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Marine harmful algal blooms, human health and wellbeing: challenges and opportunities in the 21st century

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Abstract :

Microalgal blooms are a natural part of the seasonal cycle of photosynthetic organisms in marine ecosystems. They are key components of the structure and dynamics of the oceans and thus sustain the benefits that humans obtain from these aquatic environments. However, some microalgal blooms can cause harm to humans and other organisms. These harmful algal blooms (HABs) have direct impacts on human health and negative influences on human wellbeing, mainly through their consequences to coastal ecosystem services (fisheries, tourism and recreation) and other marine organisms and environments. HABs are natural phenomena, but these events can be favoured by anthropogenic pressures in coastal areas. Global warming and associated changes in the oceans could affect HAB occurrences and toxicity as well, although forecasting the possible trends is still speculative and requires intensive multidisciplinary research. At the beginning of the 21st century, with expanding human populations, particularly in coastal and developing countries, mitigating HABs impacts on human health and wellbeing is becoming a more pressing public health need. The available tools to address this global challenge include maintaining intensive, multidisciplinary and collaborative scientific research, and strengthening the coordination with stakeholders, policymakers and the general public. Here we provide an overview of different aspects of the HABs phenomena, an important element of the intrinsic links between oceans and human health and wellbeing.

Keywords : Harmful algal blooms, human health and wellbeing, marine biotoxins, ecosystem services

1. OVERVIEW OF THE CHALLENGES

Aquatic ecosystems are supported by photosynthetic organisms (e.g., macrophytes, benthic and planktonic microalgae and cyanobacteria) that fix carbon, produce oxygen, and constitute the bases of food webs. Under certain circumstances, however, the abundance of some taxa can reach levels that may cause harm to humans and other organisms. These proliferations often are referred to as "harmful algal blooms" (HABs), a term that includes a variety of species and consequences that humans perceive as adverse. HABs occur in all aquatic environments (e.g., freshwater, brackish and marine) and at all latitudes. In this paper, we focus specifically on the threat that blooms of harmful microalgae pose to the benefits (food supplies, economic activities, tourism and recreation) that the oceans and seas provide to human health and wellbeing (**Figure 1**).

Of the many thousands of microalgal species described, about 300 are involved in harmful events (see e.g., http://www.marinespecies.org/hab/index.php). More than 100 of these species, with no apparent physiologic, phylogenetic, or structural commonalities, produce potent and persistent natural toxins that can be harmful or even lethal to humans and animals (Sournia, 1995; Moestrup *et al.*, 2009). The chemically diverse compounds synthesized by toxic HABs species have been associated with different syndromes in humans (**Box 1**), and many may also adversely affect certain fish, seabirds, reptiles, and marine mammals (**Box 2**).

In humans, toxicity is caused by the ingestion of contaminated seafood products (fish or shellfish), skin contact with toxin-contaminated water, or the inhalation of aerosolized toxins or noxious compounds. In the case of food-borne poisonings (**Figure 2**), HAB toxins are bio-concentrated, often without apparently harming the vector marine organism that ingested the toxin, and transferred up through the food web to humans. Toxic effects usually occur when the HAB species producing the toxin is present in high abundance, although seafood poisoning also can be caused by highly toxic microalgae at low abundances. In addition to the direct impacts on human health, these toxic outbreaks have associated consequences on other components of human wellbeing both in terms of their socio-economic impact and costs. Namely, HAB

occurrences can lead to the closure of important shellfisheries (e.g. Jin *et al.*, 2008) and increases in the costs of monitoring and management (Hoagland *et al.*, 2002).

Another hazardous effect of some HABs taxa is the production of excess algal biomass, which can affect individual organisms and ecosystems in different ways (**Box 2**). When large blooms decay, the subsequent degradation by bacteria of accumulated biomass reduces oxygen concentrations in marine waters, can cause hypoxia, especially in bottom waters isolated by density gradients from surface waters. In addition to the benthic faunal mortalities related to oxygen depletion, the unpleasant appearance of surface scums and bad odours associated with some HABs can dissuade tourists from visiting coastal recreation areas (Scatasta *et al.*, 2003). Phycotoxins also can cause morbidities and mortalities of wild and farmed fish (gill damage), birds (hypothermia), marine mammals, or certain invertebrates, resulting in economic losses in finfish aquaculture and tourism, and losses of the non-market, "passive" values that humans may have for protected species or extraordinary ecosystems. These examples illustrate how HABs may also decrease the non-market, passive use values of marine ecosystems and their services, thereby limiting the way in which the marine environment can enhance the quality of life and wellbeing for humans (Hoagland & Scatasta, 2006).

Blooms of microalgae, including those deemed by humans to be harmful (see for instance, http://haedat.iode.org), are a natural phenomenon (e.g. Smayda, 1997; Margalef, 1998; Gowen *et al.*, 2012 and references cited therein) and awareness of HAB events is embedded in the cultural heritage of many coastal human communities. Historically, this awareness has helped to mitigate some of the adverse effects of HABs. However, at present, there is a need to increase the information about the publich health risks and the strategies that scientists and policy makers, working together, can address to decrease the impacts of HABs on human health and wellbeing. It is important to recognize that there is not a realistic way to prevent HABs occurrence as it results from complex interactions among physical, chemical, and biological processes operating at different spatio-temporal scales in the marine environment. Over the last 50 years, human modifications of the marine environment, particularly those occurring at the

133 land-sea interface, may have influenced the incidence of HABs in certain
134 locations. These modifications include the alteration of water circulation in
135 harbors and artificial beach construction, the dispersal of species through ship
136 ballast waters, and nutrient over-enrichment (Hallegraeff & Bolch, 1992;
137 Anderson *et al.*, 2002; Davidson *et al.*, 2014).
138 Superimposed on these stresses, global warming is leading already to
139 temperature increases in some areas of the earth's oceans, and warmer waters
140 could affect the occurrence of HABs (Moore *et al.*, 2008; Backer & Moore, 2010;
141 Hallegraeff, 2010 and references cited therein; Gowen *et al.*, 2012). Specifically,
142 we can expect future changes in the frequency, intensity, and geographic extent
143 of many HABs, although the possible responses are likely to be highly species-
144 specific, given the diverse toxicity, physiology, biology, and ecology of HAB
145 organisms. Thus, the forecasting of such changes is still quite speculative,
146 requiring long time series of ecological processes, as well as more focused
147 research (including modeling).
148 This review was stimulated by discussions at the "Oceans and Human Health
149 at the beginning of the XXIst century" workshop held in Bedruthan (Cornwall,
150 United Kingdom) on March 2014 (Fleming *et al.*, 2104). This paper is not an
151 exhaustive review of all the different factors concerning the occurrence of HAB
152 events (see e.g. GEOHAB 2001; 2005; 2006; 2008; 2010; 2012; Zingone & Wyatt,
153 2005; Gowen *et al.*, 2012). Instead, we summarize the main direct impacts of
154 HABs on human health. We describe briefly the influences of HABs on human
155 wellbeing, mainly through the negative consequences to ecosystem services and
156 other marine organisms and environments. Other aspects of the possible
157 interconnections between human wellbeing and HABs have yet to be
158 investigated. Based on this evidence, we highlight the main challenges posed by
159 marine HABs, and we discuss the tools available to respond to HABs in the
160 coming years, especially within the context of climate warming.
161
162 2. DIRECT IMPACTS OF HABS ON HUMAN HEALTH.
163 As noted above, the direct impacts of HABs in marine waters on human health
164 are linked to poisonings (**Box 1**) associated with eating contaminated seafood
165 (**Figure 2**), skin contact with contaminated water, and/or inhaling aerosolised

biotoxins. In addition to human health conditions associated with known toxins produced by microalgae, there exist emerging phycotoxins and risks of poisoning through biotoxin contaminated desalinated drinking water. In the remaining text, the terms "biotoxin", "phycotoxin" or "toxin" will be used to refer to toxic compounds synthesized by the marine microalgae.

2.1. Food-borne diseases: overview.

Poisoning through the ingestion of biotoxin-contaminated seafood is the best documented impact that HABs have on humans (**Figure 2, Box 1**). The poisoning process involves the bio-concentration of the biotoxins by filter feeding fauna (mostly bivalve molluscs, e.g., *Mytilus* spp.) which themselves are generally unaffected by these compounds. Other vectors include certain marine gastropods (e.g., whelks and moon scails), some crustaceans (e.g., crabs), echinoderms and fish (e.g., some planktivorous fishes or belonging to the tetraodontidae family) that acquire biotoxins through the food web (Deeds *et al.*, 2008). Toxins accumulated in seafood tissues can remain for considerable lengths of time after the bloom has declined in the seawater. Further, these biotoxins are not destroyed by cooking or by the processing of seafood products, and because they do not have distinctive odours or taste, they can be detected only through specialised laboratory testing (Zaias *et al.*, 2010).

Most algal toxins are primarily neurotoxins (e.g., brevetoxins affecting the Na+ channels), although they are also known to affect human health through other routes (e.g., okadaic acid affecting phosphatase activity). The various toxic compounds can produce a wide range of symptoms and thus have been associated with several clinically described syndromes depending on the main symptomatic mode (**Box 1**): Amnesic (ASP), Azaspirazid (AZP), Diarrheic (DSP), Neurotoxic (NSP) and Paralytic (PSP) Shellfish Poisonings and Ciguatera Fish Poisoning (CFP). The syndromes can present with symptoms from the nervous, digestive, respiratory, hepatic, dermatologic, or cardiac systems. The effects can be acute (e.g., paralytic shellfish poisoning can occur within minutes to hours; Medcof, 1985) and can last for weeks to months (e.g., ciguatera fish poisoning; Friedman *et al.*, 2008). Although there is considerable knowledge on the acute health effects caused by HAB biotoxins, many of the toxicological mechanisms

are incompletely understood. In addition, we know little about the chronic effects of these biotoxins, either from acute exposure that produce long-lasting damages, or from chronic low level exposures over long periods of time.

For the foodborne syndromes, the prevention of contaminated shellfish reaching the markets (by monitoring the causative species and/or the presence of biotoxin in seafood in real time) is currently the only effective way to protect human health. In fact, well-structured monitoring programmes targeting the causative organisms and toxins in commercial seafood associated with the clinical syndromes (i.e., ASP, AZP, DSP, NSP and PSP) have proven effective in reducing the human exposure to biotoxins in many areas of the world. Information about operative HAB monitoring programmes is not compiled at a worldwide scale, only at regional as for the North Atlantic by the ICES (International Council for the Exploration of the Sea) – IOC UNESCO Working Group on Harmful Algal Blooms Dynamics (http://www.ices.dk/community/groups/Pages/WGHABD.aspx). However, monitoring needs to be complemented with additional actions such as informing the public in non-commercial areas affected by HABs (e.g. Reich *et al.*, 2015) and increasing the understanding of the complex processes involved the harmful events (e.g., Whyte *et al.*, 2014).

Unfortunately, due to increased human pressure on coastal marine ecosystems together with climate change, harmful blooms may occur in areas where they have not previously been reported (Campbell *et al.*, 2010; Trainer *et al.*, 2013). Also, new biotoxins are continually being identified. For these cases, toxin detection and identification of the causative organism represent new challenges for monitoring and prevention procedures (Turner *et al.*, 2015). It is also noteworthy that for ciguatera fish poisoning, the most frequent cause of HAB-associated poisoning in tropical waters, effective procedures to protect human populations are lacking (see section 2.1.b and 4.2). Increased international tourist travel and trade in seafood can lead to poisonings in areas far from where the fish is caught (Mattei *et al.*, 2014).

2.1.A. MOST COMMON BIOTOXIN SYNDROMES IN TEMPERATE LATITUDES.

In the temperate latitudes of Europe, South Africa, Asia, Australia, North America, and South America, the most common HABs cause amnesic (ASP), azaspiracid (AZP), diarrheic (DSP), neurotoxic (NSP) and paralytic (PSP) shellfish poisonings (**Box 1**).

Domoic acid, a neurotoxin produced by various species of *Pseudo-nitzschia* and *Nitzschia*, was identified as responsible for causing an outbreak of amnesic shellfish poisoning in humans (involving 107 illnesses and 3 deaths) after the consumption of blue mussels from Prince Edward Island (Canada) in 1987 (Bates *et al.*, 1989; Todd, 1993). Since then, blooms of these pennate diatoms have resulted in a range of, often large scale, shellfish toxicity events, affecting humans and other large vertebrates (see section 3.2. and **Box 2**). Symptoms of ASP poisoning in humans include short and long-term memory loss.

The azaspiracids, first identified in mussels from Ireland in 1995 (Satake *et al.*, 1998), belong to a novel group of polyether biotoxins produced by the small armoured dinoflagellate *Azadinium spinosum* (Tillmann *et al.*, 2009; see also section 4.1). This biotoxin causes symptoms similar to those displayed by DSP (Twiner *et al.*, 2008), although slowly progressing paralyses have also been observed in mouse assays. Azaspiracids has now been found in a number of other European Union countries with approximately 20 different analogues of AZA identified.

Diarrheic shellfish poisoning (DSP) was first linked to the presence of *Dinophysis fortii* in Japan *(*Yasumoto *et al.*, 1980) and to *D. acuminata* in Dutch coastal waters (Kat, 1983), and it was recorded after consumption of mussels containing DSP biotoxins from the Northern Adriatic coast in 1989 (Boni *et al.*, 1992). Diarrheic shellfish poisoning is caused by okadaic acid or its derivative dinophysistoxins, produced by ten species of the genus *Dinophysis*, two species of the genus *Phalachroma* (Reguera et al *et al.*, 2012), and *Prorocentrum lima* (Koike *et al.*, 1998). In humans, DSP biotoxins bind to phosphatase receptors, causing severe, but not usually fatal, gastrointestinal symptoms (with a rapid onset). DSP outbreaks are common in Europe, affecting shellfish consumers in at least 10 countries. On occasion, outbreaks have resulted in large numbers of people becoming ill, and shellfish harvest areas have been closed for up to 10 months (e.g., Fraga & Sánchez, 1985; Haamer *et al.*, 1990; Lassus *et al.*, 1995;

Ramstad *et al.*, 2001; Blanco *et al.*, 2005; 2013; Vale *et al.*, 2008; review by Reguera *et al.*, 2014).

For regulatory purposes, the more recently discovered pectenotoxins and yessotoxins are classified within the DSP group. Pectenotoxins are produced by some of the *Dinophysis* species including *D. acuta* and *D. acuminata*. Yessotoxins induce similar symptoms but are produced by the dinoflagellates *Lingulodinium polyedrum* and *Protoceratium reticulatum* (Paz *et al.*, 2004 and references cited there in). Recently, experts have recommended the deregulation of pectenotoxins and yessotoxins due to research results finding a non-toxic effect of the oral administration of these substances in mice (Anonymous, 2006).

Brevetoxin is the collective name given to a class of biotoxins that causes neurotoxic shellfish poisoning (NSP). Brevetoxins are produced primarily by the naked dinoflagellate *Karenia brevis*. In the Gulf of Mexico, and in isolated instances along the Southeast Atlantic coast of the United States, blooms of *K. brevis* have caused water discolouration, large-scale finfish mortality events, human poisonings due to the consumption of shellfish, and respiratory problems in asthmatics caused by inhalation of biotoxin in the form of an aerosol (Morris *et al.*, 1991; Magaña *et al.*, 2003; Kirkpatrick *et al.*, 2004; Watkins *et al.*, 2008; Fleming *et al.*, 2011). Notably, NSP has not been linked to fatalities in humans (van Dolah, 2000). The occurrence of toxic *K. brevis* red tides was recorded as early as 1648 in the Western Gulf of Mexico and since the 1840s in Florida (Magaña *et al.*, 2003; Kirkpatrick *et al.*, 2004).

Paralytic shellfish poisoning (PSP) is caused by saxitoxin and its derivatives, potent neurotoxins that can cause headache, nausea, facial numbness, and, in severe cases, respiratory failure and death. The first likely cases in the UK were in 1827 in Leith and in 1888 in Liverpool (Ayres, 1975). In British Columbia (Gaines & Taylor, 1985) and Norway (Yndestad & Underdal, 1985), the first recorded outbreaks of PSP were in 1793 and 1901 respectively. Medcof (1985) reported toxic shellfish episodes from the 1930s and 1940s. In Europe and North America, PSP is mainly associated with blooms of the thecate (armoured) dinoflagellate genus *Alexandrium,* mainly *A. tamarense/funyense/catenella* group and *A. minutum* (Medlin *et al.*, 1998; Higman *et al.*, 2001; Lilly *et al.*, 2007; Touzet *et al.*, 2007), although some *Alexandrium* species and strains are non toxic. In

297 Asia (Philippines, Malaysia, Brunei and Indonesia, Papua New Guinea), PSP is
298 mainly produced by outbreaks of the armoured dinoflagellate *Pyrodinium*
299 *bahamense* var. *compressum.* In the Philippines, this species was responsible for
300 1,995 cases with 117 deaths linked to PSP toxicity between 1983 and 1999
301 (Azanza, 1999; Azanza & Taylor (2001).
302
303 2.1.B. CIGUATERA FISH POISONING (CFP).
304 Worldwide, ciguatera fish poisoning (CFP) is the most common food poisoning
305 associated with a natural, non-bacterial chemical, and it occurs throughout the
306 tropics, particularly in vulnerable island communities such as the Pacific Island
307 Countries and Territories (PICTs). Ciguatoxins, or their precursors, are produced
308 by several species of the benthic dinoflagellate genus *Gambierdiscus* (mainly *G.*
309 *toxicus*). The biotoxins are modified through metabolic pathways in the food web
310 of coral reefs, and they tend to accumulate in fish, particularly larger carnivorous
311 species such as barracuda (*Sphyraena* spp., Heymann, 2004), but they also have
312 been found in more than 400 fish species. After consuming ciguatoxin-
313 contaminated fish, a range of acute neurologic, gastrointestinal, and cardiac
314 symptoms have been reported, with some individuals experiencing chronic
315 neurologic symptoms lasting weeks to months (e.g., Freudenthal, 1990;
316 Friedman *et al.*, 2008; Skinner *et al.*, 2011, and references cited therein).
317 Repeated exposure to ciguatoxins can reportedly exacerbate the acute ciguatera
318 symptoms (Bagnis *et al.*, 1979; Pottier *et al.*, 2001).
319 CFP is a threat to public health throughout tropical areas, and it is the most
320 widespread, and hence best described, in the island nations of the Pacific and the
321 Caribbean (for reviews, see Bruslé, 1997; Lehane & Lewis, 2000; Friedman *et al.*,
322 2008; and references therein). Unfortunately, the real extent of illness is not well
323 documented due to under-reporting and misdiagnosis (McKee *et* al, 2001; Radke
324 *et al.*, 2015). Thus, its impacts on human communities and ecosystem health are
325 still poorly understood. Data from the Health and Fisheries Authorities of 17
326 PICTs (Skinner *et al.*, 2011) estimated a mean annual incidence of 104 cases per
327 100,000 people across the region during 1973-83. Based on these estimates, the
328 recorded CFP incidence in the South Pacific should be increased by 60%, i.e., up
329 to 194 cases per 100,000 people between 1998-2008.

CFP illness rates exhibit high variability, reaching particularly elevated levels in some areas. For instance, up to 497 cases per 10,000 population per year were recorded in French Polynesia and in the Raivavae Islands (Australes) between 2000-08 (Chateau-Dégat *et al.*, 2009; Chinain *et al.*, 2010a), and up to 440 cases per 10,000 population per year in the Caribbean between 1996-2006 (Tester *et al.*, 2010). Despite uncertainty about the real incidence, data suggest that CFP constitutes an acute and chronic illness with major public health significance at both local and more widespread levels. In the future, the health problem could be exacerbated due to anthropogenic pressures, such as the increased development of the coastal zone, ocean warming (e.g. Villareal *et al.*, 2007; Kibler *et al.*, 2015), or natural disasters, such as hurricanes. These pressures can lead to the damage of coral reefs, favouring more resilient macroalgae that constitute new surfaces for the proliferation of the involved toxicogenic benthic dinoflagellates (e.g., Chateau-Degat *et al.*, 2005; Tester *et al.*, 2010).

It is inherently difficult to cope with CFP as a public health problem. For example, the risks of CFP often have been traditionally "managed" by native fishermen using their local, traditional knowledge, who may warn each other about areas where ciguatoxin-contaminated fish are known to occur. With increasing trade and coastal tourism, CFP cases could occur in non-tropical areas, where ciguatera often goes unrecognized or diagnosed only after expensive investigation (Epelboin *et al.*, 2014; Mattei *et al.*, 2014). There is neither a reliable, cost-effective method for detecting the biotoxin nor is there a biomarker to diagnose the illness in humans. A review by Friedman *et al.*, 2008, describes the clinical course of CFP and its possible treatments, many of which may be unclear to other healthcare providers and public health practitioners, even in endemic areas.

2.1.C. POISONING BY PALYTOXIN AND ANALOGUES.

Ostreopsis is a dinoflagellate genus co-occurring with *Gambierdiscus*. In tropical Indo-Pacific latitudes, *Ostreopsis* has been associated with poisoning after the ingestion of clupeid fishes, crabs, or sea urchins contaminated with palytoxin (PLTX) (see review by Deeds & Schwarz, 2010, and references cited therein). This compound and its analogues (Ciminiello *et al.* 2011; 2015 and references

therein; Brissard *et al.*, 2015;) are among the most potent biotoxins of marine origin. Nevertheless, in spite of the well-documented but very limited number of severe PLTX-related poisoning cases in these tropical areas, the true risk of PLTX poisoning through seafood consumption in humans is difficult to assess. This is because of the co-occurrence of PLTX with other seafood biotoxins (e.g., ciguatoxins, saxitoxins, and tetrodotoxin), the distribution of PLTX mainly in the tropical areas of developing nations with little surveillance and reporting, and its prevalence in reef species that are not commercially harvested.

Ostreopsis is expanding to temperate latitudes, and recurrent blooms have occurred in Mediterranean waters during the last two decades (e.g., Mangialajo *et al.*, 2011; Illoul *et al.*, 2012). In this region, *Ostreopsis* proliferations have been related to aerosol exposures at bathing beaches (section 2.3.b) and macrofaunal mortalities (**Box 2**). Fortunately, to date, food poisonings related to the PLTX-like group have not been reported in the Mediterranean, although the biotoxin has been detected in certain marine fauna (e.g., Aligizaki *et al.*, 2011; Biré *et al.*, 2013; Brissard *et al.*, 2014; Ciminiello *et al.*, 2015). The European regulation to monitor PLTX has not yet become established, although the Panel on Contaminants in the Food Chain (CONTAM Panel) of the European Food Safety Authority (EFSA, 2009) assessed the risks to human health associated with the presence of PLTX-group biotoxins in shellfish, recommending a maximum concentration of 30 µg eqPLTX/kg fresh weight. Overall, the few available data suggest a growing potential risk of seafood contamination (from commercial or recreational fishing or aquaculture) in Mediterranean coastal waters (specially in those affected by recurrent *Ostreopsis* blooms).

The possible transfer and accumulation of the PLTX-like group of biotoxins through the food web to humans should be investigated further. Because *Ostreopsis* exhibits both benthic and planktonic phases (Bravo *et al.*, 2012), its dispersion is facilitated, increasing the number of seafood types that could become contaminated and complicating its monitoring. The planktonic stage can contaminate filter-feeding bivalves (e.g., mussels), while the benthic stage can enter the food chain through herbivores (e.g., sea urchins, crabs, gastropods, salps) that feed on macroalgae (Brissard *et al.*, 2014). PLTX-like biotoxins can then be transferred to omnivores and carnivores, including humans.

2.1.D. EMERGING BIOTOXINS.

Cyclic imines.

Cyclic imines (gymnodimine, spirolides, pinnatoxins and others) have been produced reportedly by a number of dinoflagellates (*Karenia selliformis*, *Vulcanodinium rugosum, Alexandrium ostenfeldii* and *A. peruvianum*). They are classified typically as fast-acting biotoxins due to the rapid mortality occurring in the mouse bioassay for lipophilic biotoxins (Molgó *et al.*, 2014, and references cited therein). Both gymnodimine and pinnatoxins had been associated initially with acute human food poisoning events (Seki *et al.*, 1995; Uemura *et al.*, 1995). Further studies indicated that other biotoxins (i.e., brevetoxins in the case of the New Zealand shellfish poisoning assumed to be caused by gymnodimine) or bacterial (*Vibrio*) contamination (in the case of the Chinese poisoning assumed to be caused by pinnatoxins) were in fact responsible. Pinnatoxin-G has been reported worldwide (e.g., Rhodes *et al.*, 2010; 2011; Rundberget *et al.*, 2011; McCarron *et al.*, 2012), with the highest levels found in a Mediterranean Lagoon in the South of France (Hess *et al.*, 2013). It should be pointed out, however, that no food-poisoning-related events have yet been documented. The chemical stability of this biotoxin to both acids and bases (Jackson *et al.*, 2012) and the high binding affinity to the nicotinic Acetylcholine (nACh) receptor raises the spectre of potentially harmful effects to human health due to the chronic exposure of even low levels of pinnatoxins (Molgó *et al.*, 2014).

BMMA.

Although controversial, β-N-methylamino-L-alanine (BMAA) a non-protein amino acid initially reported to be produced by certain cyanobacteria proliferating in freshwater habitats (Cox *et al.*, 2005) has been recently confirmed in marine diatoms (Jiang *et al.*, 2014a) and in seafood from marine and coastal waters (Brand et al, 2010; Reveillon *et al.*, 2014; 2015). Exposure to BMAA has been linked to an increased risk of neurodegenerative diseases such as Amyotrophic Lateral Sclerosis (ALS), Parkinson's, and Alzheimer's Diseases (Bradley *et al.*, 2013). Marine cyanotoxins in general are a potential cause of unexplained acute food poisoning (Golubic *et al.*, 2010; Roué *et al.*, 2013; 2014).

Additional research is needed to confirm both these findings and the possible epidemiologic associations between BMAA and neurodegenerative diseases.

Macro-algae.

Food poisoning from macroalgae has been reported from Asian countries where such foodstuffs are traditionally consumed. Particularly important are the polycavernosides found in *Gracilaria edulis* (Louzao *et al.*, 2014, and references cited therein). As postulated by Daigo (1959), domoic acid has now been confirmed as a metabolite in *Chondria armata* following the laboratory culture of these macroalgae (Jiang *et al.*, 2014b). The occurrence of domoic acid and other glutamate receptor agonists in macroalgae may be of importance in studies on the effects of chronic exposures to subacute biotoxin concentration.

2.1.e. Effects of chronic and subacute exposure

Marine biotoxins have traditionally been known for their acute effects. Consequently, regulation at a global scale (FAO, *Codex alimentarius*) has focused on preventing acute poisoning events (Lawrence *et al.*, 2011). Only a few studies have investigated either chronic effects from an acute exposure episode or chronic exposure to sub-acute levels over time in humans. Some studies, using *in vivo* models, have shown that there may be some adverse health effects from low-level exposures (either single or repeated) to, for example, domoic acid. Levin *et al.* (2005) demonstrated that prenatal rats exposed to domoic acid exhibited postnatal effects, e.g., scopolamine susceptibility. In this study, rats showed persistent hypo-activity, and female offspring in particular showed poor performance in a maze, following a single low-dose early postnatal exposure to domoic acid. Baron *et al.* (2011) reported loco-motor disorders in rats exposed to a low level of domoic acid. Finally, low level repeated exposure over a 36-week period in zebra fish also led to gene alteration and impairment of mitochondrial function at cellular level (Lefebvre *et al.*, 2012; Hiolski *et al.*, 2014).

Subacute effects are also a potential problem for repeated or chronic ingestion of low doses of saxitoxins via drinking water produced from desalination of seawater. Until now, saxitoxins have been regulated only on the basis of their acute effects: a maximum permissible level of 3 μg L^{-1} has been established for

drinking water in Australia, Brazil and New Zealand. Recent studies suggest, however, that the effects of chronic ingestion of saxitoxins may include the alteration of antioxidant defences and the induction of oxidative stress in the brains and livers of mammals (Ramos *et al.*, 2014; Silva *et al.*, 2014). As mentioned above, the cyclic imine biotoxins also have the potential to interact with receptors involved in neurodegenerative diseases such as Parkinson and Alzheimers (Molgó *et al.*, 2014). Interestingly, in both *in vitro* and *in vivo* studies, gymnodimine and 13-desmethyl spirolide C showed some protective effects against Alzheimer's disease, and hence these compounds should be considered for further research into their possible therapeutic applications (Alonso *et al.*, 2011a; b; 2013).

2.1.F. CO-EXPOSURE AND EXPOSURE TO MIXTURES

Co-exposure to different agents can lead to confounding diagnoses in patients. For example, bacterial contamination in shellfish may lead to gastro-intestinal illness (diarrhea and vomiting) similar in degree to that caused by okadaic acid. Normally, the onset of illness following the consumption of shellfish contaminated with biotoxins is earlier (a few hours) than for those contaminated with bacterial pathogens (12-24h), because bacteria typically require a period of incubation in the patient before causing the full effect.

Exposure to mixtures of different groups of biotoxins is another issue that has not been well studied. Many studies have reported the co-occurrence of biotoxins in single algal species or shellfish that were contaminated by different algal species simultaneously, so the issue should be considered seriously (Hess, 2002; 2010; Amzil *et al.*, 2008; Twiner *et al.*, 2008; Reguera *et al.*, 2012; Suikkanen *et al.*, 2013). In particular, there is a concern that some of the compounds that do not normally cause acute shellfish poisonings in humans (e.g., yessotoxins), may be absorbed following damage to the intestinal tract caused by other biotoxins known to cause harm to humans, (e.g., okadaic acid and azaspiracids). As pure biotoxin supplies are very limited for most of the HAB biotoxins, only a few studies have investigated this potential hazard. Aasen *et al.* (2011) investigated the combination of azaspiracids with yessotoxins and did not observe any potentiation when orally co-administered at sub-acute levels to

mice. Similarly, even a combination of azaspiracids with okadaic acid, two biotoxins known for their potential to cause harm to the human digestive tract, did not cause synergistic effects when orally administered to mice at sub-acute levels (Aune *et al.*, 2012). The combination of okadaic acid and yessotoxins did not cause any increased toxicity in the oral mouse model (Sosa *et al.*, 2013). It should be noted that the digestive tract of mice differs significantly from that of humans (notably in pH), however, and further studies (possibly involving primates) may be necessary to rule out the likelihood of synergistic damage. Finally, some potentiation of domoic acid by peptaibols, a fungal metabolite, was shown in a fly larval model (Ruiz *et al.*, 2010). These varied findings are very much dependent on the biological model used, and they should be considered as very preliminary in their nature. Longitudinal studies of humans exposed naturally to mixtures of biotoxins at individually low levels over long periods of time are needed.

2.2. Waterborne diseases.

In fresh waters, cyanobacteria blooms constitute the main hazard to the health of humans (and other animals), mainly through the contamination of drinking waters by cyanotoxins, such as microcystins (see e.g., Nishiwaki-Matsushima *et al.,* 1992; Falconer, 1998; Stewart *et al.*, 2008). Direct cutaneous contact, exposure to aerosols, or swallowing water during occupational or recreational activities conducted in freshwater environments affected by cyanobacteria blooms, also can cause health problems. In contrast, there is no published evidence, at present, of risks for adverse health effects in humans from swallowing seawater containing toxic marine microalgae, but this possibility can not be discarded.

Toxic HABs have recently emerged as a potential risk for the contamination of drinking water supplied by desalination systems. Worldwide, desalination is rapidly growing to provide water for domestic consumption and industrial uses. In 2012, there were more than 14,000 desalination plants in 150 countries (Anderson & McCarthy, 2012). About 50% of this capacity was located in the West Asia Gulf region, 17% in North America, 10% in Asia (apart from the Gulf),

527 8% in North Africa, and 7% in Europe. In 2008, the installed capacity was 52.3
528 million m^3 per day. Based on a growth rate of 12% per year, the global
529 production of freshwater by desalination will have reached a capacity of 94
530 million m^3 per day by 2015.
531 Chemical and physical properties, such as the molecular weight of the
532 common HAB biotoxins (saxitoxins, brevetoxins and domoic acid, i.e., 300 to 900
533 Da), suggest that they should be efficiently removed by reverse osmosis in the
534 desalinization process. Support for this assumption was provided by Seubert *et*
535 *al.* (2012) in their study combining laboratory tests and a 5-year monitoring of
536 an operational plant in California. It has been noticed, however, that some taste
537 and odour compounds (e.g., geosmin) with low molecular weights similar to the
538 biotoxins mentioned above can pass through pre-treatment and reverse osmosis
539 membranes (Reiss *et al.*, 2006). Further, the complete removal of biotoxins is not
540 guaranteed in membranes with micro-fissures caused by, for instance, high
541 pressures within the desalination plant system. Excessive pressures can be
542 caused by the obstruction of intake filters due to high-biomass blooms, such as
543 the ones caused by *Cochlodinium polykrikoides* that occurred in the Arabian Gulf
544 and Gulf of Oman (Richlen *et al.*, 2010). Still, the data are limited (e.g., Caron *et al.*,
545 2010; Dixon *et al.*, 2011a,b; Laycock *et al.*, 2012), based mainly on laboratory
546 studies (without the appropriate up-scaling), and there are only a few studies
547 (Seubert *et al.*, 2012) from plants operating during blooms of biotoxin producing
548 HAB species. Therefore, more research is needed to ascertain the fate of
549 biotoxins during the desalination process. The potential risk of chronic exposure
550 to biotoxins requires their monitoring in drinking water produced in
551 desalination plants
552

553 **2.3. HABs and aerosolized biotoxins.**

554 2.3.A. *KARENIA BREVIS* AND BREVETOXINS.

555 Over three decades, multi-institutional and multi-disciplinary studies in the Gulf
556 of Mexico and along the coast of Florida have explored how the inhalation of
557 aerosols containing brevetoxins during high-biomass, toxic *Karenia brevis*
558 blooms can cause respiratory symptoms (e.g., Fleming *et al.*, 2005; 2006; 2011).

559 Beach visitors and full-time lifeguards have reported respiratory disorders
560 (Backer *et al.*, 2003; 2005), and studies have shown that people with asthma
561 (and possibly other lung diseases) were particularly at-risk from more severe
562 and longer-lasting symptoms (Fleming *et al,.* 2005; 2006; 2011; Milian *et al.,*
563 2007; Bean, 2011). More recent research has modeled the health costs of these
564 effects (Hoagland *et al.,* 2009; 2014).
565 The results of this research have been used to engage with stakeholders to
566 develop local response management plans to help minimise societal impacts of
567 *Karenia* blooms on human health (e.g., Kirkpatrick *et al.*, 2010; Fleming *et al.*,
568 2011; Zhao *et al.*, 2013). Information about the likelihood of health impacts has
569 been used to inform personal decisions as well. For example, the Gulf of Mexico
570 HAB Forecast (see NOAA Harmful Algal Bloom Operational Forecast System -
571 HAB-OFS-, https://tidesandcurrents. noaa.gov/hab/, accessed 26 August 2015)
572 in conjuction with a local Beach Condition Reporting System is used by
573 windsurfers and beach visitors to decide, depending on the wind, tides, and the
574 presence of a Florida red tide, whether or not to visit a particular beach on a
575 given day. Thus, current observations and forecasts of this HAB may help to
576 protect public health by decreasing exposures to toxic aerosols.
577

578 2.3.B. *OSTREOPSIS* CF. *OVATA* AND RESPIRATORY IRRITATIONS.

579 Over the past two decades, extensive blooms of *Ostreopsis* spp. have occurred in
580 the Mediterranean (e.g., Algeria, France, Italy, Tunisia). During these blooms,
581 beach users have experienced upper respiratory disorders (rhinorrhoea), eye
582 and nose irritation, fever and general malaise, and sought medical care in
583 hospital emergency departments and primary health care centres (Àlvarez *et al.*,
584 2005; Gallitelli *et al.*, 2005; Brescianini *et al.*, 2006; Durando *et al.*, 2007; Barroso
585 *et al.*, 2008; Vila *et al.*, 2008; 2012; Tichadou *et al.*, 2010; Tubaro *et al.*, 2011;
586 Illoul *et al.*, 2012;). A similar situation could be also occurring in certain beaches
587 in Brazil (Proença *et al.*, 2010). The health effects could be caused by exposures
588 to aerosols containing biotoxins or allergenic substances produced by *Ostreopsis*
589 cells fragments or accompanying microbiota (Casabianca *et al.*, 2013; Ciminiello
590 *et al.*, 2014). Reported cases of cutaneous irritation were attributed (but not

proven) to direct skin contact with seawater containing high concentrations of *Ostreopsis* cells. At present, studies (including epidemiology and ecology) are underway to improve the understanding of *Ostreopsis* bloom dynamics and the possible links to human health effects (Vila *et al.*, 2014; Berdalet *et al.*, 2015).

3. EFFECTS OF HABS ON HUMAN WELLBEING.

In addition to the risks to human health posed by exposure to biotoxins, marine HABs can impact other aspects of human wellbeing, including human commercial and recreational uses of the coastal and marine environments, such as fishing, shellfish digging and growing, and tourism, and non-market, passive uses of the ocean, such as preferences for particular ecological states. Too, marine HABs may led to complex societal responses in the affected human communities, such as the more general avoidance of coastal and ocean resources due to inadequate perceptions and communications of health risks. In this section, we refer to the economic effects resulting both from biotoxin producing species (**Box 1**) and from algal taxa involved in high biomass events (**Box 2**). Difficulties in developing estimates of the economic costs associated with HABs are considered in detail in this section.

3.1. Economic effects of HABs linked to food security and seafood related activities.

Certain HABs constitute a threat to aquaculture food production, which has become a major source of protein (linked to decreasing wild fish stocks) for expanding human populations, particularly in coastal and developing countries. Like farming, and sometimes in conjunction with it, aquaculture helps to support many local and regional economies (FAO, 2006). Currently, and with respect to the cultivation (and wild-harvest) of shellfish, the most effective way to protect humans from HAB-related seafood poisoning is to monitor for the presence of HAB species or biotoxins and to enforce periodic closures of commercial and recreational harvesting or growing areas (**Figure 3**). Contamination of seafood products can result in economic losses in shellfish digging and growing, and in the aquaculture of certain finfish. There may also be losses in downstream

industries, including processing, distribution, wholesaling. and retailing of seafood (Larkin & Adams, 2007; Morgan *et al.*, 2010).

Estimating the overall economic costs associated with the occurrence of HABs is complex. These costs vary markedly, depending on geographical region, seafood product, the frequency and intensity of HAB related events, the duration of fishery closures, and the costs of healthcare provision. As an example, Hoagland *et al.* (2002) estimated the annual economic effects of HABs in the US between 1987 and 1992. At the time, the economic effects were valued on the order of 50.0 million USD per year; this calculation has been subsequently adjusted for inflation to ~100.0 million USD per year (Hoagland & Scatasta, 2006). It is important to note that there is considerable variation in estimated impacts from year to year. This estimate was based on a compilation of the assessments of economic effects in public health, commercial fisheries, recreation and tourism, and monitoring and management. Notably, public health effects are the largest component, representing about 42% of nationwide average effects during that time period. Although the actual incidence of ciguatera fish poisoning (CFP) is very uncertain in many tropical locations, estimates of CFP illnesses comprise 99% of the total public health costs.

With regards to the specific economic costs of HAB-induced illnesses, there are very few studies available. The UNEP Global Environmental Outlook lists the worldwide economic impacts of algal biotoxins on human health from seafood alone as ~4.0 billion USD a year (GESAMP, 2001). As a comparison, the impact of infectious hepatitis from seafood consumption was estimated to be ~7.2 billion USD per year. The direct medical care costs associated with the respiratory and digestive illnesses caused by *K. brevis* blooms along the Florida coast of the Gulf of Mexico ranged from 0.1 to 0.7 million USD annually, depending on the intensity of the event (Hoagland *et al.*, 2009; 2014). Illness costs might exceed 1.0 million USD per year for large, long-lasting blooms, however, such as one that occurred during 2005-06. Assuming that the average annual illness costs of *K. brevis* blooms would persist into the future, using a discount rate of 3%, the capitalized costs of future illnesses would range between 2.0 to 24.0 million USD.

In the particular case of ciguatera fish poisoning, the average medical costs of diagnosis and treatment in traditionally non-endemic areas, as for instance in

Canada, was estimated at about 2,470 CAD per case, with about 1,000 cases per year related to tourism and food importation in 1990 (Lange *et al.*, 1992; Todd, 1995; Fleming *et al.*, 2002). Accurate estimates of the human costs of these diseases necessitate an adequate knowledge of their prevalence and incidence, as well as an understanding of their acute and chronic human health effects (Penotti *et al.*, 2013).

Any estimation of the economic effects of HABs also should include an evaluation of the costs of monitoring and management, which would include, for instance, sampling programmes or strategies to decrease the risk of HAB occurrences (e.g., reducing coastal eutrophication, sustainable use of the coastal zone, and other human-related activities) or their impacts (Hoagland *et al.*, 2002). For instance, limiting shellfish harvesting closures or varying the timing of shellfish or finfish harvesting could be useful strategies to reduce the impacts of HABs, but these actions also may have associated costs in terms of product marketability. Wessells *et al.* (1995) found that the occurrence of paralytic shellfish poisoning in blue mussels from the Canadian maritimes, leading to illnesses and subsequent harvest closures, adversely affected the market for mussels from Maine. Whitehead *et al.* (2003) found that, after consumer demand for seafood contracted upon learning of a HAB-induced fish kill, mandatory seafood inspection programs were more effective in restoring consumer confidence and expanding demand than broad public assurances of seafood safety.

Closure strategies in shellfish production areas could be beneficial over the long term, despite leading to losses in the short term. For example, this approach has been applied recently in the northern areas of Hokkaido and Tohoku (Japan) with some benefits. The region provides more than the 60% of the scallop aquaculture in Japan, accounting for about 500 thousand tonnes per year with a value of ~84.0 billion JPY (~700.0 million USD). Paralytic and diarrheic shellfish poisoning events had caused the complete closure of shellfish harvesting in the 1980s, resulting in dramatic economic impacts (Imai *et al.*, 2014). Another example is from the Galician region of NW Spain. The Rías are a highly productive ecosystem that sustain a production of 0.2-0.3 million tonnes of mussels (*Mytilus edulis*) per year. Bans on harvesting can last up to nine months

(particularly in *Dinophysis* bloom hot spot areas), when DSP biotoxin levels exceed European Union regulatory thresholds (e.g., Blanco *et al.*, 2013). NW Europe has the highest incidence of diarrheic shellfish poisoning (DSP) in the world, and intensive monitoring of biotoxins attempts to ensure that any closures of shellfish harvesting are limited to the minimum time needed.

Some data about the economic losses caused by ichthyotoxic HAB species in aquaculture are shown in **Box 2**. In most cases, fish-killing HAB species (e.g., *Karenia mikimotoi, K. brevis, Prymnesium spp. Chattonella spp.*) produce biotoxins with neurotoxic, haemolytic, or cytotoxic effects on fishes. Some HAB species have been linked directly to massive fish kills, often at aquaculture sites. In 2003, losses in European coastal waters were estimated at more than 800 million EUR in fisheries associated with HABs (Scatasta *et al.*, 2003; note that these are global data, including finfish and shellfish wild harvests and aquaculture). Analogous losses in the USA were conservatively estimated at around 4.0 million USD annually, adjusted for inflation (Hoagland 2002). Kim (2006) reported HAB-related aquaculture losses in Japan of more than 1.0 billion USD annually. Recent estimates were presented at the PICES (North Pacific Science Organization) "Workshop on Economic Impacts of Harmful Algal Blooms and Aquaculture" (Trainer & Yoshida, 2014). From 2006 to 2012, the total economic losses in farmed fish and shellfish production was estimated as ~ 94.0 million USD for Korea, Japan, and China. Note that many of these estimates are lost sales (gross revenues); they should be regarded as over-estimates of true economic losses because they do not account for the avoided costs of *not* fishing. Where commercial wild harvest fisheries are managed inadequately and therefore economically or biologically over-exploited (a common occurrence), lost net economic values, representing actual declines in human welfare, are likely to be a small fraction of reported lost sales.

There may be special impacts of high biomass HABs on the operation of desalination plants, which would result in the disruption of water production and significant economic losses. For instance, in 2008 and 2009, at least five seawater desalination plants were closed in the United Arab Emirates (UAE) due to a dense bloom of the ichthyotoxic *Cochlodinium polykrikoides* in the Arabian Gulf and Gulf of Oman that lasted for more than eight months (Richlen *et al.*,

722 2010; Anderson & McCarthy, 2012). In this particular case, algal biomass clogged
723 the filtration systems and reverse osmosis membranes.
724
725 **3.2. Impacts of HABs on non-market, passive use values of marine**
726 **ecosystems.**
727 Certain HABs have noxious, even lethal, consequences on marine organisms and
728 ecosystems (**Box 2**), thereby potentially leading to passive value losses or the
729 degradation of ecosystem services.
730 Some taxa produce particular toxic compounds that, given their high
731 concentrations in the water when the species bloom, have been involved in mass
732 mortalities of wild fauna. According to the US National Oceanic and Atmospheric
733 Administration (NOAA), more than 50% of all Unusual Mortality Events (UMEs)
734 of wild animals (turtles, dolphins, manatees, whales, birds, e.g., Scholin *et al.*,
735 2000), could have been due to microalgal biotoxins, although it is evident that
736 this is not a new phenomenon and is also a part of the natural ecosytsem
737 functioning. There are reports of mortalities of wild fish associated with HABs
738 that date back to the latter part of the 19th century (Whitelegge, 1891). In 1968,
739 mortalities of sand eels (*Ammodytes* spp.) and an estimated 80% of the breeding
740 population of shag (*Phalacrocorax aristotelis*) coincided with a bloom of
741 *Alexandrium tamarense* off the northeast coast of the United Kingdom (Adams *et*
742 *al.*, 1968; Coulson *et al.,* 1968. White (1984) documented four cases of fish kills
743 associated with saxitoxins. Other historical examples include the deaths of 19
744 humpback whales off Cape Cod (USA), and likely the deaths of pygmy, dwarf
745 sperm, and North Atlantic right whales in the same region, as well as Southern
746 right whale mortalities in Peninsula Valdés (Argentina). More recently, Scholin *et*
747 *al.* (2000) reported the deaths of over 400 California sea lions (*Zalophus*
748 *californianus*) along the central Californian coast during May and June 1998.
749 Coincident with these mortalities, a bloom of *Pseudo-nitzschia australis* was
750 reported and domoic acid was detected in planktivorous fish and in sea lion
751 body fluids.
752
753 Jessup *et al.* (2009) reported extensive marine bird mortality in the Pacific
754 Northwest (Monterey Bay, California, USA) in winter 2007 coinciding with a

755 bloom of the non-toxic dinoflagellate *Akashiwo sanguinea*. Affected birds had a
756 slimy yellow-green material on their feathers, and they were diagnosed as
757 severely hypothermic. This dinoflagellate excretes high amounts of organic
758 matter that accumulate at the sea surface. In this case, the sea foam contained
759 surfactant-like proteins, which destroyed the waterproofing and insulative
760 characteristics of the bird feathers.
761 *Ostreopsis* blooms constitute a particular case of an emerging harmful event
762 that is a growing problem in coastal environments. Since the end of the 20th
763 century in temperate waters (e.g., in the Mediterranean, Brazilian, and New
764 Zealand coasts), blooms of this benthic dinoflagellate genus have been linked to
765 damage to marine fauna (i.e., mussel mortalities, loss of spines and death of sea
766 urchins, loss of one or more arms in sea stars, and coral bleaching) and
767 subsequent alterations of the coastal ecosystems (Sansoni *et al.*, 2003; Simoni *et*
768 *al.*, 2003; Shears & Ross, 2009). In some cases, the invertebrate community of the
769 affected area has not recovered to date (Vila *et al.*, 2012). Coinciding with these
770 effects, high cell concentrations of *O.* cf. *ovata* (mainly in the Mediterranean) or *O.*
771 *siamensis* (mainly in New Zealand) were recorded in the water column. Also,
772 highly visible distinctive rusty-brown coloured mucilaginous films covered the
773 reef, macroalgae and other sedentary organisms, or floated in the water column
774 or on the surface. Oxygen depletion seems to be the most likely cause of the
775 observed effects. Direct toxicity to the fauna (via ingestion of *Ostreopsis* through
776 the food web) cannot be ruled out, given that palytoxin analogues (i.e., ostreocin
777 and ovatoxin) have been isolated from certain macrofauna at other
778 Mediterranean sites (Aligizaki *et al.*, 2008; 2011; Amzil *et al.,* 2011; Biré *et al.,*
779 2013).
780 High-biomass *Phaeocystis* blooms also have been linked to the deterioration of
781 water quality in some coastal regions of the North Atlantic and the
782 Mediterranean (e.g., Lancelot & Mathot, 1987; Arin *et al.*, 2013). This species
783 produces macroscopic colonies embedded into a mucilaginous matrix. The decay
784 of the blooms results in brownish foams containing 3-dimethylsulfoniopro-
785 pionate (DMSP), which is responsible for bad odours (Liss *et al.*, 1994). Although
786 this may result indirectly in the loss of recreational activities, no economic

assessment has been undertaken yet, and no direct harm to humans has been reported.

Finally, some studies have suggested that certain HAB species also could have subtle impacts on ecosystems, by altering fundamental physiological and biological processes (e.g., feeding behaviour, life stages, survival strategies, reproductive capacity) in other organisms of food webs, likely through allopathic effects (e.g., Fistarol *et al.*, 2003; Tillman, 2003; Granéli & Hansen, 2006). These particular effects are not easy to detect, however, and the underlying mechanisms of damage to other components of the food webs remain difficult to understand (Landsberg, 2002; Shumway *et al.*, 2003). This is due, in part, to the spatial and temporal variability of HAB events and also to the difficulty of isolating their impacts from those associated with other environmental and or anthropogenic factors (e.g., increased temperature, wave action, habitat destruction). Both long-term field studies and experimental approaches in the laboratory are required to ascertain the direct and indirect impacts of HABs in the different components of the ecosystems.

3.3. The challenges of estimating the economic costs of HABs.

As explained, HABs can lead to economic losses associated with the costs of treating human illneses, closures of commercial and recreational shellfisheries, mortalities of fish in commercial finfish aquaculture operations, declines in coastal recreation and tourism, and additional investments in environmental monitoring and the prevention, control, or mitigation of blooms or their consequences (Hoagland *et al.*, 2002). Hoagland & Scatasta (2006) estimated economic effects (adjusted for inflation into 2015 USD) on the order of 1.0 billion USD per year in Europe and 100.0 million USD per year in the United States. The European estimate was influenced largely by estimated losses to coastal tourism, which is affected mostly by high biomass, noxious (blooms causing high foam volumes, discoloration of the ocean, noxious odors, or beach closings), but not necessarily toxic, HABs. Any estimates of the scale of the economic effects of HABs should be considered very rough approximations, even in areas where they have been relatively well studied, including the United States and Europe. Estimates in other parts of the world, particularly in developing countries, are

much more speculative and uncertain. The development of comprehensive and consistent estimates of losses in economic welfare as a consequence of HABs remains a clear priority for future research.

The reasons why economic estimates often are uncertain include the wide variety of methodologies used to compile the assessments, some of which produce estimates of economic measures that may not be strictly comparable (e.g., sales, indirect or induced impacts, consumer or producer surpluses, agency budgets); the wide variety of physical and economic effects; the episodic and often unpredictable nature of blooms of different types in many areas; and the wide ranges of responses of humans to mitigate the adverse impacts, including, most importantly, switching to next-best alternative activities or foods. Moreover, these reasons tend to be context-dependent, because of differences in the capabilities of human communities for responding to HABs as a natural hazard. For example, shellfish management measures are well-practiced in many parts of the developed world, such as in Maine or Florida in the United States, but often non-existent or difficult to enforce in parts of the developing world, such as in the coastal bays of the Bohol and Visayan Seas in the Philippines. Morbidities and mortalities from shellfish poisonings, particularly among the underprivileged, are common in the latter but now exceedingly rare in the former (but see Reich *et al.*, (2015) for a modern counter-example of neurotoxic shellfish poisonings from Florida).

Other so-called non-market, "passive" uses of the coastal and marine ecosystems, such as for the conservation of protected species (including marine mammals and sea turtles), can in theory be affected by HABs. Even if favored species or unique ecosystems are not used directly, humans may experience a sense of loss that might be evaluated in economic terms. Studies of passive value losses due to the adverse effects of HABs on protected species or ecosystems are almost nonexistent. One reason for the lack of estimates of effects on passive use values is that, although *individuals* may become ill or die as a consequence of HABs, such as the deaths of endangered West Indan manatees (*Trichechus manatus*) due to *Karenia brevis* blooms in southwestern Florida, the *populations* often are largely unaffected by the mortalities (in essence, *K. brevis* blooms could be viewed as one of many natural sources of mortality). Similarly, the media

often report on "large-scale" finfish kills resulting from HABs, but the impacts on fish biomass and the growth rates of fish stocks in the wild often is minor or imperceptible.

Of greater concern to users of coastal and marine ecosystems is the loss of access to commercial or recreational fisheries, especially to high-valued shellfish stocks, such as oysters, scallops, clams, mussels, crabs, or marine snails) or to areas used to grow shellfish. Even in such cases, commercial fishermen (a market-based, direct use) tend to relocate or to switch fisheries or occupations, thereby mitigating substantial economic losses. Recreational fishermen (a non-market, direct use) choose another target or another pastime. Further, seafood consumers also can switch among food options. When switching occurs, other fisheries, recreational destinations, or food providers may benefit. Because the latter typically are not "first-best" choices, economic losses are *ipso facto* incurred in all cases, but the human behavioral switching response clearly serves to blunt the impacts. Here, policies to improve the communication of risks, say through the widespread publication of the locations of closures or the species affected, which facilitates human switching, also may help significantly to mitgate economic losses. Finally, shellfish rarely are adversely affected by blooms, and one consequence of this "immunity" to biotoxins is that areas closed to shellfish harvesting may become *de facto* fishery reserves, helping to conserve stocks, provided that the biotoxin is naturally washed out after the bloom disappears.

3.4. Social impacts of the health risks caused by toxic HABs. The case of ciguatera fish poisoning

Within the human communities whose revenue is based on aquaculture and shellfish activities, HABs may have adverse social impacts including damaged reputations, decreased incomes, employment losses, and longer term changes in seafood consumption patterns (Lipton, 1998). There has been very little study of these other human dimensions, and many social impacts remain mostly conjectural and unexplored (Bauer *et al.*, 2009).

In the case of the ciguatera fish poisoning (CFP), it has been associated with the loss of a traditional food source, losses in commercial fishing businesses, losses of tourism, increased costs of medical care, and high costs of monitoring and management (Epstein & Rapport, 1996). Fear of CFP can lead to reduced fishing in coral lagoons (Dewailly *et al.*, 2008), and to a corresponding increased reliance on pelagic fish or on a less healthy diet of lower quality, imported, canned fish or red meat. This new diet, combined with reduced levels of physical exercise, may be one factor contributing to the trend of increasing obesity among Pacific Islanders, accompanied by a rising prevalence of chronic diseases (e.g., diabetes, hypertension, and cardiovascular diseases) in indigenous Pacific populations (Lewis & Ruff, 1993).

Ciguatera fish poisoning outbreaks could hurt the economies of tropical islands, many of which are highly dependent on local reef fisheries for subsistence, export products, and tourism. Reduced fishing effort due to endemic ciguatera has been blamed for losses of traditional fishing knowledge, as new generations abandon artisanal or commercial fishing. One example concerns Rarotonga, an island located in the southern Cook Islands that exhibits the world's highest incidence of ciguatera poisoning. On Rarotonga, the per-capita fresh fish consumption decreased from 149 g/d in 1989 to 75 g/d in 2006, due to concerns about CFP (Rongo *et al.*, 2012). Consequently, the consumption of alternative proteins, particularly imported meats, increased from 1989 to 2006. The direct loss in value of marketable goods from commercial fisheries amounted to 0.8 million NZD (about 0.5 million USD) per year, and the approximate costs associated with dietary shifts amounted to 1.0 million NZD (about 0.7 million USD) per year. With a decline in cases of ciguatera poisoning in recent years, fresh fish has returned to the menus of Rarotongans, and per-capita fresh fish consumption increased to 104 g/d in 2011.

In a discussion of the effects of HABs on public health, it should be highlighted that the management of tropical waters for ciguatera fish poisoning is not well-developed. In tropical regions, fishermen usually are able to continue to access areas where finfish may have bioaccumulated ciguatoxin, leading to circumstances in which CFP illnesses may become widespread. Characterizing the extent of the CFP problem in tropical regions and developing ways to

alleviate it should be established as very high priorities for future research and management.

4. PRESENT AND FUTURE CHALLENGES, STRATEGIES AND OPPORTUNITIES.

HABs are natural phenomena that have almost certainly thousands of years before recorded history (Mudie *et al.*, 2002). To humans, HABs constitute a problem worldwide, but the idea that HABs might be prevented from occurring is often not a viable option. Improvements in our understanding of HAB dynamics during the last 40 years have led to insights for designing strategies to mitigate their impacts. These strategies must consider the present situation and the future prospects of the potential spread and increase in HAB occurrence as a result of climate and other environmental changes. Common strategies can be adapted to address specific, local problems in different parts of our world. Despite some limitations, new advances in technology and coordinated international research efforts may help to improve the management of the impacts of HABs.

4.1. Improving monitoring and research needs to forecast and predict HAB events.

Monitoring programmes for HAB species and their toxins implemented in different areas of the world have clearly reduced fatal poisonings in humans (e.g. Davidson & Bresnan, 2009). For example, in Europe, current monitoring programmes are driven by its Food Hygiene Regulations (EC) No 853/2004 and (EC) No 854/2004, which require Member States to monitor both for biotoxin concentrations in shellfish tissues and the presence of marine biotoxin-producing phytoplankton in coastal waters. Because of different capacities for undertaking local risk assessments, there are local differences in the implementation of these monitoring activities. In general, these programmes have been successful in safeguarding human health, but continued refinement will be needed in the future as environmental conditions shift (particularly climate warming) and human uses of the coastal ocean change.

A pressing need is the establishment of programmes of robust monitoring in developing countries where they are often at best rudimentary, despite

951 increasing exports of seafood products to other regions (Reich *et al.*, 2015). In
952 spite of their success, established monitoring programmes are not without
953 technical, logistical, or cost-related limitations (DeGrasse & Martinez-Diaz, 2012;
954 Hess, 2012; Suzuki & Watanabe, 2012). Since their inception, improvements
955 have been linked to advances in technologies related to sampling, taxonomic and
956 biotoxin analyses, and observing systems.
957 Light microscopy constitutes the most widespread monitoring tool for
958 harmful algal species, but it is time consuming to employ, and it requires
959 specialized training and expertise. Thus, the development of quantitative
960 biomolecular tools to facilitate monitoring is a major research need. Given the
961 number of different organisms that have to be tracked, and the lack of fully
962 quantitative molecular tools for their enumeration, monitoring agencies cannot
963 currently afford to replace light microscopy as a primary tool. In our view, this
964 strengthens the need to maintain and support the training of microscopists in
965 the identification and quantification of biotoxin-producing species.
966 While the ability to detect the presence of harmful microalgal species in
967 coastal waters can provide an excellent early warning of the likely occurrence of
968 biotoxins in, for example, shellfish (e.g., Trainer & Suddleson, 2005), many
969 uncertainties remain. These include the fact that the presence of potentially toxic
970 organisms is not always linked to toxicity in shellfish. For example, in Scottish
971 waters, morphologically indistinguishable toxic and non-toxic *Alexandrium*
972 *tamarense* cells have been known to occur simultaneously (Touzet *et al.*, 2010).
973 Furthermore, known-toxic organisms are not always detected efficiently due to
974 their benthic character, fragility when preserved, or small size. For example, the
975 azaspiracid producer *Azadinium spinosum* measures only 7x12 µm. The link with
976 its produced biotoxin was established recently in 2007 (Tillmann *et al.*, 2009),
977 only after standards for biotoxin analysis were isolated (Satake *et al.*, 2002;
978 Jauffrais *et al.*, 2012; Kilcoyne *et al.*, 2012) and biomolecular tools for tracking
979 the organism in water were developed (Kilcoyne *et al.*, 2014). Further, toxicity
980 itself is not always well described. For example, not all of the biotoxins of many
981 *Gambierdiscus* species have been described, and they may be present in complex
982 mixtures in different individual organisms and blooms. Finally, toxicity may be
983 associated with new, unexpected vectors or species. For example, in 2002, the

consumption of puffer fish from Florida caused neurologic disease in 21 people (Centers for Disease Control and Prevention, -CDCP- 2002). Initially, based on patient symptoms and reported puffer fish ingestion, the outbreak was attributed to tetrodotoxin. A mouse bioassay confirmed the presence of a Na+ channel blocking toxin, tentatively identified as tetrodotoxin (usually associated with puffer fish), in unconsumed portions of fish. Direct measurement analyses (LC/MS, immunoassay, and receptor binding assay) confirmed the unexpected presence of saxitoxin in the fish samples, however, but not tetrodotoxin. Analysis of urine samples from the victims of the outbreak confirmed these findings. This was the first confirmed report of saxitoxin poisoning associated with puffer fish ingestion in North America (Landsberg *et al.*, 2006).

Conerning biotoxin detection, bioassays (i.e., the mouse bioassay) had been used traditionally as a fast way to detect the presence of toxins in potentially contaminated seafood, thus raising warnings and preventing the harvest of contaminated shellfish. Bioassays are associated with a number of technical and ethical issues (Hess *et al.*, 2006), however, leading to their replacement recently with non-animal alternatives (i.e., cell tissue cultures; e.g. Van Dolah *et al.* 2012) in many countries, particularly in Europe (Anonymous, 2011). Research efforts are now focused on the development of multi-toxin methods for the detection of multiple groups of compounds in biosensor systems (Campbell *et al.*, 2014b, and references cited therein). The large number of compounds that need to be detected and an inability to validate new tools for detection mean that many monitoring agencies will need to continue to rely on either insensitive (and ethically questionable) mouse bioassays or on comparatively complex and expensive LC-MS/MS detection methods, neither of which can be implemented *in situ*.

A potentially useful sampling technique based on the passive capture of biotoxins by resins was developed by MacKenzie *et al.*, 2004. This method has been used successfully to trace biotoxins when the producing organisms are difficult to monitor due to their small size (e.g., *Azadinium spp*.) or their benthic setting (e.g., *Prorocentrum lima* and *Vulcanodinium rugosum*; Fux *et al.*, 2009; Zendong *et al.*, 2014). The technique has not been standardized, however, and it will need further development for hydrophilic biotoxins. At present, the passive

capture of biotoxins cannot easily be automated or adapted for *in situ* detection. Furthermore, ongoing refinement of its analytical methods will be required to meet the challenges of emerging biotoxins (Turner *et al.*, 2015).

Issues arise with the existing technologies with the frequency of representative sampling of *in situ* biotoxins and the toxin-producing microalgae, which rarely takes place more than weekly, although higher frequency sampling may be desirable in some coastal waters. In the particular case of the benthic harmful species (e.g., *Gambierdiscus, Ostreopsis, Prorocentrum lima*), sampling techniques require refinements and standardisation (e.g., Tester *et al.*, 2014). As yet automated, reliable, and affordable systems to detect harmful species or their biotoxins for routine monitoring *in situ* are lacking. While recently some promising techniques have been developed to detect biotoxin-producing organisms (e.g., Hess *et al.*, 2012 and references cited therein; ICES, 2015), they are still viewed mainly as research tools and have seldom been used in high frequency *in situ* monitoring. This is the case of the Environmental Sample Processor (ESP; Scholin *et al.*, 2009) and the Imaging Flow Cytobot (IFCB; Olson & Sosik, 2007), two automated *in situ* monitoring platforms deployed in Monterey Bay, the Gulf of Maine, Puget Sound and the Gulf of Mexico. The ESP collects and processes water samples *in situ*, using sensitive and specific molecular assays to detect target HAB cells and toxins, and transmitting the data to the laboratory in near real time. The IFCB is an imaging flow cytometer that captures the high-resolution images and fluorescence characteristics of all plankton cells (in the 5-150 μm size range) at a high frequency (3 samples per hour); the data can also be sent to a laboratory in near real time (e.g. Campbell *et al.*, 2010; 2013). At present, however, they have very high costs and cannot be distributed widely and deployed to monitor individual shellfish production areas. Although they cannot replace more traditional forms of monitoring by now, efforts are done to facilitate their eventual use for this purpose. Fortunately, these sophisticated systems are useful tools for advancing an understanding of the links between HABs and ocean dynamics.

The adoption of monitoring technologies are affected strongly by economic costs (Frolov *et al.*, 2013). Some systems are relatively simple, comprising microscopic analysis of water samples for particular HAB species and analysis of

shellfish tissues for the presence of biotoxins. Other programmes involve *in situ* monitoring of phytoplankton and model-based forecasts of bloom occurrence, such those carried out in the Gulf of Maine (e.g., Anderson *et al.*, 2005a,b; McGillicuddy *et al.*, 2005; http://www.whoi.edu/main/topic/harmful-algae-red-tides) or in California Bay (e.g., Ryan *et al.*, 2005; 2011). According to Bernard *et al.* (2014), the costs of monitoring could be on the order of 1 billion USD annually, accounting for 10% of the overall costs of HABs worldwide, estimated to be at 10 billion USD annually for marine and freshwaters. A monitoring system including satellite observations could be made more efficient by improving international cooperation in the collection, interpretation, and sharing of Earth observation information, as conceived by the Global Earth Observation System of Systems (GEOSS, Fritz *et al.*, 2008).

Monitoring, combined with operational oceanography and modelling, offers the hope of providing forecasts and early warnings and ultimately predictions of HAB events (e.g., GEOHAB, 2011; Davidson *et al.*, 2014). Achieving a predictive capability would require an adequate understanding of the ecophysiology of HAB species and the physical and chemical processes that influence the occurrence of the blooms, however. One problem is that, in many contexts, such as remote sensing from satellites, HAB species do not exhibit characteristics that distinguish them from other phytoplankters. Our understanding of the many different processes (biological, ecological, physical, chemical, meteorological) that control HAB dynamics and the dynamics of microalgae in general is incomplete, making their parameterization in numerical models extremely difficult. To date, progress has been constrained by the complexities of biological interactions and the resulting difficulties in developing ecological models. One example is the HAB operational forecast (HAB-OFS) developed by NOAA for Florida and Texas (Stumpf *et al.*, 2008; http://tidesandcurrents.noaa.gov/hab/). HAB-OFS combines satellite imagery, field observations, models, public health reports, and buoy data to help forecast *K. brevis* blooms. Another NOAA effort for forecasting *Pseudonitzschia* has incorporated input from stakeholder communities in the state of Washington (Brown *et al.*, 2012). In the Gulf of Maine, a coupled physical/biological model (e.g., He *et al.*, 2009) predicts the transport of *Alexandrium fundyense* cells, controlled by plume advection and wind forcing.

Statistically based models (Anderson *et al.*, 2009a; Lane *et al.*, 2009) have successfully hindcast *Pseudonitzschia* blooms in Monterey Bay and Chesapeake Bay. Finally, conceptual models, such as for *Phaeocystis* blooms in Vietnam (Hai *et al.*, 2010) and *Dinophysis acuminata* (Velo-Suárez *et al.*, 2014) in the Rías of northwestern Spain, have provided new insights into understanding the dynamics of blooms and designing preventive strategies.

Sustained fundamental research is needed for gaining a better understanding of HAB dynamics, to inform and improve monitoring programmes, and to design methods to mitigate the impacts of HABs on human health and well-being.

4.2. Better quantification and prevention of the impacts on human health: HAB-related disease surveillance.

Determining the true incidence of HAB-related diseases remains a very significant challenge. The lack of experience of professionals in the public health and medical communities with patients exposed to marine biotoxins has led to incorrect diagnoses and failures to report illnesses. Inexperience, in turn, likely results in the under-reporting of HAB-related disorders, even in areas where such diseases are endemic. Furthermore, in general, there is a need to improve coordination between marine biotoxin monitoring and public health surveillance activities.

Under-reporting due to erroneous diagnosis is common and widespread, and is related, in part, to the lack of diagnostic tools. For instance, the symptoms of diarrheic shellfish poisoning (DSP) are non-specific, and, except during exceptional outbreaks, neither seafood consumers nor their clinicians may recognize the incidence of DSP illness (e.g., Davidson *et al.*, 2010; Taylor *et al.*, 2013). Taylor (quoted in PICES, 2002) queries that "[n]o diarrhoeic shellfish poisoning has been diagnosed in humans in British Columbia, but, given its resemblance to diarrhoea caused by bacterial contamination (*Vibrio haemolyticus,* in particular), would DSP be detected without testing specifically for okadaic acid or dinophysistoxin?" [1]Indeed, routine methods for the detection of either biotoxins or biomarkers in human tissues or fluids are virtually absent.

[1] In 2011, nine years after Taylor had queried whether diarrheic shellfish poisoning would be detected in the absence of testing for okadaic acid or dinophysistoxin, sixty-two illnesses of

Diagnostic tools for saxitoxins in human urine have recently been developed (Johnson *et al.*, 2009). A biomarker for low-level domoic acid exposure of zebra-fish and sea lions (Lefebvre *et al.*, 2012), is a promising technology for identifying such biomarkers for humans. The verification of ciguatoxins in contaminated seafood has been particularly challenging. Recent advances suggest that an effective and reliable method will be soon available. Under the auspices of the International Atomic Energy Agency (IAEA), a radio-labelled receptor binding assay (RBA) was developed for ciguatoxin; and this assay has been tested successfully in the Caribbean and the Pacific at IAEA-UNESCO-IOC sponsored training workshops (Tester, personal communication, 2015). A more recent advance is a fluorescent RBA method that compares favourably with the radio-labelled RBA approach. The fluorescent method is analogous to a technique implemented for brevetoxins (e.g., McCall *et al.*, 2012), in that no radioactivity is involved, making it less expensive to use, and avoiding hazardous waste disposal costs that can be significant, for example, in the Pacific islands.

HAB-associated illnesses should be recognized as a public health issue, and, accordingly, public health surveillance should be coordinated with environmental monitoring. Until now, epidemiologic studies typically have been conducted after clusters of disease outbreaks have occurred (although unfortunately usually without long term follow-up to explore the chronic health effects from acute exposures). New approaches also should be multidisciplinary. They should help to identify relevant bloom events, measure biotoxins in seawater (and in some cases air) and seafood, and identify symptoms in humans and other animals associated with exposures. In addition, communications with potentially affected communities should be conducted to promote the understanding that a particular symptom may be the result of exposure to a HAB biotoxin.

An example of such an approach can be found in the Gulf of Mexico, where the link between *Karenia brevis* blooms and human exposures and health effects, particularly to contaminated aerosols, was established. These efforts facilitated the successful understanding and mitigation of the human health risks

diarrheic shellfish poisoning were reported in British Columbia. Changes were made to the shellfish monitoring program following this outbreak to include more stringent testing for DSP toxins (Taylor et al, 2013).

associated with these events. This large and costly initiative included coordination among physicians, toxicologists, and ecologists, stakeholders (including businesses, public health agencies, Poison Information Centres), and end-users (Fleming *et al.*, 2005; 2011).

Another initiative with the same aim was the Harmful Algal Bloom-related Illness Surveillance System (HABISS) (http://www.cdc.gov/hab/surveillance.htm) that the US Centers for Disease Control and Prevention (CDC) and other public health and environmental organizations established to create a coordinated human, animal, and environmental health surveillance network. The simultaneous collection of environmental and health data over time was considered to have helped public health practitioners identify long-term trends in HAB-related diseases in humans and animals. The CDC also has created a module within the National Outbreak Reporting System (NORS) to capture HAB-related illnesses. The system has been beta-tested during the summer of 2015.

In Europe, similar initiatives, although at a smaller scale, have been established in the Mediterranean region to develop tools and strategies to manage the impacts of *Ostreopsis* blooms on human health before they can have a wider impact. Examples conducted at local scale include France (Tichadou *et al.*, 2011; Lemée *et al.*, 2012) and the Spanish Catalan coast (Vila *et al.*, 2012), and the Accord RAMOGE, www.ramoge.org at Mediterranean region level (mainly on the coasts of Italy, Monaco, France and Spain).

4.3. HABs dynamics in the context of global climate change.

Climate plays a fundamental role in the physical dynamics of the water masses and energy pathways in the ocean, which in turn modulate the biogeochemical fluxes and thus nutrient supplies to microorganisms at the bases of food webs (Beaugrand *et al.*, 2010). Climate variability modulates ecological events (phenology) and ecosystem characteristics at different spatio-temporal scales (Longhurst, 2007). As a result, the dynamics of HABs, as a natural phenomenon, are also influenced by climate variability.

The Earth's climate has changed continually over scales of millions of years, as evidenced by glacial and interglacial periods. Its climate also exhibits much

shorter term cyclical changes at multiannual to decadal and multi-decadal scales, such as those reflected in the El Niño Southern Oscillation (ENSO) and the North Atlantic Oscillation (NAO).

Photosynthetic organisms have evolved and adapted with changes occurring at these different temporal scales (e.g., Beardall and Raven, 2004). In the last 200 years, however, since the industrial revolution, human activities have impacted the Earth dramatically, mainly as a consequence of the increasing release of carbon dioxide (CO_2), methane, and nitrous oxides into the atmosphere. In particular, atmospheric CO_2 concentration has increased from 280 ppm to >380 ppm at present, with values of 750–1,000 ppm predicted by 2100 (IPCC, 2008), in comparison to fluctuations between 180 ppm and 300 ppm during the previous 800,000 years.

This rapid and uncontrolled rate of increase in so-called greenhouse gases has been responsible for a significant augmentation in about 1 ^{o}C of global temperature in the past 20–30 years (data from the Hadley Centre for Climate Prediction and Research; shown in Figure 1 of Hallegraeff, 2010), with a further rise of 2-4 ^{o}C predicted over the next 100 years. Climate warming is already directly and indirectly impacting terrestrial and marine ecosystems. In the oceans, increased temperature in the upper layers can lead to changes in density which in turn affect the seasonal patterns of mixing, stratification and circulation, acidification, weakening or reinforcement of upwelling winds, and modification of the freshwater inflows to coastal regions (e.g., Bindolff *et al.*, 2007). These changes may influence many ecological processes, including the occurrences of HABs. Given the impacts that HABs have on humans, there is now an urgent need to investigate the potential effects of climate warming on microalgal-related events. In addition, it will be important to develop tools for tracking and evaluating recent and future trends in HAB dynamics at both local and global scales.

The possible impacts of climate change on toxic marine HABs include: 1) range-changes in both warm- and cold-water species; 2) changes in abundance and toxicity; and 3) changes in the timing of the seasonal window of growth (e.g. Hays *et al.*, 2005; Moore *et al.*, 2008; Hallegraeff, 2010; Anderson *et al.*, 2012; Fu *et al.*, 2012). On the other hand, the effects of climate change on other

components of the food webs (e.g., predators, competitors, parasites) could modulate the impact of climate change on the occurrence, magnitude, and duration of HABs. Some HAB species may benefit such that their impact on human health and wellbeing becomes more severe, whereas others may diminish in areas that are currently impacted (Hallegraeff, 2010). Our ability to forecast the directions of change for toxic marine HABs is constrained by inadequate understanding of the interactions among multiple climate change variables and non-climate stressors in conjunction with inadequately designed experiments for investigating decadal- or century-scale trends (Hallegraeff, 2010; Fu *et al.,* 2012).

Few studies have investigated the effects of projected future climate change conditions on individual species or genera of toxin-producing marine microalgae. Of the few studies to date that have directly investigated future climate change effects on certain HAB species or genera, most have focused on the effects of warming. For example, the 2.5-3.5 °C projected increase in sea surface temperature in the Caribbean over the coming century has been estimated to increase the incidence of CFP by 200-400% (Gingold *et al.*, 2014). In Puget Sound, warming has been projected to increase the seasonal window of growth for *Alexandrium* by ~30 days by 2040, allowing blooms to begin earlier in the year and to persist for longer periods (Moore *et al.,* 2015). It is important to remember that these projections are primarily based on projected changes to water temperature. Other aspects of bloom ecology and oceanography, such as the location of nutrient availability, competition with other phytoplankton species, grazing, and infection by parasites, were not considered. Therefore, while these initial assessments of greenhouse gas-driven changes to HAB risk provide insight into potentially important climate pathways that are relevant for bloom development, more work is needed to understand better the interactive effects of drivers other than temperature on HAB occurrence.

An emerging body of work is also focusing on the effects of ocean acidification on marine HABs. Some experiments performed on *Pseudo-nitzschia fraudulente* found significally high production of the domoic acid neurotoxin in response to a combination of low pH and some other factor that limits growth (Sun *et al.,* 2011; Fu *et al.,* 2012; Tatters *et al.,* 2012a; 2012b; 2013), provided that the limiting

resource was not needed for toxin synthesis. Saxitoxin (paralytic shellfish toxin) production increased also by elevated temperature and increased CO_2 supply (Kremp *et al.*, 2012), although the response was highly strain specific. Much more work is needed to understand the effect of increasing ocean acidification on HAB species, and thus the potential effect on human health and the ecosystems under this scenario.

In order to evaluate future trends of HAB events, there is a need to establish the present baseline. Several studies report that the occurrence and geographic distribution of toxic marine HABs has increased in certain areas during the past few decades (Hallegraeff, 1993; Van Dolah, 2000; Hallegraeff, 2010; Lewitus *et al.,* 2012). Increased awareness, expanded and better monitoring and detection of toxic HABs, and the multiple effects and interactions of human activities (including, but not limited to, increased nutrient loading to coastal waters, aquaculture development and transport of seed stock, ballast water transport) and climate warming may have contributed to this putative increase (Smayda, 1990; Hallegraeff, 1993; 2010; Sellner *et al.,* 2003; Gowen *et al.*, 2012). Direct observations of microalgae in coastal marine waters on timescales sufficient to evaluate climate change effects and to discriminate the role of other natural or anthropogenic forcings (e.g., nutrient loads) are typically lacking. This makes it difficult to establish whether the observed trends are global or local. While a few isolated time series do exist (e.g. Borkman & Smayda, 2009; Kim *et al.*, 2009), they have not yet been fully utilized to describe changes in the abundances of toxic HAB species. In some cases, the available HAB data are from offshore, such as that generated by the Continuous Plankton Recorder (CPR) in the North Atlantic (Edwards *et al.*, 2001; 2006; Hinder *et al.*, 2012). Even though humans typically encounter HABs and their toxins at the coastal margins, these offshore time series provide valuable insights into the ecological responses of HAB species on timescales relevant to climate change. A small number of toxic HAB species leave a long-term record of their abundance in bottom sediments as microfossils (Dale *et al.*, 2006) which could be used to explore time-series of bloom events. On the basis of similarities in the sediment cyst records in the Pacific and Atlantic regions of Canada, Mudie *et al.,* (2002) concluded that

climate change (including surface temperature and storminess) was a main factor stimulating blooms.

Reported illnesses are also an indicator of toxic HABs (Van Dolah, 2000); however, seafood is often consumed at long distances from where harvested. Unless robust information on the source of the seafood consumed is reported, it is difficult to identify potential relationships between foodborne HAB-related diseases and climate. Because most of the HAB-related diseases are associated with the consumption of contaminated shellfish, time series of HAB toxins in shellfish tissues provide valuable data for evaluating long-term trends and relationships to climate and in some cases date back to the 1950s (Trainer *et al.*, 2003). The interactions of weather and climate are important for understanding patterns of disease, with climate determining the range of species and weather determining the timing and intensity of outbreaks (Dobson & Carper, 1993; Epstein, 2001).

At present, it is clear that we lack sufficient scientific understanding of climate-driven changes to nearshore marine environments, as well as HAB responses to these potential changes, to provide accurate predictions of future HAB occurrences in space and time. More fundamental, multidisciplinary research and coordination including stakeholders and policy makers should be done with the objective to mitigate the impacts of HABs on human health and well-being in the near future. The concern about this need motivates discussions and meetings in different fora, such as the Symposium on "HABs and Climate Change" held in Göteborg, Sweden, May 19-22, 2015 (https://pices.int/meetings/international_symposia/2015/2015-HAB/scope.aspx).

4.4. Mitigation strategies for aquaculture.

In Japan, several strategies have been adopted to minimize economic losses to aquaculture (Imai *et al.*, 2014). In southwest Hokkaido's Funka Bay, for example, the scallop culturing industry has adapted to frequent occurrences of dinoflagellate blooms that produce the dinophysis toxin and paralytic shellfish poisoning (PSP), which typically occur in May and continue into the summer. Modified harvesting approaches were necessitated, in part, by high PSP

contamination in the 1980s that stopped shipments of all bivalves. Timing the scallop harvest every year from December to April avoids the impacts associated to the toxic bloom season. Scallops are harvested both for immediate fresh consumption, and they can be inventoried by boiling and freezing in order to provide a source of supply during the closed season.

In the Okhotsk Sea, recent occurrences of paralytic shellfish poisoning contamination of scallops have been predicted on the basis of movements of the Soya Warm Current. The strength of this current prevents the transport of *Alexandrium tamarense*, which typically resides in the offshore water masses of the Okhotsk Sea, to locations such as Monbetsu and Abashiri on the northern coast of Hokkaido. Adaptive harvesting in response to these forecasts is an effective way to avoid the impacts of toxic blooms on the bivalve aquaculture industry. This strategy is effective because of the fundamental understanding of local HAB dynamics.

Some strategies to mitigate the impacts of HABs on aquaculture may have been discounted prematurely and are worth revisiting. The use of clay to flocculate and remove toxic cells at some aquaculture sites in Asia (Lee *et al.*, 2013) is one example. This approach should be studied further to explore tradeoffs between the economic losses associated with fish kills from HABs, the environmental consequences of clay dispersal, the costs of implementing the mitigation technology, and toxin accumulation in the benthos.

4.5. Communication with the public and improving literacy about oceans and HABs.

Throughout history, humans have learned how to cope with natural phenomena, including HABs. In some areas, such as in Pacific Islands (Chinain *et al.*, 2010a), local traditional knowledge about ciguatera is functionally correct, albeit scientifically incomplete.

The Spanish explorer Alvar Núñez Cabeza de Vaca (1490?-1564) recorded a place along the northern coast of Mexico in the Gulf of Mexico, probably not far from Apalache Bay, where indigenous peoples were unable to relate the passage of time to the movements of the sun and the moon, but instead marked the

seasons by fishkills (Ferrando, 1984), which could have been caused then, as now, by blooms of *Karenia brevis*.

To people making a living around the Galician Rías, red-tides ("purgas de mar") are familiar events, traditionally compared to menstruation, through which local waters are cleansed, usually in the autumn. It was general knowledge that it was unsafe to eat shellfish gathered when the ocean exhibited a reddish-brownish hue. When mass cultivation of mussels in the Galician Rías was undertaken by developers, who were ignorant of the blooms, the dispersal of toxic mussels became more frequent. One particular extreme case occurred during the autumn of 1976 (Estrada *et al.*, 1984).

Fukuyo *et al.* (2002) note that in Northern Japan, local folklore advises not to eat shellfish during runoff of snowmelt into the sea occurring in the early spring. In the United Kingdom and the United States, there is a similar folklore: one should eat shellfish only during months that are spelled with the letter 'r', i.e., avoid shellfish consumption the summer months (May to August) when HABs are more likely to occur (although bacterial contamination of the food can not be discarded). Perhaps, as Fukuyo *et al.* (2002) suggest, such folklore has arisen because:

> "*this indicates that toxin contamination of shellfish has repeatedly occurred almost every year over a long time, leading to many tragedies among the local people. Community education resulted in self-regulating behaviour to avoid high-risk fish species and certain fishing locations.*"

Successful communication about HABs and their effects can be problematic for many different reasons. In part, this is due to the complexity of HAB phenomena, which are currently difficult to predict and to prevent or control. Most public health and medical personnel do not know enough about HABs and their potential effects on human health and wellbeing. Nowadays, many coastal communities are not fully informed of the public health risks of HABs, however, and this form of ignorance can result in a phenomenon known as the "halo effect," where human activities unrelated to the HAB hazards are scaled back or discontinued (Wessells *et al.*, 1995; Whitehead *et al.*, 2003; Parsons *et al.*, 2006). A common form of the halo effect is a reduction in the consumption of all types of

seafood, regardless of the actual risks of consuming phycotoxins. Other forms of the halo effect can influence commercial and recreational fishing behavior and coastal tourism. Consequently, it is necessary to improve the scientific messages about HABs to the many and diverse end users and stakeholders.

Fortunately, there are now examples of interesting and potentially successful dissemination and early warning activities related to safeguarding human health from HAB related toxic episodes. For example, the US National Oceanographic and Atmospheric Administration (NOAA) produces HAB Bulletins which provide forecasting of HABs for managers in the Gulf of Mexico (for *Karenia brevis*), in the Pacific Northwest (for toxic *Pseudo-nitzchia*) and the Great Lakes (for cyanobacteria). The bulletins incorporate oceanographic modelling, satellite imagery, and on-the-ground monitoring, as well as other information (e.g., real time reports from lifeguards and managers). These materials were developed with stakeholder engagement and input, so that the outputs are actually useful for and used by the people (such as beach managers) who need timely information. Another example of appropriate communication was the implementation of a toll-free, 24/7-telephone number at the Miami Poison Information Centre staffed by poison specialists trained to discuss HAB exposure and illnesses in Florida. This resource was signposted on information panels and brochures placed in beaches, hotels, and other tourist venues. Another useful aspect of this centralized information resource was that the poison control phone calls also could be incorporated into HAB human health surveillance activities to increase case reporting (Fleming *et al.*, 2011).

Examples in Europe include HAB bulletins that are produced weekly in both Ireland and Scotland for the aquaculture industries in these countries (http://www.marine.ie/Home/site-area/data-services/interactive-maps/weekly-hab-bulletin; http://www.somuchtosea.co.uk/news/bulletin_for_shellfish_farmers.aspx). In the Baltic, the Swedish Meteorological and Hydrological Institute Service offer reports and almost real time information about the algae situation in the Baltic obtained from satellite data (http://www.smhi.se/en/weather/sweden-weather/1.11631). In the NW Mediterranean, the RAMOGE Accord is working to communicate with the public and stakeholders, communicating through brochures, webpages, and with

dissemination activities about the occurrence of the *Ostreopsis* blooms and their impacts on human health and the environment, and searching to provide tools to manage them http://www.ramoge.org/fr/ostreopsis_ovata.aspx). RAMOGE also fosters the coordination of international research around the understanding and management of these events in the affected countries.

4.6. International coordination: the GEOHAB and GlobalHAB programmes.

HABs are a global challenge which needs to be addressed at local levels by implementing a broad global vision. During the last few decades, much work has been accomplished to understand HAB dynamics with the ultimate aim of predicting their occurrences and mitigate their impacts. Studies and monitoring of toxic phytoplankton and biotoxins have been conducted at local, national, and regional levels, each with their own particular resources. In addition, international and interdisciplinary cooperation has been invaluable in advancing the science of HABs. As an international exemplar, this cooperative research has been fostered from 2000 to 2014, by the GEOHAB programme, "Global Ecology and Oceanography of Harmful Algal Blooms" (www.geohab.info), with the financial support of SCOR (Scientific Committee on Oceanic Research) and IOC/UNESCO (Intergovernmental Oceanographic Commission of UNESCO). As stated in its Science Plan (GEOHAB, 2001): "[t]he scientific goal of GEOHAB was to improve the ability to predict HABs by determining the ecological and oceanographic mechanisms underlying their population dynamics, and integrating biological, chemical, and physical studies supported by enhanced observation and modelling systems."

GEOHAB acted as an umbrella and catalyst for organizing scientific research on HABs. Moreover, GEOHAB provided a common and interconnecting aim for individual needs and efforts. The initiatives sponsored by GEOHAB, including open science meetings, specific workshops, and training activities, were publicized as reports, books, and special issues in international journals (www.geohab.info).

At the termination of GEOHAB in 2014, the international scientific community agreed that a coordinated research approach to HABs was beneficial and still necessary (see GEOHAB, 2014). Starting in 2015, a new program, GlobalHAB, will

build on the GEOHAB Science Plan, incorporating the present challenges and opportunities that international research on HABs requires (**Figure 3**). Taking multidisciplinary and international perspectives, GlobalHAB will integrate key aspects of climate warming and global change on HABs within the context of the field of "oceans and human health."

5. CONCLUSIONS

Microalgal blooms are a natural part of the seasonal cycle of the marine ecosystems around the world. They are key components of the structure and dynamics of the oceans and thus sustain the benefits (food supply, recreation, commerce, livelihood,) that humans obtain from this aquatic environment.

However, some microalgal blooms can be harmful to human health, impact valued fisheries, and degrade other marine and coastal ecosystem services. The impacts of these HABs comprise acute and chronic health effects in humans, financial losses from contaminated seafood, mortalities of farmed fish, reduced coastal tourism and alter socio-cultural aspects. The losses due to HABs of passive values that humans place on protected species and extraordinary marine ecosystems are more difficult to quantify. There is evidence in some littoral areas that human pressures may have increased the occurrence of HABs. Further, global warming and changes in the climate regime also could affect HAB occurrences and toxicity, although forecasting the possible trends is still speculative.

At the beginning of the XXIst century, with expanding human populations, particularly in coastal and developing countries, there is an urgent need to prevent and mitigate the impacts that HABs pose on human health and wellbeing.

Because HABs are natural phenomena, it is not possible to prevent their occurrence. However, the scientific research conducted along the last decades, with the support of stakeholders, policy makers and the general public, has improved the understanding of HAB dynamics.

The achieved insights allow defining key priorities and designing strategies to mitigate the HABs impacts. In this paper, we have summarized part of the present knowledge and available tools to address this general objective. Major recommendations for the road map include:

* Integrate both ecosystem and human health monitoring for HAB impacts. This effort requires maintaining or expanding existing HAB and biotoxin monitoring, and implementing new monitoring programmes where necessary. Ideally this should include the monitoring of physico-chemical and meteorological variables to help ascertain the real effects of climate and other environmental changes on HAB occurrences and their impacts.

* Ascertain real trends in ciguatera fish poisoning incidence, and provide informed projections of potential future trends.

* Ascertain the risks of new emerging HABs and biotoxins (e.g., azaspiracid food-borne poisonings, BMAA and neuromuscular diseases, and respiratory irritation in new areas impacted by *Ostreopsis* blooms).

* Investigate the responses of HABs (especially regarding toxin production) to multifactorial physico-chemical climate drivers and the potential of marine microalgae to adapt genetically and phenotypically to the unprecedented rapidity of current climate and other environmental changes. This will require multidisciplinary collaboration and appropriately scaled experimental designs.

* Maintain and reinforce initiatives and local and international policies to reduce human pressures on the marine environment that may increase the occurrence of HABs and the severity of associated events.

* Investigate possible interconnections between socio-cultural aspects of human wellbeing and HAB events.

* Advance in the estimation of the economic costs of HAB events.

* Develop an increased public "ocean literacy" and expanded engagement with coastal and ocean stakeholders.

Overall, we emphasize that collaborative research across natural and social scientific disciplines, as for example, the Florida Red Tide Research Group and GEOHAB, can lead to significant advances in our understanding of HABs, helping to develop approaches at local and global levels to lessen their impacts on public health and human wellbeing.

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FIGURE LEGENDS

Figure 1. Conceptual links between the main drivers (natural dynamics, climate change and global warming and other anthropogenic forcings) involved in the occurrence of HABs, the main impacts of HABs on humans health and wellbeing, and some of the tools to decrease these effects.

Figure 2. Biotoxin transfer pathways through the marine food web to humans. A biotoxin-producing organism, such as the dinoflagellates *Dinophysis acuta* or *Alexandrium catenell*a, is bioaccumulated by shellfish, which are apparently not affected by saxitoxin or lipophilic biotoxins. Consumption of the contaminated shellfish is a traditional way of diarrheic or paralytic poisoning (DSP, PSP). Alternatively, some toxicogenic species attach to surfaces (macrophytes, corals) by an endogenous mucus (e.g., *Gambierdiscus, Ostreopsis, Prorocentrum lima*). Fragments of corals or macrophytes covered by the microalgae enter the food web through ingestion by herbivorous fish. This is the transmission mechanism of ciguatera fish poisoning (CFP). Certain fishes can also experience some sort of poisoning.

Figure 3. Main elements of the international GEOHAB (2000 – 2014) and GlobalHAB (2015-2018) programmes, that aim to contribute to the advance of the research on HABs.

Box 1. Main HAB Toxic Syndromes (in alphabetic order), Biotoxins (T), Causative Organisms (O), Symptoms (S), Route of exposure (E), Main Geographic Affected Areas (A), some References (R)

*** *Amnesic Shellfish Poisoning* (ASP):**

T: Domoic acid and isomers.

O: *Pseudo-nitzschia* spp. and *Nitzschia*.

S: Nausea, vomiting, diarrhoea, headache, dizziness, confusion, disorientation, short-term memory deficits, and motor weakness. Severe cases result in seizures, cardiac arrhythmia, respiratory distress, coma, and possibly death.

E: Consumption of shellfish (possibly, fish).

A: Worldwide, affecting seafood and fisheries activities.

R: Bates *et al.*, 1989; Martin *et al.*, 1993; Scholin *et al.*, 2000; Fehling *et al.*, 2004.

*** *Azaspiracid Shellfish Poisoning* (AZP):**

T: Azaspiracid and its derivatives

O: Amphidomataceae (*Amphidoma languida*, *Azadinium spinosum*, *Azadinium poporum*, *Azadinium dexteroporum*)

S: Nausea, vomiting, severe diarrhea, abdominal cramps; effects on mice tests include severe damage to the intestine, spleen, and liver tissues in animal tests.

E: Consumption of shellfish

A: Seafood poisoning reported from shellfish in Europe and North America.

R: Twiner *et al.*, 2008; 2012a, b; 2014; Klontz *et al.*, 2009; Tillmann *et al.*, 2009; 2014; Hess *et al.*, 2014.

*** *Ciguatera Fish Poisoning* (CFP):**

T: Ciguatoxin

O: *Gambierdiscus spp.*, *Fukuyo spp.*

S: Nausea, vomiting, diarrhoea, numbness of mouth and extremities. Neurological symptoms may persist for several months.

E: Consumption of coral reef fish

A: Endemic in the tropics and subtropics, expanding to temperate latitudes.

R: Friedman *et al.*, 2008; Litaker *et al.*, 2010; Chinain *et al.*, 2010a, b; Tester *et al.*, 2014.

*** *Diarrheic Shellfish Poisoning* (DSP):**

T: Okadaic acid and its derivatives (dinophysistoxins)

O: *Dinophysis* spp., *Prorocentrum lima*

S: Nausea, vomiting, severe diarrhoea, abdominal cramps, respiratory distress;

E: Consumption of shellfish

A: Worldwide, affecting seafood and fisheries activities.

R: Yasumoto *et al.*, 1980; Kat, 1983; Reguera & Pizarro, 2008; Raine *et al.*, 2010; Reguera *et al.*, 2014.

*** *Neurotoxic Shellfish Poisoning* (NSP) and respiratory irritation:**

T: Brevetoxins.

O: *Karenia brevis* (predominantly).

S: By seafood poisoning: nausea, temperature sensation reversals, muscle weakness, and vertigo. Exposure to aerosols related to respiratory and eye irritation particularly for asthmatics.

E: Consumption of shellfish (and fish at least for marine mammals); inhalation of marine aerosols during active blooms.

A: Particularly in the Gulf of Mexico and Japan, China, Korea, New Zealand.

R: Watkins *et al.*, 2008; Fleming *et al.*, 2011.

*** *Palytoxicosis* (foodborne poisoning) and other irritative symptoms:**

T: Palytoxin, Ostreocin, Ovatotoxin

O: *Ostreopsis* spp.

S: Associated to food-borne poisoning: nausea, vomiting, severe diarrhoea, abdominal cramps, lethargy, tingling of the lips, mouth, face and neck, lowered heart rate, skeletal muscle breakdown, muscle spasms and pain, lack of sensation, myalgia and weakness, hypersalivation, difficulty in breathing. Exposure to aerosols: eye and nose irritation, whinorrhoea, general malaise, fever . Cutaneous irritations in beach swimmers.

E: Consumption of seafood; inhalation of marine aerosols; direct contact with water.

A: Food-borne poisoning in the tropics and subtropics; respiratory and cutaneous irritations in Mediterranean beaches.

R: Deeds & Schwartz, 2010 (references there in); Tubaro *et al.*, 2011; Ciminiello *et al.*, 2010; 2013; Vila *et al*, 2012.

*** *Paralytic Shellfish Poisoning* (PSP):**

T: Saxitoxin and derivatives.

O: *Alexandrium* spp., *Pyrodinium bahamense* var. *compressum* and other species, *Gymnodinium catenatum*, some calcareous red macroalgae

S: Nausea, vomiting, diarrhoea, numbness and tingling of the lips, mouth, face and neck. Severe cases can result in paralysis of the muscles of the chest and abdomen leading to death.

E: Consumption of shellfish, crustaceans, fish.

A: Worldwide, affecting shellfish activities.

R: Ayres, 1975; Gaines & Taylor, 1985; Anderson *et al.,* 1989; 2005a; 2005b.

Box 2. Representative examples of HABs that affect marine organisms or ecosystems, with effects on wellbeing, and on human health in some cases.
Events presented following the alphabetic order of the Causative organism (CO). The Type (T) of bloom, their Effect/mode of action in the marine organisms or ecosystem (E/m-a), Effects on humans (E-h), Main Geographic Affected Areas (A) and some References (R) are indicated.

General information. Certain HABs affect marine organisms and ecosystems, due to the accumulation of biomass of particular taxa, which may or may not produce biotoxins.

In most cases, fish-killing HAB species produce haemolytic or cytotoxic biotoxins, which cause necrotizing degeneration of the fish gills. Other, more rare or more recently discovered combinations of fish-killing algae and their biotoxins include goniodomins (produced by *G. pseudogonyaulax*), amphidinols (synthesized by *Amphidinium klebsii* and *A. carteri*; reviewed by Louzao *et al.*, 2014) and karlotoxins from *Karlodinium* spp. (Bachvaroff *et al.*, 2008; Place *et al.*, 2014; Van Wagoner *et al.*, 2010). In many cases though, the toxic compound has not yet been clearly identified.

The breakdown of cells during the decline of a bloom, with the subsequent degradation and utilization of the organic matter by bacteria can result in low oxygen concentrations of isolated bottom water, causing subsequent macrofauna mortalities. Other impacts on the ecosystem include: the reduction of light penetration, production of excess ammonia, physical damage of fish gills, and hypothermia in marine birds due to the accumulation of surfactant-like proteins.

Here we list examples of many microalgae and a macrophyte involved in HAB events. More details and examples of these blooms, mainly high biomass blooms can be found, among others, in e.g. GEOHAB, 2001; 2006; 2010 (download free from www.geohab.info).

CO: *Akashiwo sanguinea* (Dinophyceae)
T: High biomass, non toxic.
E/m-a: Extensive marine birds mortality caused by hypothermia. The microalgae produced high amounts of organic matter that accumulated at the sea surface. The foam contained surfactant-like proteins, which destroyed the waterproof

and insulation characteristics of the bird feathers. E-h: Unknown R: Jessup *et al.*, 2009. A: Pacific Northwest (Monterey Bay, California, USA).
CO: *Chaetoceros wighami, C. debile* (Bacillariophyceae); *Dictyocha speculum* (Silicoflagellate). T: High biomass, non toxic. Physical damage (silicic cell cover) of the fills gills. E/m-a: Farmed fish kills. E-h: Economic losses (several million pounds). R: Bruno *et al.*, 1989; Treasurer *et al.*, 2003. A: Europe (Loch Torridon, Scotland; Shetland Isles).
CO: *Chattonella antiqua* and *C. marina* (Raphidophyceae). T: High biomass, toxic (haemolytic, haemagglutinating and neurotoxic effects, molecule similar to brevetoxin). E/m-a: Aquaculture fish and natural fauna kills. E-h: Economic losses (0.5 billion USD in 1972; Australian 45.0 million AUD losss of caged bluefin tuna in April 1996). R: Marshall & Hallegraeff, 1999, and references cited therein. A: Japan, Australia, India, Florida and China.
CO: *Cochlodinium polykrikoides, Cochlodinium* spp. (Dinophyceae) T: High biomass, toxic. The toxic compound and mechanism have not been identified yet, with controversial results (Tang & Gobler, 2008, and refs there in). Toxicity could be caused by non-hydrogen peroxide, highly reactive, labile biotoxins such as ROS-like chemicals. E/m-a: Wild and farmed fish kills; coral and shellfish. E-h: Economic losses. Hundreds of millions of USD in fisheries losses in Korea alone; more than 3.0 million USD in Vancouver (in 1999); in the Arabian Gulf and Gulf of Oman, the long lasting *Cochlodinium* bloom of 2010 killed thousands of tons of fish, limited traditional fishery operations, damaged coral reefs, impacting coastal tourism, and forcing the closure of desalination systems. R: Yuki & Yoshimatsu, 1989; Kim *et al.*, 1999; Whyte *et al.*, 2001; Gobler *et al.*, 2008; Richlen *et al.*, 2010; Kudela & Gobler, 2012, and references cited therein.

A: North America, Asia, Australia, and Europe.
CO: *Heterosigma akashiwo* (Raphidophyceae). T: High biomass, toxic. No identified toxic nor toxicity mechanism, which may affect other aquatic organisms (zooplankton, copepods, benthic larvae). E/m-a: Aquaculture fish kills. E-h: Economic losses. R: Black *et al.*, 1991, Yamochi, 1989; MacKenzie, 1991; Powers *et al.*, 2015. A: Atlantic and Pacific coast: Canada, Chile, Japan and New Zealand.
CO: *Karenia brevis* (Dinophyceae). T: High biomass, toxic (brevetoxin, haemolytic). E/m-a: Toxicity to humans and marine fauna by direct ingestion or aerosolization; manatee mortality during the active bloom phase; dolphin and manatee poisoning and mortality through the ingestion of contaminated fish and aquatic plants during the senescence phase of the bloom. Fish kills. E-h: Health costs; tourism losses, passive use losses; costs of beach cleanups. R: Tangen, 1977; Steidinger *et al.*, 1998; Bossart *et al.*, 2002; Magaña *et al.*, 2003; Flewelling *et al.*, 2005; Naar *et al.*, 2007. A: Gulf of Mexico, Florida, North Caroline.
CO: *Karenia mikimotoi* (Dinophyceae). T: High biomass, toxic (gimnocin, haemolytic). E/m-a: Fish kills. Mortalities of marine fauna. E-h: Economic losses; passive use losses. R: Dahl & Tangen, 1990, 1993; Nakamura *et al.*, 1995; Gentien, 1998; Raine *et al.*, 2001; Satake *et al.*, 2002; Silke et al,. 2005; Vanhoutte *et al.*, 2008; Davidson *et al.*, 2009Campbell *et al.*, 2014a. A: Asian and Australian, Northern European waters.
CO: *Noctiluca* (heterotrophic Dinophyceae). T: High biomass, non toxic. E/m-a: Hypoxia and excess ammonia in the environment; unpleasant odours; water colour discoloration. E-h: Economic losses (on tourism, non estimated). R: Bricelj & Lonsdale, 1997; Elbrächter & Qi, 1998; Murray & Suthers, 1999.

A: Worldwide.
CO: *Ostreopsis* cf. *ovata*, *O. siamensis* (benthic Dinophyceae) T: High biomass, toxic. E/m-a: Cells attach to corals, macrophytes or macrofauna by mucous substances. Toxicity (Palytoxin and analogues) to marine fauna by direct ingestion or by anoxia. The particular mechanisms have not been identified yet. E-h: Respiratory irritation, possible gastrointestinal illness R: Shears & Ross, 2009; Mangialajo *et al.*, 2011 and references cited therein. A: Mediterranean, New Zealand, Brasil, Japan.
CO: *Phaeocystis* (Prymnesiophyceae). T: High biomass, non toxic. E/m-a: Production of foam or mucilage (alteration of gas diffusion and rheologic properties) causing farmed fish kills; discoloration and repellent odour can impact tourism. E-h: From ~0.7 USD million in Vietnam to ~7.5 million USD in Asian aquaculture (1997, Quanzhan Bay, Fujian province, China). R: Lancelot *et al.*, 1997; Schoeman *et al.*, 2005; Hai *et al.*, 2010 and references cited there in; Arin *et al.*, 2013. A: Asian coastlines, North Sea, Antarctica.
CO: *Prymnesium parvum* (Prymnesiophyte). T: High biomass, toxic. A variety of toxic compounds with lytic effects (allelopathy) that would affect other organisms in the food webs, as well as haemolytic and cytotoxic effects on fishes (Blossom *et al.*, 2014). E/m-a: Aquaculture fish kills. E-h: Economic losses (5.0 million USD). R: Kaartvedt *et al.*, 1991. A: Norwegian fjords.
CO: *Pseudochattonella verruculosa* (Dictyochophyceae). T: High biomass, toxic. E/m-a: Aquaculture fish kills. E-h: Economic losses. R: Mackenzie *et al.*, 2011.

A: New Zealand.
CO: *Pseudo-nitzschia* spp. (Bacillariophyceae). T: High biomass, toxic (domoic acid, neurotoxic). E/m-a: Morbidity and mortality of large vertebrates, including seabirds, sea lions, sea otters, selas, and possibly whales. E-h: Possible passive use losses. R: Sierra-Beltrán *et al.*, 1997; Scholin *et al.*, 2000; Hall & Frame, 2010. A: Especially, Pacific coast of North America.
CO: *Ulva* (Ulvaceae), macroscopic benthic macroalgae. T: High biomass, non toxic. E/m-a: Hypoxia in the environment; unpleasant odours; impacts on tourism. E-h: Beach cleanup costs: 87.3 million USD in China; 10.3 to 165.9 million USD in France, depending on the extent of affected areas (approximate period 1989-2006). R: Hu & He, 2008. A: China (Qingdao) during the Olympics, Atlantic French coast. In China, disrupted activities during the Olympic games in 2008.

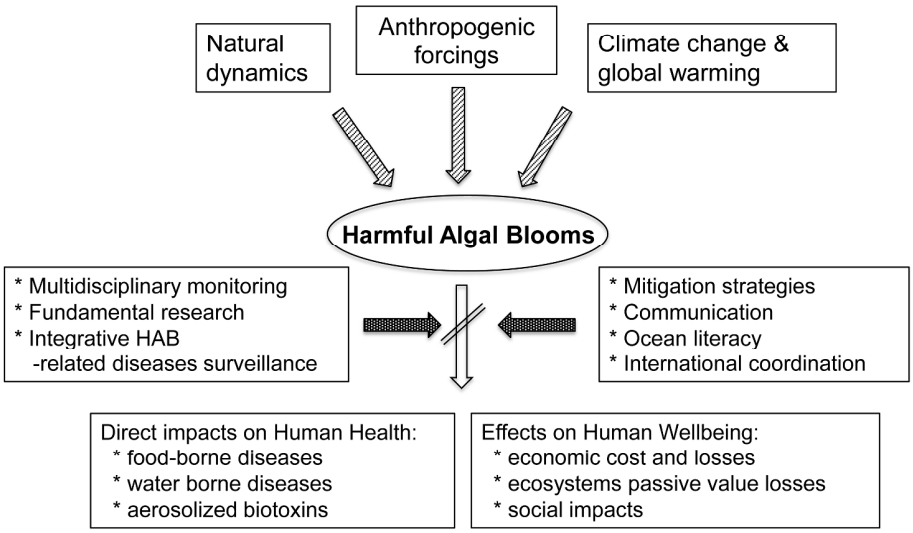

Figure 1. Conceptual links between the main drivers (natural dynamics, climate change and global warming and other anthropogenic forcings) involved in the occurrence of HABs, the main impacts of HABs on humans health and wellbeing, and some of the tools to decrease these effects.

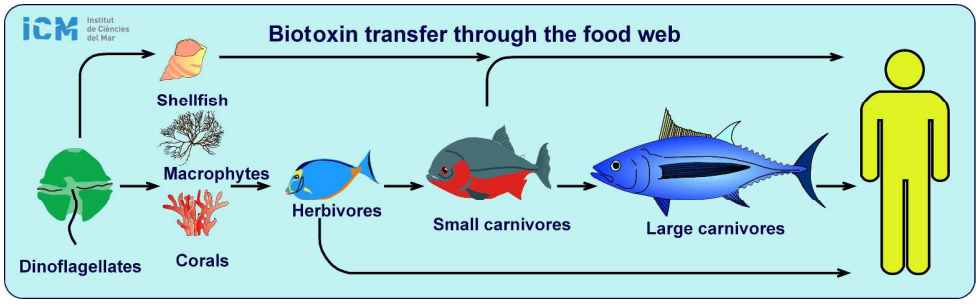

Figure 2. Biotoxin transfer pathways through the marine food web to humans. A biotoxin-producing organism, such as the dinoflagellates Dinophysis acuta or Alexandrium catenella, is bioaccumulated by shellfish, which are apparently not affected by saxitoxin or lipophilic biotoxins. Consumption of the contaminated shellfish is a traditional way of diarrheic or paralytic poisoning (DSP, PSP). Alternatively, some toxicogenic species attach to surfaces (macrophytes, corals) by an endogenous mucus (e.g., Gambierdiscus, Ostreopsis, Prorocentrum lima). Fragments of corals or macrophytes covered by the microalgae enter the food web through ingestion by herbivorous fish. This is the transmission mechanism of ciguatera fish poisoning (CFP). Certain fishes can also experience some sort of poisoning.
277x84mm (300 x 300 DPI)

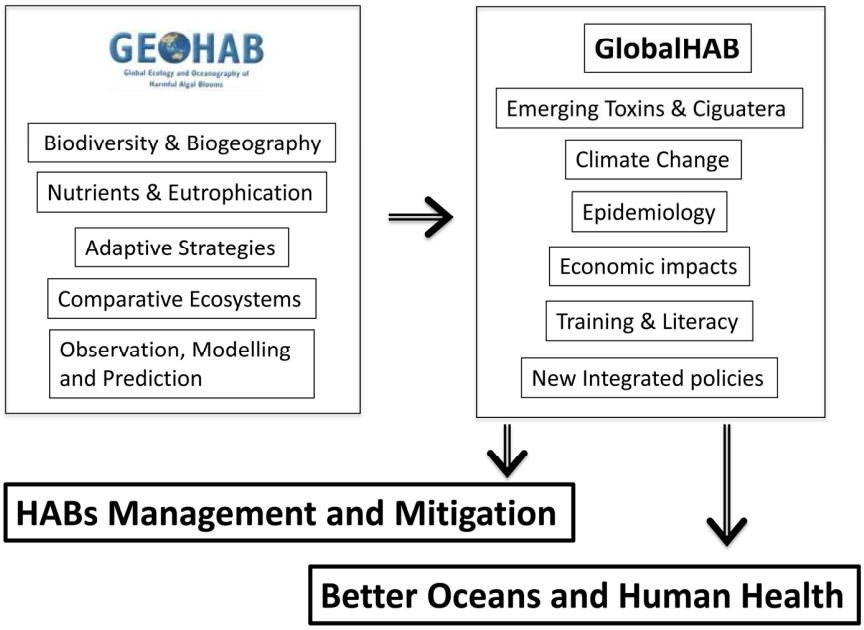

Figure 3. Main elements of the international GEOHAB (2000 – 2014) and GlobalHAB (2015-2018) programmes, that aim to contribute to the advance of the research on HABs.