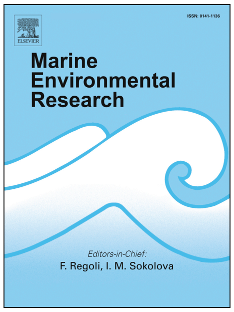


The use of *Hediste diversicolor* in the study of emerging contaminants

M.S.S. Silva, Adília Pires, Mónica Almeida, Miguel Oliveira

PII: S0141-1136(20)30163-X

DOI: https://doi.org/10.1016/j.marenvres.2020.105013

Reference: MERE 105013

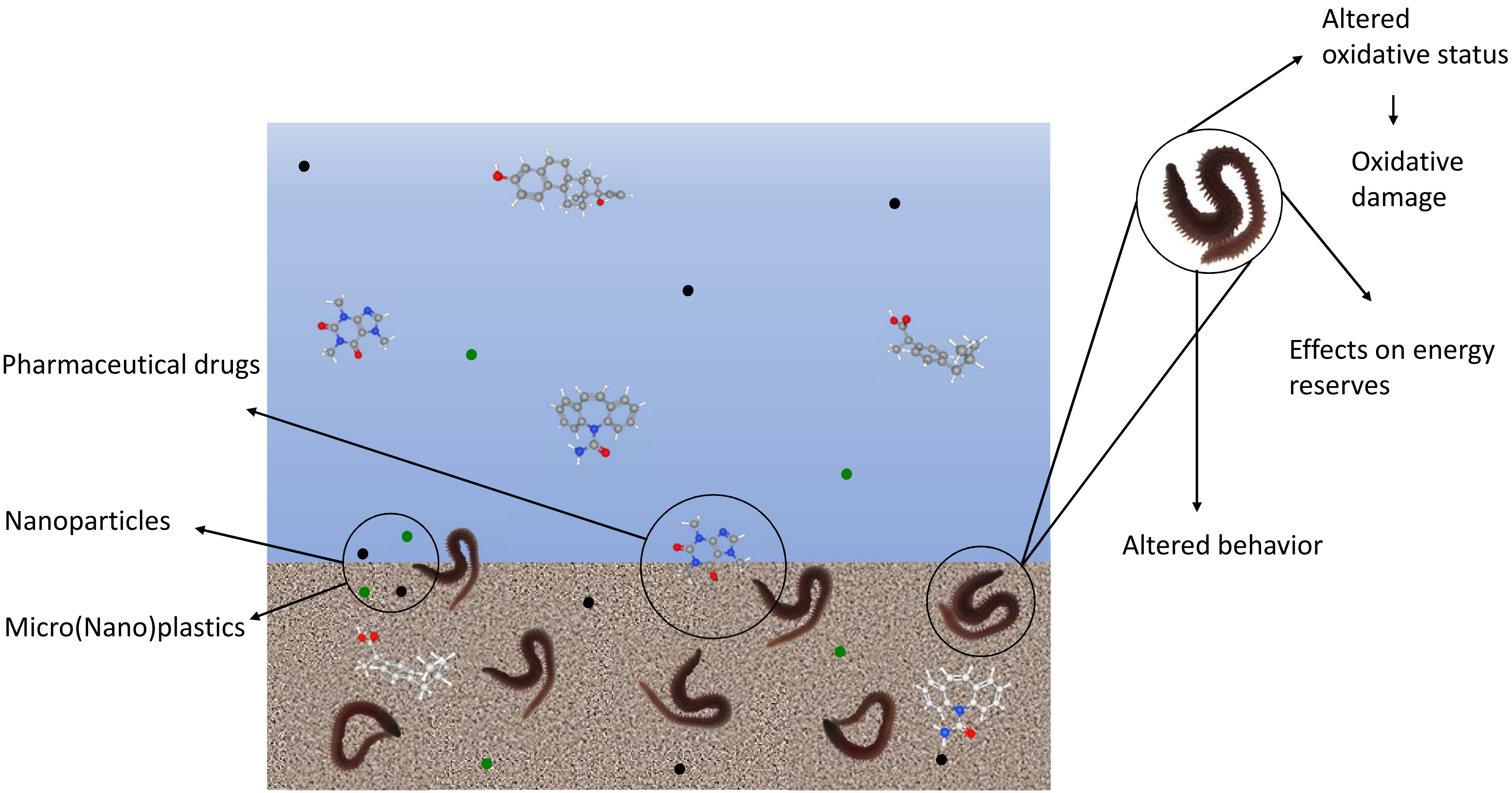
To appear in: *Marine Environmental Research*

Received Date: 20 February 2020

Revised Date: 27 April 2020

Accepted Date: 10 May 2020

Please cite this article as: Silva, M.S.S., Pires, Adí., Almeida, Mó., Oliveira, M., The use of *Hediste diversicolor* in the study of emerging contaminants, *Marine Environmental Research* (2020), doi: https://doi.org/10.1016/j.marenvres.2020.105013.


Altered oxidative status
Oxidative damage
Effects on energy reserves
Altered behavior
Pharmaceutical drugs
Nanoparticles
Micro(Nano)plastics

The use of *Hediste diversicolor* in the study of emerging contaminants

Silva, M.S.S.[1], Pires, Adília[2], Almeida, Mónica[2], Oliveira, Miguel[2,*]

[1]Departament of Biology, University of Aveiro, 3810-193 Aveiro, Portugal

[2]Centre for Environmental and Marine Studies (CESAM), Departament of Biology, University of Aveiro, 3810-193 Aveiro, Portugal

*E-mail: miguelоliveira@ua.pt

Abstract

The contamination of aquatic environments has been the focus of research to understand effects on ecosystems and its species. Benthic organisms are considered potential targets since sediments act as sources and sinks for environmental contaminants. This review presents information on the effects of three types of emerging contaminants: pharmaceuticals (tested concentrations between 0.1 ng/L – 250 mg/L and 0.01 ng/g – 2.5 µg/g), metal-based nanoparticles (< 100 nm) (tested concentrations between 10 µg/L – 1 mg/L and 5 – 140 µg/g) and micro(nano)plastics (tested concentrations between 5 µg/L – 50 mg/L and 10 – 50 mg/kg), on the polychaete *Hediste diversicolor*, a key species in estuarine/coastal ecosystems. Data shows that these contaminants promote alterations in burrowing activity (lowest concentration inducing effects: 10 ng/L), neurotransmission and damage related parameters (lowest concentration inducing effects: 100 ng/L). The characteristics of this polychaete, such as regeneration capacity, make the use this species in biomedical studies involving environmental contaminants valuable.

Keywords: polychaete, drugs, nanoparticles, plastics, bioindicator

1. Introduction

The contamination of aquatic environments has, for many years, been the focus of intense research to understand the deleterious impact in the ecosystems (Borgwardt et al., 2019; Halpern et al., 2015). The available data points to sediments as particular targets for accumulation of contaminants and as a source of contamination throughout the food web (Herrero et al., 2018; Wilkinson et al., 2018). In this perspective, species inhabiting the sediments of reservoirs and estuaries, like polychaetes, can be valuable tools to assess the impact of contaminants including emerging contaminants of concern like pharmaceuticals, nanoparticles and small plastic particles (Lewis and Watson, 2012; Silva et al., 2020a, b; Wilkinson et al., 2016). Recent studies have been using *Hediste diversicolor* as a biological model in ecotoxicity studies addressing the impact of contaminants like pharmaceuticals (Nunes et al., 2016; Pires et al., 2016a), metals, polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), pesticides (Dean, 2008; Gomiero et al., 2018) and micro(nano)plastics (Gomiero et al., 2018; Muller-Karanassos et al., 2019; Silva et al., 2020a, b) due to their sensitivity and quick response to contamination. Oxidative stress parameters have been shown responsive in *H. co npsdiversicolor* exposed to pharmaceutical drugs, such as caffeine (Pires et al., 2016a), nanoparticles, like copper oxide nanoparticles (Buffet et al., 2012a), and microplastics, such as polyvinyl chloride (PVC) (Gomiero et al., 2018). Studies addressing the effects of silver nanoparticles (Cong et al., 2014) and nanoplastics of polystyrene (PS) (Silva et al., 2020a) demonstrated a systematic impairment in behavior, a very relevant endpoint, considering that behavioral changes may reflect alterations at lower levels of biological organization, with potential considerable impact on animal fitness and survival.

Studies have also demonstrated the effects of pharmaceutical drugs, nanoparticles and plastics on other polychaete species, such as *Diopatra neapolitana* and *Arenicola marina*. Pires et al. (2016b) reported that exposure to caffeine led to alterations in oxidative stress related enzymes, decreased glycogen content and increased cell membrane damage in *D. neapolitana*, whereas in *A. marina* only increased cell membrane damage was found. *D. neapolitana* exposed to carbamazepine presented a decreased regenerative capacity, as well as an increase in the number of days necessary to fully regenerate the lost segments, which was exacerbated when it was exposed to caffeine (Pires et al., 2016c).

Regarding nanoparticles, borrowing time decreased in the polychaete *A. marina* exposed to single walled carbon nanotubes but increased in this species when organisms were exposed to titanium dioxide nanoparticles (Galloway et al., 2010). In the polychaete *Perinereis aibuhitensis* exposed to polystyrene microplastics (8-12 µm and 32-38 µm), regardless of concentration (100 and 1000 beads/mL) and size tested, the regenerative capacity was reduced to half of its normal percentage (Leung and Chan, 2018).

The easy capture and maintenance in laboratory conditions, and the high degree of responsivity make *H. diversicolor* particularly suitable to ecotoxicological studies. The present review aims to present information on laboratorial and field studies addressing the problem of environmental contamination, in terms of emerging contaminants, using *H. diversicolor* as the model species, emphasizing the importance of this model, relevant endpoints that may be addressed, and future applications.

1.1. Habitat

Hediste diversicolor (O.F. Müller, 1776), commonly called ragworm, is a polychaete species belonging to the phylum Annelida, family Nereididae. This species lives in shallow marine and brackish water ecosystems, in muddy sands, but can also be found in gravel, clay and even turf (Scaps, 2002). *H. diversicolor* has a wide distribution along the North temperate zones of the Atlantic Ocean, in Europe (from Norway to Morocco, including also the Baltic, Mediterranean, Black and Caspian Seas (Fauvel, 1923; Clay, 1967; Smith, 1977, Read)) and the eastern North American coast (Fauvel, 1923; Clay, 1967; Smith, 1977), being also reported in the Pacific Ocean (Caribbean sea, (Miloslavich et al., 2010)).

1.2. Biology

H. diversicolor reproduces only once in their lifetime and presents sexes separated throughout their life cycle (Dales, 1950; Scaps, 2002). The immature organisms have a reddish-brown color that changes to green upon maturation. Females become dark green and males have a lighter grass-green due to the production of sperm (among others Andries, 2001; Durou & Mouneyrac, 2007). These organisms reach maturity after one to two years, although in the natural environment it has been shown that individuals can live up to three years before spawning (among others Möller, 1985; Nithart, 1998). This species presents a high tolerance to salinity variations. However, at salinities lower than 10% of normal seawater salinity, osmoregulation and viability of offspring is compromised due to larval sensibility (Scaps, 2002; Smith, 1955, 1956).

H. diversicolor plays a key role in the ecosystems where it inhabits, influencing the biogeochemical cycle of nutrients, sediment oxygenation and (endo-)benthic fauna (among others Banta & Andersen, 2003; Davey, 1994; Gillet, 2012). They create U- or Y-shaped burrows, in which they live, only leaving it to search for food (Dales, 1950; Esselink and Zwarts, 1989; Kristensen and Mikkelsen, 2003). The body size and seasonal variance of water temperature influence the depth of the burrow (Esselink and Zwarts, 1989; Scaps, 2002). The ragworms are highly territorial concerning their burrows, carefully constructing them to avoid contact with others.

H. diversicolor is omnivorous and may act as a predator, actively searching for food, or as a deposit-feeder, by capturing food within the mucous secretions it produces (Fauchald and Jumars, 1979; Reise, 1979; Riisgård and Larsen, 2010). This species is highly predated by small fishes, birds, shrimps and larger crabs (Evans et al., 1979; Scaps, 2002). Predators may take only part of this animal and *H. diversicolor* has the ability to regenerate the posterior part of its body, as do other polychaete species (Bely, 2006). However, few studies have focused on the repercussions of environmental contamination on this capacity.

In addition to their ecological importance, *H. diversicolor* is also one of the polychaete species used as fish bait in recreational fishing and in aquaculture, in an integrated multitrophic approach (e.g. Pombo et al., 2018; Wang et al., 2019).

2. Ecotoxicological studies

The easy laboratorial maintenance, broad tolerance to temperature, salinity and oxygen levels, and quick response to environmental stressors, like metals, make *H. diversicolor* a good potential biological model for toxicological studies (e.g. Banta & Andersen, 2003; Dhainaut & Scaps, 2001; Gomes et al., 2013; Kristensen, 1983). However, so far, little is known about their response to emerging contaminants. In this context, emerging contaminants are defined as new natural or synthetic compounds but also those recently detected in the environment due to new detection methods and compounds only recently categorized as contaminants, and that have the potential to cause harm to ecosystems and human health (Barreto et al., 2018; Dey et al., 2019). In this review the focus will be centered on pharmaceuticals, nanoparticles (e.g. metal-based nanoparticles) and micro(nano)plastics, which have attracted an increasing number of studies aiming to assess their environmental impact (Figure 1).

2.1. *Pharmaceutical drugs*

Pharmaceutical drugs are substantially used not only for human medicine but also veterinarian, with aquaculture and livestock production the biggest contributors to their environmental release (Gomes et al., 2019; Hird et al., 2016). These compounds may reach aquatic environments in their native state (parental compound) or in the form of active secondary metabolites. Ineffective treatment of waste waters by sewage plants has been classified as a major cause for their environmental presence. Pharmaceuticals are expected to be persistent enough to reach the target site before becoming inactive and this constitutes a problem once these compounds reach the environment (Oliveira et al., 2018). Although most pharmaceuticals are designed to act on specific metabolic pathways, they may display unforeseen effects to non-target organisms, especially to invertebrates (e.g. Gomes et al., 2019; Oliveira et al., 2018).

Acetylsalicylic acid (ASA) is among the oldest and most commonly prescribed analgesics worldwide (Mahdi et al., 2006) being frequently detected in effluents and natural environments around the world in concentrations in the µg/L range and in sediments, in Europe, it was found at a concentration of 9.49 µg/kg (Ebele et al., 2017). This drug has been previously reported to cause histological alterations and oxidative stress in *Salmo trutta fario* (Nunes et al., 2015). Recently, the biochemical and histological alterations induced by this pharmaceutical on *H. diversicolor* were assessed by Gomes and colleagues (2019) after acute (96h) and chronic (28 days) exposures (Supplementary data – Table 1). The study revealed an alteration of antioxidant parameters after 96h (250 mg/L) although no peroxidative damage was reported, which may indicate that organisms were capable of counteracting the effects of this drug (Gomes et al., 2019). Additionally, these organisms demonstrated the ability to alter the levels of mucous production upon chronic exposure, as a result of increased mucous cells (Gomes et al., 2019). Although this increased mucous may constitute a good defense against some chemicals, it may lead to a heightened susceptibility to other contaminants, such as micro- and nanoparticles, that organisms may have difficulties expelling (Revel et al., 2018).

Ibuprofen is a commonly prescribed non-steroidal anti-inflammatory drug (NSAID) and as such can be frequently found in the environment. In Europe it was found with concentrations ranging from 8 ng/L up to 3.5 µg/L (Ebele et al., 2017). In order to assess the effects of ibuprofen on marine organisms, Maranho et al. (2014, 2015) chronically exposed the common ragworm to sediment contaminated with ibuprofen (Supplementary data – Table 1). Maranho et al. (2014) reported increased activity of dibenzylfluorescein dealkylase (DBF), a phase I enzyme linked to the cytochrome P450 3A4 (CYP3A4). Acetylcholinesterase (AChE) activity, an enzyme frequently used to assess effects on neurotransmission, increased in the highest concentration tested (500 ng/g), which may reflect processes of apoptosis (Zhang et al., 2012; Zhang et al., 2002). Peroxidative damage assessed as lipid peroxidation (LPO) was reported in 5 ng/g despite the lack of effects on enzymes associated with antioxidant defenses. DNA damage increased in organisms exposed to ibuprofen via spiked sediment (5 and 500 ng/g). Following studies by Maranho and colleagues (2015) demonstrated that an energy related parameter (mitochondrial electron transport (MET)) was significantly decreased in 5 ng/g and the activity of an enzyme related to inflammation (cyclooxygenase (COX)) was significantly decreased for all concentrations tested (Supplementary data – Table 1).

Carbamazepine (CBZ) is a frequently used antiepileptic drug found, in the water, in concentrations between 53 ng/L and 6.3 µg/L (among others Claessens et al., 2013; Ebele et al., 2017). Studies performed by Maranho et al. (2014) demonstrated that antioxidant enzymes respond to the exposure of CBZ (Supplementary data – Table 1). Results revealed that concentrations of 0.05, 50 and 500 ng/g increased the activity of glutathione peroxidase (GPx), responsible for catalyzing the reduction of hidrogen peroxide (H_2O_2) into water and oxygen, and glutathione S-transferase (GST), involved in the biotransformation of compounds (Oliveira et al., 2008). However, glutathione redutase (GR) activity, responsible for reducing oxidized glutathione to reduced glutathione, and that plays a major role in the reactions of GPx and GST (Bompart et al., 1990; Oliveira et al., 2009), was slightly inhibited in most concentrations (0.5 to 500 ng/g). Nonetheless, LPO was significanlty increased in the highest concentration (500 ng/g). Subsequent studies by Maranho et al. (2015), testing the same concentrations, reported a significant increase in energy related parameters (lipids and MET) in the two lowest and two highest concentrations (Supplementary data – Table 1). CBZ was reported to interfere with the activity of COX in all concentrations. Pires et al. (2016a) also exposed *H. diversicolor* for 28 days to CBZ (0.3 to 9.0 µg/L) but the via of exposure was water (Supplementary data – Table 1). Nonetheless, authors reported similar results to Maranho et al. (2014). Markers of oxidative stress (the ratio between reduced (GSH) and oxidized (GSSG) glutathione, GSH/GSSG) demonstrated a decrease in ratio, possibly leading to the increase in cell membrane damage (measured by LPO levels), in all studied concentrations. Enzymes related to biotransformation, GST and CYP3A4, were also increased in all concentrations. Energy related parameters, revealed a concentration-dependent alteration, the electron transport system (ETS) increased and glycogen content decreased, demonstrating that organisms used their energy reserves for cell functions.

Caffeine, the most consumed stimulant in the world, found in concentrations from ng/L up to 500 µg/L in water (among others Metcalfe et al., 2003; Smith et al., 2015) and 7.21 µg/kg in sediments (Ebele et al., 2017), affected parameters related to oxidative stress (Pires et al., 2016a). Pires and colleages (2016a) chronically exposed the common ragworm to three caffeine concentrations (from 0.5 to 18 µg/L) and found an increase in catalase activity (3.0 and 18.0 µg of caffeine/L) (Supplementary data – Table 1). However, the GSH/GSSG ratio was significantly decreasedin all analyzed concentrations. Nonetheless, oxidative stress, measured by superoxide dismutase (SOD) increased. Energy related parameters displayed similar responses to those reported by Pires et al. (2016a) when organisms were exposed to CBZ, in which ETS and glycogen content decreased. Biotransformation-related enzymes, GST and CYP3A4, were only significantly increased in the highest concentration (18.0 µg/L).

The effects of the combined exposure to caffeine and CBZ on *H. diversicolor* were also evaluated by Pires and colleages (2016a) (Supplementary data – Table 1). Oxidative stress enzymes such as SOD and catalase, as observed for the individual exposures, were highly responsive to contamination. SOD was found to increase, while catalase and the GSH/GSSG ratio decreased in both concentrations tested (0.3 µg CBZ/L + 0.5 µg caffeine/L and 6.0 µg CBZ/L + 3.0 caffeine/L), which demonstrated an increase in the overall oxidative stress. However, LPO levels were found to have a concentration-dependent decrease. GST and CYP3A4 also demonstrated a concentration-dependent decrease. Organims exposed to both contaminants exhibited an increase in ETS but a decrease in glycogen content. However, the combination of these two susbtances induced similar effects to those observed at the highest concentrations in individual exposures.

Cisplatin, or c -diammine-dichloroplatinum II, is one of the most prominent and widely used platinum-based anti-cancer drugs, in which 28±4% is excreted in the form of platinum complexes and 40% in the form of monoaquacisplatin (Arnesano and Natile, 2009; Gómez-Ruiz et al., 2012; Vermorken et al., 1986). When investigating the effects of this drug on the polychaete *H. diversicolor*, by exposing organisms to concentrations between 0.1 and 100 ng/L, Fonseca and colleagues (2017) found that the highest concentration of cisplatin had the most severe effects (Supplementary data – Table 1). An important yet not often analyzed parameter is the behavior. The authors reported an impaired burrowing activity in the highest concentration, with organisms unable to fully burrow. Despite the results demonstrating an increase in AChE activity in the lowest concentrations (0.1 and 10 ng/L), which may indicate cell apoptosis, a strong inhibition of this enzyme was reported in 100 ng/L, possibly explaining the impairment in burrowing behavior. As with the previous pharmaceuticals reviewed here, oxidative stress enzymes demonstrated altered responses when organisms were exposed to cisplatin, in this case in 100 ng/L. SOD and catalase were significantly decreased, while GPx was found to have an increased activity. Damage to cell membranes, reported through increased LPO levels, was found in the highest concentration of cisplatin tested. Biotransformation enzyme GST demonstrated a decreased activity when organisms were exposed to the highest concentration.

Another drug used in cancer treatments, one of the oldest and most routinely prescribed, is cyclophosphamide (CP) (Buerge et al., 2006; Česen et al., 2016; Gilard et al., 1994). About 80% of the dose taken is excreted as metabolites, frequently ending in aquatic environments where it can impact non-target organisms (Bagley et al., 1973; Steger-Hartmann et al., 1996). In order to study the effects of CP on invertebrates, Fonseca and colleagues (2018) exposed *H. diversicolor* specimens to concentrations between 10 and 1000 ng/L for 14 days (Supplementary data – Table 1). The authors reported an impairment in burrowing activity in organisms exposed to CP concentrations between 10 and 500 ng/L . However, this alteration in behavior was not accompanied by neurotoxic effects (AChE). As previously reported for other drugs, enzymes related with oxidative stress are very responsive. Although SOD activity was significantly lower in the two highest concentrations, catalase activity was increased only in 10 and 500 ng/L. GST activity was significantly decreased in organisms exposed to CP concentrations 100 up to 1000 ng/L. LPO reflected the oxidative damage caused by CP in concentrations between 100 up to 1000 ng/L. Regardless of concentration tested, organisms exposed to CP presented higher DNA damage.

One of the most commonly used contraceptive methods is the pill, which frequently contains synthetic estrogen, 17α-Ethinylestradiol (EE2). EE2 is one of the most potent estrogenic substances released into the environment, which can affect non-target species (Miyagawa et al., 2016). EE2 has been found in sewage sludge in concentrations of 48.1 µg/kg (Ebele et al., 2017). To understand the effects of EE2 in marine invertebrates, Maranho et al. (2014, 2015) exposed for 14 days the polychaete *H. diversicolor* to sediment spiked by this drug (Supplementary data – Table 1). An enzyme of the phase I of biotransformation, ethoxyresorufin O-deethylase (EROD), was found to be the main enzyme to degrade EE2, demonstrating an increased activity in organisms exposed to concentrations between 0.01 and 10 ng/g. Enzymes related to oxidative stress (GST, GR and GPx) were not very responsive to EE2 exposure. Nonetheless, LPO levels increased in the lowest concentration tested (0.01 ng/g), which may indicate an inability to prevent damage when exposed to low concentrations of EE2. An increase in AChE activity was reported in the lowest concentrations (0.01 to 1 ng/g), indicating that low concentrations of EE2 may promote cell apoptosis (Maranho et al., 2014). Later studies performed by Maranho et al. (2015) demonstrated that EE2 inhibited the activity an enzyme related with the anti-inflammatory process, COX, in all concentrations (Supplementary data – Table 1).

Cases of depression have increased over the years (WHO, 2017) and a highly prescribed selective serotonin reuptake inhibitor (SSRI) used in these cases is fluoxetine (Hird et al., 2016). As such, fluoxetine is persistingly found in the environment due to ineficient clearing in sewage plants (Arnold et al., 2014; Gardner et al., 2012), similarly to what happens with other drugs. This pharmaceutical has been found in concentrations between 2.5 and 109.2 ng/L in aquatic environments (Fekadu et al., 2019). Hird and colleagues (2016) investigated the effects of this drug on the commom ragworm by exposingspecimens, for 72 hours, to concentrations between 10 and 500 µg/L in the water, and 0.01 and 2.5 µg/g in the sediment (Supplementary data – Table 1). Fluoxetine was reported to be more bioavailable to organisms in the sediment treatment. However, regardless of treatment similar responses were reported. Polychaetes presented increased seratonin levels, which has various impacts at cell and individual levels. Organisms demonstrated altered metabolic homeostasis, reduced lipid stores and decreased feeding ability, which led to weight loss. Consequently, this can have repercussions at population level since smaller organisms may originate a smaller offspring, which may lead to a decrease of sediment bioturbation, affecting other organisms that depend of this activity.

Maranho et al. (2014) also studied the effects of fluoxetine on this polychaete by exposing organisms for 14 days to concentrations varying between 0.01 and 100 ng/g (Supplementary data – Table 1). Despite the lack of significant alterations on the oxidative stress related enzymes analyzed (GST, GPx and GR), peroxidative damage (LPO) was reported for 100 ng/g. A phase I of biotransformation enzyme, EROD, presented increased activity in all tested concentrations and the activity of AChE was significantly increased in the two highest concentrations (10 and 100 ng/g).

Propranolol is a β-blocker commonly used to treat, among others, heart diseases. Similarly to what happens with other highly prescribed drugs, propranolol is frequently found in waste water and natural environments, where it can be detected in concentrations ranging from 8 ng/L to 0.59 µg/L in water and 3.37 µg/kg in sewage sludge (Ebele et al., 2017). In order to understand the effects of this drug on the polychaete *H. diversicolor*, Maranho and team (2014, 2015) exposed specimens to sediments spiked with concentrations between 0.05 to 500 ng/g for 14 days (Supplementary data – Table 1). Phase I enzymes (EROD and DBF), related to biotransformation of pharmaceuticals, were negatively correlated. EROD activity was significantly increased in exposed organisms, while DBF had lower activity than control. Of the analyzed antioxidant enzymes (GST, GR and GPx), only GST was responsive to contamination from propranolol (0.5, 5 and 500 ng/g). LPO levels demonstrated peroxidative damage to cell membranes (0.05-5 ng/g). Lipid reserves were overall increased, a reported side effect of propranolol (England et al., 2014), and COX activity was inhibited in all tested concentrations.

Sediments act as sink, concentrating contaminants, and pharmaceuticals are no exception. Sulfamethoxazole, carbamazepine, triclosan and ciprofloxacin have been found to be more persistent in sediments that in water (Ebele et al., 2017). Such findings suggest that (endo-)benthic species are persistently exposed to pharmaceuticals.

Of the analyzed pharmaceutical drugs, *H. diversicolor* demonstrated to be more sensitive to CBZ, caffeine and fluoxetine, which promoted alterations in most of the studied parameters. The majority of pharmaceutical drugs analyzed in the scope of this review affect important biochemical parameters on *H. diversicolor*. Damages to cellular membranes and altered biochemical parameters, such as mitochondrial respiration and glycogen content, have a deleterious effect in cellular homeostasis, possibly leading to alterations at the behavioral level. In addition to lower energy production/reserves, oxidative stress and AChE increase may also contribute to behavioral changes, since an increase in AChE may be related to slower movements and thus lead to alterations in behavior. The lack of behavioral data concerning pharmaceutical drugs reveals to be a major deficiency in the field, preventing a global assessment of the impact of this type of contaminant in (endo-)benthic organisms.

2.2. *Nanoparticles*

Nanoparticles (NPs) are defined as particles with at least one dimension between 1 to 100 nm (ASTM, 2012). NPs found in the environment can originate from multiple sources since these particles are added to several everyday items like paints, sunscreen and cosmetics (Baker et al., 2014), although ash and desert dust are natural sources of NPs (Baker et al., 2014). These particles may enter marine systems directly, *via* areal deposition, effluents, dumping and run-off, or indirectly, *via* river systems (Baker et al., 2014).

Silver nanoparticles (Ag NPs) can be found in a number of products used in the everyday life, such as deodorants, cosmetics, textiles, detergents, among others (Baker et al., 2014; Mcgillicuddy et al., 2017). These particles can also be part of the sewage sludge that is later used as fertilizer, leading to run-off of NPs to aquatic environments (Mcgillicuddy et al., 2017). As these particles find their way to marine ecosystems, they can sediment and affect (endo-)benthic organisms.

Various studies have focused on the effects of Ag NPs on polychaetes. Buffet and colleagues (2014a) analyzed the effects of the chronic exposure to ionic Ag and Ag NPs (40-45 nm) on *H. diversicolor* (Supplementary data –

Table 2). Enzymes related to the immune system (laccase-type phenoloxidase (PO) and acid phosphatase (AP)) presented increased activities in organisms exposed to both forms of Ag, which highlights the danger to the health of organisms exposed to NPs. Both forms of Ag (ionic and NPs) were found able to promote increased activities of enzymes involved in defense mechanisms, leading to increased oxidative damage in the ionic Ag treatment. Caspase 3-like (CSP 3-like) has a central role in the apoptotic process and when organisms were exposed to either Ag form its activity was increased, which demonstrates that Ag promotes cellular instability. Burrowing activity was also reduced in both treatments.

Cong and team (2014) tested the effects of sediments spiked with two sizes of Ag NPs (20 and 80 nm) and ionic Ag, at concentrations between 5 and 100 µg/g, on the common ragworm (Supplementary data – Table 2). Analogously to the results reported for other NPs, Ag NPs promoted burrowing impairment, especially Ag NP_{20}. This study also demonstrated that a parameter related to cell function, lysosomal membrane stability (LMS), had a concentration-dependent decrease, which shows a great lysosomal toxicity of all the Ag forms analyzed. Similarly to the results yielded in previous studies by Cong et al. (2011), both Ag forms induced DNA damage. Such results may be more severe in smaller, and thus possibly younger, polychaetes since Cong and colleagues (2014) reported that bigger worms accumulated less Ag per body weight than smaller worms, demonstrating that size influences uptake and bioaccumulation.

Quantum dots (QDs) are a special class of NPs as they are nanoparticles with a heavy metal core (Pawar et al., 2018). Cadmium-based QDs (Cd QDs) are used, for example, in medical imaging and solar energy (Hardman, 2006). Around 15% of Cd in Cd QDs is released into the water, where they exert high toxicity levels. In order to understand the effects of cadmium sulfide (CdS) QDs, Buffet and team (2014b) analyzed the behavior and biochemical parameters of *H. diversicolor* specimens after 14 days exposure to 10 µg/L of CdS QDs and ionic Cd (Supplementary data – Table 2). Authors demonstrated that these particles promote movement impairment, which may have ecological consequences, both via waterborne and dietary exposure. Analyzed oxidative stress parameters (catalase and GST) were responsive to CdS QDs exposure, increasing their activities, and an enzyme related to the apoptotic process (CSP) had an increased activity in the waterborne and dietary treatments. Both Cd forms revealed a high bioaccumulation in tissues.

Carbon nanotubes (CNTs) are rolled up sheets of graphene and can be single-walled or have multiple concentric circles, known as multi-walled CNTs (MWCNTs) (Lawal, 2016). MWCNTs are considered one of the most interesting nanomaterials in nanotechnology due to its many chemical and physical properties (Lawal, 2016). The heightened interest may lead to environmental risks, since aquatic environments are the end destination for various contaminants, as well as human health risks.

De Marchi and colleagues (2018) analyzed how the effects of salinity changes (28 and 21) and MWCNTs (0.10 and 1.00 mg/L) affected the common ragworm (Supplementary data – Table 2). Results demonstrated that several parameters were concentration-dependent, regardless of salinity. Analyzed parameters related to energy were overall decreased, with the exception of ETS, which increased, potentially denoting an allocation of energy to defenses. Oxidative stress enzymes analyzed (SOD, catalase, GPx and GST) predominantly demonstrated an increase in activity, indicating the attempt of the organism to counteract oxidative damage. Nonetheless, LPO levels increased, particularly in salinity 28. Burrowing behavior was not analyzed but a decrease on AChE activity was observed, which suggests that MWCNTs may affect behavior.

De Marchi et al. (2019) evaluated the impact of chronic (28 days) exposure to MWCNTs, pristine and carboxylated (-COOH), in combination with an ocean acidification model (pH 7.60) on *H. diversicolor* (Supplementary data – Table 2). Pristine and functionalized MWCNTs induced neurotoxicity in both concentrations tested, revealed by a decrease in AChE activity. Functionalized MWCNTs have an increased toxicity manifested through the increase in LPO and an activation of SOD compared to pristine MWCNTs. The authors hypothesize that the oxidative stress may be due to the higher solubilization conferred by the functionalization of MWCNTs. The low pH tested (7.60) exacerbated these results and promoted a greater toxic effect of these particles, demonstrating a diminished metabolic rate.

Copper oxide nanoparticles (CuO NPs) are commonly used as bacteriocides and can be found in aquatic environments (Zhou et al., 2006). These particles have a low dissolution rate and potentially high toxicity for organisms. Buffet and colleagues (2011) analyzed the effects on behavioral and biochemical parameters of *H. diversicolor* specimens exposed for 7 days to CuO NPs and ionic Cu (10 µg/L) (Supplementary data – Table 2). Results demonstrated that oxidative stress related enzymes, catalase and GST, activities were significantly higher in organisms exposed to NPs. These particles did not cause behavioral alterations even though ionic Cu induced burrowing impairments.

Subsequent studies by Buffet and collegues (2012a) analyzed the effects of CuO NPs and ionic Cu (10 µg/L) on the polychaete *H. diversicolor* after 21 days exposure (Supplementary data – Table 2). Results demonstrated that Cu bioaccumulation was dependent on form, with uptake being higher in organisms exposed to CuO NPs. The analyzed oxidative stress endpoints (GST and LPO) were very responsive to CuO NPs and CSP was triggered by CuO NPs.

In order to analyze the effects of sediments spiked with CuO NPs, Thit and team (2015) exposed the polychaete *H. diversicolor* to three shapes of NPs (spindles, rods and spheres) and ionic Cu (7-140 µg/g) (Supplementary data – Table 2). Authors demonstrated that ionic Cu affects organisms more than CuO NPs. Although CuO NPs appeared to be accumulated in the gut of exposed organisms, these particles had little effect on bioaccumulation, behavior or mortality, regardless of the shape and size of the NPs. Ionic Cu was more bioavailable to organisms, and thus accumulated in the tissues, and promoted concentration-dependent impairment in burrowing, in which organisms spent less time inside the sediment, which makes *H. diversicolor* more vulnerable to predators.

Zinc oxide NPs (ZnO NPs) are widely used for a variety of applications: from improving toughness in polymers to products such as cosmetics and sunscreens (Jiang et al., 2018). For that reason, Buffet and team (2012b) analyzed the impact of these particles on *H. diversicolor* by exposing organisms to spiked sediments (3 mg/Kg) for 16 days (Supplementary data –

Table 2). Authors reported a significantly increased activity of GST, despite other enzymes related to oxidative stress (catalase and SOD) showing no significant alteration. Nonetheless, LPO levels were increased in organisms exposed to ZnO NPs. Apoptosis-related enzyme CSP 3-like was decreased. Although no neurotoxicity (AChE) was found due to the NPs, an impairment in the burrowing behavior was demonstrated.

Many of the NPs analyzed in this review impact behavior, which can cause severe ecological problems, but they also impact important biochemical parameters. Behavioral alterations may have serious impacts on the ecosystem, as organisms may not only be unable to perform their function in the system but also be more vulnerable to predators, risking population maintenance. Moreover, other organisms are dependent on the burrowing behavior of *H. diversicolor*, either for food or oxygen, and slower polychaetes may have negative impacts on (endo-)benthic organisms as well as on the oxygenation of the sediment itself. Metals in NPs, to which the organisms are more sensitive, are highly bioaccumulated in the tissues of organisms, which may interfere with functions of cells. GST and antioxidant defense catalase activities are frequently impacted by these contaminants, as well as CSP 3-like activity. Overall, data shows that these organisms are sensitive to different forms of NPs and have proven the importance of the nature of the xenobiotic (ionic versus NP) on the effects.

2.3. *Micro(Nano)Plastics*

Plastics are synthetic polymers based in organic polymers, usually fossil fuel, cheap and easy to manufacture. There is a wide array of plastic polymers, such as polystyrene (PS) and polyethylene (PE). They have become a part of products used in the everyday life, from packaging to cosmetics (Avio et al., 2017; de Sá et al., 2018), since plastic production began, in the 1950's (PlasticsEurope, 2019). One of the most concerning problems about plastic is its slow degradation process. In aquatic environments, where they have become ubiquitous across the globe (Bergmann et al., 2017; Eriksen et al., 2014; Waller et al., 2017), biotic and abiotic degradation processes are slow. Plastics are thus available to marine organisms, who may confuse them for food. Moreover, plastics can become brittle and break down over time: big plastic items originate microplastics (< 5 mm) and eventually nanoplastics (1-100 nm) (Oliveira and Almeida, 2019). Microplastics (MPs) and nanoplastics (NPs) can agglomerate/aggregate in seawater, leading to increased sizes and densities, which in turn leads to their sedimentation (Gigault et al., 2018; Oliveira and Almeida, 2019; Revel et al., 2018; Tallec et al., 2019). Such behavior in marine environments allows these contaminants to possibly affect (endo-)benthic fauna. Despite the increased focus on this contaminant, there are few studies focused on the effects of micro(nano)plastics on marine invertebrates, especially (endo-)benthic organisms.

Recent studies by Revel et al. (2018) analyzed the acute (96h) and chronic (10 days) effects of the combined exposure of *H. diversicolor* to PE and polypropylene (PP) MPs in water and sediment matrices (Supplementary data – Table 3). The most relevant data in this study was the higher accumulation of waterborne MPs in the guts of organisms when compared to those exposed to spiked sediments in both exposure periods. Organisms exposed via water demonstrated an increase in mucous production, leading to an increased difficulty in expelling the particles, while those exposed via sediment had the contrary response. In both treatments, authors demonstrated a decrease in immune cell viability and a decrease trend of the activity of enzymes related to the immune system, AP and PO.

Plastics can adsorb and concentrate contaminants existent in natural environments (Oliveira et al., 2019), including PAHs, which tend to accumulate in sediments in aquatic environments (Gomiero et al., 2018). An example of PAHs is benzo(a)pyrene (B[a]P), which is mutagenic and carcinogenic. Among the most frequently used plastics worldwide is PVC, used for window frames and pipes, for example. PVC is denser than seawater and sinks to the ocean floor, where it can expose (endo-)benthic organisms to contaminants.

In order to understand the single and combined effects of sediment spiked with B[a]P and PVC on the common ragworm, Gomiero and colleagues (2018) exposed organisms, for 10 and 28 days, to 5 µg/L of B[a]P and two concentrations of PVC (200 and 2000 particles/Kg of sediment) (Supplementary data – Table 3). Results demonstrated that the combination of B[a]P and plastics had a time- and dose-dependent accumulation, which further highlights the dangers of plastics to marine organisms. In organisms exposed only to B[a]P, cell function parameters, mitochondrial (MtO) and LMS activities, were reduced. In the combined treatment, these parameters (MtO and LMS) also presented a decreased activity and cell membrane damage, measured by lipofuscins content, was increased. An analysis of immune system parameters (phagocytosis assay and MtO) revealed a depression in the immune response in organisms exposed to PVC pre-incubated with B[a]P. Contrary to the results found in the combined exposure, virgin PVC particles stimulated the immune system, which may be due to the presence of natural occurring microorganisms in the sediments that may colonize virgin PVC particles (Zettler et al., 2013). Oxidative status was increased in the combined exposure, although catalase activity was only increased at the 10 days exposure period. DNA damage was significantly higher in organisms exposed to B[a]P and pre-incubated PVC.

A significant number of published studies have focused on laboratory experiments to understand effects of various contaminants on organisms. Muller-Karanassos et al. (2019) focused on analyzing environmental samples of sediment and *H. diversicolor* specimens exposed to anti-fouling paint particles (APPs) (Supplementary data – Table 3), which are composed of plastics with different metals associated to them (Muller-Karanassos et al., 2019; Turner et al., 2008a; Turner & Rees, 2016). Those particles can still leach their biocidal metals not only to the water but also to sediments, where they accumulate (Soroldoni et al., 2018; Thomas et al., 2003; Turner et al., 2008b).

Muller-Karanassos and colleagues (2019) analyzed sediment samples from two estuaries in the UK, one heavily impacted by marinas, boatyards, and abandoned boats, thus more impacted by APPs, and another a clean reference site (control). Results demonstrated that organisms had high concentrations of copper (Cu), zinc (Zn), tin (Sn) and lead (Pb) in their tissues. Similarly to what was reported by Revel and collegues (2018), organisms had

APPs of varied sizes and chemical compositions in their guts, related to a non-selective ingestion of the particles.

Very few studies have focused on the effects of NPs on marine invertebrates, particularly polychaetes. Recently Silva et al. (2020a) evaluated the chronic effects of PS NPs on *H. diversicolor* by exposing organisms to concentrations between 0.005 and 50 mg/L (Supplementary data – Table 3). Results demonstrated an increase in burrowing time in the lowest concentrations (0.005-0.5 mg/L) as well as an overall decrease in AChE activity in exposed organisms. Antioxidant enzymes were found to be less responsive than expected. Activity of SOD was increased from 0.05 to 50 mg/L, however the rest of the enzymes related to oxidative stress analyzed (GST, catalase and non-protein thiols (NPTs)) were reported to have concentration-dependent decreases. Oxidative damage measured as protein carbonylation, which was possibly a better biomarker to evaluate oxidative damage induced by PS NPs, was significantly increased from 0.05-50 mg/L. Subsequent studies by Silva et al. (2020b) demonstrated that exposure to PS NPs (0.0005-5 mg/L) significantly decreased the regenerative capacity of *H. diversicolor* exposed to 0.005-5 mg/L (Supplementary data – Table 3).

There is a big gap in knowledge when it comes to understanding the effects of plastic particles on marine invertebrates. An even bigger gap is related to comprehending the interaction of plastics with contaminants known to exist in marine habitats and their combined effects on marine organisms. Efficient methodologies to evaluate the concentrations of NPs in the oceans have yet to be created, but it is still important to understand how invertebrates, who are at the base of food webs, react to them, since NPs can accumulate along the food webs.

3. Conclusion

In this review studies with *H. diversicolor* referring to nine pharmaceutical drugs, five types of nanoparticles, and five plastic polymers were analyzed. A review of the literature from 2010 to 2019 was performed using the database Scopus and using the following combination of terms: *Hediste diversicolor* AND drugs; *Hediste diversicolor* AND nanoparticles; *Hediste diversicolor* AND plastics. The available data does not allow comparison of the role of exposure pathways on the magnitude of effects as several different non-coinciding biomarkers have been assessed. Nonetheless, these studies have shown that the polychaete *H. diversicolor* is very responsive to these emerging contaminants and thus is a good biological model to assess the effects of contaminants expected to reach the estuarine/marine environments.

Among the most frequently affected biochemical endpoints, regardless of the exposure period or contaminant, are oxidative stress related endpoints and behavior. These are important biomarkers to assess, although behavior related parameters should be more often analyzed considering its ecological importance. Alterations in the behavior of these organisms, as a result of contamination, can have serious consequences to the ecosystem and its function, possibly leading to alterations in (endo-)benthic diversity due to a reduction in sediment oxygenation. Future studies should include environmentally relevant endpoints of behavior to allow a more comprehensive understanding of the effects of contaminants. Among the endpoints scarcely evaluated on *H. diversicolor* but with promising results is regeneration. This endpoint can also provide relevant data on potential impacts on population dynamics. Moreover, *in vitro* cell culture using cells from these organisms may allow a better understanding of regeneration mechanisms as well as the impact of xenobiotic exposure on this ability.

No studies have, so far, addressed how contaminants can affect offspring in terms of number of organisms generated, organisms' size, and even if the offspring has an altered sensitivity to the contaminants to which the parents were exposed. The study of the effects on these endpoints can considerably improve the knowledge of the consequences of long-term environmental exposure.

There is a large gap in knowledge concerning the effects of plastic contamination on invertebrates, despite plastic pollution being a concerning problem. Few studies have analyzed the effects of small plastic particles on polychaetes and fewer focused on NPs, even though plastic particles tend to sediment over time and can thus affect (endo-)benthic organisms. This lack of studies may be associated with the difficulty in quantification and characterization of these particles. Detection methods are still unable to allow accurate identification and quantification of small plastic particles in water and sediment matrices. Considering the recent findings of studies with nanoplastic particles (e.g. Silva et al., 2020a), it becomes highly relevant to perform studies with behavior, which is a very sensitive endpoint. This approach may include feeding, avoidance of contaminated sediments, among others. Considering that in the environment organisms are exposed to a variety of contaminants, future studies should consider combined effects of more than one contaminant as they may interact and modulate toxic responses. This aspect is particularly relevant for nanoparticles that have their characteristics influenced by their surrounding environment (e.g. presence of contaminants, products of metabolism, pH, nutrients and organic matter). As authors De Marchi et al. (2019) demonstrated, alterations in pH may affect the response of *H. diversicolor* to nanoparticles. Substances linked to plastic have also been proved to elicit a worsening in the condition of the animal than in independent treatments (e.g. Gomiero et al., 2018). The ability of organisms to depurate environmental contaminants should also be assessed, since it has been already demonstrated that *H. diversicolor* specimens in clean sediment are able to expel environmental contaminants, like microplastic particles, when exposed via spiked sediment (Revel et al., 2018).

The available studies show that this species can be a valuable tool to assess the effects of environmental contaminants. It may be expected that, ethical considerations regarding the use of vertebrate organisms associated with sensitivity, low laboratory maintenance requirements and environmental relevance make these organisms widely used in the field of Ecotoxicology.

Acknowledgments:

Thanks are due to FCT/MCTES for the financial support to CESAM (UIDP/50017/2020+UIDB/50017/2020), through national funds.. AP was contracted under Decree-Law 57/2016 Art.23rd - Transitional Rule. MO had financial support of the program Investigador FCT, co-funded by the Human Potential Operational Programme and European Social Fund (IF/00335-2015).

This work was also financially supported by the project BIOGEOCLIM (POCI-01-0145-FEDER-029185) funded by FEDER, through COMPETE2020 - Programa Operacional Competitividade e Internacionalização (POCI), and by national funds (OE), through FCT/MCTES. This work was also funded by CYTED, through the RED Iberoamericana RIESCOS (419RT0578).

Conflict of interest: The authors declare no conflict of interest.

4. References

Andries, J.-C., 2001. Endocrine and environmental control of reproduction in Polychaeta. Can. J. Zool. 79, 254–270. https://doi.org/https://doi.org/10.1139/z00-197

Arnesano, F., Natile, G., 2009. Mechanistic insight into the cellular uptake and processing of cisplatin 30 years after its approval by FDA. Coord. Chem. Rev. 253, 2070–2081. https://doi.org/10.1016/j.ccr.2009.01.028

ASTM, 2012. Standard Terminology Relating to Nanotechnology. West Conshohocken, PA.

Avio, C.G., Gorbi, S., Regoli, F., 2017. Plastics and microplastics in the oceans: From emerging pollutants to emerged threat. Mar. Environ. Res. 128, 2–11. https://doi.org/10.1016/j.marenvres.2016.05.012

Bagley, C.M., Bostick, F.W., DeVita, V.T., 1973. Clinical pharmacology of cyclophosphamide. Cancer Res. 33, 226–33.

Baker, T.J., Tyler, C.R., Galloway, T.S., 2014. Impacts of metal and metal oxide nanoparticles on marine organisms. Environ. Pollut. 186, 257–271. https://doi.org/10.1016/j.envpol.2013.11.014

Banta, G.T., Andersen, O., 2003. Bioturbation and the fate of sediment pollutants- Experimental case studies of selected infauna species. Vie Milieu 53, 233–248.

Barreto, Â., Girão, A.V., Pereira, M. de L., Trindade, T., Soares, A.M.V.M., Oliveira, M., 2018. Microscopy Assesment of Emerging Contaminants' Effects on Aquatic Species, in: Microscopy Applied to Materials Sciences and Life Sciences.

Bely, A.E., 2006. Distribution of segment regeneration ability in the Annelida.

Integr. Comp. Biol. 46, 508–518. https://doi.org/10.1093/icb/icj051

Bergmann, M., Wirzberger, V., Krumpen, T., Lorenz, C., Primpke, S., Tekman, M.B., Gerdts, G., 2017. High Quantities of Microplastic in Arctic Deep-Sea Sediments from the HAUSGARTEN Observatory. Environ. Sci. Technol. 51. https://doi.org/10.1021/acs.est.7b03331

Bompart, G.J., Prévot, D.S., Bascands, J.-L., 1990. Rapid automated analysis of glutathione reductase, peroxidase, and S-transferase activity: application to cisplatin-induced toxicity. Clin. Biochem. 23, 501–504. https://doi.org/https://doi.org/10.1016/0009-9120(90)80039-L

Borgwardt, F., Robinson, L., Trauner, D., Teixeira, H., Nogueira, A.J.A., Lillebø, A.I., Piet, G., Kuemmerlen, M., Higgins, T.O., Mcdonald, H., Arevalo-torres, J., Luisa, A., Iglesias-campos, A., Hein, T., Culhane, F., 2019. Exploring variability in environmental impact risk from human activities across aquatic ecosystems. Sci. Total Environ. 652, 1396–1408. https://doi.org/10.1016/j.scitotenv.2018.10.339

Buerge, I.J., Buser, H.R., Poiger, T., Müller, M.D., 2006. Occurrence and fate of the cytostatic drugs cyclophosphamide and ifosfamide in wastewater and surface waters. Environ. Sci. Technol. 40, 7242–7250. https://doi.org/10.1021/es0609405

Buffet, P.E., Amiard-Triquet, C., Dybowska, A., Risso-de Faverney, C., Guibbolini, M., Valsami-Jones, E., Mouneyrac, C., 2012a. Fate of isotopically labeled zinc oxide nanoparticles in sediment and effects on two endobenthic species, the clam *Scrobicularia plana* and the ragworm *Hediste diversicolor*. Ecotoxicol. Environ. Saf. 84, 191–198. https://doi.org/10.1016/j.ecoenv.2012.07.010

Buffet, P.E., Poirier, L., Zalouk-Vergnoux, A., Lopes, C., Amiard, J.C., Gaudin, P., Risso-de Faverney, C., Guibbolini, M., Gilliland, D., Perrein-Ettajani, H., Valsami-Jones, E., Mouneyrac, C., 2014a. Biochemical and behavioural responses of the marine polychaete *Hediste diversicolor* to cadmium sulfide quantum dots (CdS QDs): Waterborne and dietary exposure. Chemosphere 100, 63–70. https://doi.org/10.1016/j.chemosphere.2013.12.069

Buffet, P.E., Richard, M., Caupos, F., Vergnoux, A., Perrein-Ettajani, H., Luna-Acosta, A., Akcha, F., Amiard, J.C., Amiard-Triquet, C., Guibbolini, M., Risso-De Faverney, C., Thomas-Guyon, H., Reip, P., Dybowska, A., Berhanu, D., Valsami-Jones, E., Mouneyrac, C., 2012b. A mesocosm study of fate and effects of CuO nanoparticles on endobenthic species (*Scrobicularia plana*, *Hediste diversicolor*). Environ. Sci. Technol. 47, 1620–1628. https://doi.org/10.1021/es303513r

Buffet, P.E., Tankoua, O.F., Pan, J.F., Berhanu, D., Herrenknecht, C., Poirier, L., Amiard-Triquet, C., Amiard, J.C., Bérard, J.B., Risso, C., Guibbolini, M., Roméo, M., Reip, P., Valsami-Jones, E., Mouneyrac, C., 2011. Behavioural and biochemical responses of two marine invertebrates *Scrobicularia plana* and *Hediste diversicolor* to copper oxide nanoparticles. Chemosphere 84, 166–174. https://doi.org/10.1016/j.chemosphere.2011.02.003

Buffet, P.E., Zalouk-Vergnoux, A., Châtel, A., Berthet, B., Métais, I., Perrein-Ettajani, H., Poirier, L., Luna-Acosta, A., Thomas-Guyon, H., Risso-de Faverney, C., Guibbolini, M., Gilliland, D., Valsami-Jones, E., Mouneyrac, C., 2014b. A marine mesocosm study on the environmental fate of silver nanoparticles and toxicity effects on two endobenthic species: The ragworm *Hediste diversicolor* and the bivalve mollusc *Scrobicularia plana*. Sci. Total Environ. 470–471, 1151–1159. https://doi.org/10.1016/j.scitotenv.2013.10.114

Česen, M., Eleršek, T., Novak, M., Žegura, B., Kosjek, T., Filipič, M., Heath, E., 2016. Ecotoxicity and genotoxicity of cyclophospamide, ifosfamide, their metabolites/transformation products and their mixtures. Environ. Pollut. 210, 192–201. https://doi.org/10.1016/j.envpol.2015.12.017

Claessens, M., Vanhaecke, L., Wille, K., Janssen, C.R., 2013. Emerging contaminants in Belgian marine waters: Single toxicant and mixture risks of pharmaceuticals. Mar. Pollut. Bull. 71, 41–50. https://doi.org/10.1016/j.marpolbul.2013.03.039

Cong, Y., Banta, G.T., Selck, H., Berhanu, D., Valsami-Jones, E., Forbes, V.E., 2014. Toxicity and bioaccumulation of sediment-associated silver nanoparticles in the estuarine polychaete, *Nereis* (*Hediste*) *diversicolor*. Aquat. Toxicol. 156, 106–115. https://doi.org/10.1016/j.aquatox.2014.08.001

Cong, Y., Banta, G.T., Selck, H., Berhanu, D., Valsami-Jones, E., Forbes, V.E., 2011. Toxic effects and bioaccumulation of nano-, micron- and ionic-Ag in the polychaete, *Nereis diversicolor*. Aquat. Toxicol. 105, 403–411. https://doi.org/10.1016/j.aquatox.2011.07.014

Dales, R.P., 1950. The reproduction and larval development of *Nereis diversicolor* O.F. Muller. Mar. Biol. Assoc. United Kingdom 29, 321–360. https://doi.org/https://doi.org/10.1017/S0025315400055405

Davey, J.T., 1994. The architecture of the burrow of *Nereis diversicolor* and its quantification in relation to sediment-water exchange. J. Exp. Mar. Bio.

Ecol. 179, 115–129. https://doi.org/https://doi.org/10.1016/0022-0981(94)90020-5

De Marchi, L., Neto, V., Pretti, C., Figueira, E., Chiellini, F., Morelli, A., Soares, A.M.V.M., Freitas, R., 2018. The influence of salinity on the effects of Multi-walled carbon nanotubes on polychaetes. Sci. Rep. 8, 1–14. https://doi.org/10.1038/s41598-018-26729-2

De Marchi, L., Pretti, C., Chiellini, F., Morelli, A., Neto, V., Soares, A.M.V.M., Figueira, E., Freitas, R., 2019. The influence of simulated global ocean acidification on the toxic effects of carbon nanoparticles on polychaetes. Sci. Total Environ. 666, 1178–1187. https://doi.org/10.1016/j.scitotenv.2019.02.109

de Sá, L.C., Oliveira, M., Ribeiro, F., Rocha, T.L., Futter, M.N., 2018. Studies of the effects of microplastics on aquatic organisms: What do we know and where should we focus our efforts in the future? Sci. Total Environ. 645, 1029–1039. https://doi.org/10.1016/j.scitotenv.2018.07.207

Dean, H.K., 2008. The use of polychaetes (Annelida) as indicator species of marine pollution: a review. Rev. Biol. Trop. 56, 11–38.

Dey, S., Bano, F., Malik, A., 2019. Pharmaceuticals and personal care product (PPCP) contamination—a global discharge inventory, in: Pharmaceuticals and Personal Care Products: Waste Management and Treatment Technology. pp. 1–26. https://doi.org/https://doi.org/10.1016/C2017-0-03544-9

Dhainaut, A., Scaps, P., 2001. Immune defense and biological responses induced by toxics in Annelida. Can. J. Zool. 79, 233–253. https://doi.org/10.1139/cjz-79-2-233

Durou, C., Mouneyrac, C., 2007. Linking steroid hormone levels to sexual maturity index and energy reserves in Nereis diversicolor from clean and polluted estuaries. Gen. Comp. Endocrinol. 150, 106–113. https://doi.org/10.1016/j.ygcen.2006.07.019

Ebele, A.J., Abdallah, M.A.-E., Harrad, S., 2017. Pharmaceuticals and personal care products (PPCPs) in the freshwater aquatic environment. Emerg. Contam. 3, 1–16. https://doi.org/10.1016/j.emcon.2016.12.004

England, R.W., Hardy, K.L., Kitajewski, A.M., Wong, A., Kitajewski, J.K., Shawber, C.J., Wu, J.K., 2014. Propranolol Promotes Accelerated and Dysregulated Adipogenesis in Hemangioma Stem Cells. Ann. Plast. Surg. 73, 1–13. https://doi.org/10.1097/SAP.0000000000000272.Propranolol

Eriksen, M., Lebreton, L., Carson, H., Thiel, M., Moore, C., Borerro, J., Galgani, F., Ryan, P., Reisser, J., 2014. Plastic Pollution in the World's Oceans: More than 5 Trillion Plastic Pieces Weighing over 250,000 Tons Afloat at Sea. PLoS One 9, e111913. https://doi.org/10.1371/journal.pone.0111913

Esselink, P., Zwarts, L., 1989. Seasonal trend in burrow depth and tidal variation. Mar. Ecol. Prog. Ser. 56, 243–254.

Evans, P.R., Herdson, D.M., Knights, P.J., Pienkowski, M.W., 1979. Short-term effects of reclamation of part of seal sands, Teesmouth, England, U.K. on wintering waders and shelduck. 1. Shorebird diets, invertebrate densities and the impact of predation on the invertebrates. Oecologia 41, 186–206.

Fauchald, K., Jumars, P.A., 1979. The diet of worms: a study of polychaetes feeding guilds. Oceanogr. Mar. Biol. - An Annu. Rev. 17, 193–284.

Fauvel, P., 1923. Polychètes errantes.

Fekadu, S., Alemayehu, E., Dewil, R., Van der Bruggen, B., 2019.

Pharmaceuticals in freshwater aquatic environments: A comparison of the African and European challenge. Sci. Total Environ. 654, 324–337. https://doi.org/10.1016/j.scitotenv.2018.11.072

Fonseca, T.G., Auguste, M., Ribeiro, F., Cardoso, C., Mestre, N.C., Abessa, D.M.S., Bebianno, M.J., 2018. Environmental relevant levels of the cytotoxic drug cyclophosphamide produce harmful effects in the polychaete *Nereis diversicolor*. Sci. Total Environ. 636, 798–809. https://doi.org/10.1016/j.scitotenv.2018.04.318

Fonseca, T.G., Morais, M.B., Rocha, T., Abessa, D.M.S., Aureliano, M., Bebianno, M.J., 2017. Ecotoxicological assessment of the anticancer drug cisplatin in the polychaete *Nereis diversicolor*. Sci. Total Environ. 575, 162–172. https://doi.org/10.1016/j.scitotenv.2016.09.185

Galloway, T., Lewis, C., Dolciotti, I., Johnston, B.D., Moger, J., Regoli, F., 2010. Sublethal toxicity of nano-titanium dioxide and carbon nanotubes in a sediment dwelling marine polychaete. Environ. Pollut. 158, 1748–1755. https://doi.org/10.1016/j.envpol.2009.11.013

Gigault, J., Halle, A. ter, Baudrimont, M., Pascal, P.Y., Gauffre, F., Phi, T.L., El Hadri, H., Grassl, B., Reynaud, S., 2018. Current opinion: What is a nanoplastic? Environ. Pollut. 235, 1030–1034. https://doi.org/10.1016/j.envpol.2018.01.024

Gilard, V., Martino, R., Malet-Martino, M.-C., Kutscher, B., Mueller, A., Niemeyer, U., Pohl, J., Polymeropoulos, E.E., 1994. Chemical and Biological Evaluation of Hydrolysis Products of Cyclophosphamide. J. Med. Chemestry 37, 3986–3993. https://doi.org/https://doi.org/10.1021/jm00049a018

Gillet, P., 2012. Preliminary Data on the Bioturbation Activity of *Hediste Diversicolor* (Polychaeta, Nereididae) from the Loire Estuary, France. Open Mar. Biol. J. 6, 53–56. https://doi.org/10.2174/1874450801206010053

Gomes, A., Correia, A.T., Nunes, B., 2019. Worms on drugs: Ecotoxicological effects of acetylsalicylic acid on the polychaeta species *Hediste diversicolor* in terms of biochemical and histological alterations. Environ. Sci. Pollut. Res. 26, 13619–13629. https://doi.org/10.1007/s11356-019-04880-1

Gomes, T., Gonzalez-Rey, M., Rodríguez-Romero, A., Trombini, C., Riba, I., Blasco, J., Bebianno, M.J., 2013. Biomarkers in *Nereis diversicolor* (Polychaeta: Nereididae) as management tools for environmental assessment on the southwest Iberian coast. Sci. Mar. https://doi.org/10.3989/scimar.03731.27f

Gómez-Ruiz, S., Maksimović-Ivanić, D., Mijatović, S., Kaluderović, G.N., 2012. On the discovery, biological effects, and use of cisplatin and metallocenes in anticancer chemotherapy. Bioinorg. Chem. Appl. 2012, 14. https://doi.org/10.1155/2012/140284

Gomiero, A., Strafella, P., Pellini, G., Salvalaggio, V., Fabi, G., 2018. Comparative Effects of Ingested PVC Micro Particles With and Without Adsorbed Benzo(a)pyrene vs. Spiked Sediments on the Cellular and Sub Cellular Processes of the Benthic Organism *Hediste diversicolor*. Front. Mar. Sci. 5, 1–12. https://doi.org/10.3389/fmars.2018.00099

Halpern, B.S., Frazier, M., Potapenko, J., Casey, K.S., Koenig, K., Longo, C., Lowndes, J.S., Rockwood, R.C., Selig, E.R., Selkoe, K.A., Walbridge, S., 2015. Spatial and temporal changes in cumulative human impacts on the world's ocean. Nat. Commun. 6, 1–7. https://doi.org/10.1038/ncomms8615

Hardman, R., 2006. A toxicologic review of quantum dots: Toxicity depends on physicochemical and environmental factors. Environ. Health Perspect. 114, 165–172. https://doi.org/10.1289/ehp.8284

Herrero, A., Vila, J., Eljarrat, E., Ginebreda, A., Sabater, S., Batalla, R.J., Barceló, D., 2018. Transport of sediment borne contaminants in a Mediterranean river during a high fl ow event. Sci. Total Environ. 633, 1392–1402. https://doi.org/10.1016/j.scitotenv.2018.03.205

Hird, C.M., Urbina, M.A., Lewis, C.N., Snape, J.R., Galloway, T.S., 2016. Fluoxetine Exhibits Pharmacological Effects and Trait-Based Sensitivity in a Marine Worm. Environ. Sci. Technol. 50, 8344–8352. https://doi.org/10.1021/acs.est.6b03233

Jiang, J., Pi, J., Cai, J., 2018. The Advancing of Zinc Oxide Nanoparticles for Biomedical Applications. Bioinorg. Chem. Appl. 2018. https://doi.org/https://doi.org/10.1155/2018/1062562

Kristensen, E., 1983. Ventilation and oxygen uptake by three species of *Nereis* (Annelida: Polychaeta). I . Effects of hypoxia. Mar. Ecol. Prog. Ser. 12, 289–297. https://doi.org/10.3354/meps012289

Kristensen, E., Mikkelsen, O.L., 2003. Impact of the burrow-dwelling polychaete *Nereis diversicolor* on the degradation of fresh and aged macroalgal detritus in a coastal marine sediment. Mar. Ecol. Prog. Ser. 265, 141–153. https://doi.org/10.3354/meps265141

Lawal, A.T., 2016. Synthesis and utilization of carbon nanotubes for fabrication of electrochemical biosensors. Mater. Res. Bull. 73, 308–350. https://doi.org/10.1016/j.materresbull.2015.08.037

Leung, J., Chan, K.Y.K., 2018. Microplastics reduced posterior segment regeneration rate of the polychaete *Perinereis aibuhitensis*. Mar. Pollut. Bull. 129, 782–786. https://doi.org/10.1016/j.marpolbul.2017.10.072

Lewis, C., Watson, G.J., 2012. Expanding the ecotoxicological toolbox: The inclusion of polychaete reproductive endpoints. Mar. Environ. Res. 75, 10–22. https://doi.org/10.1016/j.marenvres.2011.08.002

Mahdi, J.G., Mahdi, A.J., Mahdi, A.J., Bowen, I.D., 2006. The historical analysis of aspirin discovery, its relation to the willow tree and antiproliferative and anticancer potential. Cell Prolif. 39, 147–155. https://doi.org/10.1111/j.1365-2184.2006.00377.x

Maranho, L.A., André, C., DelValls, T.A., Gagné, F., Martín-Díaz, M.L., 2015. Toxicological evaluation of sediment samples spiked with human pharmaceutical products: Energy status and neuroendocrine effects in marine polychaetes *Hediste diversicolor*. Ecotoxicol. Environ. Saf. 118, 27–36. https://doi.org/10.1016/j.ecoenv.2015.04.010

Maranho, L.A., Baena-Nogueras, R.M., Lara-Martín, P.A., DelValls, T.A., Martín-Díaz, M.L., 2014. Bioavailability, oxidative stress, neurotoxicity and genotoxicity of pharmaceuticals bound to marine sediments. The use of the polychaete *Hediste diversicolor* as bioindicator species. Environ. Res. https://doi.org/10.1016/j.envres.2014.08.014

Mcgillicuddy, E., Murray, I., Kavanagh, S., Morrison, L., Fogarty, A., Cormican, M., Dockery, P., Prendergast, M., Rowan, N., Morris, D., 2017. Silver nanoparticles in the environment: Sources , detection and ecotoxicology. Sci. Total Environ. 575, 231–246. https://doi.org/10.1016/j.scitotenv.2016.10.041

Metcalfe, C.D., Miao, X.S., Koenig, B.G., Struger, J., 2003. Distribution of acidic and neutral drugs in surface waters near sewage treatment plants in the lower Great Lakes, Canada. Environ. Toxicol. Chem. 22, 2881–2889. https://doi.org/10.1897/02-627

Miloslavich, P., Díaz, J.M., Klein, E., Alvarado, J.J., Díaz, C., Gobin, J., Escobar-Briones, E., Cruz-Motta, J.J., Weil, E., Cortés, J., Bastidas, A.C., Robertson, R., Zapata, F., Martín, A., Castillo, J., Kazandjian, A., Ortiz, M., 2010. Marine biodiversity in the caribbean: Regional estimates and distribution patterns. PLoS One 5. https://doi.org/10.1371/journal.pone.0011916

Miyagawa, S., Sato, T., Iguchi, T., 2016. 17α-Ethinylestradiol, in: Handbook of Hormones. Comparative Endocrinology for Basic and Clinical Research, p. 581. https://doi.org/https://doi.org/10.1016/B978-0-12-801028-0.00243-9

Möller, P., 1985. Production and Abundance of Juvenile Nereis Diversicolor, and Oogenic Cycle of Adults in Shallow Waters of Western Sweden. J. Mar. Biol. Assoc. United Kingdom 65, 603–616. https://doi.org/doi:10.1017/S0025315400052450

Muller-Karanassos, C., Turner, A., Arundel, W., Vance, T., Lindeque, P.K., Cole, M., 2019. Antifouling paint particles in intertidal estuarine sediments from southwest England and their ingestion by the harbour ragworm, *Hediste diversicolor*. Environ. Pollut. 249, 163–170. https://doi.org/10.1016/j.envpol.2019.03.009

Nithart, M., 1998. Population Dynamics and Secondary Production of *Nereis diversicolor* in a North Norfolk Saltmarsh (UK). Mar. Biol. Assoc. United Kingdom 78, 131–143.

Nunes, B., Campos, J., Gomes, R., Braga, M., Ramos, A., Antunes, S., Correia, A., 2015. Ecotoxicological effects of salicylic acid in the freshwater fish *Salmo trutta fario*: antioxidant mechanisms and histological alterations. Environ. Sci. Pollut. Res. 22, 667–678. https://doi.org/10.1007/s11356-014-3337-2

Nunes, B., Vidal, D., Barbosa, I., Soares, A.M.V.M., Freitas, R., 2016. Pollution effects on biochemical pathways determined in the polychaete *Hediste diversicolor* collected in three Portuguese estuaries. Environ. Sci. Process. Impacts 1208–1219. https://doi.org/10.1039/c6em00297h

Oliveira, M., Almeida, M., 2019. The why and how of micro(nano)plastic research. TrAC - Trends Anal. Chem. 114, 196–201. https://doi.org/10.1016/j.trac.2019.02.023

Oliveira, M., Almeida, M., Miguel, I., 2019. A micro(nano)plastic boomerang tale: A never ending story? TrAC - Trends Anal. Chem. 112, 196–200. https://doi.org/10.1016/j.trac.2019.01.005

Oliveira, M., Cardoso, D.N., Soares, A.M.V.M., Loureiro, S., 2018. Toxic effects of human pharmaceuticals to Folsomia candida – A multigeneration approach. Sci. Total Environ. 625, 1225–1233. https://doi.org/10.1016/j.scitotenv.2017.12.319

Oliveira, M., Maria, V.L., Ahmad, I., Serafim, A., Bebianno, M.J., Pacheco, M., Santos, M.A., 2009. Contamination assessment of a coastal lagoon (Ria de Aveiro, Portugal) using defence and damage biochemical indicators in gill of *Liza aurata* - An integrated biomarker approach. Environ. Pollut. 157, 959–967. https://doi.org/10.1016/j.envpol.2008.10.019

Oliveira, M., Pacheco, M., Santos, M.A., 2008. Organ specific antioxidant responses in golden grey mullet (*Liza aurata*) following a short-term exposure to phenanthrene. Sci. Total Environ. 396, 70–78. https://doi.org/10.1016/j.scitotenv.2008.02.012

Pawar, R.S., Upadhaya, P.G., Patravale, V.B., 2018. Quantum Dots: Novel Realm in Biomedical and Pharmaceutical Industry, in: Handbook of Nanomaterials for Industrial Applications. pp. 621–637. https://doi.org/https://doi.org/10.1016/B978-0-12-813351-4.00035-3

Pires, A., Almeida, Â., Calisto, V., Schneider, R.J., Esteves, V.I., Wrona, F.J., Soares, A.M.V.M., Figueira, E., Freitas, R., 2016a. Hediste diversicolor as bioindicator of pharmaceutical pollution: Results from single and combined exposure to carbamazepine and caffeine. Comp. Biochem. Physiol. Part - C Toxicol. Pharmacol. 188, 30–38. https://doi.org/10.1016/j.cbpc.2016.06.003

Pires, A., Almeida, Â., Calisto, V., Schneider, R.J., Esteves, V.I., Wrona, F.J., Soares, A.M.V.M., Figueira, E., Freitas, R., 2016b. Long-term exposure of polychaetes to caffeine: Biochemical alterations induced in *Diopatra neapolitana* and *Arenicola marina*. Environ. Pollut. 214, 456–463. https://doi.org/10.1016/j.envpol.2016.04.031

Pires, A., Almeida, Â., Correia, J., Calisto, V., Schneider, R.J., Esteves, V.I., Soares, A.M.V.M., Figueira, E., Freitas, R., 2016c. Long-term exposure to caffeine and carbamazepine: Impacts on the regenerative capacity of the polychaete *Diopatra neapolitana*. Chemosphere 146, 565–573. https://doi.org/10.1016/j.chemosphere.2015.12.035

PlasticsEurope, 2019. Plastics – the Facts 2019.

Pombo, A., Baptista, T., Granada, L., Ferreira, S.M.F., Gonçalves, S.C., Anjos, C., Erica, S., Chainho, P., Cancela da Fonseca, L., Fidalgo e Costa, P., Costa, J.L., 2018. Insight into aquaculture's potential of marine annelid worms and ecological concerns: a review. Rev. Aquac. 1–15. https://doi.org/10.1111/raq.12307

Reise, K., 1979. Spatial configurations generated by motile benthic polychaetes. Helgoländer wissenschaftliche Meeresuntersuchungen 32, 55–72.

Revel, M., Yakovenko, N., Caley, T., Guillet, C., Châtel, A., Mouneyrac, C., 2018. Accumulation and immunotoxicity of microplastics in the estuarine worm Hediste diversicolor in environmentally relevant conditions of exposure. Environ. Sci. Pollut. Res. 1–10. https://doi.org/10.1007/s11356-018-3497-6

Riisgård, H.U., Larsen, P.S., 2010. Particle capture mechanisms in suspension-feeding invertebrates. Mar. Ecol. Prog. Ser. 418, 255–293. https://doi.org/10.3354/meps08755

Scaps, P., 2002. A review of the biology , ecology and potential use of the common ragworm *Hediste diversicolor* (O . F . Müller) (Annelida : Polychaeta). Hydrobiologia 470, 203–218. https://doi.org/10.1023/A:1015681605656

Silva, M.S.S., Oliveira, M., Valente, P., Figueira, E., Martins, M., Pires, A., 2020a. Behavior and biochemical responses of the polychaeta *Hediste diversicolor* to polystyrene nanoplastics. Sci. Total Environ. 707. https://doi.org/10.1016/j.scitotenv.2019.134434

Silva, M.S.S., Oliveira, M., Lopéz, D., Figueira, E., Martins, M., Pires, A., 2020b. Do nanoplastics impact the ability of the polychaeta *Hediste diversicolor* to regenerate? Ecol. Indic. 110. https://doi.org/10.1016/j.ecolind.2019.105921

Smith, A.J., McGowan, T., Devlin, M.J., Massoud, M.S., Al-Enezi, M., Al-Zaidan, A.S., Al-Sarawi, H.A., Lyons, B.P., 2015. Screening for contaminant hotspots in the marine environment of Kuwait using ecotoxicological and chemical screening techniques. Mar. Pollut. Bull. 100, 681–688. https://doi.org/10.1016/j.marpolbul.2015.08.043

Smith, R.I., 1956. The ecology of the Tamar estuary. VII. Observations on the interstitial salinity of intertidal muds in the estuarine habitat of *Nereis diversicolor*. Mar. Biol. Assoc. United Kingdom 35, 81–104. https://doi.org/https://doi.org/10.1017/S0025315400008985

Smith, R.I., 1955. On the distribution of Nereis diversicolor in relation to salinity in the vicinity of Tvörminne Finland and the Isefjord, Denmark. Biol. Bull. 108, 326–345. https://doi.org/https://doi.org/10.2307/1538519

Soroldoni, S., Martins, S.E., Castro, I.B., Pinho, G.L.L., 2018. Potential ecotoxicity of metals leached from antifouling paint particles under different salinities. Ecotoxicol. Environ. Saf. 148, 447–452. https://doi.org/10.1016/j.ecoenv.2017.10.060

Steger-Hartmann, T., Kümmerer, K., Schecker, J., 1996. Trace analysis of the antineoplastics ifosfamide and cyclophosphamide in sewage water by two-step solid-phase extraction and gas chromatography-mass spectrometry. J. Chromatogr. A 726, 179–184. https://doi.org/10.1016/0021-9673(95)01063-7

Tallec, K., Blard, O. eane, Gonz alez-Fern andez, C., Brotons, G., Berchel, M., Soudant, P., Huvet, A., Paul-Pont, I., 2019. Surface functionalization determines behavior of nanoplastic solutions in model aquatic environments. Chemosphere 225, 639–646. https://doi.org/10.1016/j.chemosphere.2019.03.077

Thit, A., Dybowska, A., Købler, C., Kennaway, G., Selck, H., 2015. Influence of copper oxide nanoparticle shape on bioaccumulation, cellular internalization and effects in the estuarine sediment-dwelling polychaete, *Nereis diversicolor*. Mar. Environ. Res. 111, 89–98. https://doi.org/10.1016/j.marenvres.2015.06.009

Thomas, K. V., McHugh, M., Hilton, M., Waldock, M., 2003. Increased persistence of antifouling paint biocides when associated with paint particles. Environ. Pollut. 123, 153–161. https://doi.org/10.1016/S0269-7491(02)00343-3

Turner, A., Fitzer, S., Glegg, G.A., 2008a. Impacts of boat paint chips on the distribution and availability of copper in an English ria. Environ. Pollut. 151, 176–181. https://doi.org/10.1016/j.envpol.2007.02.007

Turner, A., Rees, A., 2016. The environmental impacts and health hazards of abandoned boats in estuaries. Reg. Stud. Mar. Sci. 6, 75–82. https://doi.org/10.1016/j.rsma.2016.03.013

Turner, A., Singh, N., Millard, L., 2008b. Bioaccessibility and bioavailability of Cu and Zn in sediment contaminated by antifouling paint residues. Environ. Sci. Technol. 42, 8740–8746. https://doi.org/10.1021/es801923e

Vermorken, J.B., Vijgh, W.J.F. Van Der, Klein, I., Groeningen, H.E.G., Van, C.J., Hart, G.A.M., Pinedo, H.M., 1986. Pharmacokinetics of free and total platinum species after rapid and prolonged infusions of cisplatin. Clin. Pharmacol. Ther. 39, 136–144. https://doi.org/https://doi.org/10.1038/clpt.1986.24

Waller, C.L., Grif, H.J., Waluda, C.M., Thorpe, S.E., Loaiza, I., Moreno, B., Pacherres, C.O., Hughes, K.A., 2017. Microplastics in the Antarctic marine system: An emerging area of research. Sci. Total Environ. 598, 220–227. https://doi.org/10.1016/j.scitotenv.2017.03.283

Wang, H., Seekamp, I., Malzahn, A., Hagemann, A., Carvajal, A.K., Slizyte, R., Standal, I.B., Handå, A., Reitan, K.I., 2019. Growth and nutritional composition of the polychaete *Hediste diversicolor* (OF Müller, 1776) cultivated on waste from land-based salmon smolt aquaculture. Aquaculture 502, 232–241. https://doi.org/10.1016/j.aquaculture.2018.12.047

WHO, 2017. Depression and other common mental disorders: global health estimates, World Health Organization. https://doi.org/CC BY-NC-SA 3.0 IGO

Wilkinson, J.L., Hooda, P.S., Barker, J., Barton, S., Wilkinson, J.L., Hooda, P.S., Barker, J., Barton, S., 2016. Technology Ecotoxic pharmaceuticals , personal care products , and other emerging contaminants: A review of environmental, receptor-mediated, developmental, and epigenetic toxicity with discussion of proposed toxicity to humans. Crit. Rev. Environ. Sci. Technol. 46, 336–381. https://doi.org/10.1080/10643389.2015.1096876

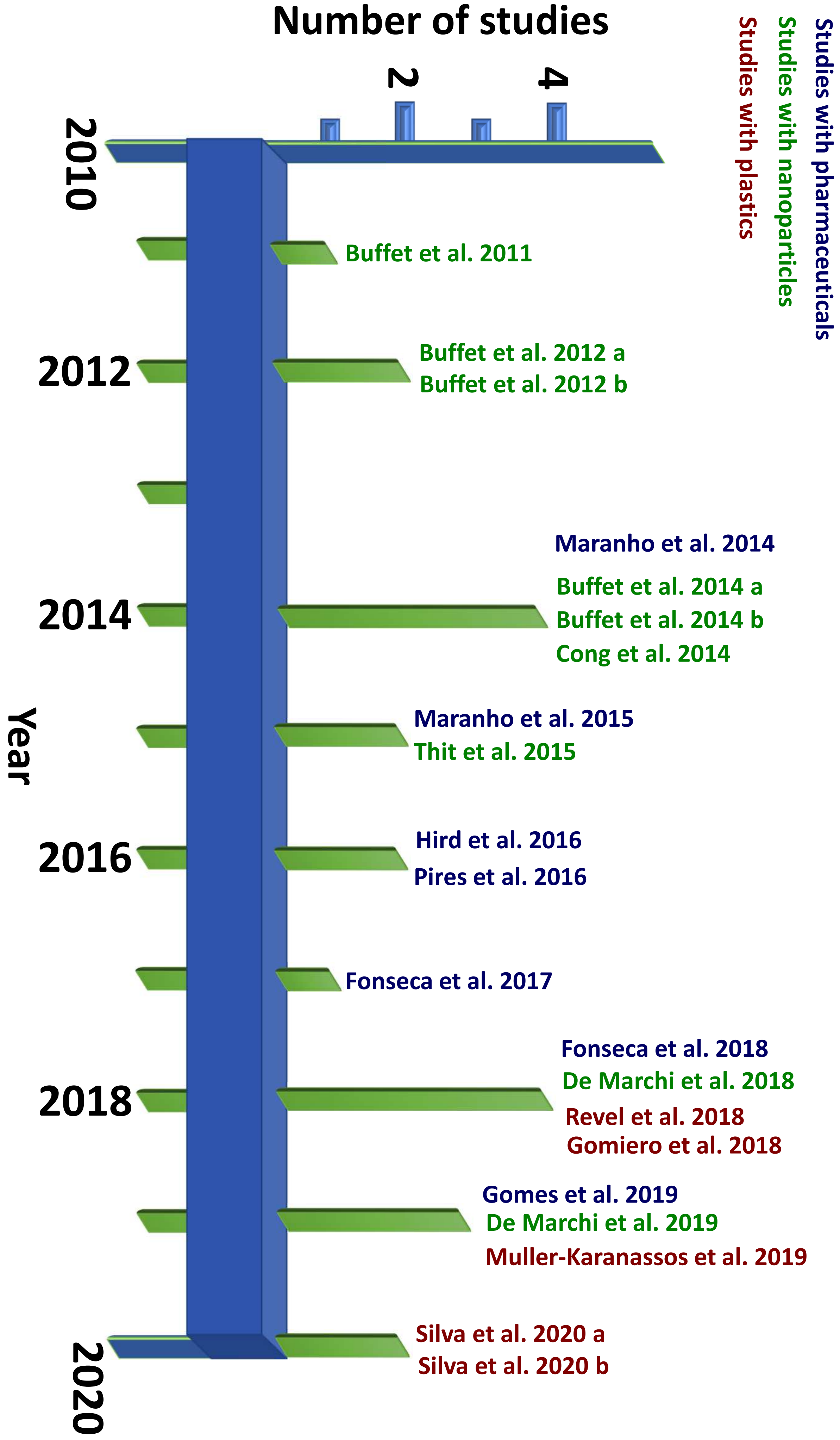
Wilkinson, J.L., Hooda, P.S., Swinden, J., Barker, J., Barton, S., 2018. Spatial (bio)accumulation of pharmaceuticals, illicit drugs, plasticisers, perfluorinated compounds and metabolites in river sediment, aquatic plants and benthic organisms.Environ. Pollut. 234, 864–875. https://doi.org/10.1016/j.envpol.2017.11.090

Zettler, E.R., Mincer, T.J., Amaral-Zettler, L.A., 2013. Life in the “plastisphere”: Microbial communities on plastic marine debris. Environ. Sci. Technol. 47, 7137–7146. https://doi.org/10.1021/es401288x

Zhang, B., Yang, L., Yu, L., Lin, B., Hou, Y., Wu, J., Huang, Q., Han, Y., Guo, L., Ouyang, Q., 2012. Acetylcholinesterase is associated with apoptosis in b cells and contributes to insulin-dependent diabetes mellitus pathogenesis. Acta Biochim Biophys Sin 44, 207–216. https://doi.org/10.1093/abbs/gmr121.Advance

Zhang, X.J., Yang, L., Zhao, Q., Caen, J.P., He, H.Y., Jin, Q.H., Guo, L.H., Alemany, M., Zhang, L.Y., Shi, Y.F., 2002. Induction of acetylcholinesterase expression during apoptosis in various cell types. Cell Death Differ. 9, 790–800. https://doi.org/10.1038/sj.cdd.4401034

Zhou, K., Wang, R., Xu, B., Li, Y., 2006. Synthesis, characterization and catalytic properties of CuO nanocrystals with various shapes. Nanotechnology 17, 3939–3943. https://doi.org/10.1088/0957-4484/17/15/055


Number of studies
2
4
Studies with pharmaceuticals
Studies with nanoparticles
Studies with plastics
Year
2010
2012
2014
2016
2018
2020
Buffet et al. 2011
Buffet et al. 2012 a
Buffet et al. 2012 b
Maranho et al. 2014
Buffet et al. 2014 a
Buffet et al. 2014 b
Cong et al. 2014
Maranho et al. 2015
Thit et al. 2015
Hird et al. 2016
Pires et al. 2016
Fonseca et al. 2017
Fonseca et al. 2018
De Marchi et al. 2018
Revel et al. 2018
Gomiero et al. 2018
Gomes et al. 2019
De Marchi et al. 2019
Muller-Karanassos et al. 2019
Silva et al. 2020 a
Silva et al. 2020 b

Highlights

Hediste diversicolor is a good model for the study of emerging contaminants.

Exposure to emerging contaminants induced oxidative stress.

Emerging contaminants affected burrowing behavior on *H. diversicolor*.

Studies on the effects of plastic contamination in marine invertebrates are scarce.

Conflict of interest: The authors declare no conflict of interest.

With the submission of this manuscript the authors would like to declare: that the reported work is original and has not been published elsewhere, accepted for publication elsewhere or under editorial review for publication elsewhere; and that the content and authorship of the manuscript has been approved by all authors.