Acquiring an evolutionary perspective in marine ecotoxicology to tackle emerging concerns in a rapidly changing ocean

Araceli Rodríguez-Romero[a, b*], Javier R. Viguri[c], Piero Calosi[d]

[a] Departamento de Química Analítica, Facultad de Ciencias del Mar y Ambientales, Universidad de Cádiz. Campus Río San Pedro, Puerto Real, 11510 Cádiz, Spain.

[b] Departamento de Ecología y Gestión Costera, Instituto de Ciencias Marinas de Andalucía (CSIC). Campus Universitario Río San Pedro, 11519, Puerto Real, Spain.

[c] Green Engineering & Resources Research Group (GER), Departamento de Química e Ingeniería de Procesos y Recursos, ETSIIT, Universidad de Cantabria, Avda. de los Castros s/n, 39005 Santander, Cantabria, Spain.

[d] Département de Biologie, Chimie et Géographie, Université du Québec à Rimouski, 300 Allée des Ursulines, Rimouski, QC G5L 3A1, Canada.

*Corresponding author: Araceli Rodríguez Romero; E-mail: araceli.rodriguezromero@uca.es

Abstract

Tens of thousands of anthropogenic chemicals and wastes enter the marine environment each year as a consequence of the ever-increasing anthropogenic activities and demographic growth of the human population, which is majorly concentrated along coastal areas. Marine ecotoxicology has had a crucial role in helping shed light on the fate of chemicals in the environment, and improving our understanding of how they can affect natural ecosystems. However, chemical contamination is not occurring in isolation, but rather against a rapidly changing environmental horizon. Most environmental studies have been focusing on short-term within-generation responses of single life stages of single species to single stressors. As a consequence, one-dimensional ecotoxicology cannot enable us to appreciate the degree and magnitude of future impacts of chemicals on marine ecosystems. Current approaches that lack an evolutionary perspective within the context of ongoing and future local and global stressors will likely lead us to under or over estimations of the impacts that chemicals will exert on marine organisms. It is therefore urgent to define whether marine organisms can acclimate, i.e. adjust their phenotypes through transgenerational plasticity, or rapidly adapt, i.e. realign the population phenotypic performances to maximize fitness, to the new chemical environment within a selective horizon defined by global changes. To foster a significant advancement in this research area, we review briefly the history of ecotoxicology, synthesis our current understanding of the fate and impact of contaminants under global changes, and critically discuss the benefits and challenges of integrative approaches towards developing an evolutionary perspective in marine ecotoxicology: particularly through a multigenerational approach. The inclusion of multigenerational studies in Ecological Risk Assessment framework (ERA) would provide significant and more accurately information to help predict the risks of pollution in a rapidly changing ocean.

Keywords: Evolutionary biology, multigenerational approach, global change, contaminants, plasticity, adaptation.

1. Introduction

The marine environment and human civilization have always been in an intimate relationship, the latter being the main beneficiaries of the resources and ecosystem services provided by the former (Visbek, 2018). However, with the advent of industrialization, this marriage has gone sour! Beyond being a provider of resources for subsistence, heat production and construction, the environment has also become the major dumping ground for our industrial, agricultural, forestry, mining and household waste products (Clayson, 2001; Ahluwalia, 2015; Gaur et al., 2020; Kedzierski et al., 2020). This results in tens of thousands of contaminants entering the marine environment each year (Álvarez-Múñoz et al., 2016; Stauber et al., 2016). In this sense, marine ecotoxicology has played a fundamental role in predicting the potential impacts of these substances on marine ecosystems (Chapman, 2016). Besides, this discipline has developed a unique perspective on the interaction between humans and the environment, as well as essential tools to rapidly assess the health status from populations to ecosystems: such as, for example, tools used in biomonitoring programs and environmental disasters impact assessment, such as mining accidents and oil spills (e.g. Blasco et al.,2002; Riba et al., 2004; Morales-Caselles et al., 2006). Currently, coastal marine environments undergo chronic low levels of contamination, with a marked upward trend due to our explosive demographic growth and ever-increasing activity levels, particularly along coastal areas (Stauber et al., 2016). For example, since 1950s, the amount of plastic waste accumulated in the coastal environment has increased between 4.8 and 12.7 million tons *per* year (Jambeck et al., 2015). However, chemical contamination is not occurring in isolation, but against a changing environmental oceanscape due to ongoing global change (GC). This will incur changes to organism and ecosystem functions and their responses to pollutants, with important implications for the reliability and usefulness of indicators developed to date. Indeed, studying interactions among environmental stressors has become a major focus in environmental studies (Piggott et al. 2015; Côté et al. 2016). In this sense, several studies have recently focused on the combined impact of GC and pollutants, addressing the potential impact of industry and household wastes within the changing environmental oceanscape (see in Noyes et al., 2009; Kimberly and Salice, 2015). However, these studies are based on short-term (within-generation) single life-stage exposure experiments. Limitations of this approach arise with respect to species possessing complex life cycles (i.e. the vast majority of marine organisms), and has been discussed (Coutellec and Barata, 2013; Calosi et al., 2016). This is particularly important in light of recent efforts to shift the focus of GC biology toward the characterization of species transgenerational plasticity and rapid evolutionary responses (Sunday et al. 2014; Munday et al., 2013; Reusch, 2014; Calosi et al., 2016).

Ecotoxicological studies conducted to date have largely overlooked the interaction of contaminants with future GC drivers, and have not considered the role that plastic and adaptive responses will play within this context. This likely under or overestimates the impacts that pollutants exert on biological systems within the rapidly changing environmental oceanscape. Here, we discuss the limitation of having largely ignored fundamental issues in the field of ecotoxicology such as: Will marine organisms be able to cope with the combined exposure to contaminants and GC drivers, whilst considering the cumulative effects over multiple life-stages and/or over multiple generations? Do organisms have the capacity for beneficial trans-generational plasticity (TGP) and to rapidly adapt to combined contaminants and GC scenarios? What are the fitness consequences of the combined exposure to contaminants and GC drivers over successive life stages and generations in marine organisms? Finally, as the central challenge for ecotoxicologists is that to acquire a critical understanding on impacts that are in the making (and even better preventively) instead of attempting to unravel its mechanisms *a posteriori*, it is important that we ask the question: Is ecotoxicology responding properly to emerging toxicological concerns in the rapidly changing environmental oceanscape?

In order to achieve our aims, we first (1) provide a brief historical perspective of ecotoxicology. (2) We then critically review our current understanding of the general biological impacts of contaminants within the context of global ocean changes by using selected representative studies. (3) We explore the advantages, challenges and limitations of using field and multigenerational approaches to investigate contaminants' impacts within the context of a rapidly changing environmental oceanscape. Finally, (4) we discuss the much-needed paradigm shift (and usefulness) required in marine ecotoxicology to acquire an evolutionary perspective on combined impacts of chemicals, whilst accounting for the multidimensionality of global changes, in order to inform future effective protection strategies and conservation policies.

2. A brief history of ecotoxicology

In the 1940s-1950s, as a response to the environmental implications of expansive human activity, emerged the field of ***Environmental Toxicology*** (Rattner, 2009) in the 1940s-1950s. It was concerned with studying the effects of toxicants on biological systems, and it focused on the screening of exogenous substances in the environment to identify those that may be potentially harmful (Leblanc, 2004). Ecological considerations were not included in these studies, and they were carried out with species easily obtained and cultured under laboratory conditions, whilst targeting parameters, endpoints and proxies easy to measure and reproduce (Chapman, 2002). However, "a single species for different purposes" is not a philosophy that allows us to reliably predict the health status of entire ecosystems under an exogenous pressure. Each ecosystem has its own set of key species and unique species-interactions. A relevant example of this approach is the widespread use of freshwater species to assess marine ecosystem health and *vice versa* (Chapman, 2002). Prominent examples of this are that of the toxicity tests carried out using (i) the freshwater water flea *Daphnia magna* (O. F. Müller, 1785), employed in many countries for biomonitoring programs to assess the impacts of wastewater discharges in marine waters, and (ii) the marine bioluminescence bacteria *Vibrio fischeri* to determine toxicity effects of contaminants in freshwater systems. The wide use of the latter has been adapted in some legal frameworks beyond marine systems, as a criterion for the characterization and classification of solid industrial waste, through the toxicity of their leachates, with implications for its management (Viguri et al., 2001; Coz et al., 2009; Abbas et al., 2018).

Derived from *Environmental toxicology*, and intending to expand beyond the effects of potentially hazardous substances at the individual level, the research field of ***Ecotoxicology*** is defined as *the assessment and prediction of the ecological and toxicological effects on natural populations, communities and ecosystems as a result of realistic exposure conditions to chemical contaminants* (Forbes and Forbes, 1994; Luoma et al., 1996; Chapman, 2002). *Ecotoxicology* informs not only on the fate of contaminants in the environment but also on the mechanisms, and ins and outs, of their transport and transformation before their final destination. This field plays a major role in decision-making within the framework of Ecological Risk Assessment (ERA) (Chapman, 2002). However, as for all disciplines it has its limitations. *Ecotoxicology* investigates the short-term biological impacts of contaminants, without taking into account organisms' long-term responses to the chronic exposure to xenobiotic substances, and ultimately their evolutionary consequences on populations. Some studies have highlighted the need to incorporate evolutionary processes in ecotoxicology studies in hopes of integrating these effects in ERA (Bickham et al., 2000 ; Van Straalen and Timmermans, 2002; Breitholtz et al., 2006; Morgan et al., 2007; Coutellec and Barata 2011; Dallinger and Höckner 2013).

Evolutionary processes can alter the responses recorded during ecotoxicological experiments. Adaptive events could appear when populations are chronically exposed to pollution, giving rise to different responses if they are compared with unexposed populations (Barata et al., 2002; Coutellec and Barata, 2011). Other issues not addressed in toxicity tests (such as genetic diversity, selective processes, inbreeding or epigenetic effects) may confound the interpretations of observed effects (Barata et al., 2000; Nowak et al., 2007; Coutellec and Barata, 2011). Severe reductions in survival and reproductive output, as well as increases in behavioural syndromes of individuals and populations are possible consequences of exposure to toxic substances, which can ultimately translate in changes in genetic diversity, allelic or genotypic frequencies, modifications in dispersal patterns or gene flow and increased mutation rates (Bickham, 2011; Oziolor et al., 2016). In the last decade, this has prompted researchers to propose the development of an ecotoxicology model considering a more holistic perspective (Chapman et al., 2002; Snape et al., 2004; Oziolor et al., 2016), to take into account the challenges that arise from a rapidly changing environment. Attaining these objectives is paramount to pursuing current and future challenges in the field of *Ecotoxicology*.

3. The fate of contaminants under ocean global change

Global change (i.e. anthropogenic global change) is mainly due to the tremendous and rapid demographic expansion of the human population since the Industrial Revolution, and the consequent changes in human society and life standards (Cohen, 2012). However, improving human well-being involves a continuous increase in the use of resources and disposal of contaminants in the natural environment which has accelerated the pace of natural changes of our planet (Waters et al., 2016). Ultimately, the great environmental changes that our planet experiences now, and in the near future will have long-lasting ecosystems effects, and in turn impact human well-being and health (Buttler and McFarlane, 2018).

GC in the ocean includes eutrophication, coastal hypoxia, ocean warming (OW), sea ice loss and sea level rise, ultraviolet (UV) radiation increase, coastal and global ocean acidification

(OA), salinity changes due to freshening (flash floods and ice melting), tropicalization of the climate, habitat loss, over exploitation of fish stocks, changes in species distributions and ecosystems structure and functioning, coastal urban sprawl and pollution (IPCC, 2014).

GC drivers can indirectly create new usage trends of chemicals products, as well as affect directly their transport and fate within the marine environment (Artigas et al., 2012: Balbus et al., 2013) and the degree of pollutant exposure to marine organisms (Noyes et al., 2009; Hooper et al., 2013; Kimberly and Salice, 2015) (see Fig.1). For example, it has been demonstrated that a reduction of pH in seawater, due to the increase of atmospheric pCO_2 levels, changes the solubility, absorption, the rate of redox processes and toxicity of metals (Millero et al., 2009). Acute seawater acidification processes impact the factors controlling the release of trace metals from sediments, enhancing the solubility of most trace metals because of the influence of pH on the dissolved organic matter, dissolution of carbonate, speciation of sulphide and iron (oxy)hydroxide minerals, the adsorption/desorption surface reactions and ion exchange processes (Martin-Torre et al., 2015). These mechanisms have been included into the kinetic modeling of Zn, Pb, Cd, Ni, Cr, Cu and As release from sediments under diverse seawater acidification scenarios, predicting important releases of these contaminants into the water column (Martin-Torre et al., 2016), thus increasing their availability to marine biota (Millero et al., 2009). In this sense, some studies have indicated that OA increases the toxicity of contaminated sediments (Roberts et al., 2013; Rodríguez-Romero et al., 2014a, b) and could exacerbate metal bioaccumulation in certain organisms (e.g. Rodríguez-Romero et al., 2014b). Simultaneously, the introduction of chemicals in seawater changes the UV radiation dynamics. Organic and inorganic chemical UV filters, that are incorporated as ingredients in the formulation of sunscreens, are released, degraded and/or transformed under solar UV radiation in the marine environment to chemicals with potentially toxic effects on marine organisms (Sánchez-Quiles and Tovar, 2014; Ramos et al., 2015). A recent study demonstrated that UV radiation plays a fundamental role in the mobilization of dissolved trace metals (i.e. Al, Cd, Cu, Co, Mn, Mo, Ni, Pb, and Ti) and inorganic nutrients (i.e. SiO_2, P-$PO_4{}^{3-}$, and N-$NO_3{}^{-}$) from sunscreen products used by beachgoers in seawater (Rodríguez-Romero et al., 2019).

On the other hand, temperature is the other environmental stressor that most impacts the environmental fate of contaminants, particularly regarding persistent organic pollutants (POP_S). Melting of glacial ice caused by warming leads to sea level rise. With the subsequent increase in intensity and frequency of storm events, further erosion of contaminated soils ultimately contributes to greater POP concentrations in coastal waters (Ma el al., 2016). Climate warming also leads to higher rates of methylation and volatilization processes of mercury from sediments accumulated from the past and in turn leads to a remobilization of this metal (Bogdal and Scheringer, 2011). As OA, OW not only affects the fate of contaminants in the environment, but also their toxicity. In general, the toxicity (e.g. higher bioaccumulation rates due to enhanced gill ventilation by organisms) increases with temperature. In contrast, an increase of temperature can also lead to higher rates of depuration and detoxification mechanisms (Stauber et al., 2016). Therefore, chemical contamination is not occurring in isolation, but occurs against a radically changing environmental oceanscape, which is significantly altering fundamental oceanic ecological processes and functions (e.g. Nagelkerken and Connell, 2015; Ullah et al., 2018; Havenhand et al., 2019).

4. Assessing the biological impacts of marine contamination under GC environmental scenarios: Multiple stressor experiments

A number of studies have investigated the implications of combined exposure to multiple environmental changes (e.g. pCO_2/pH, temperature, salinity, ultraviolet radiation) under laboratory conditions (e.g. Egilsdottir et al., 2009; Zhangh et al., 2014; Pires et al., 2015; Velez et al., 2016; Ramajo et al., 2016; Freitas et al., 2017a; Araujo et al., 2018). The results reported by these studies reflect the lack (with few exceptions) of consistent patterns describing the different responses of marine species to combinations of multiple drivers (Johson and Carpenter, 2012; Duarte et al., 2014; Kavousi et al., 2015). The interactions of these drivers often produce non-linear changes in aquatic organismal fitness and community dynamics (Boyd et al.,, 2015; Piggott et al., 2015; Côté et al., 2016; Sabater et al., 2019) and their variation patterns depend on the species and choice of response (Matozzo et al., 2013).

In the last decade, the number of studies that have addressed the combined effects of contaminants within the context of ocean GC drivers has been on the rise (e.g. Nardi et al., 2017; Malvaut et al., 2016, 2018a; Munari et al., 2020). As for studies of other environmental stressor interactions, a wide variety of results have been obtained, with metal(oid)s and OA being the most studied combination in the last years: see for example Lacoue-Labarthe et al. (2009, 2011, 2012, 2018), Houlbreque et al. (2012), Fitzer et al., 2013; Ivanina et al., 2013, 2014, 2015, 2016; Ivanina and Sokolova, 2013, 2015; Campbell et al., 2014; Lewis et al., 2013, 2016 Benedetti et al., 2016; Shi et al., 2016; Nardi et al., 2017, 2018; Dorey et al., 2018a).

On the other hand, there is no established trend describing the responses to a combined exposure of contaminants and environmental stressors. A complex pattern of response, which depends on the species, pollutant (including the concentration level of exposure) and the environmental stressor studied have been observed.

A synergistic positive pattern has been detected under the exposure to environmental stressors (i.e. OW, OA and changes in salinity levels) in combination with some metals. An increase in the toxicological effects of Cu has been found in the pale anemone *Exaiptasia pallida* (Agassiz, 1864), the harpacticoid copepod *Harpacticus sp*, the staghorn coral *Acropora cervicornis* (Lamarck, 1816) and in the Portuguese and Suminoe oysters *Crassostrea angulate* (Lamarck, 1819) and *Crassostrea rivularis* (Gould, 1861) (Patel and Bielmyer-Fraser, 2015; Sidiqqi and Bielmyer-Fraser, 2015; Bielmyer-Fraser et al., 2018; Scanes et al., 2018; Huang et al., 2018; Holan et al., 2019). The same pattern has been recorded for Cd or/and As toxicity in the Mediterranean mussel *Mytilus galloprovincialis* (Lamarck, 1819), the smooth scallop *Flexopecten glaber* (Linnaeus, 1758), C. angulata and the Japanese oyster *Crassostrea gigas* (Thunberg, 1793) (Nardi et al., 2017, 2018; Coppola et al., 2018; Moreira et al., 2018a,b,c). Notably, oxidative stress, reduced metabolism, increased energy demands and impacts on capacity to detoxify metals have been reported in bivalves among other responses (Hawkins and Sokolova et al., 2017; Coppola et al., 2018; Moreira et al., 2018a; Scanes et al., 2018).

Although the majority of studies indicate an increase of metal bioaccumulation in combination with OA (e.g. Velez et al., 2016; Duckworth et al., 2017, Cao et al., 2018), it has been demonstrated that bioaccumulation responses are specific to each metal (Lacoue-Labarthe et al., 2018; Dorey et al., 2018b). Synergistic effects of OW and OA, and Cd bioaccumulation has been also shown in the Antarctic scallop *Adamussium colbecki* (Smith, 1902) with different sensitivity among analysed tissues (Benedetti et al., 2016). In combination with OA, an increased accumulation of Co but not Cs in the Manila clam *Ruditapes philippinarum* (Adams & Reeve, 1850) has been recorded by Sezer et al., (2018). However, no differences in Hg accumulation or tolerance were found in *M. galloprovinciallis* and the sandworm polychaete *Hediste diversicolor* (O.F. Müller, 1776) when exposed to OW and OA conditions respectively (Freitas et al., 2017b, 2017c). Freitas et al. (2017b, 2017c) concluded that metal bioaccumulation could decrease when organisms are exposed to high temperature conditions for long periods *via* diminishing their metabolism. Evidence using *M. galloprovincialis* demonstrates that the impacts caused to the oxidative stress by the combination of Hg contamination and OW were similar to the ones induced by OW acting alone (Coppola et al., 2017).

On the other hand, antagonistic toxicity interactions between metals and OA have been reported in different marine organisms such as algae, corals, mollusks and crustaceans (e.g. Pascal et al., 2010; Lacoue-Labarthe et al., 2012; Gao et al., 2017; Marangoni et al., 2019). For example, Pascal et al., 2010 observed a decrease of Cd and Cu uptake in the coastal copepod *Amphiascoides atopus* (Lotufo & Fleeger, 1995) and later, Lacoue-Labarthe et al., (2012) reported similar patterns for Cd in the hatchling tissue of the common cuttlefish *Sepia officinalis* (Linnaeus, 1758). A decrease of metals uptake could be due to an increase of H^+ caused by OA, which can result in a competition for binding sites between metals and H^+, making surface sites less available to absorb metals (Pascal et al., 2010). Additionally, Gao et al. (2017) indicated that a moderate increase of pCO_2 could mitigate the toxicity of Cu in the seaweed *Ulva prolifera* (Muller, 1778).

Despite the lack of attention given to other types of chemical contaminants, findings show that the interactions between global-related abiotic change and pharmaceuticals (e.g. carbamazepine, velanfaxina) may alter organisms sensitivity and may aggravate the toxicity of a tested substance (Freitas et al., 2016; Maulvaut et al., 2018c, 2019) affecting its uptake and elimination rate (Maulvaut et al., 2018b). For example, although oxidative stress responses in adults of *R. philippinarum* and *M. galloprovincialis* were more influenced by

OA than by the combination of reduced pH and diclofenac (Munari et al., 2018), larval stage *R. philippinarum* exposed to diclofenac under OA conditions experienced higher mortality and morphological malformations compared to the exposure to single stressors in isolation (Munari et al., 2016). However, the combined effect of low pH and the pharmaceutical carbamazepine on the peppery furrow shell clam *Scrobicularia plana* (Da Costa, 1778), was lower than each stressor acting in isolation, and the impacts were more pronounced in the population of clams from the contaminated area (Freitas et al., 2015). A later study demonstrated that the toxicity of carbamazepine synergistically increased under OA conditions, with reduced survival and increased oxidative stress in *S. plana* (Freitas et al., 2016). Similarly, idiosyncratic responses have been reported for the ciliates *Euplotes* crassus *(Dujardin, 1841)* under OW conditions. On the one hand, a rise in survival rate was described after 24 h of exposure in combination with the antibiotic oxytetracycline; on the other, a decline of tolerance after 24 h of exposure in combination with copper was noted (Gomiero and Viarego, 2014).

This variety of responses is also found for other contaminants such as nanoparticles and herbicides. For example, alleviation of toxicity with a modest increase of temperature was observed on the larva of the collector sea urchin *Tripneustes gratilla* (Linneaus, 1758) exposed to nano-Zn-oxide. Nevertheless, an enhanced effect of oxidative stress in *H. diversicolor* exposed to carbon nanoparticles under OA conditions has been recorded (De Marchi et al., 2019). In the same line, Shang et al., 2020 observed an enhanced of toxicity of TiO_2 nanoparticles on the Korean mussel *Mytilus coruscus* (Gould, 1861) under acidification conditions, which could adversely affect its feeding metabolism. A one-year exposure experiment found a noticeable temperature/S-metolachlor (herbicide) and Cu toxicity relationship with significant synergistic effects on the embryo-larval development of *C. gigas*

(Gamain et al., 2017). An increased immune toxicity in the blood of the blood cockle *Tegillarca granosa* (Linnaeus, 1758) was recorded after the exposure to the persistent organic pollutant benzo[a]pyrene under future OA scenarios, which could make individuals more susceptible to pathogenic challenges (Su et al., 2017).

Despite all efforts to date, the indirect and interactive impacts of GC drivers on marine organisms' responses to environmental contaminants are scarcely explored (Nardi et al., 2017). Studies on how multiple stressors interact affecting marine and coastal ecosystems are essential to accurately identify the level of contaminants that will be detrimental for biological systems under future global ocean scenarios (Schiedek et al., 2007; Nikinmaa, 2013; Lewis et al., 2013; Campbell et al., 2014; Manciocco et al., 2014; Maulvaut et al., 2018c). However, the majority of multistressor experiments have focused on single stages of the life cycle of a marine species, which are characterized in the great majority of cases by extremely complex life cycles (c.f. Chakravarti et al., 2016, Gibbin et al., 2017a, 2017b; Thibault et al., 2020). This ultimately hinders our ability to account for organisms' capacity to cope with a changing environment by adjusting (*i.e.* acclimating *via* phenotypic plasticity) and adapting (*via* selection). Although these experiments provide important information, they may overestimate or underestimate the "real" impact associated with new GC scenarios on marine species. Long-term exposure experiments, across multiple (ideally all) life stages charactering the complex life cycles of the vast majority of marine species are required. This entails a laborious endeavor in terms of time and resources, an issue that researchers need however to face in these challenging times (Byrne and Przeslawski, 2013).

5. Approaches for acquiring an evolutionary perspective on ecotoxicology under GC stressors

The combined exposure to GC drivers and chemical pollution represents an unprecedented hazard for marine life and marine ecosystem functions and services, threatening to lower organismal physiological and ecological performances and ultimately their fitness (Noyes et al., 2009). However, to date, most studies have been focusing on short-term responses of single species to single GC stressors (Kroeker et al., 2013; Thomsen et al., 2017), largely ignoring the importance of species ability for plastic responses (and in particular the suite of responses under the umbrella of transgenerational plasticity) and rapid adaptation. These two mechanisms help define species' ability to cope under rapid environmental changes. Consequently, our understanding of the plastic and evolutionary potential of marine organisms in the face of rapid GC is extremely limited (Kelly and Hofmann, 2013; Munday et al., 2013; Sunday et al., 2014; Reusch, 2014, Kimberly and Salice, 2015; Thomsen et al., 2017). More specifically, we have so far acquired a limited understanding of carry over, cumulative and delayed effects linked to plastic responses emerging from the exposure to contaminants across different life stages and generations, in marine organisms exposed to future ocean GC scenarios. Plastic responses can be beneficial (Huey et al. 1999) and non-beneficial (Relyea, 2002), meaning they can bring an advantage or a disadvantage to the organisms expressing such plasticity in a new environment. Beneficial plastic responses can buffer the negative impacts (completely or partially) of contaminants and GC drivers (e.g. Chakravarti et al., 2016, Chen et al., 2018), effectively enabling an organism to maintain its regular functioning and ideally fitness levels, with its underlying costs (Hoffmann 1995; Jarrold et al., 2019). This 'buffering' ability is an essential mechanism enabling organisms to face periodic fluctuations and chronic changes in their natural environment (Ghalambor et al., 2007), and within the context of GC, can help organisms maintaining high performance and fitness levels, potentially gaining time for evolutionary processes to occur. The acquisition of a more in-depth understanding of the potential impacts of contaminants in the rapidly changing environmental oceanscape on marine organisms is essential.

5.1 Field experiments as a tool for long term in-situ observations

Natural analogues of future environmental conditions can be found in marine ecosystem. These natural systems can operate as tools for the characterization of the responsiveness or adaptive potential of marine organisms to the combined impacts of environmental pollution under future GC scenarios. Adaptation occurs as a result of natural selection acting on the phenotypic / genotypic combinations existing within populations. There is increasing evidence that the ability to adapt to environmental stress may depend on the environmental history of previous life stages (Marshall and Morgan, 2011). For example, on a time scale different from that at which GC is taking place, adaptation to environments with high CO_2 concentrations or high CO_2 variability has been observed in a number of marine organisms (Calosi et al., 2013; Pespeni et al., 2013; Conradi et al., 2019; c.f. Lucey et al. 2016). However, in some cases, the inability to adapt to high CO_2 conditions has been shown (see for example Lucey et al. 2016). Some examples of natural analogues of GC are included here.

1) *Estuaries and coastal areas* possess a strong space-temporal variability in terms of abiotic parameters, and display large environmental variability in temperature, salinity, pH, oxygen concentration, and nutrient load. In addition, these areas act as sinks for contaminant discharges by rivers: for example, showing high levels of diverse metal concentrations. In some cases, these metal loads discharged by rivers originate from mining activities from ancient civilizations (see Davis et al., 2000;

LeBlanc et al., 2000). However, the variability showed by coastlines and estuaries, in many cases, is already greater than projections expected under future conditions (Duarte et al. 2013).

2) *Underwater CO_2 vents* located for example in the Mediterranean Sea, Papua New Guinea, Atlantic Sea and Bay of Plenty in New Zealand are examples of vent systems which have been used as analogues for future OA (see Burrell et al., 2015, Hernández et al., 2016; Lamare et al., 2016; González-Delgado and Hernández, 2018; Rastrick et al. 2018). In some of these systems, pH gradient interacts simultaneously with other stressors, such as temperature (e.g. New Caledonia Lagoon), salinity, metal and metalloids concentrations (Vizzini et al., 2013). For example, hydrothermal seeps with high pCO_2 levels offer scenarios mimicking the toxicity of metal(oid)s under future GC ocean conditions to study acclimatization/local adaptation in organisms that have lived in these conditions for extended periods of time (Ricevuto et al., 2016; Pichler et al., 2019).

3) *Upwelling areas*. Upwelling events naturally bring low-oxygen, high-CO_2 and low-temperature waters, often undersaturated with respect to calcium carbonate, to nearshore environments (Booth et al., 2012). These waters are rich in trace elements and nutrients (Valdes et al., 2008) and therefore, these systems play an important role in the study of future impacts of multiple stressors. For example, studies suggest that natural variability in upwelling areas may promote acclimation and adaptation potential in inhabiting scallops to OA (Lardies et al., 2017).

The use of these natural systems can enable us to study the implications of organismal chronic exposure to future ocean GC scenarios in natural populations and communities. The information obtained from these studies allows us to investigate the cumulative effects of multiple stressors-induced by *in situ* evolutionary (Calosi et al., 2013) and ecological processes (Kroeker et al., 2017). Although the great advantage of this approach includes a more realistic conditions than laboratory bioassays (Barry et al., 2010), field studies are also constrained by a number of factors, such as: (i) the lack of true representative replicates and control treatments (Alexander et al., 2016); (ii) the confounding impacts of secondary environmental factors acting simultaneously in the natural environment, indistinguishable from the main factors of interest (Cornwall and Hurd, 2016). Non-controlled natural processes may lead to variation in response variables studied (Alexander et al., 2016). Despite of this, these natural systems are considered an excellent tool to validate the responses observed in laboratory experiments. This combination could avoid the complex web of confounding drivers observed in natural analogues (Rastrick et al. 2018).

5.2. Multigenerational approach as a tool to assess the long-term implications of ocean global changes: advantages and limitations

Multi-generational experiments are an effective tool to assess species' capacity for plastic responses to environmental stressors from natural and anthropogenic sources. This approach addresses the potential for evolutionary changes in species by unravelling traits that are genetically correlated with characteristics that are direct objects of selection (Gilchrist et al 1997; Munday et al., 2013). Understanding such correlated traits is crucial in making predictions of species and populations' responses to rapid ocean changes (Pistevos et al., 2011). Therefore, multi-generational experiments can provide valuable information on the evolutionary changes that may occur under new environmental scenarios (Collins and Bell, 2004; Donelson and Munday, 2015; Rodríguez-Romero et al., 2015; Chakravarti et al., 2016; Gibbin et al., 2017b; Thibault et al., 2020).

Trans-generational plasticity is a mechanism which can improve performance across generations (Salinas et al. 2013, Calosi et al. 2016), and is defined as a non-genetic process whereby the environmental conditions experienced by a parent significantly alters its own phenotype, and through this alters the fitness, the performance and the plasticity of their offspring (Badyaev and Uller, 2009). TGP has the potential for adaptive significance, facilitating trans-generational acclimation and thus improving offspring survival and fitness, but can also have deleterious effects (Marshall and Uller, 2007). For example, some studies show that offspring are better able to cope with elevated concentrations of CO_2 if their parents have experienced similar conditions (Miller et al, 2012; Parker et al, 2012; Shama et al., 2016). Nevertheless, it has also been shown that parental and grandparental effects may lead to decreased offspring capacities (Dupont et al., 2013; Shama and Wegner, 2014). On the other hand, Kelly and Hofmann (2013) suggested that some populations will display reduced plastic and adaptation capacity to face changes in temperature. Either way, TGP can be an important source of variation in performances between individuals, ultimately influencing short-term selection and the evolutionary trajectories of populations (Mousseau and Fox, 1998; Badyaev and Uller, 2009). Differently, adaptation through existing phenotypes requires genetically based variation to stress tolerance within a natural population (Sunday et al., 2014). Therefore, standing variation for multiple stressors tolerance within populations will ultimately determine their capacity to mount an evolutionary response to the ongoing GC in the oceans.

In the last years, the number of multi-generational studies spanning multiple stages of the biological cycle is increasing, which is allowing the investigation of the ability to adapt, and the extent of adaptation (e.g. Sunday et al., 2011; Fitzer et al., 2013; Foo et al., 2012; Parker et al., 2012; Rodriguez-Romero et al., 2015; Chakravarti et al 2016; Shama et al., 2016 Munday et al., 2016; Gibbin et al., 2017b).

Concerning the impact of pollutants in aquatic biotic systems, several multigenerational studies have been conducted using freshwater species (e.g. Gardestrom et al., 2008; Sowers et al., 2009; Corrales et al., 2014; Seeman et al., 2015; Knecht et al., 2017; Bal et al., 2017a, 2017b; Reátegui-Zirena et al., 2017; González-Pérez et al., 2018). In this sense, *Daphnia sp* represents the species used *par excellence* in these type of studies (see for example Clubbs and Brooks, 2007; Dietrich et al., 2010; Plaire et al., 2013; Kim et al., 2014; Jeong et al., 2015; Liu et al., 2017; Giraudo et al., 2017; Reis et al., 2018; De Liguoro et al., 2019; Chatterjee et al., 2019; Araujo et al., 2019). Marine models have not been extensively used in this sense, and only a few studies have focused on the impact of multigenerational exposure to chemical contaminants in marine organisms (Kwok et al., 2009; Sun et al., 2014, 2018; Li et al., 2015; Xu et al., 2016; Krause et al., 2017; Chen et al., 2018; Po and Chiu, 2018; Guyon et al., 2018). In this sense, copepods are the study species most used in these investigations. The results obtained from these studies have showed, for example, an increased tolerance of copepods to different contaminants such as oil, 4-methylbenzylidene camphor (ultraviolet filter), mercury, copper and tributyltin oxide (TBTO) (Krause et al., 2017; Chen et al., 2018; Sun et al., 2014; Li et al., 2015; Xu et al., 2016). Plastic physiological adaptation, transgenerational genetic and/or epigenetic changes are some suggested explanations for the tolerance acquired by copepods after a multigenerational exposure (Kwok et al., 2009; Li et al., 2015; Xu et al., 2016; Chen et al., 2018).

The increasing number of multigenerational studies is improving our understanding of marine organisms to buffer and adapt to future GC in marine ecosystems. However, due to the novelty of these studies, the majority of them only include one environmental stressor, even though the future environmental oceanscape will harbor multiple GC drivers acting in combination (Donelson et al., 2018, c.f. Chakravarti et al. 2016, Gibbin et al. 2017a, 2017b; Jarrold et al. 2019, Thibault et al., 2020).

To our knowledge, only a very limited number of publications have evaluated the multigenerational effects of chronic exposure to pollutants in combination with other environmental stressors (e.g. OA and OW) in aquatic environments (e.g. Fitzer et al., 2013; De Counter and Brander et al., 2017; Li et al., 2017; Wang et al., 2017). In some of these studies, authors indicated that the phenotypic plasticity could be responsible for the regulation of tolerance limits in response to the combined effects of multiple stressors. The endpoints measured in these cited studies are reporting in Table 1.

Although phenotypic plasticity provides an important mechanism to cope with changes in environmental conditions in the short term (Fusco and Minelli, 2010), and may itself evolve by natural selection (Scheiner, 1993), there are limits and costs to plasticity responses (Auld et al., 2010; DeWitt, 1998). So, it is unlikely to provide a long-term adaptation solution for rapid GC in oceans (Gienapp et al., 2008). Nevertheless, plastic or adaptive responses cannot be established using multigenerational experiment alone. We require employing mutual transplants assays to collect signs of adaptation (see Fig. 2), as well as collect genetic evidence for the molecular evolution of laboratory populations kept under experimental conditions (DeWitt et al., 2016). Adaptation can also be determined by using a quantitative genetic approach, which entails crossing individuals from different treatments and pedigree experimental designs (Munday et al., 2013; Sunday et al., 2014).

Another limitation of the use of multigenerational approach is represented by the difficulty in using this approach in long-lived organisms and species that are not easy to culture under laboratory conditions. The capacity for adaptation of long-generation long-lived species under GC scenarios is garnering interest due to, in many cases, a considerable commercial interest for some of these species (such as lobsters, oysters and fish among others). In these cases, conducting multigenerational experiments is too great a challenge from a logistic (e.g. investment of a greater set of material, technical and human resources) and funding perspective. These experiments can last years, for species of economic and conservation importance, if at least two or three generations are to be characterized. Consequently, multigenerational experiments are most feasible using species with short generation time. In this sense, these experiments are best used as proof of concept rather than relevant tests for specific species. To this, it must be stated that a high risk in terms of scientific productivity (i.e. number of publications) is associated with this kind of approach, where the objectives are achieved (if ever!) only on the very long term.

Despite these limitations, multigenerational studies provide an exceptional experimental tool by developing a more comprehensive understanding of the *ensemble* of carry over, cumulative, parental and selection effects. It is undeniable that this approach is an essential tool that merits integration with classic ecotoxicological studies, if we are to improve our predictions on how marine biodiversity and ecosystem functions will be affected by pollutants in combination with ongoing global changes.

6. Environmental risk assessment (ERA) in a GC framework: Conclusions and perspectives

In this paper we discuss the need to acquire a new perspective for the investigation of the effects of chemicals in a rapidly changing environmental oceanscape. This requires the development of a new comprehensive framework for the field of ecotoxicology, that fully integrates plasticity, TGP and rapid adaptation. Such a framework will be much better suited to appropriately guide and support environmental managers in their decisions making processes, promote adaptive solutions, and foster the preservation of biodiversity levels and natural resources.

It is important to recall that marine ecotoxicology plays a fundamental role in all components of ERA, even in the applied one (i.e. risk management), providing essential information about the potential impacts of stressors through toxicity tests (acute and chronic responses) as a main tool (Chapman, 2016). Controversially, within the framework of ERA, the role of these GC stressors in affecting the toxicity of chemical pollution is not considered yet. A fundamental shift in the focus and approach used in marine ecotoxicology is required in order to firmly advance our current understanding of the potential impacts caused by the interaction between pollution and other GC drivers, as well as the integration of GC evolutionary biology concepts and principles within the context of marine ecotoxicology. Furthermore, we are living in a new geological era of unprecedented environmental changes, which is driven by the exponential growth of the human population and human activities: the so called Anthropocene (Waters et al., 2016). This extends to the World's oceans, and we need to face these ongoing and emerging concerns. Thus, ERA must not be merely constrained to chemicals (Filser, 2008; Landis et al., 2013).

Marine ecotoxicology has a new challenge within the ERA framework and will need to evolve to provide useful information to empower stakeholders for making solid science-informed adaptive decisions (Chapman et al., 2017). As we know, toxicity tests used currently in ERA have several gaps, which limit our ability to accurately predict the future of marine ecosystems. Integrating a multigenerational perspective within the current ERA framework will ensure a coherent evolution of ERA in these challenging times. The inclusion of multigenerational studies in ERA should provide environmental modelers, conservationists and policy makers with new, significant and more balanced (i.e. less biased by over and under-estimations) information to help predict the risks of pollution in a rapidly changing ocean, and implement appropriate conservation guidelines and legislation to preserve natural resources and ecosystems. The complexity and diversity of the response across taxa, generations and stressors makes certainly difficult to operationalize these studies for all species, and make them applicable to all scenarios. Despite these limitations, for the implementation of multigenerational studies in ERA, two main standards should be considered: 1) the use of a number of fast generation (days to few weeks) species that can be easily cultured under global changes conditions in the laboratory, and thus used as model organisms (Krogh 1929); and 2) focus majorly on fitness measures (rather than only survival response) as endpoints. Both these aspects can be relatively easily implemented in the future ERA framework, making it more solid and reliable in providing longer-term implication of pollutant impacts within the context of global changes. Finally, in order to establish guidelines for the implementation of this new perspective within the national and international legal and management frameworks for environmental regulation of contaminants, we will require to create a discussion forum: designed specifically to rapidly identify forward solutions, and establish a sequence of stepping stones to enable the implementation of transgenerational plastic and rapid adaptation effects within ERA. This is paramount given the time-sensitive nature of the issues at stakes.

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Author contributions

All authors participated in the preliminary discussion leading to this work and in the drafting of this manuscript and discussed all topics related to this discussion manuscript.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

Abbas, M., Adil, M., Ehtisham-ul-Haque, S., Munir, B., Yameenb, M., Ghaffar, A., Abbas Shar, G., Asif Tahir, M., Iqbal, M., 2018, Vibrio fischeri bioluminescence inhibition assay for ecotoxicity assessment: A review. Sci. Total Environ. 626, 1295-1309. https://doi.org/10.1016/j.scitotenv.2018.01.066.

Ahluwalia, V. K., 2015. Environmental Pollution and Health. TERI Press, pp 130. I SBN: 978-81-7993-461-6 .

Alexander, A.C., luiker, E., Finley, M., Culp, J.M., 2016. Chapter 8 – Mesocosm and field toxicity testing in the marine context. In Marine Ecotoxicology: Blasco, J., Chapman, P.M., Campana, O., Hampel, M.B.T.-M.E. (Eds.). Academic Press, pp. 239–256. ISBN: 978-0-12-803371-5.

Álvarez-Muñoz, D., Llorca, M., Blasco, J., Barceló D., 2016. Chapter 1 – Contaminants in the marine environment, in Marine Ecotoxicology: Blasco, J., Chapman, P.M., Campana, O., Hampel, M.B.T.-M.E. (Eds.). Academic Press, pp. 2–24. ISBN: 978-0-12-803371-5.

Araújo, J.E., Madeira, D., Vitorino, R., Repolho, T., Rosa, R., Diniz, M., 2018. Negative synergistic impacts of ocean warming and acidification on the survival and proteome of the commercial sea bream, *Sparus aurata*. J. Sea Res. 139, 50–61. https://doi.org/10.1016/j.seares.2018.06.011

Araujo, G.S., Abessa, D.M.S., Soares, A.M.V.M., Loureiro, S., 2019. Multi-generational exposure to Pb in two monophyletic *Daphnia* species : Individual , functional and population related endpoints. Ecotoxicol. Environ. Saf. 173, 77–85. https://doi.org/10.1016/j.ecoenv.2019.02.001.

Artigas, J., Arts, G., Babut, M., Caracciolo, A.B., Charles, S., Chaumot, A., Combourieu, B., Dahllof, I., Despreaux, D., Ferrari, B., Friberg, N., Garric, J., Geffard, O., Gourlay-France, C., Hein, M., Hjorth, M., Krauss, M., De Lange, H.J., Lahr, J., Lehtonen, K.K., Lettieri, T., Liess, M., Lofts, S., Mayer, P., Morin, S., Paschke, A., Svendsen, C., Usseglio-Polatera, P., Van Den Brink, N., Vindimian, E., Williams, R., 2012. Towards a renewed research agenda in ecotoxicology. Environ. Pollut. 160, 201–206. https://doi.org/10.1016/j.envpol.2011.08.011.

Auld, J.R., Agrawal, A.A., Relyea, R.A., 2010. Re-evaluating the costs and limits of adaptive phenotypic plasticity. Proc R Soc B 277:503–511.

Badyaev, A. V., Uller, T., 2009. Parental effects in ecology and evolution: mechanisms, processes and implications. Philosophical Transactions of the Royal Society B: Biological Sciences 364:1169–1177.

Bal, N., Kumar, A., Du, J., Nugegoda, D., 2017a. Multigenerational effects of two glucocorticoids (prednisolone and dexamethasone) on life-history parameters of crustacean *Ceriodaphnia dubia* (Cladocera). Environ. Pollut. 225, 569–578. https://doi.org/https://doi.org/10.1016/j.envpol.2017.03.024

Bal, N., Kumar, A., Nugegoda, D., 2017b. Assessing multigenerational effects of prednisolone to the freshwater snail, *Physa acuta* (Gastropoda: Physidae). J. Hazard. Mater. 339, 281–291. https://doi.org/https://doi.org/10.1016/j.jhazmat.2017.06.024.

Balbus, J.M., Boxall, A.B.A., Fenske, R.A., McKone, T.E., Zeise, L., 2013. Implications of global climate change for the assessment and management of human health risks of chemicals in the natural environment. Environ. Toxicol. Chem. 32, 62–78. https://doi.org/10.1002/etc.2046.

Barata, C., Baird, D.J., Amat, F., Soares, A.M.V.M., 2000. Population responses to contaminants, between laboratory and field: an approach using *Daphnia magna* ephippial egg banks. Funct. Ecol. 14, 513–523

Barata, C., Baird, D.J., Soares, A.M.V.M., 2002. Determining genetic variability in the distribution of sensitivities to toxic stress among and within field populations of *Daphnia magna*. Environ. Sci. Technol. 36, 3045–3049.

Barry, J.P., Hall-Spencer, J.M.,Tyrrell, T., 2010. Chapter 8: In situ perturbation experiments: natural venting sites, spatial/temporal gradients in ocean pH, manipulative in situ *p*(CO_2) perturbations. In Guide to best practices for ocean acidification research and data reporting; Riebesell, U., Fabry, V., Hansson, L., Gattuso, J.-P., Eds.; Publications Office of the European Union: Luxembourg, pp 123-136. ISBN: 978-92-79-11118-1.

Benedetti, M., Lanzoni, I., Nardi, A., d'Errico, G., Di Carlo, M., Fattorini, D., Nigro, M., Regoli, F., 2016. Oxidative responsiveness to multiple stressors in the key Antarctic species, *Adamussium colbecki*: interactions between temperature, acidification and cadmium exposure. Mar. Environ. Res. 1 (11). https://doi.org/10.1016/j. marenvres.2016.03.011.

Bickham, J.W., Sandhu, S.S., Hebert, P.D.N., Chikhi, L., Anthwal, R., 2000. Effects of chemical contaminants on genetic diversity in natural populations: implications for biomonitoring and ecotoxicology. Mutat. Res. 463, 33-51. https://doi.org/ 10.1016/s1383-5742(00)00004-1.

Bickham, J.W., 2011. The four cornerstones of Evolutionary Toxicology. Ecotoxicology 20, 497–502. https://doi.org/10.1007/s10646-011-0636-y.

Bielmyer-Fraser, G.K., Patel, P., Capo, T., Grosell, M., 2018. Physiological responses of corals to ocean acidification and copper exposure. Mar. Pollut. Bull. 133, 781–790. https://doi.org/10.1016/j.marpolbul.2018.06.048.

Blasco, J., Arias, A.M., Sáenz, V., 2002. Heavy metal concentrations in *Squilla mantis* (L.) (Crustacea, Stomatopoda) from the Gulf of Cádiz: Evaluation of the impact of the Aznalcollar mining spill. Environ. Int. 28, 111–116. https://doi.org/10.1016/S0160-4120(02)00014-4.

Bogdal, C., Scheringer, M., 2011. Release of POPs to the Environment. In Climate Change and POPs: Predicting the Impacts. UNEP/AMAP Expert Group Report, Geneva, Switzerland.

Booth, J.A.T., Mcphee-shaw, E.E., Chua, P., Kingsley, E., Denny, M., Phillips, R., Bograd, S.J., Zeidberg, L.D., Gilly, W.F., 2012. Natural intrusions of hypoxic, low pH water into nearshore marine environments on the California coast. Cont. Shelf Res. 45, 108–115. https://doi.org/10.1016/j.csr.2012.06.009.

Boyd, P.W., Brown, C.J., Schrum, C., Krishnakumar, P.K., 2015. Modes of interactions between environmental drivers and marine biota. Front. Mar. Sci. 2, 9. https://doi.org/10.3389/fmars.2015.00009.

Breitholtz, M., Ruden, C., Hansson, S.O., Bengtsson, B.E., 2006. Ten challenges for improved ecotoxicological testing in environmental risk assessment. Ecotoxicol. Environ. Saf. 63, 324 –335. https://doi.org/10.1016/j.ecoenv.2005.12.009.

Burrell, T. J., Maas, E. W., Hulston, D. A., and Law, C. S., 2015. Bacterial abundance, processes and diversity responses to acidification at a coastal CO_2 vent. FEMS Microbiol. Lett. 362:fnv154. https://doi.org/ 10.1093/femsle/fnv154.

Butler, C.D., McFarlane, R.A., 2018. Climate Change, Food Security, and Population Health in the Anthropocene, in: Dellasala, D.A., Goldstein, M.I.B.T.-E. of the A. (Eds.), . Elsevier, Oxford, pp. 453–459. https://doi.org/https://doi.org/10.1016/B978-0-12-809665-9.09745-7.

Byrne, M., Przeslawski, R., 2013. Multistressor Impacts of Warming and Acidification of the Ocean on Marine Invertebrates' Life Histories. Integr. Comp. Biol. 53, 582–596. https://doi.org/10.1093/icb/ict049.

Calosi, P., Rastrick, S.P.S., Graziano, M., Thomas, S.C., Baggini, C., Carter, H.A., Hall-Spencer, J.M., Milazzo, M., Spicer, J.I., 2013. Distribution of sea urchins living near shallow water CO_2 vents is dependent upon species acid-base and ion-regulatory abilities. Mar. Pollut. Bull. 73, 470–84. https://doi.org/10.1016/j.marpolbul.2012.11.040.

Calosi, P., De Wit, P., Thor, P., Dupont, S., 2016. Will life find a way? Evolution of marine species under global change. Evol. Appl. 9, 1035–1042. https://doi.org/10.1111/eva.12418.

Campbell, A.L., Mangan, S., Ellis, R.P., Lewis, C., 2014. Ocean acidification increases copper toxicity to the early life history stages of the polychaete *Arenicola marina* in artificial seawater. Environ. Sci. Technol. 48, 9745–9753. https://doi.org/10.1021/es502739m.

Cao, R., Liu, Y., Wang, Q., Dong, Z., Yang, D., Liu, H., Ran, W., Qu, Y., Zhao, J., 2018. Seawater acidification aggravated cadmium toxicity in the oyster *Crassostrea gigas*: Metal bioaccumulation, subcellular distribution and multiple physiological responses. Sci. Total Environ. 642, 809–823. https://doi.org/10.1016/j.scitotenv.2018.06.126.

Chakravarti, L.J., Jarrold, M.D., Gibbin, E.M., Christen, F., Massamba-N'Siala, G., Blier, P.U., Calosi, P., 2016. Can trans-generational experiments be used to enhance species resilience to ocean warming and acidification? Evol. Appl. 9, 1133–1146. https://doi.org/10.1111/eva.12391.

Chapman, P.M., 2002. Integrating toxicology and ecology: Putting the "eco" into ecotoxicology. Mar. Pollut. Bull. 44, 7–15. https://doi.org/10.1016/S0025-326X(01)00253-3.

Chapman, P.M., 2016. Chapter 9 - Ecological risk and weight of evidence assessments, in Marine Ecotoxicology: Blasco, J., Chapman, P.M., Campana, O., Hampel, M.B.T.-M.E. (Eds.), . Academic Press, pp. 257–271. ISBN: 978-0-12-803371-5.

Chapman, P.M., 2017. Assessing and managing stressors in a changing marine environment. Mar. Pollut. Bull. 124, 587–590. /https://doi.org/10.1016/j.marpolbul.2016.10.039.

Chatterjee, N., Choi, S., Kwon, O.K., Lee, S., Choi, J., 2019. Multi-generational impacts of organic contaminated stream water on *Daphnia magna*: A combined proteomics, epigenetics and ecotoxicity approach. Environ. Pollut. https://doi.org/10.1016/j.envpol.2019.03.028.

Chen, L., Li, X., Hong, H., Shi, D., 2018. Multigenerational effects of 4-methylbenzylidene camphor (4-MBC) on the survival, development and reproduction of the marine copepod *Tigriopus japonicus*. Aquat. Toxicol. 194, 94–102. https://doi.org/10.1016/j.aquatox.2017.11.008.

Clayson, D.B., 2001. Chapter 9 - The general environment in Toxicological Carcinogenesis. Lewis Publishers, pp 93-103. ISBN: 1-56670-508-8.

Clubbs, R.L., Brooks, B.W., 2007. Daphnia magna responses to a vertebrate estrogen receptor agonist and an antagonist: A multigenerational study. Ecotoxicol. Environ. Saf. 67, 385–398. https://doi.org/10.1016/j.ecoenv.2007.01.009.

Cohen, J.E., 2012. Population and climate change. Proc Am Philos Soc. 154 (2), 158-82. https://www.jstor.org/stable/41000096.

Collins, S., Bell, G., 2004. Phenotypic consequences of 1,000 generations of selection at elevated CO_2 in a green alga. Nature 431, 566–569. https://doi.org/10.1038/nature02945

Coppola, F., Almeida, Â., Henriques, B., Soares, A.M.V.M., Figueira, E., Pereira, E., Freitas, R., 2017. Biochemical impacts of Hg in *Mytilus galloprovincialis* under present and predicted warming scenarios. Sci. Total Environ. 601–602, 1129–1138. https://doi.org/10.1016/j.scitotenv.2017.05.201.

Coppola, F., Almeida, Â., Henriques, B., Soares, A.M.V.M., Figueira, E., Pereira, E., Freitas, R., 2018. Biochemical responses and accumulation patterns of *Mytilus galloprovincialis* exposed to thermal stress and Arsenic contamination. Ecotoxicol. Environ. Saf. 147, 954–962. https://doi.org/10.1016/j.ecoenv.2017.09.051.

Corrales, J., Thornton, C., White, M., Willett, K.L., 2014. Multigenerational effects of benzo[a]pyrene exposure on survival and developmental deformities in zebrafish larvae. Aquat. Toxicol. 148, 16–26. https://doi.org/10.1016/j.aquatox.2013.12.028.

Cornwall, C.E., Hurd, C.L., 2016. Experimental design in ocean acidification research: problems and solutions. ICES J. Mar. Sci. 73, 572–581. https://doi.org/10.1093/icesjms/fsv118.

Conradi, M., Sánchez-moyano, J.E., Bhuiyan, M.K.A., Rodríguez-romero, A., Galotti, A., Basallote, M.D., 2019. Science of the Total Environment Intraspeci fi c variation in the response of the estuarine European isopod *Cyathura carinata* (Krøyer , 1847) to ocean acidification. Sci. Total Environ. 683, 134–145. https://doi.org/10.1016/j.scitotenv.2019.05.227.

Côté, I.M., Darling, E.S., Brown, C.J., 2016. Interactions among ecosystem stressors and their importance in conservation. Proc. R. Soc. B Biol. Sci. 283, 1–9. https://doi.org/10.1098/rspb.2015.2592.

Coutellec, M.A., Barata, C., 2011. An introduction to evolutionary processes in ecotoxicology. Ecotoxicology 20, 493–496. https://doi.org/10.1007/s10646-011-0637-x.

Coutellec, M.A., Barata, C., 2013. Special issue on long-term ecotoxicological effects: An introduction. Ecotoxicology 22, 763–766. https://doi.org/10.1007/s10646-013-1092-7.

Coz, A., Andrés, A., Soriano, S., Viguri, J.R., Ruiz, M.C., Irabien J.A., 2009. Influence of commercial and residual sorbents and silicates as additives on the stabilisation/solidification of organic and inorganic industrial waste. J. Hazard Mater. 164, 2–3, 755-761. https://doi.org/10.1016/j.jhazmat.2008.08.079.

Dallinger, R., Höckner, M., 2013. Evolutionary concepts in ecotoxicology: Tracing the genetic background of differential cadmium sensitivities in invertebrate lineages. Ecotoxicology 22, 767–778. https://doi.org/10.1007/s10646-013-1071-z.

Davis Jr., R.A., Welty, A.T., Borrego, J., Morales, J.A., Pendon, J.G., Ryan, J.G., 2000. Rio Tinto estuary (Spain): 5000 years of pollution. Environ. Geol. 39, 1107–1116. https://doi.org/10.1007/s002549900096.

Decourten, B.M., Brander, S.M., 2017. Combined effects of increased temperature and endocrine disrupting pollutants on sex determination, survival, and development across generations. Sci. Rep. 7, 1–9. https://doi.org/10.1038/s41598-017-09631-1.

De Liguoro, M., Maraj, S., Merlanti, R., 2019. Transgenerational toxicity of flumequine over four generations of Daphnia magna. Ecotoxicol. Environ. Saf. 169, 814–821. https://doi.org/10.1016/j.ecoenv.2018.11.077.

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.

Dewitt, T.J., 1998. Costs and limits of phenotypic plasticity: Tests with predator-induced morphology and life history in a freshwater snail 11, 465–480. https://doi.org/10.1046/j.1420-9101.1998.11040465.x.

De Wit, P., Dupont, S., Thor, P., 2016. Selection on oxidative phosphorylation and ribosomal structure as a multigenerational response to ocean acidification in the common copepod *Pseudocalanus acuspes*. Evol. Appl. 9, 1112–1123. https://doi.org/10.1111/eva.12335.

Dietrich, S., Ploessl, F., Bracher, F., Laforsch, C., 2010. Single and combined toxicity of pharmaceuticals at environmentally relevant concentrations in Daphnia magna - A multigenerational study. Chemosphere 79, 60–66. https://doi.org/10.1016/j.chemosphere.2009.12.069.

Donelson, J.M., Munday, P.L., 2015. Transgenerational plasticity mitigates the impact of global warming to offspring sex ratios. Glob. Chang. Biol. 21, 2954–2962. https://doi.org/10.1111/gcb.12912.

Donelson, J.M., Salinas, S., Munday, P.L., Shama, L.N.S., 2018. Transgenerational plasticity and climate change experiments: Where do we go from here? Glob. Chang. Biol. 24, 13–34. https://doi.org/10.1111/gcb.13903.

Dorey, N., Maboloc, E., Chan, K.Y.K., 2018a. Development of the sea urchin *Heliocidaris crassispina* from Hong Kong is robust to ocean acidification and copper contamination. Aquat. Toxicol. 205, 1–10. https://doi.org/10.1016/j.aquatox.2018.09.006.

Dorey, N., Martin, S., Oberhänsli, F., Teyssié, J.-L., Jeffree, R., Lacoue-Labarthe, T., 2018b. Ocean acidification modulates the incorporation of radio-labeled heavy metals in the larvae of the Mediterranean Sea urchin *Paracentrotus lividus*. J. Environ. Radioact. 190–191, 20–30. https://doi.org/10.1016/j.jenvrad.2018.04.017.

Duarte, C.M., Hendriks, I.E., Moore, T.S., Olsen, Y.S., Steckbauer, A., Ramajo, L., Carstensen, J., Trotter, J.A., McCulloch, M., 2013. Is Ocean Acidification an Open-Ocean Syndrome? Understanding Anthropogenic Impacts on Seawater pH. Estuaries and Coasts 36, 221–236. https://doi.org/10.1007/s12237-013-9594-3.

Duarte, C., Navarro, J.M.M., Acuña, K., Torres, R., Manríquez, P.H.H., Lardies, M.A.A., Vargas, C.A.A., Lagos, N.A.A., Aguilera, V., 2014. Combined effects of temperature and ocean acidification on the juvenile individuals of the mussel *Mytilus chilensis*. J. Sea Res. 85, 308–314. https://doi.org/10.1016/j.seares.2013.06.002.

Duckworth, C.G., Picariello, C.R., Thomason, R.K., Patel, K.S., Bielmyer-Fraser, G.K., 2017. Responses of the sea anemone, *Exaiptasia pallida*, to ocean acidification conditions and zinc or nickel exposure. Aquat. Toxicol. 182, 120–128. https://doi.org/10.1016/j.aquatox.2016.11.014.

Dupont, S., Dorey, N., Stumpp, M., Melzner, F., Thorndyke, M., 2013. Long-term and trans-life-cycle effects of exposure to ocean acidification in the green sea urchin *Strongylocentrotus droebachiensis*. Mar. Biol. 160, 1835–1843. https://doi.org/10.1007/s00227-012-1921-x.

Egilsdottir, H., Spicer, J.I., Rundle, S.D., 2009. The effect of CO_2 acidified sea water and reduced salinity on aspects of the embryonic development of the amphipod *Echinogammarus marinus* (Leach). Mar. Pollut. Bull. 58, 1187–91. https://doi.org/10.1016/j.marpolbul.2009.03.017.

Filser, Ã. J., 2008. Ecotoxicology and ecosystems: Relevance , restrictions , research needs. Basic Appl. Ecol. 9, 333–336. https://doi.org/10.1016/j.baae.2007.08.009.

Fitzer, S.C., Caldwell, G.S., Clare, A.S., Upstill-Goddard, R.C., Bentley, M.G., 2013. Response of copepods to elevated pCO_2 and environmental copper as co-stressors: A multigenerational study. PLoS ONE 8: e71257. https://doi.org/10.1371/journal.pone.0071257.

Foo, S. a, Dworjanyn, S. a, Poore, A.G.B., Byrne, M., 2012. Adaptive capacity of the habitat modifying sea urchin *Centrostephanus rodgersii* to ocean warming and ocean acidification: performance of early embryos. PLoS One 7, e42497. https://doi.org/10.1371/journal.pone.0042497.

Forbes,V.E., Forbes, T.L.,1994. Ecotoxicology in Theory and Practice. Chapman and Hall, London, 247.

Freitas, R., Almeida, Â., Calisto, V., Velez, C., Moreira, A., Schneider, R.J., Esteves, V.I., Wrona, F.J., Soares, A.M.V.M., Figueira, E., 2015. How life history influences the responses of the clam *Scrobicularia plana* to the combined impacts of carbamazepine and pH decrease. Environ. Pollut. 202, 205–214. https://doi.org/10.1016/j.envpol.2015.03.023.

Freitas, R., Almeida, Â., Calisto, V., Velez, C., Moreira, A., Schneider, R.J., Esteves, V.I., Wrona, F.J., Figueira, E., Soares, A.M.V.M., 2016. The impacts of pharmaceutical drugs under ocean acidification: New data on single and combined long-term effects of carbamazepine on *Scrobicularia plana*. Sci. Total Environ. 541, 977–985. https://doi.org/https://doi.org/10.1016/j.scitotenv.2015.09.138.

Freitas, R., De Marchi, L., Bastos, M., Moreira, A., Velez, C., Chiesa, S., Wrona, F.J., Figueira, E., Soares, A.M.V.M., 2017a. Effects of seawater acidification and salinity alterations on metabolic, osmoregulation and oxidative stress markers in *Mytilus galloprovincialis*. Ecol. Indic. 79, 54–62. https://doi.org/10.1016/j.ecolind.2017.04.003.

Freitas, R., Coppola, F., Henriques, B., Wrona, F., Figueira, E., Pereira, E., Soares, A.M.V.M., 2017b. Does pre-exposure to warming conditions increase *Mytilus* *galloprovincialis* tolerance to Hg contamination? Comp. Biochem. Physiol. Part - C Toxicol. Pharmacol. 203, 1–11. https://doi.org/10.1016/j.cbpc.2017.09.010.

Freitas, R., de Marchi, L., Moreira, A., Pestana, J.L.T., Wrona, F.J., Figueira, E., Soares, A.M.V.M., 2017c. Physiological and biochemical impacts induced by mercury pollution and seawater acidification in *Hediste diversicolor*. Sci. Total Environ. 595, 691–701. https://doi.org/10.1016/j.scitotenv.2017.04.005.

Fusco, G., Minelli, A., 2010. Phenotypic plasticity in development and evolution: facts and concepts 547–556. https://doi.org/10.1098/rstb.2009.0267.

Gamain, P., Gonzalez, P., Cachot, J., Clérandeau, C., Mazzella, N., Gourves, P.Y., Morin, B., 2017. Combined effects of temperature and copper and S-metolachlor on embryo-larval development of the Pacific oyster, *Crassostrea gigas*. Mar. Pollut. Bull. 115, 201–210. https://doi.org/10.1016/j.marpolbul.2016.12.018.

Gardestrom, J., Dahl, U., Kotsalainen, O., Maxson, A., Elfwing, T., Grahn, M., Bengtsson, B., Breitholtz, M., 2008. Evidence of population genetic effects of long-term exposure to contaminated sediments -A multi-endpoint study with copepods. Aquat. Toxicol. 86, 426–436. https://doi.org/10.1016/j.aquatox.2007.12.003.

Gao, G., Liu, Y., Li, X., Feng, Z., Xu, Z., Wu, H., Xu, J., 2017. Expected CO_2-induced ocean acidification modulates copper toxicity in the green tide alga *Ulva prolifera*. Environ. Exp. Bot. 135, 63–72. https://doi.org/10.1016/j.envexpbot.2016.12.007.

Gaur, V.K., Sharma, P., Sirohi, R., Awasthi, M.K., Dussap, C.-G., Pandey, A., 2020. Assessing the impact of industrial waste on environment and mitigation strategies: A comprehensive review. J. Hazard. Mater. 398, 123019. https://doi.org/10.1016/j.jhazmat.2020.123019.

Ghalambor C. K., Mckay J. K., Carroll S. P., and Reznick D. N. 2007. Adaptive versus non-adaptive phenotypic plasticity and the potential for contemporary adaptation in new environments. Functional Ecology 21:394–407. https://doi.org/10.1111/j.1365-2435.2007.01283.x.

Gibbin, E.M., Massamba N'Siala, G., Chakravarti, L.J., Jarrold, M.D., Calosi, P., 2017a. The evolution of phenotypic plasticity under global change. Sci. Rep. 7, 1–8. https://doi.org/10.1038/s41598-017-17554-0.

Gibbin, E.M., Chakravarti, L.J., Jarrold, M.D., Christen, F., Turpin, V., Massamba N'Siala, G., Blier, P.U., Calosi, P., 2017b. Can multi-generational exposure to ocean warming and acidification lead to the adaptation of life history and physiology in a marine metazoan? J. Exp. Biol. 220, 551 LP-563. https://doi.org/10.1242/jeb.149989.

Gienapp, P., Teplitsky, C., Alho, J. S., Mills, J. A., and Merilä, J., 2008. Climate change and evolution: disentangling environmental and genetic responses, Mol. Ecol., 17, 167–178. https://doi.org/10.1111/j.1365-294X.2007.03413.x

Gilchrist, G.W., Huey, R.B., Partridge, L., 1997. Thermal Sensitivity of *Drosophila melanogaster:* Evolutionary Responses of Adults and Eggs to Laboratory Natural Selection at Different Temperatures 70, 403–414. https://doi.org/10.1086/515853.

Giraudo, M., Dubé, M., Lépine, M., Gagnon, P., Douville, M., Houde, M., 2017. Multigenerational effects evaluation of the flame retardant tris(2-butoxyethyl) phosphate (TBOEP) using *Daphnia magna*. Aquat. Toxicol. 190, 142–149. https://doi.org/10.1016/j.aquatox.2017.07.003.

Gomiero, A., Viarengo, A., 2014. Effects of elevated temperature on the toxicity of copper and oxytetracycline in the marine model, *Euplotes crassus*: a climate change perspective. Environ. Pollut. 194, 262–71. https://doi.org/10.1016/j.envpol.2014.07.035.

González-Delgado, S., Hernández, J.C., 2018. Chapter Two - The Importance of Natural Acidified Systems in the Study of Ocean Acidification: What Have We Learned? In Advances in Marine Biology: Sheppard, C.B.T.-A. in M.B. (Ed.), . Academic Press, pp. 57–99. https://doi.org/https://doi.org/10.1016/bs.amb.2018.08.001.

González-Pérez, B.K., Sarma, S.S.S., Castellanos-Páez, M.E., Nandini, S., 2018. Multigenerational effects of triclosan on the demography of *Plationus patulus* and *Brachionus havanaensis* (ROTIFERA). Ecotoxicol. Environ. Saf. 147, 275–282. https://doi.org/10.1016/j.ecoenv.2017.08.049.

Guyon, A., Smith, K.F., Charry, M.P., Champeau, O., Tremblay, L.A., 2018. Effects of chronic exposure to benzophenone and diclofenac on DNA methylation levels and reproductive success in a marine copepod. J. Xenobiot. 8, 1–3. https://doi.org/10.4081/xeno.2018.7674.

Havenhand, J.N., Filipsson, H.L., Niiranen, S., Troell, M., Crépin, A.-S., Jagers, S., Langlet, D., Matti, S., Turner, D., Winder, M., de Wit, P., Anderson, L.G., 2019. Ecological and functional consequences of coastal ocean acidification: Perspectives from the Baltic-Skagerrak System. Ambio 48, 831–854. https://doi.org/10.1007/s13280-018-1110-3.

Hawkins, C.A., Sokolova, I.M., 2017. Effects of elevated CO_2 levels on subcellular distribution of trace metals (Cd and Cu) in marine bivalves. Aquat. Toxicol. 192, 251–264. https://doi.org/10.1016/j.aquatox.2017.09.028.

Hernández, C.A., Sangil, C., Hernández, J.C., 2016. A new CO_2 vent for the study of ocean acidification in the Atlantic. Mar. Pollut. Bull. 109, 419–426. https://doi.org/10.1016/j.marpolbul.2016.05.040.

Hoffmann, A.A., 1995. Acclimation: increasing survival at a cost. Trends Ecol. Evol. 10, 1–2. https://doi.org/10.1016/S0169-5347(00)88949-1.

Holan, J.R., King, C.K., Proctor, A.H., Davis, A.R., 2019. Increased sensitivity of subantarctic marine invertebrates to copper under a changing climate - Effects of salinity and temperature. Environ. Pollut. https://doi.org/ 10.1016/j.envpol.2019.02.016.

Houlbrèque, F., Rodolfo-Metalpa, R., Jeffree, R., Oberhansli, F., Teyssie, J.L., Boisson, F., Al-Trabeen, K., Ferrier-Pages, C., 2012. Effects of increased *p*CO_2 on zinc uptake and calcification in the tropical coral *Stylophora pistillata*. Coral Reefs 31, 101–109, http://dx.doi.org/10.1007/s00338-011-0819-2.

Hooper, M. J., Ankley, G. T., Cristol, D. A., Maryoung, L. A., Noyes, P. D., Pinkerton, K. E., 2013. Interactions between chemical and climate stressors: A role for mechanistic toxicology in assessing climate change risks. Environ. Toxicol. and Chem., 32, 32–48. https://doi.org/ 10.1002/etc.2043.

Huang, X., Jiang, X., Sun, M., Dupont, S., Huang, W., Hu, M., Li, Q., Wang, Y., 2018. Effects of copper on hemocyte parameters in the estuarine oyster *Crassostrea rivularis* under low pH conditions. Aquat. Toxicol. 203, 61–68. https://doi.org/10.1016/j.aquatox.2018.08.003.

Huey, R.B., Berrigan, D., Gilchrist, G.W., Herron, J.C., 1999. Testing the adaptive significance of acclimation: a strong inference approach. Am Zool. 39, 323–336. https://doi.org/10.1093/icb/39.2.323.

IPCC (Intergovernmental Panel of Climate Change). 2014. Climate Change 2014: Synthesis Report. Contribution of Working Groups I, II and III to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change. Ed. Core Writ. Team, RK Pachauri, LA Meyer. Geneva: IPCC.

Ivanina, A.V., Beniash, E., Etzkorn, M., Meyers, T.B., Ringwood, A.H., Sokolova, I.M., 2013. Short-term acute hypercapnia affects cellular responses to trace metals in the hard clams *Mercenaria mercenaria*. Aquat. Toxicol. 140–141, 123–133. https://doi.org/10.1016/j.aquatox.2013.05.019.

Ivanina, A.V., Sokolova ,I.M., 2013. Interactive effect of pH and metals on mitochondrial function of intertidal bivalves *Crassostrea virginica* and *Mercenaria mercenaria*, Aquat. Toxicol. 144-145C, 303-309. https://doi.org/10.1016/j.aquatox.2013.10.019.

Ivanina, A.V., Hawkins, C., Sokolova, I.M., 2014. Immunomodulation by the interactive effects of cadmium and hypercapnia in marine bivalves *Crassostrea virginica* and *Mercenaria mercenaria*. FishShellfish Immunol. 37, 299–312. https://doi.org/ 10.1016/j.fsi.2014.02.016.

Ivanina, A. V., Hawkins, C., Beniash, E., Sokolova, I.M., 2015. Effects of environmental hypercapnia and metal (Cd and Cu) exposure on acid-base and metal homeostasis of marine bivalves. Comp. Biochem. Physiol. Part - C Toxicol. Pharmacol. 174–175, 1–12. https://doi.org/10.1016/j.cbpc.2015.05.001.

Ivanina, A.V., Sokolova ,I.M., 2015. Interactive effects of metal pollution and ocean acidification on physiology of marine organisms, Curr. Zool. 61, 653e668. https://doi.org/ 10.1093/czoolo/61.4.653.

Ivanina, A. V, Hawkins, C., Sokolova, I.M., 2016. Interactive effects of copper exposure and environmental hypercapnia on immune functions of marine bivalves *Crassostrea virginica* and *Mercenaria mercenaria*. Fish Shellfish Immunol. 49, 54–65. https://doi.org/ 10.1016/j.fsi.2015.12.011.

Jambeck, J.R., Geyer, R., Wilcox, C., Siegler, T.R., Perryman, M., Andrady, A., Narayan, R., Law, K.L., 2015. Plastic waste inputs from land into the ocean. Science (80-.). 347, 768 LP – 771. https://doi.org/10.1126/science.1260352.

Jarrold, M.D., Chakravarti, L.J., Gibbin, E.M., Christen, F., Massamba-N'Siala, G., Blier, P.U., Calosi, P., 2019. Life-history trade-offs and limitations associated with phenotypic adaptation under future ocean warming and elevated salinity. Philos. Trans. R. Soc. B Biol. Sci. 374, 20180428. https://doi.org/10.1098/rstb.2018.0428.

Jeong, T.Y., Kim, T.H., Kim, S.D., 2015. Bioaccumulation and biotransformation of the beta-blocker propranolol in multigenerational exposure to *Daphnia magna*. Environ. Pollut. 216, 811–818. https://doi.org/10.1016/j.envpol.2016.06.051.

Johnson, M.D., Carpenter, R.C., 2012. Ocean acidification and warming decrease calcification in the crustose coralline alga *Hydrolithon onkodes* and increase susceptibility to grazing. J. Exp. Mar. Bio. Ecol. 434–435, 94–101. https://doi.org/10.1016/j.jembe.2012.08.005.

Kavousi, J., Reimer, J.D., Tanaka, Y., Nakamura, T., 2015. Colony-specific investigations reveal highly variable responses among individual corals to ocean acidification and warming. Mar. Environ. Res. 109, 9–20. https://doi.org/10.1016/j.marenvres.2015.05.004.

Kedzierski, M., Frère, D., Le Maguer, G., Bruzaud, S., 2020. Why is there plastic packaging in the natural environment? Understanding the roots of our individual plastic waste management behaviours. Sci. Total Environ. 740, 139985. https://doi.org/https://doi.org/10.1016/j.scitotenv.2020.139985.

Kelly, M.W., Hofmann, G.E., 2013. Adaptation and the physiology of ocean acidification 980–990. https://doi.org/10.1111/j.1365-2435.2012.02061.x.

Kim, H.Y., Yu, S., Jeong, T.-Y., Kim, S.D., 2014. Relationship between trans-generational effects of tetracycline on *Daphnia magna* at the physiological and whole organism level. Environ. Pollut. 191, 111–8. https://doi.org/10.1016/j.envpol.2014.04.022.

Kimberly, D.A., Salice, C.J., 2015. Evolutionary responses to climate change and contaminants: Evidence and experimental approaches. Curr. Zool. 61, 690–701. https://doi.org/10.1093/czoolo/61.4.690.

Knecht, A.L., Truong, L., Marvel, S.W., Reif, D.M., Garcia, A., Lu, C., Simonich, M.T., Teeguarden, J.G., Tanguay, R.L., 2017. Transgenerational inheritance of neurobehavioral and physiological de fi cits from developmental exposure to benzo [a] pyrene in zebra fish. Toxicol. Appl. Pharmacol. 329, 148–157. https://doi.org/10.1016/j.taap.2017.05.033.

Krause, K.E., Dinh, K. V., Nielsen, T.G., 2017. Increased tolerance to oil exposure by the cosmopolitan marine copepod *Acartia tonsa*. Sci. Total Environ. 607–608, 87–94. https://doi.org/10.1016/j.scitotenv.2017.06.139.

Krogh, A. *(*1929*)*. The progress of physiology. *Am. J. Physiol.* 90, 243-251.
https://doi.org/10.1152/ajplegacy.1929.90.2.243

Kroeker, K. J., Kordas, R. L., Crim, R., Hendriks, I. E., Ramajo, L., Gattuso, G. S., et al. (2013). Impacts of ocean acidification on marine organisms: quantifying sensitivities and interaction with warming. Glob. Change Biol. 19, 1884–1896, doi: 10.1111/gcb.12179.

Kroeker, K.J., Kordas, R.L., Harley, C.D.G., 2017. Embracing interactions in ocean acidification research: confronting multiple stressor scenarios and context dependence. Biol. Lett. 13, 20160802. https://doi.org/10.1098/rsbl.2016.0802.

Kwok, K.W.H., Grist, E.P.M., Leung, K.M.Y., 2009. Acclimation effect and fitness cost of copper resistance in the marine copepod *Tigriopus japonicus*. Ecotoxicol. Environ. Saf. 72, 358–364. https://doi.org/10.1016/J.ECOENV.2008.03.014.

Lacoue-Labarthe, T., Martin, S., Oberhänsli, F., Teyssie, J.-L., Markich, S.J., Jeffree, R., Bustamante, P., 2009. Effects of increased pCO_2 and temperature on trace ele- ment (Ag, Cd and Zn) bioaccumulation in the eggs of the common cuttlefish, *Sepia officinalis*. Biogeosciences 6, 2561–2573.

Lacoue-Labarthe, T., Réveillac, E., Oberhänsli, F., Teyssié, J.L., Jeffree, R., Gattuso, J.P., 2011. Effects of ocean acidification on trace element accumulation in the early-life stages of squid *Loligo vulgaris*. Aquat. Toxicol. 105, 166–76. https://doi.org/10.1016/j.aquatox.2011.05.021.

Lacoue-Labarthe, T., Martin, S., Oberhänsli, F., Teyssié, J.L., Jeffree, R., Gattuso, J.P., Bustamante, P., 2012. Temperature and pCO_2 effect on the bioaccumulation of radionuclides and trace elements in the eggs of the common cuttlefish, *Sepia officinalis*. J. Exp. Mar. Bio. Ecol. 413, 45–49. https://doi.org/10.1016/j.jembe.2011.11.025.

Lacoue-Labarthe, T., Oberhänsli, F., Teyssié, J.-L., Martin, S., 2018. Delineation of metals and radionuclides bioconcentration in eggs of seabream *Sparus aurata* and effect of environmental pCO_2. J. Environ. Radioact. 192, 426–433. https://doi.org/https://doi.org/10.1016/j.jenvrad.2018.07.010.

Lamare, M. D., Liddy, M., and Uthicke, S. 2016. In situ developmental responses of tropical sea urchin larvae to ocean acidification conditions at naturally elevated pCO_2 vent sites. Proc. R. Soc. B, 283: 20161506. https://doi.org/10.1098/rspb.2016.1506.

Landis, W.G., Durda, J.L., Brooks, M.L., Chapman, P.M., Menzie, C.A., Stahl, R.G., Stauber, J.L., 2013. Ecological risk assessment in the context of global climate change. Environ. Toxicol. Chem. 32, 79–92. https://doi.org/10.1002/etc.2047.

Lardies, M.A., Benitez, S., Osores, S., Vargas, C.A., Duarte, C., Lohrmann, K.B., Lagos, N.A., 2017. Physiological and histopathological impacts of increased carbon dioxide and temperature on the scallops *Argopecten purpuratus* cultured under upwelling influences in northern Chile. Aquaculture 479, 455–466. https://doi.org/https://doi.org/10.1016/j.aquaculture.2017.06.008.

Leblanc, M., Morales, J.A., Borrego, J., Elbaz-Poulichet, F., 2000. 4,500-year-old mining pollution in Southwestern Spain: long-term implications for modern mining pollution. Econ. Geol. 95, 655–662. https://doi.org/10.2113/gsecongeo.95.3.655.

Leblanc, G.A. 2004. Chapter 10- Elimination of toxicants. In A Textbook of Modern Toxicology: Hodgson, E. (Ed.). John Wiley & Sons, Inc., pp. 203-211. ISBN 0-471-26508-X.

Liu, Y., Fan, W., Xu, Z., Peng, W., Luo, S., 2017. Transgenerational effects of reduced graphene oxide modified by Au, Ag, Pd, Fe_3O_4, Co_3O_4 and SnO_2 on two generations of *Daphnia m*agna. Carbon 122, 669-679. https://doi.org/10.1016/j.carbon.2017.06.087.

Lewis, C., Clemow, K., Holt, W.V., 2013. Metal contamination increases the sensitivity of larvae but not gametes to ocean acidification in the polychaete *Pomatoceros lamarckii* (Quatre- fages) Marine Biology 160, 2089–2101. https://doi.org/10.1007/s00227-012-2081-8.

Lewis, C., Ellis, R.P., Vernon, E., Elliot, K., Newbatt, S., Wilson, R.W., 2016. Ocean acidification increases copper toxicity differentially in two key marine invertebrates with distinct acid-base responses. Sci. Rep. 6. https://doi.org/10.1038/srep21554.

Li, H., Shi, L., Wang, D., Wang, M., 2015. Impacts of mercury exposure on life history traits of *Tigriopus japonicus*: Multigeneration effects and recovery from pollution. Aquat. Toxicol. 166, 42–49. https://doi.org/10.1016/J.AQUATOX.2015.06.015.

Li, Y., Wang, W.-X., Wang, M., 2017. Alleviation of mercury toxicity to a marine copepod under multigenerational exposure by ocean acidification. Sci. Rep. 7. https://doi.org/10.1038/s41598-017-00423-1.

Lucey, N.M., Lombardi, C., Florio, M., DeMarchi, L., Nannini, M., Rundle, S., Gambi, M.C., Calosi, P., 2016. An in situ assessment of local adaptation in a calcifying polychaete from a shallow CO_2 vent system. Evol. Appl. 9, 1054–1071. https://doi.org/10.1111/eva.12400.

Luoma, S.N., 1996. The developing framework of marine ecotoxicology: Pollutants as a variable in marine ecosystems? J. Exp. Mar. Bio. Ecol. 200, 29–55.

Ma, J., Hung, H., Macdonald, R.W., 2016. The influence of global climate change on the environmental fate of persistent organic pollutants: A review with emphasis on the Northern Hemisphere and the Arctic as a receptor. Glob. Planet. Change 146, 89–108. https://doi.org/10.1016/j.gloplacha.2016.09.011.

Manciocco, A., Calamandrei, G., Alleva, E., 2014. Global warming and environmental contaminants in aquatic organisms: the need of the etho-toxicology approach. Chemosphere 100, 1–7. https://doi.org/10.1016/j.chemosphere.2013.12.072.

Marangoni, L.F.B., Pinto, M.M. de A.N., Marques, J.A., Bianchini, A., 2019. Copper exposure and seawater acidification interaction: Antagonistic effects on biomarkers in the zooxanthellate scleractinian coral *Mussismilia harttii*. Aquat. Toxicol. 206, 123–133. https://doi.org/https://doi.org/10.1016/j.aquatox.2018.11.005.

Marshall, D. J., Uller, T., 2007. When is a maternal effect adaptive? Oikos 116,1957–1963. https://doi:10.1111/j.2007.0030-1299.16203.x.

Marshall, D.J., Morgan, S.G., 2011. Ecological and evolutionary consequences of linked life-history stages in the sea. Curr. Biol. 21, R718–R725. https://doi.org/10.1016/j.cub.2011.08.022.

Matozzo, V., Chinellato, A., Munari, M., Bressan, M., Marin, M.G., 2013. Can the combination of decreased pH and increased temperature values induce oxidative stress in the clam *Chamelea gallina* and the mussel *Mytilus galloprovincialis*? Mar. Pollut. Bull. 72, 34–40. https://doi.org/10.1016/j.marpolbul.2013.05.004.

Maulvault, A.L., Custódio, A., Anacleto, P., Repolho, T., Pousão, P., Nunes, M.L., Diniz, M., Rosa, R., Marques, A., 2016. Bioaccumulation and elimination of mercury in juvenile seabass (Dicentrarchus labrax) in a warmer environment. Environ. Res. 149, 77–85. https://doi.org/10.1016/j.envres.2016.04.035.

Maulvault, A.L., Santos, L.H.M.L.M., Paula, J.R., Camacho, C., Pissarra, V., Fogaça, F., Barbosa, V., Alves, R., Ferreira, P.P., Barceló, D., Rodriguez-Mozaz, S., Marques, A., Diniz, M., Rosa, R., 2018a. Differential behavioural responses to venlafaxine exposure route, warming and acidification in juvenile fish (*Argyrosomus regius*). Sci. Total Environ. 634, 1136–1147. /https://doi.org/10.1016/j.scitotenv.2018.04.015.

Maulvault, A.L., Santos, L.H.M.L.M., Camacho, C., Anacleto, P., Barbosa, V., Alves, R., Pousão Ferreira, P., Serra-Compte, A., Barceló, D., Rodriguez-Mozaz, S., Rosa, R., Diniz, M., Marques, A., 2018b. Antidepressants in a changing ocean: Venlafaxine uptake and elimination in juvenile fish (*Argyrosomus regius*) exposed to warming and acidification conditions. Chemosphere 209, 286–297. https://doi.org/10.1016/j.chemosphere.2018.06.004.

Maulvault, A.L., Barbosa, V., Alves, R., Anacleto, P., Camacho, C., Cunha, S., Fernandes, J.O., Ferreira, P.P., Rosa, R., Marques, A., Diniz, M., 2018c. Integrated multi-biomarker responses of juvenile seabass to diclofenac, warming and acidification co-exposure. Aquat. Toxicol. 202, 65–79. https://doi.org/10.1016/j.aquatox.2018.06.016.

Maulvault, A.L., Camacho, C., Barbosa, V., Alves, R., Anacleto, P., Pousão-Ferreira, P., Rosa, R., Marques, A., Diniz, M.S., 2019. Living in a multi-stressors environment: An integrated biomarker approach to assess the ecotoxicological response of meagre (*Argyrosomus regius*) to venlafaxine, warming and acidification. Environ. Res. 169, 7–25. https://doi.org/10.1016/j.envres.2018.10.021.

Martín-Torre, M.C., Ruiz, G., Galán, B., Viguri, J.R., 2015. Generalised mathematical model to estimate Zn, Pb, Cd, Ni, Cu, Cr and As release from contaminated estuarine sediment using pH-static leaching tests. Chem. Eng. Sci. 138, 780–790. https://doi.org/10.1016/j.ces.2015.08.053

Martín-Torre, M.C., Ruiz, G., Galán, B., Viguri, J.R., 2016. CO_2 seawater acidification by CCS-simulated leakage: Kinetic modelling of Zn, Pb, Cd, Ni, Cr, Cu and As release from contaminated estuarine sediment using pH-static leaching tests. Int. J. Greenh. Gas Control 54, 185–199. https://doi.org/10.1016/j.ijggc.2016.09.004

Miller, G. M., Watson, S.A., Donelson, J. M., McCormick, M. I., Munday, P. L., 2012. Parental environment mediates impacts of elevated CO_2 on a coral reef fish. Nat. Clim. Change 2, 858–861. https://doi.org/10.1038/nclimate1599.

Millero, F.J., Woosley, R., Ditrolio, B., Waters, J., 2009. Effect of ocean acidification on the speciation of metals in seawater. Oceanography 22, 72–85. https://doi.org/10.5670/oceanog.2009.98.

Morales-Caselles, C., Jiménez-Tenorio, N., de Canales, M.L.G., Sarasquete, C., DelValls, T.A., 2006. Ecotoxicity of sediments contaminated by the oil spill associated with the tanker “Prestige” using juveniles of the fish *Sparus aurata*. Arch. Environ. Contam. Toxicol. 51, 652–60. https://doi.org/10.1007/s00244-005-0251-0.

Moreira, A., Figueira, E., Mestre, N.C., Schrama, D., Soares, A.M.V.M., Freitas, R., João, M., 2018a. Impacts of the combined exposure to seawater acidi fi cation and arsenic on the proteome of *Crassostrea angulat*a and *Crassostrea gigas*. Aquat. Toxicol. 203, 117–129. https://doi.org/10.1016/j.aquatox.2018.07.021.

Moreira, A., Freitas, R., Figueira, E., Volpi, A., Soares, A.M.V.M., Radaelli, M., Guida, M., Libralato, G., 2018b. Ecotoxicology and Environmental Safety Combined effects of arsenic , salinity and temperature on *Crassostrea gigas* embryotoxicity. Ecotoxicol. Environ. Saf. 147, 251–259. https://doi.org/10.1016/j.ecoenv.2017.08.043.

Moreira, A., Figueira, E., Libralato, G., Soares, A.M.V.M., Guida, M., Freitas, R., 2018c. Comparative sensitivity of *Crassostrea angulata* and *Crassostrea gigas* embryo- larval development to As under varying salinity and temperature. Mar. Environ. Res. 140, 135–144. https://doi.org/10.1016/j.marenvres.2018.06.003.

Morgan, A.J., Kille, P., Sturzenbaum, S.R., 2007. Microevolution and ecotoxicology of metals in invertebrates. Environ. Sci. Technol. 41, (4),1 085–1096. https://doi.org/10.1021/es061992x.

Mousseau, T.A., Fox, C.W., 1998. The adaptive significance of maternal effects. Trends Ecol. Evol. 13, 403–407. https://doi:10.1016/S0169-53 47(98)01472-4.

Munari, M., Chemello, G., Finos, L., Ingrosso, G., Giani, M., Marin, M.G., 2016. Coping with seawater acidification and the emerging contaminant diclofenac at the larval stage: A tale from the clam *Ruditapes philippinarum*. Chemosphere 160, 293–302. https://doi.org/10.1016/j.chemosphere.2016.06.095.

Munari, M., Matozzo, V., Gagné, F., Chemello, G., Riedl, V., Finos, L., Pastore, P., Badocco, D., Marin, M.G., 2018. Does exposure to reduced pH and diclofenac induce oxidative stress in marine bivalves? A comparative study with the mussel *Mytilus galloprovincialis* and the clam *Ruditapes philippinarum*. Environ. Pollut. 240, 925–937. https://doi.org/10.1016/j.envpol.2018.05.005.

Munari, M., Matozzo, V., Benetello, G., Riedl, V., Pastore, P., Badocco, D., Marin, M.G., 2020. Exposure to Decreased pH and Caffeine Affects Hemocyte Parameters in the Mussel *Mytilus galloprovincialis*. J. Mar. Sci. Eng. 8, 238. https://doi.org/10.3390/jmse8040238.

Munday, P.L., Warner, R.R., Monro, K., Pandolfi, J.M., Marshall, D.J., 2013. Predicting evolutionary responses to climate change in the sea. Ecol. Lett. 16, 1488–1500. https://doi.org/10.1111/ele.12185.

Munday, P. L., Donelson, J. M., Domingos, J. A., 2016. Potential for adaptation to climate change in a coral reef fish. Glob. Chang. Biol. 23, 307–317. https://doi.org/10.1111/gcb.13419.

Nagelkerken, I., Connell, S.D., 2015. Global alteration of ocean ecosystem functioning due to increasing human CO_2 emissions. Proc. Natl. Acad. Sci. 112, 13272 LP – 13277. https://doi.org/10.1073/pnas.1510856112.

Nardi, A., Mincarelli, L.F., Benedetti, M., Fattorini, D., d'Errico, G., Regoli, F., 2017. Indirect effects of climate changes on cadmium bioavailability and biological effects in the Mediterranean mussel *Mytilus galloprovincialis*. Chemosphere 169, 493–502. https://doi.org/10.1016/j.chemosphere.2016.11.093.

Nardi, A., Benedetti, M., d'Errico, G., Fattorini, D., Regoli, F., 2018. Effects of ocean warming and acidification on accumulation and cellular responsiveness to cadmium in mussels *Mytilus galloprovincialis*: Importance of the seasonal status. Aquat. Toxicol. 204, 171–179. https://doi.org/10.1016/j.aquatox.2018.09.009.

Nikinmaa, M., 2013. Climate change and ocean acidification-interactions with aquatic toxicology. Aquat. Toxicol. 126, 365–72. https://doi.org/10.1016/j.aquatox.2012.09.006.

Noyes, P.D., McElwee, M.K., Miller, H.D., Clark, B.W., Van Tiem, L.A., Walcott, K.C., Erwin, K.N., Levin, E.D., 2009. The toxicology of climate change: Environmental contaminants in a warming world. Environ. Int. 35, 971–986. https://doi.org/10.1016/j.envint.2009.02.006.

Nowak, C., Jost, D., Vogt, C., Oetken, M., Schwenk, K., Oehlmann J., 2007. Effects of inbreeding and reduced genetic variation on tolerance to cadmium stress in the midge *Chironomus riparius*. Aquat. Toxicol. 85:278–284. https://doi.org/10.1016/j.aquatox.2007.04.015.

Oziolor, E.M., De Schamphelaere, K., Matson, C.W., 2016. Evolutionary toxicology: Meta-analysis of evolutionary events in response to chemical stressors. Ecotoxicology 25, 1858–1866. https://doi.org/10.1007/s10646-016-1735-6.

Parker, L.M., Ross, P.M., O'Connor, W.A., Borysko, L., Raftos, D.A., Pörtner, H.O., 2012. Adult exposure influences offspring response to ocean acidification in oysters. Glob. Chang. Biol. 18, 82–92. https://doi.org/10.1111/j.1365-2486.2011.02520.x.

Pascal, P.-Y., Fleeger, J.W., Galvez, F., Carman, K.R., 2010. The toxicological interaction between ocean acidity and metals in coastal meiobenthic copepods. Mar. Pollut. Bull. 60, 2201–8. https://doi.org/10.1016/j.marpolbul.2010.08.018.

Patel, P.P., Bielmyer-Fraser, G.K., 2015. The influence of salinity and copper exposure on copper accumulation and physiological impairment in the sea anemone, *Exaiptasia pallida*. Comp. Biochem. Physiol. Part - C Toxicol. Pharmacol. 168, 39–47. https://doi.org/10.1016/j.cbpc.2014.11.004.

Pespeni, M.H., Sanford, E., Gaylord, B., Hill, T.M., Hosfelt, J.D., Jaris, H.K., Lavigne, M., Lenz, E. a, Russell, A.D., Young, M.K., Palumbi, S.R., 2013. Evolutionary change during experimental ocean acidification. Proc. Natl. Acad. Sci. U. S. A. 110, 6937–42. https://doi.org/10.1073/pnas.1220673110.

Pichler, T., Biscéré, T., Kinch, J., Zampighi, M., Houlbrèque, F., Rodolfo-Metalpa, R., 2019. Suitability of the shallow water hydrothermal system at Ambitle Island (Papua New Guinea) to study the effect of high *p*CO_2 on coral reefs. Mar. Pollut. Bull. 138, 148–158. https://doi.org/https://doi.org/10.1016/j.marpolbul.2018.11.003.

Piggott, J.J., Townsend, C.R., Matthaei, C.D., 2015. Reconceptualizing synergism and antagonism among multiple stressors. Ecol. Evol. 5, 1538–1547. https://doi.org/10.1002/ece3.1465.

Pires, A., Figueira, E., Moreira, A., Soares, A.M.V.M., Freitas, R., 2015. The effects of water acidification, temperature and salinity on the regenerative capacity of the polychaete *Diopatra neapolitana*. Mar. Environ. Res. 106, 30–41. https://doi.org/10.1016/j.marenvres.2015.03.002.

Pistevos, J.C. a., Calosi, P., Widdicombe, S., Bishop, J.D.D., 2011. Will variation among genetic individuals influence species responses to global climate change? Oikos 120, 675–689. https://doi.org/10.1111/j.1600-0706.2010.19470.x.

Plaire, D., Bourdineaud, J., Alonzo, A., Camilleri, V., Garcia-Sanchez, L., Adam-Guillermin, C., Alonzo, F., 2013. Comparative Biochemistry and Physiology , Part C Transmission of DNA damage and increasing reprotoxic effects over two generations of *Daphnia magna* exposed to uranium. Comp. Biochem. Physiol. Part C 158, 231–243. https://doi.org/10.1016/j.cbpc.2013.09.001.

Po, B.H.K., Chiu, J.M.Y., 2018. Transgenerational impairments of reproduction and development of the marine invertebrate *Crepidula onyx* resulted from long-term dietary exposure of 2, 20 ,4 ,40 -tetrabromodiphenyl ether (BDE-47)*. Environ. Pollut. 235, 730–738. https://doi.org/10.1016/j.envpol.2017.12.087.

Ramajo, L., Marba, N., Prado, L., Peron. S., Lardies, M.A., Rodriguez-Navarro, A.B., Vargas, C.A., Lagos, N.A., Duarte, C.M., 2016. Biomineralization changes with food supply confer juvenile scallops (*Argopecten purpuratus*) resistance to ocean acidification. Glob. Change Biol. 22, 2025–2037. https://doi: 10.1111/gcb.13179.

Ramos, S., Homem, V., Alves, A., Santos, L., 2015, Advances in analytical methods and occurrence of organic UV-filters in the environment — A review. Sci. Total Environ. 526, 278–311. http://dx.doi.org/10.1016/j.scitotenv.2015.04.0550048-9697

Rastrick, S.S.P., Graham, H., Azetsu-Scott, K., Calosi, P., Chierici, M., Fransson, A., Hop, H., Hall-Spencer, J., Milazzo, M., Thor, P., Kutti, T., 2018. Using natural analogues to investigate the effects of climate change and ocean acidification on Northern ecosystems. ICES J. Mar. Sci. 75, 2299–2311. https://doi.org/10.1093/icesjms/fsy128.

Rattner, B.A., 2009. History of wildlife toxicology. Ecotoxicology 18, 773–783. https://doi.org/10.1007/s10646-009-0354-x.

Reátegui-Zirena, E.G., Fidder, B.N., Olson, A.D., Dawson, D.E., Bilbo, T.R., Salice, C.J., 2017. Transgenerational endpoints provide increased sensitivity and insight into multigenerational responses of *Lymnaea stagnalis* exposed to cadmium. Environ. Pollut. 224, 572–580. https://doi.org/https://doi.org/10.1016/j.envpol.2017.02.040.

Reis, P., Pereira, R., Carvalho, F.P., Oliveira, J., Mendo, S., Lourenço, J., 2018. Life history traits and genotoxic effects on *Daphnia magna* exposed to waterborne uranium and to a uranium mine effluent - A transgenerational study. Aquat. Toxixol. 202, 16–25. https://doi.org/10.1016/j.aquatox.2018.06.009.

Relyea, R. A., 2002. Costs of phenotypic plasticity. Am. Nat. 159, 272–282. https://doi:10.1086/338540.

Reusch, T.B.H., 2014. Climate change in the oceans: Evolutionary versus phenotypically plastic responses of marine animals and plants. Evol. Appl. 7, 104–122. https://doi.org/10.1111/eva.12109.

Riba, I., Conradi, M., Forja, J.M., DelValls, T.A., 2004. Sediment quality in the Guadalquivir estuary: lethal effects associated with the Aznalcóllar mining spill. Mar. Pollut. Bull. 48, 144–152. https://doi.org/10.1016/S0025-326X(03)00391-6.

Ricevuto, E., Lanzoni, I., Fattorini, D., Regoli, F., Gambi, M.C., 2016. Arsenic speciation and susceptibility to oxidative stress in the fanworm *Sabella spallanzanii* (Gmelin) (Annelida, Sabellidae) under naturally acidified conditions: An in situ transplant experiment in a Mediterranean CO_2 vent system. Sci. Total Environ. 544, 765–773. https://doi.org/10.1016/j.scitotenv.2015.11.154.

Roberts, D. a, Birchenough, S.N.R., Lewis, C., Sanders, M.B., Bolam, T., Sheahan, D., 2013. Ocean acidification increases the toxicity of contaminated sediments. Glob. Chang. Biol. 19, 340–51. https://doi.org/10.1111/gcb.12048

Rodríguez-Romero, A., Jiménez-Tenorio, N., Basallote, M.D., Orte, M.R. De, Blasco, J., Riba, I., 2014a. Predicting the impacts of CO_2 leakage from subseabed storage: Effects of metal accumulation and toxicity on the model benthic organism Ruditapes philippinarum. Environ. Sci. Technol. 48, 12292–12301. https://doi.org/10.1021/es501939c.

Rodríguez-Romero, A., Basallote, M.D., De Orte, M.R., DelValls, T.Á., Riba, I., Blasco, J., 2014b. Simulation of CO_2 leakages during injection and storage in sub-seabed geological formations: Metal mobilization and biota effects. Environ. Int. 68, 105–117. https://doi.org/10.1016/j.envint.2014.03.008

Rodríguez-Romero, A., Jarrold, M.D., Massamba-N'Siala, G., Spicer, J.I., Calosi, P., 2015. Multi-generational responses of a marine polychaete to a rapid change in seawater *p*CO_2. Evol. Appl. 9, 1082–1095. https://doi.org/10.1111/eva.12344.

Rodríguez-Romero, A., Ruiz-Gutiérrez, G., Viguri, J.R., Tovar-Sánchez, A., 2019. Sunscreens as a New Source of Metals and Nutrients to Coastal Waters. Environ. Sci. Technol. 53, 10177–10187. https://doi.org/10.1021/acs.est.9b02739

Sabater, S., Elosegi, A., Ludwig, R., 2019. Chapter 1 - Defining multiplestressor implications, in: Sabater, S., Elosegi, A., Ludwig, R.B.T.-M.S. in R.E. (Eds.), . Elsevier, pp. 1–22. https://doi.org/10.1016/B978-0-12-811713-2.00001-7.

Salinas, S., Brown, S. C., Mangel, M., Munch, S. B., 2013. Non-genetic inheritance and changing environments. Non-Genetic Inheritance, 1, 38–50. https://doi.org/10.2478/ngi-2013-0005.

Sánchez-Quiles, D., Tovar-Sánchez, A., 2014. Sunscreens as a source of hydrogen Peroxide production in coastal waters. Environ. Sci. Technol. 48, 9037–9042. https://doi.org/10.1021/es5020696.

Shang, Y., Wu, F., Wei, S., Guo, W., Chen, J., Huang, W., Hu, M., Wang, Y., 2020. Specific dynamic action of mussels exposed to TiO2 nanoparticles and seawater acidification. Chemosphere 241, 1–8. https://doi.org/10.1016/j.chemosphere.2019.125104.

Scheiner, S. M., 1993. Genetics and evolution of phenotypic plasticity. Annu. Rev. of Ecol. and Syst. 24,35–68. https://doi.org/ 10.1146/annurev.es.24.110193.000343.

Schiedek, D., Sundelin, B., Readman, J.W., Macdonald, R.W., 2007. Interactions between climate change and contaminants. Mar. Pollut. Bull. 54, 1845–1856. https://doi.org/10.1016/j.marpolbul.2007.09.020.

Sezer, N., Kocaoğlan, H.O., Kılıç, Ö., Lacoue-Labarthe, T., Belivermiş, M., 2018. Acidified seawater increases accumulation of cobalt but not cesium in manila clam *Ruditapes philippinarum*. J. Environ. Radioact. 184–185, 114–121. https://doi.org/10.1016/j.jenvrad.2018.01.018.

Scanes, E., Parker, L.M., O'Connor, W.A., Gibbs, M.C., Ross, P.M., 2018. Copper and ocean acidification interact to lower maternal investment, but have little effect on adult physiology of the Sydney rock oyster *Saccostrea glomerata*. Aquat. Toxicol. 203, 51–60. https://doi.org/10.1016/j.aquatox.2018.07.020.

Seemann, F., Peterson, D.R., Witten, P.E., Guo, B., Shanthanagouda, A.H., Ye, R.R., Zhang, G., Au, D.W.T., 2015. Comparative Biochemistry and Physiology , Part C Insight into the transgenerational effect of benzo [a] pyrene on bone formation in a teleost fish (*Oryzias latipes*) ☆. Comp. Biochem. Physiol. Part C 178, 60–67. https://doi.org/10.1016/j.cbpc.2015.10.001.

Shama, L.N.S., Wegner, K.M., 2014. Grandparental effects in marine sticklebacks: transgenerational plasticity across multiple generations. J. Evol. Biol. 27, 2297–2307. https://doi.org/10.1111/jeb.12490.

Shama, L.N.S., Mark, F.C., Strobel, A., Lokmer, A., John, U., Mathias Wegner, K., 2016. Transgenerational effects persist down the maternal line in marine sticklebacks: gene expression matches physiology in a warming ocean. Evol. Appl. 9, 1096–1111. https://doi.org/10.1111/eva.12370.

Shi, W., Zhao, X., Han, Y., Che, Z., Chai, X., Liu, G., 2016. Ocean acidification increases cad- mium accumulation in marine bivalves: a potential threat to seafood safety. Sci. Rep. 6. https://doi.org/10.1038/srep20197.

Siddiqui, S., Bielmyer-fraser, G.K., 2015. Responses of the sea anemone, *Exaiptasia pallida*, to ocean acidification conditions and copper exposure. Aquat. Toxicol. 167, 228–239. https://doi.org/10.1016/j.aquatox.2015.08.012.

Stauber, J.L., Chariton, A., Apte, S., 2016. Chapter 10 – Global Change, in Marine Ecotoxicology: Blasco, J., Chapman, P.M., Campana, O., Hampel, M.B.T.-M.E. (Eds.), . Academic Press, pp. 273-314. ISBN: 978-0-12-803371-5.

Sowers, A.D., Gaworecki, K.M., Mills, M.A., Roberts, A.P., Klaine, S.J., 2009. Developmental effects of a municipal wastewater effluent on two generations of the fathead minnow, *Pimephales promelas*. Aquat. Toxicol. 95, 173–181. https://doi.org/10.1016/j.aquatox.2009.08.012.

Snape, J.R., Maund, S.J., Pickford, D.B., Hutchinson, T.H., 2004. Ecotoxicogenomics: The challenge of integrating genomics into aquatic and terrestrial ecotoxicology. Aquat. Toxicol. 67, 143–154. https://doi.org/10.1016/j.aquatox.2003.11.011.

Su, W., Zha, S., Wang, Y., Shi, W., Xiao, G., Chai, X., Wu, H., Liu, G., 2017. Benzo[a]pyrene exposure under future ocean acidification scenarios weakens the immune responses of blood clam, *Tegillarca granosa*. Fish Shellfish Immunol. 63, 465–470. https://doi.org/10.1016/j.fsi.2017.02.046.

Sun, P.Y., Foley, H.B., Handschumacher, L., Suzuki, A., Karamanukyan, T., Edmands, S., 2014. Acclimation and adaptation to common marine pollutants in the copepod *Tigriopus californicus*. Chemosphere 112, 465–471. https://doi.org/10.1016/J.CHEMOSPHERE.2014.05.023.

Sun, P.Y., Foley, H.B., Wu, L., Nguyen, C., Chaudhry, S., Bao, V.W.W., Leung, K.M.Y., Edmands, S., 2018. Long-term laboratory culture causes contrasting shifts in tolerance to two marine pollutants in copepods of the genus *Tigriopus*. Environ. Sci. Pollut. Res. Int. 25(4), 3183–3192. https://doi.org/10.1007/s11356-017-0398-z.

Sunday, J.M., Crim, R.N., Harley, C.D.G., Hart, M.W., 2011. Quantifying rates of evolutionary adaptation in response to ocean acidification. PLoS One 6, e22881. https://doi.org/10.1371/journal.pone.0022881.

Sunday, J.M., Calosi, P., Dupont, S., Munday, P.L., Stillman, J.H., Reusch, T.B.H., 2014. Evolution in an acidifying ocean. Trends Ecol. Evol. 29, 117–125. https://doi.org/10.1016/j.tree.2013.11.001.

Thomsen, J., Stapp, L.S., Haynert, K., Schade, H., Danelli, M., Lannig, G., Wegner, K.M., Melzner, F., 2017. Naturally acidified habitat selects for ocean acidification–tolerant mussels. Sci. Adv. 3 (4), e1602411. https://doi.org/ 10.1126/sciadv.1602411.

Thibault, C., Massamba-N'Siala, G., Noisette, F., Vermandele, F., Babin, M., Calosi, P., 2020. Within- and trans-generational responses to combined global changes are highly divergent in two congeneric species of marine annelids. Mar. Biol. 167, 1–17. https://doi.org/10.1007/s00227-019-3644-8.

Ullah, H., Nagelkerken, I., Goldenberg, S.U., Fordham, D.A., 2018. Climate change could drive marine food web collapse through altered trophic flows and cyanobacterial proliferation. PLoS Biol. 16, 1–21. https://doi.org/10.1371/journal.pbio.2003446.

Valdés, J., Román, D., Alvarez, G., Ortlieb, L., Guiñez, M., 2008. Metals content in surface waters of an upwelling system of the northern Humboldt Current (Mejillones Bay, Chile) 71, 18–30. https://doi.org/10.1016/j.jmarsys.2007.05.006.

Van Straalen, N.M., Timmermans, M.J.T.N., 2002. Genetic variation in toxicant-stressed populations: an evaluation of the ‘‘genetic erosion hypothesis’’. Hum. Ecol. Risk Assess. 8, 983–1002. https://doi.org/10.1080/1080-700291905783.

Velez, C., Figueira, E., Soares, A.M.V.M., Freitas, R., 2016. Combined effects of seawater acidification and salinity changes in *Ruditapes philippinarum*. Aquat. Toxicol. 176, 141–150. https://doi.org/10.1016/j.aquatox.2016.04.016.

Viguri, J., Andres, A., Ruiz, C., Irabien, A., Castro, F., 2001. Cement-waste and clay-waste derived products from metal hydroxides wastes: Environmental characterization. Process Saf. Environ. 79, 1, 38-44. https://doi.org/10.1205/095758201531121.

Visbeck, M., 2018. Ocean science research is key for a sustainable future. Nat. Commun. 9, 690. https://doi.org/10.1038/s41467-018-03158-3.

Vizzini, S., Di Leonardo, R., Costa, V., Tramati, C.D., Luzzu, F., Mazzola, A., 2013. Trace element bias in the use of CO_2 in vents as analogues for low pH environments:

Implications for contamination levels in acidified oceans. Estuar. Coast. Shelf Sci. 134, 19–30. https://doi.org/10.1016/j.ecss.2013.09.015.

Xu, X., Shi, L., Wang, M., 2016. Comparative quantitative proteomics unveils putative mechanisms involved into mercury toxicity and tolerance in *Tigriopus japonicus* under multigenerational exposure scenario. Environ. Pollut. 218, 1287–1297. https://doi.org/10.1016/j.envpol.2016.08.087.

Wang, M., Lee, J., Li, Y., 2017. Global proteome profiling of a marine copepod and the mitigating effect of ocean acidification on mercury toxicity after multigenerational exposure. Environ. Sci. Technol. 51, 10, 5820-5831 https://doi.org/10.1021/acs.est.7b01832.

Waters, C.N., Zalasiewicz, J., Summerhayes, C., Barnosky, A.D., Poirier, C., Gałuszka, A., Cearreta, A., Edgeworth, M., Ellis, E.C., Ellis, M., Jeandel, C., Leinfelder, R., McNeill, J.R., Richter, D. deB., Steffen, W., Syvitski, J., Vidas, D., Wagreich, M., Williams, M., Zhisheng, A., Grinevald, J., Odada, E., Oreskes, N., Wolfe, A.P., 2016. The Anthropocene is functionally and stratigraphically distinct from the Holocene. Science (80-.). 351, aad2622. https://doi.org/10.1126/science.aad2622.

Zhang, H., Cheung, S.G., Shin, P.K.S., 2014. The larvae of congeneric gastropods showed differential responses to the combined effects of ocean acidification, temperature and salinity. Mar. Pollut. Bull. 79, 39–46. https://doi.org/10.1016/j.marpolbul.2014.01.008.