carrying blood through the body; they have eyes with retinal structure, liver, pancreas, kidneys and intestines, backbone and more than 80% of their genes have human counterpart (FDA, 2013). A large part of the studies with *D. rerio* focus on teratogenic and development effects of substances on the larvae and on the fry. Common use to assess the toxic effect on development is due to rapid reproduction, embryos are available throughout the year, transparency of the larvae body, or easy breed, among others. D. *rerio* is now used to evaluate the potential toxic effects of ENMs.

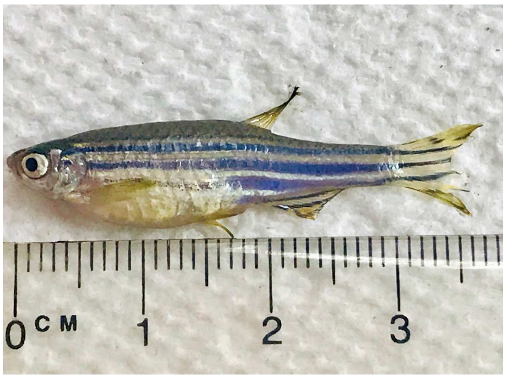

Fig. 1: Medium size adult zebrafish (D. *rerio.*)

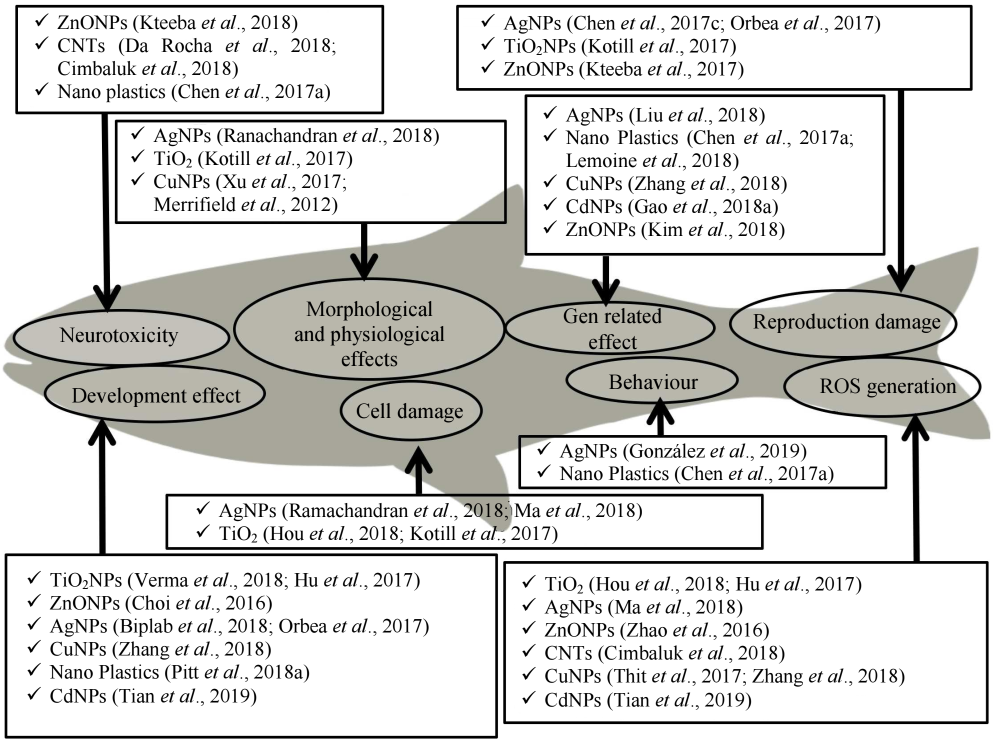

Fig. 2: Toxic effects of ENMs on D. *rerio* according to references cited in this article

Studies confirm that some ENMs share the same adverse effects on the zebrafish as show in Fig. 2. Mixtures and variations in ENMs properties could have the worst effects.

Silver Nanoparticles

Silver nanoparticles (AgNPs) are materials widely used in the development of antibacterial, paints, textiles, cosmetics, personal care products and supplements, among others. It is perhaps the most ENM used in commercials products, so it is more likely to be found in the environment. The inconsistency in the research results leads the scientific community to debate between the potential danger and the empiric evidence of the AgNPs effects. The effects depend on particle sizes, aggregation, concentrations, stages of growth of the organism, accumulation organs or tissues and the matrix where the AgNPs can interact. A bioaccumulation study by Sung *et al*. (2018) used zebrafish of ca. 2 cm long, to shortly exposed them to Au and AgNPs of 30 nm and 80nm. This research found that larger AgNPs accumulated in the liver and intestine tissue, while smaller particles were found in the gills. However, since the intestine has the largest surface area, the absorption is greater and the effect is more toxic compared to the gills and muscles (Liu *et al*., 2019). It has been proposed that the main toxicity mechanism of AgNPs in gills and intestine is due to a malfunction of related genes encoding enzymes and proteins, leading to irregularities in DNA replication, protein removal and metal ion binding (Liu *et al*., 2009). Bioaccumulation of AgNPs in zebrafish through the food chain was also evaluated by transferring brine shrimps exposed, producing as a result the metal accumulation in the liver and intestine, causing deterioration in the health of the fish (Lacave *et al*., 2017). AgNPs bioaccumulate in gonads tissues, causing an increment of Reactive Oxygen Species (ROS), inducing germ cell apoptosis (Ma *et al*., 2018). Cambier *et al*. (2018) could not find survival neither survival adverse effects in 6 days post fertilization larvae exposed to AgNPs through 15 days. The same study observed accumulation mainly on the liver blood vessels and in the interstitial tissue between the intestine and liver (Cambier *et al*., 2018). Bioaccumulation can be altered by the interaction of AgNPs with environmental matrices and change the risk potential. Gupta *et al*. (2016) showed that AgNPs can be adsorbed on clays and this complex presents higher mortality rates for zebrafish embryos compared to bare AgNPs.

On the effects of reproduction and development, AgNPs has promoted different opinions of the counterparts. At reproduction levels, Chen *et al*. (2017c) compared the effects of AgNPs and $AgNO_3$ as control and found apoptosis in ovarian follicle cells surrounding the oocyte in both cases, but the genes related to oxidative stress were more sensitive to the particles. Zebrafish from 24 to 120 h after fertilization (hpf) was approximately 200 times less sensitive to AgNPs, as compared to Ag ions and the main toxic mechanism of this acute exposure was the inhibition of Na^+ uptake (Boyle and Goss, 2018). Sarkar *et al*. (2018) propose AgNPs as a growth-stimulating agent in low doses because they found highest hatching success in low doses of nanoparticles compared to control. At higher doses, the same research reports toxic effects in embryos and larvae, including bending in myotome, deformity in tail region, somites, notochord and swelling in anterior and posterior region of embryos and larvae (Sarkar *et al*., 2018). Embryos exposed after fertilization (4-120 hpf) at concentrations between 0.03 to 3 mg/L of AgNPs, showed hyperactivity but did not present dangers for hatching, morphology, or mortality (González *et al*., 2018).

Adult zebrafish exposed to 10 µg/L of AgNPs reduced fertility and increased malformation prevalence in the embryos only after two weeks of exposure (Orbea *et al*., 2017). At the half of the LC_{50} of AgNPs during 14 days of exposure, zebrafish exhibit many negative effects, such as higher levels of ROS generations and morphological repercussions in liver and gills as cell membrane damage, irregular cell outlines, pyknotic nuclei and complete disruption of cells (Ramachandran *et al*., 2018).

As shown, the AgNPs have a huge potential risk to the environment and aquatic organisms. All applications and advantages presented by this material will continue to increase, so special attention must be paid through additional studies.

Titanium Oxide Nanoparticles

Titanium Oxide Nanoparticles (TiO_2NPs) are considered as one of the most industrially used ENMs due to its wide variety of applications. The uses of TiO_2NPs include among others: Sunscreens, paints and coatings, inks, plastics, papers, or catalysts, which results in an annual production of more than 10,000 Tm worldwide, with huge growth projections (Drobne, 2018). Due to this massive use, it is very likely that this ENM ends up being released into the environment and can lead to significant accumulations in soil or water. Some studies found potentially adverse effects and defined three main mechanisms of action in organisms: The production of ROS, the peroxidation of cell membrane lipids and cell wall damage and the incorporation of TiO_2NPs into cellular organelles and macromolecules (Hou *et al*., 2018). In zebrafish, Kotil *et al*. (2017) observed that doses of 4 mg/L of TiO_2NPs induced autophagy and necrosis in Sterli cells, therefore spermatogenic cells and testicular morphology were affected. Chen *et al*. (2018b) exposed zebrafish parents to TiO_2NPs and Bisphenol A (BPA) in mixtures and independently and found that the larvae from fish exposed to TiO_2NPs showed alterations of the metabolic pathway of glucose. This study is one of the few available on effects with adult fish. The mixture caused severe inhibitions in growth and survival of the first-generation larvae, altering activity of phagosomes and lysosomes (Chen *et al.*, 2018b). The simultaneal exposure of TiO_2NP and BPA leads to a change in the intestinal microbial community of the adult zebrafish and to the generation of oxidative stress (Chen *et al.*, 2018a). As others ENMs there is a concern about the easy mobility of these small materials through the body of an organism and through their cells, but more important is the ability to transport others substances to the cells or internal organs. Zebrafish exposed to a combination of TiO_2NP and tris(1,3-dichloro-2-propyl) phosphate (TDCIPP) resulted in an increase in the bioaccumulation of TDCIPP, affecting females, reducing certain hormones, inhibiting eggs productions and promoting the developmental toxicity in first-generation larvae (Ren *et al.*, 2018). Molecules or ions in presence of ENMs may affect organisms, although under normal conditions there would be no danger.

Additionally, different studies focus on the effects of TiO_2NPs on the development of *D rerio* embryos due to the sensitivity of the organism and the divergent results. A different conclusion about ROS has been developed by Verma *et al.* (2018), since they claim that TiO_2NPs enhance the scavenging of ROS, although it promotes deformities on embryos head trunks and tail. One-hour embryos co-exposed for 96 hours to TiO_2NPs and multi-walled carbon nanotubes show no acute toxicity, although single exposure to 100 mg/L of TiO_2NPs affected the total length of the embryo (Da Silva *et al.*, 2018). Similar results were found by Hu *et al.* (2017), that after exposing the embryos, they observed an increase in the rate of malformations and the decrease in the incubation times, while the mortality remained a control group. This study also confirms the bioaccumulation in the brain, the cell death of the hypothalamus and the generation of ROS contrary to the findings of Verma *et al.* (2018).

Zinc Oxide Nanoparticles

Zinc Oxide nanoparticles (ZnNPs) play an important role in environmental, energy and medical applications. ZnONPs are also used together with polymer nanocomposites to manufacture fuel cells, supercapacitors, energy harvesting, biomedical applications, antibacterial activities, sensors and optical, magnetic and electromagnetic protection (Ponnamma *et al.*, 2019). With such broad functions and uses, the likelihood of environmental contamination is significant and the effects on organisms as zebrafish should be thoroughly investigated. ZnONPs have been proposed as a remediation substance for aquatic systems and it is important to fully understand the potential worst toxic effects due to the nanoparticles, avoiding aggravating pollution with even more dangerous substances. Electrospun polyacrylonitrile sheets as support of ZnO nanocrystals have been used to degrade diethyl (4-nitrophenyl) phosphate, resulting in a product with less toxicity impact on zebrafish (Lakshmi *et al.*, 2019). On other hand, Misra *et al.* (2018), developed ZnONPs materials doped with Fe, impregnated on Kaolinite (ZnO/K), with the purpose of disinfecting the water in presence of zebrafish. Adult zebrafish were exposed to FeZnO/K and a photocatalytic disinfection of an enteric multidrug resistant bacteria was performed successfully without causing any intestinal damage to the fish. As expected, environmental matrices can interfere in the behavior and effects of ENMs on the organisms. The dissolved organic material can mitigate some effects of ZnONPs, even reverse abnormalities in phenotypes (Kteeba *et al.*, 2018). However, ZnONPs can cause abnormalities in secondary motoneuron axon phenotypes until the second generation (Kteeba *et al.*, 2018). Research on co-exposure of ENMs and other pollutants is also necessary and has been object of study because the mixtures outcomes can be magnified. First, the toxicity to aquatic organisms may be more significant from ZnONPs than the effects from dissolved Zn ions by themselves (Ye *et al.*, 2018). Co-exposure of ZnONPs with perfluorooctane sulfate increases the effects on oxidative stress and apoptosis that independent exposures (Du *et al.*, 2017). Zebrafish chronically exposed during development to ZnONPs and perfluorooctane sulfonate shows limited growth in body length and weight, less spawning and higher mortality. In addition, these effects are transferred to the first generation as less fertilization, less hatching, increase in mortality and malformations (Du *et al.*, 2018).

The toxicity of ZnONPs has been studied and, as analyzed in other ENMs discussed in this article, the generation of ROS is one of the most well-known mechanisms of action, but it is not the only effect. Toxic effects on zebrafish were determined by exposure to sub-lethal concentrations of ZnONPs, among them several key genes related to cancer were activated, in addition to the induction of cell differentiation and pathways associated with immune system (Kim *et al.*, 2016).

As any potential toxic substance, the main concern of the ZnONPs is the potentially adverse effect on development. Embryo hatching was reduced to 0% by the exposure to 50 mg/L of ZnONP at 72 hpf, while the same concentration at 96 hpf reduced hatching to 20% (Kteeba *et al.*, 2017). Embryos showed pericardial edema, tail edema and yolk-sac edema when exposed to concentrations as low as 0.01 mg/L of ZnONPs (Choi *et al.*, 2016). If the embryos (96 hpf) are exposed to ZnONPs, oxidative stress is induced, increasing the percentage of apoptotic cells (Zhao *et al.*, 2016).

Carbon Nanotubes

Carbon nanotubes (CNTs) are a novel and popular material widely studied and applied. The physical and mechanical properties of the CNTs allow applications in the development of sensors, filtration processes, new fabrics, nanorobots, drugs, batteries and energy, among others (Kumar *et al*., 2019). The ecotoxicological effect of the CNTs is still under study, as occurs with the others ENMs. Zebrafish, as a model organism with human homology, attends both the ecotoxicological concern and the starting point of the risk assessments for human health. As at the moment there is not an excessive amount of CNTs in the environment, science must look for chronic and neurological effects and not just focus on high concentration expositions. Zebrafish was exposed to 10 µL dose of 30 mg/kg suspension of single walled CNTs (SWCNTs), which resulted in a six-fold increase in brain levels of dopamine and serotonin, while reducing the activity of acetylcholinesterase (AchE) activity (Da Rocha *et al*., 2018). Cimbaluk *et al*. (2018), found subchronic neurotoxicity in zebrafish by decreasing the dose-response in AchE activity and the induction of oxidative stress confirmed by the increased activity of superoxide dismutase and catalase (Cimbaluk *et al*., 2018).

The main objectives of the current ENMs toxicological research are to find effects when the substances are in the same matrix. Zebrafish has been exposed to different substances in presence of CNTs to assess changes in the effects of organisms due to the mixtures. Cadmium in the presence of oxidized carbon nanotubes (oxMWCNT) was more toxic at low concentrations and induced apoptosis and necrosis in *in vitro* tests of zebrafish liver cells (Morozesk *et al*., 2018). The co-exposure of MWCNTs with fluoxetine leads to an increase in bioavailable accumulation of 46-99%, leading to an increase in metabolite formation (Yan *et al*., 2018a). The findings suggest that, once again, adverse effects with more abundant substances and ENMs can be exacerbated or mitigated. Another co-exposure experiment determined that SWCNTs decrease the accumulation of Perfluorooctane Sulfonate (PFOS) in liver, intestines, gills and brain of zebrafish but increased it in the skin, suggesting changes in bioavailability of PFOS (Li *et al*., 2017). Simultaneous exposure increased ROS generation and enhanced the AchE activity, catalase and superoxide dismutase (Li *et al*., 2017). Wang *et al*. (2017) found that MWCNTs protect early stages of the zebrafish against PFOS, which affects the hatching rate, heart rate and body length. Contrary to other studies, they observed decreases in ROS levels, the activity of superoxide dismutase and catalase. Moreover, since zebrafish has useful characteristics during development, research on co-exposures focuses on the early stages of the fish. SWCNTs functionalized with polyethylene glycol are toxic without being absorbed by the organism and the effects are shown in the mortality, the delay of the hatching, malformations, reductions in body length, the increase in ROS generation and DNA damage (Cordeiro *et al*., 2018). Otherwise 3-4 hpf zebrafish embryos show protective effects of MWCNTs by reducing the expected estrogenic response of 17β-estradiol exposures (Yan *et al*., 2018b).

Copper Nanoparticles

Copper nanoparticles (CuNPs) are used in multiple applications, including antibacterial/antimicrobial, catalysis, medical purposes, electrochemical processes, among others. Is highly probable that CuNPs impact the environment through all its applications wastes. CuNPs in environment can be easily transformed into CuS and other insoluble forms of Cu (Keller *et al*., 2017). It is suggested that the order of ecological toxicity of the Cu compounds is as follows: Copper II> nano Cu^0> nano $Cu(OH)_2$> nano CuO> micro Cu compounds and the effects at lower concentration are found in aquatic organisms (Keller *et al*., 2017). Once the CuNPs enter the free environment, they will interact with other substances based on Cu ions or Cu compounds. The independent exposure of 0.25 mg/L of CuNPs and 0.25 mg/L Cu^{+2} ions obstructs the inflammation in swimming bladders of zebrafish embryos (Xu *et al*., 2017). Both copper ions and CuNPs affect ROS production, but in general Cu ions have toxic effects at lower concentrations than CuNPs in zebrafish and fry (Thit *et al*., 2017). The median lethal concentration of CuNPs at 96 h of exposure in zebrafish larvae are 242.4 µg/L and 85.73 µg/L of $CuCl_2$, moreover the bioaccumulation of Cu is higher when co-expose to CuNPs (Chen *et al*., 2011). A comparison in the effects on embryos from CuNPs and Cu exposures, enhance hemoglobin and increase ROS generation, although CuNPs show more increases in vascular endothelial growth factor signaling and expression of vessel endothelial marker *fli1* (Zhang *et al*., 2018).

CuNPs interfere in the intestinal and digestive gut of zebrafish. Zebrafish that were exposed through food to CuNPs eradicate the intestinal microbes to undetectable levels (Merrifield *et al*., 2013). Moreover effects of CuNPs on embryos were also found, as eye hypoplasia and relatively absence of digestive gut (Zhang *et al*., 2018).

Gold Nanoparticles

Gold Nanoparticles (AuNPs) are widely used in a long list of different applications, as for example photo-electrochemistry, catalysis, sensor and medical applications, including imaging, therapy, or biosensors, among others (Caballero-Díaz and Valcárcel, 2014). Considering all the ENMs, AuNPs have the least empiric evidence of adverse effects in organisms until now, although it is also true that there are very few studies on *in vivo* toxicity (Caballero-Díaz and Valcárcel, 2014). *In vitro*, some of the mechanisms reported are: Genotoxicity, generation of ROS, mitochondrial damage, apoptosis, leakage of toxic materials, endocrine disruption, interactions with lipids and proteins, altered gene expression and cellular morphology changes (Caballero-Díaz and Valcárcel, 2014). The greatest number of experiments establishes the low or no toxicity for zebrafish. Embryos exposed to 100 µL/mL of gold nanoclusters show no toxic effects on survival, hatching rate, heart rate, malformations and gene expression (Chandirasekar *et al*., 2016). No hazard was found for zebrafish, but the soluble Au may be toxic to other organisms (García-Cambero *et al*., 2013). In comparison with AgNPs, the AuNPs have less bioaccumulation in liver tissue and intestines, but the particle size is decisive for accumulation in target organs (Sung *et al*., 2018). On the other hand, a study found that the AuNPs were not toxic to zebrafish embryos and that bioaccumulation is similar to AgNPs (Asharani *et al*., 2010).

Toxic effects are found at very high concentration, which may be far from environmental relevance. AuNPs used as anticancer agents show 100% embryo mortality at 300 mg/mL (Ramachandran *et al*., 2017). Embryos exposed to concentrations ranging from 0.08 to 50 mg/L of AuNPs, functionalized with N,N,N-trimethylammoniumeethanethiol end in cell death of the eye, smaller and malpigmented eyes, hypoactive swimming behavior and axonal growth inhibition (Kim *et al*., 2013). It is very likely that the effects of AuNPs are more related to the Au effects than the particle itself. Acute exposure to dissolved Au generates temporary changes in the behavior and swim performance (Strungaru *et al*., 2018). The progress of these investigations must necessarily be carried out through co-exposures with Au and other compounds in order to assign the real risk of AuNPs.

Nanoplastics

In recent years, questions about the impact on the environment and ecosystems of micro and nanoplastics have been rising among scientists. Materials at the nanoscale can be introduced into the environment as larger particle degradation products or by ENMs of polymers. The microscale plastics are more studied, although at the nanoscale they continue to emerge continuously. At the environment, contaminants could be adsorbed to the microplastics, however experimentally Sleight *et al*. (2017) could not found increases in bioavailability of phenanthrene and 17α-ethinylestradiol due to microplastics actions, although a reduction in zebrafish larvae was observed. Micro plastics accumulate in the gastrointestinal tract and induce changes in gene expression of zebrafish lavae (LeMoine *et al*., 2018). Effects on zebrafish larvae were greater by nanoplastic than microplastics (Chen *et al*., 2017a). When nanoplastics reach environment can be introduced in aquatics organisms through ingestion or oral exposure, dermal exposure, transference from previous generation, or biomagnification, among others. The uptake of Polystyrene Nanoparticles (PSNPs) by zebrafish is primary, through oral exposures, in comparison to dermal; however, exposures through both routes show higher abortions (Van Pomeren *et al*., 2017). Bioacumulation of PSNPs in zebrafish embryos are observed in yolk sac, gastrointestinal tract, gall bladder, liver, pancreas, heart and brain (Pitt *et al*., 2018a). First-generation embryos, that have not been directly exposed, accumulate PSNPs in the yolk sac, gastrointestinal tract, liver and pancreas (Pitt *et al*., 2018b). The PSNPs penetrate the chorion and accumulate in all body but more in lipid regions (Lee *et al*., 2019).

Nanoplasctics show toxicity mainly in the early stages of zebrafish. Nanoplasctics have adverse effects on zebrafish larvae, as shown by Chen *et al*. (2017c), that observed a reduction in larval locomotion during darkness, a reduction in body length by 6%, inhabitation of acetylcholinesterase activity and upregulated gene expressions (Chen *et al*., 2017a). PSNPs exposures during development reduce glutathione reductase activity in brain, muscle and testes and in the stages of larvae decrease the heart rate and generate hypoactivity when swimming (Pitt *et al*., 2018a). Even the first generation acquired bradycardia and reduced the level of thiols and the activity of glutathione reductase (Pitt *et al*., 2018b).

When nanoplastics are mixed with other substances, the adverse effects can be exacerbated in many ways. Co-exposures of nanoplastics with 2000 mg/L of 17 α-ethynylestradiol (EE2), increases the adsorption for EE2 and enhances hypoactivity (Chen *et al*., 2017a). Bisphenol A in co-exposure with nanoplastics increases the accumulation by 2.2 and 2.6 times in the head of zebrafish and viscera, which also accentuates neurotoxicity in the central nervous system and the dopaminergic system (Chen *et al*., 2017b). Embryos exposed to PSNP with Au compared to PSNPs alone, generate the intensification of adverse effects for survival, hatching, developmental anomalies and cell death (Lee *et al*., 2019).

Cadmium Nanoparticles

Cadmium Nanoparticles (CdNPs) have a very complex behavior in the organisms, so the mechanisms of toxicity are not fully established. Recently, studies of toxicity with Cd in zebrafish have been conducted and the results are allowing to establish the possible mechanisms. It has been observed that the effects of CdNPs can be correlated with the effects of Cd ions

(Cd^{+2}). Nanomaterials based on Cd and Cd^{+2} have been found to be responsible for the overexpression of six genes, in addition to the reduced expression of another 27 in the zebrafish (Gao *et al*., 2018a). Cd^{+2} ions have more potential of bioaccumulation than cadmium selenide quantum dots although with a homogeneous distribution along the surface of zebrafish larvae (Zarco-Fernández *et al*., 2016). Hydroxyapatite-loaded CdNPs with Cd^{+2} can generate increases in the activities of superoxide dismutase, peroxidase and catalase enzymes; furthermore it can damage liver DNA (Gao *et al*., 2018b). By itself quantum dots (QDs) retard hatching and increase the oxidative stress of embryos, as evidenced by exposure to mercaptopropionic acid-CdTe QDs and mercaptopropionic CdS-CdTe QDs (Tian *et al*., 2019).

As with others ENMs, the complexity of the environment affects the actions of the materials and the possible threat to the organism. In the case of small particles, dilution expectations are not always met. Carboxilated CdSe/ZnS QDs can agglomerate in deep well water and on the surface of fish embryos (Rotomskis *et al*., 2018). The damaging potential of an ENM is inherent to the particle, but modifications can be done to decrease or delay it. For example, possible carbon coatings on Cd nanoparticles can reduce toxicity by mitigating the release of Cd^{+2} (Balmuri *et al*., 2017).

Conclusion

ENMs are extraordinarily useful and are becoming essential for health and technology. Facing this reality, it is essential to know everything about the impact on the environment and ecosystems. Every ENM has different properties that change over time as they interact with other substances and penetrate protective barriers. Co-exposure studies of ENMs with other contaminants frequently conclude in the increment of bioconcentration of the chemicals; however this is not always the case (Naasz *et al*., 2018). Some studies showed a lower bioavailability when co-exposures are with ENMs. Small modifications of the chemical structure of ENMs may generate changes in their reactions, increasing significantly their toxicity and turning unmanageable to reach conclusions (Kabir *et al*., 2018). Some materials act as Trojan horses to other dangerous species. All these challenges make evident the urgency of generate new research, focused on the *in vivo* potential effects by the most produced ENMs.

Concentrations of environmental relevance are not commonly used, a fact that leads to one of the main criticisms that high concentration studies have no current relevance. Additional studies should be aimed at understanding sub-lethal effects and long-term exposures, evaluating natural pathways, including plants through small organisms. Every ENM should be studied in depth to evaluate the physical and chemical interactions in different environmental matrices, the effects of variations in size and concentrations, the potential effects of prolonged exposure, the coverage of ENMs, specific organisms and targeted organs. Nanomaterials are helping and, in the near future, will help even more to solve many of society's problems. That is why we must foresee the possible effects, to establish the necessary control mechanisms.

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Author’s Contributions

All authors contributed equally to this work.

Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and no ethical issues involved.

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