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Engineered nanomaterials: from their properties and applications, to their toxicity towards marine bivalves in a changing environment

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ABSTRACT

As a consequence of their unique characteristics, the use of Engineered Nanomaterials (ENMs) is rapidly increasing in industrial, agricultural products, as well as in environmental technology. However, this fast expansion and use make likely their release into the environment with particular concerns for the aquatic ecosystems, which tend to be the ultimate sink for this type of contaminants. Considering the settling behaviour of particulates, benthic organisms are more likely to be exposed to these compounds. In this way, the present review aims to summarise the most recent data available from the literature on ENMs behaviour and fate in aquatic ecosystems, focusing on their ecotoxicological impacts towards marine and estuarine bivalves. The selection of ENMs presented here was based on the OECD's Working Party on Manufactured Nanomaterials (WPMN), which involves the safety testing and risk assessment of ENMs. Physical-chemical characteristics and properties, applications, environmental relevant concentrations and behaviour in aquatic environment, as well as their toxic impacts towards marine bivalves are discussed. Moreover, it is also identified the impacts derived from the simultaneous exposure of marine organisms to ENMs and climate changes as an ecologically relevant scenario.

Keywords: emerging pollutants, nanoparticles, environmental risks, ecotoxicological effects, bivalves, marine systems.

INTRODUCTION

Engineered nanomaterials (ENMs) can be divided into two general classes: carbon-based (e.g., carbon nanotubes and fullerenes) and metal-containing (e.g., Ag, TiO_2, CeO_2, Fe) (Fadeel & Garcia-Bennett, 2010). Carbon-based nanoparticles (NPs) are allotropes of carbon with at least one dimension within the range of 1 to 100 nm. The main classes can be divided as buckyballs (spherical fullerenes), graphene (carbon sheets with nanometric thickness), carbon nanotubes (CNTs) (cylindrical fullerenes), graphene (carbon sheets with nanometric thickness), and carbon black (amorphous carbon) (Freixa et al., 2018). Regarding metals and metals oxides NPs, particles can be formed by two or more metals (Au, Ag, Cu, Pt, Pd, Zn, Ti, etc.) which are combined with each other or bonded to metalloids (Irzhak, 2016).

As a consequence of their unique characteristics, the use of ENMs in consumer, industrial, and agricultural products, as well as in environmental technology is rapidly increasing, and global production of ENMs are projected to grow to half a million tons with the number of ENMs-containing consumer products reaching 3400 by 2020 (www.nanoproject.org).

This fast expansion and use make likely their release into the environment. Of particular concern is the aquatic environment, which tend to be the ultimate sink for this type of contaminants (Selck et al., 2016). Their release can result from direct (sewage, effluents, river influx) or indirect (aerial deposition, dumping and run-off) discharges (Rocha et al., 2015) reaching different types of ecosystem compartments (water, sediments, biota). When into the aquatic system, ENMs behaviour and fate is dependent on their properties such as size, shape, chemical composition, surface charge, coating and particles state. Particle size, surface chemistry and charge, crystallinity, phase purity, solubility and shape are essential characteristics to explain the homogeneity, stability, reactivity and bioavailability of ENMs in different media (Kahru & Dubourguier, 2010). Furthermore, the behaviour of ENMs depends on the surrounding conditions including pH, temperature, ionic strength, composition and concentration of natural organic matter which affect their aggregation/agglomeration or stabilisation (Freixa et al., 2018). Generally, ENMs are transported within the water phase and easily interact with organisms. If their size is increasing by agglomeration processes they become less mobile and will tend to be deposited to the sediments, becoming less available to organisms in the water column but highly available for deposit feeders and other benthic organisms (Freixa et al., 2018). Currently, knowledge of biological effects in the aquatic environment is mainly devoted to manufactured ENMs aqueous acute and chronic toxicity using pelagic organisms (Selck et al., 2016). However, because of the settling behaviour of particulates, benthic organisms are more likely to be exposed (Selck et al., 2016). Also, a review of Minetto et al. (2016) pointed to an important asymmetry: almost 76% of published paper employed freshwater animal species and only 24% were saline water or marine species, which is related to ENM's behaviour between fresh water and salt water, with greater difficulties in their detection as well as their possible interaction with inhabiting organisms of marine environments.

Therefore, the toxic impacts of ENMs towards aquatic organisms will depend on the behaviour of the NMs as a consequence of their chemical-physical characteristics as well as on aquatic systems characteristics, which may change considering predicted climate changes. Surely, toxicological effect of ENMs are also strictly depending on the uptake by the organisms. Ward & Kach (2009) observed different behaviours by the use of 100 nm fluorescent polysterene nanoparticles delivered to *Mytilus edulis* and *C. virginica* in presence or not of aggregates: the experiment showed that aggregates induced longer retention times indicating the transfer of NP from gut to the digestive gland and the crucial role of suspended matter.

This review summarises the data available from the literature on ENMs behaviour and fate in aquatic ecosystems, specifically their ecotoxicological impacts towards marine and estuarine bivalves. The selection of this class was based on their economic importance as well as ecological relevance as nearshore groups of animals, often dominating the macrobenthos and contributing significantly to benthic-pelagic coupling and the structure of benthic food webs (Dame & Olenin, 2003). Moreover, considering the ability of these organisms to select different type of particles (Rosa et al., 2018), they can be considered ideal sentinel organisms for ENM contaminants.

The selection of ENMs presented here was based on the OECD's Working Party on Manufactured Nanomaterials (WPMN), which launched the Sponsorship Programme for the Testing of Manufactured Nanomaterials (OECD, 2010). This programme promotes international co-operation on the human health and environmental safety of manufactured nanomaterials, and involves the safety testing and risk assessment of ENMs (http://www.oecd.org/chemicalsafety/nanosafety/dossiers-and-endpoints-testing programme-manufactured-nanomaterials.htm). The OECD WPMN has published a list of ENMs, selected considering their commercial use, production volume of the materials, availability of such materials for testing and the existing information that would readily be available on the materials. This list comprised: cerium oxide; carbon nanotubes; dendrimers; nanoclays; titanium dioxide; fullerenes; silicon dioxide; zinc oxide; gold and silver nanoparticles. The following sections describe some of the most important scientific findings, relevant for hazard identification of ENMs. The purpose of this review is to summarize the current state of knowledge regarding the hazards of ENMs, based on experimental studies. The selected ENMs are: i) fullerenes (C_{60}); ii) carbon nanotubes (CNTs); iii) silver; iv) gold v) titanium dioxide; vi) zinc oxide and vii) cerium dioxide. For each selected ENMs, physico-chemical characteristics and properties, applications, environmental relevant concentrations and behaviour in aquatic environment, as well as their toxic impacts with focus on marine and estuarine bivalve species are presented. Moreover, considering that the simultaneous exposure of marine organisms to ENMs and climate changes is likely an ecologically relevant scenario, studies presented in the literature which described the possible toxic effects in bivalves simultaneously exposed to these emerging contaminants under climate change scenarios are also included here. In fact, although a research community is already able to describe some of the fundamental physical-chemical behaviour of colloids and other particles, recognising that generally the bioavailability and the ecotoxicology of chemicals (and particles) is altered by abiotic factors is an area where research is particularly lacking for ENMs.

1.1 CARBON-BASED NANOMATERIALS

1.1.1 Fullerenes

Characteristics

Carbon molecules arranged into a spherical shape resembling a geodesic dome are known as fullerenes. There are multiple spherical configurations of fullerenes (e.g., C_{60}, C_{70}, C_{80}) which depend on the number of carbon atoms, but Buckminsterfullerene (molecular formula: C_{60}) is by far the most prominent in terms of production, scientific interest, and research engagement in aquatic organisms (Petersen & Henry, 2012; Britto et al., 2015). Fullerene C_{60} is a polyhedral carbon structure composed of around 60 carbon atoms in pentagon and hexagon configuration (https://www.ncbi.nlm.nih.gov/mesh/68037741). Due to their structural characteristics, C_{60} molecule have shown unique properties, which include high electrochemical stability, small size, specific morphology and well-ordered structure. Moreover, the specific morphology gives fullerene C_{60} physical and chemical properties that differ from other traditionally used carbon ENMs, such as high electroconductivity, good thermal conductivity, and special mechanical properties (Coro et al., 2016).

Applications

As a consequence of their properties, C_{60} fullerenes are exploited in a growing number of products and applications such as biosensors (Gavalas & Chaniotakis, 2000; Zhang et al., 2013; Afreen et al., 2015; Pilehvar & De Wael, 2015), adsorption electrodes (Noked et al., 2011), screen printed systems (Petrik et al., 2010; Palanisamy et al., 2015), as well as solar cells (Brabec et al., 1999; Shaheen et al., 2001), printing technologies (Dzwilewski et al., 2009; Lawes et al., 2015), and electronic applications (mobile telephones, microwave and other devices) (Coro et al., 2016).

Environmental concentrations and behaviour

As these materials make their way into industrial and consumer products, there is also the potential for their introduction into the environment. Focusing in aquatic systems, in the study conducted by Gottschalk et al. (2009) the authors calculated predicted environmental concentrations (PECs) based on a probabilistic material flow analysis of the most ENMs (Table 1), which included fullerenes C_{60}, showing that the estimated concentrations for the surface waters were about 0.003 ng L^{-1} and more recently Sun et al. (2014) predicted the fullerenes concentrations of surface water for the EU around 0.11 ng L^{-1}. However, to assess the toxic effects of fullerenes towards aquatic organisms, it is important to understand their fate and behaviour in the water media since different factors influence their mobility and aggregation in the environment (Dwivedi & Ma, 2014). Studies showed that carbon NMs rapidly agglomerated in seawater, thus ultimately deposited onto sediments due to their lipophilic or hydrophobic characteristics generating low solubility in natural waters (solubility of fullerenes is 10–18 mol L^{-1}) (Dwivedi & Ma,2014). However, during long prolonged contact with water at pH 4-10, C_{60} molecules can crystallize to form aggregates of increased solubility. Since aggregates formed during prolonged stirring in water, C_{60} fullerene are expected to aggregate in natural waters and it has been demonstrated that these materials can be stable in aqueous solution for months under this form (Cupi et al., 2016), increasing their availability and consequent uptake by the organisms. Considering that spherical morphology of the C_{60} fullerene, it is already demonstrated from the literature that ENMs with this shape are taken up much faster and more efficiently than rod-shaped ENMs, presumably due to the longer membrane wrapping time required for the longer rod-shaped particles (Kettiger et al., 2013). Additional factors promote cellular uptake besides ENMs' shape such as size (nanoparticles with a diameter of 50 nm are more efficiently internalized by cells than smaller (about 15–30 nm) or larger (about 70–240 nm) particles) and surface functionalities (positively charged particles interact strongly with the slightly anionic plasma membrane whereas negatively charged ENMs use alternative uptake routes (e.g endocytosis)) (Kettiger et al., 2013).

Finally, it is important to stress that hydroxylated fullerene (fullerenol or fullerol) is a water-soluble carbon nanomaterial that authors like Wang et al. (2018) have shown that it is uptaken by green alga *Scenedesmus obliquus* and transferred to cladoceran *Daphnia magna* although with low efficiency.

Toxic impacts in bivalves

Studies performed to assess the C_{60} fullerenes effects towards different bivalve species are presented in Table 2. Toxicity data have been ranked and summarized according to type of NPs, exposure conditions, organisms' taxonomic group and mechanisms of interaction and effects concentrations (Table 2).

ENM effects

Concerning the toxic impacts of fullerene C_{60} in the organisms, it has been already demonstrated that their physicochemical properties support the hypothesis that this carbon NMs may induce oxidative stress following photoactivation (Usenko et al., 2008). In the presence of both visible and ultraviolet light, fullerene C_{60}, can generate reactive oxygen species (ROS) (Kamat et al., 2000; Britto et al., 2012), particularly as singlet oxygen and superoxide and these by-products can induce oxidative stress leading to a variety of detrimental downstream effects such as lipid peroxidation, DNA and protein adduction and cellular death (Pickering & Wiesner, 2005). Size, chemical composition, surface structure, solubility, shape, and aggregation can modify cellular uptake, protein binding, translocation from portal of entry to the target site, and the possibility of causing tissue injury (Nel et al., 2006).

Focusing on bivalves, it has been already demonstrated in the literature the potential toxic effects of fullerene C_{60} alone in terms of physiological and biochemical responses. Canesi et al. (2010a), exposing *Mytilus galloprovincialis* hemocytes to C_{60} fullerene at 1, 5, 10 μg mL^{-1}, showed that the NM suspensions induced a concentration-dependent lysozyme release, extracellular oxyradical and nitric oxide (NO) production. The same authors investigated other concentrations (0.05–0.2–1–5 mg L^{-1}) *in vivo,* evaluating the effects in hemocytes, digestive gland and gills, and demonstrated that these NMs were able to generated dose-dependent lysosomal membrane destabilisation in both the hemocytes and the digestive gland. Moreover, in the digestive gland, C_{60} induced lysosomal lipofuscin accumulation only at the highest concentrations, increasing the activity of the antioxidant enzyme catalase and stimulating the glutathione-S-transferases (Canesi et al., 2010b). Similar effects were reported in another mussel species (*Mytilus edulis)*, revealing that hemocytes exposed the concentration range of 1.5 and 10 μg mL^{-1} of fullerene C_{60}, generated cytotoxicity in circulating phagocytic hemocytes, which are a key component of molluscs innate immune system (Moore et al., 2009). More recently Sanchís et al. (2018) conduced an experiment trying to evaluate the metabolomic response of *M. galloprovincialis* exposed to 10 mg L^{-1} of fullerene soot. These authors confirmed the bioaccumulation of fullerenes and demonstrated that the metabolome of the exposed organisms revealed significant differences in the concentrations of several free amino acids when compared to the control group. An increase in small non polar amino acids and branched chain amino acids were observed. Also, glutamine concentrations decreased significantly, suggesting the activation of facultative anaerobic energy metabolism. Moreover, significant differences were observed in lipids content concluding that these results were consistent with hypoxia and oxidative stress. Ringwood et al. (2009), using another model species, the oyster *Crassostrea virginica*, observed that C_{60} fullerene generated dose-dependent effects (1-500 µg L^{-1} range) on embryos development and lysosomal destabilization. The authors also observed C_{60} accumulation in the hepatopancreas cells and localized in lysosomes concluding that endocytotic and lysosomal were the pathways targets of fullerenes.

"Trojan horse" effects

Different authors have devoted their research to the study of co-exposure of nanoparticles with other molecules (see references below), identified as "*Trojan horse*" mechanism, evaluating not only changes in accumulation of each element but also possible interactive effects between them. Authors like Limbach and Wick (2007) considered the ´*Trojan horse*' as the augmented of the interaction between a toxic molecule. To these authors this co-exposure will result into changes in the toxicological pathways, most of the times increasing the impacts induced in the organisms. However, other authors as Baun et al. (2008) and Sun et al. (2009), consider that in the "*Trojan horse*" mechanism the nanomaterial facilitates the entry of other molecules to the organisms and, with higher accumulation greater impacts could be provoked. Several authors have studied the combination of nanoparticles with other compounds, with not clear distinction between the effects due to their interaction or the effects due to higher accumulation. Recently, the study of Naaz et al. (2018) has made a substantial effort to clarify some ambiguities associated with the so call "Trojan Horse effect". The authors proposed seven categories of interaction between ENMs and other toxic molecules: (1) an increase in accumulation and toxicity; (2) an increase in accumulation and no change in toxicity; (3) an increase in accumulation and a decrease in toxicity; (4) no change in accumulation and toxicity; (5) no change in accumulation and a decrease in toxicity; (6) a decrease in accumulation and toxicity; (7) a decrease in accumulation and an increase in toxicity.

Authors like Henry et al. (2011) stated that C_{60} toxicity is low but highlighted the potential environmental risk of fullerenes exposure due to its capacity to act as a carrier for other contaminants. In fact, several studies showed that co-exposure with fullerene C_{60} can affect the uptake rate and toxicity of other environmental contaminants (Azvedo Costa et al., 2012; Ferreira et al., 2014). Recently, Ramos et al. (2017) have employed *in silico* approaches to predict the physico-chemical interactions of carbon nanomaterials with toxins, opening another strategy to quickly analyze the potential risk of having a 'Trojan horse' effect. Al-Subiai et al. (2012) exposed the marine mussels (*Mytilus* sp.) to fullerenes C_{60} (0.10–1 mg L^{-1}) and a model polycyclic aromatic hydrocarbon (PAH), fluoranthene (32–100 μg L^{-1}), either alone or in combination in order to determine the effects on total glutathione levels (as a measure of generic oxidative stress), genotoxicity, DNA adduct analyses in different organs, histopathological changes in different tissues (i.e. adductor muscle, digestive gland and gills) and physiological effects (feeding or clearance rate). The results showed that both fluoranthene and C_{60} on their own caused concentration-dependent increases in DNA strand breaks and the combined exposure additively enhanced the levels of DNA strand breaks and an increase in the total glutathione content. In addition, significant accumulation of C_{60} was observed in all organs, with the highest levels in digestive gland. Di et al. (2016) assessed a range of biological responses including the determination of 'clearance rates' (a physiological indicator at individual level); histopathological alterations (at tissue level; DNA strand breaks; transcriptional alterations; measurement of total glutathione in the digestive gland) after the exposure to fullerene C_{60}, either alone or in combination with a model polycyclic aromatic hydrocarbon, benzo(α)pyrene in the marine bivalve *M. galloprovincialis*. The results demonstrated significant increases in 'clearance rates' and the histopathology on selected organs (i.e. gills, digestive glands, adductor muscles and mantles) showed increased occurrence of abnormalities in all tissues types. Significantly increased levels of DNA strand breaks were also observed concluding that B(α)P and/or C_{60} induce tissue and DNA damage in exposed marine mussels, confirming their function as genotoxicants.

ENMs and climate change

Although, as mentioned before, the behaviour and toxic impacts induced by ENMs are related to their ability to interact and aggregate, creating clusters that exhibit a colloidal behaviour, which are dependent on environmental parameters such as the pH, ionic strength, type and concentrations of dissolved organic matter and sunlight (Freixa et al., 2018), up to now no studies have been published describing the possible toxic effects in marine organisms exposed to fullerene C_{60} under different climate change scenarios.

1.1.2 Carbon Nanotubes (CNTs)

Characteristics

Nanotubes are members of the fullerene structural family, which includes buckyballs and nanotubes (CNTs). While buckyballs are spherical in shape, CNTs are cylindrical and can be single-walled (SWCNT) with a diameter of less than 1 nanometer (nm) or multi-walled (MWCNT), consisting of several concentrically interlinked nanotubes, with diameters reaching more than 100 nm (McEnaney, 1999). Their length can reach several micrometers or even millimeters. CNTs are chemically bonded with sp2 bonds, that allows strong molecular interaction (Baughman et al., 2002; González-Durruthy et al., 2017).

Looking on their properties, CNTs have high thermal conductivity; high electrical conductivity; high aspect ratio; very high elasticity; high tensile strength; highly flexible — can be bent considerably without damage; low thermal expansion coefficient and are considered good electron field emitters (Ajayan & Zhou, 2001).

Applications

Commercial applications are incorporating CNT materials, which are now entering the growth phase of their product life cycle. The most promising present and future commercial applications of CNTs include: field emission; thermal conductivity; energy storage; conductive properties; conductive adhesive; thermal materials; molecular electronics based on these materials; structural applications; fibers and fabrics; biomedical applications; air and water filtration and catalyst support (De Volder et al., 2013).

Environmental concentrations and behaviour

CNTs may enter the environment directly during unintentional release, during use and consumption of CNT containing goods or as a waste from sewage treatment plants, waste incineration plants and landfills (Petersen et al., 2011). Looking at the most recent literature, the PECs of CNTs in aqueous systems were projected to approximately 0.001-1000 µg L^{-1} (Nouara et al., 2013; Zhang et al., 2017) (Table 1). Despite the virtual water insolubility of individual CNT molecules, the formed aggregates are stable under certain environmental conditions. The properties of the aggregates (size, ζ-potential, shape, surface functionalization, sedimentation rate, critical flocculation concentration, etc.) are dependent on the alteration of their surface properties (Freixa et al., 2018). Jackson et al. (2013) reported that because CNTs are difficult to disperse in water and polar matrices, many commercially available CNTs are therefore functionalized (i.e.: adding carboxyl groups) before final use preventing agglomeration in the composite matrices. Dispersants can be added to the test media to reduce CNT agglomeration (Kim et al., 2011; Najeeb et al., 2012). For example, organic matter will increase the pristine CNT dispersibility in aquatic solutions by covering the hydrophobic surface causing prolongs residence time in the water column and increasing CNT mobility which in turn, intensifies risk of exposure and toxicity (Hyung et al., 2007; Ferguson et al., 2008; Kennedy et al., 2008; Kennedy et al., 2009; Edgington et al., 2010; Zhang et al., 2011). Functionalization is achieved also through chemical modification such as amidation and esterification of the nanotube-bound carboxylic acids (Sun et al., 2002). The functionalization breaks the nanotube bundles, which is essential to solubility and the presence of functional groups on nanotubes surface therefore increases nanotubes dispersibility (Shahnawaz et al., 2010), but also sometimes increments the reactivity against proteins. Furthermore, the large specific surface area may facilitate pollutant adhesion and thus influence CNT toxicity in itself and/or toxicity of co-pollutants and influence the bioaccumulation of environmental contaminants (Ferguson et al., 2008). CNTs stability in the aquatic environment is also influenced by water characteristics such as the salinity, pH, ionic strength, type and concentrations of dissolved organic matter and sunlight (Freixa et al., 2018).

Toxic impacts in bivalves

Studies performed to assess the CNTs effects toward different bivalve species are presented in Table 2.

ENM effects

Regarding their toxicity, available data shows that CNTs can cross membrane barriers inducing harmful effects (e.g., inflammatory and fibrotic reactions). Cell and CNT interactions include cellular uptake and processing of CNTs by different routes, effects on cell signalling, membrane perturbations, production of cytokines, chemokines and reactive oxygen species (ROS), overt toxic reactivity, cell apoptosis (Zhao & Liu, 2012). In details, CNTs were reported to accumulate in various subcellular compartments, such as the cell cytosol (Al-Jamal et al., 2011), endosomes (Antonelli et al., 2010; Wang et al., 2010), the perinuclear region (Lacerda et al., 2007), mitochondria (Neves et al., 2010; Zhou et al., 2010), or the nucleus (Shi Kam et al., 2004) according to their physicochemical properties and functionalisation. Also, indirect non-specific toxic effects of CNTs, which include physical irritation and occlusion of surface tissues (e.g., gills), have been found in some studies with aquatic organisms, specifically in the marine harpacticoid copepod *Hyalella azteca*, and two fish species, fathead minnow *Pimephales promelas* and Japanese medaka *Oryzias latipes* (Oberdörster et al., 2006). Ecotoxicity by CNTs was also observed at the larvae stages the *Xenopus laevis* (e.g.

physical blockage of the gills and/or digestive tract) as well as bioaccumulation inside the intestine (Mouchet et al., 2008). Focusing on bivalves, different studies already provided biochemical and physiological responses when the organisms were exposed to different CNTs. Mwangi et al. (2012), evaluated the toxicity of different types of CNTs (SWCNTs and MWCNTs) at the concentration of 1.00 g L^{-1} (dry wt) noticing a significantly reduced survival or growth of the mussel *Villosa iris*, however no evidence was observed to support the potential of both CNTs for penetration through cell membranes. Different results were obtained by Miller et al. (2015), which comparing the toxic effects of SWCNTs and MWCNTs on *Mytilus sp*. at the concentrations of 50, 250 and 500 µg L^{-1}, showed that both CNTs generated lysosomal damage (lysosomal retention of neutral red dye) in the hemolymph. Moreover, higher toxic effect by SWCNTs in comparison to MWCNTs at 500 µg L^{-1} was observed. Moschino et al. (2014) exposed *M. galloprovincialis* to three single walled carbon nanohorns (SWCNH) concentrations: 1, 5, and 10 mg L^{-1}, demonstrating sub-lethal effects at level of physiological functions such as digestion in mussels (i.e. variations in lysosomal parameters and lipofuscin content) and the antioxidant system (i.e. glutathione peroxidase activity and malondialdehyde content). Hanna et al. (2014), investigated the potential impact of SWCNTs (1, 2, or 3 mg L^{-1}) in *M. galloprovincialis*, measuring mussel clearance rate, shell growth, and CNT accumulation in tissues and in biodeposits. The results showed that mussels decreased clearance rate of phytoplankton by 24% compared with control. However, mussel growth rate was unaffected by CNTs at concentrations up to 3 mg L^{-1}. Mussels deposited most CNTs in biodeposits, which contained >110 mg CNTs g^{-1} dry weight, and accumulated about 1 mg CNTs g^{-1} dry weight of tissue, concluding that extremely high concentrations of CNTs are needed to elicit a toxic response in mussels, although this ability may impact organisms living in/and around mussel beds. Using the mussel *Modiolus modiolus* exposed to MWCNTs (12–14 nm, MWNT concentration in sea water of 100 mg L^{-1}), Anisimova et al. (2015) observed that CNTs were ingested by the organisms. In particular, the authors found larger MWCNT aggregates in the intestinal lumen (size of 10 to 150 μm) and in the tubules of the digestive gland (10 to 50 μm), while the smallest aggregates were observed inside epithelial cells. In the intestine, digestive gland, and gills, MWCNT aggregates induced histopathological alterations in the epithelium (erosion, necrosis, trend towards increased vacuolization of the cells) and swelling of the connective tissue. Despite significant organ damage, in the study the CNTs did not modify the mussels' cellular composition of the hemolymph. Simulating in the laboratory natural environmental changes with the tidal cycle, Andrade et al. (2018) exposed *M. galloprovincialis* to carboxylated MWCNTs (0.01 mg L^{-1}) trying to understand if mussel species must either avoid or tolerate environmental changes associated with multiple stressors by developing physiological and biochemical strategies. The authors confirmed that mussels were physiologically and biochemically affected by CNTs. Moreover, when mussels were exposed to the combination of tides and MWCNTs an increase of metabolism was observed (necessary to re-establish their physiological and biochemical performance after oxygen absence) associated with a possible higher ROS production, and correlated with increased antioxidant enzymes activities, which prevented the occurrence of cellular damage, expressed as lipid peroxidation or protein carbonylation. These findings indicated that the increasing presence of CNTs in marine ecosystems can induce higher toxic impacts in intertidal organisms compared to organisms continuously submerged. De Marchi et al. (2017a) investigated the possible biochemical responses of *R. philippinarum* clams exposed to 0.01; 0.10 and 1.00 mg L^{-1} of pristine MWCNTs, and revealed that exposure to MWCNTs altered energy-related responses, with higher metabolic capacity and lower glycogen and protein concentrations in clams exposed to these CNTs. Moreover, *R. philippinarum* exposed to MWCNTs showed oxidative damage expressed in higher lipid peroxidation and lower ratio between reduced and oxidized glutathione, despite the activation of antioxidant defence mechanisms in exposed clams. Additionally, neurotoxicity was observed by inhibition of cholinesterases activity in organisms exposed to MWCNTs. De Marchi et al. (2018a) also compared two different MWCNTs: pristine and carboxylated both at concentrations of 0.01, 0.10 and 1.00mg L^{-1} with the objective to understand how surface chemistry alteration (functionalization) of CNTs may impact the toxicity of these NMs to *R. philippinarum*. The obtained results showed that exposure to both MWCNT materials altered energy-related responses, with higher metabolic capacity and lower glycogen, protein and lipid concentrations. Moreover, oxidative damage, expressed as higher lipid peroxidation and lower ratio between reduced and oxidized glutathione was observed, despite the activation of defence mechanisms (superoxide-dismutase, glutathione peroxidase and glutathione S-transferases). Finally, inhibition of cholinesterases activity in clams exposed to both CNTs was observed.

"Trojan horse" effects

"Trojan horse" effects of CNTs were also reported in the literature. In other clams' species, *Donax faba*, Sekar et al. (2016) investigated the toxic effect of pristine SWCNT and MWCNTs and bovine serum albumin (BSA) (100 µg) adsorbed by these NMs (2, 10, 50, 100 and 500 mg L^{-1}). The results showed that the median lethal concentration (LC_{50}) of SWCNT and MWCNT to *D. faba* was found to be 103 and 93 mg L^{-1}, respectively. BSA adsorbed CNTs showed LC_{50} values of 105 and 101 mg L^{-1} for BSA- SWCNT and BSA-MWCNT in comparison to pristine CNTs. In addition, CNT–BSA conjugates showed less histopathological damages a decreased effect on the cellular integrity rather than the pristine ones. Ecotoxicity of CNTs and their interaction with dissolved metals have been also observed. In a study conducted by Al-Shaeri et al. (2013), *M. galloprovincialis* was exposed to SWCNTs at the concentrations of 5, 10, 50, 100, 500 µg L^{-1}, investigating their toxic impact in the gill and hemolymph when acting alone and in combination with other two metals: cadmium chloride ($CdCl_2$ 0.001µM) and zinc sulfate ($ZnSO_4$ (1.0 µM)). The authors observed that SWCNT (> 100 µg L^{-1}) generated an increase of antioxidant responses, lipid peroxidation, and DNA strand breaks. However, the combination with both metals (SWCNT + $CdCl_2$, and SWCNT+ $ZnSO_4$ (> 100 µg L^{-1}) caused higher incidence of DNA damage in comparison to single stressor. Also, Freitas et al. (2018) evaluated the impacts of Arsenic (As) (0.1 mg L^{-1}) and carboxylated MWCNT (COOH-MWCNT: 0.1 mg L^{-1}) in the clam *Ruditapes philippinarum,* assessing the effects induced when both contaminants were acting individually and as a mixture. The results showed that the accumulation of As was not affected by the presence of the CNTs; moreover higher injuries were noticed in clams exposed to CNTs, with higher metabolic depression and oxidative stress, regardless of the presence of As. Furthermore, higher neurotoxicity was observed in clams exposed to the combination of both contaminants in comparison to the effects of As and NPs individually.

ENMs and climate change

Intertidal organisms as bivalves can be exposed to environmental changes derived from climate change. However, few studies are presented in the literature regarding the potential responses of bivalves when exposed to CNTs under a climate change scenario (De Marchi et al., 2018b; 2017). Within this context, De Marchi et al. (2018b) performed a laboratory experiment exposing *R. philippinarum* to pristine MWCNT and carboxylated MWCNT (both at the concentrations of 0.10 and 1.00 mg L^{-1}) maintained at control salinity (28) and low salinity 21. The results showed concentration dependent toxicity in individuals exposed to both types of MWCNT and under both salinities, generating alterations of energy reserves and metabolism, oxidative status and neurotoxicity compared to non-contaminated clams. Moreover, greater toxic impacts in terms of oxidative stress were observed in clams exposed to carboxylated MWCNTs compared to pristine MWCNTs under both salinities due to the presence of more amorphous carbon fragments as a result of increased oxidation of carbon, and these amorphous fragments induced higher levels of toxicity (expressed as cellular damage) to biological systems. Moreover, the authors demonstrated that salinity shifts altered the toxicity of both MWCNT materials as a consequence of the formation of large-size aggregates, which increased the state of aggregation of both CNTs. These aggregation states modified their biological effects by affecting ion release from the surface and their reactive surface area, affecting the mode of cellular uptake of NMs together with subsequent biological responses in the organisms in terms of clam metabolism, oxidative status and neurotoxicity. The same authors attempted also to evaluated a possible biochemical response of the same species when exposed to pristine MWCNT (0.10 and 1.00 mg L^{-1}) under ocean acidification conditions (control pH 8.00-low pH 7.6) (De Marchi et al., 2017b). The results obtained revealed that under low pH conditions the toxicity of MWCNTs was similar to that measured under control pH. In both cases the energy-related responses in contaminated clams were altered with an increase of their metabolism which resulted in the expenditure of their energy reserves. Moreover, *R. philippinarum* showed oxidative stress when exposed to MWCNTs expressed by higher lipid peroxidation, and activation of antioxidant defences and biotransformation mechanisms. Additionally, neurotoxicity was observed by inhibition of cholinesterase activity in organisms exposed to MWCNTs at both pH conditions.

1.2 METAL-CONTAINING NANOMATERIALS

1.2.1 Silver nanoparticles (Ag NPs)

Characteristics

Metal NPs are holding from small number of atoms to numerous metal atoms, stabilize by ligands, surfactants, polymers or dendrimers (Beyene et al., 2017). Silver (Ag) NPs are clusters of Ag atoms that range in diameter from 1 to 100 nm (Behra et al., 2013). Generally, the most commonly used are spherical Ag NPs, however diamond, octagonal and thin sheets are also well known (Graf et al., 2003). Silver NPs have distinctive physical-chemical properties, including a high electrical and thermal conductivity, surface-enhanced Raman scattering, chemical stability, catalytic activity and non-linear optical behaviour (Tran & Le, 2013).

Applications

According to the Project on Emerging Nanotechnologies (PEN, (http://www.nanotechproject.org) 313 products utilize Ag NPs, which corresponded to 24% of products listed (Tran & Le, 2013). In fact, due to their peculiar properties, they have been used for several applications, including as antimicrobial agents, industrial, household, and healthcare-related products, medical devices coatings, optical sensors, cosmetics, and have ultimately enhanced the tumor-killing effects of anticancer drugs (Korani et al., 2015). Recently, Ag NPs have been frequently used in many textiles, keyboards, wound dressings, and biomedical devices (Li et al., 2014a; Sondi & Salopek-Sondi, 2004; Broglie et al., 2015), and water purification systems (Sweet & Singleton, 2011).

Environmental concentrations and behaviour

Ag NPs have garnered public concern on their environmental implications, because they have been introduced into the aquatic environment during production, storage, and application (Zhang et al., 2018). The use of probabilistic methods for determining

PECs in Europe and in the US, based on the life cycle perspective of products containing NPs, showed current predicted environmental concentrations in Europe of 0.5−2 ng L^{-1} in surface waters (Gottschalk et al., 2009), with an estimated exponential yearly increase of Ag NP in most environmental compartment (Giese et al., 2018).

In aquatic environment, the most important processes for the bioavailability of Ag NPs and effects to aquatic organisms include agglomeration or aggregation of NPs to form larger particles, oxidation to Ag+, subsequent release of Ag+ species, speciation and solubility of Ag+ in solution and reactions modifying the reactivity of Ag(0)-NP (Navarro et al., 2008; Levard et al., 2012; Lowry et al., 2012; Piccapietra et al., 2012).

Toxic impacts in bivalves

Studies performed to assess the Ag NPs effects toward different bivalve species are presented in Table 2.

ENM effects

Silver ions cause changes in the permeability of the cell membrane to potassium and sodium ions at concentrations that do not even limit sodium, potassium, ATP, or mitochondrial activity (Kone et al., 1988). The literature also proves that Ag NPs can induce toxic effects on the proliferation and cytokine expression by human peripheral blood mononuclear cells (Shin et al., 2007). Silver NPs are also known to show severe toxic effects on the reproductive system (Auffan et al., 2009). Research showed that these materials can cross the blood-testes barrier and be deposited in the testes where they adversely affect the sperm cells. Although the mechanisms of Ag NP toxicity are not yet fully understood, there are strong indications that the release of ionic silver (Ag+) is a highly relevant factor for their toxicity and that the formation of ROS may play a role in this (Molleman & Hiemstra, 2015). Moreover, UV irradiation has been demonstrated to significantly enhance the toxicity of Ag NPs compared to that in the dark, which was explained by accelerated Ag ions release and ROS generation (Zhang et al., 2018). Looking the interaction with invertebrate species in aquatic environments, Ag NPs interact with different number of biological surfaces including skin, gills or gut tissues as well as cell walls (Zhang et al., 2018).

Looking on bivalves, in the mussels *M. galloprovincialis*, at a high concentration (10 mg L^{-1}), Ag NPs (<100 nm) showed accumulation and haemocyte damage (Gomes et al., 2013). In another study, the same authors also exposed the mussel to the same concentration of Ag NPs, measuring biomarkers of oxidative stress and metal accumulation (Gomes et al. 2014). Both Ag NPs and Ag^+ were accumulated in both gills and digestive glands. Antioxidant enzymes (superoxide dismutase, catalase and glutathione peroxidase) were activated by Ag NPs and Ag^+. Moreover, metallothionein was induced in gills, directly related to Ag accumulation, while in the digestive glands only a small fraction of Ag seems to be associated with this protein. Lipid peroxidation was higher in gills exposed to Ag NPs, whereas in the digestive glands only Ag^+ induced lipid peroxidation. A study conducted by Zuykov et al. (2011a) brought new information regarding the internal circulation of Ag NPs in bivalves. The authors demonstrated that Ag NPs can also penetrate the haemolymph. Specifically, using the radio-labelled Ag NPs (<40 nm, 0.7 mg L^{-1}), authors observed that 60% of the uptake accumulated in the soft tissues of the mussels *M. edulis* with maximum concentration in the digestive organs, whilst about 7% was found in the mussels' extrapallial fluida. Zuykov et al. (2011b) also examined the shell nacre micromorphology of adults and juveniles of *M. edulis*. However, no evidences of alteration processes were found on the nacreous layer of the young and adult mussels exposed to Ag after depuration, even if, in some cases, grains of carbonate particles were observed on the whole surface of the nacre tablets. On the other hand, not always the toxic effect was detected when bivalves were exposed to Ag NPs. This is the case of deposit-feeding clam, *Macoma balthica,* which was reared in sediments spiked with Ag NPs in different forms (aqueous ions, nanoparticles, and micrometer-sized particles) at 150–200 μg g^{-1} concentrations. In all experiments, no effects on mortality, condition index, or burrowing behaviour were observed for any concentrations (Dai et al., 2013). In the clam species *Scrobicularia plana*, Buffet et al. (2013) examined the uptake and effect of silver (soluble or as lactate Ag NPs of 40 nm) at the concentration of 10 μg L^{-1} in the organisms exposed to the contaminants directly (water) or via the diet (microalgae). The authors showed that for both forms of Ag, bioaccumulation was much more relevant for waterborne than for dietary exposure. The response of oxidative stress biomarkers (catalase, glutathione S-transferase, superoxide dismutase) was higher after dietary than waterborne exposure to Ag (soluble and NPs). Burrowing was not affected for bivalves exposed directly or through the diet to both Ag forms but feeding behaviour was impaired. Since no differences of responses to Ag either soluble or nanoparticulate were observed, it seemed that labile Ag released from Ag NPs was mainly responsible for toxicity. The same authors (Buffet et al., 2014), exposed the same bivalves to the same concentration of Ag NPs, demonstrated in this case a bioaccumulation of either Ag nanoparticulate and their ionic forms. Concerning biomarker responses, both soluble and nanoparticulate Ag forms, induced defences against oxidative stress, detoxification, apoptosis, genotoxicity and immunomodulation. Nevertheless, DNA damages in the digestive gland of *S. plana*, and Phenoloxidase were higher in the presence of Ag NPs compared to soluble Ag suggesting a specific nano effect. Another clam species (*Sphaerium corneum)* was used to investigate the chronic effects of Ag NPs (Völker et al., 2015). Animals were exposed to 0–500 μg L^{-1} assessing the effects on reproduction and behavioural changes, the effects on intracellular levels of ROS and the activity of antioxidant enzymes (superoxide dismutase, catalase, glutathione-S-transferase, glutathione peroxidase). The authors further explored the activity of the sodium–potassium adenosine triphosphatase (Na+/K+-ATPase). Chronic exposure resulted in negative effects on reproduction at concentrations of 5 and 3.18 μg L^{-1} (LOEC). ROS levels significantly increased after exposure to 10 μg L^{-1} and alteration antioxidant enzymes activities were detected. Moreover at 500 μg L^{-1} Na+/K+-ATPase activity were inhibited by 82.6 %. Using the adults and the embryos of the oysters *C. virginica* exposed to 16- 0.0016 μg L^{-1} of Ag NPs, Ringwood et al. (2010) tried to characterize their toxicity on embryonic development of oysters comparing the relative sensitivity of embryos to adults. The results showed that at 0.16 μg L^{-1} concentration, adverse effects on embryonic development were observed as well as biologically significant effects on lysosomal destabilization of adults. Significant increases in metallothionein (MT) mRNA levels were observed in both embryos and adult oysters, and MT levels were induced more in embryos. However, the authors were not able to identify if the toxicity and gene expression responses observed in this study were due to the nanoparticles themselves or the Ag ions that dissociated from the nanoparticles (Ringwood et al., 2010). Using the same species, McCarthy et al. (2013) showed that Ag NPs (20-30 nm, citrate-capped, 0.2 mg L^{-1}) increased protein levels and caused greater oxidative damage in the hepatopancreas. These results suggested an uptake of Ag NPs and transport to the hepatopancreas, where they cause damage *in situ*. Exposures (1-400 mg L^{-1}) of Ag NPs (26 nm) have shown also significantly reduced phagocytosis in the haemolymph of *C. virginica* compared to the control, with little difference between nano and ionic Ag. Phagocytosis is an important part of removal of foreign objects for health of the organism, although it can also result in pathogen uptake (Chalew et al., 2012). Impairment of physiological parameters related to bioenergetic functions after Ag NPs exposure were also demonstrated. In a study conducted by Saggese et al. (2016), the authors observed significant effects on the average respiration rate of *Brachidontes pharaonis* exposed to low doses of Ag NPs (2, 20, 40 μg L^{-1}) in mesocosm. Complex nonlinear dynamics were also detected as a function of the concentration level and time and heartbeat rates largely increased with no acclimation in animals exposed to the two highest levels with similar temporal dynamics. Moreover, a decreasing trend for absorption efficiency was observed which might indicate energetic constraints in the exposed organisms.

ENMs and climate change

As noted earlier, pH, ionic strength and composition, NOM, temperature, and nanoparticle concentration all interact to affect aggregation or stabilisation of Ag NPs (Fabrega et al., 2011). Although the advance on knowledge regarding the impacts of climate change and Ag NPs to aquatic organisms, still significant scientific uncertainties remain in understanding and ultimately predicting the long-term consequences arising from sustained modifications of climate change related factors together with pollution from contaminants of emerging concern. The understanding on the chemical nature of the exposure medium is fundamental in determining bioavailability and a consequent toxicity in exposed organisms. In this perspective the influence of salinity (15 psu vs 30 psu) in the fate and toxicity of Ag NPs towards the estuarine bivalve *Scorbicularia plana* has been recently investigated (Bertrand et al., 2016). The authors showed that at lower salinity Ag was more available for the organisms. At lower salinity the biological effects of Ag were enhanced inducing apoptosis and oxidative stress, and reducing energetic reserves and finally burrowing activities.

1.2.2 Gold nanoparticles (Au NPs)

Characteristics

Gold nanoparticles (Au NPs) are key materials in nanoscience and nanotechnology and have been extensively studied (Zhou et al., 2009). The morphology is spherical, and the versatile surface chemistry allows them to be coated with small molecules, polymers, and biological recognition molecules, thereby extending their range of application (Li et al., 2014b).

Spherical Au NPs possess optical characteristic in different aggregated states (Chen et al., 2018) which comes from the collective oscillation of electrons at their surface, and such property can be fine-tuned through control of size, composition, sharpness and chemistry (Chen et al., 2018). Due to their large surface-to-volume ratio (Yeh et al., 2012) Au NPs serve as an excellent scaffold to immobilize large quantities of specific functional groups, leading to rapid responses and high sensitivity for the targeted analyte (Chen et al., 2018). Moreover, they exhibit excellent compatibility with almost chemically and biologically active molecules (Chen et al., 2018).

Applications

As a consequence of their properties Au NPs can be fabricated as power analytic tools that are of interest to various fields. They are being widely explored for use in high technology applications such as sensory probes, electronic conductors, therapeutic agents, organic photovoltaics, drug delivery in biological and medical applications, and catalysis. They are used also as an anti-biotic, anti-fungal, and anti-microbial agent when added in plastics, coatings, nanofibers and textiles; in nanowires and catalyst applications; in therapeutic agent delivery; to connect resistors, conductors, and other elements of an electronic chip; in photodynamic therapy and in various sensors devices (Yeh et al., 2012).

Environmental concentrations and behaviour

Information available on the current levels of Au NPs in aquatic media is very limited, but predictions by Boxall et al. (2007) and Tiede et al. (2009) gave concentrations (referring to gold content) of 0.1 mg L^{-1} in surface water originating from use in consumer products (Table 1).

In natural water ecosystems, Au NPs can be degraded, transformed, transported and accumulated in a variety of ways. One main effect is that the Au NPs could form colloidal suspensions by association with substances originating from animals or from human activity as well as by the physical conditions of the water system (e.g., temperature, pH, salinity etc.) (Petosa et al., 2010).

Toxic impacts in bivalves

Studies performed to assess the Au NPs effects toward different bivalve species are presented in Table 2.

ENM effects

Gold NPs toxicity can be attributed to their interaction with the cell membrane (Goodman et al., 2004); oxidative stress leading to cytotoxicity effects (Pan et al., 2009); the inhibition of metabolic activity (e.g., leading to mitochondrial damage) (Panessa-Warren et al., 2008) and, possible damage to the nuclear condensed DNA (Kang et al., 2009). One possible explanation for the toxicity of Au NPs is that its toxicity associated with the generation of ROS may be connected to the properties of Au as a catalyst. Co-adsorbed water and O_2 generate atomic oxygen and hydroperoxy (HO_2) intermediates, considered precursors to the formation of atomically-adsorbed oxygen and hydroxyl, which activate the production of molecular oxygen and ROS (Lapresta-Fernández et al., 2012). To date, data available on the ecotoxicity of Au NPs in bivalves, showed that these NPs are uptaken and accumulated in the tissues of bivalves and capable of eliciting unexpected biological responses (Canesi et al., 2012). In *M. edulis* exposed to gold-citrate nanoparticles (GNP) (750 µg L^{-1}, average diameter 5.3 ± 1 nm), Au accumulation and oxidative stress conditions were both higher in the digestive gland and in gills. Specifically, results showed that GNP caused higher ubiquitination, induction of catalase in the digestive gland and higher ubiquitination and carbonylation in gills (Tedesco et al., 2008). In a subsequent study using smaller Au NPs (750 ppb, average diameter 5.3 ± 1 nm), the same authors showed that 95% Au was accumulated in the digestive gland, generating lipid peroxidation and decreasing thiol-containing proteins; moreover, exposure induced a significant decrease in LMS in the hemocytes (Tedesco et al., 2010). Fkiri and co-authors (2018) assessed the toxicity of two different gold Octahedra nanoparticles coated with 1.3-propandiol with polyvinyl-pyrrolidone K30 ($Au_{\_0.03}$ and $Au_{\_0.045}$) on the clam *R. decussatus* and observed an increase of oxidative stress/damage in specimen exposed only to the $Au_{\_0.045}$ form. Katsumiti and co-authors (2016) screened the cytotoxicity of four type of metal NPs (Au, ZnO and SiO_2) selected by their different physico-chemical characteristics in *M.*

galloprovincialis hemocytes and gill cells. Looking on the results related to Au NPs (at the concentrations of 0.1, 1, 10, 25, 50 and 100 mg L^{-1} and three-dimension sizes: 5, 15 and 40 nm), bulk Au and Au NPs showed relatively low toxicity to mussel hemocytes. Ionic Au was the most toxic Au form, and caused a decrease in hemocyte viability starting at 25 mg L^{-1}. The three sizes of Au NPs (5, 15 and 40 nm) decreased hemocyte viability starting at 50 mg L^{1}. Joubert et al. (2013) examined the subcellular localization in gills and digestive gland of *S. plana* using Au NPs in a range of sizes 5, 15, and 40 nm. Clams were exposed to Au NPs stabilized with citrate buffer and then diluted in seawater at the concentration of 100 μg L^{-1}. Particles were observed in gills, distributed as free in the cytoplasm, or associated with vesicles. In the digestive gland, the most striking feature was the presence of individual or small aggregates 40 nm sized within the nuclei colocalized with DNA. Depending on the size, individual or small aggregates (40 nm AuNPs) or more aggregated NPs (5 and 15 nm) were observed, with at least one of the dimensions (40–50 nm) allowing the passage through nuclear pores. In *S. plana* Au NPs were also responsible of metallothionein induction (5, 40 nm), increased activities of catalase (15, 40 nm) and superoxide dismutase (40 nm) and of glutathione S-transferase indicating defence against oxidative stress. Moreover, exposure to Au NPs impaired burrowing behavior (Pan et al., 2012). Using another clam species *R. philippinarum,* García-Negrete et al. (2013) showed accumulation of gold Au^{3+} (chloroauric acid solution) at a concentration of 50 mg L^{-1} and Au NPs (6 mg L^{-1} and 30 mg L^{-1}) in both cases within either the digestive gland or gill tissues. Moreover, electron-dense deposits (corresponding to Au NPs, as proven by X-ray microanalysis) were observed in the heterolysosomes of the digestive gland cells. *R. philippinarum* was also used as a model organism to detect the ability of Au NPs to enter cells, organelles and nuclei and trigger oxidative stress (Volland et al., 2015). Uptake, elimination and molecular effects under short-term and sub-chronic exposure conditions to an environmental relevant concentration (0.75 μg L^{-1}) of agglomerating citrate Au NPs (~20 nm) were studied. The results demonstrated that at the tested concentration, the particles are readily taken up into the digestive gland and gills generating oxidative stress and inflammatory response, measured as phase II antioxidant enzymes activity and q-PCR gene expression analysis. Simulating real estuarine mesocosm environment, Ferry et al. (2009), exposing the hard clam *Mercenaria mercenaria* to 4.3 10^{-10} M of Au nanorods, studied the distribution of Au in this species. The authors observed that the clams were able to accumulate the most nanoparticles on a *per* mass basis, suggesting that Au nanorods can readily pass from the water column to the marine food web. The internalization of Au NPs has been also thoroughly investigated in early life stages of the oyster *C. gigas* (Noventa et al., 2018). Au NPs were ingested by larvae and penetrated the cells of the digestive gland via pinocytosis-macropinocytosis. Than they undergo intracellular digestion and storage inside residual bodies, before excretion with feces or translocation for extrusion.

ENMs and climate change

The simultaneous exposure of marine organisms to Au NPs and climate changes is likely an ecologically relevant scenario. Although the importance of study how the uptake, biotransformation, elimination and effects of Au NPs in bivalves can be influenced by a variation of the environment as a consequence of climate changes, to the best of our knowledge, their combined effects have not been investigated before.

1.2.3 Titanium dioxide (TiO_2 NPs)

Characteristics

Titanium dioxide (TiO_2) exists as three different polymorphs; anatase, rutile and brookite. The primary source and the most stable form of TiO_2 is rutile. The common oxidation state of Ti is +6, +4, +3 and +2. Titanium dioxide is typically an n-type semiconductor due to oxygen deficiency (Wisitsoraat et al., 2009; Amtout & Leonelli, 1995; Asahi et al., 2000). TiO_2 is the most widely investigated photocatalyst due to high photo-activity, low cost, low toxicity and good chemical and thermal stability (Hoffmann et al., 1995; Su et al., 2006; Wang et al., 2009). TiO_2 is present in sunscreens due to its consideration as safe physical sunscreen agent, which reflects and scatters both UVB (290-320 nm) and UVA (320-400 nm), the principal cause of skin cancer. Also, TiO_2 is used to mineralize many undesired organic pollutants (Wang et al., 2008). On the other hand, as TiO_2 absorbs substantial UV radiation, in aqueous media -despite the low penetration of UV in water- it could yield to hydroxyl species that may cause substantial damage to DNA (Dunford et al., 1997; Hidaka et al., 1997; Guix et al., 2008).

Applications

Nowadays the TiO_2 NPs have different applications, including medicine, cosmetics, electronics, innovative food products and environmental remediation. TiO_2 can be used in paints, coatings, plastics, papers, inks, medicines, pharmaceuticals, food products, cosmetics, and toothpaste (Kaida et al., 2004; Wang et al., 2007a; Wolf et al., 2003). It can even be used as a pigment to whiten skim milk. TiO_2 NPs are also extensively used in sunscreens (Trouiller et al., 2009). In addition, TiO_2 has long been used as a component for articulating prosthetic implants (Jacobs et al., 1991; Sul, 2010). TiO_2 NPs can be used in catalytic reactions, such as semiconductor photocatalysis, in the treatment of water contaminated with hazardous industrial by-products (Wigginton et al., 2007). Industrial utilization of the photocatalytic effect of TiO_2 NPs has also found its way into other applications, especially for self-cleaning and anti-fogging purposes such as self-cleaning tiles, self-cleaning windows, self-cleaning textiles, and anti-fogging car mirrors (Robichaud et al., 2009). In the field of nanomedicine, TiO_2 NPs are under investigation as useful tools in advanced imaging and nanotherapeutics (Wahie et al., 2007; Kaegi et al., 2008; Robichaud et al., 2009). In addition, unique physical properties make TiO_2 NPs ideal for use in various skin care products (Wang et al., 2007b) and antibacterial properties under UV light irradiation (Kaegi et al., 2008).

Environmental concentrations and behaviour

Predicted Environmental Concentrations (PECs) for nano-TiO_2 in surface waters are of µg L^{-1} (Gottschalk et al., 2013) and up to 0.2 pg L^{-1} in seawater (Giese et al., 2018) (Table 1). Predicted environmental concentrations of TiO_2 NPs in the water compartment in different countries ranged from 0.002 µg L^{-1} to 16 µg L^{-1} (Menard et al., 2011; Sun et al., 2014).

Toxic impacts in bivalves

Studies performed to assess the TiO_2 NPs effects toward different bivalve species are presented in Table 2.

ENM effects

Principal parameters of particles affecting their physicochemical properties include shape, size, surface characteristics and inner structure. When the particles become progressively smaller, their surface areas, in turn, become progressively larger, and researchers have also expressed concerns about the harmful effects of TiO_2 NPs on human health associated with the decreased size (Andersson et al., 2011; Wang & Li, 2012). Surface modification such as coating, influences the activity of TiO_2 NPs. For example, diminished cytotoxicity was observed when the surface of TiO_2 NPs was modified by a grafting-to polymer technique combining catalytic chain transfer and thiolene click chemistry (Tedja et al., 2012). Another study confirmed the effect of surface coating on biological response endpoints of TiO_2 NPs (Saber et al., 2012).

The effects of TiO_2 NPs on marine bivalves have become issues of major concern (Wang et al., 2014; Huang et al., 2016). A study by Doyle and co-authors (2015) demonstrated that suspension feeding bivalves easily ingest TiO_2 NPs regardless their form. Besides, studies performed on *M. galloprovincialis* suggested that the gills and digestive gland are the target organs for TiO_2 NPs accumulation and toxicity (Canesi et al., 2014; Della Torre et al., 2015; Gornati et al. 2016). The NPs are also prone to biomagnification in bivalves through the food-chain (Wang et al., 2014). Furthermore, few studies demonstrated that TiO_2 NPs caused obvious oxidative damage in mussels as evidenced by the increase of the catalase activities (Barmo et al., 2013). The mechanisms that drive TiO_2 NPs toxicity are not yet fully understood, but there are evidences that UV and/or visible light exposition can generate ROS (Konaka et al., 2001; Uchino et al., 2002; Dalai et al., 2013). Sureda and coauthors (2018) exposed *M. galloproviancialis* for 24 h to environmental concentrations of sunscreen containing TiO_2 NP. Results showed an increase of metallothionein content. The activities of the antioxidant and detoxification glutathione *s*-transferases enzymes showed a bell-shape profile with increased activities at lower sunscreen concentration, while at the highest concentration the induction was abolished. In accordance with these enzyme activities, the levels of malondialdehyde, a marker of lipid peroxidation, were significantly elevated at the higher concentration of sunscreen containing TiO_2 NP. Acetylcholinesterase activity was decreased only at the highest sunscreen concentration. Moreover, D'Agata et al. (2014) carried out study on *M. galloprovincialis,* which were exposed to TiO_2 NPs (10 mg L^{-1}) for 7 day. Inductively coupled plasma-optical emission spectrometry analyses of mussel tissues showed higher Ti accumulation (>10-fold) in the digestive gland compared to gills. Nano-sized TiO_2 showed greater accumulation than bulk, irrespective of ageing, particularly in digestive gland (>sixfold higher). Despite this, transcriptional expression of metallothionein genes, histology and histochemical analysis suggested that the bulk material was more toxic. Moreover, haemocytes showed significantly enhanced DNA damage, determined by the modified comet assay, for all treatments compared to the control, but no significant differences between the treatments. Moreover, Barmo et al. (2013) demonstrated that mussels exposed for 96 h to different concentrations of TiO_2 NP (1, 10 and 100 μg L^{-1}) carried out to multiple damage as lysosomal and oxidative stress biomarkers and a decrease transcription of antioxidant and immune-related genes. Mezni et al. (2017) reported no considerable effect assessed as inuction of oxidative stress, in digestive gland of *M. galloprovincialis* treated with TiO_2 concentration gradients ranging from 1 to 100 mg L^{-1}. Indeed, the level of the superoxide anion, the activity of an antioxidant enzyme superoxide dismutase and the ratio between reduced / oxidized glutathione showed no significantly differences in digestive gland of all treated groups compared to control. However, slight modifications were observed in gill at high concentration (100 mg L^{-1}). A study performed *in vitro* on mussel hemocytes showed that TiO_2 NPs are internalized by these cell types, leading to a decrease of phagocytic activity (Marisa et al., 2015). TiO_2 NPs are also able to interfere with larval development, albeit at concentrations far from the environmental levels predicted for these NPs (Libralato et al., 2013). A recent study highlighetd the neurotoxic potential of TiO_2 NPs in *Tegillarca granosa*, through increase of neurotransmitter levels, impairment of AChE activity and down-regulation of neurotransmitter-related genes (Guan et al., 2018). Research conducted by Johnson et al. (2012) to assess the behaviour TiO_2 in sewage and toxic effects of Optisol (Oxonica Materials Ltd) and P25 (Evonik Industries AG), which are representative of forms used in sunscreen and cosmetic products. The obtained results revealed a close association of TiO_2 with activated sludge. Using commercial information on consumption, and removal rates for sewage treatment, predictions were made for river water concentrations for sunscreen TiO_2 NPs for the Anglian and Thames regions in Southern England.

"Trojan horse" effects

Nano-TiO_2 might affect aquatic organisms through its inherent properties, but also by modifying the bioavailability of other aquatic contaminants, including heavy metals (Zhang et al., 2007; Canesi et al., 2012; Yang et al., 2012) and dioxin (Canesi et al., 2014). In the case of a freshwater golden mussel *Limnoperna fortunei,* the exposure to different crystalline TiO_2 NPs (rutile and anatase; 1 mg L^{-1}) showed to enhance copper accumulation both in gills and muscle. Moreover, fractal histomorphometric analysis of muscle showed that both forms of crystaline TiO_2 NPs altered this organ (Manske Nunes et al., 2018).

ENMs and climate change

The simultaneous exposure of marine organisms to TiO_2 NPs and climate changes is likely an ecologically relevant scenario (Xia et al., 2018). Some recent studies demonstrated the influence of water acidification on the availability and toxicity of TiO_2 NPs on marine bivalves. Shi et al. (2013), showed that under low pH conitions (7.4) the accumulation of TiO_2 NPs was increased respect to normal pH in the clams *Tegillarca granosa*, *Meretrix meretrix*, and *Cyclina sinensis*. Hu and coauthors (2017) demonstrated that the effects of TiO_2 NPs on several physiological parameters of the mussel *Mytilus coruscus* were enhanced under high pCO_2 (2500–2600 µatm). Under both stressors, ammonia excretion was increased, while clearance rate, respiration rate and O:N ratio were reduced as well as the scope for growth, respect to the exposure to TiO_2 NPs at normal pH. In line with this evidence also the exposure of *M. coruscus* to TiO_2 NPs at acidified pH (7.3) induced several effects on hemocytes immune parameters (Huang et al., 2016). TiO_2 NPs exposure determined an increase of ROS levels, the reduction of phagocytosis and esterase activity and lowered lysosomal content, and such effects were exacerbated at low pH. The effects were still mantained after a recovery period under acidified conditions. Wang and coauthors (2014) investigated the effects of TiO2 NPs on *Perna viridis* exposed at different oxygen levels (hypoxia: 1.5 mg O_2 L^{-1} vs normoxia: 6.0 mg O_2 L^{-1}). Several immune parameters measured in hemocytes resulted affected as ROS levels phagocytosis and esterase activity, showing synergistic effects under both stressors.

1.2.4 Zinc oxide nanoparticles (ZnO NPs)

Characteristics

Zinc oxide nanoparticles NPs (ZnO NPs) has a hexagonal structure (space group C6mc) and its structure has a number of alternating planes composed of tetrahedrally coordinated O^{2-} and Zn^{2+} ions, stacked alternately along the c-axis. Zinc metal ions have the features of large volume to area ratio, high ultraviolet (UV) absorption, and long life-span (Yu et al., 2004) and polar surfaces (Nolan et al., 2009).

Investigation of the properties of individual ZnO nanostructures is essential for developing their potential as the building blocks for future nanoscale devices on the physical properties of ZnO nanostructures, including mechanical, piezoelectric, electrical, optical, magnetic, and chemical sensing properties (Applerot et al., 2009; Emamifar & Mohammadizadeh, 2015). A study conducted by Li & Wu (2003) showed the effects of ZnO NPs on the mechanical and antibacterial properties of PU (polyurethane) films. Moreover, Emamifar & Mohammadizadeh, (2015) tested the antimicrobial activity of LDPE (low-density polyethylene) films incorporated with ZnO NPs in orange juice.

Applications

ZnO NPs are used on a large scale in pigments, in sun screens, cosmetic, anti-virus agent in coating (Chen et al., 2003; Hu et al., 2003; Li et al., 2003) and in polymers or tires as stabilizers. Surface-coated Zn oxide has been repeatedly proposed for medical treatments such as magnetic drug targeting systems (Fujishima & Honda, 1972; Frank & Bard, 1977; Su et al., 2006) or as a contrast agent in magnetic resonance imaging (Xue et al., 2010; Petkovic et al., 2011). Zirconia is a rapidly growing ceramic nanoparticulate, with broad applications in catalysis, gas sensor (Lin et al., 1998; Xu et al., 2000) and polishing, and as additives in polymers and dental materials (Nolan et al. 2009; Andersson et al., 2011; Wang and Li, 2012).

Environmental concentrations and behaviour

Human health and environmental impacts are the potential risks of engineered ZnO NPs, which largely contribute to their current lack of public acceptance (Maynard et al. 2006). As for the other nanoparticles, the ZnO NPs environmental concentrations were calculated as probabilistic density functions and were compared to data from ecotoxicological studies (Dale et al., 2015; Coll et al., 2016; Gottschalk et al., 2015; Luo et al., 2015; Ma et al., 2013; Manzo et al., 2013; Sun et al, 2014; Wiench et al., 2009; Zheng et al., 2011). Therefore, a study by Gottschalk et al. (2009) estimated ZnO NP concentrations of 10 ng L^{-1} in natural surface water and 430 ng L^{-1} in treated wastewater in Europe (Giese et al., 2018) (Table 1). Predictions of the environmental behaviour and impacts of NPs based on results derived from laboratory-based exposures need careful consideration of the water chemistry and whether it is representative of ecologically relevant natural waters and exposure conditions. However, it is still not sure whether ZnO NPs are safe for health and the environment due to the lack of environmentally relevant conditions used in the experiments (Franklin et al., 2007).

Toxic impacts in bivalves

Studies performed to assess the ZnO NPs effects toward different bivalve species are presented in Table 2.

ENM effects

Studies demonstrated that there is with ZnO NPs an inverse relationship between concentration and oxyradical production, where this interection of ZnO with subcellular compartments, induced a dose-dependent effect with a prodcution of n-oxidase (Miller et al., 2015; Ciacci et al., 2012; Hanna et al., 2013; Matranga & Corsi, 2012; Manzo et al., 2013). Studies on the bivalves (clam, *R. philippinarum* and mussels, *Mytilus galloprovincialis*) showed the toxic effects on hemocytes and gill cells in clams and mussels when exposed to ZnO NPs *in vivo* (Katsumiti et al., 2016; Marisa, 2016). A study on *S. plana* performed by Buffet et al. (2013) showed an accumulation of 5.4 μg Zn g^{-1} when exposure at 3 mg Zn kg^{-1} and activation of antioxidant enzymes, while significant reduction of burrowing and feeding activities were detected. Moreover, Devin et al. (2017) exposing the bivalve *S. plana* to predicted doses (3 mg ZnO kg^{-1} sediment) to ZnO NPs, showed the increase of oxidative stress. Also, Trevisan et al. (2014) observed in *C. gigas* exposed at 4 mg L^{-1} of ZnO NPs for 24 and 48 h, a time-dependent accumulation of Zn in gills (49% and 80% after 24 and 48 h, respectively). Histopathological analysis showed irregular gill morphology led electron-dense vesicles near the cell membrane and loss of mitochondrial cristae and digestive gland damage complying with stress related biomarkers, probably due to both Zn ions and nano-forms. Montes et al. (2012) checked Zn uptake and accumulation in *M. galloprovincialis* exposed to 1–10 mg L^{-1} of ZnO NPs for 96 h. Up to 21% of Zn into seawater accumulated in mussels and pseudo-faces presented 63.000 μg g^{-1} of Zn; this saturation threshold for Zn were reach, thus accumulation rates did not over than excretion in mussels during exposure period. Hanna et al. (2013) exposed the *M. galloprovincialis* to 0.1, 0.5, 1 and 2 mg L^{-1} of ZnO NPs up to 12 weeks. This long-term exposure resulted in impairment feeding rate (EC50 = 1.5 mg L^{-1}) and increase of cell respiration rate (EC50 = 0.9 mg L^{-1}).

ENMs and climate change

The effects of simultaneous exposure of marine organisms to ZnO NPs and acidification has been investigated on the mussel *M. coruscus* showing different results depending on the cellular target investigated (Huang et al., 2016; Wu et al., 2018). The effects of ZnO NPs on several immune functions of hemocytes such as hemocyte mortality, ROS production, phagocytosis and esterase activities resulted enhanced under acidified conditions (pH 7.3). The effects persisted also after a recovert period of 7 days. On the contrary, in both in gills and hemocytes of *M. coruscus* expose uner the same conditions any sinergistic effects were observed on biochemical markers related to stress reposnse (superoxide dismutase, catalase, glutathione peroxidase, acid phosphatase and alkaline phosphatase (Huang et al., 2016).

1.3 RARE EARTH ELEMENTS (REES) NANOMATERIALS

1.3.1 Cerium dioxide (CeO_2 NPs)

Characteristics

Cerium (Ce) is the most abundant rare earth metal belonging to lanthanide elements. Most of the Rare earth elements (REEs) exhibit only one oxidation state in liquid form (+3). The cerium (Ce) is one of REE can exist in two oxidation states in the liquid form (Ce3+ and Ce4+). In CeO_2 NPs both states coexist on the NP surface (Sun et al., 2012). The presence of Ce^{3+}/Ce^{4+} redox couple generates oxygen vacancies which confer to this NPs catalytic and electrical properties and biological reactivity (Caputo et al., 2017).

Applications

Rare earth oxide (REO) nanoparticles (NPs) is one class of the most important nanomaterials, which are widely used in paint coating, polishing powder, catalysts, luminescent materials, between other applications (Deshpande, 2005; Zhang et al., 2012). Cerium oxide NPs (CeO_2 NPs) are used in many industrial and consumer products thanks to their unique physicochemical properties. Ceria has attracted much attention in the last years because of its numerous technological application fields such as heterogeneous catalysis an unexpected ability of Ceria to dissociate hydrogen opens new directions for the use of this promising material, where the absence of noble metal particles involves tremendous economic advantages (Trovarelli & Fornasiero, 2013; Trovarelli & Llorca, 2017). CeO_2 NPs are also used as glass polishers, as purifiers of Mischmetal, and in heat-resistant coatings (EPA, 2009) and exploited for their antibacterial properties (Jeong et al., 2005; Lee et al., 2005; Shrivastava et al., 2007). Moreover, it can be used as a catalyst itself or as a support, treatment of toxic gases and pollutants, solid oxide fuel cells, oxygen sensors, and biomedicine (Abbott et al., 2010; Amrute et al., 2012; Vile et al., 2012; Chang et al., 2013; Mann et al., 2014; Yao et al., 2014; Mullen et al., 2017). Pristine Ceria has been successfully used in alkyne semi hydrogenation reactions (Camellone et al., 2016) with high activity and selectivity to the alkene products. For instance, the excellent ultraviolet radiation absorption capability of CeO_2 NPs means that they could be used as a broad-spectrum inorganic sunscreen in personal care products (Patil et al., 2002). Cerium Oxide NPs have been introduced into gasoline to enhance combustion efficiency and to reduce pollutant release during the combustion process (Das et al., 2005). Recently, CeO_2 NPs were investigated as a free radical scavenger and have shown great promise as a nanomedicine to protect against a series of chemical and biological insults that promote the production of free radicals (Briggs et al., 1975; Telek et al., 1999; Ciofani et al., 2014).

Environmental concentrations and behaviour

Boxall et al. (2007) stated that the predicted limit of CeO_2 in the water should be < 0.0001 (µg L^{-1}). Some studies demonstrated that environmental concentration of CeO_2NPs in water should increase due to their large use in the diesel fuels, up to reach levels around 0.02 to 300 ng L^{-1} (Johnson & Park, 2012; Sun et al., 2014). This led to the recent calculation of predicted environmental concentrations as high as 1 µg L^{-1} in surface waters (O'Brien & Cummins, 2010). Anyway, the predicted environmental concentrations are rather low, and below the pg L^{-1} in seawater (Dale et., 2015; Markus et al., 2016; Meesters et al., 2016; Giese et al., 2018) (Table 1).

Some recent articles underlined that once released in natural waters, environmental modification occurring in the water media heavily influence CeO_2 NPs chemico-physical properties such as the aggregation and dissolution propensity (Quik et al., 2010; Auffan et al., 2014a; Tella et al., 2014; Booth et al., 2015). This will therefore affect the distribution of NPs in different compartments and the consequent bioavailability and toxic potential for aquatic biota (Garaud et al., 2016). Some studies also pointed out that the coating of CeO_2 NPs might be responsible for higher stability in water and modified biological consequences to organisms. As an example, citrate coating CeO_2 NPs showed different stability in freshwater exposure systems respect to bare CeO_2 NPs (Tella et al., 2015).

Toxic impacts in bivalves

Studies performed to assess the CeO_2 NPs effects toward different bivalve species are presented in Table 2.

ENM effects

Bustamante and Miramand (2005) showed levels of CeO_2 up to 3.17 µg g^{-1} (dry weight) in the digestive glands of the scallop *Chlamys varia* at clean sites in the Bay of Biscay, and up to 10.85 µg/g in contaminated sites, confirming that bivalves can significantly accumulate and could likely be affected by this contaminant. Few studies were conducted to evaluate the potential toxicity of CeO_2 NPs in aquatic organisms (Van Hoecke et al., 2009; Manier et al., 2011; Artells et al., 2013; Auffan et al., 2013, 2014a, b; Booth et al., 2015; Garaud et al., 2015; 2016; Tella et al., 2015; Peng et al., 2017; Koehlé-Divo et al., 2018). Among them, results showed that CeO_2 NPs can act as ROS scavengers, thus protecting cells from oxidative injuries, mimicking the activity of the superoxide dismutase and catalase (Das et al., 2007; Korsvik et al., 2007; Pirmohamed et al., 2010; Ciofani et al., 2014). The products of these genes are considered as among the most important components of organism antioxidant defense, playing a major role in the reduction of hydrogen peroxide and organic hydroperoxides, by using reduced glutathione (Gharib et al., 2013). For example, a well-known antioxidant as lipoic acid possess a reduction potential in the redox couple with dihydrolipoic acid could explain the observed decrease in cellular damages, a decrease which has also been shown in several works in irradiated gastrointestinal epithelium cells pre-treated with CeO_2 NPs (Colon et al., 2009, 2010). On the contrary, other studies showed that CeO_2 NPs lead to cell damages through the overproduction of ROS and the activation of anti-oxidative enzymes or genotoxic effects (Lee et al., 2009; Bour et al., 2015; Garaud et al., 2016).

Concerning marine bivalves, Bustamante and Miramand (2005) showed a levels of CeO_2 up to 3.17 µg g^{-1} (dry weight) in the digestive glands of the scallop *Chlamys varia* at clean sites in the Bay of Biscay, and up to 10.85 µg/g in contaminated sites, confirming that bivalves can significantly accumulate and could likely be affected by this contaminant.

Experiments with *M. galloprovincialis* showed that most of the CeO_2 NPs filtered from the water column were concentrated into pseudofeces, but a non-negligible fraction was also accumulated in tissues upon long-term exposure (Baker et al., 2014; Conway et al., 2014). In accordance with these observations, Montes et al. (2012) showed a significant bioaccumulation only at the highest concentration of CeO_2 NPs in marine bivalve *M. galloprovincialis* exposed over 4 days to high concentrations (1.0, 2.5, 5.0 and 10.0 mg L^{-1}). Concerning the toxicity for marine bivalves, the effects of CeO_2 NPs on the immune function of *M. galloprovincialis* have been investigated both *in vitro* (Ciacci et al., 2012; Sendra et al., 2018) and *in vivo* (Auguste et al., 2019). In hemocytes exposed *in vitro,* CeO_2 NPs reduced lysosomal membrane stability, phagocytosis capacity and extracellular ROS levels (Sendra et al., 2018). Different toxic outcomes have been observed *in vivo* such as increase of extracellular ROS, enhanced lysozyme and CAT activity and modulated some genes involved in different cellular functions (detoxification, immune response and neuroendocrine signalling) (Auguste et al., 2019). The influence of environmental conditions on the behaviour and toxicity CeO_2 NPs has been underlined (Tella et al., 2015; Briffa et al., 2018). Therefore, the uptake, biotransformation, elimination and toxicity of CeO_2 NPs in bivalves can be influenced by a variation of the environment as a consequence of climate changes.

ENMs and climate change

Yet, to the best of our knowledge, any study has been performed so far to investigate the effects of CeO_2 NPs under climate change scenarios.

FINAL CONCLUSIONS

Based on the information presented in the present study, understanding of sources, fate, and effects of ENMs in the environment has made significant progress. Available data on production volumes suggested that TiO_2 NPs are certainly the most relevant materials in terms of worldwide productions volumes (> 10000 t/a), followed by CeO_2 NPs, ZnO NPs, CNTs (100–1000 t/a) and at the end Ag NPs (55 t/a worldwide). No data are reported regarding Au NPs productions volumes (Bundschuh et al., 2018). Depending on the type and application of ENMs, they are either directly released into the environment, or indirectly via technical compartments and waste streams or enter in-use stock causing a delayed release (Keller et al., 2013; Sun et al., 2016). Considering the worldwide productions of the cited ENMs and the data reported in the present study, a summary of the PECs presented in Table 1, evidenced that the most abundant nanoparticles are Au NPs (only on the surface water), followed by TiO_2 NPs, ZnO NPs, Ag NPs, CNTs and CeO_2 NPs.

From the body of the review, it is clear that ENMs are transformed from their original status resulting from different processes, including aggregation/agglomeration, redox reactions, dissolution, exchange of surface moieties, and reactions with biomacromolecules. These dynamic transformations in turn affect the transport, fate, and toxicity of nanoparticles in the aquatic environment. Looking on their toxic effects in bivalve species, all cited ENMs can cross membrane barriers producing ROS, overt toxic reactivity, cell apoptosis and DNA damage. Moreover, it is reported that some ENMs can be accumulate in various subcellular compartments, such as mitochondria or the nucleus (fullerenes and CNTs). Other ENMs can induce inhibition of metabolic activity (Au NPs) or changes in the permeability of the cell membrane (Ag NPs). Also, indirect non-specific toxic effects which include physical irritation and occlusion of surface tissues (e.g., gills) (CNTs), bioaccumulation and growth inhibition (fullerenes, CNTs, Au NPs, Ag NPs, CeO_2 NPs, TiO_2 NPs and ZnO NPs) have been observed. Despite that most (eco)toxicity studies with ENMs observed some degree of adverse effects, it is still unclear which physical and/or chemical characteristics of ENMs are main driver of toxicity and since a very limited number of studies are made in the field of environmental fate of ENMs, their behaviour in the environment is still largely unexplored. For these reasons, it is very important to study the environmental fate of ENMs in order to understand their pathways of environmental as well as human exposure. Another urgent research need in regard to the environmental exposure of ENMs is to establish the degree of their environmental mobility and bioavailability. Understanding the environmental fate of ENMs would greatly help to assess their exposure of ecosystems and consequently toxicity in biota. Moreover, due to the scarce information presented in the literature, the impact of ENMs under current and future exposure scenarios on communities, ecosystems, ecosystem functions deserves special attention. In the near future, toxicity assays should optimize, as stated by Bondarenko et al. (2016), duration and complexity of the tests, its sensitivty, standardisation status and the required traning. Also, complementary *in silico* strategies should be incorporated to perform quick virtual screening of several nanomaterials before the execution of toxicological tests (González-Durruthy et al., 2016). Finally, the efforts and initiatives for the standardization of nanotoxicological assays (i.e: NanoReg, NANOVALID) are the paramount importance, particulary in present days where the reproducibility crisis in science is being debated (Fanelli, 2018; França & Monserrat, 2018)

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Table 1. Predicted Environmental Concentrations (PECs) of Highly Produced and Used Nanoparticles in different major pathways in the Environment (wastewater treatment plant (WWTP) effluent, surface water [1](Maurer-Jones et al., 2013)); dissolved in seawater [2](Garner et al., 2017); seawater [3](Gottschalk et al., 2015); seawater [4](Giese et al., 2018).

Nanoparticles	**PEC, pathway into environment**
Fullerenes (C60)	0.003 ng L^{-1} surface water[1]
CNTs	0.001–0.8 ng L^{-1}, surface water[1] 3.69–32.66 ng L^{-1}, WWTP effluent[1] 0.02-0.2 pg/L seawater[3]
Ag NPs	0.088–10000 ng L^{-1}, surface water[1] 0.0164–17 µg L^{-1}, WWTP effluent[1] 0-0.6 pg/L seawater[3]
Au NPs	100000 ng L^{-1}, surface water[1]
TiO_2-NPs	21–10000 ng L^{-1}, surface water[1] 1–100 µg L^{-1}, WWTP effluent[1] 10^{-12}-10^{-10} Kg/m^3 dissolved in seawater[2] 0.004-1 ng/L seawater[3]
ZnO NPs	1–10000 ng L^{-1}, surface water[1] 0.22–1.42 µg L^{-1}, WWTP effluent[1] 10^{-8}-10^{-6} Kg/m^3 dissolved in seawater[2] 0.006-0.4 ng/L seawater[3]
CeO_2-NPs	< 1000 ng L^{-1}, surface water[1] 10^{-12}-10^{-10} Kg/m^3 dissolved in seawater[2] 0.03-2 pg/L seawater[3] 0.00-0.001 ng/L seawater[4]

NPs			Bivalves		Effects [d]	Ref. [e]
Type [a]	Conc.	Time [b]	Species	Tissue [c]		
C_{60}	10 mg L^{-1}	3w	Mussels *Mitylus galloprovincialis*	O	↑ETS ↑Oxidative stress and Hypoxia; ↓glutammine; ↑LIP	Sanchís et al., 2018
	1 mg L^{-1}	3d		DG, G, H, Mt, M	↑DNA strand breaks; ↑ GSH-t; O accumulation with highest levels in DG; abnormalities in adductor M, DG and G; genetic damage	Di et al., (2016)
	1-10 µg L^{-1}	4h		H*	Lysozyme release; ↑extracellular oxyradical and NO production; no LMS damage	Canesi et al., 2010a
	0.05-5 mg L^{-1}	24h		DG, G, H	↓LMS (H, DG); lysosomal lipofuscin; ↑CAT (DG); oxidative stress	Canesi et al., 2012
	0.10–1 mg L^{-1}	3d		O, DG, M, G	↑DNA strand breaks; ↑ GSH-t; O accumulation with highest levels in DG; abnormalities in adductor M, DG and G; genetic damage	Al-Subiai et al., 2012
	10, 100, 500 and 1000 µg L^{-1}	24h	Oyster *Crassostrea virginica*	E, O, DG	↑ Lysosomal damage; ↑LPO	Ringwood et al., 2009
C_{60}, CNT	10^{-2} -10 µg mL^{-1}	1h	Mussels *Mitylus edulis*	H*	C_{60}: immunocytotoxic (↓LMS damage). CNT: no LMS damage	Moore et al., 2009
	1.00 g L^{-1}	14d	Mussel *Villosa iris*	O	Significantly reduced the growth of the mussel	Mwangi et al., 2012

CNTs	SWCNTs, MWCNTs: 50, 250 and 500 µg L-1	24h	*Mytilus sp.*	O*	↑LMS Toxicity: higher toxic effect by SWCNTs in comparison to MWCNTs at 500 µg L^{-1}	Miller et al., 2015
	SWCNHs 1, 5, and 10 mg L^{-1}	48h	Mussels *Mitylus galloprovincialis*	DG, H	↑Oxidative stress; ↓GPx; ↓LMS	Moschino et al., 2014
	MWCNTs 0.01 mg L^{-1}	14d		O	MWCNTs−COOH: ↑LPO; ↑ PC. MWCNTs−COOH+ tides: ↑ ETS; ↑SOD; ↑ GPx; ↑ GSSG; ↓LPO, ↓PC	Andrade et al., 2018
	SWCNTs: 5, 10, 50, 100, 500 µg L^{-1}; $CdCl_2$ 0.001µM; $ZnSO_4$ 1.0 µM	72h		G, H	SWCNTs (> 100 µg L^{-1}): ↑SOD; ↑ LPO; ↑DNA strand breaks in G and H. SWCNTs + $CdCl_2$, and SWCNTs+ $ZnSO_4$ (> 100 µg L^{-1}): higher degree of DNA damage in comparison to single stressor	Al-Shaeri et al., 2013
	1-3 mg L^{-1}	4w		DG, F, G, Mt, Pf	↓Clearance rate; no change in growth; Excretion in biodeposits (F and Pf)	Hanna et al., 2014
	SWCNHs 100 mg L^{-1}	48h	Mussels *Modiolus modiolus*	DG, G	Histological changes at the level of the gills, bowel and glands digestive	Anisimova et al., 2015

	SWCNT (500 µg L^{-1})	8d	Mussels *Elliptio complanata*	H*	↑DNA demage; ↑ hemocyte phagocytic efficiency; ↓hemocyte viability	Revel et al., 2018
	SWCNTs and MWCNTs: 2, 10, 50, 100 and 500 µg L^{-1}	120h	Clams *Donax faba*	O	↑(LC50) of SWCNTs and MWCNTs; ↑ toxicity effect. Histopathology of the tissues, treated with CNT–BSA conjugates has shown decreased effect on the cellular integrity	Sekar et al., 2016
	MWCNTs, MWCNTs+ pH: 0.10 and 1.00 mg L^{-1}	28d	Clams *Ruditapes philippinarum*	O	↑ETS; ↓GLY; ↑LPO; ↓ GSH-t; ↑SOD; ↓GPx (1.00 mg L^{-1}); ↓GSTs; ↓AChE	De Marchi et al., 2017a
	MWCNTs: 0.01-1.00 mg mL^{-1}	28d		O	↑ETS; ↓GLY; ↓PROT; ↑LPO; ↓ GSH-t; ↑SOD; ↓GPx (1.00 mg L^{-1}); ↓GSTs; ↓AChE	De Marchi et al., 2017b
	MWCNTs, MWCNTs−COOH: 0.01-1.00 µg L^{-1}	28d		O	↑ETS; ↓GLY; ↓PROT; ↓LIP; ↑LPO; ↓ GSH-t; ↑SOD; ↓GPx (MWCNTs), ↑GPx (MWCNTs-COOH); ↓GSTs; ↓AChE Toxicity: MWCNTs−COOH>MWCNTs	De Marchi et al., 2018a
	MWCNTs + sal. 21-28, MWCNTs−COOH+ sal. 21-28: 0.10 and 1.00 mg L^{-1}	28d		O	↑ETS; ↓GLY; ↓PROT; ↑LPO; ↓ GSH-t; ↑SOD; ↓GPx (MWCNTs), ↑GPx (MWCNTs-COOH); ↓GSTs; ↓AChE Toxicity: sal. 28+ MWCNTs−COOH> sal. 28+ MWCNTs> sal. 21+ MWCNTs−COOH> sal. 21+ MWCNTs	De Marchi et al., 2018b
	MWCNTs−COOH: 0.10 mg L^{-1} As: MWCNTs−COOH	28d		O	↑ GLY; ↑ PROT; ↓ ETS; ↑ SOD; ↑ GPx; ↓ CAT; ↓ GSTs; ↑LPO; ↓ AChE. Toxicity: MWCNTs−COOH> MWCNTs−COOH+As>As	Freitas et al., 2018

Ag	10 mg L^{-1}	7d	Mussels *Mitylus galloprovincialis*	DG, G	↑ DNA damage ↑ CAT; ↑ SOD; ↑ GPx; ↑ LPO (DG)	Gomes et al., 2013; 2014
	0.7 mg L^{-1}	3h30	Mussels *Mitylus edulis*	O, DG H, O	Increase accumulation of Ag-NPs Distinctive doughnut shaped structures (DSS) on the nacreous surface were found in the central part of shells of adult mussels after short-term exposures	Zuykov et al., 2011a; b
	2, 20, 40 μg L^{-1}	8d	Mussels *Brachidontes pharaonis*	O	↑RR; ↑HBR	Saggese et al., 2016
	150–200 μg g^{-1}	35d	Clams *Macoma balthica*	O	↑DNA damage; no mortality	Dai et al., 2013
	10 μg L^{-1}	14d	Clams *Scrobicularia plana*	O	Increase accumulation ↑DNA damages; ↑ CAT; ↑ SOD; ↑ GSTs	Buffet et al., 2013; 2014

	0–500 μg L^{-1}	28d	Clams *Sphaerium corneum*	O	↑DNA damages; ↑ CAT; ↑ SOD; ↑ GSTs; ↑ GPx	Völker et al., 2015
	1.6- 0.0016 μg L^{-1}	48h	*Oysters Crassostrea virginica*	E, O	↓Development, and lysosomal integrity of adult hepatopancreas tissues; ↑ metallothionein (MT); mRNA of embryos	Ringwood et al., 2010
	0.2 mg L^{-1}			H, O	↑ PROT; ↑ CAT; ↑ SOD; ↓GSH; ↓phagocytosis in the haemolymph	McCarthy et al., 2013
Au	750 μg mL^{-1}	24h	Mussels *Mitylus edulis*	DG, G, Mt	↑CAT (DG); ↑CP (G) ↑LPO; ↓PROT; ↓LMS	Tedesco et al., 2008; 2010
	0.1, 1, 10, 25, 50 and 100 mg L^{-1}		Mussels *Mitylus galloprovincialis*	H, G*	Reducing cell vitality	Katsumiti et al., 1016
	2 mg L^{-1}	180h	Clams *Corbicula fluminea*	O	Transferring nanoscale particles suspended in the water column to the subsurface *via* biodeposition	Hull et al., 2011
	1.6×10^{5} AuNP/cell	7d		DG, G	↑ SOD(DG); ↓GSTs (G)	Renault et al., 2008

	$100\ \mu g\ L^{-1}$	16d	Clams *Scrobicularia plana*	O, DG, G	↑DNA strand breaks; O accumulation with highest levels in DG; genetic damage	Joubert et al., 2013
				O	↑CAT ↑SOD ↑GSTs	Pan et al., 2012
	$6 - 30\ mg\ L^{-1}$	28d	Clams *Ruditapes philippinarum*	DG, G, F	Increase the accumulation of Au-NPs	García-Negrete et al., 2013
	$0.75\ \mu g\ L^{-1}$	7-14d			↑SOD; ↓CAT; ↑GPx; ↓PROT; ↑GSTs; ↓GR; genetic damage	Volland et al., 2015
	$0.1, 1\ mg\ L^{-1}$	14 d	Clams *Ruditapes decussatus*	O	↑CAT; ↑SOD; ↑GST; ↑MDA	Fkiri et al., 2018
	$0.1, 1$ and $10\ mg\ L^{-1}$	96h	Clams *Tegillarca granosa*	G	↑Neurotransmitters; ↓AChE; ↓ transcription of neurotransmitters-relate genes	Guan et al., 2018
	$0, 2.5$ and $10\ mg\ L^{-2}$	216h	Mussels *Perna viridis*	H	Effects on the immune functions: ↑Hemocyte mortality; ↓non-specific esterase activity; ↓ROS production; ↓phagocytosis and lysosomal content; ↑total hemocyte count	Wang et al., 2014
	$0, 2.5$ and $10\ mg\ L^{-1}$	14d	Mussels *Mytilus coruscus*	H	Effects on the immune functions: ↑total hemocyte count; ↑Hemocyte mortality; ↓phagocytosis and lysosomal content; ↓esterase activity; ↑ROS production Toxicity: TiO2> TiO2+pH	Huang et al., 2016

TiO_2	1 and 10 µg L^{-1}	30min	Clams *Ruditapes philippinarum*	H	Phagocytic activity	Marisa et al., 2015
	1, 10 and 100 µg L^{-1}	14d	Mussels *Mytilus galloprovincialis*	DG, H	DG: ↓ Lysosomal membrane stability; ↑ CAT; ↓ antioxidant transcription; ↓ immune-related genes. H: ↓ Lysosomal membrane stability; ↓phagocytosis; ↑ oxyradical production; ↑ antimicrobial peptides transcription; pre-apoptotic processes	Barmo et al., 2013
	1, 5 and 10 mg L^{-1}	96h		DG, G	Immune system activation (altered tissue organization; Infiltration of hemocytes); DNA damage; ROS production; inflammatory responses (presence of dense granules, residual bodies and lipid inclusions leading to apoptosis)	Gornati et al., 2016
	2.8, 28, 280 µg L^{-1}	24h		G	Low/medium concentration: ↑ Antioxidant enzymes; ↑ Metallothionein's; ↑ Oxidative damage; ↓AChE	Sureda et al., 2018
	10 mg L^{-1}	24h		DG, G	Accumulation of NPs in the tissue; Vacuolation and influx of haemocytes; DNA damage Toxicity: Bulk> TiO_2 NPs	D'Agata et al., 2013
	1, 10 and 100 mg L^{-1}	8d		DG, G	DG: No significant effects observed. G at 100 mgL^{-1}: ↑ROS production; ↑SOD; ↓GSH/GSSG ratio	Mezni et al., 2017
	0-64 mg L^{-1}	48h		L	↓ Larval development	Libralato et al., 2013

ZnO	1, 5 and 10 µg L^{-1}	4h	Mussels *Mytilus galloprovincialis*	H*	↓ Lysosomal membrane stability; ↑ ROS prodution; ↑ NO production; ↓ phagocytic activity	Ciacci et al., 2012
	0.1-2 mg L^{-1}	12w		O	↑ Respiration rate; ↑ ZnO accumulation; ↓ growth; ↑ Mortality 2 mg L^{-1}	Hanna et al., 2013
	1 and 10 µg L^{-1}	7d	Clams *Ruditapes philippinarum*	G, DG, H	↑ CAT; ↑ SOD; ↓GSTs. H at 10µg L^{-1}: ↑DNA damage. G: ↓AChE	Marisa et al., 2016
	1 mg L^{-1}	7d	Mussels *Mytilus galloprovincialis*		Cytotoxicity	Katsumiti et al., 2016
	3 mg Kg^{-1} (in sediment)	16d	Clams *Scrobicularia plana*	O	↑ZnO accumulation; ↑ CAT; ↑ CSP-3-like; ↑ LDH; ↑ MT; ↓ burrowing behaviour; ↓feeding rate	Buffet et al., 2012

	3 mg Kg^{-1} (in sediment)	2w		O	↑ Oxidative stress (Use of IBR "Integrated Biomarker Response")	Devin et al., 2016
	4 mg L^{-1}	48h	Oysters *Crassostrea gigas*	G, DG	↑ ZnO accumulation; mitochondrial disruption. G: ↓GR; ↓PROT thiols; ↑ LPO; ↑GPx. DG: ↓GR	Trevisan et al., 2014
	1-10 mg L^{-1}	96h	Mussels *Mytilus galloprovincialis*	O	ZnO uptake and accumlation	Montes et al., 2012
	0.1, 0.5, 1 and 2 mg L^{-1}	12w		O	↑ Accumulation; ↓feeding rate; ↑respiration rate	Muller et al., 2014
CeO_2	1 and 10 mg L^{-1}	96h	Mussels *Mytilus galloprovincialis*	O, G	↑Concentration of CeO_2-NPs resulted	Montes et al., 2012
	1 mg L^{-1}	21d	Mussels *Dreissena polymorpha*	O	↓GPx, ↓CAT, ↓GSts, ↓GPX	Garaud et al., 2016
	100 µg L^{-1}	6d	Clams *Corbicula fluminea*	O	↑ DNA damage; ↑LDH, ↑LIP, ↑GST	Koehlé-Divo et al., 2018

	3- 30 mg L^{-1}	8d	Mussels *Mytilus galloprovincialis*	O	↑Concentration of CeO_2-NPs in the tissues	Conway et al., 2014
	1, 10, 50 mg L^{-1}	30 min	Mussels *Mytilus galloprovincialis*	H	↓ Lysosomal membrane stability; ↓ extracellular ROS production; ↓ phagocytic activity	Sendra et al., 2018
	100 μg L^{-1}	96h	Mussels *Mytilus galloprovincialis*	H, DG	↑ CAT; ↑ SOD; ↑ lysozyme activity; ↑extracellular ROS; ↓ lipofuscin content; ↑ transcription of genes involved in detoxification immune response and cell signalling	Auguste et al., 2019

[a] CNT (Carbon Nanotubes), NCB (Nano-sized Carbon Black), C_{60} (fullerene), SWCNHs (Single walled carbon nanohorns), SWCNTs (Single walled carbon nanotubes), MWCNTs (Multi walled carbon nanotubes), MWCNTs−COOH (Carboxylated multi walled carbon nanotubes), GO (Graphene oxide), GO-PVP (Graphene oxide with polyvinylpyrrolidone), rGO-PVP (Reduced graphene oxide with polyvinylpyrrolidone).

[b] h (hours), w (weeks), d (days), min (minutes)

[c] E (Embryos), C (Carcass), EPF (Extrapallial Fluid), DG (Digestive Gland), F (Feces), G (Gill), Go (Gonad), H (Hemolymph/Hemocyte), M (Muscle), Mt (Mantle), O (Whole organism), Pf (Pseudofeces), S (Shell), Sp (Sperm), Vm (Visceral mass). *In vitro* exposure (*).

[d] MAPKs (Mitogen-activated protein kinase), LMS (Lysosomal membrane stability), NO (Nitric oxide), DNA (Deoxyribonucleic acid), CAT (Catalase), SOD (Superoxide dismutase), GPx (Glutathione peroxidase), GR (Glutathione reductase), GSH (Glutathione), GSH-t (Total glutathione), GSSG (Glutathione disulphide), GSTs (Glutatione s-transferases), LPO (Lipid peroxidation), PC (Protein Carbonyl Content), GLY (Glycogen), PROT (Protein), ETS (Electron transport system), LIP (Lipids), AChE (Acetylcholinesterase), LDH (Lactate dehydrogenase), RR (respiration rate), HBR (heart beat rate), L (larvae)